PREPARATION OF β-LACTONES

By

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Abstract

Oxetan-2-ones (β-lactones) represent important synthetic targets because they are versatile synthetic intermediates and are present in a wide variety of pharmacologically relevant natural products. Using several reported methods, a homologous series of racemic C4-monosubstituted and *trans*-1,2-disubstituted β-lactones was prepared for investigation as potential inhibitors of yeast 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) synthase. However, no general method were then available for the preparation of the corresponding *cis*-1,2-disubstituted β-lactones.

Using the mercury (II) promoted Masamune lactonization of β-hydroxy thiopyridyl ester **3-7**, *cis*-3-methyl-4-decyloxetan-2-one (**3-1**) was prepared in high yield. The requisite *syn* thiol ester was prepared starting from undecanal: (1) in one step using a titanium (IV) promoted Mukaiyama aldol condensation with silyl ketene acetal **1-28**; and (2) in three steps using a titanium (IV) promoted Evans-type aldol condensation with *N*-propionyl thiazolidinethione **4-24**, followed by conversion of the thiazolidinethione aldol adduct to thiol ester **3-7** through the corresponding free acid. Substituting *N*-propionyl thiazolidinethione **4-24** for chiral *N*-acetyl and *N*-propionyl thiazolidinethiones **4-26** and **5-16**, respectively, the Evans-type aldol condensations with undecanal proceeded with excellent diastereoselectivity (> 90 %de); this is necessary for the preparation of optically active *cis*-1,2-disubstituted and C4-monosubstituted β-lactones.

A tandem-Evans aldol-lactonization (TEAL) reaction was developed using the lithium enolates of *N*-acetyl (**5-16**) and *N*-propionyl thiazolidinethione **4-24**. Thus far, trisubstituted spiro β-lactones **6-17** and **6-19**, and C4-disubstituted spiro β-lactone **6-22**, have been successfully prepared in one-pot.

In addition to using aldol condensations to prepare the carbon skeleton for C4-monosubstituted β-lactones, a Claisen-type condensation on a glycoluril template was attempted; the advantage of this route was the potential use of well

developed asymmetric reductions of the product β-keto carboxylic acid derivative to introduce optical activity in an enantioselective preparation of C4-monosubstituted β-lactones. Unfortunately, using glycoluril **7-11**, racemic 4-nonyloxetan-2-one (**2-7v**) was produced in poor yield because of difficulties encountered removing the aldol adduct-like β-hydroxy carboxylic acid derivative from the template.

Preface

The major thrust of this thesis was to prepare 1,2-disubstituted and C4-monosubstituted β-lactones. Several key intermediates were prepared that were of interest to others, and led to several collaborative projects that will not be discussed further in this thesis. A list of relevant publications includes:

1. Mohammad Rahimizadeh, Karen Kam, **Stephen I. Jenkins**, Robert S. McDonald, Paul H. M. Harrison, "Kinetics of Glycoluril Template-Directed Claisen Condensations and Mechanistic Implications." *Can. J. Chem.*, **2002**, *80*, 517.
2. Petar A. Duspara, Cerif F. Matta, **Stephen I. Jenkins**, Paul H.M. Harrison, "Twisted Amides: Synthesis and Structure of 1,6-Dipivaloyl-3,4,7,8-Tetramethyl-2,5-Dithioglycoluril." *Org. Lett.*, **2001**, *3*, 495.
3. Paul H.M. Harrison, Petar Duspara, **Stephen I. Jenkins**, Salima A. Kassam, David K. Liscombe, Donald W. Hughes, "The Biosynthesis of Pramanicin in *Stagonospora* sp. ATCC 74235:A Modified Acyltetramic Acid." *J. Chem. Soc., Perkin Trans. 1*, **2000**, 4390.
4. William J. Leigh, Corinna Kerst, Rabah Coukherroub, Tracey L. Morkin, **Stephen I. Jenkins**, Kuangsen Sung, Thomas Tidwell, "Substituent Effects on the Reactivity of the Silicon-Carbon Double Bond. Substituted 1,1-Dimethylsilanes from Far-UV Laser Flash Photolysis of α-Silylketenes and (Trimethylsilyl) Diazomethanes." *J. Am. Chem. Soc.*, **1999**, *121*, 4744.
5. Petar Duspara, **Stephen I. Jenkins**, Donald W. Hughes, Paul H.M. Harrison, "The Biosynthesis of Pramanicin: Intact Incorporation of Serine and Absolute Configuration of the Antibiotic." *Chem. Commun.*, **1998** 2643.

Acknowledgments

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Special thanks go to my group members, both past and present, for their help and friendship over the years (in chronological order): Dr. Chris Cow, Bill Riddoch, Dr. Mohammad Rahimizadeh, Petar Duspara, Chen Hao, Adrienne Pedrech and David Liscombe. The list of fellow grad students, summer students, co-op students, post-doctoral fellows, faculty and support staff that have offered their help and friendship over the years is too long to include. I hope you all understand and accept my sincere thanks.

NSERC and McMaster University are gratefully acknowledged for their financial support.

Table of Contents

List of Abbreviations

Ac	Acetyl
Anal.	Analysis
B	Base
Bn	Benzyl
Bu	Butyl
Calcd.	Calculated
d	Doublet
dd	Doublet of Doublets
dq	Doublet of Quartets
dt	Doublet of Triplets
EIMS	Electron Impact Mass Spectrometry
equiv.	Equivalents
Et	Ethyl
EtOAc	Ethyl Acetate
FAS	Fatty Acid Synthase
FTIR	Fourier Transform Infrared Spectroscopy
h	Hour(s)
HRMS	High Resolution Electron Impact Mass Spectrometry
IC_{50}	Inhibitory Concentration for 50% Inhibition
IR	Infrared Spectroscopy
KF	Potassium Fluoride
LD_{50}	Lethal Dose for 50% Death
LDA	Lithium Diisopropylamide
LHMDS	Lithium Hexamethyldisilazide
LiO^tAm	Lithium *tert*-amylate
LiO^tBu	Lithium *tert*-Butoxide
M	Molarity

M^+	Molecular Ion
Me	Methyl
m/z	Mass / Charge Ratio
mL	Millilitre
mmol	Millimole
mp	Melting Point
MS	Mass Spectrometry
µL	Microlitre
nm	Nanometer
nmr	Nuclear Magnetic Resonance
Nu	Nucleophile
Ph	Phenyl
PKS	Polyketide Synthase
ppm	Parts Per Million
q	Quartet
quant	Quantitative
s	Singlet
s.m.	Starting Material
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl Chloride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
UV	Ultraviolet

List of Tables

List of Figures

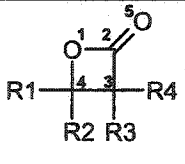
List of Schemes

Chapter 1

Introduction

Since their initial isolation, β-lactones (**1-1**) have emerged as important synthetic targets. This is not only because they have utility as versatile synthetic intermediates, but is also due to their presence in a wide variety of pharmacologically relevant natural products. Unfortunately, the utility of β-lactones has been limited by a lack of efficient methods whereby they may be prepared in both their racemic and optically active forms. It is the goal of this thesis to describe work undertaken to expand the known methods of β-lactone preparation.

In Chapter 1, the state of knowledge with respect to β-lactones is reviewed. Emphasis is placed on β-lactone reactivity, biological relevance and methods for their preparation. Preparations of poly(hydroxy) alkanoates - which are highly useful as a biodegradable and biocompatible alternative to conventional plastics derived from β-lactones - are specifically omitted in the interest of brevity.



1-1

Figure 1.1 General Structure of a β-Lactone (2-Oxetanone)

1.1 Structure of the β-Lactones

Starting in 1955, Bregman and Bauer performed one of the first structural studies using electron diffraction to determine the bond lengths and angles in the

simplest β-lactone: β-propiolactone (Figure 1.2).[1] Further studies using X-ray crystallography[2], microwave spectroscopy[3] and numerous theoretical methods[4] have supported the idea that the β-lactone ring adopts a planar conformation. This is in contrast to cyclobutane and its derivatives, which often adopt puckered conformations to avoid eclipsed interactions between hydrogens on adjacent carbons. According to Allinger, if the β-lactone is to adopt a puckered conformation, the ester bond would have to become twisted.[4b]

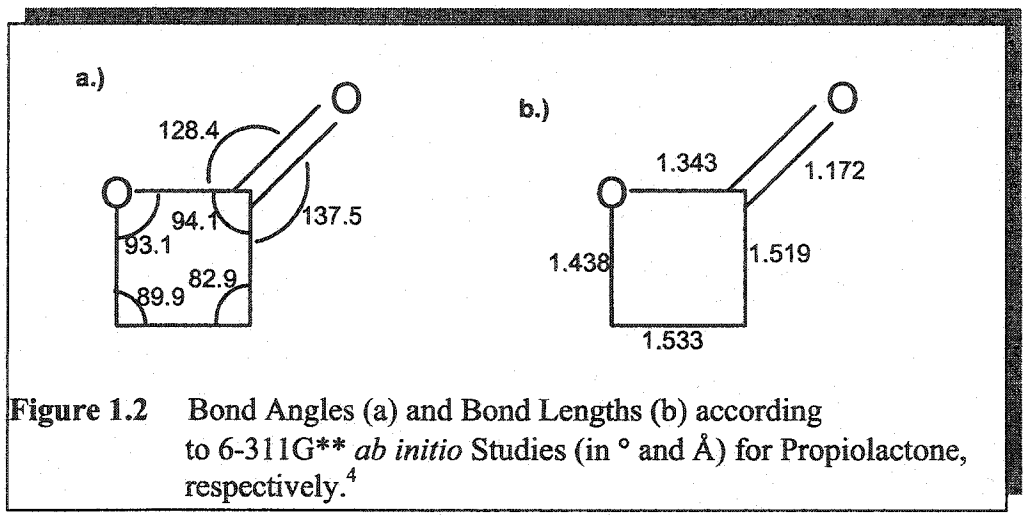
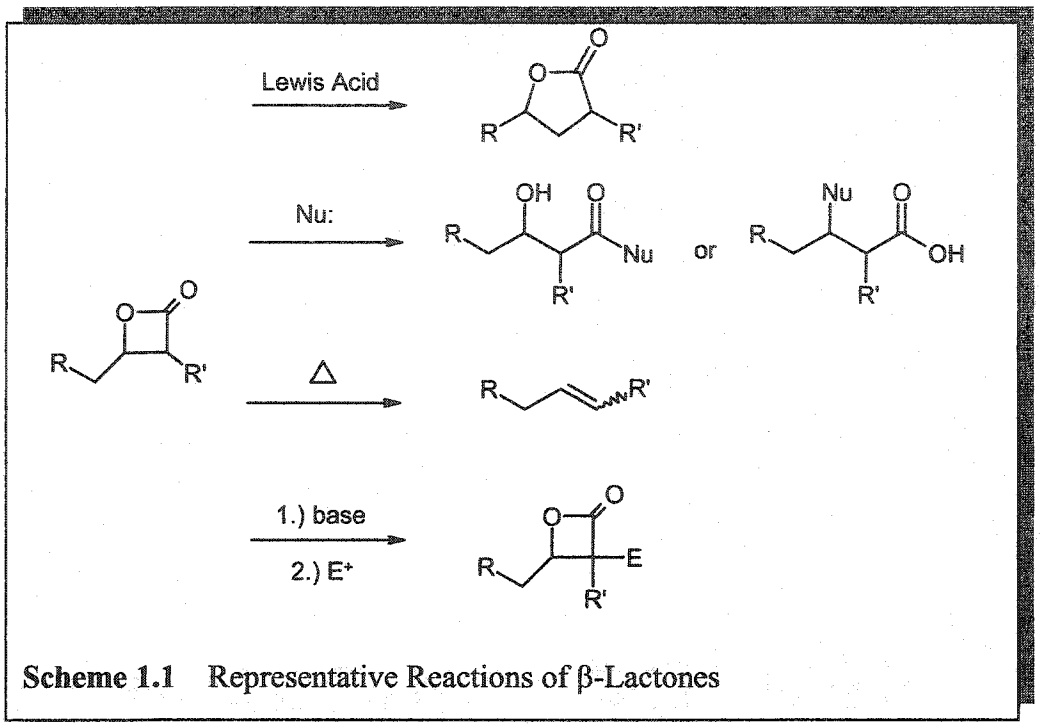


Figure 1.2 Bond Angles (a) and Bond Lengths (b) according to 6-311G** *ab initio* Studies (in ° and Å) for Propiolactone, respectively.[4]

1.2 Reactivity of β-Lactones

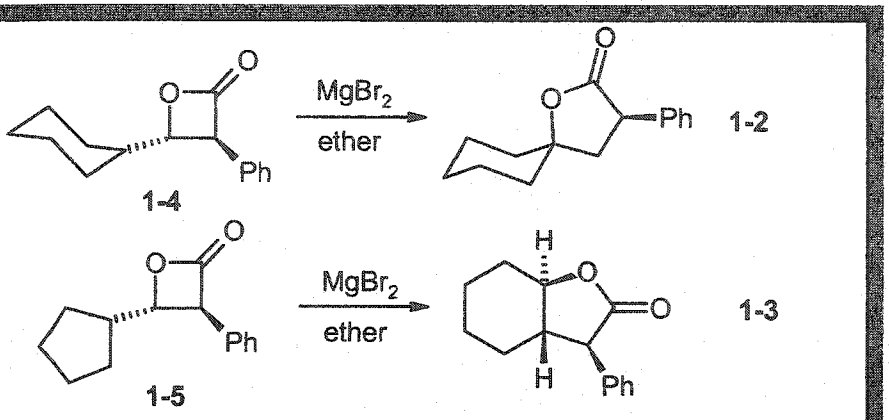
In their review of optically active β-lactones, Yang and Romo referred to β-lactones as "activated aldol products since they possess the structural features of aldol products" as well as "the inherent reactivity due to strain reminiscent of epoxides."[5] These features make β-lactones versatile intermediates capable of a wide variety of transformations that are often driven by the release of ring strain. Useful reactions of β-lactones include (Scheme 1.1): (1) Lewis acid promoted ring expansions; (2) attack by nucleophiles; (3) decarboxylation; and (4) enolate formation.



Scheme 1.1 Representative Reactions of β-Lactones

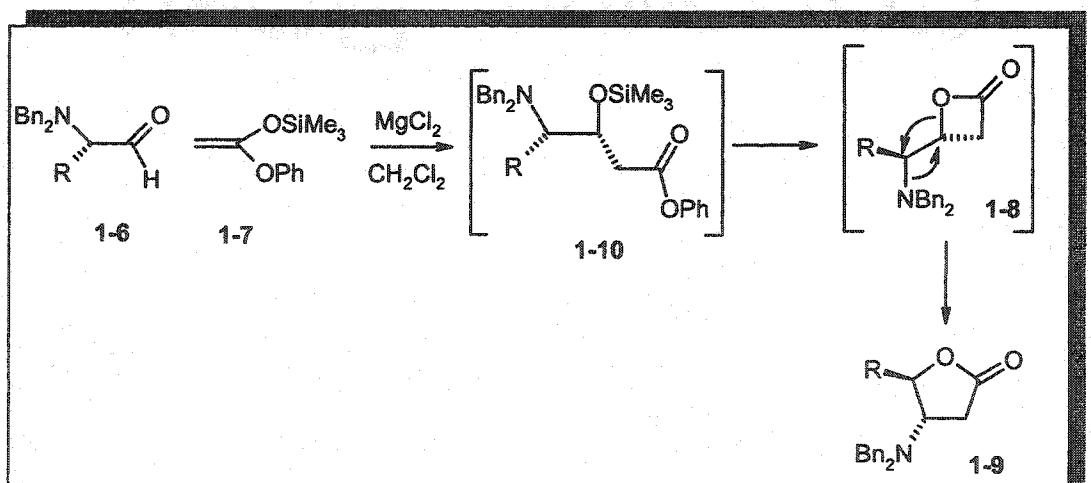
1.2.1 Lewis Acid Promoted Ring Expansion

As first demonstrated by Metzger et al. in 1967, β-lactones are capable of Lewis acid promoted rearrangement in order to relieve ring strain. Using boron trifluoride etherate, they were able to convert a β-lactone into its corresponding γ-lactone.[6] This reaction leads to either a spiro-γ-lactone (**1-2**) or a fused-γ-lactone (**1-3**) with *trans,trans* stereochemistry depending upon the size of the pendant ring (i.e. from **1-4** or **1-5**, respectively) (Scheme 1.2).



Scheme 1.2 Magnesium-Promoted Ring Expansion of β-Lactones

In 1989, Reetz et al. performed an experiment in which an *N,N*-dibenzyl protected α-amino aldehyde **1-6** underwent a non-chelation controlled aldol addition with 1-phenoxy-1-trimethylsiloxyethylene (**1-7**), to give the first example of a tandem aldolization/lactonization (Scheme 1.3).[7] Although not isolated, they proposed that intermediate β-lactone (**1-8**) immediately underwent a magnesium chloride catalyzed diatropic rearrangement to generate the corresponding optically active γ-lactone (**1-9**).



Scheme 1.3 Magnesium-Promoted Diatropic Rearrangement of a β-Lactone Prepared *In Situ* Using a Tandem Mukaiyama Aldol-Lactonization Reaction

1.2.2 Attack by Nucleophiles

The reaction of β-lactones with nucleophiles presents another fascinating route to a variety of useful organic synthons. Reaction with nucleophiles may proceed by one of two modes: (1) S_N2-like attack at C-4 leading to oxygen-alkyl bond cleavage; or (2) carbonyl substitution by attack at C-2 leading to oxygen-acyl bond cleavage (Figure 1.3).

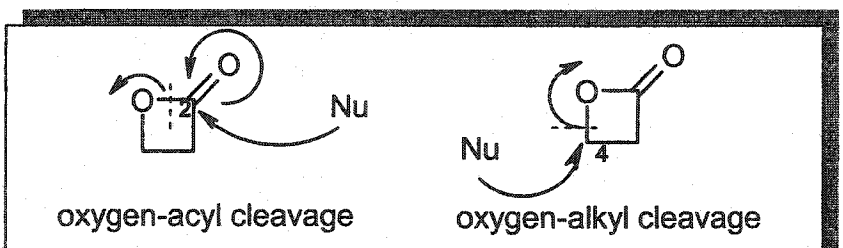
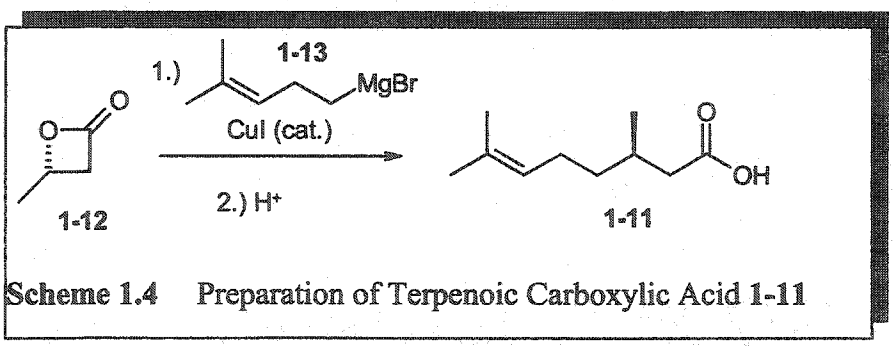
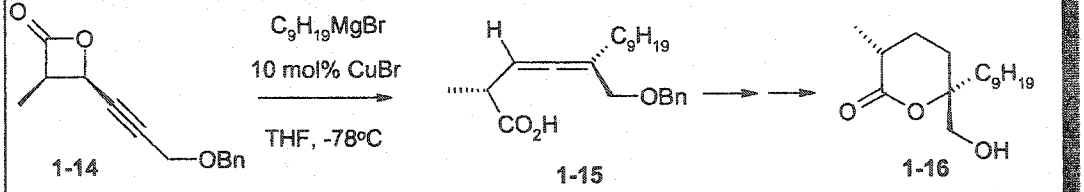


Figure 1.3 C-2 and C-4 Nucleophilic Attack of β-Lactones

Although the reaction of Grignard and organolithium reagents generally involves an initial nucleophilic attack at C-2, the final products are often complex mixtures of diols, ketones, acids and polymers. However, it has been shown that addition of a catalytic amount of Cu (I) salts to the Grignard reagent gives exclusive attack at C-4. This has been used in the preparation of terpenoic carboxylic acid **1-11** from β-lactone **1-12** (Scheme 1.4).[8] More recently, Wan and Nelson have used alkyne substituted β-lactones in the production of optically active allenes for their preparation of the naturally occurring antibiotic (-)-malyngolide (**1-13**) (Scheme 1.5).[9]



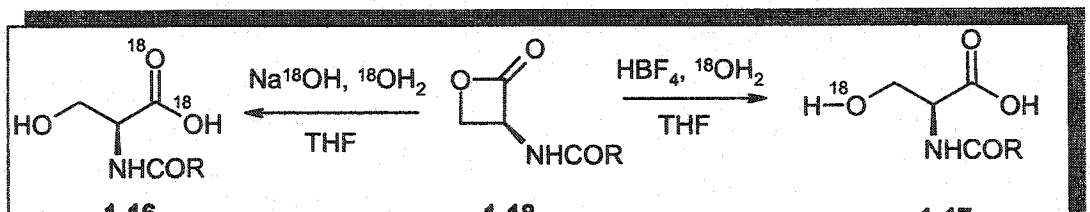
Scheme 1.4 Preparation of Terpenoic Carboxylic Acid **1-11**



1-14 1-15 1-16

Scheme 1.5 Preparation of (-)-Malyngolide (**1-16**) via Optically Active Allene **1-15** Derived from β-Lactone **1-14**

With other nucleophiles, the mechanism is highly dependent on the specific nature of the nucleophile, substrate and solvent used. During their studies on the mechanism of lactonization under Mitsunobu conditions, Ramer et al. (See Schemes 1.6 and 1.22) were able to generate ^{18}O-labelled products **1-16** and **1-17** from *N*-protected L-serine β-lactones (**1-18**) and $^{18}OH_2$. In general, they observed C-2 attack under basic or strongly acidic conditions (**1-16**), while neutral or slightly acidic conditions resulted in C-4 attack (**1-17**).[10]



1-16 **1-18** **1-17**

Scheme 1.6 Water as a Nucleophile in the Ring Opening of *N*-(Benzyloxycarbonyl)-L-Serine β-Lactones (**1-18**)

Using the same substrate, Arnold et al. went on to demonstrate that most nucleophiles, such as phenylmethyl mercaptide, pyrazole and bromide (from magnesium bromide etherate), undergo C-4 attack; only hard nucleophiles, such as sodium methoxide, were observed to preferentially attack C-2.[11] Seebach and co-workers demonstrated that enantiopure 4-methyl-2-oxetanone could undergo C-4 attack to give optically active products with aryl mercaptides, amines and azides.[12] Nelson and Spencer have used the C-4 attack of azide in the preparation of β-amino acids from a wide variety of β-lactone substrates.[13] However, Ramer et al. observed that when using β-lactones derived from L-threonine (**1-19**),

nitrogen, oxygen and carbon nucleophiles preferentially attack C-2 (Figure 1.4).[10] Presumably, the extra methyl group in **1-19** compared to **1-18**, provides steric hinderance to attack at C-4.

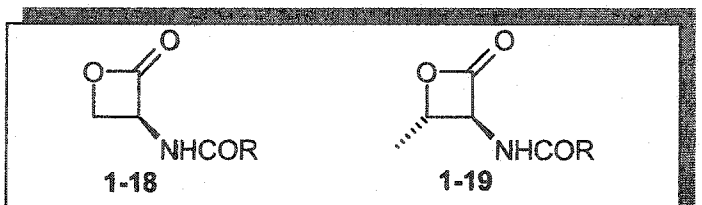
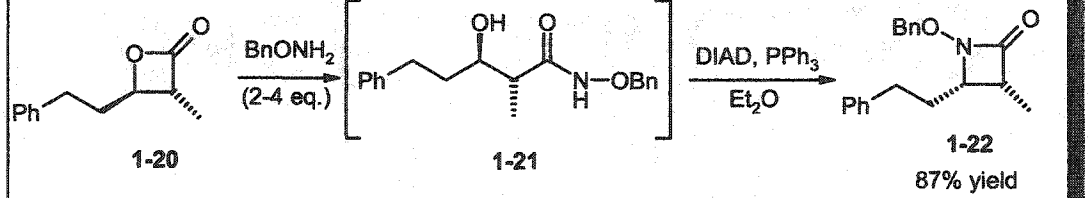


Figure 1.4 β-Lactones Derived from L-Serine (**1-18**) and L-Threonine (**1-19**)

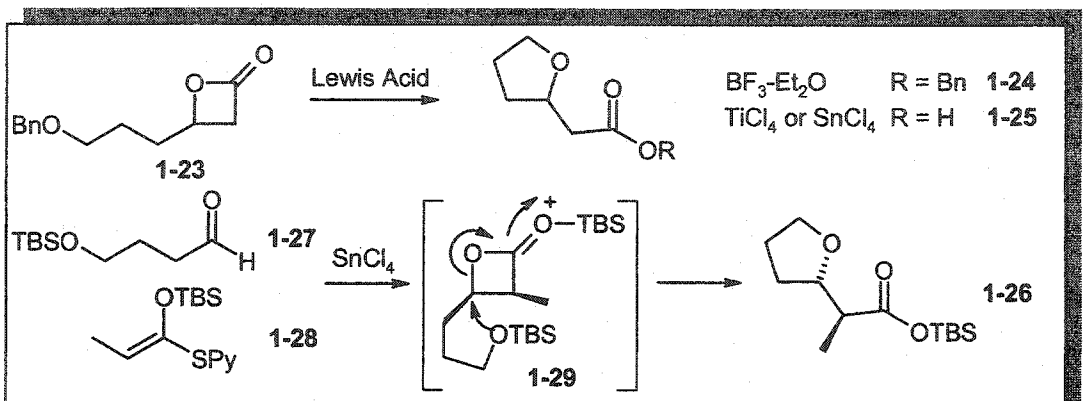
Yang and Romo have recently reported that *O*-benzylhydroxylamine (neat) preferentially attacks C-2 of **1-20** generating the corresponding optically active *N*-benzyloxyhydroxamic acid derivative (**1-21**) (Scheme 1.7). [14] They exploited this technique in the preparation of another useful class of molecule, the β-lactams, with inversion of stereochemistry at C-4 through an intramolecular Mitsunobu reaction giving **1-22**. (Reductive cleavage of the N-O bond with samarium iodide generated the *N*-unsubstituted-β-lactam in high yield.)



Scheme 1.7 Conversion of β-Lactone **1-20** to β-Lactam **1-22**

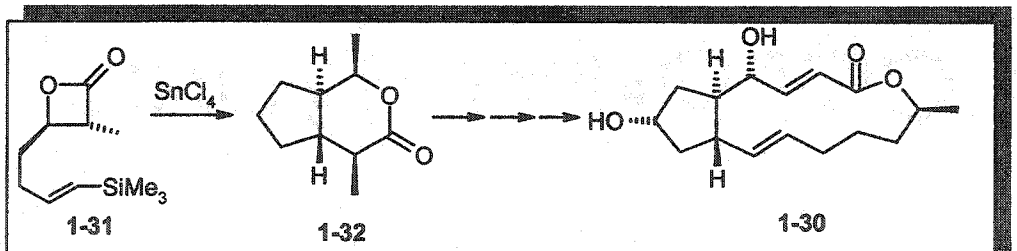
In addition, various intramolecular nucleophilic attacks have been reported (Scheme 1.8). Mead and co-workers have reported that 4(3-benzyloxypropyl)-2-oxetanone (**1-23**) may undergo ring opening via Lewis acid assisted intramolecular attack. Interestingly, the product generated depends on the Lewis acid used; boron trifluoride etherate generates the 2-benzylester substituted tetrahydrofuran (**1-24**), while other Lewis acids such as titanium tetrachloride and tin tetrachloride generate the 2-acetic acid-substituted tetrahydrofuran (**1-25**). [15,16]

Romo and Yang have recently demonstrated the utility of tin tetrachloride in a diastereoselective synthesis of tetrahydrofuran **1-26** from aldehyde **1-27** and thiopyridyl ketene acetal **1-28** (Scheme 1.8).[17]



Scheme 1.8 Lewis Acid-Promoted Intramolecular Nucleophilic Attack with Oxygen Nucleophiles

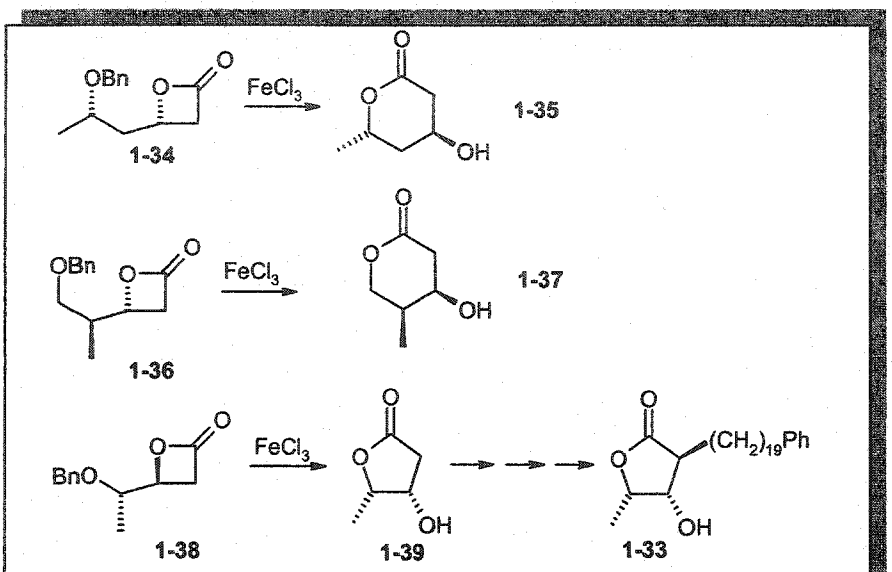
In addition to oxygen as the intramolecular nucleophile, Zhao and Romo also demonstrated that one could perform an intramolecular allylsilane addition (Scheme 1.9).[18] This sequence was used in the preparation of Brefeldin A (**1-30**), an antiviral agent capable of inhibiting protein transport, from β-lactone **1-31** via δ-lactone **1-32**.



Scheme 1.9 Preparation of Brefeldin A (**1-30**) from β-Lactone **1-31**

Zemribo *et al.* have also reported an intramolecular nucleophilic attack by oxygen on C-2 in the β-lactone moiety.[19] Using iron (III) chloride as the Lewis acid, various γ and δ-lactones (**1-35**, **1-37** and **1-39**) have been prepared from the corresponding β-lactone (**1-34**, **1-37**, and **1-38**) with excellent diastereoselectivity

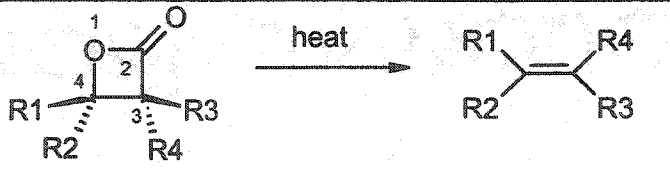
(Scheme 1.10). This method was used to prepare (-)-grandinolide (**1-33**), a natural product isolated from the bark extract of *I. grandis*.



Scheme 1.10 Iron (III) Promoted Ring Expansion of β-Lactones

1.2.3 Decarboxylation of β-Lactones

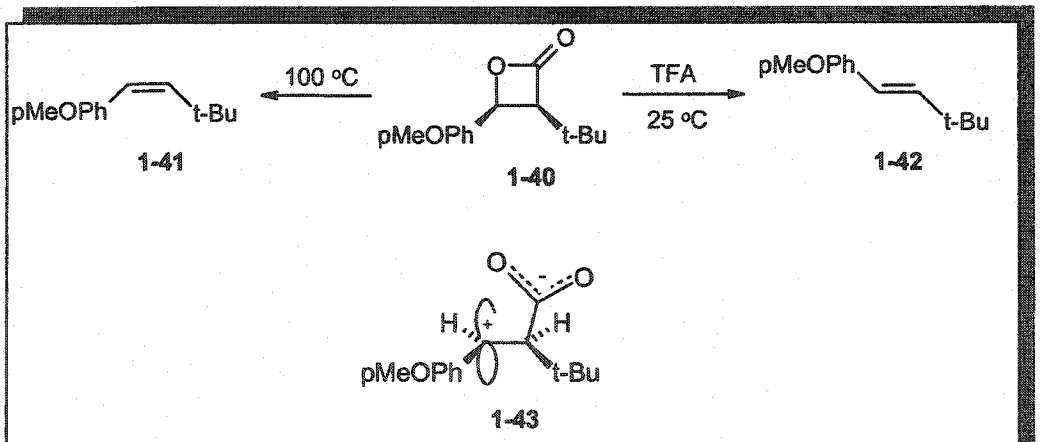
It has been known for over a century that most β-lactones will undergo decarboxylation upon mild heating.[20] Although there is presently a lot of debate over the mechanism, it is generally believed to involve *cis*-elimination of carbon dioxide to form alkenes in high yields and with high stereospecificity.[21] This approach has been used in various syntheses as an alternative to the Wittig reaction; it represents one of the very few examples of a [2 + 2] cycloreversion process that takes place with retention of configuration (Scheme 1.11).[22]



Scheme 1.11 Heat-Promoted Decarboxylation of β-Lactones

Until 1980, it was believed that the *cis*-elimination proceeded through a concerted process.[23] More recent theoretical studies describe the reaction as an asynchronous concerted process where oxygen-alkyl bond fission occurs first.[24] Electron donating substituents on C-4 promote decarboxylation, while electron withdrawing substituents slow the reaction rate.[25] This is thought to be due to stabilization of the transitory positive charge by the substituent.

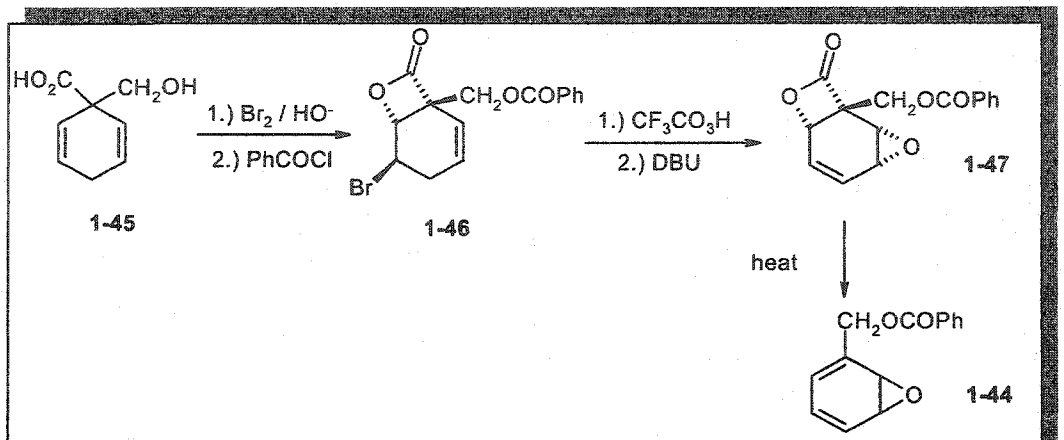
An interesting mechanistic study was performed by Mulzer and Zippel, who demonstrated that addition of 1 mol% trifluoroacetic acid (TFA) could change the decarboxylation product of *cis*-3-*t*-butyl-4-[4-methoxyphenyl]-oxetan-2-one (**1-40**) from the *Z*-olefin **1-41** to unexpected *E*-olefin **1-42** with a rate increased by a factor of 15,000 (Scheme 1.12).[26] In the production of the *Z*-olefin **1-41**, it is believed that charge interaction in the intermediate zwitterion **1-43** effectively prohibits free rotation about the C_3-C_4 bond; this rotation would relieve strong *cis* steric interaction and give rise to the *E*-olefin **1-42**. However, trifluoroacetic acid reduces this charge interaction through protonation of the intermediate carboxylate, therefore lowering the barrier to rotation.



Scheme 1.12 Stereoselectivity in the Decarboxylation of β-Lactone **1-40**

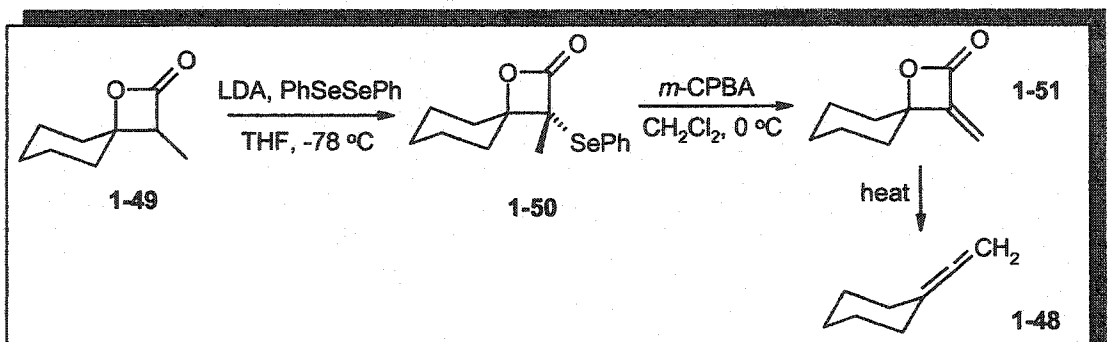
Decarboxylation of β-lactones has been used in a multitude of syntheses including the syntheses of various steroids,[27] terpenes,[28] isoflavones,[29] enol ethers[30] and benzofurans[31]. Recently, decarboxylation has been used in the

preparation of arene oxides (**1-44**) and other dihydroaromatic, as well as aromatic, compounds (Scheme 1.13).



Scheme 1.13 Preparation of an Arene Oxide **1-44** via β-Lactone **1-46**

Danheiser and co-workers have also recently reported the use of β-lactones in the production of substituted allenes (**1-48**), which represent another highly useful organic synthon (Scheme 1.14).[32]

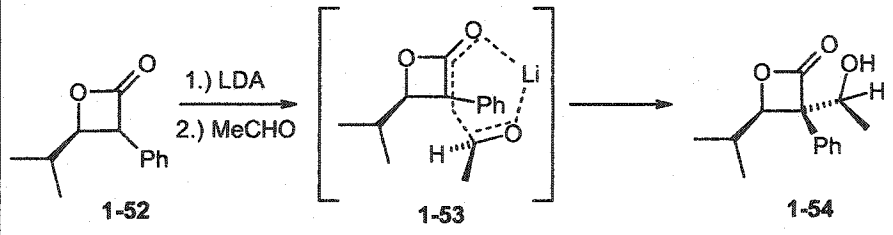


Scheme 1.14 Danheiser's Preparation Allene **1-48** via β-lactone **1-49**

1.2.4 Enolate Formation

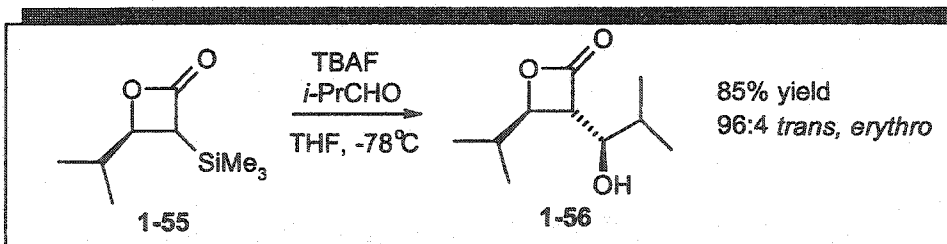
Although they represent highly strained molecules, preparative techniques for the formation of enolates from β-lactones have been known since 1980 when Mulzer et al. demonstrated that α-substituted-β-lactones could be deprotonated

with lithium diisopropylamide (LDA) at low temperature.[33] The resultant enolates are reactive to a wide variety of electrophiles, including aldehydes, alkyl halides, aryl halides and propargyl halides. Interestingly, the double chelation of lithium during the course of the reaction with aldehydes leads to a stereoselective addition in which the electrophile usually adds to the least bulky face of the enolate (Scheme 1.15).



Scheme 1.15 Reaction of the Lithium Enolate of β-Lactone **1-52** with Acetaldehyde

Mead and Yang developed a method for alkylative desilylation of α-trialkylsilyl-β-alkyl β-lactones.[34] This method eliminates the requirement for deprotonation, as the alkylation of α-unsubstituted β-lactones gives low yields. Using this one step alkylative desilylation, regardless of the starting geometry of the β-lactone, a high level of *trans* stereoselectivity is attained between the C-3 and C-4 substituents (Scheme 1.16).[35]



Scheme 1.16 One-Pot Alkylative Desilylation of α-silyl-β-Lactone **1-55**

In summary, the above examples illustrate the rich and versatile chemistry of β-lactones that make this functionality attractive in synthesis.

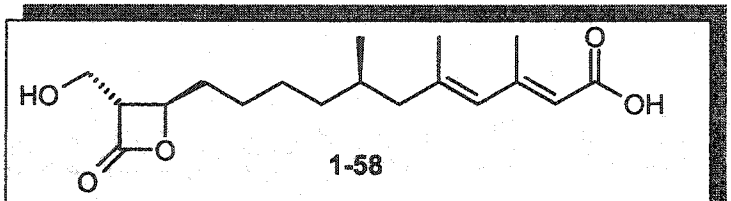
1.3 Naturally Occurring β-Lactones

Although β-lactones have been known to exist for over a century, it was long believed that this class of molecule was not found in nature. This situation changed in 1968 when anisatin (**1-57**, Figure 1.8, Chapter 1.3.2), a potent convulsant isolated from the seeds of *Illicium anisatum L.*, was fully characterized as a naturally occurring β-lactone through spectroscopy and chemical transformation experiments.[36] The last 35 years have seen a dramatic increase in the number of pharmacologically interesting naturally occurring β-lactones. Several comprehensive reviews on naturally occurring β-lactones and their preparation have recently been published, so only a brief summary of the highlights will be presented.[37] In their review of naturally occurring β-lactones, Lowe and Vederas divided the β-lactones into 3 classes according to their likely biosynthetic origin: (1) fatty acid and polyketide-like β-lactones; (2) terpenoid β-lactones; and (3) α–amino-β-lactones. This division is also used here.

1.3.1 Fatty acid and Polyketide-like β-Lactones

At present, all naturally occurring β-lactones believed to originate from a fatty acid or polyketide pathway have a *trans* relationship of substituents on the β-lactone moiety. The first member of this class was Antibiotic 1233A (**1-58**) (Figure 1.5), isolated by Aldridge et al. from *Cephalosporium* sp. in 1971.[38] Although its structure has been known since 1971, the absolute configuration of **1-58** was only recently established through the use of chemical degradation and NMR spectroscopic techniques.[39] Representing the first β-lactone to be isolated from a fungus, it has also been independently isolated from *Scopulariopsis* sp.[40] (as F-244) and *Fusarium* sp.[41] (as L-659,699). Omura and co-workers, as well as

Harrison and co-workers, have established that **1-58** is derived from four methionines and seven acetate units, using ^{13}C- and ^{2}H- labeled precursors.[42,43,44] The source of the antimicrobial activity of F-244 arises from potent specific inhibition of 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMG-CoA synthase), a key regulatory enzyme essential to the production of mevalonate in the early stages of cholesterol biosynthesis.[40,45,46] Because of its effect on cholesterol production in the body, **1-58** represents a potential drug in the treatment of hypercholesterolemia.



1-58

Figure 1.5 Structure of Antibiotic 1233A (**1-58**)

Although they bear a strong resemblance to **1-58**, the ebelactones do not exhibit any inhibitory activity against HMG-CoA synthase (Figure 1.6).[40] Ebelactones A (**1-59**) and B (**1-60**) were isolated in 1980 from *Streptomyces* sp. MG7G1 and have a polyketide origin.[47] (Through the use of ^{13}C labeled precursors, **1-59** was shown to originate from one acetate and six propionate units, while **1-60** originates from one acetate, five propionate, and one butanoate units.[48]) The structure of **1-59** was determined through X-ray crystallography of the *p*-bromobenzoate, while the structure of the homologue **1-60** was determined from spectral comparisons.[49]

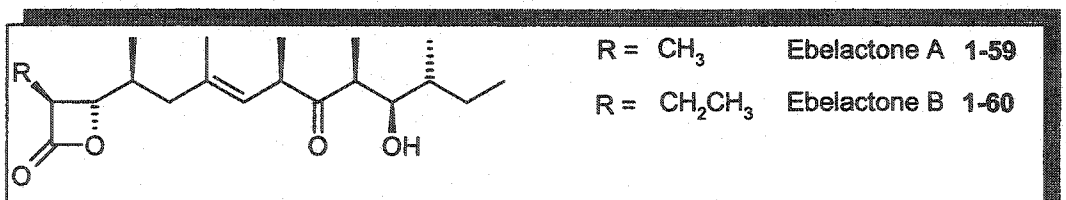


Figure 1.6 Structure of Ebelactones A (**1-59**) and B (**1-60**)

The ebelactones possess a wide range of biological activity, being potent inhibitors of esterases, lipases, carboxypeptidases, and N-formylmethionine aminopeptidases in a wide variety of animal cells.[49,50] In addition, ebelactones have also been reported to inhibit acylpeptide hydrolase[51] and cutinases[52] produced by fungal pathogens. Ebelactones may have potential as plant protection agents as all known fungal cutinases have been identified as serine hydrolases similar to esterases and lipases.[52]

Isolated from *Streptomyces* species, the natural products valilactone (**1-61**), esterastin (**1-62**) and lipstatin (**1-63**) are analogous molecules differing only in the structure of the C-4 substituent and the nature of the amino acid linked to it (Figure 1.7). These molecules represent a fatty acid derived β-lactone linked by an ester linkage to an N-acylamino acid and possess the same absolute configuration on C-3 and C-4 (oxetanone numbering) as observed in the ebelactones.

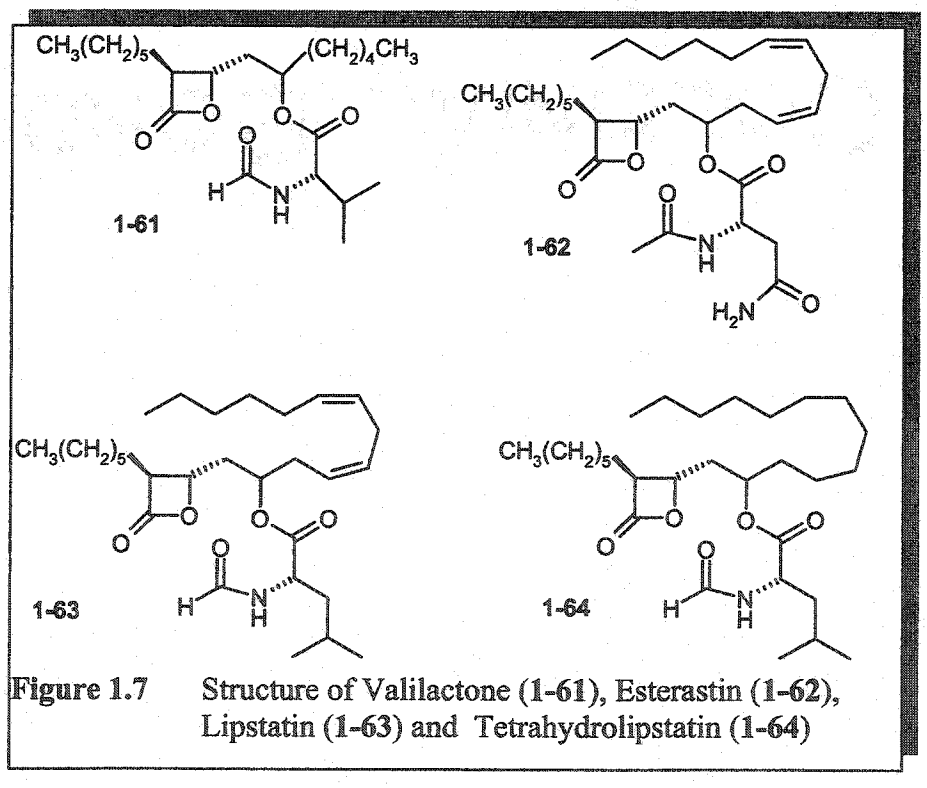


Figure 1.7 Structure of Valilactone (**1-61**), Esterastin (**1-62**), Lipstatin (**1-63**) and Tetrahydrolipstatin (**1-64**)

Valilactone (**1-61**), isolated from soil actinomycete species related to *Streptomyces alnolongus* (MD4-C1), displays esterase and lipase inhibition similar to the ebelactones.[53] Esterastin (**1-62**), isolated from *Streptomyces lavendulae*, also exhibits esterase and lipase inhibition, but differs from the ebelactones and **1-61** in that it effectively suppresses immune responses.[54,55,56] It has been used extensively to study diseases which involve lipid storage defects, such as Wolman's disease, cholesterol ester storage disease and atherosclerosis based on its inhibition of lysosomal acid lipases.[56]

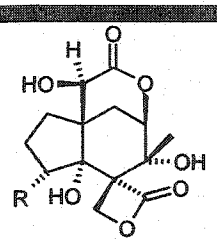
Lipstatin (**1-63**), isolated from *Streptomyces toxytricini*, is remarkably similar in structure to **1-62** and represents a highly potent irreversible pancreatic lipase inhibitor active against enzymes from a wide variety of sources, including man. [57] Because pancreatic lipase acts to cleave free fatty acids from their triglyceride precursors, **1-63** was thought to be an ideal candidate for the treatment of obesity as this should allow dietary fat to pass through the gut without being absorbed. [58] Presently the non-natural tetrahydro derivative of **1-63**, tetrahydrolipstatin (**1-64**), is used in the treatment of obesity and is marketed under the trade names Orlistat ® and Xenical® (Figure 1.7).[59] Although slightly less biologically active than **1-63**, **1-64** is still considerably potent against pancreatic lipase, and has the advantages of being more stable and easier to prepare in the laboratory.[58] Recent clinical studies have demonstrated that an appropriately modified diet supplemented with a daily intake of 50 mg **1-64** leads to sustained weight loss in humans.[60]

1.3.2 Terpenoid β-Lactone Natural Products

In nature, a number of terpenoid derived β-lactone containing natural products are known. Unfortunately, not much attention has been given to this

class of natural products; likely owing to the fact that most members of this class are potent toxins with little pharmacological potential.

In 1952, Lane et al. isolated an agent responsible for convulsant activity from the seeds of Japanese star anise (*Illicium anisatum L*).[61] In 1968, Yamada et al. used chemical transformation and spectroscopy to determine the structure of anisatin (**1-57**) and its analogue neoanisatin (**1-65**) but not their absolute stereochemistry (Figure 1.8).[36] Absolute stereochemistry was recently elucidated by Niwa et al. when they compared the product from their stereospecific synthesis to the authentic natural product.[62] These sesquiterpene-derived β-lactones represent the most powerful known poisons from plant origin (mouse LD_{50} of 1 mg/ kg) and are believed to act as non-competitive γ-aminobutyric acid (GABA) antagonists similar to the picrotoxins.[63] These molecules find use in the study of diseases such as epilepsy and Huntington's disease, which involve dysfunctions at GABA synapses.



R = OH Anisatin **1-57**

R = H Neoanisatin **1-65**

Figure 1.8 Structure of Anisatin (**1-57**) and Neoanisatin (**1-65**)

Further to these original sesquiterpenes, other β-lactone containing natural products have been isolated from this same plant. These include 2α-hydroxyneoanisatin (**1-66**),[64] 1-hydroxyneoanisatin (**1-67**),[65] 1-hydroxy-6-dehydroxyneoanisatin (**1-68**),[65] 2-oxo-6-dehydroxyneoanisatin (**1-69**)[66] and 3,4-dehydroxy-2-oxoneoanisatin (**1-70**)[65] (Figure 1.9). More recently, veranisatins A and B were isolated (**1-71** and **1-72**, respectively) from a related species, *Illicium verum*, and were also found to display convulsive effects.[67]

The only other known sesquiterpene β-lactones not related to anisatin were isolated from *Grazielia intermedia* (Figure 1.10). These include guaigrazielolide (**1-73**), [68] disynapholide (**1-74**)[69] and grazielolides A (**1-75**)[68] and B (**1-76**)[68]. To this point in time, no biological activity has been described for these compounds.

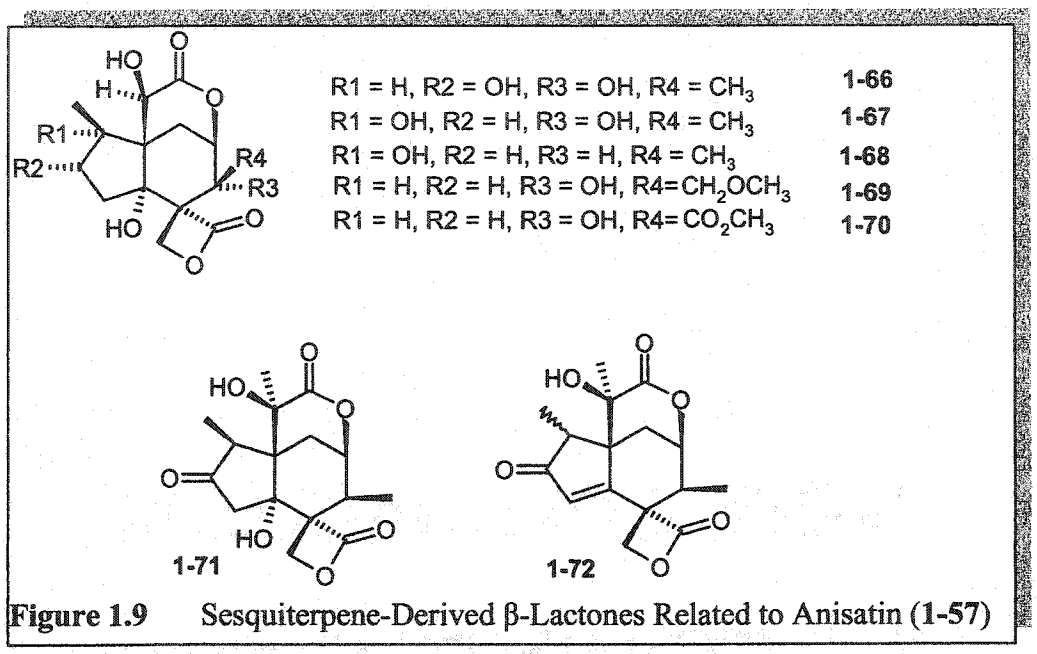


Figure 1.9 Sesquiterpene-Derived β-Lactones Related to Anisatin (**1-57**)

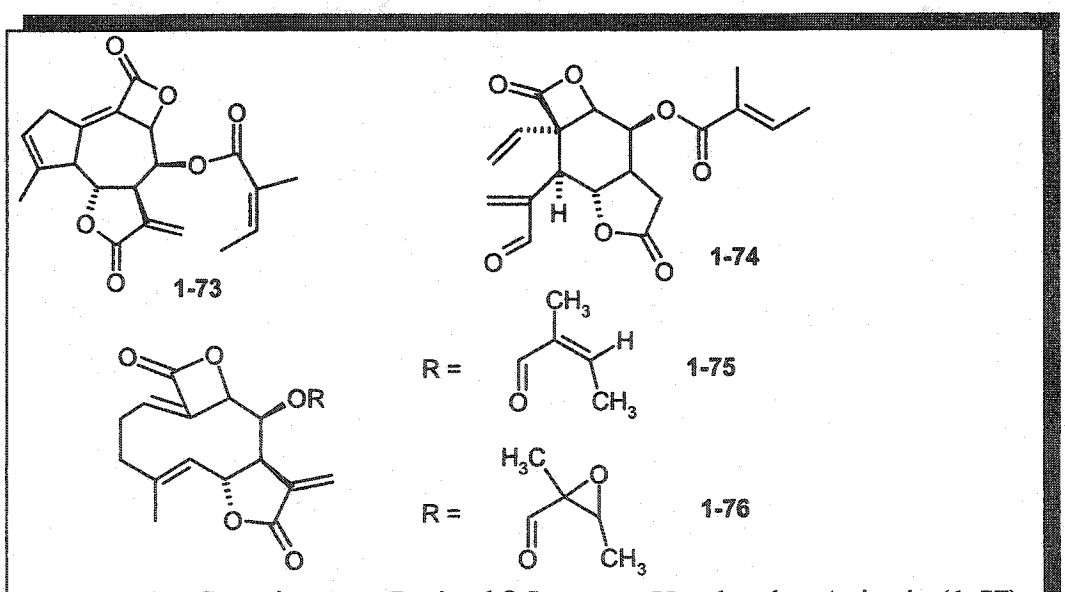


Figure 1.10 Sesquiterpene-Derived β-Lactones Unrelated to Anisatin (**1-57**)

Spongiolactone (**1-77**), isolated from the Mediterranean sponge *Spongionella gracilis*, represents the only known diterpene derived β-lactone (Figure 1.11).[70] No biological activity has been reported thus far.

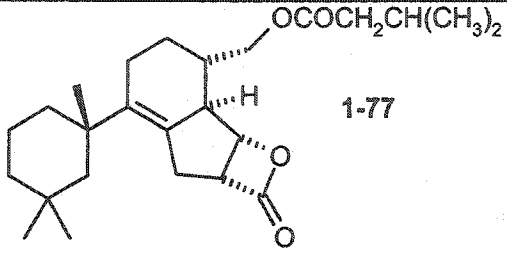
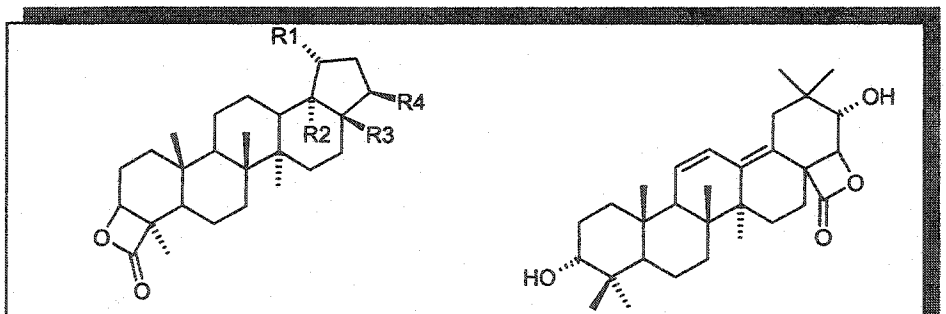


Figure 1.11 Structure of Spongiolactone (**1-77**)

Triterpene-derived β-lactones have been isolated from a wide variety of organisms. Papyriogenin G (**1-78**) was isolated from the leaves of *Tetrapanax papyriferum* and represents an oleane-type triterpene (Figure 1.12).[71] Lupeolactone (**1-79**) was isolated from *Antidesma pentandrum Merr.* and represents a lupeane-type triterpene (Figure 1.12).[72] Moretenolactone (**1-80**) was isolated from *Ficus insipidia* Willdenow and is structurally similar to **1-78**.[73]

Of the triterpene derived β-lactones, only **1-79** has any known biological activity. It has been demonstrated, on oral administration, to lower serum cholesterol levels in normal rats, as well as those artificially made hypercholesterolemic with a high fat diet.[73]



1-78 R1 = $C(CH_2)CH_3$, R3 = CH_3, R2 = R4 = H
1-80 R1 = R3 = H, R2 = CH_3, R4 = $C(CH_2)CH_3$

1-79

Figure 1.12 Triterpene Derived β-Lactones

1.3.3 α–Amino-β-lactones

The early 1980's saw the development of a new class of β-lactone containing natural products possessing an α-amino moiety. During a screening experiment in 1982 for β-lactam antibiotics, a novel N-acylated α-amino-β-lactone was isolated from Bacillus sp. SC 11,480. Named SQ 26,517, **1-81** possessed weak antimicrobial activity, and attracted attention due to its structural similarities to β-lactam antibiotics such as **1-82** (Figure 1.13).[74,75] Then in 1984, obafluorin (**1-83**) was isolated from *Pseudomonas fluorescens* (Figure 1.13).[76] Although this molecule displayed weak antimicrobial activity, it represents the first non-β-lactam antibiotic to display susceptibility to ring opening using a β-lactamase.

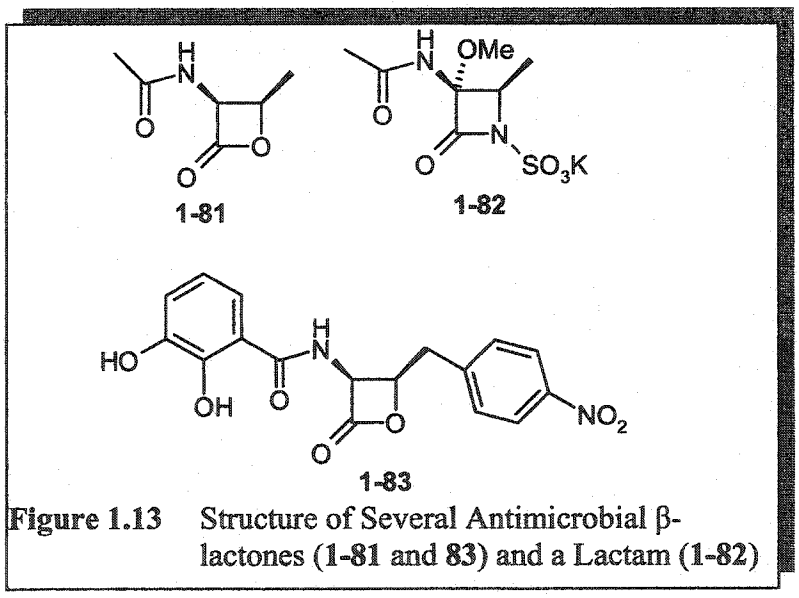


Figure 1.13 Structure of Several Antimicrobial β-lactones (**1-81** and **83**) and a Lactam (**1-82**)

In 1985 oxazolomycin (**1-84**) was discovered while screening for antibiotics with activity against Ehrlich ascites tumor (Figure 1.14).[77] Isolated from *Streptomyces* sp., its structure was elucidated using chemical modification and X-ray crystallographic studies of derivatives. It has been further suggested that resistaphylin, a potent antimicrobial agent active against Gram-positive

bacteria isolated in 1971 from *Streptomyces antibioticus*, was identical to **1-84**.[78] Further studies into the bioactivity of this molecule have revealed it to be effective in protecting plants from crown Gall disease due to its antibacterial activity against the causative agent *Agrobacterium tumefaciens*.[79] In addition to antibacterial properties, **1-84** has also been found to possess antiviral and cytotoxic activities. Its substantial biological activity is believed to lie in its ionophoric properties.[80] More recently, structurally related compounds corromycins A (**1-85**) and B (**1-86**) have been isolated from *Streptomyces hygroscopicus*.[81,82] Possessing a narrower range of antimicrobial and antitumor activity than **1-84**, they have been observed to inhibit replication of the human immunodeficiency virus (HIV).[83] The absolute and relative configuration of these analogues has yet to be determined in spite of their close structural relationship with **1-84**.

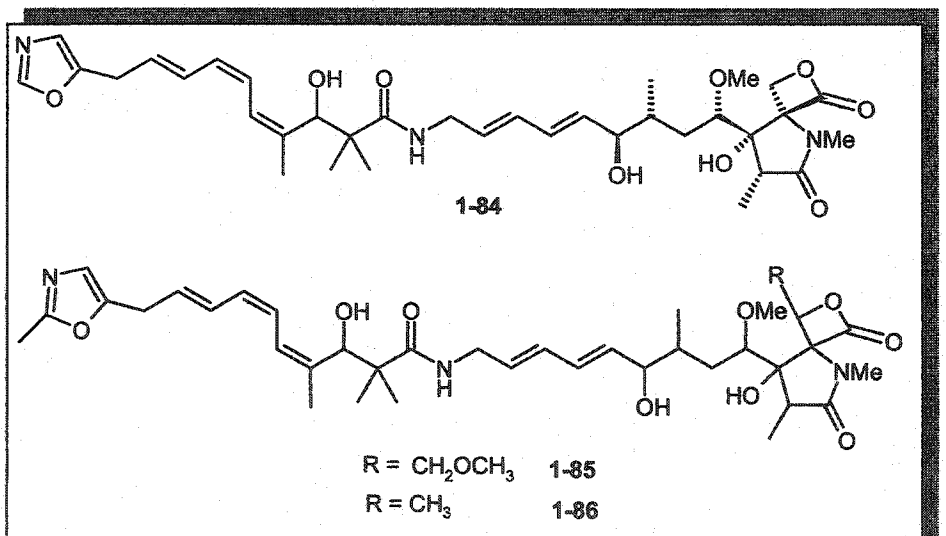


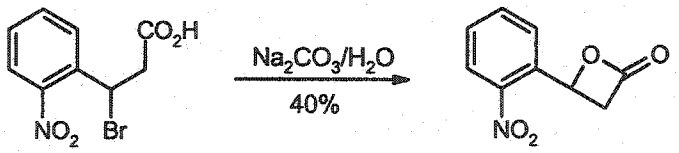
Figure 1.14 Structures of Oxazolomycin (**1-84**), and Corromycin A (**1-85**) and B (**1-86**)

In summary, there is a growing number of naturally occurring β-lactones, many of which have interesting pharmacological profiles. For this reason, and because of the application in synthesis described in Chapter 1.2, interest in

methods for the preparationof β-lactones has gained momentum. We now turn to methods for β-lactone preparation.

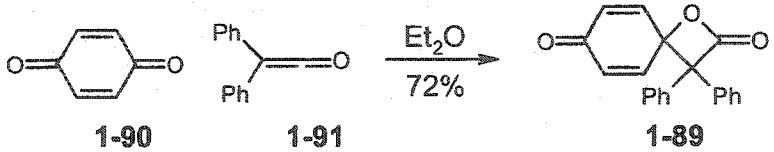
1.4 Preparation of β-Lactones

In spite of the highly strained nature of the four-membered ring in β-lactones, they have been known to exist for over a century. In 1883, Einhorn first succeeded in isolating β-lactone **1-87** from the base catalyzed cyclization of β-bromo-*o*-nitrohydrocinnamic acid (**1-88**) (Scheme 1.17).[84] Later, in 1911, Staudinger prepared β-lactone **1-89** from the [2 + 2] cycloaddition between quinone **1-90** and diphenyl ketene (**1-91**) (Scheme 1.18).[85] Until the 1950's, the [2 + 2] cycloaddition between a carbonyl compound and ketene, and the base catalyzed cyclization of β-halo carboxylic acids, represented the only known preparative methods. Since the 1950's, both the number and quality of preparative methods have increased. However, general methods for β-lactone preparation, in both optically active and inactive forms, are not as advanced as those for many other strained heterocycles.



1-88 **1-87**

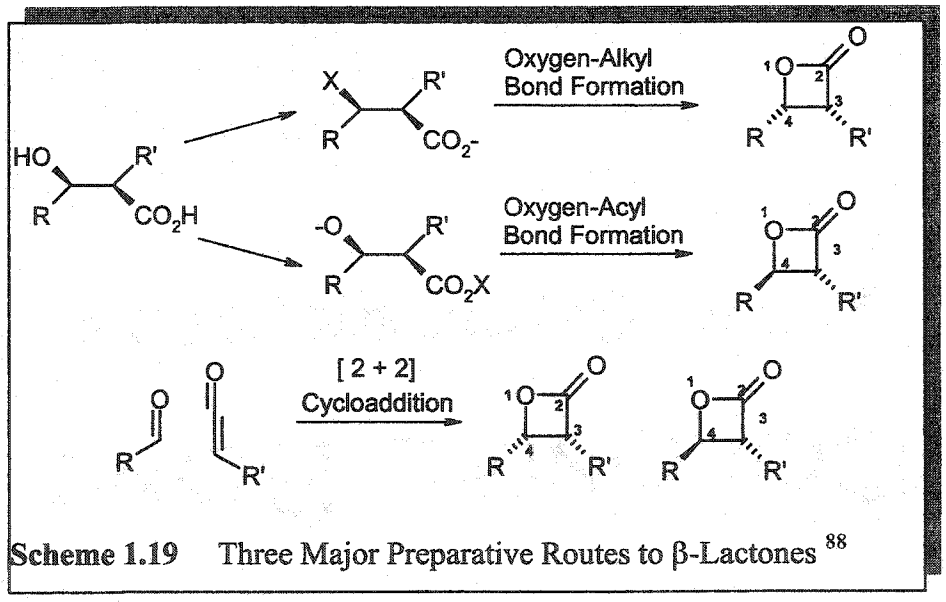
Scheme 1.17 Einhorn's Preparative Method in the Preparation of β-Lactone **1-87** from Bromide **1-88**



1-90 **1-91** **1-89**

Scheme 1.18 Staudinger's [2 + 2] Cycloaddition Approach to the Preparation of β-Lactone **1-89** from Ketene **1-91**

In the 1990's, several reviews have been published on the subject of β-lactone preparation.[86,87,88] Hence, a synopsis of the main observations along with recent developments will be presented. In their review, Pommier and Pons divided the preparative techniques into three major classes (Scheme 1.19): (1) lactonization via oxygen-acyl bond formation; (2) lactonization via oxygen-alkyl bond formation; and (3) [2 + 2] cycloaddition between a carbonyl compound and a ketene. This division is also used here.

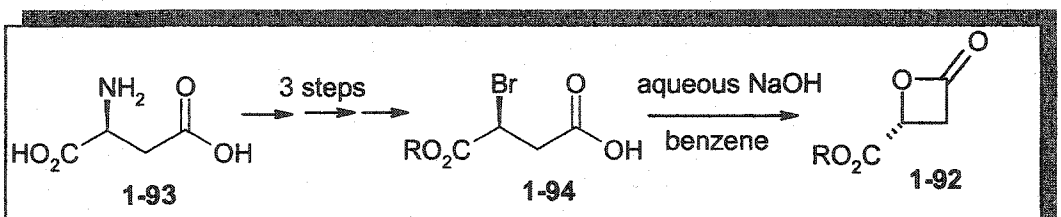


Scheme 1.19 Three Major Preparative Routes to β-Lactones [88]

1.4.1 Lactonization Via Oxygen-Alkyl Bond Formation

Lactonization via oxygen-alkyl bond formation involves the intramolecular S_N2 attack of a carboxylate onto an activated β-carbon, often with

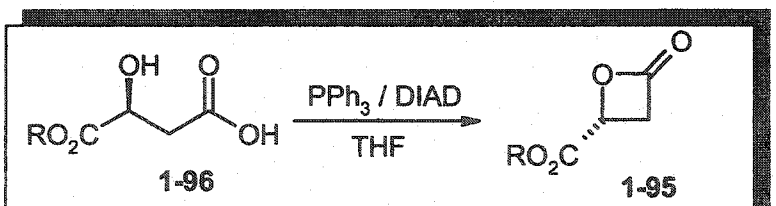
inversion of the β-stereocenter. Guerin and Vert modified Einhorn's general method using β-bromocarboxylates to produce enantiopure β-lactone precursors (**1-92**) for biodegradable polymers starting from *l*-aspartic acid (**1-93**) via bromide **1-94** (Scheme 1.20).[89] Although enantiomeric excesses greater than 99% were achieved, yields were disappointingly low.[90] Olefin production, which often accompanies β-lactone formation from β-halo carboxylic acid precursors, has made β-halo carboxylic acids unattractive substrates for lactonization.



1-93 **1-94** **1-92**

Scheme 1.20 Preparation of β-Lactone **1-92** From L-Aspartic Acid (**1-93**) via Bromide **1-94**

One of the most common oxygen-alkyl bond forming lactonization methods involves the cyclization of a β-hydroxy carboxylic acid under Mitsunobu conditions. When treated with triphenylphosphine in the presence of diethyl azodicarboxylate (DEAD), lactonization occurs with inversion at the β-stereocenter (>98% ee) via hydroxyl group activation.[91] Guerin et al. have used Mitsunobu type conditions in their preparation of optically active β-lactones (**1-95**) from the monoester of (*S*)-malic acid (**1-96**) (Scheme 1.21).[92]

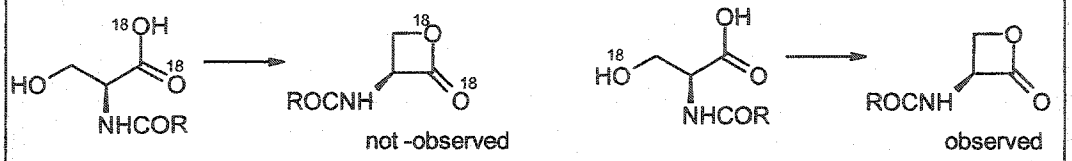


1-96 **1-95**

Scheme 1.21 Lactonization of (*S*)-Malic Acid (**1-96**) Under Mitsunobu Conditions

Arnold et al. have used Mitsunobu type conditions in their preparation of *N*-protected α-amino β-lactones.[93] Using ^{18}O labeled starting material, Ramer et

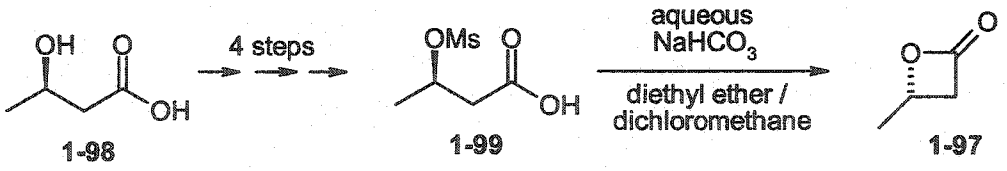
al. were able to conclude that the mechanism proceeded exclusively through hydroxyl group activation (Scheme 1.22).[94]



Scheme 1.22 Hydroxyl Activation in Serine Derivatives Occurs During Lactonization as Demonstrated by Isotope Labeling.

However, it has also been demonstrated by Mulzer *et al.* that Mitsunobu conditions may also lead to cyclization via oxygen-acyl bond formation when bulky substituents are present at C-3 and/or C-4.[95] This reaction proceeds via activation of the carboxylate and leads to retention of configuration at the β-stereocenter.

In addition to hydroxy activation by triphenylphosphine under Mitsunobu conditions, other methods are currently available. Lenz and co-workers have prepared (*S*)-butyrolactone (**1-97**) from (*R*)-β-hydroxybutyric acid (**1-98**) via mesylate **1-99** with an enantiomeric excess of >97% (Scheme 1.23).[96] Basic treatment of the mesylated β-hydroxy acid **1-98** resulted in inversion of the β-stereocenter.

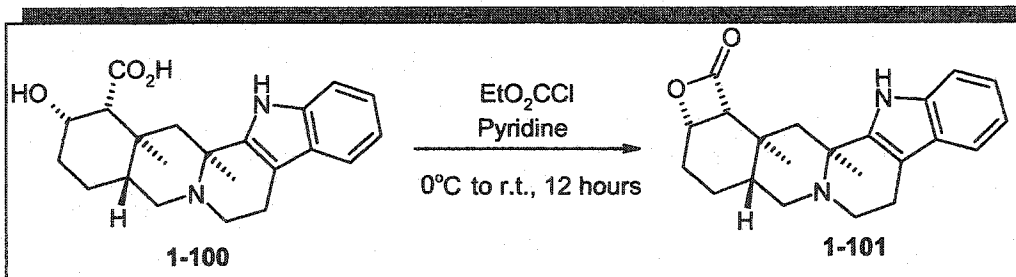


Scheme 1.23 β-Hydroxy Activation via Mesylation as a Route to β-Lactone **1-97**

1.4.2 Lactonization Via Oxygen-Acyl Bond Formation

Lactonization via oxygen-acyl bond formation involves an intramolecular attack of the hydroxyl moiety on an activated carboxyl group. This reaction occurs with retention of configuration when a β-stereocenter is present. The precursor for this type of lactonization is either a β-hydroxy carboxylic acid or β-hydroxy carboxylic acid derivative.

In 1958, Diassi and Dylion converted the carboxylic acid in yombic acid (**1-100**) to the corresponding mixed anhydride using ethyl chloroformate in pyridine. The activated carboxylic acid derivative then underwent intramolecular nucleophilic attack to give the corresponding yombic acid lactone (**1-101**) in 35% yield (Scheme 1.24). [97]

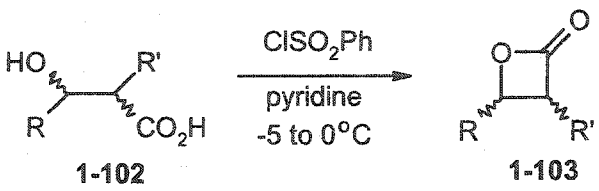


1-100 **1-101**

Scheme 1.24 Preparation of Yombic Acid Lactone **1-101** via the Mixed Anhydride of Acid **1-100**

This procedure was greatly improved by Adam and co-workers, who used benzenesulfonyl chloride in place of ethyl chloroformate (Scheme 1.25). [98] Representing the most commonly used method for preparing β-lactones in their optically active and optically inactive forms, this process is capable of generating β-lactone products in high yield from a wide variety of β-hydroxy carboxylic acid precursors. However, it is limited in its requirement for a substituent at the α-position; this is thought to be due to the need for a Thorpe-Ingold effect. In addition, this method is not compatible with small substituents at the β-position (C-4), which often result in overwhelming polyester formation. Since its development, numerous sulfonates such as *p*-toluenesulfonyl chloride,[99] *p*-

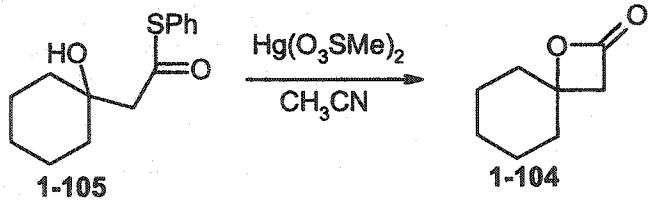
bromobenzenesulfonyl chloride[100] and methanesulfonyl chloride have been used.[101]



1-102 **1-103**

Scheme 1.25 Adam's Mixed Anhydride Lactonization Reaction

In addition to mixed anhydrides, thiol esters have been used in conjunction with various metal ions. In the late 1970's, Masamune et al. prepared spiro-β-lactone **1-104** in 94% yield from its corresponding β-hydroxy thiol ester, **1-105**, in the presence of mercury (II) methanesulfonate (Scheme 1.26).[102] Their method has a distinct advantage over Adam and co-worker's mixed anhydride strategy because there is no requirement for an α-substituent. However, due to the inherent toxicity of mercury, numerous other thiophilic metals have been substituted with less attractive results; these include silver (I) and copper (I) and -(II) salts.

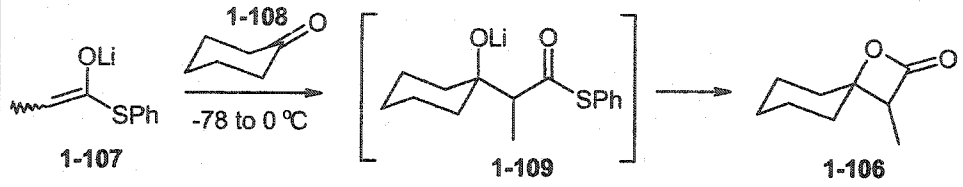


1-105 **1-104**

Scheme 1.26 Masamune's "Double-Activation" Lactonization Reaction in the Preparation of β-Lactone **1-104**

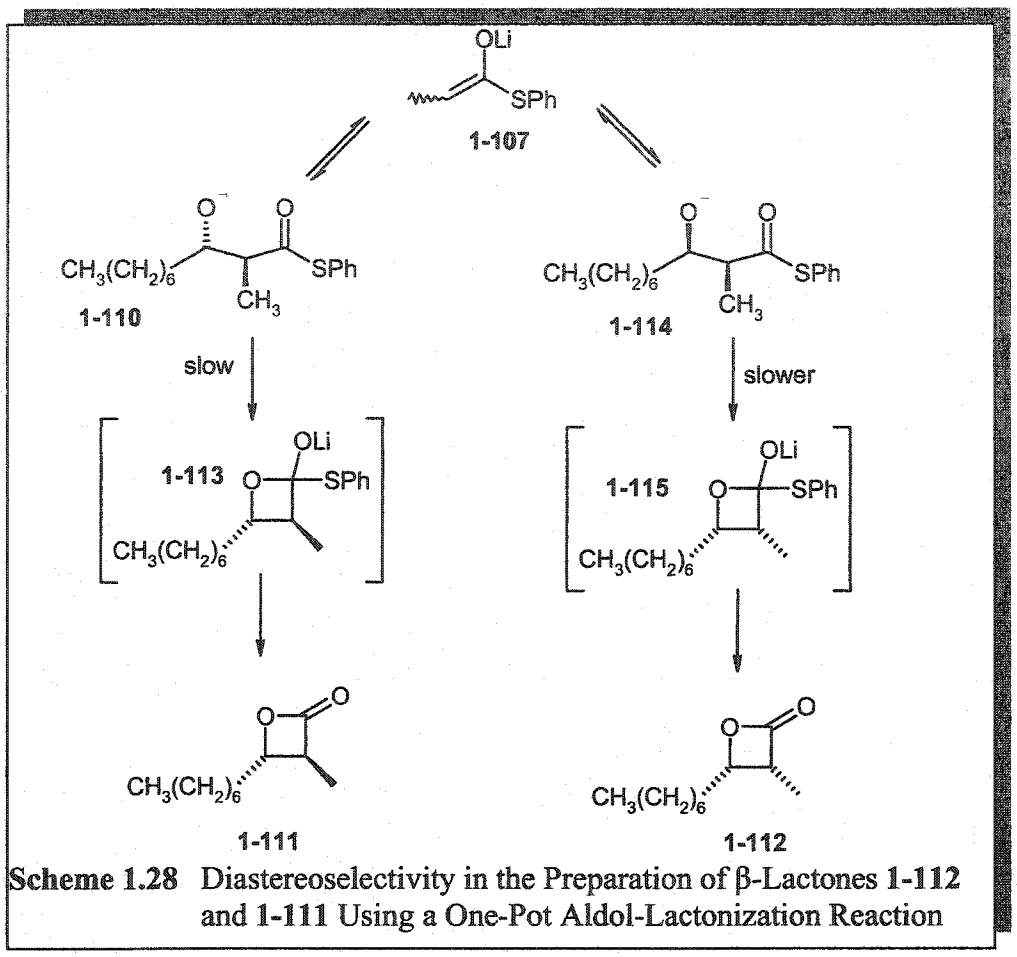
To this point, only lactonization of a pre-formed β-hydroxy carboxylic acid or acid derivative have been discussed. However, in 1991 Danheiser and Nowick developed a tandem aldol-lactonization method where spiro β-lactone **1-106** was prepared in 92% yield from enolate **1-107** and cyclohexanone (**1-108**)

(Scheme 1.27). [103] In their mercury free procedure, lactonization is a result of the intermediate alkoxide (**1-109**) attacking the thiol ester carbonyl.



Scheme 1.27 Danheiser's One-Pot Aldol-Lactonization in the Preparation of β-Lactone **1-106**

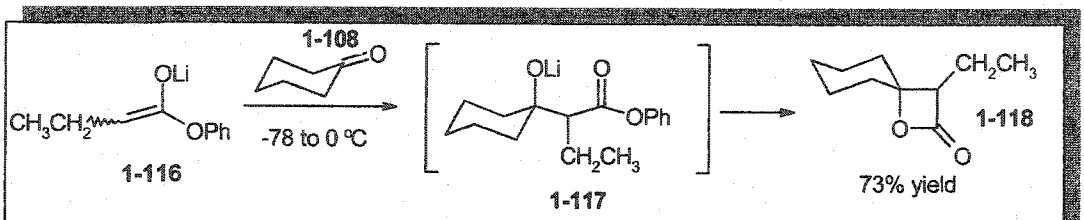
Danheiser and Nowick's preparative method generates β-lactone products in high yield using a wide variety of carbonyl compounds and thiol ester enolates with no requirement for α-substituents. However, this method exhibits poor stereospecificity as a result of the initial aldol step. Danheiser and Nowick have rationalized modest *trans* diastereoselectivity through the involvement of a rapid and reversible aldol reaction (Scheme 1.28); the less sterically congested tetrahedral intermediate in *anti*-aldolate **1-110** undergoes rapid cyclization leading via **1-113** to give *trans*-β-lactone **1-111**. By contrast, *syn*-aldolate **1-114** reacts slowly via **1-115** to give *cis*-β-lactone **1-112**. Thus, for example, octanal reacts with **1-107** to give a 2.5:1 ratio of *trans* and *cis* isomers (**1-111** and **1-112**), respectively.



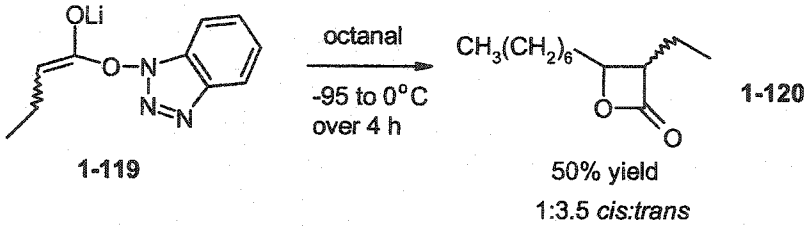
Scheme 1.28 Diastereoselectivity in the Preparation of β-Lactones **1-112** and **1-111** Using a One-Pot Aldol-Lactonization Reaction

In 1995, Welder et al. developed a less malodorous approach to the tandem aldol lactonization reaction, replacing the thiol ester with its oxygen analogue (Scheme 1.29).[104] Although similar yields were achieved using phenyl alkanoates to make tri- and tetrasubstituted β-lactones, Danheiser and Nowick's preparation was superior for mono- and disubstituted β-lactones. A year later, Welder *et al.* reacted various aldehydes with 1-acylbenzotriazoles to produce disubstituted β-lactones (e.g. **1-119** and **1-120**; Scheme 1.30). [105] Their results demonstrated that, although aldehydes could be converted into β-lactones with a yield greater than 50%, diastereoselectivity was comparable to Danheiser and Nowick's original experiments with thiol esters. Welder et al. have recently used

the lithium enolates of 1-acylbenzotriazoles (**1-119**) in their preparation of enzyme inhibitors tetrahydrolipstatin (**1-64**) and tetrahydroesterastin (**1-62**).[106]

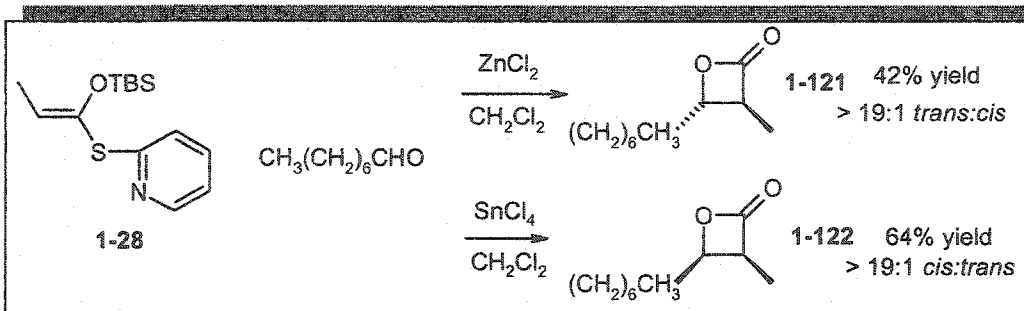


Scheme 1.29 One-Pot Aldol-Lactonization Reaction Using Phenyl Ester Enolate **1-116** in the Preparation of β-Lactone **1-118**

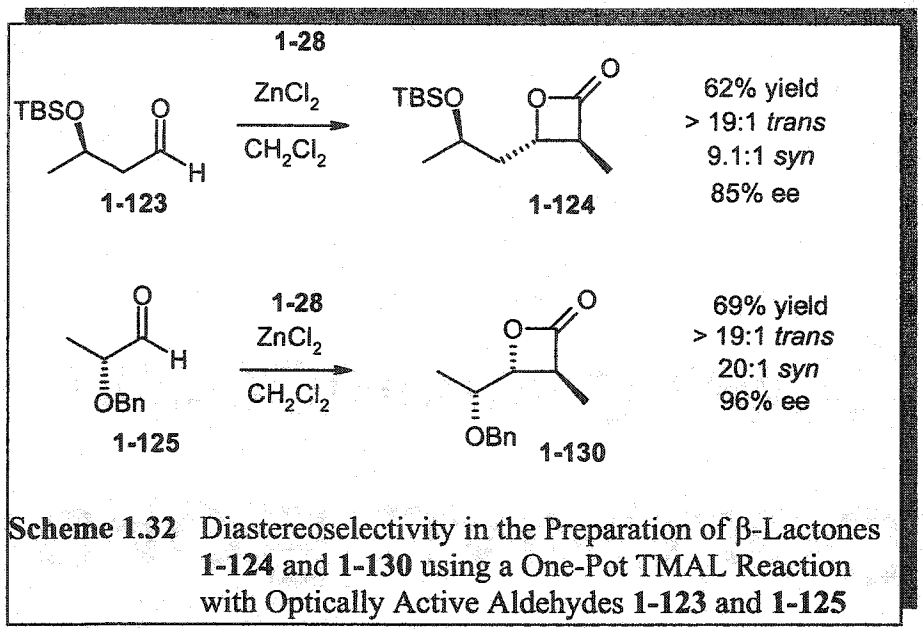


Scheme 1.30 One-Pot Aldol-Lactonization Reaction Using 1-Benzotriazole Ester Enolate **1-119** in the Preparation of β-Lactone **1-120**

The initial methodology of Danheiser and Nowick was further developed by Yang and Romo, who in 1997 used the zinc (II) chloride promoted Mukaiyama aldol reaction between various aldehydes and thiopyridyl ketene acetals to generate the requisite β-hydroxy thiol ester intermediate (Scheme 1.31). [107] Copper (II) bromide-promoted lactonization of the β-hydroxy thiol ester resulted in a high degree of diastereoselectivity in favor of the *trans*-1,2-disubstituted β-lactone (>19:1). Recently, Romo and Yang developed a complementary tandem Mukaiyama aldol-lactonization (TMAL) method using tin (IV) chloride in the diastereoselective preparation of *cis*-1,2-disubstituted β-lactones (>19:1) (Scheme 1.31).[17]



Scheme 1.31 One-Pot Tandem Mukaiyama Aldol-Lactonization Reactions in the Diastereoselective Preparation of β-Lactones **1-121** and **1-122**



Scheme 1.32 Diastereoselectivity in the Preparation of β-Lactones **1-124** and **1-130** using a One-Pot TMAL Reaction with Optically Active Aldehydes **1-123** and **1-125**

Romo and co-workers have extended the zinc (II) chloride promoted TMAL reaction to include α or β-optically active aldehydes in the preparation of optically active β-lactone products (Scheme 1.32). This preparative technique has been used in the total synthesis of the β-lactone containing natural product (-)-Panclicin D (**1-127**), a potent pancreatic lipase inhibitor (Figure 1.15).[107] Prior to the development of the TMAL reaction, Cosio et al. reacted optically active aldehydes with the lithium enolate of thiopyridyl isobutyrate (**1-128**) (Scheme 1.33).[108] However, this methodology was limited to optically active aldehydes bearing only α-stereogenic centers, and has only been applied to the preparation

of α,α-dimethyl-substituted β-lactones (likely due to the need for a Thorpe-Ingold effect for efficient lactonization).

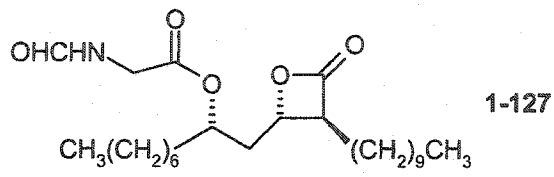
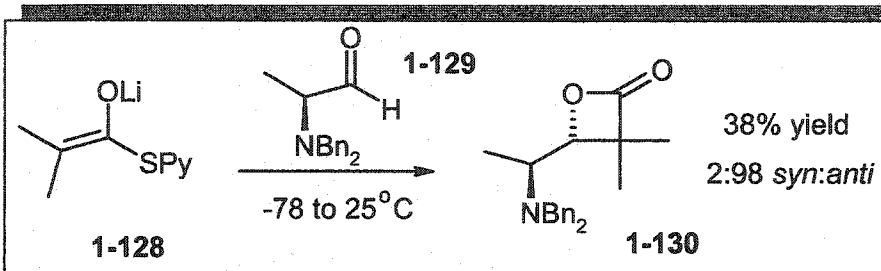
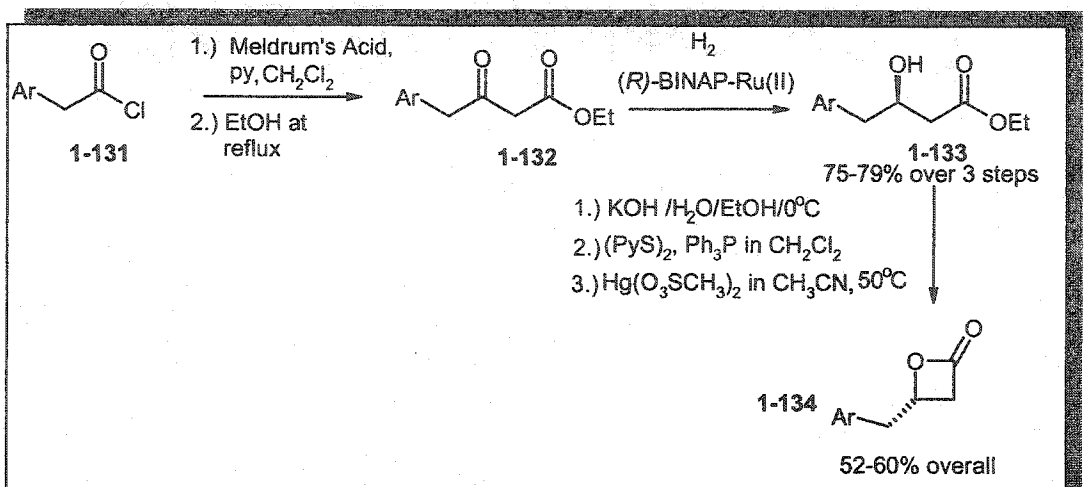


Figure 1.15 Structure of (-)-Panclicin D (**1-127**)



Scheme 1.33 Diastereoselectivity in the Preparation of β-Lactone **1-130** using a One-Pot TAL Reaction with Optically Active Aldehyde **1-129**

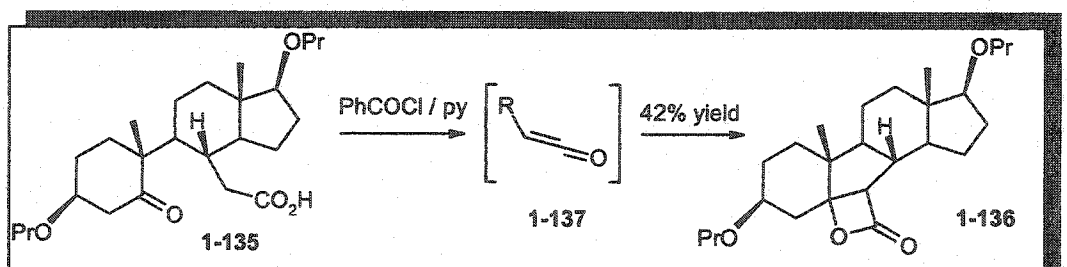
In 1993, Capozzi et al. used Noyori's asymmetric reduction of readily available β-keto esters (e.g. **1-132**) to generate optically active β-hydroxy esters (e.g. **1-133**) (Scheme 1.34).[109] Conversion to the corresponding optically active thiopyridyl esters, followed by treatment with mercury (II) methanesulfonate, provided optically active β-lactones (e.g. **1-134**) in high yield; although enantiomeric excesses were not reported, they were reasoned to be >90%. This multistep sequence represents the only general method for the preparation of optically active β-lactones from optically inactive starting materials not to involve a [2 + 2] cycloaddition between a ketene and carbonyl compound.



Scheme 1.34 Enantioselective Preparation of β-Lactone **1-134** Involving Asymmetric Reduction of β-Keto Ester **1-132**

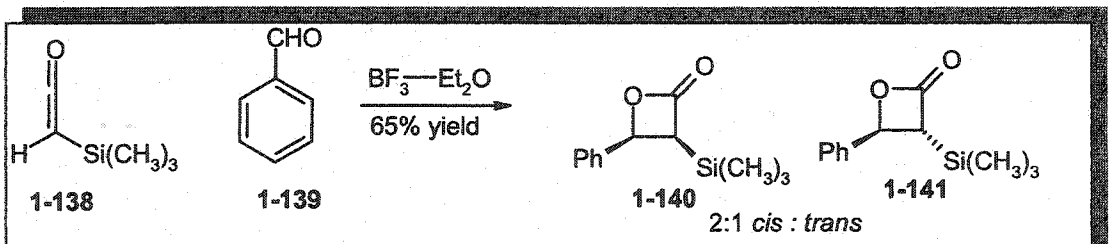
1.4.3 Lactonization Via [2 + 2] Cycloaddition

Although [2 + 2] cycloaddition reactions between ketenes and carbonyl compounds have been known for 90 years, they have been underutilized in the preparation of β-lactones; this is because few stable ketenes are reported in the literature.[110] In 1958, Kagan and Jacques generated the requisite ketene *in situ* by treating carboxylic acid **1-135** with benzoyl chloride in pyridine in the preparation of B-norsteroid **1-136** (Scheme 35).[111] Since then, pyrolysis of commercially available diketene, elimination of HCl from acid chlorides using trialkyl amines, and reductive elimination of α-halo acid chlorides using zinc have been used to generate ketenes in situ.[112]



Scheme 1.35 *In Situ* Generation of Ketene **1-137** in the Preparation of β-Lactone **1-136**

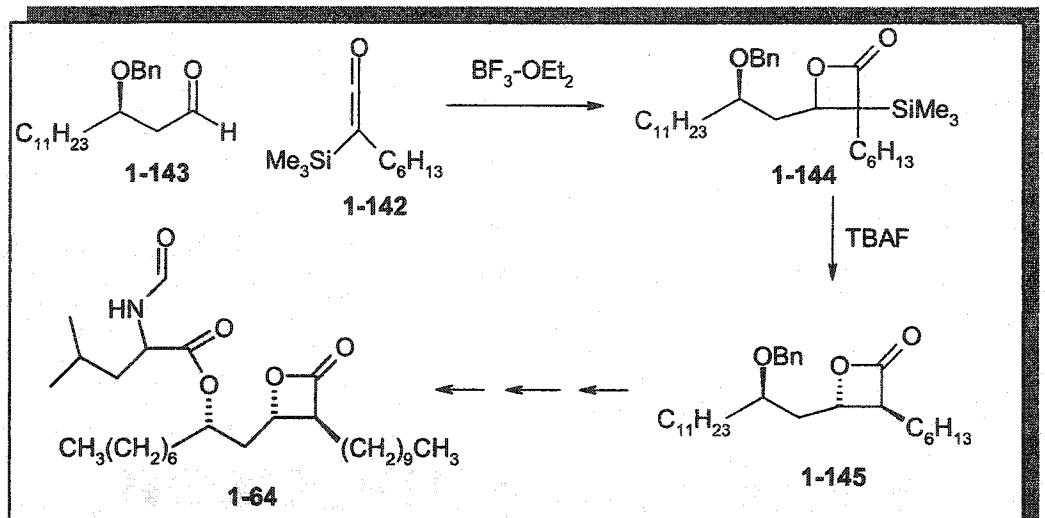
The use of ketenes in various syntheses exploded in the mid 1970's through the use of silylketenes with Lewis acid catalysts; silylketenes represent stable ketenes that can be stored for extended periods of time at low temperature.[113] In 1975, Zaitseva and co-workers developed a [2 + 2] cycloaddition between trimethylsilylketene (**1-138**) and benzaldehyde (**1-139**) in the presence of boron trifluoride dietherate (Scheme 1.36).[114] Although this reaction generates a 2:1 mixture of *cis*- and *trans*-1,2-disubstituted β-lactones (**1-140** and **1-141**, respectively), the authors found that heating at 50 °C for 6 hours diminished the amount of **1-141**. Brady and Saidi later applied this method to a wide variety of aliphatic aldehydes with similar yield and diastereoselectivity.[115] In 1992, Yamamoto demonstrated that bulky Lewis acid catalysts, such as bis(4-bromo-2,6-di-*tert*-butylphenoxy) methylaluminum, led to exclusive *cis*-1,2-diastereoselectivity.[116]



Scheme 1.36 Preparation of β-Lactones **1-140** and **1-141** using Silylketene **1-138**

In addition to trimethylsilyl ketene, alkyl(trimethylsilyl) ketenes have also been used in [2 + 2] cycloaddition reactions with various aldehydes and ketones. In 1989, Kocienski and Pons prepared (-)-tetrahydrolipstatin (**1-64**) through a boron trifluoride etherate catalyzed [2 + 2] cycloaddition reaction between *n*-hexyl trimethylsilyl ketene (**1-142**) and (3*R*)-3-(benzyloxy)-tetradecanal (**1-143**).[117] The diastereomeric cycloadducts (**1-144**) were desilylated with tetrabutylammonium fluoride and separated with ease via column chromatography; the desired diastereomer (**1-145**) represented 55-61% of β-lactones isolated (Scheme 1.37). In 1994, Kocienski, Pons and co-workers increased diastereoselectivity using ethylaluminum dichloride as a Lewis acid

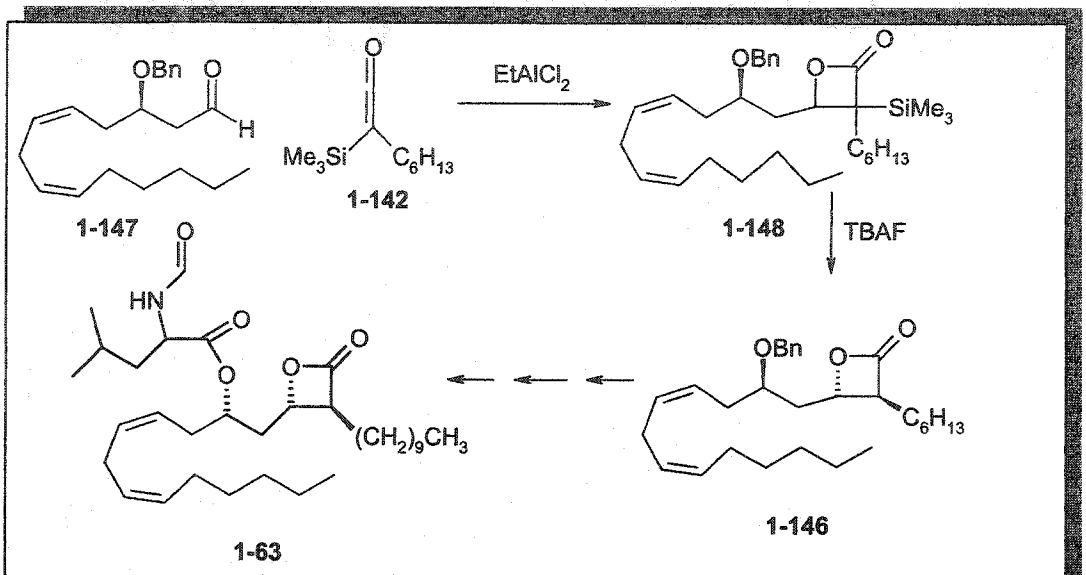
catalyst; the desired diastereomer was determined by ^{1}H NMR (500 MHz) to represent 80% of β-lactone products.[118] Pons et al. have also prepared the β-lactone moiety of another lipase inhibitor, (-)-lipstatin (**1-63**), demonstrating the ability of alkyl(trimethylsilyl) ketene to react cleanly and efficiently with the aldehyde of **1-147** even in the presence of a 1,4-diene (Scheme 1.38).[119] Desilylation of **1-148** generated 4 diastereomeric β-lactones, with the desired diastereomer (**1-146**) being separated via column chromatography in 64% overall yield from the mixture.



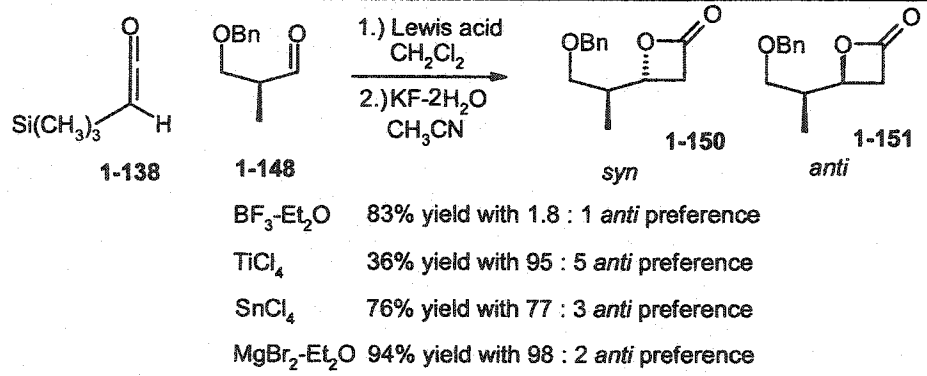
Scheme 1.37 Total Synthesis of Tetrahydrolipstatin (**1-64**) using a [2 + 2] Cycloaddition Approach with Alkyl Silyl Ketene **1-142**

In addition to mono-dentate Lewis acids, such as boron and aluminum, bi-dentate Lewis acids have been used in [2 + 2] cycloadditions between chiral aldehydes and **1-138**. In 1995, Zemribo and Romo compared tin, titanium and magnesium as Lewis acid catalysts in the [2 + 2] cycloaddition reaction between **1-138** and optically active β-and α-benzyloxyaldehydes (**1-148** and **1-149**, respectively) (Schemes 1.39 and 1.40).[120] Bi-dentate Lewis acids generated the highest diastereoselectivity, with magnesium generating the highest yield; high diastereoselectivity was rationalized as being due to facial bias from the

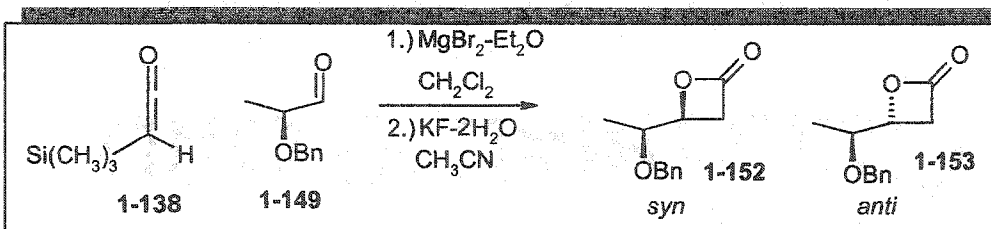
conformationally rigid chelate formed between the Lewis acid and the benzyloxyaldehyde (Figure 1.26).



Scheme 1.38 Total Synthesis of Lipstatin (**1-63**) using a [2 + 2] Cycloaddition Approach with Alkyl Silyl Ketene **1-142**



Scheme 1.39 Diastereoselectivity in the [2 + 2] Cycloaddition Reaction Between Optically Active Aldehyde **1-148** and Silylketene **1-138**



Scheme 1.40 Diastereoselectivity in the [2 + 2] Cycloaddition Reaction Between Optically Active Aldehyde **1-149** and Silylketene **1-138**

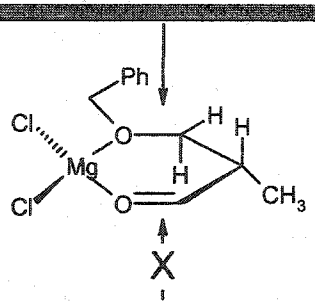


Figure 1.16 Proposed Chelate of **1-148** with Mg^{2+} where the Ketene adds *anti* to the α-Substituent

Subsequently, in 1996 Dymock et al. used optically active bissulfonamide-monoalkylaluminum complex **1-154** as a Lewis acid catalyst in the [2 + 2] cycloaddition reaction between optically inactive aldehydes and **1-138**; this generated optically active β-lactones in high yield with up to 83% ee (Figure 1.17).[121] These were similar conditions to those reported by Tamai *et al.* two years prior, who used optically active bissulfonamide-monoalkylaluminum complex **1-155** (Figure 1-17) as a Lewis acid catalyst in the [2 + 2] cycloaddition reaction between optically inactive aldehydes and ketenes; this generated optically active β-lactones with up to 74% enantiomeric excess.[122] The last seven years have seen numerous optically active Lewis acids being used to catalyze the [2 + 2] cycloaddition reaction between aldehydes and both ketenes and trimethylsilyl ketenes. These include **1-156**,[123] **1-157**,[124] **1-158**[125] and **1-159**,[126] where yield and enantiomeric excess are highly dependent upon the aldehyde used, severely limiting the generality of this approach.

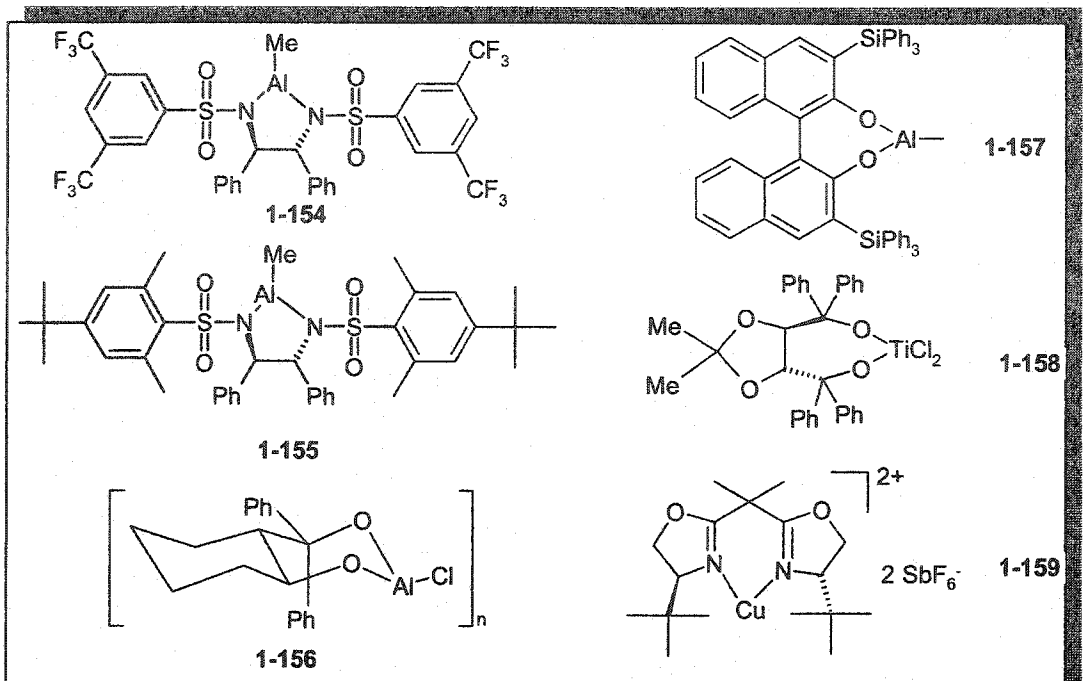
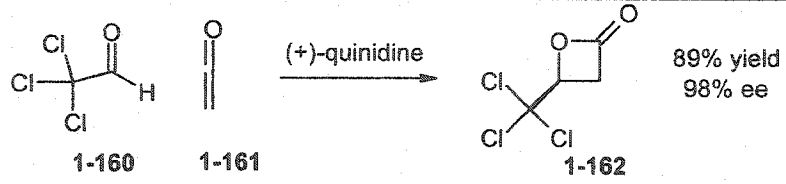


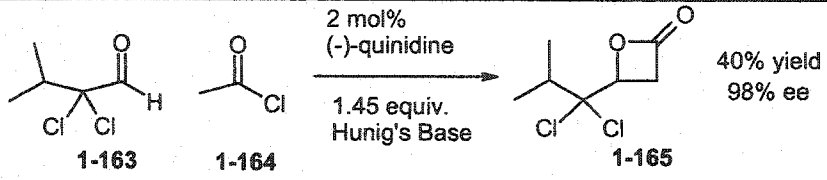
Figure 1.17 Chiral Lewis Acids Used in Enantioselective [2 + 2] Cycloaddition Reactions Involving Silylketene **1-138**

The most enantioselective [2 + 2] cycloaddition reaction to date is the procedure presented in 1982 by Wynberg and Staring (Scheme 1.41).[127] Using this procedure, β-lactones (e.g. **1-162**) were prepared in high yields with up to 98% enantiomeric excess in the presence of various cinchona alkaloid catalysts, such as quinine and quinidine. However, the procedure was limited to activated aldehydes such as chloral (**1-160**) and required fresh ketene (**1-161**) to be created in a separate flask. In 2000, Tennyson and Romo generated the requisite ketene *in situ* using acetyl chloride and Hunig's base (Scheme 1.42).[128] With (-)-quinidine as the nucleophilic catalyst, optically active β-lactones were generated from a wide variety of dichlorinated aldehydes and ketene generated *in situ*, with high yield and up to 98% enantiomeric excess. Attempts to use additional acid chlorides were unsuccessful.



1-160 **1-161** **1-162**

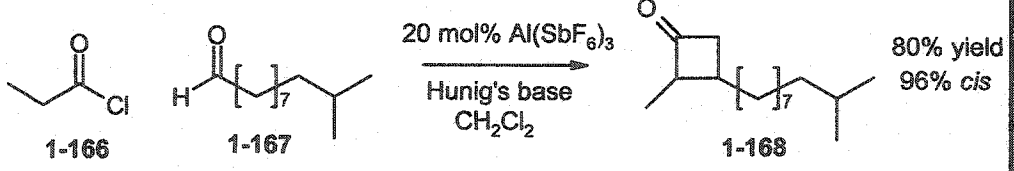
Scheme 1.41 Wynberg's Enantioselective Preparation of β-Lactone **1-162**



1-163 **1-164** **1-165**

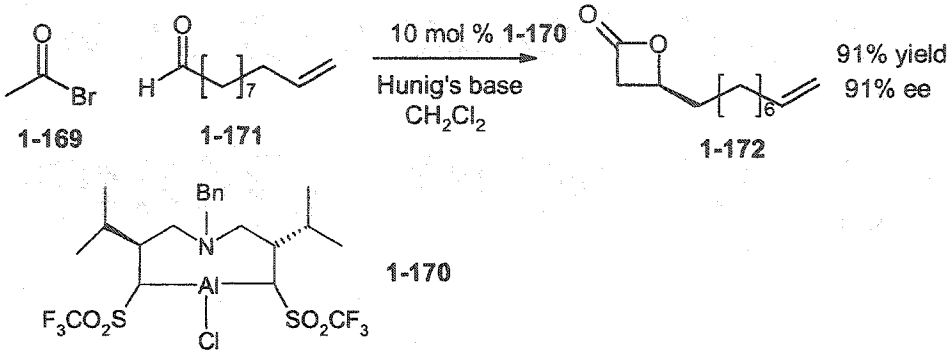
Scheme 1.42 Wynberg-type Method in the Preparation of β-Lactone **1-165**

In 1999, Nelson *et al.* generated ketenes *in situ* from acetyl (**1-164**) and propionyl chloride (**1-166**) for reaction with Lewis acid-complexed aldehydes (Scheme 1.43).[129] Their aluminum (III) catalyzed acyl halide-aldehyde cyclocondensation (AAC) reaction was capable of generating β-lactones from a large variety of aldehydes (e.g. **1-167**) in high yield from inexpensive reagents; furthermore, the reaction with **1-166** also exhibits high *cis*-diastereoselectivity. Nelson *et al.* then developed an asymmetric variant of the AAC reaction using acetyl bromide (**1-169**) and an optically active aluminum (III) triamine complex (**1-170**) to prepare optically active β-lactone **1-172** (Scheme 1.44).[130] They have recently demonstrated that the opposite enantiomer (**1-174**) can be prepared in high enantiomeric excess upon enzymatic resolution (Lipase PS Amano in benzyl alcohol) of optically inactive β-lactone **1-173** (Scheme 1.45).[131]

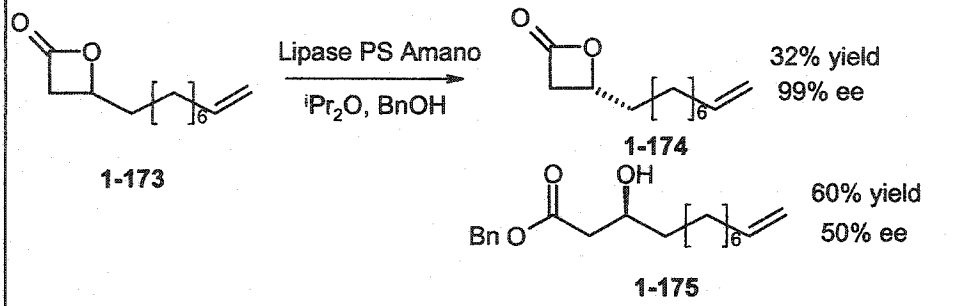


1-166 **1-167** **1-168**

Scheme 1.43 Aluminum (III) Catalyzed AAC Reaction in the Diastereoselective Preparation of β-Lactone **1-168**



Scheme 1.44 Asymmetric Aluminum (III) Catalyst **1-170** in the Enantioselective ACC Preparation of β-Lactone **1-172**



Scheme 1.45 Lipase Promoted Resolution of Racemic β-Lactone **1-173** in the Preparation of Optically Active β-Lactone **1-174**

1.5 Objectives of this Thesis

In Chapters 1.2 and 1.3, it was shown that β-lactones are interesting synthetic targets and useful synthetic intermediates. However, in Chapter 1.4, it was shown that there are many pitfalls associated with many of the available methods in β-lactone preparation, which thus limit their ease of preparation and utility. These limitations include: (1) multistep preparations: several methods required more than 1 step starting from available precursors; (2) low yield: several

methods have yields well below 50%; (3) poor generality: several methods are highly substrate-specific; (4) poor diastereoselectivity: several methods give no or little diastereoselectivity in the preparation of 1,2-disubstituted β-lactones; and (5) poor enantioselectivity: few general methods exist for the enantioselective preparation of β-lactones that are general or do not require appropriately positioned pre-existing chirality.

The overall goal of this thesis was therefore to expand the known methods of β-lactone preparation.

In Chapter 2, we discuss our involvement in a collaborative project that evaluated a homologous series of monosubstituted and 1,2-disubstituted β-lactones as potential inhibitors of 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) synthase, a key enzyme involved in cholesterol biosynthesis. This project allows us to compare known general methods for β-lactone preparation, realize their deficiencies, and narrow the focus of our goals to: (1) the development of general methods to prepare *cis*-1,2-disubstituted β-lactones; and (2) the development of general methods to prepare optically active monosubstituted β-lactones. Furthermore, our involvement in this collaborative study allows us to select target β-lactones that are of immediate future interest.

Romo and co-workers used a zinc-promoted tandem Mukaiyama aldol-lactonization (TMAL) approach in the diastereoselective preparation of *trans*-1,2-disubstituted β-lactones. In Chapter 3, we examine a possible stereo-complementary TMAL approach to the diastereo- and enantioselective preparation of *cis*-1,2-disubstituted β-lactones using non-chiral and chiral titanium, respectively. This is followed up in Chapter 4 by the examination of an Evans-type approach to the diastereo- and enantioselective preparation of *cis*-1,2-disubstituted β-lactones using non-chiral and chiral thiazolidine-2-thiones, respectively.

Chapter 5 builds on our work using an Evans-type aldol condensation in the preparation of *cis*-1,2-disubstituted β-lactones as a similar Evans-type aldol

condensation is used towards the preparation of racemic and optically active monosubstituted β-lactones.

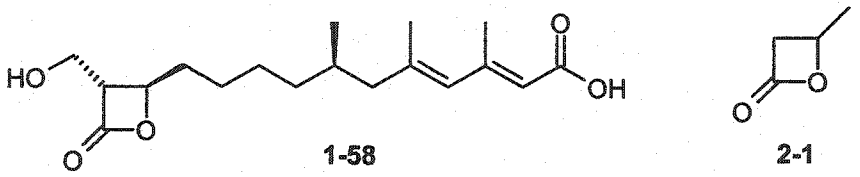
Furthermore, in Chapter 6 we use what we learned in Chapters 4 and 5 using *N*-acyl thiazolidinethiones and attempt to develop a one-pot tandem Evans-type aldol-lactonization (TEAL) reaction analogous to the TAL and TMAL reactions.

Finally, Capozi *et al.* presented the only general method capable of furnishing enantiopure β-lactones. This represents the only method for the preparation of β-lactones to use a Claisen condensation, as opposed to an aldol condensation, to make a carbon-carbon bond. In Chapter 7, we build on our laboratories development of a novel intramolecular Claisen-type condensation on a glycoluril system, to adapt this system to the potential enantioselective preparation of β-lactones.

Chapter 2

Preparation of C4-Monosubstituted and 1,2-Disubstituted β-Lactones

Our interest in β-lactone preparation started with Antibiotic 1233A (**1-58**) (Figure 2.1). As discussed in Chapter 1.3.1, this molecule irreversibly inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase, a key enzyme involved in cholesterol biosynthesis. Our laboratory has previously demonstrated that β-butyrolactone (**2-1**) is an irreversible inhibitor of HMG-CoA synthase with a similar inactivation rate constant (k_{inact}) to **1-58**, but with binding affinity (K_I) 10^5-fold higher.[132] This indicates that the β-lactone moiety in **1-58** is essential for irreversible inhibition and suggests that ring substituents only help to guide the potential inhibitor into the enzyme active site. A collaborative study was initiated to test a homologous series of C4-monosubstituted and 1,2-disubstituted β-lactones as potential inhibitors of HMG CoA synthase.



1-58 **2-1**

Figure 2-1 Structure of Antibiotic 1233A (**1-58**) and β-Butyrolactone (**2-1**); Two Potent Inhibitors of HMG-CoA Synthase

2.1 Contribution to the Study

My specific contribution was to prepare racemic β-lactones **7a-e**, **7g-o**, **7s**, **7v**, **7w** and **10t**, achiral β-lactone **17**, phenyl and thiophenyl esters **3a-d**, *tert*-butyldimethylsilyl ketene acetal **8c**, silylketenes **9a** and **9b**, and aldehydes dodecanal, tetradecanal and octadecanal. During this work, I was able to evaluate

several common general methods for the production of 1,2-disubstituted and C4-monosubstituted β-lactones directly from aldehydes. In addition, I was involved in the development of the proposed model of the HMG-CoA synthase binding/active site for β-lactone inhibitors and the choice of synthetic target molecules. R. William Riddoch and Gerard D. Wright were responsible for all biological work. The Romo research group prepared optically active C3-unsubstituted β-lactones **7aa**, **bb**, **cc**, **dd**, **e**, **s**, **x**, **y**, **z** and racemic C3-methyl substituted β-lactones **7f**, **p**, **q** and **r**.

2.2 Reprint of the Publication

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Synthesis and Inhibitory Action on HMG-CoA Synthase of Racemic and Optically Active Oxetan-2-ones (β-Lactones)

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Key words: β-lactones; HMG-CoA synthase; inhibition; asymmetric synthesis; chiral Lewis acid.

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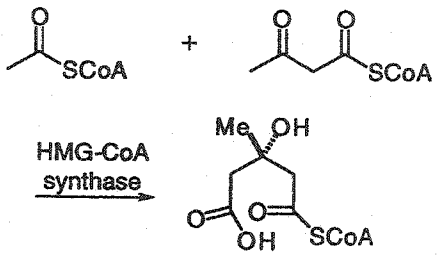
Abstract: A homologous series of both C3-unsubstituted and C3-methyl substituted oxetan-2-ones (β-lactones) was investigated as potential inhibitors of yeast 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase. Several reported methods for racemic β-lactone preparation were studied for the preparation of the target series. In addition, a novel aluminum-based Lewis acid obtained by combination of Et_2AlCl with (1R,2R)-2-[(diphenyl)hydroxymethyl] cyclo-hexan-1-ol was studied for the asymmetric [2+2] cycloaddition of aldehydes and trimethylsilylketene. This Lewis acid exhibited good reactivity but variable enantioselectivity (22-85% ee). In *in vitro* assays using both native and recombinant HMG-CoA synthase from *Saccharomyces cerevisiae*, oxetan-2-ones mono-substituted at C4 with linear alkyl chains gave IC_{50}s that decreased monotonically with chain length up to 10 carbons and then rose rapidly for longer chains. The *trans* isomers of 3-methyl-4-alkyl-oxetan-2-ones showed a similar trend but had 1.3- to 5.6-fold lower IC_{50}s. The results imply a substantial hydrophobic pocket in this enzyme that interacts with both C-3 and C-4 substituents of oxetan-2-one inhibitors.

Introduction

The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase[1] catalyzes the formal aldol condensation of 1 mol of acetyl-coenzyme A (AcCoA) and 1 mol of acetoacetyl-coenzyme A (AcAcCoA). The reaction product, (3S)-HMG-CoA, is the universal precursor of terpenes and steroids, [2] being converted by the reaction of HMG-CoA reductase to mevalonate and thence via isopentenyl diphosphate and dimethylallyl diphosphate through to geranyl (GPP), farnesyl (FPP), or other diphosphates.[2,3] GPP and FPP act as progenitors for mono- and sesquiterpenes, respectively, while in the sterol sequence, FPP is converted via

squalene and lanosterol into cholesterol and other sterols.[3] Inhibition of the many enzymes along this biosynthetic pathway thus offers the potential to regulate sterol biosynthesis; indeed the commercial statin drugs such as lovastatin and fluvastatin, which inhibit HMG-CoA reductase,[4] have proved to be highly effective at reducing sterol levels in humans.[5] Inhibitors of this pathway can also act as potent anti- microbial agents, especially for cells such as fungi which possess active sterol biosynthetic machinery.[6] HMG-CoA synthase is also involved in ketogenesis.[1a,6]

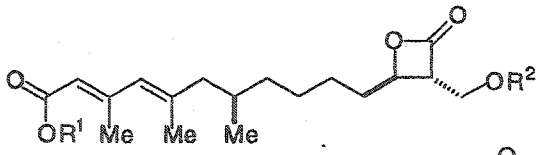


(3*S*)-HMG-CoA

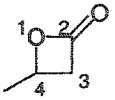
HMG-CoA synthase has been isolated from a range of species, including yeast,[7] and the livers of ox,[8] chicken[9] and man.[10] The human[10b] and avian liver[9] enzymes have been cloned and purified to homogeneity;[10] however no cloning work has been undertaken on the yeast enzyme. Detailed kinetic studies have been performed on the synthase from a range of these species to determine the sequence of events during catalysis of this condensation reaction; the enzyme exhibits BiBi ping-pong kinetics with AcCoA binding first to form an acetyl-enzyme covalent intermediate. The latter is isolable,[9] and the point of attachment has been shown to be a conserved cysteine residue (Cys-129 in both man[10a] and avian liver[9]). Binding of AcAc-CoA, via an interaction with His-264 (human enzyme residue),[11] then occurs; binding to free enzyme results in an abortive complex, accounting for the observed substrate inhibition, while binding to the acetyl-enzyme intermediate leads to aldol condensation and hence to a CoA-HMG-enzyme covalent intermediate.[12] Hydrolysis of the latter generates HMG-CoA and free synthase ready for another catalytic cycle.

As well as the statins, there exists an array of other natural products which act as inhibitors of the sterol pathway. However, aside from inhibition by one of the substrates (AcAcCoA) and other primary metabolic CoA esters such as succinyl-CoA,[13] the sole known metabolite which is specifically active against HMG- CoA synthase is the antibiotic F-244 (**1a**)[14] also known as L-659,699[14b,15] and 1233A.[16] This β-lactone, which has been isolated from *Scopulariopsis*, *Fusarium*, and *Cephalosporium* sp.,[14-16] along with a range of synthetic analogues which possess similar structures,[17] has been shown to be an irreversible inactivator of the enzyme in in vitro assays,[10a,14,15,17,18] as well as to be a potent inhibitor in in vivo systems.[14,15,17,19] The observation that both the methyl ester **1b** and O-methyl ether **1c** of F-244[14a,15b,17d,18b] exhibited little if any reduction in inhibition indicates that neither the carboxy nor hydroxy groups of F-244 participate in strong hydrogen-bond donor interactions with the enzyme active site, and therefore suggests that hydrophobic interactions are important in determining the affinity of F-244 and analogs for the enzyme. Thus a variety of non-polar substituents have been attached to the oxetan-2-one (β-lactone) C4-carbon, including 2-arylethyl[17b,c,f] and decyl.[17g] However, a systematic investigation of the effect of the length of alkyl groups attached at this site has not been conducted to the best of our knowledge. In an earlier report, we showed that β-butyrolactone (**2**), a simple β-lactone analogue of F-244, was an irreversible inhibitor of the synthase, with an inactivation rate constant (k_{inact}) similar to F-244, but with much weaker binding affinity: K_I was ca. 10^5-fold higher than that for F-244.[20] This result established that the lactone ring is the only structural component required for irreversible inhibition, and suggests that the ring substituents play a role solely in guiding the inhibitor into the enzyme active site. In order to explore the role of substituents at C3 and C4 of the oxetan-2-one ring, we thus prepared a series of β-lactones bearing either hydrogen or methyl at C-3 and alkyl chains of increasing length at C4, as well as several β-lactones containing variations on these substitution patterns. The biological activity of these simple F-244 analogs in in

vitro assays with HMG-CoA synthase is described herein.



1a: $R^1, R^2 = H$
1b: $R^1 = Me, R^2 = H$
1c: $R^1 = H, R^2 = Me$



(+/-)-2

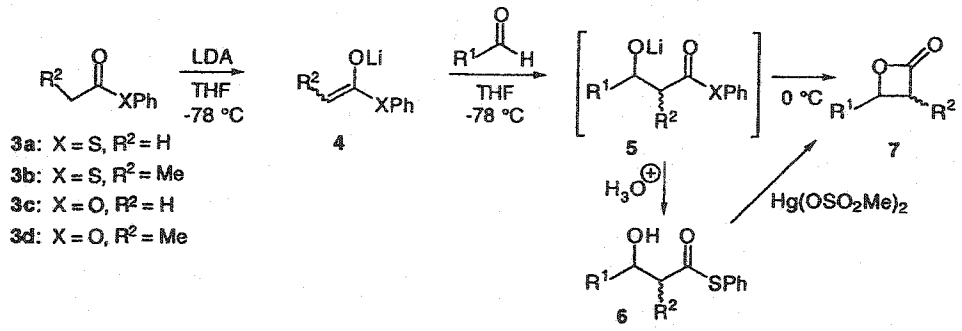
A range of methods for preparing racemic β-lactones has been reported and we investigated several of these routes to prepare our target series of compounds. This enabled a comparative study of these methods. The most efficient routes are those which involve a single-pot transformation such as the [2+2] cycloaddition of ketenes and aldehydes,[21] aldol-lactonizations,[22] and most recently the tandem Mukaiyama aldol-lactonization (TMAL) reaction.[23]

We were also interested in determining if the absolute stereochemistry of simple 4-alkyloxetan-2-ones would have a bearing on the inhibition of HMG-CoA synthase.[17a] The [2+2] cycloaddition of ketenes and aldehydes is one of the most concise routes to β-lactones. The first example of this reaction was reported by Staudinger in 1911,[21a] however more recently, Zaitseva showed that trimethylsilyl ketenes can participate in this reaction with Lewis acid catalysis.[21b] Recent studies with trimethylsilylketene and aldehydes have shown that high diastereoselectivity can be obtained with bulky, achiral Lewis acids.[24] In addition, the recent use of chiral Lewis acids has allowed access to optically active β-lactones.[25] However, a general chiral Lewis acid that provides high reactivity and enantioselectivity with a broad range of aldehyde substrates has yet to be found. We have also been studying this cycloaddition reaction as a concise entry into optically active β-lactones. In this regard, we have recently reported that the $TiCl_2$-TADDOL catalyst exhibits low to good enantioselectivity (9-80% ee) in this reaction.[26] Herein, we disclose a novel aluminum Lewis acid for this cycloaddition. While this Lewis acid provides the highest enantioselectivities reported to date for α-

unbranched, aliphatic aldehydes, it exhibits enantioselectivity which appears to be substrate dependent.

Results

Preparation of oxetan-2-ones (β-lactones). Several of the reported methods for the preparation of racemic β-lactones were investigated. The desired β-lactones were prepared by the following methods: (1) the one-pot aldol-lactonization procedure reported initially by Danheiser[22a] and subsequently modified[a] by Schick[22b] (Scheme 1, Table 1); (2) an aldol followed by a separate cyclization of the hydroxy acid derivative by the methods of Wemple[27] and Masamune[28] (Scheme 1, Table 1); (3) the tandem Mukaiyama-aldol lactonization (Scheme 2, Table 2); or (4) the catalyzed [2+2] cycloaddition of aldehydes and ketene using both $BF_3{\cdot}OEt_2$ [21] (Scheme 3, Table 3) and a new, chiral aluminum-based Lewis acid (Scheme 5, Table 4).

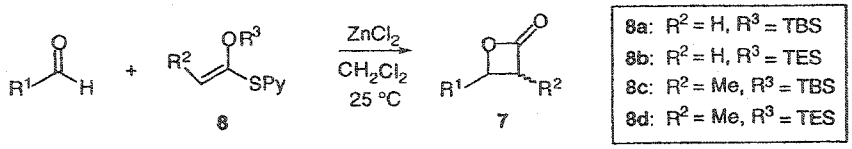


Scheme 1.

Table 1. Synthesis of racemic β-lactones via one-pot or two-step aldol-lactonizations

Entry	β-Lactone	R^1	R^2	Ester	*trans/cis* Ratio (7)	Method[a]	% Yield
1	7a	C_7H_{15}	Me	3b	>19:1[b]	A	32
2	7a	C_7H_{15}	Me	3d	>19:1[b]	B	39
3	7b	C_8H_{17}	H	3a	—	C	56[c]
4	7c	C_9H_{19}	H	3a	—	C	61[c]
5	7d	C_9H_{19}	Me	3b	>19:1[b]	A	37
6	7d	C_9H_{19}	Me	3d	>19:1[b]	B	35
7	7d	C_9H_{19}	Me	3b	1.2:1	C	66[c]

[a]Method A: Danheiser one-pot aldol-lactonization (ref 22a) but the aldehyde was added at −100 °C. Method B: Schick one-pot aldol-lactonization (ref 22b). Method C: Two-step procedure involving aldol reaction according to the method of Wemple (ref 27) and subsequent lactonization by the method of Masamune (ref 28).
[b]*trans/cis* Ratio determined by 200 MHz ^{1}H NMR on the purified β-lactones.
[c]Yields are for the two-step aldol-lactonization sequence.

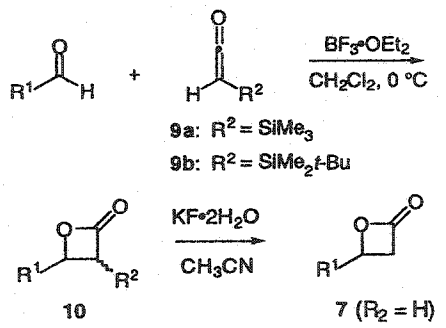


Scheme 2.

Table 2. Synthesis of racemic β-lactones via the tandem Mukaiyama aldol-lactonization (TMAL) reaction

Entry	β-Lactone	R^1	R^2	Ketene acetal	*trans/cis* Ratio (7)[a]	% Yield
1	7e[b]	$Ph(CH_2)_2$	H	8b	—	66
2	7f[b]	*t*-Bu	H	8a	—	42
3	7g[b]	C_7H_{15}	H	8b	—	65
4	7c	C_9H_{19}	H	8b	—	59
5	7h	C_4H_9	Me	8c	> 19/1	34
6	7i	C_5H_{11}	Me	8c	> 19/1	36
7	7j	C_6H_{13}	Me	8c	> 19/1	39
8	7a[b]	C_7H_{15}	Me	8d	39/1	60
9	7k	C_8H_{17}	Me	8c	> 19/1	35
10	7d	C_9H_{19}	Me	8c	> 19/1	35
11	7l	$C_{10}H_{21}$	Me	8c	> 19/1	38
12	7m	$C_{11}H_{23}$	Me	8c	> 19/1	41
13	7n	$C_{13}H_{27}$	Me	8c	> 19/1	40
14	7o	$C_{17}H_{35}$	Me	8c	> 19/1	32
15	7p[b]	*p*-NO_2Ph	Me	8c	< 1/19	36
16	7q[b]	$TBSO(CH_2)_4$	Me	8c	> 19/1	47
17	7r[b]	*c*-C_6H_{11}	Me	8c	> 19/1	16

[a]Ratios estimated or determined by ^1H NMR (200 MHz) or by GC, respectively.
[b]These β-lactones have been described previously (refs. 23b and c).



Scheme 3.

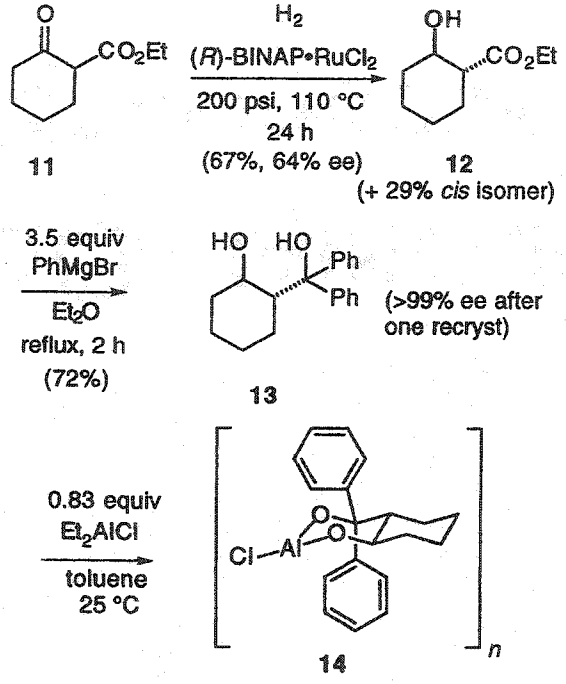
Table 3. Synthesis of racemic β-lactones via [2 + 2] cycloadditions of silylketenes and aldehydes

Entry	β-Lactone	Silylketene	R^1	% Yield (7)[a]
1	7s	9a	C_4H_9	74
2	10t	9b	C_5H_{11}	94[b]
3	7u	9a	C_6H_{13}	74
4	7g	9a	C_7H_{15}	80
5	7b	9a	C_8H_{17}	78
6	7c	9a	C_9H_{19}	84
7	7v	9a	$C_{10}H_{21}$	82
8	7w	9a	$C_{11}H_{23}$	79

[a]Yield is for the two steps of [2 + 2] cycloaddition and desilylation.
[b]Yield is for α-silyl-β-lactone **10t** as a mixture of *trans/cis* diastereomers (1/4.7).

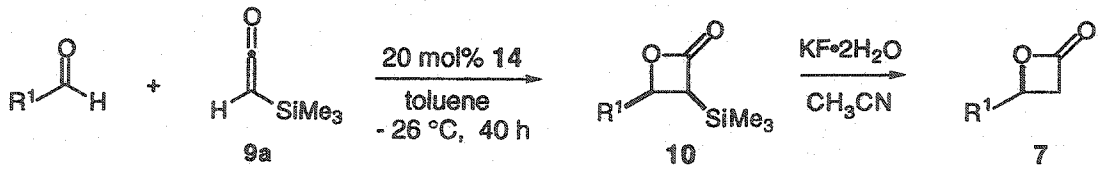
A chiral promoter based on the chiral diol, (1R,2R)-2-[(diphenyl)hydroxymethyl] cyclohexan-1-ol (**13**),[29] was studied for the [2+2] cycloaddition of trimethylsilylketene and aldehydes. Diol **13** was readily prepared in two steps from β-ketoester **11** employing the modified Noyori reduction conditions reported by Taber in 67% yield and 64% ee.[30] Addition of excess phenyl magnesium bromide to the *trans*-β-hydroxyester **12** afforded the diol **13** in 72% yield. After a

single recrystallization, the diol **13** could be enriched to 99% ee. Treatment of this diol, which was sparingly soluble in toluene with a slight deficiency of Et_2AlCl, resulted in a homogeneous solution of the presumed Lewis acid **14**. The structure of the Lewis acid has not been determined and the representation provided is meant only to show the presumed Lewis acid composition (Scheme 4).



Scheme 4.

Use of 20 mol% of this promoter led to a variety of optically active α-silyl-β-lactones **10** with enantioselectivities ranging from 22-85%. In some cases, the β-lactones were more readily isolated after desilylation which gave the monosubstituted β-lactones **7** (Table 4).



Scheme 5.

Table 4. Synthesis of optically active β-lactones via [2 + 2] cycloadditions of trimethylsilyl-ketene and aldehydes

Entry	β-Lactone	R^1	*cis*/*trans* (10)	% Yield (7)[a]	% ee	Config. (C4)
1	**7x**[b]	*c*-C_6H_{11}	>99:1[c]	83[d]	84[e]	S[f]
2	**7s**	*n*-Bu	>99:1[c]	86[d]	85[e]	R[f]
3	**7y**[b]	*t*-Bu	—	no rxn	—	—
4	**7z**	Ph	>99:1[c]	82[d]	28[e]	ND
5	**7aa**	$PhCH_2$	>19:1[g]	45[d]	75[h]	R[i]
6	**7e**[b]	$PhCH_2CH_2$	>19:1[g]	60	36[h]	S[f]
7	**7bb**	$TSBO(CH_2)_5$	>19:1[g]	55	46[j]	ND
8	**7cc**	$CH_2=CH(CH_2)_7$	>19:1[g]	71	22[j]	ND
9	**7dd**	$(CH_3CH_2)_2CH$	>19:1[g]	46	56[j]	ND

[a]Yield of **7** for two steps (not including recovered aldehyde).
[b]These β-lactones have been described previously (refs 23b–c and 26).
[c]Determined on the crude reaction mixtures by GC.
[d]Yield of **10**.
[e]% ee's are for **10** and were determined by chiral GC(TBS-cyclodextrin, ref 31).
[f]Absolute configuration were assigned after alcoholysis of **7** to the corresponding known, β-hydroxy esters and comparison of optical rotation data.
[g]Determined on the crude reaction mixtures by ^1H NMR (200 or 300 MHz).
[h]% ee's are for **7** and were determined by chiral HPLC (Chiralcel OD).
[i]Absolute configuration was assigned by comparison of optical rotation data to the known β-lactone (ref 32).
[j]% ee's of **7** determined by chiral GC (TBS-cyclodextrin).

Isolation of HMG-CoA synthase. Native HMG-CoA synthase was isolated from yeast as previously described,[20] and purified through the hydroxylapatite step to a specific activity of 0.13 mmol $min^{-1}mg^{-1}$ (units/mg). For the recombinant synthase, oligonucleotide primers complementary to the Saccharomyces cerevisiae putative HMG-CoA synthase sequence obtained from GenBank (accession no. Z50178), bearing HindIII and NdeI restriction endonuclease sites at the 3' and 5' termini, respectively, were prepared. These primers were then used to amplify the putative HMG-CoA synthase gene from a genomic *S. cerevisiae* DNA preparation by PCR. The resulting product (1.5 kb) was digested with *Hind*III and *Nde*I, purified and cloned into the corresponding restriction sites on the plasmid pET-22b. After transforming *E. coli* BL21 (DE3) cells with this plasmid, plasmid DNA from three clones was prepared. The entire 1500 bases of interest were sequenced using primers for the T7 promoter and terminator sequences present in the plasmid, and an additional primer which was complementary to a central region of the gene. The results show that in all three clones there are three silent mutations relative to the original database sequence, as well as one non-silent mutation (nt 223 from T to C) corresponding to codon

75 being changed from serine to proline. Induction of expression of HMG-CoA synthase [MW 47.5 kD] in one of these clones was achieved by IPTG as assessed by SDS-PAGE of total cell protein. After cell lysis, the crude cell-free extract possessed a specific activity of synthase of 0.04 units/mg, compared to uninduced and insert-free controls which were inactive.

The recombinant enzyme was partially purified by a sequence of ammonium sulfate precipitation, anion exchange (Q-Sepharose) and size exclusion (S-200) chromatography to a final specific activity of 0.85 units/mg protein (Table 5).

Table 5. Purification of recombinant yeast HMG-CoA synthase

Step	Vol. (mL)	Total protein (mg)	Specific activity (units/mg)[a]	Yield (%)	Fold purification
Cell-free Extract	20	30	0.04	100	1
$(NH_4)_2SO_4$ (25–40%)	5	50	0.10	104	2.5
Q-Sepharose	10	3	0.5	63	12
S-200	10	1	0.85	35	21

[a]One unit = 1 μmol/min.

IC50 values for β-lactones. Initially, we screened the β-lactones **7a-d**, **7g-o** and **7s-w** for inhibitory activity against HMG-CoA synthase using an in vitro assay against either native or recombinant enzyme. While IC_{50} is a poor measure of activity for irreversible inhibitors, this value does provide a comparison between inactivators determined with the same sample under identical conditions, as was the case in this study. Since IC_{50} is much more readily obtained, compared to the more fundamental constants of inhibition, k_{inact} and K_I, it was practical to obtain this value for all the inhibitors. All assays were performed by measuring the percentage of enzyme inhibited, relative to an inhibitor-free control, during five minutes of preincubation of inhibitor with enzyme, followed by addition of adequate substrates to prevent further inactivation of the enzyme, as demonstrated by linear substrate consumption during the assay period (Fig. 1). The IC_{50} values were then obtained by plotting % inhibition versus concentration of inhibitor for a series of assays performed at inhibitor concentrations above, below and around

the estimated IC_{50}, followed by extrapolation of the IC_{50} value (Fig. 2). For F-244, as well as several of the synthetic β-lactones studied, the IC_{50} values were determined repetitively in several independent trials, and statistical analysis gave estimates of errors associated with these determinations. The results are shown in Table 6.

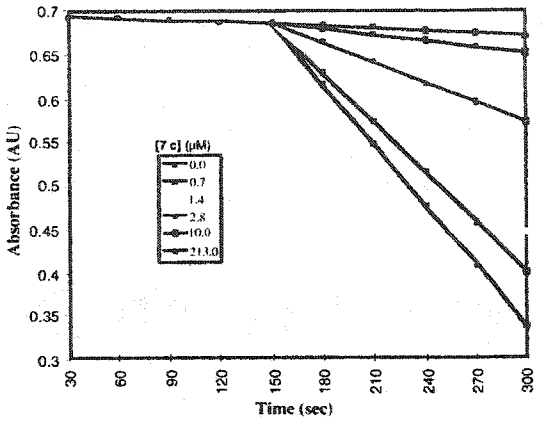


Figure 1. Inhibition of HMG-CoA Synthase by β-Lactone **7c**. Enzyme was incubated with the concentrations of **7c** shown for 5 min, then acetoacetyl-CoA (AcAcCoA) was added (time 0). Absorbance of AcAcCoA at 303 nm was monitored for 150 s (providing a control for AcAcCoA thiolase), then acetyl-CoA was added, and the reaction was monitored until time 300 s.

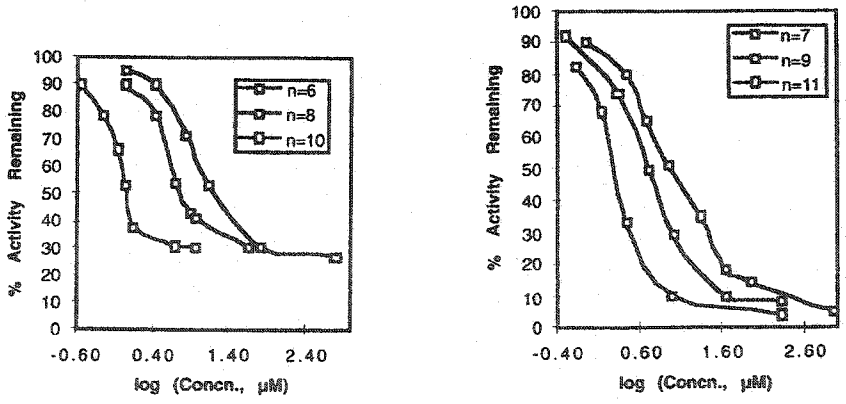
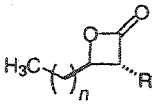


Figure 2. Representative inhibition curves for HMG-CoA synthase. Data from Figure 1 and similar plots for β-lactones **7b**, **7g**, **7u**, **7v**, and **7w** are re-plotted to show percent inhibition as a function of β-lactone concentration. IC_{50} values were determined by extrapolation.

Table 6. IC_{50} values for inhibition of HMG-CoA synthase with β-lactones of varying chain length[a]

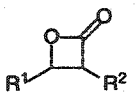


15

n	R = H				R = Me			
	Entry	β-Lactone	Enz[b]	IC_{50} (μM)[c]	Entry	β-Lactone	Enz[b]	IC_{50} (μM)[c]
—	1	**15**	N	500 (5)	13	—	—	—
0	2	**2**	N,R	2,000 (1) ± 40[d]	14	—	—	—
3	3	**7s**	R	200 (4); 150 (4)[e]	15	**7h**	R	88 (5)
4	4	**7t**	—	—	16	**7i**	R	26 (1)
5	5	**7u**	N	13 (1)	17	**7j**	R	10 (1) [g]
6	6	**7g**	N	9.0 (8)	18	**7a**	N	1.6 (1)
7	7	**7b**	N	6.3 (5)	19	**7k**	R	1.3 (1)
8	8	**7c**	N,R	2.0 (2) ± 0.17[f]	20	**7d**	N	1.0 (1) ± 0.28[d]
9	9	**7v**	N,R	1.4 (2) ± 0.08[g]	21	**7l**	R	0.28 (1)
10	10	**7w**	R	2.0 (1)	22	**7m**	R	2.7 (1)
12	11	—	—	—	23	**7n**	R	280 (8)
16	12	—	—	—	24	**7o**	R	280 (8)

[a]Determined for 5 min inactivation.
[b]Enz = enzyme source, N = native, R = recombinant.
[c]Values in parentheses are errors in the last decimal place from a single inhibition plot; errors from statistical analysis of several repeat experiments are shown as ± one standard deviation.
[d]Average and standard deviation (±) from five determinations.
[e]First value is for racemic, second for β-lactone (4*R*)-7s (85% ee).
[f]Average and standard deviation (±) from six determinations.
[g]As for note f, from four determinations.

Table 7. IC_{50} values for inactivation of HMG-CoA synthase by β-lactones with varying substitution[a]



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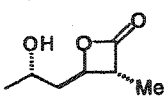

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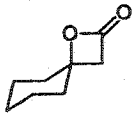

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Entry	β-Lactone	R_1	R_2	Config.	IC_{50} (μM)[b]
1	**10t**	C_5H_{11}	$SiMe_2t$-Bu	*RS-trans/cis*[c]	> 2,000
2	**7x**[d]	*c*-C_6H_{11}	H	*RS*	350 (5)
3	**7x**[d]	*c*-C_6H_{11}	H	4-*S*	184 (4)
4	**7e**[d]	$Ph(CH_2)_2$	H	*RS*	1800 (50)
5	**7bb**[d]	$Ph(CH_2)_2$	Me	*RS-trans*	1500 (50)
6	**7p**[d]	*p*-NO_2Ph	Me	*RS-cis*	> > 2,000
7	**16**[d]	$CH_2CH(OH)CH_3$	Me	3*R*,4*R*,2′*S*	283 (15)
8	**17**[d]	$-(CH_2)_5-$	H	achiral	2300 (50)[e]
9	(F-244) 1	—	—	4-*R-trans*	0.0100 ± 0.0006[f]

[a]Determined for 5 min inactivation.
[b]Values in parentheses are errors in the last decimal place from a single inhibition plot; errors from statistical analysis of several repeat experiments are shown as ± one standard deviation.
[c]This was a 4.7/1 ratio of *cis/trans* β-lactones.
[d]These β-lactones have been described previously, see refs 22a, 23c, and d.
[e]Reversible inhibitor.
[f]Average and standard deviation (±) from six determinations.

Several other synthetic β-lactones were also investigated for inhibitory efficacy against the synthase. The results for IC_{50} in these cases are shown in Table 7.

Discussion

Synthetic studies

Synthesis of racemic β-lactones. Danheiser and Nowick reported the first one-pot condensation of enolates with aldehydes to give variously substituted β-lactones.[22a] They employed thiophenyl ester enolates (**4a** or **4b**) and the presumed, initially formed aldolates **5** spontaneously lactonized on warming (Scheme 1). However, condensation of the enolate derived from phenyl thioacetate with hexanal, octanal or decanal failed to give any α-unsubstituted-β-lactones in our hands. In an analogous one-step lactonization, Schick and co-workers[22b] used the enolates of phenyl esters (**4c** or **4d**). However, this method also failed to provide the expected β-lactone **7t** by condensation of the enolate of phenyl acetate with hexanal. In contrast, addition of either octanal or decanal (-100 °C) to either the phenyl or thiophenyl propionate (**3b** or **3d**) derived enolates (**4**) gave lactones **7a** and **7d** in yields of 32-39% (Table 1, entries 1-2 and 5-6) with a *trans/cis* ratio of >19/1 (200 MHz ^{1}H NMR). The lower reaction temperature was crucial to obtain the desired β-lactones. Thus, both methods provide good selectivity but low yields in the preparation of 3,4-disubstituted oxetan-2-ones, and appear to be unsuitable for the preparation of C4-monosubstituted-β-lactones.

An alternative approach to C-4-monosubstituted oxetan-2-ones involves isolation of the aldol adduct **6**, followed by a separate lactonization (Scheme 1). Wemple condensed the enolate of phenyl thioacetate with aldehydes at low temperature, then quenched the resulting aldol alkoxide **5** to give β-hydroxythiophenyl esters **6**.[27] Masamune cyclized β-hydroxythiophenyl esters using $Hg(O_3SCH_3)_2$ to give various substituted β-lactones.[28] This sequential route furnished racemic 4-octyl-(**7b**) and 4-nonyl-oxetan-2-one (**7c**) from thiophenyl acetate and nonanal, or decanal in two steps in 56 and 61% overall yield, respectively (entries 3 and 4, Table 1). However, the corresponding condensation of phenyl thiopropionate with decanal followed by lactonization gave the lactone **7d** in a ca. 1/1.2 ratio of

cis/*trans* diastereomers and 66% overall yield. Thus, while this method provides a route to both C3, C4-disubstituted as well as C4-monsubstituted-β-lactones, undesirable features include the use of mercury salts, the low diastereoselectivity with the propionate enolate, and the fact that it is a two step process. We next investigated the use of the 2-thiopyridylketene acetals **8** for the single pot preparation of β-lactones, according to a method first reported by Hirai and further developed in our laboratories (Scheme 2, Table 2).[23] Condensation of the TBS (tert-butyldimethylsilyl) ketene acetal **8c** with a variety of aldehydes using $ZnCl_2$ as a promoter, afforded the corresponding 3-methyl-4-alkyloxetan-2-ones in yields of 32-47% with high diastereoselectivities (*trans*/*cis*, >19/1). As previously described,[23b,c] this method could also be used to access C4-monsubstituted-β-lactones unavailable by other one-pot aldol-lactonization methods described above. We have also previously reported that higher yields of β-lactones using propionate and especially acetate derived thiopyridylketene acetals could be achieved by employing the triethylsilyl (TES) ketene acetals **8b** and **8d**. This was further demonstrated in this study (i.e. entries 1, 3-4 and 8, Table 2).[23c]

The Lewis acid catalyzed [2+2] cycloaddition of trimethylsilylketene and aldehydes first reported by Zaitseva[27] was also investigated. Trimethylsilylketene[33] was prepared and its [2+2] cycloaddition with a range of saturated aldehydes afforded monosubstituted β-lactones **7b-c**, **7g**, **7s-7w** in good yields (74-84%, Table 3) after a subsequent desilylation step of the α-silyl-β-lactones **10**. This two step process provides a concise route to racemic, C4-monosubstituted β-lactones. Limitations to this method are the somewhat tedious preparation of ethoxyacetylene[34] required for the synthesis of trimethylsilylketene and the fact that it is a two step process. In summary, for *trans*-3-methyl-4-alkyloxetan-2-ones, the methods of Danheiser and Schick are comparable in both yield and diastereoselectivity, removing the requirement for diastereomer separation inherent in the method due to Wemple. The TMAL reaction provides a

concise, and highly diastereoselective route to both C4-monosubstituted and C3, C4-disubstituted-β-lactones. In most cases, these methods are complementary to one another since for example, the single-pot aldol-lactonizations proceed efficiently with ketone substrates but less so with aldehyde substrates. In contrast, the TMAL reaction provides good yields with aldehyde substrates including the use of acetic acid derived ketene acetals leading to C4-monosubstituted β-lactones. In some cases, comparable diastereoselectivity but higher yields can be obtained via the TMAL reaction in comparison to the methods of Danheiser and Schick (cf. entry 1 and 2, Table 1 and entry 8, Table 2). In addition the one step TMAL reaction gives comparable yields to the two-step aldol-lactonization (Wemple/Masamune) for the synthesis of C4-mono-substituted β-lactones (cf. entry 4, Table 1 vs entry 4, Table 2). However, the [2+2] cycloaddition of aldehydes and ketenes provides the highest overall yields for C4- monosubstituted β-lactones but is a two step procedure.

Synthesis of optically active β-lactones. In the design stages of the aluminum complex **14**, we envisioned a tetrahedral complex (**A** or **B**) formed upon complexation of the (monomeric) Lewis acid with an aldehyde (Fig. 3). In this situation, assuming the chlorine adopts a pseudoequatorial position upon complexation, the aldehyde would be in a pseudoaxial position. Two conformations are likely, **A** and **B**, and it was not clear at the outset which would predominate. These conformations avoid 1,3-diaxial type interactions between the formyl hydrogen or R group of the aldehyde and the axial phenyl group. However, it appeared that conformation **A** would provide low facial selectivity while conformation **B** may lead to high facial selectivity since the pseudoaxial phenyl effectively blocks the *Re* face of the aldehyde. The possibility of formyl C-H-O hydrogen bonding to oxygen, recently proposed by Corey to explain a number of enantioselective transformations,[35] found in conformer **B** was also considered as a possible control element to favor conformation **B**. However, analysis of the complex by ^{27}Al-NMR indicates that the Lewis acid **14** in toluene-

d_8 may exist as two species, one of which is a dimer, making a rationalization of the results more difficult.[36]

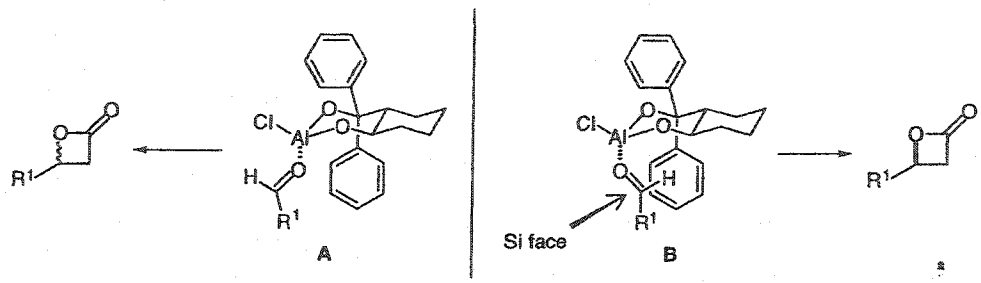

Figure 3. Proposed conformations for complexation of aldehydes with monomeric Lewis acid 14.

The Lewis acid **14** derived from diol **11** and Et_2AlCl led to good reactivity but variability in the enantioselectivity for the [2+2] cycloaddition of trimethylsilyl ketene and various aldehydes (Table 4). Interestingly, the same facial selectivity is observed with most aldehydes for which the absolute configurations have been determined (entries 1, 2 and 5 but not entry 6, Table 4) and is consistent with attack on the *Si* face of the aldehyde on conformer **B**. It should be noted that the difference in absolute configuration for the β-lactones derived from cyclohexanecarboxaldehyde and *n*-butanal (cf. entry 1 and 2, Table 4) is due to a change in substituent priority rather than a change in facial selectivity of the aldehyde. While these are the highest enantioselectivities reported to date for α-unbranched, aliphatic aldehydes (i.e. entry 2, Table 4) in this [2+2] cycloaddition, the reactivity and generality must obviously be improved before this becomes a practical procedure for the preparation of optically active β-lactones.

Inhibition studies

Although the native HMG-CoA synthase from yeast is available, as we have described previously,[20] diffculties in the purification of this enzyme to homogeneity, coupled with the availability of the sequence of the yeast genome, led us to investigate a genetic cloning approach. Cloning of the putative *S. cerevisiae* HMG-CoA synthase gene, which has ca. 40% sequence similarity to

the known human sequence, into an *E. coli* host under control of the T7 promoter, followed by induction gives HMG-CoA synthase of defined sequence, which is fully catalytically competent and resembles the native enzyme in many respects. The putative role of this gene in yeast is thus confirmed. The mutation of Ser-75 to Pro-75 which was detected in this study has little effect on the competency of the protein. The IC_{50} values for several of the β-lactone inhibitors (**2**, **7s**, **7c**, and **7v**) were determined with both recombinant and native enzyme preparations, and in each case the values obtained were found to be essentially identical. The recombinant and native HMG-CoA synthases behave similarly during purification; however the higher initial specific activity in the recombinant case allows for a purer preparation overall (ca. 25% pure based on titration with F-244). The IC_{50} for both β-lactone **2** and F- 244 (**1**) was determined at various stages of purification of both enzyme preparations, and was found to be invariant with enzyme purity, indicating that there are no interferences with inhibition through processes such as protein-protein interactions, and allowing further studies of the inhibition process with the partially purified material. An overall 21-fold purification of the recombinant synthase was obtained in three steps; completion of the purification is currently in progress.

Although the amino acid sequence for yeast synthase is substantially different than that for human enzyme, the results of this study confirm that the yeast synthase is a valid model for the human protein. Thus, the IC_{50} value for F-244 was found to be essentially identical to values reported previously.

Two sets of β-lactones bearing either hydrogen or methyl at C-3 and alkyl chains from one to 18 carbons at C-4 were evaluated for inhibitory efficacy. The results show a roughly monotonic decrease in IC_{50} with C-4 chain length until an optimum length of 10 carbons is reached. Thereafter, the IC_{50} rises sharply again. The results are most simply interpreted in terms of a substantial hydrophobic binding pocket on the enzyme; increasing alkyl chain length gives rise to tighter binding, and hence to reduced IC_{50} (Fig. 4). Alkyl chains of greater than 10

carbons "overflow" out of the pocket, perhaps into a hydrophilic region or into the aqueous environment, making this arrangement disfavored. Comparison of the C3-methyl series with the C4-mono-substituted β-lactones as inhibitors shows a consistent improved affinity for the enzyme when the 3-methyl group is present, by a factor of between 1.3 and 5.6. This result implies that a substituent at C-3 can also provide a substantial hydrophobic interaction with the enzyme. Although this study was performed largely with racemic lactones, due to ease of synthesis, lactone **7a** in enantiomerically enriched form was investigated, to establish that the inhibitors were acting enantioselectively. Comparison of the results with racemic and chiral materials shows that the enantiomer corresponding in configuration to F-244 is most effective, suggesting that the compound is binding in the synthase active site in a similar manner to F-244. It is interesting to note from Fig. 2 that β-lactones in the odd *n* series abolished synthase activity completely, but that even *n* β-lactones appeared to permit some residual enzyme activity even at high concentrations. The source of this effect is currently unclear, and investigations of this phenomenon are ongoing. The acute loss of activity for very long chains, as well as the discrimination for one enantiomer of **7a** are both inconsistent with inhibitory activity depending on aggregation of the hydrophobic β-lactones. Thus, the critical micellar concentration of long-chain β-lactones is expected to decrease with increasing chain length to 18 carbons.

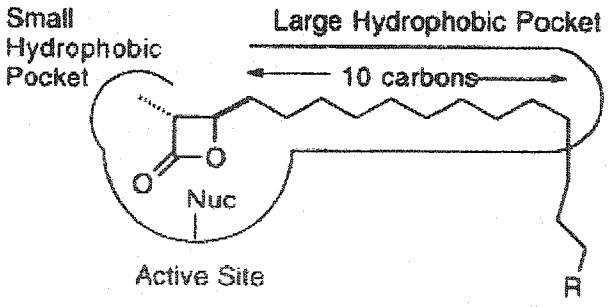

Figure 4. Proposed HMG-CoA synthase binding/active site for β-lactone inhibitors.

These results are consistent with data from a range of previous studies that have shown, for example, that F-244 methyl ester, F-244 O-methyl ether and several oxetan-2-ones possessing phenalkyl groups at C4 exhibit little loss of potency compared to the parent antibiotic. However, the present set of data rigorously establish the approximate size requirements for the hydrophobic cavity at the active site of HMG-CoA synthase. Thus, nature has selected the optimal chain length in the natural inhibitor F-244 (**1**). The results with several lactones which are reported in Table 7 demonstrate that the enzyme is not highly tolerant of major changes in structure of the inhibitor at either C3 or C4. Thus, replacement of a C3-methyl by tert-butyldimethylsilyl gives an extremely poor inhibitor (cf. entry 16, Table 6 with entry 1, Table 7). Likewise, a *p*-nitrophenyl substituent at C4 resulted in only weak activity. The results with β-lactones **7e** and **7bb** show that a phenethyl substituent at C4 gives poor activity against yeast HMG-CoA synthase. This result is in contrast to those of Hashizume with rat liver enzyme.[17b] This observation suggests a difference between the two proteins for these inhibitors, whereas F-244 shows similar activity with both enzymes. That such a difference could be exploited in species selective inhibition of the synthase is under active investigation. In contrast, 2'-hydroxypropyl or cyclohexyl substituents at C4 give inhibitory activities which approximate those of the straight-chain compounds which possess the same chain length (cf. entry 2 and 7, Table 7 with entry 3, Table 6). In the case of the cyclohexyl substituent, enantiomerically enriched material exhibited an IC_{50} of approximately one-half that of the racemic compound (entries 2 and 3, Table 7), again showing the binding to be enantioselective.

Conclusion

For the synthesis of racemic β-lactones from aldehydes, the aldol-lactonization methods of Danheiser and Schick are comparable in terms of yields and

selectivity for the preparation of C3, C4-disubstituted β-lactones. However, these methods do not allow access to C4-monosubstituted-β-lactones. The TMAL reaction provides a single step route to C4-monosubstituted-β-lactones using readily available thiopyridylketene acetals, however the two step procedure involving [2+2] cycloaddition of aldehydes and silylketenes provides higher overall yields. In addition, the TMAL reaction provides good yields and high diastereoselectivity for the synthesis of C3,C4-disubstituted-β-lactones. A new, aluminum chiral Lewis acid has been applied to the [2+2] cycloaddition of aldehydes and trimethylsilylketene and provides good reactivity but variable enantioselectivity dependent on the substrate structure. Both 4-alkyl- and 3-methyl-4-alkyl-oxetan-2-ones exhibit a logical trend in inhibition of HMG-CoA synthase with potencies which are dependent on the length of the C4 substituent; a chain of 10-11 carbons gives maximal inhibition. The results can be explained by hydrophobic interactions with the synthase active site.

Experimental

General synthetic procedures

All reactions were performed in flame-dried glassware under a positive pressure of nitrogen and magnetically stirred unless otherwise indicated. Toluene was distilled from sodium immediately prior to use. Methylene chloride was distilled from CaH_2 immediately prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl radical immediately prior to use. Acetonitrile was heated at reflux overnight with P_2O_5, distilled, and kept under argon over activated 3 Å molecular sieves. Commercially available aldehydes were purchased from Aldrich Chemical Co. and other aldehydes were prepared from the corresponding alcohols by oxidation. All aldehydes were distilled (Kugelrohr distillation) or purified by flash chromatography (silica gel) immediately prior to use. Commercial-grade reagents (Aldrich) and solvents (Caledon) were used without further purification except as indicated below. Flash

column chromatography was accomplished using Merck 60 (230-400 mesh) silica gel or Baxter S/P Silica Gel 60 Å (230-400 mesh ASTM). Thin layer chromatography was performed using Merck 60 F-254 plates, and β-lactones were visualized through treatment with a solution of phosphomolybdic acid in 10% sulfuric acid (5 g/100 mL). Mass spectra were obtained on a VG analytical 70S high-resolution, double focusing, sectored (EB) mass spectrometer at the Center for Chemical Characterization and Analysis (Texas A&M) or on a VG Analytical ZAB-E mass spectrometer (McMaster). Enantiomeric excess was determined by GC (Hewlett-Packard 5880A gas chromatograph) analysis using a TBS-β-cyclodextrin column[31] or HPLC (RAININ SD-200 with DYNAMAX UV-C detector) analysis using a Chiralcel OD column. IR spectra were recorded on a Nicolet Impact 410DSP (Texas A&M) or on a BIO-RAD FTS-40 FT-IR spectrometer (McMaster). ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) or 200E spectrometer (200 MHz) (Texas A&M) or Bruker AC-200, AC-300, or DRX-500 spectrometers (McMaster) and chemical shifts are reported in ppm using tetramethylsilane (δ 0.0) or $CHCl_3$ (δ 7.26) as internal reference. ^{13}C NMR spectra were recorded on a Varian VXR-300 (75 MHz) or XL 200E (50 MHz) and chemical shifts are reported in ppm using $CDCl_3$ (δ 77.0) as internal reference. ^{27}Al NMR spectra were recorded on a Varian XL 200 (52 MHz) in toluene-d_8 and chemical shifts are reported in ppm relative to $Al(acac)_2$ (δ 0.0) as external reference.

Methods A,[22a] B,[22b] and C[22,28] (Table 1) were performed according to the published procedures except that in method A, the aldehyde was added at -100 °C. The characterization of β-lactones prepared by these methods is described below.

General procedure for the [2+2] cycloaddition of aldehydes and trimethylsilyl ketene and desilylation as described for 4-nonyl-oxetan-2-one (7c). A solution of decanal (0.403 g, 2.62 mmol) and trimethylsilylketene **9a**[34] (0.334 g, 2.91 mmol, 1.1 equiv) dissolved in dichloromethane (5 mL) was cooled to 0 °C. While stirring, boron trifluoride etherate (0.4 mL of a 0.1 M solution in

dichloromethane) was added dropwise until IR indicated loss of trimethylsilylketene starting material (ca. 50 min). The reaction was quenched with two drops of water and the solution was filtered through a short plug of anhydrous sodium sulfate. After solvent removal on the rotary evaporator, the crude oil was dissolved in 7mL of acetonitrile. To this solution, finely crushed $KF.2H_2O$ (0.496 g, 5.23 mmol, 2.0 equiv) was added and the mixture was vigorously stirred for 20 min. The resulting mixture was filtered through florisil with ether washing and the solvent was removed on a rotary evaporator. The crude oil was purified via flash chromatography (EtOAc/hexanes, 10/90) to give 432 mg of lactone **7c** (84%) as a colorless oil. IR (thin film) 2928, 1831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.49 (m, 1H), 3.51 (dd, J=16.2,
5.7 Hz, 1H), 3.05 (dd, J=16.2, 4.3 Hz, 1H), 1.76 (m, 2H), 1.28 (m, 14H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, CDCl3) δ 168.3, 71.5, 42.8, 34.6, 29.4 (2C), 29.2, 24.8, 22.6, 14.1.

4-Butyloxetan-2-one (7s). The [2+2] cycloaddition of pentanal (0.197 g, 1.74 mmol) with trimethylsilylketene **9a** (0.215 g, 1.82 mmol) and then desilylation with potassium fluoride dihydrate (0.322 g, 3.41 mmol) was performed according to the general procedure. Work-up followed by purification afforded 187 mg (74%) of product **7s** as a colorless oil. IR (thin film) 2931, 1828 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.50 (dd, J=16.2, 5.7 Hz, 1H), 3.04 (dd, J=16.2, 4.3 Hz, 1H), 1.86 (m, 2H), 1.30 (m, 8H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 71.2, 42.8, 34.6, 31.5, 28.7, 24.7, 22.4, 13.9.

4-Hexyloxetan-2-one (7u). The [2+2] cycloaddition of heptanal (0.197 g, 1.74 mmol) with trimethylsilylketene **9a** (0.215 g, 1.82 mmol) and then desilylation with potassium fluoride dihydrate (0.322 g, 3.41 mmol) was performed according to the general procedure. Work-up followed by purification afforded 187 mg (74%) of product **7u** as a colorless oil. IR (thin film) 2931, 1828 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.50 (dd, J=16.2, 5.7 Hz, 1H), 3.04 (dd, J=16.2, 4.3 Hz, 1H), 1.86 (m, 2H), 1.30 (m, 8H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR

(50 MHz, $CDCl_3$) δ 168.3, 71.2, 42.8, 34.6, 31.5, 28.7, 24.7, 22.4, 13.9.

4-Heptyloxetan-2-one (7g). The [2+2] cycloaddition of octanal (0.217 g, 1.63 mmol) with trimethylsilylketene **9a** (0.200 g, 1.73 mmol) and then desilylation with potassium fluoride dihydrate (0.306 g, 3.24 mmol) was performed according to the general procedure. Work-up followed by purification afforded 214 mg (80%) of product **7g** as a colorless oil. IR (thin film) 2930, 1830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.50 (dd, J=16.2, 5.7 Hz, 1H), 3.04 (dd, J=16.2, 4.3 Hz, 1H), 1.80 (m, 2H), 1.27 (m, 10H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 71.4, 42.8, 34.6, 31.5, 28.9, 24.8, 22.4, 14.0.

4-Octyloxetan-2-one (7b). The [2+2] cycloaddition of nonanal (0.319 g, 2.26 mmol) with trimethylsilylketene **9a** (0.287 g, 2.52 mmol) and then desilylation with potassium fluoride dihydrate (0.413 g, 4.46 mmol) was performed according to the general procedure. Work-up followed by purification afforded 317 mg (78%) of product **7b** as a colorless oil. IR (thin film) 2928, 1831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.48 (m, 1H), 3.49 (dd, J=16.2, 5.7 Hz, 1H), 3.04 (dd, J=16.2, 4.3 Hz, 1H), 1.79 (m, 2H), 1.26 (m, 10H), 0.86 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 71.2, 42.8, 34.6, 31.7, 31.5, 29.3, 29.1, 24.8, 22.6, 14.0.

4-Decyloxetan-2-one (7v). The [2+2] cycloaddition of undecanal (0.640 g, 3.69 mmol) with trimethylsilylketene **9a** (0.475 g, 4.14 mmol) and then desilylation with potassium fluoride dihydrate (0.708 g, 7.43 mmol) was performed according to the general procedure. Work-up followed by purification afforded 651 mg (82%) of product **7v** as a colorless oil. IR (thin film) 2926, 1830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.50 (dd, J=16.2, 5.7 Hz, 1H), 3.05 (dd, J=16.2, 4.3 Hz, 1H), 1.79 (m, 2H), 1.26 (m, 16H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 71.3, 42.9, 34.7, 31.9, 29.4 (3C), 29.3, 29.1, 24.9, 22.6, 14.1.

4-Undecyloxetan-2-one (7w). The [2+2] cycloaddition of dodecanal (0.433 g, 2.32 mmol) with trimethylsilylketene **9a** (0.285 g, 2.49 mmol) and then

desilylation with potassium fluoride dihydrate (0.428 g, 4.63 mmol) was performed according to the general procedure. Work-up followed by purification afforded 413 mg (79%) of product **7w** as a colorless oil. IR (thin film) 2926, 1831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.50 (dd, J=16.2, 5.7 Hz, 1H), 3.05 (dd, J=16.2, 4.3 Hz, 1H), 1.79 (m, 2H), 1.25 (m, 18H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4, 71.3, 42.9, 34.7, 31.9, 29.6, 29.4 (3C), 29.3, 29.2, 24.9, 22.7, 14.1.

cis/trans-4-Butyl-3-tert-butyldimethylsilyloxetan-2-one (10t). The [2+2] cycloaddition of hexanal (0.242 g, 2.4 mmol) with tert-butyldimethylsilyl ketene (0.390 g, 2.5 mmol) was performed according to the general procedure with the exception that the desilylation was not performed. Purification (EtOAc/hexanes, 10/90) gave 0.561 g (94%) of β-lactone **10t** (cis/trans, 4.7/1, 200MHz ^1H NMR). IR (thin film) 2932, 1806 cm^{-1}; *cis*-**10t**: ^1H NMR (200 MHz, $CDCl_3$) δ 4.61 (m, 1H), 3.58 (d, J=6.3 Hz, 1H), 1.76 (m, 2H), 1.31 (m, 6H), 0.91 (m, 12H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 74.9, 43.8, 34.8, 32.0, 26.8, 23.2, 17.3, 14.2, 7.1, 7.3; trans-**10t**: $_1H$ NMR (200 MHz, $CDCl_3$) δ 4.36 (m, 1H), 3.58 (d, J=4.1 Hz, 1H), 1.76 (m, 2H), 1.31 (m, 6H), 0.91 (m, 12H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 73.7, 46.2, 36.3, 32.2, 26.8, 23.2, 17.3, 14.2, 7.3, 7.1.

The tandem Mukaiyama aldol-lactonization (TMAL) reaction was used to prepare the following β-lactones and was performed as described previously.[23c]

4-Heptyl-3-methyloxetan-2-one (7a). The reaction of octanal (0.216 g, 1.63 mmol) with ketene acetal **8c** (0.504 g, 1.78 mmol) was performed using 0.533 g (2.35 mmol) zinc chloride in 10mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7a** (108 mg, 39%) as a clear oil. IR (thin film) 2930, 1825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.14 (td, J=6.7, 4.0 Hz, 1H), 3.20 (qd, J=7.5, 4.0 Hz, 1H), 1.77 (m, 2H), 1.35 (d, J=7.5 Hz, 3H), 1.26 (m, 10H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.5, 50.6, 34.0, 31.5, 31.3, 29.0, 24.6, 22.4, 13.8, 12.4.

4-Nonyl-3-methyloxetan-2-one (7d). The reaction of decanal (0.104 g, 0.647 mmol) with ketene acetal **8c** (0.203 g, 0.712 mmol) was performed using 0.203 g (0.887 mmol) zinc chloride in 5mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7d** (46 mg, 35%) as a clear oil. IR (thin film) 2928, 1826 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.16 (td, J=6.7, 4.0 Hz, 1H), 3.20 (qd, J=7.5, 4.0 Hz, 1H), 1.79 (m, 2H), 1.37 (d, J=7.5 Hz, 3H), 1.26 (m, 14H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 79.6, 50.8, 34.2, 31.9, 31.6, 29.5 (2C), 29.3, 25.0, 22.7, 14.5, 12.6.

4-Butyl-3-methyloxetan-2-one (7h). The reaction of pentanal (0.125 g, 1.33 mmol) with ketene acetal **8c** (0.416 g, 1.46 mmol) was performed using 0.429 g (1.85 mmol) zinc chloride in 7 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7h** (58 mg, 34%) as a clear oil. IR (thin film) 2936, 1824 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.14 (td, J=6.7, 4.0 Hz, 1H), 3.18 (qd, J=7.5, 4.0 Hz, 1H), 1.78 (m, 2H), 1.32 (d, J=7.5 Hz, 3H), 1.24 (m, 4H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.5, 50.6, 33.7, 26.9, 22.2, 13.7, 12.4.

4-Pentyl-3-methyloxetan-2-one (7i). The reaction of hexanal (0.163 g, 1.62 mmol) with ketene acetal **8c** (0.509 g, 1.78 mmol) was performed using 0.479 g (2.12 mmol) zinc chloride in 10 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7i** (83 mg, 36%) as a clear oil. IR (thin film) 2933, 1825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.15 (dt, J=6.7, 4.0 Hz, 1H), 3.20 (dq, J=7.5, 4.0 Hz, 1H), 1.79 (m, 2H), 1.36 (d, J=7.5 Hz, 3H), 1.24 (m, 6H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.5, 50.6, 34.0, 31.3, 24.6, 22.4, 13.8, 12.4.

4-Hexyl-3-methyloxetan-2-one (7j). The reaction of heptanal (0.183 g, 1.55 mmol) with ketene acetal **8c** (0.488 g, 1.71 mmol) was performed using 0.489 g (2.15 mmol) zinc chloride in 10 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7j** (94 mg, 39%) as a clear oil. IR (thin film) 2932, 1827 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.15 (td, J=6.7,

4.0 Hz, 1H), 3.20 (qd, J=7.5, 4.0 Hz, 1H), 1.78 (m, 2H), 1.36 (d, J=7.5 Hz, 3H), 1.27 (m, 8H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 76.4, 50.6, 34.1, 31.5, 28.8, 24.9, 22.4, 13.9, 12.4.

4-Octyl-3-methyloxetan-2-one (7k). The reaction of nonanal (0.169 g, 1.19 mmol) with ketene acetal **8c** (0.34 g, 1.21 mmol) was performed using 0.364 g (1.62 mmol) zinc chloride in 5 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7k** (110 mg, 35%) as a clear oil. IR (thin film) 2929, 1826 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.14 (td, J=6.7, 4.0 Hz, 1H), 3.19 (qd, J=7.5, 4.0 Hz, 1H), 1.76 (m, 2H), 1.35 (d, J=7.5 Hz, 3H), 1.24 (m, 12H), 0.85 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.4, 50.6, 34.0, 31.7, 29.3, 29.1, 29.0, 24.9, 22.5, 14.0, 12.4.

4-Decyl-3-methyloxetan-2-one (7l). The reaction of undecanal (0.188 g, 1.04 mmol) with ketene acetal **8c** (0.328 g, 1.14 mmol) was performed using 0.336 g (1.50 mmol) zinc chloride in 5 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7l** (83 mg, 38%) as a clear oil. IR (thin film) 2928, 1827 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.15 (td, J=6.7, 4.0 Hz, 1H), 3.19 (qd, J=7.5, 4.0 Hz, 1H), 1.79 (m, 2H), 1.34 (d, J=7.5 Hz, 3H), 1.24 (m, 16H), 0.86 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.5, 50.6, 34.1, 31.8, 29.5 (2C), 29.4, 29.2, 29.1, 24.9, 22.6, 14.0, 12.4.

4-Undecyl-3-methyloxetan-2-one (7m). The reaction of dodecanal (0.291 g, 1.64 mmol) with ketene acetal **8c** (0.508 g, 1.80 mmol, 1.1 equiv) was performed using 0.649 g (2.93 mmol, 1.6 equiv) zinc chloride in 7 mL dichloromethane according to the general procedure. Work-up followed by purification gave 157 mg of β-lactone **7m** (41%) as a clear oil. IR (thin film) 2929, 1826 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.16 (dt, J=6.7, 4.0 Hz, 1H), 3.20 (dq, J=7.6, 4.0 Hz, 1H), 1.77 (m, 2H), 1.37 (d, J=7.6 Hz, 3H), 1.25 (m, 18H), 0.87 (t, J=6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 79.6, 50.7, 34.1, 31.9, 29.6 (3C), 29.4, 29.3, 29.2, 24.9, 22.7, 14.1, 12.5.

4-Tridecyl-3-methyloxetan-2-one (7n). The reaction of tetradecanal (0.270 g,

1.29 mmol) with ketene acetal **8c** (0.406 g, 1.43 mmol) was performed using 0.396 g (1.74 mmol) zinc chloride in 8 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7n** (131 mg, 40%) as a clear oil. IR (thin film) 2923, 1819 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.14 (td, J=6.7, 4.0 Hz, 1H), 3.19 (qd, J=7.5, 4.0 Hz, 1H), 1.75 (m, 2H), 1.41 (d, J=7.5 Hz, 3H), 1.23 (m, 22H), 0.86 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.5, 50.6, 34.1, 31.9, 29.6, 29.4, 29.2, 24.9, 22.6, 14.0, 12.5.

4-Heptadecyl-3-methyloxetan-2-one (7o). The reaction of octadecanal (0.179 g, 0.679 mmol) with ketene acetal **8c** (0.217 g, 0.747 mmol) was performed using 0.231 g (1.02 mmol) zinc chloride in 5 mL dichloromethane according to the general procedure. Work-up followed by purification afforded **7o** (67 mg, 32%) as a clear oil. IR (thin film) 2924, 1818 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.16 (td, J=6.7, 4.0 Hz, 1H), 3.21 (qd, J=7.5, 4.0 Hz, 1H), 1.75 (m, 2H), 1.38 (d, J=7.5 Hz, 3H), 1.25 (m, 30H), 0.90 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 79.6, 50.7, 34.1, 31.9, 31.6, 29.7, 29.4, 29.2, 24.9, 22.7, 14.1, 12.5.

Preparation of (1R,2R)-2-ethoxycarbonyl cyclohexan-1-ol (12). This β-hydroxy ester was prepared according to known procedures[30] with a few modifications. To a dried metal Parr reactor were added ethyl 2-cyclohexanonecarboxylate (10.98 g, 64.5 mmol), CH_2Cl_2 (50 mL), Ru-(R)-BINAP catalyst (4 mL; from 40mg of (*R*)-BINAP) which was prepared by the method of Taber,[30a] and Dowex-50 resin (700 mg; washed with water, methanol, diethyl ether, and methanol then dried). Hydrogenation was carried out at 200 psi H_2 and 110°C for 24 h. After cooling, the reaction mixture was filtered through celite and concentrated in vacuo. Flash chromatography (EtOAc/Hexanes, 10/90) gave a mixture of *cis*-β-hydroxy ester (3.2 g, 29%) and *trans*-β-hydroxy ester **12** (7.4 g, 67%) as pale-yellow oils. Spectral data for the *trans*-β-hydroxy ester **12** matched that previously reported:[30c] 64 %ee; R_f 0.19 (EtOAc/hexanes, 20/80); $[\alpha]_D^{22}$ -43.1° (*c* 0.58, ether); ^1H NMR (200 MHz, $CDCl_3$) δ 4.18 (q, J=7.1 Hz, 2H), 3.77 (ddd, J=4.4, 10.2, 10.2 Hz, 1H), 2.77 (bs, 1H), 2.24 (ddd, J=3.7, 10.1, 12.0

Hz, 1H), 2.04 (m, 2H), 1.75 (m, 2H), 1.30 (m, 4H), 1.25 (t, J=7.1 Hz, 3H).

Preparation of chiral diol ligand ((1R,2R)-2-[(diphenyl)-hydroxymethyl] cyclohexan-1-ol) 13. To a solution of *trans*-β-hydroxy ester **12** (1.0 g, 5.8 mmol) in anhydrous diethyl ether (60 mL) was added phenylmagnesium bromide (20.3 mL of 1.0 M in THF, 20.3 mmol) slowly and gradually at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was heated to reflux for 2 h. The mixture was cooled to ambient temperature and quenched with saturated aqueous NH_4Cl solution. The resulting precipitates were redissolved by the addition of aqueous 2 N HCl and the mixture was extracted with ether (3 x 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (EtOAc/hexanes, 10/90) gave 1.17 g (72%) of diol as a pale-yellow solid. Optically pure diol (>99.9 %ee) was obtained as white crystals after a single recrystallization from $CHCl_3$. Spectral data for this compound matched that previously reported:[29] >99.9 %ee; R_f 0.37 (EtOAc/hexanes, 20/80); mp 176.5-177.5 °C (lit. 177-178 °C); $[\alpha]_D^{22}$ -8.9 ° (*c* 1.46, CHCl3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25-7.55 (m, 10H), 3.80 (bs, 1H), 3.32 (ddd, J=4.6, 9.9, 9.9 Hz, 1H), 2.50 (ddd, J=2.7, 9.8, 12.2 Hz, 1H), 0.85-1.95 (m, 8H).

General procedure for the asymmetric [2+2] cyclo- addition reaction as described for cis-4-cyclohexyl-3-(trimethylsilyl)oxetan-2-one (10x). To a solution of chiral diol **13**, (60.4 mg, 0.214 mmol) in toluene (6 mL) was added Et_2AlCl (0.10 mL of 1.8 M in toluene, 0.178 mmol) at 0°C slowly. After stirring for 5 h at 0°C, the reaction mixture was cooled to -78°C then cyclohexanecarboxaldehyde (108 mL, 0.892 mmol) was added. After stirring for 15 min at -78°C, a solution of trimethylsilylketene **9a**[34] (153 mg, 1.34 mmol) in toluene (2 mL) was added and the mixture was further stirred for 30 min at -78°C. The resulting reaction mixture was kept in a freezer (-26°C) for 40 h. After addition of pH 7 buffer (1 mL) at -26°C, the reaction mixture was warmed to

room temperature and filtered through celite. The solution was diluted with ethyl acetate (10 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (EtOAc/hexanes, 5/95) gave 167 mg (83%) of α-silyl-β-lactone **10x** as a colorless oil. Spectral data for this compound matched that previously reported:[37] 84 %ee; R_f 0.35 (EtOAc/ hexanes, 10/90); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (dd, J=5.9, 10.5 Hz, 1H), 3.29 (d, J=5.9 Hz, 1H), 0.83- 2.09 (m, 11H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 78.0, 45.9, 40.6, 28.9, 28.6, 25.9, 25.1, 25.0, 0.85; IR (thin film) 2935, 2855, 1799, 1453, 1252, 1127 cm^{-1}.

cis-4-Butyl-3-(trimethylsilyl)oxetan-2-one (10s). This α-silyl-β-lactone was obtained from valeraldehyde (95 mL, 0.892 mmol) and trimethylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1 mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition. Flash chromatography (EtOAc/hexanes, 5/95) gave 153 mg (86%) of α-silyl-β-lactone **10s** as a colorless oil. Spectral data for this compound matched that previously reported:[26] 85% ee; R_f 0.36 (EtOAc/hexanes, 10/90); 1H NMR (300 MHz, CDCl3) δ 4.57 (m, 1H), 3.33 (d, J=6.0 Hz, 1H), 1.32-1.88 (m, 6H), 0.93 (t, J=7.2 Hz, 3H), 0.22 (s, 9H); IR (thin film) 2958, 2933, 2875, 1800, 1492, 1260, 1123 cm^{-1}.

cis-4-Phenyl-3-(trimethylsilyl)oxetan-2-one (10z). This α-silyl-β-lactone was obtained from benzaldehyde (91 mL, 0.892 mmol) and trimethylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition. Flash chromatography (EtOAc/hexanes, 5/95) gave 161mg (82%) of α-silyl-β-lactone **10z** as a colorless oil. Spectral data for this compound matched that previously reported:[37] 28% ee; R_f 0.44 (EtOAc:hexanes, 10/90); 1H NMR (300 MHz, CDCl3) δ 7.30-7.46 (m, 5H), 5.71 (d, J=6.3 Hz, 1H), 3.72 (d, J=6.3 Hz, 1H), 0.13 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 170.5, 136.8, 128.5, 128.3, 125.4, 72.6, 49.7, -1.86; IR (thin film)

3067, 3036, 2955, 2901, 1811, 1453, 1255, 1110 cm^{-1}.

cis-4-Benzyl-3-(trimethylsilyl)oxetan-2-one (10aa). This α-silyl-β-lactone was obtained from phenylacetaldehyde (104 mL, 0.892 mmol) and trimethylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1 mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition. Flash chromatography (EtOAc/hexanes, 5/95) gave 94 mg (45%) of α-silyl-β-lactone **10aa** as a colorless oil: 75 %ee; R_f 0.33 (EtOAc/hexanes, 10/90); $[\alpha]_D^{22}$ +96.1° (*c* 1.02, CHCl3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 4.83 (ddd, J=3.3, 6.3, 10.2 Hz, 1H), 3.44 (d, J=6.6 Hz, 1H), 3.15 (dd, J=10.2, 14.7 Hz, 1H), 3.05 (dd, J=3.3, 14.7 Hz, 1H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 136.7, 128.7, 128.6, 127.0, 74.0, 46.5, 39.7, -1.1; IR (KBr) 1785 cm^{-1}; HRMS calcd for $C_{13}H_{18}O_2Si$ [M+Na]: 257.0974. Found: 257.0984.

(S)-4-Cyclohexyloxetan-2-one (7x). The α-silyl-β-lactone **10x** (150 mg, 0.66 mmol) was desilylated according to the general procedure in CH_3CN (4 mL) using $KF.2H_2O$ (125 mg, 1.33 mmol) at ambient temperature. Flash chromatography (5-10% ethyl acetate in hexanes) afforded 92 mg (91%) of β-lactone **7x** as a colorless oil, which exhibited spectral data which matched that previously reported:[23c] R_f 0.22 (EtOAc/hexanes, 10/90); 84 %ee; $[\alpha]_D^{22}$ +15.9° (*c* 1.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (ddd, J = 4.2, 5.7, 8.4 Hz, 1H), 3.43 (dd, J=5.7, 16.2 Hz, 1H), 3.12 (dd, J=4.2, 16.2 Hz, 1H), 1.55-2.00 (m, 5H), 1.0-1.37 (m, 6H).

(R)-4-Butyloxetan-2-one (7s). This β-lactone was obtained from α-silyl-β-lactone **10s** (100 mg, 0.50 mmol) and $KF.2H_2O$ (94 mg, 1.0 mmol) according to the general procedure for desilylation. Flash chromatography (EtOAc/hexanes, 10/90) gave 58 mg (91%) of β-lactone **7s** as a colorless oil: 85 %ee; R_f 0.23 (EtOAc/hexanes, 10/90); $[\alpha]_D^{22}$ +24.7 ° (*c* 1.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.51 (m, 1H), 3.51 (dd, J=6.0, 16.3 Hz, 1H), 3.06 (dd, J=4.2, 16.3 Hz, 1H), 1.70-1.90 (m, 2H), 1.36-1.50 (m, 4H), 0.93 (t, J=7.2 Hz, 3H); IR (thin film)

2957, 2930, 2860, 1828, 1125 cm^{-1}.

(R)-4-Benzyloxetan-2-one (7aa). This β-lactone was obtained from α-silyl-β-lactone **10aa** (85 mg, 0.36 mmol) and $KF.2H_2O$ (68 mg, 0.73 mmol) according to the general procedure for desilylation. Flash chromatography (10/90, EtOAc/hexanes) gave 53 mg (91%) of β-lactone **7aa** as a colorless oil. Spectral data for this compound matched that previously reported:[32] R_f 0.44 (1/3, EtOAc/hexanes); $[\alpha]_D^{22}$ +6.5 ° (*c* 4.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.35 (m, 5H), 4.74 (dddd, J=4.2, 5.7, 6.3, 6.3 Hz, 1H), 3.48 (dd, J=5.7, 16.5 Hz, 1H), 3.22 (dd, J=6.3, 14.4 Hz, 1H), 3.15 (dd, J=4.2, 16.5 Hz, 1H), 3.06 (dd, J=6.3, 14.4 Hz, 1H).

4-(2-Phenylethyl)oxetan-2-one (7e). This β-lactone was obtained from hydrocinnamaldehyde (117 μL, 0.892 mmol) and trimethylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1 mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition followed by desilylation according to the general procedure. Flash chromatography (EtOAc/hexanes, 10/90) gave 94 mg (60% yield for two sequences) of β-lactone **7e** as a colorless oil. Spectral data for this compound matched that previously reported:[23c] 36 %ee; R_f 0.27 (EtOAc/hexanes, 1/5); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.36 (m, 5H), 4.45-4.55 (m, 1H), 3.48 (dd, J=5.7, 16.5 Hz, 1H), 3.03 (dd, J=4.5, 16.5 Hz, 1H), 2.65-2.88 (m, 2H), 2.01- 2.25 (m, 2H).

4-(5-tert-Butyldimethylsiloxypentyl)oxetan-2-one (7bb). This β-lactone was obtained from (6-tert-butyldimethylsiloxy)hexanal (205 mg, 0.892 mmol) and trimethylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1 mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition followed by desilylation according to the general procedure. Flash chromatography (EtOAc/hexanes, 10/90) gave 113 mg (55% yield for two sequences) of β-lactone **7bb** as a colorless oil: 46 %ee; R_f 0.47 (EtOAc/hexanes,

1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48-4.55 (m, 1H), 3.61 (t, J=6.6 Hz, 2H), 3.52 (dd, J=6.0, 16.5 Hz, 1H), 3.07 (dd, J=4.2, 16.5 Hz, 1H), 1.70-1.92 (m, 2H), 1.35-1.60 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 71.2, 62.8, 42.8, 34.6, 32.4, 25.9, 25.4, 24.6, 18.3, 5.4; IR (thin film) 1829 cm^{-1}; HRMS calcd for $C_{14}H_{28}O_3$ [M+H]: 273.1886. Found: 273.1890.

4-(8-Nonenyl)oxetan-2-one (7cc). This β-lactone was obtained from 9-decenal (138 mg, 0.892 mmol) and tri-methylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1 mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition followed by desilylation according to the general procedure. Flash chromatography (EtOAc/hexanes, 10/90) gave 124 mg (71% yield for two sequences) of β-lactone **7cc** as a colorless oil: 22 %ee; R_f 0.32 (EtOAc/hexanes, 10/90); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, J=6.6, 10.5, 17.1 Hz, 1H), 4.91-5.03 (m, 2H), 4.47-4.55 (m, 1H), 3.52 (dd, J=5.7, 16.2 Hz, 1H), 3.06 (dd, J=4.5, 16.2 Hz, 1H), 2.00-2.08 (m, 2H), 1.68-1.92 (m, 2H), 1.30-1.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 138.8, 114.1, 71.2, 42.7, 34.5, 33.6, 29.1, 28.9, 28.7, 28.6, 24.7; IR (thin film) 1829 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_2$: 219.1361. Found: 219.1359.

4-(1-Ethylpropyl)oxetan-2-one (7dd). This β-lactone was obtained from 2-ethylbutyraldehyde (110 mL, 0.892mmol) and trimethylsilylketene **9a** (153 mg, 1.34 mmol) using Lewis acid **14** prepared from Et_2AlCl (0.1 mL of 1.8 M in toluene, 0.178 mmol) and chiral diol **13** (60.4 mg, 0.214 mmol) according to the general procedure for asymmetric [2+2] cycloaddition followed by desilylation using $KF.2H_2O$ according to the general procedure. Flash chromatography (EtOAc/hexanes, 10/90) gave 58 mg (46% yield for two sequences) of β-lactone **7dd** as a colorless oil: 56 %ee; R_f 0.46 (EtOAc/hexanes, 20/80); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (ddd, J=4.6, 5.6, 8.4 Hz, 1H), 3.47 (dd, J=6.0, 16.2 Hz, 1H), 3.11 (dd, J=4.4, 16.2 Hz, 1H), 1.20-1.70 (m, 5H), 0.91 (t, J=7.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4, 73.7, 44.5, 41.5, 21.4, 20.8, 10.9, 10.2; IR (thin

film) 2971, 2936, 2871, 1835 cm^{-1}; HRMS calcd for $C_8H_{14}O_2$ [M+H]: 142.0994. Found: 142.0982.

Ethyl-(S)-3-hydroxy-3-cyclohexylpropanoate. This β-hydroxy ester was prepared by the reaction of β-lactone **7x** (26 mg, 0.17 mmol) with NaOEt (14 mg, 0.20 mmol, 1.2 equiv) in EtOH-THF at ambient temperature.[38] General work-up followed by purification by flash chromatography (EtOAc/hexanes, 20/80) gave 29 mg (86%) of β-hydroxy ethyl ester. Spectral data for this compound matched that previously reported:[39] 63 %ee; R_f 0.30 (EtOAc/hexanes, 1/6); $[\alpha]_D^{22}$ -15.2 ° (*c* 0.66, CHCl3); lit. [α] δ ^{22} -27.8 ° (*c* 0.66, $CHCl_3$) for *R*-enantiomer;[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, J=7.2 Hz, 2H), 3.74-3.81 (m, 1H), 2.88 (d, J=4.2 Hz, 1H), 2.52 (dd, J=2.7, 16.5 Hz, 1H), 2.41 (dd, J=9.3, 16.5 Hz, 1H), 1.60-1.90 (m, 5H), 1.28 (t, J=7.2 Hz, 3H), 0.98-1.42 (m, 6H).

Methyl-(*R*)-3-hydroxyheptanoate. This β-hydroxy ester was prepared by the reaction of β-lactone **7a** (45 mg, 0.35 mmol, 85 %ee) with NaOMe (22 mg, 0.42 mmol, 1.2 equiv) in MeOH-THF at ambient temperature.[38] General work-up followed by purification by flash chromatography (EtOAc/hexanes, 20/80) gave 47 mg (85%) of β-hydroxy methyl ester. Spectral data for this compound matched that previously reported:[30b] 85 %ee; R_f 0.25 (EtOAc/Hexanes, 20/80); $[\alpha]_D^{22}$ -1.67 ° (*c* 2.58, EtOH); lit. $[\alpha]_D^{22}$ -1.85 ° (*c* 2.58, EtOH) for *S*-enantiomer; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.01 (m, 1H), 3.71 (s, 3H), 2.87 (bs, 1H), 2.30-2.60 (m, 2H), 1.20-1.60 (m, 6H), 0.91 (t, J=7.3 Hz, 3H); IR (thin film) 3455, 2927, 1730 cm^{-1}.

General biochemical procedures. Biochemical reagents were purchased from Sigma and chemical reagents from Aldrich. HMG-CoA synthase assays, protein determinations and other biochemical procedures were carried out as described previously.[20] Cloning of the HMG-CoA synthase gene of *S. cerevisiae* into *E. coli* to give strain Y-HMGS was performed according to standard, established procedures.[40]

Cell growth and lysis. The *E. coli* strain Y-HMGS was grown overnight on LB-amp plates at 37°C. A single colony was then used to inoculate LB-amp liquid

medium (50 mL) which was grown overnight at 37°C with shaking (250 rpm). LB-amp liquid culture (1 L) was then inoculated with the overnight culture (7 mL) and grown to OD_{600}=0.6 (37°C, 250 rpm). Solid IPTG (95 mg) was then added and incubation was continued for a further 2.5 h. The cells were collected by centrifugation (8000 g, 5 min), washed with 0.85% NaCl, and resuspended in lysis buffer (50 mM HEPES, pH 8.0, 50 mM NaCl, 10mM EDTA, 15 mL). The cells were twice passed through the French Press (20,000 psi) and cellular debris was removed by centrifugation (8000 g, 5 min).

Ammonium sulphate precipitation. To cell-free extract (20 mL), cooled in an ice bath, was gradually added finely crushed ammonium sulphate with stirring to 25% saturation. Stirring was continued for 20 min at 4°C. The precipitate was removed by centrifugation (10,000 g, 10 min). Additional ammonium sulphate was then added to 45% saturation, and the precipitate was collected by centrifugation as above. The pellet was resuspended in 25mM HEPES (pH 8.2), and dialyzed for 3 h two times against 1 L of the same buffer.

Q-Sepharose chromatography. The dialyzed solution was applied onto a 50mL Q-Sepharose FPLC column, pre-equilibrated with loading buffer (25mM HEPES, pH 8.2). After washing with one column volume of loading buffer (10 min), the column was eluted with a continuous salt gradient (0-0.5 M NaCl, 5 mL/min, over 60 min). Fractions (5 mL) were collected and monitored for HMG-CoA synthase activity. Maximum enzyme activity was found in fractions 32-35, which were pooled and concentrated to 0.5 mL in a Gelman concentrating centrifuge tube (MW cut-off=30 kD, 10000 g, 60 min).

S-200 chromatography. The resulting solution was loaded onto a S-200 column (600 mL) which had been pre-equilibrated with loading buffer (25 mM HEPES, pH 8.2, 50mM NaCl). Elution (same buffer, 0.3 mL/min) gave fractions (6 mL). Active fractions (30-34) were pooled and concentrated as above.

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quenching of the intermediate sodium acetylide was critical for reproducible and reasonable yields (50-75%). Several other reported methods for silylketene synthesis have been studied in our laboratory but the silylation of ethoxyacetylene followed by thermolytic retro-ene reaction (ref 33) provided the highest purity and yields of silylketenes.

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2.3 Summary of Results Relevant to this Thesis

In this publication, several previously published methods were used to prepare C3-methyl substituted β-lactones. Comparing the results involving decanal, using a slightly modified version of the tandem aldol-lactonization (TAL) with *S*-phenyl thiopropionate (**3b**) initially developed by Danheiser and Nowick (Chapter 1.4.2), we were able to generate **7d** in fair yield with excellent *trans*-diastereoselectivity (37% yield, >90 %de). A two-step process involving an aldol condensation with *S*-phenyl thiopropionate (**3b**) followed by a mercury (II) catalyzed lactonization, furnished **7d** in higher yield, but with poorer diastereoselectivity (*trans*:*cis* 1.2:1, 66% yield). Using a slightly modified version of the less malodorous TAL initially developed by Welder and Schick (Chapter 1.4.2) with phenyl propionate (**3d**), we were able to generate **7d** in fair yield with excellent *trans*-diastereoselectivity (35% yield, >90 %de). A tandem Mukaiyama aldol-lactonization (TMAL) with *tert*-butyldimethylsilyl ketene acetal **8c**, initially developed by Yang and Romo (Chapter 1.4.2), furnished **7d** in fair yield with excellent *trans*-diastereoselectivity (35% yield, >90 %de)). The TMAL reaction was chosen to make further C3-methyl substituted β-lactones as it gave β-lactones in fair yield with excellent diastereoselectivity without the requirement of malodorous sulfur, toxic mercury (II) catalysts or LDA. This method was used to prepare β-lactones **7a**, **7d** and **7h-7o** in fair yield (32-47% yield).

In the preparation of C3-unsubstituted β-lactones, both tandem aldol-lactonization methods failed in our hands. Romo and co-workers demonstrated

that the tandem Mukaiyama aldol-lactonization method could be used in the preparation of racemic β-lactones **7c**, **e**, **f**, and **g** using *tert*butyldimethylsilylketene acetal **8a** or trimethylsilylketene acetal **8b** (42 – 66% yield). However, we found that the boron trifluoride diethyletherate catalyzed [2 + 2] cycloaddition reaction between an aldehyde and trimethylsilyl ketene, first reported by Zaitseva et al. (Chapter 1.4.3), gave C3-unsubstituted β-lactones **7b-c**, **7g** and **7s-w** in higher yields (74-84% yield) after desilylation of the intermediate α-silyl β-lactone. Romo and co-workers substituted boron trifluoride diethyletherate for a chiral aluminum-based Lewis acid and generated optically active C3-unsubstituted β-lactones in good yield (46-86% yield), but with highly variable enantiomeric excesses (22-85% ee).

2.4 Implication for Further Work in this Thesis

The zinc (II) chloride-promoted TMAL reaction represents a diastereoselective route to *trans*-1,2-disubstituted β-lactones, but at the time no general routes were available to prepare the corresponding *cis*-1,2-disubstituted β-lactones. Hence, we initially set out to develop general methods to prepare *cis*-1,2-disubstituted β-lactones. Our work towards the diastereo- and enantioselective preparation of *cis*-1,2,-disubstituted β-lactones using a titanium (IV) chloride-promoted TMAL approach is described in Chapter 3.

Chapter 3

Preparation of cis-1,2-Disubstituted β-Lactones

In Chapter 2, a homologous series of *trans*-1,2-disubstituted β-lactones was efficiently prepared using a zinc (II) chloride promoted TMAL reaction between silyl ketene acetal **1-28** and an aldehyde. Subsequent biological testing of the β-lactone products, in a collaborative project with Bill Riddoch, indicated *trans*-4-decanoyl-3-methyloxetan-2-one (**2-7l**) was most potent (IC_{50} 0.28 μM) against HMG-CoA synthase, a key enzyme in cholesterol biosynthesis. To test the effect of ring stereochemistry on potency, it was desirable to prepare both racemic and optically active *cis*-4-decanoyl-3-methyloxetan-2-one (**3-1**) (Figure 3.1). However, at the time there were no general diastereo- or enantioselective methods available for the preparation of *cis*-1,2-dialkyl-substituted β-lactones. In this chapter, we present our work towards the development of a diastereo- and enantioselective preparation of β-lactone **3-1** using methodology that may become a general, stereocomplementary alternative to a zinc (II) chloride promoted TMAL reaction.

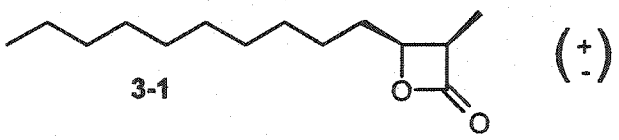
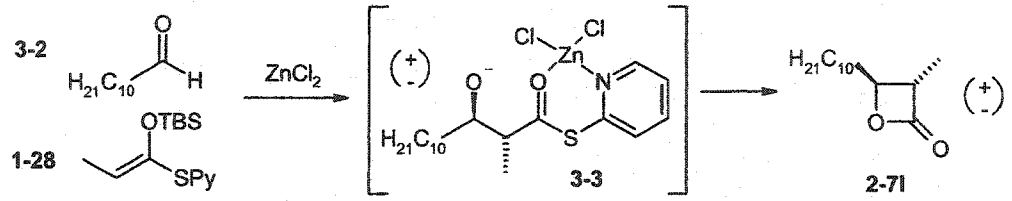


Figure 3.1 Structure of *cis*-4-Decanoyl-3-methyloxetan-2-one (**3-1**)

3.1 Retrosynthesis of Racemic *cis*-4-Decyl-3-methyloxetan-2-one

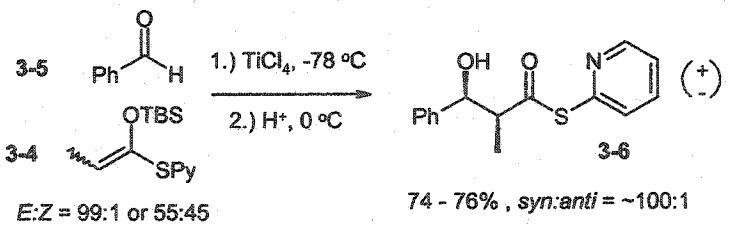
The zinc (II) chloride promoted TMAL reaction between silyl ketene acetal **1-28** and undecanal (**3-2**) must proceed through an intermediate *anti*-aldolate (**3-3**) to furnish *trans*-1,2-disubstituted β-lactone **2-7l** (Scheme 3.1).

Romo *et al.* have postulated that bidentate chelation between zinc and the thiopyridyl nitrogen and thioester oxygen atoms of **1-28** promotes lactonization in this *anti*-aldolate by increasing the electrophilicity of the carbonyl group.[102] Consequently, we searched for a Lewis acid that would furnish the requisite intermediate *syn*-aldolate, and was capable of bidentate chelation with the thiopyridyl nitrogen of **1-28**, to promote efficient lactonization.

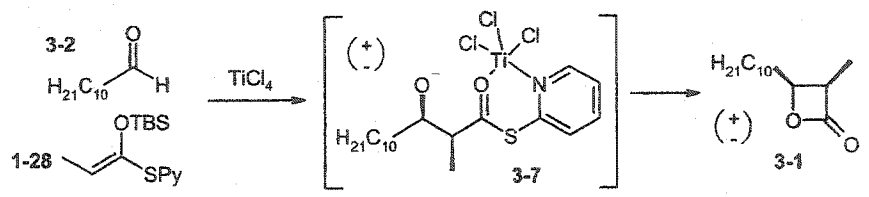


Scheme 3.1 Zinc (II) Chloride Promoted TMAL Reaction in the Preparation of β-Lactone **2-7l**

Choo and Suh reported a titanium (IV) chloride promoted stereo-convergent, *syn*-diastereoselective Mukaiyama aldol reaction of (*E*)-silyl ketene acetal **3-4** (**1-28**), and a mixture of (*E*)- and (*Z*)-silyl ketene acetal **3-4** (*E*:*Z* = 55:45), with benzaldehyde (**3-5**) (~100:1 *syn*:*anti*, 74-76% yield) (Scheme 3.2).[133] Because titanium (IV) chloride is capable of bidentate chelation with the thiopyridyl nitrogen and the thioester oxygen atoms of silyl ketene acetal **3-4**, it appeared that under appropriate conditions, titanium (IV) chloride could promote a *cis*-diastereoselective TMAL reaction between (*E*)-silyl ketene acetal **1-28** and undecanal (**3-2**) via *syn* aldolate **3-7**, giving **3-1** (Scheme 3.3).



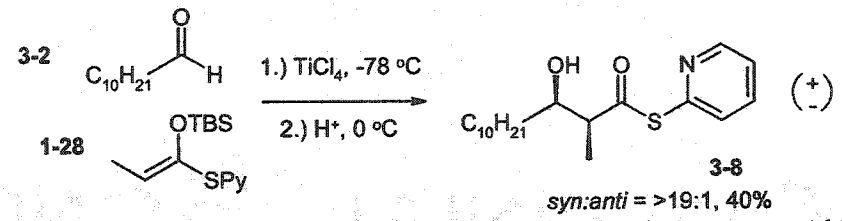
Scheme 3.2 Titanium (IV) Chloride Promoted Mukaiyama Reaction with Benzaldehyde



Scheme 3.3 Proposed Titanium (IV) Chloride Promoted TMAL Reaction

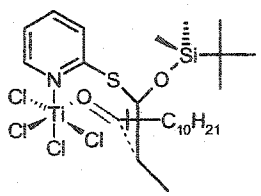
3.2 Preparation of Racemic *cis*-4-Decanoyl-3-methyloxetan-2-one

In our hands, the reaction of titanium (IV) chloride with **1-28** and **3-5** proceeded smoothly in 79% yield (>19:1 *syn* :*anti*). Similarly, we performed a titanium (IV) chloride promoted Mukaiyama aldol condensation between silyl ketene acetal **1-28** and undecanal (**3-2**) (Scheme 3.4). The *syn*-diastereomer (**3-8**) was isolated in 40% yield (>19:1 *syn:anti*, according to 200 MHz ^{1}H-NMR).



Scheme 3.4 Titanium (IV) Promoted Mukaiyama Aldol Condensation with Undecanal and Ketene Acetal **1-28**

Choo and Suh explained *syn*-diastereoselectivity to be the result of a chelated transition state where titanium (IV) chloride chelates to both the oxygen of benzaldehyde (**3-5**) and the pyridyl nitrogen of (*E*)-silyl ketene acetal **1-28**.[134] (This was supported by their observation that substitution of pyridyl for phenyl in (*E*)-silyl ketene acetal **1-28** furnished a 23:77 ratio of *syn*- and *anti*-aldolates, respectively.) We propose a similar transition state structure (**3-9**) in the titanium (IV) chloride promoted Mukaiyama condensation of undecanal (**3-2**) and silyl ketene acetal **1-28** to explain the observed *syn*-diastereoselectivity (Figure 3.2).

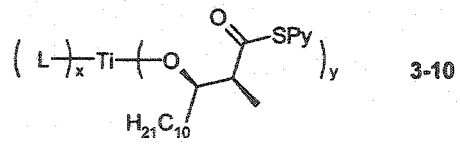


3-9

Figure 3.2 Transition State Structure for Mukaiyama Aldol Condensation with Undecanal

Because titanium (IV) chloride is a highly reactive Lewis acid, the TMAL reaction between ketene acetal **1-28** and undecanal (**3-2**) was first attempted at -78°C. Following the reaction by TLC, it appeared that the Mukaiyama aldol condensation was complete after 20 minutes. However, no β-lactone products were detected by IR analysis (characteristic carbonyl stretch expected at ~1800 cm^{-1}) after prolonged stirring at -78°C (up to 5 hours); TLC analysis indicated a majority of the product was present as the aldolate. In contrast, when the Mukaiyama aldol condensation was allowed to stir at -78°C for 30 minutes, warmed to room temperature over 1.5 hours, and stirred an additional 12 hours, the aldolate was observed to gradually decompose. Again, no β-lactone product was detected by IR analysis of the crude reaction mixture.

Unfortunately, in our hands, titanium (IV) chloride proved unsuitable for a one-pot TMAL reaction. This is likely the result of the highly oxophilic nature of titanium, which allows the aldolate to displace one or more chloride ions; the ensuing titanium ether(s) (**3-10**) simply await hydrolysis during an aqueous workup (Figure 3.3).

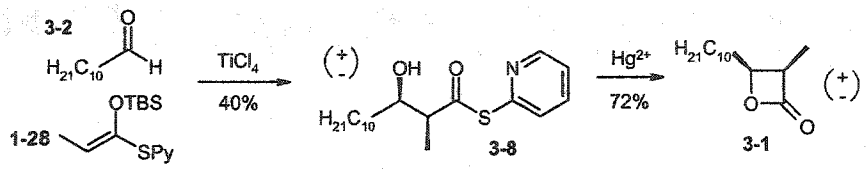


3-10

Figure 3.3 Titanium Ether of Aldolate **3-7**

Because of the highly diastereoselective nature of the titanium (IV) chloride mediated Mukaiyama aldol condensation, we decided to pursue a 2-step

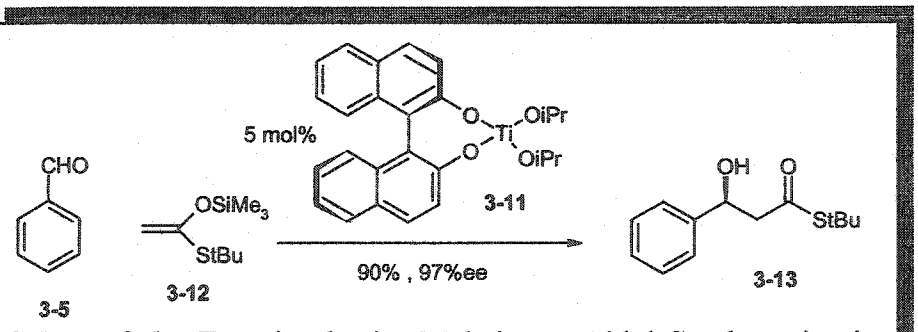
TMAL approach. Accordingly, thiol ester **3-8** was efficiently and cleanly converted to the desired *cis*-1,2-disubstituted β-lactone, *cis*-4-decyl-3-methyloxetan-2-one (**3-1**), in 72% yield upon treatment with mercury (II) methanesulfonate in acetonitrile using Masamune's "double-activation" approach (Scheme 3.5).[135] Over two steps, β-lactone **3-1** was prepared in 29% yield from undecanal (**3-2**).



Scheme 3.5 Two Step TMAL Reaction in the Preparation of β-Lactone **3-1**

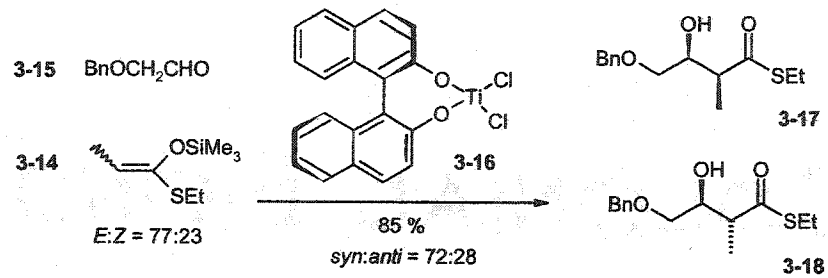
3.3 Enantioselective Preparation of *cis*-4-Decyl-3-methyloxetan-2-one

Recently, Keck and Krishnamurthy developed a chiral titanium (IV) diisopropoxide Lewis acid catalyst (**3-11**) from 1,1'-bi-2-naphthol (BINOL) that could be used to promote enantioselective Mukaiyama aldol condensations.[136] Using 20 mol% of the chiral Lewis acid catalyst, silyl ketene acetal **3-12** was condensed with benzaldehyde (**3-5**) furnishing aldol adduct **3-13** in 90% yield with an enantiomeric excess of 97% (Scheme 3.6).



Scheme 3.6 Enantioselective Mukaiyama Aldol Condensation in the Preparation of Aldol Adduct **3-13**

However, poor diastereoselectivity was observed using α-methyl silyl ketene acetal **3-14** (Scheme 3.7). Unlike the stereo-convergent, *syn*-diastereoselective titanium (IV) chloride promoted Mukaiyama aldol condensation reported by Choo and Suh, *syn* / *anti*-diastereoselectivity was observed to be sensitive to the geometry of the α-methyl silyl ketene acetal. For example, Mikami *et al.* reported the condensation of aldehyde **3-15** with an (*E*)- and (*Z*)-mixture (*E*:*Z* = 73:27) of silyl ketene acetal **3-14** in the presence of 5 mol% chiral titanium (IV) dichloride catalyst **3-16** afforded aldol adducts **3-17** and **3-18** in a ratio of 72:28 (Scheme 3.7).[137]



Scheme 3.7 Diastereoselectivity in the Mukayama Aldol Condensation Between α-Benzyloxy Aldehyde **3-15** and Ketene Acetal **3-14**

Based on our work towards a *cis*-diastereoselective titanium (IV) chloride promoted net TMAL reaction, it appeared that using a chiral BINOL-titanium (IV) catalyst we could prepare *cis*-1,2-disubstituted β-lactones with high enantiomeric purity in an analogous two-step procedure. That is, the initial Mukaiyama aldol condensation should be stereo-convergent for the *syn*-diastereomer as titanium (IV) chelates the pyridyl nitrogen as proposed in transition state structures **3-19** and **3-20** (Scheme 3.8).

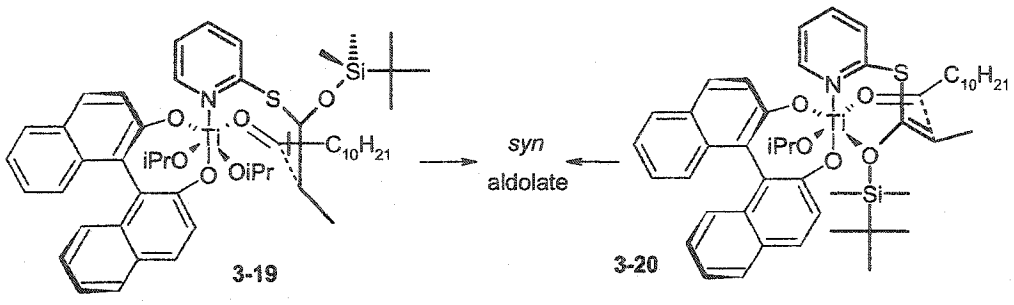
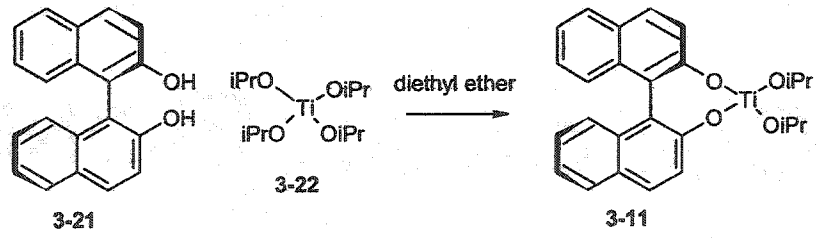


Figure 3.8 Transition State Structures Leading to Formation of the *syn*-Aldolate

To evaluate the ability of chiral titanium (IV) diisopropoxide catalyst **3-11** to promote a stereo-convergent, *syn*-diastereoselective Mukaiyama aldol condensation, we initially chose to condense benzaldehyde with (*E*)-silyl ketene acetal **1-28**; benzaldehyde (**3-5**) has no α-protons to complicate the determination of diastereoselectivity by ^{1}H-NMR.

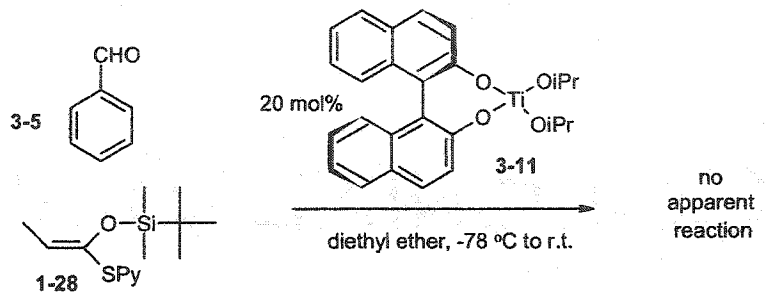
Chiral Lewis acid catalyst **3-11** was prepared immediately prior to use as a 1 M solution in toluene according to the procedure of Keck and Krishnamurthy.[136] Equimolar amounts of (*R*)-BINOL-OH (**3-21**) and titanium tetraisopropoxide (**3-22**) were dissolved in diethyl ether at 0°C and the mixture was allowed to stir for 1 h at room temperature (Scheme 3.9).



Scheme 3.9 Preparation of the BINOL-Ti Lewis Acid Catalyst **3-11**

Following the general procedure of Keck and Krishnamurthy, to a solution of benzaldehyde (**3-5**) and 20 mol% of chiral Lewis acid **3-11** in diethyl ether at -78°C, (*E*)-silyl ketene acetal **1-28** was added. The mixture was then stirred for 12 h at -20°C. No apparent reaction was observed. The reaction was then repeated at

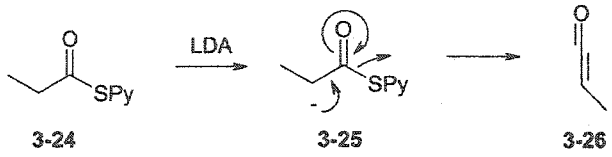
0°C, the mixture was allowed to warm to room temperature over 30 min and was then stirred for 24 h at room temperature. Again, no apparent reaction was observed.



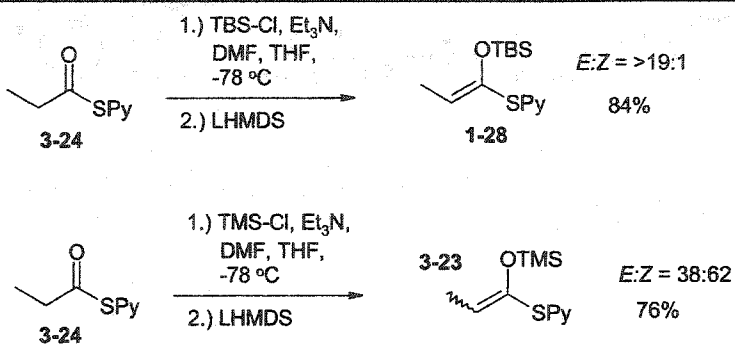
Scheme 3.10 Failed Mukaiyama Aldol Condensation using BINOL-Ti Lewis Acid with Ketene Acetal **1-28**

In our hands, *tert*-butyldimethylsilyl ketene acetal **1-28** demonstrated substantial stability to Lewis acid **3-11**. Hence, we set out to prepare the corresponding trimethylsilyl ketene acetal (**3-23**).

The enolates of thiopyridyl esters are highly susceptible to ketene formation (Scheme 3.11). To circumvent ketene formation, Hiari *et al.* reported an efficient, stereoselective preparation of (*E*)-silyl ketene acetal **1-28** using a "reverse additive" approach to "trap" the enolate of thiopyridyl ester **3-24** (Scheme 3.12).[138] (That is, *tert*-butyldimethylsilyl (TBS) chloride was added prior to lithium hexamethyldisilazane (LHMDS) to immediately trap the enolate.) Using this procedure we have stereoselectively prepared (*E*)-silyl ketene acetal **1-28** in 84% yield (Scheme 3.12). However, using trimethylsilyl (TMS) chloride, *E*-stereoselectivity was significantly diminished; a 62:38 mixture of (*E*)- and (*Z*)-silyl ketene acetals (**3-23**) was obtained in 76% yield (Scheme 3.12).

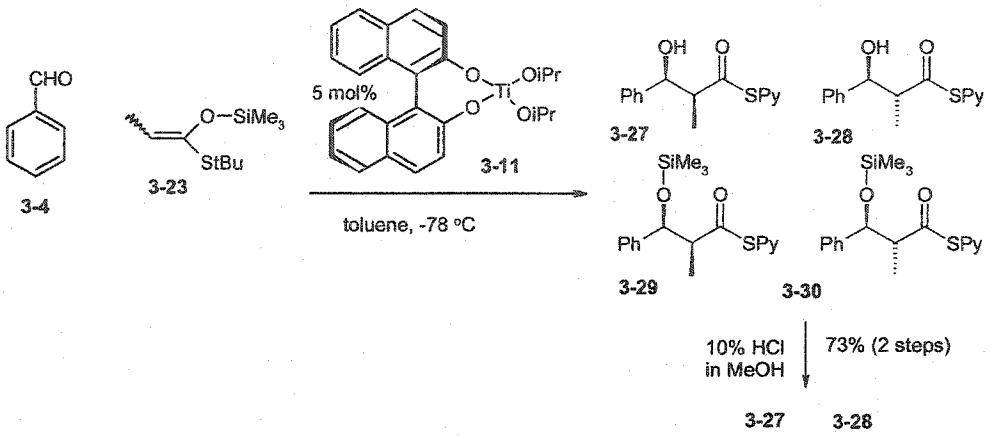


Scheme 3.11 Formation of Ketene **3-26** from 2-Pyridyl Thiol Ester **3-24**



Scheme 3.12 "Reverse Additive Approach" in the Preparation of Ketene Acetals **1-28** and **3-23**

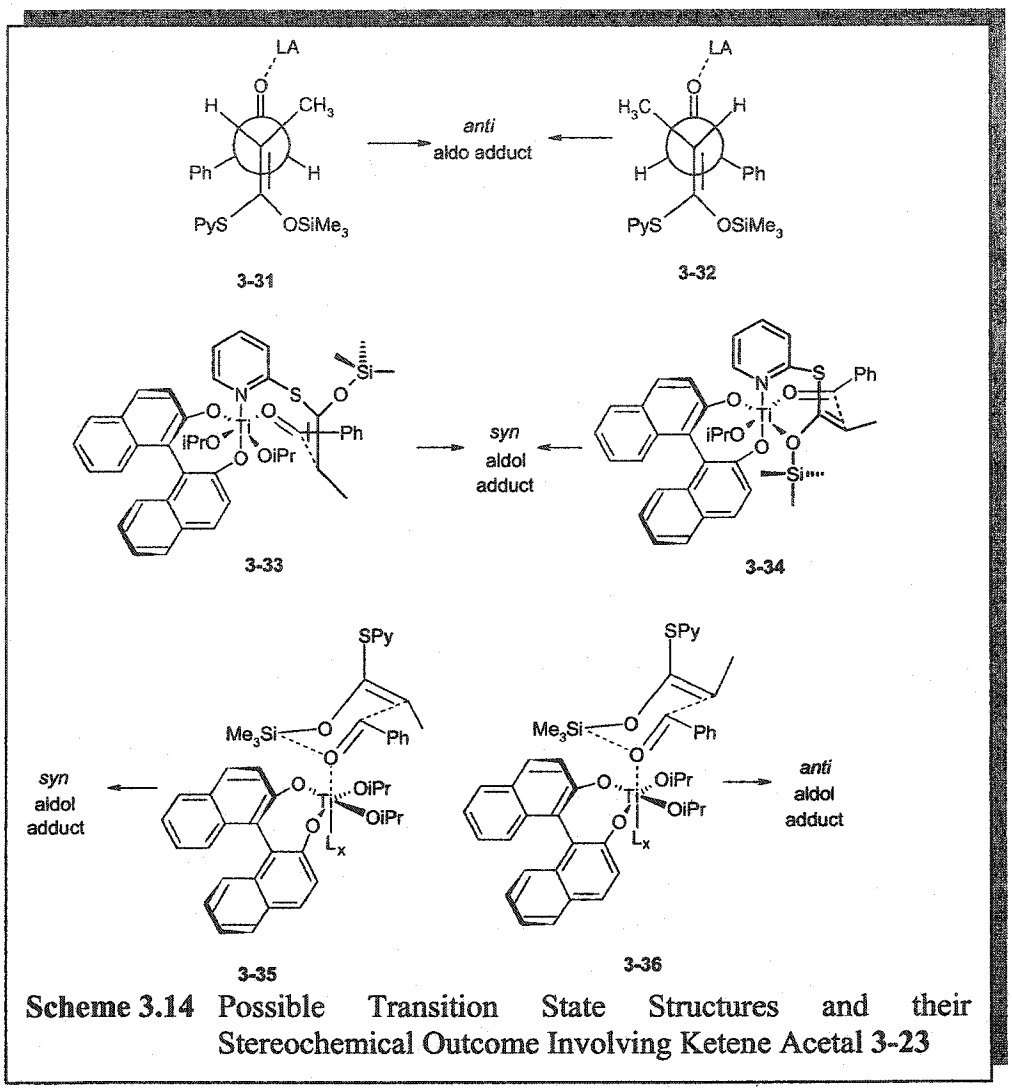
Silyl ketene acetal **3-23** cannot be stored for prolonged periods (> 1 wk at -10°C), so it was prepared immediately prior to use. Following the general procedure of Keck and Krishnamurthy, to a solution of benzaldehyde (**3-5**) and 20 mol% (*R*)-BINOL-Ti(iPrO)$_2$ (**3-11**) in toluene at -78°C, silyl ketene acetal **3-23** (*E*:*Z* = 62:38) was added. The solution was stirred 12 h at -20°C. Unfortunately, a mixture *syn*- and *anti*-diastereomers was obtained as a mixture of silylated (*syn*:*anti* = 67:33) and non-silylated (*syn*:*anti* = 61:39) aldol adducts (~ 2:3, respectively). Exposure of the crude material to 10% HCl in MeOH afforded non-silylated aldol adducts **3-27** and **3-28** in 73% yield (*syn*:*anti* = 63:37). The enantiomeric purity of the *syn*- and *anti*-diastereomers was not determined as the *syn* and *anti* diastereomers could not be separated using flash column chromatography.



Scheme 3.13 Non-Diastereoselective BINOL-Ti(IV)-Promoted Mukaiyama Aldol Condensation Involving Ketene Acetal **3-23**

As previously discussed, Suh and Choo's titanium (IV) chloride promoted stereo-convergent, *syn*-diastereoselective Mukaiyama aldol condensation was not sensitive to the geometry of the silyl ketene acetal. However, with a BINOL-Ti (IV) diisopropoxide Lewis acid, *syn*/*anti*-diastereoselectivity appears to approximately match the ratio of (*E*)- and (*Z*)-silyl ketene acetals. This implies that (*E*)-silyl ketene acetal **3-23** furnishes *syn*-aldol adducts **3-27** and **3-29**, while (*Z*)-silyl ketene acetal **3-23** furnishes *anti*-aldol adducts **3-28** and **3-30**.

These results are inconsistent with acyclic transitions state structures **3-31** and **3-32**, that would explain an *anti*-stereoconvergent Mukaiyama aldol condensation, and chelated transition state structures **3-33** and **3-34**, that would explain a *syn*-stereoconvergent Mukaiyama aldol condensation (Scheme 3.14).[139] However, the results are consistent with "chair-like" chelated Zimmermann-Traxler transition state structures **3-35** and **3-36**, where aldol adduct geometry is dependent on enolate geometry (Scheme 3.14).



Scheme 3.14 Possible Transition State Structures and their Stereochemical Outcome Involving Ketene Acetal **3-23**

Because of a lack of stereo-convergency in the Mukaiyama aldol condensation, this project was halted in order to re-evaluate the use of titanium as a Lewis acid. While we were working on this project, Romo *et al.* developed a diastereoselective, tin (IV) chloride promoted one-pot TMAL reaction for the preparation of *cis*-1,2-disubstituted β-lactones.[17] Similar to zinc (II) chloride and titanium (IV) chloride, tin (IV) chloride is capable of bidentate chelation involving the 2-pyridyl nitrogen.

3.4 Summary

In this Chapter, we presented the first diastereoselective preparation of *cis*-4-decyl-3-methyloxetan-2-one (**3-1**) using a two-step net TMAL reaction in 29% yield starting from undecanal (**3-2**) and silyl ketene acetal **1-28**. This titanium (IV) chloride promoted, *cis*-diastereoselective, net TMAL reaction is stereo-complementary to the zinc (II) chloride promoted, one-pot TMAL reaction originally developed by Romo and co-workers, and further expanded in our laboratory (Chapter 2). Unfortunately, with chiral BINOL-Ti (IV) diisopropoxide Lewis acid catalyst **3-11**, titanium appeared to lose its ability to chelate the pyridyl nitrogen in silyl ketene acetal **3-23**, thus losing its ability to promote a stereo-convergent, *syn*-diastereoselective Mukaiyama aldol condensation.

3.5 Experimental

General

All reactions were performed with flame-dried glassware under a positive pressure of nitrogen and magnetically stirred unless otherwise indicated. Air- and moisture-sensitive compounds were transferred via syringe or cannulating needle. All reagents and solvents were obtained from commercial suppliers and were used without further purification except as indicated below. All commercially available aldehydes and acid chlorides were purified via distillation (under reduced pressure where appropriate). Dichloromethane and diisopropylamine were freshly distilled under a nitrogen atmosphere from calcium hydride prior to their use. Tetrahydrofuran was freshly distilled under a nitrogen atmosphere from potassium-benzophenone ketyl radical. Diethyl ether and toluene were freshly distilled under a nitrogen atmosphere from sodium-benzophenone ketyl radical. Acetonitrile was distilled under a nitrogen atmosphere from calcium hydride and

then distilled under an argon atmosphere from phosphorus pentoxide before being stored under an argon atmosphere over 3 Å molecular sieves. Pyridine, diisopropylethylamine and triethylamine were heated under a nitrogen atmosphere at reflux over potassium hydroxide for 3 hours, distilled from potassium hydroxide and then stored over potassium hydroxide. Water was obtained from a Millipore purification system.

Flash column chromatography was performed on silica gel 60 from Silicycle (230-400 mesh). Medium pressure liquid chromatography was performed using Merck type Lobar pre-packed columns (LiChroprep Si60 20-63 μm). Radial chromatography was performed using a Chromatotron® (Harrison Research) equipped with 2 or 4 mm silica gel 60 with gypsum (EM Science) thick-layer plates. Thin-layer chromatography was performed using aluminum backed plates coated with silica gel 60 (Machery-Nagel Alugram®, Sil G/UV_{254}, 0.20 mm) using UV fluorescence, phosphomolybdic acid in 10% sulfuric acid (5 g/100 mL), 10% sulfuric acid, or iodine staining for visualization.

Proton NMR spectra were recorded on Bruker AC-200, AV-200, AC-300 or DRX-500 spectrometers and chemical shifts are reported in ppm using tetramethylsilane (δ 0.00) or $CHCl_3$ (δ 7.26) as an internal reference. Carbon-13 NMR spectra were recorded on Bruker AC-200, AV-200 or DRX-500 spectrometers and chemical shifts are reported in ppm using $CDCl_3$ (δ 77.0) as an internal reference. Electron impact mass spectra were recorded on a Finnigan 4500 quadrupole mass spectrometer and electrospray mass spectra were recorded on a Micromass Quattro-LC triple quadrupole mass spectrometer. IR spectra were recorded on a BIO-RAD FTS-40 FT-IR spectrometer.

Preparation of 2-mercaptopyridyl propionate (3-24)

Using the method of Annunziata et al.,[140] triethylamine (6.0 mL, 44 mmol) was added to a solution of 2-mercaptopyridine (4.4 g, 40 mmol) in 50 mL dichloromethane at 0°C. Then a solution of propionyl chloride (3.4 mL, 40 mmol) in 150 mL dichloromethane was added via cannulating needle over 20 minutes. The resultant solution was allowed to stir 1 hour at 0°C before being poured onto cold water (100 mL). The organic layer was washed with 5% sodium hydroxide (3 x 100 mL) and brine (100 mL), dried over sodium sulfate and concentrated using rotary evaporation. The crude oil was then purified using flash column chromatography (20% ethyl acetate in hexanes) to give **3-24** (5.8 g, 87%) as a clear yellow oil. Proton and carbon-13 NMR spectra of the product were identical to those reported by Annunziata *et al.*[141]: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.10 (3H, t, J = 5.0 Hz), 2.60 (2H, q, J = 5.0 Hz), 7.11-7.15 (1H, m), 7.47-7.49 (1H, m), 7.56-7.61 (1H, m), 8.48 (1H, d, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 196.7, 151.3, 150.0, 136.7, 129.7, 123.1, 37.3, 9.1.

Preparation of (*Z*)-1-(2-pyridyl)-1-(*tert*-butyldimethylsilyl)oxy propene (1-28)

Using the method of Hirai *et al.*,[138] *n*-butyl lithium (22.5 mL, 36 mmol, 1.6 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (7.5 mL, 30 mmol) in THF at room temperature. The solution was allowed to stir for 30 minutes before being cooled to -78°C. Then DMF (4 mL), triethylamine (8.4 mL, 60 mmol) and *tert*-butyldimethylsilyl chloride (9.0 g, 60 mmol) were added followed by a solution of **3-24** (5 g, 30 mmol) in THF (10 mL). After stirring at -78°C for 20 minutes, ethyl acetate (100 mL) was added and the solution was washed with brine (3 x 50 mL) and dried over magnesium sulfate. After the solvent was removed by rotary evaporation, the crude oil was purified using flash

column chromatography (15% ethyl acetate in hexanes) to give **1-28** (7.1 g, 84%) as a clear pale yellow oil. NMR spectra of the product were identical to that reported by Suh and Choo[133]: ^{1}H NMR (CD_2Cl_2, 200 MHz) δ: 0.09 (s, 6H), 0.89 (s, 9H), 1.73 (3H, d, J = 6.8 Hz), 5.44 (1H, q, J = 6.8 Hz), 6.98-7.04 (1H, d, J = 8.1 Hz), 7.51-7.60 (2H, m), 7.39 (1H, d, J = 3.9 Hz); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ: 159.5, 149.8, 140.7, 136.8, 121.9, 120.1, 118.4, 99.3, 25.9, 18.4, 12.6, -4.2.

Preparation 1-(2-Pyridyl)-1-(trimethylsilyl)oxy Propene (3-23)

Modifying the method of Hirai *et al.*,[138] *n*-butyl lithium (4.73 mL, 7.10 mmol, 1.5 M solution in hexanes) was added dropwise to a solution of hexamethyldisilazane (1.50 mL, 7.10 mmol) in THF (20 mL) at room temperature. The solution was allowed to stir for 30 minutes before being cooled to -78°C. Chlorotrimethylsilane (1.64 mL, 6.45 mmol) was added followed by **3-24** (1.0 g, 6.45 mmol) in THF (4 mL). The solution was allowed to warm up to room temperature over 15 minutes before being poured onto pentane (70 mL). The organic layer was treated with aqueous pH 6.8 buffer (sodium phosphate, 0.1 M) and dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude oil was submitted to high vacuum for 3 hours at room temperature to gave a mixture of (*E*)- and (*Z*)-isomers **(3-23)** (1.18 g, 76%) as a clear yellow oil that was used without further purification. Proton NMR revealed a highly pure 62:38 ratio of *E*- and *Z*-isomers; the only observed impurity was starting material (< 5%). For the *Z*-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.10 (9H, s), 1.69 (3H, J = 6.8 Hz), 4.43 (1H, q, J = 6.8 Hz), 6.98-7.00 (1H, m), 7.24-7.32 (1H, m), 7.47-7.56 (1H, m), 8.39-8.42 (1H, m). For the *E*-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.10 (9H, s), 1.76 (3H, d, J = 7.0 Hz), 4.48 (1H, q, 7.0 Hz), 6.98-7.00 (1H, m), 7.24-7.32 (1H, m), 7.47-7.56 (1H, m), 8.39-8.42 (1H, m).

Preparation of *syn*-1-(2-Pyridyl)-3-hydroxy-2-methyltridecanethioate (3-7)

Modifying the procedure of Suh and Choo,[133] undecanal (194 μL, 0.942 mmol) was added to a solution of titanium (IV) chloride in dichloromethane (4 mL, 0.25 M in dichloromethane) at -78°C. Ketene acetal **1-28** (265 mg, 0.942 mmol) was added dropwise and the solution was allowed to stir for 30 minutes. The solution was then warmed to 0°C over 30 minutes and then stirred an additional hour at 0°C before being quenched with saturated sodium bicarbonate (7 mL). The mixture was filtered and the filtrate was dried over sodium sulfate and purified using flash column chromatography (1:1 ethyl acetate-hexane) to give **3-7** (138 mg, 40%) as a clear yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.85 (t, J = 6.8 Hz, 3H), 1.23 (m, 16 H), 1.29 (d, J = 7.1 Hz, 3H), 1.46 (m, 2H), 2.28 (s, 1H), 2.81 (dq, J = 3.5, 7.0, 1H), 4.00 (m, 1H), 7.28 (m, 1H), 7.73 (m, 2H), 8.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.0, 151.0, 150.4, 137.2, 130.3, 123.6, 71.8, 53.5, 34.1, 31.9, 29.6, 25.9, 22.7

Enantioselective Preparation of 1-(2-Pyridyl)-2-methyl-3-phenyl-3-hydroxy Propanethioate (3-7)

Modifying the method of Keck and Krishnamurthy,[136] 1 M Ti(O*i*Pr)$_4$ in CH_2Cl_2 (50 μL, 0.05 mmol) was added to a solution of (*R*)-(+)-1,1'-bi-2-napthol (14.3 mg, 0.05 mmol) in diethyl ether (1 mL) at room temp. The solution was allowed to stir for 1 h at room temperature before freshly distilled benzaldehyde (26.5 mg, 0.25 mmol) was added. After stirring 5 min, the solution was cooled to -78°C and silyl ketene acetal **3-23** (*E*:*Z* = 62:38) was added. The solution was then stirred overnight (12 h) at -20°C, quenched with aqueous pH 6.8 buffer (sodium phosphate, 0.2 M), and filtered through Celite. The filtrate was then extracted with diethyl ether (3 x 1 mL) and the solvent was removed by rotary

evaporation to give crude product as the free and silylated alcohols. [For the silylated *syn*-aldol adduct (**3-29**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.00 (9H, s), 0.92 (3H, d, J = 6.5 Hz), 2.94-3.02 (1H, m), 4.77 (1H, d, J = 6.5 Hz), 7.18-7.38 (6H, m), 7.62-7.67 (2H, m), 8.54-8.56 (1H, m). For the silylated *anti*-aldol adduct (**3-30**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: -0.06 (9H, s), 1.26 (3H, d, J = 8.1 Hz), 2.98-3.06 (1H, m), 4.99 (1H, d, J = 8.1 Hz), 7.18-7.38 (6H, m), 7.62-7.67 (2H, m), 8.54-8.56 (1H, m). The ratio of *syn*- to *anti*-aldol adducts was estimated to be 67:33 by ^{1}H NMR.] The crude product was treated with 10% HCl-MeOH, concentrated by rotary evaporation, and purified by flash column chromatography (40% EtOAc in hexanes) to give a mixture of *syn*- (**3-27**) and *anti*- (**3-28**) aldol adducts as a clear and colorless oil (41 mg, 73%). Proton NMR revealed a 63:37 ratio of **3-27** and **3-28** that was identical to that reported by Annunziata *et al.* in their condensation of the titanium enolate of **3-24** with **3-5**.[141] For the *syn*-aldol adduct (**3-27**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.09 (3H, d, J = 8.8 Hz), 3.02-3.19 (1H, m), 4.88 (1H, d, J = 8.8 Hz), 7.26-7.85 (8H, m), 8.61 (1H, d, J = 4.0 Hz). For the *anti*-aldol adduct (**3-28**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.28 (3H, d, J = 4.2 Hz), 3.07-3.21 (1H, m), 5.31 (1H, d, J = 4.2 Hz), 7.26-7.85 (8H, m), 8.61 (1H, d, J = 4.0 Hz).

Preparation of Mercury (II) Methanesulfonate

The method of Capozzi *et al.* was used.[142] Mercuric acetate (32 g, 0.10 mmol) was suspended in glacial acetic acid (100 mL) at 80°C. Methane sulfonic acid (13 mL, 0.20 mmol) was then added and the suspension was allowed to stir for 1 h. The suspension was cooled to room temperature and the precipitate was filtered, rinsed with diethyl ether and dried under high vacuum at 80°C to give mercury (II) methanesulfonate (38 g, 97%) as a white powder which was used without further purification.

Preparation of *cis*-4-Decyl-3-methyloxetan-2-one (3-1)

Using a modified version of Masamune's original procedure,[102] **3-7** (96 mg, 0.28 mmol) was dissolved in chloroform (4 mL). This was added dropwise to a suspension of mercury (II) methanesulfonate (111 mg) in acetonitrile at 50°C under an argon atmosphere. After stirring 15 minutes at this temperature, the mixture was filtered and the filtrite washed with chloroform (3 x 2 mL). The solvent was removed using rotary evaporation and the crude material was purified by flash column chromatography (15% ethyl acetate in hexanes) to furnish **3-1** (46 mg, 72%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.86 (t, J = 6.8 Hz, 3H), 1.23 (m, 16H), 1.26 (d, J = 6.6 Hz, 3H), 1.67 (m, 2H), 3.71 (m, 1H), 4.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.8, 47.1, 31.9, 29.3, 25.4, 22.6, 14.1; IR (thin film) 3023, 2931, 2858, 1820 cm^{-1}.

Chapter 4

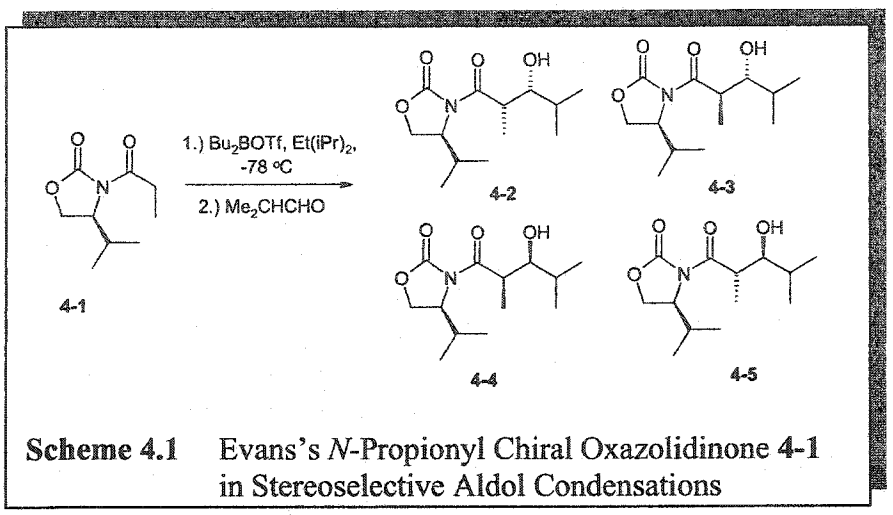
Preparation of cis-1,2-Disubstituted β-Lactones Using Thizolidinethiones

In Chapter 3, we developed a titanium (IV) tetrachloride promoted *cis*-diastereoselective TMAL approach in the preparation of *cis*-4-decyl-3-methyloxetan-2-one (**3-1**). However, this reaction could not be made enantioselective by substituting titanium (IV) chloride for a chiral BINOL-titanium (IV) Lewis acid.

We therefore searched the literature for a general, highly *syn*-diastereoselective aldol condensation that could eventually be used in an enantioselective preparation of *cis*-1,2-disubstituted β-lactones. In this Chapter, we describe our work towards the enantioselective preparation of *cis*-4-decyl-3-methyloxetan-2-one (**3-1**) using a titanium (IV) chloride promoted Evans-type aldol condensation on a chiral thiazolidinethione.

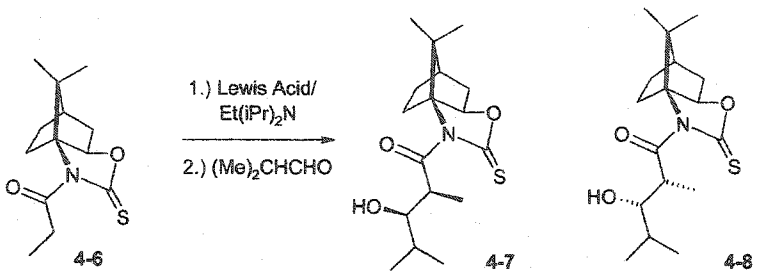
4.1 Evans and Evans-type Aldol Condensations in the Preparation of Propionate Aldol Adducts

Evans chiral oxazolidinones have been used in a wide range of asymmetric transformations, including the aldol condensation.[143] Often derived from the alcohols of naturally occurring amino acids (such as L-valine and L-phenylalanine), chiral oxazolidinones are the method of choice in the prepartion of *syn*-propionate aldol adducts.[144] For example, Evans *et al.* condensed the boron enolate derived from chiral *N*-propionyl oxazolidinone **4-1** with isobutyraldehyde in 69% yield (Scheme 4.1).[145] The diastereomeric ratio of **4-2**:**4-3**:**4-4**:**4-5** was 99.4:0.2:0.2:0.2; diastereomers **4-2** and **4-4** are often referred to as "Evans" and "non-Evans" *syn*-aldol adducts, respectively.



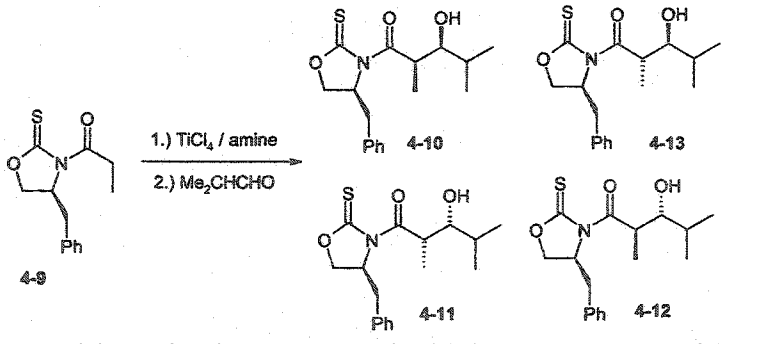
Scheme 4.1 Evans's *N*-Propionyl Chiral Oxazolidinone **4-1** in Stereoselective Aldol Condensations

Yan *et al.* developed a diastereoselective camphor-based oxazolidinethione that could "switch" in its preference for Evans and non-Evans propionate aldol adducts, thus allowing the preparation of both enantiomeric *syn*-aldol adducts (after removal of the auxiliary) from the same oxazolidinethione (Scheme 4.2).[146] The boron enolate derived from camphor-based oxazolidinethione **4-6** reacted with isobutyraldehyde to afford **4-7** and **4-8** in a ratio of 99:1 in 79% yield. Conversely, the titanium enolate derived from camphor-based oxazolidinethione **4-6** afforded **4-7** and **4-8** in a ratio of 2:98 in 85% yield. In both examples, no *anti*-diastereomers were observed (>99:1 *syn*:*anti* by ^{1}H-NMR). The "switching" between Evans (**4-7**) and non-Evans (**4-8**) diastereoselectivity was proposed to be the result of a mechanism change: condensation with the boron enolate involves a non-chelated transition state structure, while condensation with the titanium enolate involves a chelated transition state structure because of the high affinity of titanium for sulfur.



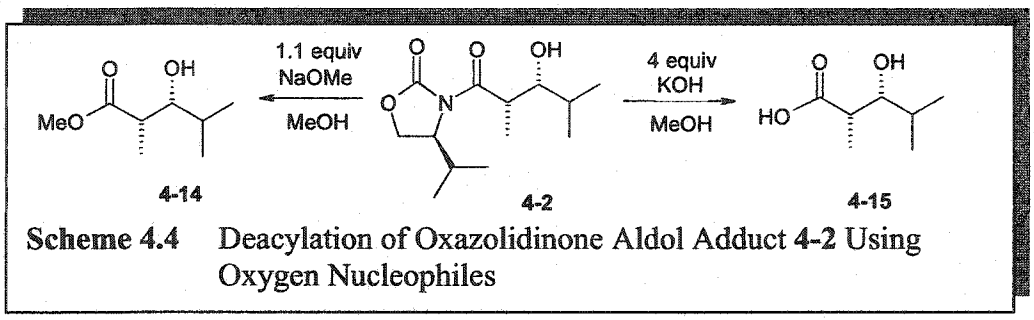
Scheme 4.2 Camphor-Derived *N*-Propionyl Oxazoldinethione **4-6** in Evans-type Aldol Condensations with Switchable *syn*-Diastereoselectivity: Boron Lewis Acids Favor **4-7** while Titanium Lewis Acids Favor **4-8**

Recently, Crimmins and co-workers reported a diastereoselective, Evans-type aldol condensation using easily accessible chiral *N*-propionyl oxazolidinethione **4-9**.[147] Both Evans and non-Evans *syn*-aldol adducts could be selectively prepared by simply varying the stoichiometry of titanium (IV) chloride and the nature of the amine base. Crimmins *et al.* condensed chiral *N*-propionyl oxazolidinethione **4-9** with isobutyraldehyde in 70-75% yield (Scheme 4.3). Using 2 equiv of titanium (IV) chloride and 1 equiv of diisopropylethylamine (Hunig's base), the diastereomeric ratio of **4-10**:**4-11**:**4-12** and **4-13** was 96.7:0.0:3.3 in favor of "non-Evans" *syn*-aldol adduct **4-10**. Conversely, using 1 equiv of titanium (IV) chloride and 2.5 equiv of (-)-sparteine, the diastereomeric ratio of **4-10**:**4-11**:**4-12** and **4-13** was 1.0:98.8:0.2 in favor of "Evans" *syn*-aldol adduct **4-11**.

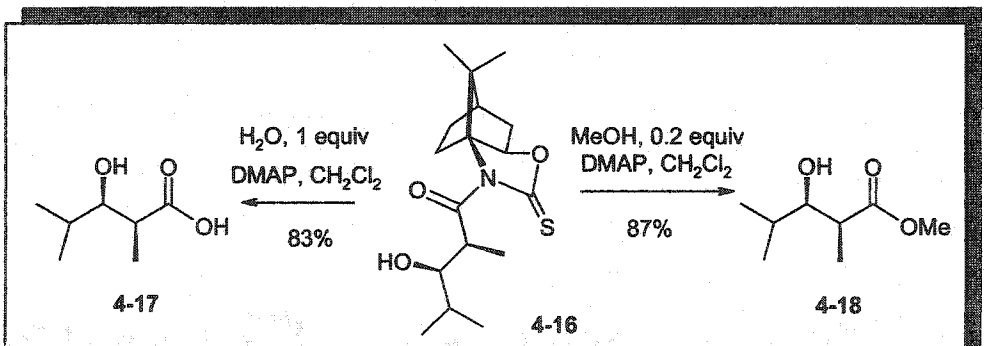


Scheme 4.3 Titanium Promoted Aldol Condensation with *N*-Propionyl Oxazolidinethione **4-9**

Oxazolidinone aldol adducts can be converted to their corresponding free acids upon exposure to aqueous hydroxide, or to their corresponding esters upon exposure to an alkoxide (Scheme 4.4).[145] Yan and coworkers have demonstrated that oxazolidinethione aldol adducts can be converted to their free acids or esters under much milder conditions with near complete recovery of the oxazolidinethione auxiliary.[148] For example, exposure of camphor-based oxazolidinethione **4-16** to water or methanol in the presence of DMAP afforded free acid **4-17** or methyl ester **4-18** in 87 or 83% yield, respectively (Scheme 4.5); no reaction was observed when the corresponding camphor-derived oxazolidinone was exposed to these same conditions.



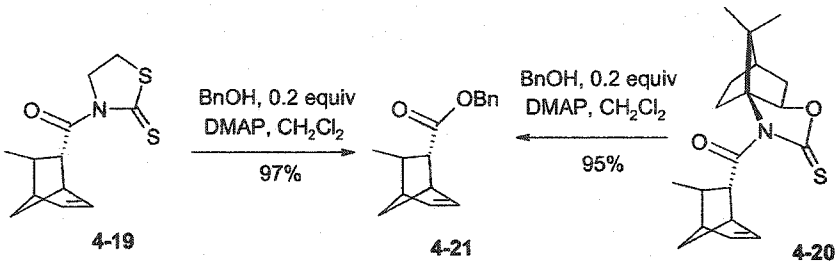
Scheme 4.4 Deacylation of Oxazolidinone Aldol Adduct **4-2** Using Oxygen Nucleophiles



Scheme 4.5 Deacylation of Oxazolidinethione Aldol Adduct **4-16** Using Oxygen Nucleophiles

Furthermore, Yan and coworkers have reported that thiazolidinethiones were efficiently deacylated under these same conditions.[149] For example, *N*-acyl thiazolidinethione **4-19** and camphor-derived *N*-acyl oxazolidinethione **4-20** were deacylated upon exposure to benzyl alcohol and 0.2 equiv DMAP in 97 and 95%

yield, respectively (Scheme 4.6); *N*-acyl thiazolidinethione **4-19** was observed to react almost 20 times faster than *N*-acyl oxazolidinethione **4-20** at room temperature, implying that thiazolidinethiones are more reactive towards deacylation compared to oxazolidinethiones.



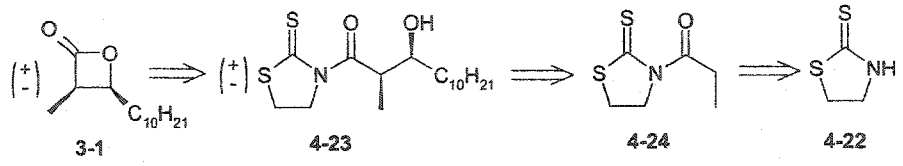
4-19 **4-21** **4-20**

Scheme 4.6 Deacylation of *N*-Acyl Thiazolidinethione **4-19** and *N*-Acyl Oxazolidinethione **4-20** Upon Exposure to Benzyl Alcohol in the Pressence of DMAP

Because the amide is so reactive in *N*-acylated thiazolidinethiones, they represent a highly attractive alternative to their corresponding oxazolidinones in the formation of versatile aldol adducts. However, at the start of this project, no titanium (IV) chloride promoted Evans-type aldol condensations had been reported in the literature using *N*-propionyl thiazolidinethiones.

4.2 Retrosynthesis of *cis*-4-Decyl-3-methyloxetan-2-one (3-1)

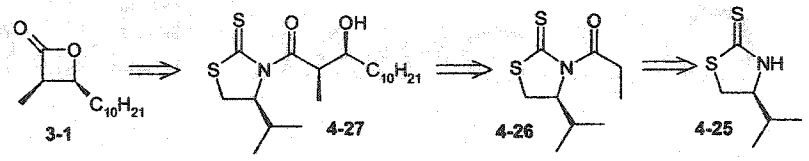
We initially proposed a retrosynthesis for racemic *cis*-4-decyl-3-methyloxetan-2-one (**3-1**) that uses commercially available thiazolidinethione **4-22** (Scheme 4.7). Building on the work of Crimmins and co-workers, it seemed reasonable that a titanium (IV) enolate derived from thiazolidinethione **4-24** would undergo a *syn*-diastereoselective aldol condensation through a highly ordered, chelated transition state to give **4-23**.



Scheme 4.7 Retrosynthesis for Racemic *cis*-4-Decyl-3-methyloxetan-2-one (**3-1**)

Enhanced reactivity of the amido carbonyl in **4-23**, compared to its oxazolidinethione and oxazolidinone analogues, could then be exploited to permit direct lactonization of **4-23**, or efficient conversion to an intermediate suitable for conventional lactonization procedures.

Once a route from aldol adduct **4-23** to β-lactone **3-1** is developed, substitution of thiazolidinethione **4-22** for chiral thiazolidinethione **4-25** should give access to the corresponding non-Evans *syn*-aldol adduct, which can eventually be used in the preparation of optically active *cis*-4-decyl-3-methyloxetan-2-one (**3-1**) (Scheme 4.8).



Scheme 4.8 Retrosynthesis for Optically Active *cis*-4-Decyl-3-methyloxetan-2-one (**3-1**)

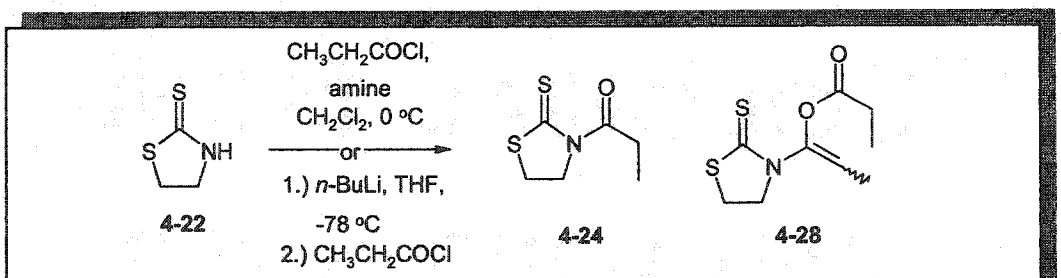
4.3 Preparation of Racemic *cis*-4-Decyl-3-methyloxetan-2-one (3-1)

4.3.1 Acylation of Thiazolidinethione 4-22

The most common acylation method for the preparation of *N*-acyl thiazolidinethiones involves exposure to the appropriate acyl chloride and

triethylamine in dichloromethane.[150] Exposure of thiazolidinethione **4-22** to propionyl chloride and triethylamine in dichloromethane at 0°C gave *N*-propionyl thiazolidinethione **4-24** in 68% yield (Scheme 4.9). However, over-acylation product **4-28** was also recovered in 26% yield as a single isomer. Exposure of thiazolidinethione **4-22** to propionyl chloride and diisopropylethylamine in dichloromethane at 0°C gave *N*-propionyl thiazolidinethione **4-24** and over-acylation adduct **4-28** in 85 and 12% yield, respectively. Improvement in yield and suppression of over-acylation may be explained by the diminished ability of the bulkier amine, diisopropylethylamine, to react with propionyl chloride to generate the corresponding ketene, and to act as a base to promote over-acylation.

This over-acylation product was surprisingly stable to aqueous base; the compound did not decompose to desired *N*-propionyl thiazolidinethione **4-24** or parent thiazolidinethione **4-22** upon exposure to 0.5 M KOH for 12 h at room temperature.

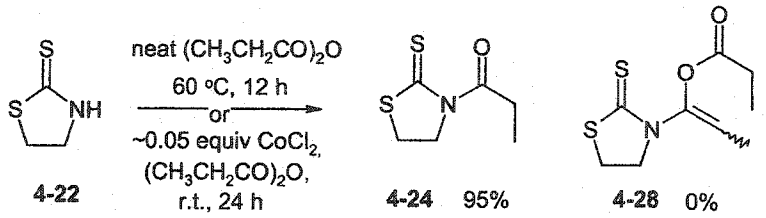


Scheme 4.9 Acylation of Thiazolidinethione **4-22** with Propionyl Chloride

Over-acylation was a concern because we planed to use a similar method with chiral thiazolidine-2-thione **4-25**; this side-reaction diminishes our ability to efficiently recycle the chiral auxiliary.

Modifying the method of Evans *et al.* for the preparation of *N*-acyl oxazolidines, thiazolidinethione **4-22** was treated with *n*-BuLi in THF at -78°C, followed by propionyl chloride, to give *N*-propionyl thiazolidinethione **4-24** in 84% yield.[151] No over-acylation adduct (**4-28**) was isolated.

We then developed a mild alternative for acylating thiazolidinethione **4-22** using propionic anhydride. Treatment of thiazolidinethione **4-22** with neat propionic anhydride at 60°C for 12 h gave *N*-propionyl thiazolidinethione **4-24** in 95% yield (Scheme 4.10). Furthermore, addition of a catalytic amount (< 1 mol%) of cobalt (II) chloride allowed the reaction to proceed at room temperature (24 h) to give *N*-propionyl thiazolidinethione **4-24**, also in 95% yield. In both reactions, the crude material could often be used without any need for purification.

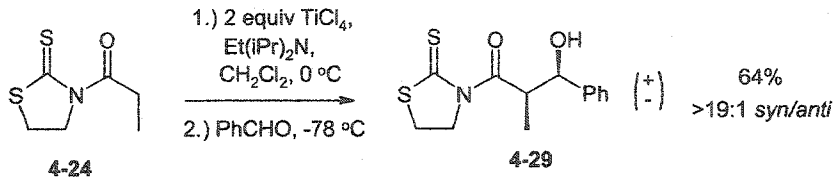


Scheme 4.10 Acylation of Thiazolidinethione **4-22** using Propionic Anhydride

4.3.2 Evans-type Aldol Condensation using *N*-Propionyl Thiazolidinethione 4-24

Our initial efforts focused on the method reported by Crimmins *et al.* for the titanium (IV) promoted Evans-type aldol condensation of benzaldehyde with chiral oxazolidinethione **4-9** (88% yield; >98:2 for *syn*:*anti*).[147]

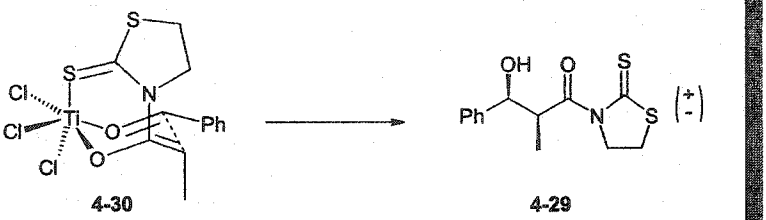
Gratifyingly, treatment of *N*-propionyl thiazolidinethione **4-24** with 2 equiv titanium (IV) chloride and 1 equiv of diisopropylamine in dichloromethane at 0°C, followed by freshly distilled benzaldehyde at –78°C, gave *syn*-aldol adduct **4-29** in 64% yield (Scheme 4.11). No *anti*-aldol adduct was observed by ^{1}H-NMR analysis of the crude reaction mixture (>19:1).



4-24 4-29

Scheme 4.11 Evans-Type Aldol Condensation with Benzaldehyde

Observed *syn*-diastereoselectivity may be explained by the chelated transition state structure **4-38** (Scheme 4.12). Similar transition state structures have been proposed for titanium (IV) promoted Evans and Evans-type aldol condensations involving oxazolidinone and oxazolidinethione systems.[147,152]

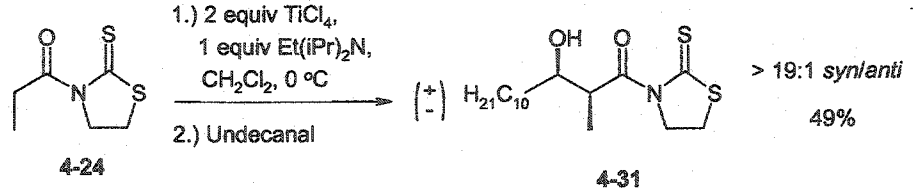


4-30 4-29

Scheme 4.12 Preparation of the *syn*-Aldol Adduct **4-29**

Purification of aldol adduct **4-29** was effortless using flash column chromatography; aldol adduct **4-29** and *N*-propionyl thiazolidinethione **4-24** - the only major impurity other than unreacted aldehyde - were bright, yellow oils.

Similarly, treatment of *N*-propionyl thiazolidinethione **4-24** with 2 equiv titanium (IV) chloride and 1 equiv of diisopropylamine in dichloromethane at 0°C, followed by freshly distilled undecanal at –78°C, gave *syn*-aldol adduct **4-31** in 49% yield (Scheme 4.13). Again, no *anti*-aldol adduct was observed by ^{1}H-NMR analysis of the crude reaction mixture (>19:1).



4-24 4-31

Scheme 4.13 Diastereoselective Evans-Type Aldol Condensation with Undecanal

Similar to aldol adduct **4-29**, purification of aldol adduct **4-31** was effortless using flash column chromatography; aldol adduct **4-31** is also a bright yellow oil.

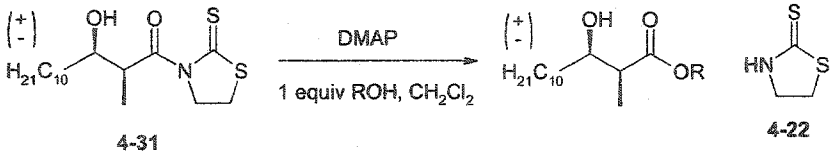
As for the Evans-type aldol condensation between *N*-propionyl thiazolidinethione **4-24** and benzaldehyde, condensation with undecanal is proposed to also proceed through a highly ordered, chelated transition state, giving high *syn*-diastereoselectivity.

4.3.3 Lactonization of Aldol Adducts of Thiazolidinethione 4-22

To the best of our knowledge, DMAP-promoted thiazolidinethione deacylation has only been performed using Diels-Alder adduct **4-19** (Scheme 4.6). In order to evaluate the reactivity of aldol adduct **4-31** towards oxygen nucleophiles in the presence of DMAP, we exposed it to methanol, benzyl alcohol, phenol and water using the methodology of Yan and coworkers (Table 4-1).[146]

Gratifyingly, aldol adduct **4-31** was reactive with all oxygen nucleophiles used regardless of their steric bulk or nucleophilicity (80-93% yield). However, 6 equivalents of water and 1 equiv of DMAP was required to give free acid **4-35** in high yield; this was likely because of the insolubility of water in the dichloromethane solvent.

With all 4 oxygen nucleophiles, the progress of the reaction could conveniently be monitored as the reaction went from clear yellow to clear and colorless upon cleavage of the amide bond.

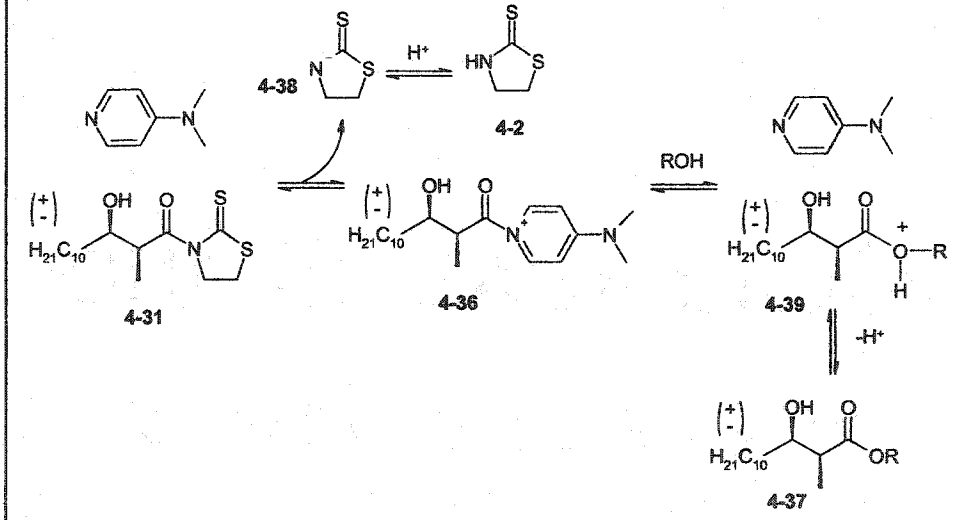


4-31 4-22

Entry	R	DMAP (equiv)	ROH (equiv)	% yield	Product
1	Me	0.2	1	91	**4-32**
2	CH_2Ph	0.2	1	89	**4-33**
3	Ph	0.2	1	93	**4-34**
4	H	1.0	6	80	**4-35**

Table 4.1 Reaction of Aldol Adduct **4-31** with Oxygen Nucleophiles

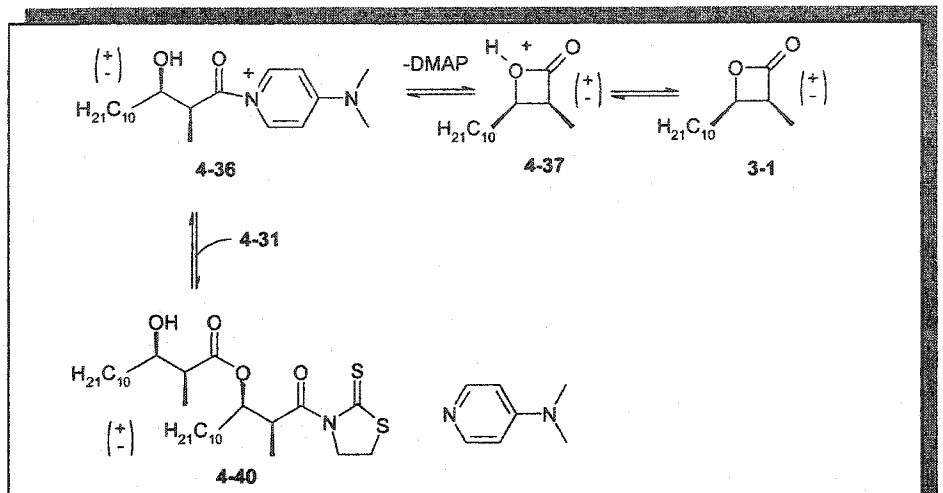
Presumably, these DMAP-promoted deacylation reactions proceed through acylium ion **4-36**, which subsequently reacts with the alcohol to give the desired product (**4-37**) (Scheme 4.14).



Scheme 4.14 Proposed Mechanism for DMAP Promoted Deacylation of *N*-Acyl Thiazolidinethione **4-31** with Oxygen Nucleophiles

We decided to investigate whether this highly reactive acylium ion could be exploited in the preparation of β-lactones under the appropriate conditions. That is, we proposed that in the presence of no additional oxygen nucleophiles, the acylium ion could undergo inter- or intramolecular nucleophilic attack with

the hydroxyl moiety in **4-31** or **4-36**, respectively (Scheme 4.15). Dilution of the reaction mixture was expected to favor intramolecular nucleophilic attack, thus furnishing the desired *cis*-1,2-disubstituted β-lactone **3-1**.

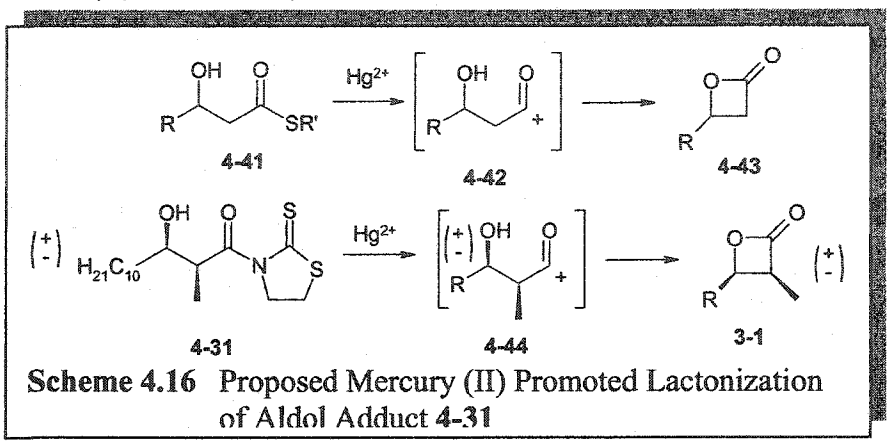


Scheme 4.15 Inter vs. Intramolecular Attack of Acylium Ion **4-36**

Unfortunately, a dilute solution of aldol adduct **4-31** (0.2 mM) in dry acetonitrile under an argon atmosphere at room temperature decomposed slowly after 7 days upon addition of 0.2 equivalents of DMAP; no β-lactone products were detected by IR analysis of the crude reaction material throughout the course of the reaction (IR displays a characteristic stretch at 1800 cm^{-1}). After work-up, *N*-acyl thiazolidinethione **4-40** was recovered in ~5% yield, demonstrating that the β-hydroxyl moiety can successfully attack acylium ion **4-36** (a control experiment without DMAP did not produce this product). Parent thiazolidinethione template was recovered intact, and the rest of the material was recovered as an inseparable mixture of organic molecules devoid of parent thiazolidinethione according to ^{1}H-NMR analysis. (This appeared to be a mixture of short chain 3-hydroxyalkanoates.)

Another strategy that we explored was the mercury (II) promoted lactonization of aldol adduct **4-31**. We proposed that thiophilic mercury would promote formation of an acylium ion, similar to Masamune's highly efficient

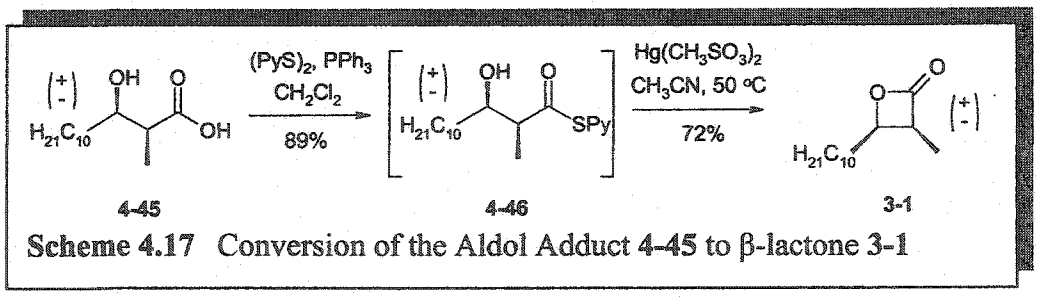
"double activation" method for preparing β-lactones from β-hydroxy thiol esters (Chapter 1.4.2) (Scheme 4.16).[102]



Scheme 4.16 Proposed Mercury (II) Promoted Lactonization of Aldol Adduct **4-31**

Unfortunately, addition of 1 equivalent of mercury (II) methanesulfonate to a dilute solution of aldol adduct **4-31** in dry acetonitrile furnished an inseparable mixture of compounds after 20 minutes at room temperature. Most notable were the absence of a β-lactone product (determined by IR analysis of the crude reaction material) and the lack of an intact thiazolidinethione ring (determined by ^{1}H-NMR analysis of the crude reaction material). Apparently, mercury promotes the rapid opening of thiazolidinethione rings, and is therefore unsuitable for the preparation of β-lactones in this case.

Using a more conventional approach, free acid **4-45** was converted to β-lactone **3-1** via mercury promoted lactonization of an intermediate thiol ester (**4-46**) (Scheme 4.17).[109] β-Lactone **3-1** was prepared in 64% yield from free acid **4-45** and in 25% overall yield from *N*-propionyl thiazolidinethione **4-24**.



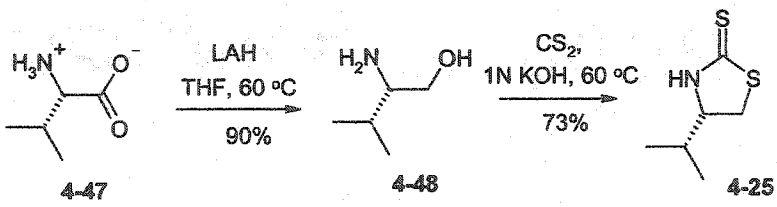
Scheme 4.17 Conversion of the Aldol Adduct **4-45** to β-lactone **3-1**

4.4 Towards the Preparation of Optically Active *cis*-4-Decyl-3-methyloxetan-2-one

In spite of the fact that racemic *cis*-4-decyl-3-methyloxetan-2-one (**3-1**) was made in only 25% yield from *N*-propionyl thiazolidinethione **4-24** in 4 steps, we decided to prepare the requisite free acid (**4-45**) from undecanal using a similar approach with chiral thiazolidinethione **4-25**. This was because, regardless of the yield, no method currently exists to prepare *cis*-4-decyl-3-methyloxetan-2-one (**3-1**), or any other optically active *cis*-1,2-disubtituted β-lactone from optically inactive building blocks.

4.4.1 Preparation of Chiral *N*-Propionyl Thiazolidinethione 4-26

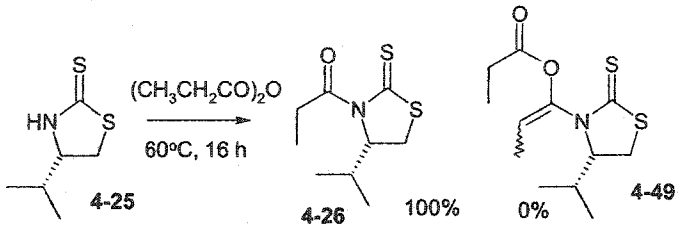
Chiral thiazolidinethiones are readily available from their corresponding amino acids (Scheme 4.18). Using the method of Harrison, L-valinol (**4-48**) was prepared in 90% yield upon exposure of L-valine (**4-47**) to lithium aluminum hydride (LAH) in THF at 60°C.[153] (Giannis and Sandhoff have reported that racemization of the α-carbon is not observed using LAH with a variety of amino acids, including **4-47**.)[154] Amino alcohol **4-48** was subsequently converted to chiral thiazolidinethione **4-25** in 73% yield upon exposure to carbon disulfide in 1 N KOH using the method of Delaunay *et al.* (Scheme 4.18).[155]



4-47 **4-48** **4-25**

Scheme 4.18 Preparation of Chiral Thiazolidinethione **4-25**

Simply heating chiral thiazolidinethione **4-25** in neat propionic anhydride at 60°C for 12 h afforded chiral *N*-propionyl thiazolidinethione **4-26** in quantitative yield with no over-acylation products observed (Scheme 4.19).

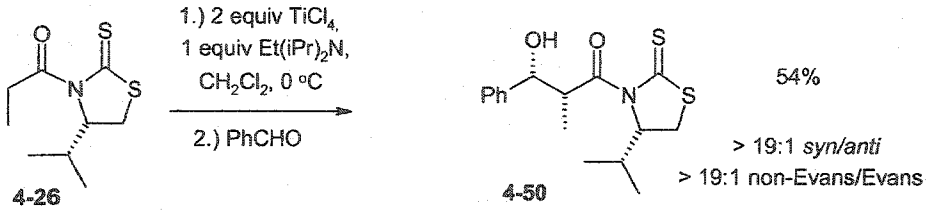


Scheme 4.19 Acylation of Chiral Thiazolidinethione **4-25** using Propionic Anhydride

4.4.2 Diastereoselective Aldol Condensation Using Chiral *N*-Propionyl Thiazolidinethione 4-26

Building on the method developed by Crimmins *et al.* for the titanium (IV) promoted non-Evans *syn*-diastereoselective condensation of chiral oxazolidinethione **4-1** with various aldehydes - and continued by us in the *syn*-diastereoselective condensation of thiazolidinethione **4-22** with undecanal and benzaldehyde - we explored a non-Evans *syn*-diastereoselective condensation of chiral thiazolidinethione **4-26** with benzaldehyde and undecanal.

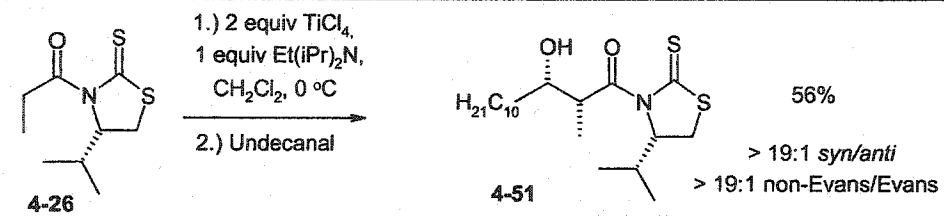
Treatment of chiral *N*-propionyl thiazolidinethione **4-26** with 2 equivalents of titanium (IV) chloride and 1 equivalent of diisopropylamine in dichloromethane at 0°C, followed by 1.1 equivalents of freshly distilled benzaldehyde at –78°C, gave desired non-Evans *syn*-aldol adduct **4-50** in 54% yield (Scheme 4.20).



4-26 **4-50**

Scheme 4.20 Condensation of *N*-Propionyl Thiazolidinethione **4-26** with Benzaldehyde

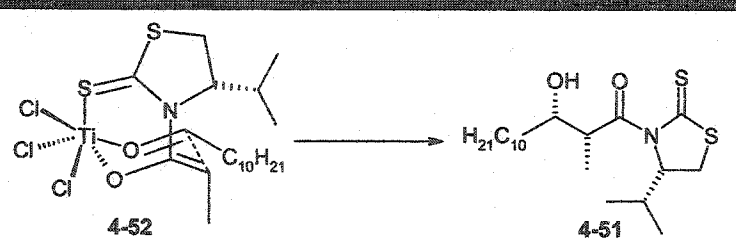
Similarly, treatment of chiral *N*-propionyl thiazolidinethione **4-26** with 2 equivalents of titanium (IV) chloride and 1 equivalent of diisopropylamine in dichloromethane at 0°C, followed by 1.1 equivalents of freshly distilled undecanal at –78°C, gave non-Evans *syn*-aldol adduct **4-51** in 56% yield (Scheme 4.21).



4-26 **4-51**

Scheme 4.21 Condensation of *N*-Propionyl Thiazolidinethione **4-26** with Undecanal

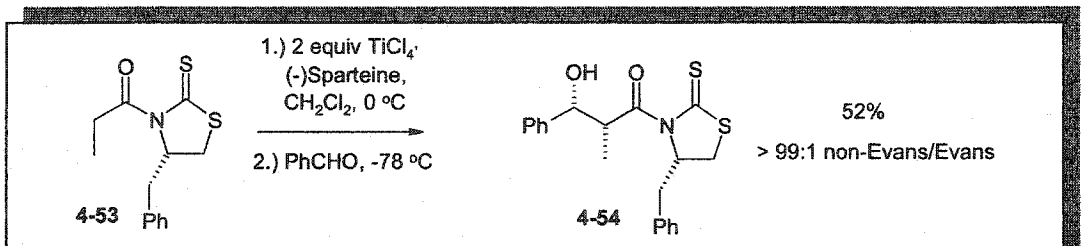
As with titanium (IV) promoted Evans and Evans-type aldol condensations using chiral oxazolidinones and oxazolidinethiones, *syn*-diastereoselectivity is proposed to be a result of the reaction proceeding through "chelated" transition structure **4-52** (Scheme 4.22). Furthermore, non-Evans diastereoselectivity is proposed to be a result of π-facial selectivity imparted by the ring isopropyl substituent.



4-52 **4-51**

Scheme 4.22 *Syn*-Diastereoselectivity in the Aldol Condensation with Titanium (IV) Chloride

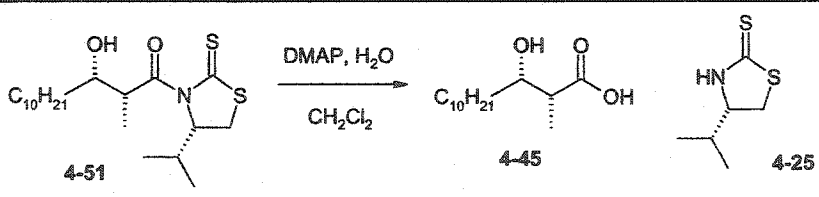
While we were finishing our work using the titanium enolate derived from chiral thiazolidinethione **4-26** in a non-Evans, *syn*-diastereoselective aldol condensation, Crimmins and Chaudhary reported their work using a similar titanium enolate derived from chiral thiazolidinethione **4-53** in a non-Evans, *syn*-diastereoselective aldol condensation (Scheme 4.23); their work fits in well with ours, further demonstrating the tremendous scope of Evans-type aldol condensations using the titanium enolates derived from chiral thiazolidinethiones.[156]



Scheme 4.23 Aldol Condensation using *N*-Propionyl Thiazolidinethione **4-53**

4.4.3 Conversion of Thiazolidinethione Aldol Adducts to their Free Acid

Similar to *N*-acyl thiazolidinethione **4-31**, treatment of chiral *N*-acyl thiazolidinethione **4-51** with 1 equivalent of DMAP in dichloromethane gave optically active *syn*-free acid **4-45** in 84% yield as a single diastereomer (Scheme 4.24).



Scheme 4.24 Removal of the Chiral Auxiliary

We have demonstrated in Chapter 4.3.3 that free acid **4-45** can be efficiently converted to the corresponding β-lactone (**3-1**) in 64% yield without epimerization of the stereocentres.

4.5 Summary of Results

In this chapter, we demonstrated that commercially available thiazolidinethione **4-22** can be efficiently used in a titanium (IV) chloride promoted, *syn*-diastereoselective Evans-type aldol condensation. Furthermore, we demonstrated that chiral thiazolidinethione **4-25** – which was easily prepared from the amino acid, L-valine – could be efficiently used in a titanium (IV) chloride promoted, non-Evans, *syn*-diastereoselective Evans-type aldol condensation.

Although the desired *cis*-4-decyl-3-methyloxetan-2-one (**3-1**) could not be prepared directly from the thiazolidinethione aldol adduct, we demonstrated that the 3-hydroxy-2-methyltridecanoyl moiety could be removed from thiazolidinethiones **4-22** and **4-51** as free acid **4-45** in 80-84% yield using relatively mild conditions that are not applicable to Evans oxazolidinones. Racemic *cis*-4-decyl-3-methyloxetan-2-one was prepared from free acid **4-45** in 62% yield using a mercury-promoted lactonization of the corresponding thiol ester.

4.6 Experimental

Preparation of L-Valinol (4-48)

Lithium aluminum hydride (730 mg, 19.3 mmol) was added portion-wise to a suspension of L-valine (**4-47**) (550 mg, 4.73 mmol) in THF (25 mL) at room

temperature. The mixture was heated at reflux for 48 h and then cooled to 0°C. Water (1.3 mL), 15% NaOH (0.75 mL) and then additional water (1.70 mL) were cautiously added drop-wise before the mixture was diluted with EtOAc (25 mL). After stirring 20 min, the suspension was filtered and the filtrite washed with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated to give L-valinol (**4-48**) (0.44 g, 90%) as a clear and colorless oil. Proton NMR indicated **4-48** was pure (> 95%) and identical to that reported by McKennon and Meyers[157]: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 1.55 (m, 1H), 2.35 (s, 2H), 2.52 (m, 1H), 3.27 (dd, J = 8.6, 10.6 Hz, 1H), 3.59 (dd, *J* = 3.8, 10.6 Hz, 1H).

Preparation of Chiral Thiazolidinethione 4-25

Using the procedure of Delaunay *et al.*[155] carbon disulfide (1.2 mL, 20 mmol) was added to a solution of L-valinol (**4-48**) (412 mg, 4.0 mmol) in 1 N NaOH (20 mL). After heating at reflux for 16 hours, the solution was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, and the mixture was concentrated using rotary evaporation. Flash column chromatography (40% ethyl acetate in hexanes) of the crude material gave chiral thiazolidinethione **4-25** as a white crystalline solid (471 mg, 73%). Proton NMR of **4-25** was identical to that reported by Delaunay *et al.*[155]: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.99 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.97 (m, 1H), 3.31 (dd, *J* = 8.3, 11.1 Hz, 1H), 3.50 (dd, *J* = 8.3, 11.1 Hz, 1H)), 4.05 (m, 1H), 8.07 (s, 1H).

Preparation of *N*-Propionyl Thiazolidinethione 4-24

Method A: A solution of 2-mercaptothiazolidine (**4-22**) (1.0 g, 8.4 mmol) in neat propionic anhydride (17 mL) was heated at 60°C for 12 h. (The progress of the reaction could be visually monitored as the clear and colorless solution became clear yellow.) The mixture was allowed to cool and was concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) of the crude material gave *N*-propionyl thiazolidinethione **4-24** (1.4 g, 95%) as a clear yellow oil. **Method B:** Anhydrous cobalt (II) chloride (~10 mg) was added to a solution of 2-mercaptothiazolidine (**4-22**) (1.0 g, 8.4 mmol) in neat propionic anhydride (17 ml). The mixture was allowed to stir at room temperature for 12 h. (The progress of the reaction could be visually monitored as the clear blue solution became clear green). The mixture was then concentrated using rotary evaporation, taken up in $CHCl_3$ (30 mL), washed with water (3 x 15 mL), dried over Na_2SO_4, and then re-concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) gave *N*-propionyl thiazolidinethione **4-24** (1.4 g, 95%) as a clear yellow oil. **Method C:** Diisopropylethylamine (7.0 mL, 40 mmol) and propionyl chloride (3.2 mL, 37 mmol) were added to a solution of 2-mercaptothiazolidine (**4-22**) (4.0 g, 34 mmol) in dichloromethane (200 mL) at 0°C. The mixture was allowed to stir 2 h, during which time the mixture warmed slowly to room temperature. The mixture was then washed with 5% aqueous HCl (3 x 150 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. Flash column chromatography of the crude material gave *N*-propionyl thiazolidinethione **4-24** (4.7 g, 85%) as a clear yellow oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.09 (t, J = 7.2 Hz, 3H), 3.17 (q, J = 7.2 Hz, 2H), 3.23 (t, J = 7.5 Hz, 2 H), 4.52 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.3, 175.2, 55.9, 32.0, 28.1, 8.6; MS(EI) *m/z*: 175, 147, 120, 57 (base). In addition, over-acylation product **4-28** (933 mg, 12%) was isolated as a clear pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.19 (t, J = 7.5 Hz, 3H),

1.66 (d, J = 7.0 Hz, 3H), 2.51 (q, J = 7.5 Hz, 2H), 3.34 (t, J = 7.7 Hz, 2H), 4.33 (t, J = 7.7 Hz, 2H), 5.40 (q, J = 7.0, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 199.3, 172.1, 138.6, 113.3, 59.2, 26.8, 10.8, 8.8; MS(EI) *m/z*: 232, 204, 174 (base), 146, 119; IR (thin film) 2987, 2946, 2887, 1760, 1699, 1406, 1267, 1117, 1008 cm^{-1}.

Preparation of Chiral *N*-Propionyl Thiazolidinethione 4-26

Similar to Method A for the acylation of 2-mercaptothiazolidine (**4-22**), a solution of chiral thiazolidinethione **4-25** (676 mg, 4.20 mmol) in neat propionic anhydride was heated at 60°C for 16 h. After cooling, the mixture was concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) of the crude material gave chiral *N*-propionyl thiazolidinethione **4-26** (911 mg, 100%) as a clear yellow oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.95 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 2.36 (m, 1H), 2.97-3.54 (m, 4H), 5.15 (m, 1H); MS(EI) *m/z*: 217, 162, 118, 57 (base).

General Procedure for the Titanium Mediated Aldol Reaction

Modifying the general procedure of Crimmins *et al.*[147] for *N*-acyl oxazolidinethiones, 2 equivalents of titanium (IV) chloride were added to a solution of *N*-propionyl thiazolidinethione in dichloromethane at 0°C. After stirring 5 min, 1 equiv diisopropylethylamine was added to the bright orange slurry. After stirring 20 min, the dark red solution was cooled to -78°C and 1.1 equivalents of freshly distilled aldehyde was added drop-wise. The mixture was allowed to stir 1 h, warmed to 0°C over 30 min, and quenched with half-saturated aqueous ammonium chloride. The organic layer was separated, dried over

$MgSO_4$, and concentrated using rotary evaporation. Flash column chromatography of the crude material gave the major diastereomer.

Preparation of Aldol Adduct 4-31

Using the general procedure for a titanium (IV) promoted aldol condensation, thiazolidinethione **4-24** (1.01 g, 5.77 mmol) in dichloromethane (60 mL) was reacted with titanium (IV) chloride (1.27, 11.58 mmol), diisopropylethylamine (1.10 mL, 6.31 mmol) and undecanal (1.33 mL, 6.44 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude material gave aldol adduct **4-31** (975 mg, 49%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.87 (t, J = 6.7 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.25 (m, 16H), 1.45 (m, 2H), 3.02 (s, 1H), 3.28 (t, J = 7.5 Hz, 2H), 3.98 (m, 1H), 4.53 (t, J = 7.5 Hz, 2H), 5.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.7, 179.0, 71.5, 56.4, 43.3, 34.0, 31.8, 29.5 (3C), 29.2 (2C), 28.1, 25.8, 22.6, 14.0, 10.1; MS(EI) *m/z*: 345, 312, 286, 226, 209, 186, 120 (base), 85; IR (thin film) 3447, 2927, 2855, 1699, 1156, 1054 cm^{-1}.

Preparation of Aldol Adduct 4-29

Using the general procedure for a titanium (IV) chloride promoted aldol condensation, a solution of chiral *N*-propionyl thiazolidinethione **4-26** (100 mg, 0.493 mmol) in dichloromethane (5 mL) was reacted with titanium (IV) chloride (0.109 μL, 0.986 mmol), diisopropylethylamine (93 μL, 0.537 mmol) and benzaldehyde (57μL, 0.549 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude material gave chiral aldol adduct **4-29** (97 mg, 64%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (d, J = 6.8 Hz, 3H), 2.16 (s, 1H),

2.92-3.01 (m, 1H), 3.06-3.14 (m, 1H), 4.19-4.39 (m, 2H), 4.82-4.91 (m, 1H), 5.02 (d, J = 5.3 Hz, 1H), 7.26-7.42 (m, 5H) ;^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.6, 178.1, 141.5, 128.1, 127.6, 126.0, 74.8, 56.1, 46.5, 28.4, 11.6; MS(EI) *m/z*: 282, 264, 248, 174, 145, 134, 120, 107, 79 (base); IR 3496, 2966, 2938, 2877, 1687, 1157 cm^{-1}.

Preparation of Aldol Adduct 4-51

Using the general procedure for a titanium (IV) chloride promoted aldol condensation, a solution of chiral *N*-propionyl thiazolidinethione **4-26** (200 mg, 0.922 mmol) in dichloromethane (10 mL) was reacted with titanium (IV) chloride (203 μL, 1.85 mmol), diisopropylethylamine (176 μL, 1.01 mmol) and undecanal (213 μL, 0.966 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude material gave chiral aldol adduct **4-51** (200 mg, 56%) as a clear yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.86 (t, J = 6.5 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.24 (m, 16H), 1.43 (m, 2H), 2.34 (m, 1H), 2.73 (s, 1H), 3.01 (d, J = 11.4 Hz, 1H), 3.48 (dd, J = 8.0, 11.4 Hz, 1H), 4.03 (m, 1H), 4.73 (dq, J = 2.3, 6.9 Hz, 1H), 5.14 (t, J = 6.7 Hz); MS(EI) *m/z*: 387, 354, 228, 162 (base), 118, 85.

Preparation of Aldol Adduct 4-50

Using the general procedure for a titanium (IV) chloride promoted aldol condensation, *N*-propionyl thiazolidinethione **4-26** (100 mg, 0.46 mmol) in dichloromethane (5 mL) was reacted with titanium (IV) chloride (101 μL, 0.92 mmol), diisopropylethylamine (88 μL, 0.50 mmol) and benzaldehyde (49 μL, 0.48 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude

material gave aldol adduct **4-50** (80 mg, 54%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.93 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.08 (d, J 6.9 Hz, 3H), 2.29 (m, 1H), 2.94 (dd, J = 11.5, 1.1 Hz), 3.01 (s, 1H), 3.42 (dd, J = 11.5, 8.0 Hz, 1H), 5.07 (m, 2H), 5.19 (d, J = 3.3 Hz, 1H), 7.19 – 7.85 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 203.0, 177.6, 141.3, 128.1, 127.3, 126.1, 73.1, 71.8, 44.3, 30.7, 29.8, 18.9, 17.4, 10.9; MS(EI) *m/z*: 324, 306, 290, 216, 162 (base), 145, 135, 118, 107, 79; IR 3496, 2966, 2938, 2877, 1687, 1157 cm^{-1}.

Preparation of Aldol Adduct 4-32

Modifying the method of Su *et al.*[148], a solution of aldol adduct **4-31** (100 mg, 0.290 mmol) in dichloromethane (1.5 mL) was treated with methanol (17.6 μL, 0.435 mmol) and DMAP (7.1 mg, 0.058 mmol). The solution was allowed to stir 6 hours at room temperature. The mixture was washed with 5% aqueous HCl (2 x 1 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) of the crude material gave β-hydroxy methyl ester **4-32** (68 mg, 91%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.86 (t, J = 6.9 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H), 1.24 (m, 16H), 1.37 (m, 1H), 1.44 (m, 2H), 2.42 (s, 1H), 2.52 (dq, J = 3.6, 7.2 Hz, 1H), 3.69 (s, 3H), 3.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 176.6, 71.7, 51.7, 44.2, 33.8, 31.9, 29.5, 29.3, 26.0, 22.6, 14.1, 10.6; MS(EI) *m/z*:259, 241, 117, 88 (base).

Preparation of Aldol Adduct 4-33

Modifying the method of Su et al.[155], a solution of aldol adduct **4-31** (50 mg, 0.145 mmol) in dichloromethane (1.5 mL) was treated with benzyl alcohol (23 μL, 0.217 mmol) and DMAP (3.5 mg, 0.029 mmol). The mixture was

allowed to stir 4 hours at room temperature. The mixture was washed with 5% aqueous HCl (2 x 1 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) of the crude material gave β-hydroxy benzyl ester **4-33** (43 mg, 89%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, J = 6.8 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.25 (m, 16H), 1.44 (m, 2H), 2.23 (s, 1H), 2.58 (dq, J = 3.5, 7.2 Hz, 1H), 3.91 (m, 1H), 5.15 (s, 2H), 7.32 (s, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 175.9, 135.8, 128.6, 128.3, 128.1, 71.8, 66.4, 44.3, 33.8, 31.9, 29.6, 29.3, 25.9, 22.7, 14.1, 10.6; IR 3409, 2927, 2856, 1755, 1197, 1162, 747, 689 cm^{-1}.

Preparation of Aldol Adduct 4-34

Modifying the method of Su et al.[148], a solution of aldol adduct **4-31** (50 mg, 0.145 mmol) in dichloromethane (1.5 mL) was treated with phenol (20 μL, 0.217 mmol) and DMAP (3.5 mg, 0.029 mmol). The mixture was allowed to stir 4 hours at room temperature. The mixture was washed with 5% aqueous HCl (2 x 1 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) of the crude material gave β-hydroxy phenyl ester **4-34** (43 mg, 93%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.87 (t, J = 6.6 Hz, 3H), 1.26 (m, 16 H), 1.36 (d, J= 7.0 Hz, 3H), 1.50 (m, 2H), 2.17 (s, 1H), 2.78 (dq, J = 3.5, 7.0 Hz, 1H), 4.04 (m, 1H), 7.05 – 7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 174.6, 150.5, 129.4, 125.9, 121.4, 71.8, 44.5, 37.9, 34.7, 34.0, 31.9, 29.6, 29.3, 26.0, 25.5, 25.5, 22.7, 14.1, 10.7; MS(EI) *m/z*: 321, 303, 227, 209, 94 (base); IR 3444, 2927, 2856, 1755, 1196, 1163, 757, 690 cm^{-1}.

Preparation of Aldol Adduct 4-35

Method A: Modifying the method of Su *et al.*[148], a solution of aldol adduct **4-31** (200 mg, 0.58 mmol) in dichloromethane (10 mL) was treated with water (63 μL, 3.5 mmol) and DMAP (71 mg, 0.58 mmol). The mixture was allowed to stir 4 hours at room temperature, and was then concentrated using rotary evaporation. Flash column chromatography (40:60:1 EtOAc-hexanes-AcOH) of the crude material gave β-hydroxy acid **4-35** (118 mg, 80%) as a clear and colorless oil. **Method B:** Modifying the method of Su *et al.*[148], a solution of chiral aldol adduct **4-51** (112 mg, 0.29 mmol) in dichloromethane (5 mL) was treated with water (31 μL, 1.7 mmol) and DMAP (35 mg, 0.29 mmol). The mixture was allowed to stir 4 hours at room temperature. The mixture was concentrated using rotary evaporation. Flash column chromatography (40:60:1 EtOAc-hexanes-AcOH) of the crude material gave β-hydroxy acid **4-35** (60 mg, 84%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.85 (t, J = 6.8 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 1.23 (m, 16H), 1.26 (m, 2H), 2.55 (dq, J = 3.5, 7.2 Hz, 1H), 3.92 (m, 1H), 8.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 177.5, 71.7, 44.1, 33.6, 31.9, 29.5, 25.9, 22.6, 20.8, 14.1, 10.4; IR 3021, 2930, 2858, 1708, 1464, 1091 cm^{-1}.

Preparation of β-Hydroxy Thiol Ester 4-46

Triphenylphosphine (115 mg, 0.438 mmol) and 2,2'-dipyridyl disulfide (90.4 mg, 0.410 mmol) were added to a solution of β-hydroxy acid **4-35** (66.9 mg, 0.293 mmol) in chloroform (4mL). The solution was allowed to stir 20 min, and was then concentrated using rotary evaporation. Flash column chromatography (25% EtOAc in hexanes) of the crude material gave β-hydroxy thiol ester **4-46** (84 mg, 89%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.85 (t,

J = 6.8 Hz, 3H), 1.23 (m, 16 H), 1.29 (d, J = 7.1 Hz, 3H), 1.46 (m, 2H), 2.28 (s, 1H), 2.81 (dq, J = 3.5, 7.0, 1H), 4.00 (m, 1H), 7.28 (m, 1H), 7.73 (m, 1H), 8.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.0, 151.0, 150.4, 137.2, 130.3, 123.6, 71.8, 53.5, 34.1, 31.9, 29.6, 25.9, 22.7.

Preparation of *cis* β-lactone 3-1

Modifying the method of Masamune, a solution of β-hydroxy thiol ester **4-46** (96 mg, 0.28 mmol) in chloroform (4 mL) was added drop-wise to a suspension of mercury (II) methanesulfonate (111 mg) in acetonitrile at 50°C under an argon atmosphere. After stirring 15 min the reaction was filtered while hot, and the filtrite washed with chloroform (3 x 2 mL). The solvent was removed using rotary evaporation and flash column chromatography (15% EtoAc in hexanes) gave β-lactone **3-1** (46 mg, 72%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.86 (t, J = 6.8 Hz, 3H), 1.23 (m, 16H), 1.26 (d, J = 6.6 Hz, 3H), 1.67 (m, 2H), 3.71 (m, 1H), 4.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.8, 47.1, 31.9, 29.3, 25.4, 22.6, 14.1; IR (thin film) 3023, 2931, 2858, 1820 cm^{-1}.

Chapter 5

Preparation of C4-Monosubstituted β-Lactones Using Thiazolidinethiones

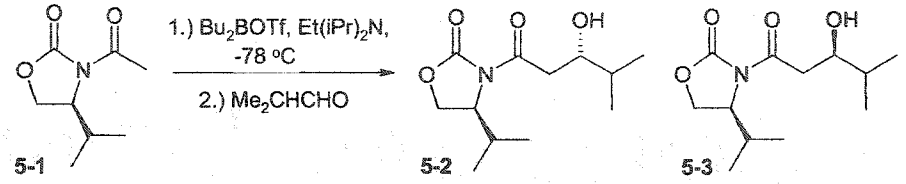
In Chapter 4 we used *N*-propionyl thiazolidinethiones in the preparation of *cis*-4-decyl-3-methyloxetan-2-one (**3-1**). At the same time, we explored an aldol condensation using *N*-acetyl thiazolidinethiones to prepare the corresponding monosubstituted β-lactone, 4-decyl oxetan-2-one (**2-7v**); this β-lactone was the most potent monosubstituted inhibitor of HMG-CoA synthase of the compounds investigated in Chapter 2.

This Chapter will deal with our use of *N*-acetyl thiazolidinethiones in the preparation of racemic 4-decyl oxetan-2-one (**2-7v**) and our work towards the use of chiral *N*-acetyl thiazolidinethiones in the preparation of optically active monosubstituted β-lactones.

5.1 Evans and Evans-type Aldol Condensations in the Preparation of Acetate Aldol Adducts

In Chapter 4.1, we briefly presented Evans and Evans-type aldol condensations in the stereoselective preparation of *syn*-propionate aldol adducts. Here, we briefly present Evans and Evans-type aldol condensations in the stereoselective preparation of acetate aldol adducts.

Although Evans' chiral oxazolidinones are highly diastereoselective in the preparation of propionate Evans *syn*-aldol adducts, minimal diastereoselectivity is observed in the corresponding acetate aldol adducts. For example, Evans *et al.* reported that the boron enolate derived from chiral *N*-acetyl oxazolidinone **5-1** gave a 52:48 mixture of **5-2** and **5-3** with isobutyraldehyde (Scheme 5.1).[158]



5-1 5-2 5-3

Scheme 5.1 Preparation of Acetate Aldol Adducts using Chiral *N*-Acetyl Oxazolidinone **5-1**

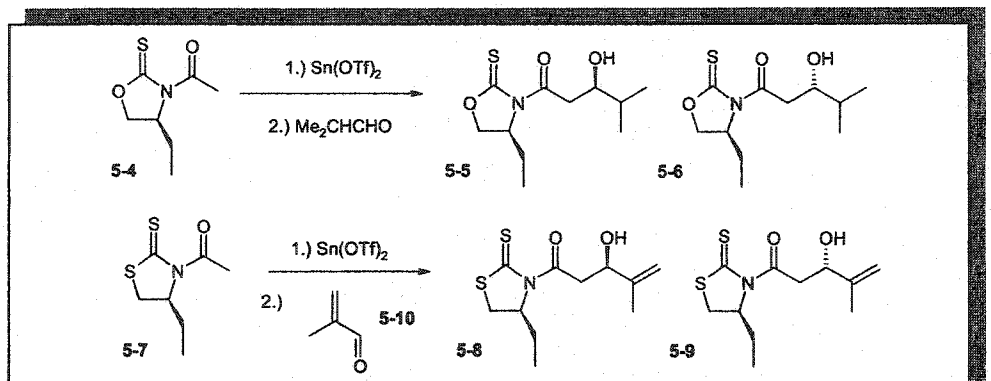
Low diastereoselectivity was attributed to the involvement of a poorly ordered transition state structure arising from the lack of an α-methyl group in the boron enolate.[159] Using the titanium enolate derived from chiral oxazolidinone **5-1**, Evans *et al.* modestly improved the diastereoselectivity, but in favor of the opposite diastereomer.[151] For example, the titanium enolate derived from chiral oxazolidinone **5-1** gave an 25:75 mixture of **5-2** and **5-3** using isobutyraldehyde. Improved diastereoselectivity - and a change in diastereomeric preference compared to the boron enolate - was attributed to a chelated transition state structure involving titanium. The minor diastereomer was believed to be the result of a competing aldol condensation where titanium was not involved in a chelated transition state structure.

Because of the greater affinity of titanium for sulfur over oxygen, several groups explored the use of chiral *N*-acetate oxazolidinethiones and thiazolidinethiones in Evans-type aldol condensations; it was presumed that increased affinity of titanium for sulfur would virtually eliminate a competing non-chelated transition state.

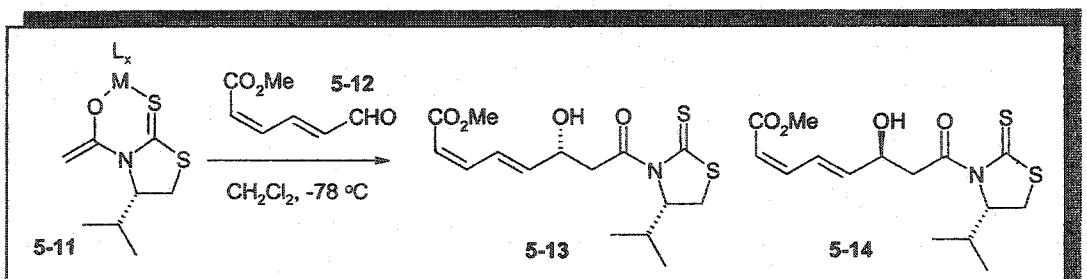
Nagao *et al.* reported that the tin enolate derived from chiral *N*-acetyl oxazolidinethione **5-4** gave a 91:9 mixture of **5-5** and **5-6** with isobutyraldehyde in 60% yield (Scheme 5.2).[160] Nagao *et al.* later reported that the tin enolate of the thiazolidinethione analogue (**5-7**) gave a 97:3 mixture of **5-8** and **5-9** using the corresponding α,β-unsaturated aldehyde (**5-10**) in 60% yield (Scheme 5.2).[161] (Nagao *et al.* cited unpublished results from their lab that indicated that the tin enolate of chiral *N*-acetyl thiazolidinethione **5-7** gave similar aldol adducts with

diastereoselectivities ranging from 92:8 to 99:1 using several aliphatic aldehydes.)[161] High diastereoselectivities observed using the tin enolates of chiral *N*-acetyl oxazolidinethiones and thiazolidinethiones are proposed to be the result of the involvement of chelated transition states.

More recently, in developing a total synthesis of macrolactin A, Gonzalez *et al.* compared *N*-acetyl thiazolidinethione enolate **5-11** in an Evans-type aldol condensation with aldehyde **5-12** (Scheme 5.3) using tin (II) and titanium (IV) as the metal ions. The tin enolate gave a 97:3 mixture of **5-13** and **5-14** in a 60% yield. The titanium enolate gave a 95:5 mixture of **5-13** and **5-14** in 84% yield. In both enolates, high diastereoselectivity was proposed to be the result of a chelated transition state.



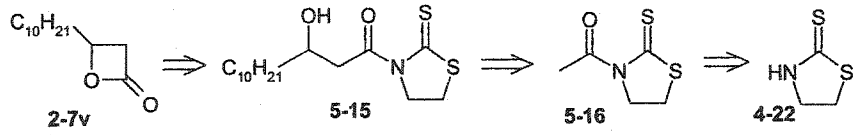
Scheme 5.2 Tin (II) Triflate Promoted Diastereoselective Aldol Condensations Involving *N*-Acetyl Oxazolidinethione **5-4** and *N*-Acetyl Thiazolidinethione **5-7**



Scheme 5.3 Preparation of Acetate Aldol Adducts **5-13** and **5-14** using Titanium and Tin Enolates of *N*-Acetyl Thiazolidinethione **5-11**

5.2 Retrosynthesis of Racemic and Optically Active 4-Decyloxetan-2-one

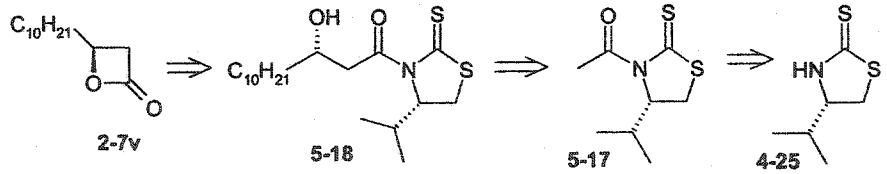
Based on our success in Chapter 4 using the titanium (IV) enolates of *N*-propionyl thiazolidinethiones in the preparation of our requisite aldol adducts for lactonization, we propose an analogous retrosynthesis using commercially available thiazolidinethione **4-22** (Scheme 5.4).



Scheme 5.4 Retrosynthesis of 4-Decyloxetan-2-one (**2-7v**) Starting From Thiazolidinethione **4-22**

Based on our work in Chapter 4, the 3-hydroxytridecyl moiety could presumably be converted to β-lactone **2-7v** through lactonization of the free acid (3-hydroxytridecanoic acid).

Once a route to β-lactone **2-7v** involving *N*-acetyl thiazolidinethione **5-16** is developed, substitution of *N*-acetyl thiazolidinethione **5-16** for chiral *N*-acetyl thiazolidinethione **5-17** should afford an optically active 3-hydroxytridecyl moiety that may eventually be used in the preparation of optically active 4-decyloxetan-2-one (**2-7v**) (Scheme 5.5).

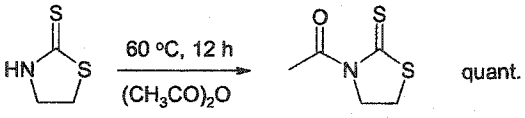


Scheme 5.5 Preparation of Optically Active 4-Decyloxetan-2-one (**2-7v**)

5.3 Preparation of Racemic 4-Decyloxetan-2-one

5.3.1 Preparation of *N*-acetyl thiazolidinethione 5-16

In Chapter 4, thiazolidinethione **4-22** was efficiently converted to *N*-propionyl thiazolidinethione **4-24** in near quantitative yield upon heating in neat propionic anhydride. Similarly, heating thiazolidinethione **4-22** for 6 h at 60°C in neat acetic anhydride gave *N*-acetyl thiazolidinethione **5-16** in quantitative yield (Scheme 5.6).



4-22 **5-16**

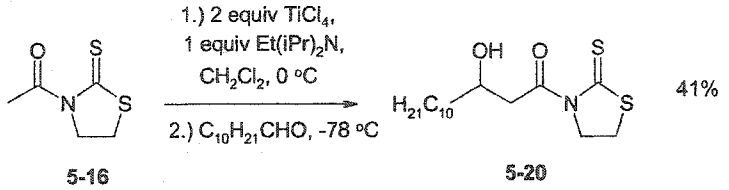
Scheme 5.6 Acetylation of Thiazolidinethione **4-22** using Acetic Anhydride

Furthermore, addition of a <1 mmol% of cobalt (II) chloride to the reaction mixture gave *N*-acetyl thiazolidinethione **5-16** in 96% yield upon exposure to acetic anhydride over 12 h at room temperature. In both reactions, the crude material could often be used without need for further purification.

5.3.2 Evans-Type Aldol Condensation of *N*-Acetyl Thiazolidinethione 5-16

Again, our initial efforts focused on the method reported by Crimmins *et al.* for the titanium (IV) promoted Evans-type aldol condensation of benzaldehyde with chiral *N*-propionyl oxazolidinethione **4-9** (88% yield, >98:2 *syn/anti*) (Scheme 4.3).

Gratifyingly, treatment of *N*-acetyl thiazolidinethione **5-16** with 2 equivalents of titanium (IV) chloride and 1 equivalent of diisopropylethylamine in dichloromethane at 0°C, followed by 1.1 equivalents of freshly distilled undecanal at -78°C, gave aldol adduct **5-20** in 41% yield (Scheme 5.7).



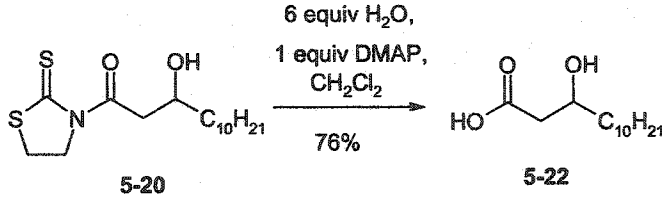
5-16 5-20

Scheme 5.7 Evans-type Condensation Between Undecanal and *N*-Acetyl Thiazolidinethione **5-16**

5.3.3 Conversion of Aldol Adduct 5-20 to β-Lactone 2-7v

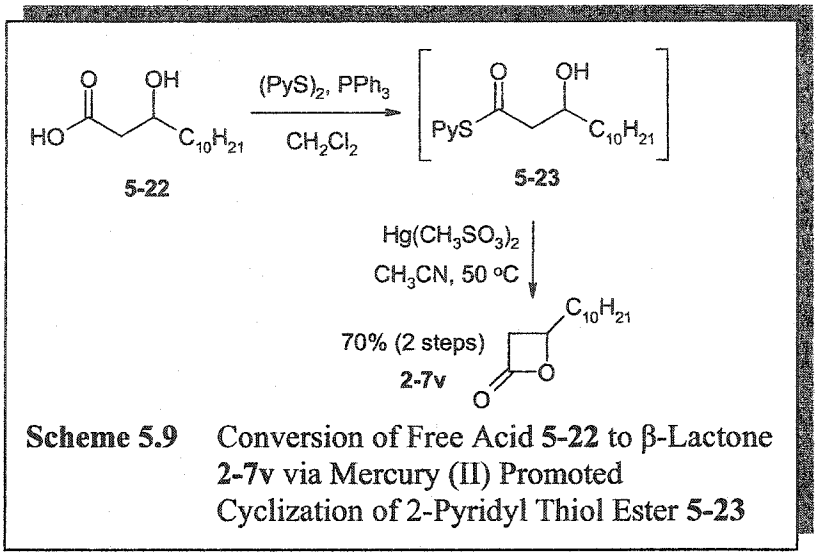
In Chapter 4.3.3, propionyl aldol adduct **4-31** was converted to β-lactone **3-1** through free acid **4-45**. Here we adopt a similar strategy.

Treatment of aldol adduct **5-20** with an excess of water in the presence of 1 equivalent of DMAP in dichloromethane gave 3-hydroxytridecanoic acid (**5-22**) in 76% yield (Scheme 5.8). Again, following the general method of Roelens *et al.*, free acid **5-22** was converted to thiol ester **5-23**. Subsequent exposure of thiol ester **5-23** to mercury (II) methanesulfonate in acetonitrile at 50°C gave β-lactone **2-7v** in 70% yield over 2 steps (Scheme 5.9).



5-20 5-22

Scheme 5.8 Preparation of Free Acid **5-22** from Aldol Adduct **5-20**



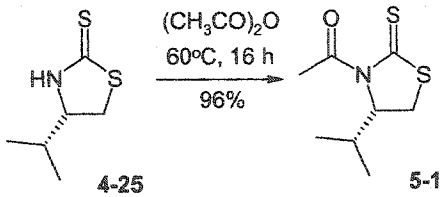
Scheme 5.9 Conversion of Free Acid **5-22** to β-Lactone **2-7v** via Mercury (II) Promoted Cyclization of 2-Pyridyl Thiol Ester **5-23**

5.4 Towards the Preparation of Optically Active 4-Decyloxetan-2-one (2-7v)

Although β-lactone **2-7v** was prepared in only 22% yield over 4 steps from *N*-acetyl thiazolidinethione **5-16**, we decided to explore diastereoselectivity in an aldol condensation involving chiral *N*-acetyl thiazolidinethione **5-17**; high diastereoselectivity in this aldol condensation is paramount to achieving high optical activity in the final β-lactone product. Presently, there are no general routes to optically active β-lactones from optically inactive starting materials involving an aldol condensation.

5.4.1 Preparation of Chiral *N*-acetyl Thiazolidinethione 5-17

Exposure of chiral thiazolidinethione **4-25** – previously prepared in Chapter 4 starting from L-valine – to neat acetic anhydride for 12 h at 60°C gave chiral *N*-acetyl thiazolidinethione **5-17** in 96% yield (Scheme 5.10). As with other *N*-acylated thiazolidinethiones we have made using this method, no further purification of the crude material was usually required.



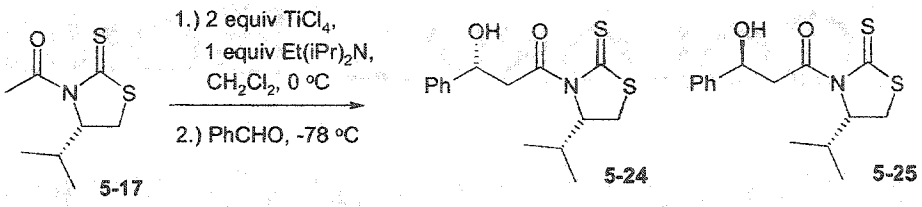
4-25 5-17

Scheme 5.10 Preparation of Chiral *N*-Acetyl Thiazolidinethione **5-17**

5.4.2 Preparation of Optically Active Thiazolidinethione Aldol Adducts

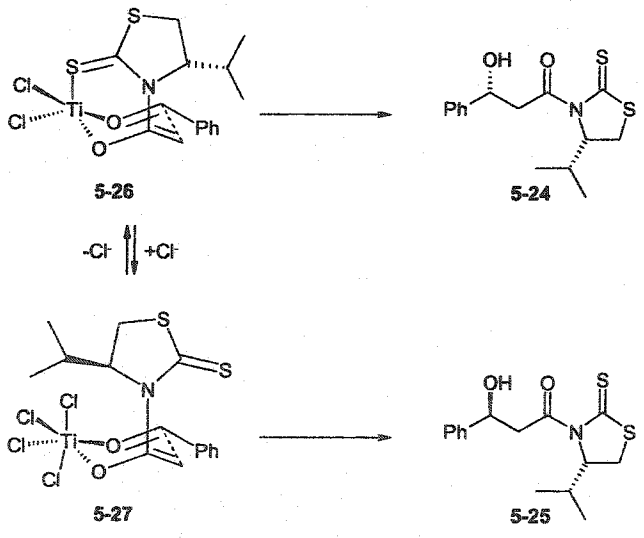
Again, building on the method developed by Crimmins *et al.* for the titanium (IV) promoted non-Evans *syn*-diastereoselective condensation of chiral oxazolidinethione **4-9** with various aldehydes - and continued by us in the condensation of *N*-acetyl thiazolidinethione **5-16** with undecanal - we explored a diastereoselective condensation of chiral *N*-acetyl thiazolidinethione **5-17**, starting with benzaldehyde.

Treatment of chiral *N*-acetyl thiazolidinethione **5-17** with 2 equivalents of titanium (IV) chloride and 1 equivalent of diisopropylethylamine in dichloromethane at 0°C, followed by 1.1 equivalents of freshly distilled benzaldehyde at –78°C, gave a 94:6 mixture of diastereomers (estimated using 500 MHz ^{1}H-NMR of the crude material). Based on the work of Nagao *et al.* with chiral titanium enolates of *N*-acetyl oxazolidinethiones and *N*-acetyl thiazolidinethiones, we assigned these diastereomers to structures **5-24** and **5-25**, respectively (Scheme 5.11). The major diastereomer (**5-24**) was isolated using simple flash column chromatography.



Scheme 5.11 Diastereoselective Aldol Condensation of Chiral *N*-Acetyl Thiazolidinethione **5-17** with Benzaldehyde

We propose that this reaction proceeds through the highly ordered, chelated transition state structure **5-26**, similar to condensations involving *N*-propionyl thiazolidinethiones (Schemes 5.12 and 4.23, respectively). Therefore, diastereoselectivity is ultimately the result of π-facial selectivity imparted by the ring isopropyl substituent. In non-chelated transition state structure **5-27**, π-facial selectivity imparted by the ring isopropyl substituent leads to the opposite diastereomer. Therefore, the minor diastereomer may be explained by the occurrence of transition state structure **5-27** and / or insufficient π-facial selectivity imparted by the ring isopropyl substituent.

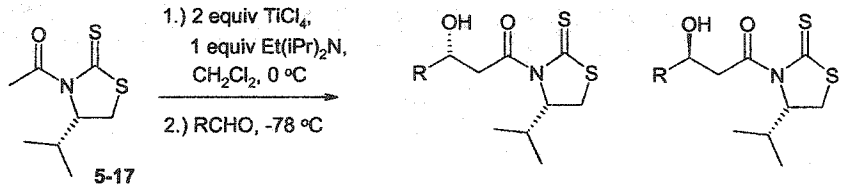


Scheme 5.12 Proposed Transition State Structures for the Titanium Promoted Evans-type Aldol Condensation of *N*-Acetyl Thiazolidinethione **5-17** and Benzaldehyde

To test the generality of this diastereoselective aldol condensation, several different aldehydes – including undecanal – were evaluated. The results are summarized in Table 5.1.

For all aldehydes used, good diastereoselectivity was observed. We propose that all condensations with these aldehydes proceed through a highly ordered, chelated transition state as described in Scheme 5.12.

However, because conversion of acetate aldol adduct **5-20** to β-lactone **2-7c** was somewhat inefficient (Chapter 5.3.3), further progress towards the preparation of optically active β-lactones using a similar strategy was halted.



R = Ph **5-28** **5-32**
R = $CH(CH_3)_2$ **5-29** **5-33**
R = $C_{10}H_{21}$ **5-30** **5-34**
R = $C(CH_3)CHPh$ **5-31** **5-35**

Entry	R	% yield	%de	major diast. (proposed)
1	Ph	64%	88 [a]	**5-28**
2	$CH(CH_3)_2$	71%	>90 [b]	**5-29**
3	$C_{10}H_{21}$	57%	>90 [b]	**5-30**
4	$CH(CH_3)CHPh$	68%	>90 [b]	**5-31**

[a] determined by 500 MHz ^{1}H-NMR of crude material
[b] determined by 200 MHz 1H-NMR of crude material

Table 5.1 Diastereoselectivity Using Chiral *N*-Acetyl Thiazolidinethione **5-17**

5.5 Summary

In this Chapter, we demonstrated that *N*-acetyl thiazolidinethione **5-16** could be used in a titanium (IV) chloride promoted aldol condensation with

undecanal. This method was further used to prepare β-lactone **2-7v** in 22% yield over 4 steps from *N*-acetyl thiazolidinethione **5-16**.

Futhermore, we demonstrated that chiral *N*-acetyl thiazolidinethione **5-17** could be used in a titanium (IV) chloride promoted diastereoselective aldol with undecanal and several other aldehydes. Using this procedure, several novel acetate aldol adducts were made in good yield (64-71%) with excellent diastereoselectivity (≥ 88 %de). These aldol adducts should eventually allow the preparation of optically active β-lactones.

5.6 Experimental

Preparation of 3-Acetyl-1,3-thiazolidine-2-thione (5-16)

Method A: A solution of thiazolidinethione **4-22** (1.0 g, 8.4 mmol) in acetic anhydride (17 mL) was heated for 12 h at 60°C during which time the solution went from clear and colorless to bright yellow. The bright yellow solution was cooled and then concentrated using rotary evaporation. Flash column chromatography of the crude material gave *N*-acetyl thiazolidinethione **5-16** (quantitative) as a bright yellow crystalline solid. **Method B:** Cobalt (II) chloride (~10 mg) was added to a solution of thiazolidinethione **4-22** (1.0 g, 8.4 mmol) in acetic anhydride (17 mL). The clear blue mixture was heated for 12 h at 60°C, during which time the mixture turned clear green. The bright green solution was cooled to room temperature and then concentrated using rotary evaporation. Flash column chromatography of the crude material gave *N*-acetyl thiazolidinethione **5-16** (1.3 g, 96%) as a bright yellow crystalline solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.78 (s, 3H), 3.29 (t, J = 7.5 Hz, 2H), 4.58 (t, J = 7.5 Hz, 2H); MS(EI) *m/z*: 161, 119, 60, 43 (base).

Preparation of (4*S*)-3-acetyl-4-isopropyl-1,3-thiazolidine-2-thione (5-17)

A solution of chiral thiazolidinethione **4-25** (676 mg, 4.20 mmol) in acetic anhydride (9 mL) was heated at 60°C, during which time the clear and colorless solution turned clear yellow. After cooling to room temperature, the mixture was concentrated using rotary evaporation. Flash column chromatography (25% EtOAc in hexanes) gave chiral *N*-acetyl thiazolidinethione **5-17** (825 mg, 97%) as a clear yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.96 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 2.29-2.40 (m, 1H), 3.01 (dd, J = 11.5, 1.0 Hz, 1H), 3.50 (dd, J = 11.5, 8.0 Hz, 1H), 5.09-5.16 (m, 1H); MS(EI) *m/z*: 203, 161, 117, 59, 43 (base).

General Procedure for the Titanium Mediated Aldol Reaction

Modifying the general procedure of Crimmins *et al.* for *N*-acyl oxazolidinethiones, 2 equivalents of titanium (IV) chloride were added to a solution of *N*-acetyl thiazolidinethione in dichloromethane at 0°C. After stirring for 5 min, 1 equiv diisopropylethylamine was added to the bright orange slurry. After stirring 20 min, the dark red solution was cooled to -78°C and 1.1 equivalents of freshly distilled aldehyde was added drop-wise. The mixture was allowed to stir 1 h, warmed to 0°C over 30 min, and quenched with half-saturated aqueous ammonium chloride. The organic layer was separated, dried over $MgSO_4$, and concentrated using rotary evaporation. Flash column chromatography of the crude material gave the major diastereomer.

Preparation of 3-(3-hydroxy-1-oxotridecyl)-1,2-thiazolidine-2-thione (5-20)

A solution of *N*-acetyl thiazolidinethione **5-16** (824 mg, 5.68 mmol) in dichloromethane (60 mL) was reacted with titanium (IV) chloride (1.25 mL, 11.39 mmol), diisopropylethylamine (1.08 mL, 6.21 mmol) and undecanal (1.30 mL, 6.34 mmol) according to the general procedure. Flash column chromatography (25% EtOAc in hexane) of the crude material gave aldol adduct **5-20** (756 mg, 41%) as a bright yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.87 (t, J = 6.8 Hz, 3H), 1.25 (m, 16H), 1.48 (m, 2H), 2.94 (s, 1H), 3.24 (m, 1H), 3.30 (t, J = 7.3 Hz, 2H), 4.08 (m, 1H), 4.59 (t, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.8, 174.3, 68.2, 55.7, 45.8, 36.5, 31.9, 29.6, 29.3, 28.3, 25.5, 22.7, 14.1; MS(EI) *m/z*: 331, 298, 169, 120 (base); IR (thin film) 3407, 3021, 2930, 2858, 1688, 1158, 1056 cm^{-1}.

Preparation of (4*S*)-3-[(3*S*)-3-hydroxy-1-oxotridecyl]-4-isopropyl-1,3-thiazolidine-2-thione (5-30)

A solution of chiral *N*-acetyl thiazolidinethione **5-17** (150 mg, 0.739 mmol) in dichloromethane (10 mL) was reacted with titanium (IV) chloride (0.163, 1.48 mmol), diisopropylethylamine (0.140 mL, 0.807 mmol) and undecanal (0.169mL, 0.824 mmol) according to the general procedure. Flash column chromatography (25% EtOAc in hexanes) of the crude material gave **5-30** (157 mg, 57%) as a bright yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.86 (t, J = 6.5 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.24 (m, 16H), 1.43 (m, 2H), 2.34 (m, 1H), 2.73 (s, 1H), 3.01 (d, J = 11.4 Hz, 1H), 3.48 (dd, J = 8.0, 11.4 Hz, 1H), 4.03 (m, 1H), 4.73 (dq, J = 2.3, 6.9 Hz, 1H), 5.14 (t, J = 6.7 Hz); MS(EI) *m/z*: 387, 354, 228, 162 (base), 118, 85.

Preparation of (4*S*)-3-[(3*S*)-3-phenyl-3-hydroxy-1-oxopropyl]-4-isopropyl-1,3-thiazolidine-2-thione (5-28)

A solution of chiral *N*-acetyl thiazolidinethione **5-17** (100 mg, 0.493 mmol) in dichloromethane (5 mL) was reacted with titanium (IV) chloride (0.109, 0.986 mmol), diisopropylethylamine (0.093 mL, 0.537 mmol) and benzaldehyde (0.057 mL, 0.549 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude material gave **5-28** (97 mg, 64%) as a yellow oil: ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 202.9, 172.5, 142.4, 128.5, 127.7, 125.7, 71.4, 70.1, 46.8, 30.8, 30.7, 19.0, 17.8.

Preparation of (4*S*)-3-[(3*S*)-4-phenyl-3-hydroxy-1-oxopentyl]-4-isopropyl-1,3-thiazolidine-2-thione (5-29)

A solution of chiral *N*-acetyl thiazolidinethione **5-17** (100 mg, 0.493 mmol) in dichloromethane (5 mL) was reacted with titanium tetrachloride (0.109 mL, 0.986 mmol), diisopropylethylamine (0.093 mL, 0.537 mmol) and isobutyraldehyde (0.0499 mL, 0.549 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude material gave **5-29** (96.4 mg, 71%) as a clear bright yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.92 (d, J = 7.1 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 7.3 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.64-1.81 (m, 1H), 2.22-2.42 (m, 1H), 2.49 (s, 1H), 3.00 (dd, J = 11.5, 1.1 Hz, 1H), 3.12 (dd, J = 17.7, 10.0 Hz, 1H), 3.50 (dd, J = 11.5, 7.9 Hz, 1H), 3.58 (dd, J = 17.7, 2.2 Hz, 1H), 3.89 (ddd, J = 10.0, 5.7, 2.1 Hz, 1H), 5.09-5.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 203.1, 173.6, 72.5, 42.8, 33.1, 30.8, 30.5, 17.8; MS(EI) *m/z*: 276, 258, 242, 214, 202, 162 (base), 118, 97; IR 3420, 3021, 2969, 2879, 1685, 1167, 1044 cm^{-1}.

Preparation of (4*S*)-3-[*trans*-(3*S*)-5-phenyl-4-methyl-3-hydroxy-1-oxopent-4-enyl]-4-isopropyl-1,3-thiazolidine-2-thione (5-31)

A solution of chiral *N*-acetyl thiazolidinethione **5-17** (100 mg, 0.493 mmol) in dichloromethane (5 mL) was reacted with titanium tetrachloride (0.109 mL, 0.986 mmol), diisopropylethylamine (0.093 mL, 0.537 mmol) and α-methyl *trans*-cinnamaldehyde (76.7 mL, 0.549 mmol). Flash column chromatography (25% EtOAc in hexanes) of the crude material gave **5-31** (118 mg, 68%) as a clear yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.92 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 1.83 (s, 3H), 2.32 (m, 1H), 2.69 (s, 1H), 2.96 (dd, J = 11.5, 1 Hz, 1H), 3.41 (dd, J = 17.3, 9.3 Hz, 1H), 3.47 (d, J = 7.9 Hz, 1H), 3.63 (dd, J = 17.3, 2.9 Hz, 1H), 4.67 (dd, J = 9.2, 2.0 Hz, 1H), 5.09 (apt t, 1H), 6.54 (s, 1H), 7.11 – 7.31 (m, 5H) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 203.1, 172.7, 138.2, 137.3, 128.1, 126.5, 125.9, 73.3, 71.5, 44.0, 30.9, 30.7, 19.1, 17.8, 14.2; MS(EI) *m/z*: 349, 332, 188, 171, 162 (base), 145, 118; IR 3445, 3020, 2970, 1686, 1166, 1043 cm^{-1}.

Preparation of 4-Decyloxetan-2-one (2-7c)

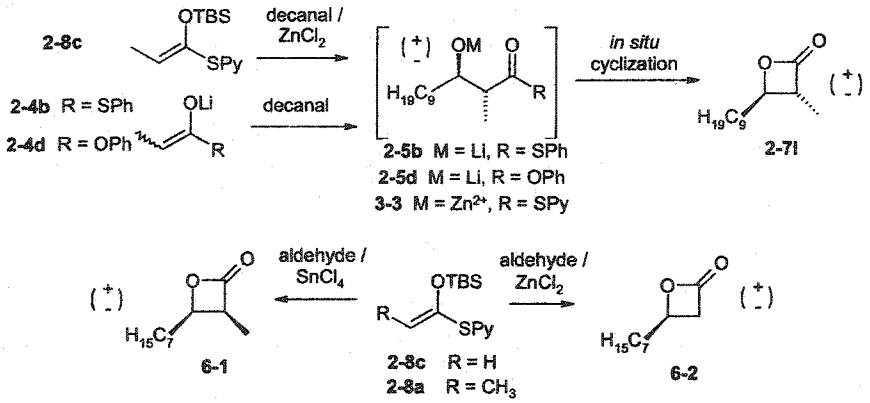
Triphenylphosphine (197 mg, 0.75 mmol) and 2,2'-dipyridyl disulfide (156 mg, 0.71 mmol) were added to a solution of β-hydroxy acid **5-22** (107 mg, 0.47 mmol) in chloroform (6 mL). After stirring for 5 minutes, the solution was added dropwise to a vigorously stirred suspension of mercury (II) methanesulfonate (370 mg) in acetonitrile (10 mL) at 50°C. After stirring an additional 10 minutes at 50°C, the reaction mixture was filtered while hot, and the filtrite was washed with chloroform (3 x 5 mL). The solvent was removed by rotary evaporation and the crude residue was purified by flash column chromatography (20% EtOAc in hexanes) to give lactone **2-7c** (69 mg, 70%) as a clear and colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.50 (m, 1H), 3.50 (dd, J =

16.2, 5.7 Hz, 1H), 3.05 (dd, J = 16.2, 4.3 Hz, 1H), 1.79 (m, 2H), 1.26 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 168.3, 71.3, 42.9, 34.7, 31.9, 29.4 (3C), 29.3, 29.1, 24.9, 22.6, 14.1; IR (thin film) 2926, 1830 cm^{-1}.

Chapter 6

Tandem Evans-Type Aldol-Lactonization Reaction in the Preparation of β-Lactones

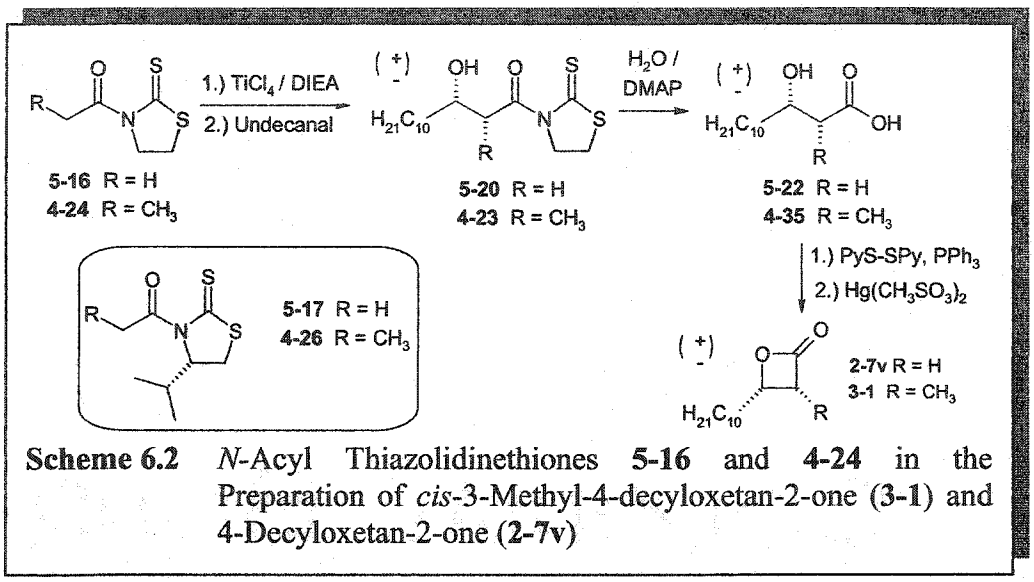
In Chapter 2, several one-pot tandem aldol-lactonization (TAL) reactions and a one-pot tandem Mukaiyama aldol-lactonization (TMAL) reaction were used in the preparation of *trans*-3-methyl-4-nonyloxetan-2-one (**2-7l**) (Scheme 6.1). Romo and co-workers have subsequently demonstrated that a one-pot TMAL reaction can be used in the preparation of *cis*-1,2-disubstituted (**6-1**) and C4-monosubstituted β-lactones (**6-2**) (Scheme 6.1).[17,162] However, these convenient one-pot reactions have thus far proved unsuitable for the preparation of optically active β-lactones from optically inactive aldehydes and ketones.



Scheme 6.1 TAL and TMAL Reaction in the Preparation of 1,2-Disubstituted (**2-7l** and **6-1**) and C4-Monosubstituted (**6-2**) β-Lactones

In Chapters 4 and 5, we used Evans-type aldol condensations between undecanal and the appropriate *N*-acyl thiazolidinethione (**4-24** and **5-16**) in the preparation of *cis*-methyl-4-decyloxetan-2-one (**3-1**) and 4-decyloxetan-2-one (**2-7v**) (Scheme 6.2). Although more steps are required compared to a TAL or TMAL approach, we have demonstrated that chiral *N*-acyl thiazolidinethiones **4-26** and **5-17** – highly recyclable chiral auxiliaries derived from relatively

inexpensive L-valine – are suitable for the preparation of optically active *cis*-1,2-disubstituted and C4-monosubstituted β-lactones from optically inactive aldehydes.



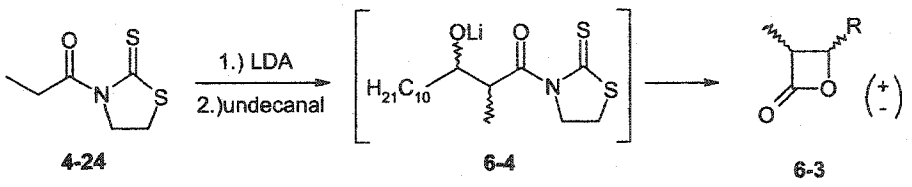
Scheme 6.2 *N*-Acyl Thiazolidinethiones **5-16** and **4-24** in the Preparation of *cis*-3-Methyl-4-decyloxetan-2-one (**3-1**) and 4-Decyloxetan-2-one (**2-7v**)

Obviously, a reaction that combined the efficiency of a TAL or TMAL reaction with the enantioselectivity of an Evans approach would be highly desirable. This Chapter will discuss our work towards the development of such a tandem Evans-type aldol-lactonization (TEAL) reaction in the preparation of β-lactones.

6.1 Retrosynthesis for 3-Methyl-4-decyloxetan-2-one (6-3)

We initially proposed a retrosynthesis for racemic 3-methyl-4-decyloxetan-2-one (**6-3**) using commercially available thiazolidinethione **4-22** in a TEAL reaction (Scheme 6.3). Building on the work of Danheiser *et al.* reacting lithium enolates with aldehydes or ketones – which, to the best of our knowledge, has been used without substantial modification in every published TAL reaction, regardless of the ester or thiol ester used – it seemed reasonable that an aldol

condensation between *N*-propionyl thiazolidinethione **4-24** and undecanal would occur with *in situ* cyclization of the lithium aldolate (**6-4**).[163,164,165] (Similar to the work of Danheiser *et al.* and others, we expected *trans*-diastereoselectivity in the preparation of 1,2-disubstituted β-lactones as the lithium enolate is not likely to undergo a chelation controlled aldol condensation.)



Scheme 6.3 Proposed TEAL Reaction in the Preparation of β-Lactone **6-3**

Once a route to 3-methyl-4-decyloxetan-2-one (**6-3**) is developed, substitution of thiazolidinethione **4-22** for chiral thiazolidinethione **4-25** should generate facial selectivity in the aldol condensation, and therefore allow the preparation of optically active 1,2-disubstituted β-lactone **6-3** from optically inactive undecanal (Figure 6.1).

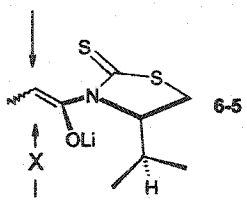
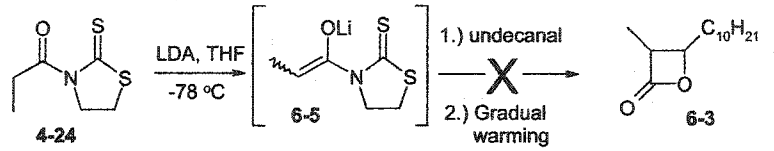


Figure 6.1 Facial Selectivity in the Aldol Step: The Aldehyde Adds *anti* to the Isopropyl Substituent on **6-5**

6.2 Preparation of 3-Methyl-4-decyloxetan-2-one (6-3)

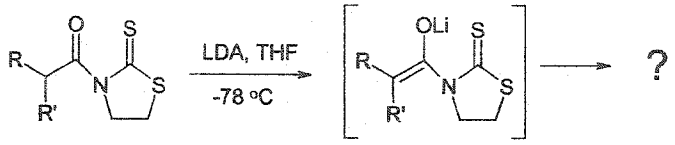
Following the TAL method described by Danheiser *et al.* for the reaction of lithium thiol ester enolates with aldehydes, a solution of *N*-propionyl

thiazolidinethione **4-24** in THF at -78°C was treated with 1.1 equiv of LDA to furnish the desired enolate (**6-5**) (Scheme 6.4). After stirring 30 minutes, a dilute, pre-cooled (-78°C) solution of undecanal in THF was added dropwise over 30 minutes. The resultant mixture was allowed to stir 30 minutes before being warmed to 0°C over 1.5 hours. Unfortunately, IR analysis of the crude material indicated no β-lactone product was produced.



Scheme 6.4 Attempted Preparation of β-Lactone **6-3** Using a TEAL Reaction

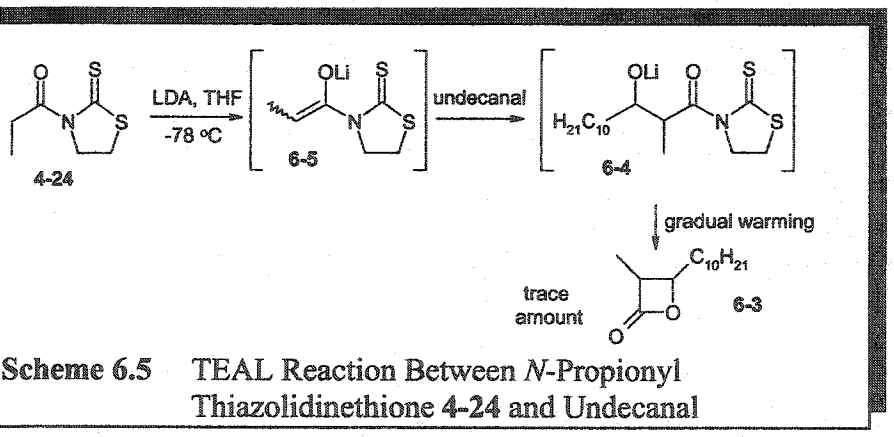
Carefully monitoring the reaction by TLC, it became obvious that *N*-propionyl thiazolidinethione **4-24** was not stable in the presence of LDA in THF at -78°C; complete decomposition was observed after ~30 minutes where ^{1}H-NMR analysis of the crude material revealed that the thiazolidinethione ring was destroyed. Several other *N*-acyl thiazolidinethiones were exposed to LDA in THF at -78°C: *N*-octanoyl thiazolidinethione **6-6**; *N*-butyryl thiazolidinethione **6-7**; *N*-methoxyacetyl thiazolidinethione **6-8**; and *N*-acetyl thiazolidinethione **5-16**. The results are summarized in Table 6.1. Although *N*-acetyl (**5-16**), *N*-octanoyl (**6-6**) and *N*-propionyl (**4-24**) thiazolidinethiones were similar in their moderate stability to LDA in THF at -78°C, *N*-isopropyl (**6-7**) and *N*-methoxyacetyl (**6-8**) thiazolidinethiones underwent complete decomposition in <5 minutes.



Entry	Enolate	R	R'	Approx. Time Until Complete Decomposition
5-16	6-9	H	H	~45 min
4-24	6-5	CH_3	H	~ 30 min
6-6	6-10	$(CH_2)_6CH_3$	H	~ 30 min
6-7	6-11	CH_3	CH_3	< 5 min
6-8	6-12	OCH_3	H	< 5 min

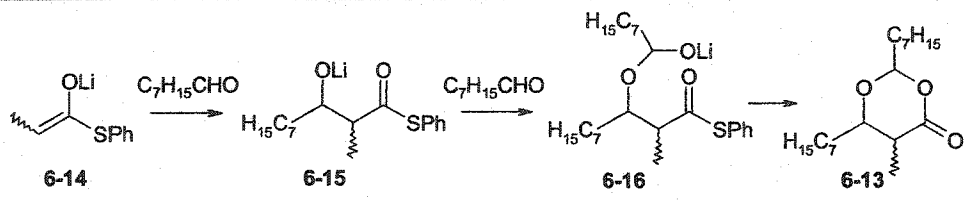
Table 6.1 Relative Stability of Several *N*-Acyl Thiazolidinethiones to LDA in THF

In an attempt to compensate for this decomposition, the TEAL reaction was repeated; a pre-cooled (-78°C) solution of undecanal in THF was added 15 minutes subsequent to exposure of *N*-propionyl thiazolidinethione **4-24** to LDA (compared to 30 minutes) dropwise over 10 minutes (compared to 30 minutes) (Scheme 6.5). The mixture was then allowed to stir 30 minutes before it was allowed to warm to 0°C over 1.5 hours. After work-up, IR analysis of the crude material indicated a possible trace amount of β-lactone product (C=O; 1810 cm^{-1}); however we were not able to isolate the product and assess the possibility of diastereoselectivity in this TEAL reaction.



Scheme 6.5 TEAL Reaction Between *N*-Propionyl Thiazolidinethione **4-24** and Undecanal

In the preparation of 3-methyl-4-decyloxetan-2-one (**6-3**), low yield in the TEAL reaction is probably the result of *N*-propionyl thiazolidinethione **4-24** decomposing in the presence of LDA in THF at -78°C. To compensate, it would be desirable to add the aldehyde neat to effectively "trap" enolate **6-5** as lithium aldolate **6-4**. Unfortunately, Danheiser *et al.* have reported that aliphatic aldehydes must be added as pre-cooled, dilute solutions to the enolate of thiophenyl ester **6-14** in order to minimize the formation of 2:1 aldehyde:enolate adduct **6-13** (Scheme 6.6).[163]



6-14 **6-15** **6-16** **6-13**

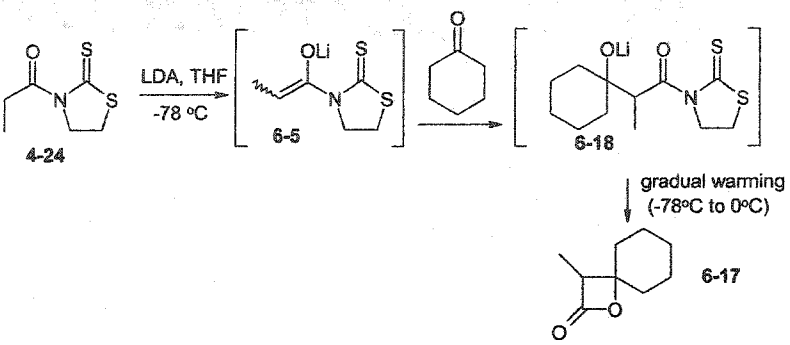
Scheme 6.6 Formation of 2:1 Aldol:Enolate Adduct **6-13** in the TAL Reaction Between Thiol Ester Enolate **6-14** and Octanal

In contrast, Danheiser *et al.* have reported that ketones can be added neat to the enolates of thiophenyl esters (**6-14**) without the formation of significant amounts of the corresponding 2:1 aldol:enolate adduct; this is likely a result of the lower reactivity of ketones relative to aldehydes towards nucleophilic attack. Hence, we decided to pursue a TEAL reaction between the lithium enolate of *N*-propionyl thiazolidinethione **4-24** and cyclohexanone.[163]

6.3 TEAL Reaction in the Preparation of spiro-β-Lactones

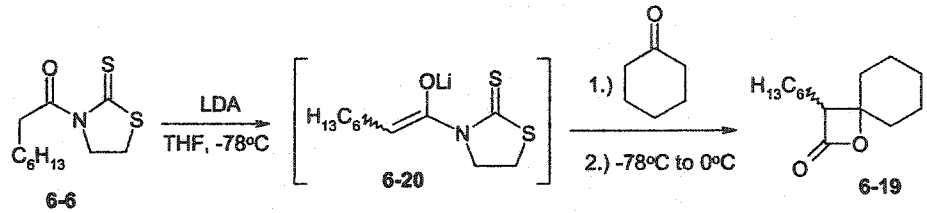
A solution of *N*-propionyl thiazolidinethione **4-24** in THF at -78°C was treated with 1.1 equiv LDA to furnish the desired lithium enolate (**6-5**) (Scheme 6.7). After stirring 15 min, cyclohexanone was added neat to the reaction mixture which was allowed to stir for 30 minutes. After gradually warming the mixture to room temperature over 1.5 hours, spiro β-lactone **6-17** was isolated in 35% yield.

This result demonstrates that thiazolidinethiones are suitable leaving groups in the spontaneous lactonization of a lithium aldolate (**6-18**).



Scheme 6.7 TEAL Reaction in the Preparation of spiro-β-Lactone **6-17** from *N*-Propionyl Thiazolidinethione **4-24**

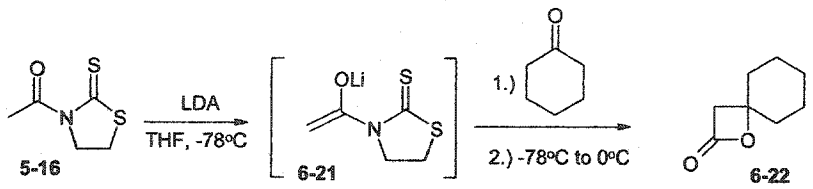
To test the tolerance of the TEAL reaction against larger α-alkyl-substituents, *N*-octanoyl thiazolidinethione **6-6** was reacted with cyclohexanone (Scheme 6.8); spiro β-lactone **6-19** was isolated in 17% yield. This lower yield is likely the result of the coiled octanoyl chain sterically shielding the α -protons in **6-6** from reacting with LDA, and its lithium enolate (**6-20**) from reacting with cyclohexanone.



Scheme 6.8 TEAL Reaction in the Preparation of spiro-β-Lactone **6-19** from *N*-Octanoyl Thiazolidinethione **6-6**

To see if this TEAL reaction could be used in the preparation of α-unsubstituted spiro-β-lactones, a solution of *N*-acetyl thiazolidinethione **5-16** in THF at -78°C was treated with 1.1 equiv LDA to furnish the desired lithium enolate (**6-21**) (Scheme 6.9). After stirring 15 min, cyclohexanone was added neat to the reaction mixture. The mixture was gradually warmed to room

temperature over 1.5 hours. Using this TEAL reaction, spiro-β-lactone **6-22** was isolated in 60% yield. This result is especially significant because it demonstrates that an α-substituent is not required to promote spontaneous, efficient lactonization of the intermediate lithium aldolate.



Scheme 6.9 Teal Reaction in the Preparation of spiro-β-Lactone **6-22** from *N*-Acetyl Thiazolidinethione **5-16**

Obviously thiazolidinethiones are excellent leaving groups that may be used in the intramolecular cyclization required to make β-lactones in a TEAL reaction. However, due to the unexpected decomposition of the lithium enolates of *N*-acyl thiazolidinethiones, this project was halted in order to re-evaluate the choice of enolate. A revised proposal for a TEAL reaction is described further in Chapter 8 that specifically addresses enolate stability.

6.4 Summary

In this Chapter, we demonstrated that thiazolidinethione **4-22** is a suitable leaving group for a one-pot tandem Evans-type aldol-lactonization (TEAL) reaction. Using this methodology, several spiro-β-lactones were prepared from the reaction of cyclohexanone with the lithium enolates of several *N*-acyl thiazolidinethiones in 17-60% yield.

Unfortunately, the lithium enolates of a variety of *N*-acyl thiazolidinethiones were quite unstable; ring opening of the thiazolidinethione ring was observed. This proved detrimental in TEAL reactions involving

aldehydes, which must be added slowly to prevent the formation of 2:1 aldehyde:enolate adducts.

6.5 Experimental

General Procedure for the TEAL Reaction

Modifying the method of Danheiser *et al.*[163], *n*-BuLi (1.1 equiv) was added to a solution of diisopropylamine (1.1 equiv) in THF at 0°C. After stirring 30 min, the mixture was cooled to -78°C and the *N*-acyl thiazolidinethione (1 equiv) was added. After stirring 15 min, freshly distilled cyclohexanone (1 equiv) was added dropwise, and the mixture was allowed to stir 30 min at -78°C. The mixture was gradually allowed to warm to room temperature over 1.5 h and was quenched with aqueous half saturated NH_4Cl. The mixture was partitioned between Et_2O and water, and the organic layer was washed with 10% aqueous K_2CO_3 and brine. The organic layer was dried over sodium sulfate and the solvent was removed by rotary evaporation. The crude material was purified using low temperature recrystallization from pentane.

Preparation of 3-Methyl-4-spirocyclohexyloxetan-2-one (6-17)

Using the general procedure for the TEAL reaction, *n*-BuLi (2.86 mmol, 1.5 M sol in hexane) was added to a solution of diisopropylamine (3.15 mmol) in 30 mL THF. To this, *N*-propionyl thiazolidinethione **4-24** (500 mg, 2.86 mmol) and cyclohexanone (296 μL, 2.86 mmol) were added, respectively. Work-up followed by purification gave **6-17** (240 mg, 60%) as a clear and colorless oil. The ^{1}H-NMR was identical to that reported by Danheiser *et al.*[163]: ^{1}H-NMR (200

MHz, $CDCl_3$) δ: 1.28 (d, J = 7.7 Hz, 3H), 1.30-1.95 (m, 10H), 3.20 (q, J = 7.7 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 172.6, 82.1, 52.5, 37.2, 31.1, 24.8, 23.1, 22.5, 8.4; IR (thin film) 3024, 2940, 2864, 1816, 1527, 1452 cm^{-1}.

Preparation of 3-Heptyl-4-spirocyclohexyloxetan-2-one (6-19)

Using the general procedure for the TEAL reaction, *n*-BuLi (2.86 mmol, 1.5 M sol in hexane) was added to a solution of diisopropylamine (3.15 mmol) in 30 mL THF. To this, *N*-hexyl thiazolidinethione **6-6** (500 mg, 2.86 mmol) and cyclohexanone (296 μL, 2.86 mmol) were added, respectively. Work-up followed by purification gave **6-19** (155 mg, 35%) as a clear and colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.86 (t, J = 6.8 Hz, 3H), 1.13-1.94 (m, 20H), 3.03 (t, J = 7.9 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 172.2, 82.0, 58.1, 37.3, 31.4, 31.2, 29.0, 27.6, 24.9, 23.9, 22.8, 22.5, 22.1, 14.0; IR (thin film) 2938, 2862, 1811, 1527cm^{-1}.

Preparation of 4-Spirocyclohexyloxetan-2-one (6-22)

Using the general procedure for the TEAL reaction, *n*-BuLi (2.86 mmol, 1.5 M sol in hexane) was added to a solution of diisopropylamine (3.15 mmol) in 30 mL THF. To this, *N*-acetyl thiazolidinethione **5-16** (565 mg, 2.16 mmol) and cyclohexanone (332 μL, 2.16 mmol) were added, respectively. Work-up followed by purification gave **6-22** (82.4 mg, 17%) as a clear and colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.37-1.59 (m, 4H), 1.61-1.97 (m, 6H), 3.06 (s, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 168.6, 78.8, 47.2, 35.8, 24.5, 23.2.

Preparation of *N*-Octanoyl Thiazolidinethione 6-6

Octanoyl chloride (1.71 mL, 10.0 mmol) was added dropwise to a solution of triethylamine (1.41 mL, 10.1 mmol) and 2-mercaptothiazolidine (**4-22**) (1.00 g, 8.39 mmol) in 30 mL dichloromethane at 0°C. The mixture was gradually allowed to warm to room temperature and was stirred for an additional 3 h. During the course of the reaction, the clear and colorless solution became clear yellow. The mixture was washed with 5% aqueous HCl (3 x 10 mL), dried over sodium sulfate, and concentrated using rotary evaporation. Flash column chromatography (20% EtOAc in hexanes) of the crude material gave *N*-octanoyl thiazolidinethione **6-6** (1.87 g, 91%) as a clear yellow oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.83 (t, J = 6.7 Hz, 3H), 1.25 (m, 10H), 1.62 (m, 2H), 3.20 (m, 2H), 3.25 (m, 2H), 4.53 (t, J = 7.5 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 201.3, 174.7, 55.9, 38.3, 31.5, 28.9, 28.2, 24.6, 22.4, 13.9; MS (EI) m/z: 245 (M^+), 212, 184, 160, 128, 119, 57 (base); IR (thin film) 3145, 2956, 1700, 1158, 1049 cm^{-1}.

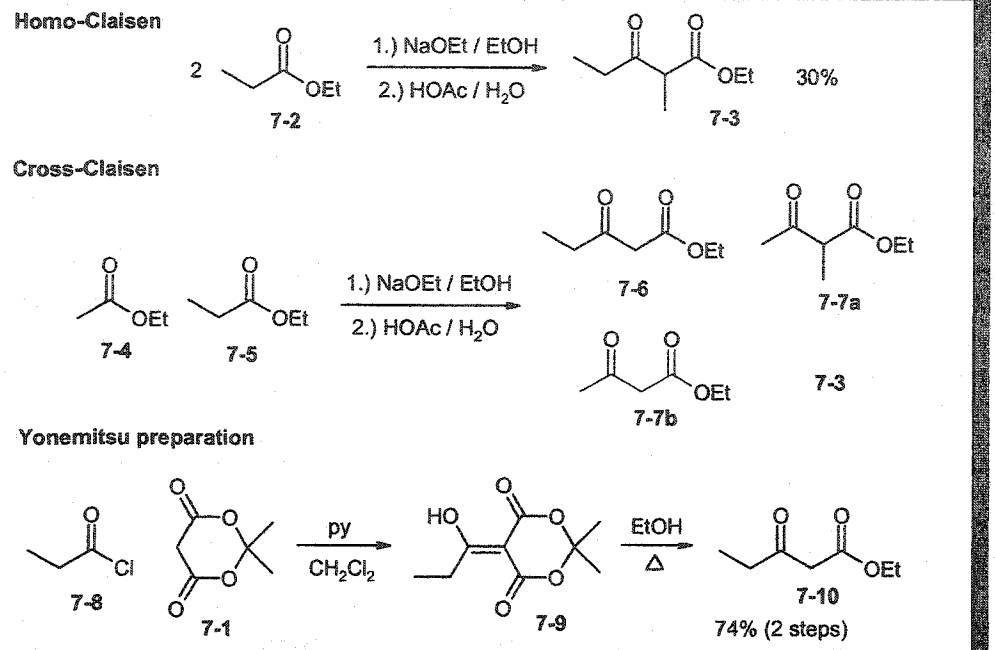
Chapter 7

Preparation of C4-Monosubstituted β-Lactones on a Glycoluril Template

In Chapters 2 to 5, the carbon-carbon bond between C-3 and C-4 in the target β-lactones was prepared through an aldol condensation or [2 + 2] cycloaddition reaction of a carbonyl compound with a carboxylic acid derivative or silyl ketene, respectively. This chapter will deal with our work towards the preparation of racemic and optically active β-lactones using a Claisen condensation to form this same carbon-carbon bond; more specifically, an intramolecular Claisen-type condensation using a glycoluril template.

7.1 Claisen Condensations in the Preparation of β-Lactones

Claisen condensations have been virtually ignored in modern organic synthesis because of the poor regioselectivity typically observed in cross-Claisen condensations (Scheme 7.1).[166] However, in 1978 Yonemitsu and co-workers demonstrated that Meldrum's acid (**7-1**) could be used in a regiospecific Claisen-type condensation to give α-unsubstituted β-keto aliphatic carboxylic acid derivatives (Scheme 7.1).[167] In 1993, Capozzi *et al.* used Noyori's asymmetric hydrogenation of α-unsubstituted β-keto esters derived from Meldrum's acid to prepare optically active β-hydroxy esters that were efficiently converted to their corresponding optically active β-lactones over 3 steps (Chapter 1.4.2, Scheme 1.34).[109] This represents the only general method for the preparation of optically active β-lactones from optically inactive starting materials not to involve a [2 + 2] cycloaddition reaction.



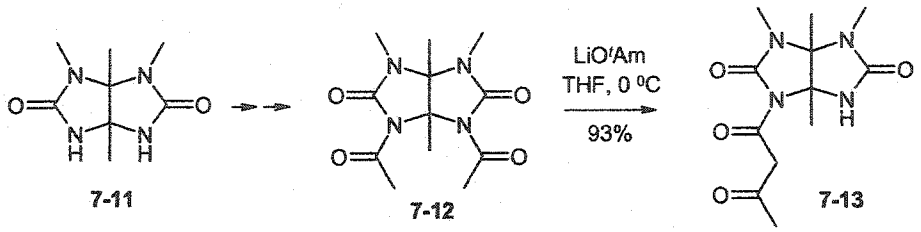
Scheme 7.1 Regioselectivity in Claisen and Claisen-Type Condensation Reactions

Using Noyori's asymmetric hydrogenation to introduce optical activity is highly attractive because it gives α-unsubstituted β-hydroxy esters in high chemical and optical yields, is compatable with a wide variety of substrates, often requires <1 mol% of commercially available BINAP-Ru(II) catalyst, and gives products of predictable absolute configuration. We decided to explore the use of a glycoluril template, previously developed in the Harrison laboratory, to prepare the requisite α-unsubstituted β-keto carboxylic acid derivatives.

7.2 Glycoluril and Monothioglycoluril Templates in Claisen-Type Condensations

In 1992 Harrison and co-workers reported a method whereby 3,4,7,8-tetramethylglycoluril (**7-11**) could be used in the biomimetic condensation of acetyl units (Scheme 7.2).[168] Glycoluril **7-11** acts as a bifunctional template with

two amide nitrogens that hold and orient two acyl groups (e.g. in **7-12**) in a manner similar to the thiols in fatty acid synthases (FAS) and polyketide synthases (PKS). When **7-12** is deprotonated to form an enolate, Claisen condensation product **7-13** is formed in nearly quantitative yield.

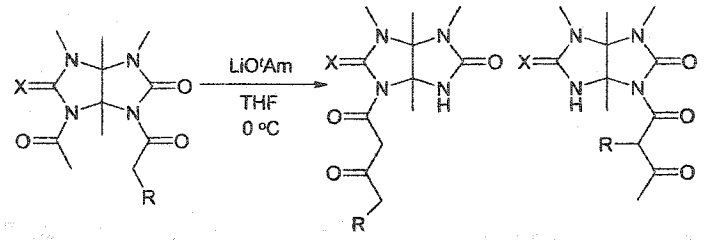


7-11 **7-12** **7-13**

Scheme 7.2 Claisen-type Condensation of Acetyl Units on a Glycoluril Template (**7-11**)

Varying one acyl group, Harrison and co-workers demonstrated that this Claisen-type condensation was regioselective (Scheme 7.3). Using this method, acetyl-decanoyl glycoluril **7-14** gave condensation product **7-15** in 65% yield as a single regioisomer.[169] However, regioselectivity was reportedly lower condensing acetyl with short-chain acyl groups such as propionyl and butanoyl. For example, acetyl-butanoyl glycoluril **7-16** gave an 81:19 mixture of regioisomers **7-17** and **7-18** in 88% yield. Both yield and regioselectivity were improved by substituting the ureido oxygen on the acetyl side of the glycoluril for sulfur; this has been demonstrated to lower the pK_a of the acetyl protons relative to butanoyl.[170] For example, acetyl-butanoyl monothioglycoluril **7-19** gave an 86:14 mixture of regioisomers **7-20** and **7-21** in 97% yield.

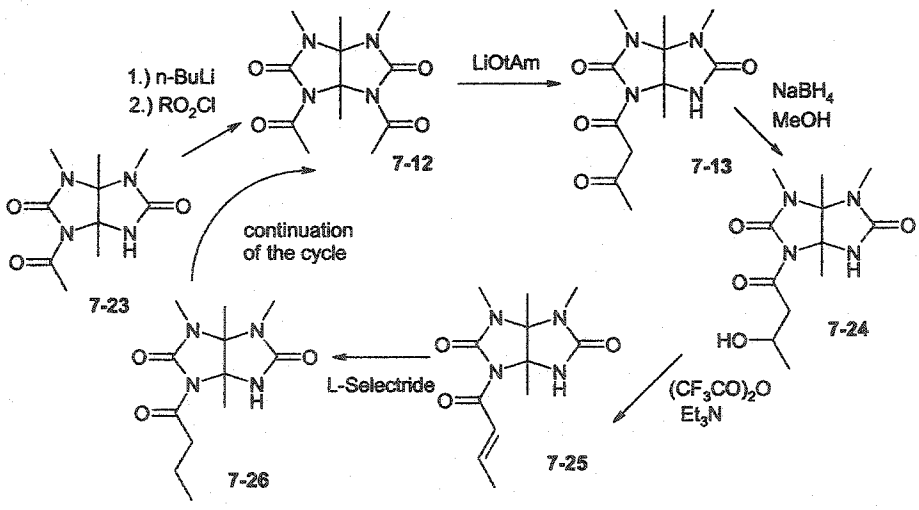
The Harrison group has also demonstrated that, through subsequent functional group manipulation, glycoluril **7-11** can be used to mimic the sequence of events that occur during iterative chain growth on polyketide synthases (Scheme 7.4).[171]



7-16: X = O, R = C_2H_5 **7-17:** X = O, R = C_2H_5 **7-18:** X = O, R = C_2H_5
7-19: X = S, R = C_2H_5 **7-20:** X = S, R = C_2H_5 **7-21:** X = S, R = C_2H_5
7-14: X = O, R = C_9H_{19} **7-15:** X = O, R = C_9H_{19} **7-22:** X = O, R = C_9H_{19}

Scheme 7.3 Cross Claisen-Type Condensations on Glycoluril and Monothioglycoluril Templates

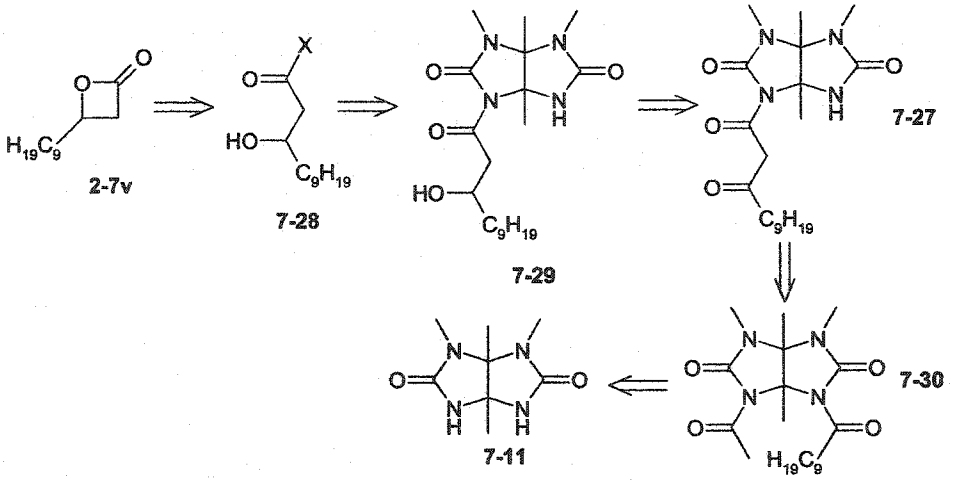
Preparing the requisite α-unsubstituted β-keto carboxylic acid derivative on a glycoluril template is attractive for several reasons: (1) a Claisen-type condensation on a glycoluril template is regioselective; (2) a glycoluril template is recyclable and could likely be attached to a solid support; (3) iterative chain growth on a glycoluril template should allow the preparation of isotopically labeled and unlabelled acyl units that are not commercially available; and (4) the process could be used for the introduction of isotopic labels into β-lactones: this is desirable for studying the mechanism of β-lactone inhibition of HMG-CoA synthase as in Chapter 2.



Scheme 7.4 Iterative Chain Growth on a Glycoluril Template

7.3 Retrosynthesis of 4-Nonyloxetan-2-one

In Chapter 5, our target molecule was 4-decyloxetan-2-one (**2-7v**), a potent inhibitor of HMG-CoA synthase. Retrosynthetic analysis of β-lactone **2-7v** involves condensation of acetyl and undecyl units on glycoluril **7-11**. However, the undecyl acyl group would have to be loaded onto the glycoluril template using commercially unavailable undecanoyl chloride. Therefore, we decided to prepare 4-nonyloxetan-2-one (**2-7c**), which involves the condensation of acetyl and decanoyl acyl units on a glycoluril template (Scheme 7.5); β-lactones **2-7c** and **2-7v** are both potent inhibitors of HMG-CoA synthase possessing IC_{50} values of 2.0 and 1.4 μM, respectively. Optical activity could eventually be introduced using Noyori's asymmetric hydrogenation of 3-oxododecanoyl glycoluril **7-27**.

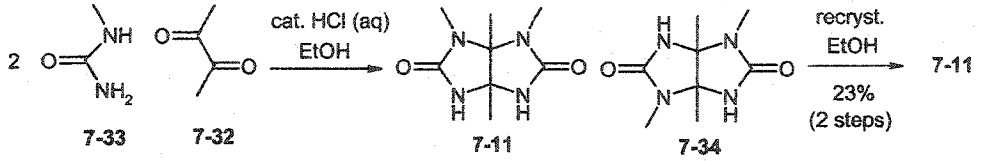


Scheme 7.5 Retrosynthesis of 4-Nonyloxetan-2-one **2-7c** Starting from Glycoluril **7-11**

7.4 Preparation of 4-Nonyloxetan-2-one Using 3,4,7,8-Tetramethylglycoluril

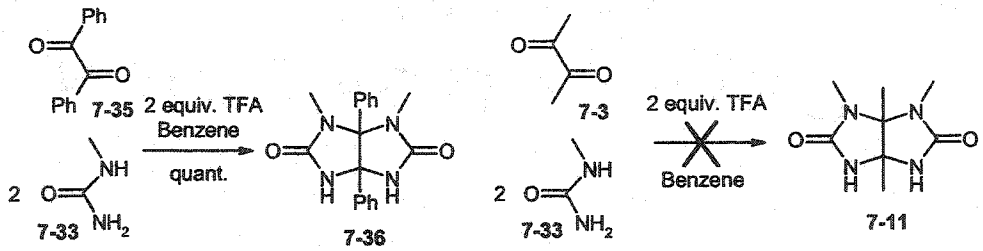
In an attempt to prepare the 14-carbon fatty acid chain of the antibiotic pramanicin, Cow reported a preparation of 3-hydroxydodecanoyl glycoluril **7-29**.

Following his synthetic method, 2,3-butanedione (**7-32**) was condensed with two equivalents of *N*-methylurea (**7-33**) in acidic ethanol to give a 1:1 mixture of regioisomers **7-11** and **7-34** (Scheme 7.6). Glycoluril **7-11** was isolated in 23% yield by recrystallization from ethanol.



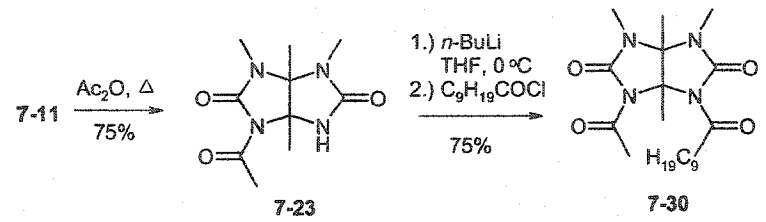
Scheme 7.6 Preparation of 3,4,7,8-Tetramethylglycoluril (**7-11**)

In 1980, Butler and Leitch condensed benzil (**7-35**) with 2 equivalents of **7-33** in the presence of an equimolar amount of trifluoroacetic acid (Scheme 7.7).[172] This gave 3,4-dimethyl-7,8-diphenylglycoluril **7-36** as a single regioisomer. However, this method was not compatible with **7-32** in the preparation of glycoluril **7-11**; an inseparable mixture of unidentified products was produced.



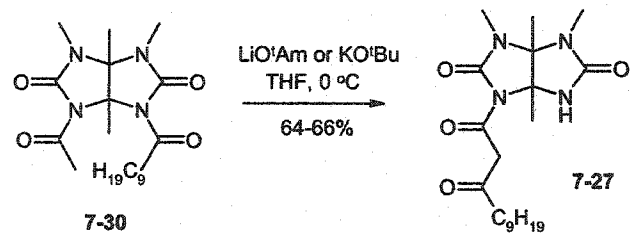
Scheme 7.7 Regioselective Preparation of Glycoluril **7-36**

Returning to the synthetic strategy of Cow, heating glycoluril **7-11** in neat acetic anhydride for 16 hours gave monoacetyl glycoluril **7-23** in 75% yield (Scheme 7.8). A second acylation reaction using LDA and decanoyl chloride gave acetyl-decanoyl glycoluril **7-30** in 75% yield (Scheme 7.8). We observed that neither acyl group could be added upon exposure of **7-11** to the corresponding acid chloride with triethylamine in chloroform.



Scheme 7.8 Acetylation and Decanoylation of Glycoluril **7-11**

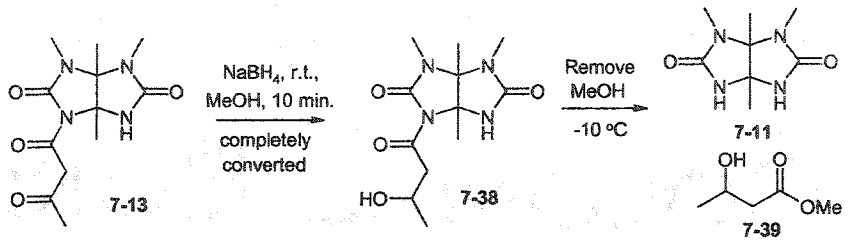
Exposure of acetyl-decanoyl glycoluril **7-30** to lithium *tert*-amylate (LiO^{t}Am) in THF according to the method of Cow gave 3'-oxododecanoyl glycoluril **7-27** in 65% yield as a single regioisomer (Scheme 7.9). Exposing acetyl-decanoyl glycoluril **7-30** to commercially available KO^{t}Bu in THF we obtained similar results (64% yield of 3'-oxododecanoyl glycoluril **7-27** as a single regioisomer).



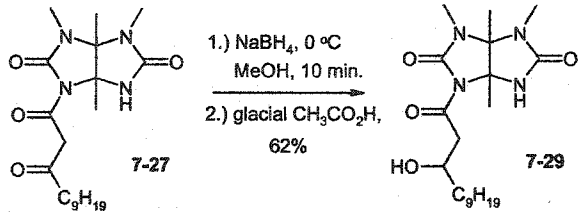
Scheme 7.9 Claisen-type Condensation of Acetyl-Decanoyl Glycoluril **7-30**

Cow reported that the reduction of 3'oxododecanoyl glycoluril **7-29** with $NaBH_4$ in methanol on a 0.1 mmol scale gave 3'-hydroxydodecanoyl glycoluril **7-37** in 79% yield. The reaction was allowed to proceed for 5 minutes before being quenched with glacial acetic acid to prevent cleavage of the 3-hydroxydodecanoyl group by sodium methoxide, as observed previously in the Harrison laboratory with 3'-oxobutanoyl glycoluril **7-13** (Scheme 7.10).[171] In our hands we obtained 3'-hydroxydodecanoyl glycoluril **7-11** in 62% yield when performed on a 1 mmol scale (Scheme 7.11). As reported by Cow, recovered starting material was the major impurity recovered, although a small amount of parent glycoluril (**7-11**) was observed, indicating cleavage. Increasing the duration of the reaction by as

little as 5 minutes significantly reduced the yield of 3'-hydroxydodecanoyl glycoluril **7-29** and the amount of starting material recovered in favor of parent glycoluril (**7-11**).



Scheme 7.10 Treatment of 3-Oxobutanoyl Glycoluril **7-13** with $NaBH_4$ Under Standard Conditions Leads to Extensive Acyl Cleavage

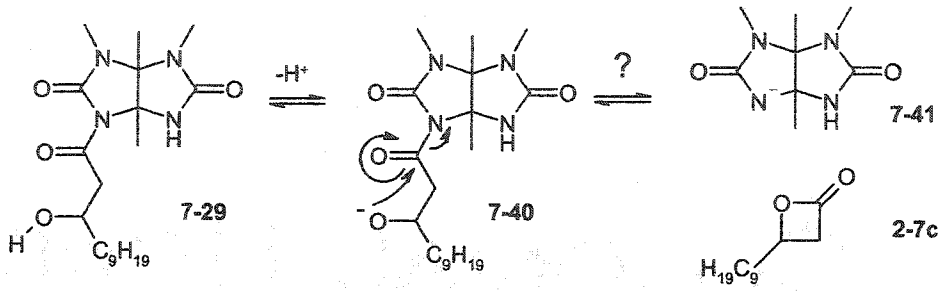


Scheme 7.11 Treatment of 3-Oxododecanoyl Glycoiluril **7-27** with $NaBH_4$

In the Harrison group a series of solvents (acetic acid, *iso*-propanol, and ethanol) and borohydride-based reducing agents ($NaBH_4$, $NaBH_3CN$ and $NaBH(OCH_3)_3$) were investigated in the reduction of 3'-oxobutanoyl glycoluril **7-13**. When the reaction was not quenched with acetic acid, 3'-hydroxybutanoyl glycoluril **7-38** was produced in <40% yield.

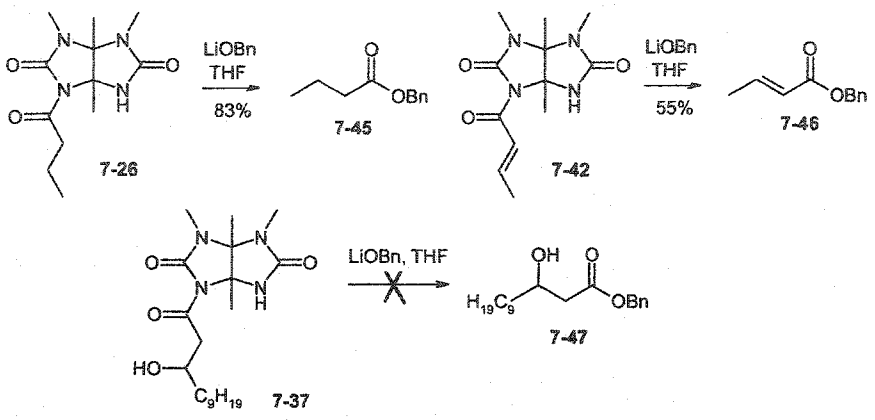
The observed sensitivity of the amido carbonyl in 3'-oxoalkanoyl glycolurils to alkoxide bases suggests that direct lactonization to form the β-lactone from the β-hydroxy acyl glycolurl template might occur if the 3-hydroxydodecanoyl moiety could effectively be converted to its alkoxide (Scheme 7.12). To test this hypothesis, 3-hydroxydodecanoyl glycoluril **7-29** was dissolved in THF and exposed to the relatively non-nucleophilic bases

triethylamine (in excess), potassium carbonate (in excess), KO^{t}Bu (1 equiv.) and LDA (1 equiv.). In all cases only starting material was recovered.

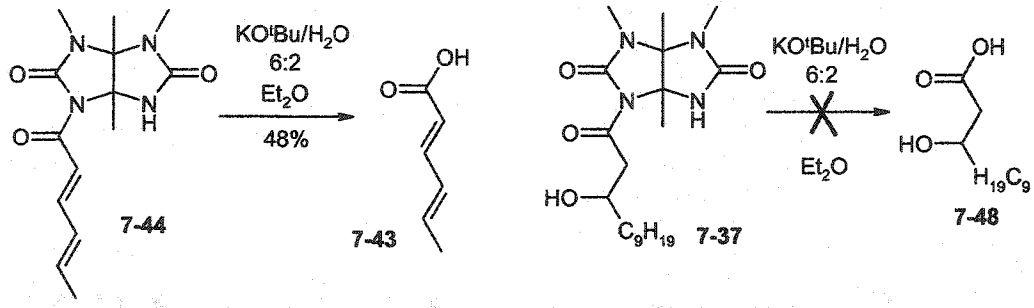


Scheme 7.12 Proposed Intramolecular Lactonization of 3'-Hydroxytridecanoyl Glycoluril **7-29**

Because LDA is certainly strong enough to furnish the requisite alkoxide, it appeared that the alkoxide was prevented from approaching the amido carbonyl at an angle acceptable for intramolecular nucleophilic attack. Hence, we attempted to remove the acyl moiety via intermolecular attack with lithium benzyloxide, which the Harrison laboratory has used to remove saturated (**7-26**) and unsaturated (**7-42**) butanoyl chains from glycoluril **7-11** (Scheme 7.13).[171] Unfortunately, only unreacted starting material was recovered upon prolonged exposure of 3'-hydroxydodecanoyl glycoluril **7-37** to lithium benzyloxide (Scheme 7.13). Similarly, prolonged exposure of 3-hydroxydodecanoyl glycoluril **7-29** to KO^{t}Bu and water, which Cow demonstrated could cleave sorbic acid (**7-43**) from monosorboyl glycoluril **7-44** in 48% yield, resulted in complete recovery of starting material (Scheme 7.14).[173]



Scheme 7.13 Lithium Benzoxide Promoted Deacylation of Acylated Glycolurils

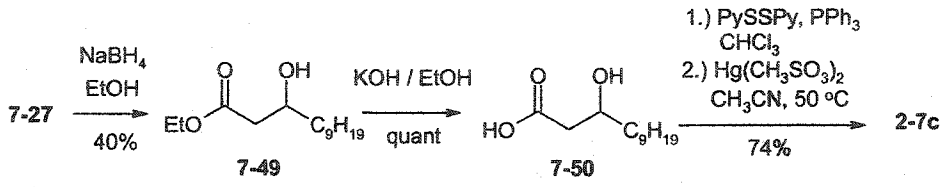


Scheme 7.14 Acyl Group Removal from Glycoluril **7-37** as the Free Acid

In contrast, we previously mentioned that overexposure to sodium borohydride in methanol quickly cleaved the 3-hydroxydodecanoyl unit from glycoluril **7-11** as its methyl ester, presumably through nucleophilic attack by sodium methoxide inadvertently generated *in situ*. This was exploited to remove the 3-hydroxydodecanoyl unit as the corresponding ester.

Gratifyingly, exposure of 3'-oxododecanoyl glycoluril **7-27** to $NaBH_4$ in ethanol for 30 minutes at room temperature afforded ethyl 3-hydroxydodecanoate (**7-49**) in 40% yield (Scheme 7.15). Following the general methodology of Roelens *et al.*[174], saponification of β-keto ester **7-49** with KOH in ethanol furnished free acid **7-50** in quantitative yield. In one pot, free acid **7-50** was

efficiently converted to its *S*-pyridyl thiol ester, and subsequently lactonized upon exposure to mercury (II) methanesulfonate to give nonyloxetan-2-one (**2-7c**) in 74% yield (Scheme 7.15).



Scheme 7.15 Conversion of 3-Oxododecanoyl Glycoluril **3-27** to β-lactone **2-7c**

In summary, a template-directed preparation of β-lactone **2-7c** on glycoluril **7-11** is possible in 10% yield from monoacetyl glycoluril **7-23**. In order to improve the practicality of the method, significant progress has to be made towards removal of the 3-hydroxyalkanoyl unit from the glycoluril template as the β-lactone, free acid, or activated carboxylic acid derivative suitable for efficient lactonization.

As discussed in Chapters 4 and 5, conversion of oxazolidinones (e.g. **4-1**, Figure 7.1) to their oxazolidinethione and thiazolidinethione (e.g. **4-25**) derivatives significantly increases the susceptibility of *N*-acyl groups to nucleophilic cleavage. Given the similarity between oxazolidinones and glycolurils, it therefore seemed reasonable to predict that *N*-acyl groups on 2,5-dithio-3,4,7,8-tetramethylglycoluril (**7-51**) would be more susceptible to nucleophilic cleavage compared to glycoluril **7-11**. We will now discuss our work towards the preparation of β-lactones using dithioglycoluril **7-51**.

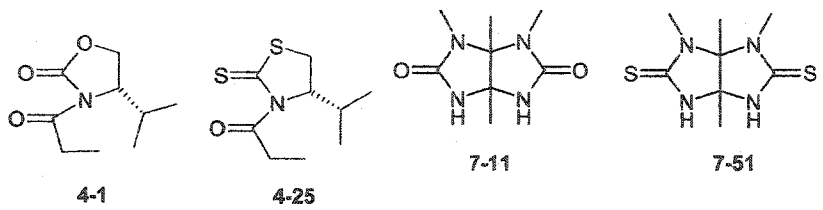
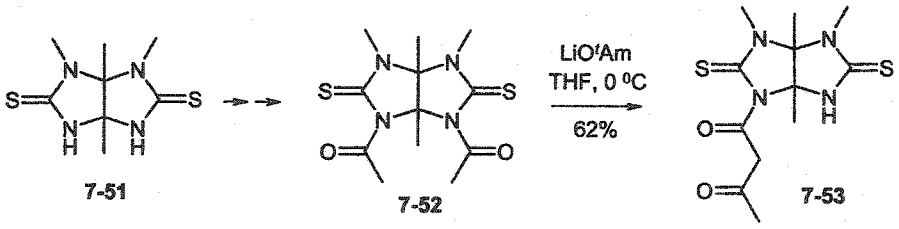


Figure 7.1 Comparison of the Structures of Several Auxiliaries: Oxazolidinone **4-1**, Thiazolidinethione **4-25**, Glycoluril **7-11** and Dithioglycoluril **7-51**

7.5 Preparation of β-Lactones Using 3,4,7,8-Tetramethyl-2,5-dithioglycoluril

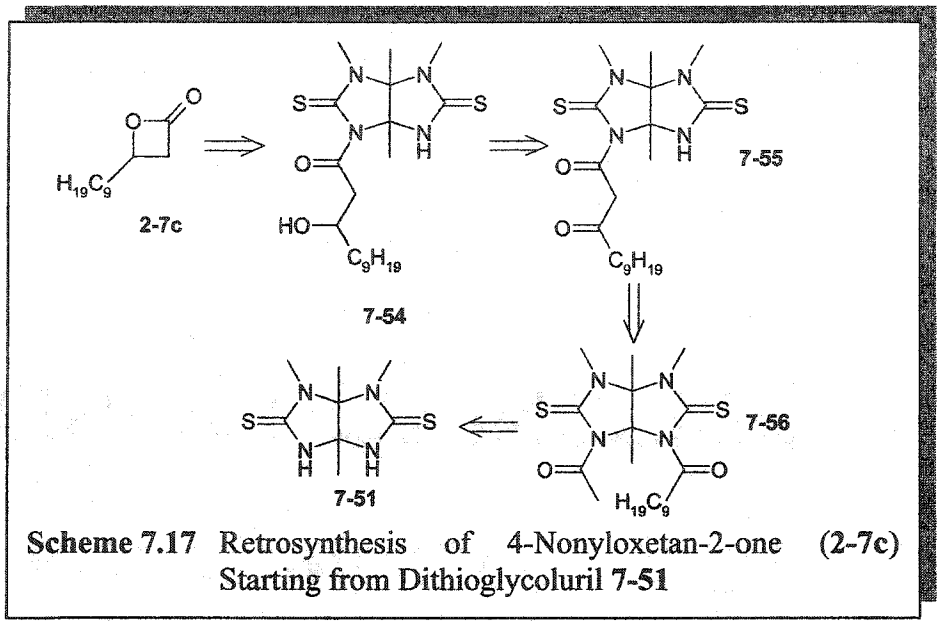
The Harrison laboratory has performed limited work using dithioglycoluril **7-51** as a template for intramolecular Claisen-type condensations. For example, diacetyl dithioglycoluril **7-52** was used in a Claisen-type condensation, but no further functional manipulations were attempted on the resulting 3'-oxobutanoyl dithioglycoluril **7-53** (Scheme 7.16).



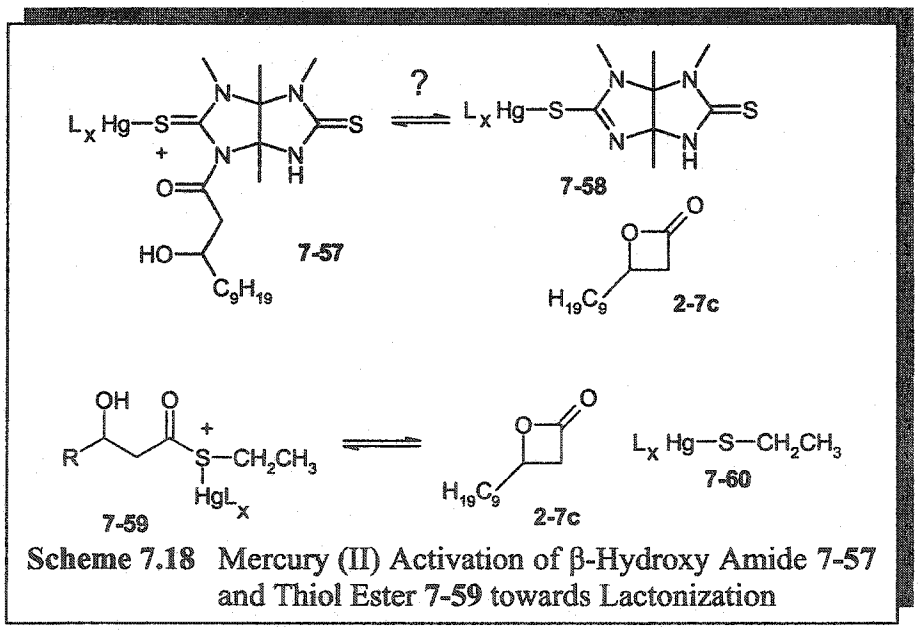
Scheme 7.16 Claisen-type Condensation on Dithioglycoluril Template **7-51**

As in Section 6.3, we chose nonyloxetan-2-one (**2-7c**) as our target lactone and proposed a similar retrosynthesis (Scheme 7.17). Dithioglycoluril **7-51** represents an attractive alternative to glycoluril **7-11** as a molecular template because of enhanced electrophilicity in the amido carbon of attached acyl

substituents. This effect should facilitate the conversion of 3-hydroxydodecanoyl dithioglycoluril **7-54** to β-lactone **2-7c** via intramolecular nucleophilic attack.



Scheme 7.17 Retrosynthesis of 4-Nonyloxetan-2-one (**2-7c**) Starting from Dithioglycoluril **7-51**



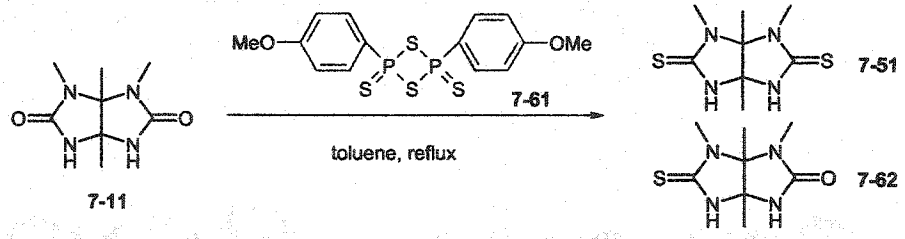
Scheme 7.18 Mercury (II) Activation of β-Hydroxy Amide **7-57** and Thiol Ester **7-59** towards Lactonization

Furthermore, we proposed that addition of thiophilic metal ions could be used to further increase electrophilicity of the amido carbonyl in **7-51**, increasing its susceptibility towards intramolecular nucleophilic attack by limiting back-

donation of the thioureido nitrogen to the amido carbonyl (Scheme 7.18). This concept is similar to Masamune's "double-activation" method for the preparation of β-lactones from β-hydroxy thiol esters (Scheme 7.18).[175]

7.5.1 Preparation of 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril

As reported in his thesis, Cow heated glycoluril **7-11** in toluene at reflux overnight with an excess of Lawesson's reagent (**7-61**) (3 equiv.) and generated dithioglycoluril **7-51** in 60% yield; these conditions have previously been reported in the preparation of thioamides from amides. However, in our hands excess Lawesson's reagent and its by-products proved difficult to remove from the desired product because dithioglycoluril **7-51** is virtually insoluble in many common organic solvents or in water.



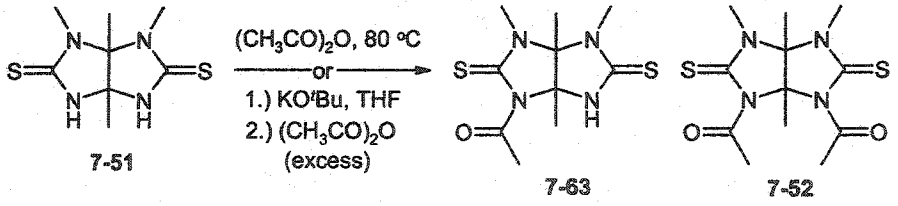
Scheme 7.19 Preparation of 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril (**7-51**)

Cow reported that if a single equivalent of Lawesson's reagent was used, the reaction gave a mixture rich in monothiol glycoluril **7-62**. Considering that 1 equivalent of Lawesson's reagent is theoretically capable of thiolating 4 equivalents of amide, this was likely the result of poor solubility of both glycolurils **7-11** and **7-61** in toluene, so a longer reaction time was used to improve the yield of dithionated product **7-51**. Upon heating at reflux for 72 h (compared to 16 h) the reaction proceeded smoothly with 1 equivalent of **7-61**. Lawesson's by-products were simply removed by washing the product with

methanol, hexanes and diethyl ether, respectively, to give a pure, 10.6:1 mixture of dithio- (**7-51**) and monothioglycoluril **7-62** in 86% yield. This material could often be used without purification (i.e. monoacetyl monothioglycolurils can be efficiently separated from monoacetyl dithioglycolurils using flash column chromatography) or recrystalized from ethanol (~100 mL ethanol / 1 g solid) (24%).

7.5.2 First Acylation Reaction of 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril

Cow reported that sulfur facilitates the rapid acetylation of glycoluril templates. Heating dithioglycoluril **7-61** in neat acetic anhydride at 80°C (compared to 120°C used to acylate glycoluril **7-11**) gave monoacetyl dithioglycoluril **7-63** in 63% yield, where the major impurity was diacetyl dithioglycoluril **7-52** (11%) (Scheme 7.20). Alternatively, Cow reacted the template with a stoichiometric amount of KO^{t}Bu in THF, followed by excess acetic anhydride, to give monoacetyl dithioglycoluril **7-63** in 85% yield (Scheme 7.20). Glycoluril **7-11** was unreactive under these conditions.



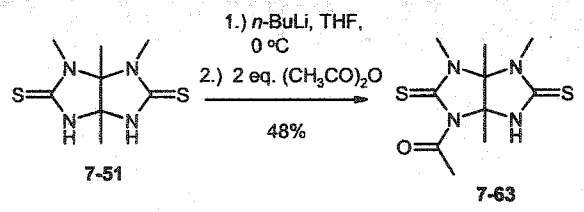
Scheme 7.20 Acetylation of Dithioglycoluril **7-51** Using Acetic Anhydride

In both methods, Cow prepared monoacetyl dithioglycoluril **7-63** on a scale <1 mmol. In our hands on a larger scale, both methods furnished monoacetyl dithioglycoluril **7-52** in somewhat lower yield: acetylation in neat

acetic anhydride and KO^{t}Bu / acetic anhydride furnished monoacetyl dithioglycoluril **7-63** in 17 and 49% yield, respectively.

Furthermore, both methods are impractical for the introduction of expensive isotopically labeled acetyl units; both require large excesses (>10 equiv) of acetic anhydride.

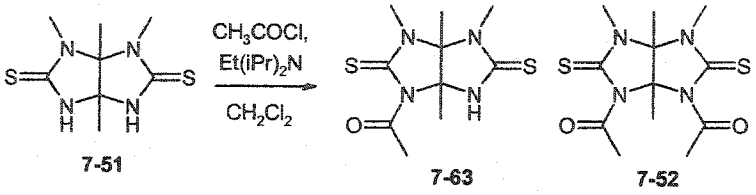
Surprisingly, exposure of dithioglycoluril **7-51** to 1 equiv KO^{t}Bu, followed by 2 equiv of acetic anhydride, gave no monoacetyl dithioglycoluril **7-63** after prolonged stirring (24 h) at room temperature. Conversely, exposing dithioglycoluril **7-51** to 1 equiv *n*-BuLi, followed by 2 equiv acetic anhydride gave monoacetyl dithioglycoluril **7-63** in 48% yield (Scheme 7.21). Presumably, HO^{t}Bu and residual KO^{t}Bu were responsible for deacylating any monoacetyl dithioglycoluril **7-63** produced and / or consuming acetic anhydride, whereas deprotonation with *n*-BuLi produces non-nucleophilic butane gas.



Scheme 7.21 *n*-BuLi Promoted Acetylation of Dithioglycoluril **7-51**

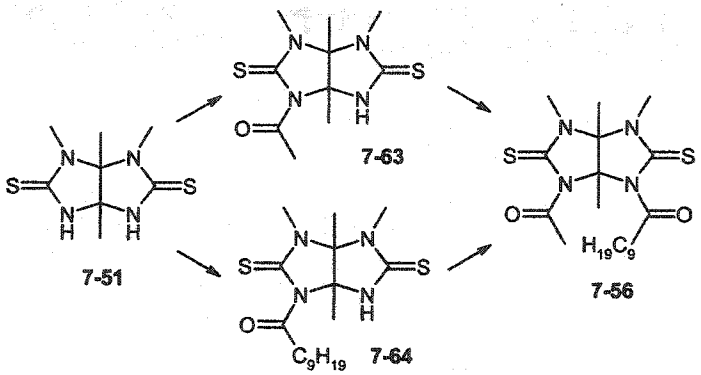
From our work in Chapters 4 and 5 involving acylation of thiazolidinethiones, we decided to expose dithiotemplate **7-51** to acetyl chloride / diisopropylethylamine in dichloromethane (Scheme 7.22). Unfortunately, exposure to 1 equivalent of acetyl chloride / diisopropylethylamine furnished a mixture of monoacetyl dithioglycoluril **7-63** and diacetyl dithioglycoluril **7-52** (~2:1, respectively). The prevalence of diacetyl dithioglycoluril **7-52** over desired monoacetyl dithioglycoluril **7-63** appears to be a result of the relative insolubility of the starting material **7-51** in organic solvents. That is, relatively insoluble starting template is initially acetylated to give soluble monoacetyl dithioglycoluril

7-63, which undergoes a relatively rapid second acetylation to give diacetyl dithioglycoluril **7-52** (Scheme 7.22).



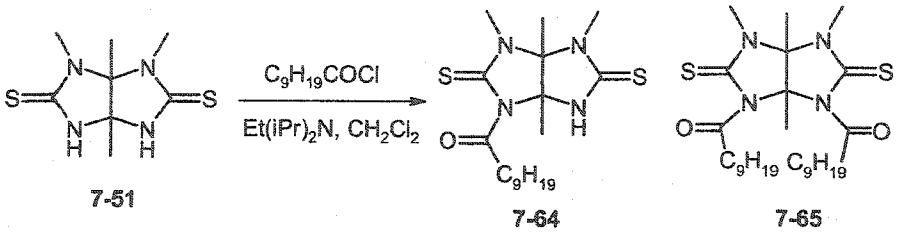
Scheme 7.22 Acetylation of Dithioglycoluril **7-51** Using Acetyl Chloride and Hunig's Base

Because there are two potential routes to acetyl-decanoyl dithioglycoluril **7-56**, we decided apply this method to the preparation of monodecanoyl dithioglycoluril **7-64** (Scheme 7.23). It was believed that because of increased steric bulk in the decanoyl moiety - compared to an acetyl moiety – the reaction would favor monodecanoyl dithioglycoluril **7-64** over didecanoyl dithioglycoluril **7-55**.



Scheme 7.23 Preparative Routes to Acetyl-Decanoyl Dithioglycoluril **7-56**

Unfortunately, decanoylation proceeded in a similar manner to acetylation. Exposure of dithioglycoluril **7-51** to decanoyl chloride / diisopropylethylamine in dichloromethane furnished didecanoyl dithioglycoluril **7-65** and monodecanoyl dithioglycoluril **7-64** (~2:1, respectively) (Scheme 7.24).

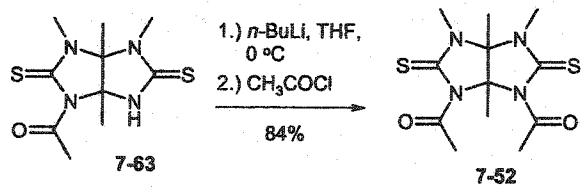


7-51 7-64 7-65

Scheme 7.24 Decanoylation of Dithioglycoluril **7-51**

7.5.3 Second Acylation Reaction of 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril

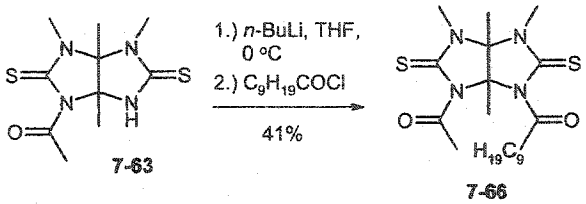
As reported in his thesis, Cow - through the addition of *n*-BuLi in THF at 0°C, followed by addition of acetyl chloride - prepared diacetyl dithioglycoluril **7-52** from **7-63** in 84% yield (Scheme 7.25). After successfully repeating this experiment, we unfortunately found the reaction inadequate for the production of mixed diacyl dithioglycolurils.



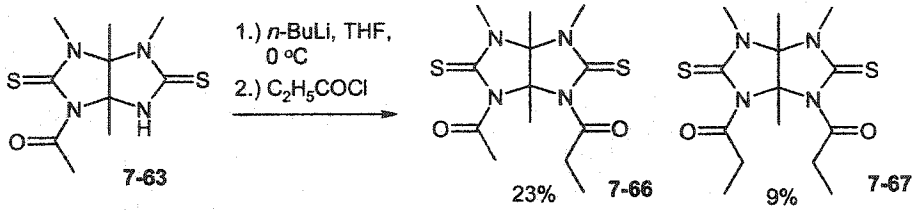
7-63 **7-52**

Scheme 7.25 Acetylation of Monoacetyl Dithioglycoluril **7-63**

Exposure of monoacetyl dithioglycoluril **7-63** to *n*-BuLi in THF at 0°C, followed by decanoyl chloride, gave acetyl-decanoyl dithioglycoluril **7-56** in 41% yield (Scheme 7.26). However, exposure of monoacetyl dithioglycoluril **7-63** to *n*-BuLi in THF at 0°C, followed by propionyl chloride, gave an inseparable 2.6:1 mixture of acetyl-propionyl (**7-66**) and dipropionyl dithioglycoluril **7-67** in 32% yield (Scheme 7.27). Similar results were obtained substituting *n*-BuLi for LDA.

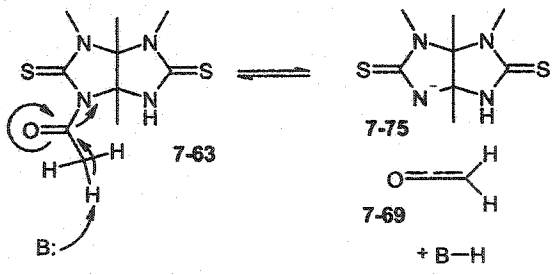


Scheme 7.26 Decanoylation of Monoacetyl Dithioglycoluril 7-63



Scheme 7.27 Propionylation of Monoacetyl Dithioglycoluril 7-63

Furthermore, exposure to *n*-BuLi or LDA at 0°C completely converted monoacetyl dithioglycoluril **7-63** to parent dithioglycoluril template in ~30 minutes. This led us to hypothesize that such strong bases remove the acetyl moiety of monoacetyl dithioglycoluril **7-63** as the ketene (**7-69**) (Scheme 7.28).



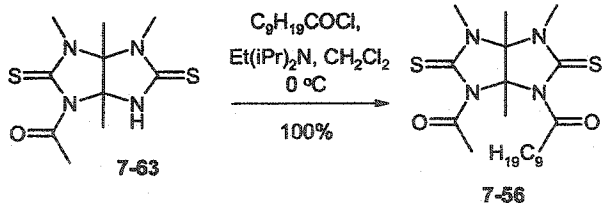
Scheme 7.28 Base Induced Deacylation of Monoacetyl Dithioglycoluril 7-63

These results can be used to explain the formation of dipropionyl dithioglycoluril **7-67** as a side-production the preparation of acetyl-propionyl dithioglycoluril **7-66**, through one of two possible mechanisms: (1) base-promoted deacetylation of monoacetyl dithioglycoluril **7-63** gives dithioglycoluril **7-51**, which then goes on to react with 2 equiv of propionyl chloride; and (2)

base-promoted deacetylation of the product acetyl-propionyl dithioglycoluril **7-67** gives monopropionyl dithioglycoluril, which goes on to react with 1 equiv of propionyl chloride. With acetyl-decanoyl dithioglycoluril **7-64**, coiling of the decanoyl chain may discourage deacetylation by shielding the α-protons of the acyl moiety.

Clearly, milder conditions are required to acylate monoacetyl dithioglycoluril **7-63**. In the previous section we discussed acylation of dithioglycoluril **7-51** upon exposure to an acid chloride in the presence of an equimolar amount of diisopropylethylamine in dichloromethane; further acylation of the desired monoacyl dithioglycoluril **7-63** could not be prevented because of its superior solubility in organic solvents relative to dithioglycoluril **7-51**. Because monoacetyl dithioglycoluril **7-63** only possesses one potential acylation site, over-acylation will not be a concern. Thus, exposure to decanoyl chloride / diisopropylethylamine in dichloromethane appears to be a mild potential route to acetyl-decanoyl dithioglycoluril **7-56**.

Exposure of monoacetyl dithioglycoluril **7-63** to two equiv of decanoyl chloride and diisopropylethylamine in dichloromethane at 0°C gave acetyl-decanoyl dithioglycoluril **7-56** in 100% yield (Scheme 7.29). Monodecanoyl (**7-64**), didecanoyl (**7-65**), or parent dithioglycoluril (**7-51**) were not isolated.



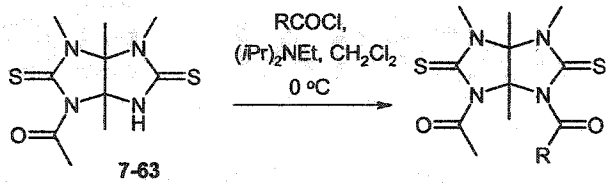
7-63 **7-56**

Scheme 7.29 Decanoylation of Monoacetyl Dithioglycoluril **7-63**

In order to test the generality of the second acylation reaction, monoacetyl dithioglycoluril **7-63** was exposed to several other acid chlorides in the presence

of diisopropylethylamine in dichloromethane at 0°C. The results are summarized in Table 7.1.

For every acid chloride used, the acylation reaction was clean, with starting material as the only other product isolated. However, exposure of monoacetyl dithioglycoluril **7-63** to 2 equiv *p*-methoxybenzoyl chloride and 2 equiv diisopropylethylamine in dichloromethane gave *p*-methoxybenzoyl-acetyl dithioglycoluril **7-76** in <10% yield; this is probably because the electron-withdrawing methoxy moiety lowers the electrophilicity of the benzoyl carbonyl. Exposure of monoacetyl dithioglycoluril **7-63** to 2 equiv *p*-methoxybenzoyl chloride and 2 equiv triethylamine in dichloromethane significantly improved the yield of *p*-methoxybenzoyl-acetyl dithioglycoluril **7-76** (43%, Entry 10) as the less bulky amine is more likely to form a highly reactive acylium ion with the acid chloride.



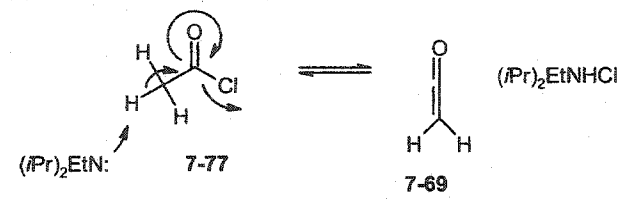
7-63

Entry	R	% yield	Product
1	CH_3	46	**7-52**
2	CH_2CH_3	98	**7-66**
3	$CH(CH_3)_2$	96	**7-70**
4	$C(CH_3)_3$	97	**7-71**
5	$CH_2(CH_2)_5CH_3$	101	**7-72**
6	$CH_2(CH_2)_7CH_3$	100	**7-56**
7	Ph	93	**7-73**
8	*p*-NO_2Ph	80	**7-74**
9	*m*-ClPh	90	**7-75**
10	*p*-MeOPh	43*	**7-76**

* 2 equiv Et_3N used

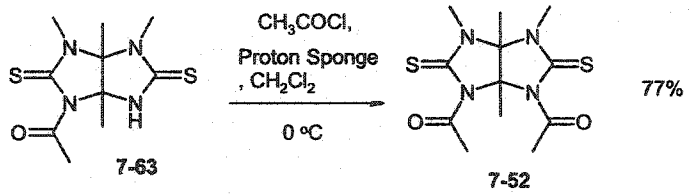
Table 7.1 Diisopropylethylamine-Promoted Acylation of Monoacetyl Dithioglycoluril **7-63**

In the exposure of monoacetyl dithioglycoluril **7-63** to 2 equiv acetyl chloride and 2 equiv diisopropylethylamine, the relatively low yield of diacetyl dithioglycoluril **7-52** produced (46%) is likely a result of acetyl chloride being consumed to give ketene **7-69** (Scheme 7.30).



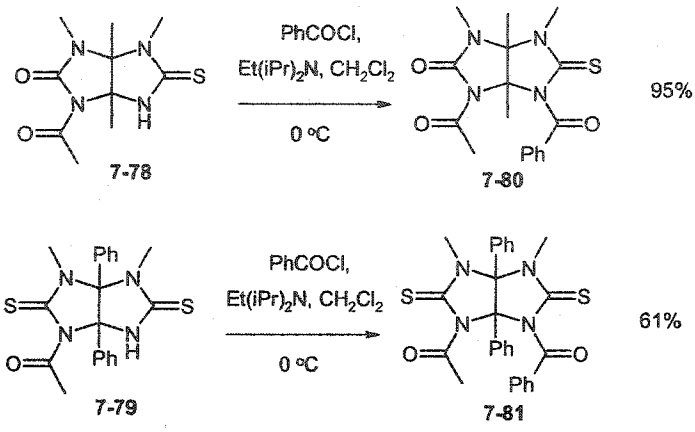
Scheme 7.30 Triethylamine-Promoted Formation of Ketene **7-69** from Acetyl Chloride (7-77)

In order to suppress ketene formation, diisopropylethylamine was replaced by 1,8-bis(dimethylamino)naphthalene (Proton Sponge®) because of the increased steric bulk and lowered pK_a value of the latter relative to diisopropylethylamine. Exposure of monoacetyl dithioglycoluril **7-63** to 2 equiv acetyl chloride and 2 equiv Proton Sponge® gave diacetyl dithioglycoluril **7-52** in 77% yield (Scheme 7.31).



Scheme 7.31 Proton Sponge Promoted Acetylation of Monoacetyl Dithioglycoluril **7-63**

In addition to monoacetyl dithioglycoluril **7-63**, other monoacetyl thiolated glycolurils have been efficiently acylated. For example, monoacetyl monothioglycoluril **7-78** and monoacetyl diphenyldithioglycoluril **7-79** were acylated upon exposure to benzoyl chloride and diisopropylethylamine in dichloromethane at 0°C in 95 and 61% yield, respectively (Scheme 7.32).

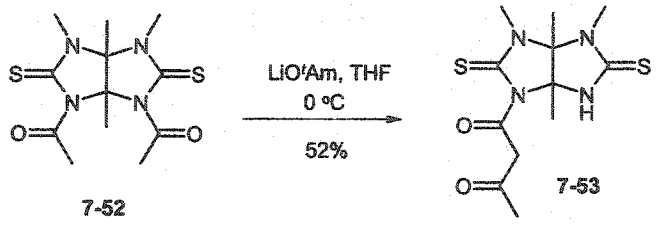


Scheme 7.32 Acylation of Monoacetyl Monothioglycoluril **7-78** and Diphenyldithioglycoluril **7-81**

Now that we have an efficient preparation of acetyl-decanoyl dithioglycoluril **7-56**, we will turn our attention towards the Claisen-type condensation of the two acyl moieties.

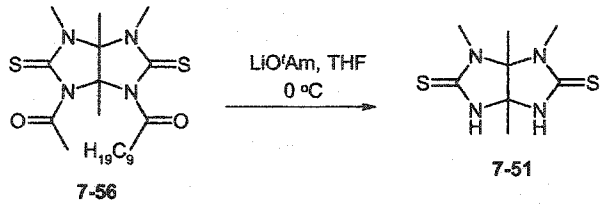
7.5.4 Claisen-Type Condensation on 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril

Cow reported that condensation of diacetyl dithioglycoluril **7-52** under standard conditions with LiO^{t}Am in THF at 0°C gave 3-oxobutanoyl dithioglycoluril **7-53** in 62% yield (Scheme 7.33). Repeating this reaction on a larger scale, we isolated 3-oxobutanoyl dithioglycoluril **7-53** in 52% yield.



Scheme 7.33 Claisen-Type Condensation of Diacetyl Dithioglycoluril **7-52**

However, exposure of acetyl-decanoyl dithioglycoluril **7-56** to LiO^{t}Am in THF at 0°C resulted in deacylation to give parent dithioglycoluril **7-51** (Scheme 7.34). Following the reaction by TLC, deacylation began with the addition of the alkoxide and was complete in less than 1 hour at 0°C; no intermediates were observed *en route* to parent dithioglycoluril **7-51** by TLC or ^{1}H-NMR (200 MHz) analysis of the crude reaction material.

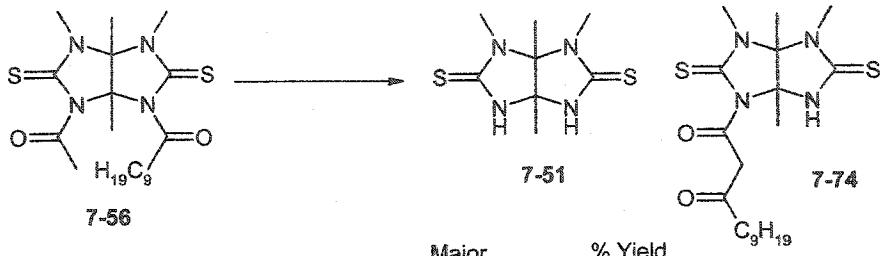


7-56 **7-51**

Scheme 7.34 Attempted Claisen-type Condensation of Acetyl-Decanoyl Dithioglycoluril **7-56**

Various condensation conditions were explored and are summarized in Table 7.3. Exposure of acetyl-decanoyl dithioglycoluril **7-56** to LiO^{t}Am, LiO^{t}Bu and KO^{t}Bu in THF at 0°C resulted in complete deacylation. Substitution of an alkoxide for the less nucleophilic base, LDA, also resulted in complete and clean deacylation. Conversely, exposure to weaker bases, such as triethylamine and diisopropylamine, furnished unreacted starting material as the only product.

Upon further experimentation exposing several diacyl dithioglycolurils to LiO^{t}Am we found that only acetyl and benzoyl groups would act as electrophilic acyl partners to undergo a Claisen-type condensation with an acetyl moiety. Other aliphatic acyl moieties appeared to undergo complete deacylation. The results are summarized in Table 7-4.



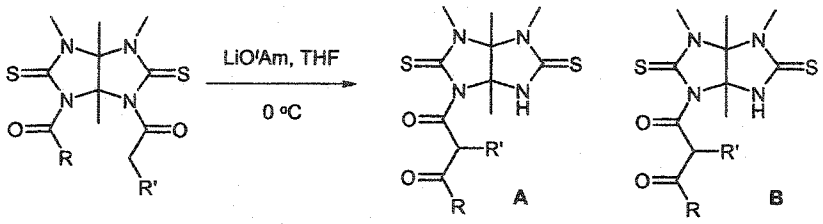
Entry	Conditions	Major Prod.	% Yield Cond. Prod.
1	LiO^{t}Am, THF, 0 °C, 1h	**7-51**	0
2	LiO^{t}Bu, THF, 0 °C, 1h	**7-51**	0
3	KO^{t}Bu, THF, 0 °C, 1h	**7-51**	0
4	LDA, THF, 0 °C, 1h	**7-51**	0
5	neat Et_3N, 48 h	**7-56**	0
6	neat $(iPr)_2NH$, 48 h	**7-56**	0

Table 7.2 Unsuccessful Claisen-Type Condensation Conditions for Acetyl-Decanoyl Dithioglycoluril **7-56**

These results have proven difficult to explain. In both successful Claisen-type condensations, varying amounts of deacetylation are observed. For diacetyl dithioglycoluril **7-52**, monoacetyl dithioglycoluril **7-63** was produced in ~15% yield. For acetyl-benzoyl dithioglycoluril **7-73**, monobenzoyl dithioglycoluril **7-76** was produced in 21% yield, and no monoacetyl dithioglycoluril **7-3** was recovered. Both results imply that deacetylation is occurring through ketene formation promoted by alkoxide bases. However, this effect does not explain how two acyl moieties can be efficiently removed using 1 equivalent of alkoxide in acetyl-propionyl (**7-66**), acetyl-octanoyl (**7-72**) and acetyl-decanoyl dithioglycoluril (**7-56**).

Comparing acetyl-benzoyl dithioglycoluril **7-73** with acetyl-decanoyl dithioglycoluril **7-56**, one could envision an initial deacetylation step furnishing amide anions **7-84** and **7-70**, respectively (Scheme 7.35). The decanoyl moiety has two α-protons that could be removed in either an inter- or an intramolecular manner, leading to formation of octanoylketene (**7-74**). The benzoyl moiety is devoid of α-protons, and therefore cannot be converted to a ketene. Such a mechanism could explain how, in acetyl-decanoyl dithioglycoluril **7-56**, 1

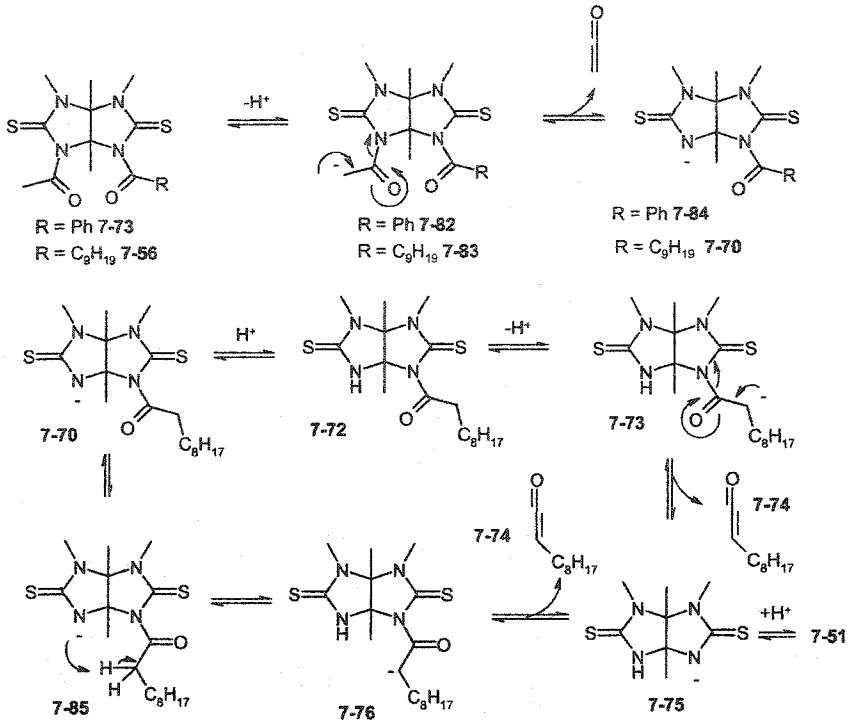
equivalent of alkoxide could remove 2 acyl moieties, while in acetyl-benzoyl dithioglycoluril **7-73**, 1 equivalent of alkoxide can deacetylate, or promote the desired intramolecular Claisen-type condensation. However, such a mechanism does not satisfactorily explain why, with the diacyl dithioglycolurils that were completely deacylated upon exposure to alkoxides, no monoacyl dithioglycolurils or condensation products were isolated.



Entry	Starting Material	R	R'	% Yield A	% Yield B	Product
1	**7-52**	CH_3	H	52	0	**7-53a**
2	**7-86**	CH_3	CH_3	0	0	**7-51**
3	**7-66**	CH_2CH_3	CH_3	0	0	**7-51**
4	**7-72**	CH_3	$CH_2(CH_2)_4CH_3$	0	0	**7-51**
5	**7-56**	CH_3	$CH_2(CH_2)_6CH_3$	0	0	**7-51**
6	**7-73**	CH_3	Ph	50	0	**7-76a**

Table 7.3 Attempted Claisen-type Condensation of Several Diacyl Dithioglycolurils

Because of the unexpected difficulties experienced with the intramolecular Claisen-type condensation, this project was halted in order to re-evaluate the overall synthetic strategy with respect to β-lactones. Alternative methods of promoting the intramolecular Claisen-type condensation are proposed in Chapter 8.2.2 that specifically address the problem of deacylation observed on a dithioglycoluril template.



Scheme 7.35 Possible Mechanism for Base-Promoted Deacylation of Diacyl Dithioglycolurils **7-56** and **7-73**.

7.6 Summary

Using glycoluril **7-11**, 4-nonyloxetan-2-one (**2-7c**) was successfully prepared in 10% yield from decanoyl chloride. Although the yield was somewhat disappointing, owing to the unanticipated additional synthetic steps required to convert the 3-hydroxydodecanoyl glycoluril derivative into a thiol ester suitable for lactonization, this sequence represents the first preparation of a β-lactone on a glycoluril template. Notably, the sequence mimics the biosynthetic assembly of more complex β-lactones, such as Antibiotic 1233 A.[176]

Substituting dithioglycoluril **7-51** for glycoluril **7-11**, we were able to develop methodology whereby acetyl and decanoyl groups could be loaded onto a glycoluril template under mild conditions (acid chloride / $Et(iPr)_2N$) in high yield.

This opens the door for a wide range of base sensitive substrates to be potentially loaded onto a glycoluril template. Unfortunately, acetyl-decanoyl dithioglycoluril **7-56**, required for the preparation of 4-nonyl oxetan-2-one (**2-7c**), and several other diacyl dithioglycolurils underwent complete deacylation upon exposure to various alkoxide bases.

7.7 Experimental

Preparation of 3,4,7,8-Tetramethylglycoluril (7-11)

Following the procedure of Sun, 2,3-butanedione (22.5 mL, 260 mmol) was added to a suspension of *N*-methylurea (38.0 g, 514 mmol) in absolute ethanol (65 mL).[177] After the addition of hydrochloric acid (15 drops), the solution clarified and an exothermic reaction took place. Product appeared as a precipitate after 20 min. The mixture was stirred for an additional 30 min before being cooled to 0°C for 1 h. The precipitate was removed by Buchner filtration and recrystallized twice from ethanol (60 mL ethanol/1 g crude solid) to give glycoluril **7-11** (11.7 g, 23%) as colorless crystals. The proton NMR spectrum of the product was identical to that reported by Sun: ^{1}H NMR (D_2O, 200 MHz) δ: 1.42 (s, 3H), 1.50 (s, 3H), 2.76 (s, 6H).

Preparation of 1-Acetyl-3,4,7,8-tetramethylglycoluril (7-23)

Method A: Using the method of Sun, glycoluril **7-11** (2.0 g, 10 mmol) was suspended in neat acetic anhydride (20 mL) and heated at reflux for 20 hours. The clear solution was then concentrated by rotary evaporation and chloroform (20 mL) was added. Solid material was filtered off and the filtrate was

concentrated by rotary evaporation. The crude material was recrystallized overnight from ethyl acetate (20 mL) to give monoacetyl glycoluril **7-23** (1.80 g, 75%) as colorless crystals. The proton NMR spectrum of the product was identical to that reported by Sun: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.56 (s, 3H), 1.69 (s, 3H), 2.48 (s, 3H), 2.87 (s, 3H), 3.02 (s, 3H), 5.99 (s, 1H).

Preparation of 1-Decanoyl-7-Acetyl-3,4,7,8-Tetramethylglycoluril (7-30)

Using the method of Cow, *n*-BuLi (8.5 mL, 12 mmol, 1.4 M in hexanes) was added to a solution of monoacetyl glycoluril **7-23** (2.57 g, 10.7 mmol) in THF (120 mL) at 0°C. After 30 min, decanoyl chloride (2.75 mL, 12.8 mmol) was added and the solution was allowed to stir for an additional hour while gradually warming to room temperature. Sodium bisulfate was added (25 mL, 1 M in water) and the solution was extracted with chloroform (3 x 60 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated using rotary evaporation. Flash column chromatography of the crude residue (30% hexanes in EtOAc) gave acetyl-decanoyl glycoluril **7-30** (3.14 g, 75%) as a colorless oil. The proton NMR spectrum was identical to that reported by Cow: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.81 (t, J = 6.6 Hz, 3H), 1.07-1.39 (m, 10H), 1.45 (s, 3H), 1.45-1.68 (m, 4H), 1.88 (s, 3H), 2.41 (s, 3H), 2.57-3.01 (m, 2H), 2.91 (s, 6H).

Preparation of 1-(3'-Oxododecanoyl)-3,4,7,8-Tetramethylglycoluril (7-27)

Using the method of Cow, *n*-BuLi (7.1 mL, 10 mmol, 1.4 M in hexanes) was added to a solution of *t*-amyl alcohol (1.74 mL, 16.0 mmol) in THF (10 mL) at 0°C. This solution was added dropwise to a solution of acetyl-decanoyl

glycoluril **7-30** (3.14 g, 8.0 mmol) in THF (130 mL), also at 0°C. After stirring 2 h, aqueous $NaHSO_4$ (20 mL, 1 M) was added and the solution was extracted with chloroform (3 x 60 mL). The combined organic layers were then washed with brine (70 mL), dried over sodium sulfate and concentrated using rotary evaporation. Flash column chromatography of the crude material (EtOAc) gave 3'-oxododecanoyl glycoluril **7-27** (2.07 g, 65%) as a white powder. The proton NMR spectrum of the product was identical to that reported by Cow: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.82 (t, J = 6.7 Hz, 3H), 1.05-1.34 (m, 12H), 1.40-1.61 (m, 2H), 1.50 (s, 3H), 1.69 (s, 3H), 2.33-2.60 (m, 2H), 2.80 (s, 3H), 2.92 (s, 3H), 3.51 (d, J = 16.2 Hz, 1H), 4.27 (d, J = 16.2 Hz, 1H), 6.03 (s, 1H).

Preparation of 1-(3'-Hydroxydodecanoyl)-3,4,7,8-Tetramethylglycoluril (7-29)

Using the method of Cow, sodium borohydride (70 mg, 1.8 mmol) was added portionwise to a solution of 3'-oxododecanoyl glycoluril **7-27** (50 mg, 0.13 mmol) in methanol (30 mL) at 0°C. After stirring 5 minutes, glacial acetic acid (1 mL) was added and the solution was concentrated using rotary evaporation. The crude material was then purified by flash column chromatography (EtOAc) to give 3'-hydroxydodecanoyl glycoluril **7-29** (31 mg, 62%) as a white solid. The proton NMR spectrum of the product was identical to that reported by Cow: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.81 (t, J = 6.7 Hz, 3H), 1.04-1.57 (m, 17H), 1.50 (s, 3H), 1.65 (s, 3H), 2.79 (s, 3H),2.79-2.90 (m, 1H), 2.94 (s, 3H), 3.20 (dd, J = 2.5, 17.0 Hz, 1H), 3.99 (m, 1H), 6.59 (s, 1H).

Preparation of 3-Hydroxy Dodecanoic Acid (7-50)

To a solution of β-hydroxy ester **7-49** (821 mg, 3.36 mmol) in ethanol at 0°C, 4 N KOH (1.5 mL) was added dropwise. The resultant solution was vigorously shaken and kept at 0°C before being carefully acidified with 1 N HCl at 0°C. The solution was saturated with NaCl, extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The solvent was removed using rotary evaporation and the crude material was recrystallized from ethyl acetate – hexanes to give β-hydroxy acid **7-50** (801 mg, 108%) as a fluffy white powder: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, J = 6.6 Hz, 3H), 1.27 (m, 14H), 1.48 (m, 2H), 2.46 (dd, J = 16.6, 8.5 Hz, 1H), 2.59 (dd , J = 16.6, 3.7 Hz, 1H), 4.04 (m, 1H), 6.27 (s, 2H); MS(EI) *m/z*: 217, 199, 181, 89 (base); IR (thin film) 3397, 3021, 2931, 2858, 1709, 1420, 1046 cm^{-1}.

Preparation of 4-Nonyloxetan-2-one (2-7c)

To a solution of β-hydroxy acid **7-50** (43.2 mg, 0.20 mmol) in chloroform (2 mL), 2,2'-dipyridyl disulfide (66 mg, 0.30 mmol) and (84 mg, 0.32 mmol) were added. After stirring for 5 min, the solution was added dropwise to a vigorously stirred suspension of mercury (II) methanesulfonate (78 mg) in acetonitrile (4 mL) at 50°C. After stirring an additional 10 minutes at 50°C, the reaction mixture was filtered while hot and the precipitate was washed with chloroform (3 x 4 mL). The solvent was removed by rotary evaporation and the crude residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to give β-lactone **2-7c** (28 mg, 74%) as a clear and colorless oil. For the intermediate thiol ester: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, J = 6.8 Hz, 3H), 1.26 (m, 16H), 1.49 (m, 2H), 2.68 (s, 1H), 2.82 (dd, J = 7.8, 15.9 Hz, 1H), 2.92 (dd, J = 3.9, 15.9 Hz, 1H), 4.12 (m, 1H), 7.31 (ddd, J = 1.2, 4.8, 7.4 Hz, 1H), 7.62

(dt, J = 1.0, 7.7 Hz), 1H), 7.76 (dt, J = 1.9, 7.7 Hz, 1H), 8.64 (m, 1H). For β-lactone **2-7c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.50 (m, 1H), 3.50 (dd, J = 16.2, 5.7 Hz, 1H), 3.05 (dd, J = 16.2, 4.3 Hz, 1H), 1.79 (m, 2H), 1.26 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 168.3, 71.3, 42.9, 34.7, 31.9, 29.4 (3C), 29.3, 29.1, 24.9, 22.6, 14.1; IR (thin film) 2926, 1830 cm^{-1}.

Preparation of 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril (7-51)

Lawesson's reagent (26.1 g, 68.1 mmol) and glycoluril **7-11** (13.5 g, 68.1 mmol) were suspended in toluene (150 mL). The solution was heated at reflux for 3 days and then stirred at room temperature for 2 days. The suspension was filtered by Buchner filtration and the filtrite was washed with methanol (100 mL), hexanes (100 mL) and diethyl ether (100 mL). This gave crude product (13.44 g, 86%) as a fine beige powder which could be used without further purification. Proton NMR of the crude product indicated a mixture of dithio- (**7-51**) and monothioglycoluril (**7-62**) products (10.6:1 ratio) that was identical to that reported by Cow. For dithioglycoluril **7-51**: ^{1}H NMR (CD_3OD, 200 MHz) δ: 1.49 (s, 3H), 1.62 (s, 3H), 3.18 (s, 6H). For monothioglycoluril **7-62**: ^{1}H NMR (CD_3OD, 200 MHz) δ: 1.49 (s, 3H), 1.59 (s, 3H), 2.89 (s, 3H), 3.16 (s, 3H). An analytical sample of dithioglycoluril **7-51** (0.78 g) was obtained recrystallizing crude material (3.0 g) from EtOH (~300 mL); the low recrystallization yield was a result of low solubility of mono- (**7-62**) and dithioglycoluril (**7-51**) in most common organic solvents.

Preparation of 1-Acetyl-3,4,7,8-Tetramethyl-2,5-dithioglycoluril (7-63)

Method A: Using the method of Cow, potassium *tert*-butoxide (580 mg, 5.16 mmol) was added to a suspension of dithioglycoluril **7-51** (1.0 g) in THF (80 mL). After stirring for 30 min, acetic anhydride (2 mL) was added and the suspension was allowed to stir for an additional 2 h before the solvent was removed using rotary evaporation. Flash column chromatography of the crude material (1:1 EtOAc-hexanes) gave monoacetyl dithioglycoluril **7-63** (572 mg, 49%) as a fine white crystalline powder. **Method B:** A solution of dithioglycoluril **7-51** (150 mg, 0.66 mmol) in THF (10 mL) at 0°C was treated with *n*-BuLi (480 μL, 1.5 M in hexanes, 0.72 mmol). After stirring for 20 min, acetic anhydride (124 μL, 1.32 mmol) was added and stirring was continued for 1 h, during which time the mixture warmed slowly to room temperature. Aqueous $NaHSO_4$ (5 mL, 1 M) was added, and the mixture was extracted with $CHCl_3$ (2 x 8 mL). The organic extracts were combined, washed with water, dried over Na_2SO_4, and concentrated using rotary evaporation. Flash column chromatography of the crude material (1:1 ethyl acetate-hexanes) gave monoacetyl dithioglycoluril **7-63** (85.2 mg, 48%) as a fine white crystalline powder. The proton NMR spectrum was identical to that reported by Cow: ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.58 (s, 3H), 1.69 (s, 3H), 2.76 (s, 3H), 3.12 (s, 3H), 3.29 (s, 3H).

Preparation of 1,7-Diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-52)

Method A: Using the method of Cow, a solution of monoacetyl dithioglycoluril **7-63** (52 mg, 0.19 mmol) in THF (10 mL) at 0°C was treated with *n*-BuLi (128 μL, 0.21 mmol, 1.5 M in hexanes). After stirring for 20 min, acetyl chloride (16 μL, 0.23 mmol) was added and the mixture was stirred for 1 h,

during which time the mixture warmed slowly to room temperature. The reaction was quenched with aqueous $NaHSO_4$ (5 mL, 1 M), and the product was extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were washed with water (10 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. Flash column chromatography of the crude material (30% hexanes in EtOAc) gave diacetyl dithioglycoluril **7-52** (47 mg, 78%) as a fine white powder. **Method B:** Proton Sponge® (79 mg, 0.18 mmol) and acetyl chloride (26 μL, 0.37 mmol) were sequentially added to a solution of monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL) at 0°C. The mixture was stirred for 4 h, during which time the mixture warmed slowly to room temperature. The mixture was then washed with aqueous HCl (3 x 2 mL, 0.5 M), dried over Na_2SO_4 and concentrated using rotary evaporation. Flash column chromatography of the crude material (30% hexanes in EtOAc) gave diacetyl dithioglycoluril **7-52** (44 mg, 77%) as a fine white powder. **Method C:** Proton Sponge® (140 mg, 0.65 mmol) and acetyl chloride (46 μL, 0.65 mmol) were added to a solution of dithioglycoluril **7-63** (50 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) at 0°C. The mixture was stirred for 3 h, during which time the mixture warmed slowly to room temperature. The mixture was then washed with aqueous HCl (3 x 2 mL, 0.5 M), dried over Na_2SO_4 and concentrated using rotary evaporation. Flash column chromatography of the crude material (30% hexanes in EtOAc) gave diacetyl dithioglycoluril **7-52** (57 mg, 84%) as a fine white powder. Proton NMR was identical to that reported by Cow: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.55 (s, 3H), 1.87 (s, 3H), 2.74 (s, 6H), 3.23 (s, 6H).

General Preparation of Mixed Diacyl Monothio- and Dithioglycolurils

Two equivalents of amine base and 2 equivalents of acyl chloride were added to a solution of the starting glycoluril in CH_2Cl_2 (~0.07 M) at 0°C. The

mixture was slowly warmed to room temperature and stirred until TLC indicated that the starting material was consumed or no further change was observed (2-4 h). The mixture was then washed with aqueous HCl (0.5 M), dried over Na_2SO_4, and concentrated using rotary evaporation. The diacyl monothio- or dithioglycoluril product was separated from unreacted starting material using flash column chromatography (EtOAc–hexanes eluent).

Preparation of 1-Acetyl-7-Propionyl-3,4,7,8-Tetramethyl-2,5-Dithioglycoluril (7-66)

Method A: A solution of monoacetyl dithioglycoluril **7-63** (380 mg, 1.40 mmol) in THF (25 mL) at 0°C was treated with *n*-BuLi (1.03 mL, 1.54 mmol). After stirring 20 min, propionyl chloride (146 μL, 1.68 mmol) was added and the solution was allowed to stir 4 h, during which time the mixture slowly warmed to room temperature. Aqueous $NaHSO_4$ (10 mL, 1 M) was added and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed using rotary evaporation. Flash column chromatography of the crude material (1:1 EtOAc-hexanes) gave a 2.62:1 mixture of acetyl-propionyl (**7-66**) and dipropionyl dithioglycoluril **7-86** (150 mg, 32%). (For dipropionyl dithioglycoluril **7-67**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ:1.17 (t, J = 7.3 Hz, 6H), 1.56 (s, 3H), 1.89 (s, 3H), 2.93 (dq, J = 7.2, 17.7 Hz, 2H), 3.23 (s, 6H), 3.44 (dq, J = 7.2, 17.7 Hz, 2H).) **Method B:** Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (65 mg, 0.24 mmol) was exposed to diisopropylethylamine (83 μL, 0.48 mmol) and propionyl chloride (42 μL, 0.48 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-propionyl dithioglycoluril **7-66** (77 mg, 98%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.15 (t, J = 7.3 Hz, 3H), 1.55 (s, 3H), 1.87 (s, 3H), 2.72 (s,

3H), 2.90 (dq, J = 7.2, 17.8 Hz), 3.22 (s, 3H), 3.46 (dq J = 7.3, 17.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 177.7, 177.1, 172.8 (2C), 87.0, 85.2, 34.2, 31.2, 31.1, 28.9, 18.7, 15.2, 8.9; MS(EI) *m/z*: 328, 143, 142 (base), 141, 86, 84; HRMS calcd. for $C_{13}H_{20}N_4S_2O_2$ 328.1028, found 328.1028; IR (thin film) 3021, 2986, 2944, 1738, 1689, 1477, 1307, 1099 cm^{-1}.

Preparation of 1-Acetyl-7-isobutyryl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-70)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to diisopropylethylamine (64 μL, 0.37 mmol) and isobutyryl chloride (39 μL, 0.37 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-isobutyryl dithioglycoluril **7-70** (59 mg, 96%) as a fine white powder: ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.10 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.54 (s, 3H), 1.91 (s, 3H), 2.70 (s, 3H), 3.17 (s, 3H), 3.31 (s, 3H), 4.39 (septet, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 180.3, 177.9, 173.1, 87.8, 85.2, 35.7, 31.5, 30.6, 29.4, 20.0, 18.7, 18.4, 15.1; MS(EI) *m/z*: 343, 273, 184, 142 (base) ; IR (thin film) 3022, 2981, 2941, 2879, 1727, 1443, 1433, 1407, 1388, 1375, 1321, 1245, 1217, 1154, 1116, 1093, 949 cm^{-1}.

Preparation of 1-Acetyl-7-pivaloyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-71)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to diisopropylethylamine (64 μL, 0.37 mmol) and pivaloyl chloride (45 μL, 0.37

mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-pivaloyl dithioglycoluril **7-71** (62 mg, 97%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.29 (s, 9H), 1.55 (s, 3H), 1.88 (s, 3H), 2.73 (s, 3H), 3.22 (s, 3H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 186.0, 180.2, 177.0, 172.3, 87.7, 86.5, 44.9, 30.8, 30.6, 28.5, 28.1, 18.0, 16.0; MS(EI) *m/z*: 356, 272, 226, 184, 142 (base); IR (thin film) 3021, 1737, 1700, 1686, 1480, 1305, 1105 cm^{-1}.

Preparation of 1-Acetyl-7-octanoyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-72)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to diisopropylethylamine (64 μL, 0.37 mmol) and octanoyl chloride (63 μL, 0.37 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-octanoyl dithioglycoluril **7-72** (73 mg, 101%) as a clear pale oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.86 (t, J = 6.6 Hz, 3H), 1.27 (m, 8H), 1.55 (s, 3H), 1.63 (m, 2H), 1.88 (s, 3H), 2.73 (s, 3H), 2.96 (ddd, J = 17.0, 8.8, 6.4 Hz, 1H), 3.22 (s, 3H), 3.24 (s, 3H), 3.41 (ddd, J = 17.0, 8.8, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 177.9, 176.3, 172.9, 87.2, 85.2, 40.3, 31.6, 31.2, 29.0, 24.8, 22.6, 18.7, 15.2, 14.0; MS(EI) *m/z*: 398, 273, 215, 184, 142 (base); HRMS calcd. for $C_{18}H_{30}N_4S_2O_2$ 398.1810, found 398.1802; IR (thin film) 2955, 2930, 2858, 1738, 1693, 1468, 1397, 1306, 1270, 1229, 1101, 1025 cm^{-1}.

Preparation of 1-Acetyl-7-decanoyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-56)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to diisopropylethylamine (64 μL, 0.37 mmol) and decanoyl chloride (76 μL, 0.37 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-decanoyl dithioglycoluril **7-56** (77 mg, 100%) as a clear pale oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.87 (t, J = 6.6 Hz, 3H), 1.11 (m, 14 H), 1.54 (s, 3H), 1.60 (m, 2H), 1.88 (s, 3H), 2.74 (s, 3H), 2.96 (ddd, J = 17.0, 8.8, 6.3 Hz, 1H), 3.22 (s, 3H), 3.25 (s, 3H), 3.41 (ddd, J = 17.0, 8.8, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 177.9, 176.3, 173.0, 87.2, 85.2, 40.3, 31.9, 31.2, 31.1, 29.4, 24.8, 22.6, 18.8, 15.2, 14.1; MS(EI) *m/z*: 426, 273, 243, 184, 142 (base); HRMS calcd. for $C_{20}H_{34}N_4S_2O_2$ 426.2123, found 426.2142; IR (thin film) 2956, 2928, 2857, 1735, 1693, 1639, 1465, 1360, 1307, 1269, 1224, 1147, 1101 cm^{-1}.

Preparation of 1-Acetyl-7-benzoyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-73)

Method A: Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to diisopropylethylamine (64 μL, 0.37 mmol) and benzoyl chloride (43 μL, 0.37 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-benzoyl dithioglycoluril **7-73** (64 mg, 93%) as a fine white powder. **Method B:** Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to Proton Sponge® (79 mg, 0.37 mmol) and benzoyl

chloride (43 μL, 0.37 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-benzoyl dithioglycoluril **7-73** (68 mg, 98%) as a fine white powder. **Method C:** Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (50 mg, 0.18 mmol) was exposed to triethylamine (51 μL, 0.37 mmol) and benzoyl chloride (43 μL, 0.37 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-benzoyl dithioglycoluril **7-73** (63 mg, 93%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.70 (s, 3H), 2.04 (s, 3H), 2.70 (s, 3H), 3.23 (s, 3H), 3.37 (s, 3H), 7.36 – 7.57 (m, 3H), 7.73 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 179.9, 172.5, 170.3, 134.6, 133.3, 130.4, 128.3, 86.8, 86.2, 31.7, 30.8, 28.2, 19.0, 16.5; MS(EI) *m/z*: 376, 246, 193, 142 (base); IR (thin film) 2985, 2938, 1712, 1689, 1485, 1402, 1368, 1350, 1333. 1306, 1270, 1240, 1111, 1101, 1023, 755 cm^{-1}.

Preparation of 1-Acetyl-7-benzoyl-3,4,7,8-tetramethyl-2-monothioglycoluril (7-80)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl monothioglycoluril **7-78** (53 mg, 0.21 mmol) was exposed to diisopropylethylamine (57 μL, 0.32 mmol) and benzoyl chloride (37 μL, 0.32 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-benzoyl monothioglycoluril **7-80** (72 mg, 95%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.66 (s, 3H), 2.04 (s, 3H), 2.37 (s, 3H), 3.12 (s, 3H), 3.20 (s, 3H), 7.33-7.54 (m, 3H), 7.71 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 179.9, 170.6, 170.3, 152.4, 134.7, 133.2, 130.2, 128.2, 82.8, 82.5, 30.9, 27.2, 25.0, 19.4, 16.4; MS(EI) *m/z*: 360, 181, 126 (base), 105, 77; HRMS calcd. for $C_{17}H_{20}N_4S_2O_3$ 360.1256, found 360.1267;

IR (thin film) 3030, 2939, 1734, 1701, 1482, 1408, 1366, 1333, 1288, 1254, 1218, 1114, 1097, 1052, 1018 cm^{-1}.

Preparation of 1-Acetyl-7-benzoyl-3,4-diphenyl-7,8-tetramethyl-2,5-dithioglycoluril (7-81)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-79** (146 mg, 0.37 mmol) was exposed to diisopropylethylamine (132 μL, 0.74 mmol) and benzoyl chloride (85 μL, 0.74 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% EtOAc in hexanes) of the crude material gave acetyl-benzoyl dithioglycoluril **7-81** (112 mg, 61%) as a fine white powder: ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.50 (s, 3H), 3.23 (s, 3H), 3.39 (s, 3H), 6.50 (d, J = 7.8 Hz, 2H), 6.70 – 7.82 (m, 13H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 182.6, 179.1, 172.2, 168.6, 134.3, 133.6, 132.6, 130.5, 130.2, 129.8, 128.8, 128.7, 128.5, 127.8, 127.6, 127.2, 125.0, 94.8, 93.3, 33.9, 33.3, 27.8; MS(EI) *m/z*: 500, 397, 396, 267, 266 (base), 265, 207, 149, 118, 105, 77; HRMS calcd. for $C_{27}H_{24}N_4S_2O_2$ 500.1341, found 500.1319; IR (thin film) 3066, 3020, 2932, 2859, 1730, 1708, 1487, 1349, 1319, 1022 cm^{-1}.

Preparation of 1-Acetyl-7-(*p*-Methoxybenzoyl)-3,4,7,8-Tetramethyl-2,5-dithioglycoluril (7-76)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (20 mg, 0.074 mmol) was exposed to triethylamine (30 μL, 0.22 mmol) and *p*- methoxybenzoyl chloride (38 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-*p*-methoxybenzoyl dithioglycoluril **7-76**

(12 mg, 43%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.68 (s, 3H), 2.01 (s, 3H), 2.67 (s, 3H), 3.24 (s, 3H), 3.35 (s, 3H), 3.83 (s, 3H), 6.87 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 180.1, 177.3, 172.4, 169.3, 163.9, 132.8, 127.1, 113.8, 86.7, 86.2, 55.4, 31.6, 30.8, 28.1, 18.9, 16.5.

Preparation of 1-Acetyl-7-(*m*-Chlorobenzoyl)-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-75)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (20 mg, 0.074 mmol) was exposed to diisopropylethylamine (38 μL, 0.22 mmol) and *m*-chlorobenzoyl chloride (39 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-*m*-chlorobenzoyl dithioglycoluril **7-75** (27 mg, 90%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.70 (s, 3H), 2.03 (s, 3H), 3.23 (s, 3H), 3.38 (s, 3H), 7.31 (t, J = 7.9 Hz, 1H), 7.47-7.49 (m, 1H), 7.54-7.56 (m, 1H), 7.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 179.7, 177.4, 172.6, 169.2, 136.5, 134.4, 133.1, 130.3, 129.4, 128.4, 86.8, 86.2, 31.8, 30.8, 28.1, 19.1, 16.5; MS(EI) *m/z*: 410, 267, 265, 224, 222, 156, 139 (base), 111, 84; HRMS calcd. for $C_{17}H_{19}N_4S_2O_2Cl$ 410.0638, found 410.0645.

Preparation of 1-Acetyl-7-(*p*-nitrobenzoyl)-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-74)

Using the general method for the preparation of diacyl dithioglycolurils, monoacetyl dithioglycoluril **7-63** (20 mg, 0.074 mmol) was exposed to diisopropylethylamine (19 μL, 0.11 mmol) and *p*-nitrobenzoyl chloride (21 mg,

0.11 mmol) in CH_2Cl_2 (2.5 mL). Flash column chromatography (30% hexanes in EtOAc) of the crude material gave acetyl-*p*-nitro benzoyl dithioglycoluril **7-74** (25 mg, 80%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.72 (s, 3H), 2.05 (s, 3H), 2.77 (s, 3H), 3.21 (s, 3H), 3.40 (s, 3H), 7.81 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 179.3, 177.4, 172.7, 168.8, 150.0, 140.2, 131.0, 123.3, 86.7, 86.3, 31.9, 30.8, 19.1, 16.4; MS(EI) *m/z*: 421, 391, 314, 272, 142 (base), 141, 120, 84; HRMS calcd. for $C_{17}H_{19}N_5S_2O_4$ 421.0878, found 421.0861.

Preparation of 1,7-Dipropionyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-86)

Diisopropylethylamine (114 μL, 0.65 mmol) and propionyl chloride (57 μL, 0.65 mmol) were added to a suspension of dithioglycoluril **7-51** (50 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) at 0°C. The solution clarified over 10 minutes and was allowed to stir for 4 h, during which time it slowly warmed to room temperature. The mixture was washed with aqueous HCl (3 x 2 mL, 0.5 M), dried over Na_2SO_4, and concentrated by rotary evaporation. Flash column chromatography of the crude material (CH_2Cl_2) gave dipropionyl dithioglycoluril **7-86** (31 mg, 41%) as a fine white powder: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (t, J = 7.3 Hz, 6H), 1.56 (s, 3H), 1.89 (s, 3H), 2.93 (dq, J = 7.2, 17.7 Hz, 2H), 3.23 (s, 6H), 3.44 (dq, J = 7.2, 17.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 177.9, 177.2, 87.2, 85.3, 34.2, 31.1, 18.8, 15.4, 9.0; MS(EI) *m/z*: 342, 198, 174, 142 (base); HRMS calcd. for $C_{14}H_{22}N_4S_2O_2$ 342.1184, found 342.1177; IR (thin film) 3022, 2981, 2942, 1741, 1691, 1477, 1305, 1068 cm^{-1}.

Preparation of 3-Oxopropanoyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-53a)

Using the method of Cow, a solution of *tert*-amyl alcohol (45 μL, 0.23 mmol) in THF (5 mL) at 0°C was treated with *n*-BuLi (53 μL, 0.23 mmol). After stirring for 30 min at 0°C, the solution was cannulated into a solution of diacetyl dithioglycoluril **7-52** (60 mg, 0.19 mmol) in THF (10 mL) at 0°C. After stirring for 2 h, the reaction mixture was quenched with $NaHSO_4$ (5 mL, 1 M), and extracted into $CHCl_3$ (3 x 10 mL). The organic layers were washed with water (10 mL) and brine (10 mL), and concentrated using rotary evaporation. Flash column chromatography (1:1 EtOAc-hexanes) of the crude material gave 3'-oxobutanoyl dithioglycoluril **7-53a** (31 mg, 52%) as a clear and colourless oil. The proton NMR spectrum of the product was identical to that reported by Cow: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.79 (s, 3H), 2.27 (s, 3H), 3.17 (s, 3H), 3.30 (s, 3H), 3.90 (d, J = 16.8 Hz, 1H), 5.09 (d, J = 16.8 Hz, 1H), 7.28 (s, 1H).

Preparation of 1-(3'-phenyl-3'-oxopropanoyl)-3,4,7,8-tetramethyl-2,5-dithioglycoluril (7-76a)

Modifying the method of Cow, a solution of *tert*-amyl alcohol (45 μL, 0.23 mmol) in THF (5 mL) at 0°C was treated with *n*-BuLi (53 μL, 0.23 mmol). After stirring for 30 min at 0°C, it was cannulated into a solution of acetyl-benzoyl dithioglycoluril **7-73** (71 mg, 0.19 mmol) in THF (10 mL) at 0°C. After stirring for 2 h, the reaction mixture was quenched with $NaHSO_4$ (5 mL, 1 M), extracted into $CHCl_3$ (3 x 10 mL), washed with water (10 mL) and brine (10 mL), and concentrated using rotary evaporation. Flash column chromatography (1:1 EtOAc-hexanes) of the crude material gave an inseparable mixture (49 mg) of 3'-oxo-3-phenylpropionyl dithioglycoluril **7-76a** (50%) and monobenzoyl

dithioglycoluril **7-87** (21%) as a clear and colourless oil. For 3-oxo-3-phenylpropionyl dithioglycoluril **7-76a** (2.77:1 mixture of keto and enol tautomers) :^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.64 (s, 3H), 1.64 (s, 3H, enol), 1.83 (s, 3H, enol), 1.86 (s, 3H), 3.18 (s, 3H), 3.19 (s, 3H, enol), 3.27 (s, 3H), 3.36 (s, 3H, enol), 3.41 (s, 1H, enol), 4.36 (d, J = 16.6 Hz, 1H), 5.79 (d, J = 16.6 Hz, 1H), 7.24 (s, 1H), 7.34-7.59 (m, 3H), 7.86 (d, J = 7.3 Hz, 2H, enol), 7.91 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 193.1, 181.3, 181.1, 178.0, 177.5, 172.0, 169.4, 136.2, 133.5, 132.4, 131.9, 129.1, 128.7, 128.2, 128.0, 126.7, 90.3, 86.6, 85.8, 83.0, 50.0, 31.8, 31.6, 30.1, 19.5, 18.7, 16.1, 16.0; MS(EI) *m/z*: 376, 334, 292, 291, 187, 147, 142, 122, 105 (base), 77; HRMS calcd. for $C_{17}H_{20}N_4S_2O_2$: 376.1028, found: 376.1018. For monobenzoyl dithioglycoluril **7-87**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.70 (s, 3H), 1.80 (s, 3H), 3.25 (s, 3H), 3.28 (s, 3H), 7.31 (s, 1H), 7.34-7.60 (m, 5H); MS(EI) *m/z*:334, 265, 152, 149, 135, 88, 86, 84 (base); HRMS calcd. for $C_{15}H_{18}N_4S_2O$: 334.0920, found: 334.0911.

Chapter 8

Conclusions and Future Work

8.1 Conclusions

As indicated in Chapter 1, the overall goal of this thesis was to expand known methods of β-lactone preparation. Because of our laboratories interest in Antibiotic 1233 A (**1-58**), we decided to focus primarily on 1,2-disubstituted and C4-monosubstituted β-lactones.

In Chapter 2, we examined known methods for the preparation of 1,2-disubstituted and C4-monosubstituted β-lactones. We found that a one-pot, tandem Mukaiyama aldol-lactonization (TMAL) reaction between an aldehyde and silyl ketene acetal **1-28** was most efficient in the preparation of *trans*-1,2-disubstituted β-lactones. Using this method, *trans*-3-methyl-4-decyloxetan-2-one (**2-7l**) was prepared in 39% yield (>90 %de). Unfortunately, no methods were available for the preparation of *cis*-1,2-disubstituted β-lactones or the enantioselective preparation of 1,2-disubstituted β-lactones taken as a whole.

Furthermore, in Chapter 2 we found that a boron trifluoride promoted [2 + 2] cycloaddition reaction between an aldehyde and silyl ketene **2-9a** was the most efficient route to C4-monosubstituted β-lactones. Using this method, 4-decyloxetan-2-one (**2-7v**) was prepared in 82% yield. Although Romo and others have used chiral Lewis acids in the enantioselective preparation of C4-monosubstituted β-lactones, enantiomeric excess values were highly variable and highly dependent on the aldehyde used.[125]

This narrowed our focus for the remainder of the thesis to the preparation of racemic and optically active *cis*-1,2-disubstituted and C4-monosubstituted β-lactones.

In Chapter 3, a titanium (IV) chloride promoted, two-pot TMAL reaction between an aldehyde and silyl ketene acetal **1-28** was developed in the

preparation of a *cis*-1,2-disubstituted β-lactone. Starting from undecanal, *cis*-3-methyl-4-decyloxetan-2-one (**3-1**) was prepared in 29% yield. Unfortunately, our attempts to prepare the corresponding optically active *cis*-1,2-disubstituted β-lactone, *cis*-(3*R*,4*R*)-3-methyl-4-decyloxetan-2-one (**3-1**), using (*R*)-BINOL-Ti(IV) were unsuccessful; *syn*-diastereoconvergency in the Mukaiyama aldol step was lost as the reaction proceeded through an unexpected non-chelated transition state structure.

However, in Chapter 4 we demonstrated that a multi-step preparation involving an Evans-type aldol condensation between an aldehyde and the titanium (IV) enolate of an achiral or chiral *N*-propionyl thiazolidinethione (**4-24** and **4-26**, respectively) could be used in the preparation of racemic or optically active *cis*-1,2-disubstituted β-lactones, respectively. Using undecanal and *N*-propionyl thiazolidinethione **4-24**, *cis*-3-methyl-4-decyloxetan-2-one (**3-1**) was prepared in 25% yield (>90 %de). Using undecanal and chiral *N*-propionyl thiazolidinethione **4-26**, the corresponding Evans-type aldol condensation gave *non-Evans* aldol adduct **4-51** in 56% yield (>90 %de).

Furthermore, in Chapter 5 we demonstrated that an Evans-type aldol condensation between an aldehyde and the titanium (IV) enolate of an achiral or chiral *N*-acetyl thiazolidinethione (**5-16** and **5-17**, respectively) could be used in the multi-step preparation of racemic and optically active C4-monosubstituted β-lactones, respectively. Using undecanal and *N*-acetyl thiazolidinethione **5-16**, 4-decyloxetan-2-one (**2-7v**) was prepared in 22% yield. Using undecanal and chiral *N*-acetyl thiazolidinethione **5-16**, the corresponding Evans-type aldol condensation gave aldol adduct **5-30** in 57% yield (>90 %de).

Although *N*-acyl thiazolidinethiones proved very useful in the preparation of racemic and optically active *cis*-1,2-disubstituted and C4-monosubstituted β-lactones (Chapters 4 and 5), the number of steps required to convert the initial aldol adduct to the product β-lactone was somewhat undesirable. Hence, in Chapter 6 we developed a one-pot, tandem Evans-type aldol-lactonization

(TEAL) reaction designed to combine the stereoselectivity of an Evans-type aldol condensation (using *N*-acyl thiazolidinethiones) with the efficiency of a tandem aldol-lactonization (TAL) reaction (using phenyl or thiophenyl esters). Unfortunately, the lithium enolates of *N*-acyl thiazolidinethiones were not sufficiently stable to withstand the gradual addition of aldehydes required for the preparation of 1,2-disubstituted or C4-monosubstituted β-lactones. However, the lithium enolates of several *N*-acyl thiazolidinethiones were sufficiently stable as to undergo an efficient TEAL reaction with cyclohexanone, which could be added neat to the reaction mixture. For example, the lithium enolate of *N*-acetyl thiazolidinethione **5-16** reacted with cyclohexanone in a TEAL reaction to give spiro-β-lactone **6-22** in 60% yield.

In Chapter 7, a Claisen-type condensation on a glycoluril template was used to prepare the carbon skeleton in the preparation of C4-monosubstituted β-lactones. We believed that an enantioselective reduction of the product β-keto amide would allow the efficient preparation of optically active C4-monosubstituted β-lactones from optically inactive acid chlorides. Although β-hydroxy amides could be efficiently prepared on glycoluril **7-11**, it proved to be a poor leaving group that was not well suited to the preparation of β-lactones. For example, 4-decyloxetan-2-one (**2-7c**) was prepared in only 10% yield from decanoyl chloride in an involved, 6-step procedure.

Glycoluril **7-11** was substituted for dithioglycoluril **7-51** to improve the efficiency of the preparation of C4-monosubstituted β-lactones on glycoluril templates by acting as a better leaving group. Although acyl halides could be added to this glycoluril template using milder conditions, deacylation during an alkoxide-promoted Claisen-type condensation using several alkyl acid halides prevented us from making our desired C4-monosubstituted β-lactones.

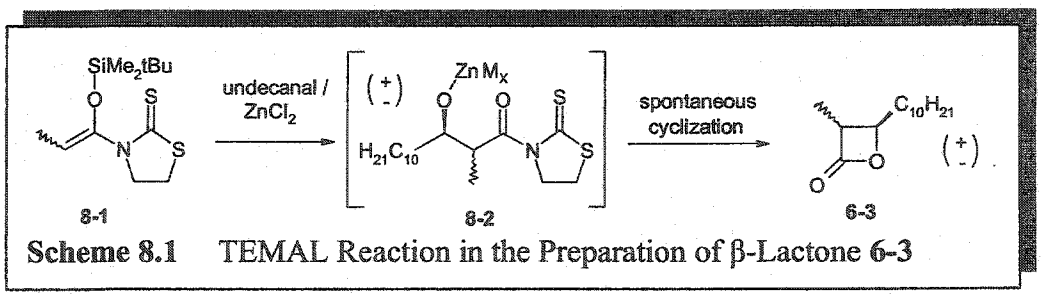
8.2 Future Work

Although numerous avenues remain to be explored in the preparation of 1,2-disubstituted and C4-monosubstituted β-lactones using thiazolidinethiones and glycolurils, two deserve more immediate attention: (1) a TEMAL reaction involving achiral and chiral *N*-acyl thiazolidinethiones; and (2) a Claisen-type reaction on a dithioglycoluril template. These will be briefly discussed below.

8.2.1 TEMAL Reaction in the Preparation of 1,2-Disubstituted β-Lactones

As previously mentioned, the TEAL reaction between cyclohexanone and the lithium enolates of several *N*-acyl thiazolidienthiones was successful in the preparation of spiro-3,4-disubstituted β-lactones (Chapter 6.3). However, the TEAL reaction between undecanal and *N*-propionyl thiazolidinethione **4-24** was not successful in the preparation of 3-methyl-4-decyloxetan-2-one (**6-3**) (Chapter 6.2). This was attributed to the instability of the lithium enolate of *N*-propionyl thiazolidinethione **4-24**.

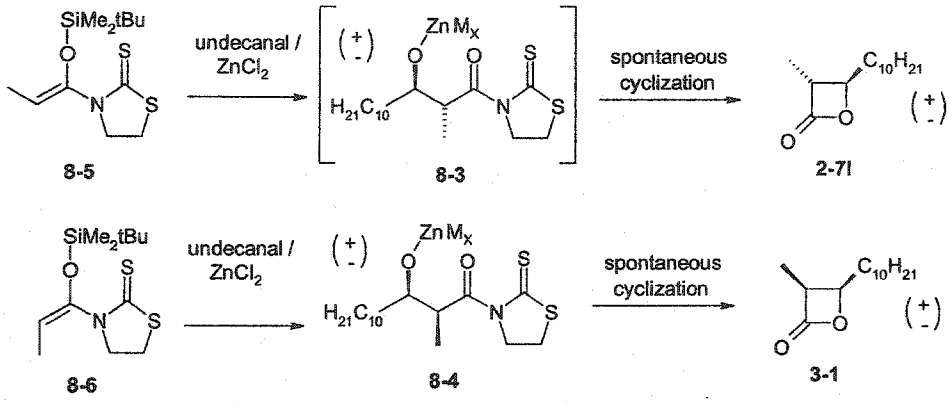
One possible solution would be to use silyl enol ether **8-1** - derived from *N*-propionyl thiazolidinethione **4-24** - in a tandem Evans-type Mukaiyama aldol-lactonization (TEMAL) reaction (Scheme 8.1).



Scheme 8.1 TEMAL Reaction in the Preparation of β-Lactone **6-3**

Similar to the TMAL reaction developed by Romo and co-workers – and further expanded in our laboratory – the zinc (II) chloride promoted Evans-type

Mukaiyama aldol condensation should proceed through an unchelated transition state structure.[17] Therefore, the geometry of the intermediate zinc aldolate (**8-3** and **8-4**) should be dependant upon the geometry of the silyl enol ether (**8-5** and **8-6**). That is, (*Z*)-silyl enol ether **8-5** should give *trans*-3-methyl-4-decyloxetan-2-one **2-7l**, and (*E*)-silyl enol ether **8-6** should give *cis*-3-methyl-4-decyloxetan-2-one **3-1** (Scheme 8.2).



Scheme 8.2 Proposed Diastereoselectivity in the TEMAL Reaction

Furthermore, substitution of achiral silyl enol ether **8-1** for chiral silyl enol ether **8-7** should generate facial selectivity in the Evans-type Mukaiyama aldol condensation required for the enantioselective preparation of 1,2-disubstituted β-lactones (Figure 8.1).

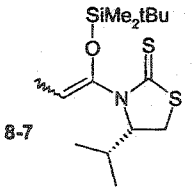


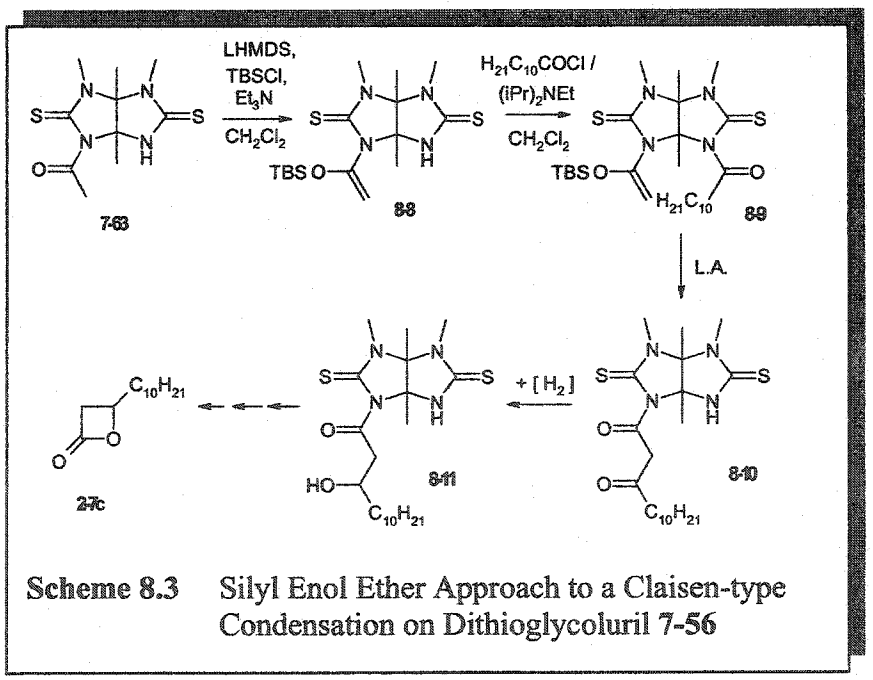
Figure 8.1 Structure of the Chiral Silyl Enol Ether Derived From *N*-Propionyl Thiazolidinethione **4-26**

This TEMAL approach may eventually be used in the preparation of C4-monosubstituted β-lactones.

8.2.2 Claisen-Type Condensation on a 3,4,7,8-Tetramethyl-2,5-Dithioglycoluril in the Preparation of C4-Monosubstituted β-Lactones

Although we used glycoluril **7-11** in the preparation of 4-nonyloxetan-2-one (**2-7c**), this template was found to be a poor leaving group (Chapter 7.4). Based on our work with thiazolidinethiones, it appeared that dithioglycoluril **7-56** represented a more suitable leaving group that could be used in the efficient preparation of C4-monosubstituted β-lactones. Unfortunately, extensive deacylation was observed using an alkoxide-promoted Claisen-type condensation to condense propionyl, octanoyl and decanoyl groups with an acetyl group on dithioglycoluril **7-56** (Chapter 7.5).

One possible solution would be to use silyl enol ether **8-8**, derived from monoacetyl dithioglycoluril **7-63**, in a Lewis acid promoted Claisen-type condensation (Scheme 8.3). Such a strategy would be advantageous in that no potentially nucleophilic or ketene forming alkoxide is required to promote the Claisen-type condensation.



Scheme 8.3 Silyl Enol Ether Approach to a Claisen-type Condensation on Dithioglycoluril **7-56**

Previous X-ray crystallographic studies of diacyl glycolurils derived from both glycoluril **7-11** and dithioglycoluril **7-56** by the Harrison group have indicated that their ground-state conformations (**8-12**) do not correspond with the conformation required for an intramolecular Claisen-type condensation (**8-13**) (Figure 8.2); rotation of the enolate about the amide bond is required in order to achieve a boat-like transition state for the reaction.[173] However, steric bulk from the *tert*-butyldimethylsilyl group in **8-14** should position the silyl enol ether in a conformation closer to that required for an efficient Claisen-type condensation.

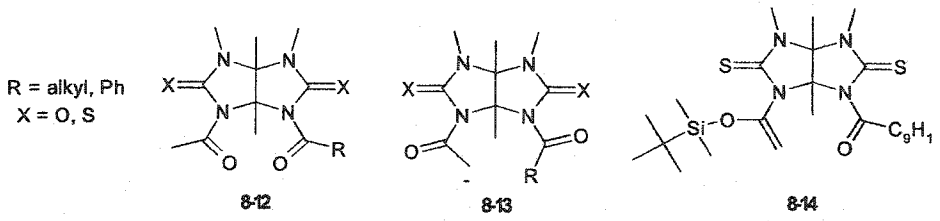
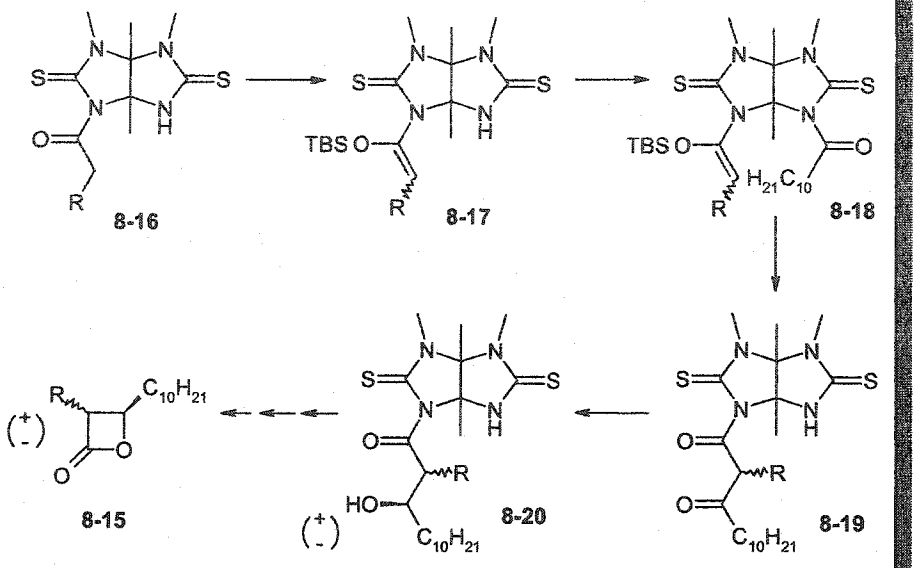


Figure 8.2 Proposed Ground State Conformation of Dithioglycolurils **8-12** and **8-14**

Furthermore, because the silyl enol ether is prepared prior to the addition of a second acyl moiety, regioselectivity in the Claisen-type condensation should be greatly improved. Such a strategy may eventually be employed in the preparation of 1,2-disubstituted β-lactones (**8-15**) on a dithioglycoluril template (Scheme 8.4).



Scheme 8.4 Regioselectivity in a Modified Claisen-type Condensation

Chapter 9

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