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Chapter~1. Alkylation chemistry of the camphor imine of tert-butyl glycinate and its derivatives. Chapter~2. Synthesis and reactions of a new carbon(2) symmetric ketone.

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CHAPTER 1 - ALKYLATION CHEMISTRY OF THE CAMPHOR IMINE OF *tert*-BUTYL GLYCINATE AND ITS DERIVATIVES

CHAPTER 2 - SYNTHESIS AND REACTIONS OF A NEW C_2 SYMMETRIC KETONE

BY

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Abstract

Factors which influence the diastereoselectivity in the alkylation of the (*R*)-camphor imine of *tert*-butyl glycinate (24) were investigated in order to further refine the alkylation model. It was demonstrated that when alkylating 24 with various benzyl bromides or allyl bromide that the diastereoselectivity was dependent on the π-electron density of the alkylating agent, the metal cation of the enolate and the cosolvent used. Inferior selectivities (de's < 85%) were obtained when using TMEDA as the cosolvent, K as the metal cation or alkylating agents with electron poor π-systems. Excellent selectivities (de's > 95%) were obtained when using HMPA as the cosolvent, Li or Na as the metal cation and alkylating agents with electron rich π-systems.

Further study included the preparation of several camphor derivatives (ketopinic acid, methyl ketopinate, 3-hydroxycamphor, 1-hydroxymethyl camphor) which were utilized as chiral auxiliaries in the alkylation of their corresponding imines of *tert*-butyl glycinate. These investigations lead to the discovery of two new and unexpected reactions of the camphor skeleton.

Finally, a new C_2 symmetric ketone, *cis,anti,cis*-tricyclo[6.3.0.$0^{3,7}$]undecan-2-one (91) was prepared in 91% ee. Initial efforts to use this ketone as a chiral auxiliary in in the alkylation of chiral imines of *tert*-butyl glycinate failed since condensation of 91 with several amines was not possible. This lead to an investigation into the utility of *cis,anti,cis*-tricyclo[6.3.0.$0^{3,7}$]undecan-2-ol (92) as a chiral auxiliary.

Summary

Chapter 1

Alkylation Chemistry of the Camphor Imine of *tert*-Butyl Glycinate and its Derivatives

Refinements to the working model of the alkylation of the camphor imine of *tert*-butyl glycinate (24) were obtained by carrying out three sets of experiments; i) imine 24 was alkylated with various *p*-substituted benzyl bromides to determine the effect of altered electrophile π-electron density on the reaction diastereoselectivity; ii) various metal enolates of 24 were prepared and alkylated to determine the role of the metal cation and the effect of replacing HMPA with TMEDA; iii) the camphor imine of α-aminoacetonitrile was alkylated to determine the importance of O-Li-N chelation on the stereoselectivity of the alkylation.

Some refinements were made to the alkylation model which account for high selectivities with unsaturated alkylating agents:

1) It was demonstrated that in general electron rich alkylating agents give better selectivities than electron poor ones.

2) Li is the best cation to use in order to obtain high selectivities with unsaturated alkylating agents.

3) When alkylating the Li enolate of 24 replacing HMPA with TMEDA results in a lower selectivity with all alkylating agents.

4) The 5-membered metallacycle generated upon enolate formation is necessary to

achieve good asymmetric induction.

Several other chiral imines of *tert*-butyl glycinate were prepared and alkylated with benzyl bromide (46, 47, 48, 49, 50). In all cases the imines were found to exist as single diastereomers at the imine double bond. The extent of asymmetric induction using these systems was found to be inferior to imine 24.

In an attempt to prepare the *tert*-butyl glycinate imine of 3-hydroxycamphor an unexpected product (52) was obtained in 80% yield. An unexpected 1-carbon ring expansion of 55 was also observed when attempting to prepare 45.

Chapter 2

Synthesis and Reactions of a new C_2 Symmetric Ketone

A new C_2 symmetric ketone (91) was prepared in the racemic form. Resolution could not be effected. The ketone (91) was reduced to alcohol 92 using LAH. Attempted separation of diastereomeric derivatives of the alcohol also failed.

The failure to resolve both 91 and 92 led to an efficient asymmetric synthesis of 91 from the readily available (+)-113. Ketone 91 was obtained in six steps in 37% overall yield from (+)-113 with 91% ee.

Imines of 91 could not be prepared and the use of alcohol 92 as a chiral auxiliary was not promising.

Appendix A

Reactions of 3,6-Dihydro-1,2-thiazine-1-oxides

Several 3,6-dihydro-1,2-thiazine-1-oxides were prepared using literature procedures. The attempted metallation and alkylation of 15 resulted in both ring

opened product (17) and rearrangement to N-phenylpyrrole. The attempted alkylation of 18 was not successful, however the aldol reaction of 18 with benzophenone gave a mixture of diastereomers (24 and 25) which were separated. We attempted the reverse Diels Alder reaction on both diastereomers. However, only diastereomer 32 would undergo cycloreversion.

For Diane

and

my parents

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I would like to thank my supervisor Dr. McIntosh for his guidance and financial support. Dr. McIntosh is a great boss, whose understanding will always be appreciated.

I would like to acknowledge the support of the technicians (especially Mike Fuerth) for their assistance in obtaining spectral data and Vince Ammoscato who was kind enough to get optical rotations run for me. I would also like to thank all of my lab mates both past and present for many thought provoking discussions.

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Finally, I would like to thank my wife, Diane for her continuous support during the last several years and many thanks to my parents for their love and guidance in order to make this all possible.

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LIST OF ABBREVIATIONS

Ac	acetate
AcOH	acetic acid
$BF_3 \cdot Et_2O$	borontrifluoride etherate
Bn	benzyl
Boc	N-tertiary-butoxycarbonyl
n-BuLi	butyllithium
^{t}BuLi	tertiary butyllithium
C_p	cyclopentadiene
CDA	chiral derivatizing agent
DBO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DCC	1,3-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
2;4-DNP	2,4-dinitrophenyl hydrazone
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DMF	N,N-dimethylformamide
EtOAc	ethyl acetate

EtOH	ethanol
Et_2O	diethyl ether
FVP	flash vacuum pyrolysis
GC	gas chromatography
Hz	hertz
HMPA	hexamethylphosphoramide
KO^{t}Bu	potassium tertiary butoxide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
mm Hg	millimeters of mercury
MoOPH	oxodiperoxymolybdenum(pyridine)-hexamethylphosphoramide
MeOH	methanol
MsCl	methanesulfonyl chloride
MS	mass spectrum
MTPA-Cl	α-methoxy-α-trifluoromethylphenylacetic acid
NBS	N-bromosuccinimide
NOE	nuclear Overhauser effect
PDC	pyridinium dichromate
PCC	pyridinium chlorochromate
pet. ether	petroleum ether (35 - 60 °C)
PTSA	*p*-toluenesulfonic acid

Ph	phenyl
PPA	polyphosphoric acid
PLE	pig liver esterase
Pd/C	palladium metal on charcoal (10%)
Ra-Ni	Raney nickel
TMS	trimethylsilyl
TBDMS	*tert*-butyl dimethylsilyl
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylene diamine

Chapter 1: The Alkylation Chemistry of the Camphor Imine of *tert*-Butyl Glycinate and its Derivatives

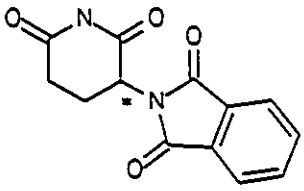
Introduction

The observation that many compounds can exist in different stereoisomeric forms has a long history which dates back to Louis Pasteur.[1] Chirality or "handedness" is a consequence of the tetrahedral arrangement of sp^3-hybidized orbitals on carbon atoms. When four different groups or atoms are attached to carbon, two different arrangements in space are possible. The two molecules formed are related to each other as non-superimposable mirror images, just as the right hand is related to the left. The two mirror images or enantiomers have identical physical properties and chemical properties in symmetric (achiral) environments. They have identical boiling points, melting points, solubilities, and reactivities with achiral chemical reagents. However, one of the first discoveries of dissimilarity between enantiomers was the fact that they rotate the plane of polarized light in opposite directions. Unlike its direction, the magnitude of rotation for the two forms is identical. Enantiomers also have identical energies. In contrast, molecules which are not related as mirror images, but which differ only in the way atoms are arranged in space are called diastereomers. Diastereomers do not have identical energies or physical or chemical properties. Enantiomers can display differences in physical and chemical properties when placed in a chiral environment where interactions with the chiral molecules can occur.

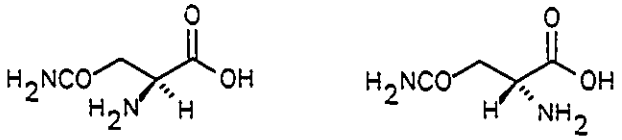
In the context of biological activity, most bio-active molecules are chiral compounds which can exist in two or more stereoisomeric forms (enantiomers or diastereomers). Whenever possible, nature uses highly developed and specific chiral

enzyme systems to effect the formation of one of the two possible stereoisomers or to take only one of the stereoisomers as a substrate. Chirality in bio-active molecules is not restricted to amino acids and enzymes since many complex carbohydrates, hormones, and steroids contain one or more chiral carbon atoms. In general only one of the optical isomers (enantiomers) of the mixture is responsible for the biological activity and frequently the other isomer (enantiomer) may either inhibit the desired effect or have adverse effects. Numerous examples of this type of behaviour exist, and can be illustrated by the often cited example of the drug thalidomide (Figure 1).[2]

Figure 1: Chirality and biological systems



Thalidomide



bitter Asparagine sweet

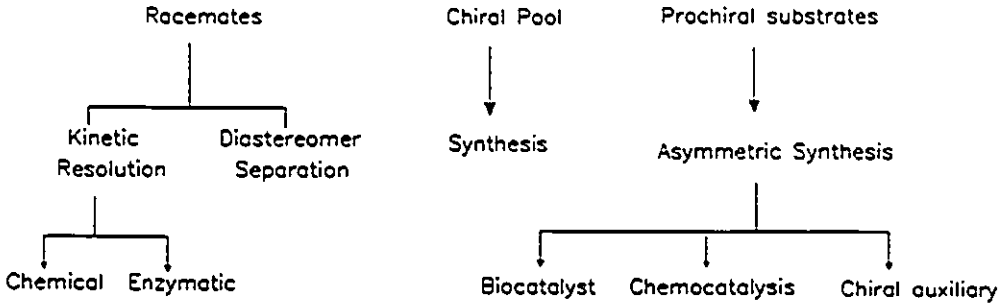
Thalidomide was marketed in the racemic form, as a drug to treat morning sickness in pregnant women. Catastrophic results (birth defects) were observed by the administration of this drug in the racemic form (both enantiomers). These results have been ascribed to the presence of two enantiomers. One enantiomer is responsible for the desired effect, whereas the other is responsible for the adverse

effects. Another, less consequential example is illustrated by the fact that the *R*-enantiomer of asparagine (Figure 1) is sweet to the taste whereas the *S*-enantiomer is bitter.[3]

The awareness that the use of racemic compounds in biological systems (chiral enviroments) may lead to unsound or misleading data has inspired many strategies for preparing enantiomerically pure compounds in order to avoid racemic mixtures altogether. This challenge of preparing optically pure compounds has thus become a major aim of the modern synthetic chemist.

Methods for obtaining molecules in the optically enriched or pure form fall into three categories; resolution, asymmetric synthesis or synthesis from chiral pool synthons (Figure 2).

Figure 2: Strategies for Optically Active Compounds



The act of separating enantiomers is called a "resolution". Resolution of racemic mixtures can be effected through a kinetic resolution or by a diastereomeric separation. A successful kinetic resolution depends on the fact that two enantiomers will react at different rates with a chiral derivatizing agent because the transition states are diastereomeric. Diastereomeric separation relies on physical differences

between diastereomeric adducts prepared from the enantiomers and the chiral derivatizing agent. Both of these methods have been extensively reviewed[4,5,6] since they constitute two of the main procedures for obtaining optically pure compounds both on an industrial scale and in the laboratory. One of the major disadvantages of these methods is that successful separation depends largely upon the nature of the racemic mixture to be resolved and the chiral derivatizing agent used and is thus often difficult to predict beforehand. Also, unless the unwanted enantiomer can be racemized to the desired one and recycled, 50% of the reaction product is virtually wasted.

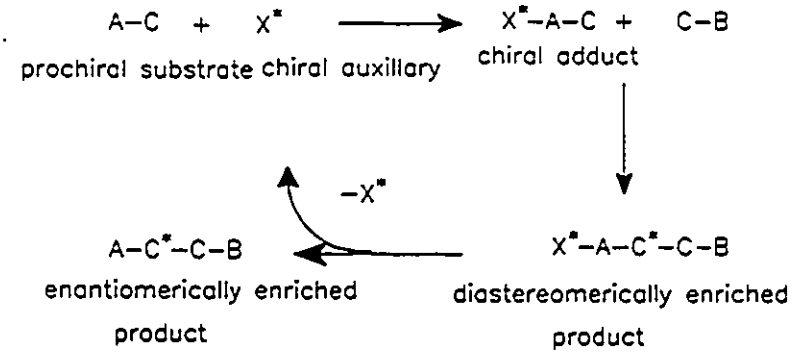
A second procedure for the preparation of optically active compounds employs chiral starting materials from the "chiral pool". The chiral pool refers to inexpensive, readily available natural products such as chiral amino acids, terpenes, tartaric acids, etc.[7] The "chiral pool" substrate is converted into the desired optically active product by conventional organic transformations which proceed by known mechanisms involving retention or inversion of configuration or chirality transfer. This strategy demands that the retrosynthetic analysis[8] of the chiral target molecule must utilize a "chiral pool" substrate as the starting material. The variety and accessibility of chiral pool synthons limits the application of this method.

The final method for obtaining optically enriched or optically pure compounds involves asymmetric synthesis. Asymmetric synthesis refers to a reaction in which a prochiral unit is converted into a chiral unit in such a manner that the stereoisomeric products are formed in unequal amounts. Most often asymmetric syntheses involve

the addition of a reagent to an unsaturated group (for example a carbonyl group) in which the addition requires the selection of enantiotopic or diastereotopic faces in the creation of the new chiral center. The chiral influence may be present as a reagent, a catalyst or as part of the the substrate itself. Numerous strategies for asymmetric synthesis have been successfully completed and these have been the subjects of many reviews.[9-12]

Two of the most utilized methods for asymmetric synthesis involve either the covalent derivatization of a prochiral molecule with a relatively inexpensive or easily prepared chiral derivatizing agent (chiral auxiliary) or the association of a chiral catalyst with a prochiral substrate in a non-covalent manner. It should be noted that a prochiral substrate refers to a molecule in which a chiral center is formed when an atom or group is replaced with a different atom or group. The process of utilizing chiral auxiliaries in asymmetric syntheses is shown in Figure 3. Note that a chiral catalyst acts in a similar fashion except the chiral influence is not bound covalently to the prochiral substrate.

Figure 3: Using a Chiral Auxiliary



In the absence of a chiral influence the reaction of a prochiral substrate with an achiral reagent proceeds through enantiomeric transition states which are of equal energy. Since the energies of the two transition states are equal, the rates of formation of the enantiomeric products must also be equal and a racemic mixture results. The covalent attachment of a chiral auxiliary to a prochiral substrate results in the formation of a chiral adduct. The reaction of the chiral adduct with an achiral reagent proceeds through diastereomeric transition states which, by definition, are unequal in energy. The magnitude of the energy difference between the two transition states ($\Delta\Delta G^{\ddagger}$) determines the ratio of the two diastereomeric products if the reaction is kinetically controlled.[13] In the ultimate case where $\Delta\Delta G^{\ddagger}$ is sufficiently large, only the pathway to one product will be attainable and total stereoselection will result. When the reaction is completed, this methodology requires that the chiral auxiliary be removed. This provides enantiomerically enriched or pure product. A useful chiral auxiliary must be available in high optical purity, be either inexpensive or recoverable without racemization and it should also be easily appended and easily removed from the prochiral substrate.

The terms enantiomeric excess (%ee), diastereomeric excess (%de) and optical purity (%op) are often used to express the ratio of enantiomers or diastereomers in a mixture. The values are calculated as follows:

ENANTIOMERIC EXCESS= ([*R*]-[*S*]/[*R*]+[*S*]) X 100
(expressed as %ee) *R* and *S* are the amounts of individual enantiomers produced

DIASTEREOMERIC EXCESS= ([A]-[B]/[A]+[B]) X 100
(expressed as %de) A and B are the amounts of individual diastereomer produced

OPTICAL PURITY = $([\alpha]_{observed}/[\alpha]_{maximum}) \times 100$

(expressed as %op) $[\alpha]_{observed}$ is the specific rotation of the sample and $[\alpha]_{maximum}$ is the specific rotation of the optically pure substance, recorded under identical conditions

It should be noted that by today's standards, an asymmetric synthesis is considered useful only if an enantiomeric excess of at least 90% is obtained (ie. 95:5 or 20:1 ratio of enantiomers).

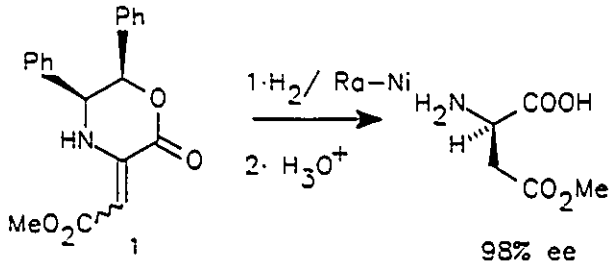
Monosubstituted α-amino acids are simple chiral molecules which are important in the formation of peptides, proteins, and other natural products.[14] Nature supplies abundant quantities of many of these, but many "unnatural" amino acids which have found increasing number of uses in pharmaceutical and agrochemical industries are only available via synthesis. Because of the different biological properties of the enantiomers and the widespread use of amino acids, efficient asymmetric syntheses are required. The remainder of the introduction is intended to illustrate some of the more advanced achievements in the synthesis of optically active amino acids and is by no means meant to be a comprehensive review. A recently published monograph by Williams[15] reviews and critically evaluates many of the best known methods for synthesizing optically active α-amino acids.

Catalytic Hydrogenation of Dehydroamino Acids

Amino acids have been prepared in optically enriched form by classical methods which involve both the asymmetric hydrogenation reactions of prochiral dehydroamino acid derivatives using chiral catalysts or the stereoselective hydrogenation of chiral non-racemic dehydroamino acids.

For example, Kagan[16] demonstrated that the hydrogenation of the chiral dehydroamino acid derivative 1 with Raney nickel when followed by acidic work-up afforded D-β-methyl aspartate with 98% ee (Figure 4).

Figure 4: Hydrogenation of Dehydroamino acids



Corey et al [17] employed the hydrazono lactone 3 (Figure 5) to obtain amino acids with de's ranging from 90-98%. The lactones were obtained by condensation of α-keto esters with compound 2. Reduction of the double bond was carried out with an aluminum-mercury amalgam and proceeded with a high degree of asymmetric induction.

Although the asymmetric inductions using dehydroamino acids are usually high, the inaccessibility of many dehydroamino acids with the requisite α-R group and the fact that a common synthon is not available for the preparation of various α-substituted amino acids makes this a rather tedious method.

A more versatile approach involves the formation of C-C bonds at the α-position by the use of nucleophilic or electrophilic glycine equivalents or the formation of α-C-N bonds using nucleophilic or electrophilic amination (Figure 6).

Figure 5: Reduction of hydrazono lactone

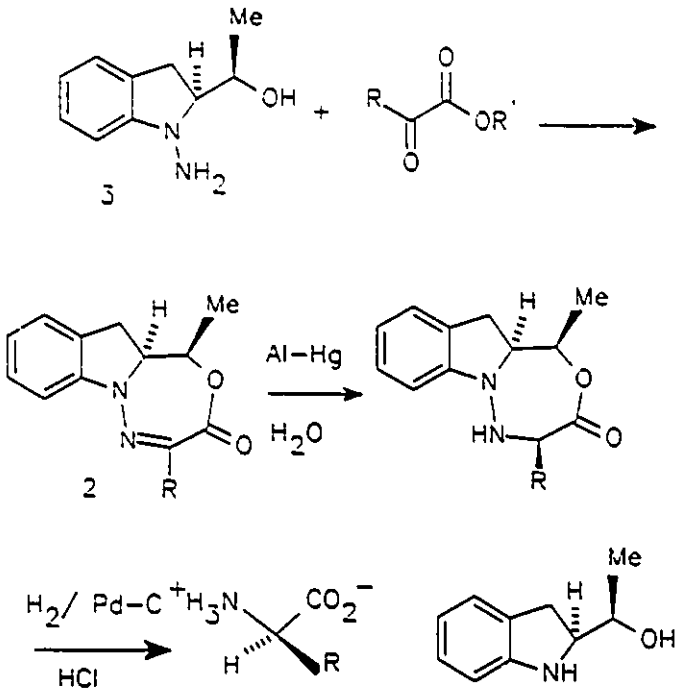
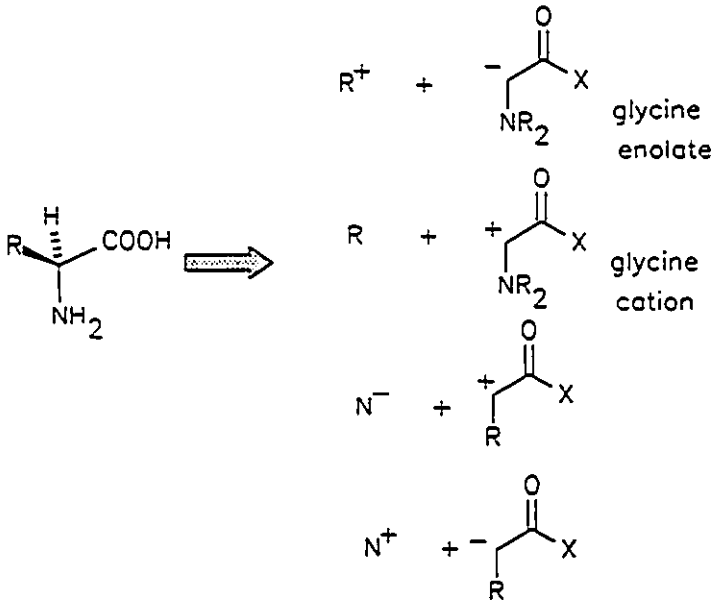


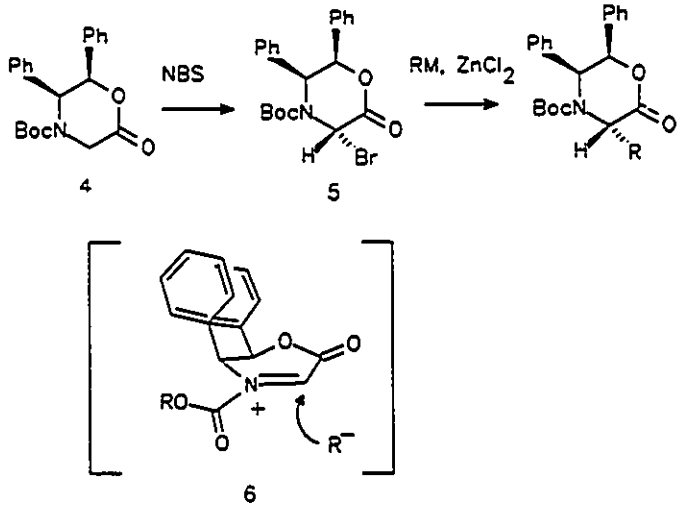
Figure 6: Strategies for Amino acids



C-C Bond Formation Using Electrophilic Glycine Equivalents

One of the most extensively studied electrophilic glycine equivalents has been oxazinone 4.[18-24] Bromination of 4 (Figure 7) proceeds stereospecifically to give the brominated product 5 with the bromine atom anti to the phenyl groups. Subsequent reaction of 5 with $ZnCl_2$ in the presence of organometallic reagents resulted in displacement of bromide with **retention** of configuration. The authors proposed that the Zn salt was coordinating to the bromine atom and ultimately provided the iminium species 6. Examination of the configuration of the resulting amino acids revealed that approach of the organometallic reagents occurred *anti* to the two phenyl rings with overall retention of configuration. Diastereomeric excesses in the range of 90-99% were often observed. The free amino acids were obtained using standard reductive procedures. The major advantage of this method lies in the availability of both antipodes of the chiral auxiliary which makes it possible to prepare both the *R* and *S* amino acids.

Figure 7: Electrophilic glycine

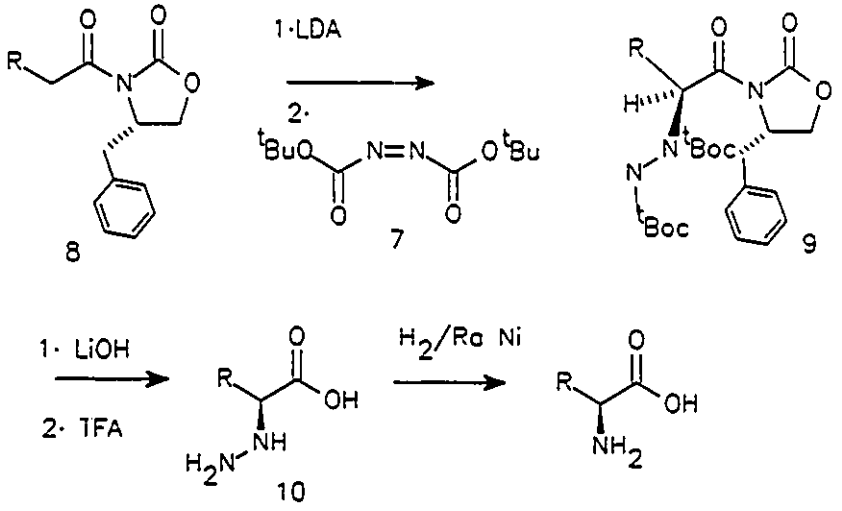


4 5 6

C-N Bond Formation *via* Electrophilic Amination

The electrophilic amination of glycine enolate equivalents is a strategy which has been recently developed for preparing α-amino acids. The lack of a ready source of "electrophilic" nitrogen has been overcome by the use of azodicarboxylate esters[25-28] (7). One of the most successful approaches using this methodology has been reported by Evans[26,27] (Figure 8). He demonstrated that the deprotonation of 8 followed by the addition of 7 provided the α-hydrazido derivatives 9 with de's in the range of 95%. It was also reported that the optical purity of 9 could be increased to over 99% by the separation of the diastereomers using column chromatography. The chiral auxiliary was most often removed by hydrolysis with LiOH and the Boc protecting groups were generally removed with trifluoroacetic acid.

Figure 8: Electrophilic Amination



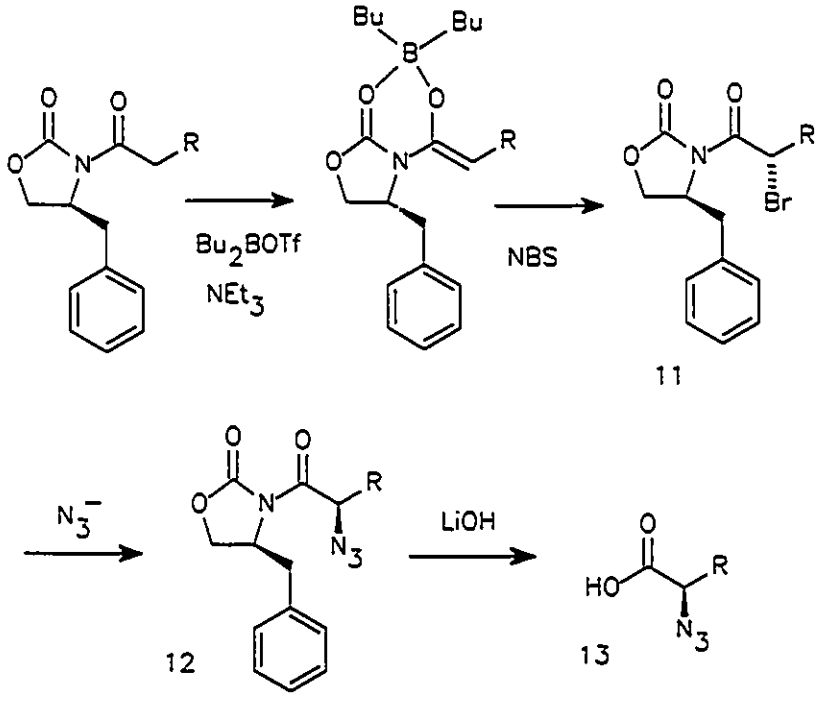
In most cases racemization did not occur during the deprotection steps. The α-hydrazino derivatives 10 were reduced to the corresponding amino acids with

hydrogen on Raney nickel.

C-N Bond Formation *via* Nucleophilic Amination

Evans[29a,29b] has made tremendous contributions in this area by utilizing azide displacement reactions of α-bromo derivatives (Figure 9). He showed that formation of the di-n-butylboron enolates followed by oxidation with NBS proceeded with high stereocontrol to give the corresponding α-bromo derivatives 11. Azide displacement was carried out using tetramethylguanidinium azide and cleanly gave 12. The chiral auxiliary was hydrolysed and gave azides 13. It was reported that reduction of the azide group gave high yields of amino acids with de's in the range of 90%.

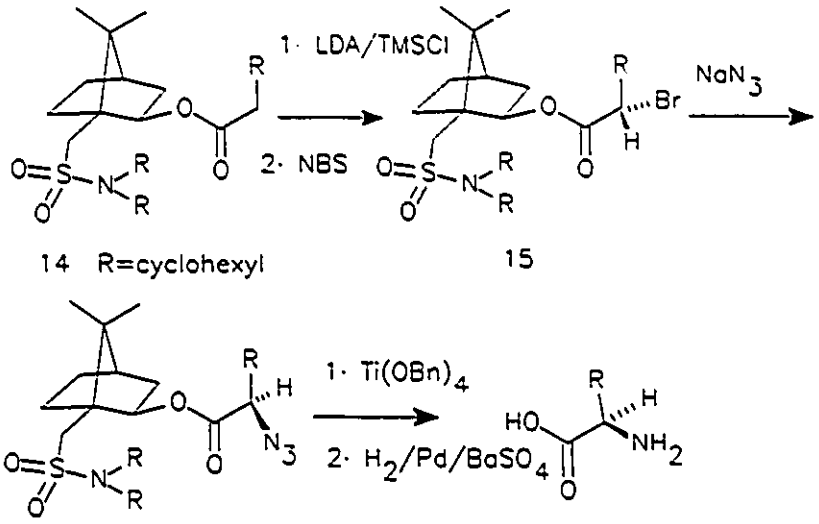
Figure 9: Evans nucleophilic amination



Oppolzer[29c,29d] has also made significant contributions to this area by utilizing the stereocontrolled halogenation of the 10-sulfonamido-isobornyl esters 14 (Figure 10).

Stereoselective halogenation of the corresponding silyl ketene acetals was reported to give the camphor derived sulfamides 15 in high yields and with excellent diastereoselectivity (de >95%). Displacement of halogen with sodium azide proceeded smoothly and gave the azido-compounds with inversion of configuration. Transesterification, followed by reduction of the azide and benzyl ester gave the corresponding α-amino acids in excellent yield and with de's of approximately 95%.

Figure 10: Oppolzer's nucleophilic amination



C-C Bond Formation via Alkylation of Chiral Glycinate Imines

During the past 15 years many groups have investigated the alkylation of chiral and achiral imine enolates derived from glycine with the objective of preparing optically active α-amino acids. In general, successful asymmetric alkylations of imines requires the stereoselective formation of a geometrically defined (*E* or *Z*) enolate. This is important because even if only one face of the enolate is accesible, the ratio of products cannot be greater than the enolate ratio. Also, of utmost

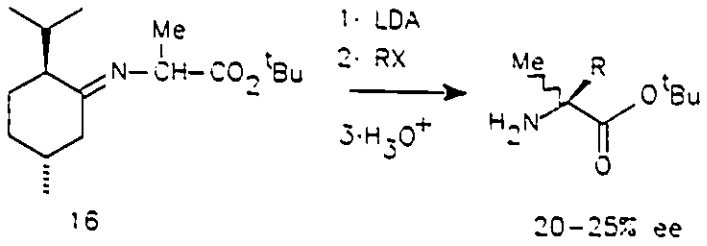
importance is the fact that in systems where enolate bond rotation can occur the diastereoselection is usually minimal. High asymmetric induction relies on the formation of a highly ordered enolate system in which the diastereotopic faces are well defined. Highly ordered enolate systems are most often formed via chelate enforced chirality transfer. This refers to the formation of a presumed 5 or 6 membered metal chelate which fulfills the role of fixing the orientation of the enolate system and the chiral moiety. In the case of imines derived from glycine it is the imino nitrogen which can provide the necessary chelation site for the formation of a 5-membered chelate of the ester enolate. In doing so, a planar 5-membered ring enolate is formed which has well defined diastereotopic faces.

Many strategies exist which utilize chiral, non-racemic aldehydes or ketones to form imines or use chiral non-racemic alcohols or amines to form chiral esters or amides of glycine imines. Combinations of the above have also been described for double asymmetric alkylations of imines. Achiral imines have been alkylated with optically active alkylating agents, or in the presence of other chiral influences and high asymmetric induction has been achieved.

One of the first alkylations of a chiral imine was reported by Yamada *et al.*[30] who used (-)-menthone as a chiral auxiliary. He showed (Figure 11) that the alkylation of the imine (16) derived from D,L-alanine *tert*-butyl ester and (-)-menthone with benzyl bromide gave (*S*)-α-methylphenylalanine *tert*-butyl ester in 55% yield after hydrolysis. The optical purity of the product was only 21%. When 3,4-dimethoxybenzyl bromide was used a 74% yield of alkylated product was

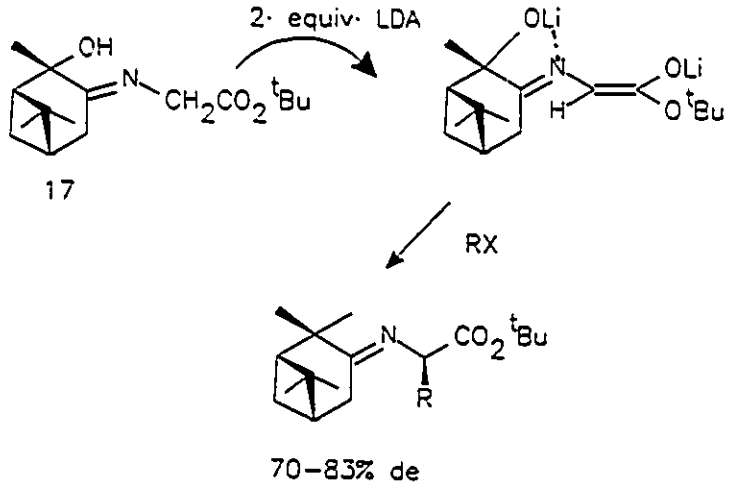
obtained with an optical purity of 24%.

Figure 11: Menthone imine



Subsequently, Yamada[31,32] reported that the alkylation of the *tert*-butyl glycinate imine of (1*S*,2*S*,5*S*)-2-hydroxypinan-2-one (17) proceeded with much higher asymmetric induction than the (-)-menthone system (Figure 12). The resulting amino acids were determined to have the *R*-configuration.

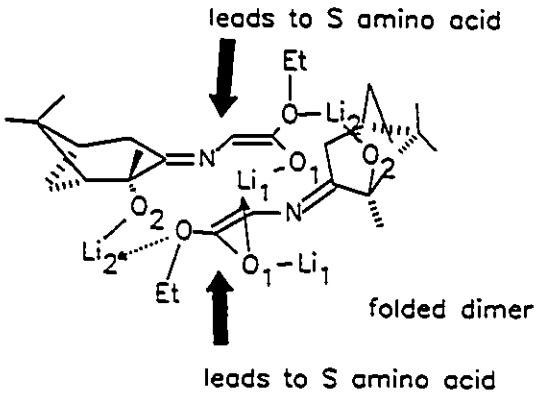
Figure 12: Pinanone imine



This implied that the alkylation of the dilithium enolate (proposed by Yamada and others[33,34]) occured from the more hindered re face of the enolate. No comment was made on this unusual direction of the approach of the electrophile or on the configuration or conformation of the enolate. However, it has been recently proposed

by Solladie-Cavallo[35] that the dilithium enolate exists as a folded dimer and that alkylation occurs from the *re* face of the enolate because the *si* face is essentially blocked (Figure 13). Although the Solladie-Cavallo model accounts for the approach of the electrophile there appears to be no relationship between the size of the alkylating agent and the observed diastereofacial selectivities. The alkylation of 17 with MeI gave a higher optical yield than the alkylation with the much larger benzyl bromide (83% and 72% respectively). This result seems to be unusual since Yamada implied that the only kinetic products were being formed.

Figure 13: Solladie-Cavallo Model

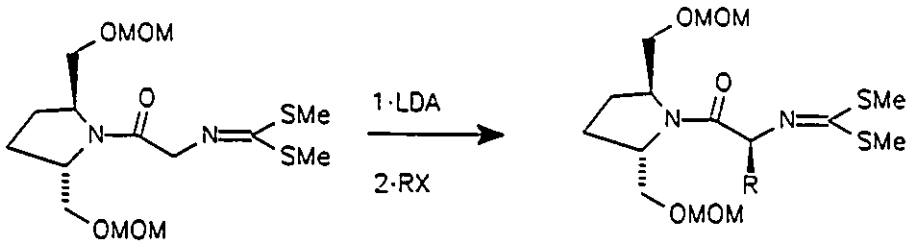


Viallefont[36,37,38] has also investigated the alkylation of 17 and its derivatives prepared from alanine, phenylglycine, leucine and valine. He has been successful in preparing many optically active α-amino acids and α,α-disubstituted amino acids but during his investigations many surprising results have been obtained which have not been fully explained. One such observation was that the alkylation of imines derived from α-amino acids in the reverse sequence preferrentially gave the same configuration at the α-position regardless of the order of the alkylation. A recent

publication by Vaillefont[39] has complicated the situation further. He found that the diastereoselectivity of the alkylation of the imine derived from alanine methyl ester and (*S*,*S*,*S*)-2-hydroxypinan-3-one with various bases was affected drastically by the choice of the base. For example, the alkylation using LDA gave amino acids with the *R*-configuration but alkylation with KO^{t}Bu gave amino acids with the *S*-configuration. The results cannot be explained easily.

Katsuki[40,41] reported that the alkylation of chiral amide 18 derived from (2*S*,5*S*)-2,5 bis(methoxymethoxymethyl)pyrrolidine[42] (Figure 14) with primary alkylating agents gave high chemical and optical yields. Secondary alkylating agents required the use of the more reactive triflates to obtain satisfactory chemical yields.

Figure 14: Katsuki's chiral amide



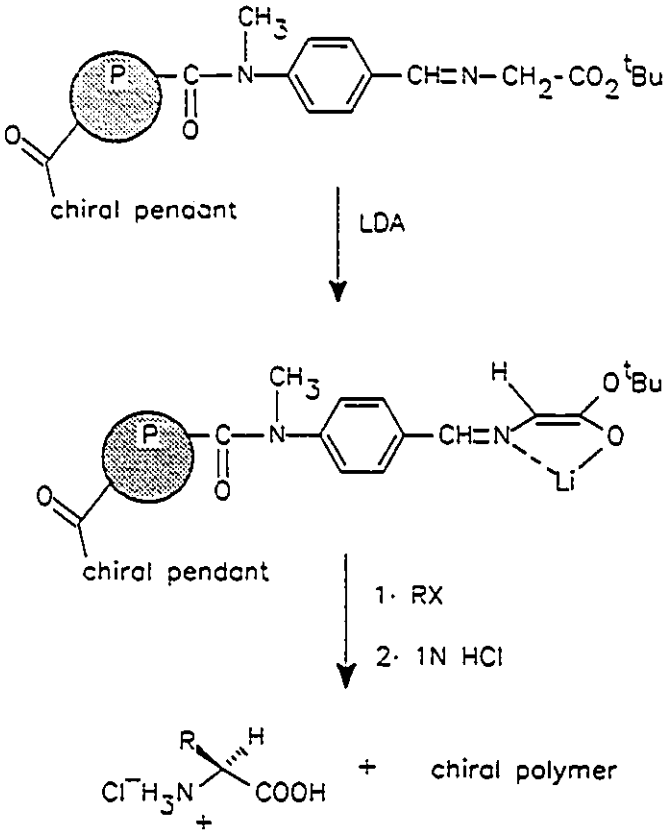
18

Although the corresponding benzophenone imine could be used for N-protection the authors found that bis(methylthio)methylenation gave the best results. Since hydrolysis of the alkylated products gave the corresponding *S*-amino acids, approach of the electrophiles to the *Z*-enolate must have occurred on the si-face. It should be noted that this chiral auxiliary possesses C_2 symmetry and the authors stated that the high induction was not the result of a chelate controlled alkylation reaction but was

due to the symmetry of the chiral auxiliary!

A novel concept for preparing optically active amino acids has been reported by Daunis.[43] His method utilized an imine derived from *tert*-butyl glycinate which is linked to a polymer chain containing a chiral pendant. In this case instead of the chirality being directly attached to the imine the chirality is located in the backbone of the polymer (Figure 15).

Figure 15: Polymer supported glycinate

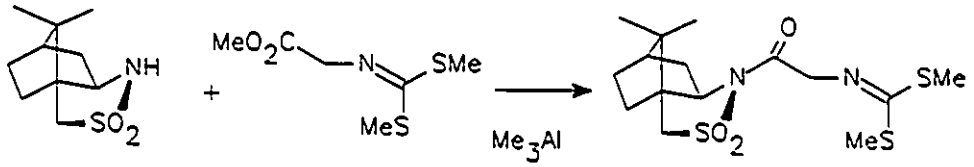


The authors reported that the chiral auxiliary was easily recovered after the hydrolysis and that it could be used in excess of 20 times without loss in optical efficiency. The diastereofacial selectivities of the alkylation products varied with the nature of the

chiral pendant. The best results were obtained when (*S*)-prolinol was used as the source of chirality. Deprotonation and alkylation at -78 °C of the (*S*)-prolinol derivative followed by hydrolysis with dilute HCl gave (*S*)-α-amino acids with de's ranging from 82-84% for saturated alkylating agents. Interestingly, the authors also reported that very little change in diastereoselectivity was observed when the alkylation was conducted at room temperature.

To date, Oppolzer[44] has reported the most efficient use of a chiral imine as a source of optically active α-amino acids. The Me_3Al-mediated acylation of Oppolzer's readily available but very expensive sultam auxiliary[45] gave, after recrystallization, the chiral "glycinate" derivative 19 which was used as the common precursor for various α-amino acids (Figure 16).

Figure 16: Oppolzer's sultam derived glycinate



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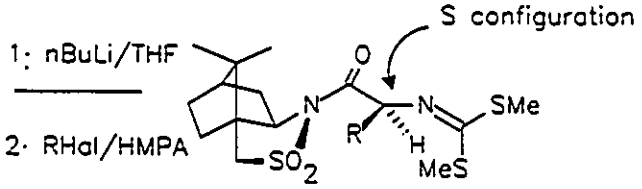


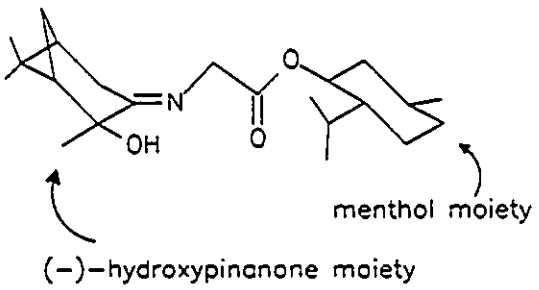
20

Oppolzer showed that treatment of 19 with *n*-BuLi and HMPA followed by either primary and secondary alkylating agents gave alkylated products (20) with de's ranging from 94-99%. The alkylated products were crystalline and the pure

crystalline (*S*)-alanine derivatives could be separated from their C(α) epimers by recrystallization. *N*-Deprotection was selective and provided the corresponding amine hydrochlorides. Saponification removed the chiral sultam and ion exchange chromatography was reported to provide **optically pure** (*S*)-α-amino acids in excellent yield.

Yaozhong[46] has described a double asymmetric induction procedure for the allylation of imine enolates derived from (+)-camphor, (+) and (-)- 2-hydroxypinan-3-ones, and (+) and (-)-menthyl glycinates. He showed that the best matched pair were the (-)-hydroxypinanone imine moiety and the (+)-menthol on the ester portion (Figure 17).

Figure 17: Double asymmetric induction



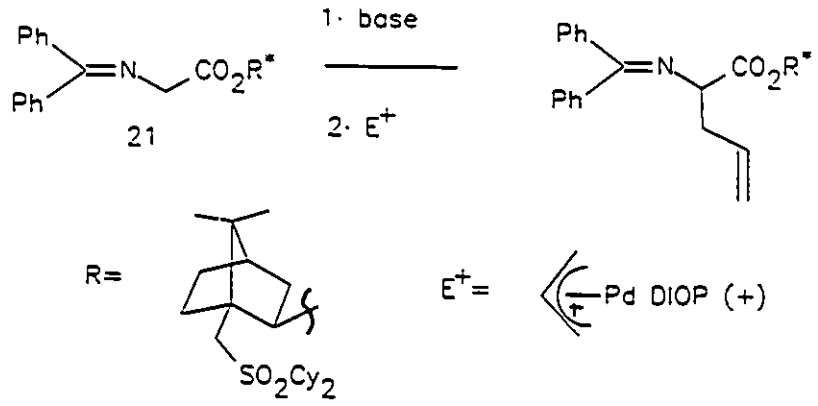
In this case (*S*)-allylglycine was isolated by hydrolysis with dilute HCl and the optical purity was calculated to be 90% by comparison of the specific rotation observed to the specific rotation of enantiomerically pure α-allylglycine.

C-C Bond Formation *via* the Alkylation of Achiral Imines

As previously noted, optically active α-amino acids have also been prepared by employing achiral imine enolates in the presence of "external" chiral influences.

Genet[47] described the allylation reaction of the benzophenone imine of methyl glycinate using catalytic amounts of chiral π-allyl Pd-complexes. It was shown that modest diastereoselectivities could be obtained by using 3 mole % $Pd(dba)_2$ and 2 (+)-DIOP ligands per Pd [2*S*,3*S*-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane]. Utilizing these conditions the *R*-allylated product was obtained with 57% ee. The enantioselectivity of the reaction was reported to be dependent on the ratio of chiral diphosphine ligand used per Pd. Dramatic results were observed when only 1 (+)-DIOP ligand was used per Pd. The allylated product of opposite configuration was isolated in good yield with 39% ee. The authors did not comment on possible structures for the active species. Genet[48] has recently reported a double-asymmetric version of this reaction (Figure 18).

Figure 18: Asymmetric allylation reaction

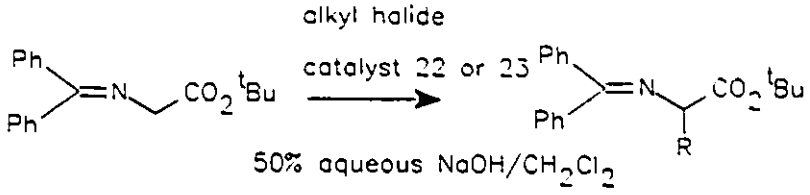


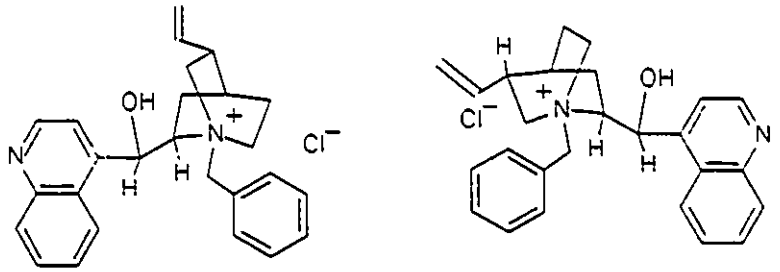
He investigated the Pd catalyzed allylation reaction of a series of imines of glycine which had been esterified with chiral auxiliary alcohols. The benzophenone imine was used as the N-protecting group. He reported that the best matched pair for the allylation of 21 was the chiral auxiliary alcohol (-)-*N*,*N*-dicyclohexylsulfamoyl-

isoborneol, and (+)-DIOP as the chiral phosphine ligand. The allylated product was obtained in high yield and 90% ee. Unfortunately, the authors did not comment on the actual experimental conditions used.

A more applicable use of catalysis in the synthesis of amino acids has been reported by O'Donnell.[49] Some years ago he demonstrated that achiral imines derived from glycinate esters could be alkylated using phase transfer conditions (KOH, achiral phase transfer catalyst). He has recently extended this methodology to include the stereoselective synthesis of α-amino acids utilizing chiral phase transfer catalysts.[50] The alkylation of the benzophenone imine of *tert*-butyl glycinate was carried out using phase transfer conditions in the presence of catalytic amounts of chiral PTC catalysts derived from cinchona alkaloids (0.1 equivalents) (Figure 19). Chiral inductions of up to 66% were observed for alkylations with benzyl bromide. It was reported that either enantiomer of the amino acid could be prepared by simply changing the catalyst from the cinchonine derivative 22 to the cinchonidine derivative 23.

Figure 19: Asymmetric alkylation of achiral imine



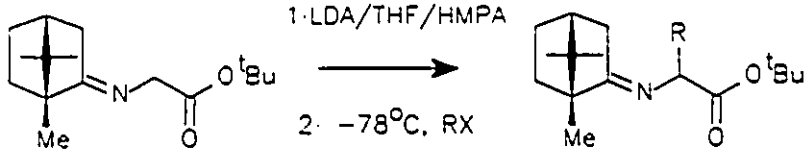


22 23

Alkylation of the Camphor Imine of *tert*-Butyl Glycinate

During the past several years our group has been focusing on the alkylation of chiral imines derived from glycine for the synthesis of optically active α-amino acids. In particular we have been interested in the alkylation chemistry of the camphor imine of *tert*-butyl glycinate (24) (Figure 20).[51-54] Initial studies of 24 showed that saturated alkyl halides gave up to 60% de. As expected, the diastereofacial selectivities increased as the steric bulk of the alkylating agent increased. Unexpectedly, the use of unsaturated alkylating agents gave products with unusually high de's when compared to saturated counterparts of equal or greater steric size. For example, allylic alkylating agents afforded de's in the range of 75% and benzyl bromide gave only one detectable diastereomer.

Figure 20: Camphor imine of t-butyl glycinate



24

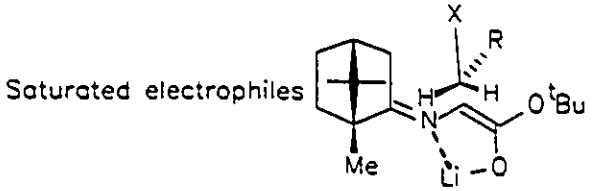
Although various conformations of the *Z*-enolate can exist it is assumed that the enolate exists in the planar chelated cyclic form as shown in Figure 21. This is not unreasonable and others[55] have depicted imine enolates in this way. Transamination of benzylated product gave (*R*)-tert-butyl-phenylalaninate which indicated that the alkylation occured from the less hindered *re* face of the enolate, the face opposite the C(8) methyl group. It was shown that kinetic products were obtained since only monosubstituted imines were formed and since attempted treatment with base followed by quenching with D_2O gave **absolutely** no deuterium incorporation. The total absence of deuterium in the alkylated products indicated that a second deprotonation was not possible under the reaction conditions.

In general the alkylations were conducted at low temperature using THF as the solvent in the presence of one equivalent of the additive HMPA (hexamethylphosphoramide). The presence of HMPA was shown to be necessary to obtain acceptable chemical yields of alkylated products, presumably due to deaggregation.[56]

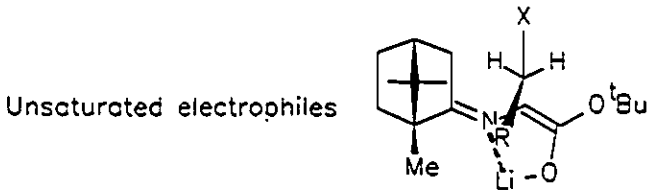
It has been proposed that the diastereofacial selectivity observed with saturated electrophiles is the result of the steric interactions between the electrophile and the

C(8)-methyl group of the camphor moiety which shields the *si* face of the enolate. As a result alkylation occurs preferentially on the *re* face (Figure 21). However, it was further proposed that if the R group of the electrophile was forced to be eclipsed with the enolate system in the transition state (Figure 21) then the steric interactions on the *si* face would be enhanced much more than on the *re* face.

Figure 21: Possible transition state structures



R group is anti to enolate on Si face



R group eclipsed with enolate on Si face

Stereoelectronic interactions between the π-system of the unsaturated alkylating agents and the enolate system have been proposed to rationalize the enhanced diastereofacial selectivities observed with allylic and benzylic electrophiles. It was postulated that an interaction between the unsaturated alkylating agents and the enolate was responsible for eclipsing the R-group of the alkylating agent with the enolate. Two models were proposed to rationalize this association, a π-π and a metal-π model. In the π-π model the eclipsing of the two groups was explained by an association between the electron-rich π-system of the enolate and the incipient positive charge

being formed in the alkylating agent due to the partial C-X bond breaking in the transition state. Alternatively, the π-metal model proposed that the association was a result of the interaction between the positive metal atom of the enolate and the π-electron density of the alkylating agents. It should be noted that all of the results can be explained using either model. Support for associations of this type in this system comes from the fact that although allyl bromides and benzyl bromide gave high selectivities, the alkylation of 24 with *p*-nitrobenzyl bromide gave a de of only 51%. It was suggested that the reduced electron density in the alkylating agent was drastically affecting the diastereoselectivity of the reaction by causing a decrease in the association of the alkylating agent with the enolate. Other evidence for association comes from the fact that when 24 was alkylated with 2 equivalents of racemic 1-phenylethyl bromide or 3-bromocyclohexene, kinetic resolution of the alkylating agent was observed. It was proposed that only an association between the alkylating agent and the π-system of the enolate could be responsible for these results.

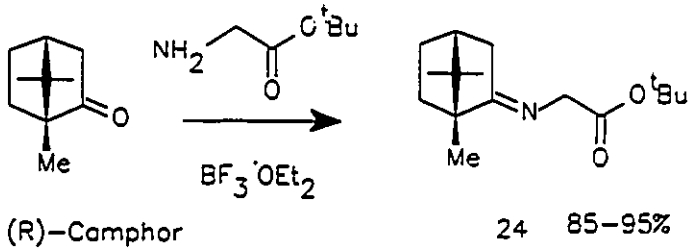
As an extension of these alkylation studies, we decided to investigate the influence of the π-electron density in the phenyl ring of benzyl bromides on the selectivities and the role that the metal cation and additive play in order to refine the alkylation model. We also chose to prepare and evaluate several chiral aldehydes and ketones as chiral auxiliaries in the alkylation reaction of the corresponding *tert*-butyl glycinate imines.

Results and Discussion

Preparation of the Camphor Imine of *tert*-Butyl Glycinate

We have previously reported[51] that the direct condensation of camphor and *tert*-butyl glycinate using Lewis acid catalysis was not possible. Imine formation was only feasible if the carbonyl group of camphor was activated as the thione.[51,52] Camphorthione is easily prepared from camphor by using Lawesson's reagent.[57] However, Lawesson's reagent has a foul odour. Recently it was reported that ketones closely related to camphor could be condensed with *tert*-butyl glycinate using BF_3 as a Lewis acid catalyst.[58,59] Reinvestigation revealed that this condensation, catalyzed by a small amount (10 mole%) of $BF_3{\cdot}Et_2O$ (in refluxing toluene using a Dean-Stark water separator), gave the camphor imine of *tert*-butyl glycinate (24) in almost quantitative yield. In the absence of the catalyst no reaction occured. This improvement made it possible to obtain multi-gram quantities of 24 without the inconvenience of preparing camphorthione (Figure 22).

Figure 22: Preparation of camphor imine of t-butyl glycinate



Refinements to the Alkylation Model

As discussed in the introduction, the alkylation of 24 using alkyl halides with a π-

system adjacent to the carbon undergoing alkylation gave products with unexpectedly high de's (75-100%), whereas alkylation with aliphatic alkylating agents gave products with de's ranging from 0-60%. Recall that the model proposed by McIntosh and Mishra[51] postulated that the high de's observed with unsaturated alkylating agents were the result of a π-π interaction between the incipient positive charge on the alkylating agent and the electron-rich π-system of the enolate. McIntosh and Leavitt[52] later suggested that the increased de's observed with unsaturated alkylating agents was the result of a Li-π interaction between the electron-rich portion of the alkylating agent and the positive lithium atom of the enolate.

To further refine the alkylation model, three sets of experiments were carried out; i) imine 24 was alkylated with various *p*-substituted benzyl bromides to observe the effect of altered electrophile π-electron density on the reaction diastereoselectivity; ii) various metal enolates of 24 were prepared and alkylated to determine the role of the metal cation and the effect of replacing the additive HMPA with TMEDA; iii) the camphor imine of α-aminoacetonitrile (25) was prepared and alkylated to determine the importance O-Li-N chelation (5-membered metallocycle) on the stereoselectivity of the alkylation.

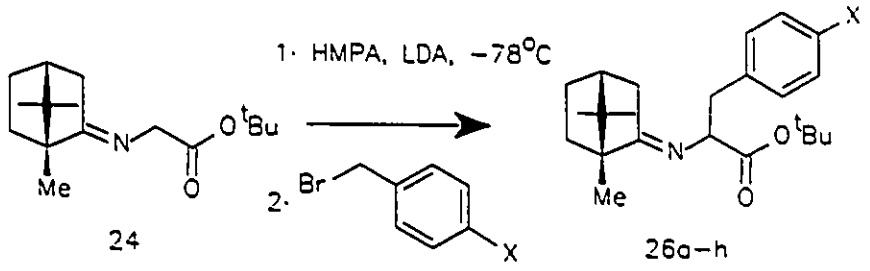
Alkylation of 24 with *p*-Substituted Benzyl Bromides

McIntosh and Leavitt[52] reported that the alkylation of 24 with *p*-nitrobenzyl bromide gave the benzylated product in good yield but the de was only 51% (compare benzyl bromide, de>98%). We decided to alkylate 24 with a series of *p*-substituted benzyl bromides where the substituents were both electron-withdrawing and electron-

donating. It was expected that a trend would be observed which would correlate the π-electron density in the phenyl ring with the selectivity. This would confirm that the low selectivity with *p*-nitrobenzyl bromide was not an anomaly.

Imine 24 was alkylated with various *p*-substituted benzyl bromides using the method previously described (Figure 23).[52]

Figure 23: Alkylation of 24



The results of the alkylation reactions are shown in Table 1. Also included in the Table are alkylation results from other workers and Hammett σ_p constants for the ring substituents.[60] The Hammett σ_p constant is a (relative) quantitative measure of the electron donating or electron withdrawing ability of a *p*-substituent. A negative σ_p constant indicates that the para-substituent is electron donating and a positive σ_p constant indicates that the para-substituent is electron withdrawing. The hydrogen atom is arbitrarily given a value of σ_p=0.00.[60]

The alkylated products were isolated in good yield and the de's ranged from 51-100%. In the cases where the diastereoselectivity was low (<60%) the de's were calculated from the integration of the overlapping diastereomeric C-11 methine proton signals or the signals from the C-8/C-9 methyl groups on camphor (Figure 24).

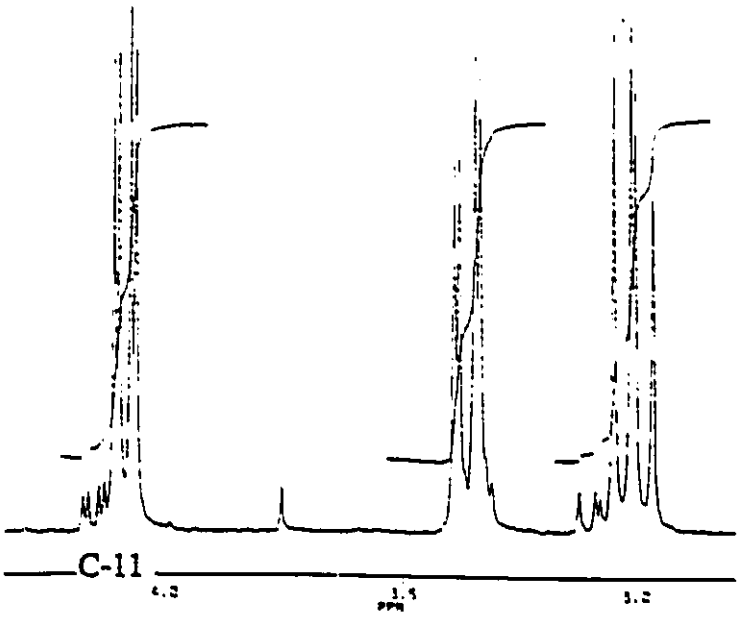
Table 1: Alkylation of 24 with p-substituted benzyl bromides					
entry	X=	cmd.	% yield	% de	σ_p value
1	F	26a	89	>98,99[a]	0.15
2	^{t}Bu	26b	71	85, 84[a]	-0.15
3	CF_3	26c	72	79 ,81[a]	0.53
4	CN	26d	75	76 ,77[a]	0.70
5	OMe	26e	83	88 ,86[a]	-0.12
6	NO_2	26f	69	51	0.81
7	H	26g	89	>98	0.00
8	Me	26h	71	>98	-0.14

[a] de values detemined from ^{19}F NMR of Mosher amides

However, when the de values were quite high the accuracy of this method became unacceptable. In order to obtain more accurate values, the imine bond was transaminated as previously described.[51] The recovered yields of the amino-esters previously obtained were modest. However it was found that the yields of the amino-esters were much improved if the crude reaction mixture was chromatographed directly (rather than using extraction techniques) to isolate camphor-oxime and the α-amino-ester (*p*-substituted phenylalanine). Using this technique yields of 80-95% were consistantly achieved. The amino-esters were derivatized with (*R*)-(+)-MTPA-Cl[61] to give the corresponding Mosher amides (Figure 25).

Employing (+)-MTPA-Cl as the chiral derivatizing agent has several advantages. Since there are no α-hydrogens, simple racemization by deprotonation is impossible. Secondly, the MTPA-derivatives have an α-CF_3 group, which makes it possible to

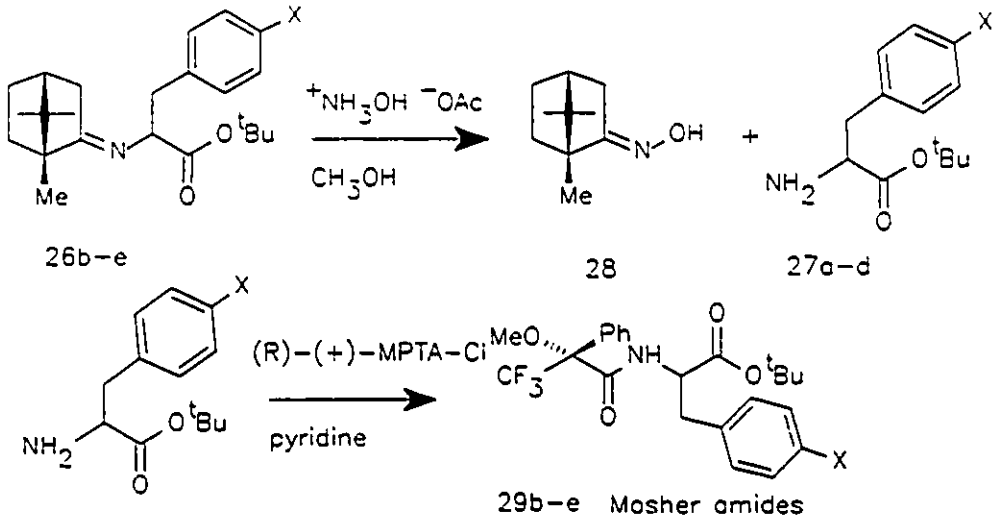
Figure 24: Calculation of de values



examine the ^{19}F NMR as well as the ^{1}H NMR. The α-CF_3 group will appear as a singlet in the ^{19}F NMR and usually the signals from diastereomers are well separated which allows accurate integration.

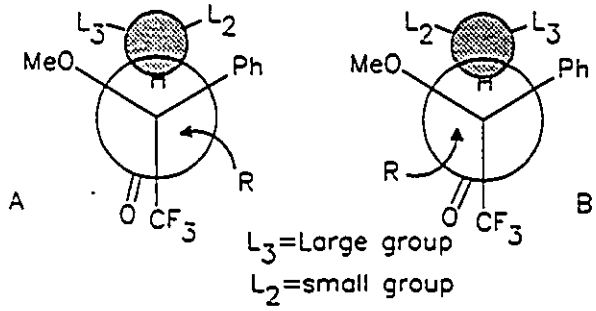
The de values obtained from the ^{1}H NMR and ^{19}F NMR for the Mosher amides are included in Table 1. The de values were internally self consistent ($\pm$2%). It was observed that the chemical shift of the α-CF_3 signal in the major diastereomer for all the MTPA-derivatives appeared at a lower field (10-20Hz) than the minor one. A model which correlates the configuration of the carbinol carbon of secondary alcohols and amines to the chemical shifts of the α-CF_3 group in MTPA-derivatives has been proposed by Mosher.[62] His concept was based on the assumption that the MTPA-derivatives (ester or amide) exist in a conformation where the α-CF_3 group, the

Figure 25: Preparation of Mosher amides



proton on the carbinol carbon and the C=O bond of the carbonyl group are located in the same plane (Figure 26). Detailed investigation revealed that the ^{19}F signal of the MTPA-derivative with configuration A appears at lower field than that with configuration B (Figure 26).

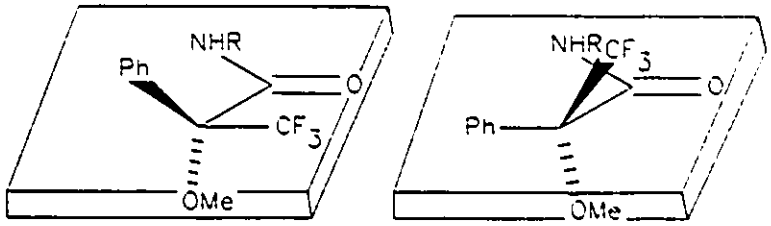
Figure 26: Mosher model



Mosher's method assumes that when the phenyl group of the MTPA fragment is eclipsed with the large group on the carbinol carbon the α-CF_3 is forced to rotate out of coplanarity with the carbonyl group. Diastereomer B represents an MTPA-derivative with this conformation and configuration (Figure 27). Diastereomer B has the α-CF_3 in a less deshielded environment of the carbonyl group and thus its resonance is upfield relative to that of

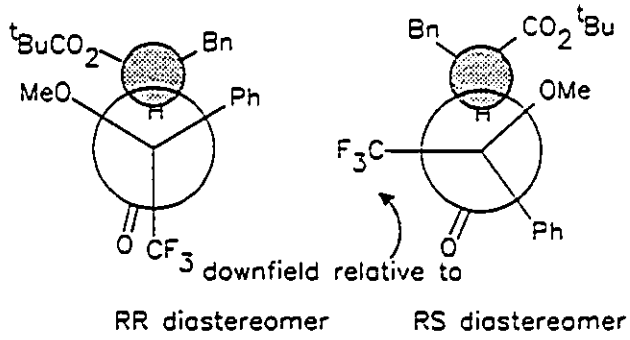
diastereomer A.

Figure 27: Chemical enviroment of α CF_3



Our results correlate well with this model. The major stereoisomers of the amino-esters formed in the alkylation reaction have been previously shown[52] to have the *R* configuration. If one utilizes Mosher's model and draws the *R* configuration of the α-aminoester, the MTPA-amide will have the benzyl group (small group) eclipsed with the phenyl group of the MTPA fragment (Figure 28). The model predicts that the *R*-isomer will exist in a conformation where the α-CF_3 group will remain coplanar with the carbonyl and thus the α-CF_3 signal in the ^{19}F NMR will be found at lower field than the other diastereomer.

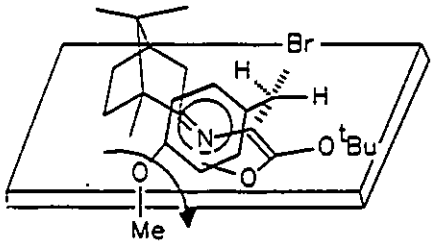
Figure 28: R-amino acids and Mosher model



Inspection of the de values (Table 1) obtained for the various *p*-substituted benzylated

products clearly shows a trend. Entries 1 and 8 show that when the σ_p-constant is weakly negative or weakly positive (*p*-Me, *p*-F), the diastereoselectivity remains very high. However, entries 3, 4 and 6 (*p*-CF_3, *p*-CN, *p*-NO_2) show that when the σ_p-constant becomes more positive (less π-electron density) the de's are reduced. Unexpectedly, entries 2 and 5 (*p*-^{t}Bu, *p*-OMe) show reduced de's in spite of the negative σ_p values. This observation suggests that an additional effect may be operating. The *p-tert*-Bu substituent and the *p*-OMe (due to rotational processes) both possess significant steric bulk above and below the plane of the phenyl ring. If the phenyl ring and the π-system of the enolate are eclipsed in the transition state as shown in Figure 29 then the steric interaction that would occur between the substituent and enolate would reduce the association between the two π-systems and result in the observed lower de.

Figure 29: Steric Hinderance in Transition state



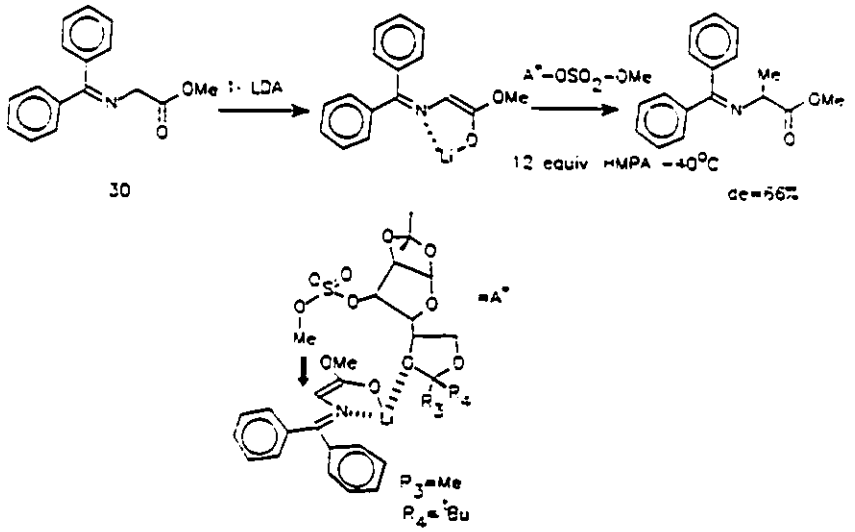
At this point one conclusion is clear. The selectivity using *p*-substituted benzyl bromides is dependant on the π-electron density of the phenyl ring and there is definitely a unique effect operating when alkylating with unsaturated alkyl halides. What is not clear at this point is whether the association is π-π in nature or whether there is the possibility of an association between the π-system of the alkylating agent and the Li atom of the enolate. In the former case electron-donating substituents would stabilize the partial positive charge formed as the C-X bond of the electrophile lengthens in the

transition state. *p*-Electron donating substituents would facilitate a larger degree of bond breaking at the transition state and consequently a larger positive charge would exist. Thus, an increase in the association of the electron rich π-system of the enolate with the π-system of the electrophile would be expected. In the metal-π case, a decrease in the π-electron density in the phenyl ring would result in a weaker Li-π association prior to reaction and in the transition state. A weaker Li-π association would result in a lower de. Both of these models can be supported by the results presented thus far.

Examples exist in the literature which suggest that a Li-π association in donor solvents like THF is possible.[63-65]

One rather interesting example by Duhamel[66] is shown in Figure 30.

Figure 30: Alkylation with chiral electrophile



An achiral glycine imine (30) was alkylated with a chiral electrophile where the chirality was in the leaving group. Good diastereoselectivity was achieved. Duhamel

interpreted his results by proposing a model where the electron-rich center on the electrophile (in his case an oxygen atom) coordinated with the Li atom of the enolate. The good diastereoselectivity was attributed to this coordination.

A recent review[67] has examined the "lithium bond" using molecular mechanics. Dicoordinate Li species of the type X_n···Li-Y where an X_1 group is σ-bonded to the lithium atom (through a lone pair of electrons) and where an X_2 group is σ-bonded to the Li atom (through a π-system) were investigated. The authors found that the most stable complexes of Li-Y and ethylene or acetylene are characterized by the perpendicular attachment of Li-Y to the middle of the multiple bond (σ-bonding). It has also been speculated that the reactions of unsaturated molecules (ethylene and acetylene) with LiH occur *via* coordination of the unsaturated unit to LiH in the transition state.[68]

In our reaction system, THF, HMPA (added) and diisopropylamine (formed in the deprotonation with LDA) are present. This is troublesome since both compounds are good donors and can coordinate to Li. It does not seem probable that the π-system of the alkylating agent could compete with these donors for a coordination site. Nevertheless, further evidence is needed in order to support or refute the possibility of Li-π association.

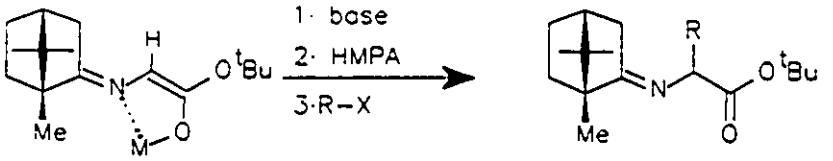
The Role of the Metal Cation and Additive in the Alkylation of the Camphor Imine of *tert*-Butyl Glycinate

The Na, K, Zn and Zr enolates of 24 were prepared and alkylated with benzyl bromide (-78°C), allyl bromide (-78°C), and isopropyl iodide (-20°C). Isopropyl iodide was chosen as the saturated alkylating agent, since any selectivity observed with the various metal enolates can only be attributed to the steric size of the alkylating agent (no π-system) and not to π-association. Any change observed in the de with isopropyl iodide upon altering the metal cation or additive (or both) can only be attributed to a change in either the reactivity or the overall gross structure of the enolate (aggregation state, bond lengths of O-Metal-N, loss of chelation). In order to observe the effect that changing the metal might have on the invoked π-π or metal-π association, the unsaturated alkylating agents benzyl and allyl bromides were chosen.

Sodium and potassium were chosen since both are weak complexing metals and these enolates should be more ionic (relative to Li). If the enhanced de observed with allyl bromide and other unsaturated alkylating agents with the Li enolate was the result of a π-π interaction, a more ionic enolate should result in an increased de. The same effect would be obtained by the formation of a smaller aggregate since there would be a higher negative charge density on the enolate oxygen atom (fewer metal atoms to *neutralize* it).

If the enhanced de's are the result of metal-π interaction then the weaker complexing metals (Na and K enolate) should result in a lower de (for benzyl and allyl bromides) since the association between the metal and π-system would be less.

Figure 31: Alkylation of various metal enolates



31a–e

M=	enolate
Li	31a
Na	31b or 31b'
K	31c
Zn	31d
Zr	31e

32	R=benzyl
33	R=allyl
34	R=isopropyl

The results of the alkylation of 24 (Figure 31) using various cations are shown in Table 2.

Table 2: Alkylation of various metal enolates of 24

Cmd. 32 R=benzyl			Cmd. 33 R=allyl			Cmd. 34 R=isopropyl		
enolate	%yield	%de	enolate	yield	%de	enolate	%yield	%de
31a	80	>98	31a	89	76	31a	86	65
31b	89	>98	31b	73	72	31b'	60	67
31b'	81	>98	31b'	75	71	31c	8	67
31c	36	66	31c	36	64			
31d	30	>98	31d	24	73			
31e	32	>98	31e	41	82			

The lithium enolate (31a) was generated by adding a THF solution of imine 24 and 1 equivalent of HMPA to 1 equivalent of LDA at -78°C. As already noted the presence of 1 equivalent of HMPA has been reported[51] to be necessary to achieve

good chemical yield.

In an attempt to prepare the sodium enolate (31b), 1 equivalent of NaH was suspended in THF and a THF solution containing 24 and 1 equivalent of HMPA was added. Very little enolate formation took place at -78°C since much of the NaH remained. An homogeneous solution of enolate 31b was obtained when a THF solution of one equivalent of *tert*-butyl alcohol was added to the mixture. In theory only a catalytic amount of alcohol was needed. However for consistency, 1 equivalent was added since in the reaction of the Li enolate, one equivalent of diisopropylamine was present and the formation of the K enolate using KO^{t}Bu generates one equivalent of *tert*-butyl alcohol. Alkylation of 31b with allyl or benzyl bromide gave 32 or 33. Both the chemical yield and diastereomeric excesses obtained (as determined by ^{1}H NMR) were identical with the de's for enolate 31a. To avoid the presence of *tert*-butyl alcohol in solution, the sodium enolate was also prepared using the sodium salt of 1,1,1,3,3,3-hexamethyldisilazane (1.0M in THF, Aldrich) as the base. The reactions of the enolate (31b') generated in this manner were identical with the reactions of enolates 31a and 31b (Table 2).

The physical nature of enolate 31c, prepared using KO^{t}Bu, depended upon the temperature of its formation. When enolate 31c was generated at -78°C in the presence of one equivalent of HMPA, a yellow-orange solution was formed which persisted for approximately 15 min, at which time a precipitate developed. The enolate was alkylated in this form. Enolate formation at -100°C in the presence of one equivalent of HMPA, gave a stable yellow-orange solution. Alkylation of 31c

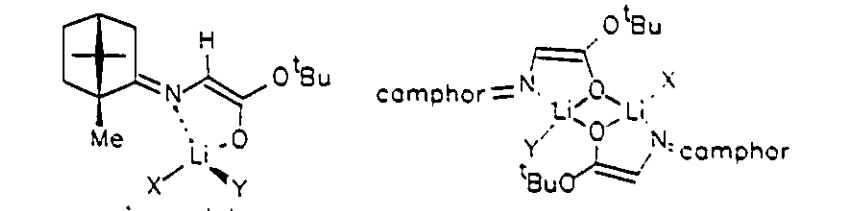
generated using either method gave the same results. In both cases alkylation with benzyl and allyl bromides gave poor chemical yields and de's inferior to those obtained with 31a, however alkylation with isopropyl iodide gave 34 with a reduced chemical yield and an optical yield similar to that obtained with 31a. (Table 2).

The Zn enolate (31d) was prepared by exchanging Zn for Li at -78°C. This was carried out by adding 1 equiv. of an ether solution of $ZnCl_2$ to enolate 31a. When 31d was alkylated, poor chemical yields were obtained but the diastereoselectivities were comparable with 31a and 31b. Finally, when enolate 31a was treated with one equivalent of Cp_2ZrCl_2 followed by either allyl or benzyl bromide, 32 and 33 were obtained. The de's were comparable with 31a and 31b. The results of these experiments are incorporated in Table 2.

In order to study the influence of the additive on the alkylation reaction one equivalent of the bidentate ligand, TMEDA was substituted for one equivalent of the monodentate ligand HMPA. TMEDA, being bidentate, has the ability to chelate the metal cation of the enolate. In the previously proposed[51,52] chelated structure of the Li enolate of 24 only two of the four coordination sites on the Li atom remain. Using one equivalent of HMPA as the additive leaves one other coordination site on the Li atom available to be taken up by solvent (THF), by diisopropylamine (generated in the formation of the enolate), by the formation of an aggregate, or by the coordination of the π-system of the incoming unsaturated electrophile (Figure 32). It would be expected however that the addition of TMEDA (bidentate ligand) rather than HMPA (monodentate ligand) would result in the loss of any possibility of association between

the incoming electrophile and the metal atom of the enolate since with TMEDA chelating, all of the coordination sites on the metal would be filled.

Figure 32: Possible enolate aggregates



monomeric enolate

X=HMPA, DIA, Solvent

Y=HMPA, DIA, Solvent

dimeric enolate

The effect of adding a bidentate ligand in the alkylation of 24 was observed when 1 equivalent of TMEDA was used in place of HMPA in the alkylation of enolates 31a, 31b' and 31c with allyl and benzyl bromides and isopropyl iodide. The results are shown in Table 3.

Table 3: Influence of TMEDA on alkylation of 24

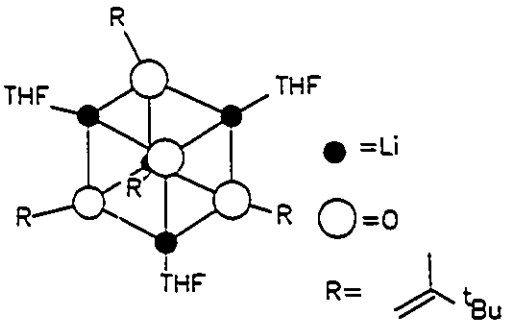
Cmd. 32 R=benzyl			Cmd. 33 R=allyl			Cmd. 34 R= isopropyl		
enolate	%yield	%de	enolate	%yield	%de	enolate	%yield	%de
31a	45	82	31a	56	69	31a	4	57
31b'	84	>98	31b'	72	73	31b'	60	64
31c	35	70	31c	45	66	31c	43	69

Up until now it has been sufficient to discuss the results of the alkylation study using the monomeric Li enolate of 24. It should be noted that it has not been assumed that the Li enolate of 24 is monomeric. However, representation of the enolate in this manner simplified the discussion of the results. When discussing the

role the cation may play or the effect that a polar coordinating additive may have on an alkylation reaction, the fact that most enolates form aggregates in slightly polar solvents (THF) is relevant.

Using low temperature X-ray crystallography and NMR techniques Seebach[69] and others[70] have shown that enolates usually exist as large aggregates in non-polar or weakly polar solvents (hydrocarbons, chlorohydrocarbons, open or cyclic ethers). The THF-solvated aggregate of the Li enolate of pinacolone (*tert*-butyl methyl ketone) was the first aggregate identified by Seebach[71] using low temperature X-ray crystallography. The aggregate was reported to be a tetrameric structure based on a Li_4O_4 cube with THF molecules coordinated at the corners (Figure 33).

Figure 33: Li_4O_4 cube

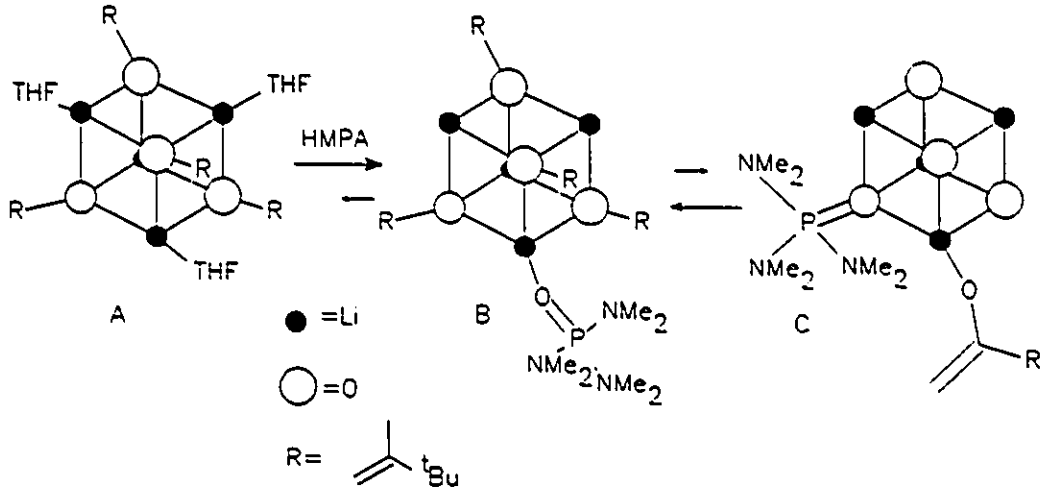


Recently, the low temperature X-ray crystal structures of the Na and K aggregates of pinacolone have also been reported.[72] It was found that the sodium pinacolone enolate crystallized from hexane (THF added) as a tetramer. However, unlike the Li case the corners of the cube were coordinated by *unenolized* ketone. The potassium enolate formed a THF solvated hexamer. These three examples indicate that the organic part of the enolate is not primarily responsible for its aggregation state. The metal (counter ion) used has a strong influence in determining the structure of the aggregate formed.

Seebach[73] and others[74-76] have also shown that the addition of polar coordinating

solvents (THF, HMPA, TMEDA) to enolates has a significant effect on the aggregation state and reactivity of the enolate. In particular, Seebach[73] discussed (speculatively) several facets of enolate chemistry using the tetrameric cube A (Figure 34).

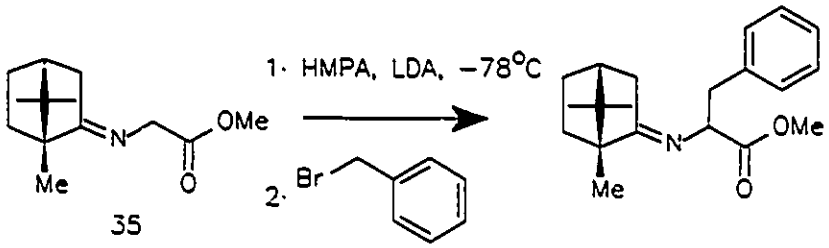
Figure 34: Effect of HMPA on Li_4O_4 cube



He points out that a polar solvent (HMPA) should be a better ligand than the O-atom of an ether (THF) and the addition of HMPA should result in the displacement of the ether from the corner of the cube (B). The polar molecule may also exchange with the enolate O-atom at the corners of the cube to form an isomeric cube (C)(Figure 34). When the enolate oxygen is situated at the edge of the cube as in C the α-carbon of the enolate is more accessible and since the enolate oxygen is being *neutralized* by only one Li atom, the enolate should be more reactive. Also in C the O-atom of the enolate is more accessible than in A or B. This assumption has been confirmed by the observed increase in O vs. C selectivity in the alkylation of ethylacetoacetate in the presence of HMPA as a cosolvent.[77] Many other examples

exist in the literature where the addition of a polar coordinating cosolvent affects the outcome of the reaction.[78,79] It has been reported by our group that addition of 0, 1, or 2 equivalents of HMPA in the alkylation of imine 35 resulted in dramatic changes in chemical and optical yields (Figure 35).[51] One equivalent of HMPA was necessary to achieve a good chemical yield and did not affect the selectivity.[51] More than one equivalent of HMPA did not affect the chemical yield further but had a negative effect on the stereoselectivity.

Figure 35: Effect of HMPA on alkylation of 35



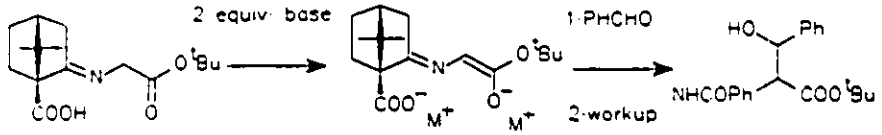
Equiv· HMPA	%yield	diast· ratio
0	40	1:3
1	73	1:3
2	70	1:2

Since Li, Na and K each have a different ionic radius (Li^+=0.60, Na^+=0.96, K^+=1.33)[80] the O-Metal-N bonds of the chelated enolate of 24 (monomer or aggregate) will be quite different, and as already noted, if an aggregate exists it is very likely that the size of aggregate for the various metal enolates may differ. In spite of these facts the alkylation of 31a, 31b, 31b' and 31c with isopropyl iodide

(where no π-association can be invoked) *all gave identical diastereoselectivities*. This result implies that the factors governing the selectivity when using unsaturated alkylating agents have not changed greatly. For example the structure of the various enolates or the aggregation state have not been altered. This is quite surprising in light of the report by Solladie-Cavallo[35] which appeared after our work was completed. Recall that she demonstrated that the stereochemistry of the alkylation of 2-hydroxypinan-3-one imine of ethyl glycinate (36) with bromoacetonitrile was dependent on the counter ion used. Under the usual conditions[81,82] (LDA, THF) the diastereoselectivity was only 20%. By changing the counter cation to Mg the diastereoselectivity was improved to 100%. The authors proposed that the Li enolate can be represented as a dimer as was previously noted (Figure 13). Solladie-Cavallo proposed that in the case of the Li enolate, the N-lone pair of bromoacetonitrile competes with O-2 for coordination to Li-2 thus allowing the "dimer" to unfold. This unfolding results in a decrease in face differentiation. The introduction of a stronger complexing metal (Mg) reinforces the folding of the dimer thus preventing competitive coordination by bromoacetonitrile.

It has also been reported[58] that the addition of benzaldehyde to the various metal enolates (Li, K, Zn) of the *tert*-butyl glycinate imine of ketopinic acid gave, after hydrolysis and derivatization, phenylserine in various chemical and optical yields (Figure 36). The authors found that the chemical and optical yields depended on the ester group (R=CH_3, Et, *tert*-butyl) and the metal. It was found that a small cation (Li) and a large ester group favoured the enantiomeric enrichment and chemical yield

Figure 36: Effect of cation on aldol stereochemistry



of the threo isomer and that a large cation (Zn) and small ester group provided enantiomeric enrichment of the erythro form of phenyl serine. Overall the structure of the intermediate enolate determined the steric course of the reaction and thus the stereoselectivity.

Alkylation of 31b and 31b' with allyl or benzyl bromides gave 32 and 33 with de's comparable to the Li case. However the alkylation of 31c (K) with the unsaturated alkyl halides showed a severe reduction in diastereoselectivity. To account for this reduction a complexation between the potassium and the *tert*-butyl alcohol formed could be considered. (As noted previously, polar coordinating additives can have a strong effect on the reactivity and selectivity of reactions.) However, two observations make this proposal untenable. First, *tert*-butyl alcohol was also present in the alkylation of 31b and had no adverse affect on the de with any of the alkylating agents. Secondly the alkylation of 31b and 31b' with any of the alkylating agents gave identical results.

The physical state of enolate 31c was found to be temperature dependent and may also account for the lower selectivity observed with allyl or benzyl bromides. The enolate was initially soluble in THF when generated at -78° C in the presence of 1

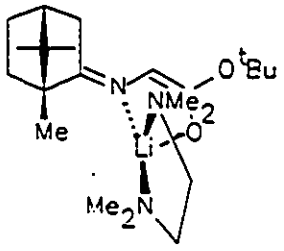
equivalent of HMPA. As time passed a precipitate formed which gave a yellow slurry which was alkylated. However, when the enolate was generated at -100°C, a homogeneous solution persisted for at least 1 hour. The enolate was alkylated at -100°C and quenched with H_2O at that temperature. The results obtained by generating and akylating the enolate at either temperature were identical. The precipitation was not a reversible process. When the enolate was warmed from -100°C to -78°C a precipitate formed. Cooling the solution to -100°C did not result in dissolution of the precipitate. It is possible that at -78°C, aggregates of the K enolate form and precipitate out of solution but at -100°C a soluble monomeric enolate persists.

The results of the alkylation of the various enolates show a definite trend. When the reaction was carried out with isopropyl iodide where no π-association with the metal cation is possible, the stereoselectivities remained consistent for all of the enolates. However, in alkylations using benzyl and allyl bromides where π-π or metal-π association is possible, only the selectivities with the K enolate (31c) were drastically reduced. Of all the metals studied potassium is the weakest complexer and should form the most ionic enolate. If the association was π-π in nature, the K enolate (31c) would be more ionic and thus the enolate should be more negative and a stronger association with the incipient positive charge on the alkyl halide would be expected. If such a process was operating an increase in selectivity (using unsaturated alkyl halides) should have been observed with 31c. This was not the case. The evidence presented suggests that the enhanced de's observed in the

alkylation of 24 with alkyl halides which have an adjacent π-system only occurs when the cation has good coordinating ability. These results support the idea that a metal-π interaction is responsible for the high de's found with unsaturated alkylating agents.

The results obtained by changing the additive from HMPA to TMEDA (Table 3) were quite interesting. Only in the case of enolate 31a did the chemical yield and diastereoselectivity in the alkylation with all three electrophiles decrease. For enolates 31b' and 31c substitution of 1 equivalent of TMEDA for 1 equivalent of HMPA showed little effect on the chemical yields or the diastereoselectivities. [Complexation of TMEDA to 31a shown in Figure 37]. As previously noted, cyclic chelation of TMEDA fills all the coordination sites on the metal atom. In such a situation, π-association with the metal is possible only if one of the coordinating N-atoms of TMEDA is displaced.

Figure 37: TMEDA chelation



Also the chelation of TMEDA to Li adds significant steric bulk to both the *re* and *si* faces of the planar enolate system near the carbon undergoing alkylation. The loss of metal-π association and the increase in steric bulk on the *re* face makes the approach of the electrophiles to the *re* face of the enolate less appealing in the case of enolate 31a and results in the observed lower de's. Coordination of TMEDA to the sodium cation should be weaker than coordination to Li and the bond lengths of the N-Na-O chelate and N-Na bonds of the TMEDA chelate will be longer (compare to Li). It is possible that the longer bond lengths in the Na enolate still allow the electrophiles to

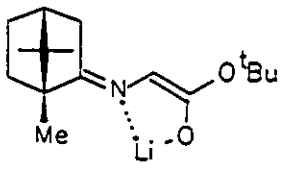
approach the *re* face relatively unobstructed.

When potassium was used as the counter ion, the selectivity was reduced to a level that seems independent of the amount and nature of the additive. It is also significant that this level of chiral induction is *the same as that which is observed with bulky saturated halides where no π-association can be invoked.*[51,52] This suggests that although the cyclic nature of the enolate may remain intact, the potassium cation is at a distance far enough from the carbon undergoing alkylation that regardless of which polar additives are coordinated to it, the diastereoselectivity is only the result of the steric interactions between the alkylating agent and camphor.

Alkylation of the Camphor Imine of α-Aminoacetonitrile

It was also of interest to study the importance of the previously proposed metallacycle formed in the deprotonation of 24 on the selectivity of the alkylation reaction (Figure 38).

Figure 38: Cyclic chelation



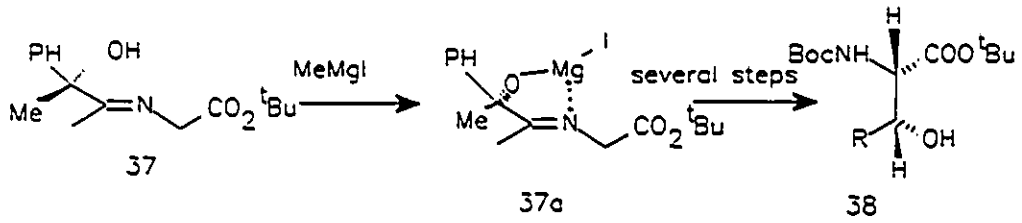
chelated enolate

In view of the high charge density on lithium it seems reasonable to propose that the transition structure for stereoselective additions could be controlled by the chelation of Li to two appropriately situated electronegative atoms. Many transition structures (for asymmetric synthesis) have been proposed which operate by intramolecular chelation control.[83] Structrural and energetic evidence for O-Li-N chelation using the lithium alkoxides of (+)-pseudoephedrine and (-)-ephedrine, their *N*-methyl analogues and a number of related compounds which cannot chelate to the Li atom have been reported

recently.[84,85] X-ray crystal structures of the Li alkoxides of *N*-methylpseudoephedrate and *N*-methylephedrate showed that in the solid state the lithium atom is chelated between the oxygen and nitrogen atoms and that the alkoxides were tetrameric.[84] The stability gained (energy lost) by chelation was estimated to be on the order of 6-8 kcal/mol by comparing the heats of deprotonation for chelates of 2-substituted-1-phenyl propanols with the appropriate non-chelatable analogues.

"Chelate enforced chirality transfer"[83] is often necessary to achieve acceptable levels of asymmetric induction in acyclic systems. For example Mukaiyama[86] found in the aldol reaction of 37 (Figure 39) that the hydroxyl group in the imine was essential for obtaining high optical yields (de 65%).

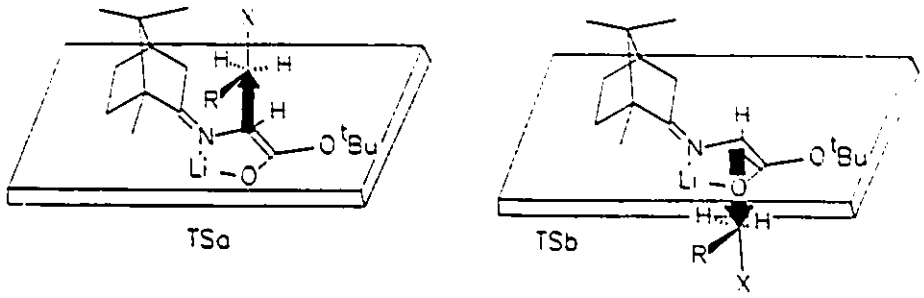
Figure 39: Selectivity as a factor of chelation



That is, the optical purity of 38 was low (5-10% ee) when the O-methylated or O-methoxymethylated imine was used in place of hydroxylated imine 37. The authors proposed that the 5-membered rigid cyclic complex 37a acts as the efficient chiral reagent.

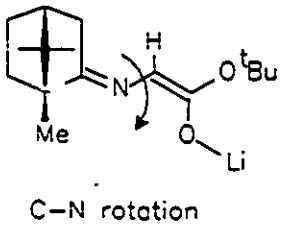
The two possible transition state structures in the alkylation of the Li enolate of 24 that invoke Li-π association (with unsaturated alkyl halides) and O-Li-N chelation are shown in Figure 40, TSa and TSb.

Figure 40: Possible transition states



Perpendicular[87] approach of the electrophile as shown in TSa results in a severe steric interaction between the incoming electrophile and camphor. The result is preferential *re* face attack. If alkylation was taking place on the extended form of the enolate rotation of the enolate as shown in Figure 41 would be possible and the approach of the incoming electrophile from the bottom face could lead to either the R or S products.

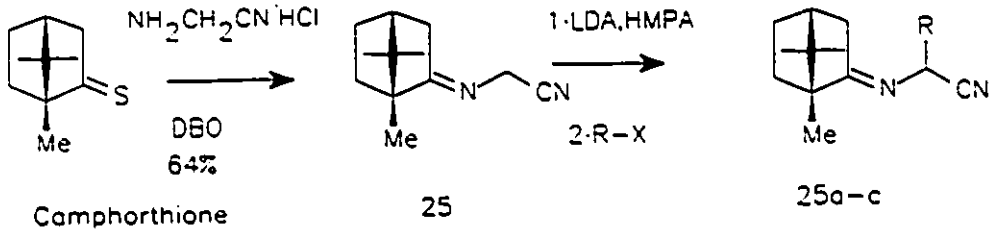
Figure 41: Extended enolate



How important is the cyclic chelated nature of the enolate to the diastereoselectivity of the alkylation reaction? In order to model the extended enolate shown in Figure 41, the camphor imine of α-aminoacetonitrile was prepared (25). Due to the geometric constraints of the nitrile group the Li enolate of 25 cannot form an intramolecular 5-membered chelate (Figure 42). The preparation and alkylation of 25 is shown in Figure 42. Camphorthione and α-aminoacetonitrile were refluxed in MeOH with DBO to afford 50-60% yield of the corresponding imine. ^{1}H NMR and ^{13}C NMR showed the presence of only one diastereomer. The imine double bond was

assigned the (*E*)-configuration based on the previous results for 24.[51] In contrast to 24, the ^{1}H NMR showed that the signal for the C-11 methylene group of 25 was a singlet rather than an AB quartet.

Figure 42: Camphor imine of α-aminoacetonitrile



This seems to indicate that the methylene protons are chemically more equivalent than C-11 protons in 24. The alkylation of 25 was carried out in the standard manner[51,52] (1 equiv. LDA, 1 equiv. HMPA, -78°C, THF) and the results are shown in Table 4.

Table 4: Alkylation of 25

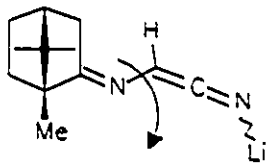
cmd.	R=	%yield	%de
25a	benzyl	67	65
25b	allyl	69	44
25c	Me	71	0

The de's were calculated from the integration of the overlapping C-11 methine protons. It is assumed that the major diastereomer resulted from *re* face attack in a manner analogous to imine 24 since the C-11 methine signal of the major diastereomer in both instances appeared at higher field. Hydrolysis of the imine bond and the nitrile (to the carboxylic acid) and comparison to known amino acids would allow rigorous specification of the configuration of the newly formed center, but this was not performed. In no case were any dialkylated products observed. The diastereoselectivities are presumed to reflect kinetic rather than thermodynamic products since attempted deprotonation of the benzylated product followed by

quenching with D_2O gave no deuterium incorporation (by mass spectroscopy and ^1H NMR). Recently however, Seebach[88] has reported a number of cases in which unexpected results were obtained with Li enolate reactions in the presence of secondary amines, mostly diisopropylamine. Addition of deuterating agents (D_2O, DX) to the Li enolates did not furnish the desired α-deuterio products, but rather more or less completely α-protonated product. It was shown[69] that the proton stems from the secondary amine (diisopropylamine). Seebach reports that "the expected products are often obtained in high yields if butyllithium is added prior to the electrophiles."[69] The addition of butyllithium in this manner would produce LDA which would be a stronger coordinator than diisopropylamine. This would not be wise in our case since, as already discussed, the addition of strong coordinators to the alkylation reaction can have adverse affects on both the chemical yield and the optical yields.

In all of the alkylations of 25 the de's were severely reduced in comparison to the alkylation reactions of the Li enolate of 24. This is presumed to be the result of the loss of the cyclic 5-membered metallacycle envisioned for the Li enolate of 24. As previously noted it is not possible to draw any type of cyclic intermediate for the enolate of 25 due to the geometric constraints (linear) of the nitrile group. This loss of intramolecular chelation results in the possibility of rotation about the C-N bond of the enolate (Figure 43). Lower diastereoselectivites follow since the diastereotopic faces of the enolate are no longer well defined.

Figure 43: C-N bond rotation



C–N rotation

Refinements to the Alkylation Model

The results of the experiments discussed lead to a more refined model for the alkylation of imine 24. These refinements are listed below.

1. The enhanced de's observed using alkyl halides which have π-systems adjacent to the carbon undergoing alkylation is the result of a weak metal-π association (not a π-π association).

2. The electrophile must be electron rich (adjacent π-unsaturation). A lower π-electron density in the phenyl ring of *p*-substituted benzyl bromides results in a lower de.

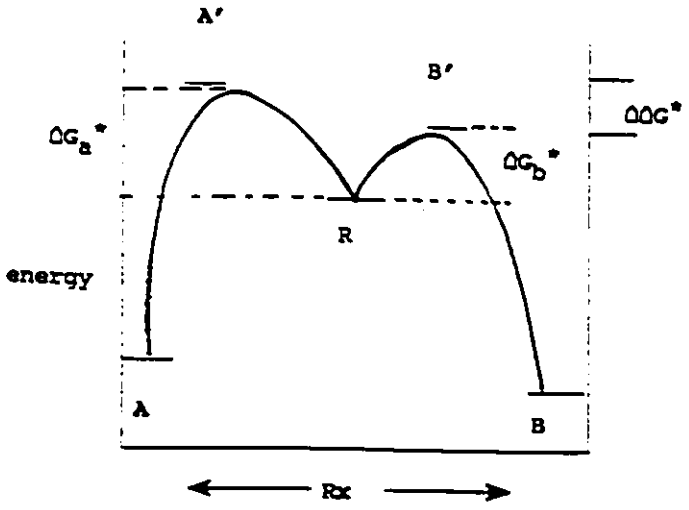
3. The cation of the enolate must be able to coordinate with the incoming electrophile. A coordination site must be available on the metal for the metal-π association to occur and the metal must be a good coordinator.

4. The rigid 5-membered metallocycle of the enolate is required for good selectivity.

The Alkylation and Preparation of Hydroxylated Camphor Imines of *tert*-Butyl Glycinates

From the foregoing results it can be concluded that when utilizing camphor as a chiral auxiliary to achieve asymmetric synthesis, very subtle changes in the reaction conditions (electronic nature of alkylating agent, enolate cation, addition of cosolvents) may cause drastic changes in the stereochemical outcome of the reaction. The energy diagram for a simple asymmetric reaction is shown in Figure 44. The chiral starting material R can react through two diastereomeric transition states A' and B' to yield diastereomers A or B.

Figure 44: Energy diagram for an asymmetric synthesis



The Gibb's free energy of activation (Figure 44) (the $\Delta G^{\ddagger}$) for the formation of diastereomeric transition states A' and B' from R are small (and not equivalent) in comparison to the $\Delta G^{\ddagger}$'s required for the formation of A' and B' from A and B respectively. If the latter two $\Delta G^{\ddagger}$'s are sufficiently large, then A and B cannot revert to R (kinetically controlled reaction) and the ratio of A and B will depend not on

their relative stabilities but on the difference in magnitude between $\Delta G^{\ddagger}_{a}$ and $\Delta G^{\ddagger}_{b}$ ($\Delta\Delta G^{\ddagger}$). In order to obtain one diastereomer in large excess, the energy difference of the diastereomeric transition states need not be very large. Using the equation $\Delta G^{\ddagger}=-RT\ln K^{\ddagger}$ (K is the ratio of stereoisomers formed) a difference in energies of only 2 kcal/mol will result in a 96:4 mixture of A and B (92% ee).[89] This very small energy difference between diastereomeric transition states can be brought into perspective by realizing that the activation energy for the interconversion of one chair form of cyclohexane to the other is 10 kcal/mol.[90]

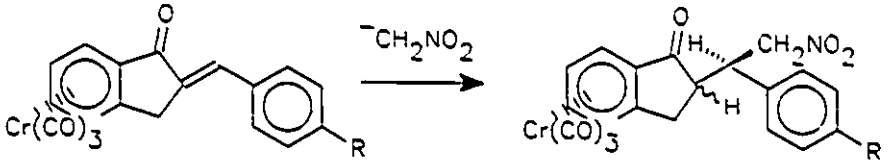
The alkylation of (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one imine of *tert*-butyl glycinate[32] has been discussed in the introduction. As previously noted, Solladie-Cavallo[35] proposed a possible structure of the lithium aggregate of the (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one imine of ethyl glycinate which accounts for the observed stereoselectivity. She speculated that the Li enolate was a folded dimer, (Figure 13) and that this aggregate accounted for the high diastereoselectivities observed with both unsaturated and saturated alkyl halides. The formation of the dimer depends upon the presence of the second anionic site (Li alkoxide) in the pinanone molecule.

With this report in mind, it was suggested that the addition of a second anionic site (O_2-Li_2) on the camphor molecule might lead to a more effective chiral auxillary for the alkylation of chiral glycinates.

The use of $Cr(CO)_3$ complexed aryl compounds substituted in the *ortho* or *meta* position have gained considerable use as efficient chiral auxiliaries.[91-93] One rather interesting report showed that the Michael addition of nitromethane to 2-arylidene-1-

tetralones complexed with $Cr(CO)_3$ was completely stereoselective[94] (Figure 45). Of the four possible stereoisomers formed only two were found. Further examination showed that the two products formed were epimeric at the carbon adjacent to the ketone. Therefore, it followed that the Michael addition was 100% stereoselective.

Figure 45: Asymmetric Michael addition



1,4 addition 100% stereoselective

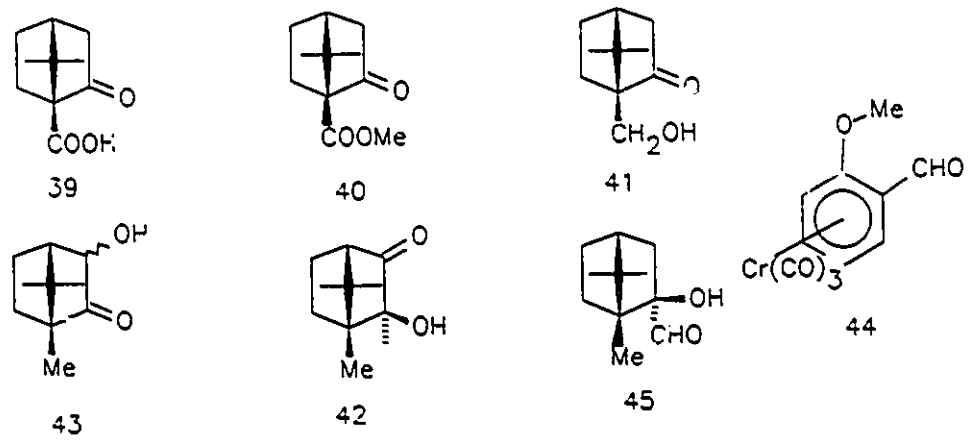
One of the most useful $Cr(CO)_3$ complexes is the complex of o-anisaldehyde. Since the preparation and resolution of the complex has been outlined in the literature[95] we decided to investigate the possible use of this chiral complexed aldehyde (as a CDA) in the alkylation of chiral glycinates.

This section of the dissertation will discuss modifications to the camphor skeleton designed to improve selectivities in the alkylation of derived glycinates. The discussion will include results obtained when various hydroxylated camphor-derivitives were used as chiral auxiliaries in the alkylation of the corresponding imines of *tert*-butyl glycinate, the alkylation of the $Cr(CO)_3$ complexed o-anisaldehyde imine of *tert*-butyl glycinate, an unexpected reaction of 3-hydroxycamphor with *tert*-butyl glycinate, and the attempted preparation of 2-hydroxy-1,7,7-trimethylbicyclo-[2.2.1]heptane-2-carboxaldehyde.

In order to study the effects that second anionic site on camphor might have on the diastereofacial selectivity of an alkylation reaction of a chiral glycinate with

benzyl bromide and to study the possible use of a chromium complexed aldehyde as a chiral auxiliary (in connection with the alkylation of chiral glycinates), we decided to prepare ketones 39-43, and aldehydes 44 and 45 (Figure 46).

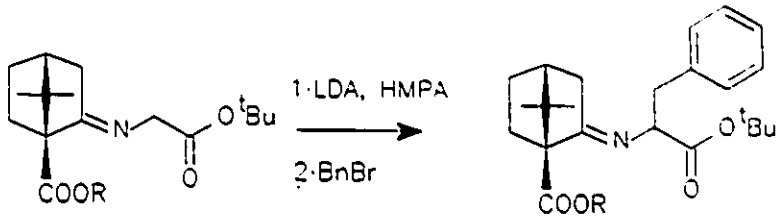
Figure 46: Possible chiral auxiliaries



Ketopinic acid (39) was prepared according to the literature procedure.[96] Oxidation of (+)-10-camphorsulfonyl chloride with $KMnO_4$ gave ketopinic acid in 38% yield. When (+)-10-camphorsulfonyl chloride was not available, it was prepared according to the literature procedure from (+)-10-camphorsulfonic acid.[97] The Lewis acid catalysed condensation of ketopinic acid with *tert*-butyl glycinate has been reported[98] and shown to give the imine with (*E*)- configuration. In our hands the reaction gave a 77% yield of imine 46. The ^1H NMR and ^{13}C NMR were consistent with the presence of only one diastereomer. The enolate of 46 was prepared in THF at -78°C using 2.1 equivalents of LDA. The enolate was alkylated with benzyl bromide in the presence of 1 equivalent of HMPA (Figure 47).

TLC and GC analysis showed that most of the imine had reacted. After column

Figure 47: Alkylation of 46 and 47



46 R=H

47 R=Me

46a de=81%

47a de=78%

chromatography a 38% yield of alkylated product (46a) was recovered along with 45% yield of ketopinic acid. Apparently prolonged exposure of the alkylated product to silica gel caused the hydrolysis of the imine double bond. This is in stark contrast to the difficulty in hydrolysis of the imine bond in 24. The presence of the acidic proton in 46 and 46a may provide catalysis for the hydrolysis. We must assume that the two diastereomers of 46a are hydrolyzed equally. Integration of the overlapping C-11 protons of the benzylated product showed a de of **81%**. Similar to the camphor imine, the methine proton (C-11) appeared as a doublet of doublets with the minor diastereomer appearing at lower field. On the basis of previous work[51,52] which found that the product of *si* face attack on the enolate showed its methylene proton absorption at lower field than the product of *re* face attack, the major diastereomer obtained from the alkylation can also be assigned as the expected product of *re* face attack. When the reaction was repeated with 2 equivalents of HMPA, the isolated chemical yield and the de remained about the same. This is in contast to the case of the camphor imine.

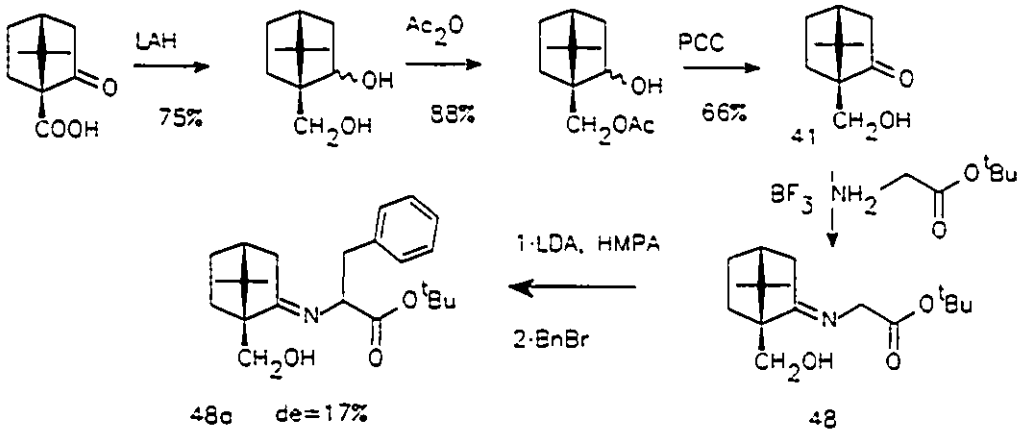
Methyl ketopinate (40) was prepared by reacting ketopinic acid with 1.2 equivalents of diazomethane in ether. After column chromatography 67% of crystalline methyl ketopinate was isolated. Lewis acid ($BF_3 \cdot Et_2O$) catalysed condensation with *tert*-butyl glycinate gave a quantitative yield of imine 47.

Again, ^1H NMR and ^{13}C NMR showed only one stereoisomer. The imine double bond was assigned the *E* configuration since, as in the camphor imine case, the C-10 substituent causes a severe steric interaction with the *N*-substituent in the *Z* configuration. Deprotonation (1.1 equivalents LDA) and alkylation with benzyl bromide at -78°C in the presence of 1 equivalent of HMPA resulted in a 78% yield of benzylated product (47a) after chromatography (Figure 47). Apparently both 47 and 47a are more stable than 46 and 46a to hydrolysis on silica gel. Interestingly, the integration of the O-Me protons of the major and minor diastereomer in the 300 MHz ^1H NMR showed that the de had not changed significantly (de=78%) in comparison to that found for 46a. It can also assumed that the major product resulted from *re* face attack on the enolate for the reasons already stated.

10-Hydroxycamphor (41) was prepared in four steps from ketopinic acid (39).[98] Ketopinic acid was reduced fully to give a diol using excess LAH in ether. The ^1H NMR of the resulting crude diol showed a mixture of epimers at C-2 (4 distinct methyl signals). When the crude diol was treated with 1 equivalent of acetic anhydride it was assumed that only the primary hydroxyl group was acetylated even though ^1H NMR indicated two singlets at about 2.1 ppm (epimers at C-2). The crude acetylated compound was oxidized with PCC (only two methyl signals) and then the

acetyl group was removed using basic conditions. 10-Hydroxycamphor was purified via column chromatography in 27% overall yield from ketopinic acid. Lewis acid catalyzed condensation of 41 with *tert*-butyl glycinate was uneventful and imine 48 was isolated in 86% yield. NMR (proton and carbon) showed only one diastereomer. The C-11 methylene protons appeared as two doublets, one at 3.95 ppm and the other at 3.64 ppm indicating that they are very diastereotopic. Alkylation with benzyl bromide at -78°C using 2.1 equivalents of LDA in the presence of 1 equivalent of HMPA gave a poor yield of 48a.

Figure 48: Preparation and alkylation of 48

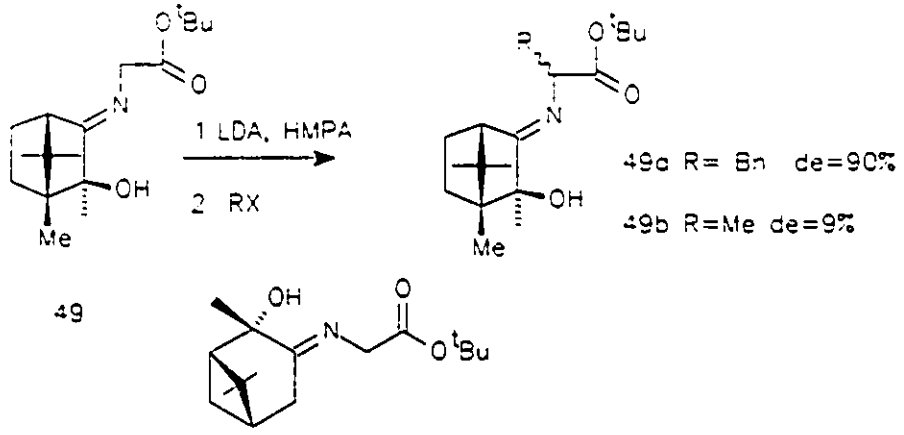


Only monoalkylated product was recovered along with starting materials (Figure 48). Surprisingly the integration of the O-*tert*-butyl group of the ester showed that the de was only 17%. The use of two equivalents of HMPA did not change the optical or the chemical yield.

The final hydroxylated imine prepared and alkylated was 49. One should note the similarities of 49 to Yamada's hydroxypinanone imine (Figure 49).

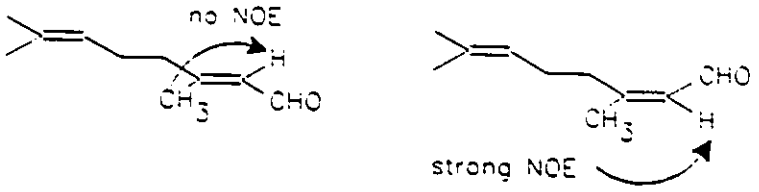
3,3-Ethylenedioxyborman-2-one was prepared from (*R*)-(-)-camphorquinone and

Figure 49: Alkylation of 49



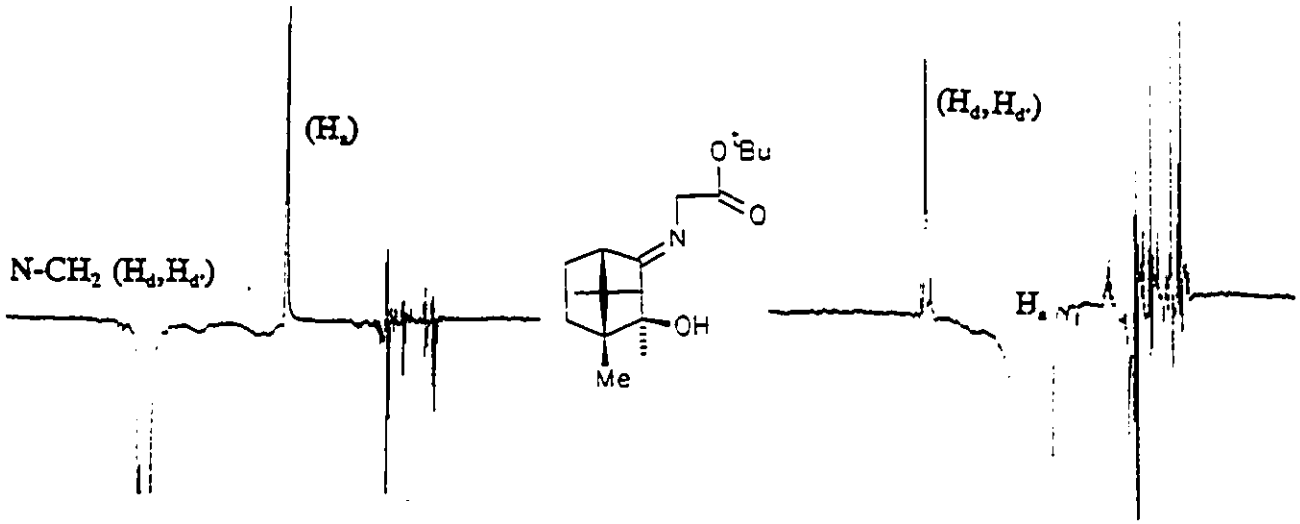
ethylene glycol according to the literature.[99] ^{1}H NMR of the crude product revealed that it was contaminated with about 5-10% of 2,2-ethylenedioxybornan-3-one. This contamination was not indicated in the literature.[99] Recrystallization from methanol gave pure 3,3-ethylenedioxybornan-3-one in 66% yield. This compound was treated with MeMgI in ether, quenched with H_2O and the acetal was hydrolysed with dilute mineral acid to give hydroxy-ketone 42 in 33% overall yield. Lewis acid catalysed condensation with *tert*-butyl glycinate gave imine 49 in excellent yield. Although the stereochemistry of the imine bond was presumed to be *E*, two ^{1}H-{^{1}H} NOE (nuclear Overhauser effect) experiments were carried out to verify this assignment. NOE is often used to obtain information about conformations or configurations. For example Ohtsuro[100] *et al* used ^{1}H-{^{1}H} NOE to determine the configuration of the two isomers of citral (Figure 50). When the CH_3 protons were irradiated and the ethylenic protons were observed, there was a signal enhancement of 18% for one isomer but no observable effect on the other. Clearly the former has the structure A and the latter is B.

Figure 50: NOE for determination of stereochemistry



Initially the protons of interest in imine 49 needed to be identified in the ^{1}H NMR. The N-CH_2 (H_d,$H_{d'}$) protons appeared a AB quartet centered at 4.05 ppm and the bridgehead proton (H_a) was observed at 2.47 ppm downfield relative to the other camphor protons and it appeared as a 1H doublet. H_a couples only to H_b (Figure 51) since the dihedral angle with H_c is about 90°. Irradiation of the methylene protons (H_d,$H_{d'}$) resulted in signal enhancement of only H_a, whereas irradiation of H_a resulted in the strong enhancement of the (H_d,$H_{d'}$) resonance and a weaker enhancement for the adjacent protons (Figure 51).

Figure 51: NOE experiments on 49

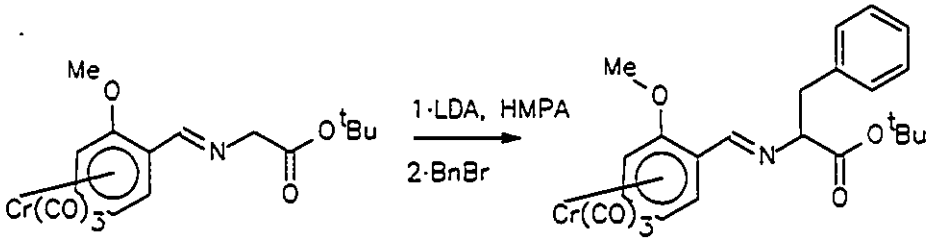


Alkylation of 49 with benzyl bromide was carried out at -78°C in the presence of 1 equivalent of HMPA using 2.1 equivalents of LDA. A 73% yield of the

monobenzylated product (49a) was isolated. No dialkylated products were detected by TLC. As determined from the integration of the overlapping C-11 proton signals in the 300 MHz ^{1}H NMR the diastereoselectivity was **90%**. Since the diastereoselectivity of the reaction was quite high 49 was also alkylated with MeI in a similar manner. The mono-alkylated product (49b) was isolated in 77% yield and the de was determined to be **9%** from the integration of the O-*tert*-butyl singlets. In analogy to the previous camphor derivatives the approach of the electrophile was expected to be predominantly from the *re* face of the enolate. This could have been demonstrated by hydrolysing the imine bond to give the corresponding amino-ester, derivatizing with MPTA-Cl[61] and comparing the ^{19}F NMR spectrum of the Mosher amide to previous results. Although the de observed for the methylated product was somewhat improved (compared to the camphor case), the selectivity did not approach the de reported for the alkylation using MeI in the 2-hydroxy-3-pinanone case.[32]

The final imine of *tert*-butyl glycinate to be prepared and alkylated was 50. Its alkylation results are shown in Figure 52.

Figure 52: Alkylation of 50



50 50a de=0%

The $Cr(CO)_3$ complex of *o*-anisaldehyde was prepared in 64% yield according to the

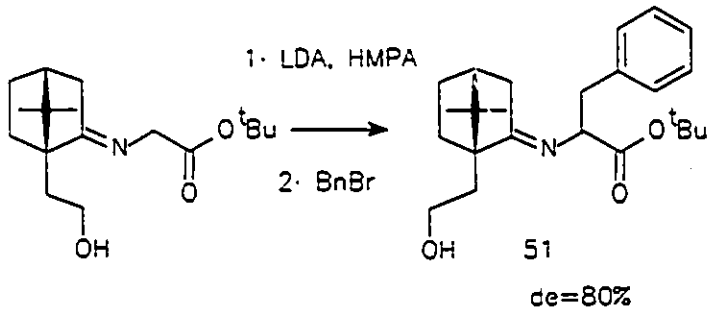
literature.[95] Although resolution of the complex has been reported,[95] in our initial studies use of the racemate was sufficient. Condensation with *tert*-butyl glycinate was facile and was accomplished by stirring the chromium complexed aldehyde with tert-butyl glycinate in ether. The deep red color of the complexed aldehyde was slowly replaced by a bright orange color. Isolation was effected by removing most of the ether and adding hexanes to precipitate the orange-colored imine. The imine was easily hydrolysed by exposure to any type of moisture or to silica gel and attempts to purify the imine by column chromatography led to isolation of the complexed aldehyde almost exclusively. ^{1}H NMR and ^{13}C NMR of the recrystallized imine showed that there was only one diastereomer present and the configuration of the imine double bond is expected to be *trans* (*E*). Alkylation with benzyl bromide in the presence of 1 equivalent of HMPA gave mostly alkylated product (50a) as determined by the ^{1}H NMR of the crude reaction mixture. However, due to the facile hydrolysis of the imine, isolation of pure benzylated product was not possible. ^{1}H NMR showed that the integration of the two diastereomeric methoxy signals of the crude benzylated product were in a 1:1 ratio. Thus the de for the benzylation reaction was 0%.

Table 5 includes the alkylation results for all of the imines discussed above. In the benzylation reactions of the C-10 substituted camphor derivatives of *tert*-butyl glycinate imines the de values obtained (17-90%) were lower than in the case of the camphor imine (24, de=99%). These results were consistent with the outcome obtained by Matassa in our laboratory who found that when the 10-hydroxymethylcamphor imine of *tert*-butyl glycinate was alkylated with benzyl

bromide 51 was obtained in 74% yield with a de of 80% (Figure 53).[101]

Table 5: Alkylation results				
entry	Cmd.	Equiv.HMPA	%yield	%de
1	46a	1	38	81
2	46a	2	30	82
3	47a	1	78	78
4	48a	1	32	17
5	48a	2	37	16
6	49a	1	73	90
7	49b	1	77	9
8	50a	1	-	0

Figure 53: Alkylation of 10-hydroxymethylcamphor imine

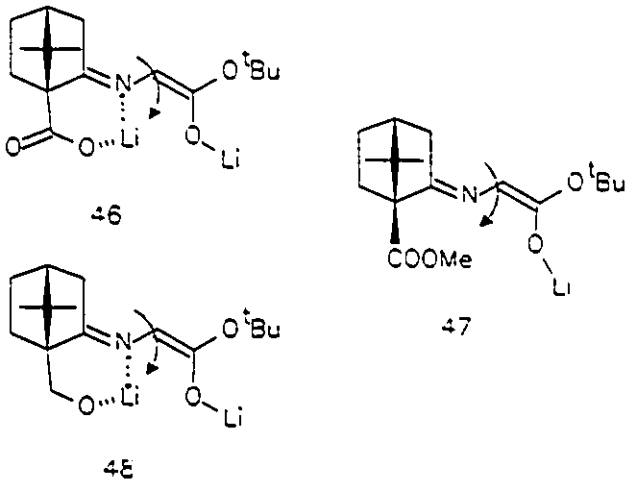


Matassa[101] also found that the addition of 2 equivalents of HMPA had no effect on the diastereoselectivity of this reaction. Our results were similar.

The precise reason for the reduced diastereoselectivity observed in the alkylation of the anions of 46,47,48 is unknown. It is conceivable that the planar 5-membered O1-Li-N chelated structure of the enolate (which has been shown previously to be vital to the diastereoselectivity in the alkylation of the camphor imine) may be

disturbed by the presence of an O2-Li bond (Figure 54) or the presence of a bulkier substituent at C-10 (as in 47) thus allowing rotation of the C-N bond of the enolate as previously proposed by Matassa.[101]

Figure 54: Possible enolate structures

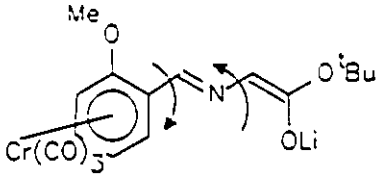


It is interesting that the presence of a second Li atom was not required for observing a reduced selectivity, since benzylation of 46 and 47 gave similar selectivity. This may suggest that the presence of a large (larger than methyl) functional group at C-10 on camphor hinders approach of the electrophile to the *re* face and thus lowers the selectivity of the reaction.

The de observed for the benzylated product (49a) was comparable to Yamada's[32] benzylated 2-hydroxypinan-3-one imine, but the de for the methylated product (49b) was significantly lower.

Finally, the complete lack of selectivity in the alkylation of 50 can attributed to the fact that the carbon undergoing alkylation is located at too far a distance from the bulky $Cr(CO)_3$ group (Figure 55). Also, one must consider that rotation of the phenyl ring is possible and discrimination of the two faces of the enolate would be negated.

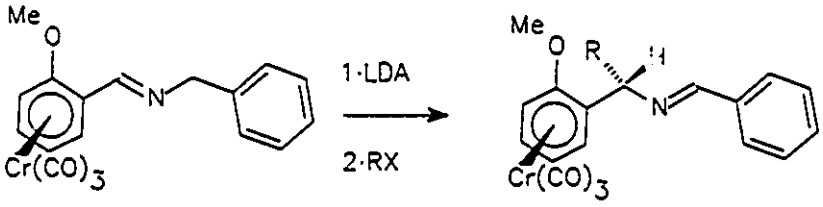
Figure 55: Lithium enolate of 50



too far from reaction site

This result was not totally unexpected since other workers have found that, in order to obtain good levels of asymmetric induction using the $Cr(CO)_3$ group as a chiral director, the carbon undergoing the reaction is most often α to the phenyl ring.[93] Rather encouraging though is that the alkylation did take place at the γ-position (relative to the phenyl ring). One literature report[102] indicates that the alkylation of the imine in Figure 56 occured preferentially at the α carbon atom (Figure 56).

Figure 56: Alkylation at the α position



In this case very high diastereoselectivities were observed even with "small" methyl group. The authors stated that alkylation in the α position was 100% regioselective and that this was probably governed by the electron-attracting effect of the $Cr(CO)_3$ group. In our case the presence of the electron withdrawing ester functionality ensured that alkylation took place at the γ position. This was confirmed by the fact

that the chemical shift of the imino-proton in both the starting material and alkylated product appeared as a singlet at about 8.3 ppm.

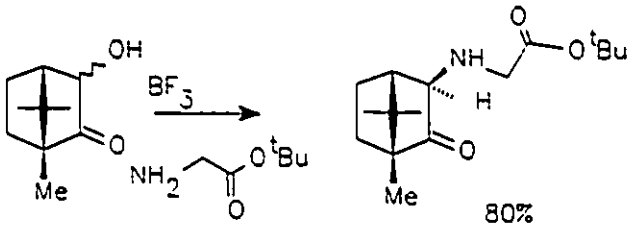
Reaction of 3-Hydroxycamphor with *tert*-Butyl glycinate

We required 3-hydroxycamphor to continue our study on the effect that a second anionic site would have on the alkylation of chiral imines of *tert*-butyl glycinate. 3-hydroxycamphor (43) was prepared by the oxidation of the Li enolate of camphor with oxodiperoxymolybdenum(pyridine)-hexamethylphosphoramide (MoOPH) as outlined in the literature (5:1 mixture of *endo* and *exo* diastereomers).[103] MoOPH oxidation was preferred since the oxidation of the enolate of camphor with other reagents[104-106] was reported to give inferior diastereoselection. The carbinol proton corresponding to the endo isomer appeared as a doublet (J= 5Hz) at lower field than the exo isomer which appears as a singlet. The angle between the carbinol proton and the bridgehead proton is about 81° in the latter and close to 45° in the former.

Attempted BF_3 catalyzed condensation of 43 with *tert*-butyl glycinate gave a single compound (by TLC and GC). The IR spectrum showed one carbonyl stretching absorption at 1740 cm^{-1}, no apparent C=N absorption, and a weak absorption that could be attributed to either OH or NH (3320 cm^{-1}). ^1H NMR spectrum showed that the camphor moiety was intac and the appearance of N-CH_2 and O^{t}Bu signals indicated that *tert*-butyl glycinate had been incorporated into the molecule. The absorption of the proton at C-3 (1H singlet, 2.86 ppm) suggested that only the *exo* stereoisomer of the compound was present since the C-3 proton of *endo* isomers shows a significant coupling to the proton at C-4. The ^{13}C NMR spectrum confirmed these facts and also indicated that two carbonyls were present, one which was clearly an ester (δ 171.6 ppm) and the other a ketone (δ 218.4, cf. camphor at δ 218.6). No

imine carbon was evident (δ 170ppm). A 2-D proton-carbon correlated NMR spectrum linked the proton signals at δ 3.43 (glycinate CH_2 group) and 2.86 with the carbon signals at δ 51.8 (t) and 69.1 (d). This clearly indicates that C-3 is substituted and that the substituent is less deshielding than an oxygen atom. Combustion data showed that the compound had the formula $C_{16}H_{27}NO_3$. All of these facts supported the structure 52 as the product (Figure 57).

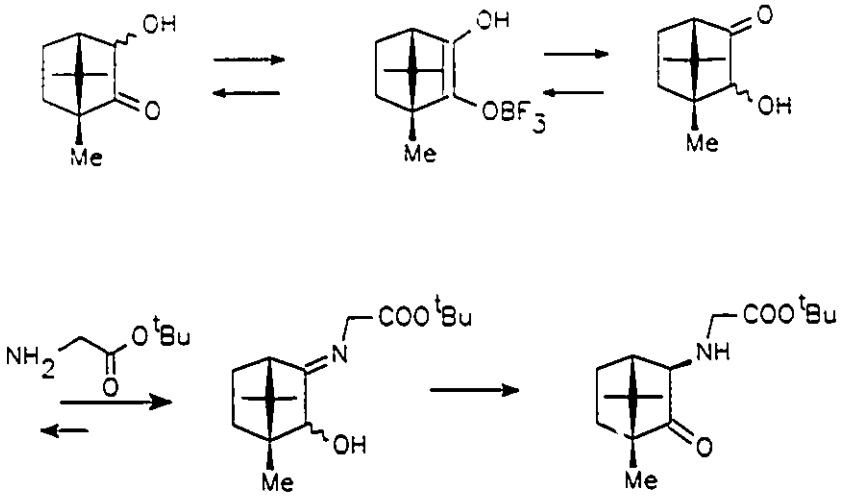
Figure 57: Formation of 52



The hydrochloride salt of 52 was prepared and the spectra were consistent with the assigned structure. In this case the protons of the N-CH_2 group were split into an AB quartet.

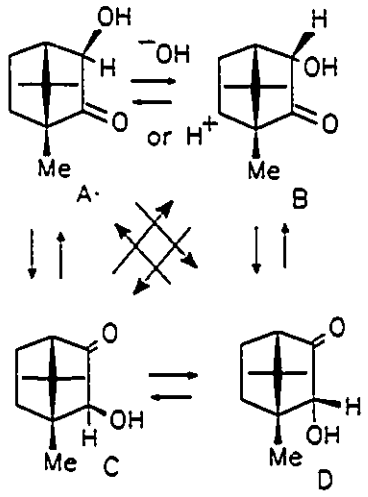
Compound 52 formally arises from the substitution of an OH group by *tert*-butyl glycinate. Although the stereochemistry of the reaction suggests that an inversion process occured (S_N2 mechanism), the nucleophilic displacement of groups from the 3-endo position of camphor are unknown. A more plausable explanation involves the intermediacy of an ene-diol, 2-hydroxyepicamphor, its imine with *tert*-butyl glycinate and retautomerization to the camphor form (Figure 58). Such sequences have been documented for other α-hydroxyketone systems[107] as well as for 3-hydroxycamphor.[108]

Figure 58: Proposed mechanism of formation of 52



Coulombeau and Rassat[108] found that in an alkaline methanol solution (and also under acid catalysed conditions), the interconversion of A-D took place without any side reactions, leading to an equilibrium mixture of all four isomers (Figure 59).

Figure 59: Isomerization of 3-hydroxycamphor

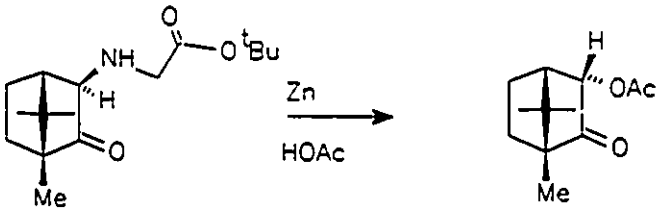


This unusual result that we have observed in the reaction of *tert*-butyl glycinate and 3-hydroxycamphor contrasts with other reports that clearly show that the condensation of 3-hydroxycamphor with benzylamine can be carried out successfully in the presence of 3Å molecular sieves.[109] Consequently, the condensation between 43 and *tert*-butyl glycinate was repeated in the absence of the Lewis acid catalysis by refluxing a toluene solution containing ground molecular sieves. Unfortunately, only small amounts of 52 were

observed by TLC and gas chromatography. The reaction mixture consisted mostly of starting materials and polyglycine.

To verify the structural assignment, 52 was treated with zinc metal in acetic acid. It was our expectation that camphor would be the product resulting from a reductive elimination.[110] Camphor was not detected in the reaction but a compound had formed which had the glycinate moiety removed (no N-CH_2 or O^{t}Bu). Furthermore, the C-3 proton had shifted from 2.86 to 5.22 ppm and was now split into a doublet. This fact in combination with the presence of a three proton singlet at 2.13 suggested structure 53 and that the acetate group was in the *endo* position (Figure 60). The assignment of 53 was easily confirmed by its hydrolysis to 3-hydroxycamphor (a 10:1 mixture of *endo:exo*) which was the starting material of the reaction sequence. The stereochemistry of the substitution reaction indicated that an inversion had taken place.

Figure 60: Attempted reduction of 52



52 53

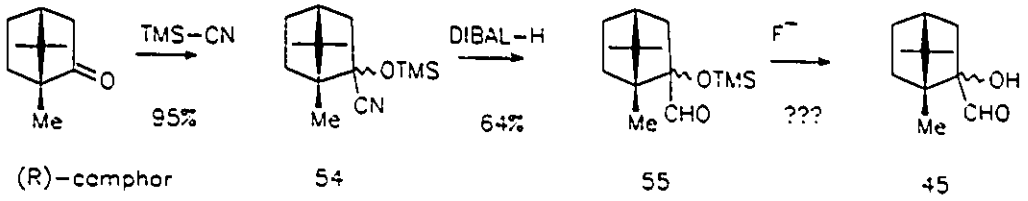
To our knowledge a reaction of this type has not been reported for camphor. In the absence of zinc metal no substitution occured. It can only be suggested that the zinc metal in some way is used to activate the glycinate moiety to substitution by

acetic acid instead of functioning as an electron source for the reduction.

Attempted Preparation of 45

We also required compound 45 to study the influence that a second anionic site would have on the alkylation reaction of its corresponding *tert*-butyl glycinate imine. The proposed synthesis of 45 is shown in Figure 61.

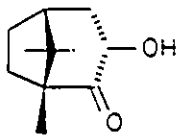
Figure 61: Attempted preparation of 45



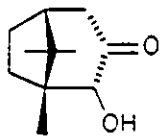
The mixture of cyanohydrin ether stereoisomers 54 was prepared in 95% yield as previously described.[111] The crude cyanohydrin was used since it has been reported[111] that attempts to purify the compound by distillation led to its decomposition. Reduction of 54 with DIBAL-H in toluene proceeded slowly at room temperature. However refluxing the reaction gave the silyl ether 55 of the desired hydroxyaldehyde 45. NMR analysis indicated that both 54 and 55 were 6:1 mixtures of epimers at C-2. The accepted mechanism[111] for the formation of cyanohydrin TMS ethers with TMS-CN involves the attack of cyanide ion on a ketone-Lewis acid complex. Assuming that the process is kinetically controlled, the isomer of 54 with the *endo*-oriented cyano group should be preferred. The desilyation of 55 proved to be anything but routine. Exposure to either BF_3 or Bu_4NF in CH_2Cl_2 gave two products (56 and 57) which were isomeric with both 45 and each other and in the same ratio as the stereoisomers 54 and 55. Neither of the two isomeric products exhibited the

expected aldehydic proton in the ^1H NMR. Both 56 and 57 (Figure 62) had a molecular weight (mass spectra) of 182 ($C_{11}H_{18}O_2$). The ^1H and ^{13}C NMR spectra for both are given in Tables 6 and 7.

Figure 62: Major and Minor Isomers



56

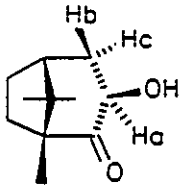


57

The IR of both compounds showed the presence of a carbonyl and an hydroxyl group. The ^{13}C NMR (both proton decoupled and DEPT-135 edited) of the major product (56) showed three quaternary methyl groups, a ketonic carbon, a secondary carbinol carbon, three methylene carbons and one methine carbon. The ^1H NMR confirmed the presence of the three methyl groups and showed a one-proton triplet at 4.21 ppm.

Decoupling experiments revealed that this signal was coupled with protons at δ 2.32 and δ 1.71 ppm. On the basis of these data, the assignments given in Table 6 were made and the structure 56 was assigned to this compound. The stereochemistry is inferred from the coupling constants calculated for the energy-minimized (MM2) conformation of 43 (Figure 63).

Figure 63: Dihedral angles



56

The dihedral angles between protons A and B (151°) and A and C (35°) respectively predict[112] coupling constants of similar magnitude (ca. 8Hz) and this agrees with the observed triplet. The dihedral angles calculated for the epimer (30° and 85°) lead to coupling constants which vary widely in magnitude and do not agree well with those observed. The Mosher ester (56a) of 56 was

Table 6: ^{1}H NMR of compounds 56 and 57

Compound 56				Compound 57			
δ ppm	mult.#H	J (Hz)	Assig.	δ ppm	mult.#H	J (Hz)	Assig.
4.21	1(t)	9.0	3-en	4.00	1(bs)		2-ex
3.50	1(d)	1.8	OH (D_2O)	3.65	1(d)	2.3	OH (D_2O)
2.32	1(m)		4-ex	2.75	1(d)	15.6	4-ex
2.14	1(m)		4-en	2.3	1(dd)	15.6, 3.1	4-en
1.95	1(m)		5	1.9	1(m)		
1.8-1.5	4(m)		6,7	1.8	1(m)		
1.00	3(s)		[11]	1.7	1(m)		
0.90	3(s)		[10]	1.4-1.25	2(m)		
0.70	3(s)		[9]	1.23	3(s)		
				0.95	3(s)		
				0.92	3(s)		

prepared from MTPA-Cl.[61] The lack of extraneous signals in the spectra of 56 and in the ^{1}H and ^{19}F NMR of its Mosher ester (56a) indicates that only one of the possible diasteromers was present.

The minor isomer (57, Figure 62) had many of the same characteristics as the major. The Mosher ester could not be formed, but NMR data ensure that only one stereoisomer was present. The most obvious differences with 57 were the presence of an AB-quartet with signals at δ 2.75 and δ 2.31 and that the secondary carbinol proton appeared as a slightly broadened singlet (δ 4.00). Decoupling experiments showed that this signal was coupled only to the OH proton. Further, the signals at δ

2.75 and δ 2.31 were coupled to each other and to a signal at δ 2.00. These data support the assignments shown in Tables 6 and 7.

Table 7: ^{13}C NMR of compounds 56,57,58

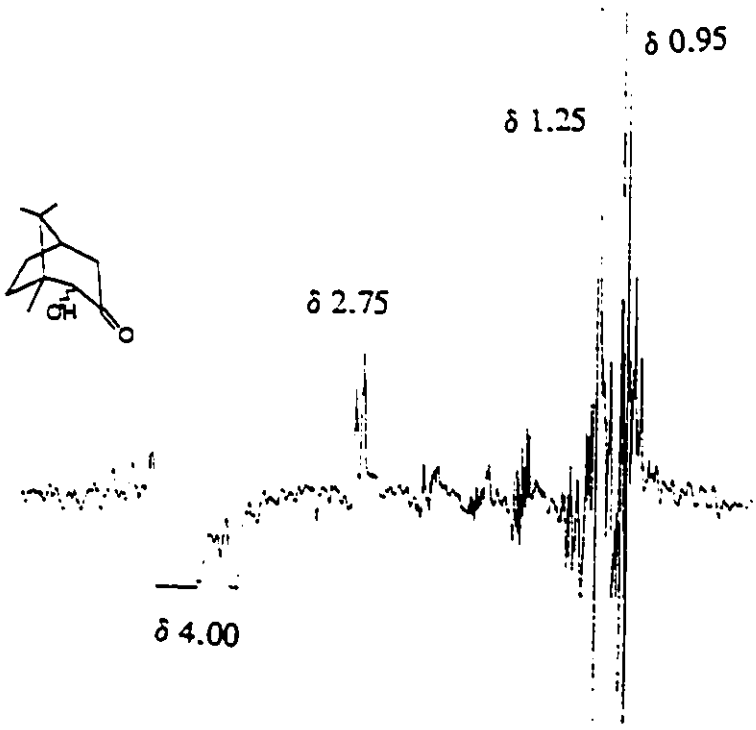
Compound 56			Compound 57			Compound 58	
δ ppm	Mult.	Assign	δ ppm	Mult.	Assign	δ ppm	Assign
215.0	s	C2	211.8	s	C3	212.6	C3
70.17	d	C3	78.9	d	C2	53.94	C2
56.8	s	C1	51.5	s	C1	44.46	C1
48.0	s	C8	46.3	d	C5	45.75	C5
44.4	d	C5	44.6	t	C4	47.04	C4
38/0	t	C7	44.4	s	C8	43.12	C8
34.1	t	C4	28.6	t	C6	27.44	C6
27.3	t	C6	26.8	t	C7	36.15	C7
23.3	q	C[10]	24.1	q	C10	23.58	C10
19.8	q	C[9]	18.4	q	C9	20.77	C9
13.4	q	[C11]	16.4	q	C11	18.84	C11

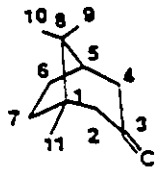
On the basis of the NMR evidence and a proposed mechanism, structure 57 was suggested for this compound. The proton and carbon NMR data for the related compound 58 (Table 7) have been reported.[113] The resonance assignments were made without comment and the values obtained for 57 were consistent with those suggested for 58 (Figure 64).

In order to assign the stereochemistry of 57, the NOE difference spectrum was obtained. The secondary carbinol proton showed a strong positive correlation with the methyl group at δ 1.25 ppm and a much weaker interaction with the methyl group

at δ 0.95 ppm. The δ 1.25 ppm methyl singlet also showed close proximity to the proton resonating at δ 2.75 ppm (Figure 64).

Figure 64: NOE experiments on 57





58

These data support the *endo* configuration of the C-2 hydroxy group in 57.

If structure 57 is correct, the methyl resonance at δ 1.25 would be due to C(9) and that at δ 0.95 would be C(11). These assignments do not correspond with those reported for compound 58. That our assignments were correct was shown in the proton-carbon correlated 2-D spectra (Figure 65) which indicated the correlations shown in Table 8.

Figure 65: 2-D spectrum of 57

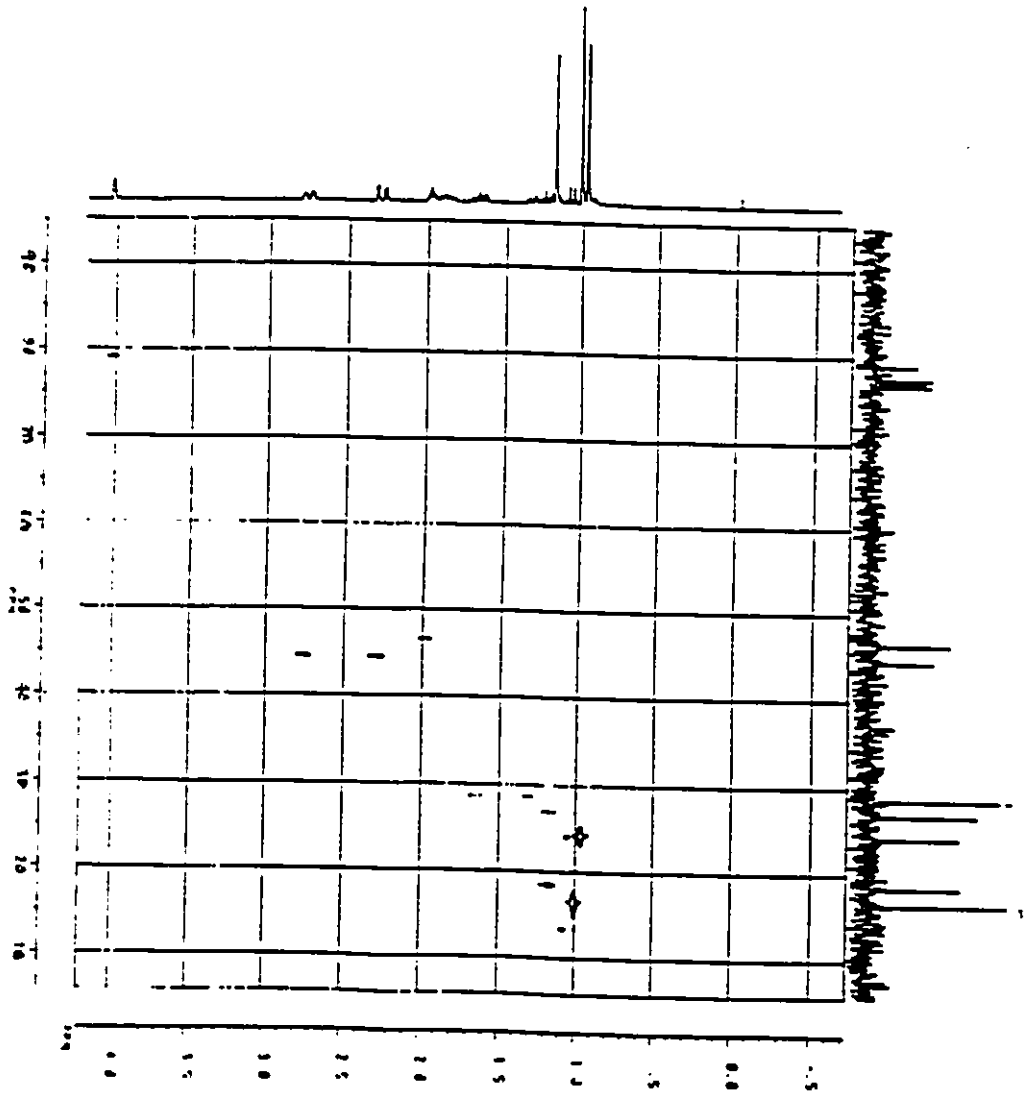
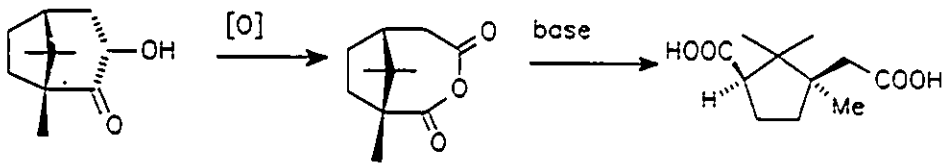


Table 8: Proton-Carbon Correlations for Compound 57	
δC (ppm)	δH (ppm)
78.9 (CH)	4.00 (bs)
46.3 (CH)	1.9 (m)
44.6 (CH_2)	2.3 (dd), 2.75 (d)
28.6 (CH_2)	1.4 (m)
26.6 (CH_2)	1.3 (m)
24.1 (Me)	0.92 (s)
18.4 (Me)	1.25 (s)
16.4 (Me)	0.95 (s)

At this point, the 2-D spectra of 56 was desired to compare with those of 57. In preparation for these experiments, the normal spectra of 56 were rerecorded and it was clear that the original material had been essentially completely converted into another compound (59, Figure 66).

Figure 66: Oxidation of 56



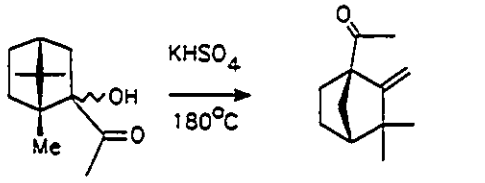
56 59 homocamphoric acid

This process had occured while crystals of 56 had been allowed to stand in air at ambient temperature for several days. This material showed a doubling of the carbonyl band in a region suggestive of a six-membered ring anyhydride but no

hydroxyl absorptions in the IR specrta was observed. Both the mass spectrum (molecular weight = 198), and DEPT-135 edited ^{13}C NMR showed the presence of only 16 protons, suggesting that an oxidation had occured. In addition, the ^{13}C NMR (Table 9) showed two carbonyl carbons at δ 173 and δ 170 ppm and no sp^3-carbon attached to oxygen. These data seemed best accommodated by homocamphoric anhydride 59. Hydrolysis of 59 provided the known[114] diacid, homocamphoric acid. The NMR spectra of homocamphoric acid have not been previously described. However, the similarity of the ^1H and ^{13}C NMR with those of known camphoric acid[115,116] and camphoric anhydride[117] and the coincidence of the melting point of our hydrolysis product to that reported[114] in the literature for homocamphoric acid ensure the structural assignment.

The facile rearrangement (example of an acyloin rearrangement[118,119]) of 55 to 56 and 57 does not seem to have been previously reported in the literature on camphor. The corresponding methyl ketone 60 ('2-acetylborneol') has been prepared.[120] No mention of stereoisomers was given. Ketone 60 rearranged under vigorously acidic conditions ($KHSO_4$, 180°C) to give 61 (Figure 67). Although a variety of ring opened products were described no ring expanded products were mentioned.

Figure 67: Rearrangement of 60



60 2-acetylcamphene

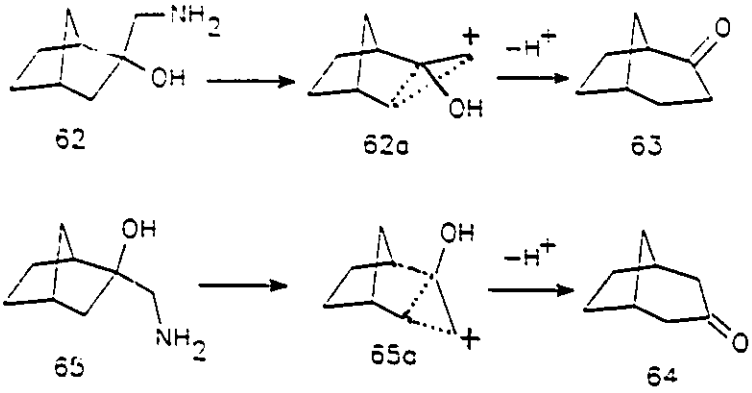
Table 9: ^{1}H NMR and ^{13}C NMR data for compound 59

^{1}H NMR				^{13}C NMR		
δ ppm	No. H Mult.	J (Hz)	Assign.	δ ppm	mult.	Assign.
2.92	1 (1/2 ABq)	14.4	4-ex	172.2	s	[C2]
2.72	1 (1/2 ABq)	14.4, 6.7	4-en	167.5	s	[C3]
2.5-2.0	3 (m)			56.23	s	C1
1.9-1.7	2 (m)			46.88	d	C5
1.27	3 (s)		[11]	46.09	s	C8
1.14	3 (s)		[9]	38.61	t	C4
1.03	3 (s)		[10]	33.10	t	C6
				26.92	t	C7
				26.01	q	C11
				20.72	q	[C9]
				20.50	q	[C10]

A recent review[121] describing one carbon ring expansions of bridged bicyclic ketones suggests that the migratory aptitudes of methylene and bridgehead bonds cannot be easily rationalized. It was reported[122] that the Tiffenau-Demjanov reaction of 2-*exo*-aminomethyl-2-*endo*-hydroxynorbanane 62 gave 63 and 64 in 86% combined yield with a 62:38 preference for methylene migrated product 63 over bridgehead product 64 (Figure 68). The epimeric hydroxy-amine 65 afforded the same products in 91:9 preference for 63 over 64. The authors describe that in the *endo* series factors favoring methylene migration are reinforced by loss of nitrogen from 65a via a

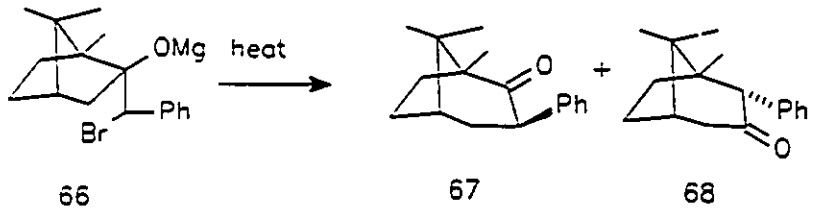
conformationally favourable chair-like transition state. In the *exo* series the loss of nitrogen from 62a involves a boat-like transition state for methylene migration; thus more bridgehead migration is observed.

Figure 68: 1-carbon ring expansion



Sisti and Rusch[123] observed both methylene and bridgehead migration in the thermal rearrangement of the magnesium salt of bromohydrin 66 (Figure 69). Methylene migrated ketone 67 (71%) was favored over bridgehead migrated ketone 68. The authors assumed that the phenyl group occupies the most stable configuration in both compounds.

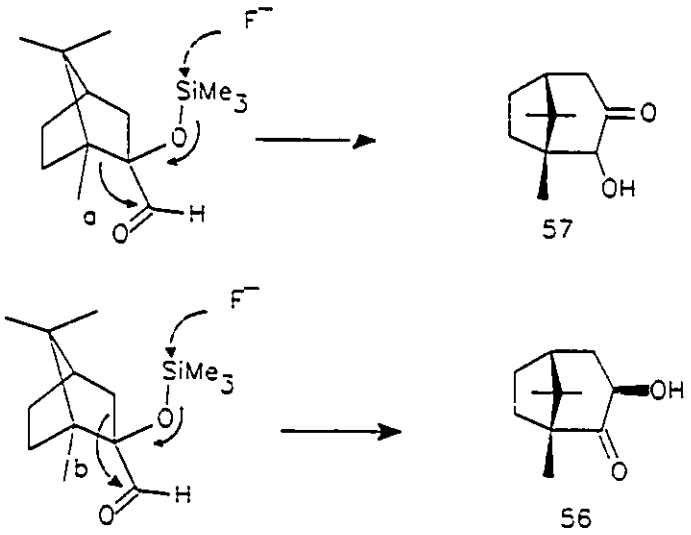
Figure 69: Ring expansion of 66



A plausible rationale for the rearrangement of 55 to 56 and 57 is given in Figure 70. Which stereoisomer of 56 or 57 is formed depends upon which of the two

diastereotopic faces of the aldehyde carbonyl group is attacked by the migrating bond. The bond (C1-C2 or C2-C3) of camphor which migrates determines which isomer (56 or 57) is formed. Although it has been noted that the ratio of 56:57 appears to be identical to the ratio of the epimers of 55 it would be fruitless to speculate on the methylene or bridgehead migratory aptitudes in our case since either epimer of 55 could yield 56 or 57.

Figure 70: Proposed mechanism for the formation of 56 and 57



It is not clear why 56 should be so sensitive to aerial oxidation. Isomer 57 does not seem to exhibit this reactivity, nor do more highly strained molecules such a 3-hydroxycamphor.[103]

As often happens in attempting to utilize chiral auxiliaries for asymmetric synthesis one cannot predict with certainty whether or not a chiral auxiliary will be effective in transferring stereochemical information. Unfortunately, it is apparent

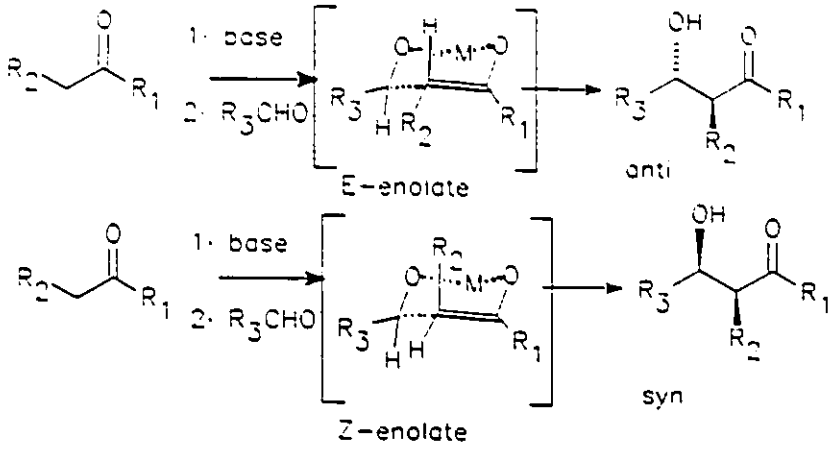
from the results obtained for the alkylations of the C-10 substituted camphor derivatives described that substituting the C-10 position of camphor adversely affects the stereochemical outcome of the reaction. However, it is noteworthy that although the chemistry of camphor has been studied extensively, the camphor molecule is still capable of providing new and unexpected chemisty as observed in the unanticipated substitution reaction of 3-hydroxycamphor and in the unforseen 1-carbon ring expansion of 55.

Chapter 2: Synthesis and Reactions of a New C_2 Symmetric Ketone

Introduction

The formation of carbon-carbon bonds in an asymmetric manner has become an important area in organic synthesis. As previously noted, the classical and most common strategy for asymmetric syntheses utilizes chiral auxiliaries or chiral inducers (cf. Chapter 1 Introduction). Recall that for an asymmetric synthesis to be considered successful the reaction must proceed with high diastereoselectivity (>90% de), and give a satisfactory chemical yield. In choosing an efficient chiral auxiliary for asymmetric syntheses (alkylation, aldol, Diels-Alder etc) it is necessary to have a sound understanding of the reaction mechanism and an idea of the most probable transition state structures. This understanding often makes it possible to predict and ultimately control the direction and extent of asymmetric induction. At this time aldol type reactions are perhaps the best understood in regard to the stereochemistry of the formation of carbon-carbon bonds. The stereochemical results obtained for the aldol reaction of lithium, boron, magnesium, and zinc enolates can be easily predicted by utilizing the Zimmerman-Traxler transition state model.[124] This model proposes that the *Z* and *E* enolates react with carbonyl compounds through one of four possible 6-membered chair-like transition states.

Figure 71: Zimmerman-Traxler model

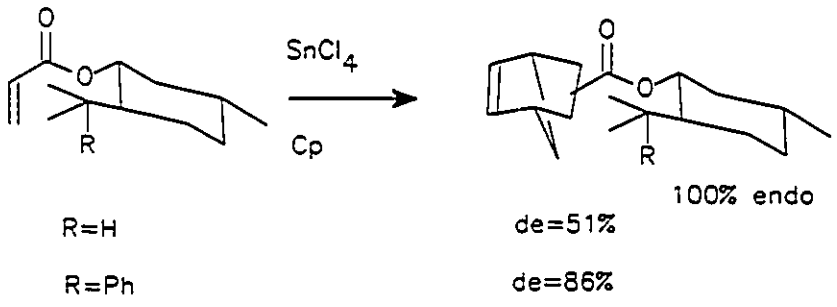


The stereochemistry of the products therefore is predicted by examination of the various possible steric interactions that may be present in these transition states. It has been demonstrated that *Z*-enolates give predominantly *syn* aldols while the *anti* aldols are predominantly obtained from *E*-enolates (Figure 71). The aldol type reaction is not the only reaction in which the stereochemistry can be explained by such a global transition state model. Other examples which can be cited are the chair-like transition states invoked for [3,3] sigmatropic rearrangements which predict the stereochemistry of products[125], the prediction of stereochemistry in additions to carbonyl groups using the Cram[126] rule and the prediction of the stereochemistry of products resulting from Diels-Alder[127] reactions.

One of the most popular methods for predicting the direction and amount of asymmetric induction is based on simple steric and/or chelation considerations. The choice of a chiral auxiliary is frequently largely empirical and based on convenience. Readily available optically active materials such as terpenes, alkaloids and amino

acids are often used. Then, if modest induction is observed with a particular system attempts may be made to optimize the selectivity by making changes to the auxiliary suggested by the evaluation of steric and/or chelation effects. For example, if it is expected that a given group behaves as a "large" group it may be useful to prepare a molecule where this group is even larger. This approach can be illustrated by Oppolzer's investigation of the asymmetric Diels-Alder reaction of acrylates derived from (-)-menthol.[128] He reports that the diastereoselectivity of the reaction was modest when menthol was chosen as the chiral auxiliary. It was assumed that the selectivity of the reaction was due to the shielding of one diastereotopic face of the acrylate group by the adjacent "small" isopropyl group. Oppolzer, then proceeded to show that the replacement the isopropyl group with a $-C(CH_3)_2Ph$ group (8-phenyl-menthol) gave a much higher diastereoselectivity (Figure 72).

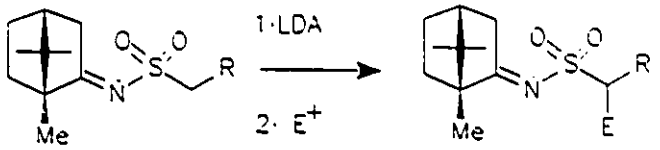
Figure 72: Asymmetric Diels-Alder reaction



Another important observation is that chiral auxiliaries function most efficiently when the asymmetric carbon atoms being formed are as close as possible to the existing center of chirality. For example, camphor has been used extensively as a chiral auxiliary.[129] However, a recent paper by Davis[130] reported that the alkylation of

camphor derived sulfonamide dianions (Figure 73) proceeded with poor induction.

Figure 73: Camphor as a chiral auxiliary



de=2-32%

The lack of chirality transfer in this case is most likely attributable to the distance separating the α-sulfonyl carbanion from the camphor moiety and to the fact that the camphorsulfonimine dianion lacks rigidity which allows the formation of competing diastereomeric conformations in the transition state.

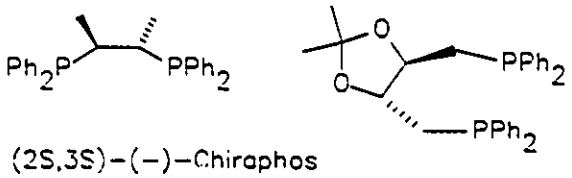
These examples point to the fact that a better understanding of the conformations and mechanisms in a reacting system is required to make rational changes in them and thus improve the stereochemical results. Such changes may take the form of imposing a larger steric bias, by introducing chelation control or by a combination of both. The goal must be a highly ordered transition state which allows prediction of preferred orientations for bond formation. The intervention of several, less ordered transition state structures, each of which may afford a different stereochemical result, must be avoided.

The presence of a C_2 symmetry axis in a chiral auxiliary simplifies the analysis of orientation of attack on a transition state structure. In most cases, this symmetry element reduces the number of possible transition state structures by removing the difference in a steric effect on two faces of a planar system (e.g. an enolate) which

would be diastereotopic in a molecule possessing an auxiliary of lower symmetry.

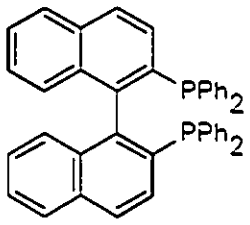
Enantiomerically pure compounds with C_2 symmetry, both monodentate and bidentate, have proven to be very efficient chiral auxiliaries in asymmetric syntheses and have been the subject of a recent review.[131] Some of the most useful bidentate auxiliaries include phosphorus based compounds[132] (Figure 74).

Figure 74: Phosphorus based auxiliaries



(2S,3S)-(-)-Chiraphos

(R,R)-(-)-DIOP



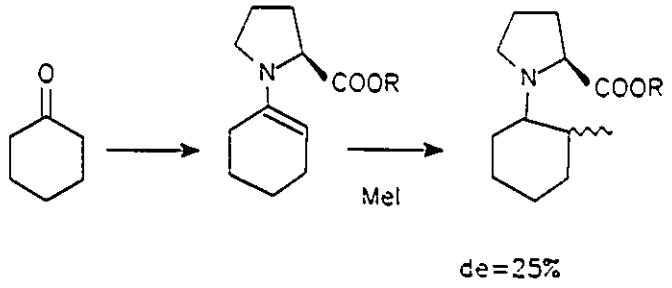
(S)-(-)-Binap

Although the area of phosphorus based auxiliaries has been very important in asymmetric syntheses, their use has concentrated on the catalytic, homogeneous reduction of alkenes and other reactions catalyzed by transition metals and this will not be discussed here. The two main types of C_2 auxiliaries which have been used most extensively in carbon-carbon bond forming reactions have been monodentate amine compounds and bidentate oxygen based auxiliaries. Parenthetically, it should be noted that the bidentate oxygen-based auxiliaries have also been the subject of a recent review.[133]

Nitrogen Based Auxiliaries

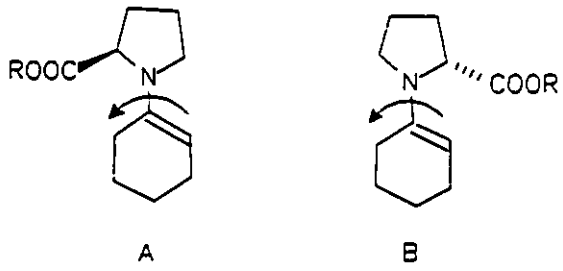
Whitesell[134] has been a seminal contributor to the field of monodentate C_2 symmetric auxiliaries. Yamada had reported[135] that alkylation of cyclohexanone enamines derived from various proline esters gave poor optical yields (10-30%) due to the presence of competing diastereomeric transition states (Figure 75).

Figure 75: Yamada's enamine alkylation



Whitesell recognized that the results of Yamada's alkylation were consistent with the participation of two sets of transition states differing by a simple rotation of the C-N bond (Figure 76).

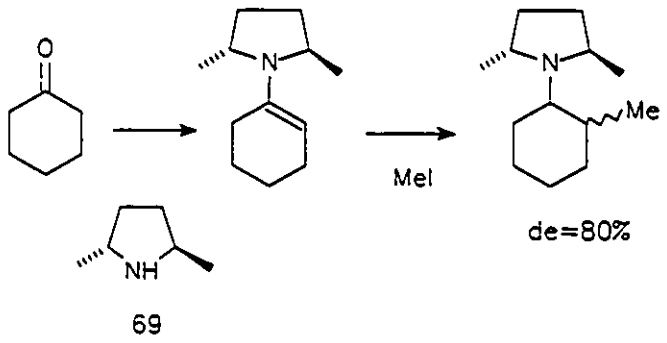
Figure 76: Two transition states



Of the four pathways of approach of the alkylating agent (both front and back of A and B), only the approach to the back face in B is blocked. By assuming that the

energies of the three remaining transition states would be nearly equivalent, the prediction of 34% de was calculated. Whitesell deduced that what was required was an amine with C_2 symmetry. He therefore introduced 2,5-dimethylpyrrolidine (69) as a chiral auxiliary to be used for the alkylation of cyclohexanone enamines (Figure 77). Utilization of this C_2 compound improved the diastereoselectivity of the alkylation reaction to 80% de. Clearly, the presence of the C_2 symmetrically placed substituents at carbons 3 and 5 on the pyrrolidine ring reduced the possible number of competing rotational conformations of the C-N bond and therefore reduced the number of competing diastereomeric transition state structures.

Figure 77: C_2 amine as auxiliary

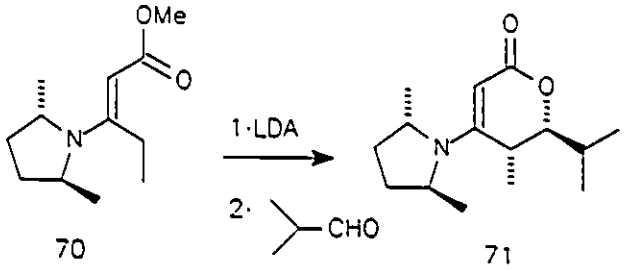


By using 2,5-dimethylpyrrolidine as an example, it should be noted at this point that, in the strictest sense, the C_2 symmetry element does not apply to monodentate amines. Nitrogen is sp^3 hybridized and does not have C_2 symmetry in the ground state. However the amines function as if C_2 symmetry were present since any atoms lying on the pseudo C_2 axis lack stereochemistry. This can also be explained by the fact that rapid inversion of the nitrogen atom would planarize the system and thus the

auxiliary functions as if a C_2 axis were present.

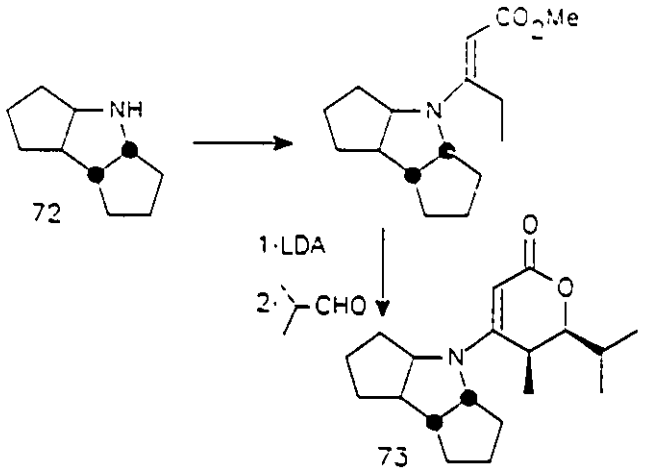
Pyrrolidine 69 has been employed successfully by others for asymmetric induction strategies. For example, Schlessinger[136,137] utilized 69 as a chiral auxiliary in the enantio- and erythro-selective aldol-lactonization of 70 with isobutyraldehyde to give 71 as a single enantiomeric product (Figure 78).

Figure 78: Selective aldol-lactonization



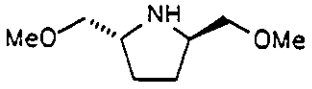
Wide application of 69 as a chiral auxiliary has been severly hampered by the lack of practical routes for its synthesis and by the fact that recovery and manipulations of the amine are made difficult due to its low boiling point[138] (bp 102 °C). In order to circumvent these shortcomings Whitesell[139] introduced a new C_2 chiral secondary amine (72) (Figure 79). The tricyclic amine 72 was prepared in the enantiomerically resolved form from simple starting materials and in a relatively small number of steps. Whitesell stated that 72 is unique among C_2 secondary amines in that a large thermodynamic preference exists for cis ring fusion in bicyclo[3.3.0]octane systems[140] which effectively prevents epimerization α to nitrogen. An application of 72 as a chiral auxiliary for asymmetric induction is illustrated in Figure 79.

Figure 79: New C_2 amine

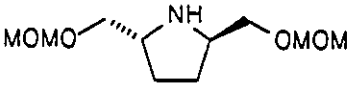


The intermediate 73 was obtained with a de of at least 95% and no other diastereomer could be detected by ^{13}C NMR.

Figure 80:
C_2 Pyrrolidines



74



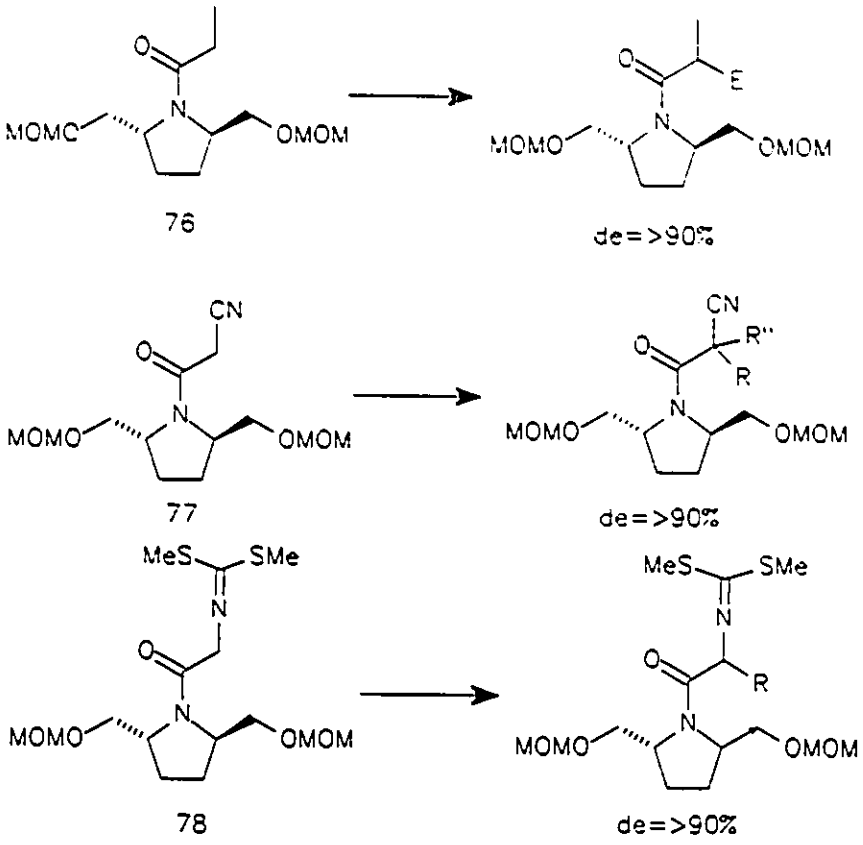
75

Many other C_2 amines have been prepared and employed as chiral auxiliaries. A number of groups have found efficient applications for trans-2,5-bis(methoxymethylene)pyrrolidine (74)[141] and trans-2,5-bis(methoxymethoxy-methyl)pyrrolidine (75)[142] and their enantiomers (Figure 80), all of which proceed with high degrees of asymmetric induction.

For example, Katsuki[143,144] reported that acylations and alkylations of propionamide 76 proceeded with high chemical yields and gave very high de's (>95%) (Figure 81). Katsuki also employed 75 as a chiral auxiliary in the asymmetric dialkylation of 77 (Figure 81).[145] He reported that the first alkylation of

77 proceeded with very low selectivity, presumably due to low *E/Z* ratios of the intermediate amide enolate. However, alkylation of the mixture of the monoalkylated amides proceeded smoothly and with high selectivity (de's=80-90%).

Figure 81: Uses of C_2 pyrrolidines

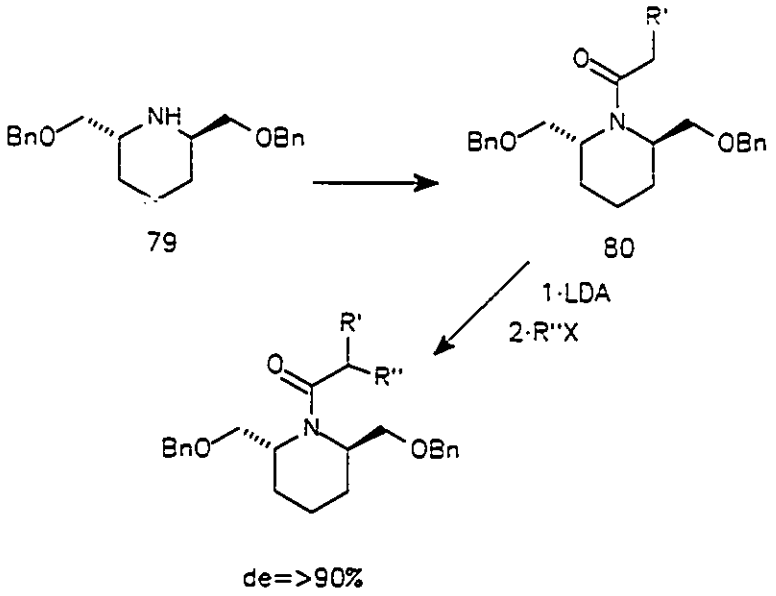


In some cases the diastereomers of the monoalkylated diastereomers were separated and alkylated separately and both diastereomers gave rise to the same major dialkylated product. Therefore the stereochemistry of the enolates derived from the monoalkylated products was presumed to be independent of the initial stereochemistry of the amide. Katsuki also used 75 as a chiral auxiliary in the preparation of α-amino acids also shown in Figure 81 (also noted in Chapter I, Introduction).[40,41] Amide 78

was alkylated smoothly with primary alkylating agents and gave only monoalkylated products with de's over 90%. Secondary alkylating agents could also be used but had to be transformed into their more reactive triflates in order to obtain satisfactory chemical yields. The corresponding α-amino acids were obtained by the hydrolysis of the imine and amide bonds.

Kurth[146] was the first to introduce piperidine 79 (and its enantiomer) and has since shown[147] that it can be used as a very efficient chiral auxiliary in the alkylation of propionamide 80 (Figure 82). Kurth points out that although C_2 symmetry in the pyrrolidine auxiliaries is obvious, his piperidine derivative manifests *functional* C_2 symmetry due to rapid chair interconversions.

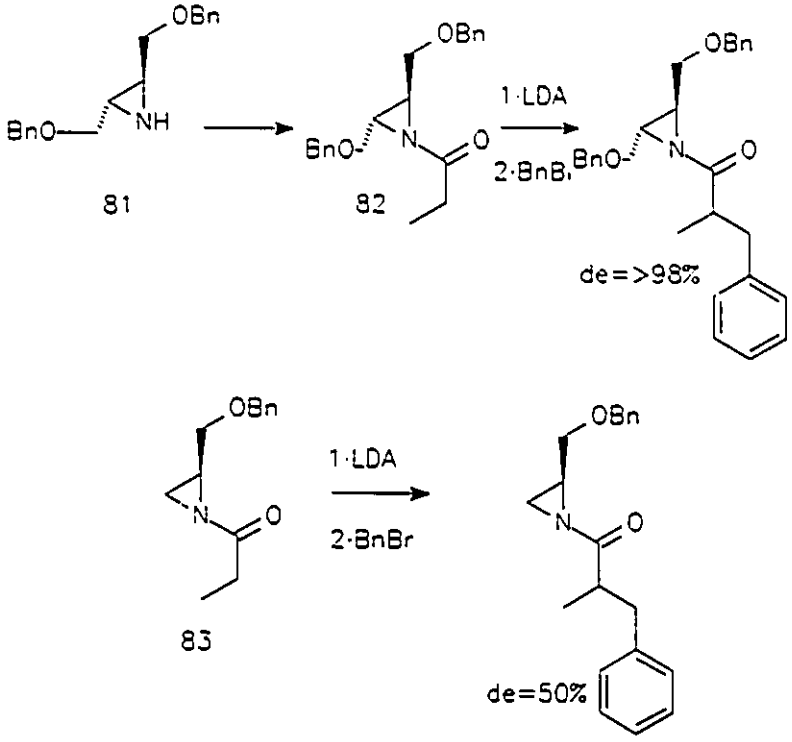
Figure 82: C_2 piperidine



Tanner[148] has introduced aziridine 81 and has not only shown that it functions as an efficient auxiliary in the alkylation of the corresponding propionamide (82), but

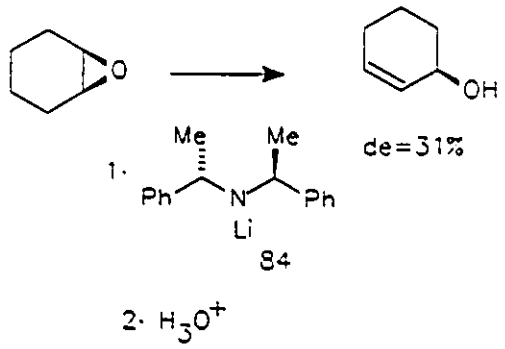
has also demonstated the importance of the C_2 symmetry element (Figure 83). Alkylation of 82 with benzyl bromide at low temperatures gave the benzylated product in high yield and with a diastereomeric ratio of >99:1 (98% de) whereas the alkylation of 83 with benzyl bromide gave a diastereomeric ratio of 75:25 (50% de) (Figure 83).

Figure 83: C_2 aziridine



Another interesting utilization of secondary C_2 amines has been in the enantioselective deprotonation and rearrangements of meso epoxides to chiral allylic alcohols. For example, Whitesell[149] has demonstrated that the enantioselective deprotonation and rearrangement of cyclohexene oxide with 84 gave optically active (*R*)-2-cyclohexen-1-ol (Figure 84).

Figure 84: C_2 lithium base

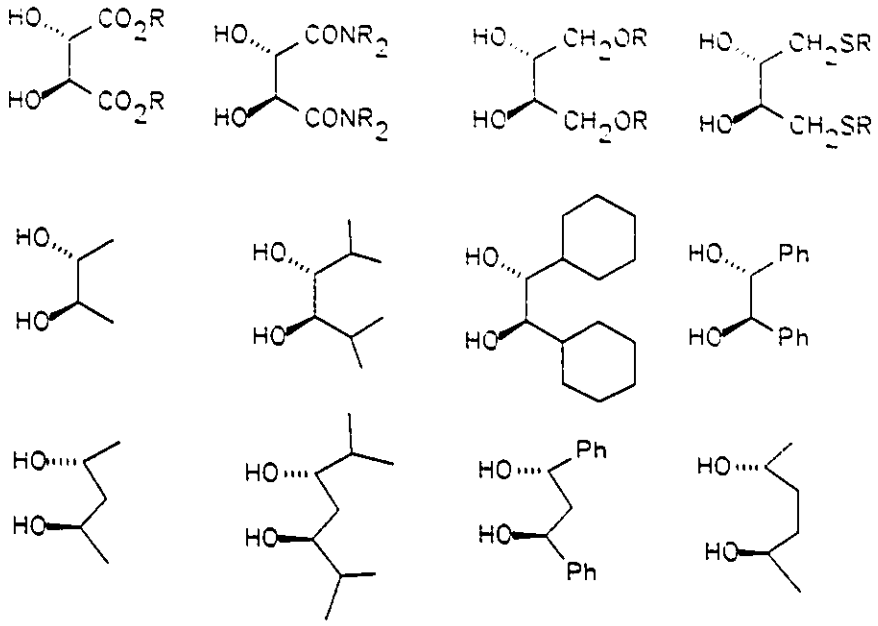


Oxygen Based C_2 Auxiliaries

During the past several years chiral acetals prepared from diols with C_2 symmetry have found increasing use in asymmetric carbon-carbon bond forming reactions. The preparation of a chiral acetal from a C_2 symmetric diol is useful since acetalization does not create a new chiral center and therefore only one acetal is formed. Chiral acetals are routinely prepared from many of the readily available diols (Figure 85). These acetals formed are frequently used in various types of reactions. Reactions which involve ring cleavage occur in the presence of strong Lewis acids[150-152] and these types of reaction will not be discussed here since, the chiral auxiliary is usually destroyed. Chiral acetals may also by used to control the stereoselectivity of a nearby prochiral center without ring cleavage and this will be discussed briefly since this allows the possibility of recycling the chiral auxiliary.

One of the first uses of a C_2 symmetric diol was the analysis of enantiomeric excesses of ketones by the formation of diastereomeric ketals[153] and also for the

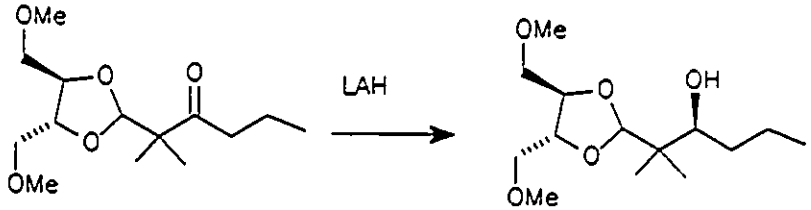
Figure 85: Chiral C_2 symmetric diols



resolution of racemic ketones.[154]

A simple example of the use of a chiral acetal in synthesis is shown in Figure 86. Reduction of the ketone which is β to the acetal auxiliary was reported to afford one diastereomer of the alcohol with 98% de.[155]

Figure 86: Asymmetric reduction



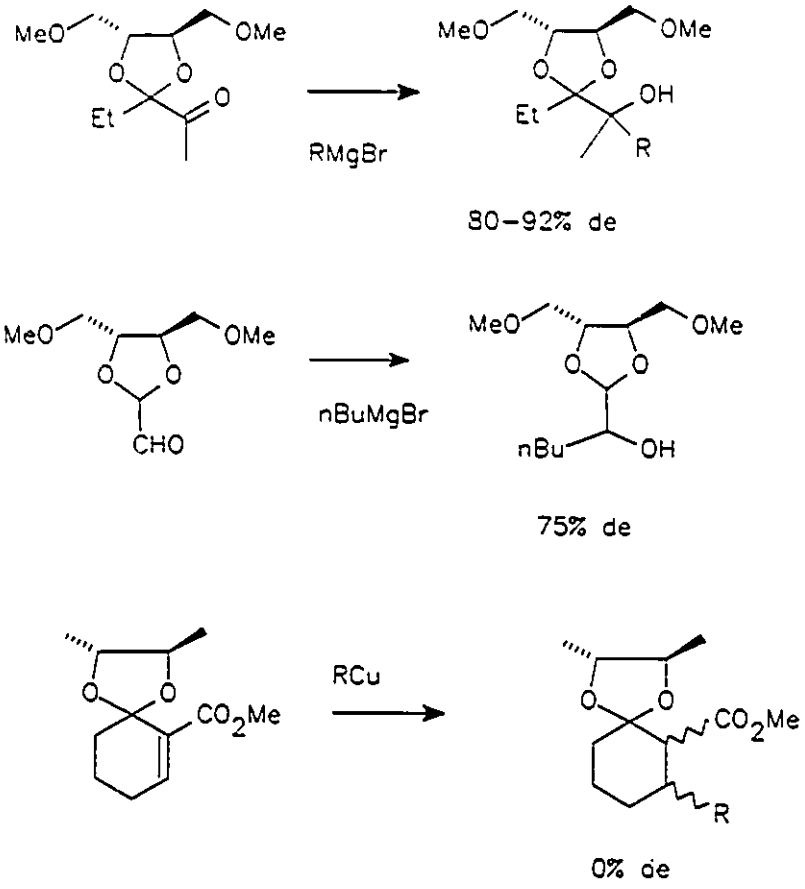
98% de

Similarily, the addition of Grignard reagents to α carbonyl groups in the examples

shown in Figure 87 have been reported to occur with 80-99% de.[156-158]

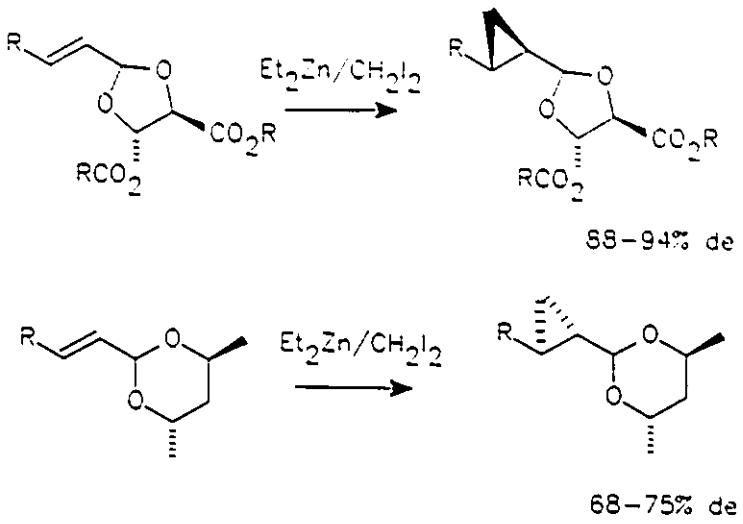
Several other groups[159,160] have found that additions to β carbon atoms have been rather inefficient, in most cases affording poor diastereoselectivities (Figure 87).

Figure 87: Addition to β-carbon



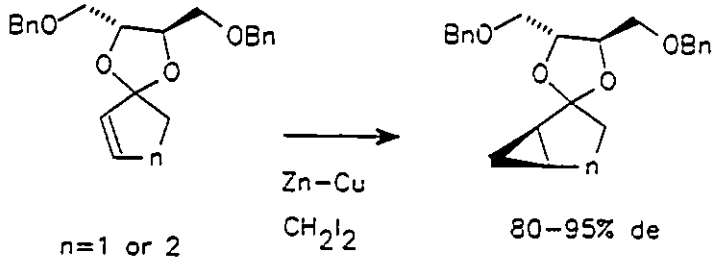
Yamamoto's group reported an asymmetric Simmons-Smith cyclopropanation reaction which employed various chiral enal acetals (Figure 88).[161,162] The reaction gave only modest selectivities and it was found that the choice of the chiral auxiliary was crucial, since the use of 2,4-pentanediol gave one diastereomer and the use of diethyl tartrate gave the opposite diastereomer (Figure 88).

Figure 88: Yamamoto's asymmetric cyclopropanation



Mash[163-165] showed that ketals derived from tartaric acid derivatives and cyclopentenones or cyclohexenones could be asymmetrically cyclopropanated with very high de's using slightly different conditions (Figure 89). Mash reported that Yamamoto's conditions gave inferior diastereoselection.

Figure 89: Mash's asymmetric cyclopropanation

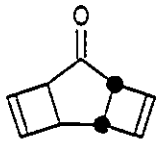


C_2 Symmetric Ketones

Our continuing interest in the alkylation of glycine derivatives has led us to consider how a C_2 symmetric chiral auxiliary might be used to control the stereochemical aspects of this alkylation process. In the previous chapter (Chapter 1) we focused on this alkylation reaction by employing various imines of *tert*-butyl glycinate derived from the readily available auxiliary, (*R*)-camphor. The advantages of using a C_2 ketone in this scenario are obvious. Primarily, the possibility of non-homogeneous imine stereochemistry is removed by using a C_2 ketone and this should make the stereochemical results more predictable. We also realized that by transforming a C_2 ketone into its corresponding alcohol derivative that a new chiral center would not be formed (note that the alcohol will not have C_2 symmetry) and that perhaps the resulting chiral alcohol may be of some use in preparing chiral esters of glycine which could be alkylated.

Very few C_2 symmetric ketones have been reported in the literature and fewer still are available in enantiomerically pure form. As a consequence, such ketones have not found wide application as chiral auxiliaries or as chiral reagents in asymmetric syntheses. Figure 90 illustrates some C_2 symmetric ketones which have been prepared but not resolved and Figure

Figure 90: Racemic C_2 ketones



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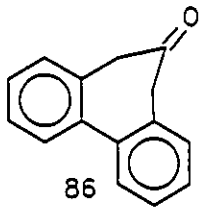
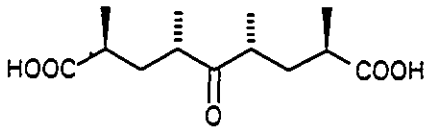


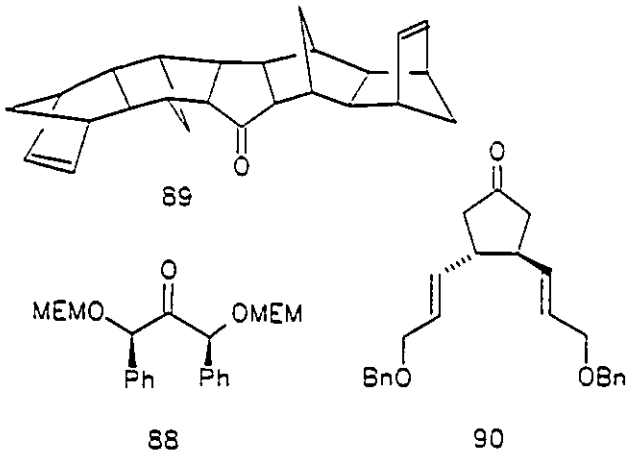
86



87

91 shows the only three C_2 symmetric ketones which have been reported to date to be available in the optically active form. None of the racemic ketones appear to be useful as possible chiral auxiliaries. For example, ketone 85 is reported[166] to be a labile material due to the highly strained *cis*-fused cyclobutene rings. Ketone 86[167] and 87[168] are also unlikely candidates as auxiliaries since epimerization is possible.

Figure 91: Optically active C_2 ketones



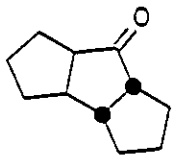
Enantiomerically pure ketone 88 was prepared by Braun[169] from a readily available chiral starting material, (*S*)-lactate.[170] The preparation however requires many steps and again racemization of 88 is possible under strongly acidic or basic conditions. Both of these facts restrict the utility of this ketone in any asymmetric scenario.

Ketones 89[171] and 90[172] (Figure 91) have also been prepared in the enantiomerically pure form. However, ketone 89 would not be an attractive candidate as a chiral auxiliary from both the spectroscopic and synthetic point of view and 90 appeared in the literature well after the project to be described was initiated.

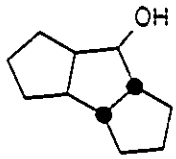
Examination of molecular models suggested to us that the C_2 symmetric tricyclic

ketone 91 and its corresponding alcohol derivative 92 might be effective as a chiral auxiliaries, especially in the alkylation of chiral glycine derivatives (Figure 92). Relative to homologs of 91 which possess either a central or two peripheral six membered rings, 91 has the advantage of avoiding ambiguous or undesirable ring fusions which could destroy the C_2 symmetry. As previously noted this is a result of the large thermodynamic preference for the cis ring fusion in bicyclo[3.3.0]octane systems.

Figure 92: Ketone 91, Alcohol 92



91



92

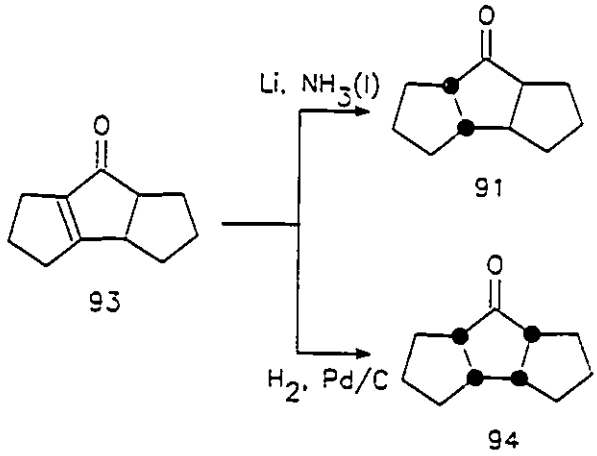
Finally, the rigid nature of the linear triquinane system should allow the simple evaluation of the stereochemical results in many asymmetric sequences. The following pages describe our approaches to the synthesis of 91 and 92 which have culminated in a short synthesis of racemic materials and an efficient synthesis of the resolved compounds.

Results and Discussion

Preparation of Racemic 91

After considering several alternatives, we selected compound 93 (Figure 93) as an excellent starting material for the synthesis of the C_2-symmetric ketone 91. The preparation of 93 in the racemic form had been previously reported by Eaton.[173] He showed that catalytic hydrogenation of 93 over palladium gave the meso (C_s) ketone (94) stereoselectively. A review[174] on the metal-ammonia reduction of conjugated ketones suggested to us that the metal-ammonia reduction of conjugated ketones leads to a preponderance of the thermodynamically more stable product. In our case, of the two possible (cis fused) ketones, 91 and 94 (Figure 93), ketone 91 is clearly the most stable due to steric effects.

Figure 93: Reduction of 93

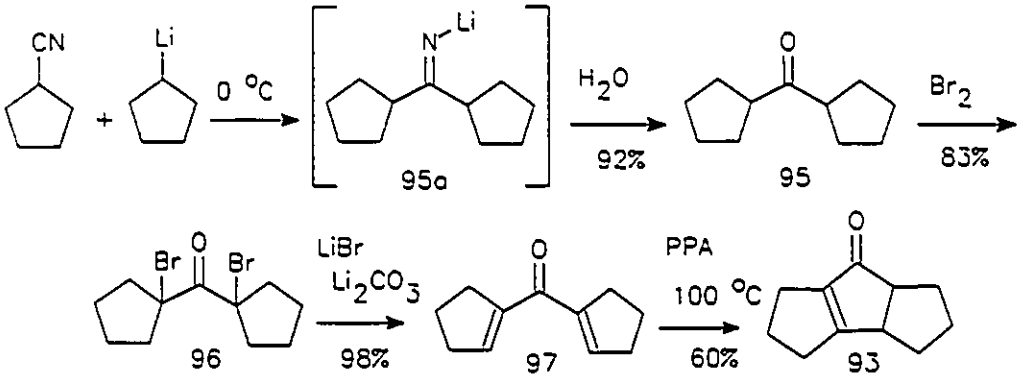


Therefore it would be expected that the metal-ammonia reduction of 93 should give the C_2 ketone in preference to the meso compound. Before attempting the metal-ammonia reduction of the tricyclic enone (93) we decided to repeat Eaton's work to

prepare an authentic sample of the meso ketone 94.

The preparation of enone 93 is shown in Figure 94. The initial Grignard reaction required the preparation of cyclopentyllithium since we found that the Grignard reaction of cyclopentylmagnesium bromide in ether with cyclopentylcarbonitrile gave poor yields (40%) of the desired product (95).

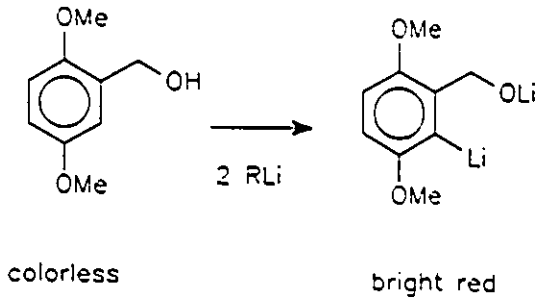
Figure 94: Preparation of 93



Although, it has been reported[175] that replacing the solvent (ether) with a benzene solution containing one equivalent of ether increased the yields of such additions, in this case it was not successful. The preparation of cyclopentyllithium was often troublesome. The use of Li metal containing 1% sodium metal was required to obtain modest yields of cyclopentyllithium. Only poor yields (20-30%) were obtained when 99.9% Li metal was used. The approximate molarity of cyclopentyllithium was determined by titrating a THF solution of 2,5-dimethoxybenzyl alcohol[176] at 0 °C with aliquots of the alkyllithium to a bright red endpoint. The development of the red color at the endpoint was reported[176] to be instantaneous and required less than 0.01 mmol equivalent of excess organolithium reagent to be visible. It has been shown[176]

that a second deprotonation of the alcohol (indicator) is responsible for the intense red color observed when the end point is reached (Figure 95). The deprotonation most likely occurs on the phenyl ring.

Figure 95: RLi titration



It is not clear why small amounts of sodium are required for the metal-halogen exchange reaction. However, early reports[177,178] note that the preparation of n-butyllithium from Li metal and n-butylchloride required the presence of high amounts (1-2%) of Na metal in the Li metal.

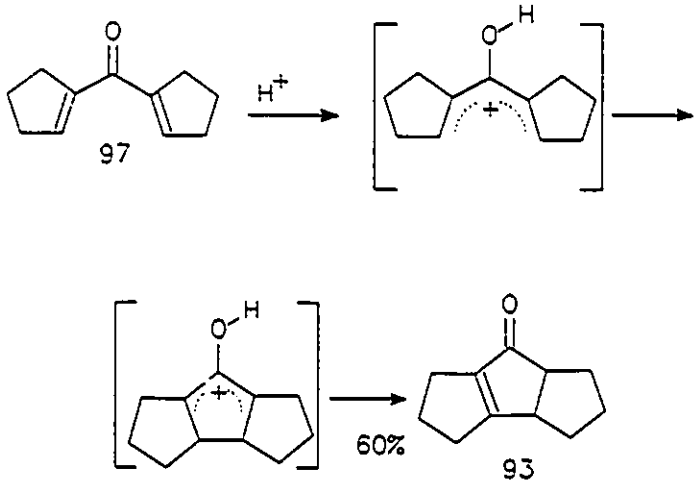
We also attempted to prepare cyclopentyllithium from Li metal and cyclopentyl bromide but found that only small amounts of cyclopentyllithium formed, presumably due to the competing Wurtz[179] coupling reaction.

The addition of cyclopentyllithium to cyclopentylcarbonitrile[180] in dry cyclohexane at 0 °C gave the ketimine salt (95a) which was immediately hydrolysed with H_2O to give 95 in excellent yield. Bromination of 95 with Br_2 in CCl_4 gave 1,1'-dibromodicyclopentyl ketone (96) (Figure 94) as a crystalline solid. Dehydrobromination was accomplished readily with a mixture of LiBr and Li_2CO_3 in DMF and gave large quantities of 1,1'-dicyclopentenyl ketone (97). Acid catalyzed cyclization was effected by stirring 97 in hot (100°C) polyphosphoric acid (PPA). After distillation, a modest yield of the desired tricyclic enone 93 was obtained.

We found that, as reported by Eaton[173], the cyclization of 97 with PPA gave 93

cleanly (with the double bond in the most thermodynamically stable position) without the intervention of any other double bond isomers. This cyclization is an example of an acid-catalyzed Nazarov[181] reaction (Figure 96). Eaton reported[173] that using methanesulfonic acid for the cyclization gave mixtures of 93 and double bond isomers and that using acids with nucleophilic counterions (X^-) to effect the cyclization led to derivatives of 91 with an X substituent α to the carbonyl group.

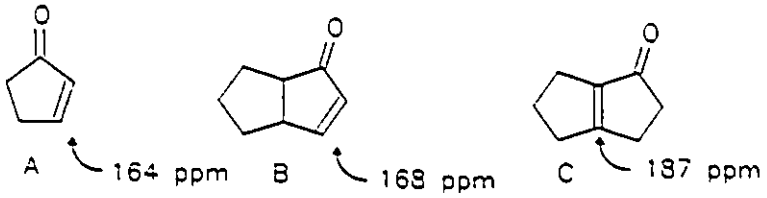
Figure 96: Nazarov reaction



The saturated ring junction of compound 93 was assigned by Eaton and ourselves to be cis since this configuration should be more thermodynamically stable than the trans fused compound. It has been reported[182] that a similar compound, *cis*-bicyclo[3.3.0]octan-1-one is 6 kcal/mol more stable than the *trans*-fused isomer. The ^{13}C NMR of 93 is worth noting. The β-carbon resonates at δ 189 ppm. This is at particularly low field, even for the β-carbon of a conjugated ketone. Examples of typical shifts are shown in Figure 97. The β-carbon of 2-cyclopentenone (A) resonates at δ 164.2 ppm[183] and the related compound, *cis*-bicyclo[3.3.0]octa-3-en-2-

one (B) the β carbon resonates at δ 168 ppm[184] (Figure 97). Interestingly, the chemical shift of the β-carbon atom of C (bicyclo[3.3.0]octa-1-en-2-one) which lacks a third 5-membered ring resonates at δ 187 ppm[184] (Figure 97). The very low field chemical shift values of the β-carbon atoms in C and in 93 indicate that there is considerable strain in these systems.

Figure 97: ^{13}C NMR of enones

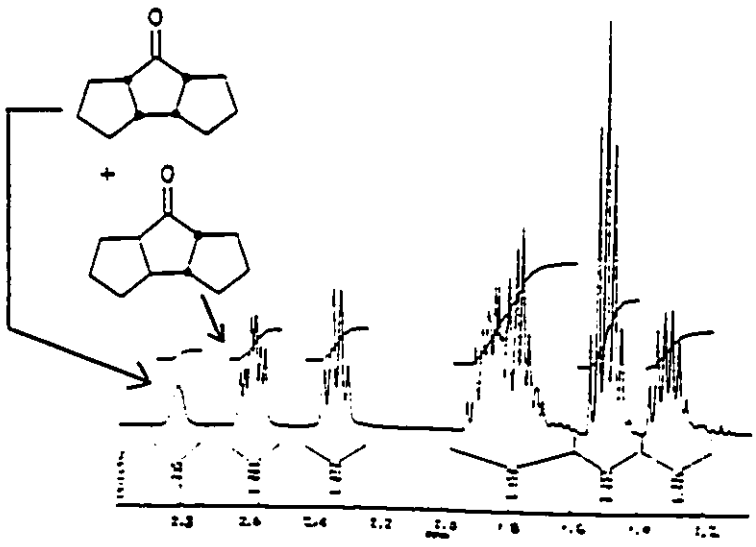


Eaton[173] showed that the catalytic hydrogenation of 93 gave *cis,syn,cis*-tricyclo[6.3.0.0^{3,7}]undecan-2-one (94) stereoselectively. He based his structural assignment on two facts. The proton-decoupled ^{13}C NMR of 94 contained only 6 resonance lines. This required that 94 have C_2 or C_s symmetry (ie. both ring fusions had to be either cis or trans). Secondly it was found that the ketal carbon atoms of the ethylene ketal[185] appeared as two separated carbon resonances in the proton-decoupled ^{13}C NMR. This indicated that the two ketal carbons are in nonequivalent chemical environments. This eliminated the isomer with C_2 symmetry and left only the *cis,syn,cis* or the *trans,syn,trans* isomers as possibilities. Since it has been previously noted that the latter is energetically less stable, the *cis,syn,cis* isomer (94) was assigned.

In our hands the catalytic hydrogenation of 93 over palladium gave two

compounds in a 9:1 ratio (as evidenced by the proton and carbon NMR). The major product was identified as 94 (the meso ketone) in full agreement with Eaton's assignment. However, since separation of the two compounds was not possible by GC or TLC techniques and since the IR spectrum of the mixture indicated that the second compound was not the alcohol derivative of 94, the minor compound (which also had only 6 resonance lines in ^{13}C NMR, and was a ketone) was tentatively assigned as the C_2 isomer (91). Verification of this assignment was made by the Li/NH_3 reduction of enone 93. Reduction in this manner furnished a 1:9 ratio of the same two ketones (94 and 91 respectively) (Figure 93, NMR in Figure 98).

Figure 98: NMR of Li/NH_3 reduction products

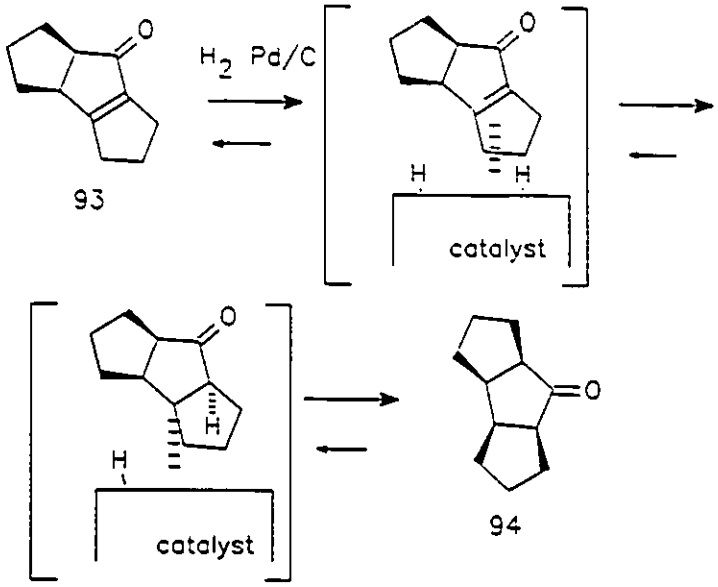


Again, although the two isomers (91 and 94) could not be separated it was apparent from the ^{13}C NMR of the ethylene ketal (of the mixture) that the major

isomer (91), which showed only one carbon resonance (δ 64.6 ppm) for the two ketal carbons, was the C_2 isomer and the minor product was the C_s isomer (94). The assignment made by Eaton[173] for the catalytic hydrogenation product of 93 and our assignment made for the major product derived from the metal-ammonia reduction of 93 follows reasonably from their synthesis.

Although the exact mechanism for heterogeneous catalytic hydrogenation of double bonds is still speculative, an accepted mechanism[186] is shown in Figure 99.

Figure 99: Catalytic Hydrogenation of 93



The olefin (93) is adsorbed onto the surface of the catalyst which also has adsorbed hydrogen atoms on it. For steric reasons the absorption of the olefin takes place with its less hindered side attached to the catalyst surface. The second step is the delivery of a hydrogen atom to the olefin forming a "half hydrogenated species". Addition of a second hydrogen atom completes the reduction and frees the olefin from the catalyst

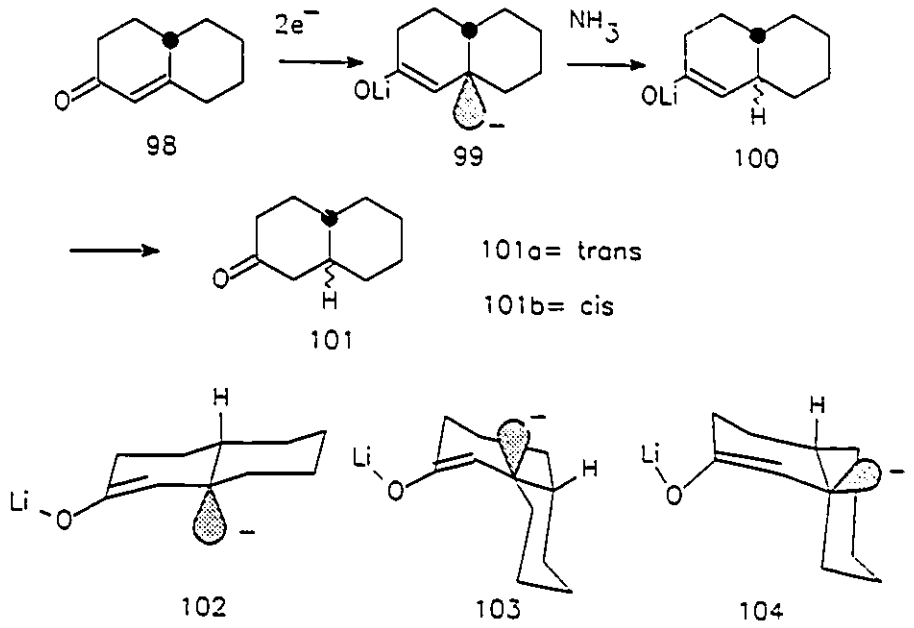
surface. This simplified mechanism clearly justifies Eaton's[173] (and our) results for the catalytic hydrogenation of 93 (Figure 99).

As previously noted, a comprehensive review[174] of dissolving metal reductions of conjugated ketones indicated that such reductions usually takes place to give a preponderance of the more stable isomer even though reversible protonation of the β-carbon atom is unlikely and steric hinderance in the protonation step is negligible. Due to these facts the rationalization of the stereochemical results of metal-ammonia reductions are often difficult.

The mechanism[174] of the chemical reduction of enones with metals (Li, Na) in liquid ammonia can be described as shown in Figure 100. The substrate 98 receives two electrons from the metal to form enolate dianion 99. The β-carbon of 99 is extremely basic and can accept a proton from ammonia to form the enolate salt 100 which is transformed into ketone 101 on addition of a proton source. In the octalone-series of type 98 the resulting enolate dianion can adopt three half-chair conformations 102, 103, 104. Only conformations 102 and 103 need be examined since these have the β-carbanion electron pair parallel to the π-orbital of the enolate system thus allowing delocalization. In this simple case the product resulting from the protonation of 102 from the bottom face would give the *trans* fused bicyclic ketone 101a. Protonation of 103 from the top face would give 101b, the *cis* fused product. Analysis[187] of the non-bonded interactions of the corresponding enolates derived from 101a and 101b indicated that the former is only 1 kcal/mol more stable than the latter. This corresponds to a 80:20 ratio of ketones 101a to 101b. However, it has been

reported[187] that metal-ammonia reduction of 98 gave 101a and 101b in a 99:1 ratio. This result shows that many other factors (solvation, charge repulsion) must be involved which influence the equilibrium in favor of enolate dianion 102 in the metal-ammonia reduction of 98.

Figure 100: Mechanism of Li/NH_3 reduction

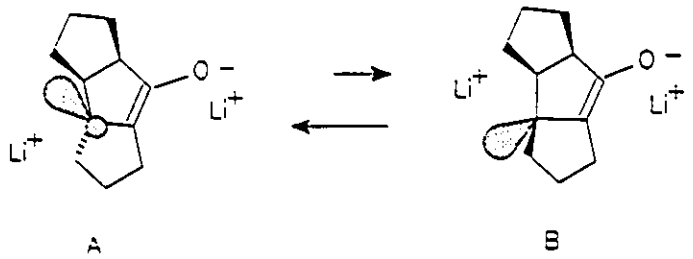


In our case, stereoelectronic or steric arguments do not adequately explain why protonation of the β-carbon occurs *syn* to the already established cyclopentane ring (Figure 101) but the experimental evidence is clear. The more stable ketone 91 is formed in large (90% of reaction mixture) excess. This observation indicates that the equilibrium of enolate dianion A (Figure 101) and enolate dianion B lies in favour of dianion A.

In order for 91 to be useful as a chiral auxiliary, it must be available in the

resolved form. To date we have not been able to achieve this resolution on a synthetically useful scale. Our attempts at this resolution are documented next.

Figure 101: Li/NH_3 reduction of 93



A B

Attempted Resolution of 91

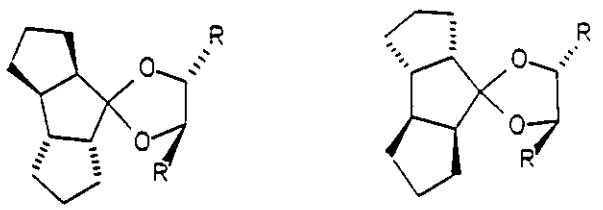
As noted in Chapter 1, diastereomeric relationships provide the basis on which chemical and physical separations of compounds can occur. Resolution of enantiomers is frequently effected by converting a mixture of enantiomers to a mixture of diastereomers by the reaction of the enantiomers with the pure enantiomer of a second reagent (the resolving agent, CDA). Since the resulting products are diastereomers they possess different physical and chemical properties and may be separated by various physical means. After separation is carried out the diastereomers are reconverted to the pure enantiomers by reversing the initial reaction with the resolving agent.

Recall that a second and often useful method for the separation of enantiomers depends on the difference in the rates of reaction between the enantiomers and the resolving agent. This process is called **kinetic** resolution. The transition state energies for the reaction of the two enantiomers with the optically pure resolving

agent are different, because they are diastereomeric. If the energy difference is large enough, the formation of one diastereomer will occur at a much faster rate than the other diastereomer. An ideal situation would exist if the reaction stopped at 50% completion and only one of the enantiomers had reacted with the resolving agent.

We attempted to use both of these methods to resolve 91. Our first effort involved its attempted ketalization with (*R*,*R*)-(+)-hydrobenzoin[188] or (2*R*,3*R*)-(-)-butanediol.[188] By examining molecular models of the diastereomeric ketals that would be formed, it appeared that the reaction of the chiral diol with a mismatched ketone (A) (Figure 102) should be slower than the reaction of the diol with a matched ketone (B).

Figure 102: Diastereomeric ketals



A B

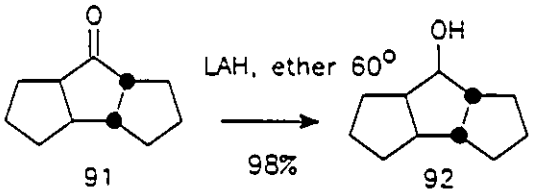
It was expected that a severe steric interaction between the R groups on the diol and the cyclopentane rings in the mismatched pair (A) would inhibit the formation of ketal A, thus making a kinetic resolution possible. However, the point is moot since we found that 91 would only react with ethylene glycol to give the ethylene ketal (105) and not with the chiral diols chosen. The steric influence of the R-groups on the chiral diols was apparently too great to allow the ketalization of 91.

Since a kinetic resolution of 91 by selective ketalization did not seem possible we decided to prepare diastereomeric derivatives of alcohol 92 (Figure 103) and separate the diastereomers. Simple cleavage of the resolving agent would recover 92 and

oxidization would give optically pure 91.

The C_2 ketone was reduced to give 92 with excess LAH in refluxing ether. We found that the reduction did not occur at 0°C and only very slowly at room temperature. This result indicated that the carbonyl group of 91 was extremely hindered (compare LAH reduction of camphor[189]).

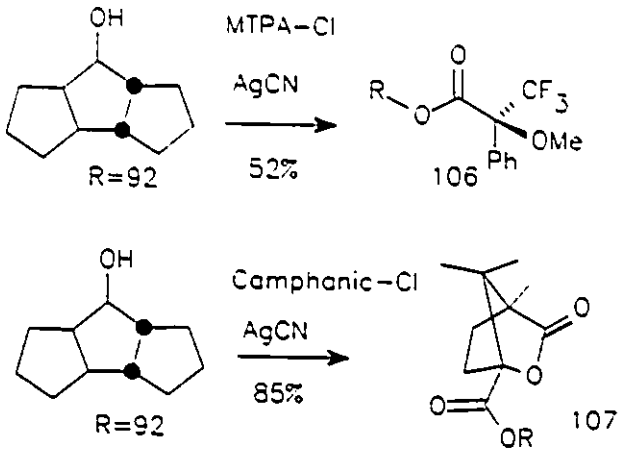
Figure 103: LAH reduction of 91



In order to prepare diastereomeric derivatives of 92 we required a chiral derivatizing agent. A good chiral derivatizing agent should be readily available, possess a state of high degree optical purity, and be easily removed from the derivatized compound. We chose (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl[61]), (1*R*)-(-)-camphanic acid chloride and (*R*)-(-)-1-(1-naphthyl)ethyl isocyanate as chiral derivatizing agents. All are commercially available in high optical purity and have been often used[190,191] to resolve mixtures of enantiomeric alcohols. Preparation of the diastereomeric esters of 92 proved to be difficult at first. It was found that the reaction of 92 with MTPA-Cl or the camphanic acid chloride would not occur under normal conditions (Et_3N, CH_2Cl_2). Even heating the reagents overnight in benzene did not provide the diastereomeric esters as was evidenced by TLC and GC. Esterification was only possible when 1 equivalent of AgCN was added to the reaction mixture (alcohol, CDA, AgCN, benzene, reflux).

This procedure provided the chiral esters (106, oil and 107, solid, Figure 104) in good yields.

Figure 104: Diastereomeric esters

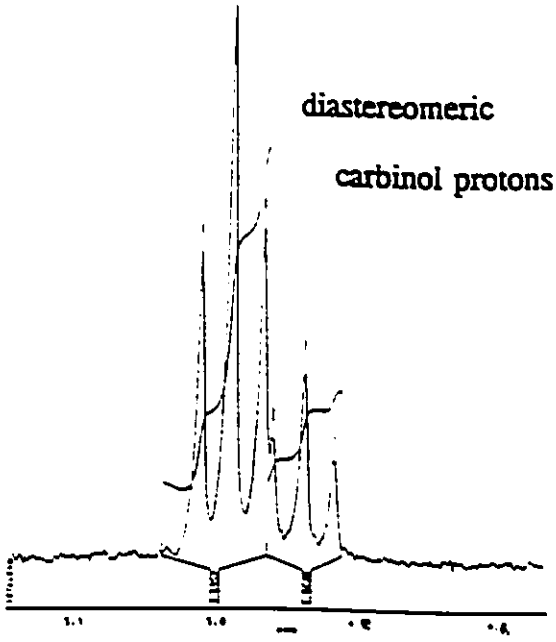


The addition of AgCN to promote rapid esterification has been used by others[192] in the preparation of highly hindered esters from acid chlorides and alcohols. It is possible that the reaction proceeds by electrophilic catalysis by silver ion on the acid chloride. The intermediacy of an acyl cyanide however must be excluded since acyl cyanides have been reported[193] to be less reactive than acyl chlorides. The apparent lack of reactivity of 92 with the acid chlorides under "normal" conditions indicated that the hydroxyl group was *very* hindered. Separation of the diastereomeric esters (106 and 107) was not possible using thin layer chromatography, column chromatography or gas chromatography.

As previously noted, of the two esters only 107 was a solid compound. Recrystallization of 107 from ethanol improved the de from 0% to 95% as evidenced by integration of the diastereomeric carbinol protons (Figure 105). Unfortunately,

large material losses (7% recovered) and the expense of the resolving agent made this resolution method inadequate for larger scale use. In spite of this, the (-)-camphanic acid chloride proved to be an excellent chiral derivatizing agent, since the ^{1}H NMR of ester 107 can be used to calculate the optical purity of alcohol 92.

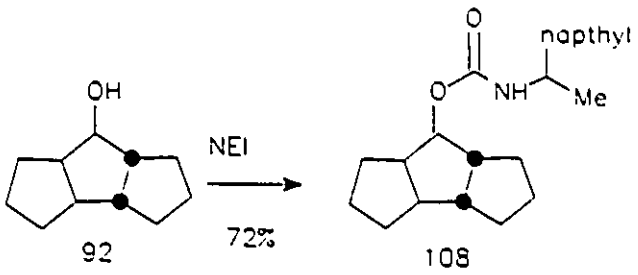
Figure 105: ^{1}H NMR of camphanic ester



Finally, we prepared carbamate 108, by refluxing 92 with (*R*)-(-)-1-(1-naphthyl)ethyl isocyanate in benzene. TLC analysis showed that all of the alcohol was consumed after 12 hours and chromatography (one spot) gave a high yield of the corresponding carbamate as a white solid (Figure 106). Diastereomeric carbamates of racemic alcohols have been reported to be separated using column chromatography.[194] However, in this instance the diastereomers of 108 were inseparable. Attempts to separate the diastereomers by recrystallization also failed to yield either diastereomer

in large excess. It was now apparent that physical separations of diastereomeric derivatives of 92 would be difficult on a laboratory scale. This failure lead us to proceed with an absolute asymmetric synthesis of 91.

Figure 106: Diastereomeric carbamate

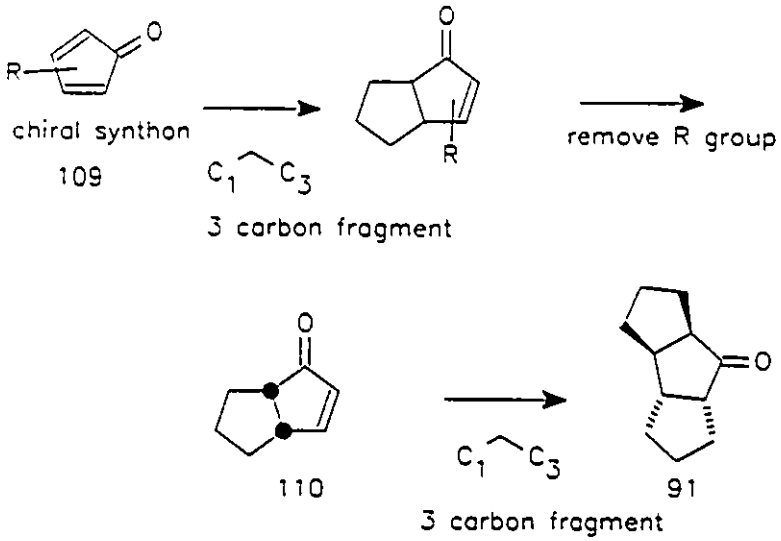


Asymmetric Synthesis of 91

Compound 91 and other compounds structurally related to it are simple examples of linear triquinanes. Many reviews[195,196] exist in the literature on the synthesis of optically pure triquinanes (mostly natural products). Unfortunately, in our case the lack of substitution in 91 makes the excellent synthetic methodology which has been developed inapplicable here.

We envisioned that the synthetic plan shown in Figure 107 could provide the C_2 ketone in a stereoselective manner. It was apparent that to prepare 91 in an optically pure state would require a chiral synthon (109) onto which a cyclopentane ring would be stereoselectively annulated. This would be carried out by the stereoselective addition of a 3-carbon fragment to 109 followed by cyclization. The removal of the directing group **R** would provide enantiomerically pure 110, a known compound which has not been previously prepared in optically pure form. The steric

Figure 107: Synthetic plan

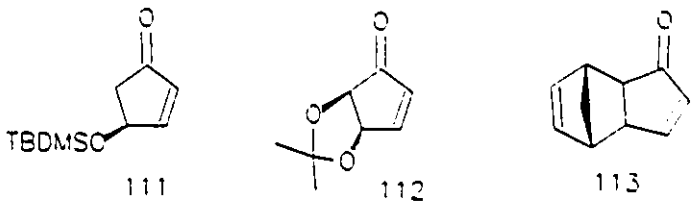


influence of the existing cyclopentane ring should direct the addition of a second 3-carbon fragment, to the opposite face of 110. Cyclization would complete the asymmetric synthesis of 91.

We located three compounds (111, 112, and 113, Figure 108) in the literature which have been prepared in optically pure form, on a relatively large scale and which might be used as a chiral synthon in the asymmetric synthesis of 91.

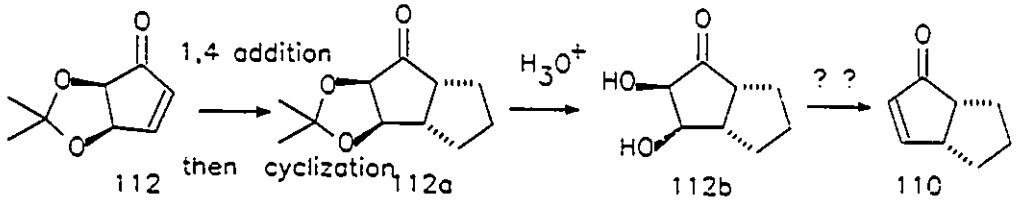
Compound 111 has been prepared and resolved by many groups using various strategies and has been used extensively in prostaglandin synthesis.[197-199] Reports in the literature[200] also indicate that compound 111 has been prepared in the optically pure form from (2*S*,3*S*)-diethyl tartrate. Although the 1,4 addition of cuprates to 111 has been shown[201] to proceed stereospecifically to give a *trans*-2,5-disubstituted cyclopentanone, the lengthy preparation of this chiral cyclopentenone using any of the published methods, made this a rather unattractive starting material.

Figure 108: Possible chiral synthons



Compound 112 is available in optically pure form from D-mannose using the method described by Borchardt.[202] Precedent[203] exists which shows that the 1,4 addition of an appropriate three carbon fragment to the enone would occur *trans* to the acetonide functionality and that cyclization to 112a should be uneventful (Figure 109). However, after the removal of the acetonide protecting group we questioned the ease of transforming 112b into 110. This left 113 as a potential starting material.

Figure 109: Transformations of 12



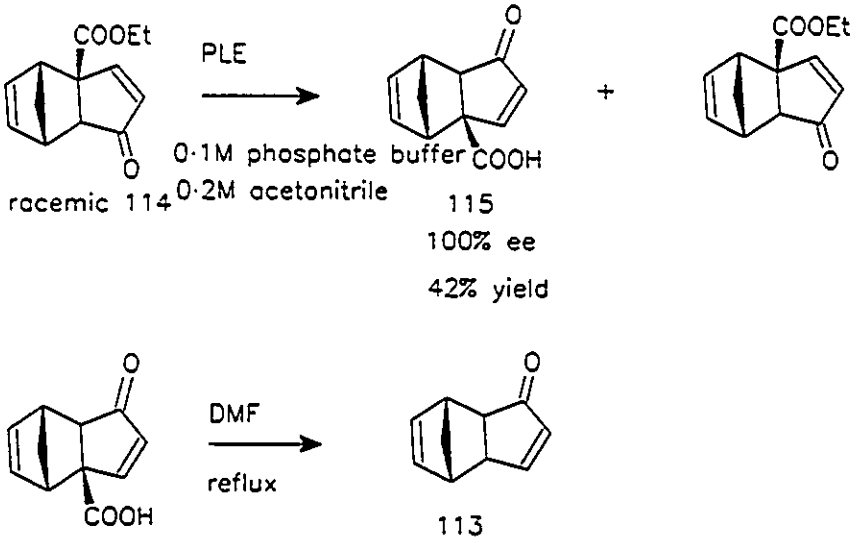
The use of enzymes as catalysts for the production of chiral synthons has been well documented.[204-206] Enzymes can be classified into six groups based on the reaction they catalyze:

1. Oxidoreductase (oxidation-reduction reactions)
2. Transferase (transfer of functional groups)
3. Hydrolase (hydrolysis reactions)
4. Lyase (addition to double bonds or the reverse)
5. Isomerase (isomerization reaction)
6. Ligase (formation of bonds coupled with pyrophosphate bond cleavage of ATP)

Although enzymes can effect a multitude of different reactions, most organic chemists have been lead to believe that enzymes only work in aqueous solutions. Recent reviews[204,205] have shown that although water is necessary for an enzyme to act efficiently, it is possible to carry out enzymatic catalysed reactions in "nearly anhydrous" organic media (monophasic) or in aqueous media containing an organic cosolvent (biphasic).

Pig Liver Esterase (PLE) has emerged as a hydrolytic enzyme which accepts a wide variety of substrates and can be used in the presence of organic cosolvents but still exibits high stereospecificity.[204-206] The preparation and PLE catalyzed kinetic resolution of 114 to (-)-115 and the decarboxylation of (-)-115 to give the chiral synthon (+)-113 has been reported[207-209] (Figure 110).

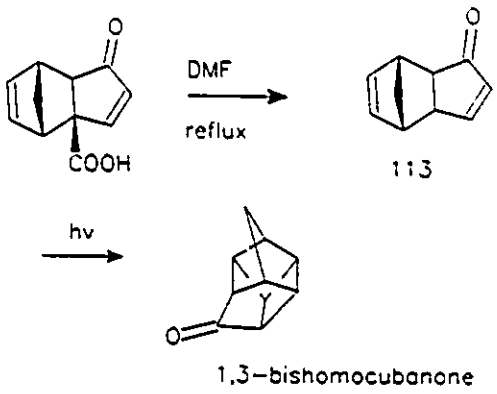
Figure 110: PLE resolution of 114



The absolute configuration of (-)-115 (and therefore (+)-113) was determined by Zwanenburg[208] by transforming (-)-115 into 1,3-bishomocubanone. It was found that

the rotation obtained for 1,3-bishomocubanone prepared from (-)-115 was $[\alpha]_D$ +11°, which was the same as that reported previously reported for (+)-bishomocubanone of known absolute configuration (1*R*,2*R*,3*S*,4*R*,5*R*,7*S*,8*S*,9*S*)(Figure 111).[210] The authors stated that this indicated that the optical purity of (-)-acid 115 obtained from the PLE catalyzed hydrolysis was 100% ee and that no racemization had occured during the decarboxylation step. It followed that the absolute configuration of (-)-115 was 1*R*,2*S*,6*R*,7*S*.

Figure 111: Absolute configuration of 115



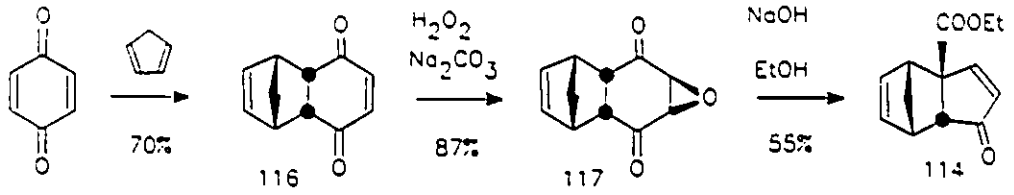
Since (+)-113 has been reported to be available in relatively few steps, from readily available starting materials and in optically pure form, we chose this compound as the starting material for the asymmetric synthesis of 91.

Synthesis of (+)-113

The ester 114 which was required for the enzyme catalyzed resolution was prepared by adapting literature procedures as shown in Figure 112.

The Diels-Alder reaction between cyclopentadiene and p-benzoquinone was carried out as described by Marchand[211] and gave the *endo*-adduct 116 in over 70%

Figure 112: Preparation of 114

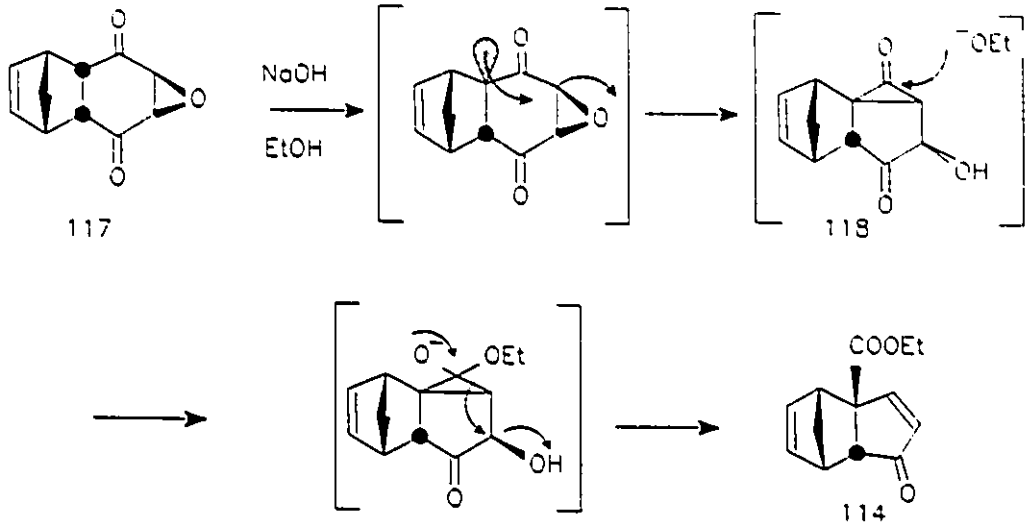


yield. Selective epoxidation of 116 was carried out according to Alder[212] by treating 116 with a basic solution of hydrogen peroxide. The reaction gave a high yield of the crystalline *exo*-epoxide 117. ^1H NMR and ^{13}C NMR ensured that only one diastereomer was present. Reaction of 117 with a small amount of NaOH in ethanol as described by Herz[213] provided 114 in 40-55% yield.

The rearrangement of 117 to 114 is thought to proceed as shown in Figure 113. Displacement of the oxirane ring by the C-1a (or C-4a) enolate occurs stereoselectively in an *anti* fashion to give the intermediate cyclopropanone, 118. Attack on the carbonyl group of 117 by ethoxide, followed by collapse of the cyclopropane ring and ejection of a hydroxyl group yields 114. This is an example of a modified Favorskii[214] rearrangement.

As noted above, the resolution of 114 (to give (-)-115)had been previously published.[208] However, a detailed description of the procedures for the selective pig liver esterase (PLE) hydrolysis of 114 did not appear until our project was well underway.[215] Zwanenburg[208] reported that a 40% yield (based on 50% maximum yield) of the resolved acid (-)-115 could be obtained with 100% ee using PLE and the conditions shown in Figure 110. He also reported that the addition of acetonitrile as a cosolvent was necessary to achieve high optical yields of 115 whereas the use of

Figure 113: Mechanism for formation of 114



acetone as a cosolvent resulted in an inferior enantiomeric excess.

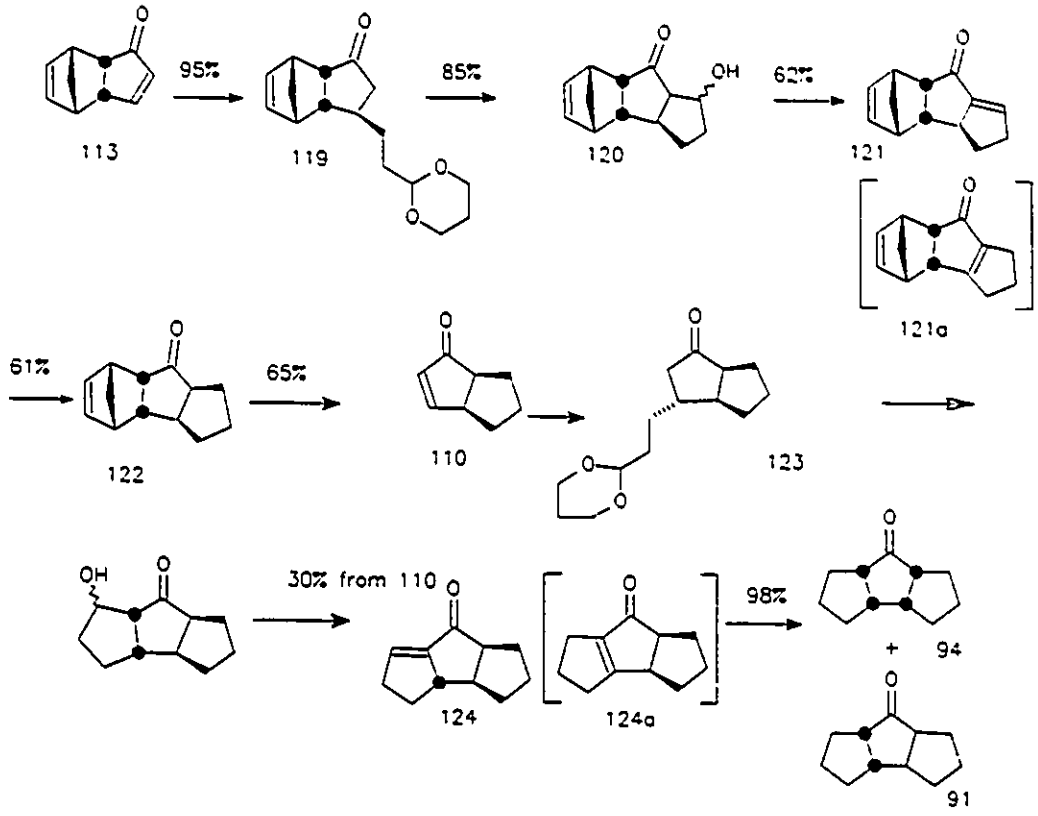
We carried out the PLE hydrolysis by stirring the racemic ester 114 vigorously in a solution of 0.1 M potassium phosphate buffer/0.2 M acetonitrile for 12 hours. The aqueous conditions made it difficult to monitor the extent of the reaction by either GC or TLC. Extraction with ethyl acetate gave optically active ester 114 and provided carboxylic acid (-)-115 in 36% yield (based on 50% maximum yield). The optical rotation of (-)-115 was found to be $[\alpha]_D$ -85° which was slightly higher than that reported by Zwanenburg ($[\alpha]_D$ -83°).[208] This suggested that we had obtained (-)-115 with very high optical purity. Decarboxylation of(-)-115 to (+)-113 was carried out by refluxing the vinylic carboxylic acid in DMF. The optical rotation we observed for (+)-113 obtained directly from the decarboxylation reaction was $[\alpha]_D$ +128°, whereas one recrystallization from hexane provided a higher melting material with $[\alpha]_D$ +139°. It should be noted that although the optical rotation reported for (-)-115

appears to be consistent throughout the literature[208,216] the optical rotations reported for (+)-113 vary considerably ($[\alpha]_D$ +141.6°[208], +150°[215], +158°[216]). It has been shown[215] that the source of this discrepency lies in the racemization of (-)-115 during the decarboxylation step, presumably via a reversible Diels-Alder reaction. The authors[215] stated that subjecting (+)-113 to the decarboxylation conditions did not result in any racemization, therefore they assumed that only carboxylic acid 115 was undergoing the cycloreversion reaction.

Synthesis of (+)-91 and (+)-92 from (+)-113

Two routes (Figures 114 and 116) from (+)-113 to optically enriched 91 and 92 have been successfully completed.

Figure 114: Initial route to optically active 91



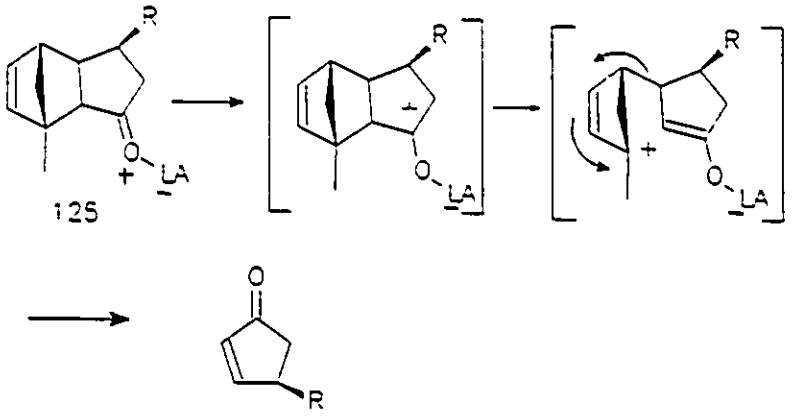
Addition of the cuprate derived from the propylene ketal of 3-bromopropanal[217] to enone (+)-113 afforded 119 (Figure 114). We chose to use the Grignard reagent derived from the propylene acetal of 3-bromopropanal rather than the ethylene ketal since the former was reported to be easier to prepare and more stable.[218] The ^{1}H NMR and ^{13}C NMR of 119 showed the presence of only one diastereomer which was

assigned the stereochemistry shown (Figure 114), since nucleophilic additions to (+)-113 are known[219] to occur in a stereoselective manner to the β-face of the enone. This is not surprising since molecular models indicate that the α-face is very hindered. Hydrolysis of 119 with 1% HCl in 90% aqueous acetone afforded the aldol product 120 as a 5:1 mixture of epimers at the carbinol carbon as evidenced by NMR. Dehydration of 120 was not spontaneous under the aldol conditions, and it was found that 120 could be best dehydrated to enone 121 by treatment of the mesylate of 120a with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). It was important to avoid isomerization of 121 to 121a as the intervention of this material would effectively negate the resolution of (-)-114. The proton NMR of 121 showed the presence of three olefinic signals and the DEPT-135 edited ^{13}C NMR confirmed the assignment of 121. Selective reduction of 121 to ketone 122 was carried out by using Li in liquid ammonia. The IR of the crude reduction product showed the presence of an alcoholic impurity which was assumed to be the product of over reduction and therefore the crude product was treated with PCC before chromatography.

The use of flash-vacuum pyrolysis (FVP) to effect the thermal reversal of Diels-Alder adducts closely allied to 122 have been reported.[220,221] However, the requisite FVP-apparatus was not available to us. Cycloreversion of compounds related to 122 has been reported by Marchand[222] to proceed in the presence of $BF_3 \cdot OEt_2$. In our hands this method was unsuccessful. No identifiable products could be isolated from the reaction mixture. Fortunately, Grieco reported[223] that using $EtAlCl_2$ as the Lewis acid in the presence of maleic anhydride for the reverse Diels-Alder reaction of

norbornene derivatives was mild and gave high yields of cyclopentenones. The reaction of 122 with $EtAlCl_2$ in the presence of maleic anhydride in refluxing 1,2-dichloroethane afforded 110 in excellent yield. The reaction may proceed by initial formation of a Lewis acid complex followed by a (concerted?) fragmentation of the strained σ-bond (Figure 115) to give an allylic carbocation. Further fragmentation occurs to give the observed products.

Figure 115: Cycloreversion reaction



This reaction mechanism is supported by the fact that the presence of a 1-methyl group in 125 has been reported[222] to facilitate the Lewis acid catalyzed cycloreversion.

The physical and spectroscopic characteristics of 110 were in full agreement with those reported in the literature[224] for the racemic compound.

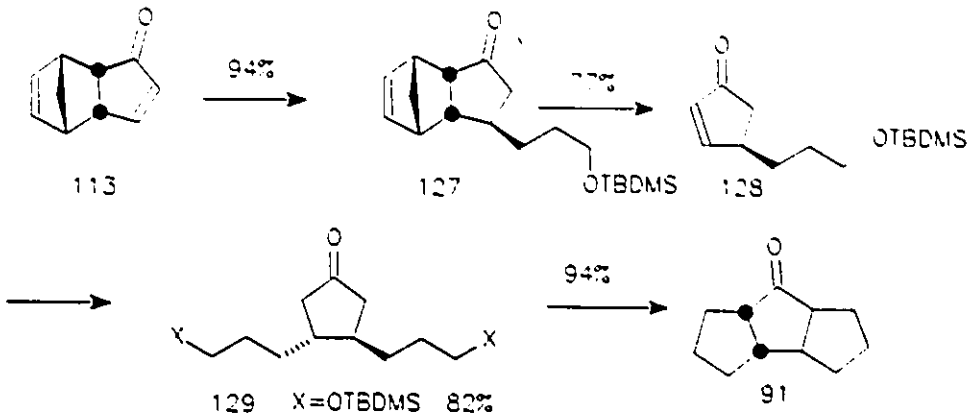
A second five membered ring was annulated using the same set of reactions to give 124 (Figure 114). The 1,4 addition of the cuprate derived from the propylene acetal of 3-bromopropanal to 110 gave a poor isolated yield of 123. However, NMR and GC analysis ensured that only one stereoisomer was present. The stereochemistry

at the 3 and 4 positions was assigned as *trans* due to the steric influence provided by the already established 5-membered ring. Cyclization and dehydration using conditions identical to those above cleanly provided 124. That 124 possessed the least substituted double bond (compare 124a) was shown in the ^{1}H NMR (δ 6.42, 1H, t) and DEPT-135 edited ^{13}C NMR (δ 138.6, CH). Catalytic hydrogenation of 124 was surprising since, a 4:1 mixture of 91 and 94 was isolated. As before the two isomers could not be separated. Although the NMR and chromatographic data for 124 indicated the presence of only one compound, the formation of two diastereomers in the hydrogenation reaction indicates either a lack of stereoselectivity in the hydrogenation reaction or the intermediacy of the isomer 124a with a fully substituted double bond. The structure of the molecule argues against the first possibility. The possibility of 124a intervening in the hydrogenation reaction requires a double bond isomerization reaction.[225] The Li/NH_3 reduction of enone 124 may have avoided this problem. However, at this point in the synthesis we were dissatisfied with the overall chemical yield of 91 from 113 using this route. The overall yield using this route was 9% from (+)-113.

In order to impove the overall yield and avoid the isomerization difficulty in the preparation of 91 an alternate *alkylative* procedure beginning from (+)-113 was employed (Figure 116). This route would be shorter and avoid the isomerization problems encountered with 124.

1,4 Addition of the cuprate derived from the TBDMS derivative of 3-bromopropanol[226] (126) proceeded selectively in over 90% yield to give 127, $[\alpha]_D$

Figure 116: Alkylative route to optically active 91



+56. Again, for steric reasons the addition was expected to occur only to the β-face of the enone. The mildly acidic work-up did not cleave the TBDMS protecting group. The retro-Diels-Alder reaction of 127 was not successful using either $EtAlCl_2$[223] or $BF_3{\cdot}OEt_2$[222]. In both cases only unidentifiable tarry products were isolated. Apparently the presence of the -OTBDMS group interfered in the cycloreversion reaction. We found however that the uncatalyzed thermal cycloreversion of 127 was successful. Compound 127 was refluxed in 1,2-dichlorobenzene for 4-5 hours. Chromatography separated the dicyclopentadiene formed and gave 128 in excellent yield (70-80%). The ^1H NMR and ^{13}C NMR of 128 had characteristic resonances at δ 7.6 ppm for the β olefinic proton and the β-carbon was observed at δ 168 ppm in the ^{13}C NMR. Subsequent, cuprate addition of 126 to 128 gave 129 in excellent yield (>80%). The addition appeared to be 100%

stereoselective since no other isomer could be detected by GC or NMR. Both the C_2 and C_s isomer would show only 9 resonance lines in the proton decoupled ^{13}C NMR. That compound 129 was the C_2 isomer rather than the C_s isomer was evidenced by the optical activity of 129 ($[\alpha]_D$ -47.7°). Removal of the TBDMS groups was accomplished by stirring 129 overnight in a solution of THF, H_2O, and HOAc. Extractive work-up resulted in large material losses, due to the solubility of 130 in water. Modified work-up then consisted of direct removal of the solvents and chromatography of the residue on Florisil. This procedure gave over 90% yield of 130, $[\alpha]_D$ -90°. We prepared three derivatives of 130 using standard methods[227,228,229](131, 132, and 133 Figure 116). After several attempts at a 5-*exo*-tet[230] cyclization, it was found that refluxing a dilute solution of 133 in ethanol with 5 equivalents of K_2CO_3 gave the best yield of (+)-91. This compound had an optical rotation of $[\alpha]_D$ +166°. The product derived from 6-*exo*-tet ring closure which would be a bridged bicylic compound was not detected in the crude reaction mixture.

Utitilizing this double *alkylative* procedure provided (+)-91 in 37% overall yield from (+)-113. Reduction of (+)-91 with LAH was routine and gave (+)-92 in over 90% yield, $[\alpha]_D$ +153. Analysis of the 300 MHz ^1H NMR spectrum of the camphanate ester (107) of 92 showed that the enantiomeric excess was **91%**. Since there are no steps in the synthesis which could lead to the racemization, the lack of optically purity can only be explained by either a lack of 100% specificity in the PLE resolution or a racemization during the decarboxylation step of the resolved acid as previously noted.

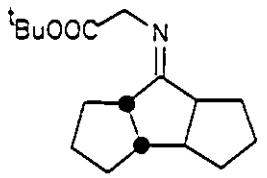
Assignment of the absolute configuration of 91 and 92 follows directly from the synthesis. The stereochemical designators change several times due to changing priorities of the substituents on the chiral centers. However, the enzyme specificity for the 2*S*-isomer of 114 leads unambiguously to the assignment of the *S*,*S*,*S*,*S* configuration of (+)-91 and (+)-92. It must be noted that the enantiomeric all-*R* series could be prepared by utilizing catalytic hydrogenation of 121a or by using the 2*R*-isomer of 114 obtained from the residue of the enzymatic hydrolysis reaction.

Attempted Imine Formation

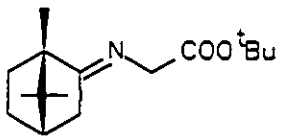
The advantages of using a C_2 symmetric chiral auxiliary have already been noted in the introduction. Along with these definite advantages, ketone 91 possesses a rigid framework which allows for simple spectroscopic analysis and which can be used to study the steric effects that the 5-membered rings of 91 might have on asymmetric reactions. In connection with previous work[51,52] on the alkylation of the camphor imine of *tert*-butyl glycinate (24) we attempted to prepare imine 134 (Figure 117).

The preparation of imines derived from hindered ketones often requires long reaction times, high temperatures, and catalysts or drying agents.[231,232] It has been shown in Chapter 1 that the formation of 24 occurs readily when camphor and *tert*-butyl glycinate are refluxed in toluene in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$.

Figure 117: Attempted imine formation



134

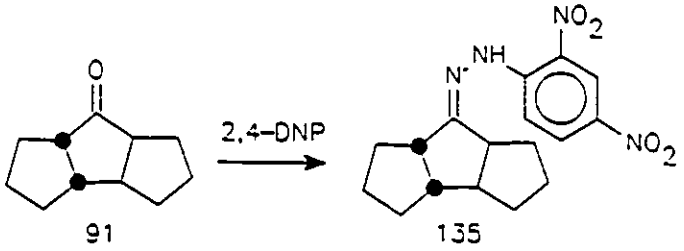


24

We treated 91 with both *tert*-butyl glycinate and benzyl amine using $BF_3{\cdot}OEt_2$ as a catalyst and were surprised by the isolation of only the starting ketone. Although the amine groups of *tert*-butyl glycinate and benzyl amine appeared to react initially with 91 (GC analysis), the imines, if formed were hydrolyzed by traces of moisture and only the starting ketone could be isolated. Though the carbonyl of 91 appears to be

quite hindered (recall sluggish LAH reduction) the corresponding imine (134, if formed) must be unstable. It appeared to us that it is possible that the condensation of amines with 91 was only proceeding to the hemiaminal intermediate. This was shown to be unlikely since the 2,4-DNP derivative of 91 (135) (Figure 118) formed readily and was isolated in good yield. The stability of the 2,4-DNP derivative of 91 is not unlike the stability of most 2,4-DNP derivatives. It is usually observed that the corresponding hydrazones of ketones or aldehydes are more stable than the corresponding alkyl imines. Benzaldehyde serves as an excellent example. The 2,4-DNP derivative of benzaldehyde[233] is quite stable to mild hydrolytic conditions, but the *tert*-butyl glycinate imine of benzaldehyde has been reported[234] to be hydrolytically unstable.

Figure 118: 2,4-DNP derivative of 91



Attempts to form the *tert*-butyl glycinate imine of 91 in the absence of catalyst was unsuccessful; only the starting ketone was recovered. The use of other catalysts (PTSA, $TiCl_4$) also did not permit the isolation of imine 134. This failure lead us to explore the possible use of alcohol 92 as a chiral auxiliary in the alkylation of glycinates.

Alkylation of a Chiral Glycinate Ester

Up to this point our group had concentrated on the alkylation of chiral imines where the chirality resided in the imine portion of the molecule. Very little work has been reported on the alkylation of chiral imines of glycine where the chirality resides in the ester portion of the molecule.

Yaozhong[46] reported on the double stereodifferentiation observed in the allylation of ketimines bearing two chiral auxiliaries (imine moiety and ester moiety) and he showed only one example of the allylation of a ketimine where the chirality is in the ester portion only (Figure 17, Chapter 1).

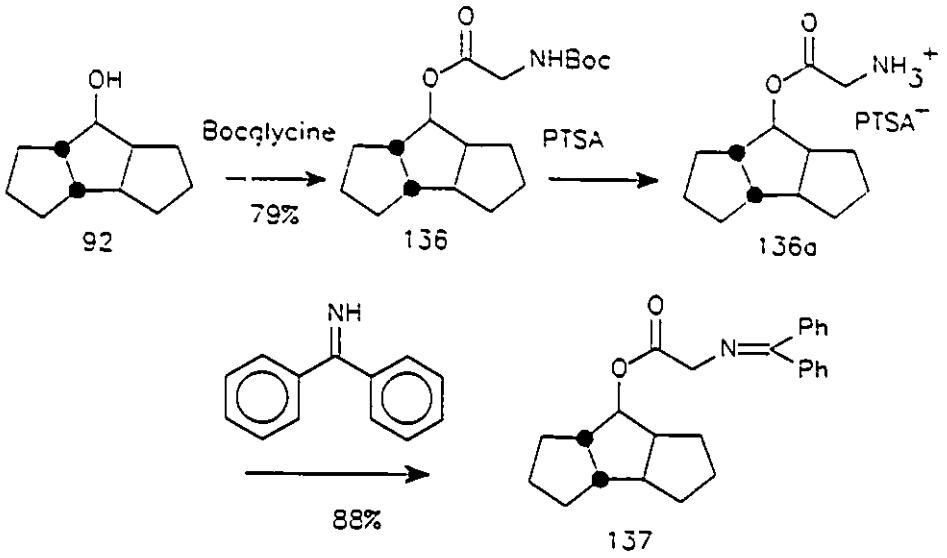
Katsuki[40,41] reported that the alkylation of a chiral amide (achiral imine moiety) with alkyl halides occured with both high chemical and optical yields. Interestingly, the chiral auxillary (trans-2,5-substituted pyrrolidine) possesses C_2 symmetry (Figure 14, Chapter 1).

We decided that the use of alcohol 92 as a chiral auxiliary in these types of alkylations might be of interest. The preparation of the chiral ester 137 is shown in Figure 119.

Esterification of 92 with Boc-glycine[235] was carried out using DCC and a catalytic amount of DMAP by adapting the procedure of Hassner[236] who has shown this method is useful in the preparation of very hindered esters. Although it has been previously noted that the hydroxyl group of 92 is quite hindered, Hassner's method gave high yields of the ester 136. The Boc protecting group was removed using standard conditions[237] to give the corresponding PTSA salt (136a). Transamination of

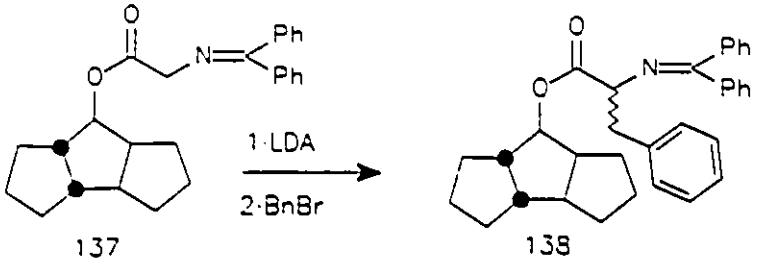
136a with diphenylmethylenimine[238] was uneventful and gave ester 137 in high yield (75%). The overall yield of 137 from the starting alcohol was 68%. The N-CH_2 protons of the imine appeared as a slightly broadened singlet at δ 4.2 ppm, a chemical shift quite typical for this type of proton. The carbinol proton appeared as a triplet (J = 6.6Hz) at δ 4.9 ppm and was well separated from all other resonances.

Figure 119: Chiral glycinate ester derivative



The alkylation reactions of imino-ester 137 with benzyl bromide were conducted in THF at low temperature employing 1.1 equivalents of LDA (Figure 120). It is important to note that enolate formation was carried out by adding a THF solution of one equivalent of 137 (with or without HMPA) to 1.1 equivalents of preformed LDA in THF at O °C, then after stirring for 30 minutes at that temperature the reaction was cooled to -78 °C and alkylated. We assumed that the *Z*-enolate would be formed not unlike the enolate formed from imine 24[51,52]. The results obtained for the alkylation reactions are shown in Table 1.

Figure 120: Alkylation with benzyl bromide



137 138

Entry 1 shows that when the alkylation was carried out with benzyl bromide at -78 °C in the absence of HMPA, no alkylation occured. Work-up afforded only the starting imine. Entry 2 shows that the addition of one equivalent of HMPA in the alkylation of 137 at -78 °C - -40 °C was also unsuccessful (as evidenced by TLC). After stirring for 1 hour at -40 °C the reaction was quenched at that temperature with water and work-up provided only the starting imine in over 90% yield. Entry 3 shows that when 137 was alkylated with benzyl bromide at 0 °C in the presence of 1 equivalent of HMPA an 88% yield of benzylated product (138) was isolated. The de was calculated by the integration of the carbinol proton at δ 4.9 ppm and found to be only 11%.

Table 1: Benzylation of 137				
entry	Eq. HMPA	Temp. °C	% yield	%de
1	0	-78	0	-
2	1	-78 → -40	0	-
3	1	0	88	11
4	0	0	68	10

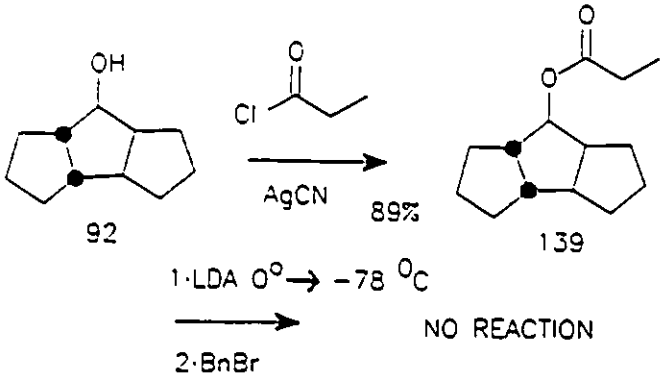
Entry 4 shows that alkylation of 137 at 0 °C in the absence of HMPA resulted in a reduction in the chemical yield but the de remained about the same.

Attempted deprotonation of 138 at 0 °C and quenching the reaction with D_2O resulted in no deuterium incorporation as evidenced by the mass spectrum and ^1H NMR. Since **absolutely** no deuterium was incorporated it can be assumed that the alkylation is operating under kinetic and not thermodynamic control. Due to the very poor selectivity observed we did not attempt to determine the configuration of the newly formed center.

The apparent lack of reactivity of the enolate of 137 can be attributed to one of two possibilities. The presence of the two phenyl rings on the imine may be impeding the alkylation reaction, or the triquinane nucleus of 137 is too sterically demanding to allow alkylation at very low temperatures. In order to distinguish between the two possibilities we prepared propionate 139 and attempted to alkylate the corresponding Li enolate at -78 °C in the presence of 1 equivalent of HMPA with benzyl bromide (Figure 121). If the steric bulk of the two phenyl rings in 137 are

responsible for the lack of reactivity in the alkylation reaction then 139 should be more reactive than 137 at -78 °C.

Figure 121: Attempted alkylation of propionate



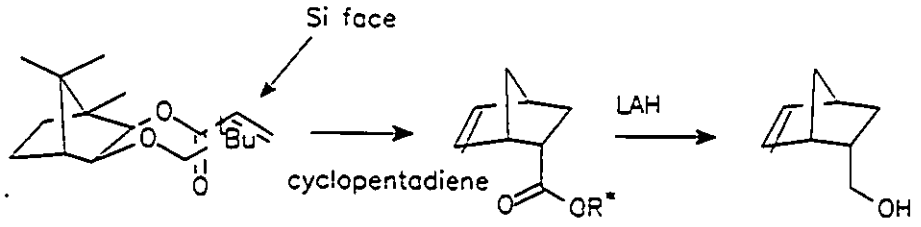
The Li enolate of 139 was prepared at 0 °C by adding a THF solution of the ester and 1 equivalent of HMPA to 1.1 equivalents of preformed LDA in THF. Upon the addition of the ester/HMPA solution the color of the reaction changed from colorless to deep yellow which may be indicative of enolate formation. The reaction was stirred at that temperature for 30 minutes and then cooled to -78 °C. Alkylation was carried out by adding a THF solution of one equivalent of benzyl bromide. After 1 hour the reaction was quenched in the usual manner (addition of H_2O at -78 °C). TLC analysis showed that only benzyl bromide and the starting ester was present. Chromatography provided an 89% yield of the starting ester (139) and no alkylated product.

The failure of the alkylation of 139 with benzyl bromide at -78 °C implies that the lack of reactivity may be due to the steric influence of the triquinane nucleus and not the phenyl rings in 137. This observation was rather surprising since inspection of

molecular models did not reveal any extreme steric hinderance which could be provided by the triquinane nucleus. Since the alkylation of ester derivatives of 92 at low temperatures (-78 °C) did not seem possible we decided to abandon the alkylation of ester derivatives and attempt to use acrylate (140, Figure 123) for asymmetric Diels-Alder reactions.

Most work in asymmetric Diels-Alder reactions has been done with optically active dienophiles, and particularly esters of acrylic acid derived from optically active alcohols. After the asymmetric Diels-Alder reaction has been carried out, the chiral auxiliary is generally removed from the adduct by reduction to recover the chiral auxiliary and obtain optically enriched alcohols. Several optically active alcohols[239,240] have been employed as chiral auxiliaries but it has been found that the best selectivities have been obtained with the neopentyl ester which was derived from camphor (Figure 122).[241,242]

Figure 122: Asymmetric Diels Alder reaction

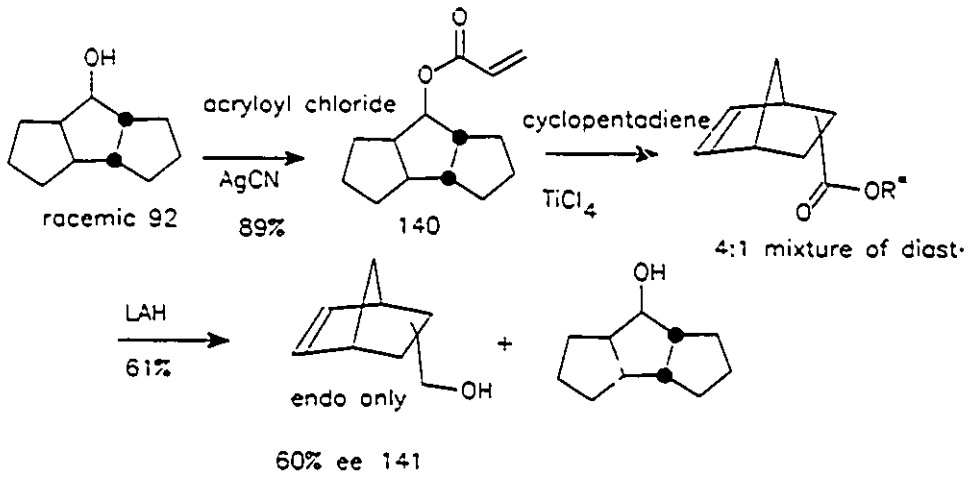


The major contributor to this field has been Oppolzer[241] who has reported that the Lewis acid catalyzed Diels-Alder reaction of cyclopentadiene with the chiral acrylate gave the cycloadduct with almost complete asymmetric induction (Figure 122). Reduction with LAH gave the optically pure endo alcohol. It was suggested by

Oppolzer that the asymmetric reaction takes place by the *endo* addition of cyclopentadiene to the ester in the conformation shown in Figure 122 in which the *re* face of the double bond is blocked by the *tert*-butyl group. This forces the addition to take place almost exclusively on the *si* face.

The preparation of **racemic** 140 from racemic 92 and the results of the Diels-Alder reactions of 140 with cyclopentadiene are shown in Figure 123 and Table 2.

Figure 123: Diels Alder reaction of acrylate



Condensation of **racemic** 92 with acryloyl chloride using the AgCN catalyzed esterification reaction previously noted provided acrylate 140 in high yield. Of all the reaction conditions attempted (Table 2) only the $TiCl_4$ catalyzed Diels-Alder reaction of 140 with cyclopentadiene was successful. The thermal cycloaddition and the $BF_3{\cdot}OEt_2$ catalyzed addition were both unsuccessful. Interestingly, for the $TiCl_4$ catalyzed reaction, TLC gave no evidence for cycloaddition at -78 °C. Only upon warming the reagents to 0 °C did a reaction occur. *In situ* reduction of the ester led to the isolation of *endo*-5-norbornenemethanol 141[243a] in 48% overall yield.

Table 2: Diels-Alder Reaction of 140 with Cyclopentadiene						
entry	solvent	Lewis Acid	# equiv.	Temp. °C	%yield	%de
1	THF	none	------	-78	0	-----
2	CH_2Cl_2	BF_3	1.1	-78	0	-----
3	toluene	none	-----	110	0	-----
4	toluene	$AlCl_3$	1.1	110	0	-----
5	CH_2Cl_2	$TiCl_4$	1.1	-78	0	-----
6	CH_2Cl_2	$TiCl_4$	1.1	0	48	60

Each of the enantiomers of 140 can give rise to two diastereomeric esters. If the activation energies of the two transition states leading to these are equal, the net result will be the formation of two racemic mixtures, related as diastereomers. The NMR of the crude mixture of Diels-Alder adduct showed that the ratio of diastereomers was 4:1 (de 60%) and the NMR of 141 indicated that the reaction occured in the *endo* fashion only. We did not attempt to determine the configuration of the newly formed centers. The poor reactivity of the acrylate with cyclopentadiene and the modest selectivity observed in the Diels-Alder reaction (compared to to the results of Oppolzers chiral auxiliaries) led us to terminate this investigation.

Conclusions and Recommendations

We have prepared a new C_2 symmetric ketone 91 and chiral alcohol 92 in racemic and optically active form. The resolution of 91 or 92 on a synthetically useful scale was not successful. This most likely is due to the fact that 91 or 92 are not highly functionalized compounds and stereochemical differences between various diastereomeric derivatives are not well recognized.

As noted however, we have been successful in preparing gram quantities of 91 and 92 with high optical purity (91% ee). Formation of imines from 91 does not seem possible. The use of alcohol 92 as a chiral auxiliary in the alkylation of chiral esters and in a Diels Alder reaction of the corresponding acrylate gave poor asymmetric inductions since the reactions would only take place at O °C. Molecular models do not reveal any type of severe steric hinderance from the triquinane nucleus of these systems therefore further work is required to determine the precise reason for this low reactivity.

The C_2 symmetry of ketone 91 appears to make this compound an ideal candidate as a chiral auxiliary in the [3,2] Wittig rearrangement[243b] and this reaction should be looked at in the future.

Experimental Procedures

General

Infrared spectra of oils were run as neat film between potassium bromide plates; solids were run as potassium bromide pellets on a Nicolet 5DX Spectrometer and only the most intense or pertinent peaks were recorded. The NMR spectra were recorded on a Bruker AC 300 Spectrometer at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 188 MHz for ^{19}F in $CDCl_3$ solution. Chemical shift values are reported as δ ppm relative to TMS as an internal standard (0 δ ppm ^{1}H NMR) or to the central line of $CDCl_3$ (77.0 δ ppm ^{13}C NMR) or CF_3COOH as an external standard (0 δ ppm ^{19}F NMR). Values in brackets ([ ]) are of the minor diastereomer. Where DEPT-135 editing of the carbon spectra was done, the multiplicities that would have been seen in the off-resonance spectra are indicated in brackets. Mike Feurth performed the C-H correlated 2-D spectra and NOE experiments. Optical rotations were performed on a Nicolet polarimeter (unthermostated) at Wayne State University, Detroit, Michigan. Mass spectra were run in the electron impact (EI), field ionization (FI) modes on a Varian MAT 5 CH instrument by the resident technician. Gas chromatographic analyses were performed on a Varian 3700 instrument using either a 1.5 ft. x 0.125 inch column packed with 5% OV-101 on Chromosorb W or a 8 ft. x 0.25 inch column packed with 20% SE-30 on Chromosorb W. Column chromatography utilized silica gel 60, 70 - 230 mesh. Melting points were recorded on a Fisher-Johns apparatus, and are uncorrected. Solvents were removed under reduced pressure and the drying agent used was anhydrous magnesium sulfate. THF and ether were dried

over potassium and benzophenone, ethanol was distilled from magnesium ethoxide, methylene chloride and carbon tetrachloride were distilled from phosphorus pentoxide. Benzene was dried over sodium metal. Pyridine was dried by storage over KOH and distilled under nitrogen. HMPA was dried over calcium hydride and distilled under nitrogen and stored over 4A molecular sieves. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. or M-H-W Laboratories, Phoenix, Az. Reagent grade chemicals were used without further purification.

Preparation of *tert*-Butyl Glycinate

tert-Butyl glycinate was prepared according to the procedure described by Moore and Rydon.[244] [bp 58-59 °C (15mm)]; IR: 3385, 3321, 2978, 1734, 1159cm^{-1}; ^{1}H NMR: 3.27 (2H, s), 1.43 (9H, s); ^{13}C NMR: 170.12, 80.42, 44.34, 27.73.

Preparation of Camphorthione and Camphor Imine of *tert*-Butyl Glycinate (*tert*-Butyl[(1*R*,4*R*)-Bornylideneamino]acetate)

Camphorthione and the camphor imine of *tert*-butyl glycinate were prepared as described by McIntosh and Mishra.[51]

Spectroscopic Data:

Camphorthione: IR: 2925, 1463, 1314, 1121cm^{-1}; ^{1}H NMR: 2.77 (1H, m), 2.38 (1H, m), 2.14 (1H, m), 1.96 (1H, m), 1.73 (1H, m), 1.30 (2H, m), 1.07 (3H, s), 1.00 (3H, s), 0.77 (3H, s); ^{13}C NMR: 226.31, 68.92, 55.35, 48.61, 45.00, 33.71, 27.03, 19.74, 19.52, 13.05.

(24) Camphor Imine of *tert*-Butyl Glycinate

IR: 2990, 1740, 1685cm^{-1}; ^{1}H NMR: 3.97 (2H, ABq, J = 16.0 Hz), 2.35 - 2.22 (1H, m), 1.95 - 1.34 (5H, m), 1.45 (9H, s), 1.25 - 1.16 (1H, m), 0.99 (3H, s), 0.91 (3H, s), 0.79 (3H, s); ^{13}C NMR: 187.42, 170.21, 80.95, 54.82, 54.32, 47.34, 43.94, 35.72, 32.18, 28.21, 27.52, 19.76, 19.04, 11.32.

BF_3·Et_2O Catalysed Preparation of the Camphor Imine of *tert*-Butyl Glycinate (24)(General Method for Imine Formation using BF_3·Et_2O)

To a 100 mL r.b flask fitted with a Dean-Stark water trap was added a 25 mL benzene solution of 1 g (6.5 mmol) of (1*R*)-camphor and 1.0 g (6.9 mmol) of *tert*-butyl glycinate. BF_3·Et_2O, (80 μl, 0.65 mmol) was added via syringe and the solution was refluxed for 24 h. The benzene was removed and the residue chromatographed (4:1 pet. ether:ether) to give 1.4 g of a thick yellow oil (81%). Spectroscopic data for this material was identical to that previously described.

General Alkylation Procedure (Preparation of Lithium Enolate of 31a)

LDA (1.1 equiv.) was prepared at 0 °C by adding BuLi (2.5 M in hexanes) to a solution of diisopropylamine in THF (10 mL) under a nitrogen atmosphere. After 10 minutes the solution was cooled to -78 °C. A solution of the appropriate imine (1.0 equiv.) and HMPA (1.0 equiv.) in THF was added dropwise via a syringe. The reaction was stirred for 30 minutes and then the appropriate alkylating agent (1.0

equiv.), dissolved in THF was added dropwise. After stirring for 1.0 - 2.0 h at -78 °C, H_20 was added. The reaction was allowed to warm to room temperature and the layers were separated. The aqueous layer was extracted with ether, the organic layers were combined, dried and concentrated. The crude product was purified by column chromatography.

Alkylation of Imine (24) with *p*-Substituted Benzyl Bromides

(26a) Camphor Imine of *tert*-Butyl *p*-Fluorophenylalaninate

Alkylation of imine 24 (1 g, 3.8 mmol) was carried out using the general alkylation procedure. *p*-Fluorobenzyl bromide was used as the alkylating agent. Chromatography (4:1 pet. ether:ether) gave 1.4 g of an oil (74%). IR: 2952, 1738, 1690, 1145cm^{-1}; ^1H NMR: 7.25 (2H, m), 6.90 (2H, m), 4.01 (1H, dd, J = 3.9, 10.2 Hz), 3.22 (1H, dd, J = 3.9, 13.5 Hz), 3.01 (1H, dd, J = 10.1, 13.4 Hz), 2.22 (1H, m), 1.81 - 1.30 (4H, m), 1.47 (9H, s), 0.99 (3H, s), 0.97 - 0.93 (2H, m), 0.98 (3H, s), 0.85 (3H, s); ^{13}C NMR: 185.05, 170.91, 159.91, 134.55, 131.18, 131.08, 114.78, 80.99, 66.63, 53.87, 47.01, 43.51, 33.85, 35.88, 31.78, 28.02, 27.21, 19.39, 18.86, 11.45; ^{19}F NMR: 4.87; FIMS: m/z 373; de >98%

(26b) Camphor Imine of *tert*-Butyl *p-tert*-Butylphenylalaninate

Alkylation of imine 24 (1 g, 3.8 mmol) was carried out following the general alkylation procedure. *p-tert*-Butylbenzyl bromide was used as the alkylating agent.

Chromatography (4:1 pet. ether:ether) gave 1.1 g of a clear oil (72%). IR: 2958, 1737, 1154cm^{-1}; ^{1}H NMR: 7.11 (4H, m), 3.97 (1H, dd, J = 3.7, 10.4 Hz), 3.21 (1H, dd, J = 3.8, 13.2 Hz), 2.99 (1H, dd, J = 10.2, 13.2 Hz, 2.15 (1H, m), 1.85 - 1.50 (3H, m), 1.40 (9H, s), 1.25 (9H, s), 1.10 - 1.01 (2H, m), 0.95 [0.91] (3H, s), 0.82 [0.84] (3H, s), 0.70 (3H, s), 0.62 (1H, m); ^{13}C NMR: 184.5, 171.2, 137.4, 129.4, 124.7, 80.4, 66.6, 46.8, 43.5, 37.8, 35.7, 34.0, 31.6, 31.4, 27.3, 19.3, 18.8, 11.4; *Anal.* Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.33; H, 10.02; N, 3.29; FIMS: m/z 411; de could not determined

(26c) Camphor Imine of *tert*-Butyl *p*-Trifluoromethylphenylalaninate

Alkylation of imine 24 (1 g, 3.8 mmol) was carried out using the general alkylation procedure. *p*-Trifluoromethybenzyl bromide was used as the alkylating agent. Chromatography (4:1 pet. ether:ether) gave 1.2 g of a solid (71%); mp 61-63 °C; IR: 2952, 1739, 1683, 1147cm^{-1}; ^{1}H NMR: 7.20 (4H, m), 4.00 (1H, dd, J = 10.0, 3.7 Hz), 3.21 (1H, dd, J = 3.7, 13.3 Hz), 3.11 (1H, dd, J = 10.0, 13.3 Hz), 2.11 (1H, bd), 1.95 - 1.50 (4H, m), 1.43 [1.45] (9H, s), 1.11 - 1.00 (2H, m), 0.96 [0.91] (3H, s), 0.85 [0.82] (3H, s), 0.74 (3H, s); ^{19}F NMR: 15.05 [14.93]; ^{13}C NMR: 185.4, 170.6, 143.2, 130.2, 129.9, 126.1, 124.8, 127.7, 81.1, 66.2, 47.0, 43.5 [43.7], 31.8, 27.1 [27.3], 19.3 [19.4], 18.8, 11.4 [11.3]; *Anal.* Calcd. for $C_{24}H_{32}F_3NO_2$: C, 68.08; H, 7.61; N, 3.30. Found: C, 67.89; H, 8.08; N, 3.15; FIMS: m/z 423; de 81%

(26d) Camphor Imine of *tert*-Butyl *p*-Cyanophenylalaninate

Alkylation of imine 24 (1.0g, 3.8mmol) was carried out following the general alkylation procedure, using α-bromo-*p*-toluonitrile as the alkylating agent. Chromatography (4:1 pet. ether:ether) gave 1.1 g of a white solid (76%). mp 88 °C; IR: 2958, 2221, 1737, 1153cm^{-1}; ^{1}H NMR: 7.41 (4H, m), 4.00 [4.09] (1H, dd, J = 9.5, 13.9 Hz), 3.29 (1H, dd, J = 4.0, 13.3 Hz), 3.12 (1H, dd, J = 9.8, 13.3 Hz), 2.25 (1H, bd), 1.95 - 1.48 (4H, m), 1.42 [1.45] (9H, s), 1.15 - 1.00 (2H, m), 0.95 (3H, s), 0.87 (3H, s), 0.74 (3H, s); ^{13}C NMR: 185.0, 170.9, 148.4, 134.5, 131.2, 118.9, 114.5, 114.4, 81.0, 66.6, 53.9, 43.5, 35.9, 31.8, 27.2, 19.4, 18.9, 11.5; *Anal.* Calcd. for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.47; N, 7.36; Found: C, 75.53; H, 8.43; N, 7.21; FIMS: m/z 380; de could not be determined.

(26e) Camphor Imine of *tert*-Butyl *p*-Methoxyphenylalaninate

Alkylation of imine 24 (1 g, 3.8 mmol) was carried out following the general alkylation procedure, using *p*-methoxybenzyl bromide as the alkylating agent. Chromatography (4:1 pet. ether:ether) gave 1.2 g of a clear oil (78%). IR: 2957, 1734, 1683, 1152cm^{-1}; ^{1}H NMR: 7.17 - 7.08 (3H, m), 6.80 - 6.73 (2H, m), 3.95 (1H, dd, J = 9.9, 4.0 Hz), 3.76 [3.75] (3H, s), 3.21 (1H, dd, J = 13.6, 3.9 Hz), 2.96 [3.05] (1H, dd, J = 13.6, 9.9 Hz), 2.25 - 1.49 (4H, m), 1.48 (9H, s), 1.20 - 0.95 (2H, m), 0.95 (3H, s), 0.85 [0.83] (3H, s), 0.73 (3H, s); ^{13}C NMR: 184.5, 171.2, 158.1, 131.0, 130.6 [130.4], 113.4 [113.5], 80.6, 66.9, 53.8, 46.9, 43.5, 35.7, 31.7, 28.0, 27.1, 19.3, 18.8, 11.4; *Anal.* Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H,

9.15; N, 3.63; Found: C, 74.49; H, 8.79; N, 3.74; FIMS: m/z 385; de 88%

Transamination of Imines

The alkylated imines were transaminated according to the method of McIntosh and Mishra.[51] The crude amino-esters were purified using column chromatography. Elution with ether gave camphor oxime. The eluting solvent was then changed to methanol and the *p*-substituted phenylalanine was obtained.

(27b) *p-tert*-Butylphenylalanine *tert*-Butyl Ester

95% yield; IR: 3438 (br), 2965, 1733, 1156cm^{-1}; ^{1}H NMR: 7.25 (4H, m), 4.10 (2H, bs), 3.72 (1H, m), 3.04 (1H, dd, J = 5.7, 13.5 Hz), 2.95 (1H, dd, J = 7.2, 13.5 Hz), 1.42 (9H, s), 1.31 (9H, s); FIMS: m/z 277.

(27c) *p*-Trifluoromethylphenylalanine *tert*-Butyl Ester

92% yield; IR: 3390 (br), 2984, 1742, 1717, 1120cm^{-1}; ^{1}H NMR: 7.52 (4H, m), 3.82 (2H, bs), 3.69 (1H, m), 3.06 (1H, dd, J = 6.0, 13.5 Hz), 2.95 (1H, dd, J = 7.1, 13.4 Hz), 1.40 (9H, s); FIMS: m/z 289.

(27d) *p*-Cyanophenylalanine *tert*-Butyl Ester

86% yield; mp 57-62 °C (hygroscopic); IR: 3391 (br), 2981, 2226, 1730, 1606, 1558, 1156cm^{-1}; ^{1}H NMR: 7.5 (4H, m), 3.64 (1H, m), 3.08 (1H, dd, J = 5.9, 13.6 Hz), 2.92 (1H, dd, J = 7.5, 13.6 Hz) 2.86 (2H, bs), 1.42 (9H, s); The amino esters

were too hygroscopic to allow elemental analysis. FIMS: m/z 246

(27e) ***p*-Methoxyphenylalanine *tert*-Butyl Ester**

94% yield; IR: 3440 (br), 2966, 1732, 1105cm^{-1}; ^{1}H NMR: 7.05 (4H, m), 4.21 (2H, bs), 3.79 (3H, s), 3.67 (1H, m), 3.07 (1H, dd, J = 5.7, 13.6 Hz), 2.97 (1H, dd, J = 7.3, 13.6 Hz), 1.42 (9H, s); FIMS: m/z 251.

Preparation of Mosher Amides

The Mosher amides (MTPA amides) were prepared from (R)-(+)-MTPA-Cl[61] according to Mosher.[61] Chromatography (1:1 pet. ether:ether) gave pure amides.

(29b) ***p*-*tert*-Butylphenylalanine MTPA Amide**

64% yield; IR: 3314, 2971, 1745, 1723, 1532, 1187, 1116cm^{-1}; ^{1}H NMR: 7.51 - 7.25 (5H, m), 7.05 (4H, m), 7.05 (1H, bs), 4.83 (1H, m), 3.41 (3H, s), 3.10 (1H, dd, J = 5.6, 13.8 Hz), 2.97 (1H, dd, J = 6.1, 13.3 Hz), 1.42 (9H, s), 1.28 (9H, s); ^{19}F NMR: 8.50 [8.43]; FIMS: m/z 493; de 85%.

(29c) ***p*-Trifluoromethylphenylalanine MTPA Amide**

71% yield; IR: 3316, 2980, 1746, 1724, 1188cm^{-1}; ^{1}H NMR: 7.55 - 7.28 (5H, m), 7.04 (4H, m), 4.83 (1H, m), 3.42 (3H, s), 3.12 (1H, dd, J = 5.6, 14.0 Hz), 2.99 (1H, dd, J = 6.6, 13.8 Hz), 2.60 (1H, bs), 1.43 (9H, s); ^{19}F NMR: 14.85 [14.80], 8.66 [8.54]; FIMS: m/z 505; de 80%.

(29d) *p*-Cyanophenylalanine MTPA Amide

58% yield; IR: 3316, 2246, 1745, 1723, 1103cm^{-1}; ^{1}H NMR: 7.71 - 6.95 (10H, m), 4.88 (1H, m), 3.5 (3H, s), 3.15 (1H, dd, J = 5.8, 14.1 Hz), 3.01 (1H, dd, J = 6.5, 13.9 Hz), 1.43 (9H, s); ^{19}F NMR: 8.72 [8.58]; FIMS: m/z 462; de 77%.

(29e) *p*-Methoxyphenylalanine MTPA Amide

65% yield; IR: 3319, 1746, 1725, 1055cm^{-1}; ^{1}H NMR: 7.54 - 7.31 (5H, m), 7.00 (1H, m), 6.75 (4H, m), 4.83 (1H, m), 3.83 (3H, s), 3.11 (1H, dd, J = 5.7, 13.9 Hz), 2.94 (1H, dd, J=6.9, 12.7 Hz), 1.47 (9H, s); ^{19}F NMR: 8.55 [8.50]; FIMS: m/z 451; de 87%.

Preparation of Metal Enolates of the Camphor Imine of *tert*-Butyl Glycinate

Na Enolate (31b)

To a cold solution of 1g (3.77 mmol) of imine 24, 1.0 equiv. of HMPA and 1.1 equiv. of oil free NaH in 5 mL of dry THF, was added 1 equiv. of *tert*-butyl alcohol under nitrogen. The slurry was stirred at 0°C for 0.5 h to give a clear yellow solution. This was cooled to -78°C and alkylated using the method described in the general alkylation procedure. The results are shown in Table 2.

Na Enolate (31b')

A cold solution of 1.0g (3.7 mmol) of imine 24 and 1 equiv. of HMPA in 5 mL of dry THF were added dropwise to a 3.8 mL solution of sodium hexamethyldisilazide (1.0M in THF, Aldrich) at 0 °C. The solution was cooled to -78 °C immediately and stirred for 15 min. Alkylation was carried out by the method described in the general alkylation procedure. The results are shown in Table 2.

K Enolate (31c)

To a -78 °C solution of 0.43 g (3.8 mmol) of potassium *tert*-butoxide in 5 mL of dry THF, was added a solution of 1.0 g (3.77 mmol) of imine 24 and 1 equiv. of HMPA . During 30 min at that temperature a precipitate formed. The precipitated enolate was alkylated as described in the general alkylation procedure. When enolate formation was carried out at -100 °C, the enolate remained in solution. The results are shown in Table 2.

Zn Enolate (31d)

To a solution of the Li enolate of imine 24 in THF, was added 1 equiv. of a solution of anhydrous $ZnCl_2$ (1.0 M in ether, Aldrich) in ether at -78 °C. After stirring for 30 min the solution changed from orange to yellow. Alkylation was carried out as described in the general alkylation procedure. The results are shown in Table 2.

Zr Enolate (31e)

To a solution of the Li enolate of imine 24 in THF, was added a THF solution of 1 equiv. of Cp_2ZrCl_2 at -78 °C under nitrogen. The color changed from orange to a deep red-brown. The reaction was stirred for 30 min at that temperature. Alkylation was carried out as described in the general alkylation procedure. The results are shown in Table 2.

Alkylation of the Camphor Imine of α-Aminoacetonitrile

(25) Camphor Imine of α-Aminoacetonitrile

A solution of 0.7 g (4.1 mmol) of camphorthione,[57] 1.1 g (12.5 mmol) of aminoacetonitrile hydrochloride and 0.5 g (4.5 mmol) of 1,4-Diazabicyclo[2.2.2]octane (DABCO) were added to 30 mL of MeOH. The reaction was refluxed for 20 h. TLC analysis (2:1 pet. ether:ether) showed the disappearance of the thione. The methanol solution was concentrated and the residue was taken up in 30 mL of ether. The ether solution was washed with H_2O, dried, and concentrated. Chromatography (4:1 pet. ether:ether) gave 0.46 g (58%) of a colorless oil. IR: 2960, 2250, 1677cm^{-1}; ^{1}H NMR: 4.07 (2H, s), 2.41 (1H, m), 2.11 - 1.63 (4H, m), 1.38 - 1.15 (2H, m), 0.95 (3H, s), 0.92 (3H, s), 0.73 (3H, s); ^{13}C NMR: 190.6 (s), 117.2 (s), 54.9 (s), 47.8 (s), 43.9 (d), 39.1 (t), 35.9 (t), 31.8 (t), 27.2 (t), 19.6 (q), 19.0 (q), 11.1 (q); *Anal.* Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; Found: C, 75.61; H, 9.61.

(25a) Benzylation of 25

Imine 25 (0.2 g, 1.0 mmol) was alkylated with benzyl bromide using the general alkylation procedure. Chromatography (4:1 pet. ether:ether) gave 0.2 g (67%) of a yellow oil. IR: 2995, 2247, 1673cm^{-1}; ^{1}H NMR: 7.41 - 7.22 (5H, m), 4.26 (1H, dd, J = 5.8, 8.5 Hz), 3.28 (1H, dd, J = 5.8, 13.3 Hz), 3.14 (1H, dd, J = 8.6, 13.3 Hz), 2.35 - 2.27 (2H, m), 1.91 - 1.02 (5H, m), 0.97 (3H, s), 0.88 (3H, s), 0.73 (3H, s); ^{13}C NMR: 188.81 (s), 136.20 (s), 129.86 (d) [129.66], 128.64 (d), 127.37 (d), 119.41 (s), 54.74 (s), 53.48 (d), 47.56 (s), 43.74 (d), 40.95 (t), 35.93 (t), 31.90 (t), 27.13 (t), 19.55 (q), 18.95 (q), 11.34 (q) [11.24]; MS(EI): m/z (M^+)280, 189, 152, 133, 108, 95, 69, 57; de 66%.

(25b) Allylation of 25

Imine 25 (0.2 g, 1.0 mmol) was alkylated with allyl bromide using the general alkylation procedure. Chromatography (4:1 pet. ether:ether) gave 0.17 g (69%) of a colorless oil. IR: 2963, 2248, 1677, 1654cm^{-1}; ^{1}H NMR: 5.92 - 5.98 (1H, m), 5.31 - 5.14 (2H, m), 4.05 - 4.12 (1H, m), 2.73 - 2.47 (3H, m), 2.00 - 1.66 (4H, m), 1.40 - 1.11 (2H, m), 0.96 (3H, s), 0.94 (3H, s), 0.70 (3H, s) [0.69 (3H, s)]; ^{13}C NMR: 188.24, 132.30, 119.44 [119.05], 54.76, 51.46 [51.75], 47.84, 43.96, 38.86, 36.25, 32.24, 27.36, 19.61, 19.02 [18.96], 11.22; MS(EI): m/z 230(M^+), 189, 133, 108, 95, 81, 69, 55; de 45%.

(25c) Methylation of 25

Imine 25 (0.2 g, 1.0 mmol) was alkylated with MeI using the general alkylation procedure. Chromatography (4:1 pet. ether:ether) gave 0.16 g (71%) of a clear oil. IR: 2959, 2939, 2242 (weak), 1675, 1448, 1060cm^{-1}; ^{1}H NMR: 4.16 (1H, m), 2.61 [2.33] (1H, m), 1.98 - 1.60 (4H, m), 1.51 [1.55] (3H, m), 1.46 - 1.13 (2H, m), 0.94 [0.93] (3H, s), 0.91 (3H, s), 0.76 [0.69] (3H, s); ^{13}C NMR: 188.76 (s), 120.22 [120.19] (s), 47.84 [47.43] (d), 46.58 [46.32] (d), 35.83 (t), 31.97 [31.69] (t), 27.38 [27.30] (t), 20.56 (q), 19.54 (q), 19.05 [18.95] (q), 11.22 (q); de 0%.

Preparation of Chiral Imines of *tert*-Butyl Glycinate.

(39) Ketopinic Acid

Ketopinic acid was prepared in 34% yield using the method of Bartlett.[96] mp 175-176 °C [lit.[96] mp 178°C]; IR: 3200 - 2400, 1751, 1691cm^{-1}; ^{1}H NMR: 10.20 (1H, bs), 2.61 (1H, m), 2.40 (1H, m), 2.21 - 1.70 (4H, m), 1.42 (1H, m), 1.15 (3H, s), 1.10 (3H, s); ^{13}C NMR: 213.52, 174.18, 66.71, 49.80, 43.98, 43.57, 27.11, 26.75, 20.77, 19.87

(46) *tert*-Butylglycinate Imine of Ketopinic Acid

The imine was prepared in 77% yield using the general $BF_3{\cdot}Et_2O$ catalyzed condensation reaction previously described (Chromatography 4:1 pet. ether:ether). TLC analysis showed the appearance of ketopinic acid after prolonged exposure of

moisture in the air. IR: 3220 -2410, 1738, 1692, 1687cm^{-1}; ^{1}H NMR: 11.20 (1H, bs), 4.09 (2H, s), 2.60 - 2.41 (2H, m), 2.21 - 1.98 (3H, m), 1.87 - 1.72 (1H, m), 1.52 (9H, s), 1.32 (3H, s), 1.25 - 1.08 (1H, m), 0.95 (3H, s); ^{13}C NMR: 186.50, 172.99, 167.67, 82.18, 60.63, 52.99, 50.63, 43.89, 35.20, 31.29, 27.92, 20.19, 19.79; FIMS: m/z 295.

(40) Methylketopinate

Diazomethane solution[245] was added via syringe under a nitrogen atmosphere to 0.05 g of 39 dissolved in 1 mL of dry ether. After 1 h at ambient temperature the reaction was concentrated. Chromatography (2:1 pet. ether:ether) gave 50 mg (81%) of a crystalline solid. mp 46 °C; ^{1}H NMR: 3.75 (3H, s), 2.61 - 2.30 (2H, m), 2.15 - 1.75 (4H, m), 1.50 - 1.36 (1H, m), 1.16 (3H, s), 1.08 (3H, s); ^{13}C NMR: 211.0, 170.1, 67.9, 51.7, 49.1, 44.2, 43.0, 26.3, 21.6, 19.67, 0.91; FIMS: m/z 196.

(47) *tert*-Butyl Glycinate Imine of Methylketopinate

The imine was prepared using the general $BF_3{\cdot}Et_2O$ catalyzed procedure. The resulting oil was chromatographed (1:1 pet. ether:ether) to give 86% yield of a colorless oil. IR: 2970, 1742, 1737, 1688, 1105cm^{-1}; ^{1}H NMR: 4.05 (2H, ABq, J =11.3 Hz), 3.78 (3H, s), 2.55 - 2.30 (2H, m), 2.05 - 1.31 (4H, m), 1.45 (9H, s), 1.35 - 1.16 (1H, m), 1.13 (3H, s), 1.05 (3H, s); ^{13}C NMR: 182.0, 171.6, 168.6, 81.0, 64.8, 54.9, 51.5, 49.4, 45.2, 36.0, 28.5, 27.9, 26.5, 21.16, 19.78; FIMS: m/z 309.

(41) 1-Hydroxymethyl Camphor

1-Hydroxymethyl camphor was prepared in four steps from ketopinic acid according to the literature in 46% overall yield.[98] IR: 3343, 2961, 1737cm^{-1}; ^{1}H NMR: 3.95 - 3.55 (2H, m), 2.60 (1H, bs), 2.42 (1H, m), 2.15 - 1.75 (3H, m), 1.60 - 1.35 (3H, m), 0.98 (3H, s), 0.97 (3H, s); ^{13}C NMR: 221.06, 60.91, 60.68, 46.87, 44.08, 43.56, 26.77, 26.07, 20.89, 19.42.

(48) *tert*-Butyl Glycinate Imine of 1-Hydroxymethyl Camphor

The imine was prepared using the general $BF_3{\cdot}Et_2O$ catalyzed condensation procedure. Chromatography (2:1 pet. ether:ether) afforded 0.95 g (77%) of a thick oil. IR: 3430, 2966, 1738, 1683, 1155cm^{-1}; ^{1}H NMR: 3.91 (1H, 1/2 ABq, J = 11.4 Hz), 3.89 (2H, s), 3.59 (1H, 1/2 ABq, J = 11.4 Hz), 2.38 (1H, m), 1.90 - 1.61 (5H, m), 1.45 (9H, s), 1.25 - 1.17 (2H, m), 0.92 (3H, s), 0.89 (3H, s); ^{13}C NMR: 187.44, 169.10, 81.24, 62.25, 57.39, 54.42, 46.98, 44.78, 35.48, 28.35, 38.02, 26.95, 20.52, 18.87; *Anal.* Calcd. for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; Found: C, 68.18; H, 9.71.

(42) 2-*exo*-Hydroxy-2-methyl-bicyclo[2.2.1]heptan-3-one

To 1.1 g (23 mmol) of Mg metal and 1 crystal of iodine suspended in 70 mL of dry ether was added an ether solution of MeI (1.5 mL, 28 mmol). When the addition was complete and after the reaction had cooled to room temperature, the reaction was heated to reflux for 1 h. The solution of the Grignard reagent was cooled to 0°C

and an ether solution of the 3-ethylene ketal of camphorquinone[188] was added slowly. After the addition, the reaction was refluxed for 4 h. The reaction was cooled to room temperature and a solution of aqueous ammonium chloride was added. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were dried and concentrated affording 4.5 g of a thick oil. This oil was dissolved in a solution containing 30 mL of EtOH and 40 mL of 3M HCl and refluxed for 3 h. The reaction was cooled and the ethanol was removed. The remaining aqueous layer containing a white precipitate was extracted with ether, and the ether extracts were combined, dried, and concentrated. Recrystallization of the residue from pet. ether gave 2.2 g (63%) of a white solid. IR: 3342, 2984, 1741, 1133cm^{-1}; ^{1}H NMR: 2.25 - 1.25 (6H, m), 1.19 (3H, s), 1.08 (3H, s), 0.96 (6H, bs).

(49) *tert*-Butyl Glycinate Imine of 42

Imine 49 was prepared from 0.5 g (2.7 mmol) of 42 using the general $BF_3{\cdot}Et_2O$ catalyzed procedure. Chromatography (3:2 pet. ether:ether) gave 0.74 g (90%) of a clear oil. IR: 3255 br, 2974, 1740, 1694, 1149cm^{-1}; ^{1}H NMR: 4.05 (1H, d, J = 5.4 Hz), 2.47 (1H, bs), 1.90 - 1.46 (4H, m), 1.43 (9H, s), 1.25 (3H, s), 1.26 - 1.20 (1H, m), 1.01 (3H, s), 0.92 (3H, s), 0.90 (3H, s); ^{13}C NMR: 188.91, 169.42, 81.41, 78.10, 55.01, 51.77, 49.92, 30.43, 28.02, 27.93, 24.50, 22.40, 22.26, 19.50, 9.30; *Anal.* Calcd. for $C_{17}H_{29}NO_3$: C, 69.11; H, 9.89; Found: C, 69.30; H, 9.81.

(44) Chromium Tricarbonyl Complex of *o*-Anisaldehyde

This compound was prepared using the three steps described by Solladie-Cavallo.[95] The overall yield from *o*-anisaldehyde was 45%. mp 96°C [lit.[95] mp 99°C]. ^{1}H NMR: 10.01 (1H, s), 6.20 (1H, d, J = 6.2 Hz), 5.94 (1H, t, J = 6.8 Hz), 5.02 (2H, m), 3.83 (3H, s); ^{13}C NMR: 230.54, 185.39, 145.68, 94.80, 92.43, 84.30, 65.70, 56.00.

(50) *tert*-Butyl Glycinate Imine of 44

To 5 mL of anhydrous ether was added 0.1 g (0.36 mmol) of the complexed aldehyde 44, 70 mg (0.54 mmole) of *tert*-butyl glycinate and 0.2 g of crushed 3A molecular sieves. After stirring for 12 h the reaction was filtered and most of the ether was removed. Hexanes was added and an orange precipitate formed. After cooling to -10 °C the precipitate was filtered off. An orange powder (0.13 g, 95%) was isolated. mp 135-137°C; IR: 3010 weak, 1955, 1898, 1870, 1735, 1615cm^{-1}; ^{1}H NMR: 8.31 (1H, s), 6.46 (1H, dd, J = 1.4, 6.5 Hz), 5.66 (1H, t, J = 6.9 Hz), 5.05 (1H, d, J = 6.8 Hz), 4.95 (1H, t, J = 6.3 Hz), 4.33 (1H, dd, J = 1.1, 15.7 Hz), 4.15 (1H, dd, J = 0.9, 15.8 Hz), 3.80 (3H, s), 1.48 (9H, s); *Anal.* Calcd. for $C_{17}H_{19}CrNO_5$: C, 52.98; H, 4.93; Found: C, 53.05; H, 5.11.

Alkylation of Chiral *tert*-Butyl Glycinate Derivatives

(46a) Benzylation of 46

Imine 46 (0.2 g, 0.7 mmol) was alkylated with benzyl bromide using the general

alkylation procedure substituting 2.1 equiv. of LDA for 1.1 equiv. of LDA. Chromatography (2:1 pet. ether:ether) afforded 0.1 g (38%) of a clear oil. IR: 3350 (br), 1738, 1690, 1675cm^{-1}; ^{1}H NMR: 9.51 (1H, bs, D_2O exchangable), 7.30 - 7.16 (5H, m), 4.09 (1H, dd, J = 3.4, 10.7 Hz), 3.36 (1H, dd, J = 3.3, 13.4 Hz), 3.00 (1H, dd, J = 10.8, 13.4 Hz), 2.43 - 2.21 (2H, m), 1.99 - 1.72 (4H, m), 1.49 (9H, s), 1.42 - 1.39 (1H, m), 1.32 (3H, s), 0.96 (3H, s); ^{13}C NMR: 185.21, 173.35, 169.27, 137.39, 129.74 [129.30], 128.76 [128.58], 126.99, 82.52, 65.89, 60.70, 50.59, 43.59 [44.04], 38.78, 35.09, 28.04, 27.85 [27.42], 20.23, 20.66, 19.72 20.03; FIMS: m/z 385; de 82%

(47a) Benzylation of 47

Imine 47 (0.15 g, 0.5 mmol) was alkylated with benzyl bromide using the general alkylation procedure. Chromatography (2:1 pet. ether:ether) gave 0.15 g (78%) of a yellow oil. IR: 2981, 1740, 1736, 1688cm^{-1}; ^{1}H NMR: 7.30 - 7.12 (5H, m), 3.95 (1H, dd, J = 4.1, 10.2 Hz), 3.75 (3H, s) [3.77], 3.18 (1H, dd, J = 4.1, 13.2 Hz), 3.00 (1H, dd, J = 10.2, 13.2 Hz), 2.41 - 1.62 (6H, m), 1.35 - 1.21 (1H, m), 1.45 (9H, s), 1.05 (3H, s), 0.95 (3H, s); ^{13}C NMR: 179.57, 171.91, 170.71, 138.80, 129.97, 128.13, 126.29, 81.03, 67.21, 64.88, 51.52, 49.26, 45.08, 38.23, 36.16, 28.36, 28.10, 26.30, 21.23, 19.51; FIMS: m/z 399; de 77%.

(48a) Benzylation of 48

Imine 48 (0.25 g, 0.9 mmol) was alkylated with benzyl bromide using the general alkylation procedure. Two equivalents of LDA were used. Chromatography (1:1 pet. ether:ether) gave 90 mg (32%) of an oil and 0.15 g of starting imine. IR: 3445 (br), 2988, 1738, 1683cm^{-1}; ^{1}H NMR: 7.31 - 7.13 (5H, m), 4.55 (1H, bs, D_2O exchangable), 3.95 (2H, m), 3.55 (1H, m), 3.22 (1H, m), 2.99 (1H, m), 2.36 (1H, m), 1.91 - 1.62 (4H, m), 1.43 (9H, s), 1.27 - 1.15 (2H, m), 0.89 (3H, s), 0.83 (3H, s); ^{13}C NMR: peaks are doubled; FIMS: m/z 371; de 17%.

(49a) Benzylation of 49

Imine 49 (0.1 g, 0.35 mmol) was alkylated with benzyl bromide using the general alkylation procedure. Two equivalents of LDA were used. Chromatography (1:1 pet. ether:ether) gave 92 mg (73%) of an oil. IR: 3250 - 3300, 2985, 1737, 1696, 1150cm^{-1}; ^{1}H NMR: 7.15 - 7.22 (5H, m), 4.11 (1H, dd, J = 3.5, 10.5 Hz), 3.25 (1H, dd, J = 3.4, 13.4 Hz), 3.04 (1H, dd, J = 10.5, 13.2 Hz), 2.41 - 2.35 (2H, m), 1.45 (9H, s), 1.41 - 1.22 (4H, m), 1.11 (3H, s), 0.99 (3H, s), 0.87 (3H, s), 0.82 (3H, s); ^{13}C NMR: 187.33, 170.88, 138.46, 129.79, 128.11, 126.34, 81.27, 77.94, 67.65, 51.60, 49.76, 47.72, 39.18, 30.77, 28.05, 24.60, 22.62, 21.13, 19.54, 9.31; MS (EI): m/z 385(M^+), 329, 294, 284, 238, 210; de 90%.

(49b) Methylation of 49

Imine 49 (0.1 g, 0.35 mmol) was alkylated with MeI using the general alkylation

procedure. Two equivalents of LDA were substituted for 1.1 equiv. of LDA. Chromatography (1:1 pet. ether:ether) afforded 0.81 g (77%) of an oil; IR: 3262 - 3306, 2987, 1736, 1695cm^{-1}; ^{1}H NMR: 4.02 (1H, m), 2.68 - 2.32 (2H, m), 2.10 - 1.52 (2H, m), 1.43 [1.42] (9H, s), 1.24 [1.32] (3H, d, J = 7.2 Hz), 1.51 - 1.40 (2H, m), 1.03 (3H, s), 1.00 (3H, s), 0.97 (3H, s), 0.87 (3H, s); ^{13}C NMR: peaks are doubled; FIMS: m/z 309; de 9%.

(50a) Benzylation of 50

Imine 50 (0.2 g, 0.5 mmol) was alkylated with benzyl bromide using the general alkylation procedure. Chromatography on silica gel (4:1 pet. ether:ether) gave only complexed aldehyde. Analysis of the crude ^{1}H NMR showed that some alkylation had taken place, and that the de was ≈0%.

Attempted Preparation of the *tert*-Butyl Glycinate Imine of 3-Hydroxycamphor

(43) 3-Hydroxycamphor.

This compound was prepared as in the literature.[103] A 5:1 mixture of endo to exo isomers was obtained. IR: 3474, 2961, 2931, 1741, 1107cm^{-1}; ^{1}H NMR: 4.15 (1H, d, J = 5 Hz) [3.69 (1H, s)], 2.93 (1H, s), 2.19 (1H, t, J = 5 Hz), 1.87 (1H, m), 1.65 (2H, m), 1.43 (1H, m), 0.95 [0.93] (3H, s), 0.87 [0.88] (3H, s), 0.82 [0.86] (3H, s); ^{13}C NMR: 220.6 (s), 74.7 [77.4] (d), 58.5 (s), 48.7 [49.4] (d), 43.2 (s), 23.7 [28.7] (t), 20.1 [21.1] (q), 18.9 (q), 18.0 (t), 9.4 [9.1] (q); FIMS: m/z 168.

Formation of (52)

3-Hydroxycamphor (0.5 g, 3 mmol) (5:1 endo:exo) was dissolved in 10 mL of dry toluene in a flask fitted with a Dean-Stark water separator under a nitrogen atmosphere. *tert*-Butyl glycinate (0.43 g , 3.3 mmol) was added followed by 40 μl of $BF_3 \cdot Et_2O$. The reaction was refluxed for 8 h at which time GC analysis indicated that all of the starting material was consumed. The mixture was concentrated to give an orange oil which was chromatographed (5:1 pet. ether:ether) to give 0.59 g of an orange-tinted oil. IR: 3319 br, 2966, 1742, 1450, 1367, 1292, 1157cm^{-1}; ^{1}H NMR: 3.43 (2H, s), 2.86 (1H, s), 2.12 (1H, d, J = 4.8 Hz), 1.89 (2H, m), 1.75 (1H, s, D_2O exchangable), 1.40 (9H, s), 1.35 (2H, m), 0.98 (3H, s), 0.89 (3H, s), 0.86 (3H, s); ^{13}C NMR: 218.4 (s), 171.6 (s), 81.3 (s), 69.1 (d), 59.9 (d), 51.8 (t), 50.4 (s), 44.4 (s), 28.2 (q), 26.5 (t), 24.2 (t), 19.2 (q), 16.1 (q), 14.0 (q); FIMS: m/z 281; *Anal.* Calcd. for $C_{16}H_{27}NO_3$: C, 68.33; H, 9.60; N, 4.98; Found: C, 68.53; H, 9.12; N, 4.61.

The hydrochloride salt of 52 was prepared by adding a solution of 52 (40 mg, 0.14 mmol) dissolved in 2 mL of ether to 20 mL of ether which had been saturated with HCl gas. The solution was stirred for 20 min and concentrated. The solid product was recrystallized from ether to give 43 mg (97%) of a white powder; mp 84-86°C; ^{1}H NMR: ca.10 (1H, very broad), 7.20 (1H, s), 4.11 (2H, d, J = 17.4 Hz), 3.61 (1H, s), 2.27 - 1.50 (5H, m), 1.44 (9H, s), 1.28 (3H, s), 0.90 (3H, s), 0.89 (3H, s); FIMS: m/z 317.

(53) 3-*endo* Acetylcamphor

To 80 mg of 52 in a 25 mL r.b. flask was added 3 mL of glacial acetic acid and 0.5 g of activated zinc dust. The mixture was stirred overnight at room temperature, diluted with 15 mL of water, filtered and the filtrate extracted with 3 X 20 mL of ether. The combined organic layers were washed with 3 X 15 mL of $NaHCO_3$ and 10 mL of brine. The organic layer was dried and concentrated to give 41 mg of an oil which had the following spectroscopic characteristics. ^1H NMR: 5.21 (1H, d, J = 5 Hz) [4.77 (1H, s)], 2.42 (1H, bs), 2.13 [2.10] (3H, s), 1.73 (3H, m), 1.45 (1H, m), 1.02 [1.00] (3H, s), 0.96 (3H, s), 0.95 (3H, s); ^{13}C NMR: 214.3 (s), 170.3 (s), 75.6 (d), 58.4 (s), 47.4 (d), 43.5 (s), 31.8 (t), 20.8 (q), 19.9 (q), 16.8 (t), 16.7 (q), 9.3 (q).

53 was hydrolysed to 43 by stirring 53 (13 mg, 0.06 mmol) in 4 mL of methanol containing 5 mg of KOH for 12 h. TLC analysis (4:1 pet. ether:ether) showed that none of the starting acetate remained. The methanol was evaporated, 2 mL of water was added to the residue and the solution was extracted with ether. The dried extracts were evaporated to give 10 mg (95%) of a solid, identical in all respects with 43

Attempted Preparation of 2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxyaldehyde (45).

(55) 2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxaldehyde TMS Ether

To a cooled solution of 62 g (0.25 mol) of 54[111] in 100 mL of dry toluene, was added 190 mL of a solution of DIBAL-H (1.5M in toluene, Aldrich) dropwise with stirring. After the addition was complete the solution was allowed to warm to room temperature. TLC analysis (4:1 pet. ether:ether) showed starting material was still present. Therefore the solution was refluxed for 3 h. After cooling to room temperature the solution was poured slowly into a cold mixture of 75 mL of H_2SO_4 in 75 mL H_2O and stirred overnight. The solution was filtered, the organic layer separated and the aqueous layer was extracted with toluene. The combined organic layers were dried and evaporated to give an oil (60 g) which was distilled to give 48 g (75%) of 55 as a 6:1 mixture of epimers; bp 75 - 80°C (0.1 mm); IR: 2957, 1731, 1251, 1124cm^{-1}; ^{1}H NMR: 9.52 [9.41] (1H, s), 2.15 (3H, m), 1.82 - 1.50 (4H, m), 0.95 [0.97] (3H, s), 0.91 [0.90] (3H, s), 0.82 (3H, s), 0.09 (9H, s); *Anal.* Calcd. for $C_{14}H_{26}O_2Si$: C, 65.88; H, 10.27. Found: C, 65.74; H, 10.32.
Chromatography did not separate the epimers.

Attempted Desilylation of 55

Formation of 56 and 57

To 10 ml of CH_2Cl_2 was added 3.5 g (14 mmol) of 55. The solution was cooled

to 0 °C in ice and 1.8 mL (15 mmol) of $BF_3 \cdot Et_2O$ was added slowly. After 15 min, GC analysis showed no starting material. The solution was allowed to warm to room temperature and then quenched by the slow addition of sat. aqueous $NaHCO_3$. The organic layer was separated, and the aqeous layer was extracted with ether. The combined organic layers were dried and evaporated to afford a white solid which showed two components on TLC anlaysis (Rf 0.37 and 0.52, 2:1 pet. ether:ether). The mixture was chromatographed to give 0.4 g (16%) of 57 [ms: m/z 182; mp 154-156 °C; IR: 3481, 2922, 1716, 1059cm^{-1}; *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; Found: C, 72.39; H, 10 10] and 1.04g (42%) of 56 [ms: m/z = 182; mp 175-180° C (dec); IR: 3475 br, 29666, 1707, 1024cm^{-1}; *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; Found: C, 74.32; H, 11.04]. The ^1H NMR and ^{13}C NMR are shown in Table 6 and Table 7. Unsatisfactory analytical data for 56 was found due to its oxidation to 59.

Compounds 56 and 57 were obtained in the same ratio when 55 was treated with 5 equiv. of $Bu_4N^+F^-$ in THF and the reaction was worked up as above.

(57a) Mosher Ester 57

To 1 mL of dry pyridine was added 100 mg of 57, the solution was cooled to 0 °C and 0.15 g of MTPA-Cl[61] was added; a precipitate formed instantly. The mixture was stirred overnight while warming to room temperature, then poured into 5 mL of 10% HCl and extracted with ether. The ether was dried and evaporated to give 0.27 g of a yellow oil which was purified by chromatography (0.21 g, 71%). IR:

2972, 1750, 1721, 1258cm^{-1}; ^{1}H NMR: 7.22 (2H, m), 7.45 (3H, m), 5.62 (1H, t, J = 9.6 Hz), 3.71 (3H, s), 2.30 - 1.05 (7H, m), 1.03 (3H, s), 0.95 (3H, s), 0.82 (3H, s); ^{13}C NMR: 207.11, 166.03, 132.41, 129.52, 128.31, 127.50, 73.83, 57.78, 55.87, 47.40, 44.29, 34.19, 33.66, 27.15, 23.15, 19.81, 13.61; ^{19}F NMR: 5.56. Compound 56 could not be esterified with MTPA-Cl!

Aerial Oxidation of 56 to give 59

After standing at room temperature in air for several days, compound 56 had been transformed into 59. This was separated from residual 56 by chromatography (1:1 pet. ether:EtOAc) and a white solid was obtained. mp 138-140°C; IR: 2972, 1782, 1745, 1118, 1041cm^{-1}; The ^{1}H NMR and ^{13}C NMR are shown in table 9.

Homocamphoric Acid

Anhydride 59 (50 mg, 0.25 mmol) was added to 1 mL of H_2O which contained 50mg of NaOH. The solution was refluxed for 1 h, allowed to cool and stirred at room temperature overnight. Acidification with conc. HCl gave a white precipitate which was dissolved in ether. The ether was separated, washed with brine, dried and evaporated to give 48 mg (81%) of homocamphoric acid. mp 237-238°C [lit.[117] mp 238 °C]; IR: 3266 - 2800, 1696, 1313, 1303cm^{-1}; ^{1}H NMR: 11.05 (2H, s), 2.41 - 2.04 (3H, m), 2.02 - 1.76 (2H, m), 1.40 - 1.15 (2H, m), 1.10 (3H,s), 0.98 (3H, s), 0.65 (3H, s); ^{13}C NMR: 177.36 (s), 174.40 (s), 54.87 (s), 44.29 (s), 43.20 (d), 35.26 (t), 31.92 (t), 26.61 (t), 21.81 (q), 21.39 (q), 19.32 (q).

Preparation of Racemic 91 and 92

Cyclopentylcarbonitrile

This compound was prepared by adapting the method of Shaw.[180] To a flame-dried 250 mL r.b flask equipped with a dropping funnel was added 80 mL of dry HMPA and 4.4 g (0.09 mole) of finely ground NaCN. In the dropping funnel was placed 8.9 g (0.06 mole) of cyclopentyl bromide in 50 mL of HMPA. This solution was added dropwise with stirring over 1 h and the reaction was stirred overnight. The reaction was worked up by adding 120 mL of H_2O and extracting the aqueous layer with 3 X 75 mL of ether. The combined ether layers were washed with brine, dried and concentrated to 4.3 g of a yellow oil. The oil was distilled at reduced pressure [bp 69-73 °C (25 mm)] [lit.[180] bp 74-75 °C (28mm)] to give 3.5 g (62%) of a clear oil; ^{1}H NMR: 2.80 - 2.52 (1H, m), 2.05 - 1.45 (8H, m); ^{13}C NMR: 123.21, 31.00, 27.64, 24.75.

(95) Dicyclopentyl Ketone

This compound was prepared by the method of Eaton[173] in 92% yield; IR: 2956, 1705cm^{-1}; ^{1}H NMR: 2.91 (2H, d, J = 7.0 Hz), 1.85 - 1.41 (16H, m); ^{13}C NMR: 216.28 (s), 50.72 (d), 29.40 (t), 26.15 (t). The only change to the published procedure was that cyclopentyl lithium had to be prepared. Preparation of cyclopentyl lithium: To 1.3 g (0.19 mole) of Li ribbon (containing 1% Na metal) suspended in 20 mL of dry cyclohexane under an argon atmosphere was added

dropwise a solution of 4.0 g (0.04 mole) of cyclopentyl chloride dissolved in 100 mL of dry cyclohexane. The reaction was stirred at ambient temperature overnight. A purple suspension was obtained. The solution was allowed to settle and an aliquot of the supernate was titrated to a red end-point using 2,5-dimethoxy benzyl alcohol as the indicator. The solution was found to be ≈ 0.46M in cyclopentyl lithium. Preparation of cyclopentyllithium replacing cyclopentyl chloride with the bromide lead to inferior yields of the alkyllithium.

(96) 1,1'-Dibromodicyclopentyl Ketone

This compound was prepared by the method described by Eaton[173] in 83% yield. ^{1}H NMR: 2.61 - 2.42 (8H, m), 2.10 - 1.76 (8H, m); ^{13}C NMR: 197.62 (s), 73.79 (s), 40.91 (t), 22.99 (t).

(97) 1,1'-Dicyclopentenyl Ketone

This compound was prepared by the method described by Eaton[173] in 98% yield. mp 57-59 °C [lit.[173] mp 61-63 °C]; IR: 2980, 1614cm^{-1}; ^{1}H NMR: 6.55 (2H, m), 2.68 - 2.50 (8H, m), 1.93 (4H, p, J = 7.1 Hz); ^{13}C NMR: 191.59 (s), 145.01 (s), 142.61 (d), 33.87 (t), 31.81 (t), 22.62 (t).

(93) *cis*-Tricylo [6.3.0.0^{3,7}]unde-1-(8)-en-2-one

This compound was prepared from 97 according to the literature procedure in 60% yield after distillation.[173] [bp 64-65 °C (0.01 mm)] [lit.[173] bp 60-63 °C (0.05

mm)]; IR: 2951, 1694cm^{-1}; ^{1}H NMR: 3.15 - 3.00 (2H, m), 2.61 - 2.43 (2H, m), 2.38 - 2.20 (4H, m), 1.90 - 1.79 (1H, m), 1.70 - 1.51 (4H, m), 1.31 - 1.09 (1H, m); ^{13}C NMR: 207.20 (s), 189.01 (s), 150.11 (s), 57.57 (d), 42.98 (d), 30.41 (t), 29.38 (t), 27.90 (t), 27.68 (t), 24.64 (t), 24.35 (t).

(94) *cis,syn,cis*-Tricyclo [6.3.0.0^{3,7}]undecan-2-one

This compound was prepared as described by Eaton[173] in 84% yield. It was obtained as a 9:1 mixture of diastereomers as indicated by ^{1}H NMR; IR: 1732cm^{-1}; ^{1}H NMR: 2.82 (4H, bs), 1.92 - 1.50 (6H, m), 1.47 (4H, pent, J = 7 Hz), 1.38 - 1.25 (2H, m); ^{13}C NMR: 223.30, 54.60 [53.50], 41.69 [46.69], 29.37 [35.00], 27.32 [30.00], 27.26 [26.32].

The 2,4-DNP derivative was prepared in the standard manner.[173] mp 162-164 °C. [lit.[173] mp 169-170 °C]

(91) *rac-cis,anti,cis*-Tricyclo[6.3.0.0^{3,7}]undecan-2-one

To 150 mL of ammonia which had been condensed in a 250 mL flask equipped with a dropping funnel and a Dry Ice condenser was added 0.27 g (40 mmol) of lithium metal. The solution was stirred for 20 min to allow complete solution of the metal. Enone 93 (2.5 g, 15 mmol) in 20 mL of dry THF was added dropwise with stirring over 1 h. The deep blue color of the solution persisted after stirring an additional 20 minutes. The reaction was quenched by the addition of 1.3 g of solid NH_4Cl and allowing the mixture to stir at -78 °C for 10 min. The condenser was

removed and the ammonia allowed to evaporate overnight. Water was added and the aqueous layer was extracted with 2 X 20 mL of ether. The organics were dried and concentrated to afford 2.4 g of a clear oil which was dissolved in 20 mL of methylene chloride containing 5.4 g of PDC. The mixture was stirred at ambient temperature overnight, 20 mL of ether was added and the solution was filtered through a pad of $MgSO_4$. Concentration and chromatography (3:1 pet. ether:ether) gave 1.8 g (70%) of 91 contaminated with 10% 94 as a clear oil; IR: 1731cm^{-1}; ^{1}H NMR: 2.59 (2H, doublet of triplets, J = 4.2, 8.9 Hz), 2.34 (2H, m), 1.95 (6H, m), 1.51 (4H, pent, J = 7 Hz), 1.32 (2H, m); ^{13}C NMR: 226.93, 53.57 [54.60], 46.59 [41.69], 34.99 [29.36], 30.30 [27.34], 26.32 [27.28]; *Anal.* Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.81; Found: C, 80.17; H, 9.66.

The 2,4-DNP derivative was prepared by standard procedures[173] and melted at 146-148 °C.

(105) Ethylene Ketal of 91

The ketal was prepared in 86% yield by using standard ketalization procedure.[185] [Kugelrohr, bp 100-120 °C (0.01 mm)] The ketal was contaminated with about 5% of the starting ketone which precluded accurate elemental analysis. ^{1}H NMR: 3.95 - 3.86 (4H, m), 2.70 - 2.39 (2H, m), 2.05 (1H, m), 1.95 - 1.30 (13H, m); ^{13}C NMR: 120.11 (s), 64.60 (t), 51.70 (d), 49.10 (d), 36.87 (t), 26.02 (t), 26.36 (t).

All attempts to prepare ketals from the chiral diols were unsuccessful.

(92) *rac-cis,anti,cis*-Tricyclo[6.3.0.$0^{3,7}$]undecan-2-ol

To a cooled (O °C) slurry of 0.25 g (7 mmol) of LAH in 4 mL of dry THF was added via syringe a THF solution of 0.5 g (3 mmol) of ketone 91. After stirring 2 h, TLC analysis (1:1 pet. ether:ether) showed only starting ketone, therefore the reaction was allowed to warm to room temperature and stir overnight. Again, TLC analysis showed mostly starting ketone, therefore the reaction was refluxed for 8 h. TLC analysis showed the disappearence of starting material, so the reaction was cooled to 0 °C in an ice bath and quenched by the addition of a fresh solution of saturated Na_2SO_4 until a fluffy white precipitate replaced the grey excess LAH (care must be taken since the reaction froths). The white precipitate was filtered and washed with ether. The ether was dried, concentrated and the residue distilled [Kugelrohr, bp 75-85 °C (0.2mm)] to give 0.5 g (98%) of a clear oil; IR: 3360-3380 (broad) cm^{-1}; ^1H NMR: 3.88 (1H, t, J = 6.8 Hz), 2.49 (1H, m), 2.27 (1H, m), 2.00 (2H, m) 1.84 - 1.23 (13H, m); ^{13}C NMR: 81.38 (d), 52.23 (d), 50.49 (d), 49.90 (d), 49.61 (d), 34.38 (t), 33.89 (t), 30.31 (t), 26.45 (t), 25.67 (t), 25.22 (t).

(106) MTPA-ester Derivative of 92

The MTPA ester (106) was prepared from 92 and MTPA-Cl in 52% yield using the standard procedure.[61] Compound 106 was obtained as an oil which ^1H NMR showed to be a 1:1 mixture of diastereomers which could not be separated; IR: 2950, 1745, 1270, 1167cm^{-1}; ^1H NMR: 7.60 - 7.15 (5H, m), 5.08 [5.06] (1H, t, J = 6.4 Hz), 3.46 [3.45] (3H, s), 2.78 (1H, m), 2.63 - 2.40 (1H, m), 2.10 (1H, m), 1.90 -

1.25 (12H, m); MS(EI): m/z 383(M^+), 189, 149, 119, 107, 93, 81, 67, 55.

(107) Camphanic-ester Derivative of 92

The camphanate (107) was prepared by refluxing 50 mg of 92, 70 mg of camphanic acid chloride and 1 equiv. of AgCN in 2 mL of dry benzene for 24 h, cooled, filtered through Hyflow and chromatographed (2:1 pet. ether:ether) to give 84 mg (85%) of a white solid. mp 88-93 °C; IR: 2942, 1790, 1743cm^{-1}; ^1H NMR: 5.00 (1H, dt, J = 6.5, 6.7 Hz), 2.80 - 2.31 (3H, m), 2.21 - 1.35 (20H, m), 1.09 (3H, s), 0.95 (3H, s); MS(EI): m/z 347(M^+), 300, 199, 148, 119, 109, 97, 93, 80, 67, 55; This material (25 mg) was recrystallized from ethanol 3 times to give 3 mg of a ≈ 40:1 mixture of diastereomers.

(108) Carbamate Derivative of 92

Carbamate 108 was prepared by adding 0.21 g (1.3 mmol) of 92 and 0.25 g (1.3 mmol) of (*R*)-(-)-(1-napthylethyl)isocyanate to 2 mL of benzene. The reaction was refluxed for 24 h after which time TLC analysis (2:1 pet. ether:ether) showed no remaining starting material. The cooled reaction mixture was poured into 5 mL of water, extracted with ether and the extracts were dried and concentrated to give 0.5 g of a thick oil. Chromatography (2:1 pet. ether:ether) gave 0.34 g (72%) of a white solid. mp 93-97°C; IR: 3348, 2943, 1684, 1539cm^{-1}; ^1H NMR: 8.1 (1H, broad), 7.80 (2H, m), 7.60 - 7.41 (4H, m), 5.62 (1H, broad), 4.95 (1H, bs), 4.78 (1H, bt), 2.70 (1H, m), 2.40 (1H, m), 2.05 (2H, m), 1.90 - 1.21 (15H, m); ^{13}C NMR: 155.9,

134.1, 128.9, 128.8, 128.2, 126.4, 125.8, 125.4, 123.5, 122.2, 83.9, 50.0, 49.6, 49.2, 48.4, 46.4, 34.3, 33.7, 30.1, 26.5, 26.0, 25.5, 21.8; MS (EI): m/z 363(M^+), 243, 229, 214, 200, 170, 149, 137, 129, 111, 97, 85, 71, 57.

Asymmetric Synthesis of 91 and 92

(116) 1,4,4a,8a-Tetrahydro-*endo*-1,4-methanonaphthalene-5,8-dione

This compound was prepared in 70% yield according to the literature procedure.[211] mp 72-73 °C (MeOH) [lit.[211] mp 76°C]; ^{1}H NMR: 6.52 (2H, s), 6.01 (2H, s), 3.49 (2H, s), 3.17 (2H, s), 1.44 (2H, ABq, J = 8.8 Hz); ^{13}C NMR: 199.32 (s), 141.96 (d), 135.23 (d), 48.67 (t), 48.76 (d).

(117) 1,4,4a,8a-Tetrahydro-*endo*-1,4-methanonaphthalene-1,4-dione-2,3-epoxide

This compound was prepared in 87% yield by adapting the literature procedure.[212] To 700 mL of acetone was added 50 g (0.29 mole) of 116. After most of the compound had dissolved, 50 mL of a 20% aqueous solution of $NaHCO_3$ was added. Through a dropping funnel 100 mL of 30% H_2O_2 was then added dropwise. The reaction was stirred for 2 h and the acetone was removed. The aqueous layer was extracted with 3 X 150 mL of EtOAc. The combined organic layers were washed with brine, dried and concentrated to give 60 g of a crude white solid. This solid was dissolved in hot MeOH/EtOAc (8:1) and cooled to -10 °C. After several hours 47.4 g of white crystals were isolated (87%). mp 117-119 °C (MeOH/EtOAc) [lit.[212] mp 120°C]; ^{1}H NMR: 6.01 (2H, s), 3.48 (2H, s), 3.40 (2H, s), 3.28 (2H, s), 1.35 (2H, ABq, J = 8.7 Hz); ^{13}C NMR: 204.19 (s), 136.65 (d), 57.81 (d), 49.45 (d), 46.31 (t), 43.24 (d).

(114) Ethyl-5-oxo-tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-2-carboxylate

This compound was prepared in 55% yield according to the literature procedure.[213] It was obtained as a thick oil [lit.[213] mp 29-30 °C]; IR: 2985, 1712 broad, 1285, 1229, 1042cm^{-1}; ^{1}H NMR: 7.35 (2H, d, J = 5.7 Hz), 6.00 - 5.89 (2H, m), 4.19 (2H, q, J = 7.2 Hz), 3.26 (3H, m), 1.80 (2H, ABq, J = 4.7 Hz), 1.26 (3H, t, J = 7.1 Hz); ^{13}C NMR: 228.31, 172.66, 161.60, 136.09, 134.61, 133.51, 64.32, 54.03, 51.09, 49.54, 45.59, 43.27, 14.11.

(-)-115 Pig Liver Esterase (PLE) resolution of 114

Racemic ester 114 was resolved using PLE (Sigma) according to the literature procedure.[215] Yields varied from 34-40% based on 50% theoretical yield in several runs; mp 121-122 °C [lit.[208] mp 125-130 °C]; ^{1}H NMR: 9.71 (1H, broad, exchangable with D_2O), 7.41 (1H, d, J = 5.7 Hz), 5.97 (3H, m), 3.29 (3H, m), 1.85 (2H, ABq, J = 9.0 Hz); ^{13}C NMR: 208.80, 178.26, 161.54, 136.35, 134.99, 133.47, 64.28, 53.97, 51.16, 49.71, 45.72.

(+)-113 Decarboxylation of (-)-115

(-)-115 was decarboxylated in 62 - 70% yield according to the literature procedure.[215] The optical rotation of (+)-113 varied depending upon the reaction time. The optical rotation could be maximized by recrystallization from n-hexane. The melting point varied from 69-76 °C [lit.[215] mp 77 °C]; $[\alpha]_D$ +139° (c = 0.5, MeOH) [lit.[208] $[\alpha]_D$ +141°]

^{1}H NMR: 7.32 (1H, m), 5.98 (2H, m), 5.72 (1H, m), 3.35 (1H, m), 3.18 (1H, m), 2.91 (1H, m), 2.73 (1H, m), 1.70 (1H, 1/2 ABq, J = 8.9 Hz), 1.52 (1H, 1/2 ABq, J = 8.9 Hz); ^{13}C NMR: 224.81, 173.96, 142.96, 138.61, 138.46. 58.80, 56.29, 53.63, 51.08, 50.11.

(119) (2*S*,5*R*,6*R*) 5-(3-oxopropyl)-Tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one Propylene acetal

The Grignard reagent from 2-(3-bromopropyl)-1,3-dioxolane was prepared by refluxing 3.9 g (20 mmol) of the acetal with 0.5 g (20 mmol) of Mg metal and a catalytic amount of iodine in 15 mL of THF for 1 h. The turbid solution was cooled to 0 °C and 0.1 g of CuCl (5 mol% based on Mg) was added. After stirring 15 min, a solution of (+)-113 (2 g, 14 mmol) in 15 mL of THF was added dropwise. After stirring 1 h at 0 °C, TLC analysis (1:1 pet. ether:ether) showed that none of the starting enone remained. The reaction was poured into 20 mL of sat. NH_4Cl solution, filtered through Hyflow and the aqueous layer was extracted with ether. After drying, and evaporation 3.4 g of a colorless oil was obtained. Chromatography (1:1 pet. ether:ether) gave 3.3 g (95%) of 119 as a thick colorless oil; IR: 2960, 1732, 1145cm^{-1}; ^{1}H NMR: 6.15 (2H, m), 4.44 (1H, t, J = 5.3 Hz), 4.12 (2H, m), 3.75 (2H, m), 3.18 (1H, m), 3.05 (1H, m), 2.92 (1H, m), 2.61 (1H, m), 2.31 - 1.90 (3H, m), 1.75 - 1.31 (8H, m); ^{13}C NMR: 220.51 (s), 136.16 (d), 135.24 (d), 102.01 (d), 66.88 (t), 54.90 (d), 52.32 (t), 48.66 (t), 48.28 (t), 47.05 (d), 46.01 (d), 36.79 (t), 33.40 (t), 31.81 (t), 25.77 (t); *Anal.* Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.45;

Found: C, 73.48; H, 8.30.

(127) (2*S*,5*R*,6*R*) 5-(3-hydroxypropyl)-Tricyclo[5.2.1.0^{2,6}] dec-8-en-3-one *tert*-butyldimethylsilyl Ether

To a suspension of 1 g of lithium wire in 20 mL of ether was added 17 g (67 mmol) of the TBDMS derivative of 3-bromopropanol[226] in 5 mL of ether in portions under an argon atmosphere. The exothermic reaction was allowed to cool before each subsequent addition. After the addition was complete, the reaction was stirred for 1 h at ambient temperature.

A solution of 6.6 g (32 mmol) of CuBr·Me_2S in 40 mL of ether was cooled to 0 °C in an ice bath. To this was added, via syringe, the solution of the lithium compound. The reaction turned orange and then dark. The mixture was stirred for 10 min and then 60 mL of Me_2S was added. After stirring for 30 min at 0 °C, a solution of (+)-113 (2.7 g , 18.5 mmol) in 40 mL of ether was added dropwise. After 1 h, TLC (3:1 pet. ether:ether) indicated that the reaction was complete. The mixture was poured into 40 mL of sat. NH_4Cl solution and filtered through Hyflow. The layers were separated, the aqueous layer was washed with ether and the combined organic extracts were dried and concentrated to give 9g of a yellow oil. Chromatography (3:1 pet. ether:ether) gave 5.5 g (94%) of 127 as a colorless oil. $[\alpha]_D$ +56° (c = 1.04, MeOH); IR: 2954, 1733, 1252, 1100, 838cm^{-1}; ^{1}H NMR: 6.15 (2H, bs), 3.54 (2H, m), 3.14 (1H, m), 3.02 (1H, m), 2.92 (1H, ddd, J = 1.6, 4.6, 9.6 Hz), 2.62 (1H, m), 2.20 (1H, dd, J = 8.9, 18.5 Hz), 1.92 (1H, ddd, J =

1.8, 6.9, 18.5 Hz), 1.72 - 1.35 (7H, m), 0.84 (9H, s), 0.02 (6H, s); ^{13}C NMR: 220.90 (s), 136.28 (d), 135.34 (d), 63.13 (t), 54.98(d), 52.43 (t), 48.91 (d), 48.42 (t), 47.22 (d), 46.22 (d), 36.80 (d), 34.22 (t), 30.96 (t), 26.07 (q), 18.47 (s), -5.18 (q); *Anal.* Calcd. for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06; Found: C, 71.31; H, 10.37.

(121) (2*S*,8*S*,9*R*) Tetracyclo[8.2.1.0^{2,9}.0^{4,8}]trideca-4,11-dien-3-one

Acetal 119 (3.15 g, 12 mmol) was refluxed overnight in 90% aqueous acetone containing 0.8 mL of conc. HCl. The acetone was evaporated and the aqueous layer extracted with 3 X 30 mL of ether, and the combined organic layers were dried and evaporated to give a brown oil (2.3 g, 85%, 120). NMR anlaylsis showed this to be a 5:1 mixture of epimers (at the carbinol carbon). IR: 3404 (br), 2961, 1721, 1184cm^{-1}; ^{1}H NMR: 6.19 (1H, m), 6.01 (1H, m), 4.28 (1H, m), 3.18 (1H, m), 3.07 (1H, m), 2.86 (1H, m), 2.68 (2H, m), 2.54 (1H, m), 2.41 - 2.05 (4H, m), 1.70 - 1.28 (3H, m); ^{13}C NMR: 223.23, 135.43, 135.14, 77.01 [76.58], 65.80, 55.71, 51.61, 48.33, 47.56, 47.50, [42.31] 41.73, [35.38] 35.33, 33.23.

Compound 120 (1.7 g, 8.5 mmol) was added to 3 mL of dry pyridine and cooled to 0 °C. Methanesulfonyl chloride (0.8 mL, 10 mmol) was added dropwise and the reaction was allowed to warm to room temperature and stirred for 10 h. The mixture was poured into 10 mL of 10% HCl, the phases separated, the aqueous phase extracted with ether and the combined organic phases were dried and evaporated. The crude mesylate was dissolved in 10 mL of dry THF, cooled to 0 °C, 1.1 equivalents of DBU were added and the reaction was allowed to warm to room

temperature. After stirring for 5 h the mixture was poured into 10% HCl, the layers separated, the aqueous phase extracted with ether and the combined organic layers dried and evaporated. There remained 1.0 g of a yellow oil which was purified by column chromatography (5:1 pet. ether:ether) to give 0.97 g (62%) of 121 as a colorless oil. IR: 2966, 1704, 1214cm^{-1}; ^{1}H NMR: ϵ 28 (1H, m), 6.10 (2H, m), 3.18 (2H, m), 3.02 (1H, s), 2.55 (4H, m), 2.35 (1H, m), 1.72 (1H, pent.), 1.58 (1H, 1/2ABq, J = 8.3 Hz), 1.39 (1H, 1/2ABq, J = 8.3 Hz); ^{13}C NMR: 203.55 (s), 153.96 (s), 135.99 (d), 135.87 (d), 133.12 (d), 60.02 (d), 52.22 (t), 49.14 (d), 46.18 (d), 45.84 (d), 45.42 (d), 37.43 (t), 36.60 (t); *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58; Found: C, 83.43; H, 7.53.

(122) (2*S*,4*S*,8*S*,9*R*)Tetracyclo[8.2.1.0^{2,9}.0^{4,8}]tridec-11-en-3-one

To a solution of 75 mg of Li wire in 20 mL of liq. NH_3 was added 121 (0.85 g, 4.5 mmol) as a solution in 10 mL of dry THF. After 20 min the blue color had disappeared and the ammonia was allowed to evaporate. Water (5 mL) was added and the aqueous phase was extracted with ether. The crude reduction product was stirred with 1 equiv. of PDC in CH_2Cl_2 overnight. Ether was added, the mixture was filtered through Hyflow and the residue from solvent removal was chromatographed (2:1 pet. ether:ether) to give 0.53 g (61%) of 122 as an oil. [Kugelrohr, bp 110-120 °C (4 mm)], ; IR: 2948, 1727cm^{-1}; ^{1}H NMR: 6.16 (1H, dd, J = 3.0, 5.6 Hz), 6.01 (1H, dd, J = 2.9, 5.6 Hz), 3.15 (1H, bs), 3.04 (1H, bs), 2.85 (1H, dd, J = 4.8, 8.6 Hz), 2.52 (1H, ddd, J = 1.4, 4.1, 8.6 Hz), 2.29 - 2.10 (2H, m), 1.95 - 1.54

(3H, m), 1.52 - 1.24 (5H, m); ^{13}C NMR: 225.00 (s), 135.69 (d), 135.07 (d), 55.93 (d), 55.90 (d), 51.64 (t), 48.10 (d), 47.48 (d), 47.27 (d), 43.20 (d), 36.21 (t), 30.36 (t), 26.57 (t); *Anal.* Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.56; Found: C, 82.58; H, 8.78.

(110) (1*S*,5*S*)-Bicyclo[3.3.0]oct-3-en-2-one

Compound 122 was converted to 110 in 65% yield using Grieco's method.[223] IR: 2947, 1706, 1185cm^{-1}; ^{1}H NMR: 7.47 (1H, dd, J = 2.7, 6.1 Hz), 6.07 (1H, dd, J = 1.7, 5.6 Hz), 3.28 (1H, m), 2.61 (1H, m), 1.96 - 1.40 (5H, m) 1.31 - 1.10 (1H, m); ^{13}C NMR: 213.19 (s), 167.60 (s), 134.50 (d), 49.62 (d), 46.61 (d), 30.14 (t), 29.33 (t), 23.54 (t).

Compound 124

124 was obtained from 110 without purification of the intermediate products using the same four steps and conditions as were utilized in the conversion of (+)-113 to 122. The yield over the four steps was 30%: IR: 2960, 1700, 1620cm^{-1}; ^{1}H NMR: 6.42 (1H, t, J = 5.5 Hz), 2.84 (2H, m), 2.75 (2H, m), 2..63 (2H, m), 1.93 - 1.41 (7H, m); ^{13}C NMR: 205.38 (s), 151.40 (s), 138.60 (s), 58.80 (d), 53.16 (d), 47.81 (d), 37.82 (t), 35.69 (t), 32.55 (t), 29.01 (t), 26.24 (t); *Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.43; H, 8.68; Found: C, 81.73; H, 8.98.

(128) (4*S*)-4-(3-*tert*-Butyldimethylsilyloxypropyl)-2-cyclopenten-1-one.

A solution of 127 (5.4 g, 16.8 mmol) in 1,2-dichlorobenzene was refluxed for 4-5 h. The reaction was monitored by TLC using 3:1 pet. ether:ether. The resulting solution was cooled then added to the top of a dry silica gel column and eluted successively with pet. ether, 8:1 pet. ether:ether, then 2:1 pet. ether:ether to give 3.3 g (77%) of 128 as a yellow oil. $[\alpha]_D$ +39.6° (c = 0.9, MeOH); IR: 2929, 1745, 836cm^{-1}; ^{1}H NMR: 7.62 (1H, dd, J = 2.4, 5.6 Hz), 6.13 (1H, dd, J = 1.8, 5.6 Hz), 3.61 (2H, t, J = 6.0 Hz), 2.92 (1H, m), 2.52 (1H, dd, J = 6.3, 18.8 Hz), 1.98 (1H, dd, J = 2.1, 18.8 Hz), 1.65 - 1.20 (4H, m), 0.88 (9H, s), 0.02 (6H, s); ^{13}C NMR: 209.83, 168.35, 133.68, 62.31, 41.94, 41.00, 31.09, 30.67, 25.90, 18.29, -5.35; *Anal.* Calcd. for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.29; Found: C, 66.37; H, 10.54.

(129) (3*S*,4*S*)-3,4-Bis(3-*tert*-butyldimethylsilyoxypropyl)-2-cyclopentan-1-one

This ketone was prepared by the method given for ketone 127. The yield after chromatography (2:1 pet. ether:ether) was 82%. $[\alpha]_D$ -47.7° (c = 0.5, MeOH); IR: 2932, 1745, 1102, 837cm^{-1}; ^{1}H NMR: 3.59 (4H, t, J = 6.4 Hz), 2.43 (2H m), 1.80 (6H, m), 1.45 (4H, m), 1.21 (2H, m), 0.87 (18H, s), 0.03 (12H, s); ^{13}C NMR: 218.60 (s), 63.11 (t), 45.24 (t), 42.66 (d), 31.34 (t), 30.25 (t), 26.04 (q), 18.43 (s), -5.19 (q); *Anal.* Calcd. for $C_{23}H_{48}O_3Si_2$: C, 64.42; H, 11.28; Found: C, 64.75; H, 11.59.

(130) (3*S*,4*S*)-3,4-Bis(3-hydroxypropyl)-cyclopentanone

A solution of 129 (3.7 g, 8.7 mmol) in a mixture consisting of 2 mL of THF, 2 mL of H_2O and 6 mL of HOAc was stirred at 25°C for 24 h. The solvents were evaporated and the residue chromatographed using Florisil (EtOAc) to afford 1.6 g (94%) of 130 as a thick oil; $[\alpha]_D$ -90.0° (c = 0.58, MeOH); IR: 3404 br, 1735, 1055cm^{-1}; ^{1}H NMR: 3.62 (4H, t, J = 6.2 Hz), 2.45 (2H, m), 2.00 (2H, bs, exchangeable with D_2O), 1.82 (6H, m), 1.55 (4H, m), 1.23 (2H, m); ^{13}C NMR: 218.72 (s), 62.68 (t), 45.15 (t), 42.60 (d), 31.11 (t), 30.14 (t).

Diol 130 was converted to the dibromide 133 in the following manner. To 15 mL of dry CH_2Cl_2 were added 1.5 g (7.5 mmol) of 130 and 5.9 g (17.8 mmol) of CBr_4. The solution was cooled in ice and 4.7 g (17.8 mmol) of triphenylphosphine in 15 mL of CH_2Cl_2 was added dropwise. The reaction was allowed to stir and warm to room temperature overnight. The solvents were evaporated and the residue triturated with 2:1 pet. ether:ether. The solution was filtered, evaporated and chromatographed (3:1 pet. ether:ether) to give 133 as a yellow oil (1.8 g, 75%) which was used without further purification; IR: 2973, 1738cm^{-1}; ^{1}H NMR: 3.41 (4H, m), 2.42 (2H, m), 1.85 (10H, m), 1.38 (2H, m); ^{13}C NMR: 217.15, 44.93, 42.10, 33.57, 32.52, 31.24.

(132) Preparation of the Dimesylate from 130

To 1 ml of CH_2Cl_2 was added 0.1 g (0.5 mmol) of 130, and 0.15 g of triethylamine. The solution was cooled to 0°C and 0.17 g (1.5 mmol of MsCl was

added. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction was poured into dilute HCl, extracted and extracted with ether. The ether was dried and concentrated to give 0.2 g of a yellow oil. Chromatography (6:1 ether:pet. ether) gave 0.1 g of the dimesylate; IR: 2982, 1739, 1150cm^{-1}; ^{1}H NMR: 4.23 (4H, t, J = 6.4 Hz), 2.96 (6H, s), 2.42 (2H, m), 1.90 - 1.63 (10H, m), 1.27 (2H, m); ^{13}C NMR: 218.74. 69.74, 44.77, 42.18, 37.49, 29.62, 27.81.

Attempted Cyclization of (132) Dimesylate

To 3 mL of dry CH_2Cl_2 was added 0.1 g (0.2 mmol) of the dimesylate and 3 equiv. of DBU. The reaction was stirred at room temperature for 6 h and TLC analysis (6:1 ether:pet. ether) showed only starting material. The reaction was refluxed for 4 h and again TLC analysis showed only starting material. Work-up, followed by chromatography (6:1 ether:pet. ether) gave 90 mg of the dimesylate.

(131) Preparation of the Diiodide

To 5 mL of acetone was added 6 equiv. of NaI and 0.1 g of the dimesylate 132. The reaction was refluxed for 2.5 h, cooled and the acetone was removed. Flash chromatography (ether) gave 95 mg of the diiodide (75%); IR: 2980, 1737cm^{-1}; ^{1}H NMR: 3.22 (4H, m), 2.42 (2H, m), 1.80 (10H, m), 1.27 (2H, m); ^{13}C NMR: 217.18 (s), 44.93 (t), 41.85 (d), 34.84 (t), 31.88 (t), 6.56 (t).

Attempted Cyclization of the Diiodide (131)

To 1 mL of THF was added 0.1 g (0.2 mmol) of diiodide 131 and 2.2 equiv. of 1,4-diazabicyclo[2.2.1]octane (DABCO). The reaction was stirred for 6 h after which time TLC analysis (ether) showed no starting material and a complex mixture of products. Attempted Kugelrohr distillation (110 °C) at reduced pressure (0.2 mm) gave none of the expected ketone.

(91) *cis,anti,cis*-Tricyclo[6.3.0.0^{3,7}]undecan-2-one from Dibromide 133

Dibromide 133 (1.7 g, 5.2 mmol) was refluxed in 100 mL of ethanol containing 5.2 g (8 equiv.) of K_2CO_3 for 18 h. The ethanol was removed, 10 mL of water was added and the aqueous solution was extracted with ether. The ethereal solution was dried and evaporated to give 0.9 g of a yellow oil which was purified by Kugelrohr distillation [bp 80-90 °C (0.2 mm)] to give 0.75 g (86%) of 91 as a colorless oil, identical in all respects except its optical activity to the racemic material; $[\alpha]_D$ +166° (c = 1.2, MeOH).

(91) *cis,anti,cis*-Tricyclo[6.3.0.0^{3,7}]undecan-2-one from 124

A solution of 27 mg of 124 in 1 mL of ethyl acetate was hydrogenated over 10 mg of 10% Pd/C overnight. Filtration and evaporation afforded 28mg of a clear oil. ^{1}H NMR showed the product to be a 4:1 mixture of 91 and 94.

(92) (*S,S,S,S*)-*cis,anti,cis*-Tricyclo[6.3.0.$0^{3,7}$]undecan-2-ol

Reduction of (+)-91 in the same manner as was used for the racemic ketone afforded alcohol 92 whose spectroscopic properties were identical with the racemic material; $[\alpha]_D$ +153° (c = 1.03, MeOH).

Reactions of 91 and 92

Attempted Formation of Imines from 91

To 25 mL of dry toluene in a 25 mL r.b. flask fitted with a Dean-Stark water separator was added 48 mg (0.3 mmol) of 91, 50 mg of *tert*-butyl glycinate and 3 drops of $BF_3{\cdot}Et_2O$. The reaction was refluxed for several hours. GC analysis showed the disappearance of the starting ketone and the appearance of a new peak with a longer retention time. All attempts to isolate this unknown compound afforded only the starting ketone. The same experiment was tried substituting benzylamine for *tert*-butyl glycinate and again only the starting ketone could be isolated by either chromatography or distillation. Both reactions were carried out in an identical manner but in the absence of $BF_3{\cdot}Et_2O$ and no imine was formed (by TLC or GC).

(137) Esterification of 92 with Boc-glycine

Esterification was carried out by adapting the literature procedure.[236] To 20 mL of dry CH_2Cl_2 was added 0.2 g (1.3 mmol) of 92, 0.24 g (1.4 mmol) of Boc-glycine[235] and 35 mg of DMAP. The solution was cooled to 0 °C and a solution of

0.29 g (1.4 mmol) of DCC in CH_2Cl_2 was added dropwise. A precipitate formed immediately. The reaction was stirred at that temperature for 2 h then allowed to warm to room temperature overnight. The precipitated dicyclohexylurea (DCU) was filtered and the solvents were removed. Addition of EtOAc gave more precipitated DCU which was filtered. The EtOAc was removed and the residue was chromatographed (4:1 pet. ether:ether) to give 0.34 g of a thick oil (79%); IR: 3376, 2946, 1718 br, 1168cm^{-1}; ^1H NMR: 5.02 (1H, bs), 4.97 (1H, t, J = 6.6 Hz), 3.84 (2H, bs), 2.68 (1H, m), 2.45 (1H, m), 2.05 (2H, m), 1.78 - 1.21 (12H, m), 1.43 (9H, s); ^{13}C NMR: 170.28 (s), 165.39 (s), 84.62 (d), 79.96 (s), 50.36 (d), 49.62 (d), 49.10 (d), 48.10 (d), 42.69 (t), 34.15 (t), 33.64 (t), 30.23 (t), 28.41 (q), 26.42 (t), 26.07 (t), 25.52 (t).

(137) Benzophenone Imine of Glycine Ester

To 10 mL of a 1:1 mixture of EtOH/Et_2O was added 0.33 g (1 mmol) of 136 and 0.23 g of PTSA·H_2O. The solution was refluxed for 24 h. TLC analysis (3:1 pet. ether:ether) showed the disappearance of the starting amide. The solvents were removed and the resulting residue was treated with a dry CH_2Cl_2 solution of 0.22 g (1.1 mmol) of diphenylmethylenimine.[238] A precipitate formed immediately. The reaction was stirred overnight. After removing the precipitate by filtration, the solvent was removed and the residue was chromatographed (4:1 pet. ether:ether) to give 0.32 g of a clear oil (86%). TLC (same solvent system) showed some benzophenone was present; IR: 2944, 1739, 1661, 1277, 702cm^{-1}; ^1H NMR: 7.98 -

7.10 (10H, m), 4.98 (1H, t, J = 6.7 Hz), 4.20 (2H, s), 2.71 (1H, m), 2.50 (1H, m), 2.11 (2H, m), 1.90 - 1.15 (10H, m), 0.88 (2H, m); ^{13}C NMR: 171.90, 170.80, 139.36, 136.06, 132.66, 130.62, 130.27, 128.90, 128.82, 128.45, 128.21, 127.64, 84.04, 55.88, 50.23, 49.41, 49.05, 48.02, 34.23, 33.70, 30.26, 26.46, 26.07, 25.56.

(138) Benzylation of 137

LDA was prepared by adding 44 μL of diisopropylamine to 0.5 mL of dry THF. The solution was cooled to -78 °C and 125 μL of n-BuLi (2.5M in hexanes) was added. The cold bath was removed for 15 min then was replaced. A THF solution of 0.1 g (0.26 mmol) of 137 and 1 equiv. of HMPA was added dropwise. A yellow solution resulted. After stirring for 45 min at -78 °C 1 equiv. of benzyl bromide in THF was added and the reaction was allowed to stir for 1 h. TLC analysis (4:1 pet. ether:ether) showed only starting materials. The reaction was allowed to warm to -40 °C and stirred for 1 h. TLC analysis (4:1 pet. ether:ether) showed only starting materials. The reaction was warmed to 0 °C and stirred for 1 hour. TLC analysis now showed the disappearance of starting material. After the addition of 10 mL of H_2O, the reaction was allowed to warm to room temperature. Ether was added and the layers were separated. The aqueous layer was extracted with ether, the combined ether layers were dried and concentrated to 0.18 g of a yellow oil. Chromatography (4:1 pet. ether:ether) gave 0.14 g (88%) of a yellow oil; IR: 2951, 1742cm^{-1}; ^{1}H NMR: 7.89 - 6.95 (13H, m), 6.56 (2H, m), 4.90 (1H, t, J = 6.3 Hz)[4.91 (1H, t, J = 6.2 Hz)], 4.23 (1H, dd, J = 4.2, 9.2 Hz), 3.29 (1H, 1/2 ABq, J = 4.2, 13.2 Hz),

3.19 (1H, dd, J = 9.3, 13.2 Hz), 2.71 (1H, m), 2.45 (1H, m), 2.06 (2H, m), 1.89 - 1.19 (11H, m), 0.90 (1H, m); ^{13}C NMR: many peaks; Cap.Column GC: 1 peak (no starting material)(70 °C for 0 min - 15 °C/min); MS (EI): m/z 477(M^+), 386, 284, 238, 182, 149, 120, 105, 91, 77; de 11%.

The reaction was repeated at 0 °C in the absence of HMPA and worked up in the manner described above. The results are shown in Table 1.

(139) Propionic Ester of Alcohol 92

Racemic 92 (0.4g, 2.4 mmol), 0.3g of AgCN and 0.33g (3.3 mmol) of propionyl chloride were added to 5 ml of dry benzene and was heated to reflux for 12 hours. After cooling, the mixture was filtered through hyflow, and the solvent was removed. Chromatography (2:1 pet. ether: ether) gave 0.45 g of a clear oil. IR: 2977, 1746, 1105cm^{-1}; ^{1}H NMR: 4.78 (1H, t, J = 6.6 Hz), 2.75 (1H, m), 2.45 (1H, m), 2.33 (2H, q, J = 7.5 Hz), 2.11 (2H, m), 1.88 - 1.15 (12H, m), 1.05 (3H, t, J = 7.5 Hz); ^{13}C NMR: 174.53, 83.23, 50.53, 49.62, 49.13, 48.03, 34.25, 33.74, 30.24, 28.01, 26.47, 26.00, 25.52, 9.41.

We attempted to alkylate ester 139 in the same manner as 137 at -78 °C and after quenching at -78 °C and work-up only the starting ester was obtained (92%).

(140) Acrylic Ester of Alcohol 92

Racemic 92 (0.4 g, 2.4 mmol), 0.3g of AgCN and 0.3 g (3.3 mmol) of acryloyl chloride were added to 5 mL of dry benzene and refluxed overnight. After cooling,

the mixture was filtered through a pad of Hyflow, concentrated and distilled [Kugelrohr, bp 60-70 °C (0.2 mm)] to give 0.48 g (89%) of 140 as a clear oil; IR: 2949, 1724, 1270, 1196cm^{-1}; ^{1}H NMR: 6.35 (1H, dd, J = 1.6, 17.5 Hz), 6.09 (1H, dd, J = 10.4, 17.5 Hz), 5.77 (1H, dd, J = 1.6, 10.3 Hz), 4.90 (1H, t, J = 6.5 Hz), 2.71 (1H, m), 2.50 (1H, m), 2.08 (2H, m), 1.85 - 1.29 (12H, m); ^{13}C NMR: 166.24, 130.14, 129.10, 83.50, 50.31, 49.63, 49.08, 48.05, 34.11, 33.59, 30.16, 26.34, 25.95, 25.43.

Successful Diels-Alder Reaction of 140 with Cylcopentadiene

A solution of $TiCl_4$ (1M in CH_2Cl_2, 0.35 mL) was added to a solution of 50 mg of racemic 140 (0.2 mmol) in toluene under a nitrogen atmosphere at 0 °C. The solution was stirred for 15 min and then 2.5 equiv. of freshly distilled cyclopentadiene was added. The mixture was stirred for 1.5 h at 0 °C and then quenched with water. The solution was extracted with ether, the extracts were dried, concentrated and flash chromatographed (20:1 hexanes:ether) to give 46 mg of a yellow oil which was contaminated with about 20% of the starting ester as judged by GC. The ^{1}H NMR showed approx. a 4:1 mixture of diastereomers of the cycloadduct. This oil was added to 18 mg of LAH in 1.5 mL of dry THF at 0°C and allowed to stir at ambient temperature overnight. Standard workup followed by chromatography gave 18 mg (61%) of a clear oil whose NMR spectra were identical to those reported for 141.[243a]

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Appendix A: Reactions of 3,6-Dihydro-1,2-thiazine-1-oxides

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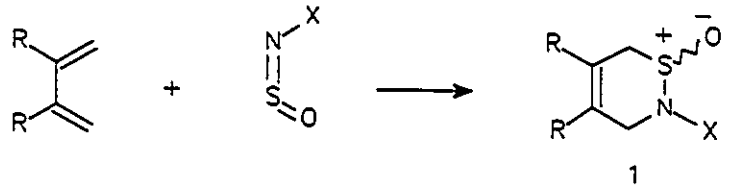
Introduction

The [4+2] cycloaddition reaction between an *N*-sulfinyl compound and a conjugated diene has been known for many years. [1-5] The product of this reaction is a 2-substituted 3,6-dihydro-1,2-thiazine-1-oxide (1) (Figure 1). Until very recently it was believed that the cycloaddition reaction was possible only if an electron withdrawing group (X= COOR, SO_2R, Ar, CN, S^+Me_2) was present on the nitrogen atom. Electron withdrawing functionalities such as acyl groups or sulfonyl groups allow the cycloaddition reaction to take place at or below room temperature. *N*-Aryl sulfinyl compounds are less reactive towards dienes and often require heating for cycloaddition to occur.

Figure 1: 3,6-dihydro-1,2-thiazine-1-oxide



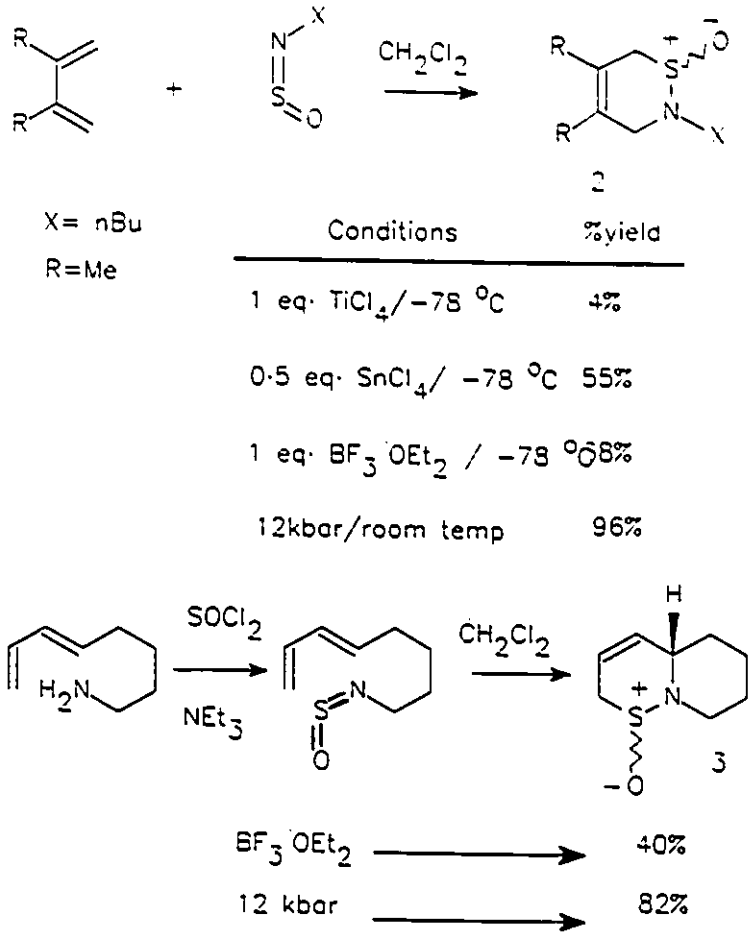
1

X=electron withdrawing group

N-sulfinyl compounds with electron donating substituents on the nitrogen (for example aliphatic *N*-sulfinylamines) have been reported to be unreactive towards 1,3-dienes under normal conditions. However, Weinreb[6] recently demonsurated that *N*-sulfinyl-n-butylamine reacted with 2,3-dimethyl-1,3-butadiene to give 2 when the cycloaddition was conducted in CH_2Cl_2 at -78 °C using one equivalent of Lewis acid as a catalyst (Figure 2). The authors reported[6] that $BF_3{\cdot}OEt_2$ gave the highest yield of the cycloadduct (68%). The same report indicated that if the reaction was carried out at

12 kbar in CH_2Cl_2 quantitative yields (96%) of the cycloadduct could be isolated.

Figure 2: Lewis acid catalyzed cycloaddition



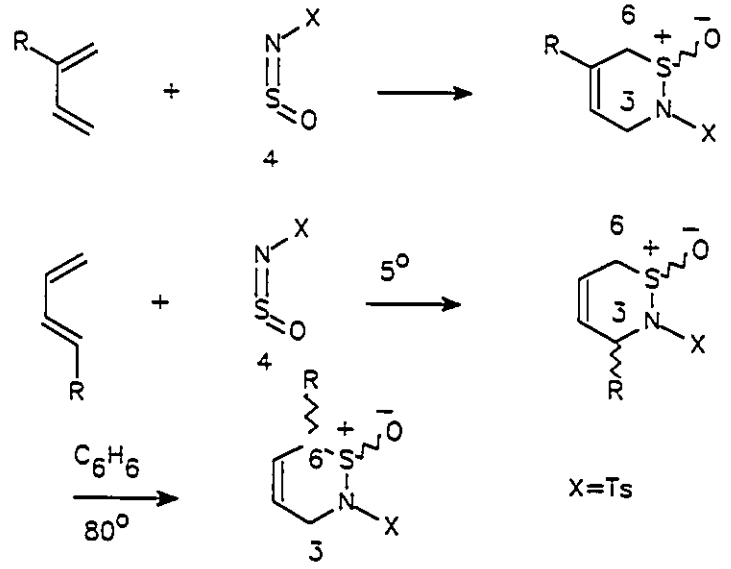
The bicyclic compound (3) was also prepared by the same group *via* an intramolecular cycloaddition using both the high pressure method or Lewis acid catalysis (Figure 2).[6]

The starting *N*-sulfinyl compounds are commonly prepared by the treatment of the parent anilines, amines, amides, urethanes or sulfonamides with thionyl chloride and pyridine.[1-3] The resulting *N*-sulfinyl compounds can often be distilled or recrystallized but are *very* water sensitive.

Two geometric isomers are possible for *N*-sulfinyl compounds. However X-ray studies have shown that *N*-sulfinylamines anilines and sulfonamides all exist in the *Z*-configuration.[3] Although ^{1}H NMR studies have shown that *N*-sulfinylanilines exist solely as the *Z*-isomer in solution[7], work by Kresze[8] using ^{13}C NMR indicated that an *E/Z* isomerization is possible for some *N*-sulfinylanilines in solution.

The regioselectivity of the cycloaddition reaction has been studied by Kresze (Figure 3).[9] He found that the reaction of *N*-sulfinyl-p-toluenesulfonamide (4) with 2-substituted-1,3-dienes gave 5-substituted dihydrothiazine oxides exclusively. Conversely, the regiochemistry of the cycloaddition of 4 with 1-substituted-1,3-dienes was found to be temperature dependent.

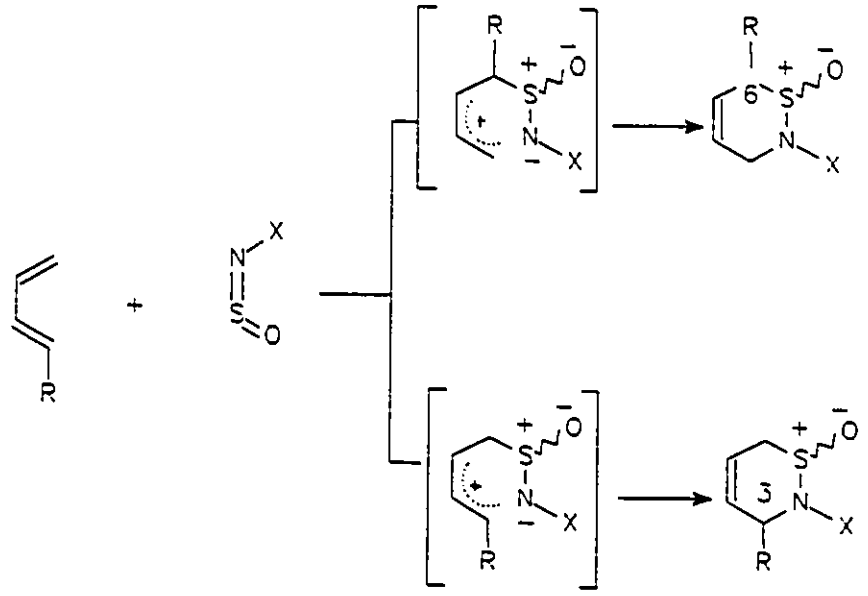
Figure 3: Regiochemistry of cycloaddition



At low temperatures (0 °C) only the 3-substituted dihydrothiazine oxides were isolated. However, heating the 3-substituted cycloadduct in benzene afforded the 6-

substituted dihydrothiazine oxide as the sole product.[1,9] Kresze[1,9] proposed that the 3-substituted adduct is the kinetic product and at higher temperatures the kinetic product is isomerized to the less sterically crowded thermodynamic product *via* a retro-Diels Alder process. Kresze also proposed[5] a mechanistic model for the cycloaddition reactions which implied that the cycloaddition is concerted but has some dipolar character (Figure 4).

Figure 4: Mechanism of formation

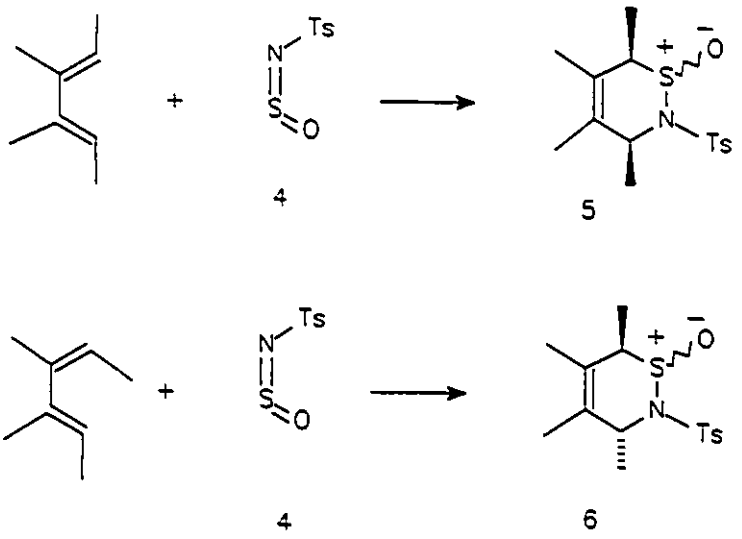


The mechanism was supported by the observation that under kinetically controlled conditions the regiochemistry of the cycloaddition was governed by the electronic characteristics of the R group in the 1-position on the diene. If the R group was electron-withdrawing (eg. COOMe), the 6-substituted isomer (kinetic product) was formed exclusively. When the R group was electron-donating the 3-substituted adduct (kinetic product) was formed exclusively since the R group stabilizes the allylic cation

formed in the transition state.

In spite of the fact that the cycloaddition is thought to proceed with some dipolar character it occurs with excellent stereospecificity with respect to the 1,3-diene.[5] For example, (*E*,*E*)-3,4-dimethyl-2,4-hexadiene reacts with 4 to give sulfonamide 5 stereospecifically. The (*E*,*Z*)-isomer reacts with 4 to give sulfonamide 6 stereospecifically (Figure 5).[5]

Figure 5: Stereospecificity of cycloaddition



Several groups have studied the conformation of the [4+2] cycloadducts using X-ray crystallography and it was shown that in the solid state the adducts exist in a half-chair conformation with the oxygen-sulfur bond in the quasi-axial position.[10,11] It was suggested that the tendency for oxygen to be quasi-axial in these adducts was due to the anomeric effect.[12] It should also be noted that the adducts formed from the cycloaddition reaction are formed as enantiomeric pairs due to the presence of configurationally stable chiral sulfur atom.

There are many well known transformations of 3,6-dihydrothiazine oxides which have been the subjects of several reviews.[1-3] Most of these involve cleavage of the sulfur-nitrogen bond since the sulfur atom is readily attacked by nucleophiles. For example, the hydrolysis of a 3,6-dihydrothiazine oxide under mildly acidic or mildly basic conditions affords a homoallylic amino compound (Figure 6). The reaction is thought to proceed through an intermediate allylic sulfinic acid which loses SO_2 *via* a retro-ene process.[13]

Figure 6: Hydrolysis reaction

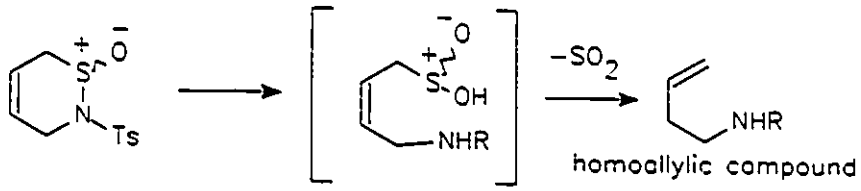
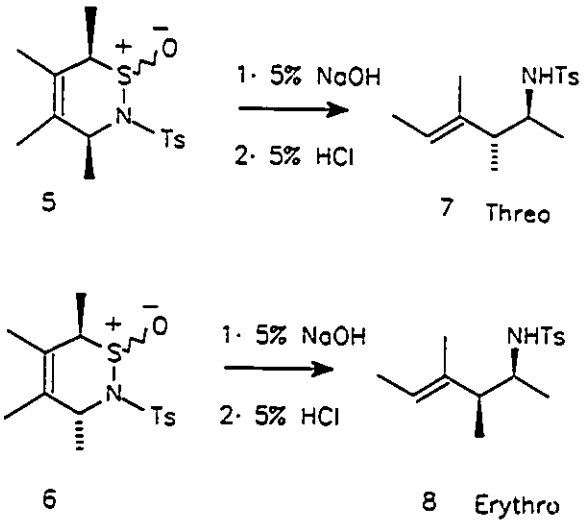


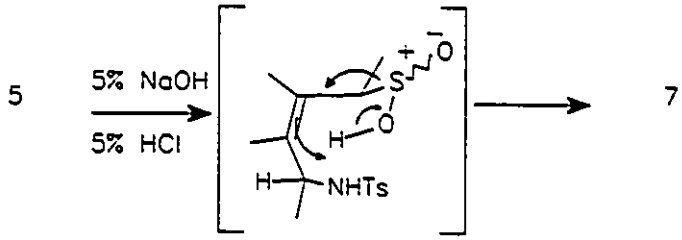
Figure 7: Homoallylic nitrogen compounds



Weinreb[5] has exploited this type of reaction in the stereoselective formation of

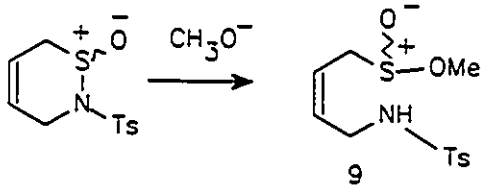
both *erythro* and *threo* homoallylic nitrogen compounds (Figure 7). When compounds 5 and 6 were treated with dilute base followed by dilute acid, the sulfonamides 7 and 8 were isolated. The stereospecificities of the reactions were rationalized by a concerted retro-ene reaction involving an intermediate sulfinic acid and the anchoring effect of the substituent at C-1 in the intermediate sulfinic acid. The C-1 substituent assumes the pseudo-equatorial position to avoid $A^{1,3}$ strain with the C-4 substiuent (Figure 8).[4]

Figure 8: Anchoring effect



The sulfur atom of 3,6-dihydrothiazine-1-oxides is also attacked readily by nucleophiles other than water and hydroxide. It has been reported by Wucherpfennig[14] that dihydrothiazine oxides can be cleaved by reaction with methoxide to afford sulfinate esters (9) (Figure 9).

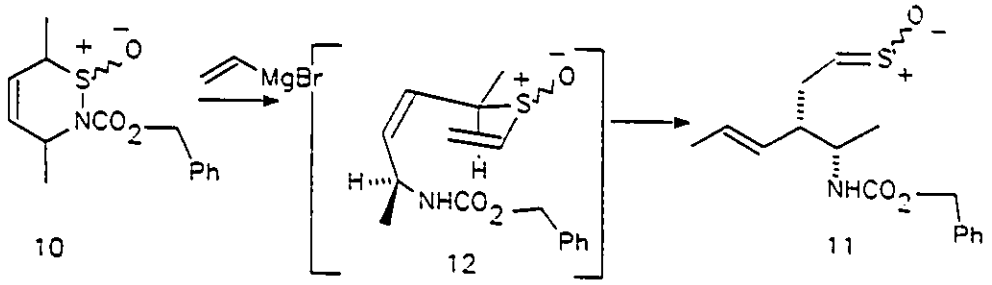
Figure 9: Sulfinate ester



Weinreb has also found that a number of *N*-acyl-dihydrothiazine oxides are susceptible to ring opening by a variety of carbon nucleophiles.[4,5,10,15,16] For example, vinyl magnesium bromide cleaves the sulfur-nitrogen bond in dihydrothiazine oxide 10 affording sulfine 11. The

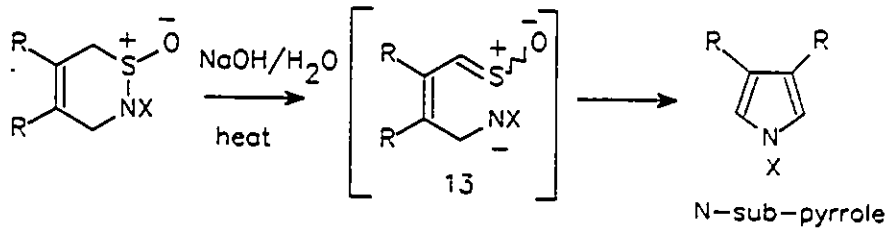
transformation was assumed to occur initially *via* an intermediate vinyl sulfoxide (12), which subsequently undergoes a [3,3] sigmatropic rearrangement *via* a chair-like transition state with the methyl group in the pseudo-equatorial position to afford 11 (Figure 10).[17]

Figure 10: Ring opening with carbon nucleophiles



Another interesting rearrangement reported in the literature involves the reaction of *N*-aryl-dihydrothiazine oxides with alkali under vigorous conditions. *N*-arylpyrroles are isolated from the reactions in modest yields (Figure 11).[1] It has been proposed that the rearrangement occurs throught an intermediate vinyl sulfine 13.[14,18,19]

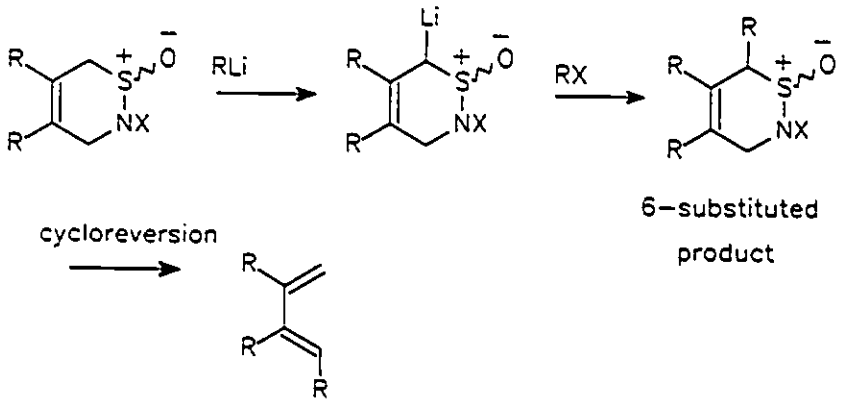
Figure 11: Rearrangement of N-arylpyrrole



Although it appears that most 3,6-dihydrothiazine-1-oxides are susceptible to nucleophilic attack at sulfur or that deprotonation α to sulfur (*N*-aryl-dihydrothiazine oxide) using vigorous conditions leads to ring opened and rearranged products, it was

our initial aim to extend the synthetic utility of these compounds. Our goal was to metallate a 3,6-dihydrothiazine-1-oxide adjacent to sulfur and react the metallated compound with an electrophile. This would provide a useful means of preparing 6-substituted 3,6-dihydrothiazine oxides from the unsubstituted analogues. A longer term goal was to effect an alkylation of the terminal position of a 1,3 diene by utilizing a retro-Diels Alder reaction of the 6-substituted thiazine oxides (Figure 12).

Figure 12: Proposed synthetic utility

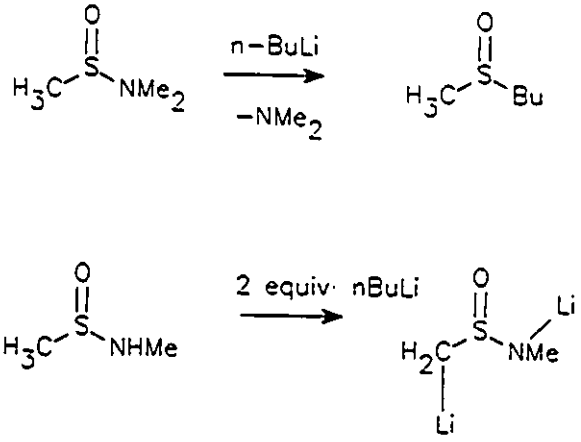


To that end, we decided to examine the alkylation reaction of 1 and the possibility of effecting the retro Diels-Alder reaction.

Results and Disscusion

Several examples appear in the literature which demonstrate that it is possible to metallate acyclic sulfinamides using alkyllithium reagents or LDA in THF at low temperatures. Corey and Durst[20] described the attempted metallation of *N,N*-dimethyl methanesulfinamide with either *n*-butyllithium or *tert*-butyllithium in THF. They found that the reaction did not lead cleanly to the α-lithio derivative. The alkyllithium reagent (*n*-butyllithium and *tert*-butyllithium) most often attacked the sulfur atom and displaced dimethylamine. However, the authors reported that *N*-monosubstituted methanesulfinamides could be easily metallated using two equivalents of alkyllithium reagent at low temperatures (Figure 13).

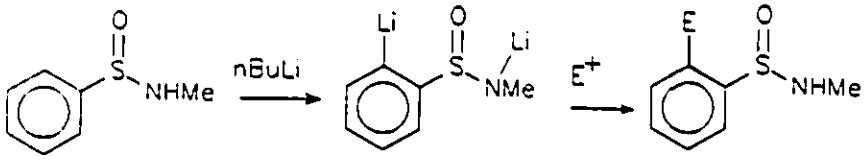
Figure 13: Corey and Durst investigation



More recently it has been shown[21] that the direct metallation of mono-*N*-substituted benzenesulfinamides could be effected using 2 equivalents of *n*-butyllithium in THF at low temperature (Figure 14). The authors commented that nucleophilic attack at sulfur by the alkyllithium reagent would be discouraged by

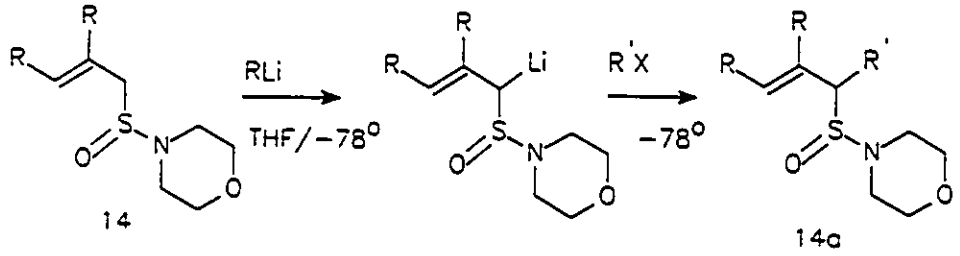
initial anion formation at nitrogen.

Figure 14: Directed metallation



A more pertinent report by Julia[22] demonstrated that *N*-alkyl sulfinamide 14 (Figure 15) could be metallated using either LDA or MeLi in THF at low temperature. The α-lithio derivative was stable at low temperatures and could be alkylated using benzylic or allylic halides to give a diastereomeric mixture of sulfinamides 14a. No comment was made about the relative stereochemistry of the newly formed center. However, the results indicated that isomerization of the carbon-double bond had not occured.

Figure 15: Julia's alkylation of N-alkyl sulfinamides



14

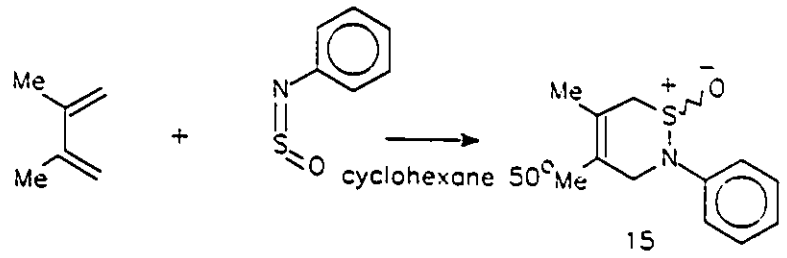
14a

Although Julia's report appeared to contradict the findings of Corey and Durst, Julia proposed that nucleophilic attack on sulfur by the base did not occur due to the increased acidity of the allylic methylene protons.

We began by examining the metallation and alkylation of *N*-phenyl-substituted dihydrothiazine oxide 15 (Figure 16). Cycloadduct 15 was prepared from *N*-

sulfinylaniline and 2,3-dimethyl-1,3-butadiene in 84% yield using a published procedure.[2]

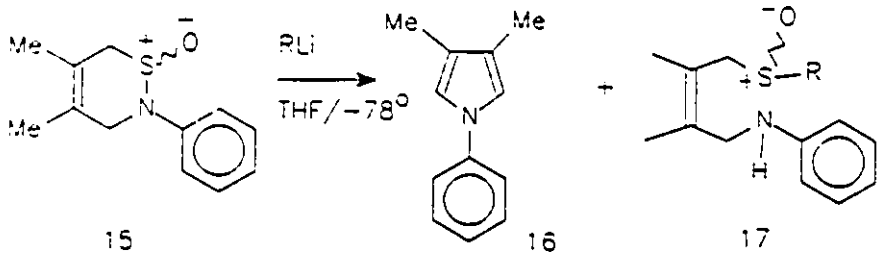
Figure 16: Preparation of 15



As previously noted, most *N*-arylsulfinylamines require some heating to effect the cycloaddition with dienes and this reaction was no exception since we found that no reaction occured at room temperature. However, it is noteworthy that extreme caution was used when heating the reaction since it has been reported that exccessively high temperatures may cause a violent decomposition.[2] The reactions of 15 with Li bases in THF at -78 °C are shown in Figure 17. In all cases a THF solution of 15 was added to a THF solution of the base which had been previously cooled to -78 °C. The reaction was stirred for 30 minutes after which time TLC analysis showed the absence of starting material. The reactions were quenched at -78 °C with water and allowed to warm to room temperature.

When *n*-butyllithium was used as the base TLC analysis revealed the presence of two compounds (16 and 17), a polar compound and a less polar compound. These compounds were separated using column chromatography and it was confirmed that the less polar compound was *N*-phenylpyrrole and the more polar compound was the sulfoxide 17 which is the product of nucleophilic attack on sulfur by *n*-butyllithium.

Figure 17: Attempted metallation of 15

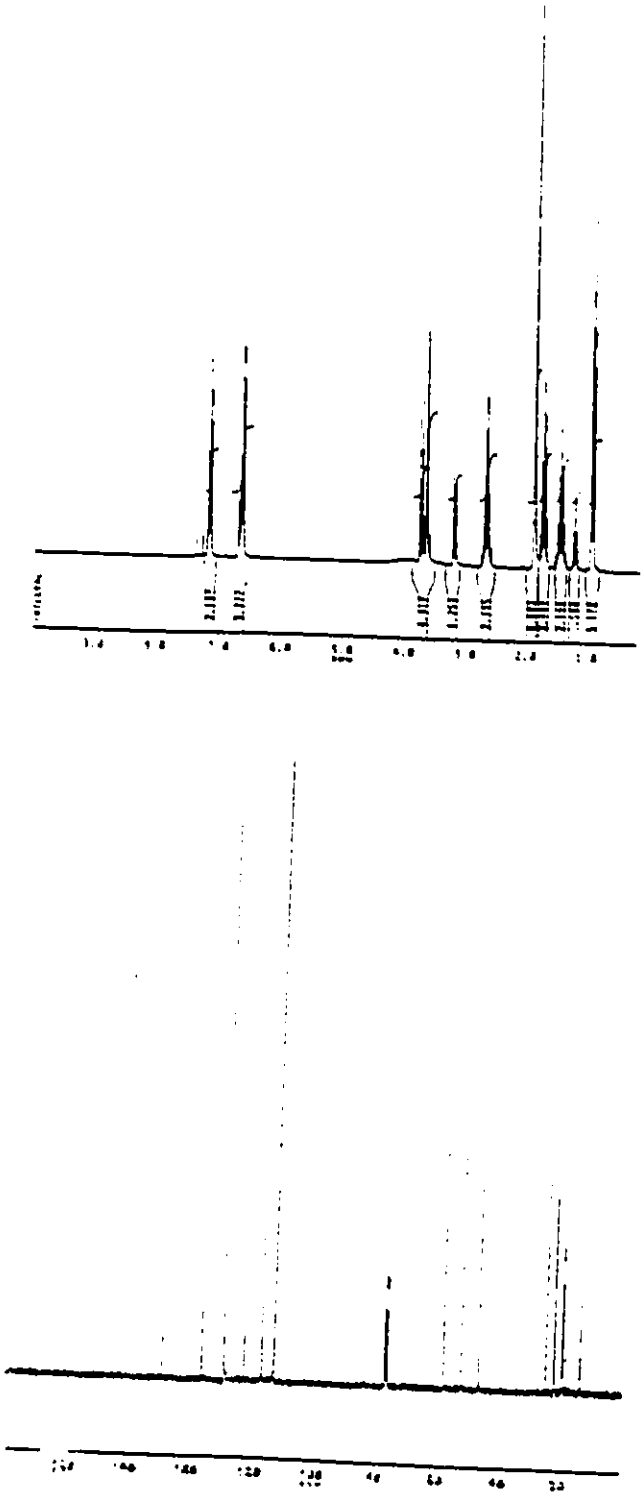


	% yield	
R=Bu	68	22
R=^{t}Bu	80	0
R=DIA	95	0

The ^{1}H NMR and ^{13}C NMR of 16 was in agreement with that in the literature.[23] The ^{1}H NMR of compound 17 (Figure 18) showed that a butyl group had been incorporated into the molecule, and the IR spectrum indicated the presence of an NH (3300 cm^{-1}) and a sulfoxide group (1040cm^{-1}). The isolation of 17 indicated that nucleophilic attack at sulfur by *n*-butyllithim was competing with the α-deprotonation and subsequent rearrangement of the intermediate vinylsulfine to *N*-phenylpyrrole.

When LDA or *tert*-butyllithium were used as the base high yields (95% and 80% respectively) of *N*-phenyl pyrrole were isolated from the reaction mixture. Apparently the steric bulk of these bases impeded nucleophilic attack on the sulfur atom. Although the use of the more sterically demanding bases eliminated the problem of nucleophilic attack on the sulfur atom and subsequent cleavage of the S-N bond, it was apparent that the monoanion of 15 was unstable even at -78 °C since in

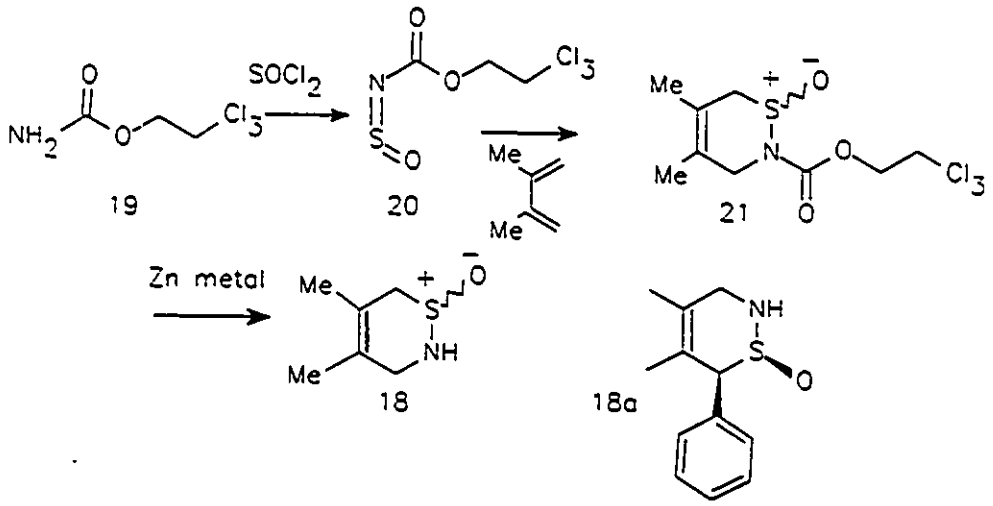
Figure 18: ^{1}H NMR and ^{13}C NMR of 17



all cases no starting material was recovered and the anion rearranged cleanly to *N*-phenylpyrrole.

It has already been noted that the initial formation of an anion on the nitrogen atom of a sulfinamide should eliminate the possibility of nucleophilic attack by base on the sulfur atom. We therefore decided to prepare 3,6-dihydro-2*H*-1,2-thiazin-1-oxide (18) (Figure 19) and attempt to alkylate the corresponding dianion. Compound 18 was prepared by adapting a literature procedure[24] (Figure 19). Urethane 19[25] was treated with thionyl chloride in ether at 0°C in the presence of 2 equivalents of pyridine.

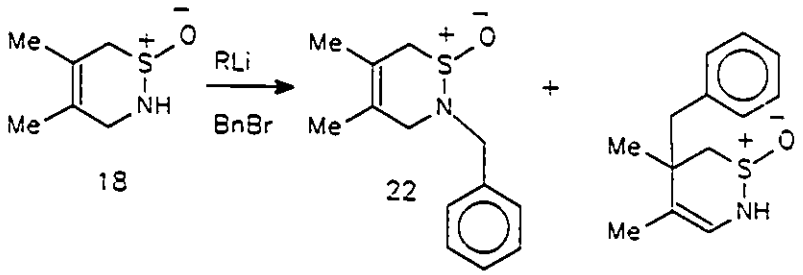
Figure 19: Preparation of 18



The corresponding sulfinyl compound 20 was isolated and distilled under vacuum to give a 73% yield of a yellow oil. To avoid hydrolytic decomposition of 20, it was immediately added to an anhydrous ether solution of 2,3-dimethyl-1,3-butadiene. After stirring the reaction under nitrogen overnight at room temperature, addition of

petroleum ether caused cycloadduct 21 to precipitate. A 94% yield of the stable cycloadduct was isolated. The methylene protons in the ^{1}H NMR of 21 appeared as AB quartets as a result of the chiral sulfur atom. The nitrogen protecting group was removed by a reductive procedure. Reduction occured readily by refluxing 21 with activated Zn metal in dry *tert*-butyl alcohol overnight and gave a 74% yield of the desired dihydrothiazine oxide 18 which was purified by recrystallization from acetone. The methylene protons of dihydrothiazine oxide 18 also appeared as AB quartets. As in 18a[26] (Figure 19) the protons *syn* to oxygen appeared at lower field (δ 3.85 J=16.1Hz and 3.40 J=16.4Hz) than the protons *anti* to oxygen (δ 3.22 J=16.1Hz, δ 2.85 J=16.4Hz) due to the deshielding effect of the sulfur-oxygen bond.

Figure 20: Attempted alkylation of 18



18 22 23

base	%yield	
2·2 equiv· BuLi	21	0
2·2 equiv· LDA	19	0

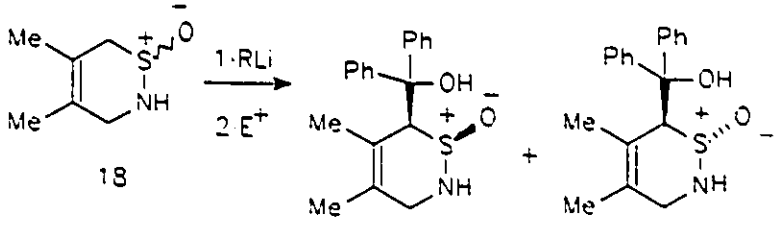
The alkylation results of 18 with benzyl bromide are shown in Figure 20. Alkylations with *n*-BuLi and LDA were carried out by adding a THF solution of 18 dropwise to a cooled (-78 °C) solution of the base. Addition of the dihydrothiazine oxide had to be slow since often times a fast addition caused the starting material to

precipitate from the cold solution. Slow addition gave a yellow solution of the presumed dianion. This solution was stirred for 30 minutes and then a THF solution of benzyl bromide was added. After stirring for 1 hour the reaction was quenched by the addition of water and allowed to warm to room temperature. As can be seen from the results in Figure 20 the formation of the dianion of 18 appears to be difficult (if dianion is forming at all). In all of the cases, only the product of *n*-alkylation (22) was isolated along with an unidentifiable mixture of products and starting material. Our results were confirmed in a subsequent publication by Weinreb[27] where he found that the deprotonation and alkylation of 18 gave mostly *n*-alkylated product. Weinreb however, did indicate that on several occasions compound 23 (Figure 20) was isolated, albeit in very low yield. Weinreb did not comment on the stereochemisty of the addition (*syn* or *anti* to oxygen).

Since it did not seem possible to **alkylate** 18 we decided to examine the use of carbonyl electrophiles. Compound 18 was lithiated using both LDA and *n*-BuLi in the same manner as described above for the alkylation reactions. The aldol reactions were carried out by adding the appropriate carbonyl compound to the dianion of 18 at -78 °C. After stirring for 1 hour at that temperature the reactions were quenched by the addition of water and allowed to warm to room temperature. The results are shown in Figure 21. The aldol reaction of the supposed dianion of 18 with benzaldehyde gave an inseparable mixture of 4 diastereomers (the ratio could not be determined by GC or ^{1}H NMR) and starting material. Mass spectral analysis and the IR spectrum (FIMS: m/z 251, IR 3380-3200, 3001, 1060) indicated that some aldol

product was present. Only in the aldol reaction with benzophenone were the aldol products separated and fully characterized. As shown in Figure 21 the aldol reaction using both *n*-BuLi and LDA as the bases gave two diastereomeric products (24 and 25) in about the same ratio (5.5:1).

Figure 21: Aldol reaction of 18



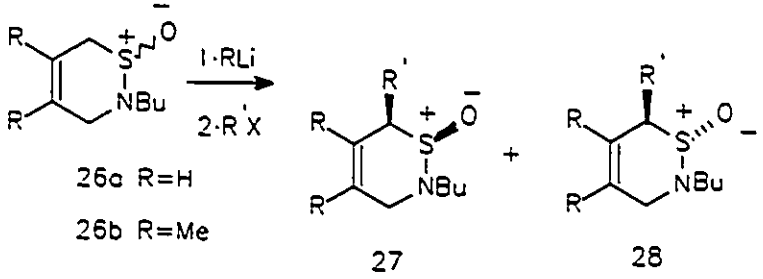
base	%yield	
2·2 equiv· BuLi	63	11
2·2 equiv· LDA	49	9

The DEPT-135 edited ^{13}C NMR of both diastereomers confirmed the presence of two quaternary olefinic carbons, and therefore indicated that the aldol reaction had taken place adjacent to sulfur. The proton NMR of the major diastereomer (24) indicated the presence of two exchangeable hydrogens (OH and NH) using D_2O exchange and had a 1 H singlet at δ 4.31 ppm corresponding to the proton adjacent to sulfur. The proton NMR of the minor diastereomer (25) was similar (two exchangeable hydrogens). The proton adjacent to sulfur appeared as a singlet and was slightly downfield at δ 4.59 ppm. Comparison of the chemical shift values of the α-protons for both diastereomers indicated that the major aldol product resulted from attack of the electrophile *syn* to the sulfur-oxygen bond and the minor product was the result of

attack *anti* to the sulfur-oxygen bond. Unfortunately, we were not successful at growing X-ray quality crystals of either diastereomer to confirm our assignments.

At about this point in the project a paper was published by Weinreb[27] which reported the successful alkylation reaction of the *N*-butylthiazine oxides 26a and 26b with both benzyl bromide and methyl iodide. He reported that both dihydrothiazine oxides could be lithiated equally well with LDA or MeLi in THF at -78 °C. Alkylation of the anions gave compounds 27 and 28 (Figure 22). Weinreb established the relative stereochemistry of the alkylated products using a combination of ^{1}H NMR europium induced shift experiments and X-ray crystallography.

Figure 22: Weinreb's alkylations

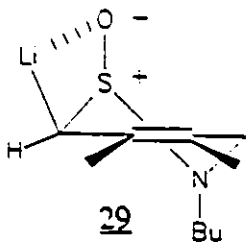


R	base	R'X	yield	ratio 27:28
H	LDA	BnBr	96%	34:66
H	MeLi	BnBr	82%	28:72
Me	LDA	BnBr	99%	11:89
Me	MeLi	BnBr	77%	9:91

He explained the observed stereochemical results by proposing that the lithium atom is bonded to both the α carbon and the quasiaxial oxygen atom and in effect the top

face of 29 (Figure 23) is blocked, thus resulting in alkylation occuring in an *anti* fashion.

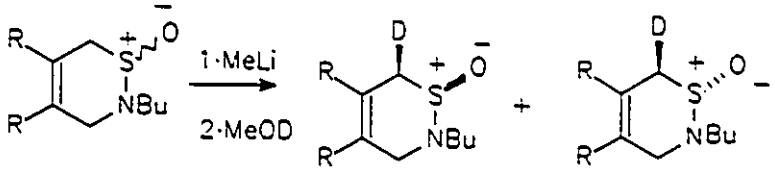
Figure 23: Li anion



29

In the same paper Weinreb investigated the analogy between 29 and metaliated sulfoxides. It has been shown that oxygenated electrophiles react with α-lithio sulfoxides in a *syn* manner via initial coordiation with the metal.[28-31] He[27] showed the reaction of the lithiated dihydrothiazine oxide 26b with MeOD gave exclusively the *syn* product 30 (Figure 24).

Figure 24: Deuteration experiment



26b R=Me

30

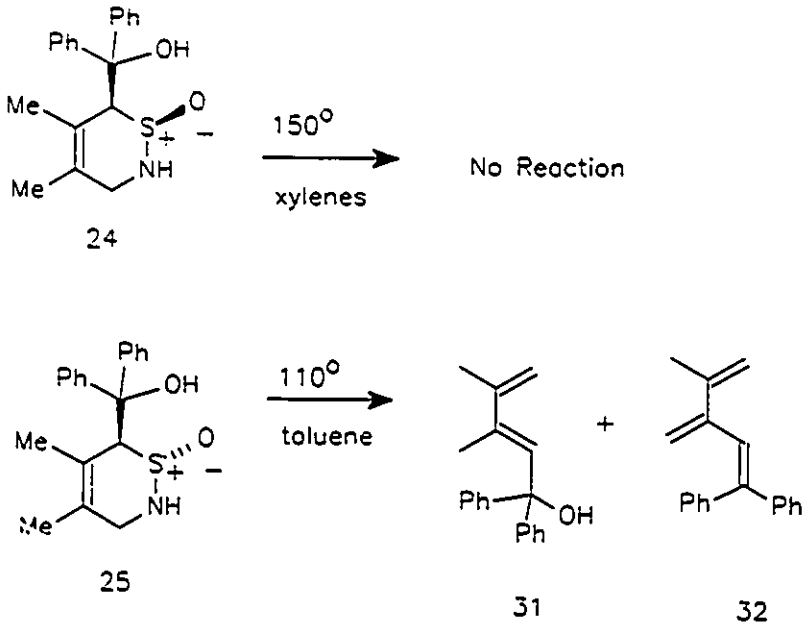
Weinreb's results agree well with our assignments of the relative stereochemistry of the aldol products 24 and 25. Our results and those of Weinreb indicate that oxygenated electrophiles react with lithiated dihydrothiazine oxides preferentially *syn* to the quasi-axial sulfur-oxygen bond by initial coordination of the oxygen to the Li atom and non-oxygenated electrophiles react preferentially in an *anti* fashion.

Attempted Reverse Diels Alder Reactions

Cycloreversion reactions are often carried out under thermal conditions.[32] In an attempt to carry out a reverse Diels-Alder reaction, compound 24 (*syn* aldol product) was refluxed in toluene or xylene for 24 hours and TLC analysis showed only starting material.

We then attempted the cycloreversion reaction conditions for 25. Compound 25 was refluxed in toluene for 12 hours. TLC analysis revealed the disappearance of the starting material and the appearance of two new compounds (polar compound and a very non polar compound, 31 and 32, Figure 25).

Figure 25: Cycloreversion reaction

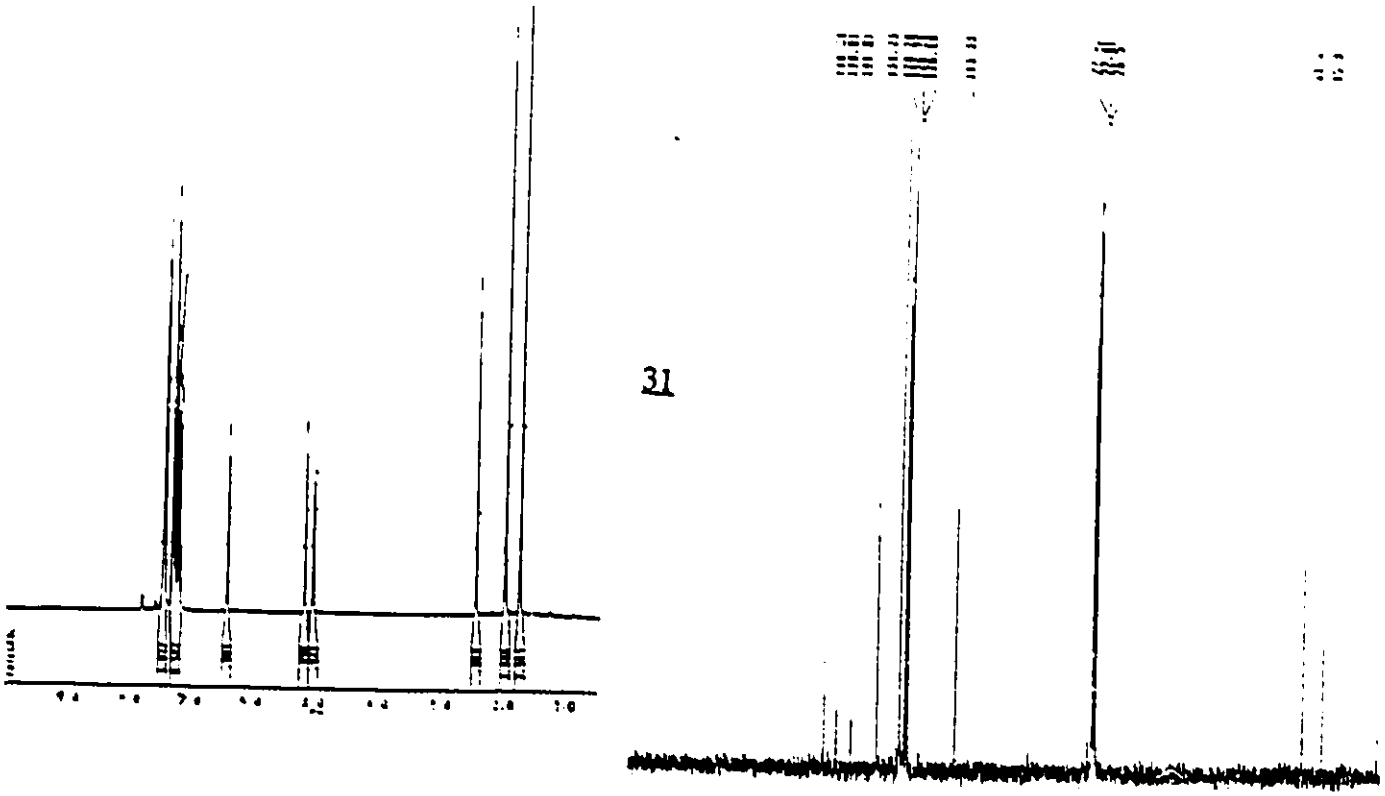


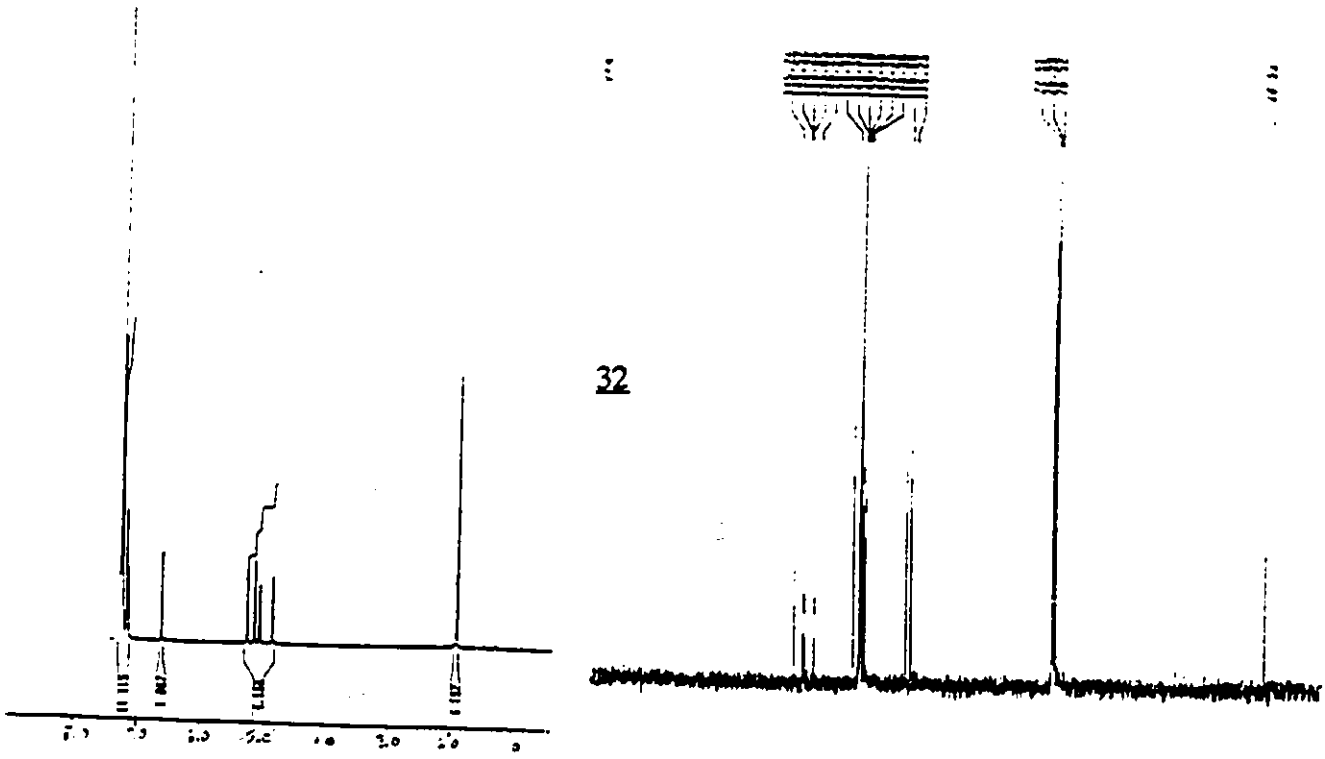
The crude NMR showed that these compounds were present in a 3:1 ratio. Column chromatography separated 31 and 32 in a combined yield of 46%. The IR of compound 32 showed the absence of any functional groups other than hydrocarbon.

From the ^{1}H NMR and ^{13}C NMR (Figure 26) compound 32 was assigned as the dehydrated reverse Diels- Alder product. The IR spectrum of the more polar compound 31 showed the presence of OH (3300cm^{-1}) and the ^{1}H NMR and ^{13}C NMR included in Figure 26 confirmed that 31 was the reverse Diels-Alder product.

Several facts complicate the discussion of these results. Very little is known about the effects of secondary orbital interactions on [4+2] cycloadditions between *N*-sulfinyl compounds and 1,3-dienes. The reactions are known to by *syn*-selective, but one cannot determine whether the *E* or *Z* sulfinyl compound is the reacting species. Therefore, for the reverse reaction, the stereochemistry one would expect is ambiguous. One can only speculate that the cycloreversion of the *syn* diastereomer 24 requires that the substituent at C6 be rotated into a more sterically demanding environment than for the *anti* diastereomer 25 and thus the activation energy for the former is too high to allow the reaction to proceed. Further work is required to define the parameters for this reaction.

Figure 26: ^{1}H NMR and ^{13}C NMR of 31 and 32





N-Sulfinylaniline

N-sufinylaniline was prepared in 91% yield according to the literature.[1] [bp 59-60 °C (0.4mm)] [lit.[1] bp 61 °C]; ^{1}H NMR: 7.28 (2H, m), 7.43 (3H, m); ^{13}C NMR: 142.64, 130.54, 129.21, 127.1.

(15) 3,6-Dihydro-4,5-dimethyl-2-phenyl-1,2-thiazine-1-oxide

Compound 15 was prepared in 84% yield according to the literature.[1] ^{1}H NMR: 7.28 (2H, m), 7.20 (3H, m), 4.21 (1H, d, J = 15.6 Hz), 3.76 (1H, d, J = 16.3 Hz), 3.55 (1H, d, J = 16.2 Hz), 3.19 (1H, d, J = 16.2 Hz), 1.82 (3H, s), 1.80 (3H, s); ^{13}C NMR: 146.81 (s), 129.42 (d), 125.05 (d), 124.60 (s), 121.82 (d), 115.31 (s), 54.80 (t), 46.69 (t), 19.62 (q), 17.34 (q).

Preparation of Lithium Diisopropyl Amide (LDA)

A 100 mL three necked r.b flask was dried in the oven and placed under a nitrogen atmosphere. To 10 mL of dry THF was added 3.4 mL of diisopropylamine (24 mmol) and the solution was cooled in an ice bath. n-butyllithium (14 mL, 22 mmol) was added dropwise and the solution was stirred for 15 min.

Deprotonation of 15

A 25 mL r.b. flask containing 10 mL of THF was cooled to -78 °C and 1.1 mL (2.5 mmol) of *n*-BuLi (2.5M in hexanes) was added. A 10 mL THF solution of 0.5 g

(2.2 mmol) of 15 was added dropwise to the base. After stirring for 30 minutes TLC analysis (2:1 ether:pet. ether) showed the disappearance of the starting material. The reaction was quenched with 5 mL of water at -78 °C and allowed to warm to room temperature. The aqueous layer was extracted with ether, the organic layers were combined, dried and concentrated to give 0.4 g of an oil. TLC analysis showed that two compounds were present. Chromatography (2:1 ether:pet. ether) gave 0.25 g of 16[32] and 0.12 g of 17.

The reaction was repeated at -78 °C on the same scale (2.2 mmol) using LDA as the base. Only compound 16 was isolated (0.36 g, 95%).

The reaction was repeated using *tert*-butyllithium as the base on the same scale (2.2 mmol). Only compound 16 was isolated (0.31 g, 80%).

Spectroscopic Data:

(16) *N*-Phenylpyrrole (3,4-dimethyl)

IR: 2931, 1601, 1530, 1050cm^{-1}; ^{1}H NMR: 7.35 (3H, m), 7.24 (2H, m), 6.83 (2H, s), 2.05 (6H, s); ^{13}C NMR: 140.73, 129.40, 124.55, 120.74, 119.44, 116.72, 10.12.

Sulfoxide 17

IR: 3300 broad, 2960, 1602, 1499, 1027cm^{-1}; ^{1}H NMR: 7.15 (2H, m), 6.62 (3H, m), 3.74 (1H, d, J = 12.5 Hz), 3.64 (3H, d, J = 2.5 Hz), 3.25 (1H, d, J = 12.5 Hz), 2.66 (2H, m), 1.88 (3H, s), 1.85 (3H, s), 1.73 (2H, m), 1.45 (2H, m), 0.92 (3H, t, J = 7.3 Hz); ^{13}C NMR: 148.64 (s), 136.07 (s), 128.98 (d), 122.48 (s),

116.97 (d), 112.91 (d), 68.17 (t), 52.41 (t), 46.73 (t), 24.64 (t), 21.95 (t), 19.35 (t), 19.21 (q), 13.56 (q).

(19) β,β,β-Trichloroethoxy Urethane

The urethane was prepared in 58% yield according to the literature procedure.[26] mp 58 °C [lit.[26] mp 57 °C]; ^{1}H NMR: 5.25 (2H, broad), 4.70 (2H, s); ^{13}C NMR: 155.30, 95.43, 74.72.

(20) *N*-Sulfinyl-O-β,β,β-trichloroethoxy Urethane

This compound was prepared by adapting a literature procedure.[25] To 50 mL of dry ether cooled in an ice bath was added 9.8 g (51 mmol) of 19 and 3.7 mL (50 mmol) of thionyl chloride under a nitrogen atmosphere. Using a dropping funnel, an ether solution of 7.8 mL of pyridine was added over 1 h. A precipitate formed immediately. The reaction was stirred at that temperature for 2 h and then allowed to warm to room temperature and stirred an additional 2 h. The precipitated pyridinium hydrochloride was filtered and the yellow solution was concentrated. Distillation (0.2 mm) at 69-70 °C gave 10.8 g (73%) of a yellow oil.

(21) 4,5-Dimethyl-2-[β,β,β trichloroethoxycarbonyl]-3,6-dihydro-2H-1,2-thiazin-1-oxide

The cycloadduct was prepared by adapting a literature[25] procedure. To 25 mL of anhydrous ether cooled in an ice bath was added 44.3 g (0.19 mole) of 20 and 18.35

g (0.22 mole) of 2,3-dimethyl-1,3-butadiene. The reaction was stirred overnight allowing the cold bath to warm to room temperature. Approximately 30 mL of pet. ether was added and 55.7 g (94%) of a white solid was filtered off. ^{1}H NMR: 4.81 (2H, ABq, J = 11.85 Hz), 4.03 (2H, ABq, J = 17.2 Hz), 3.38 (2H, ABq, J = 16.20 Hz), 1.79 (3H, s), 1.78 (3H, s); ^{13}C NMR: 152.44, 124.71, 114.91, 94.44, 75.70, 54.29, 43.32, 19.85, 17.18.

(18) 4,5-Dimethyl-3,6-dihydro-2H-1,2-thiazin-1-oxide

The *N*-protecting group was removed by modifying a literature[25] procedure. To 800 mL of *tert*-butyl alcohol was added 36 g (0.11 mole) of 21 and 58 g (0.89 mole) of Zn metal (40 mesh, activated Aldrich). The reaction was refluxed for 24 h after which a white milky solution had formed. The hot reaction mixture was filtered through a pad of Hyflow. The resulting orange tinted filtrate was concentrated under vacuum and a pink solid was obtained. This solid was added to 100 mL of water containing 25 g of Na_2CO_3. The solution was stirred for 1 h then filtered. The filtrate was extracted with $CHCl_3$ to give 25 g of a white solid. Recrystallization from acetone gave 15 g (74%) of 18. mp 111-113 °C [lit.[25] mp 112 °C]; IR: 3162, 2923, 1023, 1032cm^{-1}; ^{1}H NMR: 4.39 (1H, bs, exchangable with D_2O), 3.85 (1H, dd, J = 16.1 Hz), 3.40 (1H, dd, J = 16.4 Hz), 3.22 (1H, dd, J = 16.1Hz), 2.85 (1H, dd, J = 16.4Hz), 1.70 (3H, s), 1.66 (3H, s); ^{13}C NMR: 124.12 (s), 115.41 (s), 52.30 (t), 39.95 (t), 19.85 (q), 17.20 (q).

General Preparation of the Dianion of 18

To 5 mL of dry THF cooled to -78 °C was added 1.4 mL (3.4 mmol) of *n*-BuLi (2.4M in hexanes). A 10 mL THF solution containing 0.25 g (1.7 mmol) of 18 was added dropwise over 10 min. A yellow solution resulted. The reaction was stirred for 30 min at that temperature before 10 mL of a THF solution of the electrophile (1.8 mmol) was added.

The dianion of 18 was also prepared substituting 2.1 equivalents of LDA for 2.1 equivalents of *n*-BuLi.

Attempted Alkylation Reaction of 18 with Benzyl Bromide

The dianion of 18 (1.7 mmol) was prepared at -78 °C with *n*-BuLi as previously noted. A 10 mL THF solution of benzyl bromide was added at -78 °C and the reaction was stirred for 1 h. Water (5 mL) was added and the reaction was allowed to warm to room temperature. The aqueous layer was separated and extracted with 3 X 10 mL of EtOAc. The organic layers were combined, dried and concentrated to give 0.3 g of a black colored oil. The crude product was chromatographed (EtOAc) to give 0.1 g of a yellow oil and no other identifiable products. The oil was identified as the *N*-benzylated product (22); IR: 2923, 1123, 1023, 1037cm^{-1}; ^{1}H NMR: 7.42 - 7.29 (5H, m), 4.41 (1H, 1/2 ABq, J = 13.9Hz), 4.00 (1H, 1/2 ABq, J = 13.8Hz), 3.65 - 3.45 (2H, m), 3.12 - 3.10 (2H, broad), 1.75 (3H, s), 1.64 (3H, s); ^{13}C NMR: 136.22 (s), 128.28 (d), 128.45 (d), 127.77 (d), 124.38 (s), 114.37 (s), 58.72 (t), 54.32 (t), 46.77 (t), 19.30 (q), 16.96 (q).

Attempted alkylation substituting LDA for BuLi gave a 19% yield 22. At no time was C-alkylated product (23) isolated.

Aldol Reactions of Dianion of 18

The dilithium anion of 18 (1.7 mmol) was prepared using *n*-BuLi as described previously and a THF solution of benzophenone (1.8 mmol) was added. TLC analysis (EtOAc) showed the disappearance of most of the starting materials after 1 h at -78 °C. The reaction was quenched by the addition of 10 mL of water at -78 °C and allowed to warm to room temperature. The aqueous layer was separated and extracted with 3 X 10 mL of EtOAc. The organic layers were combined, dried and concentrated to 0.46 g of a yellow solid. Chromatography (EtOAc) gave 0.34 g of 24 (R_f = 0.35, 63%) and 0.06 g of 25 (R_f = 0.77, 11%) (total yield = 74%).

Compound 24

mp 230-234 °C (dec); IR: 3420 - 3190, 2979, 1042, 1057cm^{-1}; ^{1}H NMR: 7.78 - 7.19 (10H, m), 5.37 (1H, s, exchangable with D_2O), 4.55 (1H, s, exchangeable with D_2O), 4.31 (1H, s), 3.73 (1H, 1/2 ABq, J = 16.6 Hz), 3.50 (1H, 1/2 ABq, J = 16.5 Hz), 1.73 (3H, s), 1.07 (3H, s); ^{13}C NMR: 147.27, 146.54, 128.43, 128.10, 127.43, 127.32, 126.92, 126.35, 125.89, 119.41, 76.68, 70.53, 42.29, 21.90, 17.54; *Anal.* Calcd. for $C_{19}H_{21}NO_2S$: C, 69.68; H, 6.46; Found: C, 69.42; H, 6.58.

Compound 25

mp 158-160 °C (dec); IR: 3385 - 3161, 2978, 1057, 1008cm^{-1}; ^{1}H NMR: 7.75 -

7.50 (4H, m), 7.30 - 7.15 (6H, m), 5.32 (1H, s, exchangable with D_2O), 4.59 (1H, s), 4.28 (1H, s, exchangable with D_2O), 3.92 (1H, 1/2 ABq, J = 16.7 Hz), 3.37 (1H, 1/2 ABq, J = 16.6 Hz), 1.78 (3H, s), 1.49 (3H, s); ^{13}C NMR: 147.25, 146.94, 128.37, 128.31, 126.85, 126.47, 126.35, 125.32, 120.40, 78.62, 64.54, 42.78, 19.31, 18.29; *Anal.* Calcd. for $C_{19}H_{21}NO_2S$: C, 69.68; H, 6.46; Found: C, 69.49; H, 6.51.

The aldol reaction was repeated on the same scale (1.7 mmol) substituting 2.1 equivalents of LDA for 2.1 equivalents of *n*-BuLi. The reaction was worked up as described above and column chromatography (EtOAc) gave 0.27 g (49%) of 24 and 0.05 g (9%) of 25 (total yield = 58%).

Aldol Reaction of 18 with Benzaldehyde

The lithium dianion of 18 (1.7 mmol) was prepared from *n*-BuLi as described above. A THF solution of benzaldehyde (1.8 mmol) was added and the reaction was worked up as described above. TLC analysis showed the presence of at least 5 compounds, all of which had similar R_f values. Chromatography (EtOAc) separated the 5 compounds from benzaldehyde and gave a 0.35 g of a yellow oil. Spectral data of mixture: IR: 3300-3220, 3005, 2995, 1045, 1004cm^{-1}; FIMS: m/z 251 (75%).

Cycloreversion Reactions

Attempted Pyrolysis of 24

To 10 mL of toluene was added 50 mg of 24. The solution was refluxed for 12 h and TLC analysis (EtOAc) showed no change. The solution was concentrated and the starting material was taken up in xylenes and refluxed for 24 h. TLC analysis (EtOAc) again showed only starting materials. A small sample of 24 (50 mg) was placed in a 5 mL r.b. flask and heated to 250 °C using a Kuglrohr distillation apparatus under vacuum (0.5 mm). After 30 minutes the receiver flask remained empty. Heating was discontinued and 45 mg of a tarry residue remained in the r.b. flask. Spectral analysis revealed that all of the starting material had decomposed.

Pyrolysis of 25

To 2 mL of toluene was added 60 mg of compound 25. The solution was refluxed overnight and TLC analysis (EtOAc) showed the disappearance of the starting material. After cooling to room temperature the toluene was removed and the dark residue was chromatographed ($CHCl_3$) to give 21 mg (31) of a yellow oil and 7 mg of 32 as a yellow oil.

Spectroscopic Cata:

Compound 32

IR: 2977, 2927, 1621 weak cm^{-1}; ^1H NMR: 7.30 - 7.18 (10H, m), 6.61 (1H, s), 5.22 (1H, s), 5.09 (1H, s), 5.08 (1H, s), 4.82 (1H, s), 1.88 (3H, s); ^{13}C NMR:

145.74, 143.57, 143.24, 143.05, 140.43, 129.93, 128.10, 127.86, 126.90, 116.00, 114.73, 20.38; FIMS: m/z = 232.

Compound 31

IR: 3205 broad, 2983, 2938, 1664 weak cm^{-1}; ^{1}H NMR: 7.47 - 7.21 (10H, m), 6.41 (1H, s), 5.14 (1H, s), 5.01 (1H, s), 2.43 (1H, s), 1.98 (3H, s), 1.74 (3H, s); ^{13}C NMR: 148.24, 144.91, 141.01, 134.23, 128.20, 126.74, 126.14, 113.33, 79.21, 21.20, 15.90.

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