In compliance with the
Canadian Privacy Legislation
some supporting forms
may have been removed from
this dissertation.

While these forms may be included
in the document page count,
their removal does not represent
any loss of content from the dissertation.

A GENERAL METHOD FOR THE ASYMMETRIC SYNTHESIS OF QUATERNARY CARBONS:

REDUCTIVE FORMATION AND ALKYLATION OF α,α–DISUBSTITUTED ENOLATES

JEFFREY MICHAEL MANTHORPE

A thesis submitted to the Faculty of Graduate Studies and Research
of McGill University in partial fulfillment of the requirements of the degree of
Doctor of Philosophy

Department of Chemistry
McGill University
Montréal, Québec, Canada
March 2003

Your file Votre référence
ISBN: 0-612-88523-2
Our file Notre référence
ISBN: 0-612-88523-2

Things Which I Have Learned In My Lifetime And Not-So-Random Thoughts From My Brain

"An eye for an eye leaves everybody blind" - Dalai Lama
Watch out for falling rocks.
Bones really are white.
Free fall is good. Impact is bad.
Listen to doctors.
"Chicks" don't "dig" scars. If they did, Ronny Priefer and I would be the sexiest men alive.
By comparison to the rest of you, I'm crazy and that makes me nuts.
I seem to be missing that part of the brain which provides the self-preservation instinct.
Live your life such that if you were to die tomorrow, you would still respect yourself.
"Milk and cookies are good for you" – Robert Fulghum
It is no one else's job to clean up after me.
Heavy Metal Rocks!
Rolling a car is fun, so long as it belongs to your friend's parents!
Your life really does flash before your eyes!
There is no substitute for the love of a dog. Thanks Chippy, Dylan, and Bear! ☺

"Yeah! I'm a Freak...of Nature. Yeah! I'm a Freak...of Nature. If only I could be as cool as you, as cool as you! Body and Soul, I'm a Freak! I'm a Freak! Body and Soul, I'm a Freak! I'm a Freak!"

"Freak"- Silverchair

"I sit alone, contemplating what is missing inside me. I desperately try to remember a life that's not meant to be. I meditate and try to recapture some sense of reality, yeah. But I look around; I see numb, empty faces; the world is waiting to die. This apathy is so suffocating; the slow decay of my mind. I've searched the world for someone with answers to the questions that are plaguing me. I scream in vain at anyone who'll listen but everybody's watching TV!"

"Television"- Stabbing Westward

"You are the tear. I have no fear. You are so strange. I feel the same. Sorcerous mind, We Rise Again. We are not chained to the wheel, to the wheel. It's the way that you feel. It's the truth in your eye. You got wings upon your back and you can fly! It's the way that you feel. It's the truth in your eye, 'cause you're up against the world and still you still you Rise, and still you Rise, and still you Rise, and still you Rise!"

"Rise"- The Cult

Here for a good time, not a long time!

Kein Mehrheit Für Die Mitleid

ABSTRACT

A new, general method for the asymmetric synthesis of quaternary carbons is described. This technique involves stereocontrolled generation of α,α–disubstituted amide enolates via reduction of bicyclic α,α–disubstituted α–thioglycolate lactams using one-electron transfer reagents. A model of the geometric constraints necessary to reductively prepare α,α–disubstituted amide enolates with control of enolate *E/Z* stereochemistry is described and several chiral auxiliaries were prepared to test this design.

Successful preparation, trapping, isolation and characterization of α,α–disubstituted amide enolates is described. This reductive enolization method allows, for the first time, the stereoselective preparation of both *E*– and *Z*–acyclic α,α–disubstituted amide enolates.

Reactivity and selectivity of α,α–disubstituted amide enolates in alkylation with alkyl halides is explored. Dichotomous reactivity is observed for both *E*– and *Z*–α,α–disubstituted amide enolates. *Z*–α,α–Disubstituted amide enolates are shown to alkylate with high levels of stereoselectivity; *E*–α,α–disubstituted amide enolates alkylate with poor stereoselectivity.

Methods for isolation of the quaternary carbon-containing adducts are described. Conditions for the determination of the enantiomeric excess of chiral, non-racemic neopentyl alcohols were developed and are also described.

Development of a facile, environmentally friendly, modular synthesis of a model second-generation chiral auxiliary using simple, inexpensive starting materials is described.

RÉSUMÉ

Une nouvelle méthode pour la synthèse de carbone quaternaires asymetriques est décrite. Cette technique est basée sur la formation stéreoselective d'énolate d'amide disubstitué à travers la réduction de lactame bicyclique (α,α-disubstituted α–thioglycolate lactams) par un réactif transfèrant un électron. Un modèle des contraintes geométriques pour préparer des énolates d'amides disubstitués avec contrôle stéreochimique a également été élaboré, ainsi que plusieurs exemples d'auxiliaires chiraux pour tester ce modèle ont été synthétisés.

La préparation, l'isolement et la caractérisation des énolates sont également présentées dans ce document. Cette méthode « d'énolisation réductive » permet pour la première fois la préparation stéreoselective des deux énolates acycliques disubstitués *E* et *Z*.

La réactivité et la sélectivité des énolates disubstitués au cours de l'alkykation avec des halogènures d'alkyle ont été explorées. Une différence de réactivité a été observée pour les deux énolates *E* et *Z*. Les énolates *Z* ont démontré une grande stéreosélectivité lors de l'alkylation alors que cette sélectivité était faible pour les énolates *E*.

Des méthodes d'isolement des produits contenant ces carbones quaternaires, ainsi que leurs transformations en alcools néo-pentyliques chiraux ont été developpées et sont décrites. La mesure de l'excès énantiomérique de ces produits est également incluse.

Une nouvelle synthèse d'auxiliaires chiraux, facile a mettre en oeuvre et respectant l'environnement a été finalement developpée. Cette seconde génération d'auxiliaires chiraux peu coûteux est décrite dans le dernier chapitre.

ACKNOWLEDGEMENTS

I am deeply indebted to my research director, Prof. James Gleason, for his support over the last four and a half years. His tireless work ethic, extensive scholarly knowledge, and gifted teaching skills have been invaluable during my study. I also thank him for his performance of the molecular modeling.

I also wish to thank Profs. George Just, David Harpp, Romas Kazlauskas, Masad Damha and Karine Auclair for their kind support and helpful advice, both chemical and otherwise.

I gratefully acknowledge Professor Claude Spino (Université de Sherbrooke) for advice and helpful discussions.

The assistance of Drs. Fred Morin and Zhicheng Xia with NMR spectroscopy has been critical to the success of this work. For their assistance and technical expertise, I thank them.

I also wish to acknowledge Dr. Anne-Marie Lebuis for her solution of my X-ray crystal structure.

The administrative staff of the Chemistry department has been very wonderful to me over the years. They have treated me with kindness and respect and I hope I have returned this in kind. Thank you to Renée Charron, Chantal Marotte, Fay Nurse, Paulette Henault, Carol Brown and Sandra Aerssen for their assistance.

I would be remiss if I did not thank the fine staff of the McGill libraries, especially those of the Schulich Physical Sciences and Engineering library. Without their continuous, largely unheralded efforts, this work, as well as the work of countless other graduate students, would be greatly frustrated and delayed. Thank you all.

My labmates in 237/238 have made our lab environment a comfortable and fun climate in which to learn, live, eat, sleep (just kidding, Jim), and rock out to Iron Maiden. Thank you to Ljubomir Isakovic, Evelyn Martins, Régis Dolaine, Christopher Rescorla, Andrew Corbett, Ngiap Kie Lim, Andrew Sawayama, Alain Ajamian, Diane Burke, Wolfgang Felzmann, David Sud, James Ashenhurst, Mike Yamashita, Sally Rodrigo, Tim Cernak, Nicolas Eghbali and Ciaran O'Dahlaigh.

Thank you to James Ashenhurst for his assistance in the revision of this manuscript and to Nicolas Eghbali and Alain Ajamian for translating the abstract into French.

Financial assistance from McGill University (Alma Mater Travel Grants and Robert Zamboni Travel Grant), Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (B2 Graduate Fellowship, B3 Post-doctoral Fellowship) is gratefully acknowledged.

To my friends on sports teams such as Maassive Attack, Studly Hungwell, Ex–Men, Rybak's Rejects, and the infamous three-time defending Thompson House Softball League Champion Soft No More- Thank you for keeping me (in)sane.

To my climbing partners, Janet Macdonald, Meghan Marshall, Shabana Ali, Kermit (Joe) Lee, Tomoe Yoshihara, Michel Thibodeau and others- Thank you for not letting me die!

To my many other friends in Otto Maass, thank you all for being whom you are. My time in OMC has brought me an education completely apart from Chemistry and for that, I thank you. I wish you all well.

Over the years, I had the privilege of being taught by some very gifted teachers. I wish to thank Dr. Bill Jacobs, the late Mr. Dennis Kritzer, Mr. David Hitchon and the late Mr. Jim Hughes for giving me solid foundation in science. Their skills helped start me on this path. I also thank Mr. David Snedden and Mrs. Judy Bannon for helping me achieve the level of excellence in mathematics that it took me to get here. I also wish to thank Mr. Wayne Storms for helping me to develop the work ethic I needed to reach the completion of this degree. I have never forgotten their contributions to my development.

Thank you to the many wonderful Chemistry professors at the University of Guelph, under whom I had the pleasure of studying. My appreciation goes out to Professors Gordon Lange, Adrian Schwan, Elmer Alyea, Joe Prokipcak, Mark Baker and James Rattray.

My dearest Stephanie, without whom none of this would have happened, I thank you from the bottom of my heart. Your support and encouragement have been invaluable in so many ways. You strength carried me through many dark days and nights. I would not have made it through this degree without you.

To my father, Michael, thank you for being a constant support and for understanding all this insanity. To my mother, Judy, thank you for your contribution. To my step-mother, Caryn, thank you for being my partner-in-crime in graduate studies. Don't ever change. To my b(r)other, Ben, thanks for living in the real world and giving me the chance to get out once in a while. To my "science-geek" brother, Luke, my "go-kart driving partner" brother Christopher, my brother Thomas, a.k.a. Bob, and my "bubbly" little sister, Rebecca, thank you for all for being kids. You have been a breath

of fresh air in my little world. You are all wonderful people. I hope that I have been a good example for you.

I owe many thanks to my distant cousin, Piers, for our candid conversations of graduate school, pharmaceuticals and life in Switzerland. Cheers, Piers!

To my late grandparents, Anna and Ray, I am indebted to you for teaching me your values and your history, for it is my history too. Thank you for providing a haven when life became too much. I hope that I have made you proud.

Thank you to U2, The Cult, Matthew Good Band, Iron Maiden, K.M.F.D.M., Econoline Crush, and many others for keeping me going on the long nights of writing this monstrosity. A gargantuan thank you to the fine producers of Diet Pepsi for supporting my caffeine addiction!

Lastly, a tremendous Thank You to Ruth for getting me through me.

TABLE OF CONTENTS

ABBREVIATIONS

$A^{1,3}$	1,3-allylic
Ac	acetyl
Ar	aryl
Anal.	analysis
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2´-bis(diphenylphosphino)-1,1´-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bs	broad singlet
Bu	butyl
Bz	benzoyl
Calcd	calculated
cat.	catalyst/catalytic
Cbz	benzyloxycarbonyl
cHx	cyclohexyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CSP	chiral stationary phase
d	doublet
Δ	reflux/heat
dba	dibenzylideneacetone
d_{br}	broad doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
de	diastereomeric excess
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*–dimethylformamide

DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
e	electron
EDC•HCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
g	gram(s)
GC	gas chromatography
h	hour(s)
hfc	3-(heptafluoropropylhydroxymethylene)-camphorate
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRFABMS	high resolution fast atom bombardment mass spectrometry
Hz	hertz
i	iso
J	coupling constant
KDBB	potassium 4,4´-di-*tert*-butylbiphenylide
L	ligand, 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	milli, multiplet
M	moles per litre, metal
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
mL	millilitre
MM2	molecular mechanics 2
mmol	millimole
mol	mole
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
m/z	mass to charge ratio
n	normal
NaHMDS	sodium hexamethyldisilazide
NDA	sodium *N,N*-diisopropylamide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PhMe	toluene
Piv	pivaloyl (trimethylacetyl)
Pr	propyl
psi	pounds per square inch
pTSA	*p*-toluenesulfonic acid
R_t	retention time
RT	room temperature
s	secondary
s	singlet
t	tertiary
t	triplet
TBS	*tert*-butyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Trisyl	2,4,6-triisopropylbenzenesulfonyl
UV	ultraviolet
v/v	volume by volume comparison
w/w	weight by weight comparison

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

CHAPTER ONE

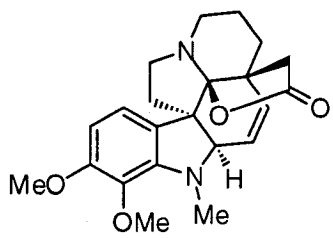
INTRODUCTION TO THE ASYMMETRIC SYNTHESIS OF QUATERNARY CARBON CENTRES

1.1 PURPOSE OF THE DEVELOPMENT OF A GENERAL METHOD FOR THE ASYMMETRIC SYNTHESIS OF QUATERNARY CARBON CENTRES

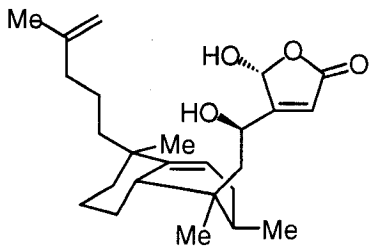
Asymmetric carbon-carbon bond construction lies at the very heart of modern synthetic organic chemistry and new approaches to this most fundamental of problems are constantly being developed. An archetypal challenge in the realm of carbon-carbon bond formation is the preparation of asymmetric quaternary carbons. Formally, quaternary carbons are bonded to four other carbon atoms and thus, contain only carbon-carbon bonds. Consequently, only asymmetric carbon-carbon bond-forming reactions may be employed in the asymmetric synthesis of quaternary carbons. While many different approaches to this very daunting problem are known,[1] very few have a broad substrate scope. This significant void in synthetic chemistry wants for a solution.

The development of a general method for the asymmetric formation of quaternary carbon stereocentres would be a great advance for the chemical community. Quaternary carbons are found in many medicinally and synthetically important molecules including aspidophytine **1**,[2] an anticockroach and insecticidal compound, dysidiolide **2**,[3] an antitumor compound, and puraquinonic acid **3**,[4] a compound shown to induce cell differentiation and a potential anti-leukemia drug. Additionally, quaternary carbons can be useful in drug candidates because they are more difficult to degrade than other functional groups, allowing for slower drug metabolism[5] and lower dosing. Thalidomide **4** ((*R*)–enantiomer shown), whose (*R*)–enantiomer relieves morning sickness and (*S*)–enantiomer causes birth deformities, is an example of a drug with a tertiary stereocentre that racemizes under physiological conditions.[6] Quaternary

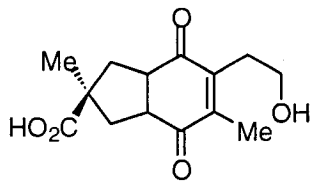
stereocentres are immune to racemization, making them advantageous over tertiary centres in terms of drug safety.



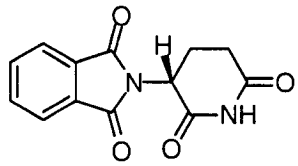
1



2



3



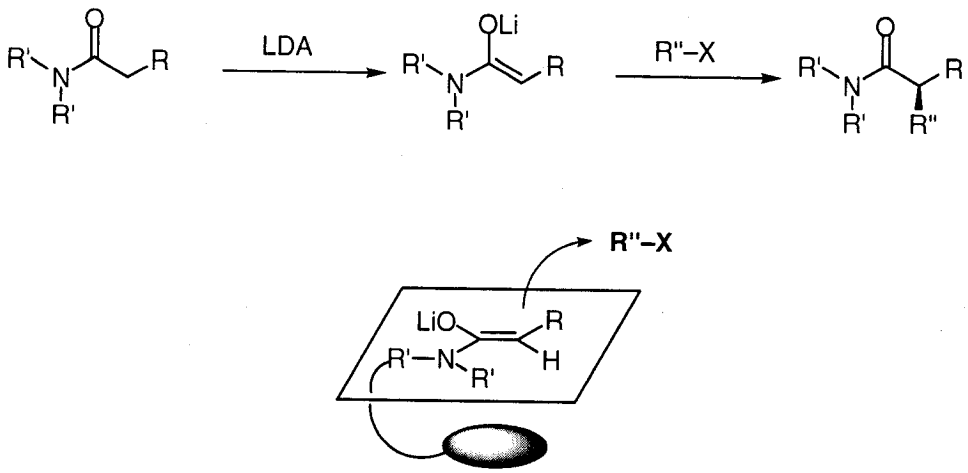
4

This research project seeks to develop a general method for the asymmetric synthesis of quaternary carbons via alkylation of acyclic α,α-disubstituted enolates. Enolates are well-known intermediates in organic synthesis and the next three sections will detail their formation and use in the preparation of asymmetric tertiary carbons.

1.2 ENOLATE ALKYLATION AS A METHOD FOR THE ASYMMETRIC SYNTHESIS OF TERTIARY CARBON CENTRES

The alkylation of an enolate with an alkyl halide is a fundamental reaction in organic chemistry for the formation of carbon-carbon bonds. The diastereoselective (or enantioselective) formation of a new stereocentre via enolate alkylation requires both enolate stereocontrol (*E* versus *Z*) and a bias for approach of the electrophile on one

π–face (*Re* or *Si*) over the other (Scheme 1). Consequently, failure to achieve high *E/Z* enolate stereocontrol or poor facial bias will result in low overall stereoselectivity. Typically, the *E/Z* ratio of enolates equates to the maximum level of stereoselectivity of the reaction; even complete facial bias will result in reaction stereoselectivity only as high as the enolate ratio. By the same token, complete enolate stereocontrol cannot compensate for poor facial bias.

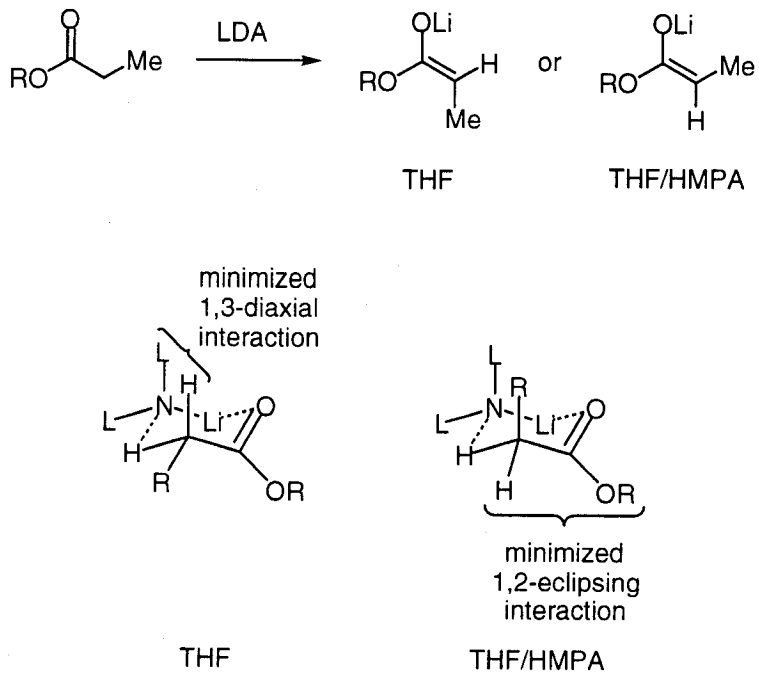


Scheme 1. Stereoselective enolate alkylation.

A useful, broad-scope enolate alkylation methodology must be amenable to the preparation of both (*R*)– and (*S*)–configurations of the new stereocentre. This can be achieved by switching the enolate geometry and using a common alkylating agent. Alternatively, the position of the alkyl groups in the starting material and alkylating agent can be reversed. There are instances where neither of these options is feasible. In this situation the use of the antipode of the auxiliary is a possible solution. However, this route is often prohibitively expensive for auxiliaries derived from chiral pool materials where only one enantiomer is readily available.

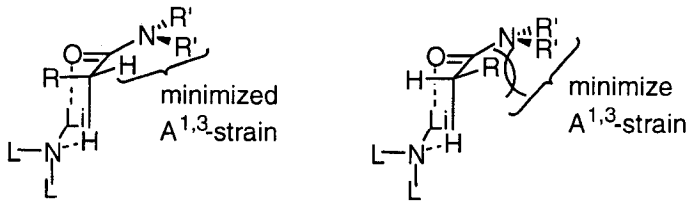
1.3 STEREOCONTROL IN α–MONOSUBSTITUTED ENOLATES

Acyclic enolate stereocontrol has been thoroughly studied in the formation of α–monosubstituted ester, ketone and amide enolates. Deprotonation of an ester or ketone with an amide base such as LDA in ethereal solvents such as THF leads to predominant formation of the *E(O)*–enolate via minimization of 1,3-diaxial interaction between the substituents on the amide base and the alkyl group on α–carbon in a chair-like transition state.[7,8] The use of a mixed solvent system containing an ethereal solvent and a polar solvent such as HMPA or DMPU results in a looser transition state and formation of predominantly the *Z(O)*–enolate where the overriding steric influence is the minimization of interaction between the alkyl group on the α–carbon and the alkoxy moiety of the ester (or alkyl moiety of the ketone) (Scheme 2).



Scheme 2. Formation of *E(O)*- and *Z(O)*-ester enolates.

In the case of amide enolate formation, the enolate geometry is governed by the minimization of $A^{1,3}$ interactions between the alkyl groups on the nitrogen atom and the alkyl group on the α-carbon. This results in exclusive formation of the Z–enolate (Scheme 3).[9]



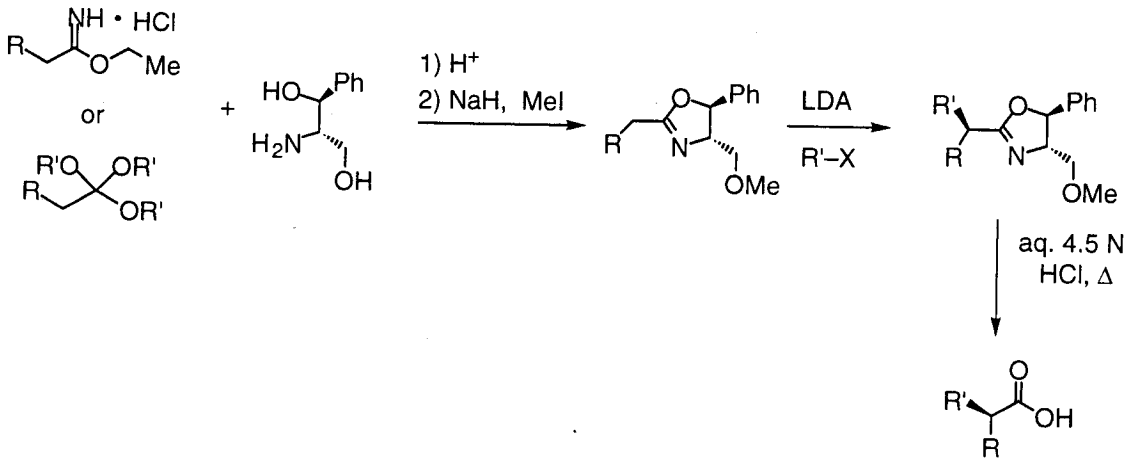
Scheme 3. Stereocontrol in formation of amide enolates.

1.4 STEREOSELECTIVE ENOLATE ALKYLATION TO FORM TERTIARY STEREOCENTRES

Asymmetric catalysis is an important sector of organic chemistry and some catalytic asymmetric enolate alkylation methodologies do exist (*vide infra*). However, these methods tend to exhibit limited scope. Broad generality in asymmetric enolate alkylation techniques remains in the domain of chiral auxiliary-based methodologies.

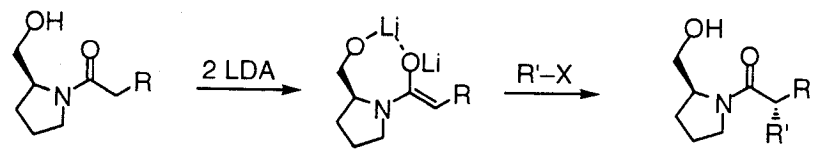
Many chiral auxiliary-based methodologies exist for the formation of tertiary stereocentres. The first, developed by Meyers and co-workers, employed chiral oxazolines.[10] These species were readily formed from a chiral aminodiol and an orthoester or imidonium chloride (Scheme 4). Alkylation takes place via deprotonation with LDA, followed by addition of an alkyl halide. This method afforded only moderate

alkylation diastereoselectivity but nevertheless provided proof that chiral pool materials could be used to influence the stereochemical outcome of enolate alkylations.

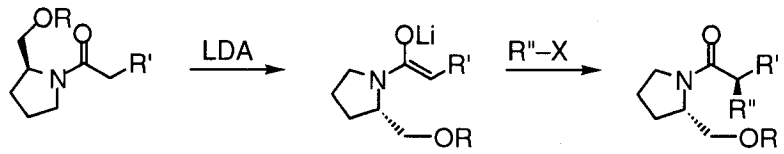


Scheme 4. Chiral oxazolines as chiral auxiliaries for enolate alkylations.

Subsequently, Evans and co-workers[9] and Sonnet and Heath[11] independently demonstrated the use of prolinol as a chiral auxiliary for enolate alkylation. In this system, the sidechain alcohol was left unmasked and two equivalents of base were used to generate a chelated enolate. In this case, the diastereoselectivity of the alkylations ranged from 88:12 to 97:3 (Scheme 5). Interestingly, the alkylation or silylation of the sidechain alcohol resulted in a switch in facial selectivity of the alkylation (albeit with diminished diastereoselectivity). This presumably results from a loss of chelation between the enolate and the sidechain oxygen (Scheme 6).

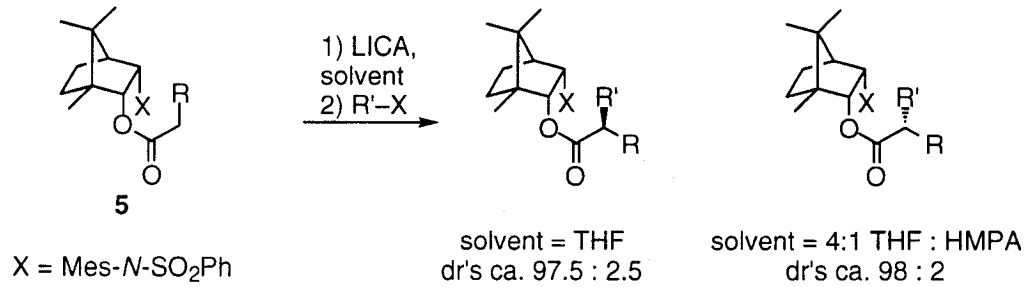


Scheme 5. Alkylation of chelated prolinol enolates.



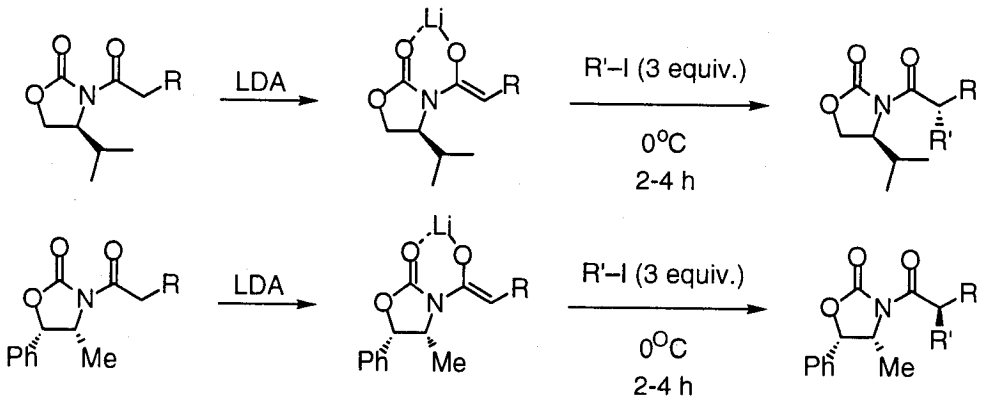
Scheme 6. Alkylation of non-chelated prolinol enolates.

Both *E(O)*– and *Z(O)*–configurations of ester enolates are accessible with high stereoselectivity. Therefore, ester-based chiral auxiliaries can be used to access both (*R*)– and (*S*)–stereochemistries by switching enolate geometries and using a common alkylating agent. Helmchen and co-workers investigated the use of several different camphor-based auxiliaries for this purpose.[12] With the ester **5**, they found that conducting the alkylation reaction in THF as solvent afforded predominantly one diastereomer with a ratio of diastereomers of approximately 97.5:2.5. The use of 4:1 THF:HMPA as solvent led to the product with primarily the opposite configuration at the new stereocentre with a diastereomeric ratio of approximately 98:2 (Scheme 7).



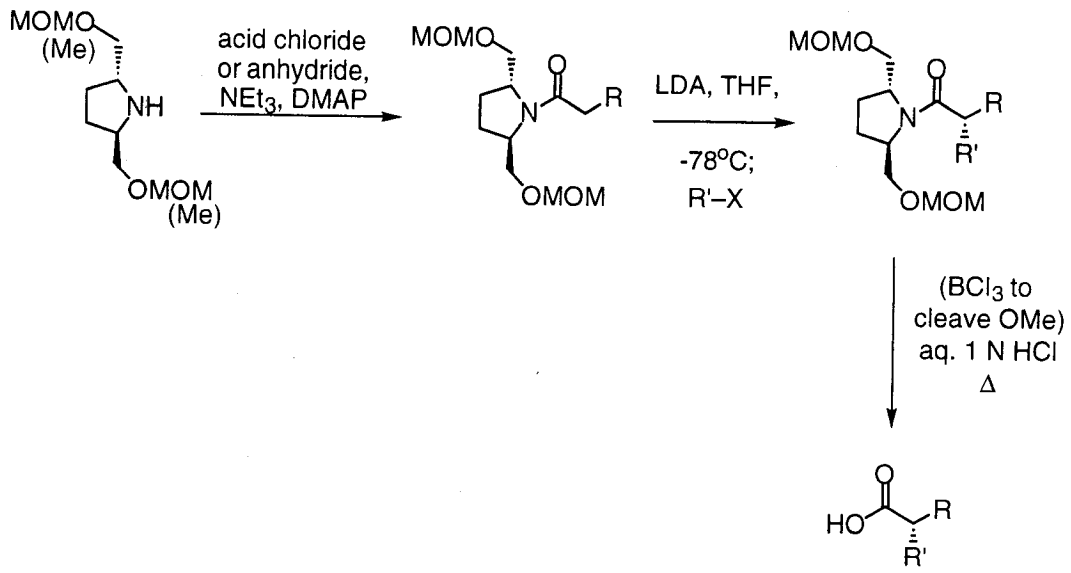
Scheme 7. Asymmetric enolate alkylation using Helmchen's camphor-derived chiral auxiliary.

Evans and co-workers later reported an oxazolidinone auxiliary, which could be easily *N*–acylated. Deprotonation of the imide to generate the enolate could be achieved with LDA or NaHMDS (Scheme 8). Imides behave similarly to amides in that they afford the *Z*-enolate upon deprotonation. Though the alkylation diastereoselectivities were high, it was found that the enolates would only react readily with activated alkyl halides only.[13,14] Because of the low reactivity of the enolates toward alkyl halides this method has found only sporadic use.



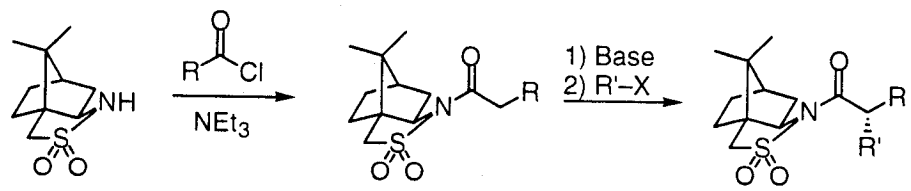
Scheme 8. Formation of tertiary carbon stereocentres via alkylation of oxazolidinone imide enolates.

Katsuki, Yamaguchi and co-workers reported an extremely selective auxiliary (Scheme 9).[15] This auxiliary was similar to prolinol but contained a second hydroxymethyl sidechain. The stereochemical configuration of the sidechain-bearing carbons was such that the auxiliary had C_2-symmetry. Although this auxiliary afforded diastereomeric excesses of >95% in all reported cases, it has seen little to no use by other researchers because it must be prepared by a lengthy synthesis involving a classical resolution.



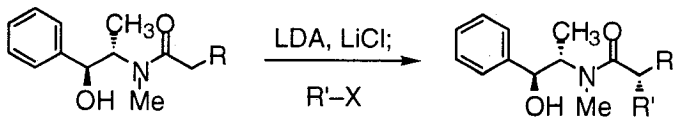
Scheme 9. A C_2-symmetric auxiliary for the formation of tertiary carbon centres.

The use of camphor sultams (readily prepared from camphorsulfonyl chloride) as chiral auxiliaries was pioneered by Oppolzer and co-workers (Scheme 10).[16] This method offers a wide range of acceptable bases and may be used with unactivated halides provided HMPA is present. After crystallization, the de of the product was typically ≥97.5%. The sultams are readily cleaved with base and aqueous hydrogen peroxide or reduced to primary alcohols with lithium aluminum hydride. Under both sets of conditions the auxiliary may be recovered and recycled.



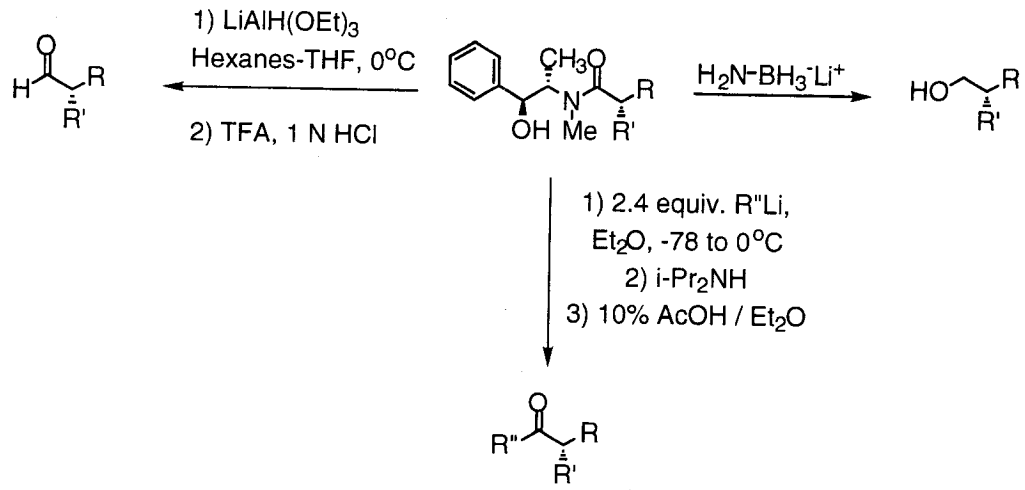
Scheme 10. The use of camphor sultams as auxiliaries for asymmetric enolate alkylation.

Pseudoephedrine is an extremely useful and practical chiral auxiliary for the asymmetric synthesis of tertiary carbon stereocentres.[17] It is a rare example of a chiral auxiliary that is readily available at reasonable cost in both enantiomeric forms. Amides of pseudoephedrine can be deprotonated with two equivalents of LDA, leading to formation of a *Z*-enolate dianion. Pseudoephedrine enolates are reactive enough to react with unactivated halides at 0°C with no need for added cosolvents (Scheme 11). Moreover, these enolates were shown to be quite stable, surviving at least 46 hours at 45 °C. This allows for the use of alkylating agents that react only sluggishly.



Scheme 11. The alkylation of pseudoephedrine amide enolates.[18]

The utility of pseudoephedrine amides was further demonstrated by the ease with which they may be transformed into a variety of products. Hydrolysis to the carboxylic acids was best achieved by sulfuric acid or tetrabutylammonium hydroxide. The auxiliary could also be cleaved under reductive conditions. The use of lithium amidotrihydroborate (LAB) afforded primary alcohols; while lithium triethoxyaluminum hydride afforded aldehydes. Ketones could be formed by the addition of excess alkyl lithium reagents (Scheme 12).



Scheme 12. Reductive cleavage of pseudoephedrine amides.

While this section has outlined the use of enolates for the asymmetric synthesis of tertiary carbons, the goal of this work was to prepare quaternary carbons. The next several sections will detail the extension of enolate alkylations to the formation of quaternary carbons.

1.5 SYNTHESIS OF α,α–DISUBSTITUTED ENOLATES

While the formation of tertiary asymmetric centres via enolate alkylation is highly developed and general, the same cannot be said about the formation of quaternary carbons. Attempted extension of enolate alkylation techniques to the formation of quaternary carbons results in two major difficulties. In the case of amides and imides, the most common classes of chiral auxiliaries, deprotonation of the α–carbon is significantly more difficult because of the increased $A^{1,3}$–strain in the transition state (Figure 2). This results in the need to employ stronger bases to effect deprotonation, which generally have

lower functional group tolerance. Enolate stereocontrol is also a concern. When attempting to form an α,α–disubstituted enolate, the steric difference between the substituents on the α–carbon (alkyl group versus alkyl group) is often much smaller than the steric difference between the substituents during the first deprotonation (alkyl group versus hydrogen). The ultimate result of this decreased difference in steric demand of the substituents is a diminished level of enolate stereocontrol. Even in the exaggerated case of 2–phenylpropionamides, where the difference in steric demand of the substituents is reasonably large (methyl versus phenyl), *E/Z* stereocontrol is very low (Scheme 13).[19] Though the deprotonation of 2–phenylpropionamides could be optimized to yield high levels of enolate stereocontrol, it was a highly specialized system and not a general example. Prior to this work, no general method for the formation of acyclic α,α–disubstituted enolates with good levels of *E/Z* stereocontrol had been published. Recall that *E/Z* stereocontrol is a required element for a successful asymmetric enolate alkylation methodology. Thus, the existing methods of asymmetric formation of quaternary carbons via enolate alkylation were all hampered by their inability to solve problem of *E/Z* stereocontrol in acyclic α,α–disubstituted enolates.

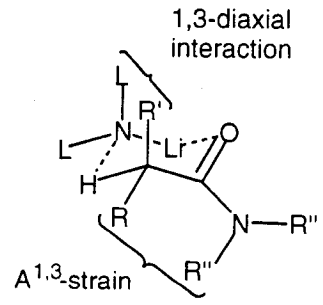
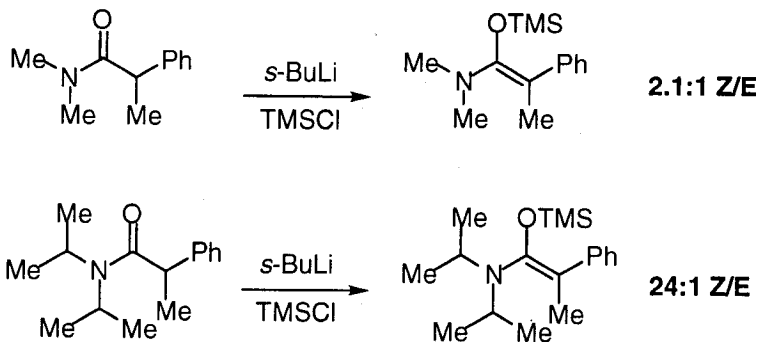


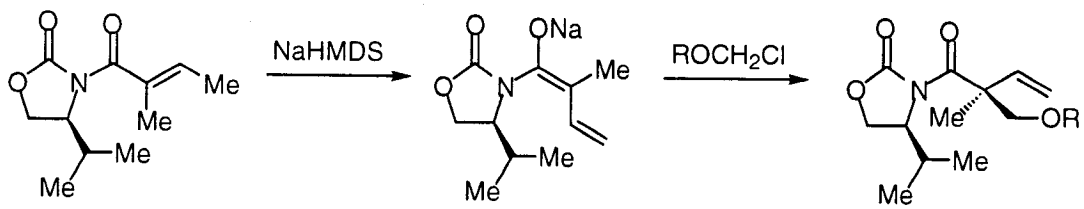
Figure 1. Depiction of increased strain in the transition state for deprotonation of α,α–disubstituted amides.



Scheme 13. The deprotonation of 2-phenylpropionamides.

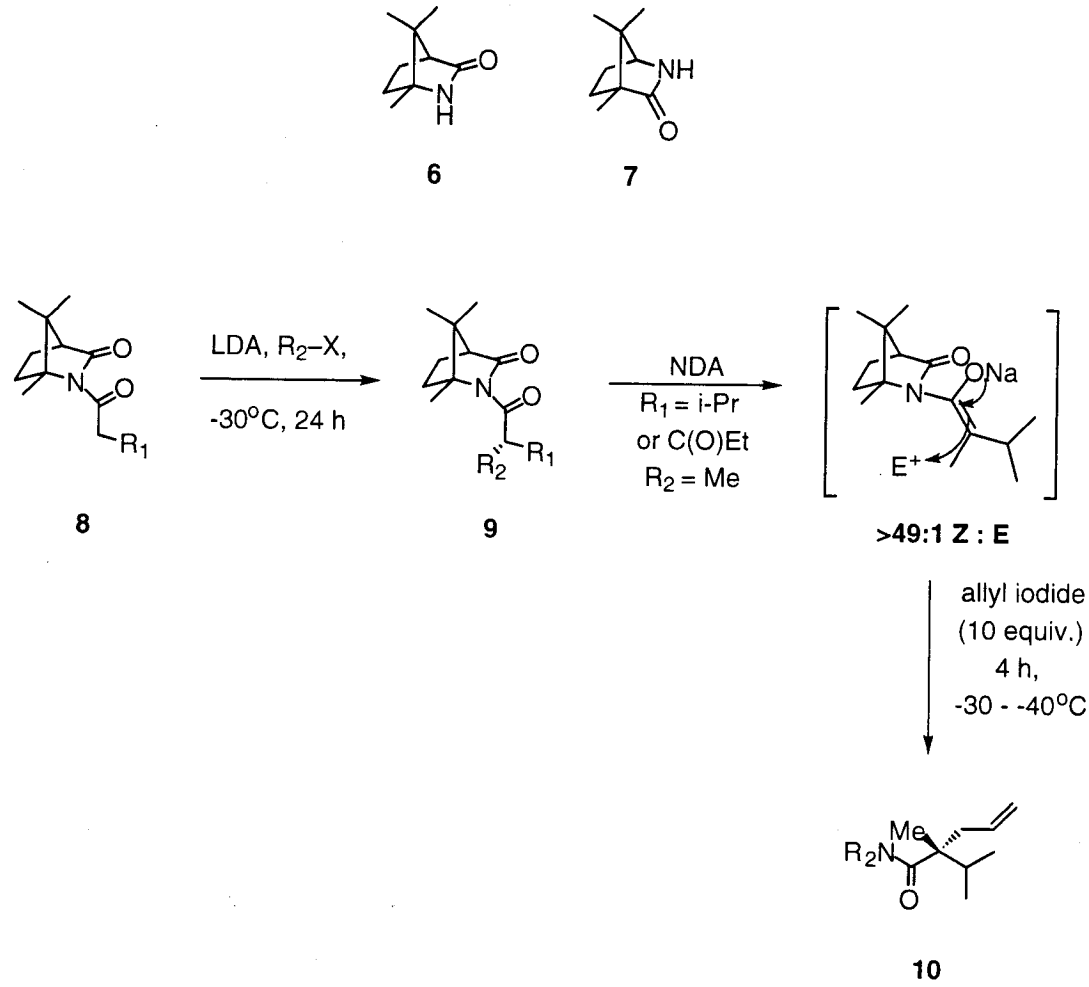
1.6 ACYCLIC α,α–DISUBSTITUTED ENOLATES

A few highly specialized examples exist in the literature for the synthesis of quaternary carbons via acyclic α,α-disubstituted enolates. Kobayashi and co-workers reported that tigloyl oxazolidinones could be deprotonated at the γ-position with NaHMDS to afford the *E*-imide enolate (Scheme 14).[20] Alkylation with methoxymethyl chloride or benzyloxymethyl chloride proceeded with good levels of diastereoselectivity. This example is striking in that it generates an *E*-imide enolate. It is however, limited to tigloyl systems and activated halides.



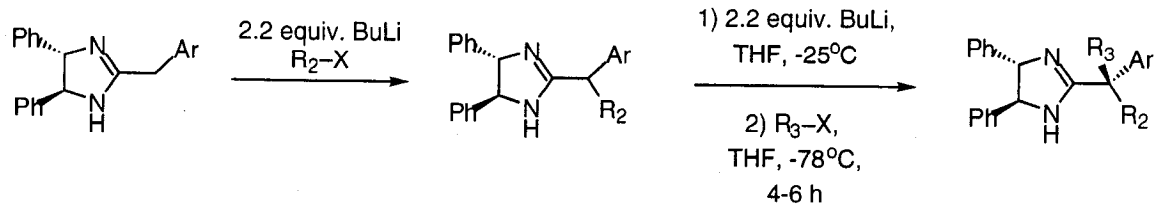
Scheme 14. Enolization and alkylation of tigloyl oxazolidinones.

Boeckman and co-workers have reported the use of camphor-based auxiliaries **6** and **7** for stereoselective Diels-Alder and [2+2] cycloadditions, as well as aldol and alkylation reactions.[21] Recently, the extension of the alkylation methodology to the formation of quaternary carbons was reported.[22] This work disclosed that imides of type **8** could be deprotonated with LDA and alkylated with activated alkyl halides to form tertiary centre–containing adducts **9** with excellent diastereoselectivity and moderate to high yield (Scheme 15). Conversion of imide **9** to quaternary adducts **10** employed sodium diisopropylamide (NDA) and required the groups resident on the α-carbon to be of significantly different steric size (methyl versus isopropyl or propionoyl). Even though the *E/Z* ratio of the α,α-disubstituted enolate was excellent, only very reactive electrophiles could be used.



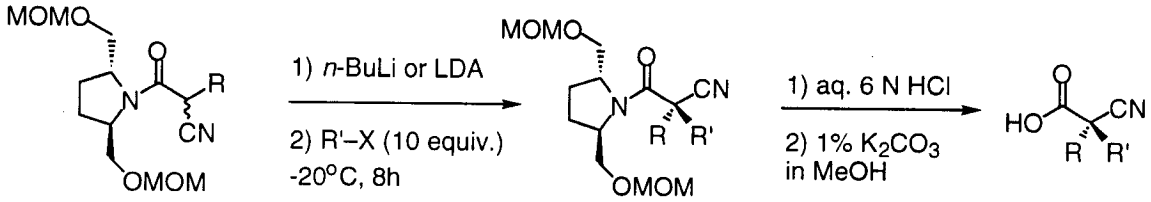
Scheme 15. Alkylation of camphor-derived imides to form quaternary carbon centres.

In another limited example, Langlois and Dalko reported the asymmetric formation of quaternary benzylic carbons using chiral imidazolines (Scheme 16).[23] Though this system was limited to the construction of benzylic quaternary centres, high de's could be obtained when either alkyl halides or activated THF (addition of 9–BBN–OTf to THF solution) were used in the final alkylation.



Scheme 16. The formation of benzylic quaternary carbons using imidazolines.

Katsuki and co-workers reported the synthesis of α-cyano-α-quaternary carboxylic acids (Scheme 17).[24] This limited example had the advantage that the α–proton's acidity was increased by the presence of the nitrile group and the small steric size of the nitrile group allowed for reasonable *E/Z* stereocontrol. Notably, the diastereoselectivity of the quaternary carbon-forming reactions (80-90% de) was not nearly as high as the tertiary carbon-forming reactions (>95% de).



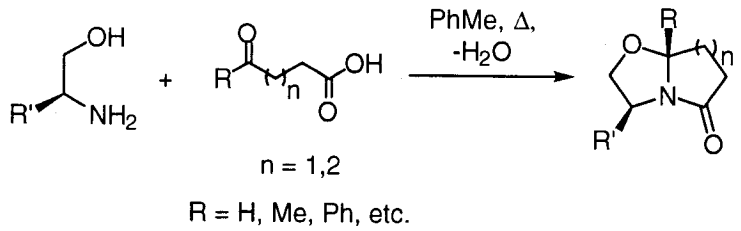
Scheme 17. The formation of α-cyano,α-quaternary carboxylic acids.

1.7 CYCLIC α,α–DISUBSTITUTED ENOLATES

The examples in the previous section serve to illustrate the difficulty in generating α,α-disubstituted enolates and the very poor substrate scope for these methods. The most common solution to poor *E/Z* stereocontrol in the formation of α,α-disubstituted enolates

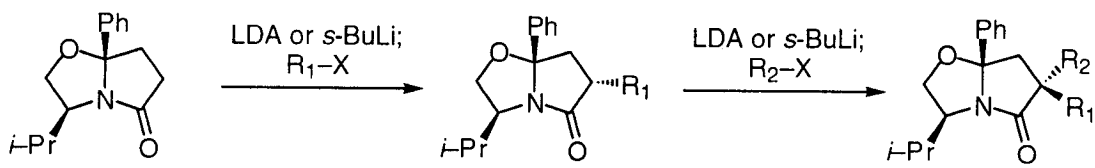
is to employ a cyclic structure in the enolate, either a permanent ring or a temporary metal chelate.

The most widely known method of asymmetric quaternary carbon formation via the alkylation of cyclic α,α-disubstituted enolates was developed by Meyers and co-workers.[25] This technique uses chiral bicyclic lactams which are prepared from a chiral amino alcohol and a γ- or δ-keto acid (Scheme 18) or a cyclic anhydride.



Scheme 18. The formation of chiral bicyclic lactams from a keto acid.

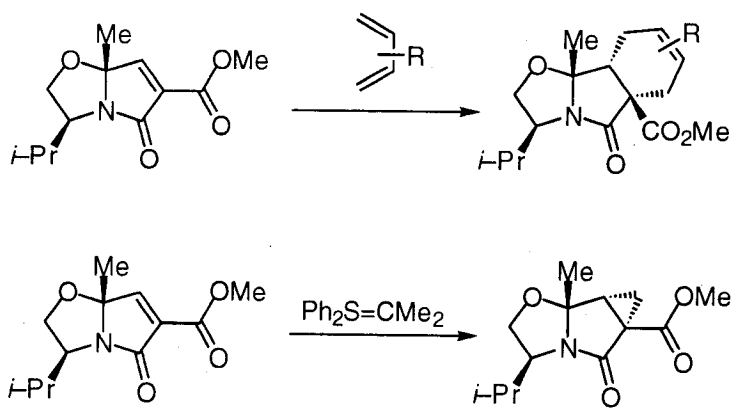
Alkylation of these bicyclic systems can be achieved by deprotonation with LDA or *s*-BuLi followed by alkylation with various alkyl halides (Scheme 19). Diastereoselectivities are generally good to excellent in both the first and second alkylations and yields are typically high. Unreactive alkylating agents, such as isopropyl iodide, were also investigated but required more forcing conditions, resulting in diminished diastereoselectivity.



Scheme 19. The formation of quaternary carbon centres via the dialkylation of chiral bicyclic lactams.

An immediately interesting feature of this alkylation system is that the alkylation occurs on the endo face of the bicycle. Many experiments and theoretical calculations have been carried out to determine the source of this selectivity. Unfortunately, there appears to be many factors at play and no simple explanation has been put forward.[26] It is known however that the apical group and position of the oxygen in the five-membered ring are critical for endo alkylation to occur.

Meyers and co-workers also investigated the chemistry of α,β-unsaturated chiral bicyclic lactams in Diels-Alder and cyclopropanation reactions (Scheme 20). In these systems, substitution of the α-carbon with an ester group was often necessary to obtain high diastereoselectivity. Again, predominantly endo products were obtained.



Scheme 20. The Diels-Alder and cyclopropanation reactions of Meyers' chiral bicyclic lactams.

It is important to point out that although the Meyers chemistry is highly selective, applicable to a wide range of reactions and that conditions have been developed to convert these lactams into a variety of materials (Figure 2), the γ- or δ-keto functionality is always required and must be incorporated into the final product or subsequently

transformed after cleavage. This represents a significant limitation to this otherwise very potent technique.

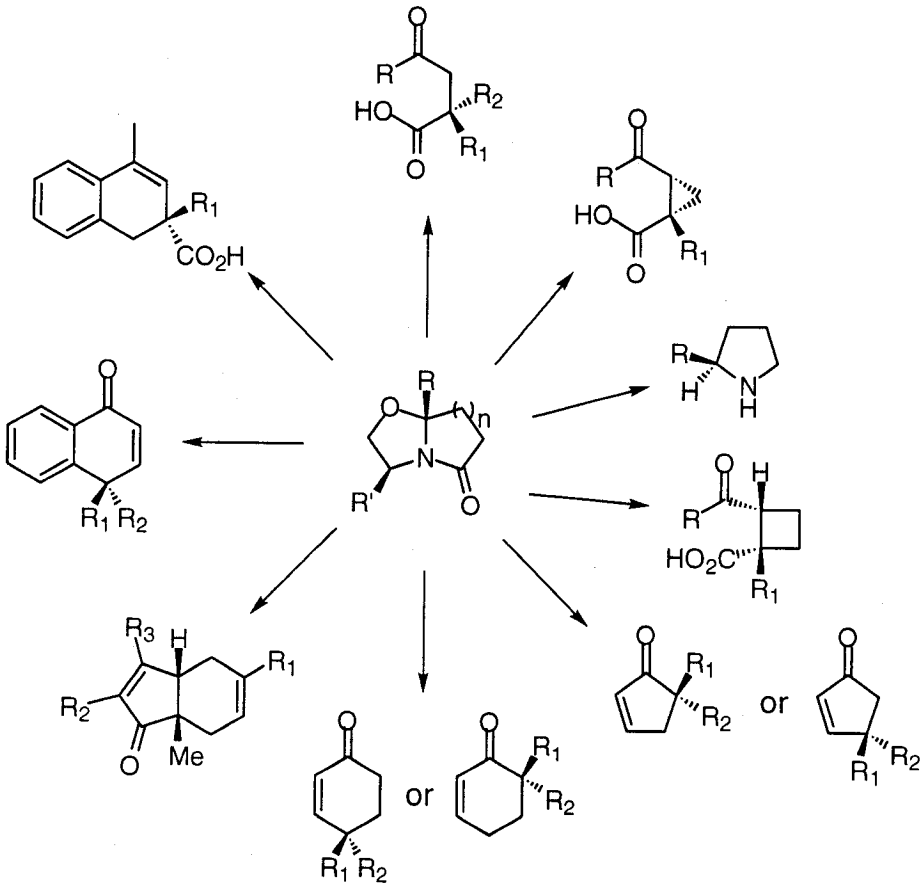
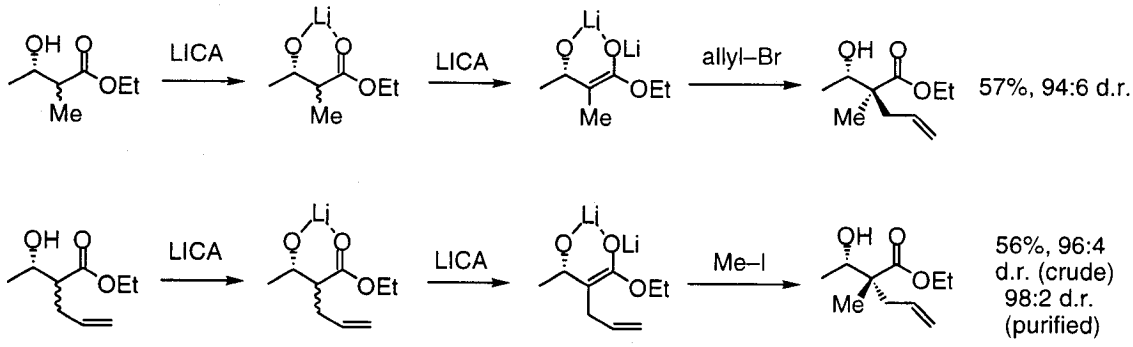


Figure 2. Utility of Meyers' bicyclic lactams.

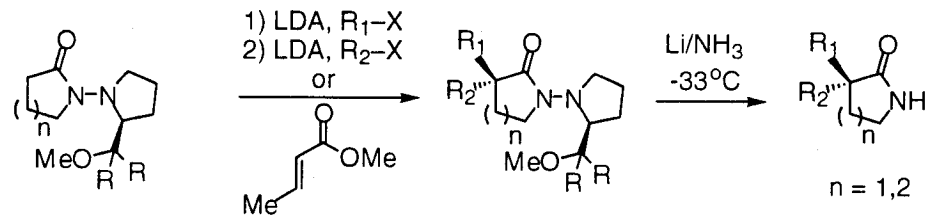
In more limited work, Fráter demonstrated the use of metal chelates as a form of temporary ring to control *E/Z* enolate stereochemistry in the deprotonation and alkylation of β–hydroxyesters[27] (Scheme 21).[28] Here, the alcohol moiety was deprotonated first and the resulting lithium alkoxide chelated to the ester carbonyl. This chelate fixed the conformation around the carbonyl carbon-α-carbon bond and allowed for deprotonation with good *E/Z* stereocontrol. The addition of activated halides resulted in highly

diastereoselective formation of quaternary centres. This method has very limited substrate scope and yields are consistently low.



Scheme 21. Diastereoselective alkylation of β-hydroxyesters to form quaternary carbon centres.

Enders and co-workers have demonstrated the asymmetric synthesis of quaternary carbon-containing pyrrolidinones.[29] Using stepwise dialkylation followed by reduction, the known lactams **11**[30] could be transformed into quaternary carbon containing materials (Scheme 22). This method was limited to the use of allyl bromide or ethyl crotonate as the electrophile in the second alkylation.

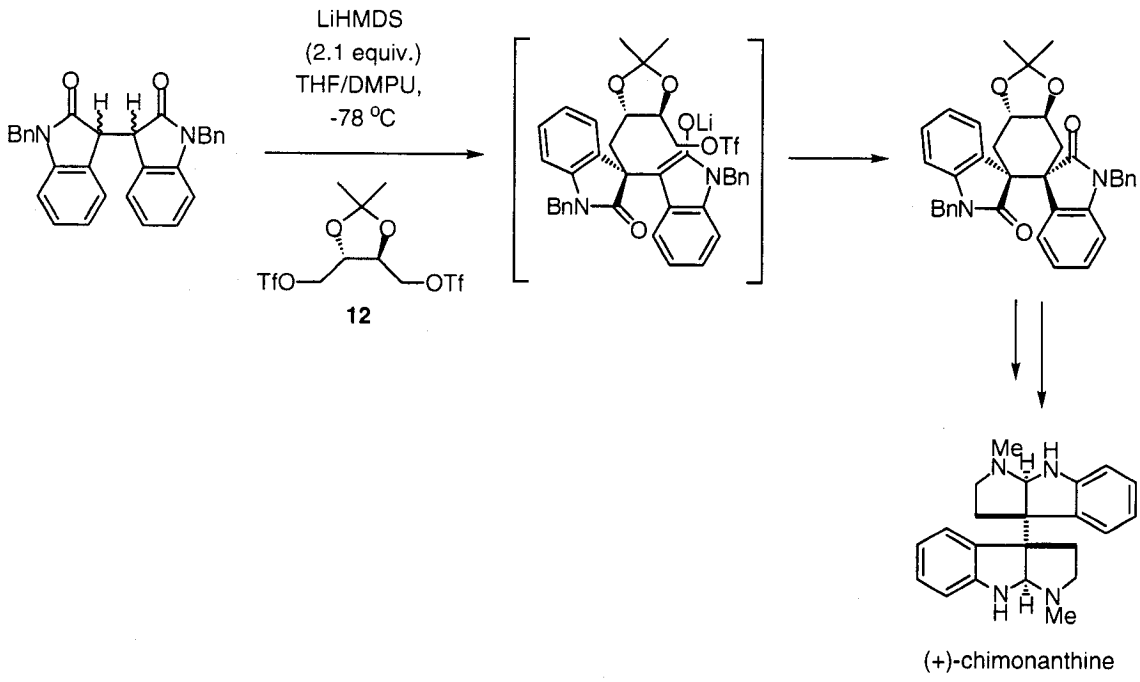


11

Scheme 22. The synthesis of α-quaternary pyrrolindinones.

The use of bis-electrophiles to generate contiguous quaternary carbon centres has been reported by Overman and co-workers.[31] This methodology was used in the total

synthesis of (+)- and *meso*-chimonanthine (Scheme 23). This procedure consisted of generation of a dienolate and alkylation with a tartrate-derived bis-electrophile **12**. Typically, in diastereoselective enolate alkylation the enolate contains the chiral auxiliary. This example is notable because the diastereoselectivity of the alkylation is governed by the chirality of the electrophile and the dienolate contains no stereocentres.

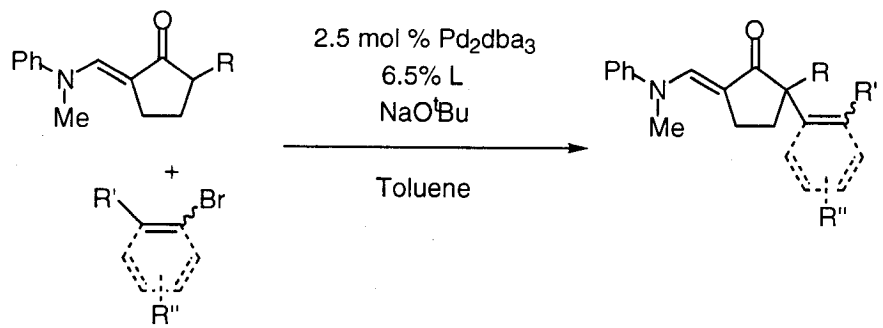


Scheme 23. The use of a bis-electrophile to generate vicinal quaternary stereocentres.

In addition to the traditional technique of alkylation using alkali metal enolates, recent work by the groups of Buchwald[32] and Hartwig[33] has seen the use of palladium enolates to install aryl and vinyl groups and form quaternary centres. These groups cannot directly be installed by traditional enolate alkylation techniques because they virtually never undergo S_N2 reactions. This system works by generating the enolate under traditional means then transmetallating the enolate to palladium.[33] In the presence

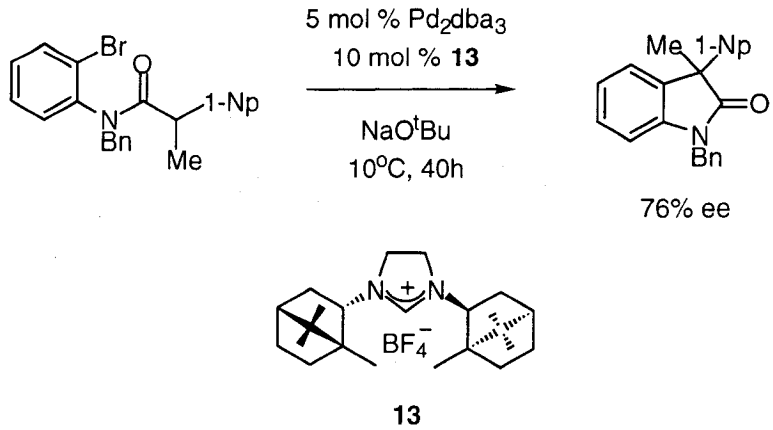
of a chiral ligand with a high affinity for palladium, asymmetric coupling of the enolate and the vinyl (aryl) halide results.

By using α′-blocked ketones, Buchwald and co-workers have developed a technique to arylate or vinylate a the α-position of a ketone by using stoichiometric NaO^{t}Bu, catalytic palladium(0), and catalytic amounts of a chiral phosphine ligand (Scheme 24). This catalytic method has led to vinylations with up to 96% ee and arylations with up to 94% ee. Unfortunately, to date the substrate scope is limited: only α′-blocked cyclopentanones and tetralones have been reported.



Scheme 24. The vinylation / arylation of ketone enolates.

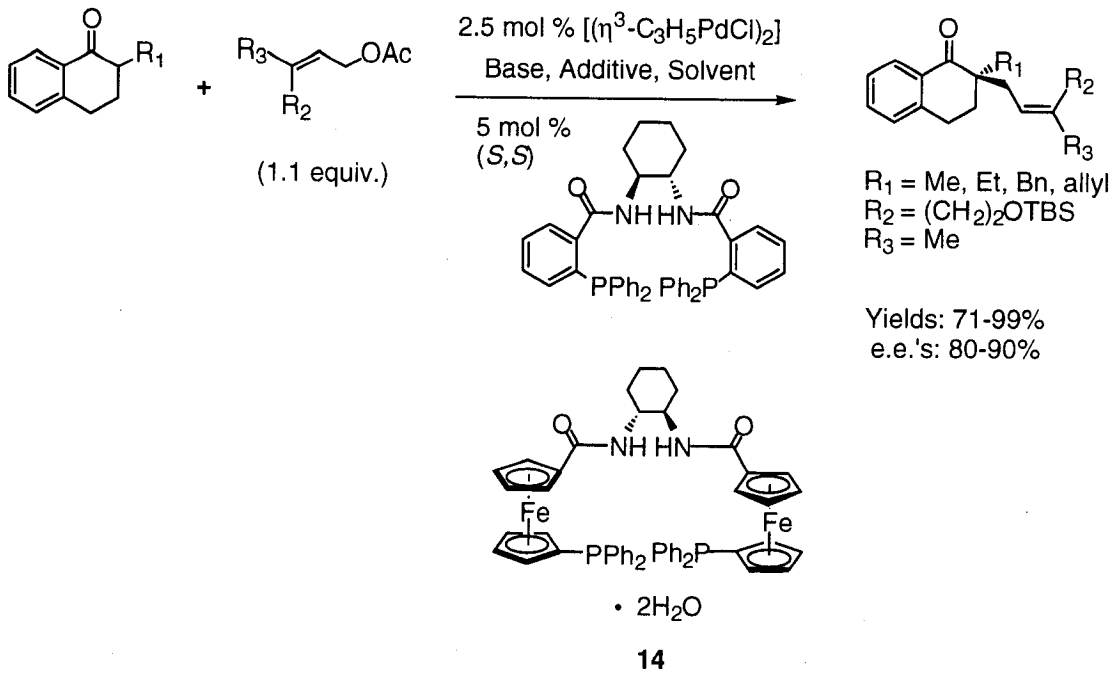
Hartwig and co-workers have developed a technique for the intramolecular arylation of α,α-disubstituted amide enolates (Scheme 25). This technique favoured the use of a bornylamine-derived Arduengo-type carbene[34] ligand **13** for asymmetric induction.



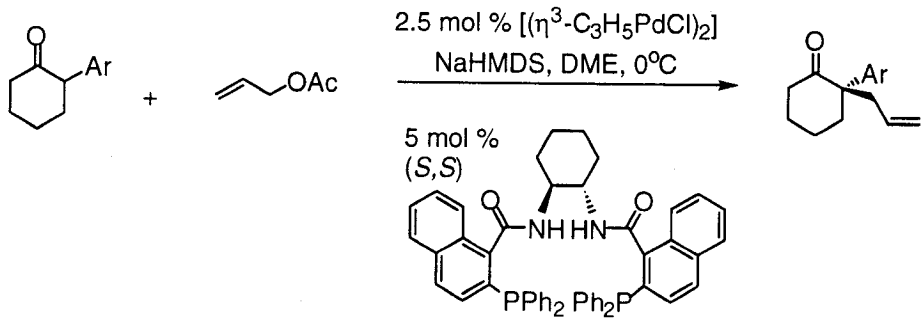
13

Scheme 25. The asymmetric arylation of α,α-disubstituted amide enolates.

In a related method, Trost and co-workers have developed techniques for the palladium-catalyzed asymmetric allylation of ketone enolates (Scheme 26).[35] The additive (usually a mild Lewis acid such as Me_3SnCl) is not crucial but moderately increases the reaction rate and increases the ee by a few percentage points. The enolates were generated by simple deprotonation with LDA or NaHMDS. Initial reports cited only the use of α′-blocked ketones but more recent work[36] showed that α′-blocking is not required in the case of α-aryl ketones (Scheme 27). In research very similar to that of Trost, Hou and Dai[37] found that high ee's (up to 95% ee) could be obtained in the allylation of α-methyltetralone using their bis-*N*-[2-(diphenylphosphino)ferrocenylcarbonyl]-diaminocyclohexane ligand **14**.



Scheme 26. The palladium-catalyzed asymmetric allylic alkylation of ketone enolates.



Scheme 27. Catalytic asymmetric allylation of α-aryl ketones.

This section has reviewed many of the methods of asymmetric formation of quaternary carbons using enolates formed by deprotonation. Because of the challenging nature of the problem, many other researchers have taken non-enolate approaches to

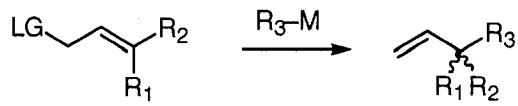
asymmetric quaternary carbon synthesis and these will be briefly outlined in the next section.

1.8 NON-ENOLATE METHODS FOR THE ASYMMETRIC SYNTHESIS OF QUATERNARY CARBON CENTRES

Many researchers have investigated the development of both general and specific methods for the asymmetric formation of quaternary carbon centres and this section will detail several of the more general techniques that do not employ enolates. Many additional methods do exist, however as the goal of this work has been to develop a general method, only methods that present or have the potential to present generality are discussed here.

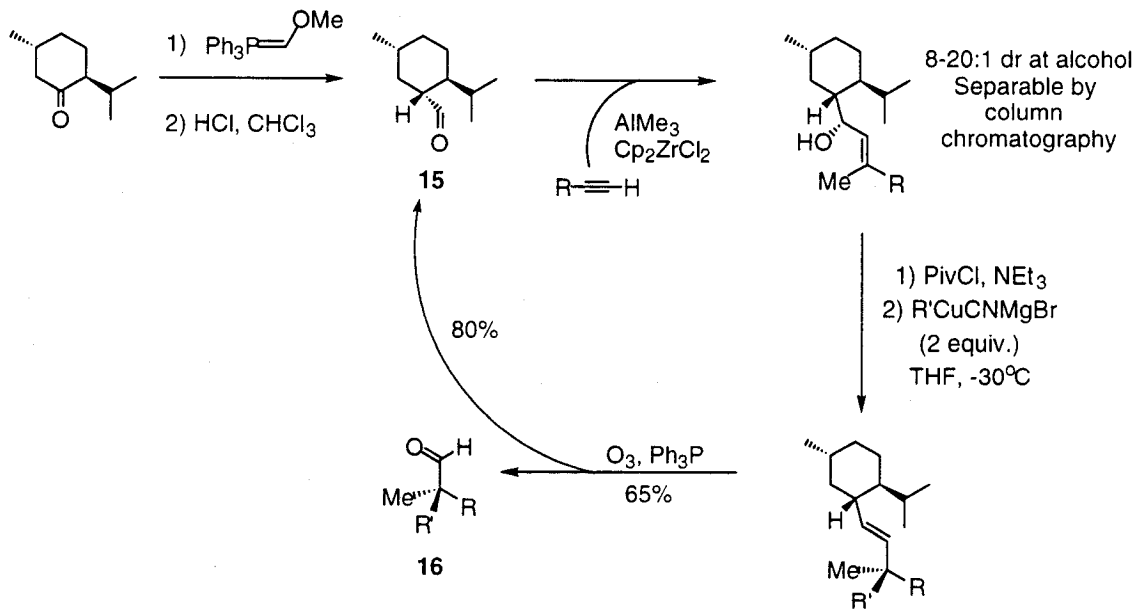
1.8.1 S_N2' DISPLACEMENTS

A potential method for quaternary carbon synthesis is to perform an allylic or S_N2' displacement on a system which is disubstituted at the 3-position. This motif requires that the reaction take place at the 3-position, which is the softer of the two potential reaction sites (Scheme 28). The alkene geometry and π-facial attack must also be controlled in order to obtain high stereoselectivity. Copper is known to react preferentially at soft sites over hard sites,[38] making it an ideal metal for this transformation. Two groups have developed methods based upon this rationale, one a chiral auxiliary based method, the other a catalytic method.



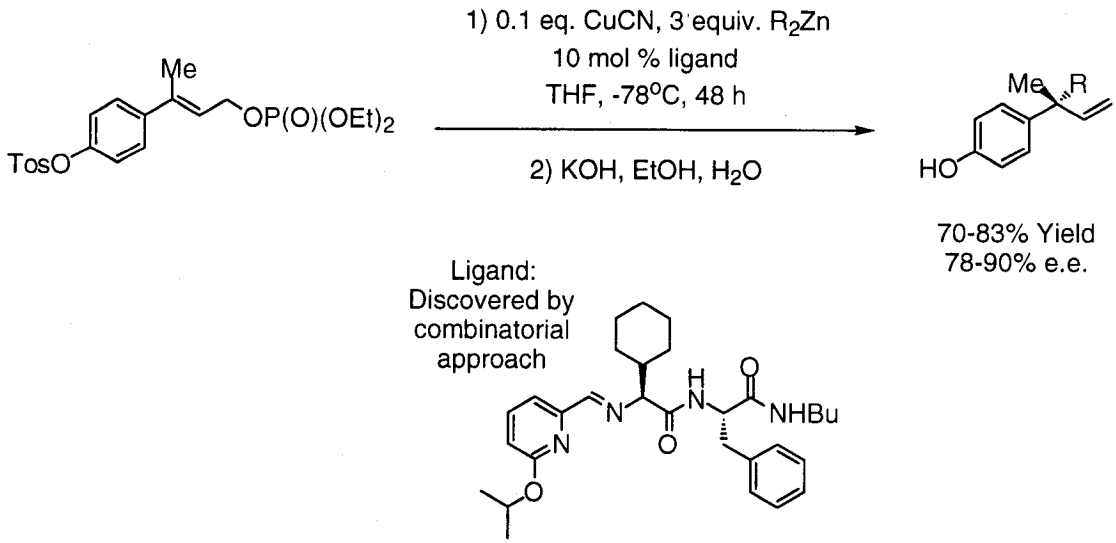
Scheme 28. S_N2' displacements as a technique for quaternary carbon synthesis.

An homologated (-)-menthone auxiliary **15**, reported by Spino and Beaulieu, was shown to undergo highly diastereoselective additions of vinyl alanes (Scheme 29).[39] It was also reported that after acylation of the secondary alcohol, addition of cyanocuprates derived from the corresponding Grignard reagents resulted in an S_N2' displacement of the ester with high diastereoselection (up to 98% de). Ozonolysis led to the recovery of the auxiliary and isolation of the desired α–quaternary aldehyde **16**. One drawback of this method is that a methyl group must be resident on the quaternary carbon because only trimethylaluminum is regioselective in the carboalumination of alkynes.



Scheme 29. The asymmetric formation of quaternary stereocentres via diastereoselective addition of cyanocuprates to allylic esters.

In a related method, Hoveyda and co-workers demonstrated the formation of quaternary carbons via enantioselective S_N2' displacement of allylic phosphates via the copper-catalyzed addition of dialkylzinc reagents in the presence of an unnatural peptide (Scheme 30)[40]. This method only allowed for the use of methyl and aryl groups on the starting alkene. No other substituents were reported.

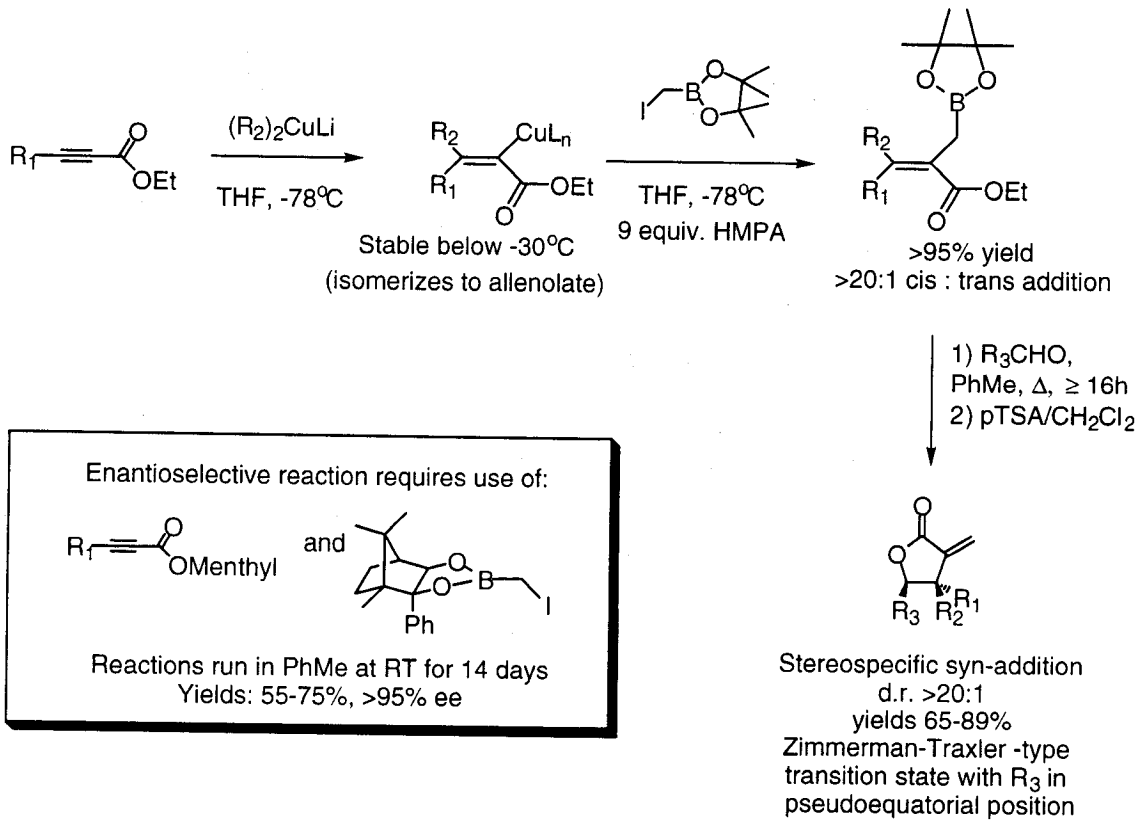


Scheme 30. The formation of asymmetric quaternary stereocentres via the enantioselective copper-catalyzed addition of dialkylzinc reagents to allylic phosphates.

1.8.2 ADDITION OF NUCLEOPHILIC ALLYLMETALOID SPECIES TO ALDEHYDES

While the previous two methods dealt with the use of allylic electrophiles, techniques have also been developed that use nucleophilic allylmetalloid species. Hall and Kennedy reported the addition of allylboronate species to aldehydes for the diastereoselective synthesis of quaternary carbon-containing γ-lactones (Scheme 31).[41]

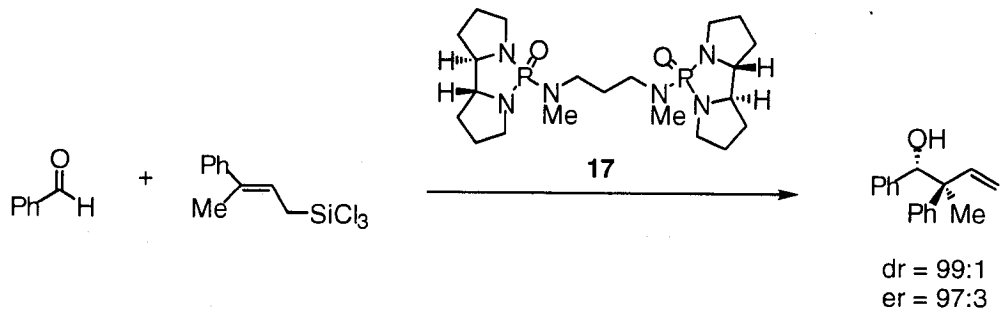
Despite high diastereoselection, the combined use of both a menthyl propargyl ester and a camphor-derived chiral boronate was required to effect high enantioselection.



Scheme 31. The use of allylboronates for the synthesis of quaternary carbon-containing γ-lactones.

Denmark and co-workers have developed a catalytic enantioselective synthesis of quaternary carbons by allylation of aromatic or α,β-unsaturated aldehydes by allylic trichlorosilanes (Scheme 31).[42] In this system the stereochemistry is controlled by catalytic amounts of a tethered chiral bisphosphoramide (e.g. **17**), a chiral Lewis base. In this system *E*-allylsilanes afforded almost exclusively *anti* addition products. *Z*-Allylsilanes afforded *syn* adducts with similarly high selectivity. One substrate was utilized in the synthesis of LY426965, a serotonin antagonist. This method was limited

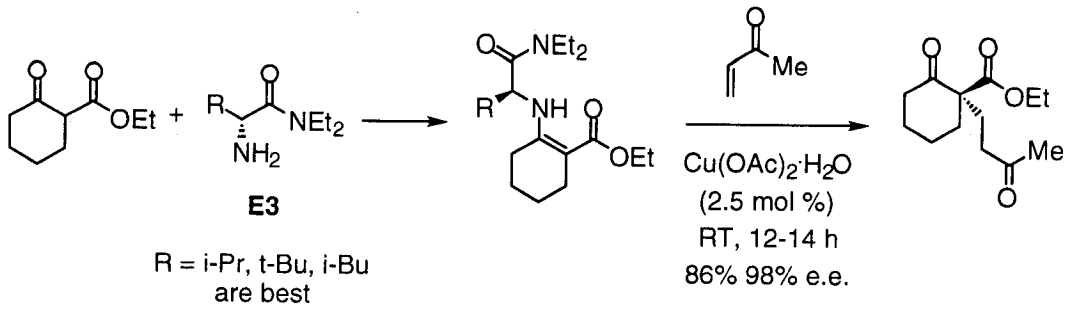
to the use of aromatic aldehydes as aliphatic aldehydes afforded O-silylated chlorohydrins.



Scheme 32. The Lewis base-catalyzed addition of allylic trichlorosilanes to aldehydes.

1.8.3 ASYMMETRIC MICHAEL ADDITIONS

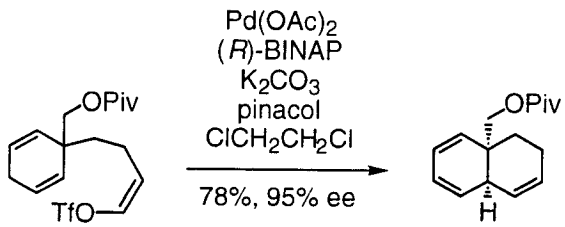
Asymmetric Michael reactions using chiral enamines have been reported.[43] These reactions are useful as they often take place under mild reaction conditions and are tolerant of many functional groups. 1-Phenylethylamine is a readily available chiral amine that has been used for this type of reaction since 1985.[43b] α-Aminocarboxamides such as **18** were recently introduced in copper-catalyzed asymmetric Michael reactions (Scheme 33).[44] These reactions were shown to proceed with up to 98% ee. Similar levels of enantioselectivity were obtained with open-chain 1,3-dicarbonyl compounds.[45] This technique allows for the generation of quaternary stereocentres at ambient temperature, under mild reaction conditions, using catalytic amounts of a "green" metal and an amino acid-derived auxiliary that is cleaved upon reaction workup. It is nevertheless limited to 1,3-dicarbonyl species.



Scheme 33. The copper-catalyzed asymmetric Michael addition of enamines to enones.

1.8.4 INTRAMOLECULAR HECK COUPLING

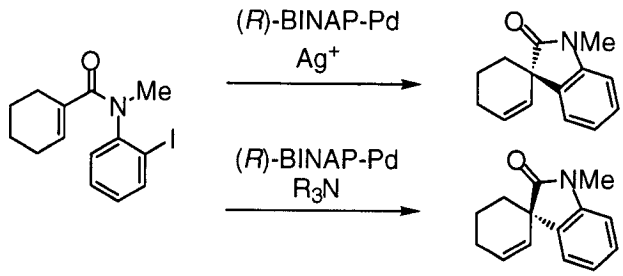
The use of Heck couplings for the synthesis of quaternary carbons has been reported by both Shibasaki[46] and Overman.[47] Shibasaki reported the desymmetrization of trienyl triflates using palladium(0) and (*R*)-BINAP as a chiral ligand (Scheme 34). Although this method did allow for high enantioselection, it was limited to the formation of [4.4.0] bicycles.



Scheme 34. Enantioselective Heck desymmetrization.

Overman and co-workers found that cyclohexenyl carboxamides of iodoaniline would undergo enantioselective Heck cyclization in the presence of palladium(0), (*R*)–BINAP and a silver(I) salt, producing a spiro centre in up to 81% ee (Scheme 35). It is very interesting to note that by adding an amine base in place of the silver salt, the

sense of enantioselection is reversed. The use of 1,2,2,6,6-pentamethylpiperidine as base led to enantioselection as high as 95% ee. No explanation for this phenomenon has been published.



Scheme 35. Enantioselective Heck cyclization of cyclohexenyl carboxamides of iodoaniline.

1.9 OVERVIEW OF PROJECT

Quaternary carbons are found in many pharmaceutically relevant natural products and are seen in non-natural source drugs as well. As mentioned above, the number of general methods for the asymmetric synthesis of quaternary carbons is small and most of the known methods have significant limitations.

We are interested in developing a versatile, efficient method for generating acyclic α,α–disubstituted enolates with *E/Z* stereocontrol. Subsequent diastereoselective alkylation of these enolates would afford quaternary carbons with high diastereomeric excess. Such a methodology would be a strong contribution to the field of asymmetric synthesis and of great value to the pharmaceutical community.

We began this study, as described in Chapter Two, with studies of *E/Z* stereocontrol in the reductive enolization of various thioglycolate lactams, as there is

precedence for the reductive enolization of thioglycolate esters. Our results in this area led us to investigate the alkylation of these enolates with alkyl halides and this is presented in Chapter Three.

---

[1] For reviews on asymmetric quaternary carbon synthesis, see a) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; b) Corey, E.J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388; c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

[2] He, F.; Bo, Y.; Altom, J.D.; Corey, E.J. *J. Am. Chem. Soc.* **1999**, *121*, 6771 and references cited therein.

[3] Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228 and references cited therein.

[4] a) Becker, U.; Erkel, G.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 229. For synthetic approaches to puraquinonic acid see b) Clive, D.L.J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954; c) Hisaindee, S.; Clive, D.L.J. *Tetrahedron Lett.* **2001**, *42*, 2253; d) Clive, D.L.J., Yu, M. *Chem. Comm.* **2002**, 2380; e) Kraus, G.A.; Choudhury, P.K. *J. Org. Chem.* **2002**, *67*, 5857.

[5] Most drugs are initially metabolized by P450 enzymes, which oxidize carbon-hydrogen bonds. See a) Anzenbacher, P.; Anzenbacherová, E. *Cell. Mol. Life Sci.* **2001**, *58*, 737 and references cited therein; b) Guengerich, F.P. *Chem. Res. Toxicol.* **2001**, *14*, 611 and references cited therein.

[6] Eliel, E.L.; Wilen, S.H. Mander, L.N. *Stereochemistry of Organic Compounds*; Wiley: Toronto, **1994**, p. 204 and references cited therein.

[7] The *E(O)* notation is used to denote that the alkyl group on the α-carbon is anti or (*E*) to the alkoxide oxygen. Formally, an *E(O)*-enolate is a *Z*-ester enolate because the alkoxide

has a lower priority than the ether moiety. Because the alkoxide has a higher priority than the dialkylamino moiety in the discussion of amide enolates, an amide enolate with the alkyl group syn to the alkoxide functionality is termed a *Z*-enolate. The *E(O)* notation for ester enolates is then very useful when discussing both amide and ester enolates simultaneously because it allows for all enolates in which the alkyl group is syn to the alkoxide oxygen to be referred to as *Z*-enolates.

[8] a) Ireland, R.E.; Muller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976**, *98*, 2868; b) Ireland, R.E.; Wipf, P.; Armstrong, J.D. *J. Org. Chem.* **1991**, *56*, 650. For a model explaining this selectivity see c) Zimmerman, H.E.; Traxler, M.D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[9] 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.

[10] a) Meyers, A.I.; Knaus, G.; Kamata, K.; Ford, M.E. *J. Am. Chem. Soc.* **1976**, *98*, 567; b) Meyers, A.I.; Yamamoto, Y.; Mihelich, E.D.; Bell, R.A. *J. Org. Chem.* **1980**, *45*, 2792 and references cited therein.

[11] Sonnet, P.E.; Heath, R.R. *J. Org. Chem.* **1980**, *45*, 3137.

[12] Schmierer, R.; Grotemeier, G.; Helmchen G.; Selim, A. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 207.

[13] Evans, D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

[14] Alkyl halides with minimal steric hindrance (Me–I) or a group that can readily stabilize a δ^+ (BnBr, allyl-Br, MOM–Cl, *etc.*) are often classified as activated alkyl halides because of their significantly higher levels of reactivity.

[15] a) Kawanami, Y; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857; b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015; c) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343.

[16] Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.

[17] Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.J., Gleason, J.L *J. Am. Chem. Soc.* **1997**, *118*, 6496 and references cited therein.

[18] Lithium chloride was used (6 equivalents) because it was found to accelerate reactions and in some cases, increase the reaction diastereoselectivity.

[19] Vedejs, E.; Kruger, A.W.; Lee; N.; Sakata, S.T.; Stec, M.; Suna, E. *J. Am. Chem. Soc.* **2000**, *122*, 4602.

[20] Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron* **2000**, *41*, 6429.

[21] a) Boeckman, R.K. Jr.; Liu, Y. *J. Org. Chem.* **1996**, *61*, 7984; b) Boeckman, R.K. Jr.; Wrobleski, S.T. *J. Org. Chem.* **1996**, *61*, 7238; c) Boeckman, R.K. Jr.; Connell, B.T. *J. Am. Chem. Soc.* **1995**, *117*, 12368; d) Boeckman, R.K. Jr.; Johnson, A.T.; Museelman, R.A. *Tetrahedron Lett.* **1994**, *35*, 8521; e) Boeckman, R.K. Jr.; Nelson, S.G.; Gaul, M.D. *J. Am. Chem. Soc.* **1992**, *114*, 2258.

[22] Boeckman, R.K. Jr.; Boehmler, D.J.; Musselman, R.A. *Org. Lett.* **2001**, *3*, 3777.

[23]a) Dalko, P.I.; Langlois, Y. *Chem. Comm.* **1998**, 331; b) Dalko, P.I.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 8107.

[24] Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463.

[25] The chemistry of Meyers' chiral bicyclic lactams has been reviewed: a) Romo, D.; Meyers, A.I. *Tetrahedron* **1991**, *47*, 9503; b) Groaning, M.D.; Meyers, A.I. *Tetrahedron* **2000**, *56*, 9843. More recent advances in this area have been reported: c) Meyers, A.I.; Downing, S.V.; Weiser, M.J. *J. Org. Chem.* **2001**, *66*, 1413.

[26] Meyers, A.I.; Seefeld, M.A.; Lefker, B.A.; Blake, J.F., Williard, P.G. *J. Am. Chem. Soc.* **1998**, *120*, 7429.

[27] The depicted β-hydroxyesters were formed by the reduction of the corresponding β–keto esters by Baker's yeast. The reduction is highly stereoselective at the β-carbon but poorly selective at the α-carbon. The low selectivity at the α-carbon is inconsequential because the α-carbon becomes sp^2 in the enolate.

[28] a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825; b) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2829; c) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.

[29] a) Enders, D.; Zamponi, A.; Schäfer, T.; Nübling, C.; Eichenauer, H.; Demir, A.S.; Raabe, G. *Chem. Ber.* **1994**, *127*, 1707; b) Enders, D.; Teschner, P.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2001**, 4463.

[30] Enders, D.; Brauer-Scheib, S.; Fey, P. *Synthesis* **1985**, 393.

[31] Overman, L.E.; Larrow, J.F.; Stearns, B.A.; Vance, J.M. *Angew. Chem. Int. Ed.* **2000**, *39*, 213.

[32] a) Åhman, J.; Wolfe, J.P.; Troutman, M.V.; Palucki, M.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 1918; b) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox. J.M.; Buchwald, S.L. *Org. Lett.* **2001**, *3*, 1897; c) Hamada, T.; Buchwald, S.L. *Org. Lett.* **2002**, *4*, 999; d) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

[33] Lee, S.; Hartwig, J.F. *J. Org. Chem.* **2001**, *66*, 3402.

[34] Arduengo, A.J., III; Rasika Dias, H.V.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *112*, 5530.

[35] Trost, B.M.; Schroeder, G.M. *J. Am. Chem. Soc.* **1999**, *121*, 6759.

[36] Trost, B.M.; Schroeder, G.M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492.

[37] a) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, Z.-Z. *Org. Lett.* **2001**, *3*, 149; for other catalytic, asymmetric alkylations of tetralone enolates, see b) Koga, K.; Sirai, R. *Mater. Integ.* **2001**, *14*, 68.

[38] Lipsutz, B.H.; Sengupta, S. *Org. React.* **1992**, *41*,135.

[39] Spino, C.; Beaulieu, C. *Angew. Chem. Int. Ed.* **2000**, *39*, 1930.

[40] Luchaco-Cullis, C.A.; Mizutani, H.; Murphy, K.E.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1456.

[41] Kennedy, J.W.J.; Hall, D.G. *J. Am. Chem. Soc.* **2002**, *124*, 898.

[42] a) Denmark, S.E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488; b) Denmark, S.E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951. For a mechanistic study see c) Denmark, S.E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *123*, 12021.

[43] For reviews on this subject see a) Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051; b) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

[44] a) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2752; b) Christoffers, J.; Rößler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701. Additional reviews: c) Christoffers, J. *Synlett* **2001**, 723; d) Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259.

[45] Christoffers, J.; Mann, A. *Chem. Eur. J.* **2001**, *7*, 1014.

[46] Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737.

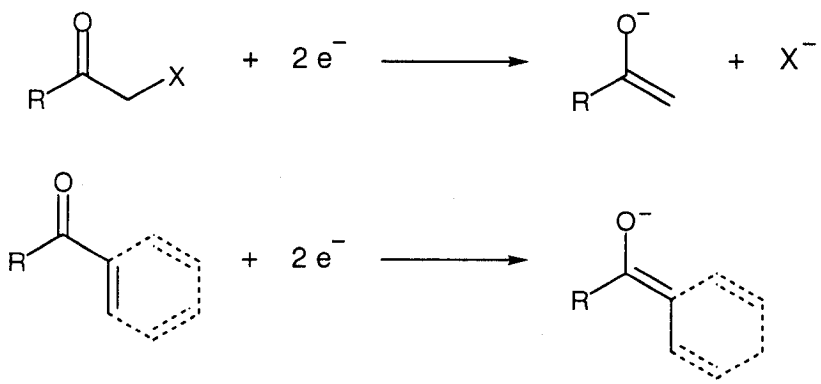
[47] Ashimori, A.; Bachand, B.; Overman, L.E.; Poon, D.J. *J. Am. Chem. Soc.* **1998**, *120*, 6477; b) Matsuura, T.; Overman, L.E.; Poon, D.J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.

CHAPTER TWO

STEREOCONTROLLED REDUCTIVE GENERATION OF α,α–DISUBSTITUTED AMIDE ENOLATES

2.1 REDUCTIVE GENERATION OF ENOLATES

The previous chapter outlined the complications in generating α,α-disubstituted enolates, both in terms of difficulty of the deprotonation and *E/Z* stereocontrol. Reductive enolate generation is an alternative to enolate formation by deprotonation. This method functions by transferring electrons from a reductant such as an alkali metal to carbon-carbon multiple bonds or a carbon-heteroatom bond (Scheme 36). Electron transfer enolate generation is not subject to steric concerns that plague deprotonation techniques and therefore this enolization strategy has greater potential to be developed into a broad-scope technique for the generation of α,α–disubstituted enolates.

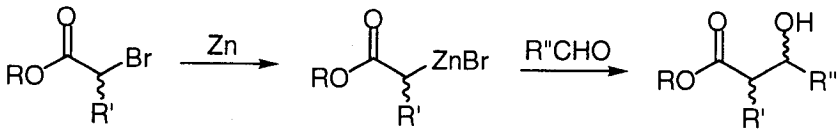


Scheme 36. Reductive enolization.

Several different functionalities have been reduced to generate enolates. These include α–halo esters, enones, benzoic acid derivatives, and α–thio esters.

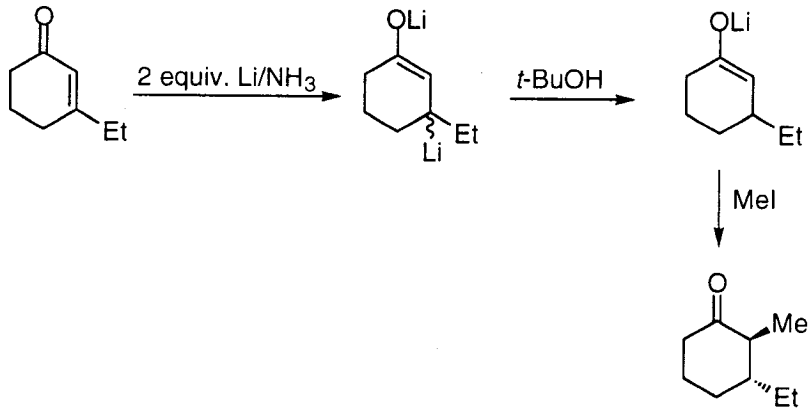
In the Reformatsky reaction, α-halo esters are reduced to the zinc enolate with metallic zinc, which are then typically allowed to react with an aldehyde to form aldol

adducts (Scheme 37).[1] Other reducing agents, such as indium, titanium, manganese, and samarium diiodide have also been employed in Reformatsky-type chemistry.[2]



Scheme 37. The Reformatsky reaction.

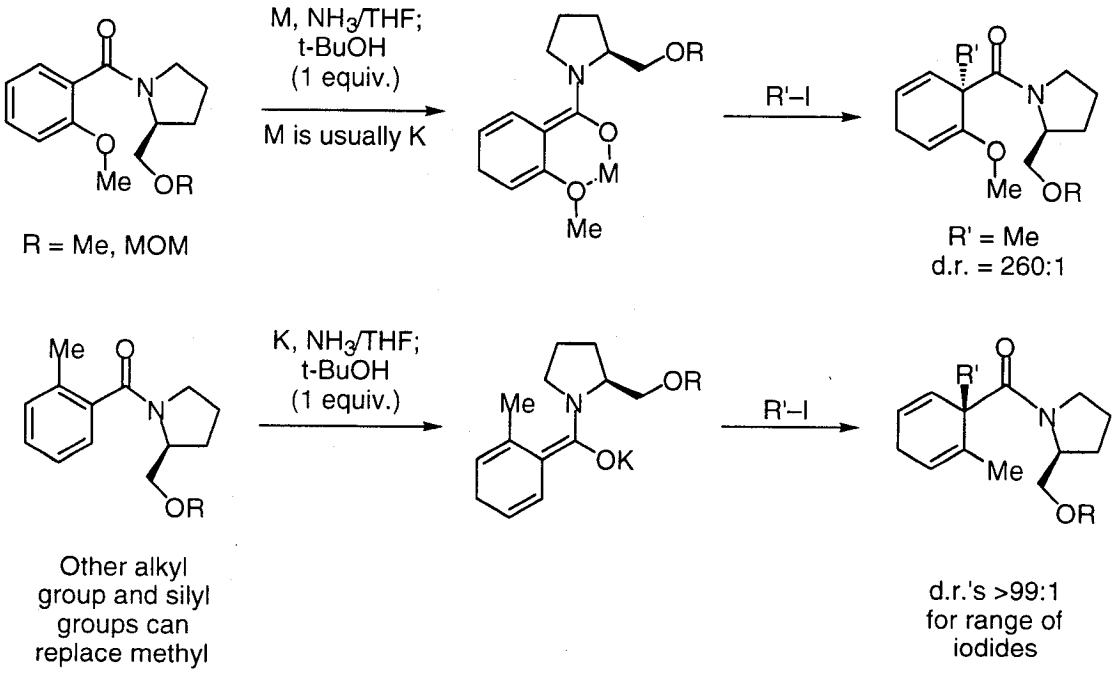
Cyclic enones can be reduced under dissolving metal conditions to afford enolate dianions (Scheme 38).[3] One equivalent of an alcohol is typically present during the reduction process so that the carbanion is quenched upon its formation. Subsequent alkylation is typically diastereoselective.



Scheme 38. Reductive enolization and alkylation of cyclic enones.

The Birch reduction is a well-known method for producing 1,4–cyclohexadienes.[4] Exposure of an aromatic system to two equivalents of an alkali metal and two equivalents of an alcohol in liquid ammonia results in the formation of 1,4–cyclohexadienes. When a Birch reduction is performed on benzoic acid derivatives, an α,α-disubstituted enolate is generated. Schultz and co-workers developed this enolate formation technique into a

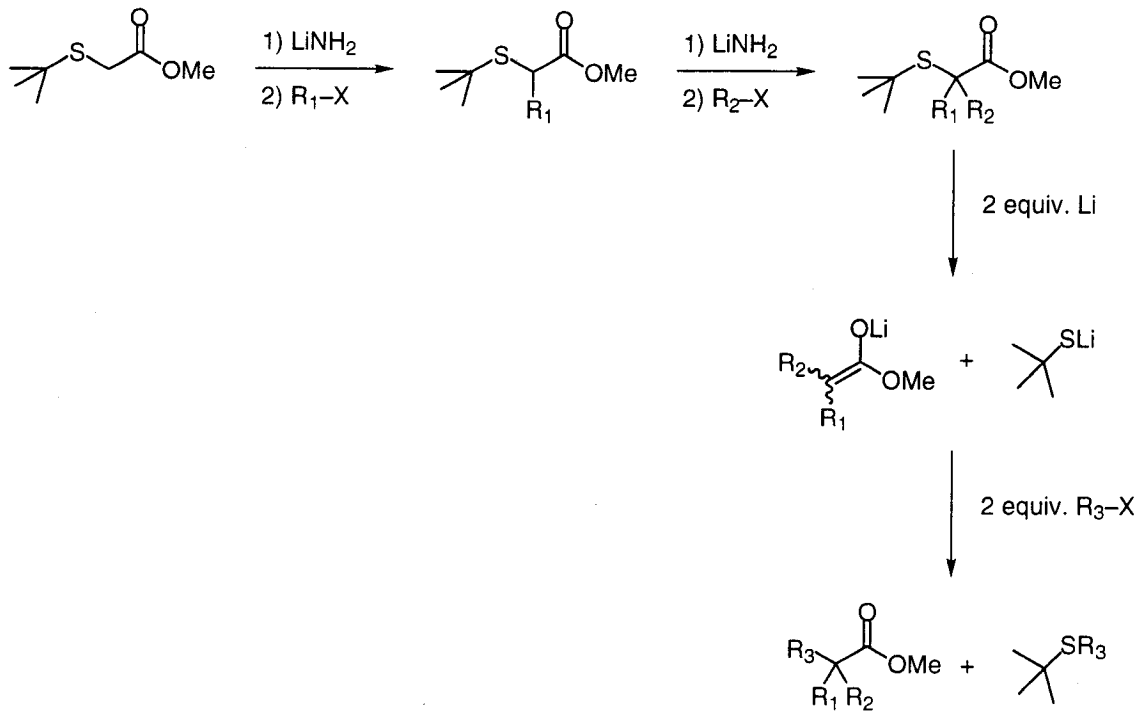
method for the asymmetric synthesis of quaternary carbons (Scheme 39).[5] This technique, although highly successful, is limited to the preparation of chiral cyclohexadienes, which must usually be subjected to further significant synthetic manipulation. This results in lengthy, linear syntheses making this a less efficient methodology.



Scheme 39. The asymmetric synthesis of quaternary carbons via Birch reduction.

Nagata and co-workers also developed a method of quaternary carbon synthesis using a reductive enolization method.[6] In this work, they showed that α,α–dialkylated α–*tert*-butylthio esters, nitriles and ketones could be prepared via stepwise alkylation of their unalkylated counterparts using lithium amide as base. Subsequent reduction using stoichiometric amounts of lithium in liquid ammonia and THF led to formation of an

α,α–disubstituted enolate.[7] Alkylation or acylation of these enolates afforded quaternary carbons in good yield (Scheme 40).



Scheme 40. Formation of quaternary carbons via reductive enolization of α–*tert*–butylthio carbonyl compounds.

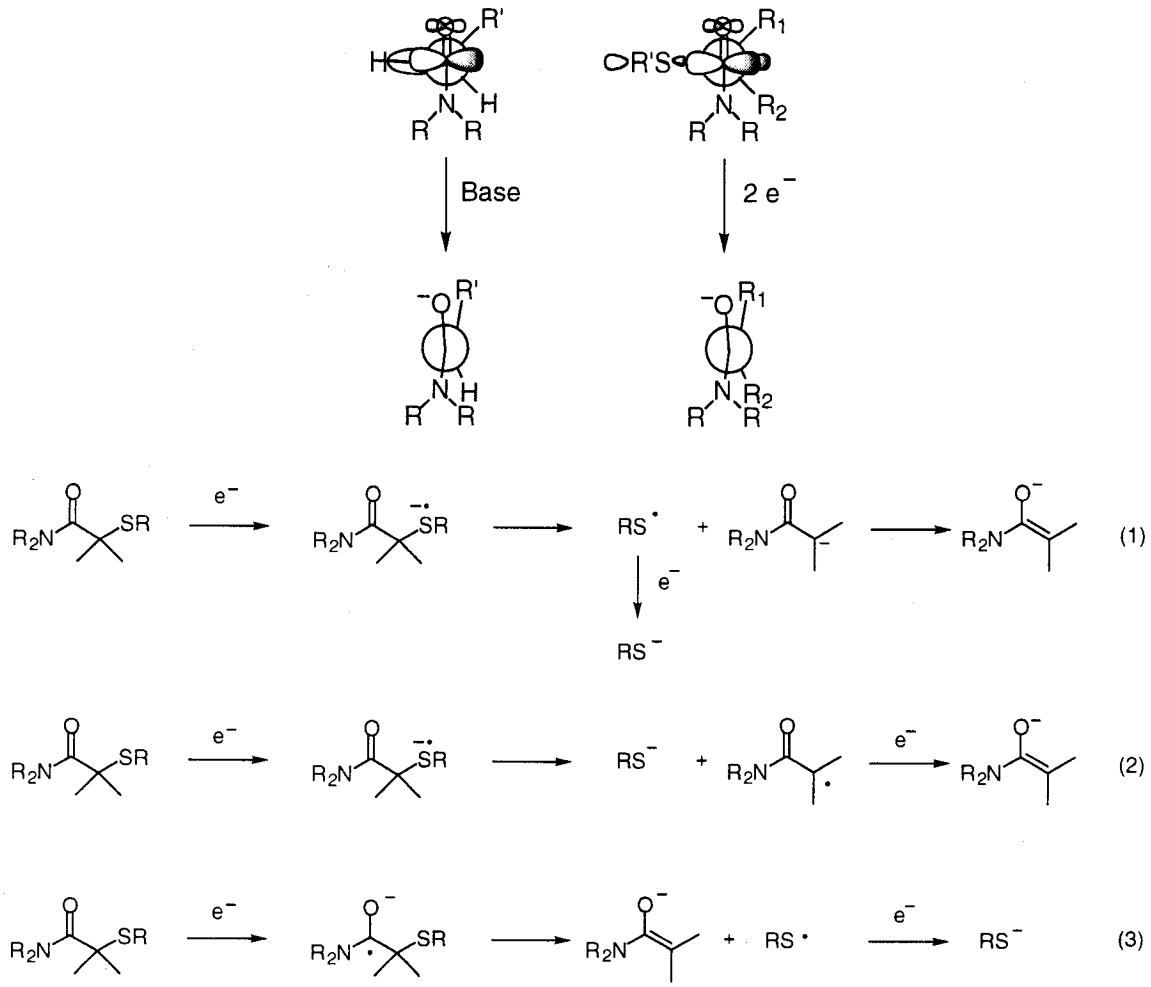
It is important to point out that all the quaternary centres prepared by Nagata's technique were either achiral or chiral but racemic. In those substrates where the R_1 and R_2 groups were different, the level of *E/Z* stereocontrol was likely poor (*vide infra*). These enolates also lacked a chiral source to favour attack on one π-face of the enolate over the other. As mentioned in Chapter One, *E/Z* enolate stereocontrol discrimination of the two diastereotopic faces of the enolate are the two elements required for an asymmetric enolate alkylation methodology.

The goal of this work was to extend Nagata's method of reductive enolization and alkylation of α–thioglycolate species to an asymmetric methodology for the synthesis of quaternary carbons. This Chapter will detail our rational design of a chiral auxiliary system and investigation of *E/Z* stereocontrol in the reductive generation of α,α–disubstituted enolates.

2.2 DESIGN OF A CHIRAL AUXILIARY SYSTEM FOR THE STEREOSELECTIVE FORMATION OF α,α–DISUBSTITUTED ENOLATES VIA REDUCTIVE ENOLIZATION

The initial phase of this project was to identify a chiral auxiliary system that would enable us to control *E/Z* stereochemistry during reductive formation of α,α–disubstituted enolates. Use of an amide- or ester-based chiral auxiliary would avoid regioisomeric deprotonation issues associated with ketone enolates. In many cases, amide enolates are preferable to ester enolates, as they are more stable; ketene formation can be a problem with ester enolates.[8] Therefore, the decision was made to pursue this research using an amide-based chiral auxiliary system.

During enolization by deprotonation, the two electrons from the breaking carbon-hydrogen bond add to the π* orbital of the corresponding carbonyl. The deprotonation occurs when the π* orbital of the carbonyl is aligned with the breaking carbon-hydrogen bond, allowing the more stable *O*–enolate (as opposed to the *C*–enolate) to form directly (Scheme 41). Thus the ideal O–C–C–H dihedral angle is 90°.



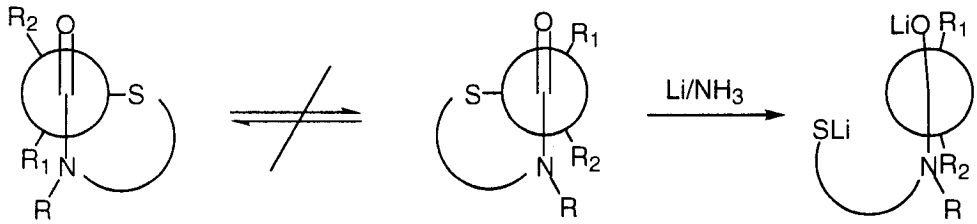
Scheme 41. Desired orbital alignment in deprotonation and reductive enolizations and potential modes of enolate formation.

A deprotonation enolization involves a single transfer of two electrons. A reductive enolization, on the other hand, involves the two discrete single electron transfers. This results in many different mechanistic possibilities and the exact mechanism of the reductive enolization of α–thioglycolates is not known. The α–carbon-sulfur bond may be cleaved after the transfer of one or two electrons.[9] Regardless of the exact mechanism, three possibilities may occur upon breakage of the

α–carbon-sulfur bond. The first two pathways involve carbon-sulfur bond cleavage with simultaneous formation of an anion or a radical on the α–carbon (Scheme 41, equations 1 and 2, respectively). The third involves concurrent carbon-sulfur bond scission and enolate formation through β–elimination of thiol radical from the amide ketyl (Scheme 41, equation 3). In the first scenario, an O–C–C–S dihedral angle of 90° in the starting amide (analogous to a deprotonation mechanism) (Scheme 41) would allow for direct formation of the *O*–enolate, resulting in little to no rotation around the carbonyl carbon-α–carbon bond. Minimizing rotation around this bond is critical, as would result in scrambling of enolate geometry (*vide infra*). In the case of formation of a radical on the α–carbon upon cleavage of the α–carbon-sulfur bond, a 90° O–C–C–S dihedral angle would align the radical with the amide's π* orbital. It is known that α–carboxy radicals are stabilized to a modest degree.[10] Thus, the 90° O–C–C–S dihedral angle and the consequent alignment of the radical with the carbonyl may slow rotation around the carbonyl carbon-α–carbon bond and help control enolate geometry. Once the radical is reduced by the addition of a second electron, a stable enolate would be formed, locking the enolate geometry. The third possible scenario for reductive enolate formation from thioglycolate species involves the formation of a ketyl radical. In this instance, an O–C–C–S dihedral angle of 90° would be ideal for extrusion of the sulfur as a radical, allowing for direct formation of the enolate.

In order to develop a stereoselective reductive enolization technique, we sought to design a system which would maintain O–C–C–S dihedral angle as close to 90° as possible by tethering the sulfur and amide nitrogen together in a ring. In addition, the method would require the stereoselective installation of R_1 and R_2 on the α–carbon to

afford a lactam of type **19** (Scheme 42). Upon reduction of lactam **19**, the alkyl groups R_1 and R_2 would maintain their relative proximities to the amide oxygen and nitrogen respectively and the stereochemical information of the α–carbon of the starting material would be transferred to the enolate **20** (principle of least motion[11]). Importantly, this would mean that inversion of stereochemistry at the α–carbon would result in inversion of enolate geometry. Implicit in this argument is a requirement that rotation about the O–C–C–S dihedral in the starting material and reduction intermediates be minimized. If the system were flexible enough to allow the sulfur to move to the opposite side of the amide plane (conformer **21**), the positioning of the alkyl groups with respect to the amide oxygen and nitrogen would be reversed. Hence, conformer **21** would afford the opposite enolate geometry to conformer **19**. It was postulated that a small bicyclic framework would incorporate sufficient structural rigidity to maintain the sulfur on one side of the amide plane. Moreover, there is significant precedent in the work of Meyers and others that a chiral bicyclic lactam framework can allow for stereoselective introduction of the two alkyl groups on the α–carbon.[12] Finally, it was also desired that the residue of the bicycle act as a chiral auxiliary for subsequent alkylation of the α,α–disubstituted enolate to form the desired quaternary carbon.



21 **19** **20**

Ideal conformation
for reduction:
S–C–C–O dihedral = 90°

Scheme 42. Model for the reductive enolization of thioglycolate lactams.

2.3 MODELING STUDIES OF BICYCLIC THIOGLYCOLATE LACTAMS

Prefacing our search for a chiral auxiliary with the requirement of a bicyclic structure, we modeled several series of bicyclic lactams using the MM2 force field (Macromodel). The size of both rings (one of those rings being the tether between the nitrogen and sulfur atoms) was varied, in search of a system with an O–C–C–S dihedral angle of as close to 90° as possible. In order to ascertain the level of conformational rigidity, as well as the simple ground state dihedral angle, the weighted average (Boltzmann distribution) of the dihedral angles of all conformations found within 2 kcal/mol of the ground state at –78 °C was calculated. For the sake of simplicity and consistency, the two alkyl substituents on the α–carbon of the modeled systems were methyl groups. The results of our modeling survey are shown in Figure 3. It is necessary to recognize that the search for compounds affording an O–C–C–S dihedral angle of 90° operated on the premise that the dihedral angle of the reduction transition state was similar to the O–C–C–S dihedral angle of the starting lactam. This may not be valid assumption. Nevertheless, it did seem to be a reasonable and logical starting point.

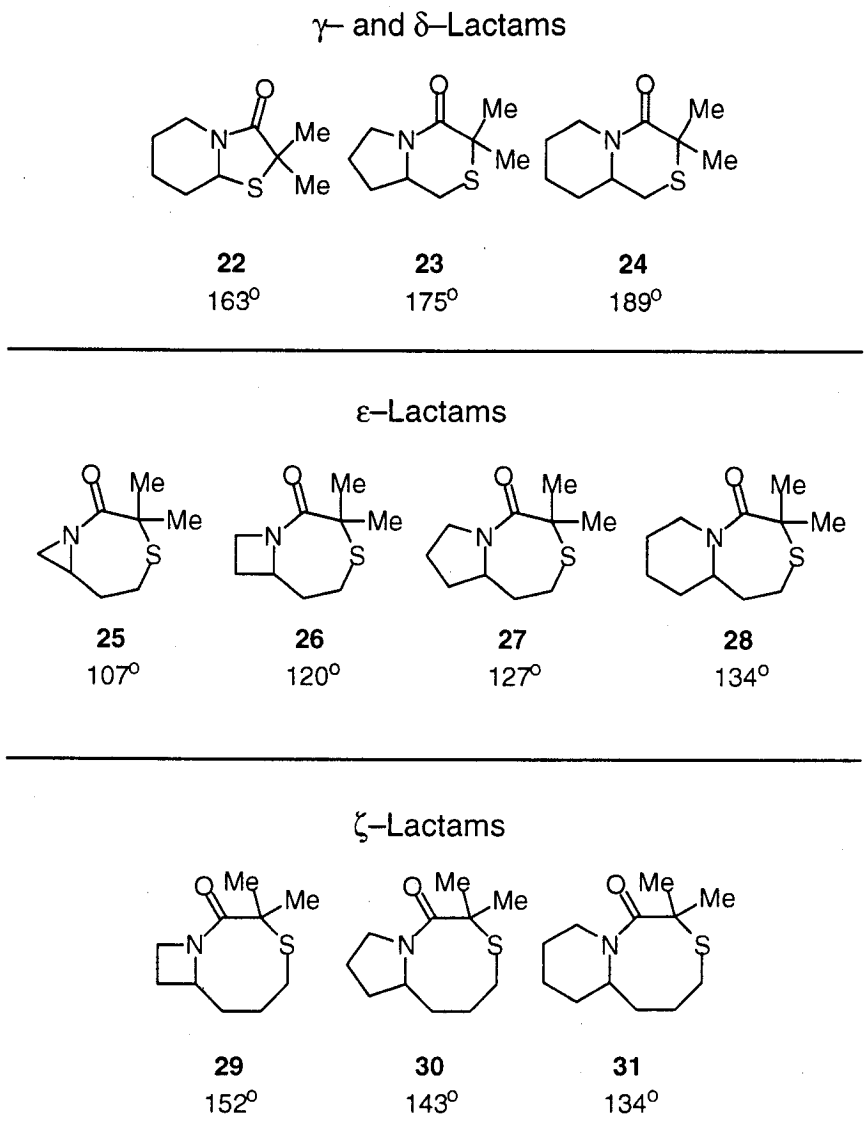


Figure 3. Dihedral angles (O–C–C–S) of various bicyclic thioglycolate lactams.

Among the optimal γ– and δ–lactams listed in the top row of Figure 3, all displayed O–C–C–S dihedral angles much larger than 90°. It was decided that one of these systems could be selected as a control system. The demethylated variant of lactam **23** is known in the literature and is prepared in two simple steps from (*S*)–prolinol (*vide infra*).[13] Therefore the ring system of lactam **23** was selected for synthesis.

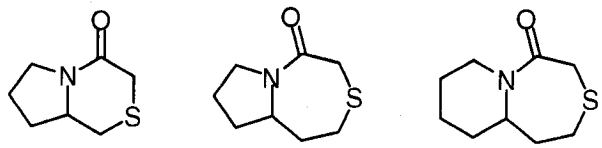
All of the ε-lactams listed in Figure 3 showed reasonable dihedral angles. Of these lactams, it was felt that 5,7-lactam **27** could be expeditiously prepared in an asymmetric fashion from (*S*)–proline. This lactam was selected as the primary candidate for our investigation. Lactam **28** presented a slightly larger dihedral angle of 137°. This was deemed to be acceptable for initial study purposes as well. This system could be prepared in analogy to system **27**, starting from pipecolic acid. Unfortunately, enantiomerically pure (*S*)-pipecolic acid is prohibitively expensive.[14] For the purposes of initial study, diastereoselectivity was the main issue, enantioselectivity was not. This system could be readily prepared in racemic fashion in a cost-effective manner (*vide infra*). Lactams **25** and **26** were not pursued because their synthesis would have been more involved and very costly. Lactam **25** also presents a stability problem. Neither of these qualities bodes well for a synthetic methodology.

The eight-membered ring-containing bicycles **29**, **30**, and **31** present dihedral angles ranging from a reasonable 134° to a less desirable 152°. None of these systems were investigated in our initial study. It was thought that synthesis of the eight-membered ring might present problems, as it is well known that eight-membered rings are often quite difficult to prepare.[15]

2.4 SYNTHESIS OF BICYCLIC THIOGLYCOLATE LACTAMS

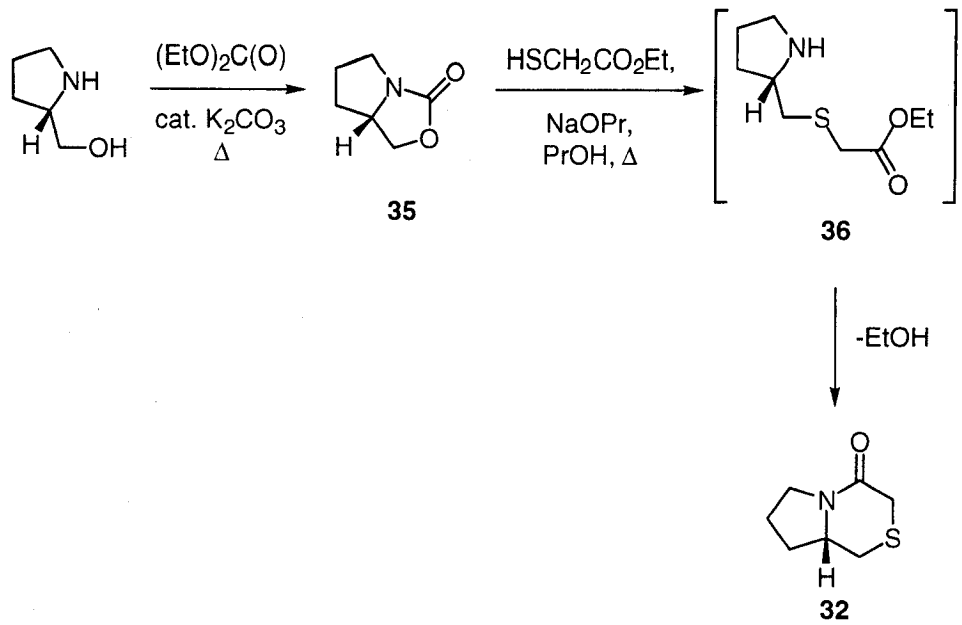
Having selected three bicyclic lactams for investigation in our reductive enolization study, the next step was to prepare the unalkylated versions of **23**, **27** and **28** (**32**, **33**, and

34 respectively). As previously mentioned, **32** was known in the literature,[13] while syntheses of **33** and **34** would have to be developed.



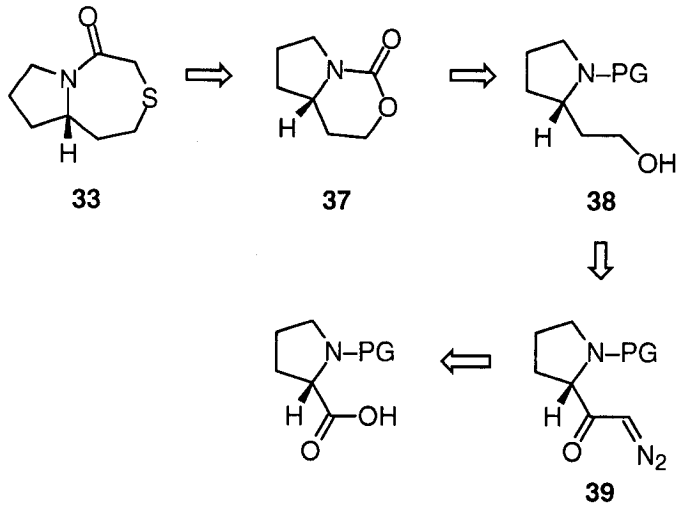
32 **33** **34**

Ishibashi's procedure for the synthesis of **32**[13] was very straightforward (Scheme 43). (*S*)–Prolinol was converted to the carbamate **35** using diethyl carbonate and catalytic potassium carbonate. The carbamate was then heated at reflux in *n*-propanol with sodium *n*–propoxide and ethyl thioglycolate. These reaction conditions presumably form the thiolate of ethyl thioglycolate, which then attacks the sp^3 carbon of the carbamate in an S_N2 fashion, resulting in loss of CO_2. This is a good example of a soft nucleophile attacking the soft site of an ambident electrophile. The resulting amine **36** then undergoes intramolecular acylation with the ester to afford **32**.



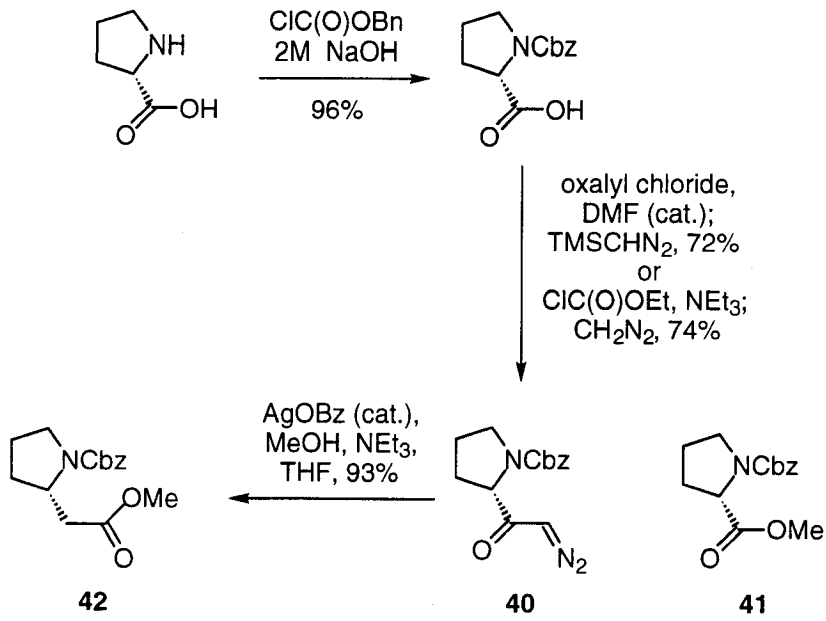
Scheme 43. Synthesis of bicyclic thioglycolate lactam **32**.

The synthesis of bicyclic thioglycolate lactam **33** was expected to be somewhat more involved. The initial route to **33** (Scheme 44) was designed to go through the carbamate **37**, the homologue of **35**. This cyclic carbamate was envisioned as arising from homologated prolinol **38**. We envisioned alcohol **38** as arising from an Arndt-Eistert[16] homologation of *N*–protected (*S*)–proline, using diazoketone **39**.



Scheme 44. Retrosynthesis of 5,7-bicyclic thioglycolate lactam **33**.

Initially, the nitrogen of (*S*)–proline was protected in high yield with a Cbz group using benzyl chloroformate (Scheme 45). This group was chosen because it is typically removed under mild hydrogenolysis conditions. Conversion of the carboxylic acid moiety into the diazoketone **40** was performed in good yield using oxalyl chloride and catalytic DMF followed by addition of trimethylsilyldiazomethane or by addition of ethyl chloroformate and triethylamine followed by the addition of diazomethane.[17] A complication arose in this protocol from the formation of Cbz-proline methyl ester **41**. Despite vigorous attempts to ensure complete formation of the acid chloride or mixed anhydride, the formation of this undesired side product could not be prevented. The situation was further complicated by the difficulty of the removal of undesired ester **41** from the desired diazoketone **40**. This required very judicious column chromatography.



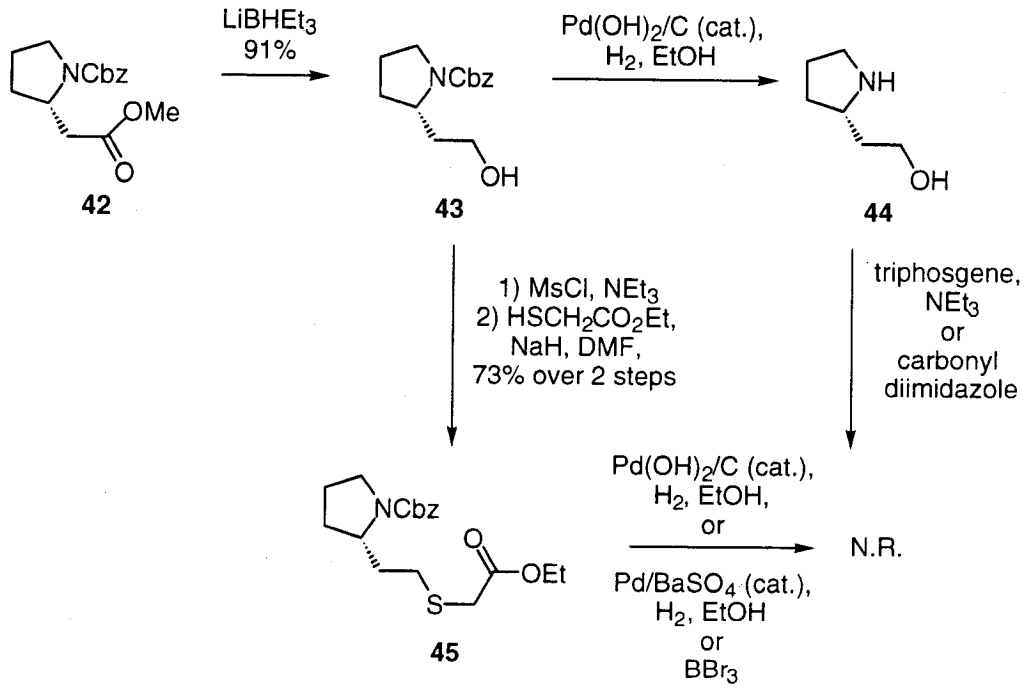
Scheme 45. Preparation of homologated proline ester **42**.

After several failed attempts at thermal Wolff rearrangements[18] of the diazoketone **40**, a silver (I)-catalyzed procedure was adopted.[19] The addition of silver benzoate in triethylamine to a solution of diazoketone and 4 equivalents of methanol in THF afforded the homologated ester **42** in high yield.

Removal of the ester contaminant **41** before completion of the Arndt/Eistert process proved to be obligatory. Once the Wolff rearrangement had been performed, the homologated ester **42** was indistinguishable from the unhomologated material **41** by silica gel chromatography. In all the subsequent reactions, both materials behave identically and thus both compounds would be carried through the reaction sequence. This problem was only discovered after a batch of material containing this contaminant was converted to lactam **33**. The previously prepared lactam **32** was found as a minor

component in the NMR spectrum **33**. Separation of lactams **32** and **33** by chromatography or distillation was unsuccessful.

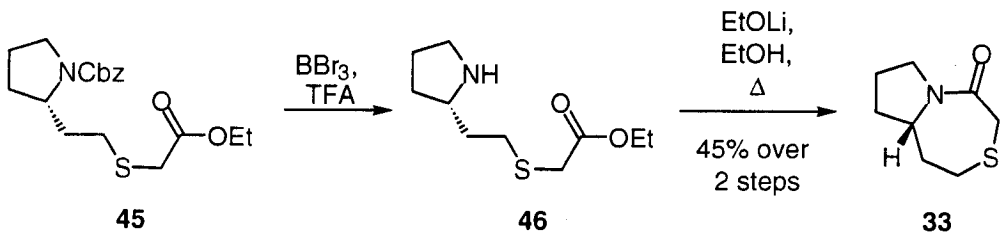
Reduction of the ester **42** with DIBAL was initially investigated. Despite the presence of a large excess of DIBAL the reaction would only proceed to 60% completion. The remainder of the starting material was recovered unchanged. Switching to lithium triethylborohydride (Super-Hydride) as the reducing agent resulted in high yields of the desired alcohol **43** (Scheme 46). The use of hydrogen and catalytic palladium hydroxide on carbon effectively removed the Cbz protecting group from alcohol **43**. However, the desired carbamate could not be formed using either triphosgene and triethylamine or carbonyldiimidazole. This prompted a change in synthetic strategy, abandoning the carbamate opening sequence.



Scheme 46. Attempts to form carbamate **37** and preparation of sulfide **45**.

It was believed that by installing the thioglycolate moiety prior to protecting group removal, a peptide coupling or amine acylation could be performed to form the lactam ring. To achieve this, the alcohol **43** was converted to the corresponding mesylate using mesyl chloride and triethylamine. Addition of the mesylate to a solution of the sodium thiolate of ethyl thioglycolate led to formation of the desired sulfide **45** in good yield.

Attempted removal of the Cbz group under typical hydrogenolysis conditions (H_2, catalytic $Pd(OH)_2/C$) was ineffective. It was proposed that the sulfide was poisoning the palladium catalyst.[20] Palladium on barium sulfate is known to be more resistant to poisoning by sulfur.[21] However, in this instance it proved to be ineffective. Boron tribromide is also known to remove Cbz protecting groups[22] but this was also unsuccessful. Removal of the protecting group was ultimately achieved using boron tribromide and trifluoroacetic acid (Scheme 47).[23] The vigorous conditions required to remove the Cbz group would ultimately prompt a change in protecting group strategy (*vide infra*).



45 **46** **33**

Scheme 47. Cyclization to form bicyclic α–thioglycolate lactam **33**.

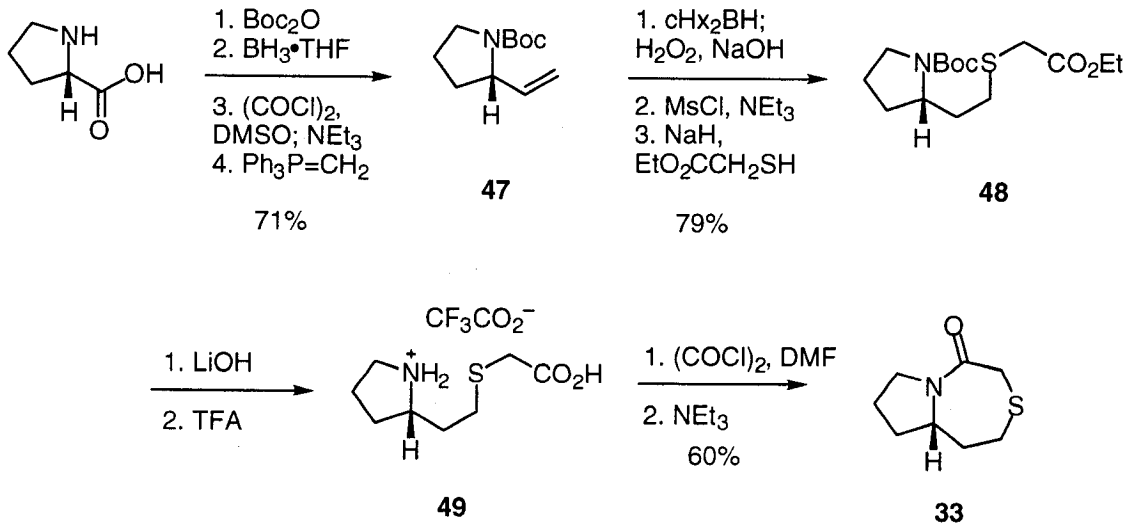
Based upon conditions for formation of the 5,6–lactam **32**,[12] it was felt that a small amount of base and an alcoholic solvent would be useful conditions for the

formation of the desired lactam **33**. Indeed, refluxing the amino ester in ethanol with lithium ethoxide afforded the desired lactam **33** in moderate yield over two steps.

Though the previous synthetic sequence was effective in preparing thioglycolate lactam **33**, the reaction conditions were often harsh and impractical. Some of the reaction yields were also less than desirable. This prompted a change in protecting groups. The decision was made to use a Boc protecting group on the nitrogen atom. It was also decided to employ a Wittig reaction to homologate the proline system. This would provide a significant difference between the homologated (alkene) and unhomologated (aldehyde) materials (if unreacted starting material remained).

(*S*)–Proline was Boc-protected (Scheme 48). Reduction of the carboxylic acid moiety with borane was followed by Swern oxidation[24] to the aldehyde. Subsequent Wittig methylenation resulted in a 4-step yield of 71% of alkene **47**. This sequence required purification only after the Wittig reaction. Hydroboration/oxidation with dicyclohexylborane afforded the desired *N*–Boc–2-(2-pyrrolidine)ethanol in 93% yield. Mesylation followed by displacement with the thiolate ion derived from ethyl or methyl thioglycolate provided sulfide **48** in 85% yield. Ester saponification was followed by cleavage of the Boc group with TFA. It was found that the amino acid trifluoroacetate salt **49** could be converted to the corresponding acid chloride with oxalyl chloride and catalytic DMF without affecting the protonated amine moiety. Addition of the acid chloride to a solution of triethylamine in methylene chloride resulted in a 60% yield of the desired bicyclic lactam **33**. The trifluoroacetate salt of the amino acid **49** could also be cyclized via slow addition to a solution of EDC•HCl, NEt_3, and HOBt. This

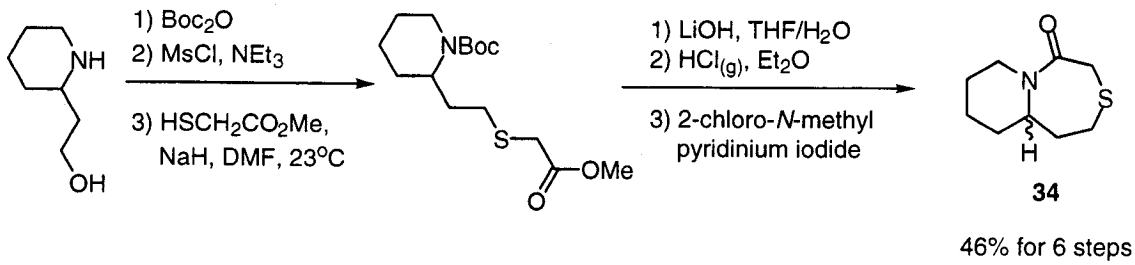
procedure, although providing yields as high as 62%, proved to be unreliable and costly. Other peptide coupling agents provided only very low yields of lactam **33**.



Scheme 48. The synthesis of bicyclic thioglycolate lactam **33**.

With an acceptable synthetic route to lactam **33** in hand, our attention turned to the synthesis of the 6,7-lactam **34**. As previously mentioned, the enantioselective synthesis of lactam **34** would require the use of the highly expensive (*S*)–pipecolic acid. For the purposes of initial investigation diastereoselectivity was more important than enantioselectivity. Therefore the synthesis of **34** could be performed in a racemic fashion using a much less expensive starting material, 2-(2-piperidine)ethanol (Scheme 49).[25] Selective *N*–Boc protection of 2-(2-piperidine)ethanol was followed by *O*-mesylation. Mesylate displacement by the thiolate ion derived from deprotonation of methyl thioglycolate was followed by ester saponification. Removal of the Boc group was carried out by bubbling gaseous HCl through an ethereal solution of the carboxylic acid. Coupling of the amino acid was best achieved using Mukaiyama's peptide coupling

reagent, 2-chloro-*N*-methylpyridinium iodide.[26] The resulting lactam **34** was produced in multi-gram quantities with an overall yield of 46% for six steps.



Scheme 49. Synthesis of bicyclic thioglycolate lactam **34**.

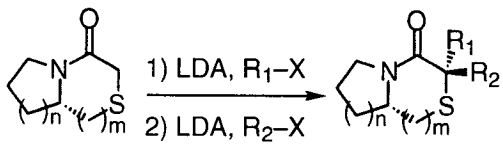
2.5 ALKYLATION OF BICYCLIC THIOGLYCOLATE LACTAMS

With lactams **32**, **33** and **34** in hand, a study of their alkylations was undertaken. Standard enolization conditions were to use a slight excess of LDA as base in the presence of 5 equivalents of LiCl in THF. Addition of a primary alkyl halide resulted in *C*–alkylation. No *O*–alkylation was ever observed. Although dialkylation is possible during the first alkylation reaction, this was rarely observed and occurred only with the use of allyl bromide as the electrophile.

The results of the alkylation survey are found in Table 1. From the table it can be seen that alkylations of the 5,6–lactam **32** proceeded in >80% yield in all cases. Interestingly, the second alkylation step was less selective than the first. Alkylations of 5,7–lactam **33** occurred in good to excellent yield. Notably, alkylations of the ε–lactam **33** were more stereoselective than alkylations of the corresponding δ–lactam **32**. This may be due to the very rigid structure of the 5,6-bicyclic system and the high O–C–C–S dihedral angle. In both **32** and **33**, alkylations occurred primarily on the exo-face of the

bicycle. This facial selectivity was determined by observation of NOE enhancements in ^{1}H NMR experiments (Figure 4) and an X-ray crystal structure of **51f** (Figure 5, left).

Table 1. Alkylation of bicyclic lactams.



32 n=1, m=1
33 n=1, m=2
34 n=2, m=2

50 n=1, m=1
51 n=1, m=2
52 n=2, m=2

Series
a R_1= *n*-Pr R_2= Me
b R_1= Me R_2= *n*-Pr
c R_1= Allyl R_2= Me
d R_1= Me R_2= Allyl
e R_1= Bn R_2= Me
f R_1= Me R_2= Bn
g R_1= *n*-Pr R_2= Et
h R_1= Et R_2= *n*-Pr
i R_1= *n*-Bu R_2= Me
j R_1= Et R_2= Me

lactam	R_1–X	yield	de[a]	R_2–X	product	yield	de[b]
32	*n*-PrI	84%	88%	MeI	**50a**	94%	72%
32	MeI	88%	81%	*n*-PrI	**50b**	88%	72%
32	allyl–Br	88%	85%	MeI	**50c**	91%	79%
32	MeI			allyl–Br	**50d**	86%	78%
33	*n*–PrI	76%	88%	MeI	**51a**	90%	90%
33	MeI	86%	93%	*n*-PrI	**51b**	72%	86%
33	allyl–Br	88%	85%	MeI	**51c**	85%	95%
33	MeI			allyl–Br	**51d**	96%	87%
33	BnBr	96%	>95%	MeI	**51e**	88%	>99%[c]
33	MeI			BnBr	**51f**	91%	>99%[c]
33	*n*–PrI			EtI	**51g**	75%	88%
33	EtI	80%	87%	*n*-PrI	**51h**	76%	94%
33	*n*–BuI	80%	94%	MeI	**51i**	86%	98%[c]
33	EtI			MeI	**51j**	89%	90%
34	*n*–PrI	95%	68%	MeI	**52b**	81%	50%[a,c,e]
34	MeI	95%	87%	*n*-PrI	**52a**	81%	62%[a,c,e]
34	BnBr	80%	>95%	MeI	**52f**	89%	66%[a,c,e]
34	MeI			BnBr	**52f**	69%[d]	10%[a,c]

[a] Determined by integration of ^{1}H and/or ^{13}C NMR resonances.
[b] Determined by capillary gas chromatography on a Chiralsil Dex or 5% crosslinked phenyl, methyl siloxane column. Unless otherwise noted, diastereomers were not separable by flash column chromatography.
[c] These substrates were separable by column cromatography.
[d] Lactam **52f** was isolated in 38% yield and lactam **52e** was isolated in 31% yield. [e] Alkylation selectivity is reversed for these substrates.

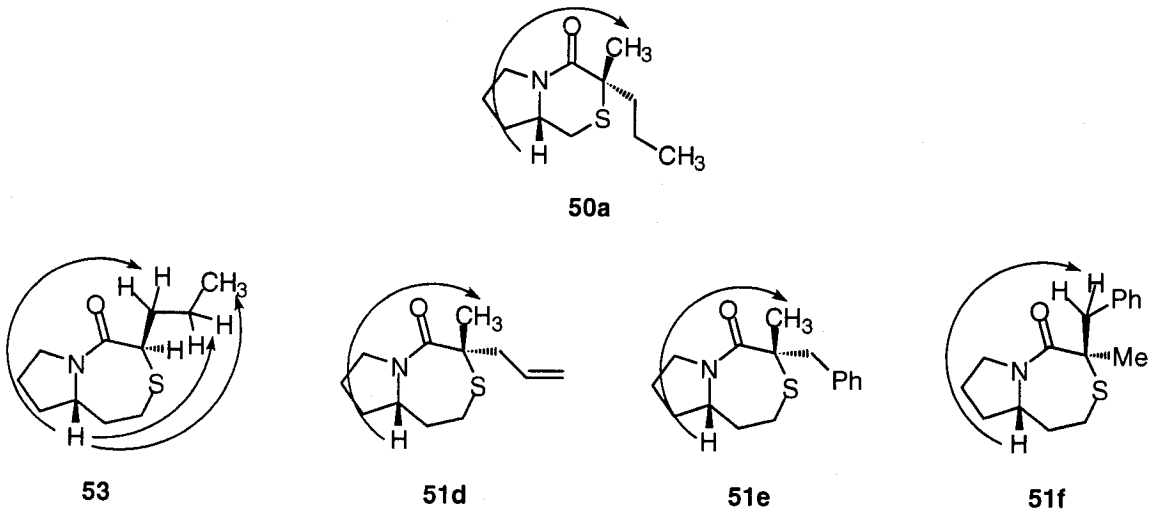
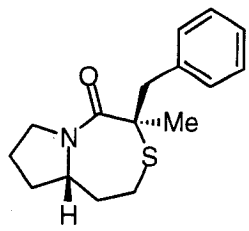


Figure 4. Observed NOE enhancements in 5,6– and 5,7–bicyclic thioglycolate lactams.



51f

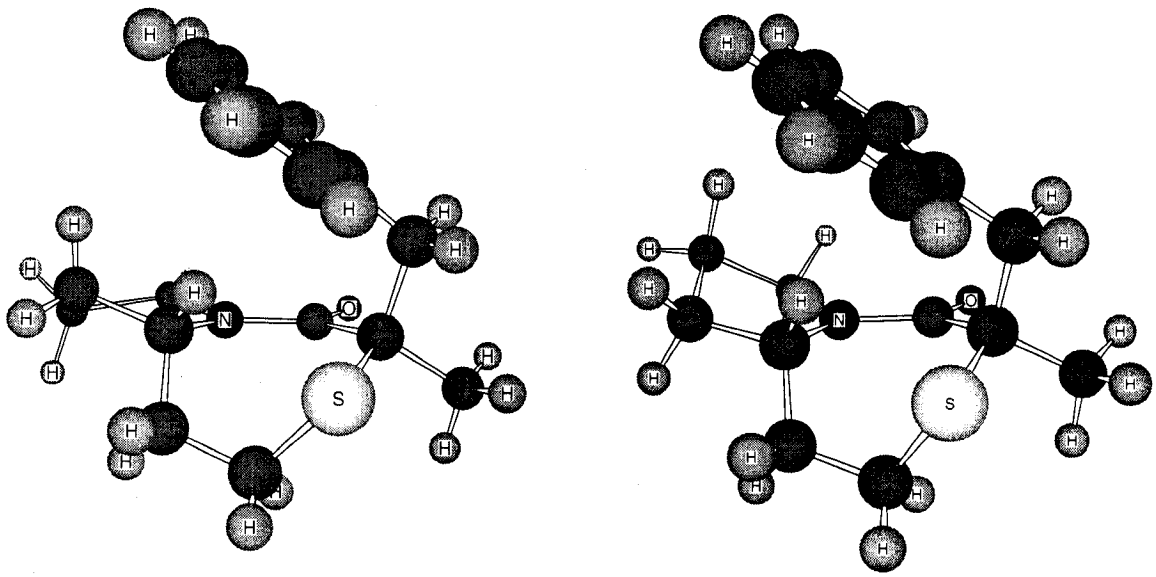


Figure 5. X-ray crystal structure (left) and MM2-predicted conformation of the ground state (right) of bicyclic thioglycolate lactam **51f**.

It is very interesting to note the similarity between the X–ray structure (Figure 5, left) and the ground state conformation of **51f** predicted by the MM2 force field (Figure 5, right). In both cases the conformation of the seven-membered ring is very similar and the phenyl group is positioned over the bicycle. The only significant difference between the two structures in the envelope conformation of the five-membered ring. However, of crucial importance is that the O–C–C–S dihedral angle is highly similar between the two structures (X-ray: 156.6°, MM2: 153.3° (N.B. The dihedral angles listed in Figure 3 and

Table 1 are the weighted average (Boltzmann distribution) of all conformations within 2 kcal/mole of the ground state)). It is important to point out that the X–ray structure is a solid-state structure and the MM2–predicted structure is a gas–phase structure. The crucial reduction process occurs in between the two states, in the solution phase. Nevertheless, the homology of these two structures provided evidence that gave higher confidence in our MM2 calculations.

Alkylations of our last system, 6,7–lactam **34**, produced some intriguing results. Curiously, the initial alkylation of lactam **34** would occur on the exo-face of the bicycle with moderately good diastereoselectivity while the second alkylation usually occurred on the endo-face of the bicycle with low diastereoselectivity. The outcome of the alkylation was determined by NOE enhancements (Figure 6). Although the diastereomeric excesses of lactams of type **52** were low, the diastereomers were separable by flash column chromatography. Hence, these substrates could still be used in the investigation of *E/Z* selectivity in the reductive enolization step. Unfortunately, the low diastereoselectivity of the alkylations did not lend itself well to making **34** a good, general chiral auxiliary for this project. Nevertheless, the reductive enolizations of lactams **52a**, **52b**, **52e** and **52f** were examined.

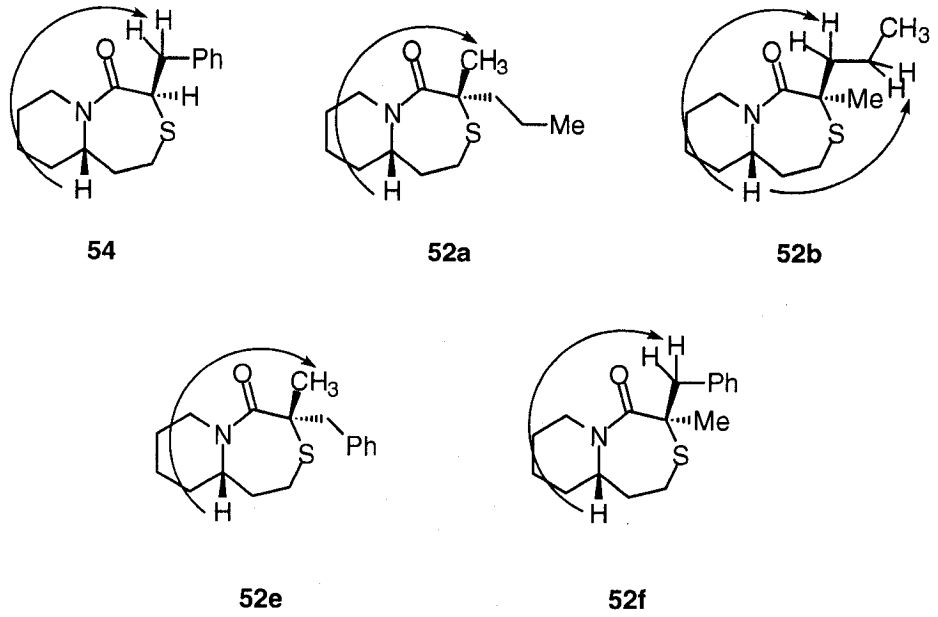


Figure 6. NOE enhancements observed in 6,7–bicyclic thioglycolate lactams.

2.6 REDUCTIVE ENOLIZATION AND TRAPPING OF BICYCLIC α,α–DISUBSTITUTED α–THIOGLYCOLATE LACTAMS

Having prepared all of the lactams listed in Table 1, an investigation of their reductive enolization was undertaken. The plan was to generate the α,α–disubstituted enolates, trap them as the corresponding silyl ketene aminals and examine their *E/Z* ratios by NMR. Careful consideration was given to the experimental conditions under which the enolizations would be carried out. The initial plan, which was developed during the early stages of the development of this project, was to use lithium in liquid ammonia as the reduction conditions. While this technique may be more useful and practical on large scale, particularly process scale, it was felt the ability of ammonia to act as a nucleophile toward trapping agents and the potential for it to quench the enolates via proton transfer

might present problems in the study. Various aromatic compounds are known in the literature for their ability to accept an electron from an alkali metal, forming a radical anion and subsequently transfer the electron to a substrate. Among the aromatic compounds known to form relatively stable radical anions are naphthalene,[27] 1–(*N*,*N*–dimethylamino)naphthalene,[28] anthracene,[29] and 4,4′–di–*tert*–butylbiphenyl.[30] These aromatic reagents can be used stoichiometrically or catalytically. Moreover, these aromatic-based radical anions can be used in THF, a useful solvent for manipulating (*e.g.* trapping) enolates.[31]

For the purposes of this study, lithium 4,4′–di–*tert*–butylbiphenylide (LDBB)[30a–d] was selected as the reducing agent of choice. It has higher stability than other one-electron transfer reagents and as such could be prepared in large batches and readily stored for several weeks at a time. This was highly advantageous in terms of efficiency.

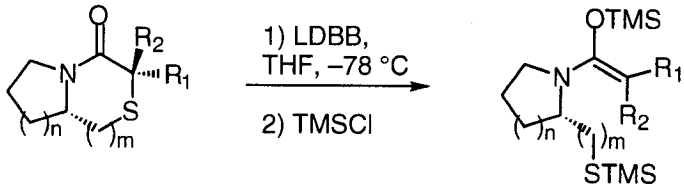
Careful consideration was also given to the manner in which the reduction was to be carried out. The reduction could be carried out by adding LDBB to a solution of the lactam ("normal addition") or vice versa ("inverse addition"). Inverse addition would require the titration of the LDBB solution,[32] while normal addition would see the lactam reduced titrametrically by the LDBB. Thus, normal addition was chosen for the sake of greater convenience.

The manner in which the enolate ratio was to be examined was also considered. It was believed that ^{1}H and ^{13}C NMR spectroscopy on the silyl ketene aminals would be the most informative techniques. Woodbury and Rathke[31] observed great difficulty in trapping amide enolates with TBSCl (ten hours in THF at room temperature in the presence of HMPA). In contrast, Woodbury and Rathke found that trimethylsilyl

chloride (TMSCl) was a useful reagent for trapping amide enolates in less than one hour, starting at –78 °C and warming to room temperature. For this reason TMSCl was selected as the trapping agent for our experiments.

The best reduction and trapping conditions for this investigation were to slowly add a solution of the radical anion LDBB in THF to a THF solution of the lactam at –78 °C until the dark green colour of the LDBB solution persisted. Then excess trimethylsilyl chloride (three equivalents) was added to the solution of dianion. After ten minutes at –78 °C the cooling bath was removed and stirring was continued for another 30 minutes. After 30 minutes, the solvent was pumped off from the reaction. After sufficient drying time (approximately two hours), benzene-d_6 was added and the mixture was stirred for 10 minutes. After allowing 5 minutes for settling of the residual solids to occur, the supernatant layer was transferred to an argon-purged NMR tube via syringe. This technique allowed for isolation of the silyl ketene aminals in such a manner that they were stable for approximately one week without detectable decomposition. The results of our reductive enolization survey using the enolization, trapping and isolation technique described above are shown in Table 2. With only one exception (lactam **51d**) all of the lactams reduced and trapped smoothly. In all cases, several peaks were useable for integration of the ^{13}C signals to determine the *E:Z* ratio. Unfortunately, ^{1}H NMR could not be used for quantitation. However, we were able to use ^{1}H NMR to assign *E*- or *Z*-stereochemistry to the major enolates in solution (*vide infra*).

Table 2. Reductive enolization of bicyclic thioglycolate lactams.



n	m	lactam	R_1	R_2	Z/E[a]	O-C-C-S[b]	lactam	R_1	R_2	Z/E[a]	O-C-C-S[b]
1	1	**50a**	*n*-Pr	Me	48:52	174	**50b**	Me	*n*-Pr	64:36	182
1	1	**50c**	Allyl	Me	43:57	175	**50d**	Me	Allyl	68:32	178
1	2	**51a**	*n*–Pr	Me	87:13	141	**51b**	Me	*n*–Pr	20:80	128
1	2	**51c**	Allyl	Me	87:13	140	**51d**	Me	Allyl	26:74[c]	138
1	2	**51e**	Bn	Me	92:8	145	**51f**	Me	Bn	12:88	149
1	2	**51g**	*n*–Pr	Et	80:20	139	**51h**	Et	*n*–Pr	12:88	137
1	2	**51i**	Et	Me	90:10						
1	2	**51j**	*n*–Bu	Me	n.d.						
2	2	**52a**	*n*–Pr	Me	83:17	140	**52b**	Me	*n*–Pr	37:63	133
2	2	**52e**	Bn	Me	92:8	143	**52f**	Me	Bn	53:47	139

[a]Enolate Ratios determined by integration of ^{13}C resonances. [b]Weighted Average (calculated at -78 °C) Dihedral Angle of all conformations within 2 kcal/mole of the ground state as determined by Monte Carlo calculations. [c]Reduction of **51d** produced a byproduct (ca. 30%) that could not be fully characterized.

As expected, the 5,6-lactams of type **50** afforded poor *E/Z* selectivity. The O–C–C–S dihedral angle of almost 180° in the 5,6-lactams of type **50** positions the oxygen between the two alkyl groups (Figure 7). It was expected that this would lead to an almost equal distribution of *E*– and *Z*–enolates upon cleavage of the carbon-sulfur bond. The series of lactams **50** did however demonstrate a small switch in the major isomer formed when the stereochemistry of the α–carbon was inverted. Although not a clear proof of principle, it does indicate that there is some correlation between geometry

and stereochemistry of the starting material and the stereochemistry of the α,α–disubstituted enolate.

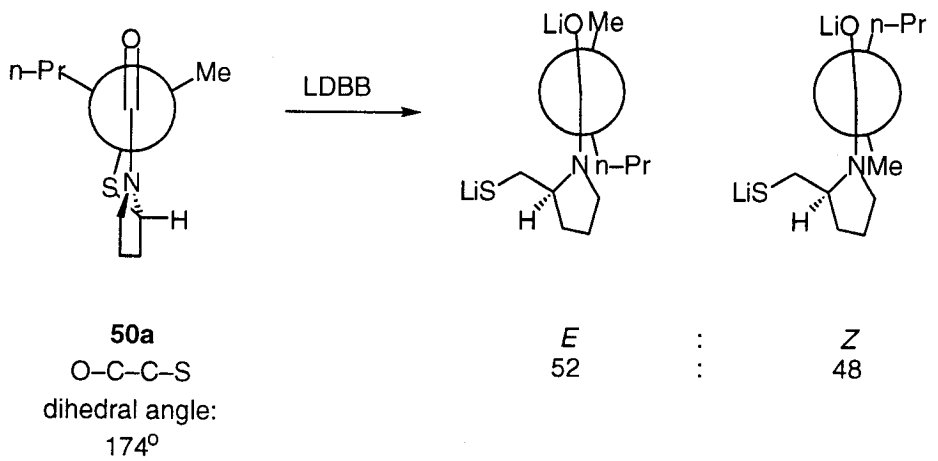
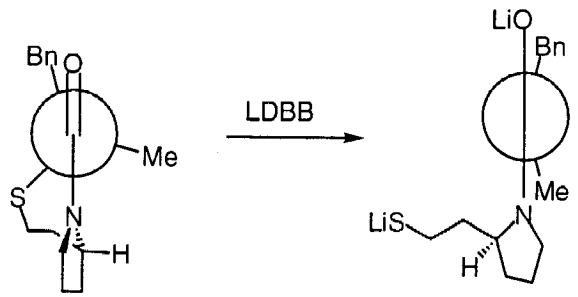


Figure 7. Three-dimensional representation of the reductive enolization of lactam **50a**.

Gratifyingly, reduction of 5,7-lactams led to formation of α,α–disubstituted enolates with high levels of *E*/*Z* stereocontrol. Moreover, we observed that inversion of stereochemistry of the α–carbon of the lactam led to a switch in the major enolate formed. This constituted a clear proof-of-principle for our enolization strategy. We demonstrated, for the first time, the ability to kinetically control enolate geometry in the reductive generation of acyclic α,α–disubstituted enolates. These results clearly show that when certain geometric constraints are employed, it is possible to translate the stereochemistry of the α–carbon of the starting material to the stereochemistry of an acyclic enolate.

A very clear pattern was observed in the reduction of the 5,7-lactams. Those substrates in which the smaller of the two alkyl groups was installed in the second alkylation afforded predominantly the *Z*–enolate. Those substrates in which the larger of

the two alkyl groups was installed in the second alkylation afforded predominantly the *E*–enolate. This meant that the alkyl group installed in the first alkylation was consistently positioned *syn* to the oxygen of the silyl ketene aminal and the alkyl group installed in the second alkylation was consistently positioned *syn* to the nitrogen of the silyl ketene aminal (Figure 8).



51e

Figure 8. Positioning of the alkyl groups and dihedral angle of lactam **51e** translating to enolate geometry.

The inverse addition enolization technique was examined using lactam **51f**. While addition of LDBB to a solution of the lactam afforded a 12:88 *Z:E* ratio of enolates, the alternative technique of addition of a solution of the lactam to LDBB afforded a 20:80 *Z:E* ratio of enolates. The inverse addition reduction technique was not pursued any further due to the fact that it did not offer any improvement in the enolate ratio and it was more tedious to set up.

It is very interesting to note that after significant emphasis was placed on dihedral angle, the series of compounds in which the dihedral angle was smaller (i.e. closer to 90°) often afforded poorer *E/Z* selectivity. For example, lactam **51a** has a weighted average O–C–C–S dihedral angle of 141° and affords a *Z:E* ratio of 87:13. Meanwhile, diastereomeric lactam **51b** has a smaller O–C–C–S dihedral angle (128°) but affords a

Z:E ratio of 20:80. The best hypothesis that can be put forward at this time is that the species undergoing α–carbon-sulfur bond cleavage has a different conformation than the unreduced material.

The 6,7-lactams (**52** series) produced an interesting series of results. Lactams **52a** and **52e** correlated well with their 5,7-lactam counterparts **51a** and **51e**, affording primarily *Z*–enolates in 83:17 and 92:8 *Z:E* ratios respectively. The attempted formation of *E*–enolates via reduction of lactams **52b** and **52f** resulted in poor *E/Z* selectivity. Reduction of lactam **52f** actually afforded a small excess of the *Z*–enolate. This may arise from increased flexibility of the 6,7-ring system, leading to potentially different conformations of the starting lactam and the intermediate radical-anions.

The assignment of *E*– and *Z*–enolate geometries was accomplished using NOE experiments on the trapped enolates derived from lactams **51e**, **51f**, **51g**, and **51h**. The observed enhancements are shown below in Figure 9. Importantly, all observed NOE enhancements were bi-directional. The remaining silyl ketene aminals were assigned by analogy. A noteworthy trend was observed in the ^{13}C NMR resonances of the silyl ketene aminals. The carbons of the *Z*–silyl ketene aminal were more shielded than those of the *E*–silyl ketene aminal. The only exception to this was the C_1-signal of the silyl ketene aminals obtained by reduction and trapping of lactams **51g** and **51h**, where the signal did not resolve.

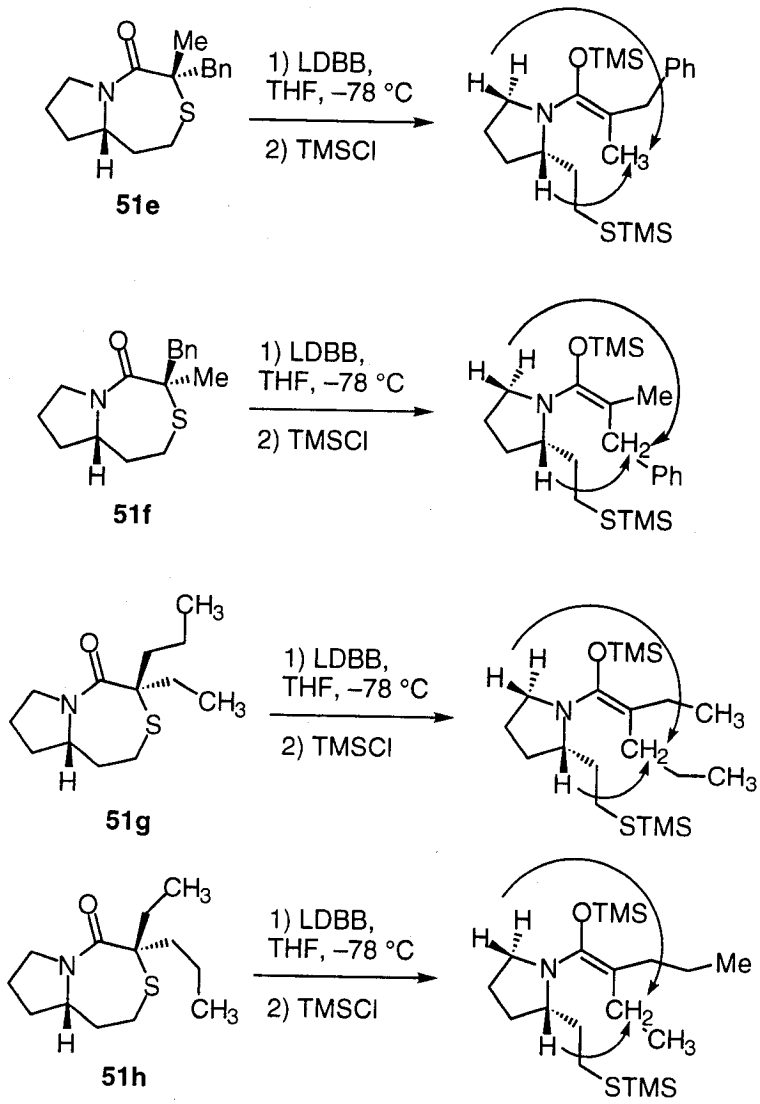


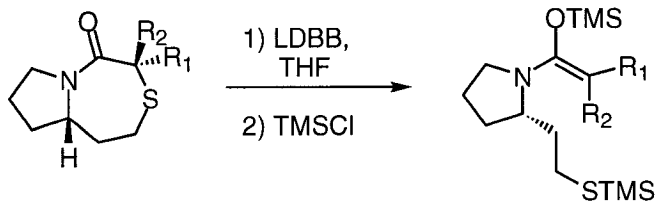
Figure 9. Observed NOE enhancements in the trapped enolates of bicyclic thioglycolate lactams.

These results demonstrate for the first time that the *E/Z* geometry of enolates can be controlled by employing certain geometric constraints in the starting material and constitute a proof of principle for one of the two major goals of this research project. A communication detailing the results of this study has been published.[33]

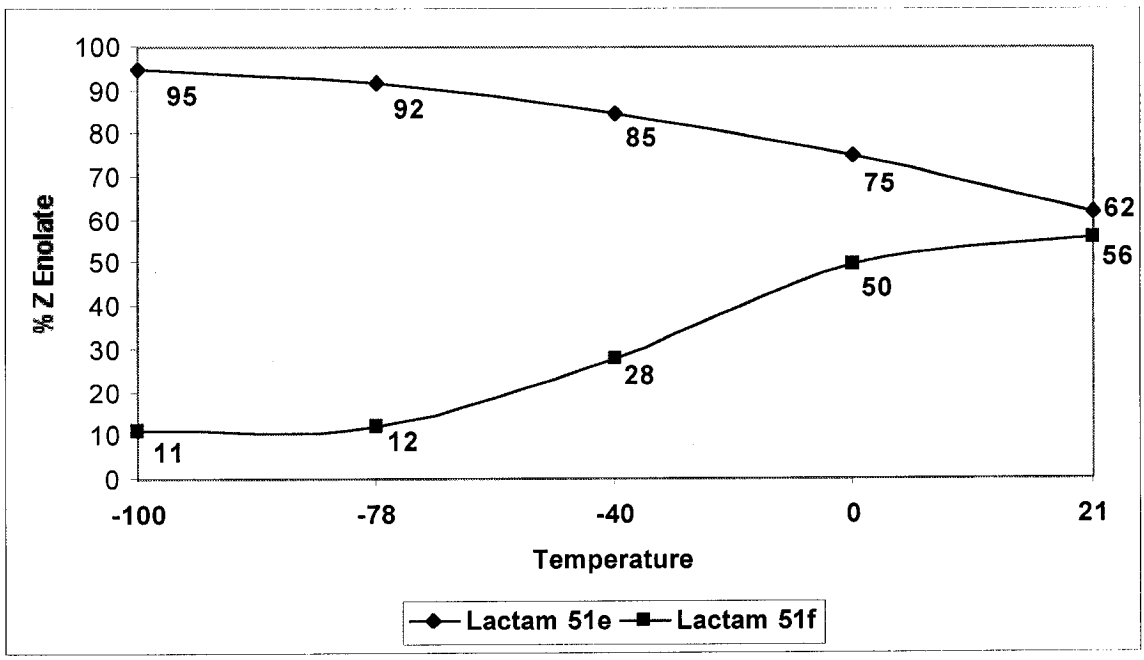
2.7 TEMPERATURE EFFECTS IN THE REDUCTIVE FORMATION OF α,α–DISUBSTITUTED ENOLATES

In an attempt to discover the thermodynamic *E/Z*–ratio of these α,α–disubstituted enolates, it was decided to investigate the effect of temperature on the reduction of diastereomeric α–thioglycolate lactams **51e** and **51f**. These experiments would also serve to investigate the thermal stability of these highly strained α,α–disubstituted enolates. The results of this temperature survey are shown below (Table 3).

Table 3. The effect of temperature on the *E/Z*–ratio of enolates generated by reduction of thioglycolate lactams **51e** and **51f**.



	Temperature				
	-100 °C	-78 °C	-40 °C	0 °C	21 °C
R_1= Bn R_2= Me (**51e**) *Z:E* Ratio	95:5	92:8	85:15	75:25	62:38
R_1= Me R_2= Bn (**51f**) *Z:E* Ratio	11:89	12:88	28:72	50:50	56:44



The results in Table 3 demonstrate a clear diminution of *E/Z* selectivity in enolate generation as the temperature increases. It is interesting to note that even at room temperature there is not a complete convergence of the enolate ratios. However, lactam

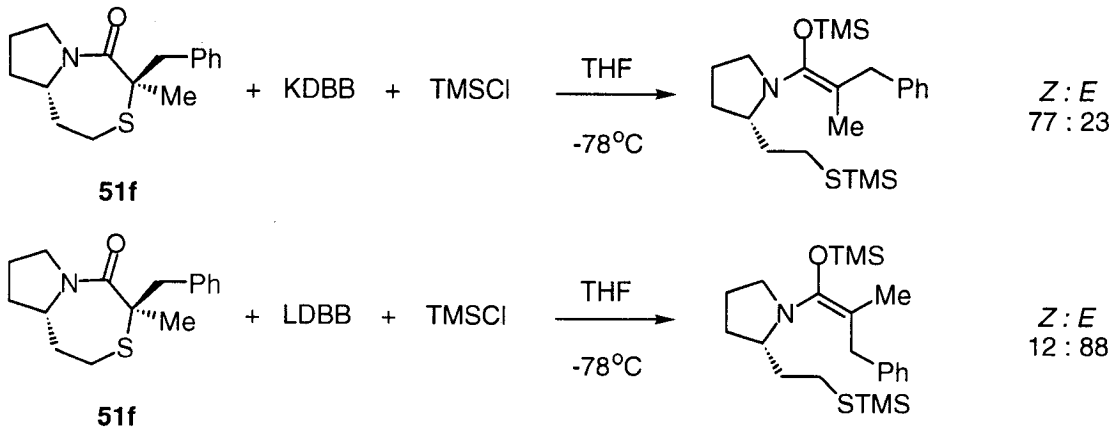
51f does afford primarily the *Z*–enolate at room temperature, contrary to lower temperature results. Ultimately, there is a clear trend toward a thermodynamic *Z:E* ratio of approximately 60:40. It is to be expected that the *Z*–enolate would be thermodynamically favoured. The positioning of the methyl group cis to the silyl ketene aminal nitrogen affords less $A^{1,3}$–strain than the benzyl group affords in the *E*–enolate.

2.8 USE OF OTHER REDUCING AGENTS FOR THE FORMATION OF α,α–DISUBSTITUTED ENOLATES FROM α–THIOGLYCOLATE LACTAMS

In another attempt to increase the selectivity in the generation of *E*–enolates, the use of potassium 4,4´–di–*tert*–butylbiphenylide (KDBB)[30e,f] and samarium diiodide in the reductive enolization were investigated. It was felt that perhaps a change in metal ion would have some subtle effect on the reduction. Potassium enolates are known to be far less aggregated than their lithium counterparts[34] and potassium is much less oxophilic.[35] Samarium diiodide is also a very common one-electron transfer reagent.[36] For the sake of consistency, lactam **51f** was again used as the substrate for this procedure.

Upon (normal addition) reduction of lactam **51f** with KDBB at –78 °C and trapping with TMSCl the silyl ketene aminal formed was found to have a *Z:E* ratio of ***77:23*** (Scheme 50)! This is in contrast to the same reduction and trapping using LDBB; which afforded a ***12:88*** ratio! Needless to say, this was a completely unexpected outcome. At this point, little can be offered to explain this result beyond the statement that this result is likely due to decreased oxophilicity of potassium and decreased aggregation state. It is possible that the lower oxophilicity of potassium may change the

mechanism of the reductive enolization process. It is unlikely that the potassium enolates are undergoing *E/Z* equilibration. Although potassium enolates are known to equilibrate more readily and rapidly than lithium enolates,[37] it is unlikely that the thermodynamic equilibrium of the potassium enolates would be so far removed from the equilibrium point of 60:40 (*Z:E*) found for the corresponding lithium enolates.



Scheme 50. The effect of the metal ion on *E:Z* ratio in the reductive enolization of α–thioglycolate lactam **51f**.

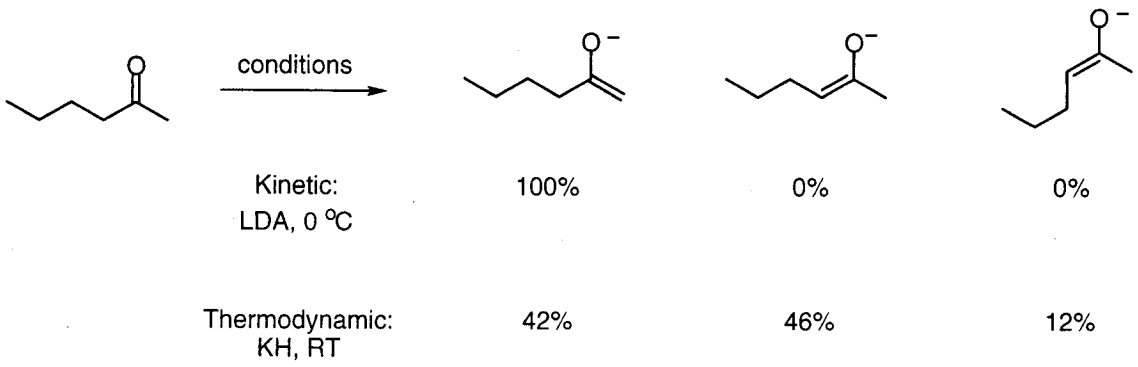
Samarium diiodide was also investigated as a potential reducing agent for reductive enolization of our lactams. However, it proved to have insufficient reduction potential to carry out this reductive enolization.

2.9 ENOLATE *E/Z* EQUILIBRATION

An important issue in enolate chemistry is *E/Z* equilibration. Because this was the first time that acyclic α,α–disubstituted amide enolates (in particular, the highly strained acyclic α,α–disubstituted ***E***–amide enolates) were being generated, probing the rate of enolate equilibration was deemed to be important. Moreover, some unusual results in the alkylation of our α,α–disubstituted *E*–enolates (*vide* Chapter 3) prompted us to investigate the possibility of enolate equilibration. The startling results obtained by reduction of lactam **51f** with KDBB placed further importance on investigating the rate of *E/Z* equilibration in this system. Again, lactam **51f** was chosen as the substrate for this experiment. It affords predominantly the more strained *E*–enolate in with a high 88:12 ratio, making observation of any diminution of the *E/Z* enolate ratio more readily observable.

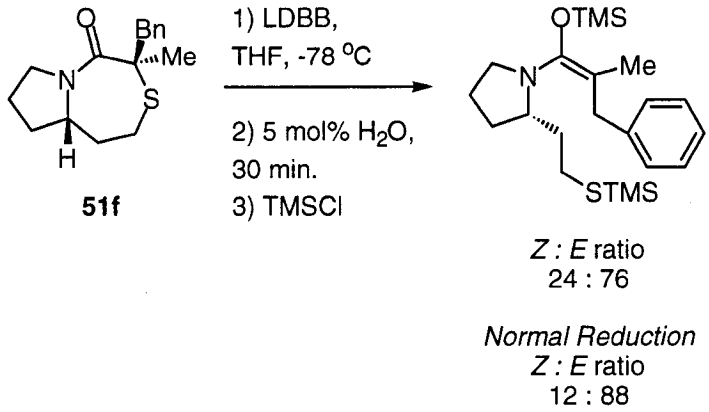
This experiment is derived from the analogy of ketone enolates, where it is known that the presence of a proton source can lead to the regiochemical and/or stereochemical equilibration of enolates. For example, deprotonation of 2–hexanone with LDA at 0 °C (kinetic conditions- low temperature, excess base) leads to the formation of the less substituted enolate. Conversely, the use of thermodynamic conditions (excess ketone, room temperature) leads to the predominant formation of the more substituted enolate (Scheme 51).[34c] Under thermodynamic conditions, equilibration occurs via transfer of a proton from a ketone molecule to an enolate, generating a new enolate and reforming a molecule of ketone. Eventually, the system reaches an equilibrium state that typically favours the more substituted enolate. Our reductive enolization conditions lead to the

formation of the kinetic enolate. However, it is possible that the presence of a small amount of a proton source (*e.g.* adventitious water) may lead to *E/Z* enolate equilibration.



Scheme 51. Kinetic versus thermodynamic formation of enolates from 2-hexanone.

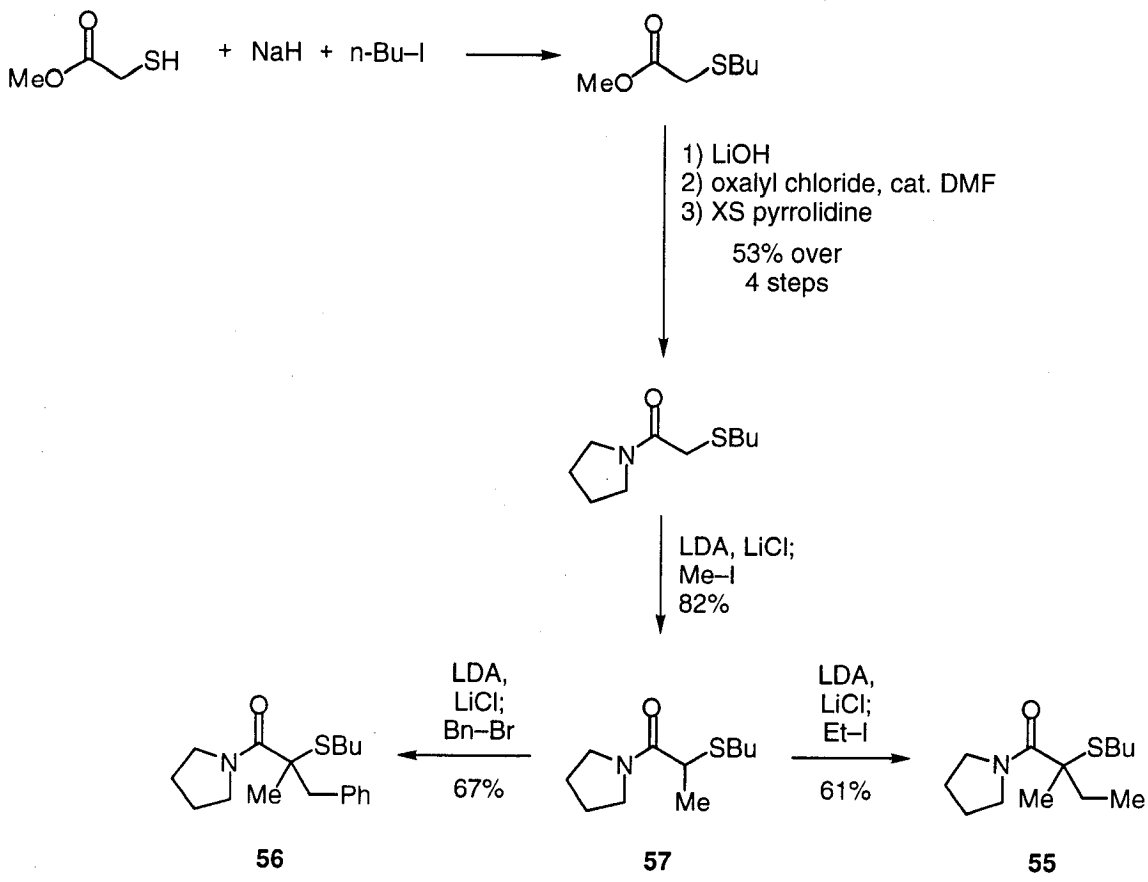
In this experiment (Scheme 52), the reductive enolization of **51f** was performed under standard conditions (titration of lactam with LDBB at –78 °C) and then 5 mol% of water was added to partially protonate the enolate mixture. After stirring at –78 °C for 30 minutes, distilled TMSCl was added. As per usual, stirring was continued at –78 °C for 10 minutes after the addition of TMSCl, then the cooling bath was removed and stirring was continued for 30 minutes. After removal of the volatiles, integration of the ^{13}C NMR spectrum showed a 24:76 ratio of enolates, still in favour of the thermodynamically less stable *E*–enolate; thus indicating that *E/Z* isomerization of this enolate (and presumably other enolates generated by this technique) is a slow process at –78 °C, even in the presence of a significant amount of a proton source. If enolate equilibration were a more rapid process in this system, an enolate ratio of 60:40 in favour of the *Z*–enolate would be expected, as determined by the temperature experiments (*vide supra*).



Scheme 52. Equilibration of enolates in the presence of a catalytic amount of water.

2.10 AN ACYCLIC CONTROL SYSTEM

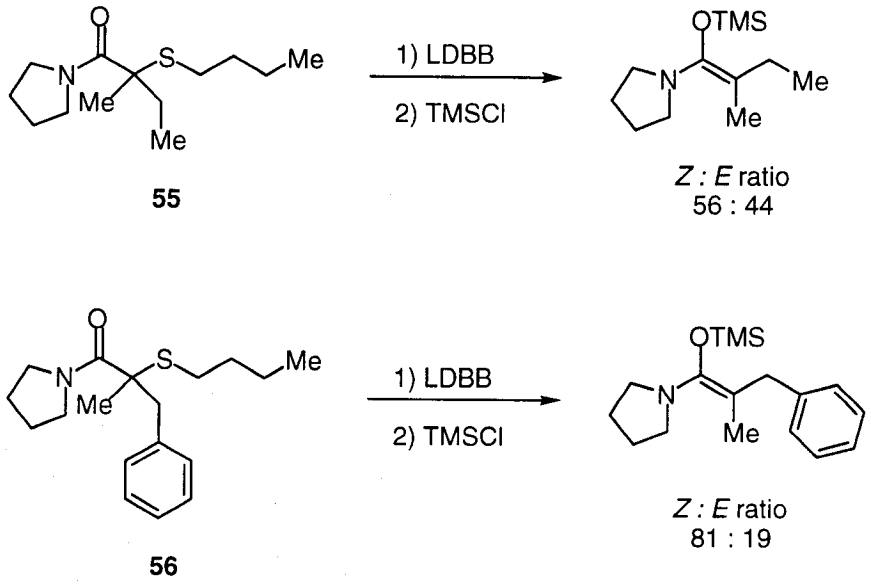
In addition to lactams **50a** – **50d**, it was felt that an acyclic control system would be beneficial and informative. We sought to use a system similar to our bicyclic thioglycolate lactams yet not containing the lactam ring. Therefore α–thio pyrrolamides were selected as the substrate for this model study. It was decided that two substrates should be used; one in which the α–carbon substituents were of similar steric size and another in which one of the two alkyl groups substituting the α–carbon had considerably more steric demand. Amides **55** and **56** were prepared from methyl thioglycolate (Scheme 53). The successful deprotonation and alkylation of amide **57** is likely due to the small steric size of the sulfur substituent. Recall that deprotonation of an α,α–dialkyl amide requires rather forcing conditions (*vide supra*). The conditions used here were intermediate between those used for a typical α–monoalkyl amide and an α,α–dialkyl amide.



Scheme 53. Preparation of α,α–disubstituted α–thio pyrrolamide control substrates.

Upon reductive enolization and trapping (Scheme 54), amide **55** afforded a 56:44 *Z*:*E* ratio.[38] By comparison, amide **56** afforded a startlingly high *Z*:*E* ratio of silyl ketene aminals of 81:19. Thus, when the difference in steric demand between the substituents on the α–carbon is small (Me versus Et) there is virtually no *E*/*Z* stereocontrol in the reductive enolization. This clearly demonstrates that the geometric constraints provided by the lactam ring are a necessity to obtain *E*/*Z* stereocontrol in this reductive enolization process. The moderate selectivity in the reduction of amide **56** demonstrates that it is possible to obtain some degree of *E*/*Z* stereocontrol when there is a large difference in steric demand between the substituents on the α–carbon. However, the goal of this work

was to develop a general method that did not rely upon large steric differences between the α–carbon substituents to obtain *E/Z* stereocontrol.



Scheme 54. The reductive enolization and trapping of amides **55** and **56**.

2.11 CONCLUSIONS

Having prepared a series of α,α–disubstituted α–thioglycolate lactams, we demonstrated for the first time that it is possible to influence *E/Z* ratio of enolates in a reductive enolization process by employing certain geometric and stereochemical constraints. It was shown that under kinetic conditions, we could produce either *Z*– or *E*–α,α–disubstituted amide enolates simply by inverting the alkylation order in the preparation of the requisite α,α–disubstituted α–thioglycolate lactams. We also demonstrated that we could reliably produce acyclic *E*–amide enolates, something that cannot be accomplished using other methodologies.

By varying the temperature at which the reductive enolization was performed, we were able to demonstrate that the selectivity observed in the enolization at lower temperatures is indeed a kinetic effect. By increasing the enolization temperature, a trend toward a thermodynamic product mixture was observed.

It was also demonstrated that the reductive enolization technique and the metal ion of the reducing agent are of paramount importance in the enolization process. While the reduction technique had a small effect on the *E/Z* ratio of the enolates, the metal ion was shown to have a dramatic effect on the *E/Z* ratio, resulting in a switch of the major enolate formed.

Furthermore, it was demonstrated that enolate equilibration is a slow process at –78 °C. This has important implications for reactions that require longer timeframes to reach completion.

Lastly, by reducing acyclic α,α–disubstituted α–thio amides, we demonstrated that the lactam ring is indeed required to obtain usable levels of *E/Z* selectivity in the reductive formation of α,α–disubstituted enolates when there is a small steric difference between the alkyl groups on the α–carbon. If this method is to be a general technique for the preparation of α,α–disubstituted enolates and asymmetric quaternary carbons, these high levels of *E/Z* selectivity are required.

---

[1] For reviews see a) Fürstner, A. *Synthesis*, **1989**, 571; b) Rathke, M.W. *Org. React.* **1975**, *22*, 423; c) Gaudemar, M. *Organomet. Chem. Rev. Sect. A* **1972**, *8*, 183.

[2] Smith, M.B.; March, J. *March's Advanced Organic Chemistry*; Wiley: Toronto, **2001**, p. 1212.

[3] a) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979 and references cited therein; b) Stork, G.; Rosen, P.; Goldman, N.L. *J. Am. Chem. Soc.* **1961**, *83*, 2965; c) Stork, G.; Darling, S.D. *J. Am. Chem. Soc.* **1964**, *86*, 1761; d) Balme, G. *Tetrahedron Lett.* **1985**, *26* 2309.

[4] a) Akhrem, A.A.; Reshotova, I.G.; Titov, Yu.A. *Birch Reduction of Aromatic Compounds*; Plenum: New York, **1972**; For reviews see: b) Birch, A.J. *Pure Appl. Chem.* **1996**, *68*, 553; c) Rabideau, P.W. *Tetrahedron* **1989**, *45*, 1579; d) Birch, A.J.; Subba Rao, G. *Adv. Org. Chem.* **1972**, *8*, 1; d) Kaiser, E.M. *Synthesis* **1972**, 391; e) Harvey, R.G. *Synthesis* **1970**, 161.

[5] a) Schultz, A.G. *Chem. Commun.* **1999**, 1263; b) Schultz, A.G. *Acc. Chem. Res.* **1990**, *23*, 207; c) Schultz, A.G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855; d) Schultz, A.G.; Macielag, M.; Sunderarараman, P.; Taveras, A.G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

[6] Kamata, S.; Uyeo, S.; Haga, N.; Nagata, W. *Synth. Commun.* **1973**, *3*, 265.

[7] The quasi-halogen nature of nitriles necessitated that the reductive enolization be carried out in THF using stoichiometric lithium and catalytic amounts of naphthalene or trimesitylborane. Reduction in liquid ammonia led to a variety of products including reductive loss of the nitrile group.

[8] Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* **1977**, *42*, 2038 and references cited therein.

[9] a) Holy, N.L. *Chem. Rev.* **1974**, *74*, 243; b) Truce, W.E.; Tate, D.P.; Burdge, D.N. *J. Am. Chem. Soc.* **1960**, *82*, 2872; c) Screttas, C.G. *J. Chem. Soc. Chem. Comm.* **1972**, 809.

[10] a) Wu, L.; Fischer, H. *Helv. Chim. Acta* **1983**, *66*, 138; b) Camaioni, D.M.; Walter, H.F.; Jordan, J.E.; Pratt, D.W. *J. Am. Chem. Soc.* **1973**, *95*, 7978; c) Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379.

[11] This principle states that "those elementary reactions will be favoured that involve the least change in atomic position and electronic configuration." a) Hine, J. *J. Org. Chem.* **1966**, *31*, 1236; b) For a review of this principle see Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1.

[12] 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.

[13] Ishibashi, H.; Uegaki, M.; Sakai, M. *Synlett* **1997**, 915.

[14] The current Aldrich Chemical, Canada price of (*S*)-pipecolic acid is $67.90 for 100 mg.

[15] For references on the rates of ring formations see a) Illuminati, G.; Mandolino L. *Acc. Chem. Res.* **1981**, *14*, 95 and references cited therein; b) Winnik, M.A. *Chem. Rev.* **1981**, *81*, 491 and references cited therein.

[16] a) Ardnt, F.; Eistert, B.; Partale, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1364; b) Ye, T.; McKervey, M.A. *Chem. Rev.* **1994**, *94*, 1091. For previous preparations of **D35** see c) Pluciñska, K.; Liberek, B. *Tetrahedron* **1987**, *43*, 3509; d) Cassal, J.M.; Fürst, A.; Meyer, W. *Helv. Chim. Acta* **1976**, *59*, 1917, e) Ye, J.; McKervey, M.A. *Tetrahedron*, **1992**, *48*, 8007.

[17] Guibourdenche, C.; Podlech, J.; Seebach, D. *Liebigs Ann.* **1996**, 1121.

[18] Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4461.

[19] Newman, M.S.; Beal, P.F., III *J. Chem. Soc.* **1950**, *72*, 5163.

[20] Meienhofer, J.; Kuromizu, K. *Tetrahedron Lett.* **1974**, 3259.

[21] Bodanszky and Bodanszky recommend the use of palladium on barium sulfate for the hydrogenolysis of Cbz groups from methionine-containing peptides. See Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis* (2nd Edition); Springer: New York, **1994**, p.131 and references cited therein.

[22] Felix, A.M. *J. Org. Chem.* **1974**, *39*, 1427.

[23] Pless, J.; Bauer, W. *Angew. Chem. Int. Ed. Eng.* **1973**, *12*, 147.

[24] For a review of the Swern and related activated DMSO oxidations see Tidwell, T. *Org. React.* **1990**, *39*, 297.

[25] The current price of 25 g racemic 2-(2-piperidine)ethanol from Aldrich Chemical Co. is $69.60.

[26] a) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163; b) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, *1465*; c) Mukaiyama, T. *Angew. Chem. Int. Ed. Eng.* **1979**, *18*, 707.

[27] For lithium naphthalenide 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 naphthalenide 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 naphthalenide see c) Merrill, B.A. In *Encyclopedia of Reagents for Organic Synthesis*. (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 4269 and references cited therein.

[28] Ferguson, M.D. In *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 3104 and references cited therein.

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

[30] For references on LDBB see: a) Freeman, P.K.; Hutchinson, L.L. *Tetrahderon Lett.* **1976**, 1849; b) Freeman, P.K.; Hutchinson, L.L. *J. Org. Chem.* **1980**, *45*, 1924; c) Ferguson, M.D. In *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 3076 and references cited therein; d) Donohoe, T.J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015. For references on KDBB (potassium 4,4'–di–*tert*–butylbiphenylide) see: e) Karaman, R.; He, G.-X.; Chu, F.; Blaskó, A.; Bruice, T.C. *J. Org. Chem.* **1993**, *58*, 438; f) Karaman, R.; Kohlman, D.T.; Fry, J.L. *Tetrahedron Lett.* **1990**, *31*, 6155.

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

[32] For a method of titration of lithium naphthalenide see Screttas, C.G.; Micha-Screttas, M. *J. Organomet. Chem.* **1983**, *252*, 263.

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

[34] For references on enolate aggregation see a) Seebach, D. *Angew. Chem. Int. Ed. Eng.* **1988**, *27*, 1624 and references cited therein; b) Boche, G. *Angew. Chem. Int. Ed. Eng.* **1989**, *28*, 277 and references cited therein; c) Caine, D. In *Carbon-Carbon Bond Formation.* (Augustine, R.L. Editor) Marcel Dekker: New York, **1979**, p. 85-352 and references cited therein; d) Jackman, L.M.; Lange, B.C. *Tetrahedron* **1977**, *33*, 2737; e) Evans, D.A. In *Asymmetric Synthesis.* (Morrison, J.D. Editor) Academic: Orlando, **1984**,

vol. 3, p. 1-110 and references cited therein; f) Williard, P.G.; Hintze, M.J. *J. Am. Chem. Soc.* **1990**, *112*, 8602; g) Arnett, E.M.; Fischer, F.G.; Nichols, M.A.; Ribiero, A.A. *J. Am. Chem. Soc.* **1990**, *112*, 801; h) Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* **1993**, *34*, 5213; i) Edwards, A.J.; Hockey, S.; Mair, F.S.; Taithby, P.R.; Snaith, R.; Simpkins, N.S. *J. Org. Chem.* **1993**, *58*, 6942. See also reference 3a.

[35] a) House, H.O.; Prabhu, A.V.; Phillips, W.V. *J. Org. Chem.* **1976**, *41*, 1209; b) Zook, H.D.; Grumby, W.L. *J. Am. Chem. Soc.* **1960**, *82*, 1386; c) Zook, H.D.; Russo, T.J. *J. Am. Chem. Soc.* **1960**, *82*, 1258; d) Zook, H.D.; Russo, T.J.; Ferrand, E.F.; Stotz, D.S. *J. Org. Chem.* **1968**, *33*, 2222; e) Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* **1968**, *33*, 3477; f) Zook, H.D.; Miller, J.A. *J. Org. Chem.* **1971**, *63*, 1112. See also reference 33d.

[36] Molander, G.A.; Harris, C.R. In *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 4428 and references cited therein.

[37] House, H.O.; Trost, B.M. *J. Org. Chem.* **1965**, *30*, 1341 and references cited therein.

[38] Assignments of these silyl ketene aminal geometries were made by analogy of their ^{13}C NMR spectra (enolate carbons) to the ^{13}C NMR spectra of the silyl ketene aminals generated by reduction of the corresponding lactams (**55**: **51i**; **56**: **51e** and **51f**).

CHAPTER THREE

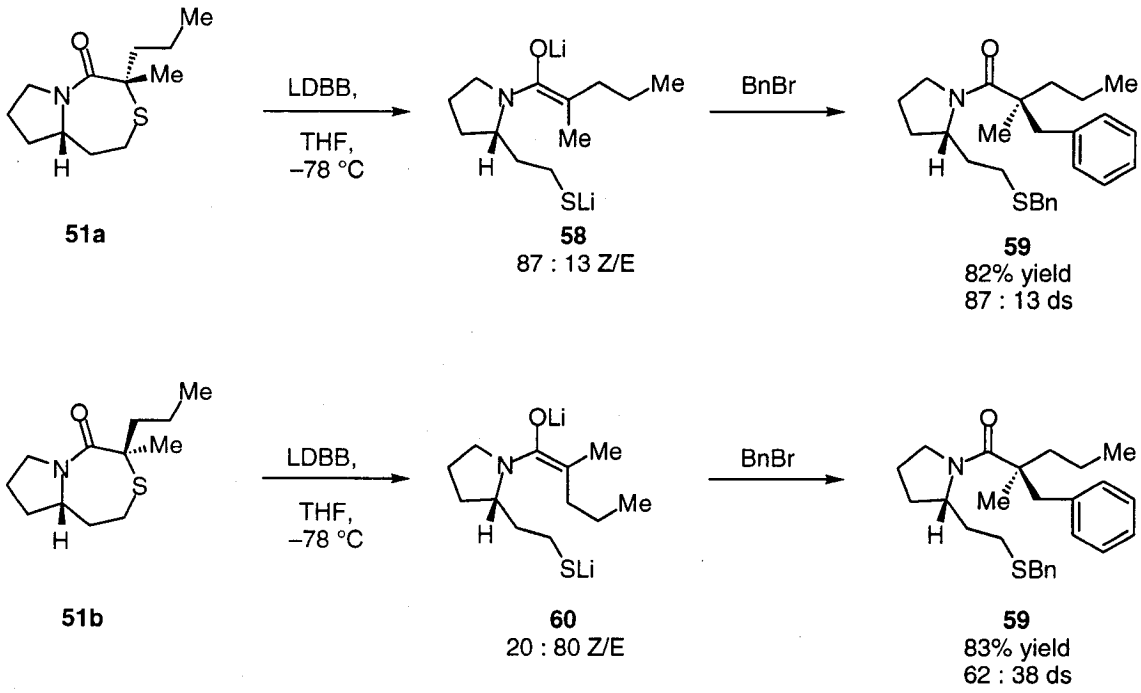
STEREOSELECTIVE ALKYLATION OF α,α–DISUBSTITUTED ENOLATES GENERATED BY REDUCTIVE ENOLIZATION OF α,α–DISUBSTITUTED α–THIOGLYCOLATE LACTAMS

3.1 INTRODUCTION

Chapter 2 detailed our success in the project's first phase, the stereocontrolled generation of α,α–disubstituted enolates. This Chapter will detail the second stage of the research, the stereoselective alkylation of the α,α–disubstituted enolates to form quaternary carbons in high diastereomeric excess. Because the ultimate goal of this research was a general, broad-scope method of asymmetric quaternary carbon synthesis, it was deemed necessary to be able to access both (*R*)– and (*S*)–configurations of the new quaternary centres. The final stage was to develop a method to efficiently remove the chiral auxiliary.

3.2 ALKYLATION OF α,α–DISUBSTITUTED ENOLATES WITH ACTIVATED ALKYL HALIDES

The initial alkylation experiments involved lactams **51a** and **51b**. These lactams were previously demonstrated to afford *Z:E* enolate ratios of 87:13 and 20:80, respectively. Upon alkylation with 3 equivalents of benzyl bromide, *Z*–enolate **58** afforded an 87:13 ratio of C,S–dialkylated quaternary carbon-containing adducts **59** (Scheme 55). Three equivalents of alkylating agent are required in this reaction because alkylations at carbon and sulfur occur at comparable rates (*vide infra*).[1] This ratio is perfectly in line with the enolate ratio and was a very promising result. In an intriguing twist, *E*–enolate **60** afforded the same major adduct **59** as that afforded by **58**, albeit with a lower ratio of 62:38![2]

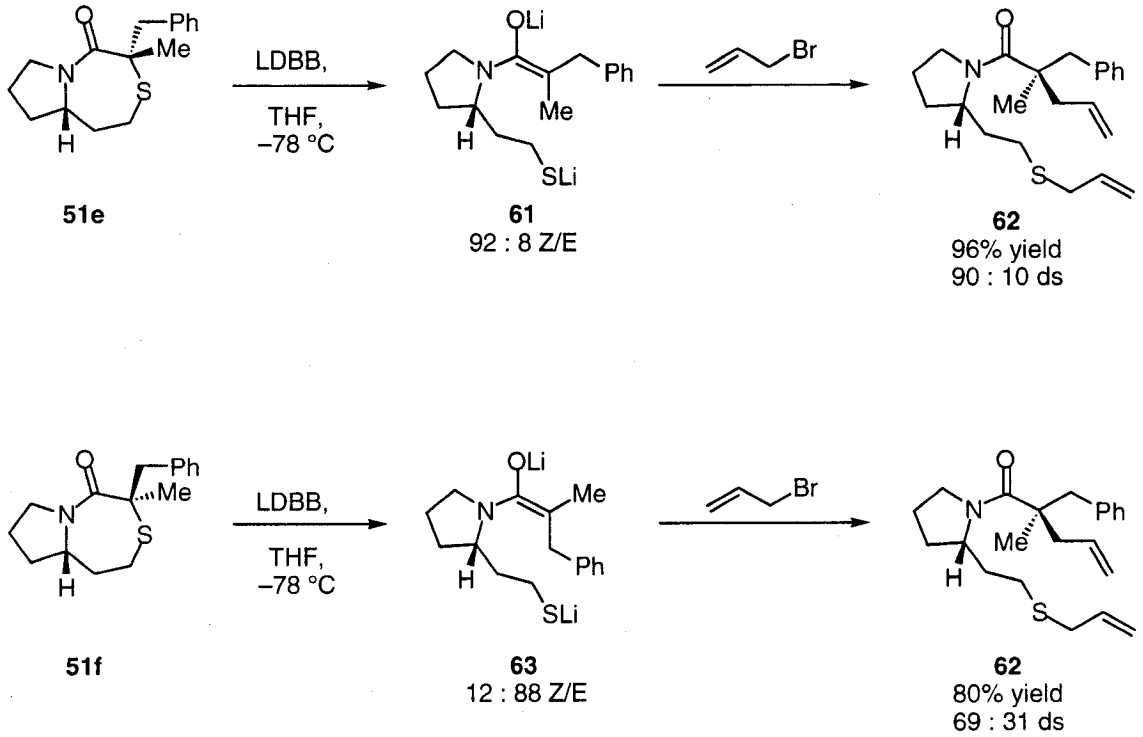


Scheme 55. The reductive enolization and alkylation of lactams **51a** and **51b**.

The inverted facial selectivity in the alkylation of enolate **60** was startling and disappointing. These experiments were actually carried out before the enolization and trapping study presented in Chapter Two and their results prompted us to step back and study the enolization process. We recognized the need to determine that we were indeed obtaining reversal of *E/Z* selectivity in the reductive enolization process by inverting the order of the first two alkylations.

After completing our study of the enolization process that was outlined in Chapter Two, we returned to the study of the alkylation of these α,α–disubstituted enolates. At this point, we chose to investigate the behaviour of lactams **51e** and **51f**, as these two lactams were most commonly used for the enolization studies and they offered the highest *E/Z* selectivity in the reductive enolate generation process. Upon reductive

enolization and alkylation with three equivalents of allyl bromide *Z*–enolate **61** afforded a 90:10 mixture of quaternary carbon adducts **62** (Scheme 56). This was similar to the result obtained from the alkylation of **58**, another *Z*–enolate and 90:10 was felt to be reasonable diastereoselectivity of the product **62**, given that it arose from a 92:8 ratio of enolates.



Scheme 56. Reductive enolization and alkylation of lactams **51e** and **51f**.

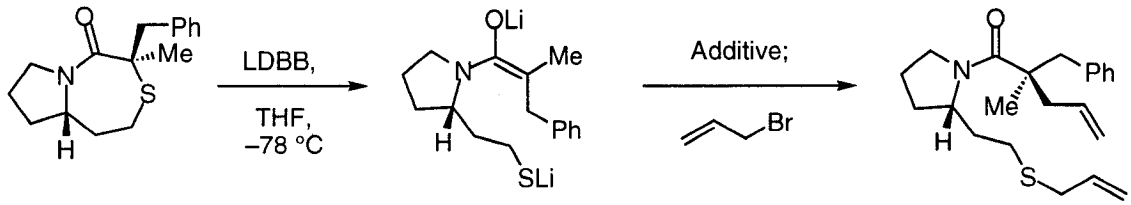
When lactam **51f** was exposed to the same reaction conditions as those with lactam **51e**, the C,S–dialkylated product was again obtained in good yield. Once again however, the diastereoselectivity of the alkylation was poor and again slightly in favour of the same major stereoisomer formed in alkylation of the *Z*–enolate **61**. This result confirmed that we were not able effectively alkylate the *E*–enolates to form the desired quaternary carbon adducts with the opposite stereochemistry of those arising from the

Z–enolates. At this stage it was evident that the problem lay in the alkylation step and not in the enolization process. This prompted the study of the effect of additives on the alkylation reaction, particularly with *E*–enolates. We were suspicious that the aggregation state of the reaction was influencing the stereochemical outcome of the reaction and thus we felt that the investigation of the influence of additives that are known to alter or break up aggregates would be useful and potentially fruitful.

3.3 THE INFLUENCE OF ADDITIVES ON THE ALKYLATION OF α,α–DISUBSTITUTED ENOLATES WITH ACTIVATED ALKYL HALIDES

Suspecting that the aggregation state of the alkylation reaction or the formation of an intramolecular chelate were affecting the stereoselectivity of the reaction, a study of the effects of additives was performed. The additives selected were hexamethylphosphoramide (HMPA),[3] 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[4] and lithium chloride.[5,6] All of these reagents break up aggregates and chelates in enolate alkylation reactions. In the cases of HMPA and DMPU, the cosolvent was added after the reductive enolization was performed but before the alkyl halide had been added. This was done to ensure consistency in the reductive enolization process. Again, lactams **51e** and **51f** were selected for this study. As previously demonstrated, lactam **51f** afforded a 69:31 ratio of quaternary carbon adducts in the absence of a cosolvent. The effects of different cosolvent conditions are shown in Table 4.

Table 4. The effect of additives on the stereochemical outcome of the reductive enolization and alkylation of lactam **51f** with allyl bromide.



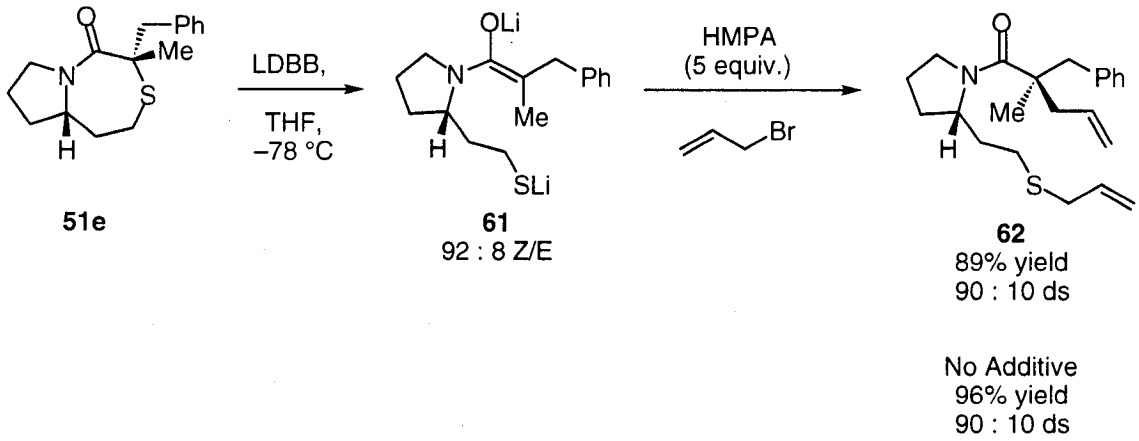
51f → **63** 12 : 88 Z/E → **62**

Additive	Yield	Product Ratio
none	80%	69 : 31
HMPA (5 equiv.)	66%	47 : 53
HMPA (20 vol%)	74%	39 : 61
DMPU (45 vol%)	72%	45 : 55
LiCl (10 equiv.)	32%	68 : 32

The results of Table 4 show a decrease in yield when any additive is used. However, this decrease is minor in all instances except the case of lithium chloride. More important were the effects of the additives on the product ratio. The use of five equivalents of HMPA resulted in a nearly one to one ratio of adducts, while the use of a larger amount of HMPA (20 vol%) resulted in a larger switch- a 39:61 ratio. Unfortunately, this is still not a useful level of stereoselectivity. Adding 45 vol% of DMPU to the enolate solution resulted in nearly the same level of stereoselectivity as five equivalents of HMPA. Ten equivalents of lithium chloride had no discernible effect on the stereochemical outcome of the reaction. Because the use additives in the alkylation reaction did not afford levels of product stereoselectivity that were in line with the enolate ratio, we believed that enolate aggregates and intramolecular chelates may only

be partially responsible for the observed poor alkylation diastereoselectivity. The low stereoselectivity was presumed to arise from the *E*–enolate reacting via different conformation(s) than the analogous *Z*–enolate.

In contrast to the results of the use of cosolvents with *E*–enolates, the addition of five equivalents of HMPA had no noticeable effect on the stereochemical outcome of the alkylation reaction of the *Z*–enolate **61** with allyl bromide to produce amide **62** (Scheme 57).



51e

61
92 : 8 Z/E

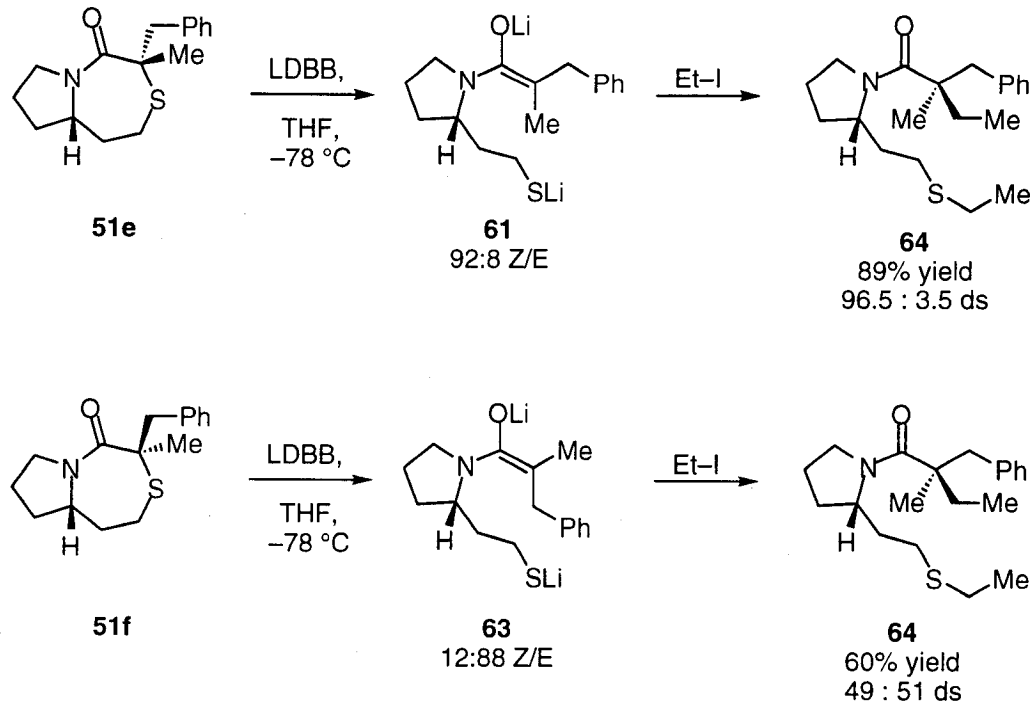
62
89% yield
90 : 10 ds

No Additive
96% yield
90 : 10 ds

Scheme 57. The effect of five equivalents of HMPA on the alkylation of enolate **61**.

3.4 ALKYLATION OF α,α–DISUBSTITUTED ENOLATES WITH UNACTIVATED ALKYL HALIDES

Our investigation of alkylation of our α,α–disubstituted enolates with activated alkyl halides produced some rather intriguing results. This prompted us to explore the behaviour of our α,α–disubstituted enolates when the reactivity of the alkylating agent was decreased. Initially we chose to investigate the alkylation of enolates **61** and **63** with ethyl iodide (four equivalents).[7] This research produced some startling data (Scheme 58).



Scheme 58. The alkylation of enolates **61** and **63** with ethyl iodide.

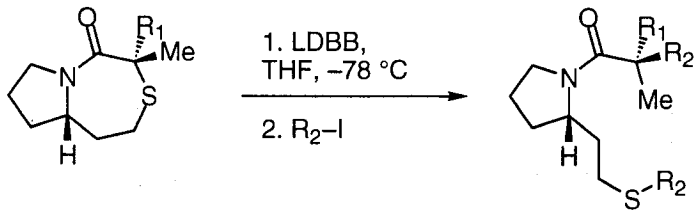
Upon alkylation of enolate **61** with four equivalents of ethyl iodide it was found that the amide adduct **64** had a diastereomeric ratio of 96.5:3.5. This was a fantastic discovery because the *E/Z* ratio of the intermediate enolate (**61** in this case) is usually the upper limit of stereoselectivity in an alkylation reaction. In this instance that limit had been exceeded for some reason. We were already aware that our *E*– and *Z*–enolates exhibited different behaviour when alkylated with activated alkyl halides. The initial supposition was that the minor *E*–enolate was a contributing factor in the "excessive" selectivity.

When the *E*–enolate **63** was exposed to the same set of reaction conditions dichotomous reactivity was again observed. The diastereoselectivity of the reaction was 49:51. This supported the speculation that the minor *E*–enolate was involved in the

abnormally high diastereoselectivity of the alkylation of **61** with ethyl iodide. Using the approximation that the *E*–enolate alkylates in a stereorandom fashion, the eight percent *E*–enolate in **61** should afford about four percent each of the minor and major diastereomer of the quaternary carbon adduct. Assuming that the major component, the *Z*–enolate, alkylates with nearly perfect selectivity, a ratio of 96:4 should be observed for amide **64**. At 96.5:3.5, the observed ratio is nearly identical to this estimate.

The next stage was to determine if this enrichment observed by alkylating a *Z*–enolate with an unactivated alkyl halide was a general phenomenon. A variety of lactams and alkyl halides were investigated. As mentioned in Chapter Two, in order to generate a *Z*–enolate, the larger of the first two alkyl groups must be installed in the first alkylation and the smaller alkyl group should be installed in the second alkylation step. The results of our survey as shown below in Table 5.

Table 5. The alkylation of *Z*–α,α–disubstituted amide enolate dianions with unactivated alkyl halides.



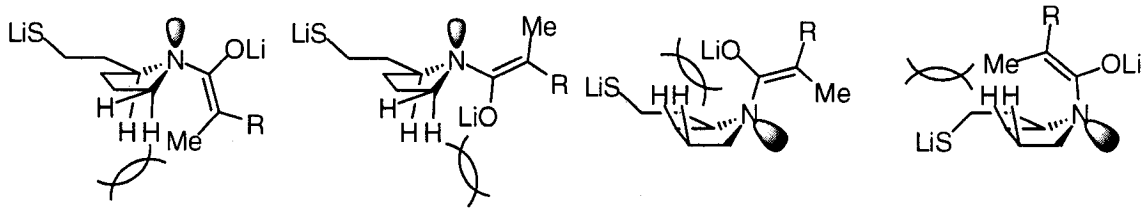
R_1	Z/E	Enolate de (%)	R_2–I	Product	Yield	de
Bn	92 : 8	84	Et–I	**64**	89%	93%
Bn	92 : 8	84	*n*-Bu–I	**65**	76%	>95%
Et	90 : 10	80	*n*-Pr–I	**66**	83%	>95%
n-Pr	87 : 13	74	Et–I	**67**	85%	89%
n-Pr	87 : 13	74	*n*-Bu–I	**68**	71%	95%
n-Bu	n.d.	n.d.	*n*-Pr–I	**69**	88%	95%
Allyl	87 : 13	74	Et–I	**70**	84%	88%
Allyl	87 : 13	74	*n*-Bu–I	**71**	80%	91%
n-Pr	87 : 13	74	*i*-Bu*	**72**	60%	87%

*see text

As can be seen from Table 5, we observed that the enrichment of diastereoselectivity in the alkylation of **61** with an unactivated alkyl halide is indeed general to all of the *Z*–enolates that have been examined thus far. In all cases, the de of the quaternary carbon-containing adduct has a higher de than the intermediate enolate.

It is also very important to point out that these reactions were conducted at –78 °C over four hours without added cosolvents. Unactivated alkyl halides do not normally react with amide enolates under these conditions. This unprecedented level of reactivity is hypothesized to arise from the unusually high level of $A^{1,3}$–strain in these α,α–disubstituted enolates (Scheme 59), as well as their dianionic nature. The lone

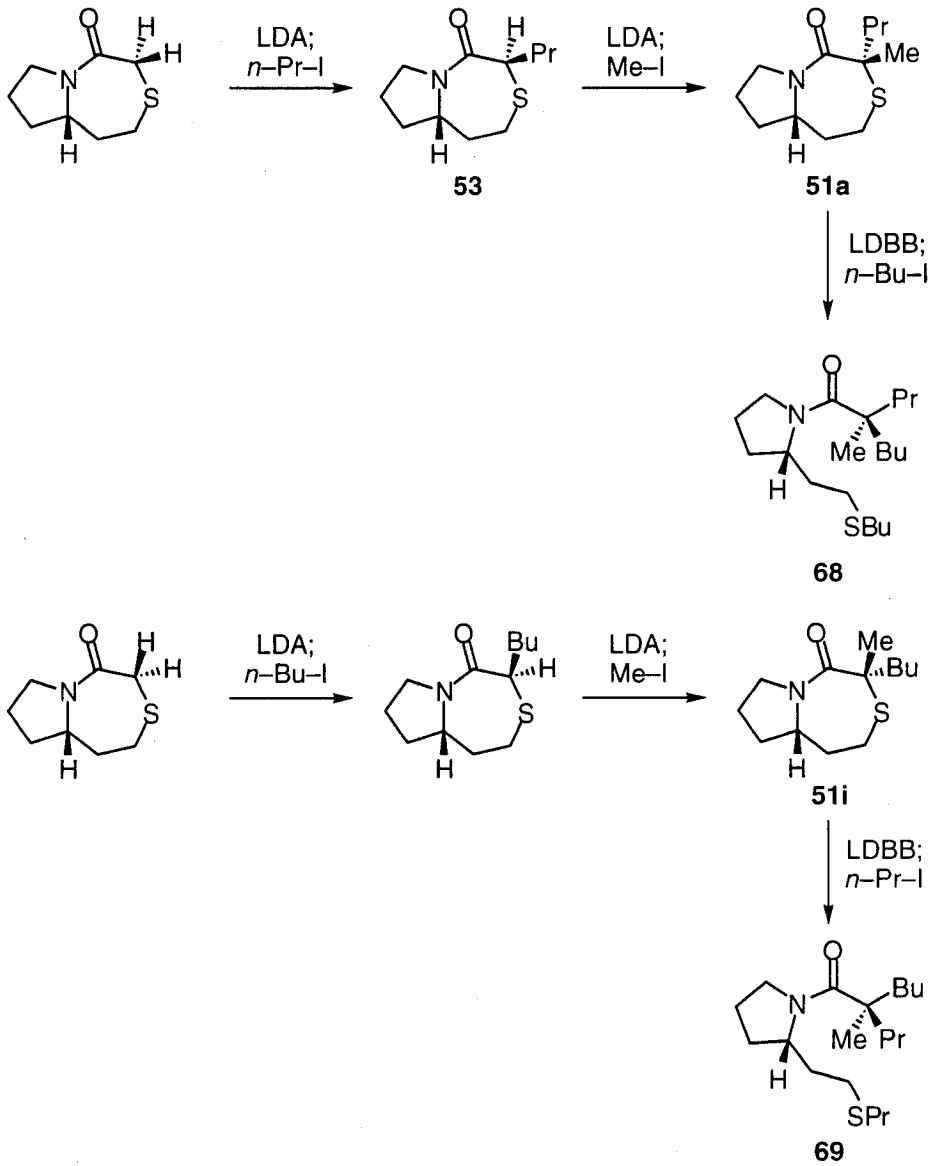
exception, which required a cosolvent, was the β–branched isobutyl iodide, a very unreactive alkyl halide.[5] The use of isobutyl iodide as the alkylating agent required the use of 23 vol% HMPA in order to obtain high reaction rate. The presence of HMPA affected only the reaction yield and not the overall diastereoselectivity of the reaction.



Scheme 59. Several potential conformations of α,α–disubstituted amide enolates that depict significant $A^{1,3}$–strain.

As previously mentioned, a major goal for this project was to be able to produce both the (*R*)– and the (*S*)–configurations of quaternary carbons. The initial plan was to reverse the order of the first two alkylations, generating analogous *E*– and *Z*–enolates. Use of a common alkylating agent in the final reaction would lead to selective formation of both (*R*)– and (*S*)–configurations of the quaternary carbon. Though our results with *E*–enolates make this route unworkable, it is possible to form both stereochemical configurations of the quaternary centre by inverting the overall alkylation order (Scheme 60). For example, the pair of amides **68** and **69** (see Table 5), while not true diastereomers (they contain different alkyl groups on the sulfur), do contain the same three alkyl groups on the α–carbon and they afford the opposite stereochemical configuration of the α–carbon with 95% de (**68** is (*S*) and **69** is (*R*)). The same can be said for the pair of amides **66** and **67**. Thus, even though the *E*–α,α–disubstituted enolates are not suitable substrates for this alkylation strategy, it is still generally feasible

to prepare both stereoisomers of the quaternary carbon. While this process allows for access to both (*R*)– and (*S*)–configurations of the quaternary carbon, only cases in which the final alkylating agent is unactivated will lead to a product with a diastereomeric excess higher than the diastereomeric excess of the intermediate enolate.

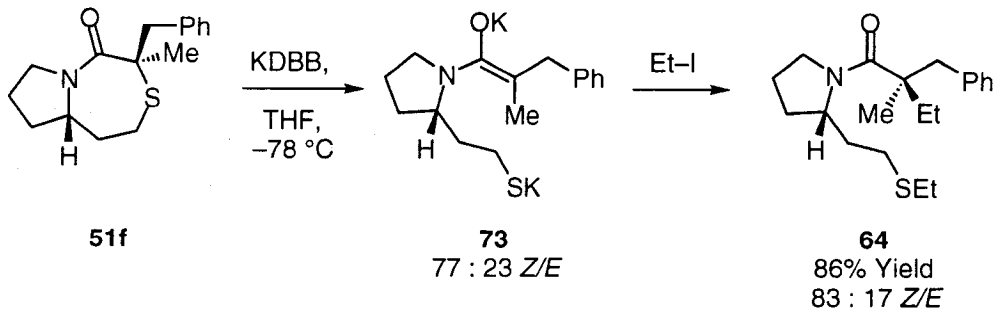


Scheme 60. Inversion of alkylation order to access both (*R*)– and (*S*)–stereochemical configurations of the quaternary carbon.

3.5 THE EFFECT OF POTASSIUM AS THE METAL CATION ON THE STEREOCHEMICAL OUTCOME OF ALKYLATION REACTIONS

It was pertinent to investigate the effect of the metal cation on the stereochemical enrichment phenomenon observed during alkylation of *Z*–enolates with unactivated alkyl halides. We were curious about the degree of metal-dependency of the enrichment pattern. Changing from a lithium enolate to potassium might change the aggregation state of the enolate (potassium enolates are known to be far less aggregated than their lithium counterparts[6.8]).

Recall that in a dramatic result, which is contradictory to reduction with LDBB, lactam **51f** affords predominantly the *Z*–potassium enolate dianion **73** (77:23 *Z/E*) upon reduction with KDBB (*vide supra*). Alkylation of potassium enolate **73** with four equivalents of ethyl iodide led to the C,S–dialkylated product in 86% yield and 83:17 ds (in the same direction as *Z*–enolates with lithium as the metal counterion) (Scheme 61). Again, the enrichment of diastereoselectivity beyond the enolate ratio was observed. This result demonstrated that the enrichment process is not completely restricted to lithium counterions.



51f

73
77 : 23 *Z/E*

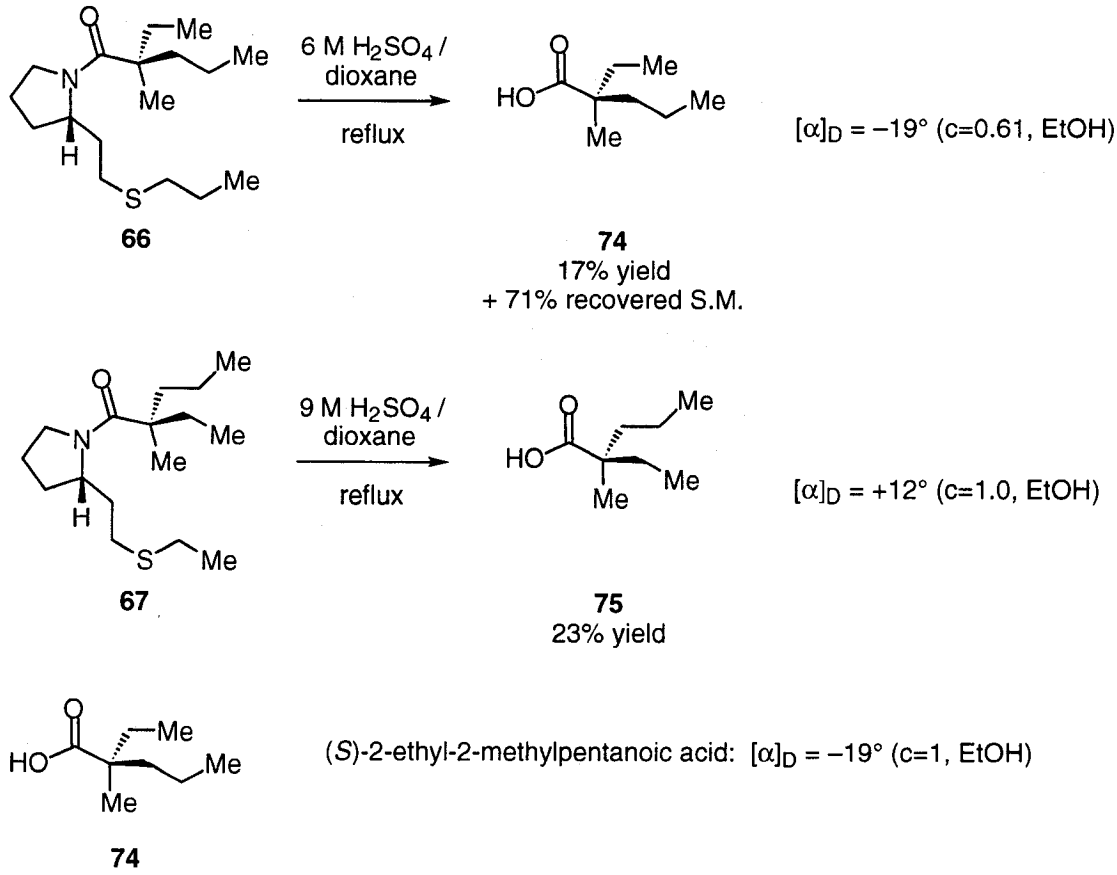
64
86% Yield
83 : 17 *Z/E*

Scheme 61. The alkylation of a *Z*–potassium enolate with ethyl iodide.

3.6 ISOLATION OF QUATERNARY CARBON ADDUCTS VIA AMIDE HYDROLYSIS

Having developed a method for preparing many quaternary chiral, non-racemic carbon centres with greater than 90% de, we focussed on isolation of substrates as their carboxylic acid derivatives. However, hydrolysis of tertiary amides is a notoriously difficult process, as evidenced by the lack of amide-based enolate alkylation methodologies that lack assisted hydrolysis.[9] This, combined with the steric hindrance of an α–quaternary centre, made the hydrolysis of our products the most difficult scenario for amide hydrolysis. Fortunately, quaternary carbons are immune to epimerization during hydrolysis so extremely forceful hydrolysis conditions could be used with little concern.

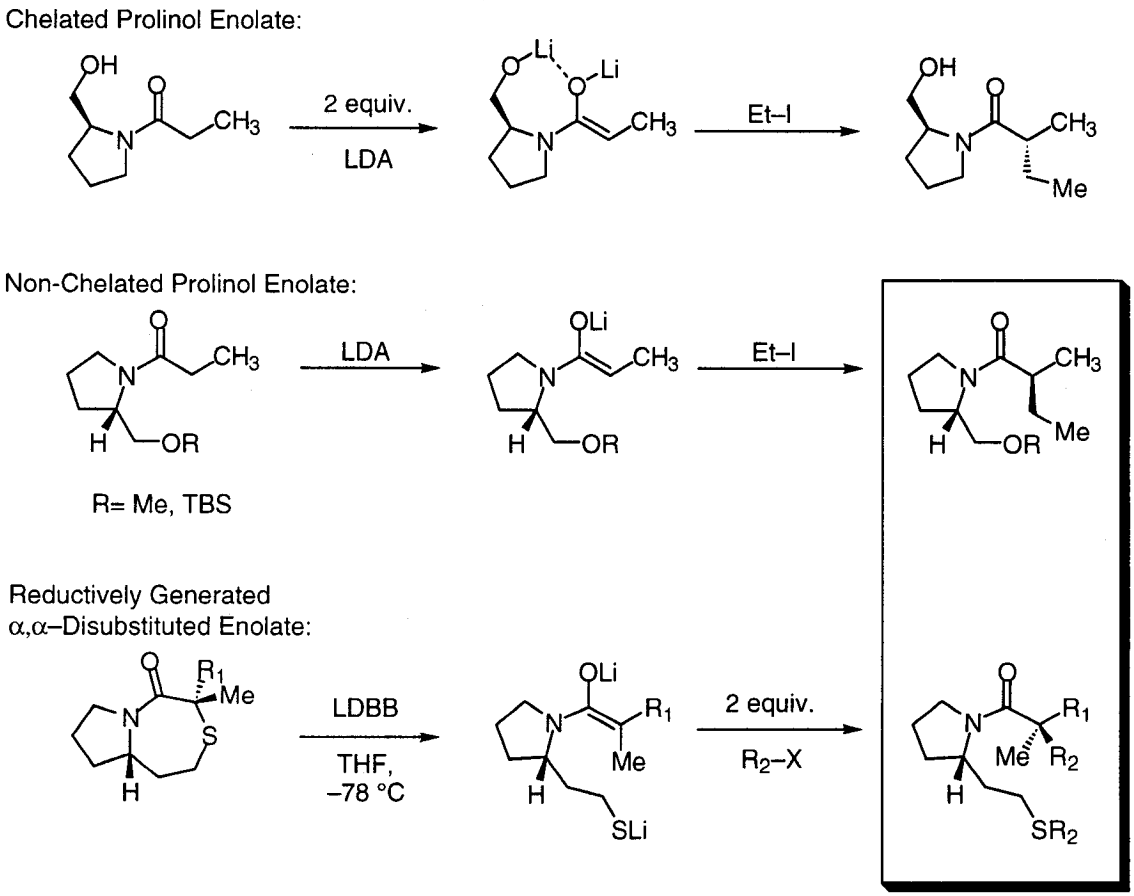
Acidic hydrolysis of amide **66** in 1:1 6 M aqueous H_2SO_4:1,4-dioxane at reflux afforded 17% of 2-ethyl-2-methylpentanoic acid **74**[10] and 71% recovered starting material (Scheme 62). Despite the use of these vigourous conditions only a small amount of desired carboxylic acid product was isolated. Use of more vigourous conditions, 1:1 9 M aqueous H_2SO_4:1,4–dioxane at reflux, still afforded only 23% yield of the desired 2–ethyl-2-methylpentanoic acid **75**. It was felt at this point that acidic hydrolysis would not prove to be an effective means of isolation of the quaternary carbon products and it was not pursued any further.



Scheme 62. Acidic hydrolysis of amides **66** and **67**.

While acidic hydrolysis did not prove to be a practical process for the formation of α–quaternary carboxylic acids, it did afford enough material to measure the optical rotation of our samples of 2-ethyl-2-methylpentanoic acid. Comparison of the optical rotation of our sample of acid **74** with the value obtained by Fuganti and co-workers[10] demonstrated that our sample was of (*S*)-configuration. Acid **75** was shown to be the enantiomer, (*R*)–2-ethyl-2-methylpentanoic acid.

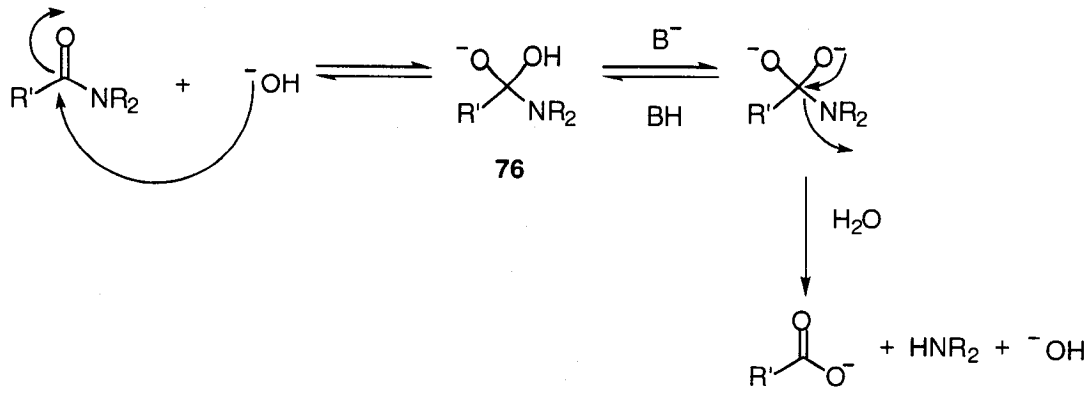
Now knowing the absolute stereochemical outcome of our alkylation reactions, the direction of stereoselection was compared with a similar chiral auxiliary, (*S*)–prolinol amides (Scheme 63).[9d-f] It was shown in Chapter One that the use of two equivalents of LDA with an (*S*)–prolinol amide led to a chelated enolate and alkylation occurred on the less hindered *Si*–face of the enolate. In contrast, if the sidechain alcohol was *O*–protected, a non-chelated enolate formed and alkylation occurred on the *Re*–face, now the less hindered face of the enolate.



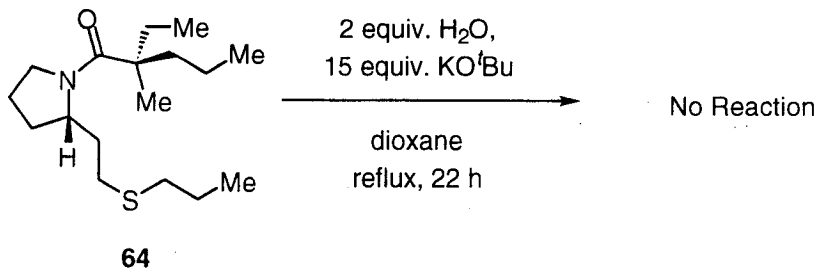
Scheme 63. Facial selectivity in alkylation of α,α–disubstituted enolates.

If the α,α–disubstituted enolates formed in this work are drawn in the same manner, it appears that the alkylation process is occurring via a non-chelated transition structure and alkylation is occurring on the *Re*–face. All stereochemical assignments in this body of work have been made in analogy to these results. To date, we have not been able to offer a satisfactory depiction of this transition structure. However, it is noteworthy that no transition state model has been proposed for the non-chelated prolinol enolates despite the fact that this work was published more than 20 years ago.

The low efficiency of acid hydrolysis of our amides prompted us to investigate basic hydrolysis of our α–quaternary tertiary amides. Typically, the base hydrolysis of amides is slow. If hydroxide adds to an amide carbonyl, hydroxide is still a better leaving group than the amine moiety in the tetrahedral intermediate **76** (Scheme 64). Gassman and co-workers reported that the combined use of anhydrous potassium hydroxide[11] and potassium *tert*–butoxide effectively hydrolyses tertiary amides in THF at room temperature.[12] This method uses potassium *tert*–butoxide, a much stronger base than potassium hydroxide, to deprotonate the orthoamide intermediate **76**. This leads to faster formation of the desired carboxylate. Hydrolysis of *N,N*–dimethylpivalamide (the simplest α–quaternary tertiary amide) was reported by Gassman and co-workers to proceed in good yield in refluxing THF. Unfortunately, Gassman's conditions and a more vigourous variant of them (two equivalents of KOH and 13 equivalents of KO^{t}Bu in 1,4-dioxane at reflux for 22 hours) afforded only quantitative recovery of starting amide **64** (Scheme 65).



Scheme 64. Mechanism of amide hydrolysis under basic conditions.



64

Scheme 65. Attempted hydrolysis of α–quaternary tertiary amide **64**.

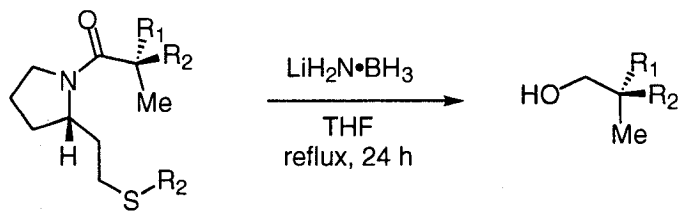
3.7 ISOLATION OF QUATERNARY CARBON ADDUCTS VIA REDUCTIVE AMIDE CLEAVAGE

An alternative to hydrolytic cleavage of amides is reduction. With hydrolysis proving to be an inefficient method of isolation of our quaternary carbon adducts we chose to investigate reduction as a means of quaternary carbon isolation.

Strong reducing agents (such as lithium aluminum hydride[13] and diborane[14]) typically reduce tertiary amides to their corresponding tertiary amines. However, several reagents (lithium triethylborohydride,[15] 9-borabicyclo[3.3.1]nonane (9-BBN),[16] and metal amide-borane complexes[17]) are known to produce the corresponding alcohol. Recently, Schwartz' reagent, bis(cyclopentadienyl)zirconium chloride hydride, was also shown to reduce tertiary amides to aldehydes.[18] It was believed that 9–BBN would be too hindered to effectively reduce our amides. However, the reductions with lithium triethylborohydride, Schwartz' reagent and a metal amide-borane complex- lithium amidotrihydroborate (LAB)[19] were pursued.

Although our α–quaternary amides proved to be inert to lithium triethylborohydride and Schwartz' reagent, they could be reduced using LAB. This reagent is readily prepared by deprotonation of commercially available borane-ammonia complex with LDA. Reaction of our amides with four equivalents of LAB in refluxing THF for 24 hours led to the clean formation of the desired neopentyl alcohols in good to excellent yields (Table 6).

Table 6. The reduction of tertiary α–quaternary amides by lithium amidotrihydroborate.



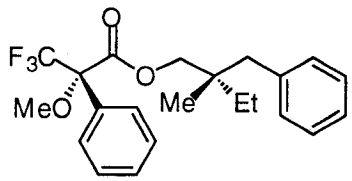
Amide	R_1	R_2	Alcohol	Yield	ee
64	Bn	Et	**77**	96%	94%[a]
65	Bn	*n*-Bu	**78**	97%	96%[a]
68	*n*-Pr	*n*-Bu	**79**	99%	96%[b]
69	*n*-Bu	*n*-Pr	**80**	87%	95%[b]
71	Allyl	*n*-Bu	**81**	74%	93%[b]

a) determined by HPLC using a CSP,
b) determined by GC using a CSP, via corresponding carboxylic acid

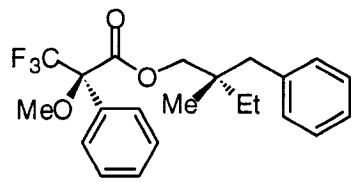
3.8 DETERMINATION OF ENANTIOMERIC EXCESSES OF CHIRAL, NON-RACEMIC NEOPENTYL ALCOHOLS

Once a method for the isolation of the quaternary carbon-containing adducts had been discovered, we sought to determine their enantiomeric excess precisely. This would serve to validate the ^{13}C NMR data for the corresponding amides and give unequivocal proof of the level of stereoselectivity of the final alkylation reaction.

Determination of the enantiomeric excesses of alcohols **77** and **78** was relatively straightforward. The phenyl group provided a useful chromophore for HPLC using a CSP with UV detection. Use of a Chiracel OD column and an isopropanol/hexanes solvent system allowed for clean separation of the enantiomers of **77** and **78**. Integration of the signals revealed the products to be 94% ee and 96% ee respectively. These values correlate very well with the data obtained by integration of the high temperature ^{13}C NMR signals on the corresponding amides **64** (93% de) and **65** (>95% de). The enantiomeric excess of **77** was confirmed by integration of the diastereotopic carbinol proton signals in the proton spectra of both corresponding Mosher esters[20] **82** and **83**.

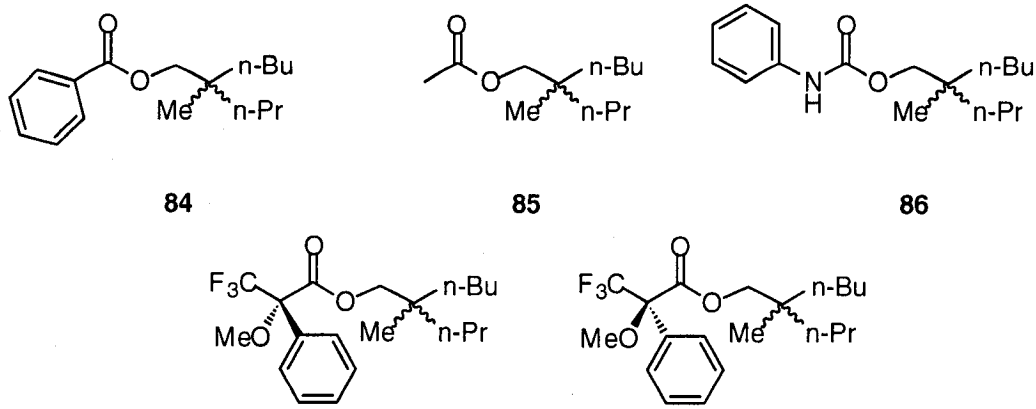


82



83

Determination of the enantiomeric excesses of alcohols **79**, **80** and **81** proved to be a far more challenging task. These substrates lacked a chromophore that would be useful for UV detection. Therefore, HPLC using a CSP on these alcohols was not an option. Moreover, these alcohols contained a three-carbon chain and a four-carbon chain resident on the quaternary centre. This resulted in only a very subtle difference between the two enantiomers in terms of chromatographic behaviour. After GC using a CSP proved on alcohols **79-81** to be futile, a mixture of **79** and **80** was prepared and many derivatives of this quasi-racemic mixture were synthesized. These included the corresponding benzoate **84**, acetate **85**, phenyl carbamate **86** and Mosher esters **87** and **88** (from both (*R*)– and (*S*)–Mosher's acid chloride).



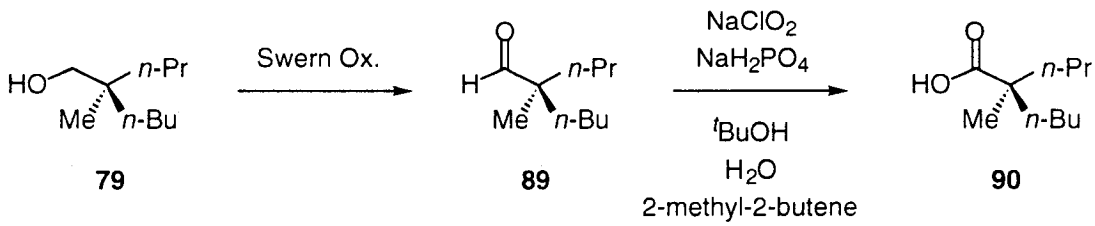
84 **85** **86**

87 **88**

In the case of benzoates **84**, none of normal phase HPLC using a CSP, reverse phase HPLC using a CSP or GC using a CSP proved to be an effective means of separation. Acetates **85** were not detectable by UV on the HPLC and the enantiomers were not separable by GC. Phenyl carbamates **86** were not separable by normal phase HPLC using a CSP or GC.

The Mosher esters **87** and **88** were readily separable as two pairs of diastereomers by HPLC using a CSP. However, this separation was based solely upon the stereochemistry of the Mosher acid residue and not based upon the stereochemistry of the alcohol residue. GC using a CSP, ^{1}H, ^{13}C and ^{19}F NMR techniques were also ineffective. The addition of Eu–(+)–$(hfc)_3$[21] had no discernible effect on the NMR spectra of esters **87** and **88**. The addition of Eu–(+)–$(hfc)_3$ to a mixture of alcohols **79** and **80** was also investigated. Proton, ^{13}C, and ^{19}F NMR spectra were acquired. Unfortunately, this too proved to be an unsuccessful means of determining the enantiomeric excess of the sample.

Upon a suggestion from Professor Claude Spino,[22] we chose to investigate the separation of the carboxylic acids corresponding to **79**, **80** and **81**, using GC. A single step Jones oxidation[23] of alcohol **79** was unsuccessful, as was the use of Dess-Martin periodinane[24] to form the aldehyde **89**. Swern oxidation[25] of alcohol **79** (Scheme 66) proved to be very clean; as was the subsequent oxidation of aldehyde **89** with sodium chlorite[26] to produce carboxylic acid **90** (acids **91** and **92** were prepared analogously). The enantiomeric carboxylic acids **90** and **91** were readily separable on a Chirasil-Dex GC column. Acid **90** was found to have 96% ee, while enantiomeric acid **91** was found to have 95% ee. Intriguingly, the enantiomers of acid **92** were not on a Chirasil-Dex GC column. Hence, they were converted to a mixture of **90** and **91** using catalytic palladium hydroxide on carbon under a hydrogen atmosphere. Effective separation was then observed and the sample derived from acid **92** was found to have 93% ee. The peaks of **90** and **91** did tail somewhat, resulting in an estimated accuracy of ±2%. As was the case with alcohols **77** and **78**, the ee values that were determined for the derivatives of alcohols **79**, **80** and **81** concurred with the NMR integration data for the corresponding amides.



Scheme 66. The conversion of chiral neopentyl alcohols to their corresponding carboxylic acids.

3.9 CONCLUSIONS

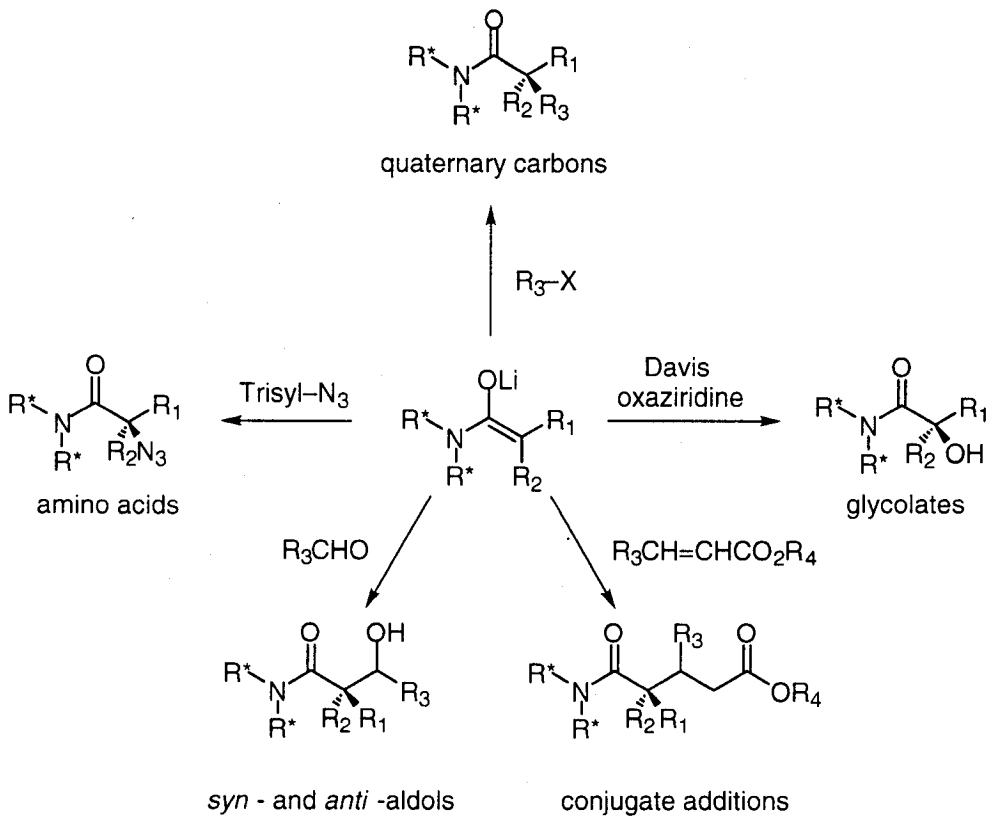
This work demonstrated that acyclic α,α–disubstituted amide enolates could be readily alkylated with both activated and unactivated alkyl halides in good yield. Moreover, these enolates proved to be highly reactive, reacting with unactivated alkyl halides at –78 °C without added cosolvents. This reactivity is believed to arise from high allylic strain or the absence of amines or both.

Remarkably, when *Z*–α,α–disubstituted amide enolates were alkylated with unactivated halides the alkylation stereoselectivity was higher than the ratio of the intermediate enolates. Poor stereoselectivity was observed in the alkylation of *E*–enolates. This poor selectivity of the minor *E*–enolate is proposed to be the source of the enriched stereoselectivity in the alkylation of the *Z*–enolates. The low stereoselectivity of the alkylation of the *E*–enolates is presumed to arise from the *E*–enolate reacting via different conformation(s) than the analogous *Z*–enolate.

Reductive amide cleavage was established as the most effective means of isolation of the quaternary carbon adducts. Methods of determining the enantiomeric excess were also established. The enantiomeric excesses of the quaternary carbon adducts were in agreement with the diastereomeric excess values obtained by integration of the high temperature NMR data.

The results of this enolate alkylation study and isolation of the quaternary carbon adducts were published in 2002.[27] The success of this study has led to projects for other students who are investigating other reactions that employ enolate intermediates (Scheme

67). Currently under investigation is the aldol reaction. Future directions for this work include the investigation of Michael reactions. Synthesis of α,α–disubstituted amino acids may also be probed using azido-transfer reagents. Enolate oxidation would lead to the formation of α,α–disubstituted glycolates.



Scheme 67. Future uses of α,α–disubstituted amide enolates.

---

[1] The diastereoselectivity of quaternary carbon-forming reactions was determined by integration of high temperature (105 °C in toluene-d_8 or 100 °C in a sealed tube in benzene-d_6) ^{13}C magnetic resonances.

[2] At no point were diastereomeric quaternary carbon-containing adducts separable by column chromatography.

[3] Dykstra, R.R. In *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 2668 and references cited therein.

[4] Beck, A.K.; Seebach, D. In *Encyclopedia of Reagents for Organic Synthesis.* (Paquette, L. Editor) Wiley: Toronto, **1995**, p. 2123 and references cited therein.

[5] Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.J., Gleason, J.L *J. Am. Chem. Soc.* **1997**, *118*, 6496 and references cited therein.

[6] Seebach, D. *Angew. Chem. Int. Ed. Eng.* **1988**, *27*, 1624 and references cited therein.

[7] Similarly to activated alkyl halides, unactivated alkyl halides had nearly identical rates of C– and S–alkylation.

[8] For references on enolate aggregation see a) Boche, G. *Angew. Chem. Int. Ed. Eng.* **1989**, *28*, 277 and references cited therein; b) Caine, D. In *Carbon-Carbon Bond Formation.* (Augustine, R.L. Editor) Marcel Dekker: New York, **1979**, p. 85-352 and references cited therein; c) Jackman, L.M.; Lange, B.C. *Tetrahedron* **1977**, *33*, 2737; d) Evans, D.A. In *Asymmetric Synthesis.* (Morrison, J.D. Editor) Academic: Orlando, **1984**, vol. 3, p. 1-110 and references cited therein; e) Williard, P.G.; Hintze, M.J. *J. Am. Chem. Soc.* **1990**, *112*, 8602; f) Arnett, E.M.; Fischer, F.G.; Nichols, M.A.; Ribiero, A.A. *J. Am. Chem. Soc.* **1990**, *112*, 801; g) Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* **1993**, *34*, 5213; h) Edwards, A.J.; Hockey, S.; Mair, F.S.; Taithby, P.R.; Snaith, R.; Simpkins, N.S. *J. Org. Chem.* **1993**, *58*, 6942; i) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979 and references cited therein.

[9] The most common amide-based enolate alkylation methodologies, pseudoephedrine (reference 5), Meyers' bicyclic lactams [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] and prolinol [d) Evans, D.A.; Takacs, J.M. *Tetrahedron Lett.* **1980**, *21*, 4233; e) Evans D.A.; Dow, R.L.; Shih, T.L.; Takacs, J.M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290; f) Sonnet, P.E.; Heath, R.R. *J. Org. Chem.* **1980**, *45*, 3137] all employ N→O acyl transfer hydrolysis.

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

[11] Anhydrous KOH in THF with excess potassium *tert*-butoxide is prepared by addition of two equivalents of water to six equivalents of potassium *tert*-butoxide in anhydrous THF. Poor solubility of anions in THF renders the hydroxide ion extremely reactive and nucleophilic.

[12] Gassman, P.G.; Hodgson, P.K.G.; Balchunis, R.J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

[13] For an example of a reduction of a tertiary amide to a tertiary amine see Cope, A.C.; Ciganek, E. *Org. Synth.* **1963**, *IV*, 339.

[14] a) Brown, H.C.; Heim, P. *J. Am. Chem. Soc.* **1964**, *86*, 3566; b) Brown, H.C.; Narasimhan, S.; Choi, Y.M. *Synthesis* **1981**, 441; c) Brown, H.C.; Narasimhan, S.; Choi, Y.M. *Synthesis* **1981**, 996.

[15] Brown, H.C.; Kim, S.C. *Synthesis* **1977**, 635.

[16] Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. *J. Org. Chem.* **1976**, *41*, 1778.

[17] a) Hutchins, R.O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* **1984**, *49*, 2438; b) Fisher, G.B.; Harrison, J.; Fuller, J.C.; Goralski, C.T.; Singaram, B. *Tetrahedron*

Lett. **1992**, *33*, 4533; c) Fisher, G.B.; Fuller, J.C.; Harrison, J.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 1091; d) Fisher, G.B.; Fuller, J.C.; Harrison, J.; Alvarez, S.G.; Burkhardt, E.R.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378.

[18] White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2000**, *122*, 11995.

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

[20] Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

[21] Quimpère, M.; Jankowski, K. *J. Chem. Soc., Chem. Comm.* **1987**, 676.

[22] Professor Claude Spino, Université de Sherbrooke. Personal communication.

[23] a) Bowden, K.; Heilbron, I.M.; Jones, E.R.H.; Weedon, B.C.L. *J. Chem. Soc.* **1946**, 39; b) Bowers, A.; Halsall, T.G.; Jones, E.R.H.; Lemin, A.J. *J. Chem. Soc.* **1953**, 2548.

[24] Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155.

[25] For a review of the Swern and related activated DMSO oxidations see Tidwell, T. *Org. React.* **1990**, *39*, 297.

[26] a) Bal, B.S.; Childers, W.E.; Pinnick, H.W. *Tetrahedron* **1981**, *37*, 2091; b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567; c) Bayle, J.P.; Perez, F.; Courtieu, J. *Bull. Soc. Chim. Fr.* **1990**, 565.

[27] Manthorpe, J.M.; Gleason, J.L. *Angew. Chem. Int. Ed.* **2002**, *41*, 2338.

CHAPTER FOUR

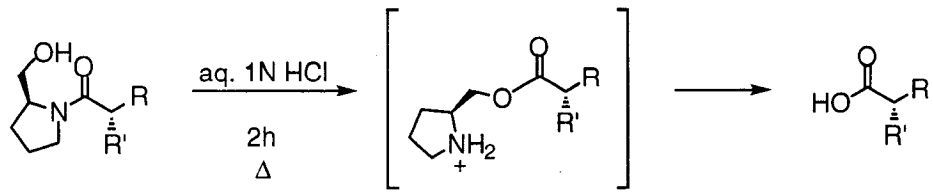
APPROACHES TO A SECOND-GENERATION AUXILIARY

4.1 INTRODUCTION

In Chapters Two and Three, we developed a method for selective generation of acyclic *E*– or *Z*–α,α–disubstituted amide enolates and subsequent formation of asymmetric quaternary carbon centres with excellent levels of diastereoselectivity. These studies showed that a seven-membered α–thioglycolate lactam was requisite to obtain high levels of *E/Z* stereocontrol and that a fused 5,7-bicyclic ring system was optimal.

Though the previous Chapter outlined a successful method for the asymmetric synthesis of quaternary carbons, two problems were encountered: the synthesis of the auxiliary was lengthy (9 to 10 steps) and the hydrolytic cleavage of the amide bond of the α–quaternary amides proved to be a very challenging task. In developing a second-generation auxiliary, we sought to create a system that could be more readily synthesized from inexpensive starting materials and would allow for isolation of the desired quaternary carbons using simple acidic or alkaline hydrolysis.

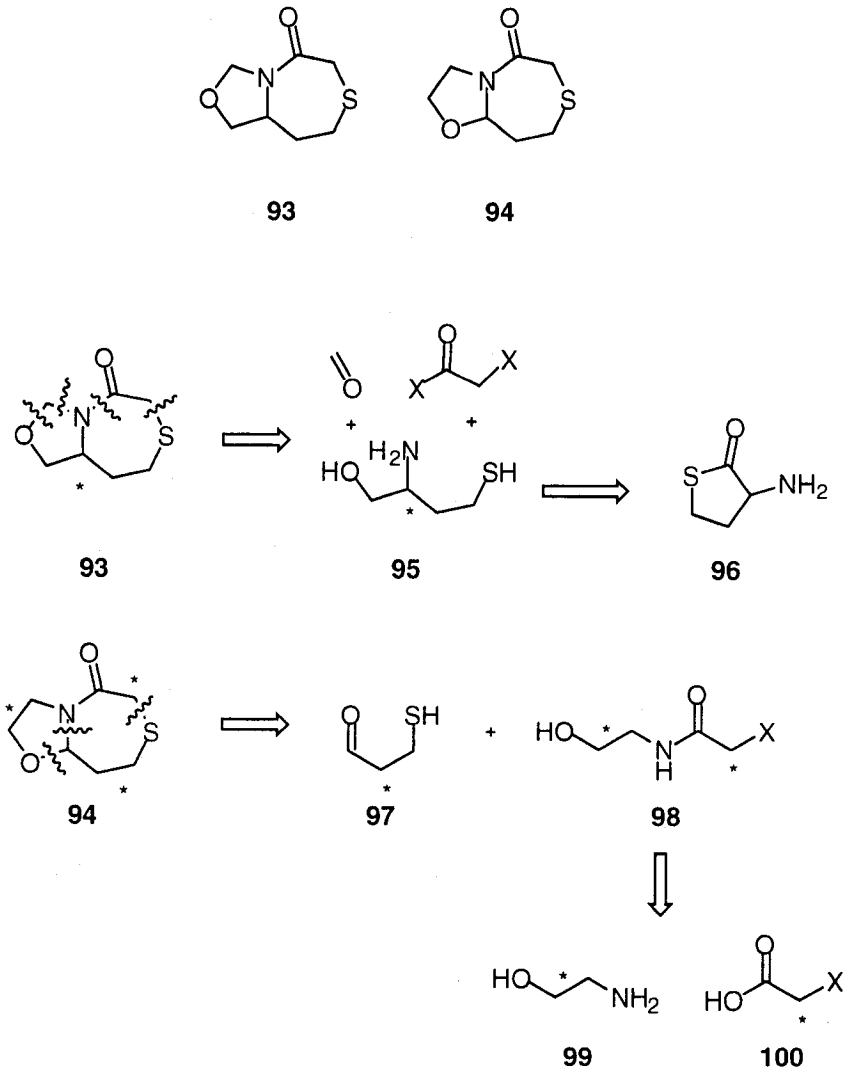
We envisioned that more facile hydrolysis of the asymmetric α–quaternary amides could be achieved using *N*→*O* acyl transfer hydrolysis (Scheme 68). This type of hydrolysis has been demonstrated with prolinol[1] and pseudoephedrine[2] amides. The presence of an ethanolamine moiety allows an acid-promoted *N*→*O* acyl shift to proceed via a five-membered ring transition state, resulting in an ester and an amine. Under the acidic conditions, the amine is immediately protonated (to afford intermediate **92**), rendering the acyl shift irreversible. The resulting ester is much more readily hydrolyzed than the corresponding amide, resulting in highly accelerated hydrolysis.



92

Scheme 68. *N→O* acyl transfer-assisted hydrolysis in prolinol amides.

Knowing that the presence of an alcohol is incompatible with the alkylation process, we envisioned the use of the ethanolamine moiety in an *N*–acyl aminal, in analogy to the work Meyers and co-workers.[3] Under acidic conditions, the aminal would hydrolyze and unmask the ethanolamine moiety. The aminal could be incorporated into the five-membered ring, leading to two general structures, **93** and **94**. Retrosynthetically, chiral lactam **93** was envisioned to arise from a chiral α–amino-δ-thio alcohol (**95**), a derivative of homocysteine or its corresponding thiolactone **96** (Scheme 69). Meanwhile, the generic structure of lactam **94** could be envisioned as arising from a β–oxothiol **97** and an α–halo ethanolacetamide **98**. It is possible to have chirality on all of the fragments **97** or **99** or **100** or any combination thereof. The three potential sites of chirality would allow for exploration of many different lactams in our search for a general auxiliary. The general structure of lactam **94** was pursued over lactam **93** because it was more attractive synthetically and appeared to offer greater potential for the exploration of different chiral influences.



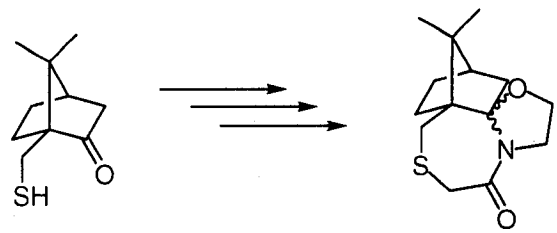
Scheme 69. Retrosynthesis of generic lactams **93** and **94**.

The ability to investigate the influence of different chiral fragments is of paramount importance; and not simply for their influence on the selectivity of alkylations. Formation of the aminal results in a new stereocentre at the aminal carbon. It is critical that this stereocentre be formed with high diastereoselectivity. High diastereoselectivity in the formation of this stereocentre would minimize difficult separations during the auxiliary synthesis. Therefore, we require that the β–oxothiols

and/or chiral amino alcohols exert strong influence on the diastereoselective formation of the aminal.

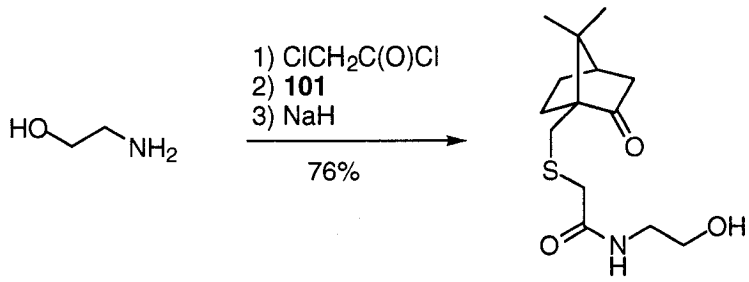
4.2 INVESTIGATION OF A CAMPHOR-BASED CHIRAL AUXILIARY

For our first auxiliary of type **94** we decided to synthesize a chiral β–oxothiol and use an achiral amide of type **98**. In examining the chiral pool, we realized that commercially available camphorsulfonyl chloride could be readily converted to camphor 10–thiol **101** in a single step.[4] Once attached to an amide of type **98**, we envisioned formation of the aminal to afford our chiral auxiliary **102**.



101 **102**

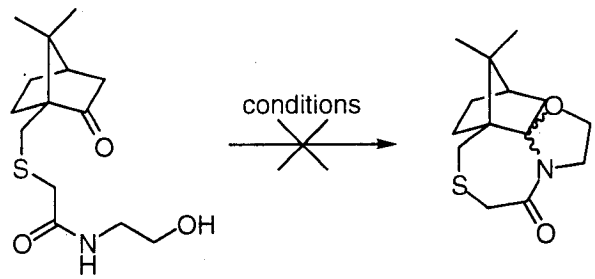
With the chiral β–oxothiol **101** in hand, we developed a one-pot synthesis of α–thioethanolamide **103** (Scheme 70). Sequential addition of chloroacetyl chloride, (*R*)–camphor 10–thiol and sodium hydride to a THF solution of excess ethanolamine resulted in formation of amide **103** in good yield. This one-pot route was chosen because α–chloroethanolacetamide proved to be miscible with water and difficult to isolate.



103

Scheme 70. Synthesis of camphor-based α–thioethanolamide **103**.

With our desired amide **103** in hand, we set about to form the aminal. Notably, the formation of the aminal would result in contiguous quaternary centres. It is known that the formation of vicinal quaternary centres is an extraordinarily difficult task.[5] Steric interference in these reactions is extreme. Undaunted, we attempted to form our requisite aminal to produce our auxiliary **102**. Many different sets of conditions, including catalytic *p*–toluenesulfonic acid in benzene or toluene with azeotropic removal of water, catalytic *p*–toluenesulfonic acid with copper sulfate as dehydrating agent, catalytic sulfuric acid and magnesium sulfate as drying agent, or trimethylsilyl trifluoromethanesulfonate, were investigated. Unfortunately, we were unable to form the aminal and auxiliary **102** under any of the attempted sets of conditions (Scheme 71).

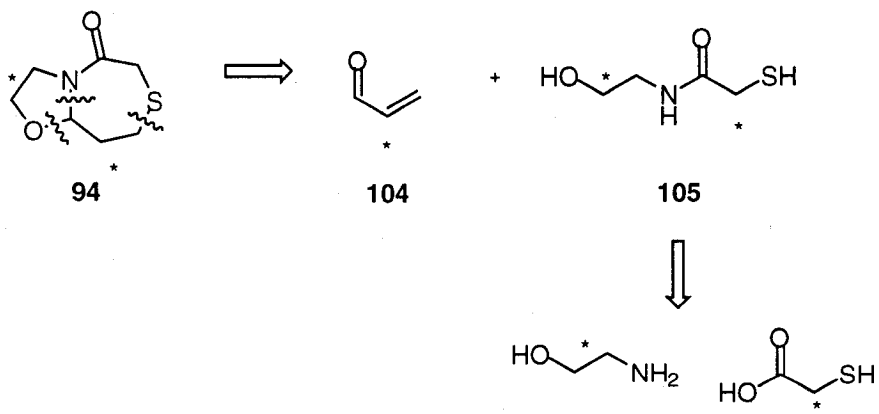


103 **102**

Scheme 71. Attempted formation of aminal **102**.

4.3 DEVELOPMENT OF A GENERAL SYNTHETIC ROUTE TO SECOND-GENERATION AUXILIARIES

Our inability to form aminal **102** prompted us to re-examine our retrosynthesis of our generic lactam **94**. Very importantly, we realized that by disconnecting the opposite sulfide bond to the one previously described (to afford β–oxothiol **95** and α–haloethanolamide **97**), the acetal precursor could be derived from a Michael addition of a thiolate to an enone (Scheme 72). This would still enable the potential use of two different chiral sources- the enone **104** and the α–thioethanolamide **105**. It is also conceivable that a chiral thioglycolate moiety could be used. However, chiral pool sources of these materials are not available. Moreover, the use of a chiral thioglycolate would limit the generality of the auxiliary for the preparation of a range of quaternary carbon-containing adducts. Therefore the use of this type of chiral influence would preferably be avoided.

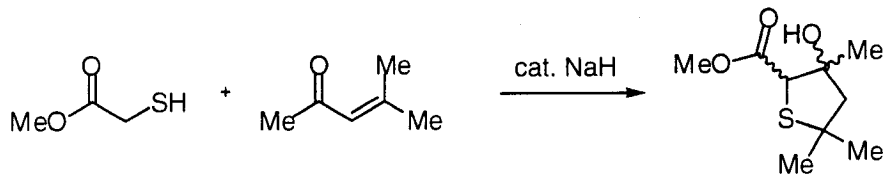


94 **104** **105**

Scheme 72. Second retrosynthetic plan for generic lactam **94**.

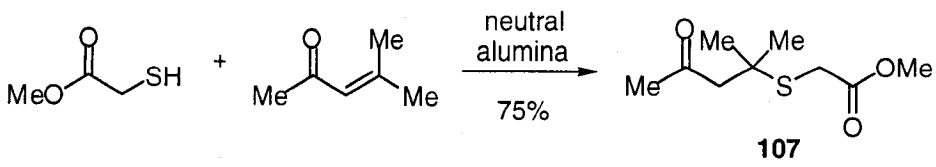
In contrast to our previous attempt at a second-generation auxiliary, the decision was made to develop a generic synthetic plan using achiral materials. With two potential sites for incorporation of chirality, we needed to develop a synthetic route that would be amenable to rapid synthesis of a variety of auxiliaries. This would facilitate the investigation of the influence of chirality at different positions in the lactam on aminal formation diastereoselectivity, as well as alkylation diastereoselectivity.

The study was begun by investigating the conjugate addition of methyl thioglycolate onto mesityl oxide. Use of a catalytic amount of sodium hydride (10 mol%) led to Michael addition (Scheme 73). However, under the reaction conditions, the conjugate addition product underwent a base-catalyzed intramolecular aldol to form tetrahydrothiophene **106**, which was isolated in 98% yield as a mixture of stereoisomers. It was possible to prevent the intramolecular aldol reaction by using the mild conditions developed by Ranu and Bhar.[6] Adsorption of methyl thioglycolate onto neutral alumina, followed by addition of mesityl oxide gave sulfide **107** in 75% yield (Scheme 74). Advantageously, this reaction takes place in the absence of solvent, which would be very useful for large scale applications.



106

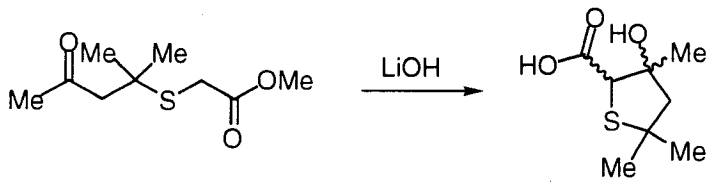
Scheme 73. Michael addition of methyl thioglycolate onto mesityl oxide.



107

Scheme 74. Michael addition of methyl thioglycolate onto mesityl oxide under neutral conditions.

With our desired keto ester **107** in hand, we attempted to hydrolyze the ester so that coupling with ethanolamine could be performed (Scheme 75). Unfortunately, while the ester hydrolysis did take place, the aldol side-reaction again occurred. Careful monitoring of this reaction appeared to show that the aldol was occurring more rapidly than ester saponification. Thus, the formation of aldol adduct **108** could not be avoided. As a result, this pathway to the ethanolamide was abandoned.

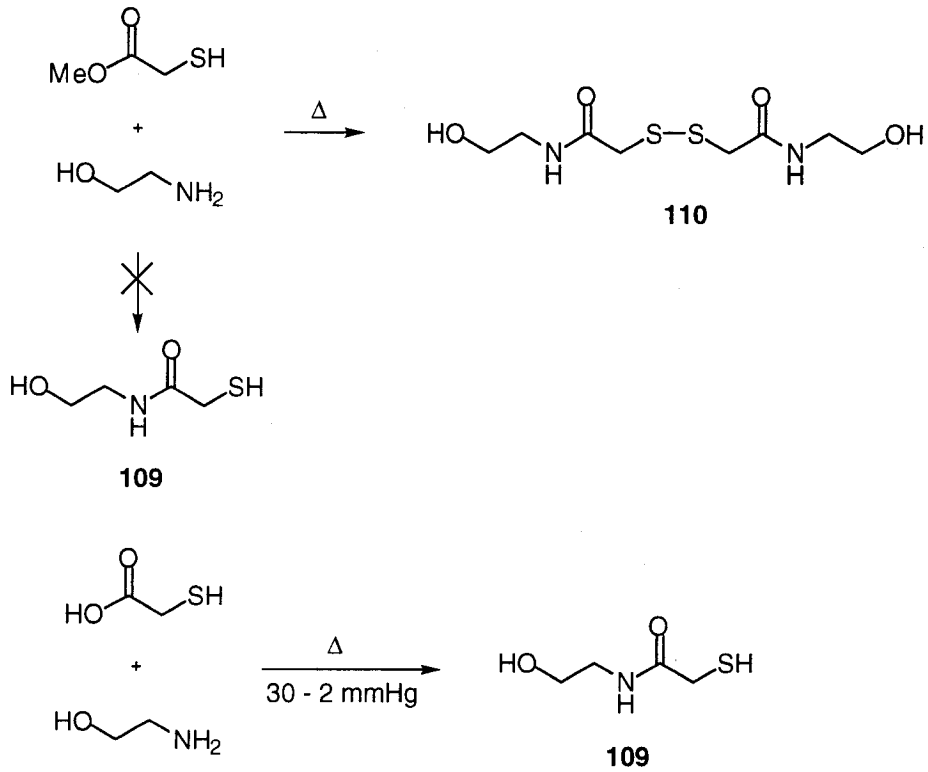


107 **108**

Scheme 75. Attempted saponification of ester **107**.

After encountering difficulty in the late installation of the ethanolamine moiety, we elected to investigate its installation prior to the conjugate addition. This required the preparation of the highly functionalized, water miscible amide **109**.[7] The miscibility of amide **109** with water necessitated the avoidance of aqueous workup. Preparation of amide **109** by heating methyl thioglycolate and ethanolamine in the absence of solvent

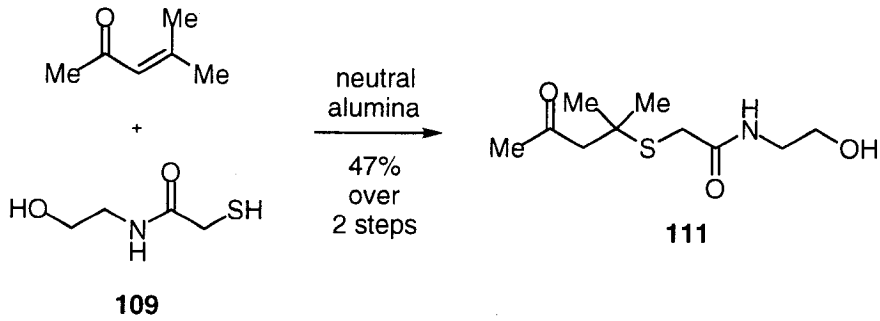
with concomitant distillation of methanol has been reported (Scheme 76).[7a] However, in our hands, this procedure afforded only disulfide **110**. This disulfide has been reported to form from thiol **109** very rapidly in the presence of oxygen.[7b] A more successful protocol was to heat thioglycolic acid and ethanolamine under vacuum in the absence of solvent.[7b]



Scheme 76. Synthesis of α–thioethanolamide **109**.

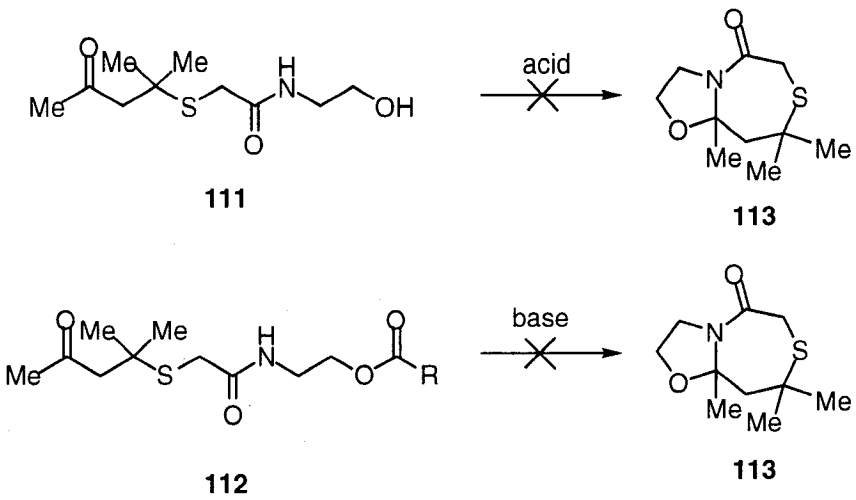
Having solved the problem of the synthesis of air-sensitive thiol **109**, we attempted to use it in conjunction with mesityl oxide the alumina-promoted conjugate addition reaction (Scheme 77). This reaction proceeded in an unoptimized two-step yield of 47%. This synthesis afforded multi-gram quantities of keto amide **111**. It is important to add that amide **111** also has significant water solubility. This makes this solid phase procedure highly practical because the products are simply eluted off of the alumina and

purified by column chromatography as necessary, without the need for aqueous extraction. Moreover, it proceeds under neutral conditions in the absence of solvent. These characteristics make this approach very attractive for large scale preparation.



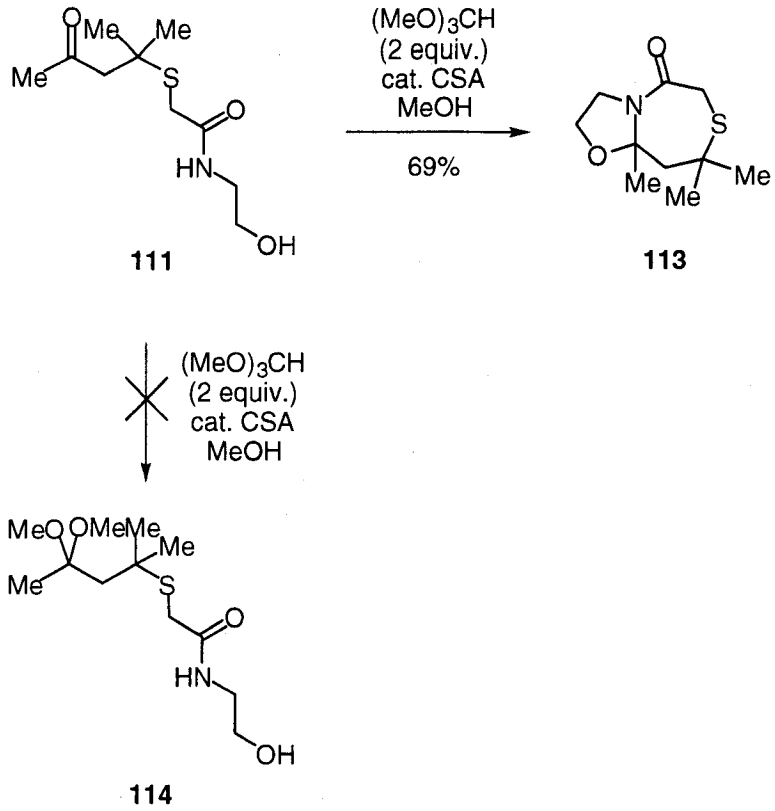
Scheme 77. Michael addition of thiol **109** onto mesityl oxide.

Having prepared amide **111**, the formation of the *N*–acyl aminal was investigated. Eight different sets of protic or Lewis acid-catalyzed conditions all failed to produce the desired aminal **113** (Scheme 78). There was literature precedent for the formation of an *N*–acyl aminal 5,7–ring system by acylating the oxygen (to afford **112**) and then adding excess base.[8] This protocol and variations thereof, led to aldol products, retro-Michael reactions, or decomposition.



Scheme 78. Attempted formation of aminal **113** under acidic and basic conditions.

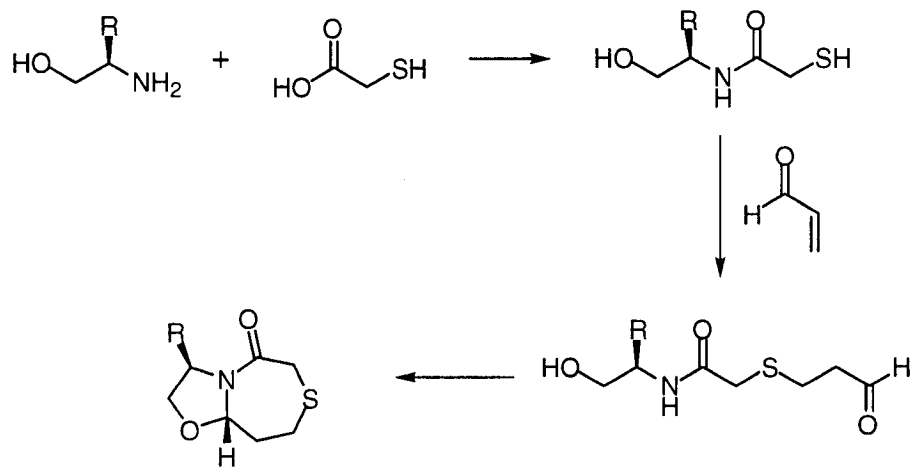
Unable to directly form the desired aminal, we elected to investigate the formation of the dimethyl acetal of the ketone in keto amide **111** and subsequent trans-acetalization. Serendipitously, attempting to form the dimethyl acetal **114** using trimethyl orthoformate and catalytic CSA in methanol resulted in formation of lactam **113** as the sole product in an unoptimized yield of 69% (Scheme 79).



Scheme 79. Formation of aminal-containing α–thioglycolate lactam **113**.

Having developed conditions to form the requisite *N*–acyl aminal of the second-generation auxiliary, the formation of camphor-based aminal **102** from amide **103** was revisited. Unfortunately but not surprisingly, these conditions did not lead to the formation of the desired aminal **102**. Rather, **103** was recovered, along with some of the corresponding dimethyl acetal. The difficulty in the formation of aminal **102** is not believed to be a demonstration of a lack of generality of our conditions for the formation of aminals. It is believed that the absence of aminal formation is due to the steric hindrance of the adjacent quaternary carbon. This should not affect our ability to form auxiliaries, as we plan on avoiding systems with an adjacent quaternary centre.

This research is now continuing with another student investigating the formation of 5,7-bicylic thioglycolate lactam aminals using chiral amino alcohols to form thioglycolate amides and acrolein as a Michael acceptor (Scheme 80). Progress in this research will be reported in due course.



Scheme 80. Current investigation of the synthesis of chiral bicyclic thioglycolate lactam aminals.

4.4 CONCLUSIONS

This Chapter described our development of a synthetic route to a model second-generation auxiliary system. This synthetic pathway is three steps, including two that are solvent free, and proceeds in an overall, unoptimized yield of 32%. This method should be amenable to the rapid synthesis of a variety of auxiliaries, facilitating the rapid discovery of an optimal system that will allow for the formation of a variety of quaternary carbons in high diastereomeric excess. This auxiliary system also contains an *N*–acyl aminal, which should unmask an ethanolamide moiety upon reaction with aqueous acid. This ethanolamide functionality should promote N→O acyl transfer

hydrolysis, thus bypassing the difficult hydrolysis of the α–quaternary amide adducts, the second problem encountered in our first generation chiral auxiliary system.

---

[1] 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; c) Sonnet, P.E.; Heath, R.R. *J. Org. Chem.* **1980**, *45*, 3137.

[2] Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.J., Gleason, J.L *J. Am. Chem. Soc.* **1997**, *118*, 6496 and references cited therein.

[3] The chemistry of Meyers' chiral bicyclic lactams has been reviewed: a) Romo, D.; Meyers, A.I. *Tetrahedron* **1991**, *47*, 9503; b) Groaning, M.D.; Meyers, A.I. *Tetrahedron* **2000**, *56*, 9843. More recent advances in this area have been reported: c) Meyers, A.I.; Downing, S.V.; Weiser, M.J. *J. Org. Chem.* **2001**, *66*, 1413.

[4] Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802.

[5] a) Overman, L.E.; Larrow, J.F.; Stearns, B.A.; Vance, J.M. *Angew. Chem. Int. Ed.* **2000**, *39*, 213; b) Lemieux, R.M.; Meyers, A.I. *J. Am. Chem. Soc.* **1998**, *120*, 5453.

[6] Ranu, B.C.; Bhar, S. *Tetrahedron* **1992**, *48*, 1327.

[7] a) Shroot, Braham; Hensby, Christopher; Maignan, Jean; Lang, Gerard; Colin, Michel. EP 342115 A1 (1989); b) Martin, H. US 3148126 (1964).

[8] Chodynski, M.; Grzeszczyk-Morzycka, B.; Morzycki, J.W.; Boncza-Tomaszewski, Z.; Rodewald, W.J. *Heterocycles* **1985**, *23*, 2335.

CONTRIBUTIONS TO KNOWLEDGE

1. A model for a general method of stereoselective reductive generation of acyclic α,α–disubstituted enolates and asymmetric quaternary carbon synthesis was developed.

2. Three series of chiral bicyclic α,α–disubstituted-α–thioglycolate lactams (based upon one previously known and two previously unknown lactams) were prepared to test this model.

3. Reduction of the chiral bicyclic α–thioglycolate lactams demonstrated that both *E*– and *Z*–α,α–disubstituted amide enolates could be stereoselectively generated under kinetic conditions. This is the first general method for stereoselective preparation of *E*– and *Z*–α,α–disubstituted amide enolates and constituted proof-of-principle of our stereoselective reductive enolization method.

4. A general method of asymmetric quaternary carbon synthesis was developed. Asymmetric alkylation of *Z*–α,α–disubstituted enolates led to quaternary carbons in high diastereomeric excess.

5. Amide reduction was established as an effective means of isolation of quaternary carbon adducts. New chiral, non-racemic neopentyl alcohols were synthesized.

6. A rapid, inexpensive, modular synthesis of a model second-generation chiral auxiliary was developed.

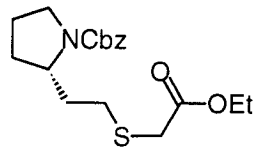
All research described in this thesis was carried out by Jeffrey Michael Manthorpe, under the supervision of Professor James Gleason, except the molecular modeling, which was performed by Professor James Gleason.

CHAPTER FIVE

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, oxalyl chloride, dimethyl sulfoxide, methylene chloride, diisopropylamine, hexamethylphosphoramide and triethylamine were distilled from calcium hydride. Benzene-d_6 and toluene-d_6 were stored over flame-activated 4Å molecular sieves. *n*-Butyllithium was titrated with *sec*-butanol in toluene using 2,2'–dipyridyl as an indicator. Alkylation and enolate trapping substrates were dried via azeotropic removal of water using dry toluene. All Schlenk flasks and lithium chloride were flame-dried under vacuum. Alkyl halides were filtered through basic alumina immediately prior to addition. All reactions were conducted under argon. 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, 100, or 125 MHz for ^{13}C. Elemental analyses were performed Quantitative Technologies Inc., Whitehouse, NJ, USA. High resolution mass spectrometry was performed by the Université de Sherbrooke, Sherbrooke, QC, Canada or McGill University, Montréal, QC, Canada.

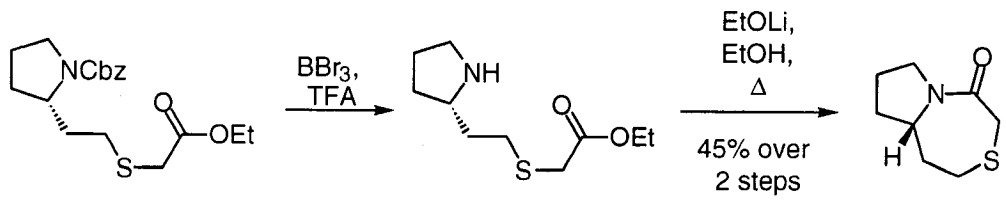
Ethyl 5-((2*S*)-2-(*N*-benzyloxycarbonyl)pyrrolidine)-3-thiapentanoate 45.



Methanesulfonyl chloride (0.184 mL, 2.39 mmol, 1.1 equiv.) was added dropwise to a stirred solution of (2*S*)-2-(2-(*N*-benzyloxycarbonyl)pyrrolidine)ethanol[1] **43** (0.540 g, 2.17 mmol, 1.0 equiv.) and triethylamine (0.400 mL, 2.87 mmol, 1.3 equiv.) in dichloromethane (10 mL) at 0 °C. After 25 minutes, saturated ammonium chloride solution (10 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

Ethyl thioglycolate (0.357 mL, 3.26 mmol, 1.5 equiv.) was added to a slurry of sodium hydride (60% w/w in mineral oil, 0.174 g, 4.34 mmol, 2.0 equiv.) and the mesylate prepared above in *N,N*-dimethylformamide (10 mL) at 23 °C. After stirring for 17 h, saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 25% ethyl acetate in hexanes to afford the ethyl 5-((2*S*)-2-(*N*-benzyloxycarbonyl)pyrrolidine)-3-thiapentanoate **45** (0.560 g, 1.59 mmol, 73%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.29-7.36 (m, 5H), 5.12-5.14 (m, 2H), 4.15-4.20 (m, 2H), 3.97 (m, 1H), 3.37-3.43 (m, 2H), 3.24 (m, 1H), 3.05 (m, 1H), 2.61-2.87 (m, 2H), 1.81-2.26 (m, 4H), 1.63-1.70 (m, 2H), 1.27 (t, 3H, J = 7.0 Hz); ^{13}C NMR (C_6D_6) δ 170.1, 155.0, 138.0, 128.7, 128.2, 66.8, 60.9, 57.2, 34.7, 24.4, 30.7, 29.7, 23.0, 14.2.

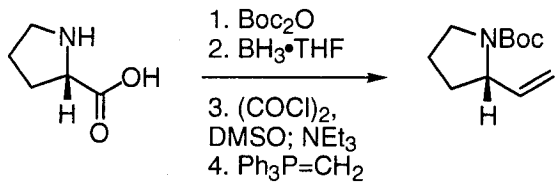
(7*S*)-1-Aza-4-thiabicyclo[5.3.0]-2-decanone 33 via deprotection of (2*S*)-*N*-(benzyloxycarbonyl)-2-(3-thiapentanoate)-pyrrolidine 45 and ester amination.



Boron tribromide in methylene chloride (1.0 M, 16.12 mL, 16.1 mmol, 4.0 equiv.) was added to stirred trifluoroacetic acid (4.66 mL, 60.4 mmol, 15 equiv.) at 0 °C. After 3 minutes, the volatiles were removed in vacuo and a solution of (2*S*)-*N*-(benzyloxycarbonyl)-2-(3-thiapentanoate)-pyrrolidine **45** (1.418 g, 4.03 mmol, 1.0 equiv.) in trifluoroacetic acid (15 mL) was added via cannula. The mixture was stirred at 0 °C for 1 h, at which time methylene chloride (15 mL) and aqueous sodium hydroxide solution (2 M, 125 mL) were sequentially added. The mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. To the residue was added ethanol (absolute, 30 mL) and lithium (0.28 g, 40.3 mmol, 10.0 equiv.). The mixture was heated at reflux for 18 h, cooled to room temperature, saturated aqueous sodium bicarbonate solution (5 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (50 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 50%→100% ethyl acetate in hexanes to afford

(7*S*)-1-Aza-4-thiabicyclo[5.3.0]-2-decanone **33** (0.308 g, 1.80 mmol, 45% over two steps) as a white solid. ^{1}H NMR ($CDCl_3$) δ 3.82 (m, 1H), 3.65 (m, 1H), 3.40-3.48 (m, 2H), 3.15 (dd, 1H, J = 1.8, 14.7 Hz), 2.92 (m, 1H), 2.78 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.67-1.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.2, 58.6, 47.0, 36.5, 36.0, 34.8, 33.1, 23.1.

(2*S*)-*N*–*tert*–butoxycarbonyl-2-ethenylpyrrollidine 47.



71%

Di–*tert*–butyldicarbonate (10.4 g, 47.8 mmol, 1.1 equiv.) was added in several portions to a stirred solution of (*S*)–proline (5.00 g, 43.4 mmol, 1.0 equiv.) in p–dioxane (85 mL) and aqueous sodium hydroxide solution (0.5 M, 85 mL) at 23 °C. After 1 h, the solution was concentrated in vacuo to approximately 50 mL, then acidified to pH 1 using aqueous hydrochloric acid solution (6 M). The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

Borane-tetrahydrofuran complex (1.0 M in tetrahydrofuran) was added to a stirred solution of the protected amino acid prepared above in tetrahydrofuran (75 mL) at 0 °C. The reaction was warmed to 23 °C and stirred for 3 h then cooled to 0 °C. 12 mL of distilled water was added pipetwise, followed by 9.1 g of anhydrous potassium carbonate. The mixture was stirred for 30 minutes, transferred to a separatory funnel and the layers

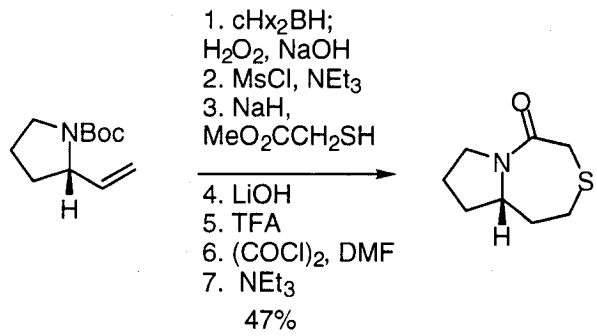
were separated. The aqueous phase was extracted with diethyl ether (2 x 25 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

Dimethyl sulfoxide (6.61 mL, 93.1 mmol, 2.2 equiv.) in methylene chloride (20 mL) was added to a stirred solution of oxalyl chloride (4.52 mL, 50.8 mmol, 1.2 equiv.) in methylene chloride (150 mL) at –78 °C. After 20 minutes, the alcohol prepared above was added via cannula as a solution in methylene chloride (45 mL). After stirring for 75 minutes at –78 °C, triethylamine (23.6 mL, 169.3 mmol, 4.0 equiv.) was added and the reaction was allowed to warm to 23 °C. The mixture was extracted with aqueous hydrochloric acid solution (1 M, 2 x 100 mL), distilled water (4 x 100 mL), and brine (2 x 100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

Sodium hexamethyldisilazide (1.0 M in tetrahydrofuran, 58.7 mL, 58.7 mmol, 1.4 equiv.) was added to a stirred suspension of methyl triphenylphosphonium bromide (22.47 g, 62.90 mmol, 1.50 equiv.) in tetrahydrofuran (150 mL) at –78 °C. After 30 minutes, the mixture was warmed to 0 °C, stirred for 30 minutes, then cooled to –78 °C. A solution of the aldehyde prepared above in tetrahydrofuran (30 mL) was added via cannula. After 1 h, the mixture was warmed to 23 °C, stirred for 1 h, then diluted with distilled water (100 mL) and diethyl ether (100 mL). The phases were separated and the aqueous phase was washed with diethyl ether (2 x 100 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford the desired (2*S*)-*N*–*tert*–butoxycarbonyl-2-ethenylpyrrollidine **47** as a

colourless oil (6.12 g, 31.0 mmol, 71% for 4 steps). ^{1}H NMR δ ($C_6D_5CD_3$, 105 °C) 5.61 (m, 1H), 4.84-4.97 (m, 2H), 4.13 (m, 1H), 3.21-3.26 (m, 2H), 1.11-1.75 (m, 4H), 1.36 (s, 9H). ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 153.6, 139.5, 112.8, 78.0, 58.8, 46.1, 31.5, 28.2, 22.9.

(7*S*)-1-Aza-4-thiabicyclo[5.3.0]-2-decanone 33 via peptide coupling.



Borane-tetrahydrofuran complex (1.0 M in tetrahydrofuran, 131.8 mL, 131.8 mmol, 1.3 equiv.) was added to a stirred solution of cyclohexene (27.7 mL, 273.7 mmol, 2.7 equiv.) in tetrahydrofuran (400 mL) at 0 °C. After 1.5h, a solution of (2*S*)-*N*–*tert*–butoxycarbonyl-2-ethenylpyrrollidine (20.00 g, 101.4 mmol, 1.0 equiv.) in tetrahydrofuran (150 mL) was added via cannula. After 10 minutes the reaction was to 23 °C and stirred for 1 h. The mixture was warmed to 35 °C and aqueous sodium hydroxide solution (3 M, 60 mL) and 30% aqueous hydrogen peroxide (125 mL) were added via pipette. The pH of the mixture was adjusted to pH 12 using 3 M aqueous sodium hydroxide solution and the mixture was stirred at 35 °C for 1.5 h. After cooling to 23 °C, the mixture was saturated with solid sodium chloride and diethyl ether (300 mL) was added. After separating the layers, the aqueous phase was extracted with diethyl ether (2 x 150 mL). The combined organic phases were dried over anhydrous

sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica eluting with 25% ethyl acetate in hexanes to afford the known (2*S*)-2-(2-(*N*-*tert*-butoxycarbonyl)pyrrolidine)ethanol[2] as a colourless oil (20.14 g, 93.55 mmol, 92%).

Methanesulfonyl chloride (2.80 mL, 36.2 mmol, 1.2 equiv.) was added dropwise to a stirred solution of (2*S*)-2-(2-(*N*-*tert*-butoxycarbonyl)pyrrolidine)ethanol (6.50 g, 30.2 mmol, 1.0 equiv.) and triethylamine (5.47 mL, 39.2 mmol, 1.3 equiv.) in dichloromethane (100 mL) at 0 °C. After 2 h, saturated ammonium chloride solution (50 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

Methyl thioglycolate (5.67 mL, 63.4 mmol, 2.1 equiv.) was added to a slurry of sodium hydride (60% w/w in mineral oil, 0.242 g, 60.4 mmol, 2.0 equiv.) in *N,N*–dimethylformamide (100 mL) at 23 °C. After 10 minutes, the mesylate prepared above was added as a solution in *N,N*-dimethylformamide (50 mL) via cannula. After stirring for 3.5 h, aqueous hydrochloric acid solution (0.2 M, 10 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned between water (100 mL) and 2:1 diethyl ether:hexanes (150 mL). The layers were separated and the aqueous layer was extracted with 2:1 diethyl ether:hexanes (2 x 150 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford methyl 5-((2*S*)-2-(*N*-benzyloxycarbonyl)pyrrolidine)-3-thiapentanoate **48** (7.75 g, 25.5 mmol, 85%). ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 3.75 (m, 1H), 3.38 (s, 3H), 2.97-3.36 (m, 2H), 2.97 (AB, 2H, J = 17.3 Hz), 2.36-2.62 (m, 2H), 1.98 (m, 1H), 1.19-

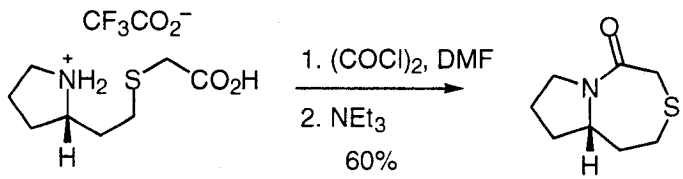
1.66 (m, 5H), 1.42 (s, 9H). ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 169.8, 154.0, 78.3, 56.5, 51.0, 46.2, 34.3, 33.2, 30.4, 29.5, 28.3, 23.3. HRFABMS *m/z* 304.1583 ($M+H^+$, $C_{14}H_{26}NO_4S$ requires 304.1581).

Methyl 5-((2*S*)-2-(*N*-benzyloxycarbonyl)pyrrolidine)-3-thiapentanoate **48** (5.48 g, 18.1 mmol, 1.0 equiv.) was combined with lithium hydroxide monohydrate (1.52g, 36.2 mmol, 2.0 equiv.) in tetrahydrofuran (25 mL) and water (25 mL) at 23 °C. After stirring for 5.5 h, the mixture was concentrated in vacuo and the residue was partitioned between aqueous sodium hydroxide solution (0.5 M, 35 mL) and dichloromethane (25 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 25 mL). The combined organic layers were extracted with aqueous sodium hydroxide solution (0.2 M, 5 x 15 mL). The combined aqueous layers were acidified to pH 2 by addition of aqueous hydrochloric acid solution (1 M) and the resulting solution was extracted with ethyl acetate (3 x 75 mL). Combined ethyl acetate layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was dissolved in trifluoroacetic acid (20 mL) at 23 °C. After stirring for 30 min, the mixture was concentrated in vacuo.

A solution of the residue and triethylamine (5.04 mL, 36.3 mmol, 2.0 equiv.) in dichloromethane (45 mL) was added over 10 h to a stirred solution of hydroxybenzotriazole (3.18 g, 23.5 mmol, 1.3 equiv.) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.51 g, 23.5 mmol, 1.3 equiv.) in dichloromethane (15 mL) at 23 °C. After stirring for a total of 24 h, the sample was diluted with diethyl ether (50 mL) and extracted sequentially with aqueous hydrochloric acid solution (0.2 M, 3 x 50 mL), saturated aqueous sodium bicarbonate solution (3 x 50 mL), and brine (1 x

50 mL). The combined brine and sodium bicarbonate layers were extracted with dichloromethane (1 x 50 mL). The combined aqueous hydrochloric acid layers were extracted with dichloromethane (1 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of 50% ethyl acetate in hexanes to ethyl acetate to afford (7*S*)-1-aza-4-thiabicyclo[5.3.0]-2-decanone **33** (1.92 g, 11.21 mmol, 62% for 3 steps) as a white solid. ^{1}H NMR ($CDCl_3$) δ 3.82 (m, 1H), 3.65 (m, 1H), 3.40-3.48 (m, 2H), 3.15 (dd, 1H, *J* = 1.8, 14.7 Hz), 2.92 (m, 1H), 2.78 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.67-1.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.2, 58.6, 47.0, 36.5, 36.0, 34.8, 33.1, 23.1. Anal. Calcd for $C_8H_{13}NOS$: C, 56.10; H, 7.65; N, 8.18. Found: C, 56.26; H, 7.79; N, 7.98.

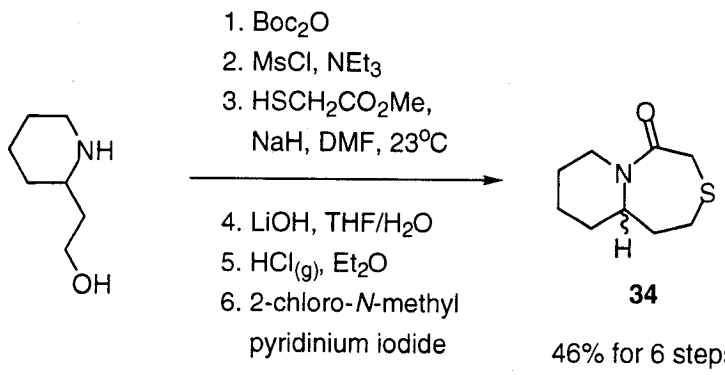
(7*S*)-1-Aza-4-thiabicyclo[5.3.0]-2-decanone 33 via intramolecular amine acylation with an acid chloride prepared from amino acid trifluoroacetate salt 49.



Oxalyl chloride (0.332 mL, 3.80 mmol, 1.05 equiv.) was added to a stirred solution of *N,N*–dimethylformamide (10% v/v in methylene chloride, 0.056 mL, 0.072 mmol, 0.02 equiv.) and amino acid trifluoroacetate salt **49** (prepared by the procedure above, 1.10 g, 3.62 mmol, 1.0 equiv.) in methylene chloride (30 mL). Gas evolution was observed and the mixture was stirred at room temperature for 3.5 h and concentrated in vacuo. The residue was diluted with methylene chloride (250 mL) and triethylamine

(1.51 mL, 10.9 mmol, 3.0 equiv.) was added over 3 minutes. The mixture was stirred at room temperature for 13.5 h, heated at reflux for two hours, cooled to room temperature and extracted with aqueous hydrochloric acid solution (1 M, 3 x 40 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel to afford (7*S*)-1-Aza-4-thiabicyclo[5.3.0]-2-decanone **33** (405 mg, 2.36 mmol, 65% (60% over 3 steps)) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 3.82 (m, 1H), 3.65 (m, 1H), 3.40-3.48 (m, 2H), 3.15 (dd, 1H, *J* = 1.8, 14.7 Hz), 2.92 (m, 1H), 2.78 (m, 1H), 2.22 (m, 1H), 2.04 (m, 1H), 1.67-1.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.2, 58.6, 47.0, 36.5, 36.0, 34.8, 33.1, 23.1.

1-Aza-4-thiabicyclo[5.4.0]-2-undecanone 34.



34

46% for 6 steps

Di-*tert*-butyl dicarbonate (2.66 g, 12.2 mmol, 1.05 equiv.) was added to a stirred solution of ±-2-(2-piperidine)ethanol (90%, technical grade, 1.50 g, 11.6 mmol, 1.0 equiv.) and triethylamine (1.78 mL, 12.8 mmol, 1.1 equiv.) in tetrahydrofuran at 23 °C. After stirring for 3 h, 15 mL of 0.2 M aqueous hydrochloric acid solution was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

The residue was dissolved in dichloromethane (15 mL) at 0 °C and triethylamine (2.42 mL, 17.4 mmol, 1.5 equiv.) and methanesulfonyl chloride (0.813 mL, 16.3 mmol, 1.4 equiv.) were added sequentially. After stirring for 2.5 h, saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexanes to provide the desired mesylate (2.91 g, 9.11 mmol, 87% for 2 steps based on 90% (w/w) purity of ±-2-(2-piperidine)ethanol).

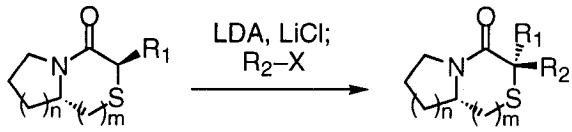
Methyl thioglycolate (1.71 mL, 19.1 mmol, 2.1 equiv.) was added to a slurry of sodium hydride (60% w/w in mineral oil, 0.729 g, 18.2 mmol, 2.0 equiv.) in *N,N*–dimethylformamide (40 mL) at 23 °C. After 10 minutes, the mesylate prepared above was added as a solution in *N,N*-dimethylformamide (15 mL) via cannula. After stirring for 3 h, aqueous hydrochloric acid solution (0.2 M, 10 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned between aqueous sodium hydroxide solution (1.0 M, 20 mL) and diethyl ether (40 mL). The layers were separated and the organic layer was extracted with aqueous sodium hydroxide solution (1.0 M, 15 mL). The combined aqueous layers were extracted with 2:1 diethyl ether:hexanes (35 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford the desired product contaminated with disulfide byproducts and was used directly in the subsequent lactamization process.

The thioether was combined with lithium hydroxide monohydrate (0.765 g, 18.2 mmol, 2.0 equiv.) in tetrahydrofuran (25 mL) and water (25 mL) at 23 °C. After stirring for 4 h, the mixture was concentrated in vacuo and the residue was partitioned between aqueous sodium hydroxide solution (0.5 M, 35mL) and dichloromethane (25 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 25 mL). The combined organic layers were extracted with aqueous sodium hydroxide solution (0.2 M, 5 x 15 mL). The combined aqueous layers were acidified to pH 1 by addition of aqueous sulfuric acid solution (6 M) and the resulting solution was extracted with ethyl acetate (3 x 75 mL). Combined ethyl acetate layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

The residue was dissolved in diethyl ether (50 mL) at 23 °C. Hydrogen chloride gas was bubbled through the solution for 2 h. The solvent was removed in vacuo and the residue was combined with triethylamine (2.88 mL, 20.7 mmol, 3.0 equiv.) and 2-chloro-*N*-methylpyridinium iodide (2.00 g, 7.82 mmol, 1.25 equiv.) in dichloromethane (80 mL) at 23°C. After stirring at 23 °C for 16 h, the mixture was diluted with ethyl acetate (150 mL) and extracted with aqueous hydrochloric acid solution (1 M, 3 x 15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 50% ethyl acetate in hexanes to afford 1-aza-4-thiabicyclo[5.4.0]-2-undecanone **34** (0.882 g, 4.76 mmol, 46% overall based on 90% (w/w) purity of ±-2-(2-piperidine)ethanol) as a white solid. ^{1}H NMR ($CDCl_3$) δ 4.17 (d_{br}, 1H, J = 14.9 Hz), 3.96 (m, 1H), 3.72 (d, 1H, J = 12.4 Hz), 3.09 (d, 1H, 12.4 Hz), 2.39-2.65 (m, 3H), 2.06 (m, 1H), 1.26-1.75 (m, 7H); ^{13}C

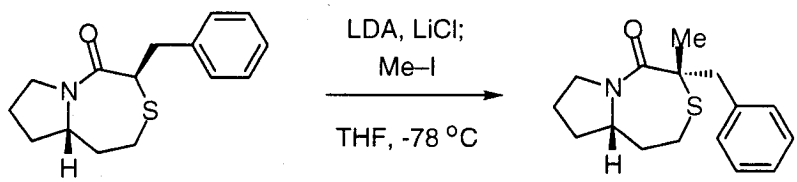
NMR ($CDCl_3$) δ 169.3, 53.0, 38.1, 33.4, 30.7, 28.9, 28.6, 24.0, 19.1. Anal. Calcd for $C_9H_{15}NOS$: C, 58.34; H, 8.16; N, 7.56. Found: C, 58.67; H, 8.24; N, 7.50.

Sample procedure for alkylation with alkyl halides:



m,n = 1,2
R_1 = H, alkyl

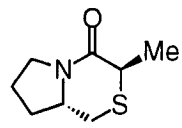
Synthesis of (3*S*,7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51e via alkylation of (3*R*,7*S*)-1-aza-3-benzyl-4-thiabicyclo[5.3.0]-2-decanone with methyl iodide.



A solution of *n*-butyllithium in hexanes (2.51 M, 0.408 mL, 1.02 mmol, 1.10 equiv.) was added to a slurry of diisopropylamine (0.150 mL, 1.07 mmol, 1.15 equiv.) and lithium chloride (.197 g, 4.65 mmol, 5.0 equiv.) in tetrahydrofuran (8 mL) at –78 °C. After 30 minutes, a solution of (3*R*,7*S*)-1-aza-3-benzyl-4-thiabicyclo[5.3.0]-2-decanone (243 mg, .930 mmol, 1.0 equiv.) in tetrahydrofuran (4 mL) was added via cannula. The resulting mixture was stirred for 30 minutes, at which time, methyl iodide (64 μL, 1.04 mmol, 1.1 equiv.) was added dropwise. Stirring was continued for 2.5 h at –78 °C, until TLC showed no reaction progress. Saturated aqueous ammonium chloride solution (5 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 20% ethyl acetate in hexanes to afford (3*S*,7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51** (224 mg, .813 mmol, 88%) as a colourless oil. ^{1}H

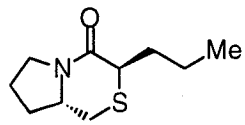
NMR ($CDCl_3$) δ 7.35-7.38 (m, 2H), 7.10-7.21(m, 3H), 4.53 (m, 1H), 3.57 (d, 1H, J = 13.2 Hz), 3.40-3.53 (m, 2H), 2.82 (d, 1H, J = 13.2 Hz), 2.45 (m, 1H), 1.93-2.05 (m, 2H), 1.38-1.77 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 171.7, 138.1, 132.0, 127.6, 126.5, 55.8, 54.2, 49.1, 48.0, 33.8, 32.8, 28.0, 26.7, 21.7. Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.64; N, 5.06. The product was determined to have >99% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 200 °C, R_t = 18.9 minutes (minor diastereomer), 19.7 minutes (major diastereomer)).

(3*R*,6*S*)-1-Aza-3-methyl-4-thiabicyclo[4.3.0]-2-nonanone.



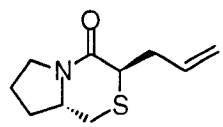
The alkylation was carried out at –78 °C over 3 h using 1.15 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 50% ethyl acetate in hexanes to afford (3*R*,6*S*)-1-aza-3-methyl-4-thiabicyclo[4.3.0]-2-nonanone as a colourless oil in 88% yield. The product was determined to have 81% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 3.27 (m, 1H), 2.88-3.01(m, 2H), 2.30 (m, 1H), 2.09 (m, 1H), 1.61 (m, 1H), 1.15-1.41 (m, 2H), 1.00 (m, 1H), 0.88 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 61.5, 46.2, 37.2, 33.7, 31.0, 21.8, 18.7. Anal. Calcd for $C_8H_{13}NOS$: C, 56.10; H, 7.65; N, 8.18. Found: C, 55.78; H, 7.73; N, 8.10.

(3*R*,6*S*)-1-Aza-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone.



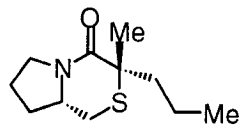
The alkylation was carried out at –40 °C over 3 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*R*,6*S*)-1-aza-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone as a pale yellow solid in 84% yield. The product was determined to have 88% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 3.59 (m, 1H), 3.14-3.27 (m, 2H), 2.53 (m, 1H), 2.27 (m, 1H), 1.86 (m, 1H), 1.56-1.72 (m, 2H), 1.06-1.48 (m, 5H), 0.57 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 167.5, 60.8, 46.6, 43.1, 36.0, 33.9, 31.3, 22.0, 20.1, 13.7. Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.23; H, 8.43; N, 6.93.

(3*R*,6*S*)-1-Aza-3-allyl-4-thiabicyclo[4.3.0]-2-nonanone.



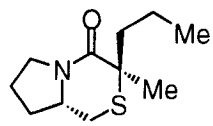
The alkylation was carried out at –78 °C over 3 h using 1.15 equiv. of allyl bromide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*R*,6*S*)-1-aza-3-allyl-4-thiabicyclo[4.3.0]-2-nonanone as a pale yellow solid in 88% yield. The product was determined to have 85% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 5.45 (m, 1H), 4.70-4.81(m, 2H), 3.47 (m, 1H), 3.13-3.28 (m, 2H), 2.43-2.55 (m, 2H), 1.16-2.32 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 166.5; 134.6, 117.6, 61.3, 46.6, 42.7, 37.8, 33.9, 31.1, 22.0. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found: C, 60.51, H, 7.45, N, 7.10.

(3*S*,6*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone 50a.



The alkylation was carried out at –78 °C over 2 h using 1.2 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford (3*S*,6*S*)-1-aza-3-methyl-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone **50a** as a colourless oil in 94% yield. ^{1}H NMR ($CDCl_3$) δ 3.50 (m, 1H), 3.16-3.21 (m, 2H), 2.27-2.63 (m, 2H), 1.81 (m, 1H), 0.96-1.66 (m, 7H), 1.08 (s, 3H), 0.55 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.7, 62.3, 48.1, 46.6, 44.6, 34.1, 30.2, 27.7, 22.1, 18.3, 14.3. Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.93; H, 8.98; N, 6.57. Found: C, 61.55; H, 9.03; N, 6.54. The product was determined to have 72% de by GC analysis (HP-5 column (Crosslinked 5% Ph Me Siloxane), He carrier gas, 14 psi, oven temperature = 92 °C, R_t = 150.8 minutes (minor diastereomer), 153.6 minutes (major diastereomer)).

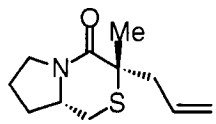
(3*R*,6*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone 50b.



The alkylation was carried out at –78 °C over 30 min then 0 °C over 1.25 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford (3*R*,6*S*)-1-aza-3-methyl-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone **50b** as a colourless oil in 88% yield. ^{1}H NMR ($CDCl_3$) δ 3.57 (m, 1H), 3.24-3.32 (m, 2H), 2.36-2.66 (m, 2H), 1.89 (m, 1H), 0.98-1.71 (m, 7H),

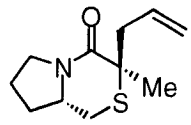
1.29 (s, 3H), 0.62 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.6, 62.5, 48.9, 46.7, 43.4, 34.1, 29.4, 29.4, 22.3, 18.4, 14.3. Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.93; H, 8.98; N, 6.57. Found: C, 61.70; H, 8.98; N, 6.41. The product was determined to have 72% de by GC analysis (HP-5 column (Crosslinked 5% Ph Me Siloxane), He carrier gas, 14 psi, oven temperature = 92 °C, R_t = 150.8 minutes (major diastereomer), 153.6 minutes (minor diastereomer)).

(3*S*,6*S*)-1-Aza-3-methyl-3-allyl-4-thiabicyclo[4.3.0]-2-nonanone 50c.



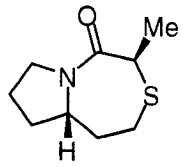
The alkylation was carried out at –78 °C over 2 h using 1.2 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexanes to afford (3*S*,6*S*)-1-aza-3-methyl-3-allyl-4-thiabicyclo[4.3.0]-2-nonanone **50c** as a colourless oil in 91% yield. ^{1}H NMR ($CDCl_3$) δ 5.47 (m, 1H), 4.67-4.75 (m, 2H), 3.46 (m, 1H), 3.05-3.20 (m, 2H), 2.23-2.44 (m, 3H), 2.02 (dd, 1H, J = 8.1, 13.6 Hz), 1.75 (m, 1H), 1.55 (m, 1H), 1.38 (m, 1H), 1.16 (m, 1H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.0, 133.9, 118.3, 62.3, 47.3, 46.6, 46.1, 34.0, 29.8, 27.0, 22.1. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.39; H, 8.14; N, 6.62. The product was determined to have 79% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 10.2 minutes (major diastereomer), 10.6 minutes (minor diastereomer)).

(3*R*,6*S*)-1-Aza-3-methyl-3-allyl-4-thiabicyclo[4.3.0]-2-nonanone 50d.



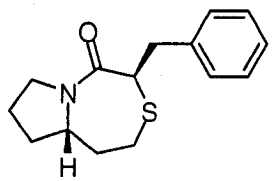
The alkylation was carried out at –78 °C over 3 h using 1.2 equiv. of allyl bromide. The reaction was purified by chromatography on silica gel eluting with 35% ethyl acetate in hexanes to afford (3*R*,6*S*)-1-aza-3-methyl-3-allyl-4-thiabicyclo[4.3.0]-2-nonanone (**4d**) as a colourless oil in 86% yield. ^{1}H NMR ($CDCl_3$) δ 5.50 (m, 1H), 4.82-4.86 (m, 2H), 3.54 (m, 1H), 3.16-3.28 (m, 2H), 2.33-2.69 (m, 3H), 2.13 (dd, 1H, J = 7.4, 14.0 Hz), 1.85 (m, 1H), 1.65 (m, 1H), 1.48 (m, 1H), 1.25 (s, 3H), 1.23 (m, H); ^{13}C NMR ($CDCl_3$) δ 170.0, 133.5, 118.5, 62.3, 46.6, 45.1, 34.1, 29.4, 28.4, 22.2. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.43; H, 8.14; N, 6.57. The product was determined to have 78% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 10.2 minutes (minor diastereomer), 10.6 minutes (major diastereomer)).

(3*R*,7*S*)-1-Aza-3-methyl-4-thiabicyclo[5.3.0]-2-decanone.



The alkylation was carried out at –78 °C over 2 h using 1.2 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 50% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a white solid in 86% yield. The product was determined to have 93% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 4.0 (m, 1H), 3.32-3.58 (m, 3H), 2.84 (m, 1H), 2.49 (m, 1H), 2.04 (m, 1H), 1.51-1.92 (m, 5H), 1.46 (d, 3H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.2, 56.2, 48.6, 43.2, 35.6, 34.5, 26.6, 22.2, 16.8. Anal. Calcd for $C_9H_{15}NOS$: C, 58.34; H, 8.16; N, 7.56. Found: C, 58.37; H, 8.18; N, 7.40.

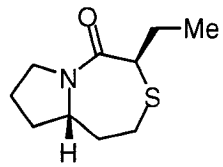
(3*R*,7*S*)-1-Aza-3-benzyl-4-thiabicyclo[5.3.0]-2-decanone 53.



The alkylation was carried out at –78 °C over 3 h using 1.2 equiv. of benzyl bromide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-benzyl-4-thiabicyclo[5.3.0]-2-decanone **53** as a white solid in 90% yield. The product was determined to have >95% de by ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$) δ 7.26-7.17 (m, 5H), 4.07 (m, 1H), 3.88 (m, 1H), 3.42-3.45 (m, 2H), 2.89 (m, 1H), 2.55 (m, 1H), 1.59-2.03 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 170.4, 137.9, 129.4, 128.6, 127.1, 55.8, 50.8, 48.5, 36.9, 35.3, 33.9, 26.9, 22.1. Anal. Calcd for

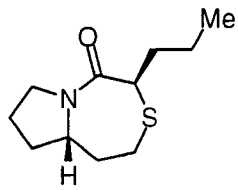
$C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.83; H, 7.42; N, 5.07.

(3*R*,7*S*)-1-Aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone.



The alkylation was carried out at –40 °C over 3 h using 2.0 equiv. of ethyl iodide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 80% yield. The product was determined to have 87% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 3.92 (m, 1H), 3.18-3.41 (m, 3H), 2.76 (m, 1H), 2.36 (ddd, 1H, J = 3.8, 6.3, 14.8 Hz), 1.46-2.03 (m, 8H), 0.84 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 56.1, 50.7, 48.5, 36.0, 34.5, 26.1, 23.0, 22.2, 12.2. Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.02; H, 8.69; N, 6.71.

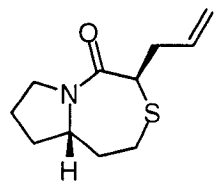
(3*R*,7*S*)-1-Aza-3-propyl-4-thiabicyclo[5.3.0]-2-decanone.



The alkylation was carried out at –40 °C over 3 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-ethyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 76% yield. The product was determined to have 88% de by ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$) δ 3.90 (m, 1H), 3.21-3.40 (m, 3H), 2.75 (m, 1H), 2.34 (ddd,

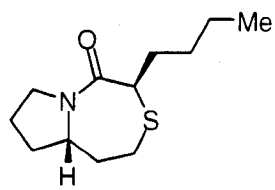
1H, J = 3.8, 6.3, 14.8 Hz), 1.97 (m, 1H), 1.08-1.83 (m, 9H), 0.73 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 56.1, 48.7, 48.5, 36.0, 34.5, 26.2, 22.2, 20.7, 13.8. Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.93; H, 8.98; N, 6.57. Found: C, 62.05; H, 8.90; N, 6.47.

(3*R*,7*S*)-1-Aza-3-allyl-4-thiabicyclo[5.3.0]-2-decanone.



The alkylation was carried out at –78 °C over 3 h using 1.2 equiv. of benzyl bromide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-allyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 86% yield. The product was determined to have 85% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.09-5.19 (m, 2H), 4.19 (m, 1H), 3.49-3.67 (m, 3H), 2.59-3.01 (m, 4H), 2.02 (m, 1H), 1.70-1.87 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.8, 134.4, 117.6, 56.1, 48.5, 48.5, 35.7, 34.6, 34.4, 26.5, 22.2. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.61; H, 8.25; N, 6.32.

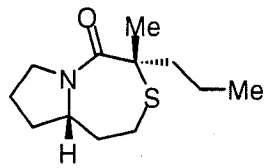
(3*R*,7*S*)-1-Aza-3-butyl-4-thiabicyclo[5.3.0]-2-decanone.



The alkylation was carried out at –40 °C over 3 h, 15 minutes using 2.0 equiv. of *n*–butyl iodide. The reaction was purified by chromatography on silica gel eluting with 30%

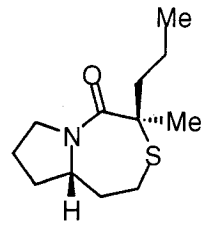
ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-butyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 80% yield. The product was determined to have 94% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 4.14 (m, 1H), 3.48-3.61 (m, 3H), 2.95 (ddd, 1H, J = 3.7, 9.5, 15.0 Hz) 2.58 (ddd, 1H, J = 3.7, 6.7, 15.0 Hz), 2.18 (m, 1H), 1.69-2.05 (m, 7H), 1.30-1.54 (m, 4H), 0.91 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 56.1, 49.0, 48.4, 36.0, 34.5, 29.6, 29.4, 26.2, 22.3, 22.2, 14.0.

(3*S*,7*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51a.



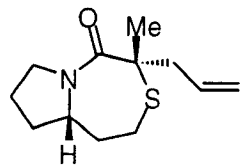
The alkylation was carried out at –78 °C over 4 h using 1.2 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 35% ethyl acetate in hexanes to afford (3*S*,7*S*)-1-aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone **51a** as a colourless oil in 90% yield. ^{1}H NMR ($CDCl_3$) δ 4.50 (m, 1H), 3.42-3.59 (m, 2H), 2.83 (m, 1H), 2.62 (m, 1H), 1.99-2.16 (m, 2H), 1.41-1.84 (m, 8H), 1.48 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 65.4, 56.0, 48.7, 45.8, 34.2, 32.9, 28.6, 26.4, 21.8, 18.5, 14.7. Anal. Calcd for $C_{12}H_{21}NOS$: C, 63.39; H, 9.31; N, 6.16. Found: C, 63.67; H, 9.32; N, 6.07. The product was determined to have 90% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 14.1 minutes (minor diastereomer), 14.9 minutes (major diastereomer)).

(3*R*,7*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51b.



The alkylation was carried out at 0 °C over 4.5 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 35% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone **51b** as a white solid in 90% yield. ^{1}H NMR ($CDCl_3$) δ 4.25 (m, 1H), 3.43-3.48 (m, 2H), 2.87 (ddd, 1H, *J* = 4.7, 7.4, 14.9 Hz), 2.52 (ddd, 1H, *J* = 4.7, 7.4, 14.9 Hz), 2.07 (m, 1H), 1.54-1.94 (m, 7H), 1.14-1.47 (m, 2H), 1.40 (s, 3H), 0.82 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 56.1, 51.7, 49.0, 40.4, 35.1, 33.9, 27.6, 27.5, 21.8, 18.0, 14.4. Anal. Calcd for $C_{12}H_{21}NOS$: C, 63.39; H, 9.31; N, 6.16. Found: C, 63.38; H, 9.25; 6.08. The product was determined to have 90% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 14.1 minutes (major diastereomer), 14.9 minutes (minor diastereomer)).

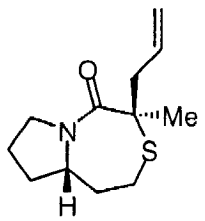
(3*S*,7*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51c.



The alkylation was carried out at –78 °C over 3.5 h using 1.2 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*S*,7*S*)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51c**

as a colourless oil in 85% yield. The product was determined to have 95% de by GC analysis: ^{1}H NMR ($CDCl_3$) δ 5.95 (m, 1H), 5.04-5.13 (m, 2H), 4.43 (m, 1H), 3.48-3.54 (m, 2H), 2.78-2.87 (m, 2H), 2.63 (m, 1H), 2.42 (dd, 1H, *J* = 7.8, 13.1 Hz), 2.12 (m, 1H), 1.61- 1.86 (m, 5H) 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 135.2, 118.4, 56.2, 51.8, 49.0, 47.0, 34.7, 33.5, 28.4, 25.1, 21.8. Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50; N, 6.22. Found: C,63.85; H, 8.47; N, 6.09. The product was determined to have 95% de by chiral GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 14.7 minutes (major diastereomer), 15.5 minutes (minor diastereomer)).

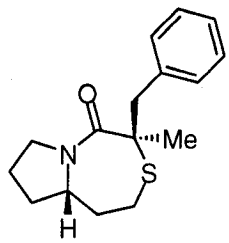
(3*R*,7*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51d.



The alkylation was carried out at –78 °C over 2 h using 1.1 equiv. of allyl bromide. The reaction was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51d** as a white solid in 96% yield. The product was determined to have 87% de by chiral GC analysis: ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 1H), 5.00-5.07 (m, 2H), 4.29 (m, 1H), 3.45-3.48 (m, 2H), 2.40-2.95 (m, 4H), 2.09 (m, 1H), 1.58-1.91(m, 5H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 132.9, 118.7, 56.4, 51.3, 49.2, 42.4, 35.1, 34.1, 27.8, 27.8, 21.9. Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50; N, 6.22. Found: C, 63.85; H, 8.47; N, 6.09. The product was determined to have 87% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 14.7 minutes (minor diastereomer),

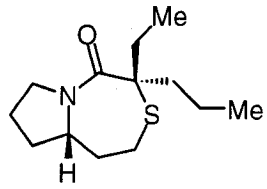
15.5 minutes (major diastereomer)).

(3*R*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51f.



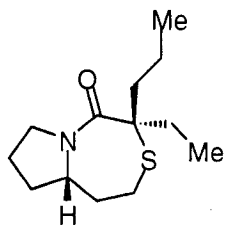
The alkylation was carried out at –78 °C over 2.5 h using 1.3 equiv. of benzyl bromide. The reaction was purified by chromatography on silica gel eluting with 20% *e*thyl acetate in hexanes to afford (3*R*,7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51f** as a white solid in 91% yield. ^{1}H NMR ($CDCl_3$) δ 7.11-7.19 (m, 5H), 3.88 (m, 1H), 3.50 (m, 1H), 3.32 (m, 1H), 2.97 (AB, 2H, J = 13.5 Hz), 2.80 (m, 1H), 2.59 (m, 1H), 1.49-1.62 (m, 6H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 136.9, 130.5, 128.0, 127.1, 55.3, 54.9, 48.9, 46.4, 34.0, 32.5, 30.6, 27.3, 21.7. Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.69; N, 4.97. The product was determined to have >99% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 200 °C, R_t = 18.9 minutes (major diastereomer), 19.7 minutes (minor diastereomer)). (3*R*,7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51f** was recrystallized from toluene at room temperature via passive evapouration of solvent. The resulting crystal was analyzed by X–ray crystallography (see Appendix).

(3*S*,7*S*)-1-Aza-3-ethyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51g.



The alkylation was carried out at –78 °C over 6 h using 2.0 equiv. of ethyl iodide. The reaction was purified by chromatography on silica gel eluting with 25% ethyl acetate in hexanes to afford (3*S*,7*S*)-1-aza-3-ethyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone **51g** as a colourless oil in 76% yield. ^{1}H NMR ($CDCl_3$) δ 4.50 (m, 1H), 3.37-3.51 (m, 2H), 2.76 (m, 1H), 2.54 (m, 1H), 1.81-2.04 (m, 3H), 1.35-1.74 (m, 9H), 0.83 (t, H, J = 7.4 Hz), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0, 58.0, 55.6, 48.6, 42.5, 33.9, 32.7, 31.7, 28.0, 21.6, 18.2, 14.8, 9.5. Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80. Found: C, 64.67; H, 9.35; N, 5.41. The product was determined to have 88% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 15.7 minutes (minor diastereomer), 16.3 minutes (major diastereomer)).

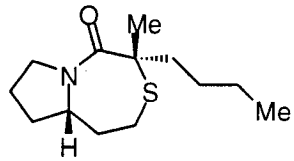
(3*R*,7*S*)-1-Aza-3-ethyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51h.



The alkylation was carried out at –78 °C over 6 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 25% ethyl acetate in hexanes to afford 3-(*R*)-7-(*S*)-1-aza-3-ethyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone **51h** as a colourless oil in 76% yield. ^{1}H NMR ($CDCl_3$) δ 4.48 (m, 1H), 3.32-3.47 (m,

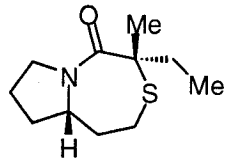
2H), 2.72 (m, 1H), 2.53 (m, 1H), 1.96-2.01 (m, 2H), 1.54-1.72 (m, 8H), 1.18-1.25 (m, 2H), 0.87 (t, 3H, J = 7.0 Hz), 0.75 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0, 58.0, 55.6, 48.5, 40.9, 33.9, 33.4, 32.6, 28.0, 21.6, 18.2, 14.6, 9.5. Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80. Found: C, 64.47; H, 9.61; N, 5.67. The product was determined to have 94% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 15.7 minutes (major diastereomer), 16.3 minutes (minor diastereomer)).

(3*S*,7*S*)-1-Aza-3-butyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51i.



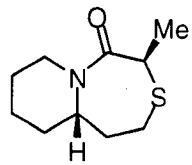
The alkylation was carried out at –78 °C over 3 h using 1.1 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford (3*S*,7*S*)-1-aza-3-butyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51i** as a colourless oil in 86% yield. ^{1}H NMR ($CDCl_3$) δ 4.52 (m, 1H), 3.46-3.60 (m, 2H), 2.86 (m, 1H), 2.65 (m, 1H), 1.20-2.17 (m, 10H), 1.50 (s, 3H), 0.90 (dt, J = 1.8, 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 55.5, 52.5, 48.3, 42.9, 33.8, 32.5, 28.2, 27.0, 25.9, 23.0, 21.3, 13.9. The product was determined to have 98% de by GC analysis after chromatography and 93% de by GC analysis before chromatography (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 180 °C, R_t = 12.1 minutes (minor diastereomer), 12.9 minutes (major diastereomer)).

(3*S*,7*S*)-1-Aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51j.



The alkylation was carried out at –78 °C over 3 h using 1.1 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford (3*S*,7*S*)-1-aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone as a colourless oil in 89% yield. ^{1}H NMR ($CDCl_3$) δ 4.52 (m, 1H), 3.44-3.59 (m, 2H), 2.84 (m, 1H), 2.63 (m, 1H), 2.08-2.17 (m, 2H), 1.73-1.83 (m, 4H), 1.58-1.71 (m, 2H) 1.48 (s, 3H), 1.02 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 55.7, 53.2, 48.4, 35.8, 33.9, 32.6, 28.3, 25.8, 21.5, 9.5. The product was determined to have 90% de by GC analysis (Chirasil Dex column, He carrier gas, 14 psi, oven temperature = 170 °C, R_t = 15.7 minutes (minor diastereomer), 16.3 minutes (major diastereomer)).

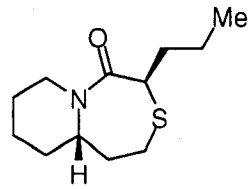
(3*R,7*S**)-1-Aza-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone.**



The alkylation was carried out at –78 °C over 3 h using 1.1 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexanes to afford (3*R**,7*S**)-1-aza-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone as a white solid in 95% yield. The product was determined to have 87% de by ^{13}C NMR analysis: ^{1}H NMR (CDCl3) δ 4.27 (m, 1H), 3.90-3.97 (m, 2H), 2.61-2.70 (m, 2H), 2.44

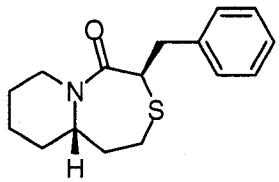
(m, 1H), 2.10 (m, 1H), 1.23-1.71 (m, 7H), 1.41 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 52.3, 42.6, 40.1, 29.6, 28.9, 28.2, 24.8, 20.6, 19.0. Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.16; H, 8.52; N, 6.89.

(3*R,7*S**)-1-Aza-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone.**



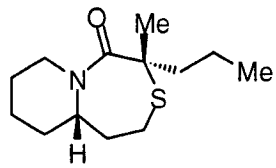
The alkylation was carried out at –40 °C over 2.25 h and 0 °C over 1.5 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexanes to afford (3*R**,7*S**)-1-aza-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone as a colourless oil in 95% yield. The product was determined to have 68% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 4.39 (m, 1H), 4.11 (m, 1H), 3.87 (dd, 1H, J = 6.8, 9.0 Hz), 2.64 (m, 1H), 2.31-2.53 (m, 2H), 2.09 (m, 1H), 1.88 (m, 1H), 1.53-1.73 (m, 5H), 1.21-1.48 (m, 5H), 0.83 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.2, 51.5, 49.3, 39.5, 36.2, 29.4, 28.5, 28.2, 24.9, 21.5, 20.2, 14.0. Anal. Calcd for $C_{12}H_{21}NOS$: C, 63.39; H, 9.31; N, 6.16. Found: C, 63.43; H, 9.28; N, 5.99.

(3*R,7*S**)-1-Aza-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone 54.**



The alkylation was carried out at –78 °C over 6 h and overnight at 23 °C using 1.1 equiv. of benzyl bromide. The reaction was purified by chromatography on silica gel eluting with 10%→20%→30% ethyl acetate in hexanes to afford (3*R**,7*S**)-1-aza-3-benzyl-4-thiabicyclo[5.4.0]-2-undecanone **54** as a colourless oil in 80% yield. The product was determined to have >95% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 7.19-7.32 (m, 5H), 4.51 (m, 1H), 4.29 (m, 1H), 4.18 (m, 1H), 3.34 (ddAB, 1H, *J* = 1.6, 9.5, 13.8 Hz), 3.08 (ddAB, *J* = 1.6, 9.4, 13.8 Hz), 2.50-2.78 (m, 3H), 2.19 (m, 1H), 1.35-1.84 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 168.9, 138.5, 128.8, 126.6, 51.5, 50.1, 39.4, 39.2, 28.8, 28.2, 28.7, 24.5, 19.9.

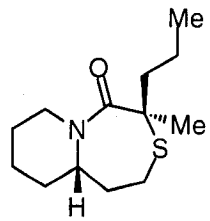
(3*S,7*S**)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone 52a.**



The alkylation was carried out at –40 °C over 21 h using 2.0 equiv. of *n*-propyl iodide. The reaction was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford (3*S**,7*S**)-1-aza-3-methyl-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone **52a** as a colourless oil in 81% yield. The product was determined to have 62% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 4.67 (m, 1H), 4.23 (d_{br}, 1H, *J* = 12.6

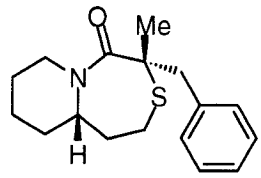
Hz), 2.64 (dd, 1H, J = 6.4, 15.1 Hz), 2.19-2.40 (m, 2H), 2.02 (dt, 1H, J = 5.2, 12.6 Hz), 1.08-1.88 (m, 11H), 1.42(s, 3H), 0.77 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9, 53.2, 51.4, 46.9, 38.9, 29.7, 28.4, 28.0, 27.1, 24.8, 19.9, 18.1, 14.6. Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80. Found: C, 64.66; H, 9.43; N, 5.81.

(3*R,7*S**)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone 52b.**



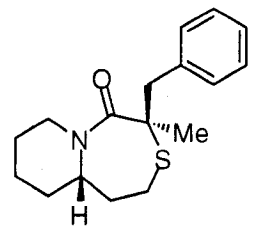
The alkylation was carried out at –78 °C over 3 h using 1.1 equiv. of methyl iodide. The reaction was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford (3*R**,7*S**)-1-aza-3-methyl-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone **52b** as a colourless oil in 81% yield. The product was determined to have 50% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 4.79 (m, 1H), 4.38 (m, 1H), 2.78 (dd, 1H, J = 5.9, 15.2 Hz), 2.46-2.55 (m, 2H), 2.17 (m, 1H), 1.97 (m, 1H), 1.24-1.83 (m, 10H), 1.56 (s, 3H), 0.92 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 53.5, 51.6, 47.2, 39.2, 29.9, 28.6, 28.3, 27.4, 25.1, 20.2, 18.3, 14.8. Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80. Found: C, 64.62; H,9.23; N, 5.76.

(3*S,7*S**)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone 52e.**



The alkylation was carried out at –78 °C over 6 h and overnight at 23 °C using 1.1 equiv. of benzyl bromide. The reaction was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford (3*S**,7*S**)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone **52e** as a white solid in 31% yield. The product was determined to have >95% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 7.19-7.44 (m, 5H), 4.89 (m, 1H), 4.41 (m, 1H), 3.36 (AB, 1H, J = 13.4 Hz), 3.16 (AB, 1H, J = 13.4 Hz), 2.68 (dd, J = 6.5, 15.2 Hz), 2.55 (m, 1H), 2.26 (m, 1H), 2.15 (m, 1H), 1.22-1.84 (m, 7H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 137.8, 132.1, 127.2, 126.2, 53.3, 51.4, 48.6, 39.2, 29.2, 28.3, 27.8, 26.5, 24.6, 19.8. Anal. Calcd for $C_{17}H_{23}NOS$: C, 70.54; H, 8.01; N, 4.84. Found: C, 70.22; H, 8.17; N, 4.75.

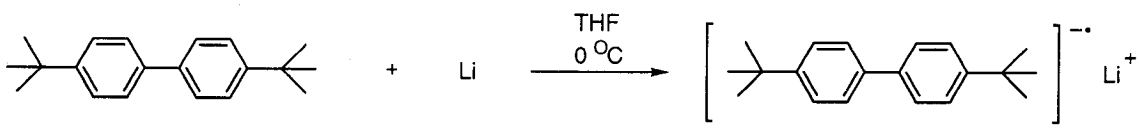
(3*R,7*S**)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone 52f.**



The alkylation was carried out at –78 °C over 6 h and overnight at 23 °C using 1.1 equiv. of benzyl bromide. The reaction was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford (3*R**,7*S**)-1-aza-3-benzyl-3-methyl-4-

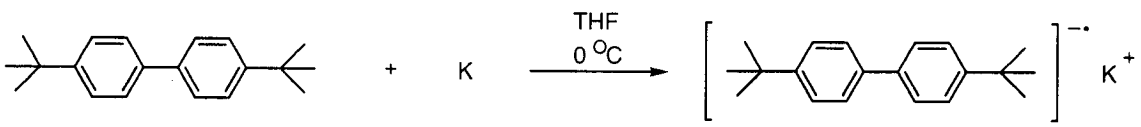
thiabicyclo[5.4.0]-2-undecanone **52f** as a colourless oil in 38% yield. The product was determined to have >95% de by ^{13}C NMR analysis: ^{1}H NMR ($CDCl_3$) δ 7.21-7.29 (m, 5H), 4.86 (m, 1H), 4.38 (m, 1H), 3.28 (AB, 1H, J = 13.8 Hz), 3.08 (AB, 1H, J = 13.8 Hz), 2.81 (dd, J = 6.5, 15.2 Hz), 2.51-2.59 (m, 2H), 2.18 (dt, 1H, J = 5.1, 12.3 Hz), 1.25-1.85 (m, 7H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0, 136.5, 130.2, 127.9, 126.8, 54.0, 51.7, 46.3, 39.2, 30.7, 28.5, 27.9, 26.5, 24.8, 19.7. Anal. Calcd for $C_{17}H_{23}NOS$: C, 70.54; H, 8.01; N, 4.84. Found: C, 70.67; H, 8.13; N, 4.71.

Preparation of Lithium 4,4′-di-*tert*-butylbiphenylide.



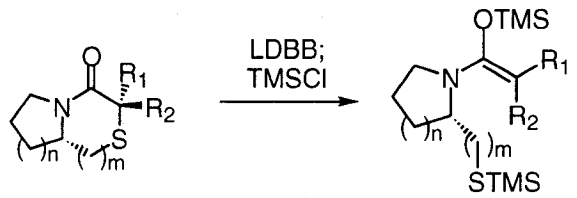
Lithium (0.172 g, 24.8 mmol, 1.1 equiv.) was pressed into thin sheets, rinsed in hexanes, tetrahydrofuran, methanol, and tetrahydrofuran and then added to a solution of 4,4′–di-*tert*-butylbiphenyl (6.0 g, 22.5 mmol, 1.0 equiv.) in tetrahydrofuran (50.0 mL) at 0 °C. Stirring was continued at 0 °C for 5 h, at which point the solution was stored under argon in a cryobath at 0 °C.

Preparation of Potassium 4,4′-di-*tert*-butylbiphenylide.

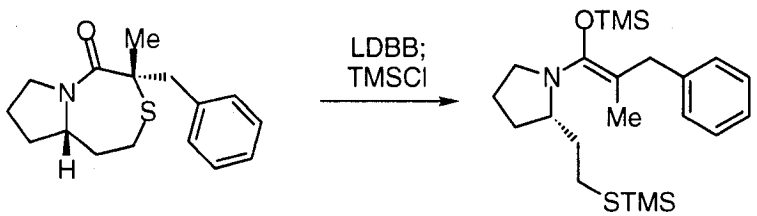


4,4′–Di-*tert*-butylbiphenyl (0.145 g, 0.546 mmol, 1.0 equiv.) was added to a Schlenk flask containing potassium (32 mg, 0.819 mmol, 1.5 equiv.) (pressed into thin sheets and rinsed in hexanes) and tetrahydrofuran (11.0 mL) at 0 °C. Stirring was continued at 0 °C for 4 h prior to use.

Sample procedure for sequential reductive enolization and trapping:



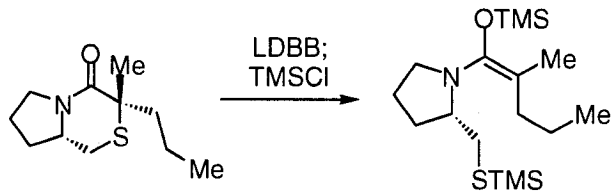
Reduction and trapping of (3*S*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51e.



A solution of lithium di-*tert*-butylbiphenylide (LDBB) in THF was added dropwise via glass syringe to a solution of (3*S*,7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone **51e** (68.5 mg, 249 μmol, 1.0 equiv.) in tetrahydrofuran (2.5 mL) in a Schlenk flask at –78 °C until the green colour of LDBB briefly persisted. Trimethylsilyl chloride (95 μL, 750 μmol, 3 equiv.) was immediately added and the mixture was stirred for 10 minutes at -78°C, at which point the cooling bath was removed and stirring was continued for 30 minutes. The solvent was removed by placing the contents of the flask under vacuum. After 1 h the flask was flushed with argon, the residue was triturated into C_6D_6 and the supernatant was transferred to an NMR tube. ^1H, ^{13}C and NOE difference NMR spectra were acquired. Note: The spectra of the product usually contain di-*tert*-butylbiphenyl and residual tetrahydrofuran, which may obscure some product resonances. ^1H NMR (C_6D_6) δ 7.05 (m, 5H), 3.26 (m, 2H), 3.14 (d, 1H, J = 14.7 Hz), 2.94 (m, 1H), 2.67 (m, 1H), 2.26-2.41 (m, 2H), 1.84 (m, 1H), 0.75-1.64 (m), 0.00-0.11 (m, 18H); ^{13}C

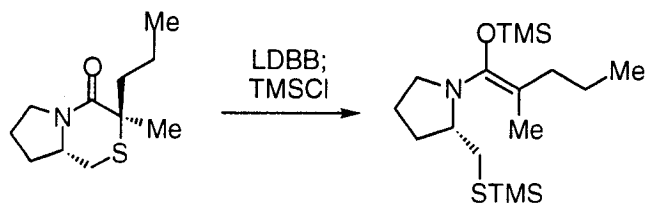
NMR (C_6D_6) δ 145.26, 141.71, 104.80, 57.53, 51.07, 39.26, 38.44, 31.16, 25.78, 24.45, 23.46, 16.42, 1.02, 0.95.

Reductive enolization and trapping of (3*S*,6*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone 50a.



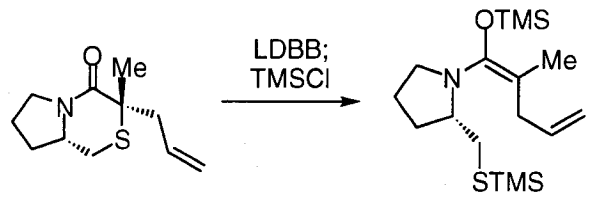
^{1}H NMR (C_6D_6) δ 3.48 (m, 1H), 3.12 (m, 1H), 2.81-2.97 (m, 2H), 2.04-2.42 (m, 3H), 0.89-1.78 (m, 12H), 0.09-0.45 (m, 18H); ^{13}C NMR (C_6D_6) δ 144.04, 109.25, 60.62, 52.05, 34.65, 31.18, 30.93, 24.02, 21.83, 15.92, 14.35, 0.95, 0.88.

Reductive enolization and trapping of (3*R*,6*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[4.3.0]-2-nonanone 50b.



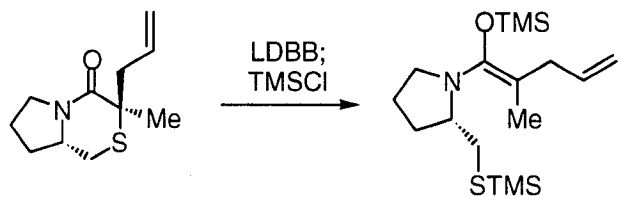
^{1}H NMR (C_6D_6) δ 3.50 (m, 1H), 3.13 (m, 1H), 2.81-2.96 (m, 2H), 2.01-2.42 (m, 3H), 0.90-1.80 (m, 12H), 0.30 (s, 9H), 0.24 (s, 9H); ^{13}C NMR (C_6D_6) δ 143.54, 107.56, 60.54, 51.14, 34.26, 30.97, 30.84, 24.12, 21.45, 16.48, 14.32, 1.04, 0.88.

Reductive enolization and trapping of (3*S*,6*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[4.3.0]-2-nonanone 50c.



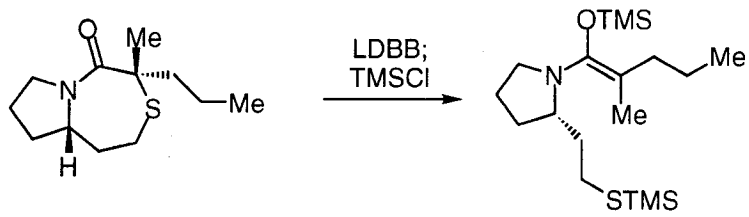
^{1}H NMR (C_6D_6) δ 5.88 (m, 1H), 5.05-5.15 (m, 2H), 3.54 (m, 1H), 2.78-3.22 (m, 3H), 2.38 (m, 1H), 2.08 (m, 1H), 0.98-1.80 (m, 8H), 0.01-0.49 (m, 18H). ^{13}C NMR (C_6D_6) δ 144.72, 138.09, 114.72, 114.72, 106.83, 60.32, 52.2, 37.60, 24.06, 16.12, 1.03, 0.82.

Reductive enolization and trapping of (3*R*,6*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[4.3.0]-2-nonanone 50d.



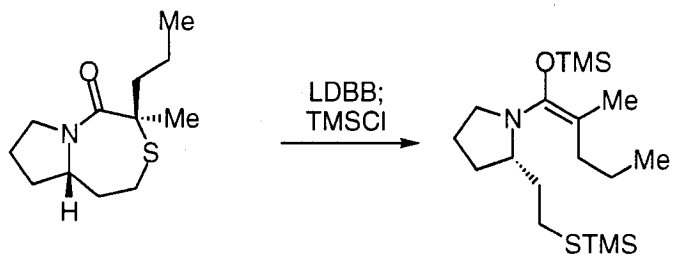
^{1}H NMR (C_6D_6) δ 5.89 (m, 1H), 5.05-5.17 (m, 2H), 3.58 (m, 1H), 2.81-3.22 (m, 3H), 2.40 (m, 1H), 2.09 (m, 1H), 0.98-1.82 (m, 8H), 0.07-0.46 (m, 18H); ^{13}C NMR (C_6D_6) δ 144.05, 137.28, 114.97, 104.38, 60.47, 51.24, 37.02, 24.25, 16.49, 1.00, 0.80.

Reductive enolization and trapping of (3*S*,7*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51a.



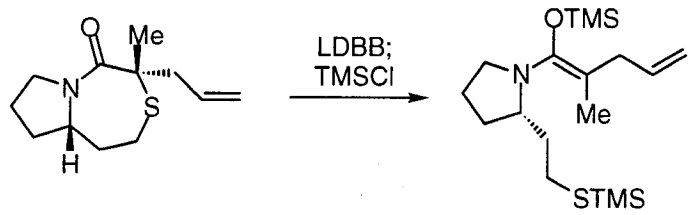
^{1}H NMR (C_6D_6) δ 3.36 (m, 1H), 3.09 (m, 1H), 2.84 (m, 1H), 2.52-2.58 (m, 2H), 0.91-2.18 (m), 0.08-0.43 (m, 19H); ^{13}C NMR (C_6D_6) δ 144.24, 106.85, 57.65, 50.89, 39.21, 31.05, 24.22, 23.46, 21.54,16.49, 14.40, 0.96, 0.92.

Reductive enolization and trapping of (3*R*,7*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51b.



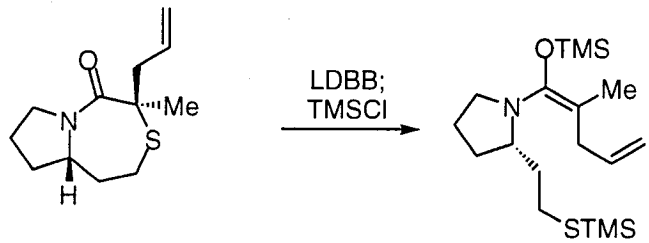
^{1}H NMR (C_6D_6) δ 3.31 (m, 1H), 2.77-3.07 (m, 2H), 1.96-2.58 (m, 5H), 0.85-1.79 (m), 0.00-0.34 (m, 18H); ^{13}C NMR (C_6D_6) δ 144.59, 108.83, 57.98, 51.59, 38.93, 34.85, 30.94, 24.00, 23.59, 21.86, 15.94, 14.40, 0.96, 0.92.

Reductive enolization and trapping of (3S,7S)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51c.



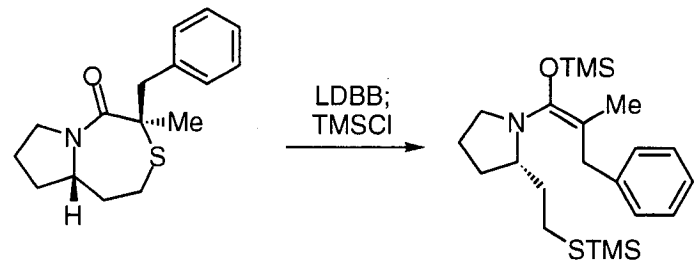
^{1}H NMR (C_6D_6) δ 5.90 (m, 1H), 5.00-5.12 (m, 2H), 3.36 (m, 1H), 3.10 (m, 1H), 2.72-3.00 (m, 2H), 2.47-2.53 (m, 2H), 0.84-2.03 (m), 0.01-0.46 (m, 18H); ^{13}C NMR (C_6D_6) δ 144.58, 137.17, 114.78, 103.34, 57.35, 50.80, 39.08, 36.79, 30.97, 24.19, 23.26, 16.26, 0.82, 0.72.

Reductive enolization and trapping of (3*R*,7*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51d.



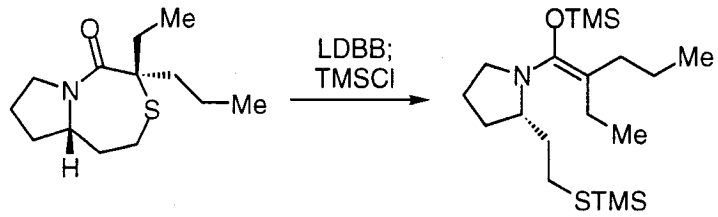
^{1}H NMR (C_6D_6) δ 5.77 (m, 1H), 4.90-5.08 (m, 2H), 2.78-3.54 (m), 2.43-2.57 (m), 0.80-2.25 (m), 0.11-0.43 (m, 18H); ^{13}C NMR (C_6D_6) δ 145.11, 137.99, 114.56, 105.99, 57.56, 51.62, 38.81, 37.53, 30.74, 23.87, 23.36, 15.86, 0.88, 0.80.

Reductive enolization and trapping of (3*R*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51f.



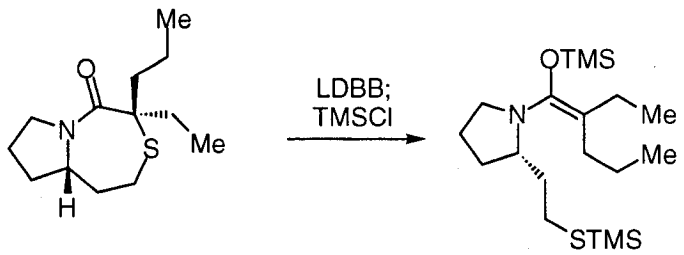
^{1}H NMR (C_6D_6) δ 7.14 (m, 5H), 3.81 (d, 1H, *J* = 14.7 Hz), 3.44 (d, 1H, *J* = 14.7), 3.34 (m, 1H), 3.06 (m, 1H), 2.94 (m, 1H), 2.50-2.60 (m, 2H), 2.07 (m, 1H), 1.84 (m, 1H), 0.96-1.72 (m), 0.10-0.44 (m, 18H); ^{13}C NMR (C_6D_6) δ 145.96, 141.78, 107.68, 58.13, 51.73, 39.10, 38.83, 30.90, 23.98, 23.65, 16.07,1.06, 0.98.

Reductive enolization and trapping of (3*S*,7*S*)-1-Aza-3-ethyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51g.



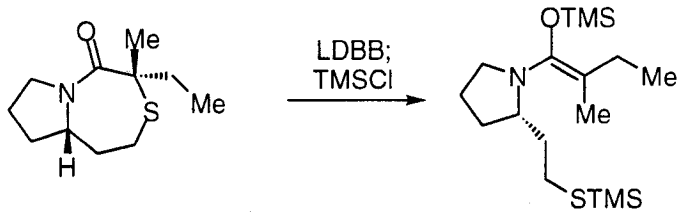
^{1}H NMR (C_6D_6) δ 3.23 (m, 1H), 2.98 (m, 1H), 2.81 (m, 1H), 2.42-2.53 (m, 2H), 2.32 (m, 1H), 2.06-2.18 (m, 2H), 1.91-2.01 (m, 2H), 1.72 (m, 1H), 0.79-1.69 (m), 1.01 (t, 3H, *J* = 7.6 Hz), 0.95 (t, 3H, *J* = 7.5 Hz), -0.14-0.36 (m, 18H); ^{13}C NMR (C_6D_6) δ 144.18, 114.46, 57.74, 51.75, 39.09, 31.05, 24.12, 23.64, 23.22, 21.60, 14.63, 13.96, 1.04, 0.97.

Reductive enolization and trapping of (3*R*,7*S*)-1-Aza-3-ethyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51h.



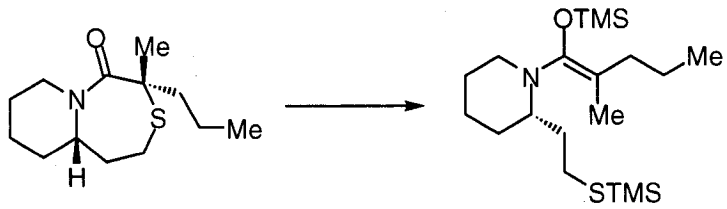
^{1}H NMR (C_6D_6) δ 3.31 (m, 1H), 3.08 (m, 1H), 2.89 (m, 1H), 2.53-2.58 (m, 2H), 2.39 (m, 1H), 2.15-2.26 (m, 2H), 2.00-2.10 (m, 2H), 1.82 (m, 1H), 0.78-1.71 (m), 1.10 (t, 3H, *J* = 7.4 Hz), 1.01 (t, 3H, *J* = 7.2 Hz), 0.01-0.32 (m, 18H); ^{13}C NMR (C_6D_6) δ 144.17, 114.53, 57.94, 51.64, 39.02, 31.89, 31.09, 24.08, 23.69, 22.45, 22.08, 14.66, 12.9, 1.01, 0.92.

Reductive enolization and trapping of (3*S*,7*S*)-1-Aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51j.



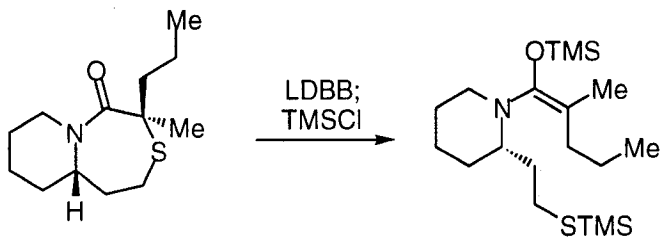
^{1}H NMR (C_6D_6) δ 3.28 (m, 1H), 3.03 (m, 1H), 2.76 (m, 1H), 2.48 (t, 3H, *J* = 7.8 Hz), 2.07 (q, 2H, 7.4 Hz), 1.93 (m, 1H), 0.81-1.76 (m), 1.70 (s, 3H), 0.22 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (C_6D_6) δ 143.55, 108.26, 57.58, 50.83, 39.19, 25.69, 25.12, 24.15, 23.43, 15.94, 12.83, 0.94, 0.83.

Reductive enolization and trapping of (3*S,7*S**)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone 52a.**



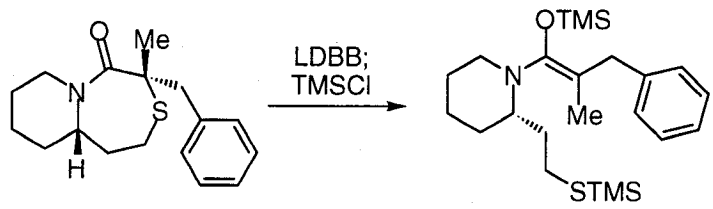
^{1}H NMR (C_6D_6) δ 2.45-2.80 (m), 2.05-2.14 (m), 1.88-1.95 (m), 1.74-1.82 (m), 1.76 (s, 3H), 0.84-1.58 (m), 0.96 (t, 3H, *J* = 7.0 Hz), -0.20-0.38 (m); ^{13}C NMR (C_6D_6) δ 146.93, 108.85, 56.53, 52.21, 37.20, 34.14, 31.17, 31.05, 26.62, 24.62, 23.13, 21.24, 16.31, 14.64, 1.06, 0.95.

Reductive enolization and trapping of (3*R,7*S**)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.4.0]-2-undecanone 52b.**



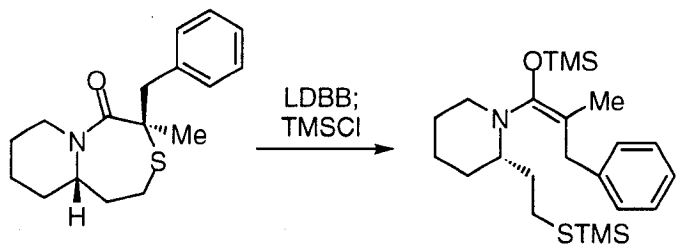
^{1}H NMR (C_6D_6) δ 2.43-2.80 (m), 1.80-2.15 (m), 0.80-1.78 (m), 1.55 (s, 3H), -0.20-0.40 (m); ^{13}C NMR (C_6D_6) δ 147.32, 109.56, 57.01, 53.12, 37.76, 34.84, 26.46, 24.89, 23.44, 21.65, 15.71, 14.52, 1.15, 1.10.

Reductive enolization and trapping of (3*S,7*S**)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone 52e.**



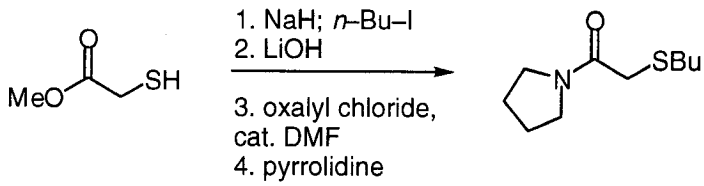
^{1}H NMR (C_6D_6) δ 7.03-7.30 (m, 5H), 3.14 (AB, 1H, *J* = 14.6 Hz), 2.42-2.80 (m, 4 or 5H), 2.04 (m, 1H), 1.79 (m, 1H), 1.64 (s, 3H), 1.02-1.55 (m), -0.07 (s, 9H); ^{13}C NMR (C_6D_6) δ 147.89, 141.23, 129.01, 128.53, 107.71, 56.35, 52.10, 38.22, 36.95, 26.63, 24.43, 23.00, 16.15, 1.16, 0.99.

Reductive enolization and trapping of (3*R,7*S**)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.4.0]-2-undecanone 52f.**



N.B. Though the reductive enolization of **52f** predominantly yields the *Z*–enolate, that data can be found in the preceding entry. The data presented in this entry is for the *E*–enolate. ^{1}H NMR (C_6D_6) δ 7.05-7.30 (m, 5H), 3.97 (AB, 1H, *J* = 13.8 Hz) 3.41 (AB, 1H, *J* = 14.8 Hz), 2.47-2.77 (m, 4 or 5H), 2.09 (m, 1H), 1.53 (s, 3H), 1.12-1.95 (m); ^{13}C NMR (C_6D_6) δ 148.47, 141.76, 128.89, 128.43, 108.74, 57.06, 53.02, 39.10, 37.69, 26.37, 24.75, 23.51, 15.84, 1.18, 1.10.

***N*–(3-thiaheptanoyl)-pyrrolidine.**



Methyl thioglycolate was added to a stirred suspension of sodium hydride (60% w/w in mineral oil, 1.54 g, 38.4 mmol, 1.0 equiv.) in a mixture of tetrahydrofuran (160 mL) and *N,N*–dimethylformamide (40 mL) at 23 °C. After 15 minutes, *n*–butyl iodide was added and the mixture was stirred for 17 hours. The mixture was diluted with distilled water (10 mL) and tetrahydrofuran and residual *n*–butyl iodide were removed in vacuo. The mixture was diluted with distilled water (25 mL) and extracted with a mixture of diethyl ether and hexanes (1:1, 3 x 50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The sulfide was used without further purification.

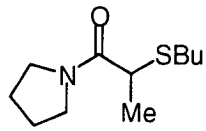
Lithium hydroxide monohydrate (3.22 g, 76.8 mmol, 2.0 equiv.) was added to solution of the crude sulfide prepared above in tetrahydrofuran (67 mL), distilled water (67 mL), and methanol (67 mL). The mixture was stirred at 23 °C for 2 h, concentrated in vacuo to 1/3 volume, diluted with distilled water (100 mL) and extracted with methylene chloride (3 x 25 mL). The aqueous phase was acidified to pH 1 (aqueous sulfuric acid solution, 6M) and extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude carboxylic acid was used without further purification.

Oxalyl chloride (4.01 mL, 46.1 mmol, 1.2 equiv.) was added to a stirred solution of *N,N*–dimethylformamide (0.60 mL, 0.77 mmol, 0.02 equiv.) and the crude carboxylic acid prepared above in methylene chloride (250 mL) at 23 °C. The mixture was stirred at

23 °C for 2 h and the solvent was removed. The crude acid chloride was used without further purification.

Pyrrolidine (8.01 mL, 96.0 mmol, 2.5 equiv.) was added to a stirred solution of the acid chloride prepared above in methylene chloride (250 mL) at 23 °C. After 2 h, saturated ammonium chloride solution (20 mL) was added and the methylene chloride was removed in vacuo. The residue was extracted with diethyl ether (2 x 75 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 30% ethyl acetate in hexanes to afford *N*–(3-thiaheptanoyl)-pyrrolidine (4.06 g, 20.2 mmol, 53%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 3.43-3.52 (m, 4H), 3.20 (s, 2H), 2.64 (t, 2H, J = 7.4 Hz), 1.82-2.02 (m, 4H), 1.57 (m, 1H), 1.39 (m, 1H), 0.88 (t, 3H, 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 167.8, 46.7, 46.0, 34.4, 31.8, 31.2, 26.2, 24.4, 21.9, 13.7.

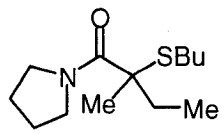
_N_–(2-methyl-3-thiaheptanoyl)-pyrrolidine 57.



The reaction was conducted according to the general alkylation procedure above, with the following exceptions: The alkylation was carried out at –78 °C over 3 h using 1.2 equiv. of methyl iodide. After 3 h, an additional 0.1 equiv. of methyl iodide was added and the reaction was stirred at 23 °C for 15 minutes. The reaction was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford (±)–*N*–(2-methyl-3-thiaheptanoyl)-pyrrolidine **57** in 82% yield. ^{1}H NMR ($CDCl_3$) δ 3.45 (m, 1H), 3.07-3.23 (m, 4H), 2.19-2.36 (m, 2H), 1.52-1.72 (m, 4H), 1.01-1.26 (m,4H),

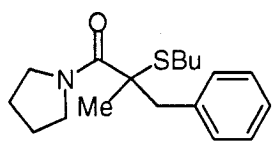
1.16 (d, 3H, J = 7.0 Hz), 0.58 (t, 3H, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.1; 45.5, 45.4, 38.9, 31.0, 27.8, 25.5, 23.6, 21.3, 17.0, 13.0.

_N_–(2-ethyl-2-methyl-3-thiaheptanoyl)-pyrrolidine 55.



The reaction was conducted according to the general alkylation procedure above, with the following exceptions: The deprotonation was carried out at 0 °C for 1 h. The alkylation was carried out at 0 °C over 2 h using 2.0 equiv. of ethyl iodide. The reaction was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford (±)-_N_–(2-ethyl-2-methyl-3-thiaheptanoyl)-pyrrolidine **55** as a colourless oil in 61% yield. ^{1}H NMR (C_6D_6, 100 °C, sealed tube) δ 3.67 (m, 2H), 3.48 (m, 2H), 2.47 (dt, 2H, J = 1.0, 7.3 Hz), 2.04 (m, 1H), 1.70 (m, 1H), 1.59 (s, 3H), 1.38-1.54 (m, 6H), 1.20-1.33 (m, 2H), 0.91 (t, 3H, J = 7.4 Hz), 0.77 (t, 3H, J = 7.2 Hz); ^{13}C NMR (C_6D_6, 100 °C, sealed tube) δ 170.0, 52.5, 47.6 (2C), 31.8, 31.4, 28.8, 25.0 (2C), 23.9, 21.9, 13.1, 8.8.

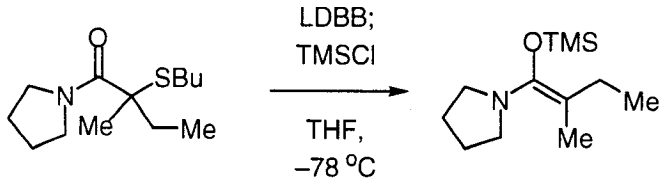
_N_–(2-benzyl-2-methyl-3-thiaheptanoyl)-pyrrolidine 56.



The reaction was conducted according to the general alkylation procedure above, with the following exceptions: The deprotonation was carried out at 0 °C for 1 h. The alkylation was carried out at 0 °C over 5 h using 1.2 equiv. of benzyl bromide. The reaction was

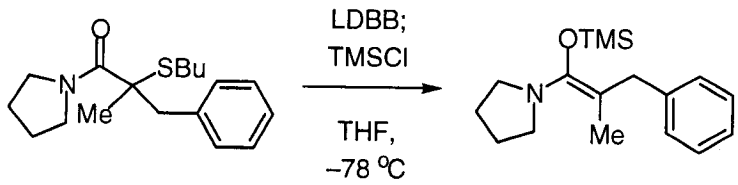
purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to afford (±)-*N*–(2-benzyl-2-methyl-3-thiaheptanoyl)-pyrrolidine **56** as a colourless oil in 67% yield. ^{1}H NMR (C_6D_6, 100 °C, sealed tube) δ 7.05-7.27 (m, 5H), 3.55-3.64 (m, 5H), 2.98 (AB, 1H, J = 11.6 Hz), 2.53 (t, 2H, J = 7.2 Hz), 1.47 (s, 3H), 1.23-1.45 (m, 8H), 0.78 (t, 3H, J = 7.3 Hz); ^{13}C NMR (C_6D_6, 100 °C, sealed tube) δ 169.3, 137.9, 130.7 (2C), 127.8 (2C), 126.3, 52.6, 48.0 (2C), 44.8, 31.7, 29.1, 25.0 (2C), 24.3, 21.9, 13.2.

Reductive enolization and trapping of *N*–(2-ethyl-2-methyl-3-thiaheptanoyl)-pyrrolidine 56.



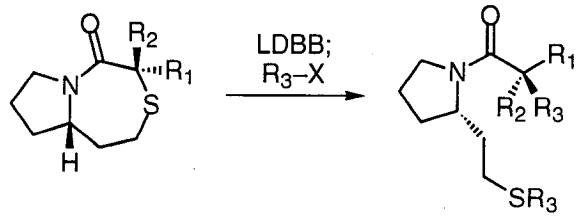
The reductive enolization was carried out according to the general procedure above. ^{1}H NMR (C_6D_6) δ 2.76-2.96 (m, approx. 6H), 2.24 (t, 3H, J = 7.0 Hz) (minor isomer), 2.16 (t, 3H, J = 7.6 Hz) (major isomer), 1.72 (s, 3H) (major isomer), 1.68 (s, 3H) (minor isomer), 1.49-1.56 (m, approx. 6H), 0.77-1.40 (m), 0.18 (s); ^{13}C NMR (C_6D_6) δ 145.2 (minor isomer), 144.9 (major isomer), 106.5 (minor isomer), 104.5 (major isomer), 50.0 (minor isomer), 49.4 (major isomer), 40.0, 25.5 (major isomer), 25.4 (minor isomer), 16.0 (minor isomer), 15.8 (major isomer), 1.0 (minor isomer), 0.9 (major isomer).

Reductive enolization and trapping of *N*–(2-benzyl-2-methyl-3-thiaheptanoyl)-pyrrolidine 57.

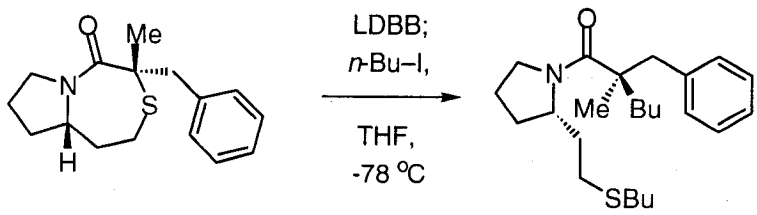


The reductive enolization was carried out according to the general procedure above. ^{1}H NMR (C_6D_6) δ 6.97-7.27 (m, 5H), 3.25-3.28 (m, 4H), 3.05-3.10 (m ,2H), 2.64-2.68 (m, 2H), 2.42-2.54 (m, 7H), 2.36 (t, 1H, 7.3 Hz), 1.58 (s, 3H), 0.67-1.53 (m), 0.19 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (C_6D_6) δ 147.1 (minor isomer), 146.6, (major isomer), 128.9 (major isomer), 128.8 (minor isomer), 128.4, 104.4 (minor isomer), 100.9 (major isomer), 49.8 (minor isomer), 49.3 (major isomer), 38.8 (minor isomer), 38.7 (major isomer), 25.4 (major isomer), 25.1 (minor isomer), 16.2 (minor isomer), 16.1 (major isomer), 0.9 (minor isomer), 0.8 (minor isomer), 0.7 (major isomer).

General Procedure for Reduction and Alkylation of Thioglycolate Lactams:



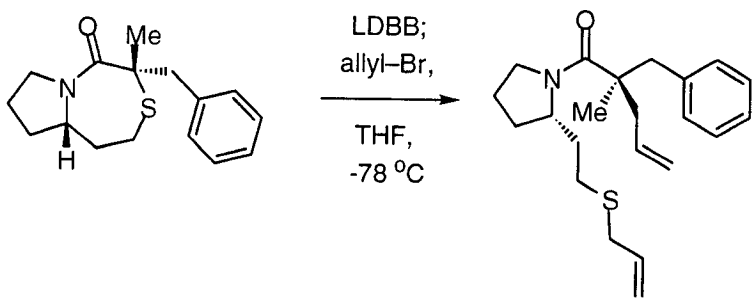
(2*S*)-*N*-((2*R*)-2-butyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiaheptyl)-pyrrolidine 65 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51e.



A solution of lithium di-*tert*-butylbiphenylide (LDBB) in THF was added dropwise via glass syringe to a solution of (3*S*,7*S*)-1-aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone (243 mg, 882 μmol, 1.0 equiv.) in tetrahydrofuran (8.8 mL) in a Schlenk flask at –78 °C until the green colour of LDBB briefly persisted. *n*-Butyl iodide (402 μL, 3.53 mmol, 4.0 equiv.) was added dropwise and the solution was stirred at –78 °C for 4 h. 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 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 3% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*R*)-2-butyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiaheptyl)-pyrrolidine **65** (260 mg, 670 μmol, 76%) as a colourless oil in 76% yield. The product was determined to have >95% de by ^{13}C NMR analysis: ^{1}H NMR

($C_6D_5CD_3$, 105 °C) δ 6.95-7.08 (m, 5H), 4.24 (m, 1H), 2.93-3.11 (m, 3H), 2.38-2.51 (m, 5H), 1.97-2.16 (m, 2H), 1.07-1.60 (m, 14H), 1.13 (s, 3H), 0.76-0.88 (m, 6H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.8, 138.8, 130.3, 127.7, 126.0, 58.8, 48.2, 46.9, 46.3, 41.3, 34.3, 31.9, 31.8, 29.3, 28.8, 27.0, 25.0, 23.2, 22.6, 21.8, 13.6, 13.2. Anal. Calcd for $C_{24}H_{39}NOS$: C, 73.98; H, 10.09; N, 3.59. Found: C, 74.31; H, 9.98; N, 3.60.

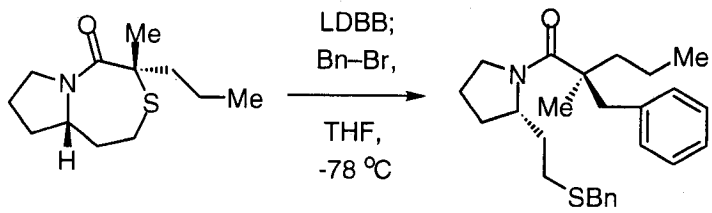
(2*S*)-*N*-((2*R*)-2-allyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiahex-5-enyl)-pyrrolidine 62 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51e.



The reaction was carried out at –78 °C over 3 h using 3 equiv. of allyl bromide. The reaction was purified by column chromatography on silica gel eluting with 8% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*R*)-2-allyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiaheptyl)-pyrrolidine **62** as a colourless oil in 96% yield. The product was determined to have 80% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 6.96-7.10 (m, 5H), 5.64-5.86 (m, 2H), 4.89-5.06 (m, 4H), 4.24 (m, 1H), 2.85-3.13 (m, 5H), 2.78 (dd, 1H, J = 6.5, 13.9 Hz), 2.50 (d, 1H, J = 13.4 Hz), 2.32-2.40 (m, 2H), 1.98-2.15 (m, 2H), 1.14-1.46 (m, 5H), 1.13 (s, 3H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.4, 138.6, 135.3, 135.0, 130.3, 127.7, 126.1, 116.7, 115.7, 58.7, 48.0, 46.9, 45.9, 45.9, 34.6, 33.8, 28.7, 28.1, 24.9,

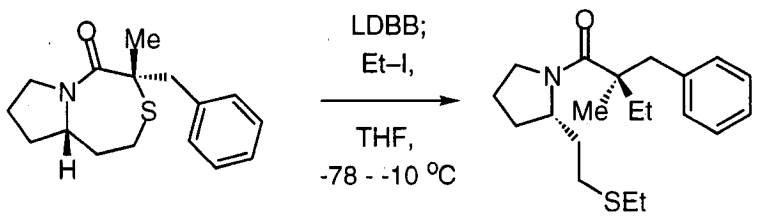
22.3. Anal. Calcd for $C_{22}H_{31}NOS$: C, 73.90; H, 8.74; N, 3.92. Found: C, 73.92; H, 8.85; N, 3.93.

(2*S*)-*N*-((2*S*)-2-methyl-2-propyl-2,3-dihydrocinnamoyl)-2-(4-phenyl-3-thiapropyl)-pyrrolidine 59 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51a.



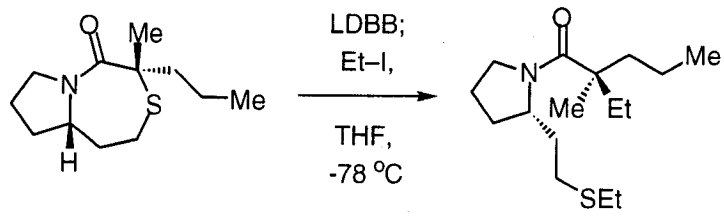
The reaction was carried out at –78 °C over 17.5 h using 2.2 equiv. of benzyl bromide. The reaction was purified by column chromatography on silica gel eluting with 10%→15% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*S*)-2-methyl-2-propyl-2,3-dihydrocinnamoyl)-2-(3-thiaheptyl)-pyrrolidine **59** as a colourless oil in 82% yield. The product was determined to have 74% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 6.96-7.25 (m, 5H), 4.22 (m, 1H), 3.58 (s, 2H), 3.29 (m, 1H), 3.12 (AB, 1H, *J* = 13.6 Hz) 2.97 (m, 1H), 2.50 (AB, 1H, *J* = 13.5 Hz), 2.08-2.34 (m, 3H), 1.16-1.52 (m, 7H). 1.13 (s, 3H), 0.82-0.87 (m, 3H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.5, 139.0, 138.9, 130.4, 128.9, 128.1, 127.7, 126.4, 126.0, 58.6, 48.0, 46.8, 45.9, 42.0, 36.2, 33.5, 28.6 (2C), 24.9, 23.4, 17.9, 14.3.

(2*S*)-*N*-((2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiapentyl)-pyrrolidine 64 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51e.



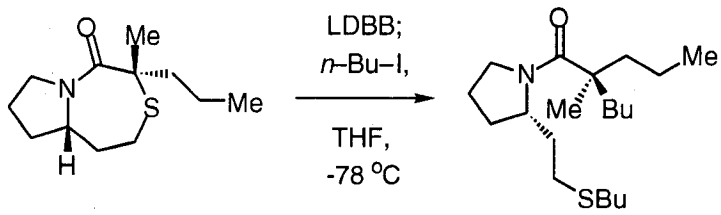
The reaction was carried out at –78 °C for 2 h and then warmed to –10 °C over 2 h using 4.0 equiv. of ethyl iodide. The reaction was purified by column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiapentyl)-pyrrolidine **64** as a colourless oil in 89% yield. The product was determined to have 93% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 6.95-7.09 (m, 5H), 4.24 (m, 1H), 2.91-3.08 (m, 3H), 2.33-2.54 (m, 5H), 1.91-2.16 (m, 2H), 1.08-1.59 (m, 9H), 1.10 (s, 3H), 0.82 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.6, 138.2, 130.3, 127.7, 126.0, 58.8, 48.6, 46.9, 45.9, 34.3, 33.8, 28.8, 28.7, 25.7, 25.0, 22.0, 14.5, 8.8. Anal. Calcd for $C_{20}H_{31}NOS$: C, 72.02; H, 9.37; N, 4.20. Found: C, 71.67; H, 9.52; N, 4.23.

(2*S*)-*N*-((2*R*)-2-ethyl-2-methylpentanoyl)-2-(3-thiapentyl)-pyrrolidine 67 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-*n*-propyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51a.



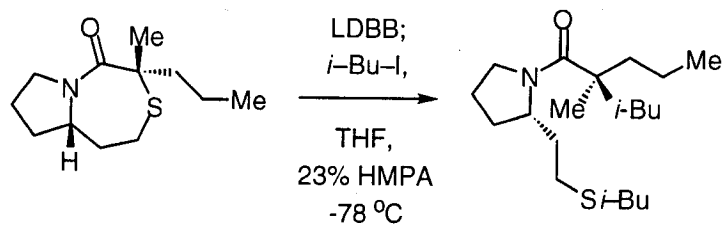
The reaction was carried out at –78 °C over 4 h using 4 equiv. of ethyl iodide. The reaction was purified by column chromatography on silica gel eluting with 10% ether in hexanes to afford (2*S*)-*N*-((2*R*)-2-ethyl-2-methylpentanoyl)-2-(3-thiapentyl)-pyrrolidine **66** as a colourless oil in 85% yield. The product was determined to have 89% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 4.23 (m, 1H), 3.37 (m, 1H), 3.13 (m, 1H), 2.33-2.44 (m, 4H), 1.19-1.78 (m, 11H), 1.13 (s, 3H), 1.10 (t, 3H, J = 7.1 Hz), 0.77-0.89 (m, 6H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.6, 58.4, 47.0, 46.7, 41.5, 34.3, 31.9, 28.8, 28.7, 25.7, 25.1, 22.8, 14.4 (2C), 8.6. Anal. Calcd for $C_{16}H_{31}NOS$: C, 67.31; H, 10.94; N, 4.91. Found: C, 67.19; H, 11.11; N, 4.83.

(2*S*)-*N*-((2*S*)-2-propyl-2-methylhexanoyl)-2-(3-thiaheptyl)-pyrrolidine 68 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-*n*-propyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51a.



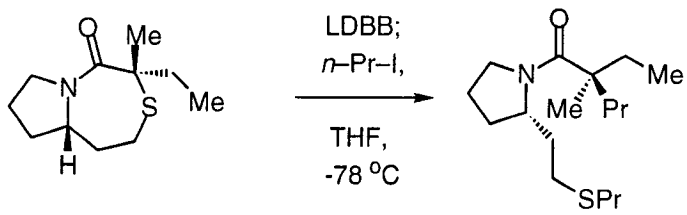
The reaction was carried out at –78 °C over 4 h using 4 equiv. of *n*-butyl iodide. The reaction was purified by column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*S*)-2-propyl-2-methylhexanoyl)-2-(3-thiaheptyl)-pyrrolidine **68** as a colourless oil in 71% yield. The product was determined to have 95% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 4.24 (m, 1H), 3.41 (m, 1H), 3.15 (m, 1H), 2.38-2.45 (m, 4H), 2.13 (m, 1H), 1.10-1.74 (m, 19H), 1.16 (s, 3H), 0.62-0.87 (m, 9H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.7, 58.4, 46.7 (2C), 41.9, 39.3, 34.4, 31.9, 31.8, 29.2, 28.7, 26.9, 25.1, 23.4, 23.2, 21.8, 17.8, 14.4, 13.5, 13.1. Anal. Calcd for $C_{20}H_{39}NOS$: C, 70.32; H, 11.51; N, 4.10. Found: C, 70.38; H, 11.15; N, 3.98.

(2*S*)-N-((2*S*)-2,4-dimethyl-2-propylpentanoyl)-2-(5-methyl-3-thiahexyl)-pyrrolidine 72 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-methyl-3-propyl-4-thiabicyclo[5.3.0]-2-decanone 51a.



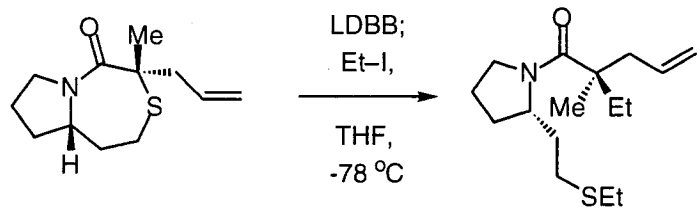
The reaction was carried out at –78 °C over 5h using 4 equiv. of *i*-butyl iodide and 23% (v/v) HMPA. The reaction was purified by column chromatography on silica gel using 3% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*S*)-2,4-dimethyl-2-propylpentanoyl)-2-(5-methyl-3-thiahexyl)-pyrrolidine **72** as a colourless oil in 60% yield. The product was determined to have 87% de by ^{13}C NMR analysis: ^{1}H NMR (C_6D_6, 100 °C, sealed tube) δ 4.20 (m, 1H), 3.42 (m, 1H), 3.07 (m, 1H), 2.39 (t, 2H, J = 7.8 Hz), 2.30 (d, 2H, 6.8 Hz), 2.20 (m, 1H), 1.38-1.72 (m, 8H), 1.15-1.31 (m, 5H), 1.19 (s, 3H), 0.80-0.88 (m, 15H); ^{13}C NMR (C_6D_6, 100 °C, sealed tube) δ 173.9, 58.8, 48.7, 46.9, 46.8, 42.9, 41.7, 34.3, 29.9, 28.8, 28.7, 25.2, 24.9, 24.9, 24.2, 23.6, 21.8, 21.8, 17.7, 14.7. Anal. Calcd for $C_{20}H_{39}NOS$: C, 70.32; H, 11.51; N, 4.10. Found: C, 69.92; H, 11.35; N, 3.89.

(2*S*)-*N*-((2*S*)-2-ethyl-2-methylpentanoyl)-2-(3-thiahexyl)-pyrrolidine 66 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-ethyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51j.



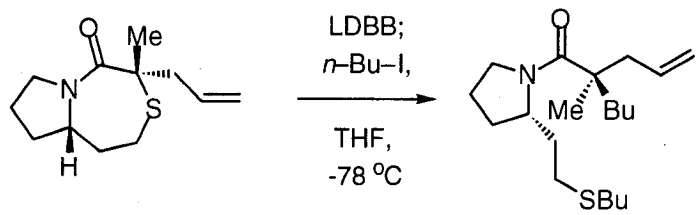
The reaction was carried out at –78 °C over 4 h using 4 equiv. of *n*-propyl iodide. The reaction was purified by column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*S*)-2-ethyl-2-methylpentanoyl)-2-(3-thiahexyl)-pyrrolidine **66** as a colourless oil in 83% yield. The product was determined to have >95% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 4.23 (m, 1H), 3.38 (m, 1H), 3.13 (m, 1H), 2.34-2.43 (m, 4H), 2.12 (m, 1H), 1.01-1.71 (m, 13H), 1.13 (s, 3H), 0.78-0.89 (m, 9H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.5, 58.4, 47.0, 46.6, 41.6, 34.4, 34.3, 31.6, 29.2, 28.7, 25.1, 22.9, 22.8, 17.9, 14.4 , 12.9, 8.5. Anal. Calcd for $C_{17}H_{33}NOS$: C, 68.17; H, 11.11; N, 4.68. Found: C, 68.15; H, 10.80; N, 4.48.

(2*S*)-*N*-((2*R*)-2-ethyl-2-methylpent-4-enoyl)-2-(3-thiapentyl)-pyrrolidine 70 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51c.



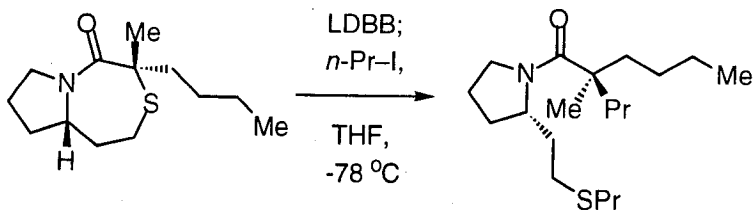
The reaction was carried out at –78 °C over 4 h using 4 equiv. of ethyl iodide. The reaction was purified by column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*R*)-2-ethyl-2-methylpent-4-enoyl)-2-(3-thiapentyl)-pyrrolidine **70** as a colourless oil in 84% yield. The product was determined to have 88% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 105 °C) δ 5.77 (m, 1H), 4.92-4.98 (m, 2H), 4.23 (m, 1H), 3.35 (m, 1H), 3.10 (m, 1H), 2.33-2.46 (m, 5H), 2.06-2.17 (m, 2H), 1.08-1.75 (m, 13H), 1.12 (s, 3H), 0.80 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($C_6D_5CD_3$, 105 °C) δ 173.1, 135.3, 116.3, 58.5, 46.7, 46.7, 43.2, 34.2, 31.5, 28.8, 28.7, 25.7, 25.1, 22.6, 14.4, 12.9, 8.6. Anal. Calcd for $C_{16}H_{29}NOS$: C, 67.79; H, 10.31; N, 4.94. Found: C, 67.52; H, 10.44; N, 5.08.

(2*S*)-*N*-((2*R*)-2-allyl-2-methylhexanoyl)-2-(3-thiaheptyl)-pyrrolidine 71 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-allyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51c.



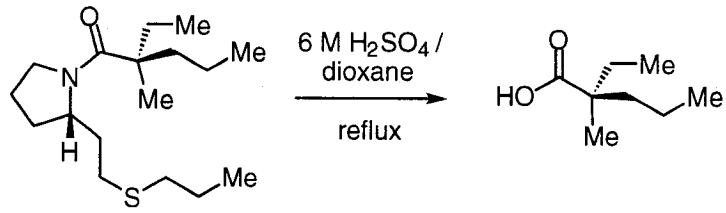
The reaction was carried out at –78 °C over 4 h using 4 equiv. of butyl iodide. The reaction was purified by column chromatography on silica gel eluting with 3% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*R*)-2-allyl-2-methylhexanoyl)-2-(3-thiaheptyl)-pyrrolidine as a colourless oil in 80% yield. The product was determined to have 91% de by ^{13}C NMR analysis: ^{1}H NMR (C_6D_6, 100 °C, sealed tube) δ 5.83 (m, 1H), 4.97-5.00 (m, 2H), 4.30 (m, 1H), 3.31 (m,1H), 3.06 (m, 1H), 2.41-2.50 (m,4H), 2.22 (m, 1H), 2.13 (dd, 1H, J = 14.2, 7.8 Hz), 1.66 (m, 1H), 1.20-1.54 (m, 15H), 1.18 (s, 3H), 0.831 (t, 3H, J = 6.8 Hz), 0.78 (t, 3H, J = 7.3 Hz); ^{13}C NMR (C_6D_6, 100 °C) δ 173.4, 135.5, 116.8, 58.6, 46.9, 46.3, 43.7, 38.8, 34.1, 32.0, 31.8, 29.2, 28.6, 27.0, 25.3, 23.5, 23.4, 22.0, 13.9, 13.5. Anal. Calcd for $C_{20}H_{37}NOS$: C, 70.74; H, 10.98; N, 4.12. Found: C, 70.69; H, 10.85; N, 4.06.

(2*S*)-*N*-((2*R*)-2-ethyl-2-methylhexanoyl)-2-(3-thiahexyl)-pyrrolidine 69 via reduction and alkylation of (3*S*,7*S*)-1-Aza-3-butyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51i.



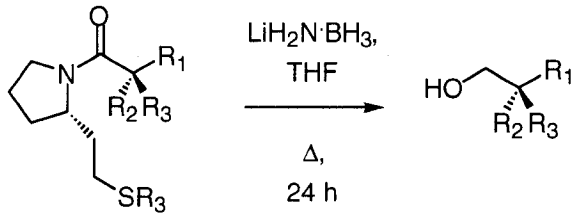
The reaction was carried out at –78 °C over 4 h using 4 equiv. of *n*-propyl iodide. The reaction was purified by column chromatography on silica gel eluting with 3% ethyl acetate in hexanes to afford (2*S*)-*N*-((2*R*)-2-ethyl-2-methylhexanoyl)-2-(3-thiahexyl)-pyrrolidine **69** as a colourless oil in 88% yield. The product was determined to have 95% de by ^{13}C NMR analysis: ^{1}H NMR ($C_6D_5CD_3$, 100 °C) δ 4.25 (m, 1H), 3.38 (m, 1H), 3.14 (m, 1H), 2.35-2.44 (m, 4H), 2.16 (m, 1H), 1.15-1.75 (m, 17H), 1.17 (s, 3H), 0.85-0.90 (m, 9H); ^{13}C NMR ($C_6D_5CD_3$, 100 °C) δ 173.8, 58.6, 46.9, 46.8, 42.2, 39.3, 34.4 (2C), 29.3, 28.9, 27.0, 25.4, 23.8, 23.6, 23.2, 18.2, 14.7, 13.9, 13.2. Anal. Calcd for $C_{19}H_{37}NOS$: C, 69.67; H, 11.39; N, 4.28. Found: C, 70.04; H, 11.40; N, 4.01.

(2*S*)-2-Ethyl-2-methyl-pentanoic acid 74 via hydrolysis of (2*S*)-*N*-((2*S*)-2-ethyl-2-methylpentanoyl)-2-(3-thiahexyl)-pyrrolidine 66.

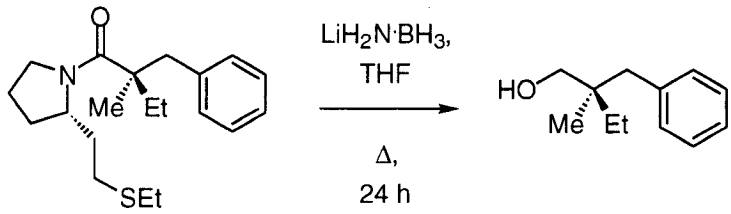


A solution of (2*S*)-*N*-((2*S*)-2-ethyl-2-methylpentanoyl)-2-(3-thiahexyl)-pyrrolidine **66** (78 mg, 0.26 mmol, 1.0 equiv.) in *p*-dioxane (3 mL) and aqueous sulfuric acid solution (6 M, 3 mL) was heated at reflux for 24 h, cooled to 23 °C and extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was partitioned between diethyl ether (10 mL) and aqueous sodium hydroxide solution (0.5 M, 10 mL). The phases were separated and the organic phase was extracted with aqueous sodium hydroxide solution (0.5 M, 1 x 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford (2*S*)-*N*-((2*S*)-2-ethyl-2-methylpentanoyl)-2-(3-thiahexyl)-pyrrolidine **66** (55 mg, 0.18 mmol, 71%). The combined aqueous phases were acidified to pH 1 (6 M aqueous hydrochloric acid solution), extracted with diethyl ether (3 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford (2*S*)-2-ethyl-2-methyl-pentanoic acid **74** (6.7 mg, 0.46 mmol, 18%) as a colourless oil with an odour of fudge. ^{1}H NMR ($CDCl_3$) δ 1.14-1.93 (m, 6H), 1.12 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 183.6, 46.1, 41.1, 31.8, 20.5, 17.9, 14.6, 9.0.

General Procedure for Amide Reduction using Lithium Amidotrihydroborate:



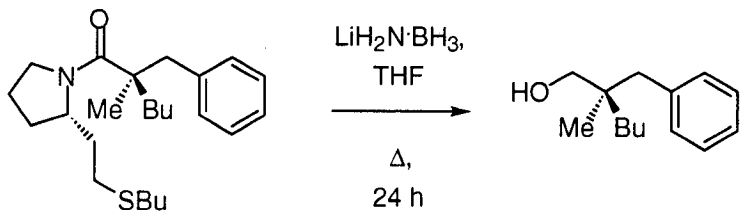
(2*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamyl alcohol 77 via reduction of (2*S*)-*N*-((2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiapentyl)-pyrrolidine 64.



A solution of *n*-butyllithium in hexanes (2.27 M, 2.39 mL, 5.42 mmol, 3.90 equiv.) was slowly added to a stirred solution of diisopropylamine (799 μL, 5.70 mmol, 4.10 equiv.) in tetrahydrofuran (2.5 mL) at 0 °C. After stirring for 10 minutes, borane-ammonia complex (90%, 191 mg, 5.56 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*S*)-*N*-((2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiapentyl)-pyrrolidine **64** (464 mg, 1.39 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 (3 M, 5 mL). The resulting mixture was warmed to 23 °C and stirred for 30 minutes, at which point aqueous sodium hydroxide (3 M, 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 30% diethyl ether

in pentane afforded (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **77** (239 mg, 1.34 mmol, 96%) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 7.19-7.31 (m, 5H), 3.33 (s, 2H), 2.61 (AB, 2H, *J* = 24.6 Hz), 1.58 (bs, 1H), 1.27-1.40 (m, 2H), 0.93 (t, 3H, *J* = 7.5 Hz), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.0, 130.8, 128.1, 126.2, 68.4, 42.8, 39.1, 29.1, 21.0, 8.3. HRFABMS *m/z* (M+H, 179.14359 $C_{12}H_{19}O^+$ requires 179.14359). $[\alpha]^{25}_D$ = –5.9° (c = 14.2, CH_2Cl_2). The product was determined to have 94% ee by HPLC analysis (Chiralcel OD column, eluting with 1% isopropanol in hexanes at 0.7 mL/minute- R_t= 20.5 minutes (major enantiomer), 22.8 minutes (minor enantiomer)).

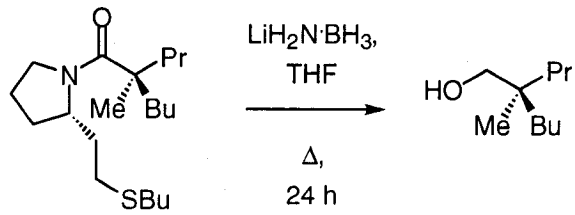
(2*R*)-2-Butyl-2-methyl-2,3-dihydrocinnamyl alcohol 78 via reduction of (2*S*)-*N*-((2*R*)-2-butyl-2-methyl-2,3-dihydrocinnamoyl)-2-(3-thiaheptyl)-pyrrolidine 65.



The reaction was carried out according to the general procedure above. The residue was purified by column chromatography on silica gel eluting with 30% diethyl ether in pentane to afford (2*R*)-2-butyl-2-methyl-2,3-dihydrocinnamyl alcohol as a colourless oil in 97% yield: ^{1}H NMR ($CDCl_3$) δ 7.20-7.32 (m, 5H), 3.34, (s, 2H), 2.63 (AB, 2H, *J* = 25.3 Hz), 1.87 (bs, 1H), 1.24-1.34 (m, 6H), 0.97 (t, 3H, *J* = 6.6 Hz), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.1, 130.8, 128.1, 126.2, 68.9, 43.1, 39.0, 36.7, 26.1, 23.9, 21.7, 14.5. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.18; H, 10.73. The product was determined to have 96% ee by HPLC analysis (Chiralcel OD column, eluting with 0.4% isopropanol in hexanes at 0.7 mL/minute- R_t= 30.6 minutes (major enantiomer),

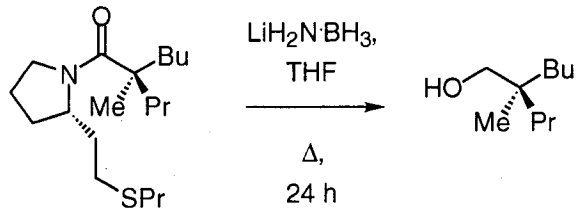
33.1 minutes (minor enantiomer)).

(2*R*)-2-Methyl-2-propylhexanol 79 via reduction of (2*S*)-*N*-((2*S*)-2-propyl-2-methylhexanoyl)-2-(3-thiaheptyl)-pyrrolidine 68.



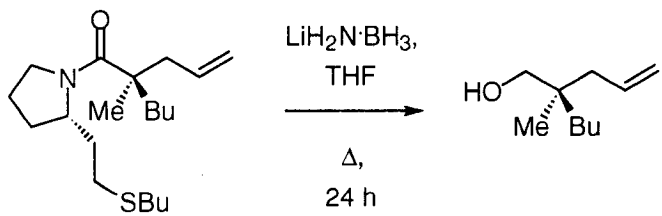
The reaction was carried out according to the general procedure above. The residue was purified by column chromatography on silica gel eluting with 30% diethyl ether in pentane to afford (2*R*)-2-methyl-2-propylhexanol **79** as a colourless oil in 87% yield: ^{1}H NMR ($CDCl_3$) δ 3.34 (s, 2H), 1.57 (bs, 1H), 1.18-1.31 (m, 10H), 0.90 (m, 6H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 70.2, 39.2, 37.5, 36.4, 25.9, 23.9, 22.1, 16.9, 15.3, 14.4. HRFABMS *m/z* 141.14627 ($M + H^+ - H_2O$, $C_{10}H_{21}^+$ requires 141.14632.). The product was determined to have 95% ee by GC analysis of the corresponding carboxylic acid (*vide infra*) (Chirasil Dex column, He carrier gas, 25 psi, oven temperature =100 °C, R_t = 40.2 minutes (minor enantiomer), 41.0 minutes (major enantiomer)).

(2*S*)-2-Methyl-2-propylhexanol 80 via reduction of (2*S*)-*N*-((2*R*)-2-ethyl-2-methylhexanoyl)-2-(3-thiahexyl)-pyrrolidine 69.



The reaction was carried out according to the general procedure above. The residue was purified by column chromatography on silica gel eluting with 30% diethyl ether in pentane to afford (2*S*)-2-methyl-2-propylhexanol **80** as a colourless oil in 99% yield: ^{1}H NMR ($CDCl_3$) δ 3.34 (s, 2H), 1.18-1.31 (m, 10H), 0.90 (m, 6H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 70.2, 39.2, 37.5, 36.4, 25.9, 23.9, 22.1, 16.9, 15.3, 14.4. The product was determined to have 96% ee by GC analysis of the corresponding carboxylic acid (*vide infra*) (Chirasil Dex column, He carrier gas, 25 psi, oven temperature = 100 °C, R_t = 39.3 minutes (major enantiomer), 42.4 minutes (minor enantiomer)).

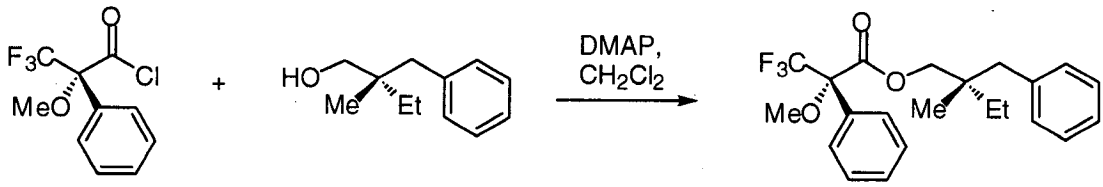
(2*R*)-2-Allyl-2-methylhexanol 81 via reduction of (2*S*)-*N*-((2*R*)-2-allyl-2-methylhexanoyl)-2-(3-thiaheptyl)-pyrrolidine 71.



The reaction was carried out according to the general procedure above. The residue was purified by column chromatography on silica gel eluting with 30% diethyl ether in pentane to afford (2*R*)-2-allyl-2-methylhexanol **71** as a colourless oil in 74% yield: ^{1}H

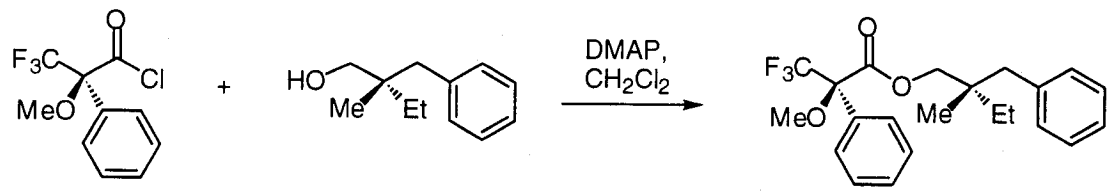
NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.03-5.08 (m, 2H), 3.36 (s, 2H), 2.04 (d, 2H, J = 7.7 Hz), 1.41 (bs, 1H), 1.25-1.32 (m, 6H), 0.91 (t, 3H, J = 7.1 Hz), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.3, 117.1, 69.8, 41.4, 37.8, 36.3, 25.6, 23.6, 21.6, 14.1. HRFABMS *m/z* 157.1587 ($M + H^+$, $C_{10}H_{21}O^+$ requires 157.1592.). The product was determined to have 95% ee by GC analysis of the corresponding hydrogenated carboxylic acid (*vide infra*) (Chirasil Dex column, He carrier gas, 25 psi, oven temperature = 100 °C, R_t = 39.3 minutes (minor enantiomer), 42.4 minutes (major enantiomer)).

(2*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate 82.



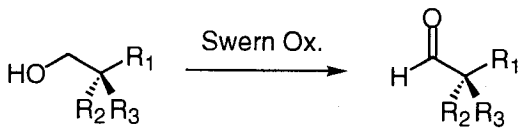
(*R*)–α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (36 mg, 0.143 mmol, 1.5 equiv.) and 4–(dimethylamino)pyridine (35 mg, 0.285 mmol, 3.0 equiv.) were added to a solution of (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **77** (17 mg, 0.095 mmol, 1.0 equiv.) in methylene chloride (2 mL) at 23 °C. After 1.5 h, the reaction was diluted with diethyl ether (15 mL) and extracted with saturated ammonium chloride solution (2 x 2 mL) and saturated sodium bicarbonate solution (2 x 2 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate **82** (37 mg, 0.94 mmol, 99%) as a colourless oil. The crude ester was determined to have 96% de by ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 7.48-7.59 (m, 2H), 7.41-7.46 (m, 3H), 7.12-7.25 (m, 3H), 6.97-7.03 (m, 2H), 4.05 (AB, 1H, *J* = 11.1 Hz), 3.95 (AB, 2H, *J* = 11.7 Hz) (minor isomer), 3.88 (AB, 1H, *J* = 10.9 Hz), 3.57 (s, 3H), 2.54 (AB, 2H, *J* = 13.5 Hz), 1.19-1.39 (m, 2H), 0.87 (t, 3H, *J* = 7.3 Hz), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.5, 137.5, 130.4, 129.6, 128.4, 127.9, 127.5, 126.1, 124.9, 70.9, 55.4, 42.6, 37.4, 29.0, 20.8, 7.8. Anal. Calcd for $C_{22}H_{25}F_3O_3$: C, 69.99; H, 6.39. Found: C, 67.03; H, 6.53. (As a mixture of (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate **82** and (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate **83**.)

(2*R*)-2-Ethyl-2-methyl-2,3-dihydrocinnamyl (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate 83.



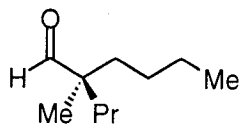
(*S*)–α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (21 mg, 0.084 mmol, 1.5 equiv.) and 4–(dimethylamino)pyridine (21 mg, 0.168 mmol, 3.0 equiv.) were added to a solution of (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **77** (10 mg, 0.056 mmol, 1.0 equiv.) in methylene chloride (2 mL) at 23 °C. After 3 h, the reaction was diluted with diethyl ether (10 mL) and extracted with saturated ammonium chloride solution (2 x 5 mL) and saturated sodium bicarbonate solution (2 x 5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate **83** (21.7 mg, 0.55 mmol, 98%) as a colourless oil. The crude ester was determined to have 94% de by ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 7.56-7.57 (m, 2H), 7.43-7.44 (m, 3H), 7.18-7.26 (m, 3H), 6.97-6.98 (m, 2H), 3.98 (AB, 1H, *J* = 11.2 Hz), 3.92 (AB, 1H, *J* = 11.7 Hz), 3.58 (s, 3H), 2.58 (AB, 1H, *J* = 13.2 Hz), 2.50 (AB, 1H, *J* = 13.2 Hz), 1.20-1.39 (m, 2H), 0.89 (t, 3H, *J* = 7.6 Hz), 0.83 (s, 3H). Anal. Calcd for $C_{22}H_{25}F_3O_3$: C, 69.99; H, 6.39. Found: C, 67.03; H, 6.53. (As a mixture of (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate **82** and (2*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate **83**.)

General Procedure for Alcohol Oxidation using Swern Oxidation Conditions.



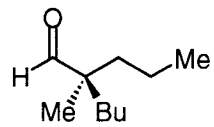
Dimethyl sulfoxide (2.4 equiv.) in methylene chloride (3:1 v/v) was added to a solution of oxalyl chloride (1.4 equiv.) in methylene chloride at –78 °C. After 45 minutes a solution of alcohol **79**, **80** or **81** (1.0 equiv.) in methylene chloride (final concentration: 0.1 M with respect to the alcohol) was added via cannula. After 60 minutes, triethylamine (4.0 equiv.) was added dropwise and the reaction was warmed to 23 °C. The mixture was diluted with ether and washed with aqueous hydrochloric acid (1 M, 2 x) and water (3 x). The combined aqueous layers were washed with ether (1 x). The combined organic layers were extracted with brine (1 x), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford the corresponding aldehyde was oxidized to the carboxylic acid without further purification.

(2*S*)-2-Methyl-2-propylhexanal *ent*-89.



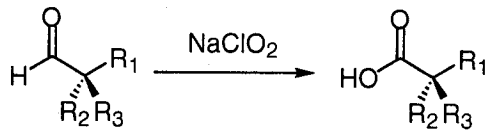
Prepared according to the general procedure above. ^{1}H NMR ($CDCl_3$) δ 9.40 (s, 1H), 1.13-1.47 (m, 10H), 1.00 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 206.8, 49.1, 38.8, 35.3, 26.2, 23.4, 18.1, 17.4, 14.9, 14.1.

(2*R*)-2-Methyl-2-propylhexanal 89.



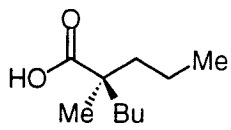
Prepared according to the general procedure above. ^{1}H NMR ($CDCl_3$) δ 9.40 (s, 1H), 1.13-1.47 (m, 10H), 1.00 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 206.8, 49.1, 38.8, 35.3, 26.2, 23.4, 18.1, 17.4, 14.9, 14.1.

General Procedure for Aldehyde Oxidation using Buffered Sodium Chlorite.



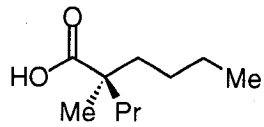
A freshly prepared solution of sodium chlorite (2.0 equiv.) and sodium dihydrogen phosphate monohydrate (4.0 equiv.) in water (1 part) was added dropwise to a solution of the crude aldehyde prepared above from alcohol 79, 80 or 81 (1.0 equiv.) in *tert*-butanol (2.33 parts) and 2-methyl-2-butene (1 part) (final concentration: 0.016 M with respect to the aldehyde) at 23 °C. The reaction was stirred at 23 °C for 5 h, diluted with distilled water and extracted with ethyl acetate (3 x). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford the corresponding carboxylic acid.

(2*S*)-2-Methyl-2-propylhexanoic acid 90.



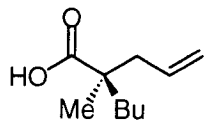
Prepared according to the general procedure above. ^{1}H NMR ($CDCl_3$) δ 1.16-1.67 (m, 10H), 1.14 (s, 3H), 0.91 (t, 3H, J = 7.2 Hz), 0.90 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 183.9, 45.8, 41.5, 39.0, 26.8, 23.3, 21.1, 17.9, 14.7, 14.1.

(2*R*)-2-Methyl-2-propylhexanoic acid *ent*-90.



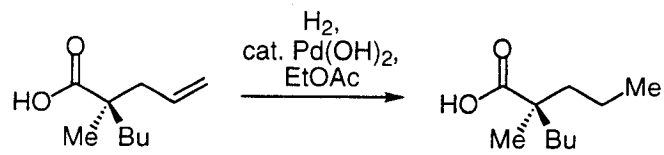
Prepared according to the general procedure above. ^{1}H NMR ($CDCl_3$) δ 1.16-1.67 (m, 10H), 1.14 (s, 3H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.90 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 183.9, 45.8, 41.5, 39.0, 26.8, 23.3, 21.1, 17.9, 14.7, 14.1.

(2*R*)-2-allyl-2-methylhexanoic acid.



Prepared according to the general procedure above. ^{1}H NMR ($CDCl_3$) δ 5.48 (m, 1H), 5.05-5.08 (m, 2H), 2.40 (dAB, 1H, *J* = 6.8, 13.7 Hz), 2.21 (dAB, 1H, *J* = 7.6, 13.9 Hz), 1.16-1.66 (m, 6H), 1.13 (s, 3H), 0.89 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 183.2, 133.8, 118.1, 45.7, 43.0, 38.5, 26.6, 23.1, 21.1, 13.9.

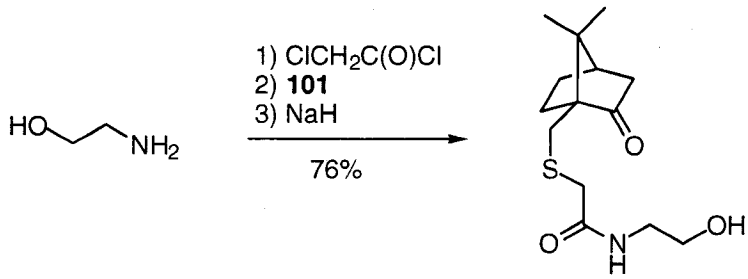
Procedure for Hydrogenation of (2*R*)-2-Allyl-2-methylhexanoic acid.



Catalytic $Pd(OH)_2$/C was suspended in a solution of (2*R*)-2-allyl-2-methyl hexanoic acid in ethyl acetate and the mixture was stirred vigorously under an atmosphere of hydrogen

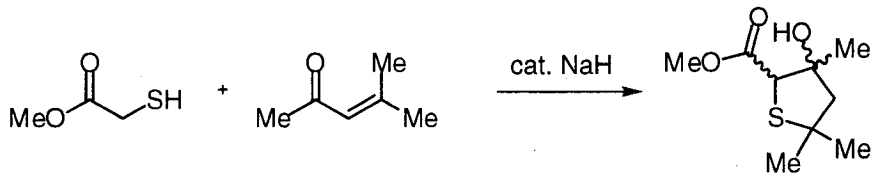
for 18 h, filtered through a pad of Celite® and concentrated to afford (2*S*)-2-methyl-2-propylhexanoic acid.

_N_-(2-hydroxyethyl)-_S_-(10-(1_S_)-camphoryl))-mercaptoacetamide 103.



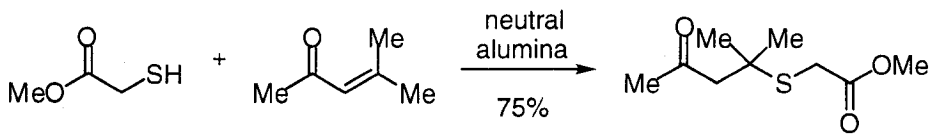
Chloroacetyl chloride (0.285 mL, 3.58 mmol, 1.5 equiv.) was added dropwise to a stirred solution of ethanolamine (0.577 mL, 9.56 mmol, 4.0 equiv.) in tetrahydrofuran (6.0 mL) at 23 °C. After twenty minutes, (1*S*)-camphor-10-thiol **101** (440 mg, 2.39 mmol, 1.0 equiv.) in tetrahydrofuran (6 mL) was added via cannula and sodium hydride (60% w/w, 0.239 g, .598 mmol, 2.5 equiv.) was added in one portion. The mixture was stirred at 23 °C for 28 h and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 50%→100% ethyl acetate in hexanes to afford *N*-(2-hydroxyethyl)-*S*-(10-(1*S*)-camphoryl))-mercaptoacetamide **103** (519 mg, 1.82 mmol, 76%) as a pale rose-coloured oil. ^{1}H NMR ($CDCl_3$) δ 7.70 (bs, 1H), 3.99 (m, 1H), 3.44-3.48 (m, 2H), 3.19-3.21 (m, 2H), 3.02 (AB, 2H, J = 11.6 Hz), 2.53 (AB, 1H, J = 12.4 Hz), 2.36 (AB, 1H, 12.7 Hz), 2.13 (m, 1H), 1.61-1.86 (m, 4H), 1.32 (m, 1H), 1.15 (m, 1H), 0.78 (s, 3H), 0.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.1, 60.7, 60.2, 60.0, 47.4, 42.9, 42.5, 42.0, 36.9, 29.4, 26.6, 26.3, 19.7, 19.2.

3-Hydroxy-3,5,5-tetramethyltetrahydrothiophene-2-carboxylic acid methyl ester 106.



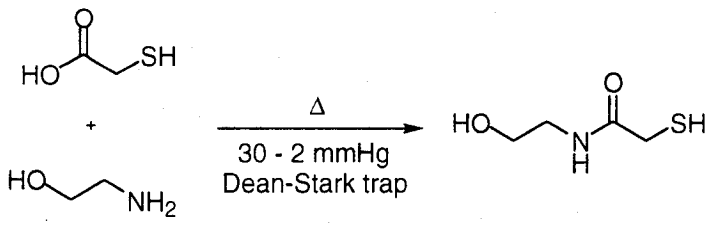
Methyl thioglycolate (0.421 mL, 4.71 mmol, 1.0 equiv.) was added dropwise to a stirred suspension of sodium hydride (60% w/w in mineral oil, 19 mg, 0.471 mmol, 0.1 equiv.) in tetrahydrofuran (20 mL) at 23 °C. After 5 minutes, the mixture was cooled to 0 °C and mesityl oxide (90% v/v, 0.72 mL, 5.65 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C over 2 h, at which point saturated sodium bicarbonate solution (10 mL) and ethyl acetate (40 mL) were added. The phases were separated and the organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexanes to afford 3-hydroxy-3,5,5-tetramethyltetrahydrothiophene-2-carboxylic acid methyl ester **106** as a mixture of stereoisomers (943 mg, 4.62 mmol, 98%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 1H), 3.64 (s, 1H), 3.54 (s, 3H), 2.05 (m, 1H), 1.75 (m, 1H), 1.39 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 82.3, 57.6, 56.9, 52.0, 51.3, 33.3, 32.8, 26.6.

4,4-Dimethyl-6-oxo-3-thiaheptanoate 107.



Methyl thioglycolate (0.421 mL, 4.71 mmol, 1.0 equiv.) was added dropwise and dispersed onto stirred, flame-dried neutral alumina (Brockmann I, standard grade, ≈150 mesh, 2.355 g) under argon. After 10 minutes, mesityl oxide (0.599 mL, 4.71 mmol, 1.0 equiv.) was added via syringe and dispersed onto the alumina. The mixture was stirred for 1.5 h, poured onto a column of silica gel and eluted with methylene chloride. Removal of the methylene chloride in vacuo afforded methyl 4,4-dimethyl-6-oxo-3-thiaheptanoate **107** (0.72 g, 3.52 mmol, 75%) as a pale yellow oil contaminated with small amounts of mesityl oxide. ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.24 (s, 2H), 2.65 (s, 2H), 2.07 (s, 3H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 205.3, 170.5, 53.6, 51.9, 43.8, 31.5, 30.4, 27.6.

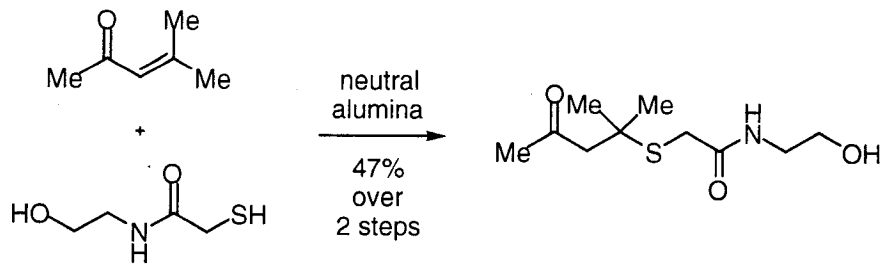
***N*-(2-hydroxyethyl)-mercaptoacetamide 109.**



Ethanolamine (8.68 mL, 144 mmol, 1.0 equiv.) was added to stirred mercaptoacetic acid (10.0 mL, 144 mmol, 1.0 equiv.) under argon at 23 °C (***N.B.*** This is a very exothermic process). The stirred mixture was heated to 130 °C, at which point the pressure was reduced to 30 mm Hg. After 2 h, the temperature was increased to 170 °C and the

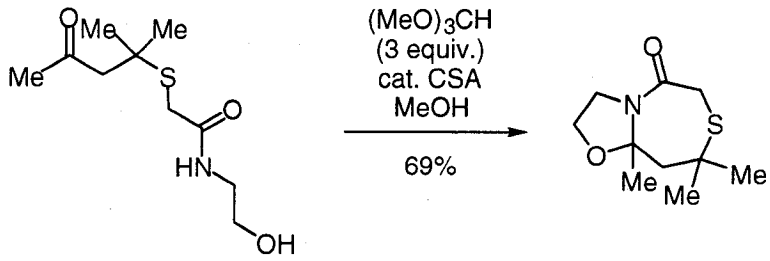
pressure was reduced to 2 mm Hg. The mixture was stirred for an additional 4 hours, then cooled to 23 °C under argon to afford *N*-(2-hydroxyethyl)-mercaptoacetamide **109** as a viscous yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.73 (m, 2H), 3.44 (m, 2H), 3.26 (s, 2H), 2.00 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 170.4, 61.9, 42.6, 28.3.

***N*-(2-hydroxyethyl)-4,4-dimethyl-6-oxo-3-thiaheptanomide.**



N-(2-hydroxyethyl)-mercaptoacetamide **109** (5.00 g, 36.99 mmol, 1.0 equiv.) was added to was added dropwise and dispersed onto mechanically stirred, flame-dried neutral alumina (Brockmann I, standard grade, ≈150 mesh, 18.5 g) under argon. After 10 minutes, mesityl oxide (4.70 mL, 36.99 mmol, 1.0 equiv.) was added via syringe and dispersed onto the alumina. The mixture was mechanically stirred at 23 °C for 7 h and allowed to stand for 14 h. The mixture was poured onto a column of sand and eluted with 5% methanol in ethyl acetate to afford *N*-(2-hydroxyethyl)-4,4-dimethyl-6-oxo-3-thiaheptanomide **111** (4.01 g, 17.2 mmol, 47% over 2 steps) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.41 (bs, 1H), 4.01 (bs, 1H), 3.53 (t, 2H, J = 5.1 Hz), 3.25 (dd, 2H, J = 5.3, 10.6 Hz), 3.12 (s, 2H), 2.57 (s, 2H), 2.01 (s, 3H), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 206.3, 170.0, 60.8, 53.5, 44.3, 42.1, 32.6, 31.8, 28.0 (2C).

5,5,7-Trimethyl-1-aza-8-oxa-4-thiabicyclo[5.3.0]-2-decanone 113.



Trimethyl orthoformate (1.76 mL, 16.18 mmol, 3.0 equiv.) and (1*S*)-10-camphorsulfonic acid (92.3 mg, 0.397 mmol, 0.074 equiv.) were sequentially added to a stirred solution of *N*–(2-hydroxyethyl)-4,4-dimethyl-6-oxo-3-thiaheptanomide **111** (1.25 g, 5.36 mmol, 1.0 equiv.) in methanol (110 mL) under argon. The mixture was stirred at 23 °C for 40 h, at which point, solid potassium carbonate (40 mg) was added and the solvent was removed in vacuo. The residue was partitioned between 3/4 saturated sodium chloride solution (4 mL) and ethyl acetate (75 mL). The phases were separated and the organic phase was extracted with 3/4 saturated sodium chloride solution (2 x 4 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 80% ethyl acetate in hexanes to afford 5,5,7-trimethyl-1-aza-8-oxa-4-thiabicyclo[5.3.0]-2-decanone **113** (797 mg, 3.71 mmol, 69%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 3.90-4.00 (m, 2H), 3.73 (m, 1H), 3.60 (m, 1H), 3.52 (AB, 1H, J = 15.1 Hz), 3.03, (AB, 1H, J = 14.6 Hz), 2.16 (AB, 2H, J = 15.1 Hz), 1.54 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.7, 93.2, 61.6, 52.0, 45.8, 41.9, 31.8, 31.7, 30.8, 25.8.

---

[1] For references on the preparation of (2*S*)-2-(2-(*N*-benzyloxycarbonyl)pyrrolidine)ethanol, including an Arndt-Eistert homologation see

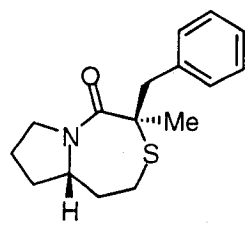
a) Cassal, J.M.; Fuerst, A.; Werner, M. *Helv. Chim. Acta* **1976**, *59*, 1917; b) Davies, S.B.; McKervey, M.A. *Tetrahedron Lett.* **1999**, *40*, 1229.

[2] (a) Leyendecker, F; Jesser, F.; Laucher, D.; Ruhland, B. *Nouv. J. Chim.* **1985**, *9*, 7. (b) Devita, R.J.; Goulet, M.T.; Wyvratt, M.J.; Fisher, M.H.; Lo, J-L.; Yang, Y.T.; Cheng, K.; Smith, R.G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621.

APPENDIX I

COORDINATES OF STRUCTURES OF

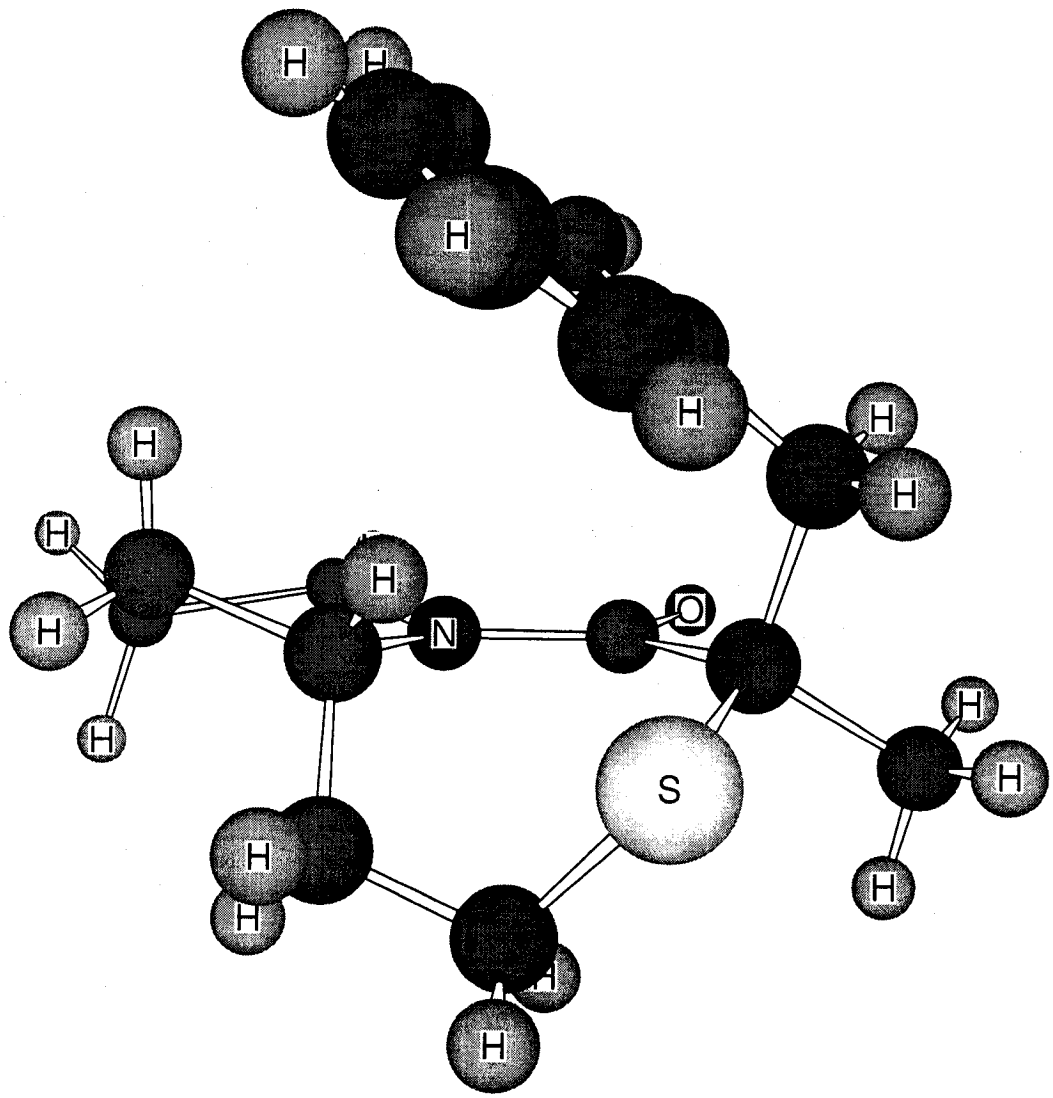
(3*R*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51f



51f

X-ray Crystal Structure of

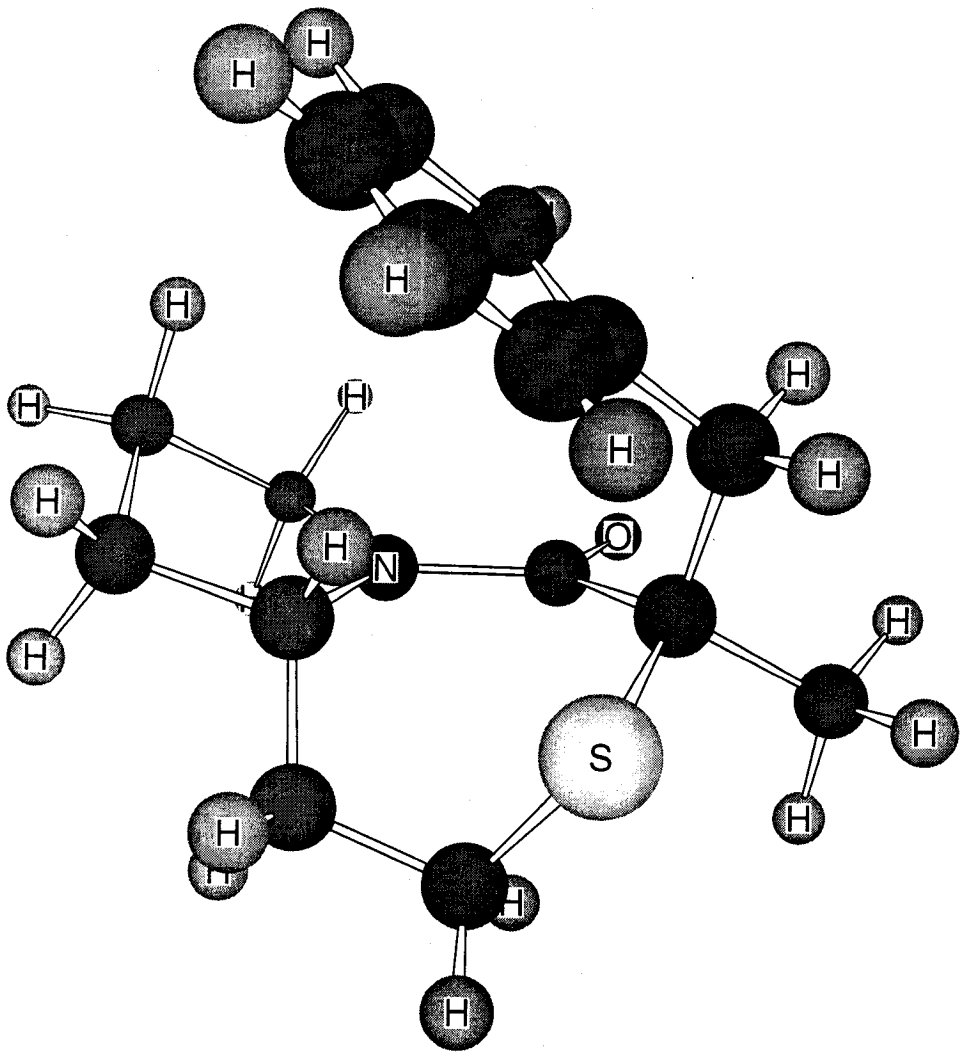
(3*R*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51f



```
CRYST1   8.002  11.364  15.941  90.00  90.00  90.00
SCALE1     0.124966 0.000000 0.000000      0.000000
SCALE2     0.000000 0.088000 0.000000      0.000000
SCALE3     0.000000 0.000000 0.062732      0.000000
ATOM      1 S4        0      7.891  -0.564   2.787 1.000  4.68
ATOM      2 O2        0      5.904   2.505   1.222 1.000  5.28
ATOM      3 N1        0      5.161   0.418   1.357 1.000  3.53
ATOM      4 C2        0      6.043   1.378   1.665 1.000  3.67
ATOM      5 C3        0      7.243   1.148   2.616 1.000  3.96
ATOM      6 C5        0      7.518  -1.281   1.173 1.000  4.78
ATOM      7 H5A       0      7.615  -0.596   0.492 1.000  5.74
ATOM      8 H5B       0      8.160  -1.983   0.981 1.000  5.74
ATOM      9 C6        0      6.114  -1.859   1.101 1.000  4.67
ATOM     10 H6A       0      6.112  -2.742   1.503 1.000  5.60
ATOM     11 H6B       0      5.856  -1.955   0.171 1.000  5.60
ATOM     12 C7        0      5.088  -0.984   1.815 1.000  3.57
ATOM     13 H7        0      5.230  -1.027   2.783 1.000  4.28
ATOM     14 C8        0      3.637  -1.370   1.482 1.000  4.64
ATOM     15 H8A       0      3.567  -2.316   1.283 1.000  5.57
ATOM     16 H8B       0      3.044  -1.158   2.220 1.000  5.57
ATOM     17 C9        0      3.306  -0.534   0.266 1.000  5.23
ATOM     18 H9A       0      3.654  -0.942  -0.543 1.000  6.28
ATOM     19 H9B       0      2.348  -0.417   0.173 1.000  6.28
ATOM     20 C10       0      3.989   0.785   0.546 1.000  4.61
ATOM     21 H10       0      3.729   1.633   0.269 1.000  5.53
ATOM     22 C11       0      8.402   2.042   2.126 1.000  5.85
ATOM     23 H11       0      8.695   1.741   1.262 1.000  8.77
ATOM     24 H11       0      9.133   1.989   2.747 1.000  8.77
ATOM     25 H11       0      8.101   2.951   2.063 1.000  8.77
ATOM     26 C12       0      6.824   1.638   4.033 1.000  4.73
ATOM     27 H12       0      7.581   1.530   4.629 1.000  5.67
ATOM     28 H12       0      6.627   2.586   3.981 1.000  5.67
ATOM     29 C13       0      5.639   0.941   4.643 1.000  4.03
ATOM     30 C14       0      4.351   1.354   4.364 1.000  4.82
ATOM     31 H14       0      4.214   2.109   3.838 1.000  5.78
ATOM     32 C15       0      3.260   0.658   4.857 1.000  6.12
ATOM     33 H15       0      2.399   0.942   4.653 1.000  7.34
ATOM     34 C16       0      3.445  -0.450   5.647 1.000  6.50
ATOM     35 H16       0      2.713  -0.926   5.966 1.000  7.80
ATOM     36 C17       0      4.727  -0.851   5.961 1.000  6.29
ATOM     37 H17       0      4.861  -1.590   6.510 1.000  7.55
ATOM     38 C18       0      5.804  -0.162   5.467 1.000  5.20
ATOM     39 H18       0      6.664  -0.440   5.690 1.000  6.24
```

MM2 Force Field Ground State Structure of

(3*R*,7*S*)-1-Aza-3-benzyl-3-methyl-4-thiabicyclo[5.3.0]-2-decanone 51f



C(1)							
N(5)	C(1)	1.447					
C(2)	C(1)	1.548	N(5)	101.658			
C(3)	C(2)	1.538	C(1)	104.980	N(5)	-18.123	Dihedral
C(4)	N(5)	1.453	C(1)	116.040	C(2)	-6.178	Dihedral
C(6)	N(5)	1.399	C(1)	124.839	C(4)	119.003	Pro-S
C(8)	C(6)	1.546	N(5)	124.442	C(1)	-6.673	Dihedral
O(7)	C(6)	1.221	N(5)	117.419	C(8)	118.113	Pro-R
S(9)	C(8)	1.843	C(6)	118.518	N(5)	29.631	Dihedral
C(10)	C(1)	1.537	N(5)	113.075	C(2)	111.111	Pro-S
C(11)	C(8)	1.548	C(6)	107.482	S(9)	109.599	Pro-R
C(12)	C(8)	1.551	C(6)	107.752	S(9)	105.629	Pro-S
C(13)	C(10)	1.533	C(1)	114.503	N(5)	51.517	Dihedral
C(14)	C(11)	1.512	C(8)	115.112	C(6)	62.248	Dihedral
C(15)	C(14)	1.398	C(11)	120.509	C(8)	-88.381	Dihedral
C(19)	C(14)	1.397	C(15)	118.688	C(11)	120.801	Pro-S
C(16)	C(15)	1.395	C(14)	120.727	C(19)	-0.655	Dihedral
C(17)	C(16)	1.393	C(15)	120.084	C(14)	0.084	Dihedral
C(18)	C(19)	1.395	C(14)	120.781	C(15)	0.790	Dihedral
H(20)	C(1)	1.114	C(2)	107.697	N(5)	109.747	Pro-S
H(21)	C(2)	1.116	C(1)	112.695	C(3)	112.690	Pro-R
H(22)	C(2)	1.115	C(1)	111.204	C(3)	107.737	Pro-S

H(23)	C(3)	1.116	C(2)	113.244	C(4)	112.710	Pro-S
H(24)	C(3)	1.116	C(2)	109.255	C(4)	109.956	Pro-R
H(25)	C(4)	1.114	C(3)	112.106	N(5)	109.387	Pro-S
H(26)	C(4)	1.116	C(3)	110.278	N(5)	114.321	Pro-R
H(27)	C(10)	1.116	C(1)	110.400	C(13)	107.120	Pro-R
H(28)	C(10)	1.117	C(1)	107.888	C(13)	110.074	Pro-S
H(29)	C(11)	1.115	C(8)	109.625	C(14)	107.909	Pro-R
H(30)	C(11)	1.115	C(8)	110.111	C(14)	108.934	Pro-S
H(31)	C(12)	1.115	C(8)	112.498	C(6)	59.512	Dihedral
H(32)	C(12)	1.114	C(8)	111.930	H(31)	105.783	Pro-S
H(33)	C(12)	1.115	C(8)	111.857	H(31)	106.997	Pro-R
H(34)	C(13)	1.115	S(9)	110.062	C(10)	109.244	Pro-R
H(35)	C(13)	1.115	S(9)	111.872	C(10)	111.110	Pro-S
H(36)	C(15)	1.102	C(14)	120.171	C(16)	119.102	Pro-R
H(37)	C(16)	1.103	C(15)	119.938	C(17)	119.978	Pro-R
H(38)	C(17)	1.103	C(16)	120.151	C(18)	120.155	Pro-S
H(39)	C(18)	1.102	C(17)	119.977	C(19)	120.001	Pro-S
H(40)	C(19)	1.103	C(14)	120.205	C(18)	119.014	Pro-S

APPENDIX II

WAIVERS OF COPYRIGHT

American Chemical Society

Publications Division
Copyright Office

FAX:

DATE: March 13, 2003

TO:

FROM: C. Arleen Courtney, Copyright Associate C. Arleen Courtney

Thank you for your request for permission to include **your** paper(s) or portions of text from **your** paper(s) in your thesis. Permission is now automatically granted; please pay special attention to the implications paragraph below. The Copyright Subcommittee of the Joint Board/Council Committees on Publications approved the following:

> Copyright permission for published and submitted material from theses and dissertations
> ACS extends blanket permission to students to include in their theses and dissertations their own articles, or portions thereof, that have been published in ACS journals or submitted to ACS journals for publication, provided that the ACS copyright credit line is noted on the appropriate page(s).
>
> Publishing implications of electronic publication of theses and dissertation material
> Students and their mentors should be aware that posting of theses and dissertation material on the Web prior to submission of material from that thesis or dissertation to an ACS journal may affect publication in that journal. Whether Web posting is considered prior publication may be evaluated on a case-by-case basis by the journal's editor. If an ACS journal editor considers Web posting to be "prior publication", the paper will not be accepted for publication in that journal. If you intend to submit your unpublished paper to ACS for publication, check with the appropriate editor prior to posting your manuscript electronically.

If your paper has **not** yet been published by ACS, we have no objection to your including the text or portions of the text in your thesis/dissertation in **print and microfilm formats**; please note, however, that electronic distribution or Web posting of the unpublished paper as part of your thesis in electronic formats might jeopardize publication of your paper by ACS. Please print the following credit line on the first page of your article: "Reproduced (or 'Reproduced in part') with permission from [JOURNAL NAME], in press (or 'submitted for publication'). Unpublished work copyright [CURRENT YEAR] American Chemical Society." Include appropriate information.

If your paper has already been published by ACS and you want to include the text or portions of the text in your thesis/dissertation in **print or microfilm formats**, please print the ACS copyright credit line on the first page of your article: "Reproduced (or 'Reproduced in part') with permission from [FULL REFERENCE CITATION.] Copyright [YEAR] American Chemical Society." Include appropriate information.

Note: If you plan to submit your thesis to UMI or to another dissertation distributor, you should not include the unpublished ACS paper in your thesis if the thesis will be disseminated electronically, until ACS has published your paper. After publication of the paper by ACS, you may release the entire thesis (**not the individual ACS article by itself**) for electronic dissemination; ACS's copyright credit line should be printed on the first page of the ACS paper.

SUMMARY: The inclusion of your ACS unpublished or published manuscript is permitted in your thesis in print and microfilm formats. If ACS has published your paper you may include the manuscript in your thesis on an intranet that is not publicly available. Your ACS article cannot be posted electronically on a publicly available medium, such as but not limited to, electronic archives, Internet, intranet, library server, etc. The only material from your paper that can be posted on a public electronic medium is the article abstract, figures, and tables.

Thank you for writing. Questions?

2/25/03

aren Buehler

From: Jeff Manthorpe [quatcarbon@yahoo.ca]
Sent: Thursday, March 13, 2003 3:10 PM
To: copyright@acs.org
Subject: request for permission

Dear A.C.S. representative,

I, Jeffrey Manthorpe, a Ph.D. candidate at McGill University, am writing to request permission to include a copy of my J. Am. Chem. Soc. paper (J. Am. Chem. Soc. 2001, vol. 123, 2091.) in an appendix of my thesis. I am planning to reprint the complete, unaltered article, including the A.C.S. copyright credit. Thank you for your consideration in this matter. If you have any questions or concerns, do not hesistate to contact me via email, phone

Sincerely,

Jeff Manthorpe

Subject: Antwort: request for permission
To: "Jeff Manthorpe" <quatcarbon@yahoo.ca>
From: "Claudia Rutz" <CRutz@wiley-vch.de>
te: Tue, 18 Mar 2003 08:39:53 +0100

Dear Mr. Manthorpe,

Thank you for your e-mail dated March 17.

We hereby grant permission for the requested use. We expect that due credit will be given to the original source.

With kind regards

Sincerely yours,

Claudia Rutz

****

Claudia Rutz
Copyright/Licensing Manager
WILEY-VCH Verlag GmbH
Boschstraße 12

2

Jeff Manthorpe <quatcarbon@yaho o.ca>

An:
Kopie:
Thema: request for permission

17.03.2003 23:24

Guten Tag Frau Rutz,

Ich heisse Jeff Manthorpe. Ich bin ein student doctorat aus Universitat McGill nach Montreal, Canada. I am writing to request permission to include an article I published in Angewandte Chemie (Angew. Chem. 2002, vol. 114, 2444; Angew. Chem. Int. Ed. 2002, vol. 41, 2338) in my doctoral thesis. I am planning to include the entire, unaltered article, including the Wiley-VCH copyright notice, as an appendix. Please understand that my thesis is ready for submission once I receive this waiver. Accordingly, I would greatly appreciate a response via fax at (514) If you have any concerns, please do not hesitate to contact me via email, or by phone

Danke schon,

Jeff Manthorpe

Ph.D. Candidate
McGill University
Dept. of Chemistry

APPENDIX III

PUBLISHED PAPERS

Stereoselective Generation of E- and Z-Disubstituted Amide Enolates. Reductive Enolate Formation from Bicyclic Thioglycolate Lactams

Jeffrey M. Manthorpe and James L. Gleason*

Department of Chemistry, McGill University
801 Sherbrooke St. West, Montreal, QC, Canada H3A 2K6

Received November 27, 2000

The formation of enolates is a process that is fundamental to a multitude of chemical transformations. In many cases, the stereochemistry of an enolate (E or Z) is an integral part of stereoselective reactions (e.g., syn/anti control in aldol reactions). For monosubstituted ester and ketone enolates, stereochemistry can often be influenced by judicious choice of solvent, base, and temperature.[1] For monosubstituted tertiary amide enolates, minimization of A-1,3 interactions usually favors Z-enolate formation.[2] Stereocontrol in disubstituted enolates is a more difficult task and must often be evaluated on a case-by-case basis. Highest levels of stereocontrol are usually associated with cyclic frameworks,[3] including metal chelates,[4] while control based on differential steric environments is less reliable.[5,6] We have initiated a project to develop stereoselective quaternary carbon forming reactions based on enolate transformations. The goal is to develop a general method that does not rely on specific enolate features such as chelating functionality or a large steric difference between enolate substituents. In this communication, we report a method for controlling enolate geometry in disubstituted amide enolates where the E/Z selectivity is dependent only on the geometry and stereochemistry of the enolate precursor.

Our design utilizes a two-electron reduction of α,α-dialkylated bicyclic thioglycolate lactams to provide disubstituted amide enolates (Figure 1).[7] Assuming that (a) two alkyl groups (R_1 and R_2) are installed stereoselectively at the α-position, (b) the O−C−C−S dihedral angle is held as close to 90° as possible by the bicyclic system, and (c) significant bond rotation does not occur about the carbonyl-carbon/α-carbon bond during the two-electron reduction process, the E/Z stereochemistry of the enolate should be controlled by the relative positions of R_1 and R_2 in the starting lactam. Importantly, this should afford kinetic E/Z stereocontrol that is independent of the relative stabilities of the two enolates

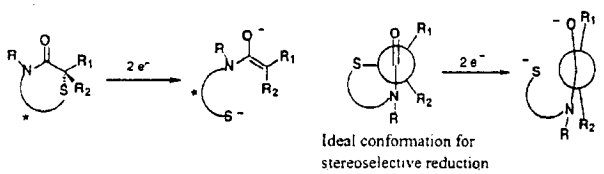
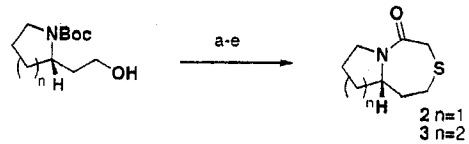


Figure 1. Model for stereoselective enolate generation.

Scheme 1. Synthesis of 5,7- and 6,7-Bicyclic Lactams

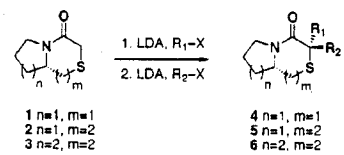


[a] MsCl, NEt_3, CH_2Cl_2. [b] MeO_2CCH_2SH, NaH, DMF. [c] LiOH, THF/H_2O. [d] TFA (or HCl/Et_2O). [e] EDC-HOBT (or 2-chloro-1-methylpyridnium iodide), NEt_3, CH_2Cl_2. 53% yield (5 steps) for **2**. 46% yield (5 steps) for **3**.

and does not depend on a large difference in size of the two alkyl groups. Significantly, switching the position of R_1 and R_2 by inverting the order of their installation should lead to a reversal of enolate geometry. In many regards, our model resembles the preferred transition state for deprotonation adjacent to a carbonyl group, with sulfur transposed for hydrogen. The significant difference is that deprotonation is a concerted (two-electron) process whereas the reductive process undoubtedly involves two separate one-electron-transfer steps and thus bond rotation is a potential competing process in the intermediate radical anion resulting from C−S bond scission.

Molecular modeling calculations (MM2) using a Monte Carlo conformational search (Macromodel) were used to identify suitable candidates for this stereoselective reduction process. Several classes of bicyclic thioglycolate lactams were analyzed for desirable O−C−C−S dihedral angles both at the ground state and as a weighed average of all stable conformations within 2 kcal/mol of the ground state. From these calculations, the 5,6-, 5,7- and 6,7-bicyclic lactams **1**−**3** were identified as candidates for study (see Table 1). Of these, the 5,7- and 6,7-bicyclic lactams **2** and **3** appear to be reasonable candidates (O−C−C−S dihedral angles of 120−150°), while the 5,6-bicyclic lactam **1** has an

Table 1. Alkylation of Bicyclic Lactams



1 n=1, m=1
2 n=1, m=2
3 n=2, m=2

4 n=1, m=1
5 n=1, m=2
6 n=2, m=2

Series
a R_1 = n-Pr R_2 = Me
b R_1 = Me R_2 = n-Pr
c R_1 = Allyl R_2 = Me
d R_1 = Me R_2 = Allyl
e R_1 = Bn R_2 = Me
f R_1 = Me R_2 = Bn
g R_1 = n-Pr R_2 = Et
h R_1 = Et R_2 = n-Pr

lactam	R_1−X	yield	de[a]	R_2−X	product	yield	de[b]
1	*n*-PrI	84%	88%	MeI	**4a**	94%	72%
1	MeI	88%	81%	*n*-PrI	**4b**	88%	72%
1	allyl-Br	88%	85%	MeI	**4c**	91%	79%
1	MeI			allyl-Br	**4d**	86%	78%
2	*n*-PrI	76%	88%	MeI	**5a**	90%	90%
2	MeI	86%	93%	*n*-PrI	**5b**	72%	86%
2	allyl-Br	88%	85%	MeI	**5c**	85%	95%
2	MeI			allyl-Br	**5d**	96%	87%
2	BnBr	96%	>95%	MeI	**5e**	88%	>99%
2	MeI			BnBr	**5f**	91%	>99%
2	*n*-PrI			EtI	**5g**	75%	88%
2	EtI	80%	87%	*n*-PrI	**5h**	76%	94%
3	*n*-PrI	95%	68%	MeI	**6b**	81%	50%[a,c]
3	MeI	95%	87%	*n*-PrI	**6a**	81%	62%[a,c]
3	BnBr	80%	>95%	MeI	**6f**	89%	66%[a,e]
3	MeI			BnBr	**6f**	69%[d]	10%

[a] Determined by integration of ^1H and/or ^{13}C NMR resonances. [b] Determined by capillary gas chromatography on a Chirasil Dex column. Unless otherwise noted, diastereomers were not separable. [c] Alkylation selectivity is reversed for these substrates. These substrates were readily separable by flash chromatography. [d] Lactam **6e** was isolated in 31% yield and lactam **6f** was isolated in 38% yield.

(1) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. (c) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *24*, 495. (d) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(2) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.

(3) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.

(4) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829. (b) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

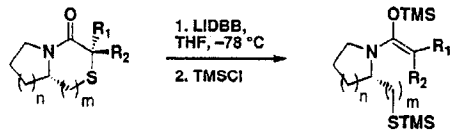
(5) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, S. T.; Stec, M.; Suna, E *J. Am. Chem. Soc.* **2000**, *122*, 4602.

(6) For a stereoselective enolization of tiglate oxazolidinone imides, see: Hosoawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429.

(7) Kamata, S.; Uyeo, S.; Haga, N.; Nagata, W. *Synth. Commun.* **1973**, *3*, 265.

10.1021/ja0058280 CCC: $20.00
Published on Web 02/10/2001

Table 2. Reductive Enolization of Bicyclic Thioglycolate Lactams



series	n	m	lactam	R_1	R_2	O−C−C−S dihedral[a]	Z/E ratio[b]	lactam	R_1	R_2	O−C−C−S dihedral[a]	Z/E ratio[b]
1	1	1	**4a**	*n*-Pr	Me	174	47:53	**4b**	Me	*n*-Pr	182	64:36
2	1	1	**4c**	Allyl	Me	175	44:56	**4d**	Me	Allyl	178	68:32
3	1	2	**5a**	*n*-Pr	Me	141	87:13	**5b**	Me	*n*-Pr	128	20:80
4	1	2	**5c**	Allyl	Me	140	87:13	**5d**	Me	Allyl	138	26:74
5	1	2	**5e**	Bn	Me	145	92:8	**5f**	Me	Bn	149	12:88
6	1	2	**5g**	*n*-Pr	Et	139	80:20	**5h**	Et	*n*-Pr	137	12:88
7	2	2	**6a**	*n*-Pr	Me	140	83:17	**6b**	Me	*n*-Pr	133	37:63
8	2	2	**6e**	Bn	Me	143	92:8	**6f**	Me	Bn	139	53:47

[a] Weighted average (calculated at −78 °C) of all conformations within 2 kcal/mol of the ground state as determined by Monte Carlo calculations. [b] Determined by integration of ^{13}C resonances.

unfavorable dihedral angle (175−180°) and thus was expected to serve as a control.

Lactam **1** was prepared in two steps from prolinol following the procedure of Ishibashi.[8] Lactams **2** and **3** were prepared from *N*-Boc-2-(2-pyrrolidine)ethanol and *N*-Boc-2-(2-piperidine)ethanol, respectively, by displacement of the corresponding mesylates with methyl thioglycolate followed by a straightforward lactamization protocol (Scheme 1). Sequential alkylation of lactams **1**−**3** was performed in THF with LDA (1.1 equiv) in the presence of LiCl (5 equiv).[9] Excellent yields and good to excellent diastereoselectivities were obtained for the alkylations of 5,6- and 5,7-bicyclic lactams (Table 1). The expected stereochemical outcome of these alkylations, wherein the electrophile approaches from the exo-face of the bicyclic system,[3] was confirmed through NOE studies. Alkylation of the 6,7-bicyclic lactam **3** was not only less selective but the facial selectivity in the second alkylation reaction was reversed relative to that of the 5,7-bicyclic system.

Reduction of the thioglycolate lactams was best accomplished by titrating with lithium di-*tert*-butylbiphenylide (LiDBB) in THF at −78 °C. The resulting enolate dianions were trapped as the silyl ketene aminals by addition of trimethylsilyl chloride followed by warming the reaction slowly to 23 °C over 0.5 h.[10] The silyl ketene aminals were isolated by removal of solvent in vacuo and trituration into C_6D_6 and the E/Z ratio of the products was determined by ^{13}C NMR.[11] The stereochemistry for the silyl ketene aminals derived from **5e**−**h** (Table 2, Series 5−6) was definitively assigned by observation of NOE enhancements. Assignments for the remaining products were made by analogy and by comparison of the ^{13}C NMR shifts for the ketene aminal carbons among related series.

Reduction and trapping of amides **4a**−**d** proceeded with low levels of E/Z selectivity, consistent with the large O−C−C−S dihedral angle in these substrates (Series 1−2, Table 2). In contrast, reduction of lactam **5a** afforded the *Z*-2-methylpentanamide enolate with 87:13 selectivity. *Importantly, reduction of the stereoisomeric lactam (**5b**) produced the E-enolate, also with good levels of stereocontrol (80:20 E/Z).* A similar trend was observed for all 5,7-bicyclic lactams studied (Series 3−6, Table 2). Reduction of the 6,7-bicyclic lactams **6a** and **6e** produced *Z*-enolates cleanly. However, *E*-enolate selectivity was reduced for reduction of diatstereomers **6b** and **6f**. Overall, the results are in accord with our proposed model and indicate that bond rotation in the intermediate radical anions is at most a minor competing factor in the reductive enolization process. The reasons for reduced selectivity with lactams **6b** and **6f** are unclear, but may reflect a higher degree of flexibility in the 6,7-bicyclic ring system.

In conclusion, we have developed a method for stereoselective generation of disubstituted amide enolates wherein the E/Z selectivity is determined by the stereochemistry and geometry of the starting bicyclic lactams. The method affords both *E*- and *Z*-amide enolates without relying on a steric difference between the two substituents. The high levels of alkylation selectivity of the 5,7-bicyclic system and the excellent levels of stereocontrol for enolate generation appear to earmark it for future development. In this regard, it is important to note that the reduction generates an enolate structure that is reminiscent of prolinol amide enolates[2] and may serve as a template for subsequent stereoselective transformations.[12] We expect that this new enolate preparation will find use in numerous reactions including alkylations and aldol reactions.

Acknowledgment. Support for this research from NSERC, FCAR, Research Corporation and Merck Frosst Inc. is gratefully acknowledged. J.M.M. acknowledges support from FCAR in the form of a postgraduate scholarship.

Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0058280

(8) Ishibashi, H.; Uegaki, M.; Sakai, M. *Synlett* **1997**, 915.

(9) For the use of LiCl in alkylations of amide enolates, see: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(10) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 881.

(11) Generally the reduction of the amides was complete and ≤5% of enolate quenching was observed. Reduction of **5d** produced a byproduct (ca. 30%) that could not be fully characterized.

(12) For example, reduction of **5e** with LiDBB followed by addition of allyl bromide (3 equiv) and stirring at −78 °C for 3 h affords the corresponding C,S-dialkylated product in 96% yield and 90:10 diastereoselectivity. Complete studies on this alkylation reaction will be reported in due course.

fluoride ions were 1 to 2 mM. The protonation constant of fluoride in water is: $\log K_{HF/F} = 3.15$.

NMR Measurements: ^{1}H NMR spectra were recorded on a Bruker AM500 spectrometer at 500 MHz. Binding constants were obtained by NMR titrations of **L** with fluoride from 25 measurements in D_2O at pD = 5.0 ± 0.1. Initial concentrations were $[\mathbf{L}]^0 = 2$ mM and titrations were performed using aliquots from a 20 mM stock solution of NaF. A solution of the sodium salt of [2,2,3,3-D_4]-3-(trimethylsilyl)propionic acid (TPS) in D_2O in a capillary tube was used as an external reference. The pD value was adjusted with a concentrated solution of TsOH and NaOD in D_2O. All spectra were recorded at room temperature. The association constants K_s were calculated by fitting f to δ_{obs} (consisting of several independent NMR signals) with a 1:1 association model using Sigma Plot software. Equations (1) and (2) were used, where **L** is the ligand and A^- is the anion, and the error limit in K is less than 10%:

$$c = ([A^-]^0 + [\mathbf{L}]^0 + 1/K_s - \{([A^-]^0 + [\mathbf{L}]^0 + 1/K_s)^2 - 4[\mathbf{L}]^0[A^-]^0\}^{1/2})/2 \quad (1)$$

$$f = (\delta_{LA} - \delta_L)c/[\mathbf{L}]^0 + \delta_L \quad (2)$$

The Job's plot was performed by examining different concentration ratios of **L** and NaF in D_2O at pD = 5.0 ± 0.1, while maintaining the total concentration of the ligand plus NaF at 10 mM. The pD value was adjusted with a concentrated solution of TsOH and NaOD in D_2O. NMR measurements were recorded at room temperature.

Received: October 22, 2001
Revised: April 12, 2002 [Z18101]

[1] B. Dietrich, J. Guilhem, J.-M. Lehn, C. Pascard, E. Sonveaux, *Helv. Chim. Acta* **1984**, *67*, 91 – 104.
[2] Nomenclature: M = *m*-xylyl, P = *p*-xylyl, and Fu = furan spacers; E = ethyl links within the tren unit between amine groups; A = amine; cryp = cryptand.
[3] a) S. Mason, T. Clifford, L. Seib, K. Kuczera, K. Bowman-James, *J. Am. Chem. Soc.* **1998**, *120*, 8899 – 8900; b) T. Clifford, A. Danby, J. M. Llinares, S. Mason, N. W. Alcock, D. Powell, J. A. Aguilar, E. García-España, K. Bowman-James, *Inorg. Chem.* **2001**, *40*, 4710 – 4720.
[4] T. Clifford, S. Mason, J. M. Llinares, K. Bowman-James, *J. Am. Chem. Soc.* **2000**, *122*, 1814 – 1815.
[5] J. A. Aguilar, T. Clifford, A. Danby, J. M. Llinares, S. Mason, E. García-España, K. Bowman-James, *Supramol. Chem.* **2001**, *13*, 405 – 417.
[6] a) J.-M. Lehn, S. H. Pine, E. I. Watanabe, A. K. Willard, *J. Am. Chem. Soc.* **1977**, *99*, 6766 – 6768; b) J.-M. Lehn, *Pure Appl. Chem.* **1980**, *52*, 2441 – 2459.
[7] a) J. Jazwinski, J.-M. Lehn, D. Lilienbaum, R. Ziessel, J. Guilheim, C. Pascard, *J. Chem. Soc. Chem. Commun.* **1987**, 1691 – 1692; b) D. McDowell, J. Nelson, *Tetrahedron Lett.* **1988**, *29*, 385 – 386; c) D. Chen, A. E. Martell, *Tetrahedron* **1991**, *47*, 6895 – 6902.
[8] V. Amendola, E. Bastianello, L. Fabbrizzi, C. Mangano, P. Pallavicini, A. Perotti, A. M. Lanfredi, F. Ugozzoli, *Angew. Chem.* **2000**, *112*, 3039 – 3042; *Angew. Chem. Int. Ed.* **2000**, *39*, 2917 – 2920.
[9] X-ray data for **1**: A crystal of dimensions 0.64 × 0.42 × 0.21 mm was selected for structural analysis. Crystal data: $M_r = 1161.31$; triclinic space group, $P\bar{1}$, $a = 9.8302(11)$, $b = 15.9973(19)$, $c = 17.417(2)$ Å, $\alpha = 84.404(3)°$, $\beta = 89.959(3)°$, $\gamma = 77.098(2)°$, $V = 2656.5(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.452$ g cm^{-3}, $F(000) = 1232$. A total of 12226 observed reflections ($I > 2\sigma(I)$) were collected. The refinement converged at $R1(F$, observed data) = 0.0443, and $wR2$ (F^2, all data) = 0.1189, and GOF = 0.974. Diffraction data were collected using a Bruker SMART APEX CCD area detector mounted on a Bruker D8 goniometer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) at 100(2) K.[S] Intensity data were measured as a series of ω and θ oscillation frames each of 0.3° for times of 5 s per frame. The detector was operated in a 512 × 512 mode and was positioned 5.04 cm from the sample. Coverage of unique data was close to 99.4% complete to 26.00° in θ. Cell parameters were determined from a least-squares fit of 9504 peaks in the range $2.40 < \theta < 30.58°$. Virtually no decay was observed, based on data obtained for a number of peaks monitored at both the beginning and end of data collection. The data were corrected for absorption by the semi-empirical method.[9] Lorentz and polarization corrections were applied. The data were merged to form a set of 15608 independent data with $R_{int} = 0.0248$. The space group was determined by statistical tests, and the structure was solved by direct methods and refined by full-matrix least-squares methods on F^2.[10] Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. CCDC-172118 (**1**) and CCDC-172119 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[10] Data collection: SMART Software Reference Manual, Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA, **1994**. Data reduction: SAINT Software Reference Manual, Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA, **1995**.
[11] G. M. Sheldrick, SADABS. Program for Empirical Absorption Correction of Area Detector Data, University of Göttingen, Göttingen (Germany), **1996**.
[12] G. M. Sheldrick, SHELXTL Version 5 Reference Manual, Bruker AXS 5465 E. Cheryl Parkway, Madison, WI 53711-5373, USA, **1994**, using *International Tables for Crystallography, Vol. C*, Kluwer, Boston, **1995**, Tab. 6.1.1.4, 4.2.6.8, and 4.2.4.2.
[13] N. Alcock in *Bonding and Structure*, Ellis Horwood, West Sussex, England, **1990**, p. 316.
[14] Synthesis, characterization, and structural results for **2** are given in the Supporting Information.
[15] Protonation constants for PEAcryp have been reported as $\log K_1 = 9.6(1)$, $\log K_2 = 9.00(4)$, $\log K_3 = 8.62(8)$, $\log K_4 = 7.3(1)$, $\log K_5 = 6.7(1)$, and $\log K_6 = 6.52(9)$ using Et_4NClO_4 as the electrolyte: F. Arnaud-New, S. Fuangswasdi, B. Maubert, J. Nelson, V. McKee, *Inorg. Chem.* **2000**, *39*, 573 – 579.
[16] R. J. Motekaitis, A. E. Martell, J.-M. Lehn, E.-I. Watanabe, *Inorg. Chem.* **1982**, *21*, 4253 – 4257.
[17] P. Gans, A. Sabatini, A. Vacca, *J. Chem. Soc. Dalton Trans.* **1985**, 1195 – 1200.

Stereoselective Formation of Quaternary Carbon Centers: Alkylation of α,α-Disubstituted Amide Enolates**

Jeffrey M. Manthorpe and James L. Gleason*

The stereoselective formation of quaternary carbon centers is one of the most challenging tasks in organic chemistry and can only be achieved using methods which employ some form of carbon – carbon bond forming reaction.[1] One of the most straightforward methods for the formation of carbon – carbon bonds is the alkylation of an enolate with an alkyl halide and,

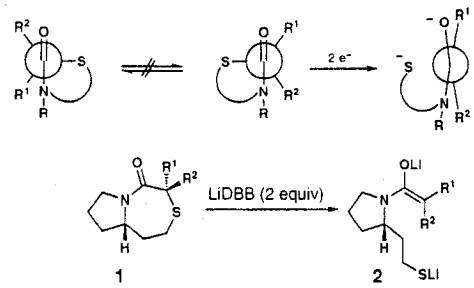
[*] Prof. J. L. Gleason, J. M. Manthorpe
Department of Chemistry
McGill University
801 Sherbrooke St. West, Montreal, QC, H3A 2K6 (Canada)
Fax: (+1) 514-398-3797
E-mail: jim.gleason@mcgill.ca

[**] We thank NSERC, Research Corporation, and Merck Frosst Therapeutic Inc. for support of this research. J.M.M. acknowledges support from FCAR in the form of a postgraduate fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

indeed, several methods for the stereoselective formation of quaternary carbon centers have been based on this approach.[2-17] One of the most significant problems in any approach based on enolate alkylation is to control enolate stereochemistry (*E* vs. *Z*). This control is necessary, as it works in tandem with π-facial selectivity to a stereoselective reaction. Many methods solve this problem by employing cyclic enolates or metal chelates.[2-11] Although this works well, the final alkylation products usually contain specific functional group residues that were necessary to form the cyclic enolate. This often limits the scope of these methods.

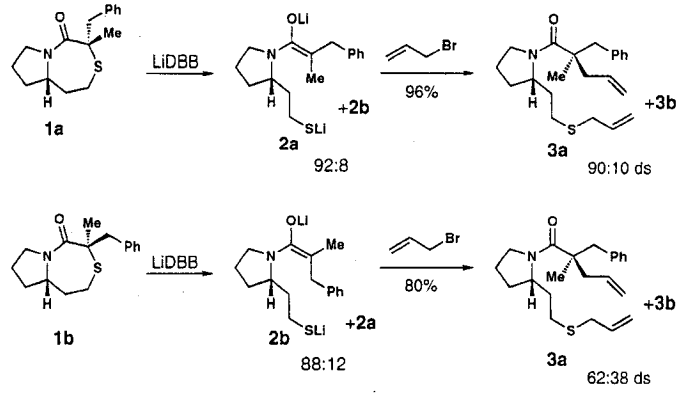
Recently, we reported a method for the preparation of α,α-disubstituted amide enolates by reduction of bicyclic thioglycolate lactams.[18] This method was based on a simple operational model wherein the bicyclic system constrains the sulfur so that it is held rigidly on one face of the carbonyl plane (Scheme 1). Upon two-electron



Scheme 1. Operational model for the stereocontrolled synthesis of α,α-disubstituted amide enolates **2** by reduction of bicyclic thioglycolate lactams **1**.

reduction, carbon–sulfur bond cleavage occurs to form an enolate dianion and the *E*/*Z* stereochemistry of the enolate is governed by the relative locations of the α-alkyl groups in the starting lactam. Good to excellent levels of stereocontrol are observed and both *E* and *Z* amide enolates **2** may be prepared (Scheme 1). Importantly, this method removes the requirement for a cyclic enolate or chelating functionality to control enolate stereochemistry; any alkyl groups may be present at the R^1 and R^2 positions. A feature of our design is that the reduction step liberates a chiral auxiliary which is reminiscent of a prolinol amide. Prolinol amides have been used to control stereochemistry in alkylations which form tertiary carbon stereocenters.[19] Here, we report that high stereoselectivities may be achieved for the formation of quaternary carbon centers by the alkylation of our α,α-disubstituted enolates, which in many cases even exceed the stereoisomer ratio of the intermediate enolates.

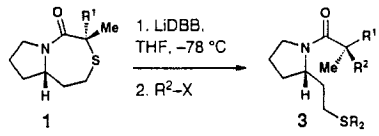
As previously reported, reduction of diastereomeric lactams **1a** and **1b** with lithium di-*tert*-butyldiphenylide (LiDBB)[20] in THF at −78 °C affords the corresponding *Z* and *E* enolates with 92:8 and 88:12 selectivity, respectively (Scheme 2).[18] Addition of allyl bromide to the enolates



Scheme 2. Alkylation to form quaternary carbon stereocenters.

resulted in the formation of C,S-dialkylated products in high yields.[21] Intriguingly, alkylation of either enolate, **2a** or **2b**, afforded *the same major product* **3a**. The alkylation of *Z* enolate **2a** showed good stereoselectivity (90:10) which was roughly in line with the ratio of the intermediate enolates. Alkylation of *E* enolate **2b** was only poorly selective (62:38).[22] Additives had only a modest effect on the alkylation selectivity of the *E* enolate. Conducting the reaction in the presence of 20% hexamethylphosphoramide (HMPA) reversed the stereoselectivity slightly (39:61 ratio), while addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 45%) or LiCl (10 equiv) had minimal effects. The addition of HMPA had no discernable effect on either the yield or the stereoselectivity in the alkylation of the *Z* enolate.

A significant and practical improvement in the stereoselectivity of the alkylation was observed when the *Z* enolates are allowed to react with unactivated alkyl halides [Eq. (1), Table 1]. For instance, reaction of enolate **2a** with ethyl iodide instead of allyl bromide afforded the corresponding product **3c** with 96.5:3.5 diastereoselectivity (93% *de*). Similar selec-



(1)

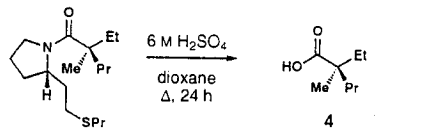
Table 1. Alkylations using unactivated electrophiles [Eq. (1)].

Lactam	R^1	*Z*/*E* Ratio of **2**[a]	*de* [%] of **2**	R^2X	Product	Yield [%]	de [%][c]
1a	Bn	92:8	84	EtI	**3c**	89	93
1a	Bn	92:8	84	*n*BuI	**3d**	76	>95
1c	*n*Pr	87:13	74	EtI	**3e**	85	89
1c	*n*Pr	87:13	74	*n*BuI	**3f**	71	95
1c	*n*Pr	87:13	74	*i*BuI	**3g**	59[b]	87
1d	Et	90:10	80	*n*PrI	**3h**	83	>95
1e	allyl	87:13	74	EtI	**3i**	84	88
1e	allyl	87:13	74	BuI	**3j**	80	91
1f	*n*Bu	–[c]	–	*n*PrI	**3k**	88	>95

[a] Determined by ^{13}C NMR spectroscopy. [b] HMPA (23%) was added during the alkylation step. [c] Not determined.

tivities were observed for a series of *Z* enolates and unactivated *n*-alkyl halides. The yields were high and in most cases the reactions proceeded to completion within 4 h at −78 °C without added polar co-solvents.[23] Branched alkyl halides such as isobutyl iodide were slower to react, but gave acceptable yields at −78 °C in the presence of HMPA.[24] Importantly, in all cases explored with unactivated alkyl iodides the alkylation selectivities were higher than the *Z*/*E* ratios of the intermediate enolates. This selectivity enhancement presumably has its origin in the low alkylation selectivity of the minor *E* enolates (1:1 selectivity was observed for reaction of **2b** with EtI). From a practical standpoint, the poor selectivity of the *E* enolates is not a significant issue, as a judicious choice of the alkylation sequence can allow stereoisomeric products to be prepared. For example, alkylation products **3f** and **3k** were prepared with high diastereoselectivity by simply inverting the overall alkylation sequence. These molecules are not true diastereomers, as they have different alkyl groups on sulfur. However, upon cleavage of the amide auxiliary (vide infra), the final products were isolated as a pair of enantiomers.

Hydrolysis of the alkylation products proved to be difficult. Heating **3h** in a 1:1 mixture of 6 M H_2SO_4 and dioxane for 24 h resulted in formation of the acid **4** [Eq. (2)] in 18% yield



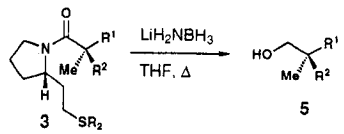
(2)

3h

$[\alpha]_D^{20} = -18$ (*c*=0.6, EtOH)

along with recovery of 71% of the starting material. Although this direct hydrolysis was not practical, it did allow the stereochemistry of the alkylation process to be elucidated. Comparison of the optical rotation of **4** with literature data established that the *S* isomer was formed in the alkylation step.[25] Thus, the alkylation occurs from the top face of the enolate [as drawn in Eq. (2)]. Similar facial selectivity was observed by Evans and Takacs in the reactions of O-alkylated prolinol *Z* amide enolates.[19a] In the latter case, masking the prolinol hydroxyl group as an ether resulted in a switch in facial selectivity, presumably due to a loss of chelation. Given the similar facial selectivity and that chelation here would require an eight-membered ring, our results seem most consistent with an unchelated enolate.

An effective method for removal of the chiral auxiliary proved to be reductive cleavage. Treatment of the amides with lithium amidotrihydroborate[26] in THF at reflux [Eq. (3)] afforded the corresponding primary alcohols in high yields (Table 2). The enantiomeric excess of the products was assessed either directly or on the corresponding carboxylic acids (see Table 2 and Supporting Information). In all cases, the enantiomeric excess of the products was consistent with the diastereomeric excess of the alkylation products, indicating that no significant kinetic resolution occurred during the reductive cleavage of the chiral auxiliary.



(3)

Table 2. Reductive cleavage of the chiral auxiliary with lithium amidotrihydroborate [Eq. (3)].

Amide	R^1	R^2	Product	Yield [%]	*ee* [%]
3c	Bn	Et	**5a**	96	94[a]
3d	Bn	*n*Bu	**5b**	97	96[a]
3f	*n*Pr	*n*Bu	**5c**	99	96[b]
3k	*n*Bu	*n*Pr	**5d**	87	95[b]
3j	allyl	*n*Bu	**5e**	74	93[b]

[a] Determined by HPLC analysis (Chiracel OD column). [b] Determined by capillary GC analysis (ChirasilDex column) on the corresponding carboxylic acid. Due to peak tailing, the GC analyses are accurate to within ±2%.

In conclusion, we have developed a highly stereoselective enolate alkylation process for the generation of quaternary carbon centers. The stereoselectivities are highest for reactions of α,α-disubstituted *Z* amide enolates with unactivated *n*-alkyl iodides. The method is notable in that high selectivities are obtained without the need for cyclic enolates or metal chelates, thus allowing any alkyl group to be incorporated into the final product. The resulting alkylation products may be cleaved in high yield to the corresponding primary alcohols using lithium amidotrihydroborate. Finally, enantiomeric pairs of molecules may be formed simply by inverting the order of alkylation followed by cleavage of the chiral auxiliary. Further studies in this area will focus on the extension of the method to other carbon–carbon bond forming reactions.

Experimental Section

Reduction/alkylation procedure [Eq. (1)]: A solution of LiDBB in THF was added dropwise with a glass syringe to a solution of lactam **1a** (243 mg, 882 μmol, 1 equiv) in THF (8.8 mL) in a Schlenk flask at −78 °C until the green color of LiDBB briefly persisted. *n*-Butyl iodide (402 μL, 3.53 mmol, 4.0 equiv) was added dropwise and the solution was stirred at −78 °C for 4 h. Saturated ammonium chloride solution (10 mL) was added and the resulting mixture was warmed to room temperature and extracted with ethyl acetate (3 × 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 3% ethyl acetate in hexanes to afford 260 mg of **3d** as a colorless oil in 76% yield. The product was determined to have >95% *de* by ^{13}C NMR analysis. ^1H NMR ($C_6D_5CD_3$, 105 °C): δ = 6.95–7.08 (m, 5H), 4.24 (m, 1H), 2.93–3.11 (m, 3H), 2.38–2.51 (m, 5H), 1.97–2.16 (m, 2H), 1.07–1.60 (m, 14H), 1.13 (s, 3H), 0.76–0.88 ppm (m, 6H); ^{13}C NMR ($C_6D_5CD_3$, 105 °C): δ = 173.8, 138.8, 130.3, 127.7, 126.0, 58.8, 48.2, 46.9, 46.3, 41.3, 34.3, 31.9, 31.8, 29.3, 28.8, 27.0, 25.0, 23.2, 22.6, 21.8, 13.6, 13.2 ppm. $C_{14}H_{19}NOS$: C 73.98, H 10.09, N 3.59; found: C 74.31, H 9.98, N 3.60.

Reductive cleavage of the chiral auxiliary [Eq. ((3)]: A solution of *n*-butyllithium in hexanes (2.27 M, 2.39 mL, 5.42 mmol, 3.90 equiv) was slowly added to a stirred solution of diisopropylamine (799 μL, 5.70 mmol, 4.10 equiv) in THF (2.5 mL) at 0 °C. After stirring for 10 min, borane–ammonia complex (90%, 191 mg, 5.56 mmol, 4.0 equiv) was added in one portion. After stirring at 0 °C for 15 min the mixture was warmed to 23 °C and after 10 min a solution of **3c** (464 mg, 1.39 mmol, 1 equiv) in THF (5 mL) was added with a cannula. The mixture was heated at reflux for

  1433-7851/02/4113-2340 $ 20.00+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 13

24 h, then cooled to 0 °C, and quenched with aqueous hydrochloric acid (3 M, 5 mL). The resulting mixture was warmed to 23 °C and stirred for 30 min, at which point aqueous sodium hydroxide (3 M, 10 mL) was added. The mixture was stirred at 23 °C for 30 min and extracted with diethyl ether (3 × 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 pentane afforded (*R*)-2-ethyl-2-methyl-2,3-dihydrocinnamyl alcohol **5a** (239 mg, 1.34 mmol, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.19-7.31$ (m, 5H), 3.33 (s, 2H), 2.61 (AB, 2H, $J = 24.6$ Hz), 1.58 (bs, 1H), 1.27–1.40 (m, 2H), 0.93 (t, 3H, $J = 7.5$ Hz), 0.82 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 139.0$, 130.8, 128.1, 126.2, 68.4, 42.8, 39.1, 29.1, 21.0, 8.3 ppm. High-resolution FAB-MS: *m/z* (*M*+H): 179.14359 ($C_{12}H_{19}O^+$ requires 179.14359). $[\alpha]_D^{25} = -5.9$ (*c* = 14.2, CH_2Cl_2). The product was determined to have 94% *ee* by HPLC (Chiralcel OD column, eluting with 1% 2-propanol in hexanes at 0.7 mL min^{-1}; $R_t = 20.5$ min (major enantiomer), 22.8 min (minor enantiomer)).

Received: October 26, 2001
Revised: April 11, 2002 [Z18123]

[1] For reviews, see: a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

[2] a) A. I. Meyers, M. Harre, R. Garland, *J. Am. Chem. Soc.* **1984**, *106*, 1146; b) D. Romo, A. I. Meyers, *Tetrahedron* **1991**, *47*, 9503; c) M. D. Groaning, A. I. Meyers, *Tetrahedron*, **2000**, *56*, 9843.

[3] a) A. G. Schultz, M. Macielag, P. Sundararaman, A. G. Taveras, M. Welch, *J. Am. Chem. Soc.* **1988**, *110*, 7828; b) A. G. Schultz, *Acc. Chem. Res.* **1990**, *23*, 207; c) A. G. Schultz, *Chem. Commun.* **1999**, 1263.

[4] G. Frater, *Helv. Chim. Acta* **1979**, *62*, 2825.

[5] a) K. Tomioka, K. Ando, Y. Takemasa, K. Koga, *J. Am. Chem. Soc.* **1984**, *106*, 2718; b) K. Kato, H. Suemune, K. Sakai, *Tetrahedron* **1994**, *50*, 3315.

[6] M. Ihara, M. Takahashi, H. Niitsuka, N. Taniguchi, K. Yasui, K. Fukumoto, *J. Org. Chem.* **1989**, *54*, 5413.

[7] a) J. Aahman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918; b) A. Chieffi, K. Kamikawa, J. Ahman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897.

[8] a) B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **1999**, *121*, 6759; b) S.-L. You, X.-L. Hou, L.-X. Dai, X.-Z. Zhu, *Org. Lett.* **2001**, *3*, 149.

[9] a) A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem.* **1986**, *98*, 442; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476; b) U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446; c) Y. Yamashita, K. Odashima, K. Koga, *Tetrahedron Lett.* **1999**, *40*, 2803.

[10] a) L. E. Overman, J. F. Larrow, B. A. Stearns, J. M. Vance, *Angew. Chem.* **2000**, *112*, 219; *Angew. Chem. Int. Ed.* **2000**, *39*, 213; b) S. B. Hoyt, L. E. Overman, *Org. Lett.* **2000**, *2*, 3241.

[11] D. Enders, P. Teschner, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **2001**, 4463.

[12] S. Hosoawa, K. Sekiguchi, M. Enemoto, S. Kobayashi, *Tetrahedron Lett.* **2000**, *41*, 6429.

[13] S. G. Davies, J. C. Walker, *J. Chem. Soc. Chem. Commun.* **1986**, 495.

[14] P. I. Dalko, Y. Langlois, *J. Org. Chem.* **1998**, *63*, 8107.

[15] T. Hamamoto, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 2463.

[16] D. Enders, A. Zamponi, T. Schäfer, C. Nübling, H. Eichenauer, A. S. Demir, G. Raabe, *Chem. Ber.* **1994**, *127*, 1707.

[17] R. K. Boeckman, D. J. Boehmler, R. A. Musselman, *Org. Lett.* **2001**, *3*, 3777.

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

[19] a) D. A. Evans, J. M. Takacs, *Tetrahedron Lett.* **1980**, *21*, 4233; b) P. Sonnet, R. R. Heath, *J. Org. Chem.* **1980**, *45*, 3137; c) D. A. Evans, R. L. Dow, T. S. Shih, J. M. Takacs, R. Zahler, *J. Am. Chem. Soc.* **1990**, *112*, 5290.

[20] P. K. Freeman, L. L. Hutchinson, *Tetrahedron Lett.* **1976**, 1849.

[21] Greater than two equivalents of electrophile must be added, as the S- and C-alkylations occur at similar rates.

[22] The reasons for this dichotomous behavior are unclear. We have been unable to detect significant *E*/*Z* isomerization under the reaction conditions. Other effects such as aggregation state and/or different reactive conformations of the *E* and *Z* enolates cannot be ruled out.

[23] Alkylation of amide enolates with unactivated electrophiles often requires the addition of HMPA or LiCl for useful reaction rates to be observed. For examples see ref. [19] and a) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496; b) W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.* **1989**, *30*, 5603.

[24] Addition of HMPA affected only the reaction rate. Conducting the reaction without HMPA resulted in the identical diastereoselectivity but the yield of **3g** was only 20%.

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

[26] a) A. G. Myers, B. H. Yang, D. J. Kopecky, *Tetrahedron Lett.* **1996**, *37*, 3623; b) A. G. Myers, B. H. Yang, H. Chen, D. J. Kopecky, *Synlett* **1997**, *5*, 457; see also: c) G. B. Fisher, J. C. Fuller, J. Harrison, S. G. Alvarez, E. R. Burkhardt, C. T. Goralski, B. Singaram, *J. Org. Chem.* **1994**, *59*, 6378.

The Chemistry of the Oxychlorination Catalyst: an In Situ, Time-Resolved XANES Study**

Carlo Lamberti,* Carmelo Prestipino, Francesca Bonino, Luciana Capello, Silvia Bordiga, Giuseppe Spoto, Adriano Zecchina, Sofia Diaz Moreno, Barbara Cremaschi, Marco Garilli, Andrea Marsella, Diego Carmello, Sandro Vidotto, and Giuseppe Leofanti

Almost all of the world production of vinyl chloride today is based on cracking of 1,2-dichloroethane. For many decades, this compound has been produced by catalytic oxychlorination of ethylene with hydrochloric acid and oxygen [Eq. (1)]. The reaction is performed at 490–530 K and 5–6 atm (1 atm ≈ 1.01×10^5 Pa) using both air and oxygen in fluid- or fixed-bed reactors.[1]

$$C_2H_4 + 2HCl + \tfrac{1}{2}O_2 \rightarrow C_2H_4Cl_2 + H_2O \qquad (1)$$

[*] Dr. C. Lamberti,[+] C. Prestipino,[+] F. Bonino, L. Capello,[+]
Prof. Dr. S. Bordiga, Prof. Dr. G. Spoto, Prof. Dr. A. Zecchina
Dipartimento di Chimica IFM
Via P. Giuria 7, 10125 Torino (Italy)
and
INSTM Research unit of Turin University
Fax: (+39) 011-670-7855
E-mail: carlo.lamberti@unito.it
Dr. S. Diaz Moreno
ESRF
BP 220, 38043 Grenoble (France)
B. Cremaschi, M. Garilli, A. Marsella, D. Carmello, S. Vidotto, G. Leofanti[++]
EVC Technological Centre
Via della Chimica 5, 30175 Porto Marghera/Venezia (Italy)
[+] Also with INFM UdR di Torino Università (Italy)
[++] Consultant: Via Firenze 43, 20010 Canegrate/Milano (Italy)

[**] L.C. was supported by an INFM grant for her stay at the ESRF. We are indebted to R. Weigel for his fundamental support during data acquisition and to M. Sanchez Del Rio for his important support on the complex data handling.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.