DEVELOPMENT OF A PRACTICAL METHOD FOR THE ASYMMETRIC SYNTHESIS OF QUATERNARY CARBON CENTERS:

A SECOND GENERATION AUXILIARY

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ABSTRACT

Despite significant progress in the field of organic chemistry, the asymmetric formation of all-carbon quaternary centers still represents a considerable challenge. Our group previously reported the stereocontrolled generation and alkylation of α,α-disubstituted amide enolates to form quaternary centers. This reaction takes place via the reduction of bicyclic α,α-dialkylated α-thioglycolate lactams using one-electron transfer reagents.

This method suffered from several limitations to practicality, thus this research project has focused on the development of a second-generation chiral auxiliary system which would overcome the first generation auxiliary shortcomings.

The design and synthesis of a new chiral auxiliary system is described. The design is modular and allows the auxiliary to be synthesized in a few shorts steps from commercially available materials. Alkylation of the new auxiliary, reductive enolization and the subsequent final alkylation to form quaternary centers is achieved with high levels of stereocontrol for both enolate intermediates. Two sets of conditions are described to cleave the auxiliary and liberate the products containing the quaternary centers.

The methodology that has been developed is versatile and represents a practical solution to the enantioselective formation of quaternary carbon centers. It also overcomes all the shortcomings of the first generation.

RÉSUMÉ

Malgré les importants progrès reportés en synthèse organique, la formation énantioselective de carbones quaternaires demeure un défi de taille. Notre groupe de recherche a récemment publié des travaux portant sur l'alkylation d'énolates α,α-disubstitués par le biais d'une réduction de lactams bicycliques α-thioglycolés α,α-disubstitués afin de former des carbones quaternaires énantiosélectivement.

Cette méthode présentant d'importantes limitations pratiques, le but de ce projet de recherche a consisté en le développement d'une seconde génération d'auxiliaire chiral qui contrera les inconvénients du premier.

Ce document présente le développement ainsi que la synthèse du nouvel auxiliaire chiral. L'alkylation ainsi que la réduction et l'alkylation finale de l'auxiliaire permettent la formation de carbones quaternaires et ce, avec une très grande sélectivité pour les deux énolates. De plus, deux types de conditions sont proposées afin d'enlever l'auxiliaire et de libérer les carbones quaternaires sous forme d'acides carboxyliques ou d'alcools primaires.

La méthodologie developpée est versatile et s'avère être une solution pratique pour la synthèse énantiosélective de carbones quaternaires et ce, sans les inconvénients rencontrés avec l'auxiliaire de première génération.

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To my dad, and my *future husband*, Jonathan, thank you both for your patience, love and support over these years. My dear mother, thanks for the faith that you always had in me. I hope you can see me from where you are and that you are proud of me.

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ABBREVIATIONS

$A^{1,3}$	1,3-allylic
Ac	acetyl
Ar	aryl
Anal.	analysis
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bs	broad singlet
Bu	butyl
Bz	benzoyl
Calcd	calculated
cat.	catalyst/catalytic
cHx	cyclohexyl
CSA	camphorsulfonic acid
d	doublet
Δ	reflux/heat
dd	doublet of doublets
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide

dr	diastereomeric ratio
e	electron
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
g	gram(s)
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRFABMS	high resolution fast atom bombardment mass spectroscopy
Hz	hertz
i	iso
J	coupling constant
KDBB	potassium 4,4'-di-*tert*-butylbiphenylide
L	litre
LAB	lithium amidotrihydroborate
LDA	lithium *N,N*-diisopropylamide
LDBB	lithium 4,4'-di-*tert*-butylbiphenylide
LG	leaving group
LICA	lithium *N*-isopropyl-*N*-cyclohexylamide
LiHMDS	lithium hexamethyldisilazide

m	mili, multiplet
M	moles per litre, metal
Me	methyl
*m*CPBA	*meta*-chloroperbenzoic acid
mL	mililitre
MM2	molecular mechanics 2
mmol	milimole
mol	mole
m/z	mass to charge ratio
NaHMDS	sodium hexamethyldisilazide
NDA	sodium *N,N*-diisopropylamide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PhMe	toluene
Pr	propyl
psi	pounds per square inch
*p*TSA	*p*-toluenesulfonic acid
R_t	retention time
RT	room temperature
s	singlet
t	tertiary
t	triplet

TBS	*tert*-butyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
UV	ultraviolet

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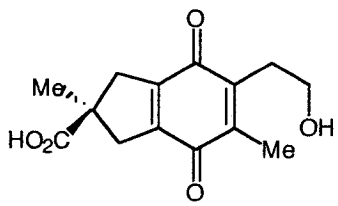
CHAPTER ONE

INTRODUCTION TO THE ENANTIOSELECTIVE SYNTHESIS OF QUATERNARY CARBON CENTERS

1.1 USEFULNESS OF QUATERNARY CENTERS

The asymmetric formation of quaternary carbon centers has always represented a considerable challenge for synthetic chemists. Despite significant progress in the field of organic chemistry, there is still a need for a general method which would allow for the highly stereoselective synthesis of quaternary carbon centers.

Quaternary carbons are found in a wide variety of biologically active molecules such as puraquinonic acid **1**,[1] a potential anti-leukemia drug which is known to induce cell differentiation, dysidiolide **2**,[2] an antitumor compound, and gallopamil **3**,[3] an important calcium antagonist.



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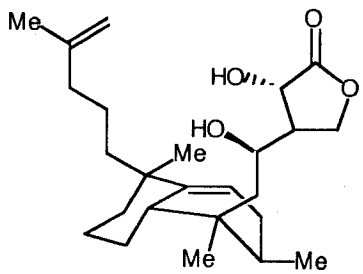

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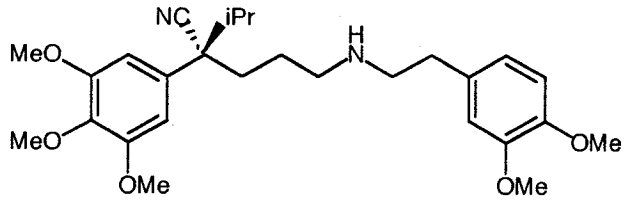
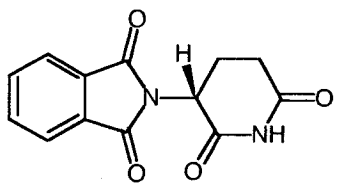


3

Quaternary centers can be very useful in potential drug candidates because they are more stable, allowing for slower metabolism.[4] It is known that some tertiary centers are prone to racemization under physiological conditions. A very important example of this is thalidomide **4** where the (*R*)-enantiomer (shown) is known to relieve pregnancy morning sickness while its enantiomer, which is slowly formed at physiological pH, can cause birth deformities.[5] Quaternary stereocenters can be advantageous over tertiary ones since they are immune to racemization.



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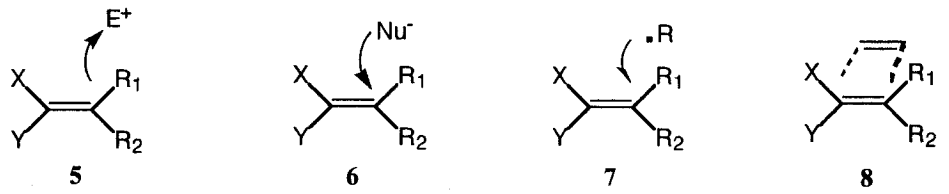
1.2 Possible Pathways Available for Quaternary Centers Formation

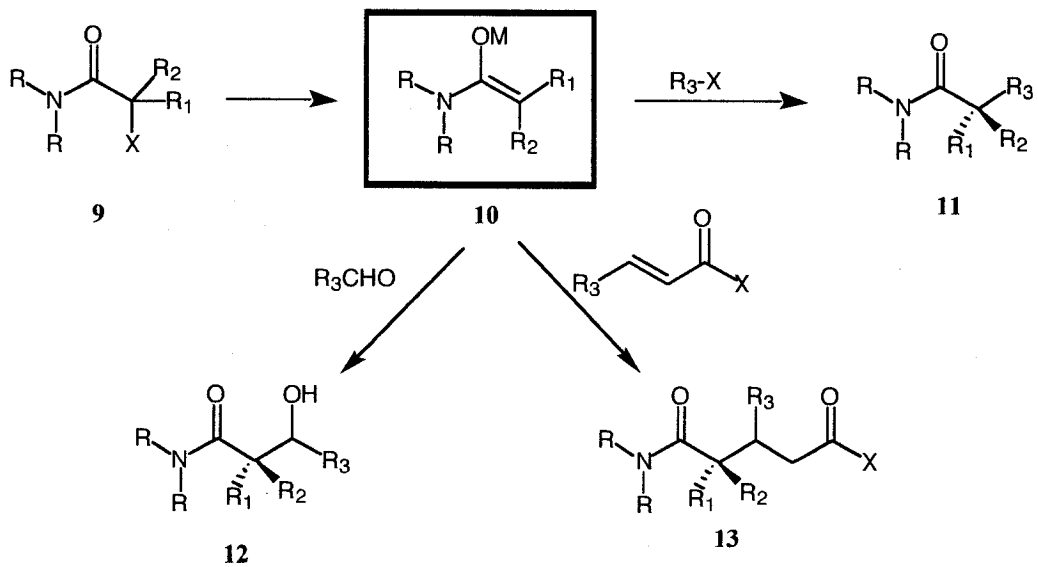
Carbon-carbon bond formation can theoretically be achieved in many ways. Addition to sp^2 atoms to create the quaternary stereocenter is the more convenient way, as the use of sp^3 centers will results in problems due to sterics and/or the need to control and maintain stereochemistry in reaction precursors. Several approaches are possible by using sp^2 centers (Scheme 1). A radical approach (**7**) may result in difficulties to control stereoselectivity. Pericyclic reactions can also be used to form quaternary centers (**8**). Some very interesting results have been achieved using addition of nucleophilic allylmetalloid species to aldehydes,[6] S_N2' displacements,[7] Michael additions[8] and more recently, organocatalysis.[9] However, the scope of these methods tends to be limited. Addition of an electrophile on an sp^2 center remains one of the best methods to form

quaternary centers with high selectivity (**5**), especially when a heteroatom is present (enamines, enolates).



Scheme 1. Carbon-carbon bond forming.

α,α-Disubstituted enolates are a useful way to access quaternary centers via carbon-carbon bond forming reactions. Alkylations with alkyl halides (**11**), Michael additions (**13**), and aldol reactions (**12**) are some examples of routes that are commonly used for quaternary carbon synthesis (Scheme 2). This research project will focus on the development of a general method for quaternary centers formation via the alkylation of α,α-disubstituted enolates with alkyl halides.



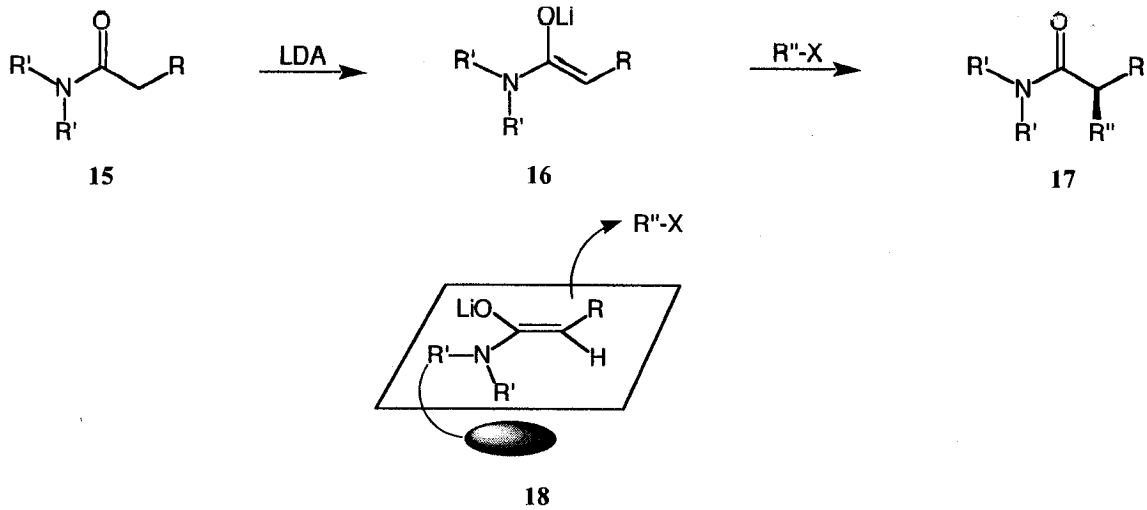
Scheme 2. α,α-Disubstituted enolates as precursors for quaternary centers.

Catalytic enantioselective enolate functionalizations have received lots of attention. Numerous methods are available for the allylation, vinylation or arylation[10] of enolates with very high stereocontrol. However, these methods are often limited to sp^2-hybridized electrophiles. Recently, the Jacobsen group reported a highly selective catalytic method for alkylation of tin enolates with sp^3-hybridized electrophiles.[11] However, this method, like many metal-catalyzed methods, works only with activated alkyl halides.

Chiral auxiliary based methods have proven to be more reliable and more general, particularly when dealing with unactivated alkyl halides. This research project will focus on the development of a chiral auxiliary system for the asymmetric synthesis of quaternary carbon centers.

1.3 Stereoselective Enolate Alkylation

Formation of a new stereocenter via the alkylation of an enolate with an alkyl halide has been extensively studied over the past two decades. Two requirements are needed in order to achieve the alkylation with high selectivity. First, good stereocontrol in the formation of the enolate is required; second, a bias for the approach of the electrophile on one π-face over the other (*si* or *re*) is also important (Scheme 3). A failure in one of these two requirements will result in low overall stereoselectivity.



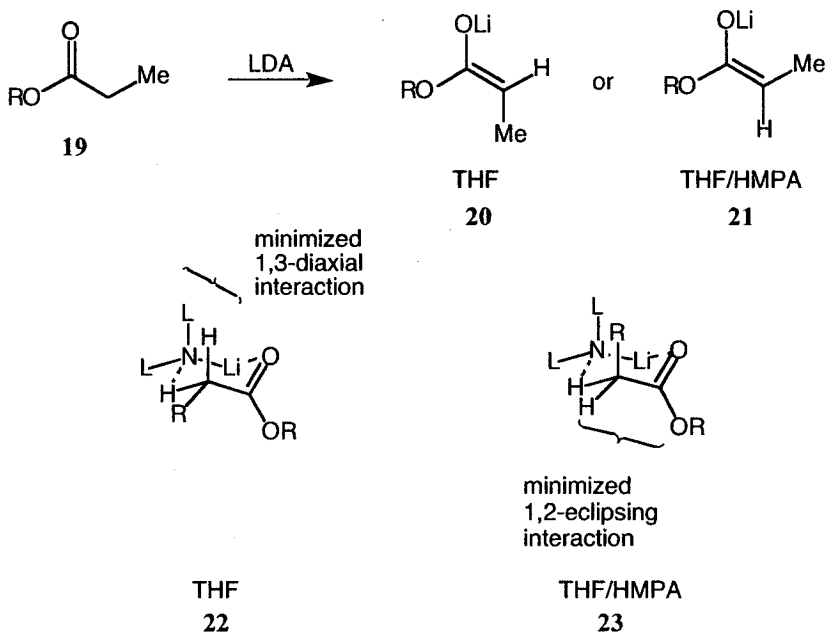
Scheme 3. Stereoselective enolate alkylation.

A good and general methodology should have several important characteristics. The auxiliary should be readily synthesized from inexpensive materials, should possess a broad substrate scope and auxiliary cleavage should occur easily. Ideally, it should be possible to recycle the auxiliary. More importantly, it should provide access to both configurations (*R* and *S*) of the new stereocenter. This can usually be achieved by switching the enolate geometry, inverting the order of alkylation or using the antipode of the auxiliary. The latter case is often very expensive.

1.4 Stereoselective Formation of Monosubstituted Enolates

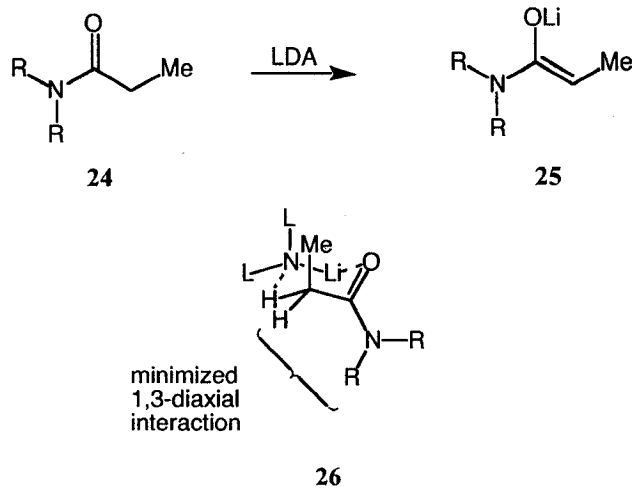
Deprotonation of a ketone or an ester with a strong amide base such as LDA in a polar aprotic solvent such as THF at low temperature will result in the predominant formation of the *E(O)*-enolate. In this case, there is a minimization of 1,3-diaxial interactions between the alkyl group on the α-carbon of the enolate and the substituent

on the amide base in the chair-like transition state (Scheme 4). The addition of a polar co-solvent such as HMPA will result in a looser transition state and the *Z(O)*-enolate will form predominantly. In this case, the overriding steric influence is the minimization of 1,2 eclipsing interactions between the alkyl group on the α-carbon of the enolate and the alkoxy moiety of the ester (alkyl in the case of a ketone).[12] Because of regiochemistry problems, ketone enolates have not found a popular use as chiral auxiliaries.



Scheme 4. Formation of *E(O)*- and *Z(O)*-ester enolates.

In the case of amide enolates, the enolate geometry is governed by the minimization of $A^{1,3}$ interactions between the alkyl group on the nitrogen atom and the alkyl group on the α-carbon. This results in the exclusive formation of the *(Z)*-enolate (Scheme 5).[13]



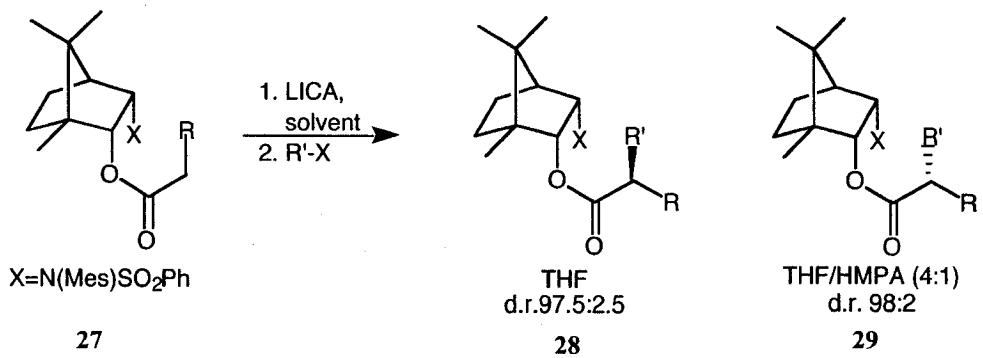
Scheme 5. Formation of *Z(O)*-amide enolate.

1.5 Stereoselective Enolate Alkylation to Form Tertiary Centers

Many useful chiral auxiliary based methods do exist for the asymmetric formation of tertiary carbon centers. The first method was developed by Meyers and used chiral oxazolines as auxiliaries.[14] Even if this method only afforded moderate selectivity, it provided the proof that chiral materials can be used to control the stereochemical outcome of enolate alkylations.

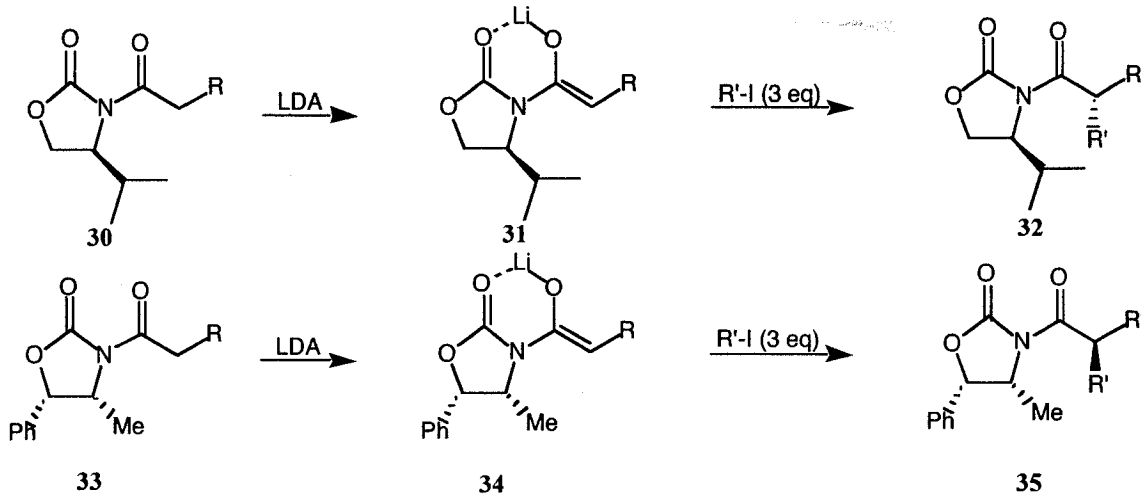
Since it is possible to have access to both *E(O)*- and *Z(O)*-enolates by choosing the appropriate deprotonation conditions, ester-based chiral auxiliaries can be used to access both *(R)* and *(S)* configurations by switching the enolate geometry. Helmchen and co-workers developed a camphor-based auxiliary, which afforded high selectivity for asymmetric tertiary carbon formation.[15] In this particular case, a bulky group blocks the back face of the auxiliary for the approach of the electrophile, resulting in high

selectivity. By using THF as the only solvent, the *(E)*-enolate predominates, whereas the formation of the *(Z)*-enolate is almost complete with the addition of HMPA. Both (*R*) and (*S*) configurations are thus accessible with high levels of stereocontrol (Scheme 6).



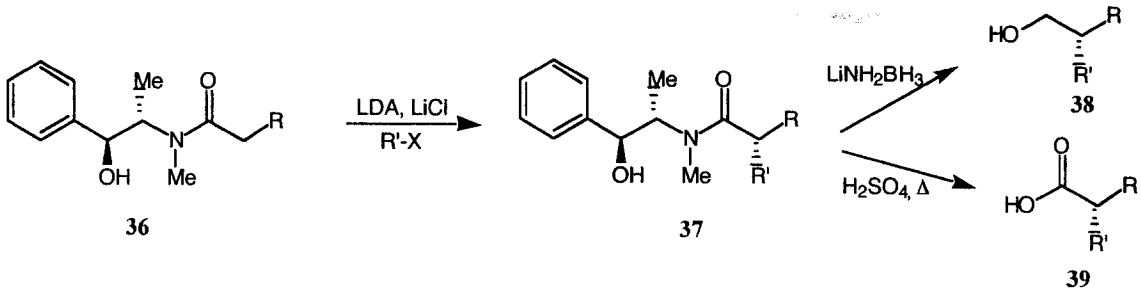
Scheme 6. Asymmetric enolate alkylation with camphor-based auxiliary.

After having developed prolinol-derived chiral auxiliaries,[16] Evans and co-workers reported the use of oxazolidinones to control the selectivity during the deprotonation and alkylation of imides.[17] The use of different amino alcohols to make the chiral auxiliaries allowed for the formation of both the *(R)* and the *(S)* configurations at the new stereocenter. This method afforded high selectivity, but due to the low nucleophilicity of imide enolates, this method was restricted to the use of activated alkyl halides such as benzyl bromide and methyl iodide (Scheme 7).



Scheme 7. Asymmetric enolate alkylation with oxazolidinone imide enolates.

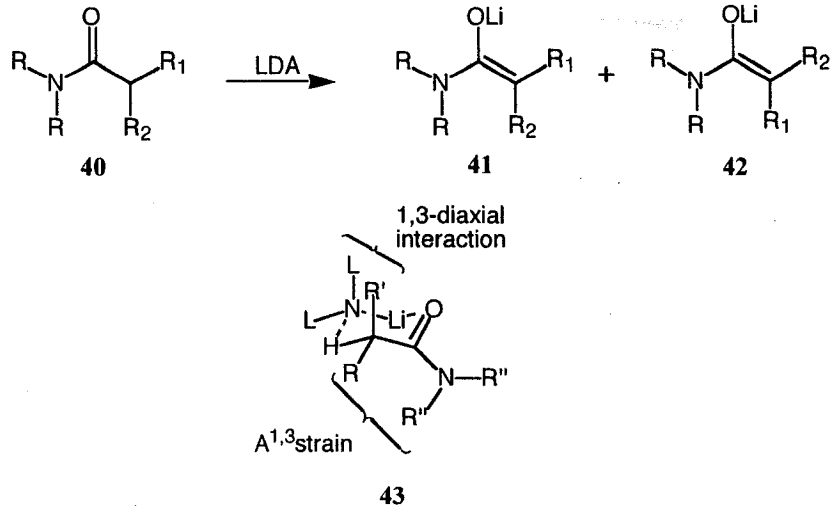
The use of pseudoephedrine amides as chiral auxiliaries for stereoselective enolate alkylation turned out to be one of the more practical methods.[18] It is a rare example where the auxiliary is available in both enantiomeric forms at a reasonable cost. Pseudoephedrine amides can be deprotonated with 2 equivalents of LDA to afford exclusively the *(Z)*-enolate, which is reactive enough to undergo electrophilic addition with both unactivated and activated alkyl halides at 0 °C in the presence of lithium chloride (Scheme 8).[19] The selectivities obtained are very high, as the majority of halides alkylate with >95% de. Numerous auxiliary cleavage conditions which lead to different functionalities (alcohols, ketones, aldehydes and carboxylic acids) further demonstrated the usefulness of pseudoephedrine amides.



Scheme 8. Alkylation of pseudoephedrine amides.

1.6 Formation of α,α-Disubstituted Enolates

While several good methods are available for the stereoselective formation of monosubstituted enolates, achieving high stereocontrol in generating α,α-disubstituted enolates still remains a difficult task. Enolization using traditional deprotonation techniques is significantly more difficult since there is an increase of $A^{1,3}$ strain in the transition state (for amide enolates) (Scheme 9). Thus, stronger bases have to be used, consequently resulting in lower functional group tolerance. Moreover, the steric difference between two alkyl groups is smaller than it was for the previous deprotonation where a hydrogen atom was present. This will result in a lower enolate stereocontrol.[20]

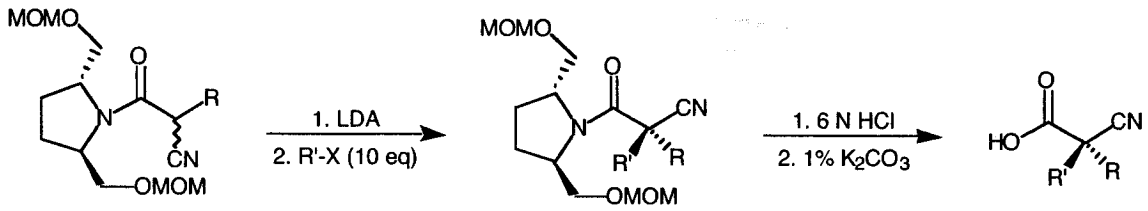


Scheme 9. Formation of α,α-disubstituted enolates.

1.7 Acyclic α,α-Disubstituted Enolates

There are a few methods that have been developed for the formation of quaternary carbon centers which use acyclic disubstituted enolates. Most of these methods are, however, limited to the use of activated alkyl halides and, thus, not very general.[21]

Katsuki and co-workers reported the use of a C_2-symmetric auxiliary for the formation of α-cyano-α-quaternary carboxylic acids (Scheme 10).[22] Because of the small size of the cyano moiety and also the increased acidity of the α-carbon, overall good stereocontrol was achieved. However, the selectivity for this particular reaction was not as high as it was with the propionate auxiliary, which showed very high levels of stereocontrol in the formation of tertiary centers (80-90% de vs >95% de).[23]



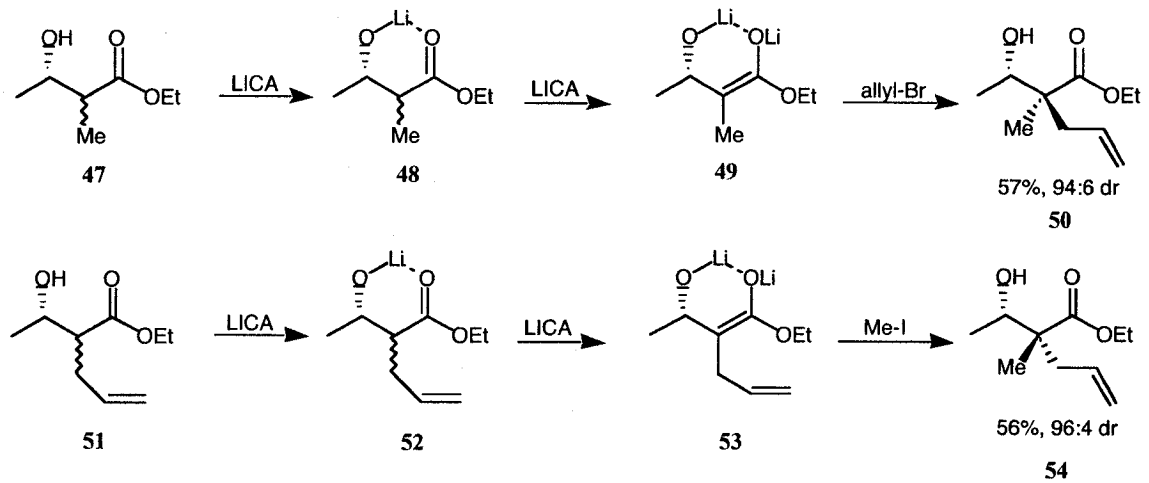
44 45 46

Scheme 10. Formation of α-cyano-α-quaternary carboxylic acids.

1.8 Cyclic α,α-Disubstituted Enolates

It has been mentioned in the previous section that it is very difficult to control the enolate geometry when attempting to generate acyclic disubstituted enolates. The most common solution to this problem is to use a cyclic structure, which can be either a permanent ring or a temporary metal chelate.

Fràter demonstrated the use of metal chelates as a temporary ring to control the enolate *E/Z* stereochemistry during the deprotonation of β-hydroxyesters (Scheme 11).[24] Unfortunately, this method displays a very limited substrate scope and low yields.

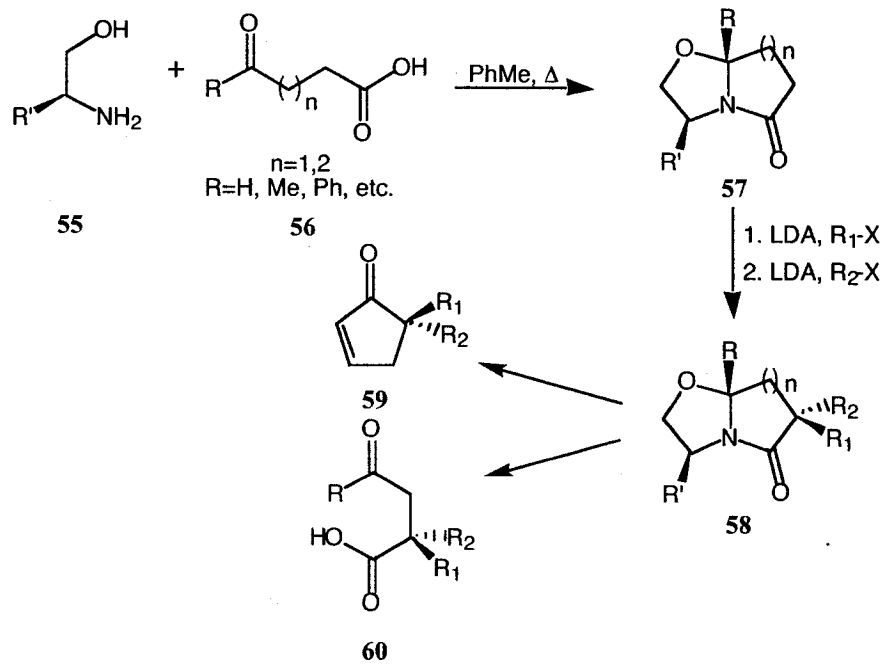


47 48 49 50

51 52 53 54

Scheme 11. Stereoselective alkylation of β-hydroxyesters.

Alkylation of bicyclic lactams turned out to be the most general method for quaternary carbon synthesis.[25] The bicyclic lactams are easily prepared via the condensation of a keto acid or a cyclic anhydride and an amino alcohol. Installation of both alkyl groups with either activated or unactivated halides is achieved in high yields and most importantly, high stereocontrol (Scheme 12).



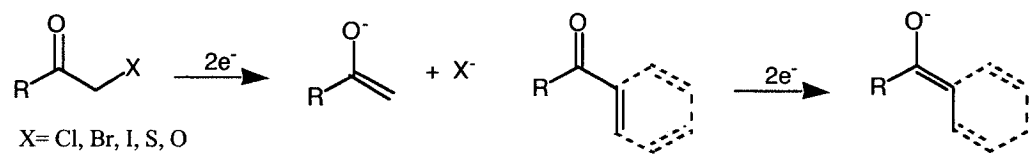
Scheme 12. Bis-alkylation and cleavage of chiral bicyclic lactams to form quaternary centers.

These lactams can be hydrolyzed or cleaved under numerous sets of conditions to afford a wide variety of functional groups. The only real limitation of this methodology resides in the fact that it uses a cyclic enolate, which leaves an extra functionality in the final product.

The previous examples demonstrate the limitations met while attempting to form disubstituted enolates. When these enolates are cyclic, *E/Z* stereocontrol can be higher, but using cyclic enolates represents a limitation by itself. The goal of this project is to develop a highly practical method that uses enantioselective alkylation of acyclic disubstituted amide enolates to form quaternary centers based on a method that was previously developed in our research group.

1.9 Reductive Enolization as a Powerful Deprotonation Surrogate

Our research group has been working on the development of a chiral auxiliary based method for the enantioselective formation of quaternary carbon centers. Over the past years, a functional but impractical methodology has been developed. The initial idea behind the project was to access to disubstituted enolates with high stereocontrol by using reductive enolization conditions. Examples of reductive enolization include electron transfer to carbon-carbon multiple bonds or a carbon-heteroatom bond cleavage by a reductant such as an alkali metal (Scheme 13).



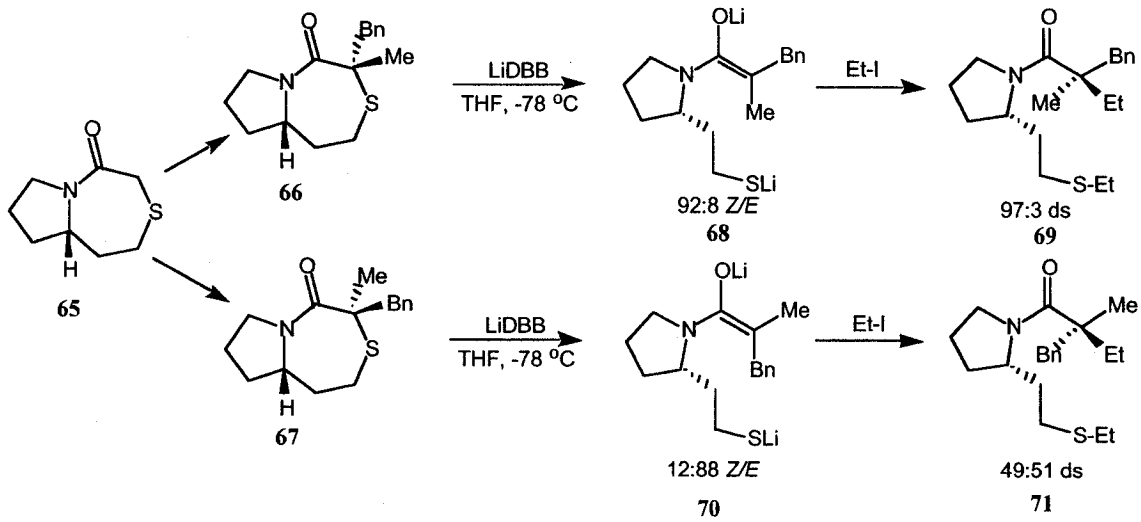
Scheme 13. Reductive enolization.

A very well known example of this is the Reformatsky reaction, in which an α-halo ester is reduced to the zinc enolate with metallic zinc and, usually, that enolate reacts with an aldehyde to form an aldol adduct.[26] The most widely known electron-transfer reduction reaction is probably the Birch reduction.[27] Schultz and co-workers developed a method for quaternary carbon formation in which disubstituted enolates were generated upon treatment of benzoic acid derivatives with two equivalents of an alkali metal.[28] This method was restricted to the synthesis of chiral cycohexadienes.

Nagata and co-workers developed a method for racemic quaternary carbon synthesis based on the reductive enolization of α-*tert*-butylthiocarbonyl compounds.[29] Extension of Nagata's methodology to an asymmetric method to reductively enolize and alkylate α-thioglycolate species to form quaternary centers was developed in our laboratories by Jeffrey Manthorpe and is described below.

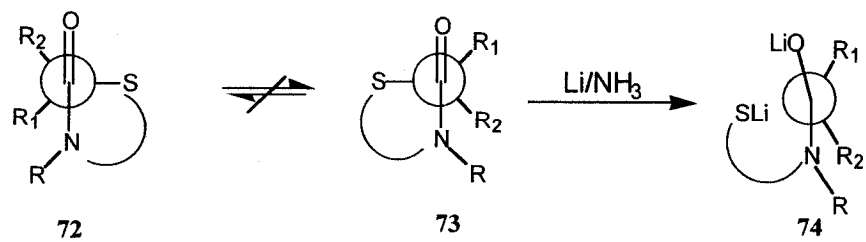
1.10 Design of a First-Generation Chiral Auxiliary System

Our group previously reported the use of bicyclic thioglycolate lactams as chiral auxiliaries for controlling selectivity in the formation of disubstituted enolates.[30] More recently, we expanded the methodology to make quaternary carbon centers (Scheme 14).[31] The method involves synthesis of bicyclic lactam **65** and alkylation to form a disubstituted thioglycolate. Reduction forms a disubstituted enolate which can be alkylated with high stereoselectivity forming α-quaternary amides. Although hydrolysis of these amides is not efficient, they can be reduced with lithium amidoborohydride to afford α-quaternary primary alcohols in high yields and high ee.



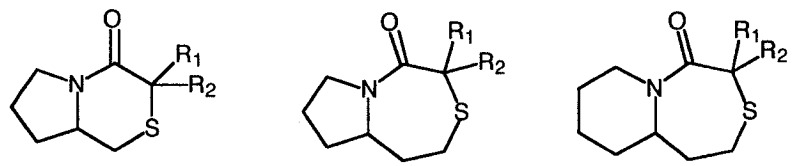
Scheme 14. Alkylations and reductive enolization of auxiliary.

A key to this process is the stereoselective generation of α,α-disubstituted enolates in the reductive enolate formation. Stereoselectivity is predicted by a simple model in which the bicyclic system offers enough rigidity to constrain the sulfur on one side of the amide plane. Upon reduction, assuming that the initial two alkyl groups are installed stereoselectively, the least motion principle results in stereoselective enolate formation (Scheme 15). The relative positions of the alkyl groups are key to this process, as inverting the configuration of the thioglycolate lactam results in a switch in enolate geometry.



Scheme 15. Model for reductive enolization of bicyclic thioglycolate lactams.

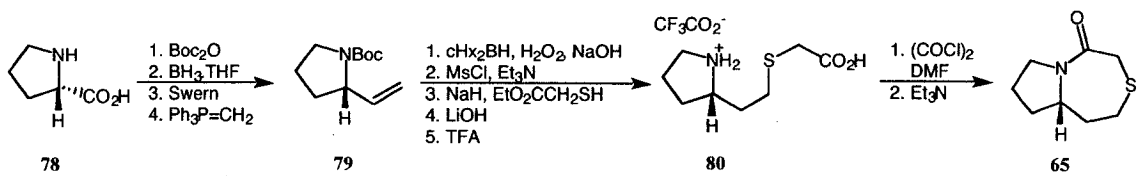
Following the assumption that the ideal O-C-C-S dihedral angle should be as close as possible to 90° during the reduction process, numerous bicyclic systems were modeled using the MM2 force field and three candidates were chosen for investigation (Figure 1). Among these, lactam **76** was the most promising candidate, and indeed afforded the highest enolate stereoselectivities.



O-C-C-S	175°	127°	134°
	75	**76**	**77**

Figure 1. Dihedral angles of best candidates.

One disadvantage of a 5,7 bicyclic thioglycolate lactam such as **65** is that their synthesis was challenging. Starting from (*S*)-proline **78** as a chiral pool material, a one-carbon homologation was required in order to form the correct ring size. In the end, the synthesis took approximately 10 steps (Scheme 16). Although yields for the individual steps were high, this synthesis is much too long for a practical chiral auxiliary.

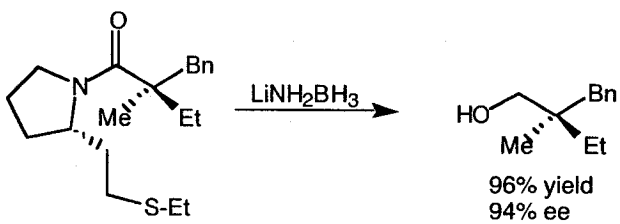


78 **79** **80** **65**

Scheme 16. Synthesis of bicyclic thioglycolate lactam **65**.

A second limitation to the method was that while alkylation of *(Z)*-enolates afforded high selectivity, alkylation of the corresponding *(E)*-enolates resulted in nearly 1:1 mixtures (Scheme 14). Preliminary experiments indicated that enolate equilibration, aggregates or intramolecular chelates could only partially explain this lack of selectivity. Free rotation around the C-N bond in amides resulting in different reactive conformations was viewed as a possible main source of the low selectivity.[32] This limitation could be partially overcome by inverting the overall alkylation order (vs. inverting R_1 and R_2 installation to revert the enolate geometry) to access both (*R*) and (*S*) configurations of the new quaternary center.[33]

Because of the high stability of tertiary amides combined with the steric bulk at the quaternary center, removal of the auxiliary via hydrolysis of the amide to the carboxylic acid turned out to be very difficult and afforded dramatically low yields. It was however possible to cleave the auxiliary by using reducing conditions. Lithium amidotrihydroborate (LAB) afforded primary alcohols in high yields (Scheme 17).[34]



69 **81**

Scheme 17. Cleavage of the auxiliary.

Overall, this method was functional and allowed for the stereoselective formation of quaternary carbon centers with high selectivity. However, the low *(E)*-enolate selectivity, the inability to directly hydrolyze the quaternary adducts and most

importantly the lengthy 10-step synthesis of the auxiliary constituted serious limitations to this otherwise very potent method. The goal of this project was to design a second-generation auxiliary, which would overcome these shortcomings.

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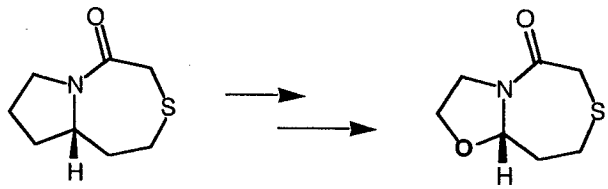
CHAPTER TWO

DEVELOPMENT OF A SECOND-GENERATION CHIRAL AUXILIARY SYSTEM FOR ENANTIOSELECTIVE SYNTHESIS OF QUATERNARY CARBON CENTERS

2.1 Design of a Second-Generation Chiral Auxiliary System

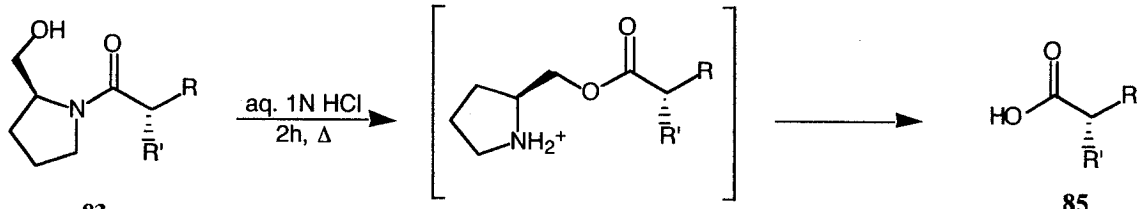
The goal of this project was to design a new auxiliary system, which would overcome the first generation auxiliary's shortcomings. The new auxiliary would have to afford high selectivity for both the *(E)*- and the *(Z)*-disubstituted enolate during the final alkylation. The new auxiliary should also be easily synthesizable from commercially available and inexpensive starting materials and afford an easier hydrolysis of the quaternary carbon products.

The first-generation auxiliary provided excellent proof-of-principle for our stereoselective disubstituted enolate formation and provided reasonable diastereoselectivty in subsequent alkylations. Thus, in attempting to develop a practical auxiliary, we sought to modify the original system rather than develop a totally new design. To this end, incorporation of an oxygen atom in the five-membered ring, forming an aminal moiety might allow for both easier synthesis and hydrolysis (Figure 2). For the synthesis, the auxiliary could potentially be built in a modular fashion from small, commercially available components. This structure is closely related to those developed by Meyers, although efforts to directly condense a 5,7 bicyclic lactam were reported to proceed in low yield and selectivity.[1] For hydrolysis, acetal cleavage would reveal a β-hydroxyamide, which would be expected to hydrolyze via N to O acyl-transfer. Similar examples have been described by Evans and co-workers for hydrolysis of prolinol amides used for asymmetric formation of tertiary carbon centers (Scheme 18).[2]



65 82

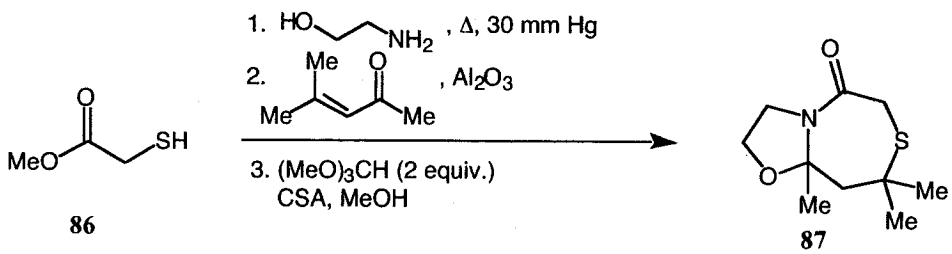
Figure 2. Oxygen-incorporation to promote O to N and N to O acyl transfers.



83 84 85

Scheme 18. N to O acyl transfer-assisted hydrolysis in prolinol amides.

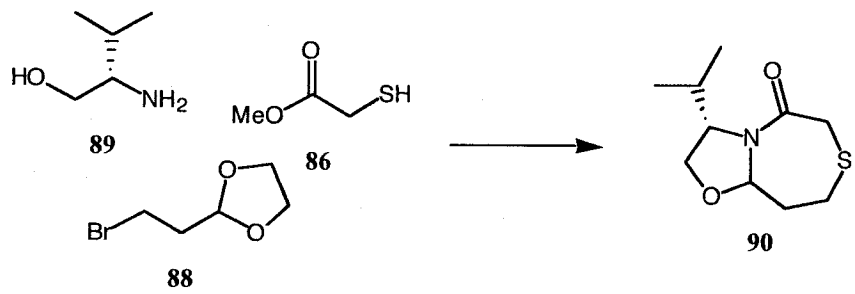
The synthesis of a racemic aminal containing α-thioglycolate lactam **87** was achieved by Jeffrey Manthorpe in three steps from condensation of an amino acid, a thioglycolate **86** and mesityl oxide (Scheme 19).[3] Although the synthesis was facile, the presence of the angular methyl group and/or the gem-dimethyl in **87** negatively affected alkylation and reductive enolization.[4]



86 87

Scheme 19. Synthesis of a racemic aminal-containing auxiliary.

To further develop this system, we thought that the presence of angular methyl group should be avoided in order to regain the previous levels of stereocontrol. Addition of chirality in the starting materials also had to be considered to avoid a racemic synthesis. It was postulated that the isopropyl group of valine should be of an appropriate size to control the stereochemistry during the acetal formation while not adversely affecting subsequent alkylation reactions. Thus, condensation of an acrolein equivalent **88**, valinol **89** and methyl thioglycolate **86** should afford a synthesis of the second-generation auxiliary in two or three steps (Scheme 20).



Scheme 20. Condensation to afford auxiliary.

An additional design feature is that upon reductive enolization, this particular α-thioglycolate lactam could also form a pseudo-C_2-symmetric auxiliary, which should help for the third alkylation selectivity. Assuming the *trans*-acetal isomer could be prepared, C-N bond rotation in the subsequent enolate would consistently block one π-face of the enolate (Figure 3). As described in Chapter 1, C_2-symmetric enolates have been shown to be highly selective in the formation of tertiary carbon stereocenters (Figure 4).[5]

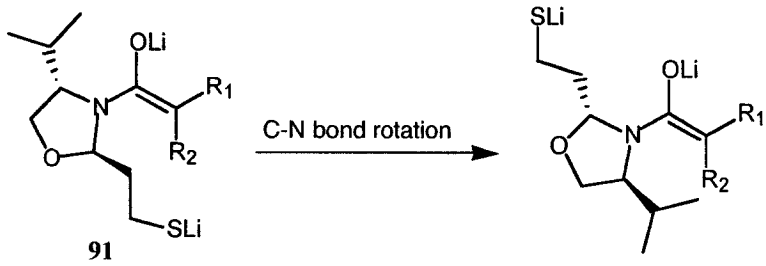


Figure 3. Pseudo C_2-symmetric enolate.

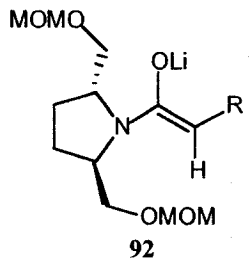
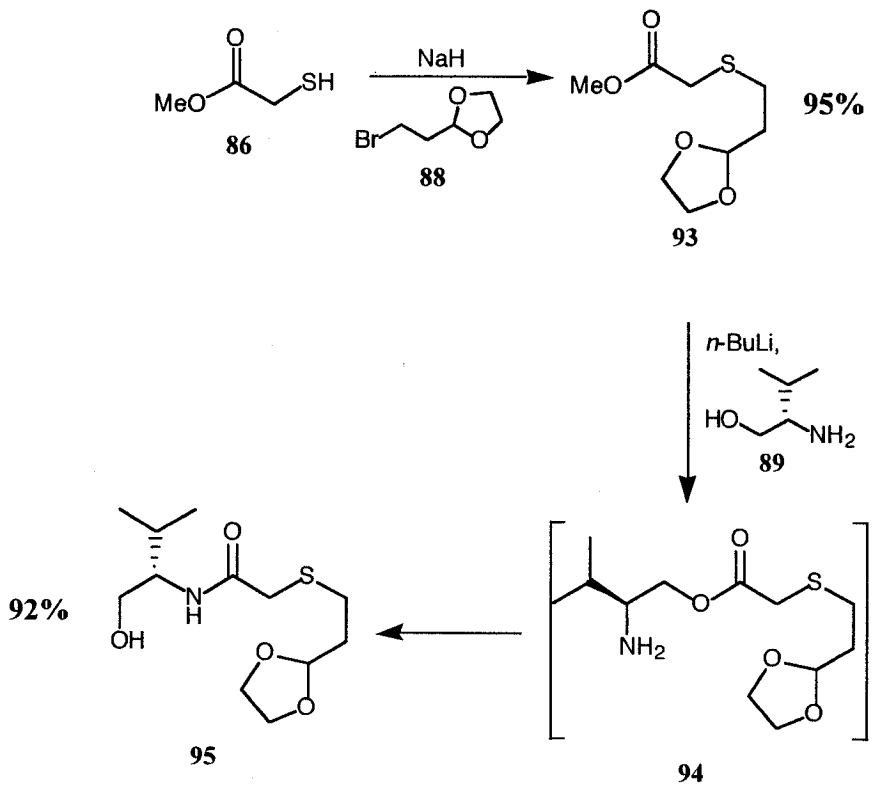


Figure 4. Yamaguchi's C_2-symmetric chiral auxiliary.

2.2 Synthesis of a Second-Generation Chiral Auxiliary System

The synthesis of bicyclic lactam **90** was expected to be straightforward. The initial route to **90** was designed to proceed via auxiliary precursor **95,** which would be formed via *S*-alkylation and amide-bond formation. *S*-Alkylation of methyl thioglycolate with 2-(2-bromoethyl)-1,3-dioxolane using sodium hydride as a base was very straightforward and afforded the desired α-thiomethylester **93** in good yield. In situ transesterification followed by O to N acyl transfer could be achieved by simply adding valinol to the above reaction mixture, provided that a slight excess of sodium hydride was present. However, only modest yields of **95** were observed with this one-pot protocol (31% yield from **86**). In contrast, conducting the second step separately using a

catalytic amount of *n*-butyllithium afforded auxiliary precursor **95** in 92% yield (Scheme 21).

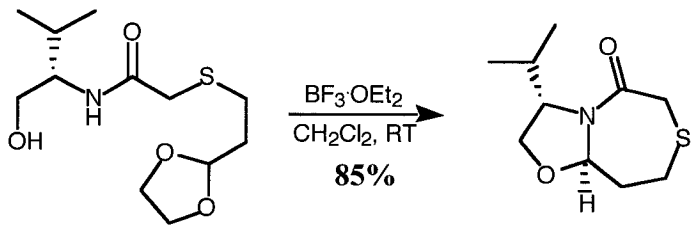


86 **88** **93** **89** **95** **94**

Scheme 21. Synthesis of auxiliary precursor **95**.

It was believed that the cyclization of the auxiliary precursor **95** to form the desired auxiliary **90** could be achieved via transacetalization under acidic conditions. After several attempts, it was clear that the use of protic acids such as *p*-toluenesulfonic acid and camphor-sulfonic acid were not the best choices. Cyclization of the seven-membered ring was never observed. In contrast, the use of boron trifluoride diethyletherate, an aprotic lewis acid, afforded the desired auxiliary in 85% yield as a single diastereomer (Scheme 22). The ease and high stereoselectivity of closure to the bicyclic lactams is in surprising contrast to prior attempts to form 5,7-bicyclic lactams

lacking the sulfur.[1] This could possibly be explained by the fact that both rings are formed in an intramolecular fashion with the 7-member ring being formed first.



95 **90**

Scheme 22. Cyclization of auxiliary.

The stereochemistry of the bicyclic lactam **90** was determined by NOE studies and was found to be the *trans* product by NOE enhancements between the angular hydrogen and the methyl groups of the isopropyl unit (Figure 5). The selectivity was determined by GC analysis and found to be >99% de.

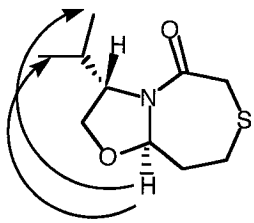
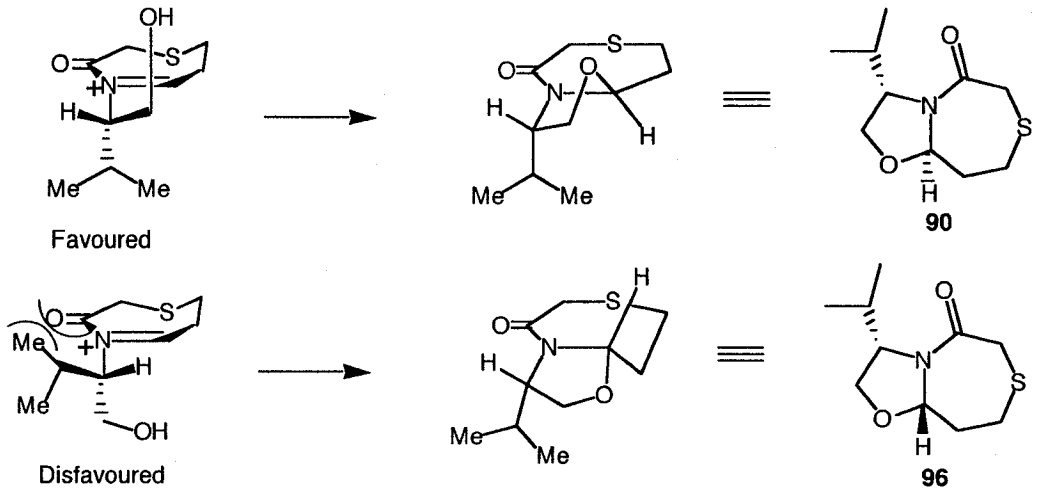


Figure 5. Observed NOE enhancements in **90**.

The bicyclic lactam that was obtained turned out to be the kinetic product, as extended treatment with boron trifluoride diethyletherate afforded the other diastereomer **96** as the thermodynamic product. The kinetic formation of **90** can be explained by the steric interactions between the carbonyl and the isopropyl group that are taking place upon formation of compound **96** (Scheme 23). This gears the hydroxymethyl chain such

that it attacks the cation from the top face. The lower stability of the kinetic product **90** over the thermodynamic one **96** could be explained by the fact that the bicycle **90** is more concave than the bicycle **96**, leading to more important interactions in **90**.



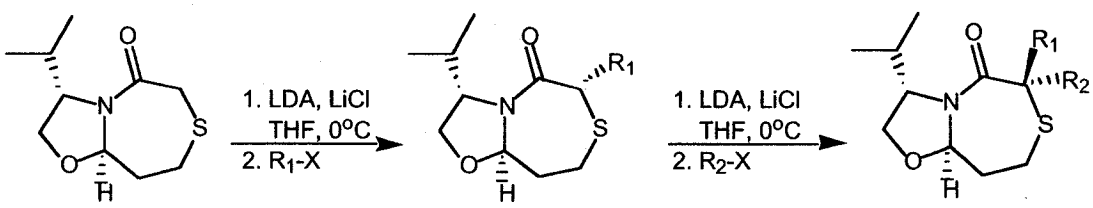
Scheme 23. Diastereoselectivity obtained upon cyclization.

The synthesis of the auxiliary could be achieved in three steps in an overall yield of 71%, which represented a significant improvement over the first generation auxiliary, which required more than 10 steps to synthesize and proceeded in 34% overall yield.[6] Very importantly, the new auxiliary can be synthesized without need for any column chromatography. The final product **90** can be crystallized directly from diethyl ether.

2.3 Alkylation of the Second-Generation Lactam

With the new auxiliary **90** in hand, a study of its alkylation chemistry with different alkyl halides was undertaken. It was decided to use the same alkylation conditions as with the previous auxiliary,[6] consisting of a slight excess of LDA as base in THF in the presence of 5 equivalents of lithium chloride.[7] Upon addition of primary alkyl halides, *O*-alkylation was never observed, nor was dialkylation. Results of the alkylation investigation are depicted in Table 1. It was observed that the first and the second alkylations both proceeded in >86% yield in all cases. Both alkylations are highly selective, both in the case of unactivated and activated alkyl halides.

Table 1. Alkylation of auxiliary.



90 **97** **98**

R_1–X	Product	Yield	dr[a]	R_2–X	Product	Yield	dr[a]
Et–I	**97a**	95%	98:1	Me–I	**98a**	90%	99:1
				Pr–I	**98b**	92%	98:2
Me–I	**97b**	90%	99:1	Et–I	**98c**	86%	99:1
Pr–I	**97c**	89%	99:1	Et–I	**98d**	89%	97:3
Bn–Br	**97d**	88%	98:2	Me–I	**98e**	95%	98:2
				Et–I	**98f**	92%	99:1

[a] Determined by GC using a Chirasil Val column.

For both alkylations, the approach of the electrophile occurs on the *exo* face of the bicycle, as was also observed with the first generation auxiliary. This indicates that the isopropyl group plays no significant role in facial discrimination and is similar to the selectivity observed by Meyers and co-workers.[1] This facial selectivity was determined by observation of NOE enhancements in ^{1}H NMR experiments (Figure 6) and an X-ray structure of **98c** (Figure 7). The NOE enhancements between the angular hydrogen and the protons on the ethyl group as well as interactions between the methyl groups of the isopropyl unit and the ethyl group confirmed the facial selectivity.

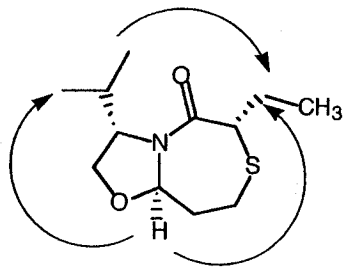


Figure 6. NOE enhancements observed in lactam **97a.**

The X-ray structure also demonstrated that the O-C-C-S dihedral angle of the dialkylated lactam was 111°. The dihedral angle is also closer to 90° than it was for the first generation 5,7 lactam, which was greater than 153°.[8] Thus, the selectivity during the reductive enolization should be higher (*vide supra*).

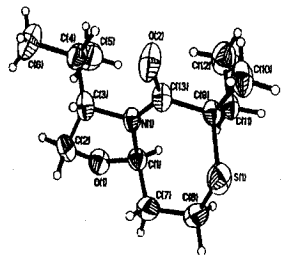
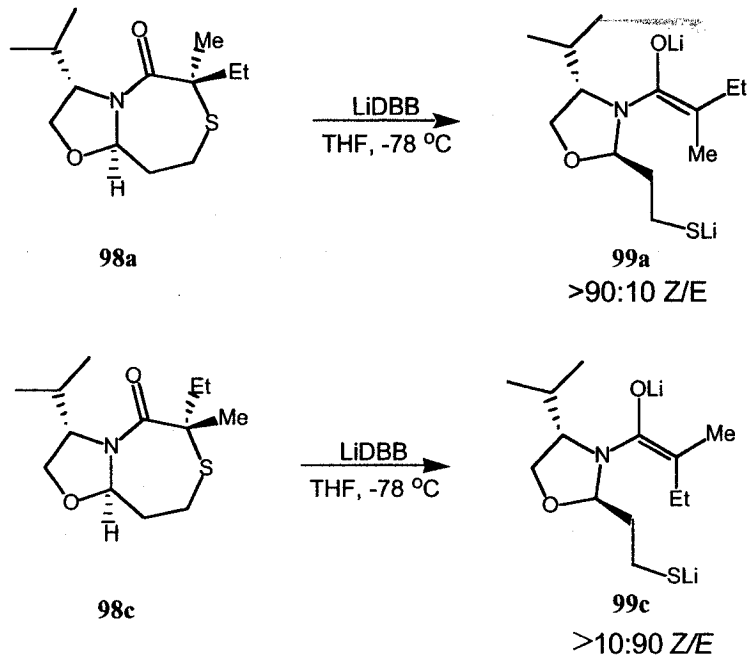


Figure 7. X-ray crystal structure of lactam **98c.**

2.4 Reductive Enolization and Enolate Trapping of α,α-Disubstituted Bicyclic Thioglycolate Lactams

With the dialkylated lactams in hand, the plan was to study their behavior under reductive enolization conditions and trap the enolates as the corresponding silyl ketene aminals. Numerous aromatic systems are known in the literature for their ability to form a radical anion after accepting an electron form an alkali metal. Naphtalene,[9] anthracene[10] and 4,4-di-*tert*-butylbiphenyl[11] are some examples that are commonly used because of their ability to form relatively stable radical anions. For this study, 4,4-di-*tert*-butylbiphenyl (LDBB) was selected as the reagent of choice because of its higher stability and its ability to be stored over a long period of time. It also afforded great results with the first generation auxiliary.[6]

Treatment of dialkylated lactams **98** with LDBB in THF followed by enolate trapping with TMSCl and warming to room temperature formed silyl ketene aminals.[12] However, while these trapping experiments afforded good results with the first-generation lactams, some problems occurred when attempting to trap the second-generation auxiliary disubstituted enolate intermediates. Analysis by ^{1}H and ^{13}C NMR revealed the presence of the desired silyl ketene aminals but the reaction was not clean. The selectivity was estimated at >9:1 for both the *(E)*- and the *(Z)*-enolates (Scheme 24). It was not possible to get a more precise measurement due to the presence of side-products. The reactivity/instability of the aminal moiety could possibly be the reason why the trapping results were not clear, even though extended treatment of lactam **98a** with a large excess of TMSCl at room temperature did not seem to affect the aminal.



Scheme 24. Reductive enolization and enolate trapping of dialkylated bicyclic lactams.

To clearly understand the reductive enolization process, it is imperative that the enolate ratios are exactly known. In the future, other enolate trapping methods will be investigated. While the proof that the use of geometric constraints to control the *E/Z* geometry of an enolate was demonstrated with the first generation auxiliary,[6] it was gratifying to see that the same trend could be observed with the second-generation system.

2.5 Reductive Enolization and Alkylation of α,α-Disubstituted Bicyclic Thioglycolate Lactams to Form Quaternary Adducts

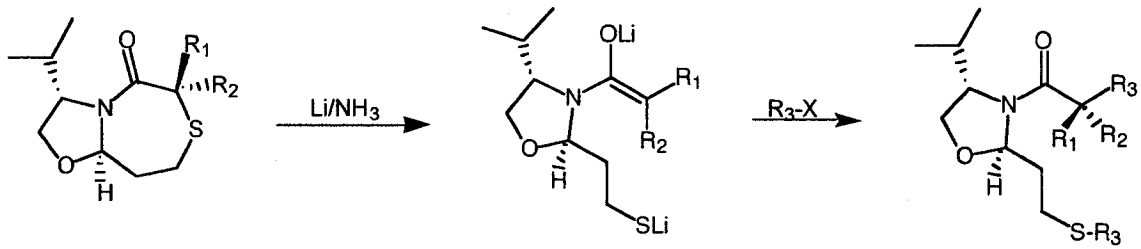
The previous section demonstrated the ability to reduce the lactam to form α,α-disubstituted enolates with high selectivity. One of the goals of this project was to have access to both enolate alkylation products with high selectivity. While the first generation 5,7 lactam was only selective during the alkylation of the *(Z)*-enolate, it was proposed that the pseudo C_2-symmetric nature of the disubstituted enolate should improve the *(E)*-enolate selectivity during the final alkylation (*vide infra*).

Although reductive enolization with LDBB afforded high selectivity, the reduction did not go to completion as it did with the first generation auxiliary. Indeed, in the subsequent alkylation, yields around 60% were observed. Tremendous efforts were made to remove adventitious moisture from the reaction mixture in order to optimize the yields, but they were without success. Particular care to the shape of the lithium, its concentration in THF and the purity of DBB were also considered. In every attempt, we failed to get more than 70% yields. We then decided to investigate other reductants.

Using Birch reduction conditions (lithium in liquid ammonia) with 2.1 equivalents of lithium followed by alkylation afforded only modest yields of alkylation products. However, during these reactions, the blue color of the dissolved lithium disappeared partway through. Increasing the lithium concentration up to four equivalents afforded complete reduction and higher alkylation yields (Table 2). This constituted a considerable improvement over the first generation lactam for which the Birch conditions

did not afford good results. These conditions can be much more practical in large-scale processes.

Table 2. Reductive enolization and alkylation of dialkylated lactams.



98 **99** **100**

Entry	Lactam	R^1	R^2	R^3–X	Product	Yield	dr[a]
	Z-Enolates						
1	**98a**	Et	Me	Bn–Br	**100a**	92	93:7
2	**98a**	Et	Me	Pr–I	**100b**	88	99:1
3	**98a**	Et	Me	$TBSO(CH_2)_3I$	**100c**	86	96:4
4	**98a**	Et	Me	$Cl(CH_2)_4)I$	**100d**	79	95:5
5	**98d**	Pr	Et	Allyl-Br	**100e**	91	95:5
6	**98e**	Bn	Me	Et–I	**100f**	87	97:3
	E-Enolates						
7	**98c**	Me	Et	Bn–Br	**100g**	85	93:7
8	**98c**	Me	Et	Pr–I	**100h**	91	99:1
9	**98c**	Me	Et	$Cl(CH_2)_4I$	**100i**	81	95:5
10	**98c**	Me	Et	$TBSO(CH_2)_3I$	**100j**	84	95:5
11	**98b**	Et	Pr	Allyl-Br	**100k**	89	96:4

[a] Diastereoselectivities were determined by chiral HPLC and/or GC analysis of products after auxiliary removal. See supporting information for details.

As shown in Table 2, the final alkylation afforded high selectivity with either unactivated or activated halides, which in itself constituted an improvement over the first-generation auxiliary where the addition of very activated electrophiles such as

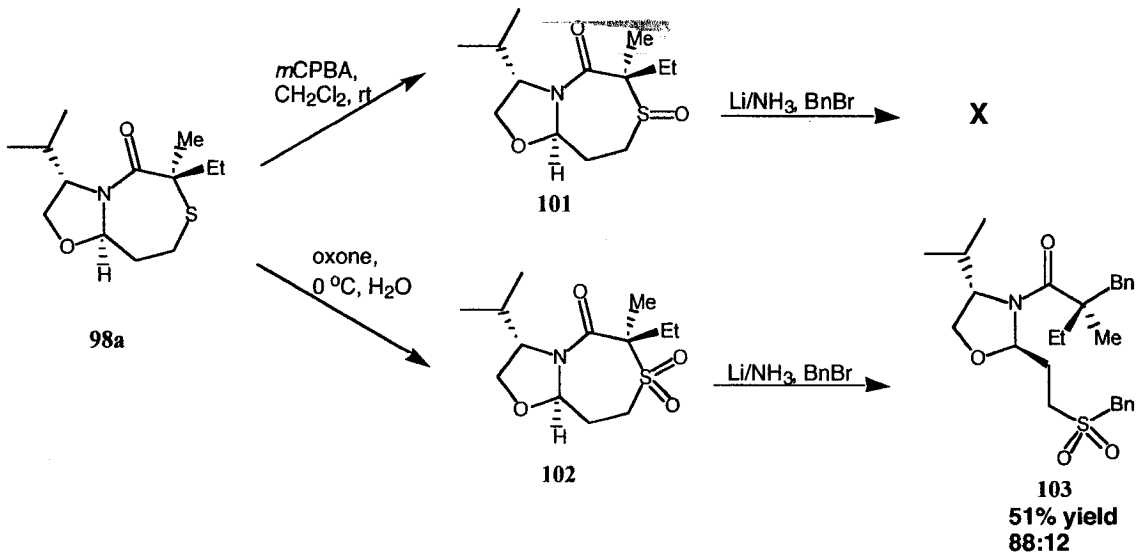
benzyl bromide afforded only moderate selectivity.[13] Very importantly, high levels of selectivity were observed for both the *(E)*- and the *(Z)*-disubstituted enolate alkylation products. This higher selectivity for the *(E)*-enolate presumably resulted from the pseudo C_2-symmetric nature of the enolate, which compensates for rotational isomerism about the enolate C-N bond.[14] It was also possible to incorporate functional groups such as protected alcohols or halogens in the final alkylation step (entries 3,4 and 9,10). The fact that the quaternary adducts are not limited to the presence of a methyl group also constituted an advantage over the first-generation auxiliary. Moreover, the investigation showed that the method could produce a quaternary stereocenter with three groups of nearly identical size (entries 5 and 11). In some cases, altering the overall order of alkylation improved the selectivity in the formation of stereoisomeric products (entry 1 vs. entry 6).[15] In all cases, the diastereomeric products were not separable by chromatography.

Determination of selectivity on tertiary amides is not straightforward due to amide rotamers which complicate the NMR spectrum. In addition, due to the relatively low stability of the reduced-alkylated products **100**, determination of the selectivity directly on substrates **100** was not possible. The use of high temperature NMR spectroscopy required heating at temperatures higher than 100 °C in order to reach the coalescence temperature of all the rotamers, and this resulted in decomposition of the products. Thus, the selectivity had to be determined by analysis of the cleaved products (*vide infra*).

Investigation of different one-electron reducing agents was also conducted. Whereas the use of LDBB afforded products which were not as clean as with lithium in liquid ammonia, the use of another alkali metal, potassium in liquid ammonia afforded

the same yield and selectivity. It is important to note that the use of potassium as a metal cation with the first generation auxiliary afforded an inversion of the enolate geometry and a significant change in the alkylation selectivity.[3]

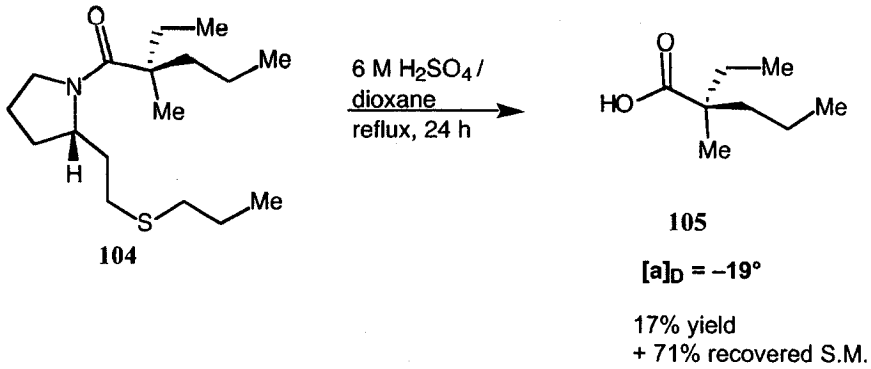
The oxidation state of the sulfur atom was also a point of interest. In our constant search of the best selectivity, an investigation of the reduction potential of sulfides, sulfoxides and sulfones was undertaken. Starting from dialkylated lactam **98a**, oxidations were achieved to obtain either the sulfoxide **101** and the sulfone **102**. Oxone was used to oxidize directly to the sulfone, whereas treatment of lactam **98a** with 1.0 equivalent of *m*CPBA afforded an inseparable mixture of sulfoxide diastereomers. Reduction of **101** with lithium in liquid ammonia and subsequent alkylation with benzyl bromide did not afford the desired product. However, reduction of **102** and addition of excess benzyl bromide resulted in the formation of the desired sulfone **103** in 50% yield (Scheme 25). Whereas sulfinic acids can easily undergo alkylation, sulfenic acids are highly unstable, and can immediately undergo further side reactions.[16] Theoretically, it was expected that the presence of the sulfone should render the reductive enolization and the alkylation more selective, as modeling studies indicated that the bicycle's rigidity is increased. However, upon auxiliary cleavage the selectivity was determined to be slightly lower (88:12 vs. 93:7).[17]



Scheme 25. Oxidation and reductive enolization on lactam **98a**.

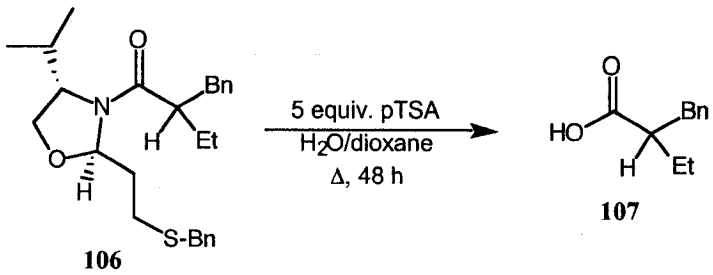
2.6 Isolation of Quaternary Adducts via Amide Hydrolysis

The previous section outlined the ease with which the methodology that we developed gives access to a variety of quaternary adducts with high levels of stereocontrol. Because of the high stability of tertiary amides, direct hydrolysis did not turn out to be an effective means of cleavage with the first-generation auxiliary. (Scheme 26). It did afford enough material, however, to determine the absolute stereochemistry of the α-quaternary carboxylic acid by comparison to the literature value.[18]



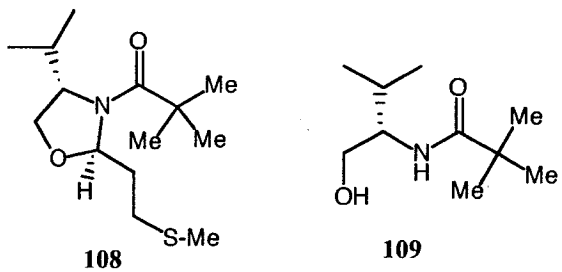
Scheme 26. Acidic cleavage with first generation auxiliary.

With the incorporation of an oxygen atom in the five-membered ring, we hoped that the hydrolysis would be easier due to N to O acyl transfer chemistry. Numerous attempts with different reaction conditions initially did not afford the desired carboxylic acids. Treatment with different acids such as *p*TSA, $FeCl_3$, HCl and sulfuric acid at different concentrations either in water, dioxane or methanol did not afford any of the desired acids or esters. However, we observed that treatment of our auxiliary bearing a tertiary center at the α-carbon with 5 equivalents of *p*-TSA at reflux for two days in a water/dioxane solvent mixture afforded the carboxylic acid in 60% yield (Scheme 27). This indicated that the steric environment around the quaternary center was slowing down the hydrolysis and it might simply be a matter of forcing the reaction conditions to induce the hydrolysis to proceed on our desired alkylated products.



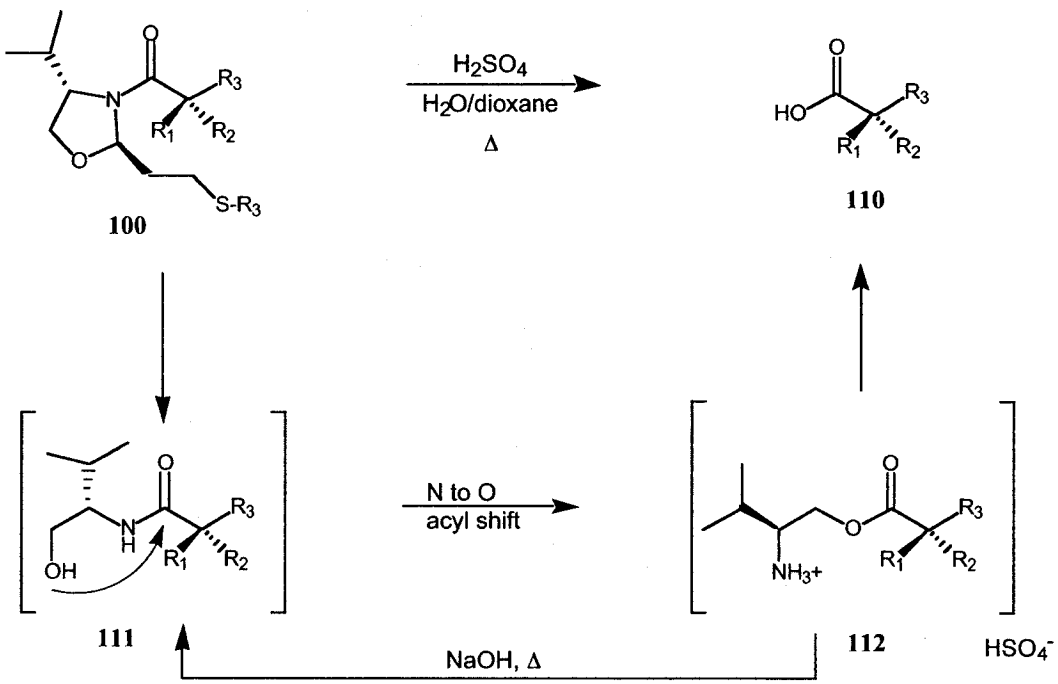
Scheme 27. Hydrolysis of a tertiary center.

We then decided to carefully monitor the reaction by NMR spectroscopy using trimethylated lactam variants **108** and **109** as control systems. While product **108** was easily synthesized using our methodology, product **109** was obtained via coupling between pivaloyl chloride and valinol with catalytic DMAP and triethylamine as a base in dichloromethane at 0 °C for 2 h. In both cases, presence of a *t*-butyl group would considerably simplify the ^{1}H NMR spectra. Pivalic acid was obtained in satisfying yields upon treatment of **108** and **109** with aqueous sulfuric acid in *p*-dioxane at reflux for 8 hours.



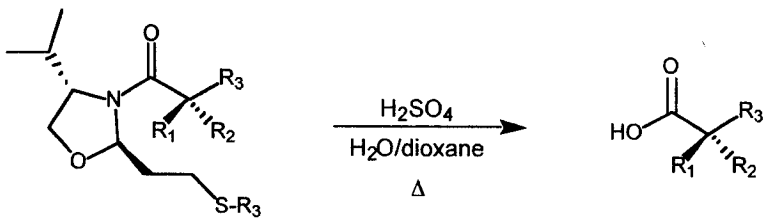
NMR studies revealed, as expected, that the reaction occurs by acetal cleavage to form a β-amidoalcohol **111** followed by N to O assisted acyl-transfer to form a β-aminoester **112** which finally undergoes acid hydrolysis to reveal the carboxylic acid (Scheme 28). Intermediate **112** could even be isolated upon treatment of **108** with 1 M

HCl or sulfuric acid in a water/dioxane mixture at room temperature. As expected, treatment of aminoester **112** with sodium hydroxide at reflux shifted the equilibrium towards the amidoalcohol **111**. When applied to our alkylated products, the above conditions afforded carboxylic acids in excellent yields (Table 3). The products could be isolated by distillation or by treatment with diazomethane followed by column chromatography. In the case of alkylated products **100c** and **100j** (entries 3 and 7, Table 3), TBS cleavage occurred and the products were isolated as δ-lactones.



Scheme 28. Mechanism of the acidic hydrolysis.

Table 3. Acidic auxiliary cleavage



100 **110**

Entry	R^1	R^2	R^3	Product	Yield	e.r.	$[\alpha]_D$
1	Et	Me	Bn	**110a**	81%	93:7	-7.4 °
2	Et	Me	Pr	**110b**	79%	99:1	-18.0 °
3 [a]	Et	Me	$TBSO(CH_2)_3$	**110c**	79%	96:4	+173 °
4	Et	Me	$Cl(CH_2)_4$	**110d**	80%	95:5	-13.2 °
5	Me	Et	Bn	**110g**	60%	93:7	+8.5 °
6	Me	Et	Pr	**110h**	82%	99:1	+16.0 °
7 [a]	Me	Et	$TBSO(CH_2)_3$	**110i**	81%	95:5	-154 °
8	Me	Et	$Cl(CH_2)_4$	**110j**	81%	95:5	+14.8 °

[a] Product isolated as the δ-lactone resulting from TBS cleavage and cyclization.

The absolute stereochemistry of the α-quaternary acids was determined by comparison of the optical rotation values with the ones obtained with the first generation auxiliary and the value reported in the literature for acid **110b**. The enantioselectivity was determined by GC for acids **110d** and **110j** as well as for lactones **110c** and **110i**. With the benzyl group acting as a good chromophore, HPLC was used to determine the selectivity on acids **110a** and **110g**. With three groups of similar size (ethyl, methyl and propyl), enantiomers **110b** and **110h** were barely separable using a chiral cyclodextrin column in a GC. Once transformed into their corresponding benzyl esters, however, both enantiomers were easily separable. It is known that benzyl groups fit well into

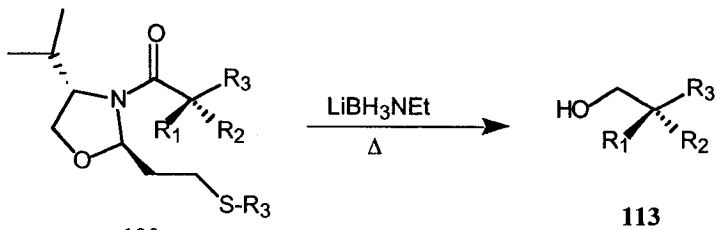
cyclodextrin residues and thus may have increased the affinity of these substrates for the chiral stationary phase.

2.7 Isolation of Quaternary Adducts via Reductive Amide Cleavage

Although the new methodology afforded direct access to carboxylic acids under acidic conditions, we envisioned that it would be useful to have two sets of conditions for auxiliary cleavage in case some adducts were acid sensitive.

Since amide reduction with lithium amidoborohydride[19] was used to remove the auxiliary during the first generation auxiliary, it was applied to the new system and afforded good yields of primary alcohols (Table 4). The enantioselectivity of the liberated primary alcohols was determined easily using chiral HPLC for alcohols **113a**, **113f** and **113g**. Without the presence of a decent chromophore, HPLC monitoring was not suitable for alcohols **113e** and **113k**. However, when transformed into their corresponding benzoates, enantiomers **113e** and **113k** were readily separable by chiral GC.

Table 4. Reductive cleavage of auxiliary.



100 **113**

Entry	R^1	R^2	R^3	Product	Yield	e.r.	$[\alpha]_D$
1	Et	Me	Bn	**113a**	85%	93:7	+8.0 °
2	Pr	Et	Allyl	**113e**	84%	95:5	+14.4 °
3	Bn	Me	Et	**113f**	87%	97:3	-7.2 °
4	Me	Et	Bn	**113g**	85%	93:7	-7.2 °
5	Et	Pr	Allyl	**113k**	84%	96:4	-15.1 °

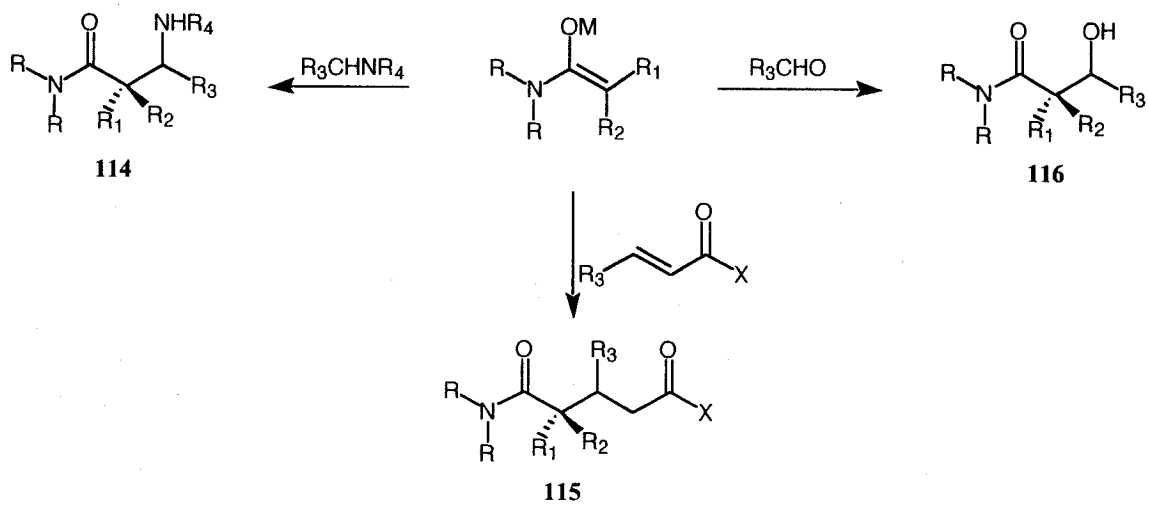
2.8 CONCLUSIONS

The goal of this project was to develop a practical second-generation chiral auxiliary system for the enantioselective synthesis of quaternary carbon centers. Where the first-generation auxiliary included a lengthy synthesis, a low selectivity for the *(E)*-enolate final alkylation and a harsh hydrolysis, we sought to design a newer version of the bicyclic lactam, which would overcome the first generation shortcomings.

It was demonstrated that the new auxiliary could be synthesized in two or three steps from readily available starting materials. Moreover, its synthesis does not require any column chromatography or other purification other than a simple recrystallization. Subsequent alkylations of the bicyclic lactams were achieved with excellent yields and selectivities leading to a variety of α,α-disubstituted enolate precursors. Reductive

enolization of the dialkylated lactams under Birch conditions and subsequent alkylation afforded quaternary adducts cleanly with high levels of selectivity for both the *(E)*- and the *(Z)*-enolates. The auxiliary can be cleaved under acidic or basic conditions to reveal either the α-quaternary carboxylic acids or the primary alcohols. This methodology represents a considerable improvement over the first generation auxiliary system as it overcomes almost all of its shortcomings.

The results of this new methodology were submitted for publication in 2005. The success of this second-generation chiral auxiliary system has led to different projects that use enolate intermediates (Scheme 29).



Scheme 29. Future uses of α,α-disubstituted enolates.

The aldol reaction (**116**) showed good results with the first-generation auxiliary.[20] Preliminary investigations have shown that these reactions are also selective with the new auxiliary.[21] Future directions of this research project include the use of Michael acceptors (**115**) and imines (**114**) as electrophiles.

[1] a) Romo, D.; Meyers, A.I. *Tetrahedron*, **1991**, *47*, 9503; b) Groaning, M.D.; Meyers, A.I. *Tetrahedron*, **2000**, *56*, 9843; c) Meyers, A.I.; Downing, S.V.; Weiser, M.J. *J. Org. Chem.* **2001**, *66*, 1413; d) Meyers, A.I.; Seefeld, M.A.; Lefker, B.A.; Blake, J.F; Willard, P.G. *J. Am. Chem. Soc.* **1998**, *120*, 7429.

[2] a) Evans, D.A.; Takacs, J.M. *Tetrahedron Lett.* **1980**, *21*, 4233; b) Evans, D.A.; Dow, R.L.; Shih, T.L.; Takacs, J.M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

[3] Manthorpe, J.M. *A General Method for the Asymmetric Synthesis of Quaternary Centers: Reductive Formation and Alkylation of α,α-Disubstituted Enolates*, Ph.D. Thesis, McGill University, **2003**, p.115.

[4] Manthorpe, J. M. *unpublished results.*

[5] Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857.

[6] Manthorpe, J.M.; Gleason, J.L. *J. Am. Chem. Soc.* **2001**, *123*, 2091.

[7]Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.G.; Gleason, J.L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

[8] These dihedral angles are not directly comparable since they were measured for the benzyl/methyl lactam for the first-generation auxiliary and with the methyl/ethyl lactam for the second-generation auxiliary. However, these angles can be compared on a qualitative basis. In addition, the behavior of a compound in solution vs. in a crystal structure can be really different.

[9] For lithium naphtalenide see a) Sort, K.M. in *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 3151 and references cited therein; for sodium naphtalenide see b) Molander, G.A.; Harris, C.R. in *Encyclopedia of*

Reagents for Organic Synthesis. (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 4602 and references cited therein; for potassium naphtalenide see c) Merrill, B.A. in *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 4269 and references cited therein.

[10] For sodium anthracenide see Merrill, B.A. in *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 4508 and references cited therein.

[11] For references on LDBB see a) Ferguson, M.D. in *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 3076 and references cited therein; b) Donohoe, T.J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015. For references on KDBB see c) Karaman, R.; He, G.-X.; Chu, F.; Blasko, A.; Bruice, T.C. *J. Org. Chem.* **1993**, *58*, 438; d) Karaman, R.; Kohlman, D.T.; Fry, J.L *Tetrahedron Lett.* **1990**, *31*, 6155.

[12] Woodbury, R.P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 881.

[13] Manthorpe, J.M.; Gleason, J.L. *Angew. Chem. Int. Ed.* **2002**, *114*, 2444.

[14] Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* **1999**, *1*, 2069.

[15] Products **100a** and **100f** are not true stereoisomers, as alkylation on sulfur produces compounds with different molecular formulas. However, upon cleavage of the auxiliary, the products are identical.

[16] a) Shank, K. *The Chemistry of Sulphones and Sulphoxides.* (Patai, P.; Rappoport, Z. and Sterling, C. Editors) Wiley: New-York, **1988**, p.165 and references cited therein; b) Kulhe, E. *The Chemistry of th Sulfenic Acids.* Georg Thiemes Publishers Stuggart: Germany, **1973**, p.43.

[17] Product **103** was submitted to a reductive cleavage with lithium amidoboroydride to afford (*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **113a** (see section 2.7 and chapter 3).

[18] Fronza, G.; Fogliato, G.; Fuganti, C.; Grasselli, P.; Rigoni, R. *Tetrahedron*, **1996**, *52*, 14281.

[19] Myers, A.G; Yang, B.H.; Kopecky, D.J. *Tetrahedron Lett.* **1996**, *37*, 3623.

[20] Burke, E.D.; Gleason, J.L. *Org. Lett.* **2004**, *6*, 405.

[21] Burke, E.D. *unpublished results*.

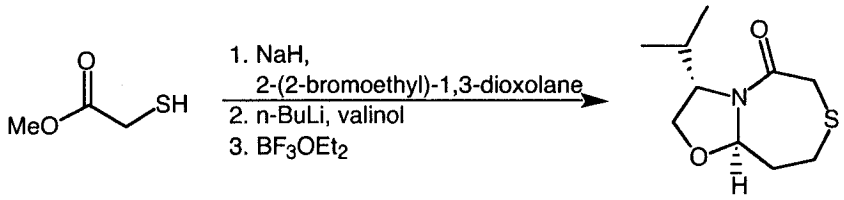
CHAPTER THREE

EXPERIMENTAL SECTION

General Experimental.

All reagents were commercial materials and were used without further purification with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Toluene and methylene chloride were distilled from calcium hydride. Valinol can be purchased from Aldrich or synthesized via the methodology published by A. I. Meyers.[1] Alkylation and reductive enolization substrates were dried via azeotropic distillation of water using dry toluene. All Schlenk flasks and lithium chloride were flame-dried under vacuum. Alkyl halides were passed through basic alumina prior to addition. Chromatography was conducted using 230-400 mesh silica gel. NMR spectra were recorded at 270, 300, 400 or 500 MHz for ^{1}H and 67.5, 75 or 100 MHz for ^{13}C. GC analyses were conducted on a CP Chiralsil-dex column (25 m x 0.25 mm) using He (14 psi) as carrier gas unless mentioned. Elemental analyses were obtained from Quantitative Technologies Inc., Whitehouse, NJ. High-resolution mass spectroscopy experiments were conducted by M. Gaston Boulay at Université de Sherbrooke.

Synthesis (7*R*,10*S*)-1-Aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (90).



Methyl thioglycolate **86** (12.61 mL, 141.0 mmol, 2.0 equiv.) was added slowly to a mixture of 60% NaH (5.64 g, 141.0 mmol, 2.0 equiv.) in tetrahydrofuran (200 mL) at 23 °C resulting in a vigorous evolution of hydrogen. Once the gas evolution had ceased, 2-(2-bromoethyl)-1,3-dioxolane **88** (8.28 mL, 70.5 mmol, 1.0 equiv.) was added slowly via a glass syringe. The resulting mixture was stirred for 16 h. Saturated aqueous sodium bicarbonate (150 mL) was added and the mixture was extracted with ethyl acetate (3 X 150 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 15% ethyl acetate in hexanes to afford (2-[1,3]dioxolan-2-yl-ethylsulfanyl)-acetic acid methyl ester **96** (13.81 g, 67.2 mmol) in 95% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ, 5.00 (t, 1H, J = 4.5 Hz), 3.97 (m, 2H), 3.89 (m, 2H), 3.73 (s, 3H), 3.24 (s, 2H), 2.74, (t, 2H, J = 7.8 Hz), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ, 170.9, 103.2, 65.3, 52.7, 34.0, 33.8, 30.0, 27.5. HRMS calc. for $C_8H_{14}O_4S$: 206.0613. Found: 206.0619 ±0.0006.

A 2.50 M solution *n*-butyllithium in hexanes (5.38 mL, 13.4 mmol, 0.2 equiv.) was added to a solution of valinol **89** (8.31 g, 80.7 mmol, 1.2 equiv.) in tetrahydrofuran (150 mL) at 0 °C. The mixture was stirred for 5 minutes, at which time, a solution of (2-[1,3]dioxolan-2-yl-ethylsulfanyl)-acetic acid methyl ester **96** (13.81 g, 67.2 mmol, 1.0 equiv.) in tetrahydrofuran (25 mL) was added via cannula. The resulting mixture was

stirred for 16 h at 23 °C. Saturated aqueous ammonium chloride (150 mL) was added and the mixture was extracted with ethyl acetate (3 X 75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 60% ethyl acetate and 5% methanol in hexanes to afford 2-(2-[1,3]dioxolan-2-yl-ethylsulfanyl)-N-(1-hydroxymethyl-2-methyl-propyl)-acetamide **94** (17.09 g, 61.8 mmol) in 92% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ, 7.12 (d, 1H, J = 9.2 Hz), 4.95 (t, 1H, J = 3.9 Hz), 3.95 (m, 2H), 3.85 (m, 2H), 3.69 (m, 3H), 3.28 (s, 2H), 2.67, (m, 2H), 2.45 (bs, 1H), 1.95 (m, 3H), 0.97 (d, 3H, J = 7.0 Hz), 0.95 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ, 169.5, 103.0, 65.3, 64.0, 57.7, 36.9, 33.7, 29.3, 28.5, 19.9, 19.1. HRMS calc. for $C_{12}H_{23}NO_4S$: 277.1348. Found: 277.1353 ±0.0008.

Boron trifluoride diethyletherate (9.40 mL, 74.2 mmol, 1.2 equiv.) was added dropwise to a solution of 2-(2-[1,3]dioxolan-2-yl-ethylsulfanyl)-N-(1-hydroxymethyl-2-methyl-propyl)-acetamide **94** (17.09 g, 61.8 mmol, 1.0 equiv.) in dichloromethane (150 mL) at 23 °C. After 18 h, saturated aqueous sodium bicarbonate (75 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 X 100 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The product was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **90** (11.31 g, 52.5 mol) in 85% yield as a white solid. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.26 (d, 1H, J = 9.0 Hz), 4.18 (m, 1H), 3.95 (m, 2H), 3.28 (d, 1H, J = 14.5 Hz), 3.20 (dd, 1H, J = 1.6, 14.5 Hz), 2.99 (m, 1H), 2.82, (m, 1H), 2.48 (m, 1H), 2.26 (m, 1H), 2.09 (m, 1H), 0.90 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 6.7 Hz); ^{13}C NMR

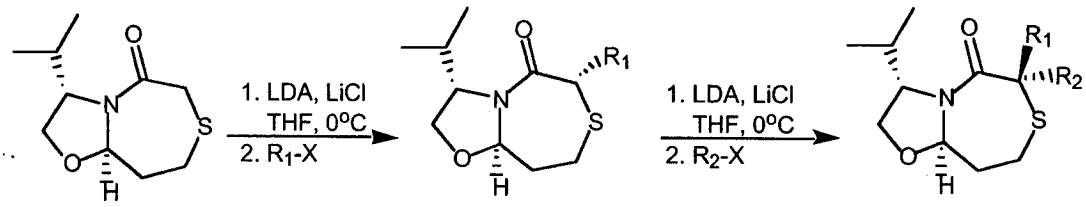
($CDCl_3$) δ, 168.1, 90.54, 65.7, 62.1, 37.0, 36.6, 30.0, 27.9, 19.7, 16.3. $[\alpha]^{25}_{D}$=+17.2° (c=6.79, CH_2Cl_2). Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.87; H, 7.96; N, 6.64. mp: 138-139 °C.

Rapid synthesis of (7*R*,10*S*)-1-Aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (90) without purification.

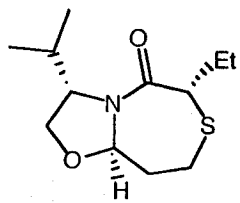
Methyl thioglycolate **86** (16.85 mL, 188.0 mmol, 2.0 equiv.) was added slowly to a mixture of 60% NaH (7.52 g, 188.0 mmol, 2.0 equiv.) in tetrahydrofuran (300 mL) at 23 °C resulting in a vigorous evolution of hydrogen. Once the gas evolution had ceased, 2-(2-bromoethyl)-1,3-dioxolane **88** (11.04 mL, 94.0 mmol, 1.0 equiv.) was added slowly via a glass syringe. The resulting mixture was stirred for 16 h. Saturated aqueous sodium bicarbonate (200 mL) was added and the mixture was extracted with ethyl acetate (3 X 150 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. A 2.50 M solution *n*-butyllithium in hexanes (7.24 mL, 18.1 mmol, 0.2 equiv.) was added to a solution of valinol **89** (11.20 g, 108.6 mmol, 1.2 equiv.) in tetrahydrofuran (150 mL) at 0 °C. The mixture was stirred for 5 minutes, at which time, a crude solution of (2-[1,3]dioxolan-2-yl-ethylsulfanyl)-acetic acid methyl ester **94** (18.57 g, 90.5 mmol, 1.0 equiv.) in tetrahydrofuran (25 mL) was added via cannula. The resulting mixture was stirred for 16 h at 23 °C. Saturated aqueous ammonium chloride (150 mL) was added and the mixture was extracted with ethyl acetate (3 X 75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. Boron trifluoride diethyletherate (13.08 mL, 103.2 mmol, 1.2 equiv.) was added dropwise to a crude solution of 2-(2-[1,3]dioxolan-2-yl-

ethylsulfanyl)-N-(1-hydroxymethyl-2-methyl-propyl)-acetamide **94** (23.77 g, 86.0 mmol, 1.0 equiv.) in dichloromethane (150 mL) at 23 °C. After 18 h, saturated aqueous sodium bicarbonate (100 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 100 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The product was crystallized out from diethyl ether to afford **90** (13.36 g, 62.0 mmol) in 71% yield as a white solid. The product was determined to have >99% de by GC chiral analysis.

Sample procedure for alkylation with alkyl halides:



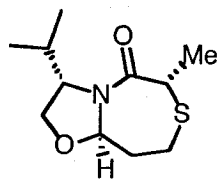
Synthesis of (3*S*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (97a).



A solution of *n*-butyllithium in hexanes (2.50 M, 204 μL, 1.10 equiv.) was added to a slurry of diisopropylamine (74.8 μL, .53 mmol, 1.15 equiv.) and lithium chloride (98.0 mg, 2.32 mmol, 5 equiv.) in tetrahydrofuran (4 mL) at 0 °C. After 5 minutes, a solution of (7*S*,10*S*)-1-aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone **90** (100 mg, 0.46 mmol, 1.0 equiv.) in tetrahydrofuran (6 mL) was added via cannula. The resulting mixture was stirred for 15 minutes, at which time, ethyl iodide (74.5 μL, .93 mmol, 2.0 equiv.) was added dropwise. Stirring was continued for 12 h at 0 °C. Saturated aqueous ammonium chloride solution (10 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 X 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*S*,7*S*,10*S*)-1-aza-3-ethyl-10-isopropyl-[8-oxa-4-thiabicyclo[5.3.0]-2-decanone **97a** as a white solid (106 mg, .44 mmol) in 95% yield. The product was determined to

have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.39 (dd, 1H, J = 1.6, 10.2 Hz), 4.28 (m, 1H), 3.89 (m, 2H), 3.34 (t, 1H, J = 7.5 Hz), 2.97-2.63 (m, 2H), 2.42, (m, 1H), 2.30 (m, 1H), 2.14-1.98 (m, 2H), 1.88 (m, 1H), 1.07, (t, 3H, J = 7.2 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 170.0, 88.8, 64.5, 62.9, 50.0, 35.8, 28.1, 23.7, 23.5, 19.6, 16.3, 12.1. HRMS calc. for $C_{12}H_{21}NO_2S$: 243.1293. Found: 243.1297 ±0.00087. mp: 106-107 °C.

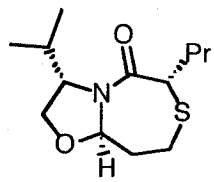
(3*S*,7*R*,10*S*)-1-Aza-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo [5.3.0]-2-decanone (97b):



A solution of *n*-butyllithium in hexanes (2.50 M, 2.04 mL, 1.10 equiv.) was added to a slurry of diisopropylamine (748 μL, 5.3 mmol, 1.15 equiv.) and lithium chloride (984 mg, 23.2 mmol, 5 equiv.) in tetrahydrofuran (10 mL) at 0 °C. After 5 minutes, a solution of (7*S*,10*S*)-1-aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone **90** (1.00 g, 4.6 mmol, 1.0 equiv.) in tetrahydrofuran (20 mL) was added via cannula. The resulting mixture was stirred for 15 minutes, at which time, methyl iodide (376 μL, 6.0 mmol, 1.2 equiv.) was added dropwise. Stirring was continued for 12 h at 0 °C. Saturated aqueous ammonium chloride solution (25 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 X 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to

afford (3*S*, 7*S*,10*S*)-1-aza-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone **97b** (0.96 g, 4.2 mmol) in 90%yield as a white solid. The product was determined to have >98% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.32 (d, 1H, J = 9.8 Hz), 4.28 (m, 1H), 3.85 (m, 2H), 3.57 (q, 1H, J = 7.4 Hz), 2.90-2.77 (m, 2H), 2.40, (m, 2H), 2.06 (m, 1H), 1.59 (d, 3H, J = 7.8 Hz), 0.88 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 170.8, 88.9, 64.7, 62.6, 41.7, 35.0, 28.2, 24.2, 19.3, 17.2, 16.4. Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.61; H, 8.35; N, 6.11. Found: C, 57.68; H, 8.42; N, 6.09. mp: 107-108 °C.

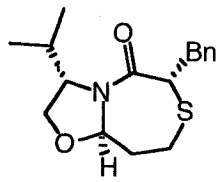
(3*S*,7*R*,10*S*)-1-Aza-10-isopropyl-3-propyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (97c):



The alkylation was carried out following the general procedure above starting from **90** (100 mg, .46 mmol) at 0 °C over 16 h using 2.0 equiv. of propyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **97c** (106 mg, .41 mmol) as a white solid in 89% yield. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.41 (d, 1H, J = 10.2 Hz), 4.27 (m, 1H), 3.87 (m, 2H), 3.42 (t, 1H, J = 7.4 Hz), 2.94 (m, 1H), 2.64, (m, 1H), 2.42 (m, 1H), 2.02 (m. 2H), 1.82 (m, 1H), 1.52, (m, 1H), 1.41 (m, 1H), 0.98 (t, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 170.0, 88.7, 64.5, 62.8, 48.2, 35.9, 32.2, 28.1, 23.7, 20.8, 19.6, 16.4, 14.1. Anal. Calcd

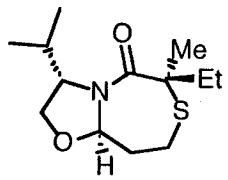
for $C_{13}H_{23}NO_2S$: C, 60.66; H, 9.01; N, 5.44. Found: C, 60.79; H, 9.12; N, 5.41. mp: 77-78 °C.

(3*S*,7*R*,10*S*)-1-Aza-3-benzyl-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (97d):



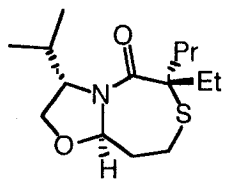
The alkylation was carried out following the general procedure above starting from **90** (100 mg, .46 mmol) at 0 °C over 16 h using 1.2 equiv. of benzyl bromide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **97d** (125 mg, .41 mmol) as a white solid in 88% yield. The product was determined to have 97% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 7.30-7.18 (m. 5H), 5.33 (dd, 1H, J = 1.8, 9.6 Hz), 4.19 (m, 1H), 3.95 (m, 2H), 3.39 (m, 2H), 3.10 (m, 1H), 2.88-2.73 (m, 2H), 2.36 (m, 1H), 2.20-2.01 (m, 2H), 0.84 (d, 3H, J = 7.0 Hz), 0.73 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ, 169.2, 139.2, 129.3, 128.4, 126.7, 90.2, 65.7, 61.8, 49.2, 36.8, 36.2, 30.5, 28.3, 19.6, 16.2. HRMS calc. for $C_{17}H_{23}NO_2S$: 305.1449. Found: 305.1456 ±0.0009. mp: 135.5-136 °C.

(3*R*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98a):



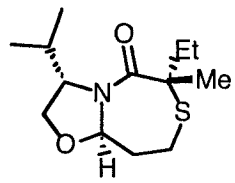
The alkylation was carried out following the general procedure above starting from **97a** (100 mg, .41 mmol) at 0 °C over 16 h using 1.2 equiv. of methyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **98a** (95 mg, .37 mmol) as colorless oil in 90% yield. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.64 (dd, 1H, J = 2.3, 9.8 Hz), 4.28 (m, 1H), 3.93-3.81 (m, 2H), 2.85-2.67 (m, 2H), 2.42-2.25 (m, 2H), 1.93 (m, 3H), 1.51 (s, 3H), 1.06 (t, 3H, J = 7.4 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 6.7 Hz; ^{13}C NMR ($CDCl_3$) δ, 172.5, 88.9, 64.4, 62.9, 52.6, 34.7, 33.2, 27.8, 24.8, 24.6, 19.5, 16.3, 9.4. HRMS calc. for $C_{13}H_{23}NO_2S$: 257.1449. Found: 257.1454 ±0.0008.

(3*S*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-3-propyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98b):



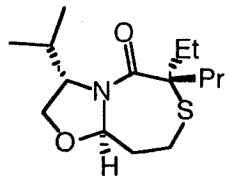
The alkylation was carried out following the general procedure above starting from **97a** (100 mg, .41 mmol) at 0 °C over 16 h using 2.0 equiv. of propyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **98b** (108 mg, .38 mmol) as a white solid in 92% yield. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.72 (dd, 1H, J = 2.7, 9.8 Hz), 4.28 (m, 1H), 3.88 (m, 2H), 2.85-2.64 (m, 2H), 2.43 (m, 1H), 2.22 (m, 1H), 2.00-1.77 (m, 5H), 1.37-1.25 (m, 2H), 1.03 (t, 3H, J = 7.4 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 171.3, 88.7, 63.7, 63.0, 57.2, 39.8, 34.2, 30.9, 27.4, 24.1, 19.7, 18.2, 16.0, 14.8, 9.1. Anal. Calcd for $C_{15}H_{27}NO_2S$: C, 63.12; H, 9.53; N, 4.91. Found: C, 63.29; H, 9.60; N, 4.90. mp: 58-59 °C.

(3*S*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98c):



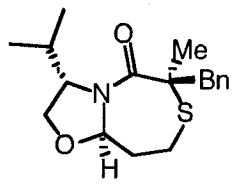
The alkylation was carried out following the general procedure above starting from **97b** (100 mg, .44 mmol) at 0 °C over 16 h using 2.0 equiv. of ethyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **98c** (97 mg, .37 mmol) as a white solid in 86% yield. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.55 (dd. 1H, J = 1.9, 9.8 Hz), 4.31 (m, 1H), 3.85 (m, 2H), 2.93 (m, 1H), 2.69 (m, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 2.05-1.87 (m, 3H), 1.49 (s, 3H), 0.97 (t, 3H, J = 7.4 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 172.0, 89.1, 63.9, 63.5, 51.8, 35.4, 27.8, 25.9, 24.1, 19.8, 16.2, 9.3. Anal. Calcd for $C_{13}H_{23}NO_2S$: C, 60.66; H, 9.01; N, 5.44. Found: C, 60.70; H, 8.99; N, 5.43. mp: 106-107.5 °C.

(3*R*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-3-propyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98d):



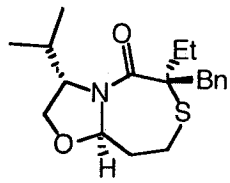
The alkylation was carried out following the general procedure above starting from **97c** (100 mg, .39 mmol) at 0 °C over 16 h using 2.0 equiv. of ethyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **98d** (99 mg, .35 mmol) as colorless oil in 89% yield. The product was determined to have 94% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 5.70 (dd, 1H, J = 2.7, 9.8 Hz), 4.28 (m, 1H), 3.86 (m, 2H), 2.86-2.64 (m, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 1.99-1.74 (m, 5H), 1.50 (m, 3H), 0.98-0.84 (m, 11H); ^{13}C NMR ($CDCl_3$) δ, 171.1, 88.7, 63.7, 63.1, 57.1, 40.2, 34.3, 30.9, 27.5, 24.2, 19.7, 17.9, 16.0, 14.9, 9.4. HRMS calc. for $C_{15}H_{27}NO_2S$: 285.1762. Found: 285.1769 ±0.0008.

(3*S*,7*R*,10*S*)-1-Aza-3-benzyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98e):



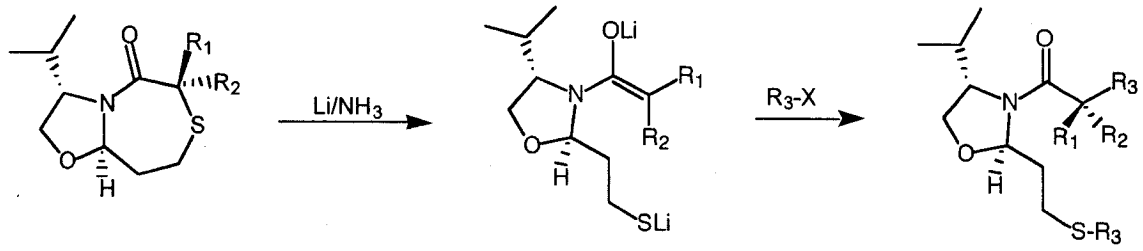
The alkylation was carried out following the general procedure above starting from **97d** (100 mg, .33 mmol) at 0 °C over 16 h using 1.2 equiv. of methyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **98e** (99 mg, .31 mmol) as colorless oil in 95% yield. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 7.37-7.21 (m, 5H), 5.73 (dd, 1H, J = 2.5, 9.6 Hz), 4.30 (m, 1H), 3.86 (m, 2H), 3.36 (d, 1H, J = 13.7 Hz), 3.10 (d, 1H, J = 13.7 Hz), 2.64 (m, 1H), 2.44 (m, 1H), 2.20 (m, 1H), 1.85 (m, 1H), 1.48 (s, 3H), 0.90 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 172.0, 137.2, 131.9, 127.9, 126.8, 88.8, 64.2, 63.2, 54.6, 45.6, 34.2, 27.7, 26.0, 25.0, 19.6, 16.4. HRMS calc. for $C_{18}H_5NO_2S$: 319.1606. Found: 319.1611 ±0.0010.

(3*R*,7*R*,10*S*)-1-Aza-3-benzyl-3-ethyl-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (98f):

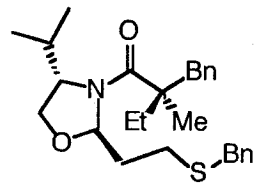


The alkylation was carried out following the general procedure above starting from **97d** (100 mg, .33 mmol) at 0 °C over 16 h using 2.0 equiv. of ethyl iodide. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford **98f** (101 mg, .30 mmol) as a colorless oil in 92% yield. The product was determined to have >99% de by GC chiral analysis: ^{1}H NMR ($CDCl_3$) δ, 7.39 (d, 2H, J = 8.2 Hz), 7.23 (m, 3H), 5.80 (dd, 1H, J = 2.7, 9.8 Hz), 4.29 (m, 1H), 3.86 (m, 2H), 3.44 (d, 1H, J = 13.6 Hz), 2.99 (d, 1H, J = 13.6 Hz), 2.65-2.52 (m, 2H), 2.32 (m, 1H), 2.13 (m, 1H), 1.92-1.79 (m, 3H), 1.02 (t, 3H, J = 7.4 Hz), 0.91 (d, 3H, J = 7.0 Hz), 0.87 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ, 170.4, 137.4, 131.9, 127.8, 126.7, 88.5, 63.6, 63.4, 58.7, 43.6, 33.6, 32.1, 27.4, 24.3, 19.9, 16.2, 9.6. HRMS calc. for $C_{19}H_{27}NO_2S$: 333.1762. Found: 333.1766 ±0.0010.

General procedure for sequential reductive enolization and alkylation of dialkylated substrates:



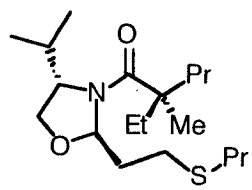
[2*R*,4*S*]-((2*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamoyl)-4-isopropyl-2-(4-phenyl-3-thiapropyl)-oxazolidine (100a):



Lithium wire (54 mg, 7.8 mmol, 4.0 equiv.) was pressed into thin sheets and rinsed in hexanes, tetrahydrofuran, methanol and tetrahydrofuran and then added in liquid ammonia (25 mL). After 1 hour of stirring at -78 °C, dialkylated lactam **98a** (500 mg, 1.94 mmol, 1.0 equiv.) in tetrahydrofuran (8 mL) was cannulated into the lithium-ammonia solution. The resulting mixture was stirred for 10 minutes, at which time benzyl bromide (692 μL, 5.8 mmol, 3.0 equiv.) was added dropwise. Stirring was continued for 4 h at -78 °C. Saturated aqueous ammonium chloride solution (15 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100a** (613 mg, 1.78 mmol) in 92% yield as a colorless oil. The product was determined to have 93:7 dr by analysis of the

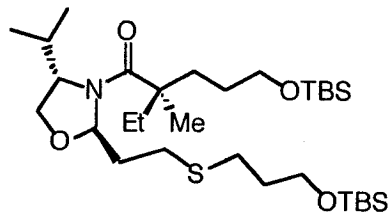
corresponding carboxylic acid. ^{1}H NMR ($CD_3S(O)CD_3$, 100 °C) δ, 7.32-7.18 (m, 10H), 5.45 (d, 1H, J = 8.1 Hz), 3.98-3.46 (m, 6H), 3.13 (d, 1H, J = 13.1 Hz), 2.68 (d, 1H, J = 13.1 Hz), 2.45 (m, 3H), 2.06-1.94 (m, 2H), 1.73 (m, 2H), 1.68 (m. 1H), 1.19 (s, 3H), 0.91(t, 3H, J = 7.3 Hz), 0.83 (d, 3H, J = 6.9 Hz), 0.72 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.1, 138.3, 138.2, 130.9, 130.6, 129.1, 128.7, 127.1, 126.5, 90.5, 66.9, 64.7, 61.3, 49.6, 47.0, 43.6, 36.7, 33.2, 32.8, 27.3, 22.2, 19.9, 15.9, 9.9. HRMS calc. for $C_{27}H_{37}NO_2S$: 439.2545. Found: 439.2549 ±0.0013.

[2*R*,4*S*]-((2*R*)-2-Ethyl-2-methyl-pentanoyl)-4-isopropyl-2-(3-thiahexyl)-oxazolidine (100b):



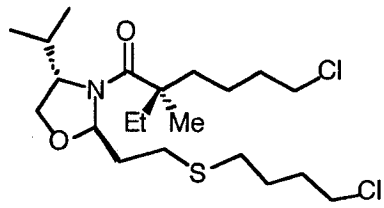
The reaction was carried out following the general procedure above starting from **98a** (100 mg, .39 mmol) at -78 °C over 4 h using 4.0 equiv. of propyl iodide. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100b** (117 mg, .34 mmol) in 88% yield as a colorless oil. The product was determined to have 99:1 dr by analysis of the corresponding carboxylic acid. ^{1}H NMR (C_6D_6, 110 °C) δ, 5.78 (d, 1H, J = 8.1 Hz), 3.88 (m, 1H), 3.51 (m, 3H), 2.56 (m, 2H), 2.35 (m, 4H), 1.75 (m. 3H), 1.52 (m, 2H), 1.35 (m, 3H), 1.19 (s, 3H), 0.88 (m, 12H), 0.60 (d, 3H, J = 7.0 Hz); ^{13}C NMR (C_6D_6, 110 °C) δ, 175.1, 90.4, 64.3, 61.4, 48.3, 43.3, 34.6, 34.2, 32.5, 30.6, 27.9, 22.9, 22.4, 19.0, 17.7, 15.2, 14.3, 12.8, 8.6. HRMS calc. for $C_{19}H_{37}NO_2S$: 343.2545. Found: 343.2543 ±0.0010.

[2*R*,4*S*]-((2*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-2-ethyl-2-methylpentanoyl)-4-isopropyl-2-(6-(*tert*-butyl-dimethyl-silanyloxy)-3-thiahexyl)-oxazolidine (100c):



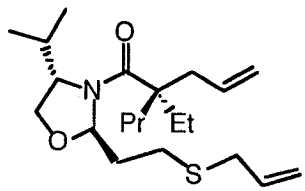
The reaction was carried out following the general procedure above starting from **98a** (100 mg, .39 mmol) at -78 °C over 4 h using 4.0 equiv. of *tert*-butyl-(3-iodo-propoxy)-dimethylsilane. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100c** (200 mg, .34 mmol) in 86% yield as a yellow oil. The product was determined to have 96:4 dr by analysis of the corresponding δ-lactone. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 5.58 (d, 1H, J = 9.4 Hz), 4.06-3.90 (m, 3H), 3.70-3.55 (m, 4H), 2.59 (m, 3H), 2.02 (m, 2H), 1.82-1.70 (m, 4H), 1.59-1.42 (m, 4H), 1.26 (s, 3H), 0.89 (m, 27H), 0.05 (d, 12H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.6, 63.8, 61.9, 61.3, 48.0, 37.5, 33.1, 32.9, 29.1, 28.4, 28.2, 26.4, 26.3, 22.6, 20.0, 18.7, 16.0, 9.5, -4.9. HRFABMS *m/z* 604.4265 ($M + H^+$, $C_{31}H_{66}NO_4SSi_2^+$ requires 604.4251).

[2*R*,4*S*]-((2*R*)-6-Chloro-2-ethyl-2-methylhexanoyl)-4-isopropyl-2-(7-chloro-3-thiaheptyl)-oxazolidine (100d):



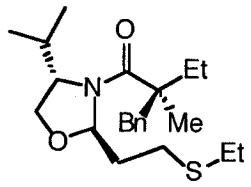
The reaction was carried out following the general procedure above starting from **98a** (100 mg, .39 mmol) at -78 °C over 4 h using 4.0 equiv. of 1-chloro-4-iodobutane. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100d** (136 mg, .31 mmol) in 79% yield as a yellow oil. The product was determined to have 95:5 dr by analysis of the corresponding carboxylic acid. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 5.51 (d, 1H, J = 8.6 Hz), 4.02-3.81 (m, 4H), 3.45 (m, 4H), 2.47 (m, 3H), 2.04 (m, 2H), 1.83-1.14 (m, 14H), 0.83-0.731 (m, 9H); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.4, 90.6, 65.2, 61.3, 51.8, 48.3, 45.3, 44.9, 33.3, 33.2, 31.8, 31.7, 27.9, 26.9, 22.3, 22.2, 21.7, 20.1, 19.9, 15.9, 9.4. HRFABMS *m/z* 440.2164 (M + H^+, $C_{21}H_{40}Cl_2NO_2S^+$ requires 440.2157).

[2*R*,4*S*]-((2*R*)-2-Ethyl-2-propyl-pent-4-enoyl)-4-isopropyl-2-(3-thiahex-5-enyl)-oxazolidine (100e):



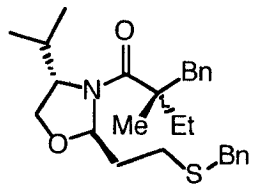
The reaction was carried out following the general procedure above starting from **98d** (100 mg, .35 mmol) at -78 °C over 4 h using 3.0 equiv. of allyl bromide. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100e** (117 mg, .32 mmol) in 91% yield as a colorless oil. The product was determined to have 95:5 dr by analysis of the corresponding alcohol. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 5.76 (m, 2H), 5.48 (d, 1H, J = 8.5 Hz), 5.10 (m, 3H), 4.29-3.75 (m, 7H), 3.16 (dd, 2H, J = 3.5 Hz, 7.0 Hz), 2.69-1.25 (m, 11H), 1.05-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 174.9, 134.4, 118.0, 117.3, 89.5, 65.3, 61.5, 51.8, 48.3, 45.9, 39.1, 35.2, 33.1, 28.5, 26.8, 22.2, 20.2, 17.9, 16.2, 15.1, 9.3. HRFABMS *m/z* 368.2626 (M + H^+, $C_{21}H_{38}NO_2S^+$ requires 368.2623).

[2*R*,4*S*]-((2*S*)-2-Ethyl-2-methyl-2,3-dihydrocinnamoyl)-4-isopropyl-2-(3-thiapentyl)-oxazolidine (100f):



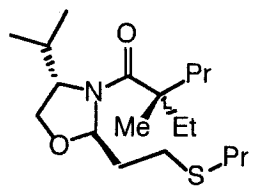
The reaction was carried out according to the general procedure above starting from **98e** (100 mg, .31 mmol) at -78 °C over 4 h using 4.0 equiv. of ethyl iodide. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100f** (103 mg, .27 mmol) as a colorless oil in 87% yield. The product was determined to have 97:3 dr by analysis of the corresponding primary alcohol. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 7.26-7.14 (m, 5H), 5.56 (d, 1H, J = 9.9 Hz), 3.97 (m, 1H), 3.84 (m, 2H), 3.31 (d, 1H, J = 12.9 Hz), 2.48 (m, 4H), 2.10 (m, 1H), 1.41 (m, 1H), 1.36 (m. 8H), 0.86 (t, 3H, J = 7.8 Hz), 0.70 (bs, 3H), 0.61 (bs, 3H); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.0, 138.5, 130.8, 128.3, 126.6, 90.7, 64.8, 61.4, 50.8, 47.9, 38.0, 33.0, 27.6, 26.4, 20.6, 19.8, 16.2, 15.1, 9.4. HRFABMS *m/z* 378.2473 ($M + H^+$, $C_{22}H_{35}NO_2S^+$ requires 378.2467).

[2*R*,4*S*]-((2*S*)-2-Ethyl-2-methyl-2,3-dihydrocinnamoyl)-4-isopropyl-2-(4-phenyl-3-thiapropyl)-oxazolidine (100g):



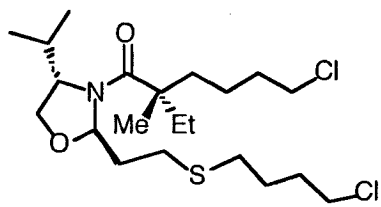
The reaction was carried out following the general procedure above starting from **98c** (100 mg, .39 mmol) at -78 °C over 4 h using 3.0 equiv. of benzyl bromide. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100g** (162 mg, .37 mmol) as a colorless oil in 85% yield (the product was slightly contaminated with methylene chloride). The product was determined to have 93:7 dr by analysis of the corresponding carboxylic acid. ^{1}H NMR ($CD_3S(O)CD_3$, 100 °C) δ, 7.31-7.22 (m, 10H), 5.44 (d, 1H, J = 8.1 Hz), 3.99-3.70 (m, 5H), 3.17 (d, 1H, J = 13.2 Hz), 2.45 (m, 2H), 1.91 (m, 2H), 1.72 (m, 2H), 1.60 (m. 2H), 1.21 (s, 3H), 0.83 (t, 3H, J = 7.3 Hz), 0.70 (d, 3H, J = 6.8 Hz), 0.60 (d, 3H, J = 6.4 Hz)); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 174.9, 138.6, 138.5, 130.9, 130.8, 130.6, 130.5, 129.4, 129.1, 128.7, 128.6, 128.3, 128.2, 128.1, 127.2, 126.6, 126.5, 66.9, 61.4, 50.8, 47.9, 47.0, 38.0, 36.8, 33.2, 32.6, 32.5, 27.8, 27.5, 27.3, 20.7, 20.5, 19.9, 15.3, 9.9, 9.7, 9.5. HRMS calc. for $C_{27}H_{37}NO_2S$: 439.2545. Found: 439.2549 ±0.0013.

[2*R*,4*S*]-((2*S*)-2-Ethyl-2-methylpentanoyl)-4-isopropyl-2-(3-thiahexyl)-oxazolidine (100h):



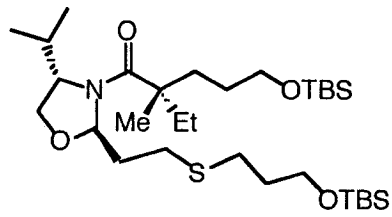
The reaction was carried out following the general procedure above starting from **98c** (100 mg, .39 mmol) at -78 °C over 4 h using 4.0 equiv. of propyl iodide. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100h** (122 mg, .36 mmol) as a colorless oil in 91% yield. The product was determined to have 99:1 dr by analysis of the corresponding carboxylic acid. ^{1}H NMR (C_6D_6, 90 °C) δ, 5.75 (dd, 1H, J = 1.6, 8.6 Hz), 3.91 (m, 1H), 3.67 (m, 2H), 2.57 (m, 2H), 2.41 (m, 2H), 2.24 (m, 2H), 1.77 (m. 3H), 1.52 (m, 2H), 1.32 (m, 3H), 1.68 (s, 3H), 0.86 (m, 12H), 0.83 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.3, 90.1, 66.7, 64.4, 61.3, 61.0, 48.2, 48.1, 43.5, 42.6, 34.5, 34.4, 34.3, 33.1, 32.8, 30.2, 30.0, 28.0, 27.7, 23.8, 22.9, 22.2, 22.1, 21.1, 20.2, 19.6, 18.7, 18.0, 17.9, 17.8, 15.6, 14.8, 14.7, 13.5, 10.7, 9.1, 8.0. HRMS calc. for $C_{19}H_{37}NO_2S$: 343.2545. Found: 343.2543 ±0.0010.

[2*R*,4*S*]-((2*S*)-6-Chloro-2-ethyl-2-methylhexanoyl)-4-isopropyl-2-(7-chloro-3-thiaheptyl)-oxazolidine (100i):



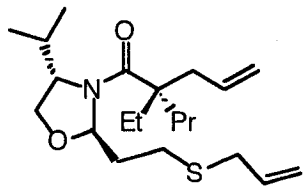
The reaction was carried out following the general procedure above starting from **98c** (100 mg, .39 mmol) at -78 °C over 4 h using 4.0 equiv. of 1-chloro-4-iodobutane. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100i** (139 mg, .31 mmol) in 81% yield as a yellow oil. The product was determined to have 95:5 dr by analysis of the corresponding carboxylic acid. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 5.51 (d, 1H, J = 8.6 Hz), 4.02-3.81 (m, 4H), 3.45 (m, 4H), 2.47 (m, 3H), 2.04 (m, 2H), 1.83-1.14 (m, 14H), 0.83-0.731 (m, 9H); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.4, 90.6, 65.2, 61.3, 51.8, 48.3, 45.3, 44.9, 33.3, 33.2, 31.8, 31.7, 27.9, 26.9, 22.3, 22.2, 21.7, 20.1, 19.9, 15.9, 9.4. HRFABMS *m/z* 440.2164 (M + H^+, $C_{21}H_{40}Cl_2NO_2S^+$ requires 440.2157).

[2*R*,4*S*]-((2*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-2-ethyl-2-methylpentanoyl)-4-isopropyl-2-(6-(*tert*-butyl-dimethyl-silanyloxy)-3-thiahexyl)-oxazolidine (100j):



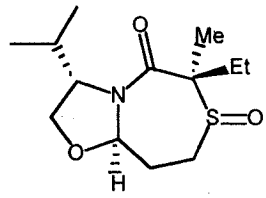
The reaction was carried out following the general procedure above starting from **98c** (100 mg, .39 mmol) at -78 °C over 4 h using 4.0 equiv. of *tert*-butyl-(3-iodo-propoxy)-dimethylsilane. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100j** (199 mg, .33 mmol) in 84% yield as a yellow oil. The product was determined to have 95:5 dr by analysis of the corresponding δ-lactone. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 5.56 (d, 1H, J = 9.3 Hz), 4.03-3.89 (m, 3H), 3.70-3.57 (m, 4H), 2.58 (m, 3H), 2.01 (m, 2H), 1.82-1.70 (m, 4H), 1.59-1.42 (m, 4H), 1.26 (s, 3H), 0.89 (m, 27H), 0.05 (d, 12H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 175.5, 63.8, 61.8, 61.3, 48.0, 37.5, 33.1, 32.9, 29.1, 28.4, 28.2, 26.4, 26.3, 22.6, 20.0, 18.7, 16.0, 9.5, -4.8. HRFABMS *m/z* 604.4265 ($M + H^+$, $C_{31}H_{66}NO_4SSi_2^+$ requires 604.4251).

[2*R*,4*S*]-((2*S*)-2-Ethyl-2-propyl-pent-4-enoyl)-4-isopropyl-2-(3-thiahex-5-enyl)-oxazolidine (100k):



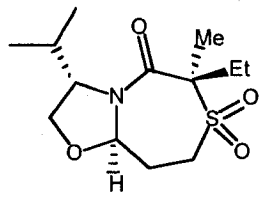
The reaction was carried out following the general procedure above starting from **98b** (100 mg, .35 mmol) at -78 °C over 4 h using 3.0 equiv. of allyl bromide. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **100k** (115 mg, .31 mmol) in 89% yield as a colorless oil. The product was determined to have 96:4 dr by analysis of the corresponding alcohol. ^{1}H NMR ($CDCl_3$, 23 °C) δ, 5.78-5.58 (m, 3H), 5.06 (m, 4H), 4.05-3.85 (m, 4H), 3.14 (d, 2H, J = 7.0 Hz), 2.59-2.38 (m, 4H), 2.18-2.04 (m, 3H), 1.71-1.52 (m, 2H), 1.25 (m, 3H), 0.92-0.82 (m, 9H); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 174.9, 134.5, 118.1, 117.3, 88.4 65.3, 61.5, 51.8, 48.3, 45.9, 39.1, 38.2, 35.2, 28.5, 26.8, 22.2, 20.2, 20.0, 17.9, 15.1, 9.3. HRFABMS *m/z* 368.2626 ($M + H^+$, $C_{21}H_{38}NO_2S^+$ requires 368.2623.

(3*R*, 7*R*, 10*S*)-1-Aza-3-ethyl-10-isopropyl-3-methyl-8-oxabicyclo-4-sulfinyl-[5.3.0]-2-decanone (101)



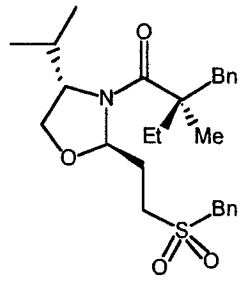
Methylene chloride (5.0 mL) was added in a 10 mL schlenk flask under argon. A solution of lactam **98a** (200 mg, 0.78 mmol, 1.0 equiv.) in 5 mL methylene chloride was added via cannula. *m*CPBA (134 mg, 0.78 mmol, 1 equiv.) was added in one portion and the solution turned red. The resulting mixture was stirred at room temperature for 11 h at which point saturated aqueous sodium bicarbonate (10 mL) was added and the resulting mixture and extracted with methylene chloride (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford **101** (68 mg, 0.25 mmol) in 41% yield as white solid: ^{1}H NMR ($CDCl_3$) δ, 5.42 (d, 1H, J = 10.2 Hz), 4.44 (m, 1H), 3.98-3.85 (m, 2H), 3.12 (m, 2H), 2.60 (m, 2H), 2.34 (m, 1H), 2.06 (m, 1H), 1.68 (s, 3H), 1.05 (t, 3H, J = 7.3 Hz), 0.90 (d, 3H, J = 7.0 Hz), 0.85 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ, 172.1, 88.7, 66.9, 65.3, 53.4, 37.3, 35.0, 28.8, 27.7, 25.5, 19.9, 16.5, 9.8. HRMS calc. for $C_{13}H_{23}NO_3S$: 273.1439. Found: 273.1454 ±0.0008.

(3*R*, 7*R*, 10*S*)-1-Aza-3-ethyl-10-isopropyl-3-methyl-8-oxabicyclo-4-sulfanyl-[5.3.0]-2-decanone (102)



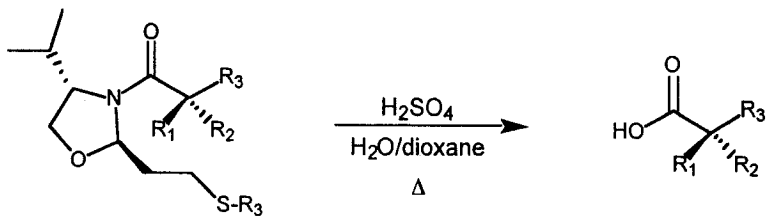
To a solution of lactam **98a** (200 mg, 0.78 mmol, 1.0 equiv) in methanol (3.0 mL) at 0 °C, a solution of Oxone (1.43g, 2.3 mmol, 3.0 equiv.) in distilled water (5.0 mL) was added slowly. The resulting mixture was stirred at 0 °C for 4 h, at which point distilled H_2O was added until the solution became clear and the resulting mixture was warmed to 23 °C and extracted with methylene chloride (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 75% ethyl acetate in hexanes to afford **102** (203 mg, 0.70 mmol) in 90% yield as a white solid: ^{1}H NMR ($CDCl_3$) δ, 5.55 (d, 1H, J = 9.8 Hz), 4.42 (m, 1H), 3.91 (m, 2H), 3.60 (m, 1H), 3.21 (m, 1H), 2.45-2.28 (m, 4H), 1.71 (s, 3H), 1.13 (t, 3H, J = 7.4 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.83 (d, 3H, J = 6.7 Hz; ^{13}C NMR ($CDCl_3$) δ, 173.5, 89.6, 67.4, 65.9, 53.6, 37.7, 35.2, 28.8, 27.6, 25.9, 19.9, 16.8, 9.5. HRMS calc. for $C_{13}H_{23}NO_4S$: 257.1449. Found: 257.1454 ±0.0008.

[2*R*, 4*S*]-((2*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamoyl-4-isopropyl-2-(2-phenylmethanesulfonylethyl)-oxazolidine (103):

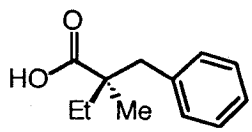


Lithium wire (18 mg, 2.6 mmol, 4.0 equiv.) was pressed into thin sheets and rinsed in hexanes, tetrahydrofuran, methanol and tetrahydrofuran and then added in liquid ammonia (15 mL). After 1 hour of stirring at -78 °C, dialkylated lactam **102** (185 mg, 0.64 mmol, 1.0 equiv.) in tetrahydrofuran (4 mL) was cannulated into the lithium-ammonia solution. The resulting mixture was stirred for 10 minutes, at which time benzyl bromide (228 μL, 1.9 mmol, 3.0 equiv.) was added dropwise. Stirring was continued for 4 h at -78 °C. Saturated aqueous ammonium chloride solution (10 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford **103** (154 mg, 0.32 mmol) in 51% yield as a colorless oil. The product was determined to have 88:12 dr by analysis of the corresponding carboxylic acid. ^{1}H NMR ($CDCl_3$) δ, 7.44-7.18 (m, 10H), 5.46 (d, 1H, J = 8.1 Hz), 4.61-3.77 (m, 6H), 3.26 (d, 1H, J = 12.9 Hz), 2.67 (d, 1H, J = 12.9 Hz), 2.30-1.63 (m. 6H), 1.29 (s, 3H), 1.00 (t, 3H, J = 7.3 Hz), 0.87 (d, 3H, J = 7.0 Hz), 0.80 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 23 °C) δ, 176.1, 138.9, 139.2, 132.1, 130.9, 129.7, 128.9, 127.9, 126.5, 91.5, 67.6, 64.0, 62.3, 49.9, 47.6, 43.6, 36.7, 33.7, 32.8, 27.8, 22.9, 20.9, 16.5, 10.7. HRMS calc. for $C_{27}H_{37}NO_4S$: 471.2495. Found: 471.2549 ±0.0013.

General procedure for acidic hydrolysis:

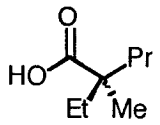


Synthesis of (*R*)-2-Benzyl-2-methylbutyric acid (110a):



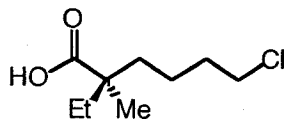
A solution of [2*R*,4*S*]-((2*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamoyl)-4-isopropyl-2-(4-phenyl-3-thiapropyl)-oxazolidine **100a** (240 mg, .64 mmol, 1.0 equiv) in *p*-dioxane (3 mL) and aqueous sulfuric acid solution (5.3 M, 3mL) was heated at reflux for 8 h, cooled to 23 °C and extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by distillation under vacuum (150 °C, 0.5 mmHg) to afford (*R*)-2-benzyl-2-methylbutyric acid **110a** (106 mg, .52 mmol) in 81% yield as colorless oil. ^{1}H NMR ($CDCl_3$) δ, 11.42 (bs, 1H), 7.14-7.36 (m, 5H), 3.08 (d, 1H, J = 13.3 Hz), 2.77 (d, 1H, J = 13.3 Hz), 1.84 (m, 1H), 1.53 (m, 1H), 1.13 (s, 3H), 0.98 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 183.6, 137.6, 130.7, 128.2, 126.7, 46.5, 41.4, 32.1, 20.8, 18.2, 15.0, 9.3. $[\alpha]^{25}_D$=-7.4° (c=26.0, CH_2Cl_2). The product was determined to have 93:7 dr by chiral HPLC analysis (Chiralcel OD column, eluting with 1% isopropanol + 0.01% trifluoroacetic acid in hexanes at 0.7 ml/minute) R_t=11.78 minutes (minor enantiomer), 12.32 minutes (major enantiomer). HRMS calc. for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1147 ±0.0005.

(*R*)-2-Ethyl-2-methylpentanoic acid (110b):



The reaction was carried out according to the general procedure above starting from **100b** (252 mg, .73 mmol) to afford (*R*)-2-ethyl-2-methylpentanoic acid **110b** (83 mg, .58 mmol) in 79 % yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 9.81 (bs, 1H), 1.22-1.73 (m, 6H), 1.12 (s, 3H), 0.91 (t, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 184.6, 46.5, 41.4, 32.1, 20.8, 18.2, 15.0, 9.3. $[\alpha]^{25}_D$=+16.4° (c=20.0, EtOH), lit.[2] $[\alpha]^{20}_D$= +19.7° (c=1, EtOH). The product was determined to have 99:1 dr by GC chiral analysis of the corresponding benzyl ester (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 130 °C, Rt = 13.13 minutes (major enantiomer), 15.97 minutes (minor enantiomer). HRFABMS *m/z* (M+H, 145.1232 $C_8H_{16}O_2^+$ requires 145.1228).

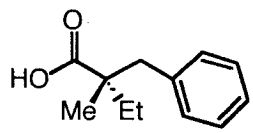
(*R*)-6-Chloro-2-ethyl-2-methylhexanoic acid (110d):



The reaction was carried out according to the general procedure above starting from **100d** (150 mg, .34 mmol) to afford (*R*)-6-Chloro-2-ethyl-2-methyl-hexanoic acid **110d** (53 mg, .27 mmol) in 80% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 11.12 (bs, 1H), 3.53 (t, 2H, J = 6.7 Hz), 1.67-1.36 (m, 8H), 1.15 (s, 3H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 183.8, 46.4, 45.1, 38.0, 33.3, 32.1, 22.3, 20.9, 9.3. $[\alpha]^{25}_D$=+14.8° (c=3.35, CH_2Cl_2). The product was determined to have 95:5 dr by chiral GC (Chirasil Dex column, He carrier gas, 25 psi, oven temperature = 100 °C), Rt= 6.67 minutes

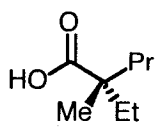
(major enantiomer), 10.68 minutes (minor enantiomer). HRFABMS *m/z* 193.1000 (M + H^+, $C_9H_{18}ClO_2^+$ requires 193.0995).

(*S*)-2-Benzyl-2-methylbutyric acid (110g):



The reaction was carried out according to the general procedure above starting from **100g** (234 mg, .53 mmol) to afford (*S*)-2-benzyl-2-methylbutyric acid **110g** (81 mg, .42 mmol) in 60% yield as a colorless oil (the product contained residual diethyl ether and dioxane which were not removed due to volatility of the product). ^{1}H NMR ($CDCl_3$) δ, 11.42 (bs, 1H), 7.14-7.36 (m, 5H), 3.08 (d, 1H, J = 13.3 Hz), 2.77 (d, 1H, J = 13.3 Hz), 1.84 (m, 1H), 1.53 (m, 1H), 1.13 (s, 3H), 0.98 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 183.6, 137.6, 130.7, 128.2, 126.7, 46.5, 41.4, 32.1, 20.8, 18.2, 15.0, 9.3. $[\alpha]^{25}_D$=+8.5° (c=35.0, CH_2Cl_2). The product was determined to have 93:7 dr by chiral HPLC analysis (Chiralcel OD column, eluting with 1% isopropanol + 0.01% trifluoroacetic acid in hexanes at 0.7 ml/minute) R_t=11.78 minutes (major enantiomer), 12.32 minutes (minor enantiomer). HRMS calc. for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1147 ±0.0005.

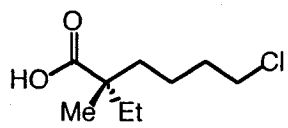
(*S*)-2-Ethyl-2-methylpentanoic acid (110h):



The reaction was carried out according to the general procedure above starting from **100h** (239 mg, .70 mmol) to afford (*S*)-2-ethyl-2-methylpentanoic acid **110h** (81 mg, .57

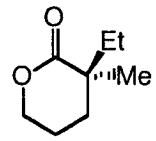
mmol) in 82% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 9.81 (bs, 1H), 1.22-1.73 (m, 6H), 1.12 (s, 3H), 0.91 (t, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 184.9, 46.5, 41.4, 32.1, 20.8, 18.2, 15.0, 9.3. $[\alpha]^{25}_D$=-18.0° (c=10.5, EtOH), lit.[2] (for enantiomer **110b**) $[\alpha]^{20}_D$= +19.7° (c=1, EtOH). The product was determined to have 99:1 dr by GC chiral analysis of the corresponding benzyl ester (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 130 °C, Rt = 13.13 minutes (minor enantiomer), 15.97 minutes (major enantiomer). HRFABMS *m/z* (M+H, 145.1232 $C_8H_{16}O_2^+$ requires 145.1228).

(*S*)-6-Chloro-2-ethyl-2-methylhexanoic acid (110j):



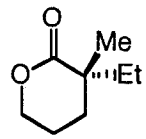
The reaction was carried out according to the general procedure above starting from **100i** (200 mg, .45 mmol) to afford (*S*)-6-Chloro-2-ethyl-2-methyl-hexanoic acid **110j** (69 mg, .36 mmol) in 81% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 11.12 (bs, 1H), 3.53 (t, 2H, J = 6.7 Hz), 1.67-1.36 (m, 8H), 1.15 (s, 3H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 183.8, 46.4, 45.1, 38.0, 33.3, 32.1, 22.3, 20.9, 9.3. $[\alpha]^{25}_D$=-13.2° (c=10.0, CH_2Cl_2). The product was determined to have 95:5 dr by chiral GC (Chirasil Dex column, He carrier gas, 25 psi, oven temperature = 100 °C), Rt= 6.76 minutes (minor enantiomer), 10.75 minutes (major enantiomer). HRFABMS *m/z* 193.1000 (M + H^+, $C_9H_{18}ClO_2^+$ requires 193.0995).

Synthesis of (*S*)-3-Ethyl-3-methyl-tetrahydropyran-2-one (110c):



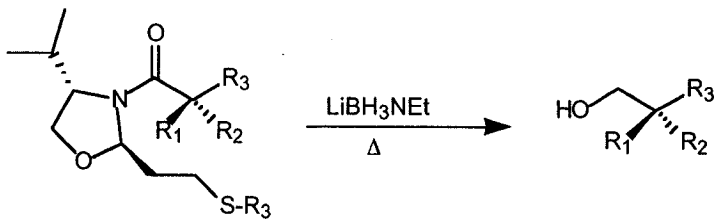
A solution of [2*R*,4*S*]-((2*R*)-5-(*tert*-butyl-dimethyl-silanyloxy)-2-ethyl-2-methyl-pentanoyl)-4-isopropyl-2-(6-(*tert*-butyl-dimethyl-silanyloxy)-3-thiahexyl)-oxazolidine **100c** (150 mg, .25 mmol, 1.0 equiv) in methanol (10.4 mL) and concentrated sulfuric acid (0.60 mL) was stirred at 23 °C for 18 at which point the methanol was evaporated. The residue was dissolved in ethyl acetate (10 mL) and extracted with a saturated solution of aqueous ammonium chloride (3 X 15 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 50% ethyl acetate in hexanes to afford (*S*)-3-ethyl-3-methyltetrahydropyran-2-one **110c** (29 mg, .20 mmol) in 79% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 4.17 (m, 2H), 1.91-1.55 (m, 6H), 1.27 (s, 3H), 0.92 (t, 3H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.7, 70.6, 43.0, 33.2, 31.7, 26.4, 21.0, 9.0. $[\alpha]^{25}_D$= +173° (c=3.75, CH_2Cl_2). The product was determined to have 96:4 dr by chiral GC analysis (Chirasil Dex column, 14 psi, oven temperature = 80 °C) Rt = 16.21 minutes (major enantiomer), 17.81 minutes (minor enantiomer). HRFABMS *m/z* 143.1077 (M + H$^+$, $C_8H_{15}O_2^+$ requires 143.1072).

(*R*)-3-Ethyl-3-methyl-tetrahydropyran-2-one (110i):

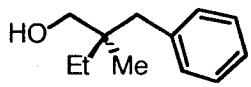


The reaction was carried according to the general procedure above starting from **100j** (150 mg, .25 mmol) to afford (*R*)-3-ethyl-3-methyl-tetrahydropyran-2-one **110i** (29 mg, .20 mmol) in 81% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 4.17 (m, 2H), 1.91-1.55 (m, 6H), 1.27 (s, 3H), 0.92 (t, 3H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.7, 70.6, 43.0, 33.2, 31.7, 26.4, 21.0, 9.0. $[\alpha]^{25}_{D}$= -154° (c=4.95, CH_2Cl_2). The product was determined to have 95:5 dr by chiral GC analysis (Chirasil Dex column, 14 psi, oven temperature = 80 °C) Rt = 16.09 minutes (minor enantiomer), 17.61 minutes (major enantiomer). HRFABMS *m/z* 143.1077 ($M + H^+$, $C_8H_{15}O_2^+$ requires 143.1072).

General procedure for reduction to the primary alcohol with lithium amidoborohydride:



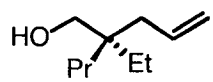
Synthesis of (*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamyl alcohol (113a):



A solution of *n*-butyllithium in hexanes (2.50 M, 813 μL, 1.87 mmol, 3.9 equiv.) was slowly added to a stirred solution of diisopropylamine (275μL, 1.96 mmol, 4.1 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C. After stirring for 10 minutes, borane-ammonia complex (90%, 60 mg, 1.9 mmol, 4.0 equiv.) was added in one portion. After stirring at 0 °C for 15 minutes the mixture was warmed to 23 °C and a solution of [2*R*,4*S*]-((2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamoyl)-4-isopropyl-2-(4-phenyl-3-thiapropyl)-oxazolidine **100a** (210 mg, .48 mmol, 1.0 equiv.) in tetrahydrofuran (5 mL) was added via cannula. The mixture was heated at reflux for 24 hours, then cooled to 0 °C and quenched with aqueous hydrochloric acid (3M, 5 mL). The resulting mixture was warmed to 23 °C and stirred for 30 minutes, at which point aqueous sodium hydroxide (3M, 10 mL) was added. The mixture was stirred at 23 °C for 30 minutes and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography on silica gel eluting with 30% diethyl ether in hexanes afforded **113a** (72 mg, .41 mmol,) in 85%

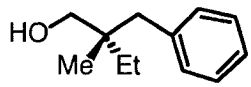
yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ, 7.17-7.27 (m, 5H), 3.34 (d, 1H, J = 11.0 Hz), 3.32 (d, 1H, J = 10.6 Hz), 2.63 (d, 1H, J = 13.3 Hz), 2.58 (d, 1H, J = 12.9 Hz), 1.28-1.42 (m, 3H), 0.93 (t, 3H, J = 7.4 Hz), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 130.7, 128.1, 126.1, 68.5, 42.9, 39.2, 29.3, 21.2, 8.5. $[\alpha]^{25}_D$=+8.0° (c=69.5, CH_2Cl_2). The product was determined to have 93:7 dr by chiral HPLC analysis (Chiralcel OD column, eluting with 1% isopropanol in hexanes at 0.7 ml/minute- R_t=21.1 minutes (major enantiomer), 23.7 minutes (minor enantiomer). HRMS calc. for $C_{12}H_{18}O$: 178.1358. Found: 178.1362 ±0.0005.

(*R*)-2-Ethyl-2-propyl-pent-4-en-1-ol (113e):



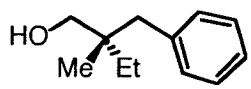
The reaction was carried out according to the general procedure above starting from **100e** (783 mg, 2.12 mmol) to afford (*R*)-2-ethyl-2-propyl-pent-4-en-1-ol **113e** (280 mg, 1.79 mmol) in 84% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ, 5.84 (m, 1H), 5.04 (m, 2H), 3.38 (s, 2H), 2.02 (d, 2H, J= 7.4 Hz), 1.33-1.17 (m, 7H), 0.90 (t, 3H, J = 7.1 Hz), 0.83 (t, 3H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 135.5, 117.2, 67.4, 40.6, 39.3, 36.1, 26.3, 16.6, 15.4, 7.9. $[\alpha]^{25}_D$=+14.4.° (c=8.0, CH_2Cl_2). The product was determined to have 95:5 dr by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 80 °C) R_t= 14.96 minutes (minor enantiomer), 16.53 minutes (major enantiomer). HRFABMS *m/z* 157.1597 ($M + H^+$, $C_{10}H_{21}O^+$ requires 157.1592).

(*S*)-2-Ethyl-2-methyl-2,3-dihydrocinnamyl alcohol (113f):



The reaction was carried out according to the general procedure above starting from **100f** (39 mg, .10 mmol) to afford (*S*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **113f** (17 mg, .09 mmol) in 87% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ, 7.17-7.27 (m, 5H), 3.34 (d, 1H, J = 11.0 Hz), 3.32 (d, 1H, J = 10.6 Hz), 2.63 (d, 1H, J = 13.3 Hz), 2.58 (d, 1H, J = 12.9 Hz), 1.28-1.42 (m, 3H), 0.93 (t, 3H, J = 7.4 Hz), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 130.7, 128.1, 126.1, 68.5, 42.9, 39.2, 29.3, 21.2, 8.5. $[\alpha]^{25}_D$=-7.1° (c=69.5, CH_2Cl_2). The product was determined to have 97:3 dr by chiral HPLC analysis (Chiralcel OD column, eluting with 1% isopropanol in hexanes at 0.7 ml/minute-R_t=21.3 minutes (minor enantiomer), 23.7 minutes (major enantiomer). HRMS calc. for $C_{12}H_{18}O$: 178.1358. Found: 178.1362 ±0.0005.

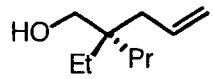
(*S*)-2-Ethyl-2-methyl-2,3-dihydrocinnamyl alcohol (113g):



The reaction was carried out according to the general procedure above starting from **100g** (212 mg, .48 mmol) to afford (*S*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **113g** (73 mg, .41 mmol) in 85% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ, 7.17-7.27 (m, 5H), 3.34 (d, 1H, J = 11.0 Hz), 3.32 (d, 1H, J = 10.6 Hz), 2.63 (d, 1H, J = 13.3 Hz), 2.58 (d, 1H, J = 12.9 Hz), 1.28-1.42 (m, 3H), 0.93 (t, 3H, J = 7.4 Hz), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.9, 130.7, 128.1, 126.1, 68.5, 42.9, 39.2, 29.3, 21.2, 8.5. $[\alpha]^{25}_D$=-7.1° (c=14.2, CH_2Cl_2). The product was determined to have 93:7 dr by chiral HPLC analysis

(Chiralcel OD column, eluting with 1% isopropanol in hexanes at 0.7 ml/minute- R_t=24.4 minutes (major enantiomer), 22.2 minutes (minor enantiomer). HRMS calc. for $C_{12}H_{18}O$: 178.1358. Found: 178.1362 ±0.0005.

(*S*)-2-Ethyl-2-propyl-pent-4-en-1-ol (113k):



The reaction was carried out according to the general procedure above starting from **100k** (40 mg, .11 mmol) to afford (*S*)-2-Ethyl-2-propyl-pent-4-en-1-ol **113k** (15 mg, .09 mmol) in 84%yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ, 5.84 (m, 1H), 5.04 (m, 2H), 3.38 (s, 2H), 2.02 (d, 2H, *J*= 7.4 Hz), 1.33-1.17 (m, 7H), 0.90 (t, 3H, *J* = 7.1 Hz), 0.83 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 135.5, 117.2, 67.4, 40.6, 39.3, 36.1, 26.3, 16.6, 15.4, 7.9. $[\alpha]^{25}_D$=-15.1° (c=8.6, CH_2Cl_2). The product was determined to have 96:4 dr by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 80 °C) R_t= 14.18 minutes (major enantiomer), 16.18 minutes (minor enantiomer). HRFABMS *m/z* 157.1597 ($M + H^+$, $C_{10}H_{21}O^+$ requires 157.1592).

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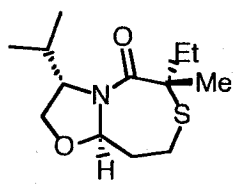
[1] Meyers, A.I.; McKennon, M.J. *J. Org. Chem.* **1993**, *58*, 3568-3571.

[2] Fronza, G.; Fogliato, G.; Fuganti, C.; Grasselli, P.; Rigoni, R. *Tetrahedron* **1996**, *52*, 14281-14286.

APPENDIX

COORDINATES OF STRUCTURE OF

(3*S*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone 98c



X-RAY CRYSTAL STRUCTURE OF

(3*S*,7*R*,10*S*)-1-Aza-3-ethyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone 98c

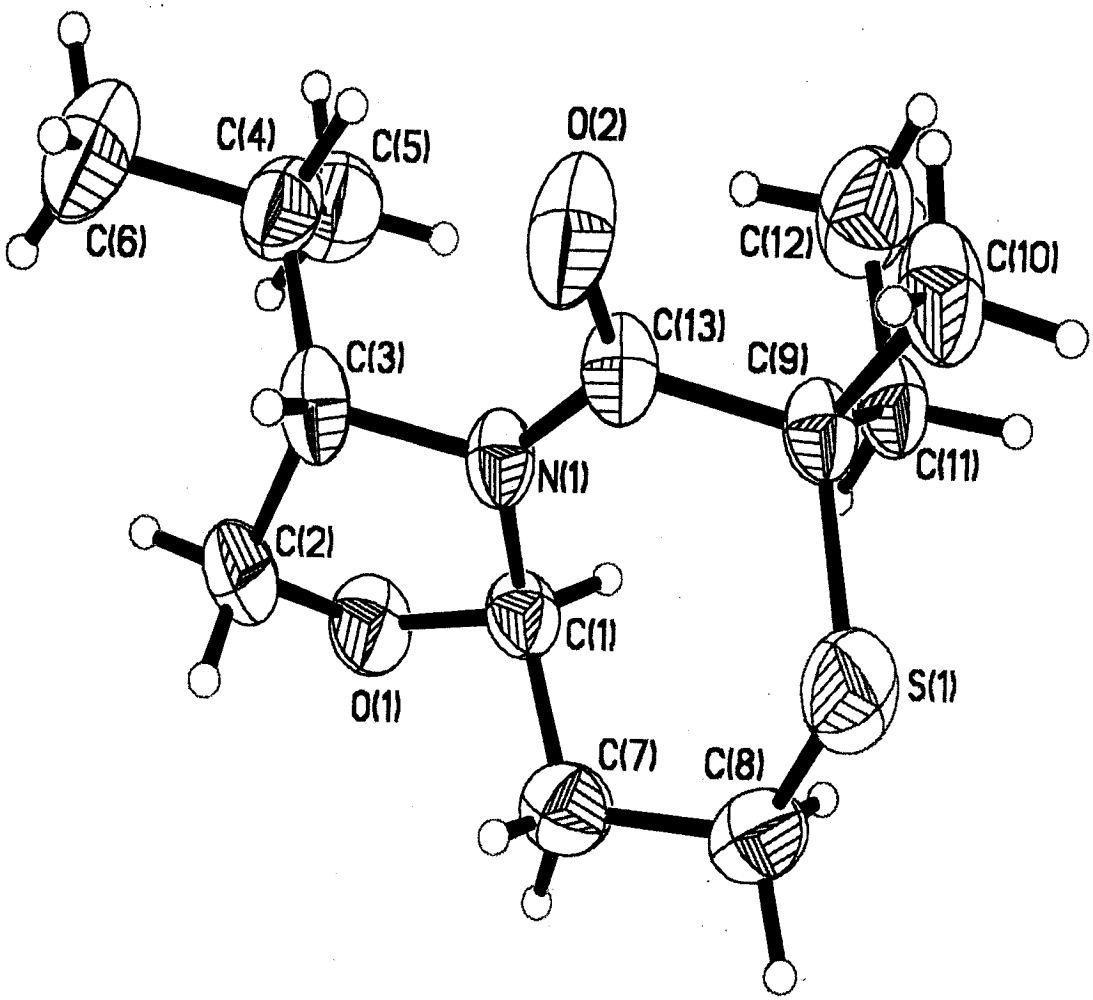


Table1. Crystal data and structure refinement for z1.

Identification code	z1
Empirical formula	C13 H23 N O2 S
Formula weight	257.38
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system, space group	?, ?
Unit cell dimensions	a = 6.0663(14) A alpha = 90 deg.
	b = 13.068(3) A beta = 90 deg.
	c = 17.860(4) A gamma = 90 deg.
Volume	1415.8(5) A^3
Z, Calculated density	4, 1.207 Mg/m^3
Absorption coefficient	0.220 mm^-1
F(000)	560
Crystal size	? x ? x ? mm
Theta range for data collection	1.93 to 25.00 deg.
Limiting indices	-7<=h<=7, -15<=k<=15, -21<=l<=21
Reflections collected / unique	10667 / 2488 [R(int) = 0.0551]
Completeness to theta = 25.00	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2488 / 0 / 155
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.0899
R indices (all data)	R1 = 0.0819, wR2 = 0.1071
Absolute structure parameter	-0.08(13)
Extinction coefficient	0.0002(9)
Largest diff. peak and hole	0.186 and -0.159 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for z1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	1706(2)	4563(1)	4290(1)	68(1)
O(1)	3785(4)	4872(2)	1754(1)	56(1)
O(2)	-1820(4)	6045(2)	3104(1)	78(1)
N(1)	1237(4)	5447(2)	2575(1)	41(1)
C(1)	3481(5)	5023(2)	2528(2)	44(1)
C(2)	1702(6)	4658(3)	1437(2)	57(1)
C(3)	107(5)	5352(3)	1846(2)	48(1)
C(4)	-325(6)	6372(3)	1464(2)	58(1)
C(5)	1782(7)	6959(3)	1277(2)	76(1)
C(6)	-1737(7)	6216(4)	768(2)	88(1)
C(7)	3792(8)	4027(3)	2940(2)	71(1)
C(8)	4091(8)	4130(3)	3781(2)	76(1)

C(9)	1189(5)	5848(2)	3946(2)	43(1)
C(10)	-524(6)	6266(3)	4506(2)	70(1)
C(11)	3231(6)	6526(3)	3970(2)	49(1)
C(12)	2881(8)	7584(3)	3657(2)	85(1)
C(13)	110(5)	5788(2)	3176(2)	45(1)

Table 3. Bond lengths [A] and angles [deg] for z1.

S(1)-C(8)	1.799(4)
S(1)-C(9)	1.815(3)
O(1)-C(1)	1.409(3)
O(1)-C(2)	1.412(4)
O(2)-C(13)	1.224(4)
N(1)-C(13)	1.348(4)
N(1)-C(1)	1.472(4)
N(1)-C(3)	1.477(4)
C(1)-C(7)	1.507(4)
C(2)-C(3)	1.514(5)
C(3)-C(4)	1.519(5)
C(4)-C(6)	1.524(5)
C(4)-C(5)	1.528(5)
C(7)-C(8)	1.520(5)
C(9)-C(11)	1.524(4)
C(9)-C(13)	1.526(4)
C(9)-C(10)	1.542(4)
C(11)-C(12)	1.507(5)
C(8)-S(1)-C(9)	105.04(16)
C(1)-O(1)-C(2)	107.7(2)
C(13)-N(1)-C(1)	129.7(2)
C(13)-N(1)-C(3)	119.6(2)
C(1)-N(1)-C(3)	110.3(2)
O(1)-C(1)-N(1)	103.3(2)
O(1)-C(1)-C(7)	110.0(2)
N(1)-C(1)-C(7)	114.3(3)
O(1)-C(2)-C(3)	105.1(2)
N(1)-C(3)-C(2)	100.3(3)
N(1)-C(3)-C(4)	113.7(3)
C(2)-C(3)-C(4)	114.8(3)
C(3)-C(4)-C(6)	110.2(3)
C(3)-C(4)-C(5)	113.2(3)
C(6)-C(4)-C(5)	111.0(3)
C(1)-C(7)-C(8)	114.9(3)
C(7)-C(8)-S(1)	115.5(3)
C(11)-C(9)-C(13)	113.8(3)
C(11)-C(9)-C(10)	108.8(3)
C(13)-C(9)-C(10)	108.3(3)

C(11)-C(9)-S(1)	112.8(2)
C(13)-C(9)-S(1)	109.4(2)
C(10)-C(9)-S(1)	103.0(2)
C(12)-C(11)-C(9)	114.1(3)
O(2)-C(13)-N(1)	119.5(3)
O(2)-C(13)-C(9)	119.4(3)
N(1)-C(13)-C(9)	121.1(3)

Symmetry transformations used to generate equivalent atoms

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for z1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	93(1)	67(1)	46(1)	8(1)	8(1)	-10(1)
O(1)	49(1)	72(2)	46(1)	-9(1)	12(1)	8(1)
O(2)	27(1)	158(3)	48(1)	-21(2)	1(1)	11(2)
N(1)	34(2)	57(2)	33(1)	-7(1)	2(1)	-4(1)
C(1)	41(2)	50(2)	41(2)	-7(1)	4(2)	4(2)
C(2)	70(3)	58(2)	44(2)	-16(2)	4(2)	-2(2)
C(3)	40(2)	68(2)	37(2)	-9(2)	4(1)	-16(2)
C(4)	52(2)	80(3)	42(2)	-4(2)	-3(2)	15(2)
C(5)	87(3)	63(3)	78(3)	10(2)	-5(3)	-8(3)
C(6)	63(3)	150(4)	52(2)	3(2)	-8(2)	15(3)
C(7)	96(3)	61(2)	55(2)	-3(2)	1(2)	26(2)
C(8)	107(4)	64(3)	55(2)	8(2)	-2(2)	28(2)
C(9)	34(2)	59(2)	37(2)	-9(2)	2(1)	-3(2)
C(10)	48(2)	117(4)	46(2)	-23(2)	9(2)	6(2)
C(11)	42(2)	63(2)	41(2)	-12(2)	-6(2)	-4(2)
C(12)	106(4)	74(3)	75(3)	4(2)	-20(3)	-22(3)
C(13)	31(2)	66(2)	38(2)	-6(2)	5(2)	-7(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for z1.

	x	y	z	U(eq)
H(1A)	4545	5529	2711	53
H(2A)	1312	3945	1511	69
H(2B)	1701	4804	905	69
H(3A)	-1295	4992	1917	58
H(4A)	-1176	6794	1814	70
H(5A)	2627	7061	1725	114
H(5B)	1407	7610	1064	114
H(5C)	2638	6573	923	114
H(6A)	-1993	6864	530	132

H(6B)	-3122	5917	909	132
H(6C)	-986	5768	427	132
H(7A)	5073	3682	2735	85
H(7B)	2521	3596	2845	85
H(8A)	5291	4603	3875	91
H(8B)	4528	3469	3980	91
H(10A)	-910	6954	4370	106
H(10B)	91	6262	5001	106
H(10C)	-1818	5844	4495	106
H(11A)	3717	6586	4486	58
H(11B)	4401	6195	3690	58
H(12A)	4228	7967	3693	127
H(12B)	1748	7925	3937	127
H(12C)	2445	7535	3142	127

Table 6. Torsion angles [deg] for z1.

C(2)-O(1)-C(1)-N(1)	-30.4(3)
C(2)-O(1)-C(1)-C(7)	92.1(3)
C(13)-N(1)-C(1)-O(1)	-176.1(3)
C(3)-N(1)-C(1)-O(1)	10.8(3)
C(13)-N(1)-C(1)-C(7)	64.4(4)
C(3)-N(1)-C(1)-C(7)	-108.6(3)
C(1)-O(1)-C(2)-C(3)	38.5(3)
C(13)-N(1)-C(3)-C(2)	-163.0(3)
C(1)-N(1)-C(3)-C(2)	10.9(3)
C(13)-N(1)-C(3)-C(4)	74.0(4)
C(1)-N(1)-C(3)-C(4)	-112.1(3)
O(1)-C(2)-C(3)-N(1)	-29.0(3)
O(1)-C(2)-C(3)-C(4)	93.3(3)
N(1)-C(3)-C(4)-C(6)	-173.0(3)
C(2)-C(3)-C(4)-C(6)	72.3(4)
N(1)-C(3)-C(4)-C(5)	62.0(4)
C(2)-C(3)-C(4)-C(5)	-52.7(4)
O(1)-C(1)-C(7)-C(8)	165.0(3)
N(1)-C(1)-C(7)-C(8)	-79.3(4)
C(1)-C(7)-C(8)-S(1)	67.9(5)
C(9)-S(1)-C(8)-C(7)	-63.8(3)
C(8)-S(1)-C(9)-C(11)	-51.3(3)
C(8)-S(1)-C(9)-C(13)	76.5(3)
C(8)-S(1)-C(9)-C(10)	-168.5(2)
C(13)-C(9)-C(11)-C(12)	52.1(4)
C(10)-C(9)-C(11)-C(12)	-68.8(4)
S(1)-C(9)-C(11)-C(12)	177.5(2)
C(1)-N(1)-C(13)-O(2)	-174.7(3)
C(3)-N(1)-C(13)-O(2)	-2.2(5)