PREPARATION OF β-LACTONES

DEVELOPMENT OF A STEREOSELECTIVE METHOD FOR THE PREPARATION OF β-LACTONES

By

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ABSTRACT

β–Lactones are present in a number of biologically interesting natural products. They also have inherent reactivity due to their strained ring system and act as important synthetic intermediates. In this current work, we focus on the development of an efficient stereoselective route for the synthesis of β-lactones. A Tandem Evans-type Aldol-Lactonization (TEAL) method was developed and various di- and tri-substituted β-lactones were successfully synthesized in a one pot process, using the lithium enolates of *N*-acetyl- (**2-8**) and *N*-propionyl- (**2-20**) thiazolidine-2-thione and a variety of ketones with moderate to good yields. Substitution of these *N*-acyl thiazolidine-2-thiones with chiral *N*-acetyl and *N*-propionyl thiazolidine-2-thiones (**2-41** and **2-42** respectively) produced β-lactones with good enantioselectivity (up to 83% e.e.) and also showed an improvement of diastereoselectivity indicating the potential of the developed method.

ACKNOWLEDGMENTS

I would like to express my earnest thanks and appreciation to my supervisor Dr. P. H. M. Harrison, for his guidance and encouragement throughout this thesis. I also wish to thank to my committee member, Dr. Fred Capretta for his valuable suggestions and comments along the way.

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Chapter 1

Introduction

β–Lactones (oxetan-2-ones) are four-membered cyclic esters (Figure 1.1). They constitute the key structural feature in many natural products that are pharmacologically interesting.[1,2] Thus, there are a number of fatty acid-, polyketide-, terpenoid- and α-amino acid-derived β-lactones present in nature; these are described in Section 1.1. Furthermore, the strained oxetanone ring undergoes nucleophilic cleavage under mild conditions with a variety of reagents and these reactions have been used for the preparation of a number of synthetic targets.[3] β–Lactones also undergo stereospecific decarboxylation upon thermolysis to produce various types of substituted and functionalized alkene.[4] These reactions of β-lactones are described in Chapter 1.2.

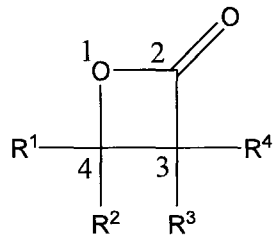


Figure 1.1: General Structure of β-lactones (2-Oxetanones).

Because of these applications, demand for the development of a simple and efficient synthetic route to optically active β-lactones is growing rapidly. Unfortunately, the utility of β–lactones has been limited by a lack of efficient methods whereby they may be prepared in desired stereoselective forms. The known methods for preparation of β-lactones are reviewed in Section 1.3.

The aim of this thesis is to describe work carried out to develop a stereoselective method for the preparation of β-lactones in both racemic and optically active forms. This work is described in Chapter 2.

1.1: β–Lactones in Natural Products:

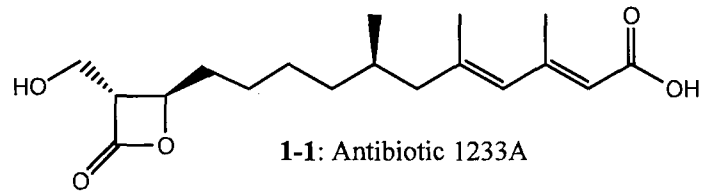
During the last 40 years, a dramatic increase in the number of pharmacologically interesting β–lactones has occurred. According to their likely biosynthetic origin they can be classified into different classes. These classes are described very briefly here.

1.1.1: Fatty Acid- and Polyketide- like β–Lactones:

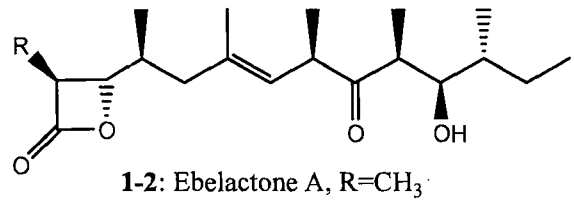
The first member of this class was antibiotic 1233A (**1-1,** Figure 1.2), isolated by Aldridge *et al.* from *Cephalosporium* sp. in 1971[5] and subsequently as F-244 from *Scopulariopsis sp*[6] and as L-659,699 from *Fusarium sp.*[7] The absolute configuration of **1-1** was established in 1988[8] by chemical degradation and NMR techniques. Harrison and co-workers as well as Omura and co-workers have established that **1-1** is derived from four methionine and seven acetate units, using ^{13}C- and ^{2}H- labeled precursors.[9,10] 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.[11] Because of its effect on cholesterol production in the body, **1-1** represents a potential drug in the treatment of hypercholesterolemia.

Ebelactones A (**1-2**) and B (**1-3**) (Figure 1.2) were isolated in 1980 from *Streptomyces* sp. MG7G1 and have a polyketide origin.[12] Using ^{13}C labeled precursors, it was found that ebelactone A originates from one acetate and six propionate units and

ebelactone B originates from one acetate, five propionate, and one butanoate units.[13] The ebelactones are potent inhibitors of esterases, lipases, carboxypeptidases and *N*-formylmethionine aminopeptidases in a wide variety of animal cells.[14] They have also been reported to inhibit acylpeptide hydrolase[15] and cutinases[16] produced by fungal pathogens. These properties make them potential plant protection agents, as all known fungal cutinases have been identified as serine hydrolases similar to esterases and lipases.[16]



1-1: Antibiotic 1233A



1-2: Ebelactone A, R=CH_3
1-3: Ebelactone B, R=CH_2CH_3

Figure 1.2: Fatty Acid and Polyketide Like β-Lactones

The natural products valilactone (**1-4**), esterastin (**1-5**) and lipstatin (**1-6**) are analogous molecules differing only in the structure of the C-4 substituent (Figure 1.3). Valilactone displays esterase and lipase inhibition similar to ebelactone.[17] Esterastin exhibits esterase and lipase inhibition, but differs from the ebelactones in that it effectively suppresses the immune response.[18] Lipstatin represents a highly potent irreversible pancreatic lipase inhibitor active against enzymes from a wide variety of sources, including man[19] and an ideal candidate for the treatment of obesity as this drug

should allow dietary fat to pass through the gut without being absorbed.[20] The non-natural tetrahydrolipstatin (orlistat, **1-7**, Figure 1.3) is now used for preventing obesity and hyperlipidemia[21] and marketed as Xenical® or the over the counter drug as 'alli'.

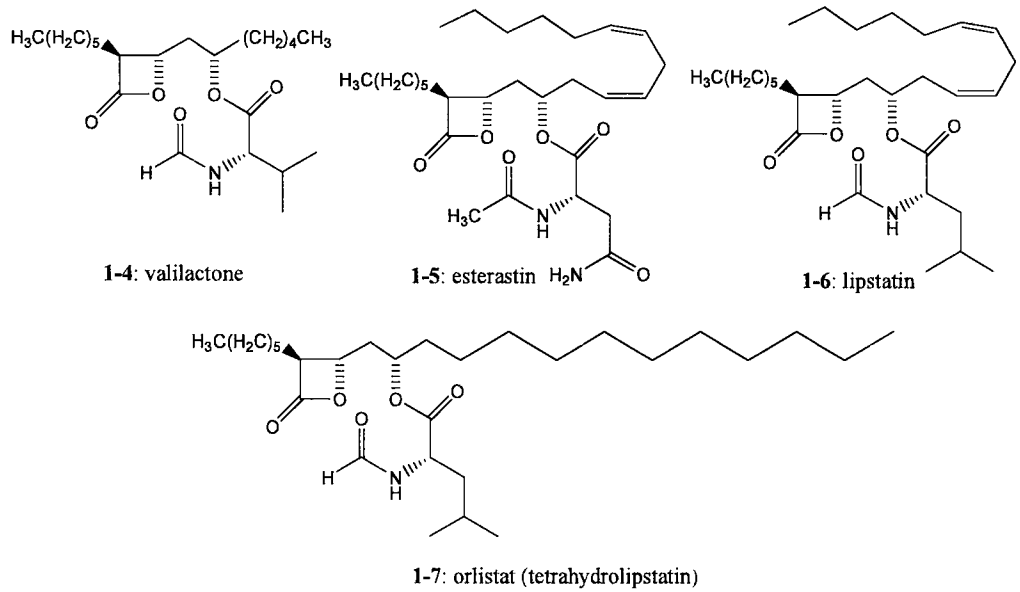
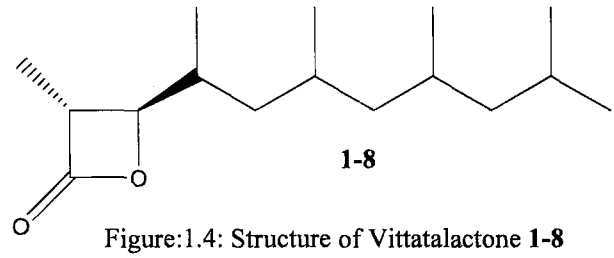


Figure 1.3: Some More Fatty Acid and Polyketide Like ß-Lactones

Recently, in 2005, a novel β-lactone, vittatalactone, **1-8** (Figure 1.4) was isolated from the volatile compound released by male beetles, *Acalymma vittatum*.[22] The structure of **1-8** was determined by microderivatization, GC-MS and NMR studies and found to have the closest structural relationship with ebelactone A. It possibly acts as an aggregation pheromone for *A. vittatum*.

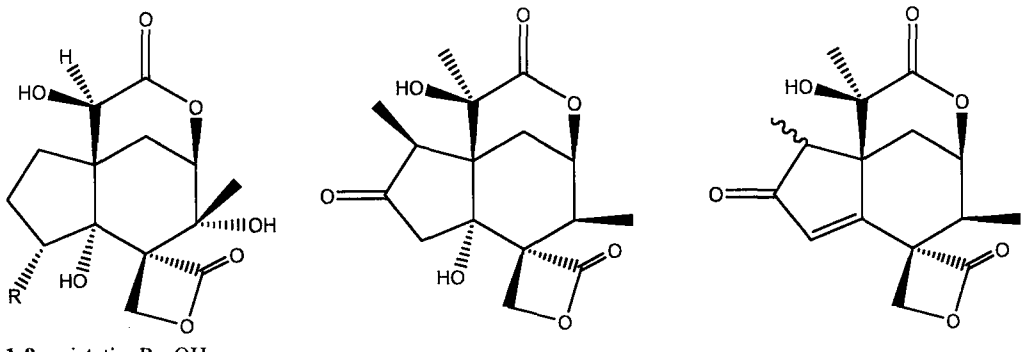


1-8

Figure:1.4: Structure of Vittatalactone **1-8**

1.1.2: Terpenoid β–Lactones:

The major sesquiterpene-derived β–lactones are anistatin (**1-9**) and neoanistatin (**1-10**),[23] isolated from *Illicium anistatum L*, and varanistatin A (**1-11**) and varanistatin B (**1-12**),[24] isolated from *Illicium veru* (Figure 1.5). Anistatin and neoanistatin are useful in the study of diseases such as epilepsy and Huntington's disease which involve dysfunction of γ–aminobutyric acid synapses because, similar to the picrotoxins, they act as non-competitive γ–aminobutyric acid (GABA) antagonists.[25]



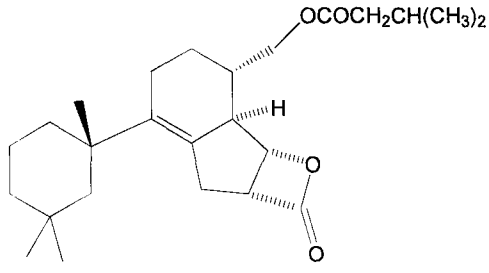
1-9: anistatin, R= OH
1-10: neoanistatin, R=H

1-11: varanistatin A

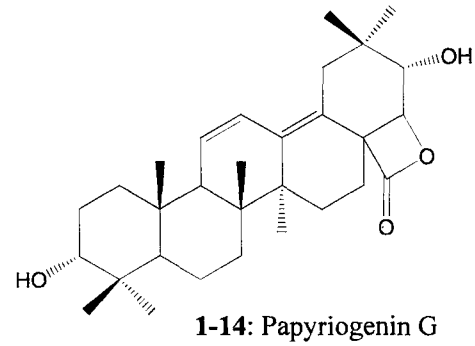
1-12: varanistatin B

Figure 1.5: Terpenoid β-Lactones

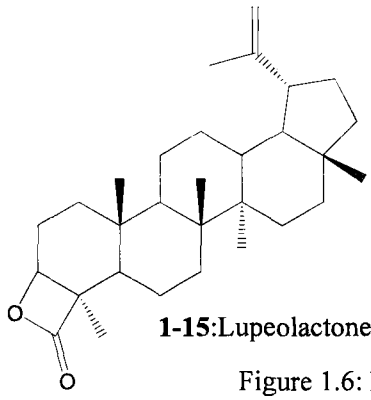
Spongiolactone (**1-13**) is the only known diterpene β-lactone; it has been isolated from *Spongionella gracilis*.[26] There are a number of triterpene derived β–lactones isolated from a wide variety of organisms. Some examples are papyriogenin G (**1-14**), isolated from *Tetrapanax papyriferum*[27] and lupeolactone (**1-15**), isolated from *Antidesma pentandrum Merr.*[28] Lupeolactone has been found to be effective in lowering serum cholesterol level in normal rats. Moretenolactone (**1-16**), isolated from *Ficus insipidia,*[29] has a similar structure to that of lupeolactone.



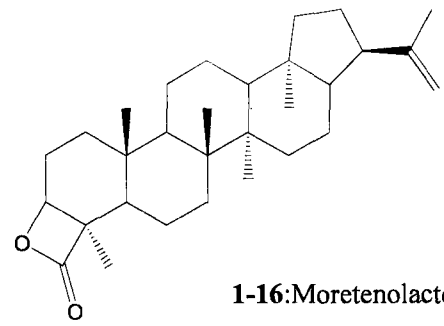
1-13:Spongiolactone



1-14: Papyriogenin G



1-15:Lupeolactone



1-16:Moretenolactone

Figure 1.6: Di- and Triterpene Derived β-Lactones

1.1.3: α-Amino-β-Lactones:

β-Lactone natural products possessing an α-amino moiety are also known in nature. SQ 26,517 (**1-17**) from *Bacillus* sp. SC 11,480[30] and obafluorin (**1-18**) from *Pseudomonas fluorescens*[31] display weak antimicrobial activity. Oxazolomycin (**1-19**) isolated from *Streptomyces* sp (Figure 1.7) in 1985[32] exhibits strong antibacterial activity and is effective in protecting the plant from crown gall disease.[33] It was also found to have antiviral and catatonic activity.[34] The structure of oxazolomycin was established by X-ray cystallographic studies of its derivatives.[32]

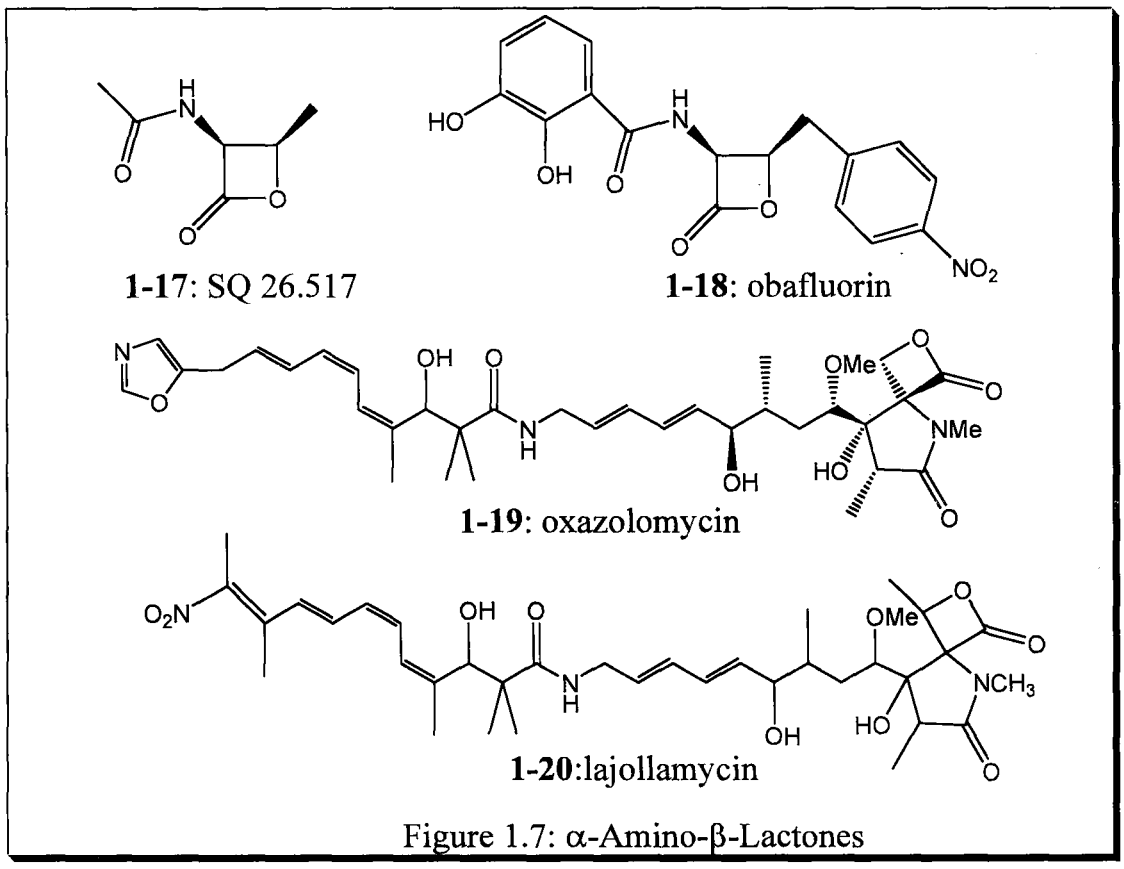
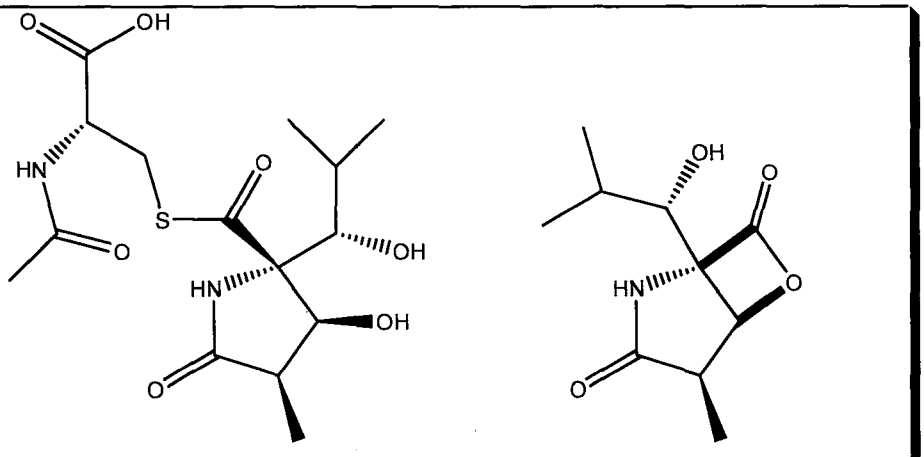


Figure 1.7: α-Amino-β-Lactones

Lajollamycin (**1-20**), a structurally related compound to oxazolomycin, has been isolated from *Streptomyces nodosus* (NPS007994) in 2004 by Potts *et al.*.[35] It is a nitro-tetraene spiro-β-lactone-γ-lactam. The structure of **1-20** was elucidated by complete spectroscopic analysis and comparison with oxazolomycin and some other structurally related known antibiotics like 16-methyloxazolomycin and triedimycin. Lajollamycin showed antimicrobial activity against both drug-sensitive and –resistant microorganisms and inhibits the growth of murine melanoma cell line B16-F10.[35]

1.1.4: Bicyclic β-Lactones of Mixed Origin:

A new class of β-lactones containing a fused 4/5 ring system emerged when Omura and his colleagues discovered lactacystin (**1-21**) in 1991,[36] a natural product isolated from the culture broth of *Streptomyces sp.* OM-6519. It inhibits the mammalian 20S and 26S proteasomes over a wide range of concentrations.[37] It acts as a pro-inhibitor. The thiol ester function of lactacystin allows spontaneous conversion to the *clasto*-lactacystin-β-lactone (**1-22**), called omuralide, which in turn is able to directly inhibit the proteasome.[38] The inactivation involves acylation of the *N*-terminal threonine subunit, a key participant in proteolytic catalysis.[39]



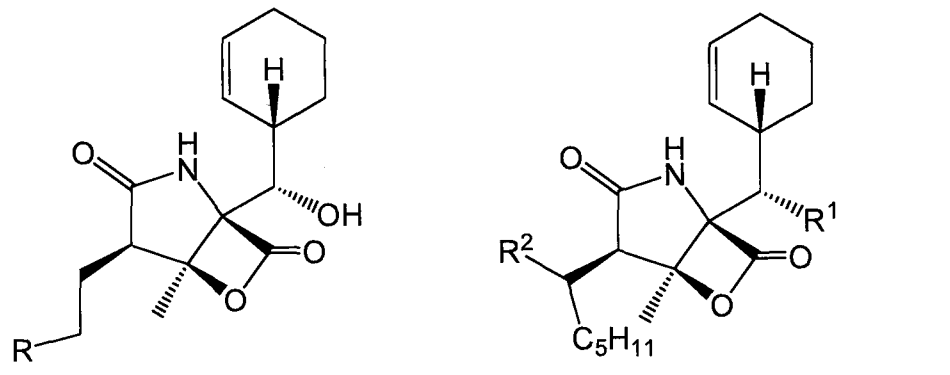
1-21:lactacystin **1-22**:omuralide

Figure 1.8: Stucture of Lactacystin **1-21** and Omuralide **1-22.**

Salinosporamides, containing a fused γ-lactam-β-lactone core structure have been isolated from a new genus of marine bacterium, Salinospora, found in ocean sediment.[40] Among them, salinosporamide A (**1-23**), isolated from *Salinospora tropica*[41] by Fenical *et al.*, was found to be 35 times more potent as an inhibitor of the 20S proteasome than omuralide and recently entered phase I clinical trials for treatment of human cancer.[42] Both salinosporamide A and omuralide inhibit the proteolytic activity of the 20S subunit of the proteasome without affecting any other protease activity.[41] Extensive testing confirms that the β-lactone is the crucial pharmacophore responsible for their activity.[43] The inhibition by salinosporamide involves acylation of the active site of threonine by the β-lactone, followed by cyclization of the alkoxide at C13 with the loss of the chloro substituent, leading to a tetrahydrofuran.[44] Salinosporamide B (**1-24**), the deschloro analogue of A, has been found to have 500 times less cytotoxic activity than **1-23** indicating importance of the chloroethyl group for cytotoxicity.[41]

By ^{13}C feeding experiments, Moore *el al* showed that salinosporamide A originates from acetate, β-hydroxy-2′-cyclohexenylalanine and a tetrose-derived chlorinated unit; on the other hand salinosporamide B originated from acetate, β-hydroxy-2′-cyclohexenylalanine and butyrate, suggesting a convergent biosynthesis of these two natural products in *S. tropica.*[45]

The cinnabaramides A-C (**1-25-1-27**), isolated from a terrestrial strain of *Streptomyces*[46] also have the same bicyclic ring structure and biological properties as salinosporamide A and omuralide.



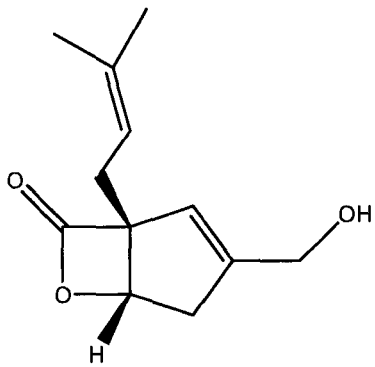
1-23:salinosporamide A, R=Cl
1-24:salinosporamide B, R=H

1-25:cinnabaramides A, R^1=OH, R^2=H
1-26:cinnabaramides B, R^1=R^2=OH
1-27:cinnabaramides C, R^1=R^2= H

Figure 1.9: Bicyclic ß-Lactones

Another unusually fused β-lactone, vibralactone (**1-28**) was isolated from the culture broth of the polypore *Boreostereum vibrans* by Liu e*t al.* in 2006.[47] The structure of **1-28** was established by spectroscopic and computational methods, and found to have a fused 4/5 ring system like salinosporamide A. It showed inhibition of pancreatic lipase

with an IC_{50} of 0.4 μg/mL. Therefore, like orlistat, vibralactone exhibits potential for inhibition of fat absorption in the treatment of obesity.



1-28

Figure:1.10: Structure of Vibralactone **1-28**

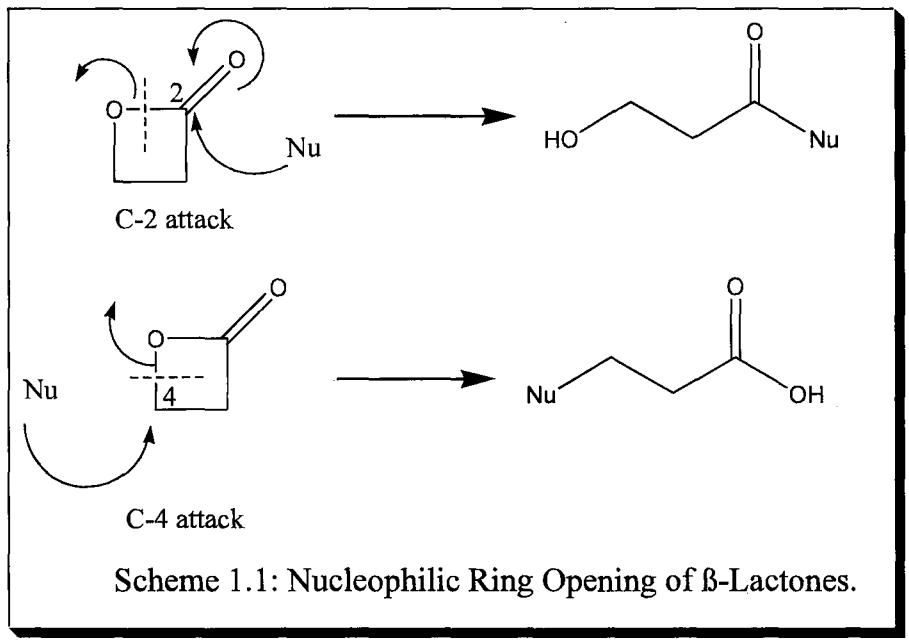
In summary, the number of naturally occurring β-lactones having interesting pharmacological activity is rapidly increasing and creating interest in the methods for preparing them.

1.2: Reactivity of β–Lactones:

β–Lactones combine the structural features of a masked aldol product with the exceptional reactivity of a strained ring system.[48] These features make β–lactones versatile intermediates capable of a wide variety of transformations that are often driven by release of the ring strain. In this section, the important reactions of β-lactones will be discussed in brief.

1.2.1: Cleavage by Nucleophilic Attack:

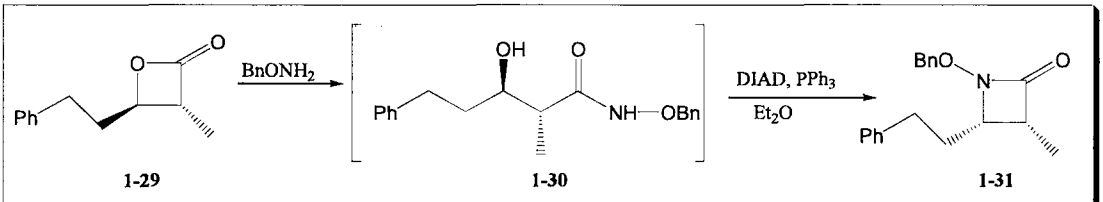
Nucleophilic cleavage of the strained 2-oxetanone ring takes place under relatively mild conditions with a variety of organometallic reagents and heteroatom nucleophiles. Soft nucleophiles typically add to β-lactones at the C (alkyl)-O bond (C-4 attack) with inversion of configuration, thereby furnishing β-functionalized carboxylic acids which can be chiral; hard nucleophiles cleave the C (acyl)-O bond (C-2 attack) and unmask the aldol structure. In general C-2 attack takes place under basic or strongly acidic conditions, while neutral or slightly acidic conditions result in C-4 attack (Scheme 1.1).[49]



Scheme 1.1: Nucleophilic Ring Opening of ß-Lactones.

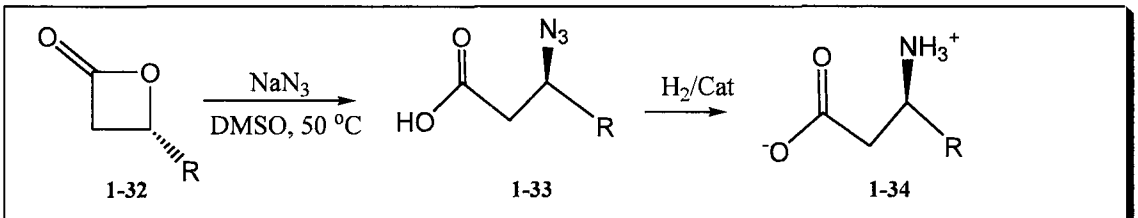
These reactions of β–lactones with nucleophiles provide a fascinating route to a variety of useful organic synthons like propionic acid derivatives,[50] tetrahydrofurans,[51] amino acids,[52] etc. As an example, Yang and Romo recently made the useful β-lactam **1-31** using preferential attack of O-benzylhydroxylamine at C-2 of the β-lactone **1-29** with

inversion of stereochemistry at C-4. An intramolecular Mitsunobu reaction then furnishes the desired lactam (Scheme 1.2).[53]

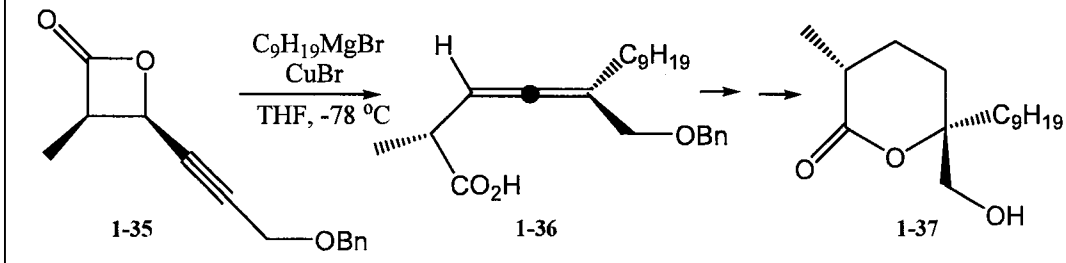


Scheme 1.2: Use of C-2 Nucleophilic Ring Opening in the Conversion of a ß-Lactone to a β-Lactam

More recently Nelson and colleagues have used C-4 attack of azide in the preparation of β-amino acids from a wide variety of β-lactone substrates.[52] They also employed this reaction in the preparation of optically active allenes in the synthesis of (-)-malyngolide **1-37,** a naturally occurring antibiotic (Scheme 1.4).[54]



Scheme:1.3: Nucleophilic Ring Opening of the β-Lactone **1-32** with Azide and Formation of ß-Amino acids.

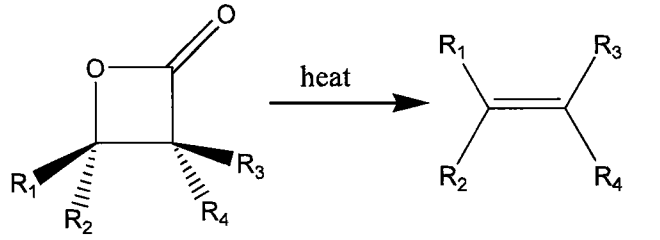


Scheme 1.4:Preparation of (-)-Malyngolide from β-lactone **1-35** by Nucleophilic Ring Opening

Moreover, intramolecular nucleophilic attack on the β-lactone moiety leads to various important organic molecules, including natural products.[55.56.57]

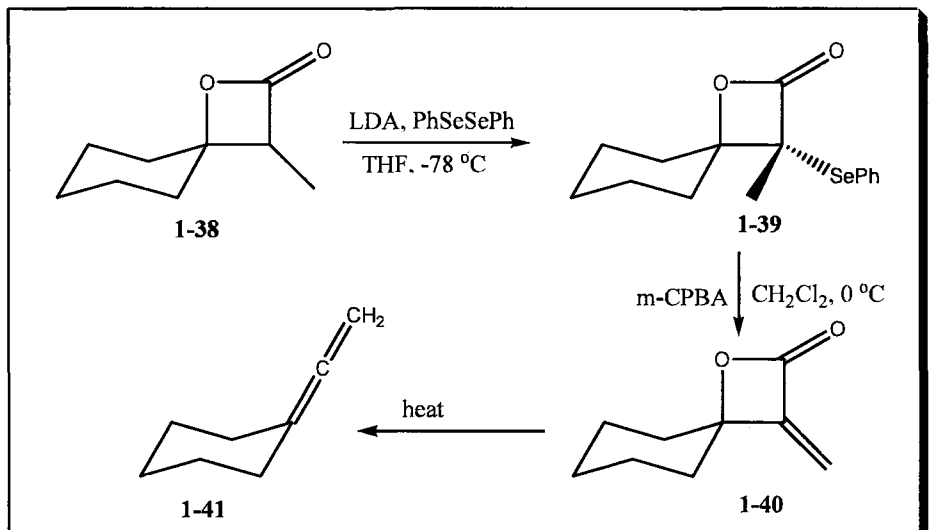
1.2.2: Decarboxylation of β-Lactones by Thermolysis:

β-Lactones undergo decarboxylation under mild heating.[58] This reaction is generally believed to involve *cis*-elimination of carbon dioxide, and forms alkenes in high yields and with high stereospecificity (Scheme 1.5). This approach has been used in various syntheses to prepare stereospecifically functionalized double bonds as an alternative to, e.g., the Wittig reaction.[59]



Scheme 1.5: Formation of Alkenes from β-Lactones

Decarboxylation of β-lactones has been used in the synthesis of various steroids,[60] terpenes,[61] isoflavones,[62] enol ethers,[63] benzofurans[64] and substituted allenes.[65] For example, recently Danheiser and co-workers used this reaction in the production of substituted allenes which are highly useful organic synthons (Scheme 1.6).[65]

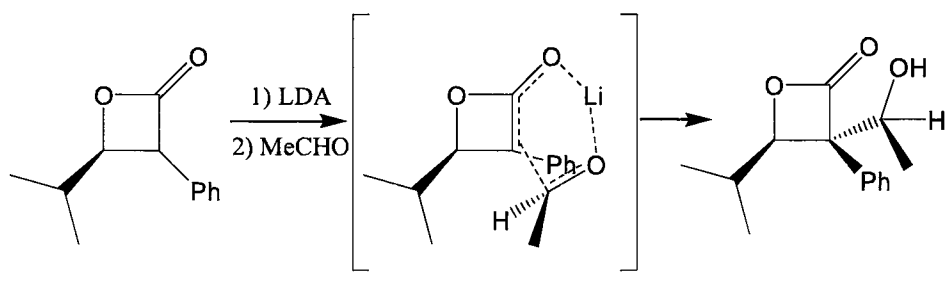


1-38 **1-39** **1-40** **1-41**

Scheme:1.6: Preparation of Allene **1-41** fron β-Lactone **1-38**

1.2.3: Enolate Formation:

In 1980 Mulzer *et al.* showed that α-substituted β-lactones could be deprotonated with LDA at low temperature.[66] The resulting enolates react with a variety of electrophiles such as aldehydes, alkyl halides, etc.. In the reaction with aldehydes (Scheme 1.7), the chelation of lithium leads to a stereoselective addition of the electrophiles to the least bulky face of the enolate, i.e. favoring transition state **1-43**.

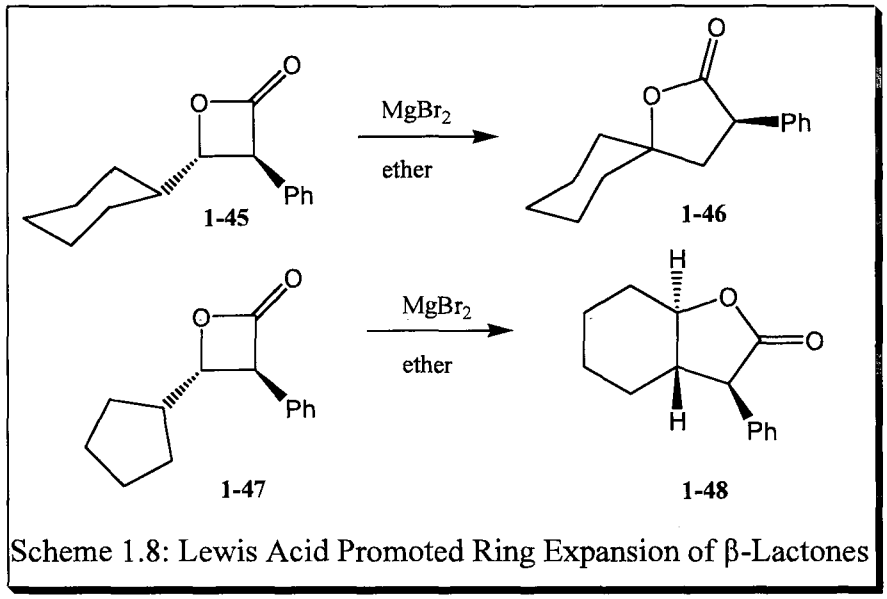


1-42 **1-43** **1-44**

Scheme 1.7: Reaction of Li-Enolate of β-Lactone **1-42** with Acetaldehyde

1.2.4: Lewis Acid Promoted Ring Expansions:

β–Lactones are capable of Lewis acid promoted rearrangement in order to relieve strain.[67] These reactions lead to either a spiro-γ-lactone (**1-46**) or a fused-γ-lactone (**1-48**) (Scheme 1.8).



Scheme 1.8: Lewis Acid Promoted Ring Expansion of β-Lactones

From the discussion above, it is obvious that the opportunity to employ β-lactones as versatile chiral synthons in the synthesis of both natural and synthetic molecules is large, making this functionality attractive in synthesis.

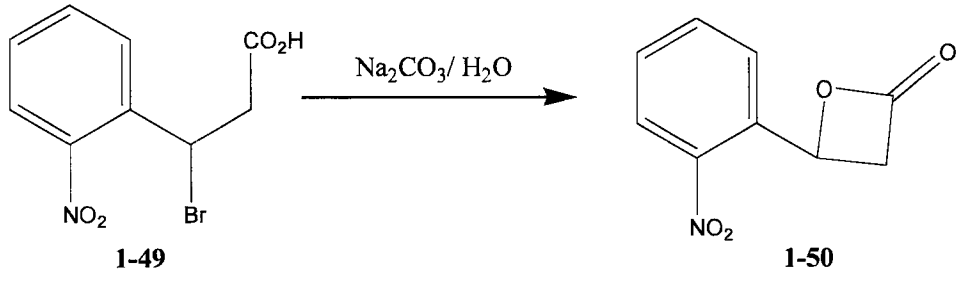
1.3: Methods for Synthesis of β-Lactones:

In spite of the fact that β-lactones possess rich and versatile chemistry which make them very important in synthetic organic chemistry, general methods for the direct synthesis of β-lactones are not as developed as those for other strained heterocyclic molecules. The only known preparative methods for β-lactones, until the last few

decades, were the intramolecular lactonization of β-halo-carboxylic acid salts under basic conditions and [2 + 2] cycloaddition between carbonyl compounds and ketenes. In the 1990's the preparation of β-lactones gained momentum and several reviews have been published during this time. Here we will highlight these methods briefly.

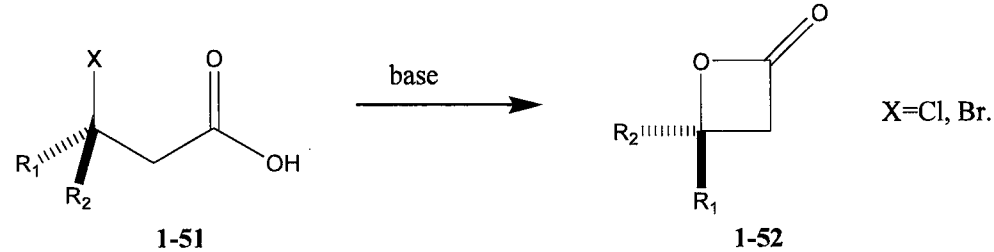
1.3.1: Lactonization by Intramolecular Cyclization of β-Haloacid Salts:

Einhorn in 1883 reported the first example of cyclization of β-bromo-*o*-nitrohydrocinnamic acid to the corresponding 4-(2-nitrophenyl)oxetan-2-one, **1-50** (Scheme 1.9).[68] Using this method, several chiral β-lactones have been prepared from chiral β-halocarboxylic acids (Scheme 1.10).[69, 70, 71]



1-49 **1-50**

Scheme 1.9: Einhorn's Method for β–Lactone Preparation

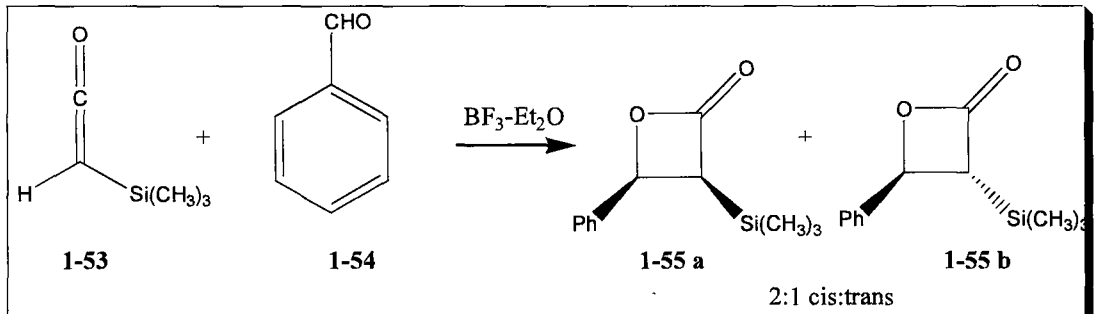


1-51 **1-52**

Scheme 1.10: Optically Active β–Lactones Prepared from β-Halocarboxylic Acids

1.3.2: Formation of β-Lactones by [2+2] Cycloaddition:

[2+2] Cycloaddition of carbonyl compounds and ketenes has been known for the preparation of β-lactones for almost a century, but due to unavailability of stable ketenes, the method was not utilized extensively until recently. In 1975, Zaitseva and his colleagues used trimethylsilylketene and benzaldehyde in the presence of boron trifluoride for preparation of β-lactones. (Scheme 1.11).[72]



Scheme 1.11: Preparation of β-Lactones Using Trimethylsilylketene

Later it was found that the use of a bulky Lewis acid, such as bis(4-bromo-2,6-di-tert-butylphenoxy) methylaluminum, produces exclusively *cis*-1,2-diastereoselectivity.[73] Moreover bi-dentate Lewis acids like magnesium chloride generate exclusively the *anti* diastereomer when a chiral aldehyde is used in this reaction by producing a conformationally rigid chelate in which the ketene adds *anti* to the α-substituent (Figure 1.11).[74]

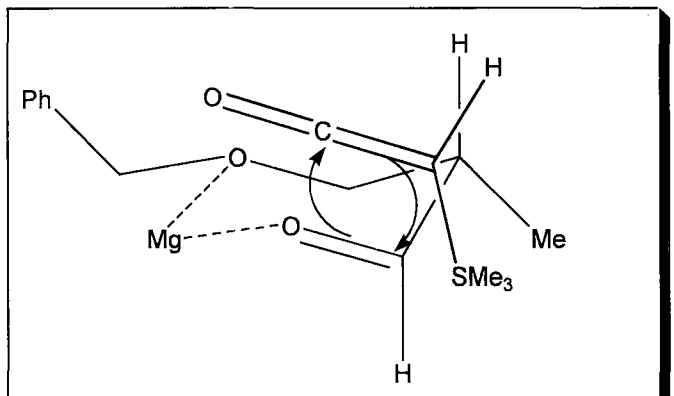
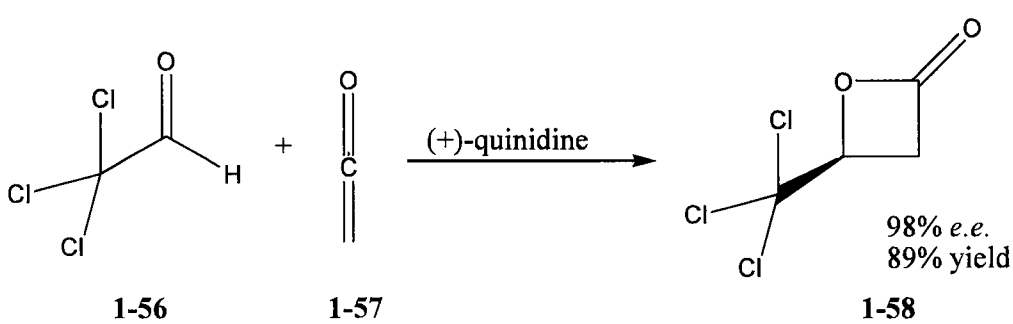


Figure 1.11: *Anti* Addition of Ketene, Relative to α-Substituent

Use of optically active Lewis acids in this method generates optically active β-lactones from optically inactive aldehydes and ketenes,[75,76,77] but the *e.e.* values are highly variable and highly dependent on the carbonyl compounds used.

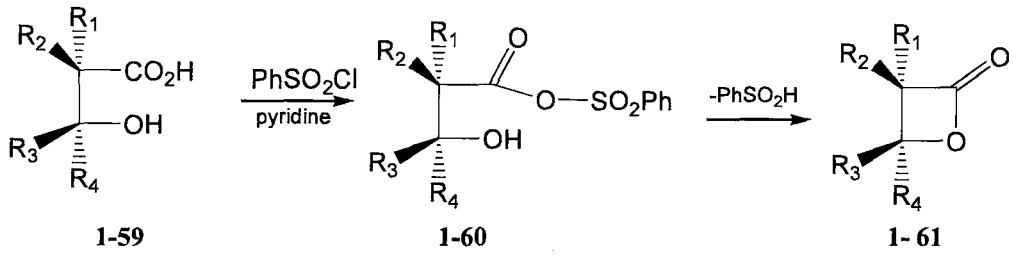
In the presence of various cinchona alkaloid catalysts, such as quinine and quinidine, β-lactones were prepared in high yield with 98% enantiomeric excess by [2+2] cycloaddition (Scheme 1.12).[78] However, the requirement for activated aldehydes, like chloral, limits the use of this procedure in general.



Scheme 1.12: Enantioselective β-Lactone Preparation from Chloral and Ketene

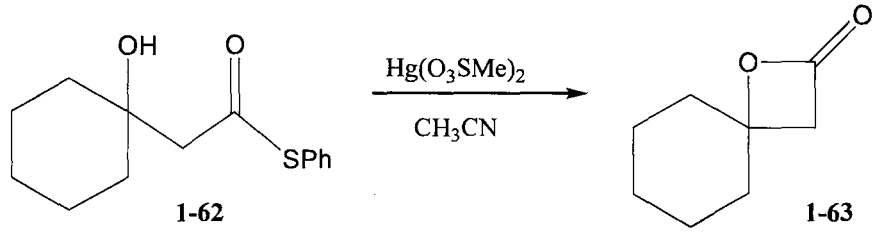
1.3.3: Lactonization by Oxygen-Acyl Bond Formation:

In this method β-lactones are formed by the intramolecular attack of the hydroxyl group of a β-hydroxy acyl moiety on to the activated carboxyl group. This method was first successfully used by Adams *et al.* by activating the β-hydroxyacid using benzenesulfonyl chloride. The β-hydroxy group serves as the internal nucleophile, displacing the benzenesulfonate ion in the mixed anhydride **1-60** (Scheme 1.13 a).[79] Retention of the configuration of the initial β -hydroxy acid in the β-lactone product is obtained in this reaction, but mono- or disubstitution at the α-carbon of the hydroxy acid is essential for cyclization into a β-lactone due to the need for a Thorpe-Ingold effect.[79] Masamune, in the 1970's overcame this problem by using β-hydroxy thiol esters in the presence of mercury (II) methanesulfonate (Scheme 1.13 b).[80] However, the toxicity of mercury reduced the attractiveness of the process.



1-59 **1-60** **1- 61**

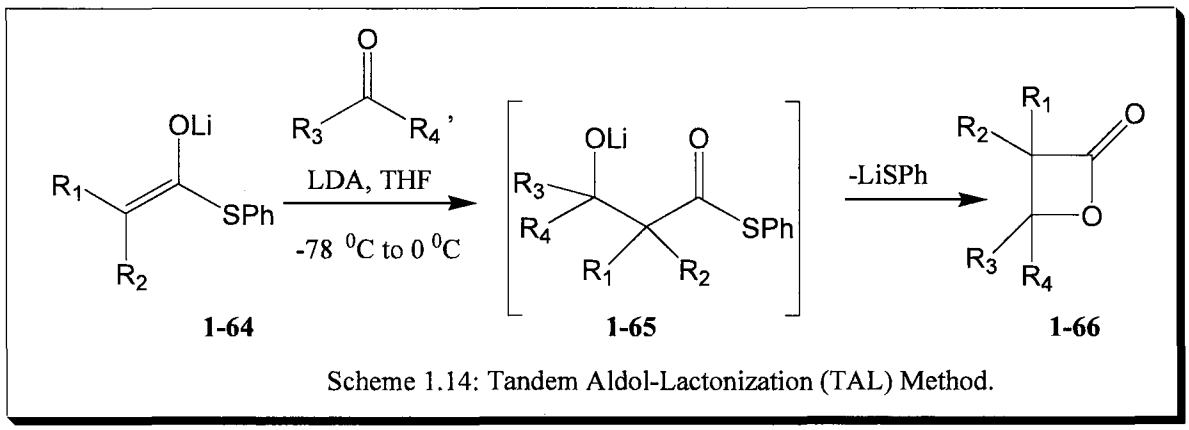
Scheme 1.13 a: Adams' Mixed Anhydride Method for β-Lactone Preparation



1-62 **1-63**

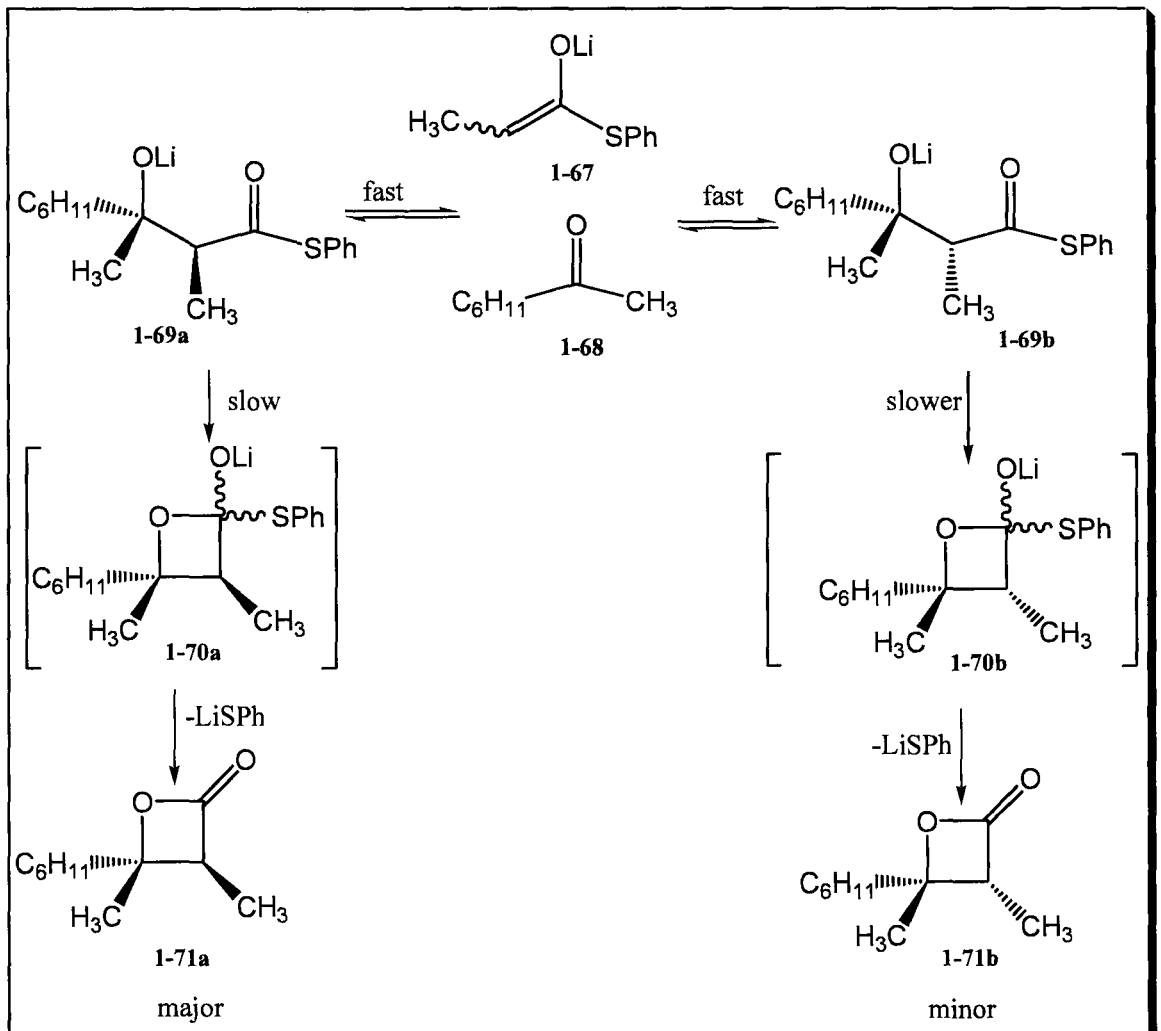
Scheme 1.13 b: Masamune's Lactonization Method for β-Lactone Preparation

In 1991 Danheiser and Nowick developed a mercury-free tandem aldol-lactonization (TAL) method where β-lactones were prepared from the lithium enolate of thiophenyl propionate.[81] In this procedure, lactonization is a result of the intermediate alkoxide attacking the thiol ester carbonyl as an internal nucleophile, displacing the thiophenyl group (Scheme 1.14).



Scheme 1.14: Tandem Aldol-Lactonization (TAL) Method.

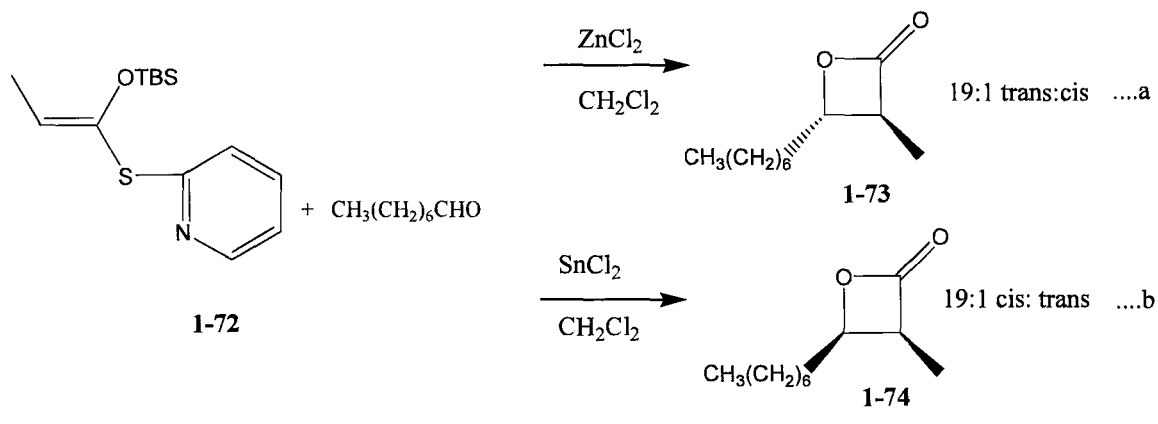
This method generates β-lactone products in high yield using a wide variety of carbonyl compounds and thiol ester enolates. However, this method exhibits poor stereospecificity, because of the initial aldol step with the thiophenyl entity. Danheiser and Nowick suggest that the observed *anti* selectivity with ketones is due to a rapid and reversible aldol condensation step followed by a subsequent cyclization which is more rapid for the *anti* aldolate **1-69a,** than the *syn* aldolate **1-69b,** giving the less sterically congested lactone **1-71a** as major product (Scheme 1.15).



Scheme1.15: Mechanism for Diastereoselectivity in the TAL Method

This tandem aldol-lactonization method was further developed by Romo and Yang, in 1997. They used a tandem Mukaiyama Aldol-Lactonization (TMAL) reaction between various aldehydes and thiopyridyl ketene acetals, using zinc (II) chloride.[82] A high degree of *anti* diastereoselectivity was obtained in this reaction (Scheme 1.16a).

When this TMAL reaction was performed with tin (II) chloride they succeeded in obtaining *syn* diastereoselectivity (Scheme 1.16b).



Scheme 1.16: Tandem Mukaiyama Aldol-Lactonization Method for Preparation of β-Lactones

This method has been used for the preparation of optically active β-lactones from optically active aldehydes bearing α-stereogenic centers; however, this requirement limits its use in the preparation of enantiomerically enriched β-lactones from optically inactive aldehydes. Another pitfall associated with this process is the requirement of α-substituents in the enolate, due to the Thorpe-Ingold effect being required for cyclization to the lactone.

1.4. Objective of the present work:

As discussed, the importance of β-lactones, both as reaction intermediates and as a key structural feature in a number of biologically interesting natural products, is increasing rapidly. However, there is no efficient method available for the enantioselective preparation of mono- or 1, 2-disubstituted β-lactones taken as a whole. There are many drawbacks associated with the available methods for β-lactone preparation, which limit their ease of preparation and utility. These limitations include some or all of: multi-step preparation, low yield, poor generality, poor diastereoselectivity, and poor enantioselectivity.

Thus the focus of the present work is to develop an efficient, facile, one-pot synthesis of β-lactones by which these highly desirable compounds can be prepared in a stereoselective manner. A method called Tandem Evans type Aldol Lactonization (TEAL) was developed by Jenkins and Harrison for the synthesis of racemic and optically active β-lactones. However, only a few preliminary examples were tested. In this present work we developed this method, tested the general applicability of the process, and explored the diastereo- and the enantio- selectivity of a chiral version of the method.

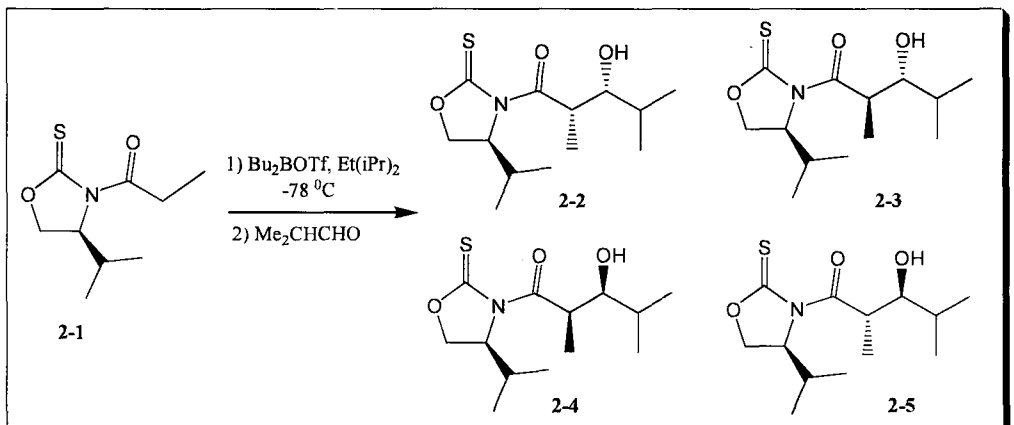
Chapter 2

Results and Discussion

2.1 Tandem Evans-type Aldol Lactonization (TEAL) Method:

Preparation of β-lactones by the method of Danheiser *et al.* (Scheme 1.14) using the reaction of lithium enolates with aldehydes or ketones (TAL) combined with *in situ* cyclization is very desirable because it is a one-pot technique, with good ease of purification and generality towards various aldehydes and ketones.[81]

On the other hand, asymmetric synthesis using Evans chiral oxazolidinones has been used in a wide range of transformations, including the aldol condensation.[83] For example, Evans *et al.* condensed the boron enolate derived from chiral *N*-propionyloxazolidinones (**2-1**) with isobutyraldehyde in 69% yield, with a diastereomeric ratio of **2-2: 2-3: 2-4: 2-5** of 99.4: 0.2: 0.2: 0.2 (Scheme 2.1).[84]

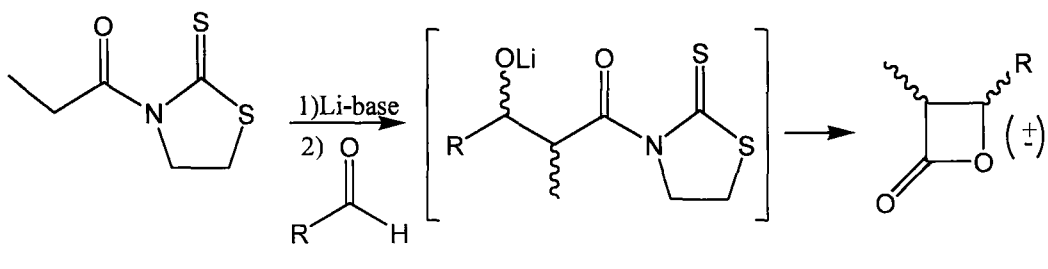


Scheme 2.1: Evans' Chiral Auxiliary in Stereoselective Aldol Addition

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. Subsequent activation of the acid and cyclization has been used to generate β-lactones with high *d.e.*'s and *e.e.*'s; however, this process requires a multi-step sequence.

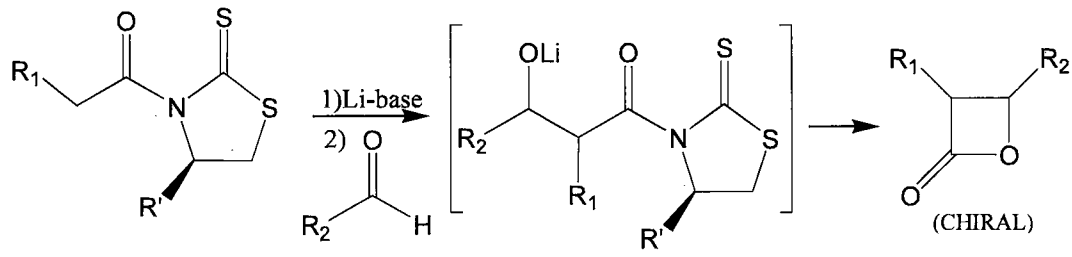
Furthermore, Yan and coworkers have reported that thiazolidinethiones were more efficiently deacylated under the same conditions as used for oxazolidinones.[85] This implies that the thiazolidinethiones represent a highly attractive alternative to their corresponding oxazolidinones in the formation of versatile aldol adducts.

Thus the concept of using thiazolidinethione auxiliaries in asymmetric synthesis can be adopted to the TAL method using a thiazolidinethione in place of the thiophenyl group of Danheiser. The auxiliary could both control the stereochemistry in the initial aldol step, providing control of the stereochemistry of the final product, **and** allow for spontaneous cyclization of the alkoxide. From this analysis, a one-pot tandem Evans-type aldol-lactonization (TEAL) reaction was proposed (Scheme 2.2).



Scheme 2.2: Proposed TEAL Reaction in the Preparation of β-Lactones

The proposed method was investigated first with the unsubstituted thiazolidinethione. Once a route to preparation of racemic β-lactones had been developed, it was expected that substitution of chiral thiazolidinethiones for the unsubstituted thiazolidinethione should generate facial selectivity in the aldol condensation, and thus allow the preparation of optically active 1, 2-substituted β-lactones from optically inactive carbonyl compounds (Scheme 2.3).



Scheme 2.3: Proposed TEAL Reaction for the Preparation of Optically Active β-Lactones.

This stereoselectivity was expected to be achieved by *anti*-addition of carbonyl compounds resulting from the steric hindrance of the chiral group at the 4-position of the Z-enolate (Figure 2.1), in accord with a non-chelated enolate. Further, the thiazolidinethiones should be easily recoverable in this one-pot TEAL reaction and lack the stench associated with the thiophenol produced in Danheiser's method.

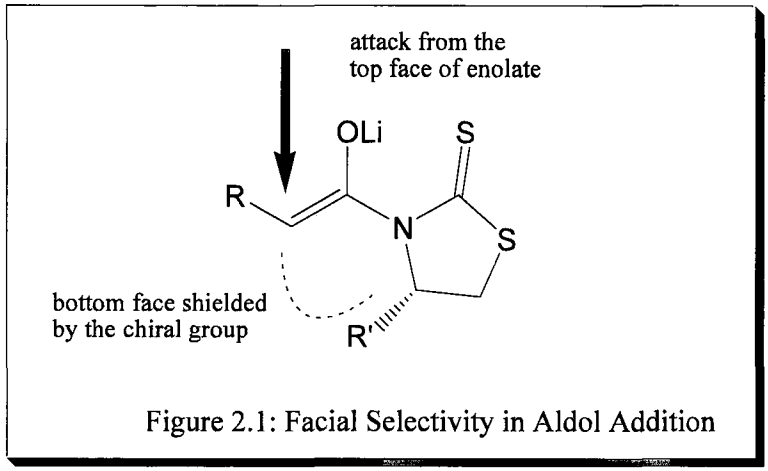
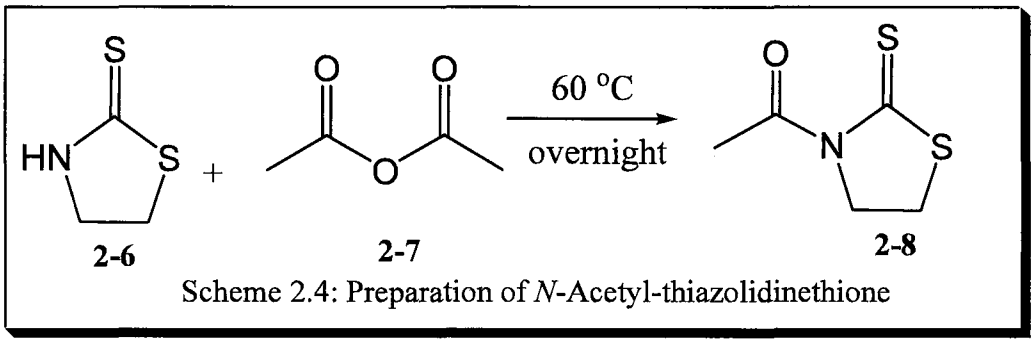


Figure 2.1: Facial Selectivity in Aldol Addition

2.2: Development of the Method:

2.2.1: Preparation of *N*-Acetyl-thiazolidinethione:

In the development of the TEAL reaction, this method was first investigated with *N*-acetyl thiazolidinethione (**2-8**) which was prepared by heating a solution of thiazolidinethione (**2-6**) in neat acetic anhydride (**2-7**) overnight at 60 °C (Scheme 2.4).[86] After evaporation of the excess acetic anhydride, *N*-acetyl thiazolidinethione was obtained in quantitative yield and was used in the next TEAL reaction without need for further purification.

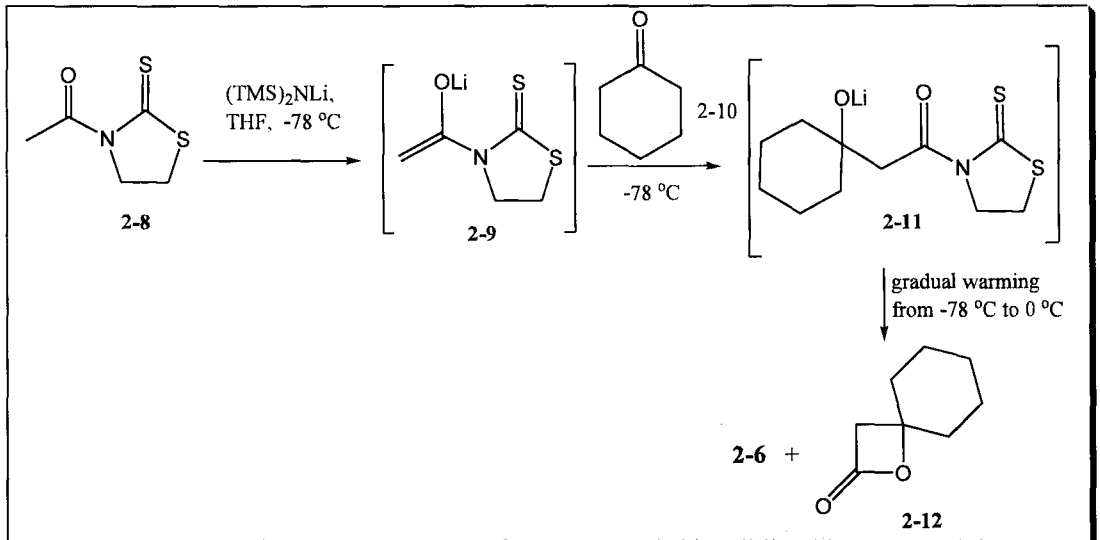


2-6 **2-7** **2-8**

Scheme 2.4: Preparation of *N*-Acetyl-thiazolidinethione

2.2.2: Preparation of β-Lactones Using *N*-Acetyl thiazolidinethione:

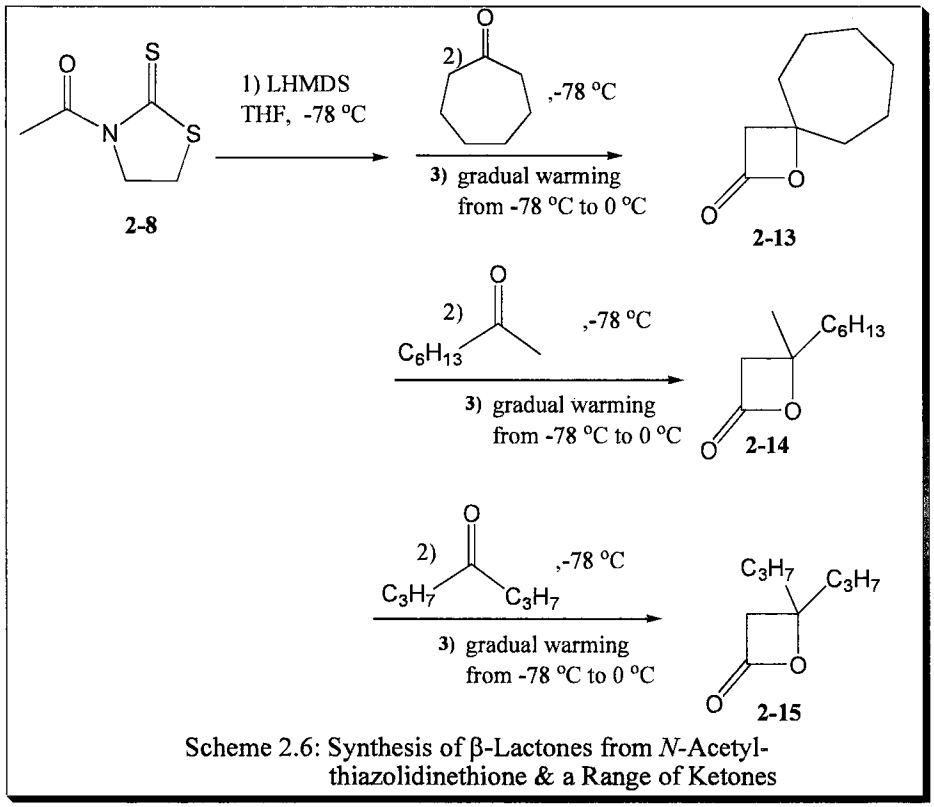
Following the TAL method described by Danheiser *et al.*,[81] a solution of *N*-acetyl thiazolidinethione **2-8** in THF at -78 °C was treated with 1.1 equiv. of lithium hexamethyldisilazide to furnish the desired lithium enolate **2-9** (Scheme 2.5). After stirring for 15 min, freshly distilled cyclohexanone (**2-10**) was added neat to the reaction mixture. The resulting presumed aldolate, **2-11,** was warmed gradually to 0 °C over 1.5 hour. We were happy to find that the 4-spirocyclohexyloxetan-2-one **2-12** was obtained in 86% yield (Table 1, entry 1).



Scheme 2.5: Synthesis of β-Lactone **2-12** from *N*-Acetyl-thiazolidinethione & Cyclohexanone

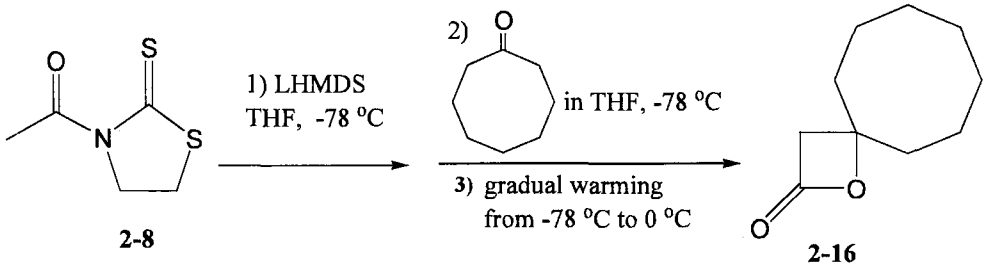
LHMDS was found to be a better base than LDA in this reaction, probably because of the fact that *N*-acyl-thiazolidinethiones are not stable in the presence of LDA in THF at -78 °C, as revealed from the study of Jenkins.[86] As expected, the thiazolidinethione auxiliary (**2-6**) was recovered in high yield in this reaction.

To test the tolerance of the reaction to structural changes in the ketone, this reaction was then investigated with a range of ketones. We found moderate to good yields with cycloheptanone (Table 1, entry 2), octan-2-one (Table 1, entry 4), and heptan-4-one (Table 1, entry 5).



Scheme 2.6: Synthesis of β-Lactones from *N*-Acetyl-thiazolidinethione & a Range of Ketones

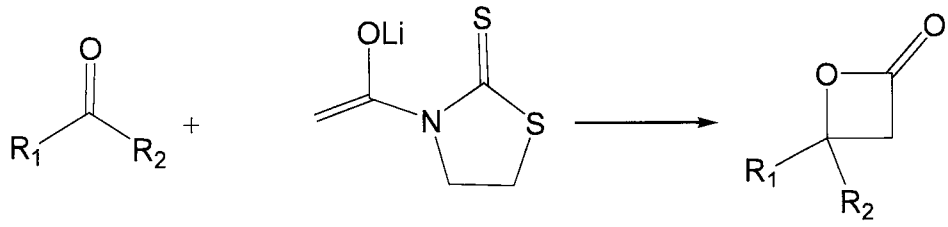
Only a poor yield was obtained with the solid substrate cyclooctanone (Table 1, entry 3), which was added as a solution in THF (Scheme 2.7). This is again probably the result of decomposition of the Li-enolate of thiazolidinethione in THF at -78 °C. [87] To compensate for this problem it has been suggested to add the carbonyls neat to "trap" the enolate as the aldolate, which was not feasible with solid ketones.



2-8 **2-16**

Scheme 2.7: Synthesis of β-Lactone **2-16** from *N*-Acetyl-thiazolidinethione & Cyclooctanone

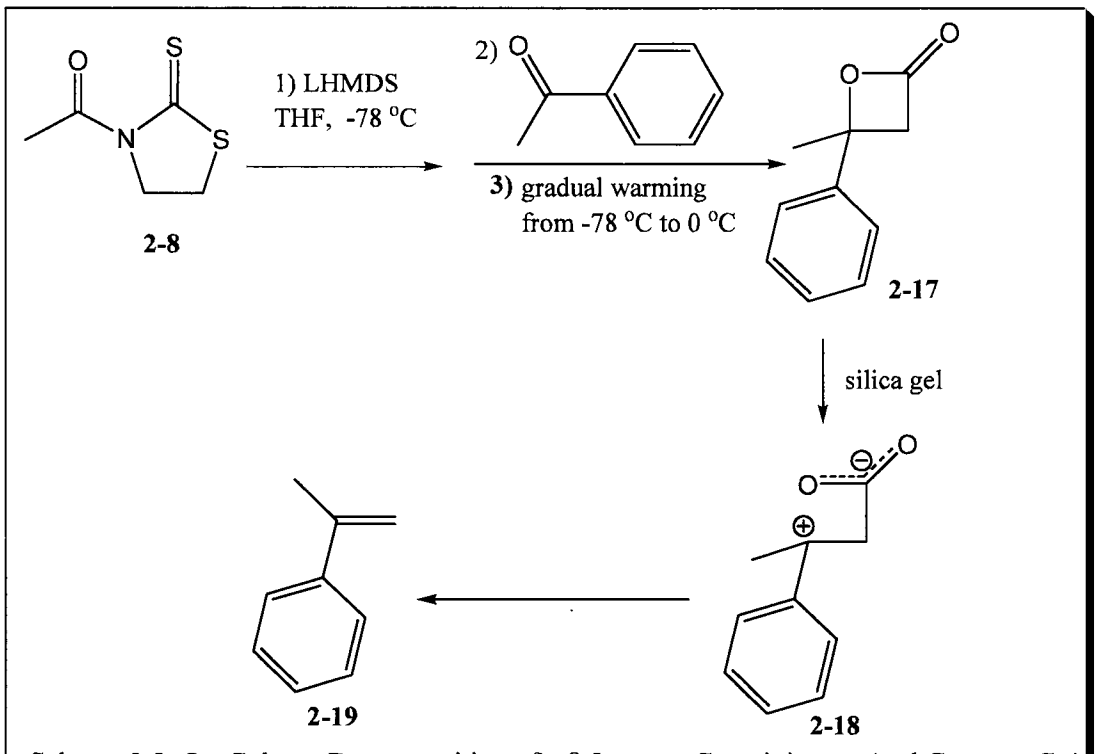
Table 1: Synthesis of β-Lactones via the Tandem Evans-type Aldol Lactonization (TEAL) Method Using *N*-Acetyl-thiazolidinethione.



Entry no	R_1	R_2	% Yield
1	Cyclohexyl		86
2	Cycloheptyl		67
3	Cyclooctyl		6
4	Me	Hexyl	45
5	Propyl	Propyl	39
6	Me	Ph	26 Lactone (decomposed; methyl styrene isolated)

When tested with the aromatic ketone acetophenone, the alkene methylstyrene **2-19** was formed instead of the expected β-lactone. It has been noted that β-lactones with

cation stabilizing substituents (e.g. aryl groups) at the C-4 (β) position decompose unless the chromatographic purification is carried out at -20 °C to suppress on-column decarboxylation of the labile lactone assisted by silica gel (Scheme 2.8).[87] In this particular reaction it is likely that the aromatic ring at C-4 promotes decomposition of the lactone by stabilizing the transitory positive charge in zwitterion **2-18**. Thus acetophenone gave 26% of α-methyl styrene **2-19** (Table 1, entry 6) with *N*-acetyl thiazolidinethione.

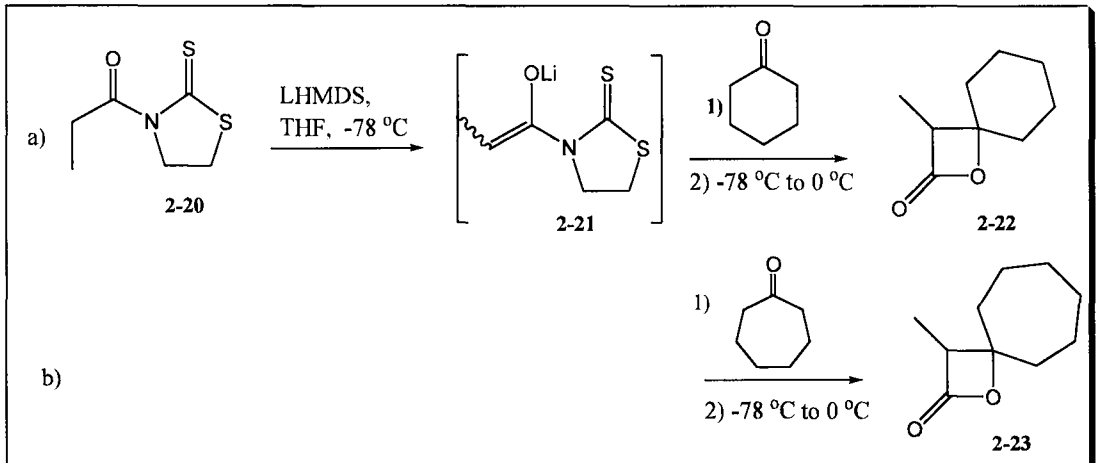


Scheme 2.8: On-Column Decomposition of a β-Lactone Containing an Aryl Group at C-4

2.2.3: Preparation of β-Lactones Using *N*-Propionyl Thiazolidinethione:

Next we tested the versatility of the TEAL reaction with respect to acyl group on the auxiliary. Thus when *N*-propionyl-thiazolidinethione (**2-20**) was prepared from thiazolidinethione (**2-6**) and propionic anhydride and then condensed with **2-10** following the same procedure as described above, lactonization occurred giving an 80% yield of 3-methyl-4-spirocyclohexyloxetan-2-one **2-22** (Scheme 2.9 a, Entry 1, Table 2) as a colorless oil.

Cycloheptanone, when condensed with **2-20** gave 46% of 3-methyl-4-spirocycloheptyloxetan-2-one **2-23** (Scheme 2.9 b, Entry 2, Table 2).



Scheme 2.9: Synthesis of β-Lactones from *N*-Propionyl thiazolidinethione

The success of the TEAL reaction with both *N*-acetyl thiazolidinethione and *N*-propionyl thiazolidinethione, and the higher yield with *N*-acetyl-thiazolidinethione, clearly indicate that, unlike the TMAL method, no α-substituent (Figure 2.2) is required for the effective lactonization of the lithium aldolate.

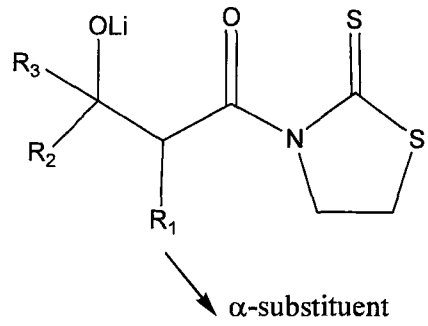
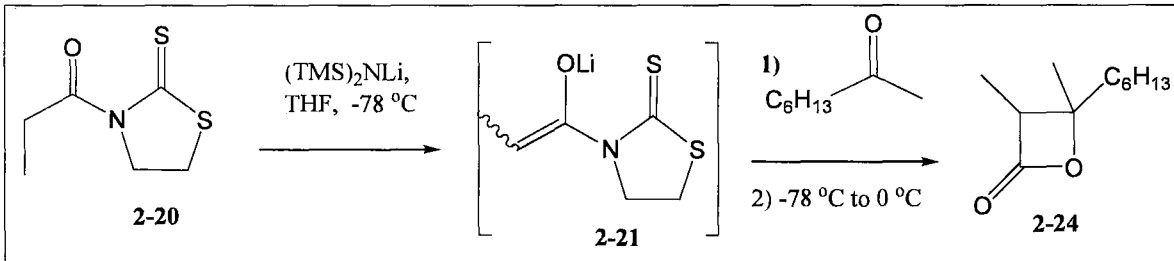


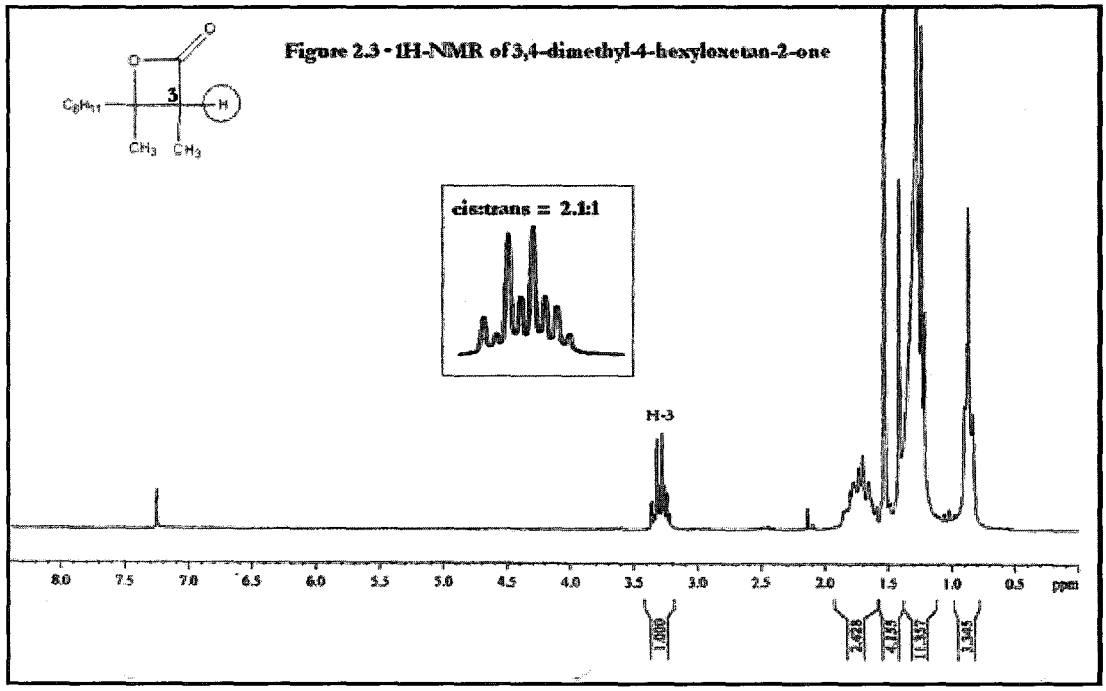
Figure 2.2: α-substituent in the Aldolate

The diastereoselectivity of the TEAL reaction with unsubstituted auxiliary **2-20** was next tested by condensing *N*-propionyl-thiazolidinethione with octan-2-one. 3, 4-Dimethyl-4-hexyl-oxetan-2-one (**2-24**) (Entry 3, Table 2) was obtained in 38% yield.



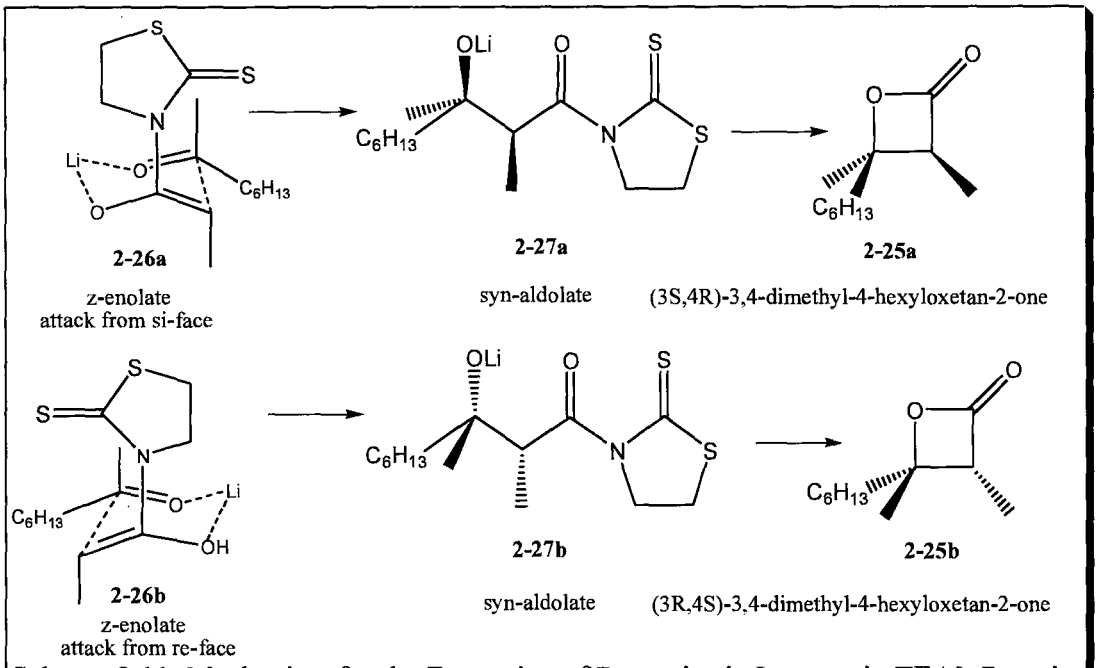
Scheme 2.10: Synthesis of β-Lactone **2-24** from *N*-Propionyl-thiazolidinethione & 2-Octanone

Compound **2-24** can be formed in two diastereomeric forms, each of which has two enantiomers. The diastereomeric ratio was determined by measuring the relative peak heights of the peaks at δ 3.29 and 3.31 corresponding to the diastereomeric H-3s of the two isomers, in the ^{1}H NMR spectrum (Figure 2.3). The ratio was found to be 2.1:1, indicating selective formation of one isomer over the other.



A non-chelated Zimmerman-Traxler-like transition state involving a Z-enolate was postulated,[88] so in the absence of a facial directing group within the auxiliary, it was assumed that both Evans and non-Evans *syn* aldolates would be formed, leading to racemic *cis*-3,4-dimethyl-4-hexyl-oxetan-2-one (**2-25a** and **2-25b**) over the *trans*-products. This is mainly due to reduced steric hindrance in the chair-like transition states **2-26a** and **2-26b** of Scheme 2.11, compared to those leading to the *trans*-lactone. The minor *trans*-isomer would be formed from the E-enolate which formed in the absence of any substitutuent at the 4-position of the auxiliary.

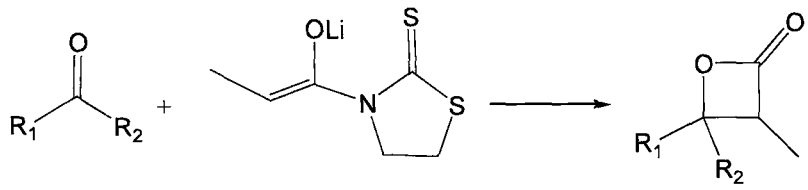
Proof that the *cis* isomer was the major product came subsequently from nOe experiments (see below).



Scheme 2.11: Mechanism for the Formation of Racemic cis-Lactone in TEAL Reaction

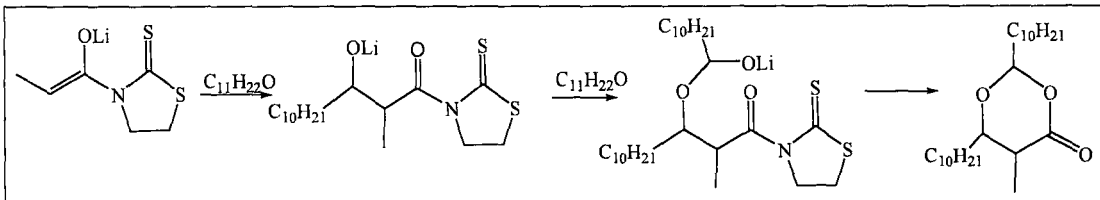
Table 2, entry 4 again shows that formation of α, β-dimethyl styrene rather than the desired β-lactone occurred when acetophenone was condensed with *N*-propionyl thiazolidinethione (**2-20,** cf. Scheme 2.8).

Table 2: Synthesis of β-lactones via the Tandem Evans-type Aldol Lactonization (TEAL) Method Using *N*-propionyl-thiazolidinethione.



Entry no	R_1	R_2	% Yield
1	Cyclohexyl		80
2	Cycloheptyl		46
3	Me	Hexyl	38
4	Me	Ph	21 lactone (decomposed; dimethyl styrene isolated)

One of the features of the TEAL reaction that was revealed by Jenkins' study, is that enolizable aldehydes (e.g. decanal) may form a 2:1 aldehyde: enolate adduct (**2-30**) when added to the solution of enolate **2-21** at -78°C (Scheme 2.12). Only pivalaldehyde (lacking α-protons) gave 37% of the corresponding β-lactone with *N*-acetyl-thiazolidinethione and 62% with *N*-propionyl-thiazolidinethione.[89] In the event, experiments with aldehydes in the current work also failed to give β-lactones.



2-21 2-28 2-29 2-30

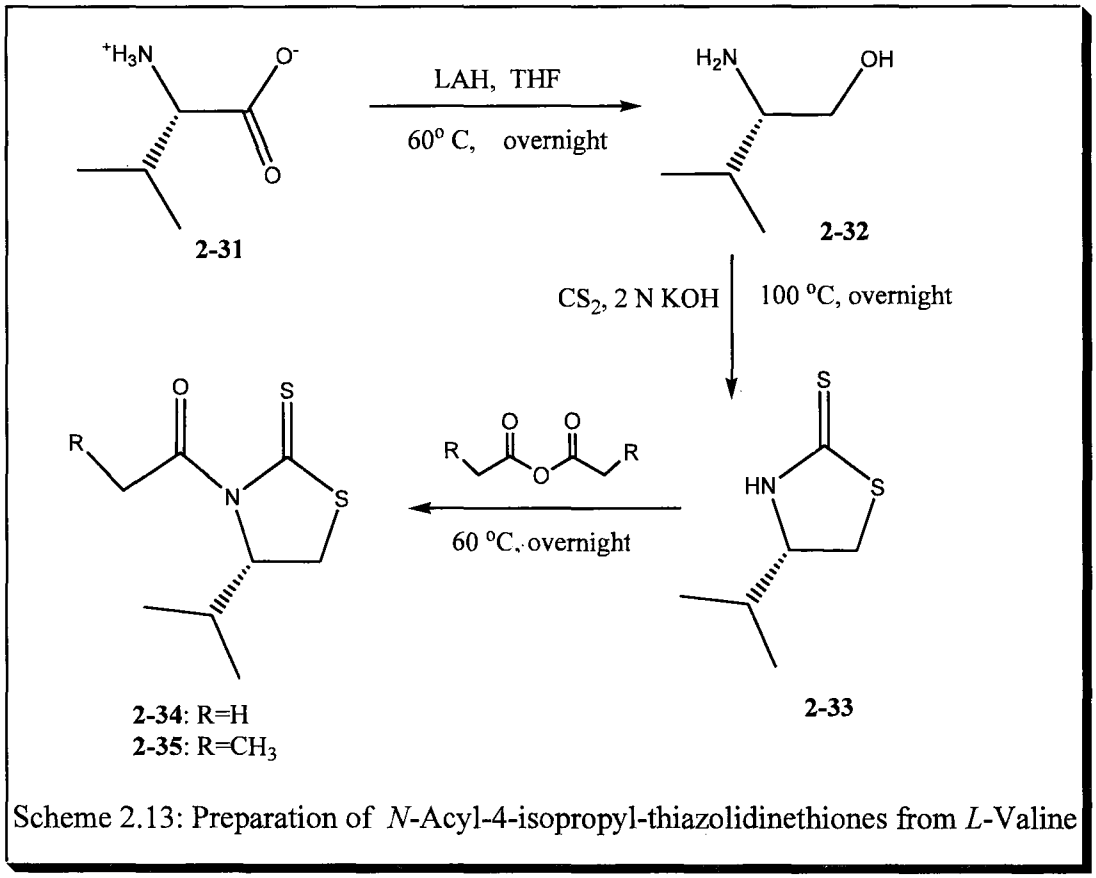
Scheme 2.12 : Formation of 2:1 Adduct of Aldehyde and Enolate

2.3: Approach Using Chiral Thiazolidinethiones:

After establishing the standard reaction conditions for the TEAL method using unsubstituted thiazolidinethione, our next step was to use a chiral thiazolidinethione, (*S*)-4-isopropyl-thiazolidinethione, derived from *L*-valine,[90] in order to impart facial selectivity in the initial aldol step to form enantiomerically enriched β-lactones.

2.3.1 Synthesis of Chiral Auxiliary:

L-valine (**2-31**) was first reduced to *L*-valinol (**2-32**) by heating at reflux with lithium aluminium hydride in THF overnight. A yield of 91% of **2-32** was obtained after work-up. This was subsequently converted to (*S*)-4-isopropyl-thiazolidinethione **2-33**, upon exposure to carbon disulphide in 2 *N* KOH, following the method of Delaunay *et al.*.[91] A solution of **2-33** in neat acetic anhydride was then heated at reflux overnight. Work-up followed by purification gave 99% *N*-acetyl-4-isopropyl-thiazolidinethione (**2-34**) as a yellow oil.[92] *N*-propionyl-4-isopropyl-thiazolidinethione (**2-35**) was also prepared following the same procedure, in a yield of 95% (Scheme 2.13).

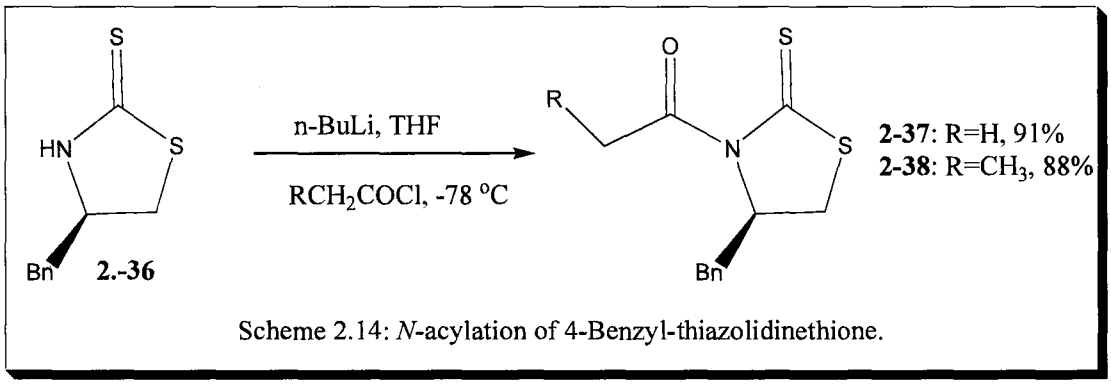


Scheme 2.13: Preparation of *N*-Acyl-4-isopropyl-thiazolidinethiones from *L*-Valine

Unfortunately no β-lactones were detected when either of the *N*-acylated thiazolidinethiones (**2-34 or 2-35**) was condensed with cyclohexanone in the TEAL reaction, despite numerous attempts. The failure of this reaction could be attributed to the bulky isopropyl group causing steric hindrance in cyclization of the lithium aldolate to form the strained four-membered ring of the β-lactone.

Considering this, our next choice was (*R*)-4-benzyl-thiazolidine-2-thione, for producing facial selectivity. We expected that the bulky phenyl group would be further away from the reaction site as a result of the CH_2 group spacer, compared to the

isopropyl group in **2-33**. Following the method of Crimmins *et al.*,[87] 4-benzyl-thiazolidinethione (**2-36**) was acylated by adding n-BuLi at -78 ^{0}C in THF followed by acyl chlorides. After 15 min the reaction mixtures were allowed to warm to room temperature and stirred for another 30 min. The reactions were quenched with 5 mL of 10% K_2CO_3. Work-up and purification gave the desired *N*-acyl thiazolidinethiones **2-37** and **2-38** (Scheme 2.14).



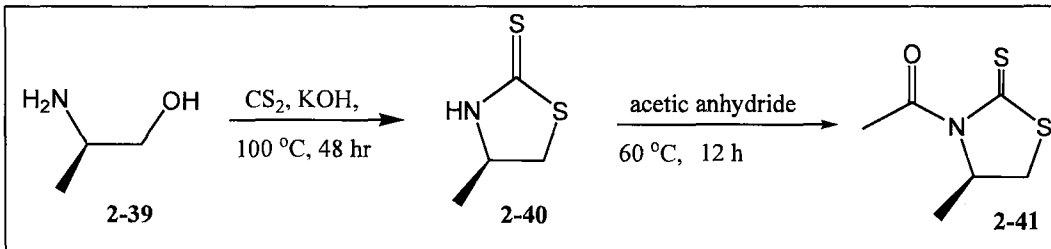
Scheme 2.14: *N*-acylation of 4-Benzyl-thiazolidinethione.

However, both of these derivatives of (*R*)-benzyl-thiazolidinethione also failed to produce the desired β-lactones when condensed with cyclohexanone.

2.3.2 Synthesis of β-Lactones with 4-Methyl-thiazolidinethione:

The size of the chiral directing group in the 4-position was then reduced to a methyl group, expecting that the small methyl group should not produce significant steric hindrance for aldolate cyclization, but at the same time facial selectivity can be achieved in the aldol step because of the chirality in the substrate.

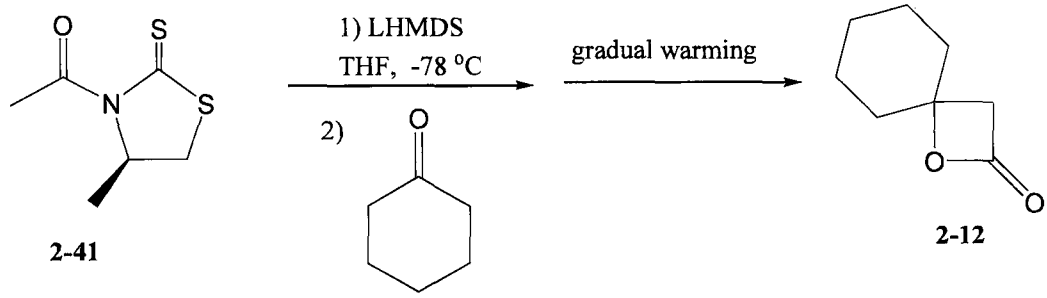
(*R*)-4-Methyl-thiazolidinethione was prepared by refluxing commercially available *D*-alaninol (**2-39**) and CS_2 in aqueous 2 *N* KOH for 48 hours.[91] Work-up followed by crystallization afforded (*R*)-4-methyl-thiazolidinethione (**2-40**) as colorless crystals in 81% yield. This material was then acylated by heating with neat acetic anhydride at 60 °C for overnight to give (4*R*)-*N*-acetyl-4-methyl-thiazolidinethione (**2-41**) in 99% yield. (Scheme 2.15)



2-39 **2-40** **2-41**

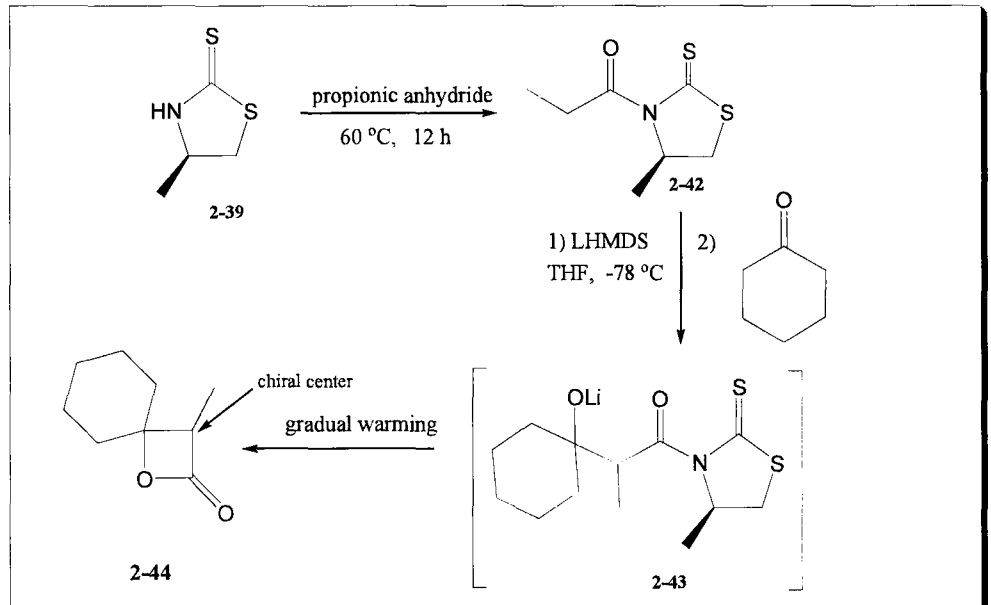
Scheme 2.15: Preparation of (4*R*)-*N*-Acetyl-4-methyl-thiazolidinethione **2-41** from D-Alaninol

To our pleasure we found that when **2-41** reacted with cyclohexanone following the TEAL method, 4-spirocyclohexyloxetan-2-one (**2-12**) was obtained in 64% yield (Scheme 2.16, Table 3, entry 1).



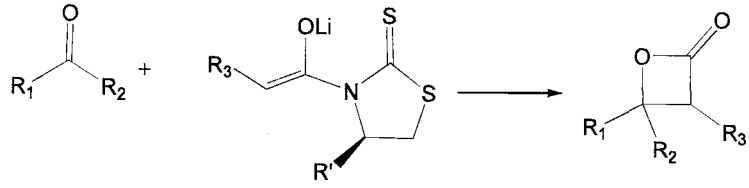
Scheme 2.16: TEAL Reaction of (*R*)-*N*-Acetyl-4-methyl-thiazolidinethione with Cyclohexanone.

When (*R*)-4-methyl-thiazolidinethione, **2-40** was converted to (*R*)-*N*-propionyl-4-methyl-thiazolidinethione (**2-42**) by heating at reflux with neat propionic anhydride and this product then reacted with cyclohexanone, it gave the more interesting 3-methyl-4-spirocyclohexyloxetan-2-one (**2-44**) in 69% yield (Scheme 2.17, entry 2, Table 3), bearing one chiral center at the α-position.



Scheme 2.17: Reaction of (*R*)-*N*-propionyl-4-methyl-thiazolidinethione with cyclohexanone.

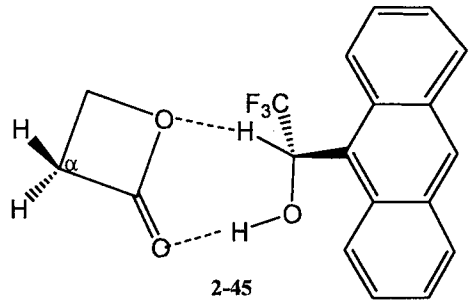
Table 3: Synthesis of β-lactones via theTEAL Method Using Chiral Thiazolidinethiones.



Entry No	R_1	R_2	R_3	R′	*e.e.*	(*cis: trans*)	Yield (%)
1	Cyclohexyl		H	Me	-	-	64
2	Cyclohexyl		Me	Me	81	-	69
3	Cyclohexyl		Me	Et	63	-	A
4	Me	Hexyl	H	Me	40	-	34
5	Me	Hexyl	Me	Me	-	3.9:1	31

[a] The yield was not determined due to difficulties in the purification

The specific rotation of **2-44** was found to be + 41.1° (c=0.1, MeOH) which strongly indicated the predominance of one enantiomer over the other. To determine the enantiomeric excess (*e.e.*) we employed the method of using a chiral shift reagent in NMR-experiments. However, the commonly used shift reagent $Eu(fod)_3$ failed to cause shift of any signal in the ^{1}H-NMR spectrum of 2-44. A shift reagent, (*S*)-2,2,2-trifluoro-1-anthrylethanol, also called Pirkle's reagent,[93] was then used as our next choice. It has two acidic protons which can form two hydrogen bonds with a compound that has two basic sides, such as a β-lactone, and forms a rigid complex such as **2-45** (Figure 2.4).



2-45

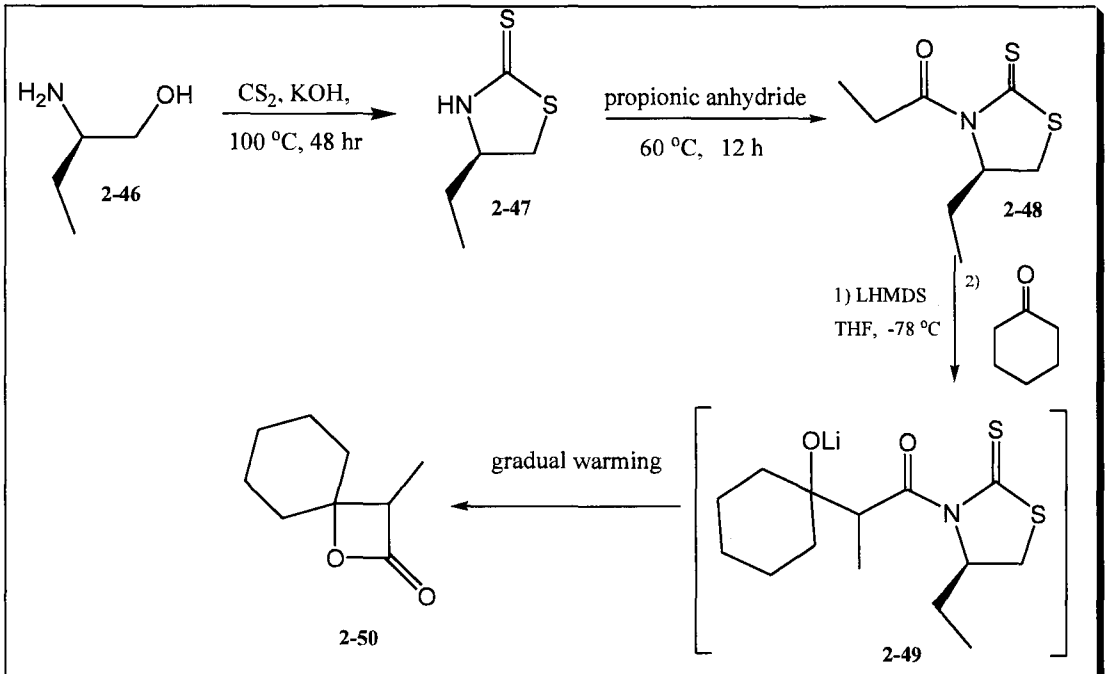
Figure 2.4: Complex Between β–Lactone and Pirkle's Reagent

Therefore, the α-proton of the β-lactone that is on the same side as the anthryl group should show a different chemical shift than the α-proton on the opposite side due to ring anisotropy. Thus, when about 12 mg of (*S*)-2,2,2-trifluoro-1-anthrylethanol was added into a solution of 15 mg of racemic β-lactone **2-21** in $CDCl_3$, the quartet for the α-protons at δ 3.19 (Figure 2.5) of the two enantiomers was split into two separate quartets of equal intensity (Figure 2.6 a). In contrast, the same compound prepared from the chiral auxiliary **2-39** was split into two quartets of different intensity (Figure 2.6 b). From the ratio of the integrals of these two signals, the *e.e.* of this particular TEAL reaction was determined to be 81%. This implies that, as expected, introduction of the chiral auxiliary indeed provided facial selectivity in the TEAL reaction leading to one enantiomer predominantly over the other.

Next, the group at the 4-position of the auxiliary was changed from methyl to ethyl, expecting that a bulkier group would achieve more facial selectivity in the aldol step, and thereby would increase the *e.e.* of the resulting β-lactone.

(4*R*)-*N*-Propionyl-4-ethyl-thiazolidinethione (**2-48**) was prepared from (*R*)-(−)-2-amino-1-butanol (**2-46**) by first heating with CS_2 in 2 N KOH at 110 °C. Then the

resulting (4*R*)-4-ethyl-thiazolidinethione (**2-47**) was heated with neat propionic anhydride at reflux. **2-48** was then condensed with cyclohexanone following the TEAL method to give 3-methyl-4-spirocyclohexyloxetan-2-one (**2-50**) (Scheme 2.18, Table 3, entry 3).



Scheme 2.18: TEAL Reaction of (4*R*)-*N*-Propionyl-4-ethyl-thiazolidinethione with Cyclohexanone

To our surprise, the methyl group was found to be a more efficient stereo-directing group than the ethyl group at position 4 of the thiazolidinethione moiety. Thus, the reaction of cyclohexanone with (4*R*)-*N*-propionyl-4-ethyl-thiazolidinethione gave a lower *e.e.* (63%, Figure 2.5 c), and $[\alpha]^{21}_{D}$ + 10.6 (c=0.1, MeOH). The optical rotation is of the same sign (positive) for both samples, indicating the same sence of stereoinduction, although the absolute configuration could not be readily determined because no literature data is available for this compound.

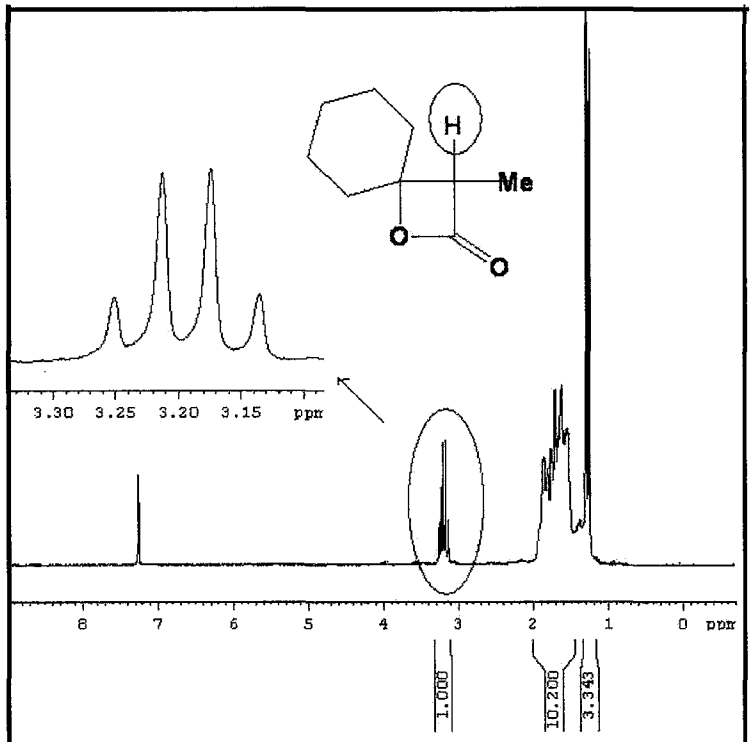


Figure 2.5: 1H NMR of 3-methyl-4-cyclohexyloxetan-2-one

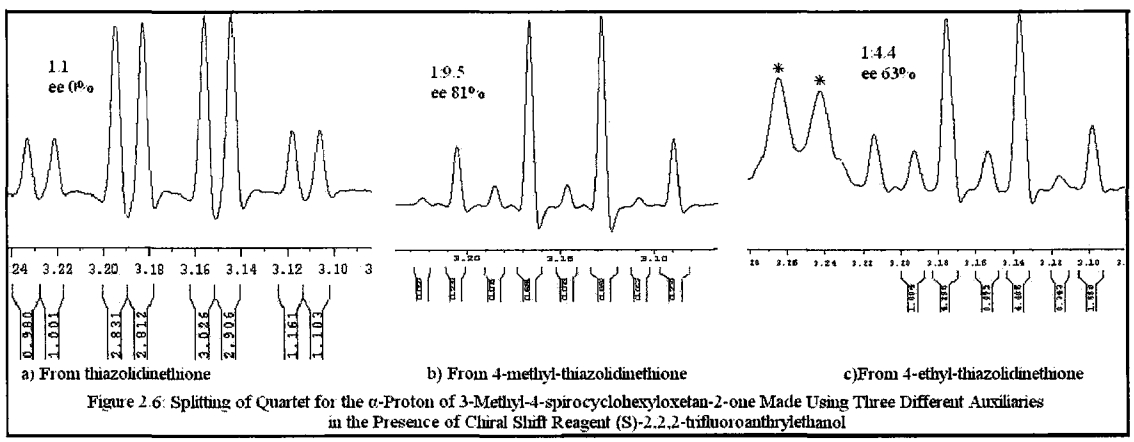
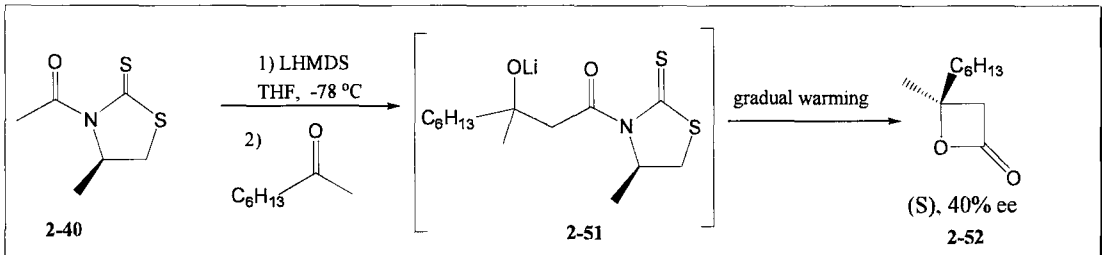


Figure 2.6: Splitting of Quartet for the α-Proton of 3-Methyl-4-spirocyclohexyloxetan-2-one Made Using Three Different Auxiliaries in the Presence of Chiral Shift Reagent (S)-2,2,2-trifluoroanthrylethanol

* peaks from the shift reagent.

To determine which enantiomer is forming predominantly, a known lactone,[94] 4-methyl-4-(n-hexyl)-oxetan-2-one (**2-52**) was then prepared by reacting *N*-acetyl-4-

methyl-thiazolidinethione (**2-40**) and octan-2-one. The desired lactone **2-52** was isolated in 34% yield (Scheme 2.19, Table 3, entry 4).



2-40 **2-51** **2-52**

Scheme 2.19: TEAL Reaction of (*R*)-*N*-Acetyl-4-methyl-thiazolidinethione with 2-Octanone

The optical rotation was measured in methanol and under the literature conditions and found to be $[\alpha]^{21}_{D}$= -4.6 (c=0.1, MeOH) & -6.3 (c= 1.2, $CHCl_3$). The sign of the optical rotation indicates that we prepared (*S*)-(-)-4-methyl-4-(n-hexyl)-oxetan-2-one predominantly, since the (*R*)- enantiomer has a literature rotation of $[\alpha]^{21}_{D} = +4.8°$(*c* 1.17, $CHCl_3$).[94]

A separation of the signals for the α–protons (ab at δ 3.05 and at 3.06) of the two enantiomers was observed in the presence of the chiral shift reagent (*S*)-2,2,2-trifluoro-1-anthrylethanol (Figure 2.7 a & b). From this data, the *e.e.* of this reaction was determined to be 40%. This result is consistent with the proposed mechanism for strereocontrol (Scheme 2.11). This is discussed further below, in context of the next experimental result.

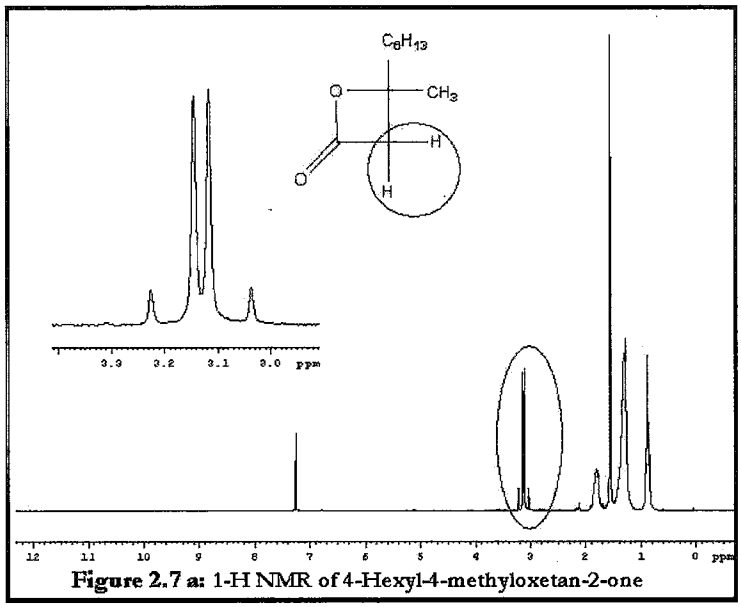


Figure 2.7 a: 1-H NMR of 4-Hexyl-4-methyloxetan-2-one

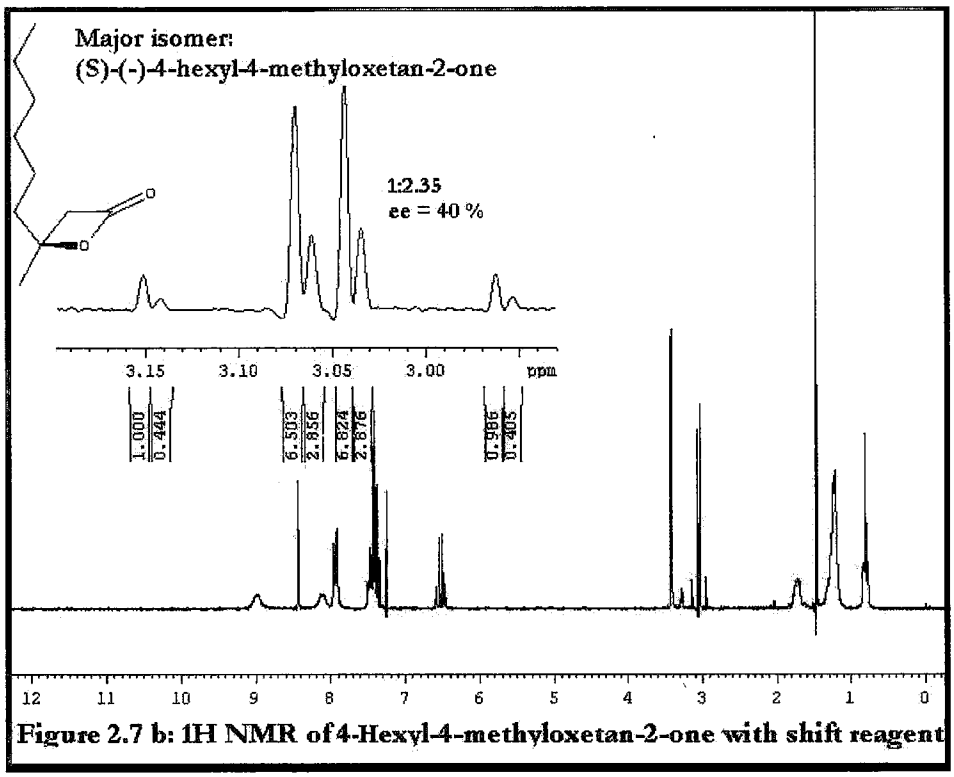
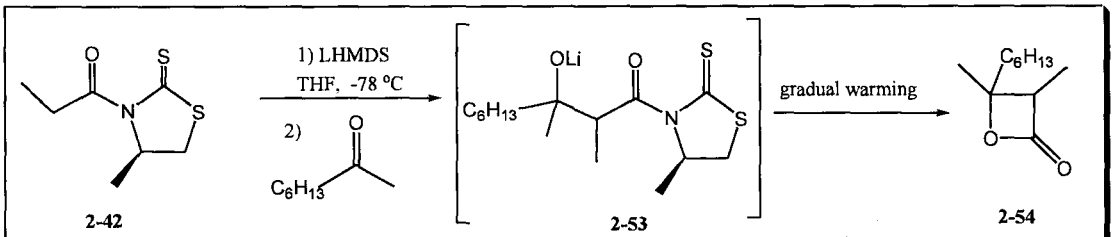


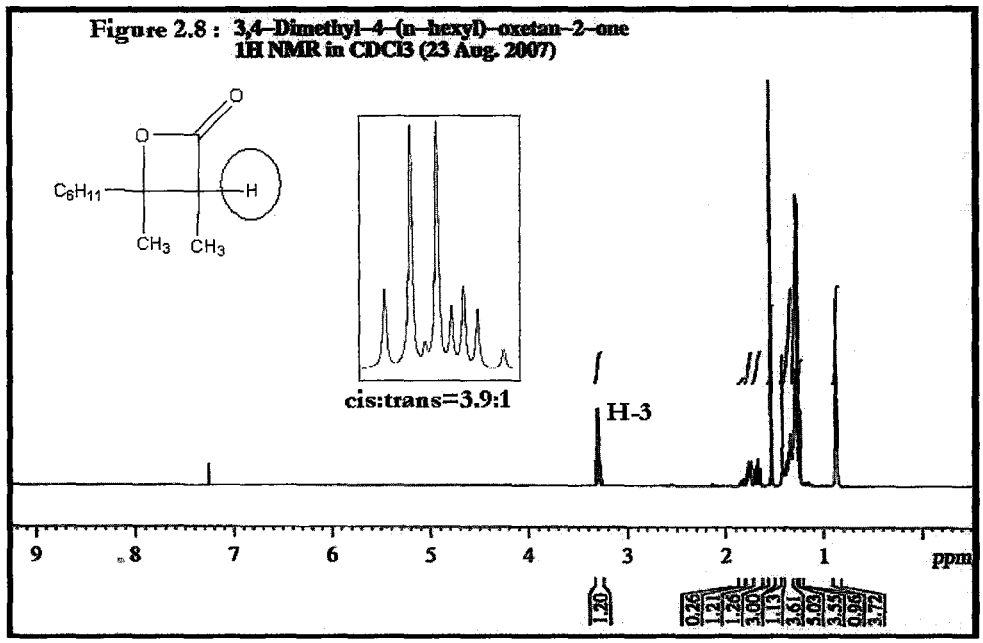
Figure 2.7 b: 1H NMR of 4-Hexyl-4-methyloxetan-2-one with shift reagent

Next (*R*)-*N*-propionyl-4-methyl-thiazolidinethione, **2-42** was condensed with octan-2-one to give 3, 4-dimethyl-4-(n-hexyl)-oxetan-2-one (**2-54**) in 31% yield (Scheme 2.20, Table 3, entry 5).



Scheme 2.20: TEAL Reaction of (*R*)-*N*-Propionyl-4-methyl thiazolidinethione with 2-Octanone

Measurement of peak heights for the signals at δ 3.28 and δ 3.30 in the ^{1}H-NMR spectrum for the α-protons in each of the two diastereomers (Figure 2.8) revealed that the diastereomeric ratio was 3.9:1. Thus, comparing the same reaction with *N*-propionylthiazolidinethione (**2-20,** Scheme 2.10 and Figure 2.3), we see that there was improved diastereoselectivity for (*R*)-*N*-propionyl-4-methyl-thiazolidinethione.



These two distereomers were separated by MPLC using silica gel as stationary phase and 20% ethyl acetate in hexane as eluent. The stereochemistry of each isomer was determined by nOe experiments. For the major diastereomer, irradiation of the H-3 proton signal at δ 3.31 ppm caused an enhancement of the signals at 1.54 ppm and 1.26 ppm (Figure 2.10 b). These two signals are for the two methyl groups, CH_3-6 and CH_3-5, positioned at C-4 and C-3 respectively (Figure 2.9). This implies that the proton at position 3 and the methyl group at position 4 are on the same side of the molecule, so this is *cis*-3, 4-dimethyl-4-(n-hexyl)-oxetan-2-one, **2-54a**. This result is supported by the nOe experiment for the minor isomer, where irradiation of the H-3 signal at δ 3.30 ppm does not cause any enhancement of the signal at δ 1.43 for the protons of the methyl group CH_3-6 at position 4. On the contrary it enhances the signal for the H-7 protons (CH_2 group of the hexyl chain, connected to C-4) (Figure 10 d) which clearly indicates that the C_6H_{13} chain is on the same side as the H-3 proton, and the opposite side to the methyl group at position 3. Irradiation of CH_3-5 also led to an nOe at CH_3-6, confirming that these two substituents are *cis* on the lactone ring. Thus the minor isomer is *trans*-3, 4-dimethyl-4-(n-hexyl)-oxetan-2-one (**2-54b**).

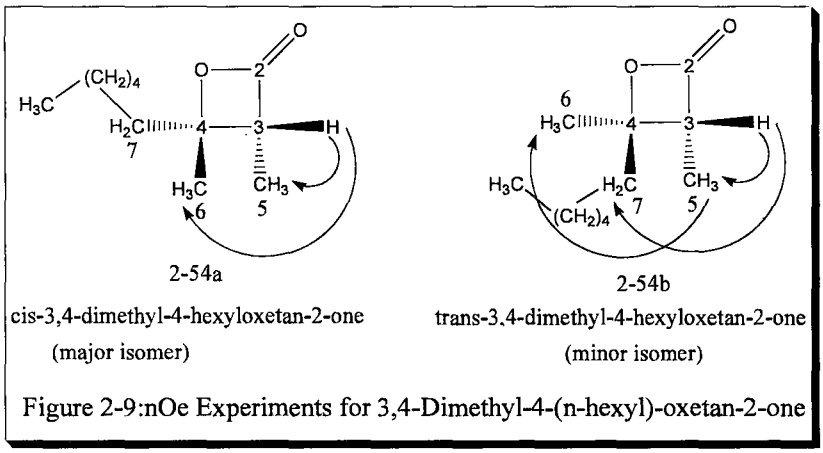
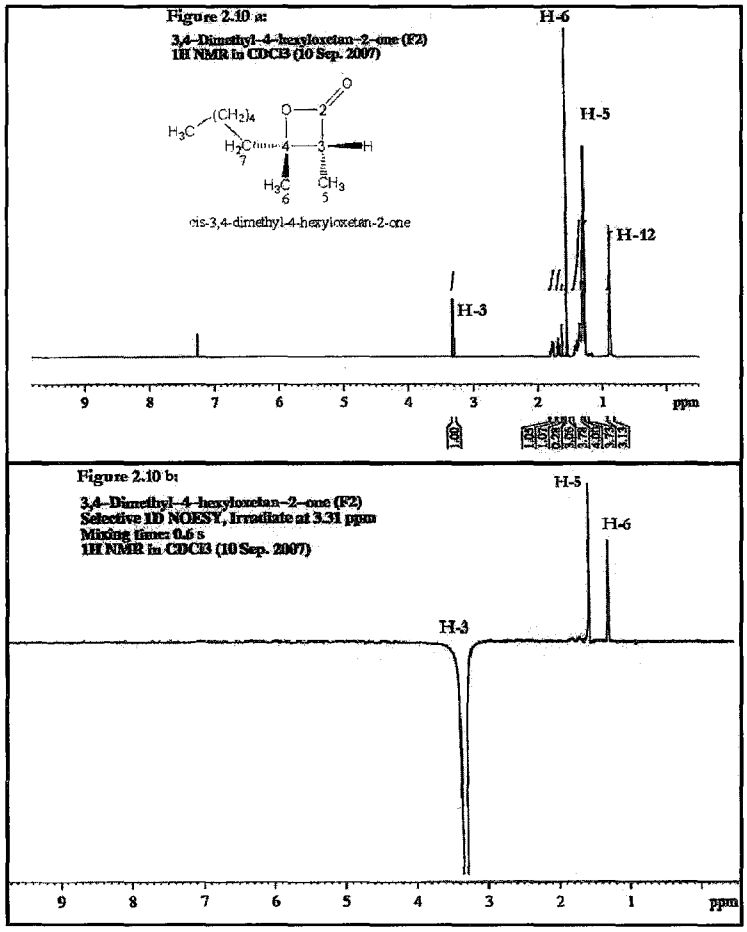
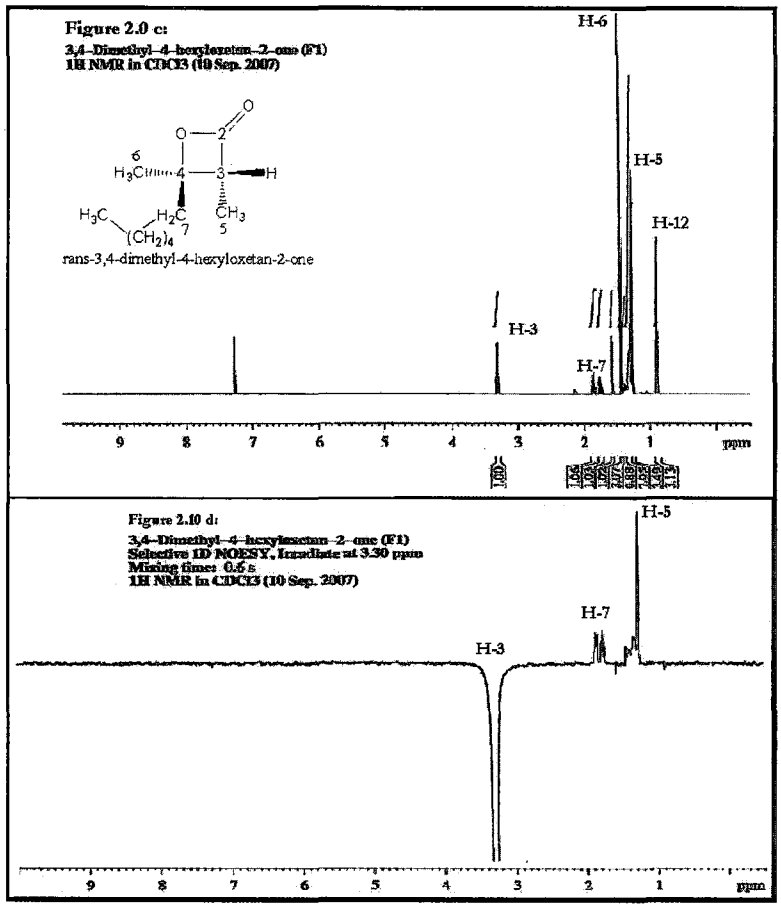
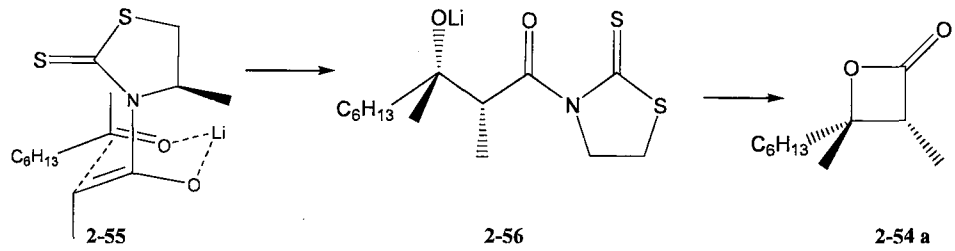


Figure 2-9:nOe Experiments for 3,4-Dimethyl-4-(n-hexyl)-oxetan-2-one





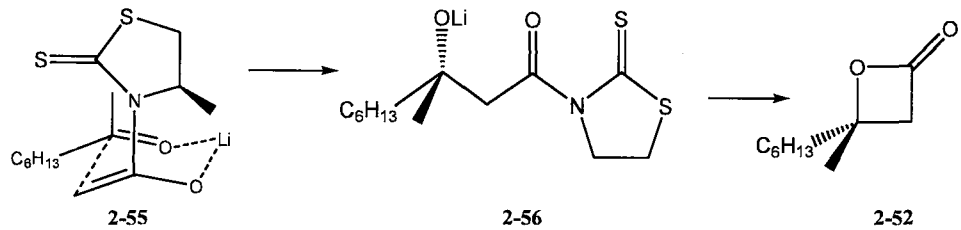
The formation of the *cis*-isomer as the major product supports the mechanism predicted earlier (Scheme 2.11). The methyl group at position 4 of the auxiliary suppresses the formation of the E-enolate to some degree and thereby suppresses the formation of *trans* product. Also it is expected that π-facial selectivity increases to some extent giving optically active product (Scheme 2.21).



2-55 attack from re-face | **2-56** syn-aldolate | **2-54 a** (3*R*,4*S*)-3,4-dimethyl-4-hexyloxetan-2-one

Scheme 2.21: Formation of *cis*-Lactone Through a Non-Chelated Transition State Where Re-Face Addition is Favored for Aldol Addition.

The proposed mechanism also supports the formation of (*S*)-4-hexyl-4-methyloxetan-2-one (**2-52**) as the major product, which forms through the transition state **2-55** where the carbonyl compound is added from the re-face of the aldolate (Scheme 2.22).



2-55 | **2-56** | **2-52** (*S*)-4-hexyl-4-methyloxetan-2-one

Scheme 2.22: Mechanism for Enantioselective TEAL Reaction in the Preparation of β–Lactone **2-52**

In the presence of the chiral shift reagent (*S*)-2,2,2-trifluoro-1-anthrylethanol, the quartet at δ 3.30 of *cis*-3,4-dimethyl-4-(*n*-hexyl)-oxetan-2-one (**2-54a**) split into two quartets and from the ratio of the integrals of these two signals, the *e.e.* was measured to be 14%. In the same experiment with the *trans* diastereomer, **2-54b,** the *e.e.* was found to be 62%. The observed preference for the 4*S* enantiomer in the preparation of **2-52** and the

predominance of *cis*-isomer in the preparation of **2-54** suggest the formation of (3*R*,4*S*)-3,4-dimethyl-4-hexyloxetan-2-one (**2-54a**) as the major isomer. However, more experimental data needed to confirm the absolute configurations of these four enantiomers.

2. 4: Summary:

Using the lithium enolates of *N*-acetyl- (**2-8**) and *N*-propionyl-thiazolidine-2-thione (**2-20**), several spiro-, di- and tri- substituted β-lactones were successfully prepared in fair to good yield by the TEAL method. The method worked well with various types of ketones. However, cyclooctanone, when condensed with **2-8** gave a disappointing yield (6%), owing to the need for adding the ketone 'neat' to the reaction mixture. The developed methodology has a simple purification process and good recovery of the auxiliary.

Substituting chiral *N*-acetyl- (**2-41**) and *N*-propionyl-4-methyl-thiazolidine-2-thione (**2-42**) for **2-8** and **2-20**, we were able to prepare optically active β-lactones **2-44, 2-52 and 2-54.** The enantioselectivity in forming β-lactones bearing chiral centers at the α-position (**2-44,** 83% *e.e.*) is promising. A degree of diastereoselection was also observed, forming *cis* lactone. Therefore, with the progress reported herein, there is scope for further improvement of the Tandem Evans type Aldol Lactonization methodology towards the efficient synthesis of chiral β-lactones.

Chapter 3.

Conclusion and Future Work

3.1: Conclusion:

In our present work, we demonstrated that the introduction of thiazolidinethiones as achiral or chiral auxiliaries in a Tandem Aldol Lactonization method worked well, giving moderate to good yields of β-lactones in a one-pot synthesis. The thiazolidinethiones are found to be **both** good auxiliaries for aldol reaction **and** excellent leaving groups; they can thus be used to promote the intramolecular cyclization of the aldolate intermediates required in the TEAL reaction. The cyclization method is also versatile, with various cyclic and open chain ketones and acyl thiazolidinethiones with or without a substituent at the α-position all giving lactones. This implies that, unlike other methods, α-substituents do not play any role for efficient cyclization (no Thorpe-Ingold effect required), as in almost all cases *N*-acetyl-thiazolidinethione gave better yields that *N*-propionyl-thiazolidinethione. Thione functionality in imides is required for spontaneous cyclization of the intermediate as the reaction with oxazolidinones has previously failed in our lab and acetyl-oxazolidinethione gave a poor yield compared to acetyl-thiazolidinethione.[89]

The TEAL reaction was developed in order to combine the stereoselectivity of an Evans-type aldol condensation with the efficiency of a tandem aldol-lactonization (TAL) reaction. Unfortunately the lithium enolates of common *N*-acyl thiazolidinethiones, **2-34,**

2-35, 2-37 and **2-38** failed to produce any β-lactone in the TEAL method. However, with *N*-acyl-4-methyl-thiazolidinethiones we were succesful in producing β-lactones with improved de over that of the corresponding *N*-acyl-thiazolidinethiones, and with some degree of enantioselectivity.

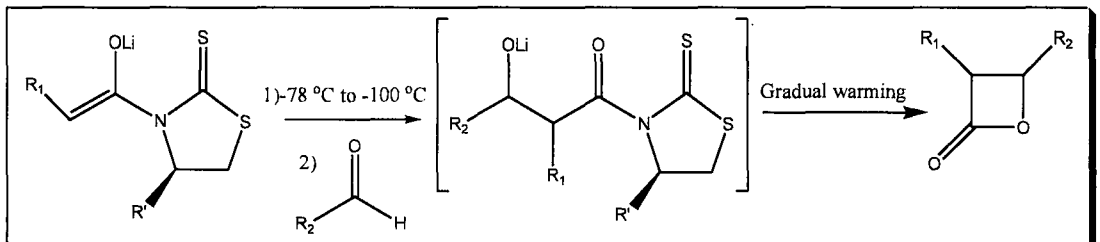
3.2: Future Work:

A number of aspects remain to be investigated in order to improve the preparation of β-lactones by the TEAL method. Some of them are: application of this method with aldehydes to produce 3, 4-disubstituted and 4-monosubstituted β-lactones, improvement of both diastereoselectivity and enantioselectivity in the aldol step, and determination of absolute stereochemistry of the resultant lactones.

3.2.1: Problems with Aldehydes and Plausible Solutions:

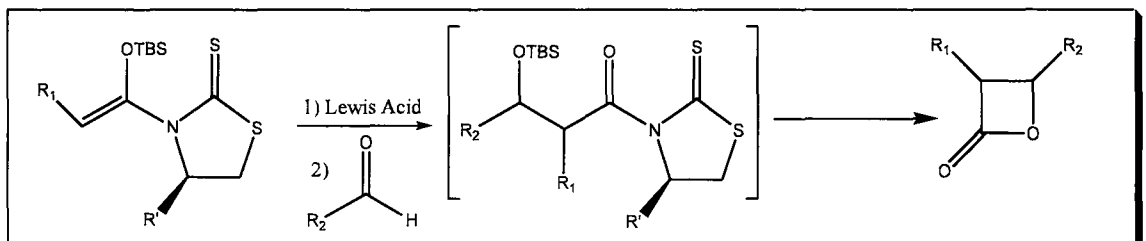
Trace amounts of β-lactone were obtained (detected by IR spectroscopy) when the lithium enolate of *N*-propionylthiazolidinethione was condensed with undecanal in the TEAL reaction.[86] The low yield was probably because of the decomposition of *N*-propionylthiazolidinethione in the presence the LDA at -78 °C. To suppress this reaction it is important add the aldehyde neat in order to trap the lithium enolate as the lithium aldolate. However, as mentioned earlier, formation of the 2:1 aldehyde: enolate adduct **2-30** occurs when aliphatic aldehydes are not added as a pre-cooled dilute solution (Scheme 2.12).

Therefore, one possible solution to this dilemma might involve cooling the enolate to -100 °C or lower after formation of the enolate at -78 °C, and then slowly adding the aldehyde as a pre-cooled solution in THF to avoid decomposition of the thiazolidinethione enolate moiety (Scheme 3.1).



Scheme 3.1: Proposed TEAL Reaction with Modified Conditions.

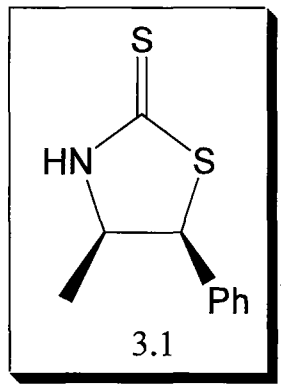
Another possible solution is to use the silyl enol ether of the *N*-acyl-thiazolidinethiones in a Mukaiyama-like aldol-lactonization, analogous to the approach used by Romo *et al.* in the synthesis of β-lactones with thiopyridyl ketene acetals.[95] The silyl enol ether should be much less reactive than the lithium enolate, thus allowing the reaction to proceed towards the desired direction (Scheme 3.2).



Scheme 3.2 : Combination of Mukaiyama Aldol Reaction and TEAL Reaction in the Preparation of β-Lactones

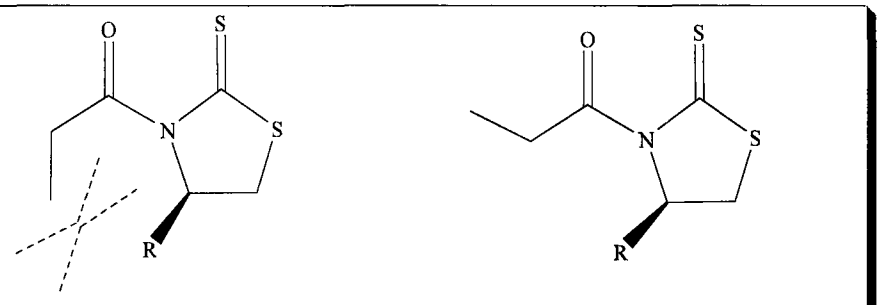
3.2.2: Improvement of Stereoselectivity:

The reactions using 4-methyl-thiazolidinethione as a chiral auxiliary have higher *e.e.*'s than those with 4-ethyl-thiazolidinethione. This is consistent with the fact that a bulky group at the 4-position of the auxiliary is not desirable for the lactonization. Thus, from the pool of available chiral thiazolidinethiones, the next choice should be one in which the methyl group remains constant at position 4 but a bulky group can be introduced at a remote site to increase the diastereotopic face selectivity, thereby increasing the *e.e.* value. Hence, the next choice should be 4-methyl-5-phenylthiazolidinethione **3-1,** a compound that has been reported by Le Corre.[91]



3.1

On the other hand, the reaction producing 3-methyl-4-spirocyclohexyloxetan-2-one with a chiral center at the 3-position has a higher *e.e.* than that producing 4-methyl-4-(n-hexyl)-oxetan-2-one with a chiral center at the 4-position. It has been proposed that the reaction with the lithium enolate has a non-chelated transition state where the chiral group at the 4-position of the auxiliary regulates the orientation of the alkyl group at the α-position (Figure 3.1).



s-trans: disfavoured by steric crowding

s-cis: favoured

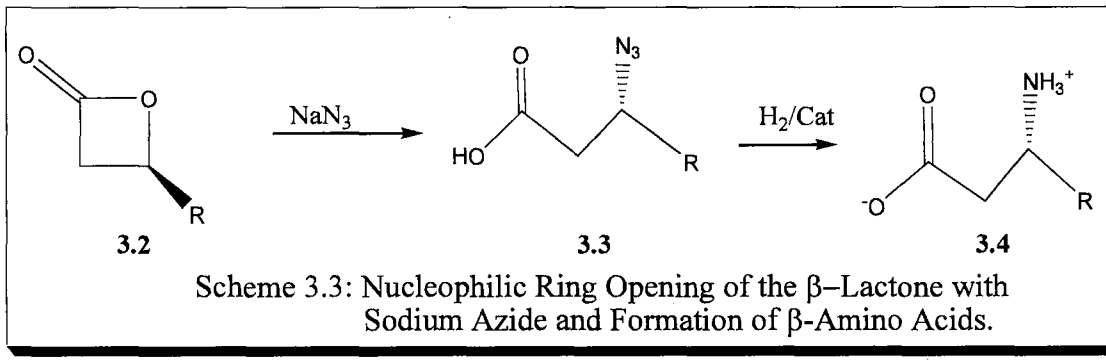
Figure 3.1:Orientation of the Alkyl Group at the alpha-Position

High diastereoselectivities in aldol reactions with chiral enolates are controlled by two elements: enolate diastereotopic selectivity and relative facial selectivity between enolate and aldehyde. Good control of both these elements can produce high selectivity. Hence, it is anticipated that use of strong Lewis acids could result in the formation of bidentate, chelated rigid transition states and thereby increase the diastereoselectivity of the aldol step. In addition the diastereoselectivity can be controlled by changing the nature and stoichiometry of the Lewis acid. It may then be possible to cyclize the resulting aldols using strongly basic conditions.

3.2.3: Determination of Absolute Stereochemistry:

As described in Chapter 2, the enantiomeric excess of β-lactones can be determined using the chiral shift reagent (*S*)-2,2,2-trifluoro-1-anthrylethanol (TFAE). However, to determine the absolute stereochemistry of unknown lactones, it is important to derivatize the synthesized lactone as a crystalline compound to facilate the use of x-ray crystallography. It is well known that β-lactones undergo nucleophilic ring opening to

give a variety of β-hydroxyester or amide adducts depending on the nature of the nucleophile (Chapter 1). Though hard nucleophiles have a higher affinity for the carbonyl center, soft nucleophiles such as azide attack the β-carbon giving S_N2-like displacement of the carboxylate residue to afford β-azido acids (**3-3**) with inversion of configuration at the β-center (Scheme 3.3).[96] The resultant acid **3-3** can be reduced to a β-amino acid **3-4** by catalytic hydrogenation:



3.2 **3.3** **3.4**

Scheme 3.3: Nucleophilic Ring Opening of the β–Lactone with Sodium Azide and Formation of β-Amino Acids.

Since these acids are crystalline, and have a high melting point, the absolute stereochemistry of the β-amino acid could then be determined using x-ray crystallography. From this it should be possible to determine the absolute stereochemistry of the 3, 4 di- or tri-substituted β-lactones produced in the TEAL reaction.

Great opportunities lie with β-lactones in synthetic chemistry. Successful development of this asymmetric route to β-lactones can make these compounds versatile chiral intermediates in the synthesis of various pharmacologically relevant natural products as well as a range of important synthetic compounds.

Chapter 4:

Experimental

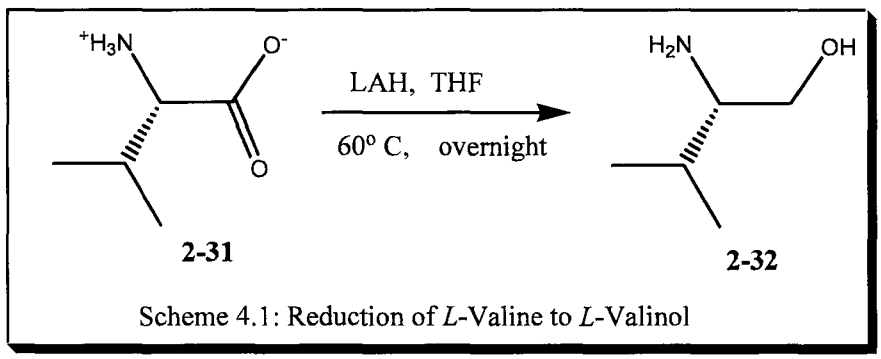
4.1 General Synthetic Procedures:

All reactions were performed in oven-dried glassware and magnetically stirred. THF and diethyl ether were distilled from sodium-benzophenone ketyl radical immediately prior to use. Commercially available ketones were purchased from Aldrich Co. and distilled prior to use. Other commercial grade reagents (Aldrich) were used without further purification. Flash column chromatography was accomplished using Merck 60 (230-400 mesh) silica gel. 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). NMR spectra were recorded on a Bruker AV-200 spectrometer (200 MHz) or a Bruker AV-600 spectrometer (600 MHz). Infra-red spectra were recorded on a Bio-Rad FTS 40 machine. Mass spectra were obtained on a Kratos MS890MS spectrometer. Specific rotations were measured on a Perkin-Elmer 241 polarimeter installed with a sodium lamp (λ = 389 nm). The enantiomeric excesses (*e.e.*'s) of the chiral lactones were determined using *(S)*-2,2,2-trifluoro-1-anthrylethanol as a chiral shift reagent in ^{1}H NMR experiments[93].

4.2 Preparation of compounds

4.2.1 Reduction of *L*-Valine:

Using the method of Harrison,[91] lithium aluminum hydride (1.3 g, 34.74 mmol) was added with caution (small amount at a time) to a suspension of *L*-valine (**2-30**) (1 g, 8.6 mmol) in 50 mL THF. The mixture was heated at reflux for overnight and then cooled

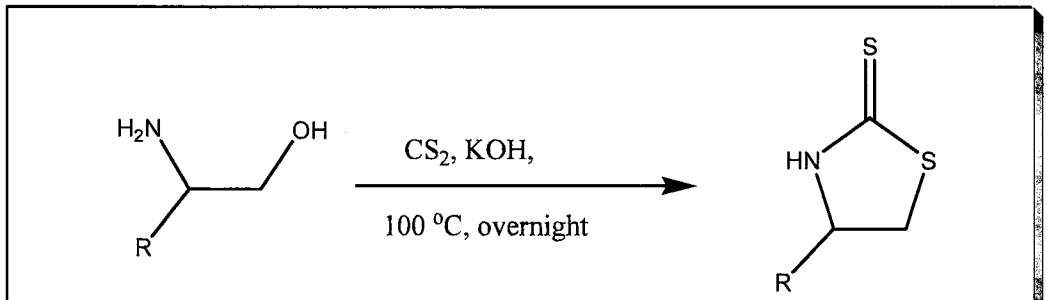


Scheme 4.1: Reduction of *L*-Valine to *L*-Valinol

to 0 ^{0}C with ice-water. Water (2.3 mL) was added very cautiously, (giving a white precipitate) followed by 1.35 mL of 15% NaOH and 3 mL of additional water. Then the mixture was diluted with 50 mL EtOAc and was stirred for 20 minutes and filtered. The residue was washed with ethyl acetate (25 mL x 2 times). The combined organic extracts were then dried over anhydrous sodium sulfate. Then the mixture was filtered and concentrated on the rotatory evaporator to give valinol (**2-32**) (0.8 g, 91%) as a colorless semi-solid material, which was used directly in the next reaction. The ^{1}H NMR spectrum was identical to that reported by Mayers.[97] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.66 (m, 1H), 2.40 (bs, 3H), 2.65 (m, 1H), 3.39 (dd, J = 8.5, 10.6 Hz, 1H), 3.73 (dd, J = 3.7, 10.6 Hz, 1H).

4.2.2 General Procedure for the Preparation of Chiral Thiazolidinethiones:

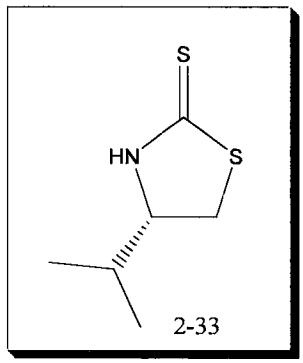
To a solution of the amino alcohol in 2 N KOH was added 10 equiv. of CS_2. The reaction mixture was stirred at 100 °C (bath temp 110 °C and with an efficient reflux condensation) overnight. After cooling to room temperature, the thiazolidinethione was



Scheme 4.2: Preparation of Chiral Thiazolidinethiones from Chiral 2-Aminoethanols

extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated using the rotatory evaporator. White crystals of thiazolidinethiones were obtained by recrystallization from chloroform.

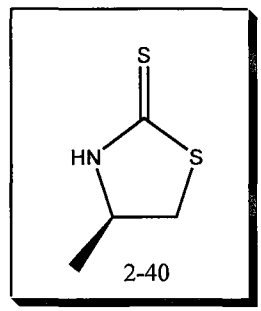
(4*S*)-4-Isopropyl-thiazolidinethione (2-33):



The reaction of *L*-valinol (0.8 g, 7.8 mmol) and CS_2 (2.3 mL, 10 equiv.) in 100 mL of 2 N KOH was performed according to the general procedure. Work-up followed

by crystallization afforded 4-isopropylthiazolidinethione (1.03 g, 6.4 mmol, 83%). Proton NMR was identical to that reported by Delaunay *et al.*[91] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.96 (m, 1H), 3.31 (dd, J = 8.3, 11.1 Hz, 1H), 3.50 (dd, J = 8.3, 11.1 Hz, 1H) 4.04 (m, 1H), 7.9 (s, 1H).

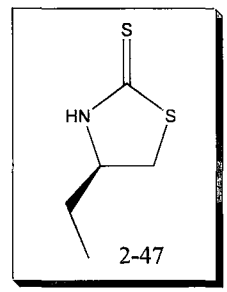
(4*R*)-Methyl-thiazolidinethione (2-40):



2-40

The reaction of *D*-alaninol (2.00 g, 26.7 mmol) and CS_2 (16 mL, 10 equiv.) in 200 mL aqueous 2 N KOH was performed according to the general procedure. Work-up followed by crystallization afforded 4-methyl-thiazolidinethione (2.87 g, 21.6 mmol, 81%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (d, J = 4.4 Hz, 3H), 3.24 (dd, J = 7.6, 11.0 Hz, 1H), 3.69 (dd, J = 7.6, 11.0 Hz, 1H), 4.48 (m, 1H), 8.55 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.7, 40.3, 60.2, 200.1. MS (EI) m/z: 133 (M^+), 84, 74, 41 (base).

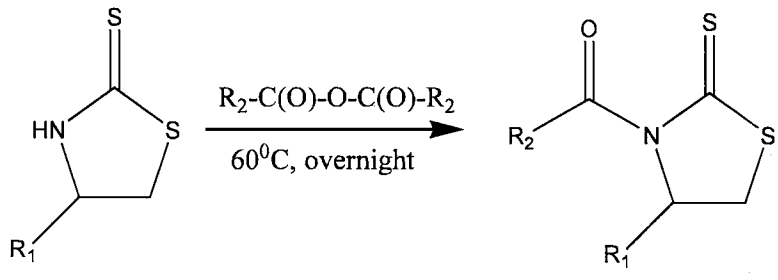
(4*R*)-4-Ethyl-thiazolidinethione (2-47):



2-47

The reaction of (*R*)-(−)-2-amino-1-butanol (2.00 g, 22.7 mmol) and CS_2 (14 mL, 10 equiv.) in 200 mL aq. 2 N KOH was performed according to the general procedure. Work-up followed by crystallization afforded 4-ethyl-thiazolidinethione (2.6 g, 17.7 mmol, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.5 Hz, 3H), 1.74 (m, 2H), 3.20 (dd, J = 10.8, 7.8 Hz, 1H), 3.56 (dd, J = 10.8 , 8.3 Hz, 1H), 4.16 (m, 1H), 8.67 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 10.0, 27.1, 38.0, 65.9, 200.4. MS (EI) m/z: 147 (M^+), 117, 100, 73, 57 (base).

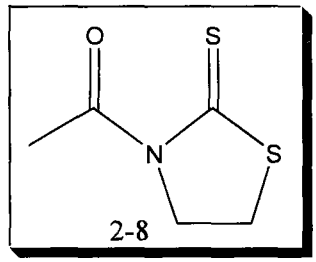
4.2.3 General Procedure for the Preparation of *N*-Acylated Thiazolidinethiones:



Scheme 4.3: General Procedure for the *N*-Acylation of Thiazolidinethiones

A solution of thiazolidinethione in neat acetic or propionic anhydride was heated at 60 ^{0}C overnight (Scheme 4.3). The progress of the reaction could be visually monitored as the clear and colorless solution became bright yellow. The unreacted anhydride was removed on the rotatory evaporator to give the desired *N*-acylated thiazolidinethione as a yellow oil which was further purified using flash column chromatography (20% EtOAc in Hexane).

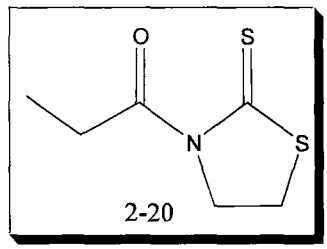
_N_-Acetyl-thiazolidinethione (2-8):



2-8

A solution of thiazolidinethione (1.0 g, 8.4 mmol) in neat acetic anhydride (17 mL) was heated according to the general procedure. Removal of excess acetic anhydride gave the desired *N*-acetyl thiazolidinethione (1.25 g, 7.8 mmol, 93 %) which was used in the next reaction without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.75 (s, 3H), 3.27 (t, J = 7.5 Hz, 2H), 4.55 (t, J = 7.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.0, 28.2, 55.6, 171.5, 202.0. MS (EI) m/z: 161 (M^+), 119, 60, 44 (base).

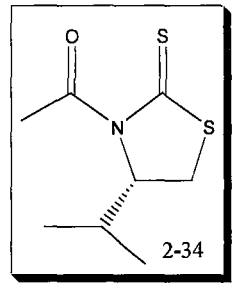
_N_-Propionyl-thiazolidinethione (2-20):



2-20

A solution of thiazolidinethione (1.0 g, 8.4 mmol) in neat propionic anhydride (17 mL) was heated according to the general procedure. Work-up followed by purification gave the desired *N*-propionyl thiazolidinethione (1.4 g, 8.0 mmol, 95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.11 (t, J = 7.2 Hz, 3H), 3.19 (q, J = 7.2 Hz, 2H), 3.26 (t, J = 7.5 Hz, 2H), 4.54 (t, J = 7.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 8.8, 28.3, 32.3, 56.1, 175.6, 201.6. MS (EI) m/z: 175 (M^+), 147, 57(base).

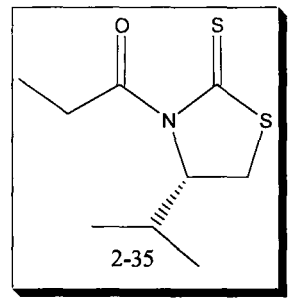
(4*S*)-*N*-Acetyl-4-isopropyl-thiazolidinethione (2-34):



2-34

A solution of (4*S*)-4-isopropyl-thiazolidinethione (1.0 g, 6.2 mmol) in neat acetic anhydride (15 mL) was heated according to the general procedure. Work-up followed by purification gave *N*-acetyl-4-isopropyl-thiazolidinethione as a yellow oil[86] (1.3 g, 6.1 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.08 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 2.43 (m, 1H), 2.87 (s, 3H), 3.13 (dd, J = 1.0, 11.5 Hz, 1H), 3.61 (dd, J = 8.0, 11.5 Hz, 1H), 5.25 (m, 1H).

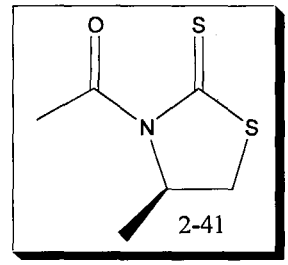
(4*S*)-*N*-Propionyl-4-isopropyl-thiazolidinethione (2-35):



2-35

A solution of (4*S*)-4-isopropyl-thiazolidinethione (1.0 g, 6.2 mmol) in neat propionic anhydride (20 mL) was heated according to the general procedure. Work-up followed by purification gave *N*-propionyl-4-isopropylthiazolidinethione[86] (1.3 g, 6.0 mmol, 97%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.57 (m, 1H), 3.09-3.66 (m, 4H), 5.27 (m, 1H).

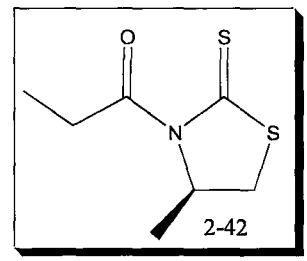
(4*R*)-*N*-Acetyl-4-methyl-thiazolidinethione (2-41):



2-41

A solution of (4*R*)-4-methyl-thiazolidinethione (1.0 g, 7.5 mmol) in neat acetic anhydride (17 mL) was heated according to the general procedure. Work-up followed by purification gave *N*-acetyl-4-methyl-thiazolidinethione (1.3 g, 7.4 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.48 (d, J = 4.4 Hz, 3H), 2.84 (s, 3H), 2.9 (dd, J = 0.7, 11.2 Hz, 1H), 3.62 (dd, J = 7.4, 11.2 Hz, 1H), 5.31 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.1, 27.1, 35.5, 63.2, 170.7, 201.3. MS(EI) *m/z*: 175 (M^+), 161, 133, 119, 74, 43 (base)

(4*R*)-*N*-Propionyl-4-methyl-thiazolidinethione (2-42):

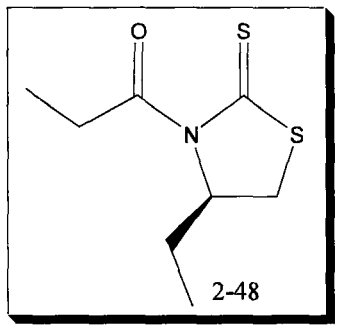


2-42

A solution of (4*R*)-4-methyl-thiazolidinethione (1.0 g, 7.5 mmol) in neat propionic anhydride (17 mL) was heated according to the general procedure. Work-up followed by purification gave *N*-propionyl-4-methyl-thiazolidinethione (1.4 g, 7.4 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.14 (t, J = 7.2 Hz, 3H), 1.48 (d, J = 6.4 Hz, 3H), 2.77 (dd, J = 0.8, 11.2 Hz, 1H), 2.95-3.44 (m, 2H), 3.61 (dd, J = 7.2, 11.2 Hz, 1H), 5.31

(m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 8.8, 18.2, 32.3, 35.6, 63.6, 174.9, 200.9. MS(EI) *m/z*: 189 (M^+), 175, 161, 133, 74, 43 (base).

(4*R*)-*N*-propionyl-4-ethyl-thiazolidinethione (2-48):



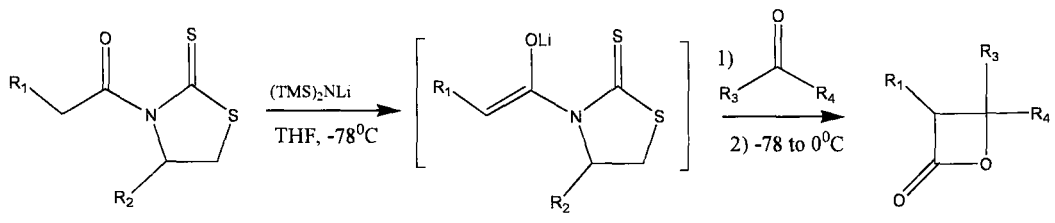
2-48

A solution of (4*R*)-4-ethyl-thiazolidinethione (1.0 g, 6.8 mmol) in neat propionic anhydride (17 mL) was heated according to the general procedure. Work-up followed by purification gave *N*-propionyl-4-ethyl-thiazolidinethione (1.1 g, 5.4 mmol, 80%). ^1H NMR (200 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.6 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H), 1.65-1.98 (m, 2H), 2.89 (d, J = 11.3 Hz, 1H), 2.90-3.42 (m, 2H), 3.50 (dd, J = 7.6, 11.3 Hz, 1H), 5.05 (approx. dt, J = 4.3, 8.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 8.9, 10.2, 24.5, 32.2, 32.5, 68.8, 174.7, 201.4. MS(EI) *m/z*: 203 (M^+), 147, 117, 100, 73, 57 (base).

4.2.4 General procedure for the TEAL reaction:

A 100 mL round-bottom flask with a magnetic stirrer was flushed with dry nitrogen and fitted with a rubber septum and nitrogen inlet adapter. Freshly distilled THF, followed by *N*-acyl thiazolidinethione (1 equiv.) were added by syringe. The solution was then cooled to -78 °C. Then lithium bis(trimethylsilyl)-amide (1.1 equiv., 1 M in THF) was added dropwise, slowly over 5 minutes. After stirring for 15 minutes, freshly distilled ketone (1 equiv.) was added in neat form, dropwise and slowly. After 30 minutes

the reaction mixture was gradually warmed to 0 °C over 1.5 h by adding room temperature acetone to the dry ice-bath occasionally.

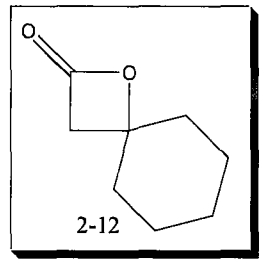


Scheme 4.4: General Procedure for the Preparation of β-Lactones Using TEAL Method

The reaction was then quenched at 0°C with half saturated NH_4Cl and the mixture was partitioned between diethyl ether and water. The organic layer was washed with 10% aqueous potassium carbonate and then with brine. It was then dried over anhydrous sodium sulfate, filtered and the solvent was removed by rotary evaporation. The crude material was then purified by flash column chromatography (10% ethyl acetate in hexane). (Low temperature crystallization from pentane gave very pure lactone samples but lower yield).

Preparation of β–Lactones using Thiazolidinethiones:

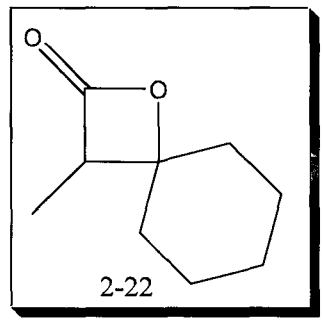
4-Spirocyclohexyloxetan-2-one (2-12):



2-12

To a solution of 460 mg (1 equiv., 2.86 mmol) of *N*-acetyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3.0 mL, 1.1 equiv.) and 296 μL of cyclohexanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 4-spirocyclohexyloxetan-2-one (348.1 mg, 87%) as a clear and colorless oil. (Wax-like solid crystals below 0^0 C). ^{1}H NMR (200 MHz, $CDCl_3$). δ: 1.57-1.33 (m, 4H), 1.92-1.59 (m, 6H), 3.03 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 23.3, 24.5, 35.8, 47.25, 78.9, 168.6. IR (KBr) 2943, 2870, 1813, 1459 cm^{-1}. MS(EI) *m/z*: 140 (M^+), 122, 98, 96, 81, 80, 67, 55 (base).

3-Methyl-4-spirocyclohexyloxetan-2-one (2-22):

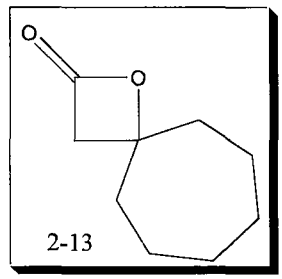


2-22

To a solution of 500 mg (1 equiv., 2.86 mmol) of *N*-propionyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3.0 mL, 1.1 equiv.) and 296 μL

cyclohexanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 3-methyl-4-spirocyclohexyloxetan-2-one (352.4 mg, 80%) as a clear and colorless oil. The ^{1}H NMR was identical to that reported by Danheiser *et al.*.[83] ^{1}H NMR (200 MHz, $CDCl_3$). δ: 1.27 (d, J = 7.7 Hz, 3H), 1.30-1.93 (m, 10H), 3.19 (q, J = 7.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 8.4, 22.5, 23.1, 24.8, 31.1, 37.1, 52.5, 82.1, 172.6. IR (KBr) 2933, 2874, 1824, 1442 cm^{-1}.

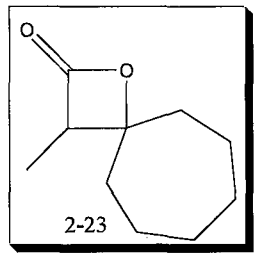
4-Spirocycloheptyloxetan-2-one (2-13):



2-13

To a solution of 460 mg (1 equiv., 2.86 mmol) of *N*-acetyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 320 μL of cycloheptanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 4-spirocycloheptyloxetan-2-one (294.6 mg, 67%) as a clear and colorless oil. ^{1}H NMR (200 HHz, $CDCl_3$). δ: 1.49-1.94 (m, 8H), 2.15 (m, 4H), 3.11 (s, 2H).

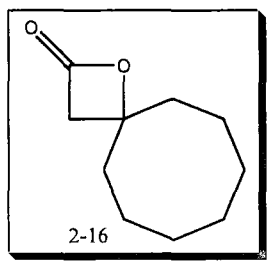
3-Methyl-4-spirocycloheptyloxetan-2-one (2-23):



2-23

To a solution of 500 mg (1 equiv., 2.86 mmol) of *N*-propionyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 296 μL cyclohexanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 3-methyl-4-spirocycloheptyloxetan-2-one (224.4 mg, 46%) as a clear and colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$). δ: 1.40 (d, J = 7.7, 3H), 1.45-1.89 (m, 8H), 1.91-2.67 (m, 4H), 3.40 (q, J = 7.7Hz , 1H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 9.1, 21.8, 22.1, 28.2, 28.3, 34.2, 40.1, 53.6, 85.3, 172.8. IR (KBr) 2932, 2862, 1819, 1469 cm^{-1}. MS(EI) *m/z*: 168 (M^+), 153, 150, 140, 139 (base).

4-Spirocyclooctyloxetan-2-one (2-16):

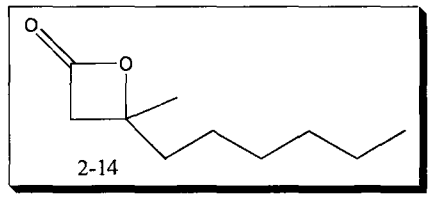


2-16

To a solution of 460 mg (1 equiv., 2.86 mmol) of *N*-acetyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 350 μL of cyclooctanone (1 equiv., 2.86 mmol) were added using the general procedure for the

TEAL reaction. Work-up followed by purification gave 4-spirocyclooctyloxetan-2-one (28.6 mg, 6%) as a clear and colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$). δ: 1.40-1.77 (m, 12H), 1.85-2.1 (m, 2H), 2.09-2.25 (m, 2H), 3.07 (s, 2H).

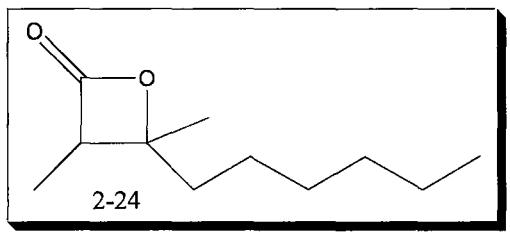
4-Methyl-4-hexyloxetan-2-one (2-14):



2-14

To a solution of 460 mg (1 equiv., 2.86 mmol) of *N*-acetyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 456 μL 2-octanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 4-methyl-4-hexyloxetan-2-one (217 mg, 45%) as a clear and colorless oil. The ^{1}H NMR was identical to that reported by Doyle *et al.*.[94] ^{1}H NMR (200 MHz, $CDCl_3$). δ: 0.89 (t, J = 6.6 Hz, 3H), 1.24-1.44 (m, 8H), 1.56 (s, 3H), 1.74-1.90 (m. 2H), 3.08 (d, J = 16.1 Hz, 1H), 3.18 (d, J =16.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.0, 22.5, 24.2 (2C), 29.2, 31.6, 39.4, 47.4, 78.8, 168.3.

3, 4-Dimethyl-4-hexyloxetan-2-one (2-24):

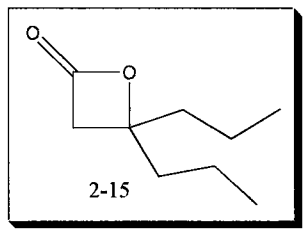


2-24

To a solution of 500 mg (1 equiv., 2.86 mmol) of *N*-propionyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 456 μL 2-

octanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave a mixture of *trans* and *cis* 4-methyl-4-hexyloxetan-2-one (198 mg, 38%) as a clear and colorless oil. The ratio of *cis*:*trans* isomers was determined by ^{1}H-NMR to be 2.1:1. ***Cis*-3,4-dimethyl-4-hexyloxetan-2-one** ^{1}H NMR (200 MHz, $CDCl_3$). δ: 0.87 (t, J =6.9 Hz, 3H), 1.25 (d, J = 7.7Hz), 1.25-1.40 (m, 8H), 1.53 (s, 3H), 1.63-1.86 (m, 2H), 3.30 (q, J = 7.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 8.6, 14.0, 22.5, 23.8, 24.6, 29.5, 31.6, 35.0, 53.4, 82.3, 172.4. ***Trans*-3,4-dimethyl-4-hexyloxetan-2-one**: ^{1}H NMR (200 MHz, $CDCl_3$). δ: 0.87 (t, J = 6.9 Hz, 3H), 1.24 (d, J = 7.7 Hz), 1.20-1.40 (m, 8H), 1.42 (s, 3H), 1.63-1.86 (m, 2H), 3.28 (q, J= 7.7 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$). δ: 9.3, 19.4, 22.5, 23.8, 24.2, 29.3, 31.6, 40.7, 51.6, 82.3, 172.4.

4, 4-dipropyloxetan-2-one (2-15):



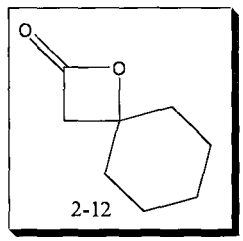
2-15

To a solution of 460 mg (1 equiv., 2.86 mmol) of *N*-acetylthiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 326 μL 4-heptanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 4,4-dipropyloxetan-2-one (160.6 mg, 39%) as a clear and colorless oil. ^{1}H NMR (50 MHz, $CDCl_3$). δ: 1.06 (t, J = 7.2 Hz, 6H), 1.41-1.56 (m, 4H), 1.76 (m, 4H), 3.04 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 15.7, 16.2, 41.6,

45.2, 81.4, 168.1. IR (KBr) 2959, 2873, 1824, 1463 cm^{-1}. MS(EI) *m/z*: 156 (M^+), 112, 84, 69, 56 (base).

Preparation of β–lactones using 4-methyl-thiazolidinethiones:

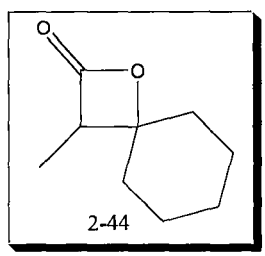
4-spirocyclohexyloxetan-2-one (2-12):



2-12

To a solution of 500 mg (1 equiv., 2.86 mmol) of *N*-acetyl-4-methyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 296 μL of cyclohexanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 4-spirocyclohexyloxetan-2-one (256 mg, 64%) as a clear and colorless oil. ^1H NMR (200 MHz, $CDCl_3$). δ: 1.57-1.33 (m, 4H), 1.92-1.59 (m, 6H), 3.04 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 23.3, 24.5, 35.8, 47.3, 78.9, 168.6.

3-methyl-4-spirocyclohexyloxetan-2-one (2-44):

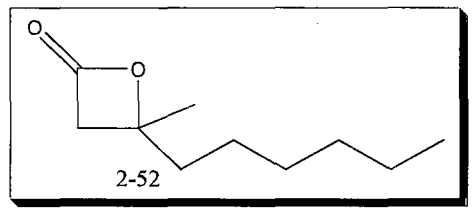


2-44

To a solution of 540 mg (1 equiv., 2.86 mmol) of *N*-propionyl-4-methyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.)

and 296 μL cyclohexanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 3-methyl-4-spirocyclohexyloxetan-2-one (302 mg, 69%, 81% *e.e.*) as a clear and colorless oil. $[\alpha]^{21}_{D}$= + 41.1^{0} (c=0.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$). δ: 1.22 (d, *J* = 7.7 Hz, 3H), 1.27-1.86 (m, 10H), 3.15 (q, *J* = 7.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 8.4, 22.5, 23.1, 24.8, 31.1, 37.1, 52.5, 82.1, 172.6.

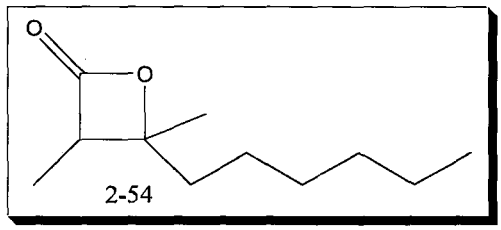
4-methyl-4-hexyloxetan-2-one (2-52):



2-52

To a solution of 500 mg (1 equiv., 2.86 mmol) of *N*-acetyl-4-methyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 456 μL 2-octanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave 4-methyl-4-hexyloxetan-2-one (164 mg, 34%, 40% *e.e.*) as a clear and colorless oil. The ^{1}H NMR was identical to that reported by Doyle *et al.*. [94] $[\alpha]^{21}_{D}$ = - 4.6^{0} (c=0.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$). δ: 0.89 (t, *J* = 6.6 Hz, 3H), 1.24-1.44 (m, 8H), 1.56 (s, 3H), 1.74-1.90 (m. 2H), 3.08 (d, *J* = 16.1 Hz, 1H), 3.18 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 14.0, 22.5, 24.2 (2C), 29.2, 31.6, 39.4, 47.4, 78.7, 168.2.

3,4-dimethyl-4-hexyloxetan-2-one (2-54):

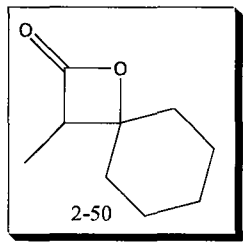


2-54

To a solution of 540 mg (1 equiv., 2.86 mmol) of *N*-propionyl-4-methyl-thiazolidinethione in 3.0 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 456 μL 2-octanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by purification gave a mixture of *trans* and *cis* 4-methyl-4-hexyloxetan-2-ones (154 mg, 31%) as a clear and colorless oil. The ratio of *cis*:*trans* isomers was determined by ^{1}H-NMR to be 3.9:1. The isomers were separated by MPLC using silica gel as stationary phase and 20% ethyl acetate in hexane as eluent. ***Cis*-3,4-dimethyl-4-hexyloxetan-2-one** (102 mg, 14% *e.e.*): ^{1}H NMR (600 MHz, $CDCl_3$). δ: 0.89 (t, J =6.9 Hz, 3H), 1.27 (d, J = 7.8 Hz), 1.29-1.43 (m, 8H), 1.54 (s, 3H), 1.65-1.79 (m, 2H), 3.31 (q, J = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$). δ: 8.7, 14.1, 22.6, 23.9, 24.8, 29.7, 31.7, 35.2, 53.6, 82.4, 172.5. ***Trans*-3,4-dimethyl-4-hexyloxetan-2-one** (31 mg, 62% *e.e.*): ^{1}H NMR (600 MHz, $CDCl_3$). δ: 0.89 (t, J = 6.9 Hz, 3H), 1.26 (d, J = 7.8 Hz, 3H), 1.27-1.40 (m, 8H), 1.43 (s, 3H), 1.73-1.88 (m, 2H), 3.30 (q, J = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 9.4, 14.2, 19.5, 22.7, 24.4, 29.4, 31.8, 40.9, 51.8, 82.5, 172.5. IR (KBr) 2930, 2860, 1821cm^{-1}. MS(EI) *m/z*: 184 (M^+), 171, 113, 85, 83, 49 (base).

Preparation of β–lactones using 4-ethyl-thiazolidinethione:

3-methyl-4-spirocyclohexyloxetan-2-one (2-50):



2-50

To a solution of 580 mg (1 equiv., 2.86 mmol) of *N*-propionyl-4-ethyl-thiazolidinethione in 30 mL THF, lithium bis(trimethylsilyl)-amide (3 mL, 1.1 equiv.) and 296 μL cyclohexanone (1 equiv., 2.86 mmol) were added using the general procedure for the TEAL reaction. Work-up followed by column chromatography (10% EtOAc in hexane) gave 3-methyl-4-spirocyclohexyloxeten-2-one with impurities having the same R_f value in the hexane: ethyl acetate system. Further chromatography gave 16 mg of pure 3-methyl-4-spirocyclohexyloxetan-2-one, using Methanol: EtOAc: Hexane (6:4:90) (63% *e.e.*). $[\alpha]^{21}{}_D = +10.6^0$ (c=0.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$). δ: 1.28 (d, J = 7.7 Hz, 3H), 1.34-1.96 (m, 10H), 3.19 (q, J =7.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$). δ: 8.4, 22.4, 23.1, 24.8, 31.1, 37.1, 52.5, 82.2, 172.6.

Chapter 5

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