1988

Part I. Synthesis of homochiral 2-methyl-1-azoniatricyclo(4.4.3.0(1,6))tridecane and 2-methyl-1-azoniatricyclo(4.4.4.0(1,6))tetradecane and their applications in phase transfer catalysis. Part II. Enamines and iminium salts from amido acids.

Samuel Osafo Acquaah

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PART I - SYNTHESIS OF HOMOCHIRAL
2-METHYL-1-AZONIATRICYCLO[4.4.3.0\(^{1,6}\)]TRIDECANE AND
2-METHYL-1-AZONIATRICYCLO[4.4.4.0\(^{1,6}\)]TETRADECAINE AND THEIR
APPLICATIONS IN PHASE-TRANSFER CATALYSIS

PART II - ENAMINES AND IMINIUM SALTS FROM
AMIDO-ACIDS

by
Samuel Osafo Acquaah

A Dissertation
Submitted to the Faculty of Graduate Studies through
The Department of Chemistry and Biochemistry
In Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy at
The University of Windsor
Windsor, Ontario, Canada
1988
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Abstract

Part I

Synthesis of homochiral 2-methyl-1-azoniatricyclo [4.4.3.01,6]-tridecane and 2-methyl-1-azoniatricyclo [4.4.4.01,6]tetradecane and their applications in phase-transfer catalysis.

The synthesis of homochiral 2-methyl-1-azoniatricyclo[4.4.3.01,6]-tridecane and 2-methyl-1-azonia-tricyclo[4.4.4.01,6]tetradecane salts 6 and 7 starting from L-glutamic acid and L-alanine respectively and their applications in phase-transfer catalysis are described. The application of these salts in the enantioselective phase-transfer catalyzed cyclopropanation reaction between diethyl bromomalonate and methyl vinyl ketone, 2-chloroacrylonitrile or acrolein gave products in good chemical yields, but the enantiomeric excess of the products was very low. Alkylation reactions with ethyl 2-oxocyclopentanecarboxylate or ethyl 2-oxocyclohexanecarboxylate and allyl bromide proceed to give products in good yields but with very low enantiomeric excess. Possible reasons for these results are discussed.
Part II

Enamines and Iminium Salts from Amido-Acids

The synthesis of some N-(ω-carboxyalkyl)lactams and N-(ω-carbethoxyalkyl)lactams and their pyrolysis over soda lime to give enamines are described. This investigation took place as part of a general investigation of the effectiveness of this carbon-carbon bond forming reaction in the synthesis of enamines and iminium salts and the ability to utilize this method in the synthesis of 1-azapropellanes with different ring sizes.
To the Glory of God

"Because He lives, I can face tomorrow"
Acknowledgments

I would like to express my sincere thanks and gratitude to my research supervisor, Dr. John M. McIntosh for his guidance and support in this project.

I would also like to thank Mr. Dave Hill and the entire technical staff, especially Mr. Mike Fuerth, Mr. Ron New and Mr. Jerry Vriesacker for their assistance.

Dr. R. Lintvedt (Wayne State University) provided the facilities of a Nicolet QE300 NMR instrument for running some of the high field NMR spectra and Dr. R.D. Bach (Wayne State University) provided the facilities for obtaining the optical rotations. These are very much appreciated.

I would like to acknowledge the support and cooperation of my lab partners and the other members of the department.

I am also indebted to Miss R.A. Loomis for helping in typing portions of this work.

The financial support of the University of Windsor in the form of a Graduate Scholarship and teaching assistantships is also acknowledged.
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Bu</td>
<td>benzyll</td>
</tr>
<tr>
<td>CBZ</td>
<td>benzyloxycarbonyl</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminoypyridine</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylyphosphoramid</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
<td>Mes</td>
<td>mesyl</td>
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<tr>
<td>MS</td>
<td>Mass spectra</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Phthaloyl</td>
<td>phthaloyl</td>
</tr>
<tr>
<td>RaNi</td>
<td>Raney Nickel</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TEA</td>
<td>triethyl amine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>t-BOC</td>
<td>tert-butyloxy carbonyl</td>
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<td>Ts</td>
<td>tosyl</td>
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CHAPTER I

SYNTHESIS OF HOMOCHIRAL

2-METHYL-1-AZONIATRICYCLO[4.4.0]\(^{1,6}\)TRIDECEANE AND

2-METHYL-1-AZONIATRICYCLO[4.4.4]\(^{0,6}\)TETRADECANE AND THEIR

APPLICATIONS IN PHASE-TRANSFER CATALYSIS
INTRODUCTION

The technique of phase-transfer catalysis was first demonstrated by Jarouse (1) and extensively pioneered by Makoza (2), Brandstrom (3), and Starks (4). It has been of tremendous value to the practising organic chemist. The technique has been applied advantageously to circumvent problems encountered when reactions are performed with reagents which are mutually insoluble. Although the technique provides no new reactions, it facilitates or accelerates reactions which, under usual conditions, may proceed at very slow rates or give low yields of products. The application of this technique offers several practical improvements over earlier procedures. Higher reaction yields, better selectivity, shorter reaction times, milder conditions, cheaper reagents and greater convenience are among the advantages frequently encountered.

The unique nature of phase-transfer catalysis lies in the elimination of the problems encountered in reactions performed under heterogeneous conditions where water-soluble reagents are required to interact with water insoluble organic compounds. The ability of the phase-transfer agent to solubilize anions in organic solvents by forming organophilic ion pairs results in very large increases in the reaction rates for such heterogeneous reactions in the presence of small amounts of the phase-transfer catalyst.

During the past decade, the technique has been proven very versatile. It has been applied in reactions such as alkylation (5), condensation (6), oxidation (7), reduction (8), etherification (9), Wittig olefination (10),
and Darzen's condensation (11) as well as others (12).

Three distinct methodologies have been developed in phase-transfer catalysis. These are liquid-liquid, liquid-solid and gas-liquid phase-transfer catalysis. In liquid-liquid phase-transfer catalysis (LL-PTC) (13), the reaction is performed in a two-phase system which contains one reactant in the organic phase and the nucleophile or base (usually as an alkali metal salt) in the aqueous phase. In solid-liquid phase-transfer catalysis (SL-PTC) (14) the reaction is performed in a heterogeneous solid-solvent system. This situation requires a solid salt as the source of the reactive anion while the organic reagent is dissolved in the solvent. In gas-liquid phase-transfer catalysis (GL-PTC) (15), the reaction is performed without solvent and the organic reagent is located in the gas phase.

The common phase-transfer catalysts are lipophilic quaternary ammonium and phosphonium salts, and crown ethers. Crown ethers have proven to be most effective catalysts in solid-liquid phase-transfer reactions (16) whilst quaternary ammonium and phosphonium salts are most effective in LL-PTC reactions (13).

The mechanism of phase-transfer catalysis involves two steps:

1. Transfer of one reagent from a medium in which it is soluble into another medium or phase in which it is normally insoluble.

2. Reaction of the transferred reagent with the non-transferred reagent.

This can be represented schematically as in Fig. 1 (17).
AQUEOUS $Q^+X^- + Nu^- \rightleftharpoons [Q^+Nu^-] + X^-$

PHASE

ORGANIC $[Q^+X^-] + NuB \rightleftharpoons [Q^+Nu^-] + BX$

PHASE

Figure 1. Mechanism of Phase-transfer Catalysis

The water soluble nucleophile $Nu^-$ is transferred as an ion-pair, $Q^+Nu^-$, into the organic phase in the presence of the phase-transfer catalyst cation $Q^+$. A reaction takes place between the organic substrate, BX and the ion-pair, $Q^+Nu^-$ (equation 1).

$$Q^+Nu^- + BX \longrightarrow B-Nu + Q^+X^- \quad \text{Eqn. 1}$$

Migration of the cationic catalyst as the ion-pair $Q^+X^-$, back to the aqueous phase completes the cycle. This process continues until equilibrium is reached or until one of the reactants has been consumed.

The success of the technique depends on the reactivity of $Q^+Nu^-$ and on the concentration of the reacting salt $Q^+Nu^-$ in the organic medium. The latter in turn relies on two factors: the distribution coefficients of $Q^+Nu^-$ and $Q^+X^-$ between the organic and aqueous phases and the concentration of the alkali metal salt in the aqueous phase.

For best results, the distribution coefficient $K$ of $Q^+Nu^-$ between the aqueous and organic phases should be large while that of $Q^+X^-$ should be
small.

\[
\text{Distribution, } K = \frac{Q^+\text{Nu}^- \text{ (organic)}}{Q^-\text{Nu}^+ \text{ (aqueous)}}
\]

Figure 2. Distribution coefficient calculation

In addition to these factors, optimum results are obtained if the concentration of the nucleophile Nu\(^{-}\) in the aqueous phase is as high as possible.

The magnitude of the distribution coefficient depends on the organic solvent used and the nature of the cation Q\(^{+}\) and the nucleophile Nu\(^{-}\).

Studies by Brandstrom (18) on the distribution of tetrabutyl-ammonium bromide (TBAB) between water and other solvents indicate that aprotic solvents that are virtually immiscible with water (e.g. chloroform, methylene chloride) show by far the most favorable extraction behaviour and are preferable to aromatic solvents like benzene, toluene and o-dichlorobenzene which have also been utilized in PTC reactions. Many solvents cannot be used because of their partial solubility in water and the risk of side reactions.

Structural features have been observed to influence the catalytic activity of quaternary salts in PTC reactions (19). An important requirement is that the bulk property of the nitrogen or phosphorus substituents should have appreciable organic character to transfer the anions into the organic phase. The chain length of the substituent groups
affects the distribution coefficient for these ions. For example, Gibson and Weatherburn (20) in their studies on the effect of chain length on distribution coefficients of triphenylphosphonium salts between chloroform and water showed that the coefficient increased by a factor of about two for each CH₂ group added in a given homologous series. Similar results have been obtained for quaternary ammonium picrates (19).

An effective PTC catalyst should contain 15 or more carbon atoms. Thus a phase-transfer agent with only a small degree of organic character such as (CH₃)₄N⁺ will not have enough lipophilic interaction with the organic phase to bring much of the desired anion into the organic phase. At the other extreme, a highly organic catalyst such as (C₁₆H₃₃)₄N⁺ would be soluble in even the most non-polar media but will be difficult to purify and handle. Salts having long alkyl groups and three methyl or ethyl groups are generally poor phase-transfer catalysts since they tend to form micelles and remain in the aqueous phase. If salted out of the aqueous phase, a third phase may result. Herriot and Picker (21) have provided data on the distribution coefficients between benzene and water for several quaternary ammonium hydroxides.

The anion can also affect the distribution coefficient of the ion-pair (22). A specific amount of water of solvation migrates into the organic medium with the anion and there influences both the relative and absolute reaction rates. Studies indicate that anions are hydrated to different degrees. This depends mostly on their charge to mass ratio. The more the anion is hydrated, the more strongly it is attracted to the
aqueous phase and the less reactive it is in the organic phase.

For the past decade, chemists have been actively involved in the synthesis of enantiomerically pure organic compounds because of the growing demand for these materials in the pharmaceutical and chemical industries. In this regard biogenetic and biomimetic considerations have been routinely applied in synthetic design. Most of the transformations of achiral reactants to chiral products or from one chiral material to another have been achieved with stoichiometric amounts of a chiral reagent. Catalysts capable of stereospecific transformations have only recently become available (23). Although nature has provided an abundance of chiral catalysts (i.e. enzymes) their isolation, purification, identification and stabilization present problems which have precluded their wide application in synthesis. In addition to these problems, there are some transformations which are not possible through enzymatic processes. For example, S-(−)-malic acid is readily available from the achiral and inexpensive fumaric acid through an enzymatic process (Fig. 3) (24). However, no enzyme has been found to give the other enantiomer “unnatural” R-(+)-malic acid. Both enantiomers of malic acid or other chiral compounds are valuable substances as well as chiral synths and the necessity to design and synthesize this type of material is inevitable.

A possible approach to a realization of this synthetic goal is the utilization of chiral ammonium salts in performing absolute asymmetric syntheses or kinetic resolutions under phase-transfer catalyzed conditions.

Reports in the literature on the utilization of chiral phase-transfer
catalysts to achieve asymmetric induction in some organic reactions indicate varying degrees of success. Some of the more successful results using quaternary ammonium compounds as catalysts are shown in Fig. 4. It must be emphasized that these results are balanced by a much larger number in which little or no asymmetric induction has been obtained. (Fig. 5)

Some successful kinetic resolutions have also been reported in the alkylation of some racemic alcohols to give ethers. (32) and in the N-alkylation of potassium phthalimide with rac ethyl 2-bromopropionate (33). (Fig. 6)
Figure 4. Some Examples of Successful Asymmetric Inductions in Phase-transfer Catalyzed Reactions
1. (a) \[
\text{C}=\text{C}\xrightarrow{\text{CCl}_4/\text{HCl}/\text{CaCl}_2, \text{H}_2\text{O}}\text{Cl}-\text{C}-\text{C}-\text{Cl}
\]
\text{(ref. 30)}

catalyst: N-dodecyl-N-methylephedrinium bromide

(b) \[
\text{R-CHO} \xrightarrow{\text{KCN/\text{Ac}_2\text{O}}} \text{R-CH-OAc}
\]
\text{(ref. 30)}

catalyst: Benzyl cinchonidinium chloride

2. \[
\text{Ph-CH}=\text{CH-C(O)-Ph} + \text{CH}_3\text{NO}_2 \rightarrow \text{PhCH}-\text{CH}_2\text{-C(O)-Ph}
\]
\text{(ref. 31a)}

catalysts: \(\text{CH}_3\text{S(X)-CH}_2\text{CH}_2\text{-CH-CH}_2\text{-OH}\) , \(X = \text{O or ()}\)

3. \[
\text{Me}_2\text{CH-CH}_2\text{-C(O)-Me} \xrightarrow{\text{(Cl-CH}_2\text{)}_2/\text{NaOH}} \text{Me}_2\text{CH-CH}_2\text{-CH(OH)-Me}
\]
\text{(ref. 31b)}

catalyst: L-N-methyl-N-ethylephedrinium bromide

Figure 5. Some Examples of Unsuccessful Asymmetric Inductions in Phase-Transfer Catalyzed Reactions (ee's < 2%)
Some of the most impressive results have been published by Cram and his coworkers using chiral crown ethers (34). (Fig. 7) The improved enantioselectivities found under these conditions can be ascribed to multi-
site complexation of the catalysts which Crum terms "host-guest" interactions. Such three-dimensionally complex complexations are not applicable to simple quaternary ammonium salts although it has been shown (35) that the presence of the hydroxy group in the cinchona alkaloid catalyzed reaction is necessary for the observed asymmetric inductions. In general, catalysts with a polar group in the $\beta$-position produce higher asymmetric induction. Other examples include the Darzen's reaction using (-)-(R)-dimethyl-N-dodecylamphetaminium bromide 2a (36) and the $\gamma$-hydroxy derivative 1 as catalysts in the epoxidation reaction which afforded
optically inactive products, whereas the β-hydroxy derivative 2b yielded enantiomerically enriched products. (Fig. 8) The same general results are found in the borohydride reductions of carbonyl compounds under phase-transfer conditions (28).

\[ \text{Me} \quad \text{Me} \]
\[ \text{PhCH-CH-N}^+\text{-Me Br} \quad \text{PhCH-CH_2-CH-N}^+\text{-Me} \]
\[ \text{Y} \quad \text{R} \quad \text{OH} \quad \text{R} \]

2a \( Y = H \), 2b \( Y = OH \)

\[ \text{R = n-C}_{12}\text{H}_{25} \quad \text{O} \]
\[ \text{RC}-\text{R'}+\text{p-MeC}_6\text{H}_4\text{SO}_2\text{-CH}_2\text{Cl} \quad \text{NaOH-H}_2\text{O} \]
\[ \text{O} \quad \text{MeCN} \quad \text{R'} \]

\[ \text{ee } Q^+X^- = 2\text{a.b} = 0\% \]
\[ \text{O}^+X^- = 2\text{b} = 2.5\% \]

\( R = \text{Me, Et, Ph.} \quad R' = \text{H, Me, Et, }^1\text{Pr, Ph} \)

Figure 8. Effect of Presence of hydroxy group on asymmetric induction in Darzen's Condensation. (36)

The mechanistic picture of catalysis by 'onium' salts (35) involves a tight ion-pair between the site of the positive charge and the working anion \( X^- \). This proposal has been elegantly illustrated by crystal data (29). Molecular modeling studies have also been used to explain the
functional group interactions in intimate ion pairs and the efficiency of chiral phase-transfer catalysts in asymmetric induction (29).

It has also been observed that higher optical yields are obtained in reactions performed in solvents of low dielectric constants (35). This suggests a solvent effect on conformer population or a proximity effect. In solvents of low dielectric constant, the anion should be more tightly associated with the chiral cation, and polar interactions should be stronger and therefore reaction of the anion should be more strongly affected stereochemically.

The generally low optical yields observed in phase-transfer-catalyzed reactions may be attributed to the small differences in the stability and population of the possible conformations of these small molecules, each of which might lead to a different stereochemical result. The rigid stereochemical nature of Wynberg’s catalysts (quaternary salts derived from cinchona alkaloids (35) (Fig. 9)) may reduce the conformational possibilities and be responsible for the improved enantiomeric excesses obtained although it must be noted that these catalysts also possess a previously unnoted feature—a chiral nitrogen atom.

All of the chiral catalysts examined to date have their chirality in the carbon skeleton. Most have been derived from readily available naturally occurring chiral amines (eg. ephedrine). Since, in solution, the anion should be closest to the positive nitrogen atom, chirality at this point would be expected to influence the reactions more strongly. However, as has been pointed out (37), simple chiral ammonium
Figure 9. Cinchona Alkaloids Whose Derivatives Have Been Used as Phase-Transfer Catalysts
salts should not be effective in inducing asymmetry. The tetrahedral nitrogen atom of such cations must have two right-handed and two left-handed faces, and since association of the anion must be with a face of the tetrahedron, unless access to three of these faces is restricted, little asymmetric induction can be expected. A catalyst with a chiral nitrogen atom and only one open face, but with little other chirality which might affect the reacting center, would be an ideal choice to begin a rational examination of the effect of structure and other parameters on asymmetric induction in phase-transfer reactions.

McIntosh (38) has proposed that for a simple quaternary ammonium salt to be expected to be capable of significant asymmetric induction and be useful in an interpretative way, it must fulfill the following criteria:

(a) It must have a chiral nitrogen atom.

(b) It should be as rigid as possible to facilitate interpretation of stereochemical results and reduce conformational effects.

(c) Three of the four faces of the nitrogen atom should be blocked.

(d) The introduction of various substituents in stereochemically defined ways should be possible.

Molecules which fulfill these criteria are not easy to envisage and the catalysts derived from cinchona alkaloids do not completely satisfy all the conditions. For example, salts based on the quinuclidine ring system can be modified to satisfy conditions (a), (b) and (d), but not (c).

Molecules possessing the propellane structure, especially those
incorporating a quaternary nitrogen at the bridgehead position appear to offer a viable choice since they fulfill condition (c). All the carbocyclic compound $\mathcal{C}$ (39), $\mathcal{D}$ (40), and $\mathcal{E}$ (40) and their nitrogen analogues (37) are known. (Fig. 10)

The compound $\mathcal{D}$ possesses D$_3$ symmetry and is chiral (41). When one bridgehead carbon is replaced with a nitrogen atom, an ammonium salt $\mathcal{A}$ is generated which possesses C$_3$ symmetry and which is chiral even though no obvious asymmetric center is present.

Although the molecules $\mathcal{A}$ and $\mathcal{B}$ are chiral, the exposed face of the nitrogen atom is not. In $\mathcal{A}$, the three equatorial hydrogens alpha to the nitrogen project into the area of the nitrogen face. Approach of a reagent to this face will encounter no asymmetry. However, substitution of other, dissimilar groups on these bonds will produce a chiral environment on that face. The propellane structure offers a system with possibilities of examining the effect of such structural changes. The interaction of a chiral quaternary ammonium salt as an ion-pair can occur in two ways, depending upon the type of reaction involved. The anion of the extracted ion-pair $Q^+X^-$ must lie between the chiral nitrogen and the (prochiral) substrate. Therefore the ultimate contact between $Q^+$ and substrate required for transmission of stereochemical information when $X^-$ is a primary reactant (as, for example, in SN2 reactions of $X^-$ with 2-bromobutane) will be exceedingly difficult. However, if the function of $X^-$ is to deprotonate a substrate, a different situation arises. The product of this process is a new ion-pair in which the chiral $Q^+$ is in close
Figure 10. Known Examples of 1-Azatricycloalkane Systems
proximity to the prochiral substrate and a much larger effect of the catalyst should be anticipated. Thus the propellane structure offers a system with possibilities of examining the effect of structural changes on their asymmetric induction.

The lack of a "handle" in 3C has precluded attempts at its resolution and no direct information on its optical activity is available. Although the synthesis of racemic 3N (42b) and the methyl substituted analogue (42a) have been accomplished, the resolution of these compounds via diastereomeric salts has proved futile (41).

X-Ray and NMR data showed the structure of the azapropellane 3N cation to be a slightly flattened all-chair form which undergoes chair-chair ring inversion of all three rings with a first order rate constant of 0.7 sec⁻¹ (43). A report by Alder (43) indicates that the barrier to this process is 17.6 kcal mol⁻¹. Since this process corresponds to the racemization process for this chiral C3 molecule, its resolution is not feasible. However, models indicate that an axially oriented substituent at any position is severely strained, and thus the substituted ring should be constrained to the chair form possessing an equatorial substituent. Models further suggest that in the presence of one "frozen" ring, sufficient rigidity is imparted to the entire system to prevent the inversion of the other two rings, thus making the system optically stable. Such a substituent will render its attached ring carbon chiral, and the presence of two diastereomeric pair of enantiomers is indicated. However, if an axial substituent is forbidden, the situation simplifies to one
enantiomeric pair of ions.

The objective of the work to be described has been the preparation of the non-racemic ammonium salts 6 and 7 (Fig. 11) and to examine their use as chiral phase-transfer catalysts.

![Figure 11. Target Chiral Azapropellanes](image)

The term "homochiral" has been used by many authors to describe compounds which are enantiomerically pure at one or more sites and to distinguish these from compounds which are inherently chiral but obtained only in a racemic form. This terminology will be used in this dissertation.

The synthesis of the compact azapropellane skeleton is an interesting problem involving the creation of two contiguous quaternary centers. Steric factors dictate that the creation of such a center adjacent to a pre-existing one will be best achieved by an intramolecular reaction (cyclization). Previous work had shown that approaches via cycloaddition reactions (e.g., Diels-Alder reactions of dehydroquinolizidine) were futile (44). However, unlike the propellanes themselves, the azapropellanes have
a "handle" - the nitrogen atom - which can be used to complete the assembly of the structure. Thus if the molecules are viewed as bridged quinolizidines, generation of this system with the appropriately functionalized alkyl chain at position 9a of the quinolizidine nucleus might be expected to lead to the desired system. A particularly attractive feature of this approach is the ability to generate different ring sizes in the azapropellane from a common precursor. A potential difficulty which was anticipated lies in the fact that many 9a-substituted quinolizidines exist predominantly in the trans-fused, axially substituted conformation (45). However, since nitrogen inversion is a facile process, it was expected that cyclization might occur. This prediction was born out by the synthesis of 3N from dehydroquinolizidine as shown in Fig. 12.

Considering this general pathway for application to salts which contain substituents adjacent to nitrogen adds further complexity to the synthetic design. Additional steric bulk will be present to impede the final cyclization. The substituent could be present in either one of the existing rings or in the cyclizing ring. In either case, lower yields might be expected. The earlier synthesis of racemic 7 (42) involved the latter approach and the yields obtained reflected the increased difficulty in the cyclization. If this approach is used and the substituted center is to be enantiomerically pure, two conditions must be fulfilled. Since the cyclization is a substitution reaction, the reacting carbon must be homochiral AND the substitution must occur stereospecifically. This implies a Sn2 reaction on an optically active halide. Since Sn2 reactions
are very subject to steric hindrance, and considering the situation outlined above, such an approach seems doubtful at best.

Figure 12. Nitrogen Inversion in Quinolizidine Systems.

When the alternative approach is considered, two favorable factors become important. Some compounds containing homochiral centers adjacent to nitrogen are readily available in the form of amino acids and this approach
would not require a stereospecific cyclization with all the difficulties previously mentioned. Further, the cyclization reaction itself might be expected to be facilitated since, if the introduction of the 9a-substituent into a 4-substituted quinolizidine occurred in a trans manner, it would lead to a cyclization geometry wherein the substituent is as far removed from the electrophilic center as possible.

If this approach is entertained, one must consider how the chiral quinolizidine derivative may be prepared. In this regard, the work described in Part II of this dissertation was of great importance. Miyano,(46) and Murakoshi (47) had shown that N-ω-carboxyalkylglutams can be cyclized to the materials we required by pyrolysis over soda lime. Most importantly, this process occurs without disturbing the existing C-N bond.

Figure 13. Retention of Stereochemistry in Soda Lime Pyrolysis

Therefore the synthesis of 6 and 7 was projected as occurring as shown in
Fig. 14. The details of this synthesis, with the modifications which were required as the work proceeded, leading to the final preparation of 6 and 7 are detailed in the next section of this dissertation.

Figure 14. Projected Syntheses of Target Salts 6 and 7.
RESULTS

A: 2-methyl-1-azoniatriacyclo[4.4.3.0\(^1,6\)]tridecane salt (6).

The synthesis of salt 6 was achieved using the procedures depicted in Schemes 1 and 2. Lactam 15 was the key intermediate. It has previously been prepared in two ways (48,49), neither of which was suitable for preparation on the scale which we required. Therefore the preparation of 15 was effected as shown in Scheme 1 which is largely the method developed by Silverman (51).

Esterification of S-(+)-glutamic acid followed by neutralization and cyclization of the amino acid diester gave S-(+)-5-carbethoxy-2-pyrrolidinone. (50) The ester carbonyl group was selectively reduced to S-(+)-5-hydroxymethyl-2-pyrrolidinone (10) with lithium borohydride in 70% yield (51). Tosylation of the primary hydroxyl group proceeded to give 11 in 35% yield, but all attempts at the reduction of the tosylate to give 15 (52) failed. Treatment with NaBH\(_4\) in DMSO (53) or under phase-transfer conditions (54) with tetrabutyl ammonium bromide were unsuccessful. The tosylate 11 was converted to the thiophenyl derivative 12 but reduction with Raney-Nickel required severe conditions and a mixture of products was obtained. An alternative method was explored using the iodide which was obtained from 11 in 40% yield with sodium iodide in acetone. Hydrogenation with hydrogen and palladium on carbon in the presence of triethyl amine gave a quantitative yield of 15 (48,49). The low overall yield in this sequence of steps was overcome by direct conversion of the alcohol 10 to the bromide 14 in 75% yield using triphenylphosphine and carbon.
Scheme 1. Synthesis of R-(-)-5-methyl-2-pyrrolidinone

tetabromide. (51) Reduction of 14 with hydrogen and palladium on carbon gave 15 in 90% yield and 95% enantiomeric excess as judged by comparison of its specific rotation with that reported (48). It should be noted that the
Scheme 2. Synthesis of 2- methyl-1-azoniatricycl[4.4.3.0^{1,6}]-
tridecane Salt 6
final step changes the absolute configuration of the material from the S series to the R series, and the product obtained must necessarily be R-5-methyl-2-pyrrolidinone. The (+)-isomer of this material had originally been assigned the S-configuration (48). However, this assignment has been reversed based on CD measurements (48) and its chromatographic (HPLC) mobility on a chiral column (49). The present work unambiguously confirms the reversed assignment.

Alkylation of 15 with ethyl 5-bromovalerate (Scheme 2) in DME using KH as the base gave 16. Pyrolysis over soda-lime gave the enamine 17 in 75% yield. In most reactions, the enamine 17 was not isolated but was converted directly to the perchlorate 18 (49%). The iminium salt 18 afforded cyanoamine 19 in 73% yield on treatment with aqueous KCN.

Spectroscopic data support the formation of the trans-fused isomer of the indolizidine ring system in accordance with literature data (55). The infrared spectrum of nitrile 19 showed strong Bohlmann bands in the region of 2700 - 2800 cm⁻¹ attributable to the α-hydrogens oriented trans and antiperiplanar to the nitrogen lone pair of electrons (56). The ¹H NMR spectrum of 19 (Fig. 15) also indicated predominantly the trans-fused configuration. The methyl group signal appeared as a doublet at 1.12 ppm with a coupling constant of: J = 6.5 Hz as expected for the trans indolizidine ring system. The broad doublet at 3.14 ppm can be reasonably assigned to the equatorial protons on the carbon of the six-membered ring and adjacent to the nitrogen atom (57). The multiplet at 2.65 ppm corresponds to the proton in the five-membered ring and adjacent to the
nitrogen. The absence of any other absorptions down-field from this region unequivocally confirms the trans indolizidine structure.

Figure 15. 300 MHz $^1$H NMR Spectrum of 9a-cyano-3-methyl-indolizidine 19
The reaction of the nitrile with 4-phenoxybutyl magnesium bromide gave ether 20 in 42% yield. The stereochemistry of the quaternary center in 19 and 20 were of no concern at this point since the planned cyclization (21) destroys any distinction between the cis and trans isomers of 19 or 20. Compound 20 was smoothly cleaved to 21 in hot concentrated hydrobromic acid. Treatment of 21 with silver oxide gave the 6-hydroxide. The trifluoroacetate, prepared by the addition of trifluoroacetic acid to the hydroxide salt was a semi-solid but using concentrated hydrobromic acid gave the 6-bromide as a crystalline solid. In analogy with the reported (42) data of the unsubstituted analogue 4N, 6-bromide has only limited solubility in water, was insoluble in chloroform and melted at a temperature above 300° C. The structure was confirmed by its elemental analysis, field desorption mass spectrum (one peak at m/z = 194), 13C NMR and 300 MHz 1H NMR spectra. The 13C NMR spectrum of 6-trifluoroacetate is given in Table 3. This showed signals for 13 carbons whose chemical shifts correlated with the 13C NMR signals reported, for the unsubstituted compound. (42) The 1H NMR spectrum is shown in Fig. 15 and is summarized in Table 1. The assignments were made by analogy with the spectrum of the unsubstituted system (42) and confirmed by complete spin-decoupling measurements. The proton spectrum at 60 MHz showed all protons adjacent to nitrogen as broad multiplets which were clearly not first order. At 300 MHz, part of the spectrum became amenable to first order analysis. The integrated spectrum showed a doublet at 1.35 ppm for the methyl group attached to the carbon adjacent to the bridgehead nitrogen. The single
Figure 16. 300 MHz $^1$H NMR Spectrum of 2-methyl-1-azonia-
tricyclo[4,4,3,0$^{1,6}$]tridecane Salt $\delta$ (X = OH)
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<th>No. of Protons</th>
<th>Multiplicity</th>
<th>Coupling Constant, J (Hz)</th>
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<td>3</td>
<td>q</td>
<td>m</td>
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<tr>
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<td>13</td>
<td>m</td>
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<td>Me</td>
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<td>17.6</td>
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<tr>
<td></td>
<td>48.9</td>
<td>19.1</td>
<td>17.0</td>
<td>29.2</td>
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</tr>
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</table>

Table 2: $^{13}$CNMR spectrum of 6 and 7 (X' = O-H) in CDCl$_3$
proton absorption at 4.58 ppm which appeared as an apparent quartet was assigned to the methine hydrogen adjacent to the methyl group. Spin-decoupling experiments confirmed this assignment. The hydrogens attached to the six-membered ring carbons alpha to the nitrogen at the bridgehead appeared as diastereomeric pairs. Two doublet of doublet of doublets appeared at 3.79 and 3.22 ppm. Their coupling constants (13.4 and 13.0 Hz respectively) identified them as being axial. The higher field of these two signals partially overlapped with those for the two equatorial hydrogens which occurred as broadened doublets at 3.11 and 3.09 ppm respectively. One proton whose chemical shift and coupling constants identified it as an axial proton adjacent to the carbon bridgehead resonated at 2.24 ppm, but the remainder of the protons were unresolved. Most importantly, when the signal at 3.78 ppm was irradiated in a decoupling experiment, the integrated intensity of its geminal partner (at 3.02 ppm) did not decrease. This lack of spin saturation transfer is good evidence that ring inversion is not occurring as has previously been discussed (58).

B. 2-methyl-1-azoniatricyclo[4.4.0.1,6]tetradecane salt (7)

The preparation of optically pure S-(+)-6-methyl-2-piperidinone (28) for further elaboration into 7 proved to be unexpectedly difficult. However, the successful synthesis of this compound was achieved using the procedures outlined in Schemes 5 and 6. Our initial strategy for the synthesis of 28 (Scheme 3) involved reduction of imine 26 which was
prepared from the known 25 (59a). Reducing reagents examined included catalytic hydrogenation over palladium on carbon, sodium borohydride, sodium cyanoborohydride and Redal [sodium bis(2-methoxyethoxy)aluminum hydride]. Sodium cyanoborohydride, a hydride reducing reagent which is stable in mildly acidic solutions, has been used extensively for the reduction of imines which exist in the activated protonated form in acidic media (59b). Reports of the asymmetric reduction of imines using Redal (59b) prompted an investigation of this reducing agent. Although it was expected that the ester function would also be reduced, it could be re-oxidized to the oxidation state required for cyclization to lactam 28. However, in all cases, the diastereomeric excesses obtained were less than 25% and using Redal, several other unidentified products were also seen. Furthermore, the diastereomers could not be separated by medium pressure chromatography, a result consistent with previous reports (59c).

The strategy was utilized however in the preparation of racemic 28 which was then converted to the target compound to pretest the methodology.

A recent procedure developed by Husson and coworkers (60) which utilizes the chiral oxazolidine synthon 30 (Scheme 4) was examined. Preparation of 32 was carried out as described in the literature (60). However, the sensitive silylated material 33 could not be deprotonated to allow its conversion to 34 by the literature procedure (61). All attempts led to the formation of 32 and other unidentified products after work-up with acidic stannous chloride. After this route had been abandoned, the original authors reported problems similar to these and provided a modified
method to achieve such deprotonations. (62).

Scheme 3. Synthesis of (−)-6-methyl-2-piperidinone

Other synthetic plans ultimately resulted in failure or gave very low yields of the expected products and finally we adopted the procedures outlined in Schemes 5 and 6.
Scheme 4. Attempted Synthesis of 6-methyl-2-piperidinone Using chiral oxazolidine 30
S-(+)-2-amino-1-propanol (alaninol) (25), was prepared by the reduction of L-alanine using lithium aluminum hydride in THF in 65% yield (63). Initially, the sequence of reactions shown in Scheme 5 was attempted using the phthaloyl group as the nitrogen protecting group. However, after compound 38 (R = phthaloyl) had been prepared, this route had to be abandoned due to unsatisfactory yields in all the steps. The amino group was protected as the benzyl carbamate in 88% yield and the hydroxyl function was converted to the bromide 37a or the tosylate 37b in 60% and 88% yield respectively. The nitrile 38 was obtained by the reaction of the bromide with NaCN impregnated on alumina (64) or by the displacement of the tosylate with NaCN in DMF. Refluxing the nitrile in concentrated hydrochloric acid overnight gave the amino-acid hydrochloride which was protected as the carbamate (65). The ester was reduced to the amidoalcohol 40 and then converted to the bromide with triphenylphosphine and carbon tetrabromide. The two carbon homologation with the sodium salt of diethyl malonate gave the diester 42 which was deprotected by hydrogenolysis to afford lactam ester 43. Decarbethoxylation of 43 under neutral conditions (66) gave the optically active lactam 28. An alternative procedure for the synthesis of 28 is shown in Scheme 6. The protected amino acid 44 (67) was converted to the diazoketone 45 (68) (70%) by first forming the anhydride and subsequent treatment of this with ethereal diazomethane.

Wolff rearrangement in the presence of catalytic amounts of silver benzoate in triethyl amine and methanol gave the ester 29b in 72% yield. (69) Dibal reduction of the ester in toluene at -78°C gave the aldehyde
Scheme 5. Synthesis of S-(+)-6-methyl-2-piperidinone

(70) (not isolated). Two carbon homologation using Wittig-Horner reaction conditions, followed by reduction with hydrogen in the presence of palladium on carbon gave 47 in 48% overall yield (71). Deprotection and
Scheme 6. Alternative Synthesis of S-(+)-6-methyl-2-piperidone
Scheme 7. Synthesis of 2-methyl-1-azonia[4.4.4.0^1,6]-tetradecane Salt 2

cyclization gave the optically active lactam 28 in 92% yield.

Comparison of the methods shown in Schemes 5 and 6 showed that the
structure of this compound, obtained as the iodide was confirmed by its field desorption mass spectrum (one peak at m/z = 208), \(^{13}\text{C}\) NMR and 400 MHz \(^1\text{H}\) NMR spectra. The latter correlated with that published previously for the racemic material (42). The \(^{13}\text{C}\) NMR spectrum of the trifluoroacetate is given in Table 2. This showed signals for 14 carbons. The 300 MHz \(^1\text{H}\) NMR spectrum is given in Fig. 17 and is summarized in Table 3. It showed a doublet at 1.04 ppm for the methyl group attached to the carbon adjacent to the bridgehead nitrogen atom. The multiplet at 4.21 ppm was assigned to the methine proton at the point of attachment of the methyl group. The protons adjacent to the nitrogen on the unsubstituted rings exist as two diastereomeric pairs and this is reflected in their different chemical shifts. Spin decoupling experiments showed that the protons causing absorptions B and C (Table 3) are situated geminally to those causing absorptions D and E respectively. The identification of which of the unsubstituted rings is giving rise to these pairs of signals is not possible at this time. Again, integration of the \(^1\text{H}\) NMR spectrum under decoupling conditions showed no sign of spin-transfer saturation indicating that at least on the NMR time scale, ring inversion of all three rings is not occurring.
Figure 17. 300 MHz $^1H$ NMR Spectrum of Homochiral 2-methyl-1-azoniatricyclo[4,4,0,1.6]tetradecane Salt $\mathcal{Z}$ ($X = OH$)
<table>
<thead>
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The enantiomeric excesses of lactams 15 and 28 are 93% and 92% respectively based upon comparison of their specific rotations with literature values. Since none of the reactions leading from 15 to 6, or from 28 to 7 affect the chiral centers, the optical purities of 6 and 7 are assumed to be 93% and 92% also. In an attempt to demonstrate this point, salt 7 (X⁻ = OH⁻) was treated with R-(+)-camphorsulfonic acid. Although the methyl region of the ¹H NMR spectrum was complicated by the strong signals from the camphor moiety, no signals could be discerned which could be ascribed to a second diastereomeric methyl group in 7. Previous work had shown (72) that other chiral anions (e.g. mandelate) did not give spectra which were useful in determining the optical purity of 7. Therefore the best estimate of the enantiomeric excesses of 6 and 7 is 92%.

**Application of Salts 6 and 7 to Phase-transfer Catalysis**

The possibility of achieving enantioselectivity using catalysts 6 and 7 was examined in a cyclopropanation and an alkylation reaction.

**Cyclopropanation Reaction (73) (Fig. 18)**

The cyclopropanations were performed with diethyl bromomalonate and the appropriate unsaturated compound in the presence of aqueous alkali, the chiral catalyst and toluene as the solvent. Toluene was chosen because of its low dielectric constant which has been shown to favor larger asymmetric inductions (35). The results obtained are presented in Table 4. All reactions were performed at 0°C and a control reaction was also run under the same conditions. A significant amount of reaction occurred even though no catalyst was present.
It must be noted that the optical rotation for the pure enantiomer of the products of these reactions are unknown. Attempts were made to determine the enantiomeric excesses of some products using a chiral lanthanide shift reagent (LIS), tris[3-(heptadecyl)-hydroxy-3,5,5-trimethylcyclohexyl]europium(III) (Eu(hfc)_3). However, in no case could the results of these experiments be used to assign definitive values to the enantiomeric excesses. The strong proton signals due to the europium ligand obscured much of the area of interest and when higher ratios of LIS reagent to product were used, assignment of the NMR signals which could be resolved to specific protons in the molecule was tenuous at best. The number of sites in these molecules which could complex with the LIS reagent may be responsible for these ambiguous results. Since it is possible that the pure enantiomers may have very low specific rotations, the low values observed may not indicate that low enantiomeric excesses have been achieved. However, such a conclusion is not warranted by the data.

Alkylation Reactions (Fig. 19)

These were performed with ethyl 5-oxocyclopentanecarboxylate or ethyl 6-oxocyclohexanecarboxylate (74) and allyl bromide in the presence of base and the chiral catalyst. The results are presented in Table 5. A blank experiment was performed with no catalyst and in this case very little reaction took place. In this case the optical rotation for the same product obtained by a phase transfer reaction catalyzed by an ephedrine derivative is available (25a). In that report, a specific rotation of
Figure 18. Cyclopropanation Reactions.

Table 4. Asymmetric Induction in Cyclopropanation Reactions (a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Reagent</th>
<th>Yield</th>
<th>$\left[\alpha\right]_{D}^{25}$ (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CH}_2=\text{C(Cl)CN} )</td>
<td>70</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>( \text{CH}_2=\text{C(CHO)} \text{CH}_3 )</td>
<td>65</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>( \text{CH}_2=\text{CHO} )</td>
<td>72</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>( \text{CH}_2=\text{C(Cl)CN} )</td>
<td>55</td>
<td>1.2</td>
</tr>
</tbody>
</table>

(a) All compounds show IR and $^1$H NMR spectra identical to those reported in the literature. Products were purified by silica gel chromatography.

(b) Optical rotations were measured in CHCl$_3$, c = 1.0
-8.2° was obtained and the enantiomeric excess was determined to be 5-6%. On that basis, the enantiomeric excess of the product obtained in this work would be <1%. Considering the uncertainty in the specific rotation measurements and in the determination of enantiomeric excesses in general, the most accurate statement would be that essentially no asymmetric induction has been achieved.
Figure 19. Alkylation Reactions

**Table 5. Asymmetric Inductions in Alkylation Reactions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Yield</th>
<th>$\left[\alpha\right]_D^{25}$</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>6</td>
<td>80</td>
<td>1.3</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>6</td>
<td>76</td>
<td>1.0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>7</td>
<td>60</td>
<td>0.8</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

(a) All compounds show 1R and $^1$H NMR spectra identical to those reported in the literature. Products were purified by silica gel chromatography.

(b) Optical rotations were measured in CHCl$_3$, $c = 1.5$

(c) Substrate A is ethyl 2-oxocyclopentancarboxylate and substrate B is ethyl 2-oxocyclohexancarboxylate.

(d) Reaction performed under identical conditions using (-)-N-benzyl-N-methylephedrinium bromide gave the same product in 85% yield, $\left[\alpha\right]_D^{25} = -8.2^\circ$ (CHCl$_3$, $c = 1.5$) (25a) whose ee was assigned as 67%.

(e) Based on the optical rotation in footnote (d)
DISCUSSION AND CONCLUSIONS

The homochiral salts of 2-methyl-1-azonia[4.4.3.0^{1,6}]tridecane (6) and 2-
methyl-1-azonia[4.4.4.0^{1,6}]tetradecane (7) have been synthesized using the
methodology outlined. As part of these syntheses, new and effective
method for the preparation of the chiral synthons 15 and 28 have been
developed. The overall chemical yield and enantiomeric excess for 15 and
28 are high and these compounds will be useful additions to the pool of
chiral intermediates which will prove very useful in future asymmetric
syntheses. In addition, the methodology previously developed for the
cyclization of amido acids to enamines and/or iminium salts using soda-
lime pyrolysis has been shown to be applicable to chiral lactams. The
cyclization does not disturb the configuration of the carbon adjacent to
nitrogen.

Although the syntheses required many steps and the overall yield was
disappointing, the materials have been obtained and their proton and carbon,
NMR spectra support the postulate that substituents on the rings will stop
the interconversion of conformations which was observed in the
unsubstituted heterocycles. The ability of these salts to act as phase-
transfer catalysts has been confirmed and their ability to transfer
chirality during these reactions has been investigated in cyclopropanation
and alkylation reactions. As seen in Tables 4 and 5, optically active
compounds were obtained in all cases. In the cyclopropanation reaction,
products were obtained in good yield, but since there is no literature data
for the pure enantiomers, and since LIS reagent experiments were
unsuccessful, the enantiomeric excesses have not been assigned. It should be noted that the assignment of optical purity can also be achieved using chiral HPLC columns. (75) This technique should be applicable here, but we do not have access to this equipment. In the alkylation reactions, the products were obtained in moderate yields which, however, are comparable to the yields previously obtained using the ephedrine-derived catalysts (25a). Again, the enantiomeric excesses obtained were very low.

The results obtained suggest that the rules proposed by McIntosh (38) previously alluded to do not completely describe the requirements for effective chirality transfer. The catalysts prepared fulfilled all the stated requirements and yet effective chirality transfer was not observed. However, as previously noted, literature results (35) indicate that the presence of a second, polar group near the quaternary nitrogen in the catalyst seems necessary for high asymmetric induction in phase-transfer reactions. The function of this group is presumably to present another coordination site so that the substrates can be held in a very specific orientation at the transition state. It was our hope that the rigid nature of the salts 6 and 7, and the restriction of the site of the anionic species to one face of the nitrogen atom would create the same type of chiral environment and lead to improved asymmetry transfer. Clearly this hope has not been fulfilled. However, the choice of conditions used in the phase-transfer reactions was arbitrary and it is possible that improved results may be obtained if other conditions are chosen. In particular, the choice of solvent could be examined to see if lowering the dielectric
constant produces favorable results. It has not been possible to pursue this due to an insufficient amount of the chiral catalysts.

Another suggestion for future work would be to prepare molecules of the azapropellane type which also contain polar functional groups on the exposed face of the molecule. Such compounds may combine both effects and lead to improved results.

In retrospect, the suggestion that one molecule might be capable of inducing asymmetry in several or many different reactions appears optimistic. The most effective producer of asymmetric catalysts, i.e. Mother Nature, uses a different catalyst (enzyme) for almost every reaction. Therefore, it may be that the catalysts prepared in this work may be effective, but in an as yet unexamined reaction.
CHAPTER 2

ENAMINES AND IMINUM SALTS FROM AMIDO-ACIDS
Introduction

The ability of enamines to function as synthetic intermediates was first demonstrated by Stork (76) in 1954. Since that time the enamine functionality has proven to be a highly versatile synthetic intermediate for carbon-carbon bond forming processes in organic synthesis. It has found many applications, particularly in the biomimetic elaboration of alkaloids (77) and in the synthesis of heterocyclic compounds (78). Recent reports (79) indicate considerable interest in the utility of this intermediate in asymmetric synthesis, an area which is of wide application in the synthesis of pharmacologically and biologically active compounds. Several excellent reviews (80) which provide wide coverage of the structure, reactivity, spectroscopic information, reactions and synthetic applications of enamines have appeared. The structures of enamines have been characterized by IR, $^1$H NMR, $^{13}$C NMR, $^{15}$N NMR, UV, Mass spectrometry and other techniques. The infrared absorptions of enamines appear as medium to strong bands in the region 1610-1675 cm$^{-1}$. This absorption is shifted to higher wave numbers on protonation due to the formation of the iminium salt (1640-1690 cm$^{-1}$). The ultraviolet spectrum of both free enamines and iminium salts give absorptions in the region 220 - 235 nm ($\epsilon$ 4000-10,000) and N-protonation causes a hypsochromic shift in the $\lambda_{\text{max}}$ value. The mass spectra of enamines show M-1, M and M+1 ions, but the base peak usually that due to the formation of an eniminium ion.

\[ \text{N-CH=CH-CH}_2\text{-R} \rightarrow \text{R}_2\text{N}^+\text{CH=CH-CH}_2\text{+ R} \]

The 1H NMR spectra show signals for the C1 olefinic carbon in the range
124-156 ppm and the C2 carbon in the range 79-131 ppm (downfield from TMS). Substituents deshield the olefinic carbon to which they are attached (α-effect) but the magnitude varies greatly. The chemical shift of the iminium group (C=N⁺) appears in the region 188-195 ppm. The vinylic protons in the ¹H NMR spectrum appear in the region 3.9-5.3 ppm. These values depend on the degree of overlap between the electron pair on the nitrogen atom and the double bonds. The greater the overlap, the higher the field at which the protons appear. The three atom π-system of enamines is susceptible to attack by an electrophile on the nitrogen or β-carbon. Protonation takes place rapidly on nitrogen to give the enammonium ion. This is followed by a relatively slow transfer of the proton to the carbon to give the more stable iminium ion. This result indicates that the formation of enammonium salts is kinetically controlled, while protonation on the β-carbon is subject to thermodynamic control. This behaviour reflects the marked similarity in the reactions of enamines and enolate ions toward electrophiles. The reactivity of the iminium salt is also comparable to that of a protonated carbonyl group. The interconversion between the iminium and enamine forms is a facile process which can easily be controlled. Choice of the proper forms allows site specific bond formation at either of two centers. Thus, reactions can be performed on the iminium form which forms bonds alpha to the nitrogen by employing nucleophilic reagents (e.g. Grignard reagents), or with electrophilic reagents (e.g. acyl or alkyl halides) on the enamine form which leads to bond formation beta to the nitrogen atom. (Fig. 20).
Fig. 20. Interconversion of Enamine and Iminium Forms.

The most common method used for the synthesis of enamines has been the condensation of a secondary amine with aldehydes or ketones. The water generated in these reactions has been removed by various methods - e.g. azeotropic distillation with benzene or toluene, or the use of drying agents such as potassium carbonate, molecular sieves or titanium chloride (81). Other methods for the preparation of enamines are the addition of secondary amines to polarized acetylenes (particularly acetylenic ester and
sulfonyl (82), the addition of secondary amines to allenes (83), or the application of the Wittig-Horner reaction (84) which can be utilized in the synthesis of both aldehyde and ketone enamines.

The synthesis of bicyclic enamines presents different synthetic problems, especially when the nitrogen is at a bridgehead position. Formation of these by the standard methods requires starting materials which are tedious to prepare and has inherent regiochemical problems. Leonard and coworkers (85) have developed a method for the synthesis of such compounds by the oxidation of tertiary amines with mercuric acetate.

(Fig. 21)

Figure 21. Enamines from the Mercuric Acetate Oxidation of Tertiary Amines.
However, this method requires many steps for the preparation of the requisite starting material and the overall yield is very low. Furthermore, the reaction is not regiospecific and is suitable when only one tertiary hydrogen atom alpha to the nitrogen exists (i.e. in symmetrical systems). Otherwise a mixture of enamines is formed.

Rapoport and coworkers (86) have recently described the preparation of bicyclic enamines by the decarbonylation of N-alkylated α-amino acid (Fig. 22). This useful process is effective only for the

\[
\text{Figure 22. Enamines from the Decarbonylation of N-Alkylated α-Amino-Acids}
\]
cyclization of 5- and 6-membered rings. The cyclization of 7-membered rings is not feasible, a result which limits the synthetic application of the methodology.

For the formation of 1-azabicyclo[5.4.0]undecanes, the annulation of a 6-membered ring onto an existing 7-membered ring requires several steps for the preparation of the starting material, hexahydro-1H-2-azepine-2-carboxylic acid and the yield is extremely low (87).

We have been interested (Chapter 1) in the synthesis of substituted ammonium salts of type 53. A retrosynthetic analysis suggested that the bicyclic salts 54 might function as suitable precursors. (Fig. 23)

---

**Figure 23. Retrosynthetic Analysis of the 1-azapropellane Skeleton**

The feasibility of this proposal has been demonstrated in a series of reports. Compounds 56 - 59 containing all possible combinations of 5- and
6-membered rings were prepared (42) (Fig. 24). However, the need to synthesize 53 with other ring sizes and with substituents present in the rings necessitated the search for other viable and practical procedures for the preparation of the requisite iminium salts. Syntheses using Leonard's procedure (85) were not promising since they appeared to be tedious and the regiochemical problems previously alluded to were present in the oxidation of bicyclic amines when different ring sizes or unsymmetrically situated substituents were present.

![Diagram of chemical structures](image)

56  57  58  59

Figure 24. Known 1-azapnellane Ring Systems

Other, more unusual, methods for enamine synthesis have been reported. In particular, Miyano and coworkers (46) have reported the preparation of dehydropyrrolizidines and dehydroindolizidines by a simple two-step procedure. The first step involves the alkylation of lactams with $\gamma$-butoxylactone in the presence of sodium. The amido-acids so formed were
cyclized by pyrolysis over soda lime (Fig. 25) to give bicyclic enamines 60. Unlike the standard procedures, the enamines are formed by the formation of a new carbon-carbon bond.

A literature review showed that Miyano's reaction procedure had been previously investigated by Murakoshi in the late 1960's (47). However, this work attracted little attention because it appeared largely in Japanese. The reports indicated that 5-, 6-, and 7-membered rings could be formed, that the stereochemistry at the C-N center was retained and that the presence of a N-H bond did not interfere with the cyclization. In

\[
\begin{align*}
\text{Na} & \quad \text{Na} \\
\text{butyl lactone} & \quad \text{Soda-lime} \\
\Delta & \quad \Delta \\
n = 1 \text{ or } 2 & \quad R = H \text{ or } CH_3
\end{align*}
\]

Figure 25. Enamines from Amido-Acids

addition, both Murakoshi and Alder (88) have shown that esters can be substituted for acids. This method provides a useful approach to the desired type of heterocyclic enamines and iminium perchlorates. A
particularly attractive aspect of the method is the regiospecific formation of iminium salts which contain other tertiary hydrogens adjacent to the nitrogen atom.

In view of the potential utility of this procedure in alkaloid synthesis and in the preparation of the tricyclic ammonium salts 53 and the paucity of information on procedures to 1-azabicycloalkanes, it was decided to investigate the general applicability of this procedure.

One can envisage a variety of amido-acids which might undergo the reaction. Both C- and N-(ω-carboxyalkyl)lactams, as well a ω-acylamino-carboxylic acids are possible substrates for the reaction. In each of these, the effect of ring size of both the existing and the cyclizing rings, and substituents on nitrogen and/or the chains are possible variants.

Pillon and others in this group (89) have studied the annulation of a combination of 5- and 6-membered rings from N-(ω-carboxyalkyl)lactams and also the cyclizations of some C-(ω-carboxyalkyl)lactams. The annulation of a 7-membered ring onto an existing 6-membered ring proceeded in moderate yields. Thus the ring closure of 61 afforded the crude enamine 62 in 49% yield. Acidification with ethanolic perchloric acid gave the perchlorate 63 in 30% yield and a small amount of the ring-opened product 64 was also obtained. (Fig. 26)
Figure 26. Annulation of a 7-Membered Ring

In general, the formation of seven membered rings proceeds with some difficulty. This problem is evident in the report by Rapoport (86) and in other pyrolysis reactions although it has been possible to form the 7-membered imine from 6-acetamidohexanoic acid (47c,d). As an alternative to cyclizing a 7-membered ring onto a pre-existing 5-membered ring and as a part of our general studies on this methodology, we investigated the annulation of a 5-membered ring onto an existing 7-membered one. The results of this investigation and other aspects of the method form this section of the dissertation.
RESULTS

The alkylation of 6-methyl-2-piperidinone with 6-chlorohexene (65) under phase-transfer conditions (92) gave 66 in 60% yield. Oxidation of 66 with KMnO₄ in acetic acid gave a moderate yield of the acid 67 which, on pyrolysis over soda lime gave the enamine 68 in 60% yield which was then directly converted to the known perchlorate 49. (Scheme 8) The low overall yield of the enamines with this procedure led us to

Scheme 8. Synthesis of Enamine 68 Starting from Olefinic Lactam 65
reinvestigate Alder's (90) method for the preparation of N-(ω-carbethoxyalkyl)lactams and their cyclizations to bicyclic enamines. These reactions afforded better yields than the route via the corresponding acids and required fewer steps. Thus, the alkylation of 2-piperidinone or 2-pyrrolidinone with ethyl 5-bromovalerate in the presence of potassium hydride and dry DME as solvent gave 69a and 69b in 61% and 70% yield respectively. Pyrolysis of the esters over soda lime gave the corresponding enamines 70a and 70b in 70% and 72% yield.

Since the completion of our work, but before its publication, the formation of 70c and 70d and other homologues were reported. (91) (Fig. 27)

As mentioned previously, the low yield in the annulation of a 7-membered ring onto an existing 6-membered ring and our inability to cyclize a 7-membered ring on a 5-membered one led us to examine the alternative annulation of a 5-membered ring onto an existing 7-membered ring.

N-alkylation of hexahydro-1H-azepine-2-one (ε-caprolactam) with 5-chloro-1-pentene under phase transfer conditions (92) gave 71 in 62% yield. (Scheme 9) Oxidation of 71 with KMnO₄ under either liquid-liquid or liquid-solid phase transfer conditions gave 72 in very low yields. When KMnO₄ was used in the presence of acetic acid, a moderate yield of 72 was obtained. Pyrolysis over soda lime gave the enamine 73 in 65% yield.
Figure 27. Synthesis of Enamines from N-(ω-carbethoxyalkyl)-Lactams
Scheme 9. Annulation of a 5-Membered Ring Onto a 7-Membered Ring.
DISCUSSION

As noted, reports from our group and others have shown the pyrolysis of amido-acids over soda lime to be useful in the annulation of 5- and 6-membered rings and the formation of bicyclic enamines. The work reported here expands the knowledge of the scope of the reaction and suggests that for the preparation of fused ring systems which contain a 7-membered ring, the best route will involve annulation onto an existing caprolactam moiety. (However, it should be noted here that successful formation of a 7-membered ring has been reported (93).) The process is simple and yields are good relative to other existing procedures. Since the configuration of the existing C-N bond is not disturbed during the cyclization, application of the method to the synthesis of optically active nitrogen-containing compounds (e.g. ammonium salts) seems possible.

Determination of the mechanism of a reaction run at high temperature under heterogeneous conditions is difficult and any proposal must be regarded as being speculative. Nonetheless, the report by Mundy et al. (94) on the base-induced ring opening reaction of acyl lactams and our previous results suggest that the mechanism for these cyclizations is similar to the classical Ruzicka pyrolysis (95) of dicarboxylic acid salts over barium, calcium or thorium oxide. (Fig. 28)
Figure 28. Suggested Mechanism for the Cyclization Reaction
CONCLUSION

The formation of bicyclic enamines by this pyrolysis process is an important and convenient method for the synthesis of 1-azabicyclo compounds. It is noteworthy that the heterocyclic enamines were formed by a carbon-carbon bond forming reaction unlike the common methods which require the 1-azabicycloalkanes as starting materials. The importance of the current methodology has been demonstrated in the syntheses of some chiral tricyclic ammonium salts (Chapter 1).
CHAPTER III
EXPERIMENTAL
GENERAL INFORMATION

All melting points and boiling points are uncorrected. Infrared spectra were run on a Perkin-Elmer model 180 instrument in chloroform solution or in the FT mode on a Nicolet 5 DX spectrometer as neat samples. The $^1$H NMR spectra were run at 60 MHz on a Varian EM 360 spectrometer or on a Nicolet QE300 spectrometer at 300 MHz in chloroform-d with tetramethylsilane (TMS) as the internal standard. The data are presented in the format: chemical shift (multiplicity, number of protons, coupling constant) and are included as an appendix at the end of this section. The abbreviations used are: s-singlet, d-doublet, t-triplet, dd-doublet of doublets, m-multiplet, bs-broad singlet. $^{13}$C NMR spectra were recorded at 22.64 MHz on a Bruker CXP 100 spectrometer or a Nicolet QE300 spectrometer at 75 MHz. Gas chromatographic analyses were performed on a Varian Model 3700 instrument using a 1.5 ft x 1/8 in column packed with 5% OV-101 on Chromosorb W or a column packed with 20% SE30 on Chromosorb W. Mass spectra were run on a Varian MAT CH5 instrument in the field ionization (FI), field desorption (FD) or electron impact (EI) mode. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Concentrations in g/100 mL of solvent are included following the measured optical rotations.

Microanalyses were done by Guelph Chemical Laboratories, Guelph, Ontario and Galbraith Laboratories, Knoxville, Tennessee. For column chromatography, silica gel (Merck silica gel 60) 70-230 mesh was used. Reagent grade chemicals were used without further purification unless
otherwise specified. Tetrahydrofuran or dimethoxyethane were dried with potassium and benzophenone and distilled under nitrogen. Diisopropyl amine was stored over potassium hydroxide. Methylene chloride, chloroform and carbon tetrachloride were distilled from calcium hydride. Dimethyl formamide was distilled over barium oxide and stored over molecular sieves. For reactions which involved aqueous work-up, the drying agent was magnesium sulfate.

**EXPERIMENTAL PROCEDURES**

(S)-(5-hydroxymethyl)-2-pyrrolidinone (10)

This compound was prepared in 70% yield according to the literature procedure described by Silverman (51); mp 66-68°C (lit. (51) mp 65-67°C); $^1$H NMR: 1.4-2.6 (m, 4H), 3.13-4.06 (m, 3H), 3.86 (br s, 1H), 7.63 (s, 1H).

(S)-(5-phenylthiomethyl)-2-pyrrolidinone (12)

S-(5-p-toluenesulfonylmethyl)-2-pyrrolidinone (prepared in 30% yield according to the literature procedure (52)) (3g, 0.01 mol) was dissolved in 50 mL THF. A solution of sodium thiophenoxide (1.5 g, 0.01 mol) in THF (10 mL) was added dropwise with stirring. The mixture was stirred overnight and filtered. The solvent was evaporated to leave a yellow oil in 65% yield. $^1$H NMR: 1.26-2.46 (m, 5H), 2.57-2.93 (m, 1H), 3.23-3.87 (m, 2H), 7.23 (s, 5H).
(S)-(5-iodomethyl)-2-pyrrolidinone (13).

This compound was prepared in 40% yield by the literature procedure (52); mp 80-82 °C (lit. (52) mp 86-87 °C); \(^1\)H NMR: 1.6-2.53 (m, 4H), 3.23 (d, 2H, J = 6 Hz), 3.43-4.03 (m, 1H), 7.5 (br s, 1 H).

(S)-(5-bromomethyl)-2-pyrrolidinone (14).

This compound was prepared in 75% yield using the literature procedure (51); mp 70-72 °C (lit. (51) mp 71-74 °C); \(^1\)H NMR: 1.53-2.67 (m, 4H), 3.4 (d, 2H, J = 6 Hz), 3.73-4.13 (m, 1H), 5.43 (br s, 1 H).

(R)-(5)-5-methyl-2-pyrrolidinone (15).

**Method A**

Compound 12 (2.0 g, 0.001 mol) in ethanol (100 mL) was reduced with Raney Nickel (96) under reflux for two days. The reaction was only about 40% complete and the product was contaminated with starting material and other unidentified products.

**Method B**

Bromide 14 (8.8 g, 0.05 mol) in ethanol (150 mL) and triethylamine (5.06 g, 0.05 mol) was reduced with hydrogen in the presence of a catalytic amount of 10% palladium on carbon for 36 h at one atmosphere pressure and ambient temperature. The mixture was filtered through Celite and the solvent evaporated. The residue was extracted with ether (3 x 100 mL), the ether evaporated and the residue was distilled under reduced pressure to give 4.1 g (85%) of 15 as a colorless oil, bp 90 °C (1.8 mm); [\(\alpha\)]\(_D^{25}\) +24.8
(c=0.9, water) (lit.48) [\(\alpha\)]\(_D^{25}\) +26.6 (c=0.9, water)); MS (Fl): m/z=99.
The \(^1\)H NMR, IR and \(^{13}\)C NMR spectra are given in Tables 6, 7 and 8 respectively.

(R)-N-(4-carboxybutyl)-5-methyl-2-pyrrolidinone (16).

This compound was prepared in the same manner as described for 69b using 5-methyl-2-pyrrolidinone. A colorless oil was obtained in 70% yield, bp 140-142\(^\circ\) C (1 mm); [\(\alpha\)]\(_D^{25}\) +6.5\(^\circ\) (c= 2.0, ethanol); MS (Fl): m/z = 227

The \(^1\)H NMR and IR data are given in Tables 6 and 7.

Anal. Calcd. for C\(_{12}\)H\(_{21}\)NO\(_3\): C, 63.39; H, 9.31; N, 6.16. Found: C, 63.65; H, 9.98; N, 6.35.

**General Procedure for the Soda Lime Pyrolyses.**

The procedure was the same in all cases. The acid was thoroughly mixed with twice its weight of finely ground soda lime. The soda lime used contained an indicator which turned blue in the presence of carbon dioxide. Frequently the mixture became sticky and turned blue as soon as the mixing began. The pasty mass was transferred to a flask which was fitted with a short-path distillation apparatus, purged with nitrogen and the flask was heated with a free flame. The contents of the flask turned blue, evolved carbon dioxide, and then turned white again. Water distilled, followed by organic material (head temperature 140-200\(^\circ\) C). After all the material had distilled, the two-phase distillate was diluted with ether, the phases separated, and the aqueous phase was extracted with ether. The combined ethereal extracts were dried and evaporated to give the crude enamine which was treated with 70% perchloric acid in ethanol (1:1). Fresh samples
were used for all spectroscopic investigations. 

(3R)-3-methyl-4,4-dehydroindolizidinium perchlorate (18).

The enamine was obtained as a colorless oil in 65% yield. The perchlorate was obtained by treatment of a freshly prepared sample of the enamine in ethanol (20 mL) at 0°C with cold 70% perchloric acid. The precipitated salt was filtered and recrystallized from ethanol to give 18 in 45% overall yield from the lactam ester 16, mp 215-218°C.

(3R)-9-cyano-3-methylindolizidine (19).

This was prepared according the procedure described by Leonard for 70b (97). The nitrile was obtained in 78% yield from the perchlorate, bp 80-84°C (4.5 mm); [α]D 25 -62.3 (c = 1.06, chloroform); MS (Fl): m/z = 164. The spectroscopic data for 19 are given in Tables 6, 7 and 8.

(3R,9S)/(3R,9R)-(4-phenoxbutyl)-3-methylindolizidine (20).

This was prepared in 45% yield in the manner described by McIntosh (42); [α]D 25 -39.5° (c = 1.5, chloroform); MS (Fl): m/z = 287. The spectroscopic data are given in Tables 6, and 7.

Anal. Calcd. for C19H29NO: C, 79.39; H, 10.16; N, 4.88. Found: C, 80.12; H, 11.09; N, 5.03.

Ethyl 5-ketoheptanoate (25).

A mixture of 5-oxocapronitrile (prepared according to the literature procedure (98)), (61.5 g, 0.55 mol), 30 mL of concentrated sulfuric acid and 150 mL of ethanol was refluxed for 30 h. The solvent was removed and 200 mL of cold water was added followed by 10% sodium carbonate solution until the solution was neutral. The mixture was extracted with ether and
the extracts dried. Evaporation of the solvent and distillation of the residue under reduced pressure gave 66 g (75%) of 25 as a colorless liquid, bp 68-72° C (0.95 mm) (lit. (59a) bp 107° C(15 mm)); IR (neat): 3000, 2960, 2920, 1730, 1450, 1420, 1375, 1200, 1100, 1070, 1035, 945, 860 cm\(^{-1}\); \(^1\)H NMR: 4.33-3.93 (q, 2H, J = 7 Hz), 2.80-2.23 (m, 8H), 2.13 (s, 3H), 2.03-1.67 (t, 2H, J = 7 Hz), 1.36-1.13 (t, 3H, J = 7 Hz).

**Attempted Preparation of R-(-)- or S-(+)-6-methyl-2-piperidinone (28) from Ethyl 5-keto hexanoate (25).**

The imine prepared from 25 and S-(+)-\(\alpha\)-methylbenzyl amine as outlined in Method A was subjected to reduction with hydrogen in the presence of a catalytic amount 10% of palladium on carbon, sodium borohydride, sodium cyanoborohydride and Redal. The diastereomeric excess in each case was below 25%. However, the diastereomers could not be separated by column chromatography. The reaction was adapted for the preparation of the racemic compound as described below.

(+) 6-Methyl-2-piperidinone (28).

**Method A**

Compound 25 (10.0 g, 0.06 mol), (+)\-\(\alpha\)-methylbenzylamine (12.0 g, 0.09 mol) in 75 mL of benzene was refluxed for 12 h under a Dean Stark water separator. The excess amine was removed in vacuo and the residual imine was reduced with 2.0 g of 10% palladium on carbon in ethanol at an initial pressure of 40 psi. The reduction was stopped after 36 h at which time there was complete hydrogenation and hydrogenolysis of the amine. The
solvent was removed and the colorless liquid was stored in the freezer. The white solid obtained was recrystallized from ethyl acetate to give 4.2 g (59%) of the pure racemic lactam 28, mp 80-82° C (lit. 48 mp 81-82° C). The spectroscopic data are given in Tables 6, 7 and 8.

**Method B**

A solution of 25 (10.0 g, 0.06 mol) in 50 mL absolute ethanol was saturated with ammonia and reduced with hydrogen in the presence of palladium on carbon (2.0 g) at an initial pressure of 40 psi. The reduction was complete in 24 h. Excess ammonia was allowed to evaporate and the solvent was removed. The residue was stored in the freezer to give a white solid which was recrystallized from ethyl acetate to give 6.9 g of lactam 28.

**Attempted preparation of 34.**

Heterocycle 22 was prepared as described by Husson (60). However, all attempts at deprotonation of the O-silylated amino nitrile 33 with BuLi or LDA according to the literature procedures for such deprotonations were unsuccessful (61). It was therefore not possible to effect the oxidation of the anion to give the lactam. Subsequently, the original authors have reported similar problems in the deprotonation reaction (62) and have given modifications to the procedure which allows successful deprotonation. The possibility of oxidizing the anion from 33 to the lactam remains unexplored.
S-(+)-2-amino-1-propanol (S-(+)-alaninol (35)).

This was prepared by LAH reduction of L-alanine according to the procedure given in the literature for the reduction of valine and phenylalanine (63). The product (35) was obtained as a colorless oil in 64% yield, bp 83-84°C (14 mm); [α]$_D^{25}$ +20.5° (c = 5, ethanol) (lit.(96) [α]$_D^{25}$ +20.1°); IR (KBr): 3349 (broad), 2964, 1594, 1461, 1377, 1059 cm$^{-1}$; $^1$H NMR: 1.07 (d, 2H, J = 7 Hz), 2.86 (s, 3H), 3.01-3.73 (m, 3H).

(S)-N-(benzylxycarbonyl)-2-amino-1-propanol (36).

Benzylchloroformate (24.5 g, 0.14 mol) was added to a mixture of S-(+)-3-amino-1-propanol (10 g, 0.13 mol), water (100 mL), and Na$_2$CO$_3$ (17.1 g). The mixture was stirred for 4 h at room temperature and extracted with ethyl acetate (3 x 100 mL). The solution was dried, filtered and evaporated under reduced pressure to give an oil which crystallized on standing. Recrystallization from petroleum ether - ethyl acetate gave 24 g (85%) of the product, mp 80-82°C; [α]$_D^{25}$ -7.9° (c = 1, ethanol). The spectroscopic data can be found in Tables 6 and 7.

Anal. Calc. for C$_{11}$H$_{15}$NO$_3$: C, 63.15; H, 7.22; N, 6.70. Found: C, 63.30; H, 7.20; N, 6.87.

(S)-N-(benzylxycarbonyl)-2-aminopropyl bromide (37a).

The protected amino alcohol 36 (20 g, 0.1 mol) was added to triphenylphosphine (26 g, 0.1 mol) in dry acetonitrile (200 mL) and placed in an ice bath. Carbon tetrabromide (33.1 g, 0.1 mol) in the same solvent (100 mL) was added dropwise. After the addition, the resulting light yellow solution was stirred at ambient temperature overnight. The solvent
was removed under reduced pressure and the residue chromatographed on silica gel using ethyl acetate - hexane to afford 16 g (65%) of a solid, \([a]_D^{25} -26.6^\circ\) (c = 1, chloroform). The spectroscopic data can be found in Tables 6 and 7.

**Anal.** Calcd. for C_{11}H_{14}BrNO_2: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.3; H, 5.40; N, 5.28.

(S)-N-(benzyloxyacarbonyl)-2-aminopropyl p-toluene sulfonate (37b)

Tosyl chloride (28.5 g, 0.15 mol) was added in small amounts to a solution of the amido alcohol 26 (20.8 g, 0.1 mol) in methylene chloride at 0°C. The mixture was stirred at that temperature for 8 h and then poured on ice. The organic layer was separated, washed with 20% hydrochloric acid, saturated NaHCO_3 solution, brine and then dried. Solvent was removed and the residue chromatographed on silica gel using ethyl acetate-hexane (1:4) to give 27 g (75%) of a white solid, mp 66-67°C. MS (EI): m/z 101, 102, 262. The \(^1\)H NMR spectrum and IR data can be found in Tables 6 and 7.

**Anal.** Calcd. for C_{18}H_{17}NO_2S: C, 60.15; H, 4.77; N, 3.90. Found: C, 59.91; H, 4.41; N, 4.04.

(S)-N-(benzyloxyacarbonyl)-3-aminobutyronitrile (38).

**Method A**

Sodium cyanide impregnated on alumina (64) (100 g) was added to the bromide 37a (10 g) in toluene (100 mL) at 90°C. The mixture was stirred for 8 h and the residue was filtered off, washed with ethyl acetate (3 x 100 mL) and the solvent was evaporated to give an oil which was chromatographed on silica gel using 4:1 hexane - ethyl acetate to give 5 g
(63%) of the product.

**Method B**

Sodium cyanide (3.01 g, 0.06 mol) in dry DMF (150 mL) was placed in an oil bath at 95-100°C. The tosylate \((27b)\) (14.9 g, 0.04 mol) was added and stirring was continued overnight. Solvent was removed under reduced pressure and 200 mL of methylene chloride was added. The mixture was washed with brine \((2 \times 75 \text{ mL})\), the organic layer was separated and dried. Filtration and removal of solvent gave a residue which was chromatographed on silica gel using ethyl acetate - hexane \((4:1)\) to give 5.6 g (63%) of the product. The \(^1^H\) NMR and IR data are summarized in Tables 6 and 7.


\((S)\)-N-(\(^1^\text{butoxy} \text{carbonyl})\)-3-aminobutanol \((40a)\).

**Method A**

The nitrile \((38)\) (5 g, 0.023 mol) was refluxed in concentrated hydrochloric acid overnight. The solvent was evaporated under reduced pressure to give a viscous residue which was dissolved in methanol in the presence of a catalytic amount \((100 \text{ mg})\) of p-toluenesulfonic acid. The mixture was stirred overnight and the solvent evaporated under reduced pressure to give the amino ester hydrochloride. This was then dissolved in methylene chloride \((100 \text{ mL})\) and di-\(^\text{sec}\)-butyl carbonate \((5.01 \text{ g}, 0.023 \text{ mol})\) and triethyl amine \((2.3 \text{ g}, 0.023 \text{ mol})\) were added. The mixture was stirred at room temperature for 4 h. Ether was added and the precipitated triethylamine hydrochloride was filtered off, washed with ether and the
solvents evaporated. The residue was chromatographed over silica gel using ether - petroleum ether (1:3) to give 2.9 g (58%) of the ester (39a). This material (3.0 g, 0.014 mol) was added to a suspension of LiAlH₄ (0.52 g, 0.014 mol) in THF and stirred for 1 h at room temperature. The reaction was quenched with water and filtered. The solvent was evaporated and chromatography of the residue on silica gel using ethyl acetate - hexane (1:2) gave the alcohol in 65% yield, mp 55-56°C. (lit. (97) mp 56°C).

**Method B**

The diazoketone 45 (16 g, 0.08 mol) prepared from L-alanine via the mixed anhydride prepared with ethyl chloroformate according to the literature procedure (68) was dissolved in dry methanol (120 mL) and treated with a few drops of a solution of silver benzoate (1g) in triethylamine (11.6 mL). A vigorous reaction occurred with the evolution of nitrogen. When the reaction had subsided, the mixture was treated with charcoal, boiled for a few minutes and then filtered. The solvent was removed and ether (150 mL) was added and the mixture was washed with dilute HCl, saturated NaHCO₃, and then brine. The solution was dried, the ether evaporated and the residue chromatographed over silica gel using petroleum ether - ether (3:1) and crystallized in pentane to give the homologated ester (39a) in 75% yield, mp 42°C; [α]D²⁵ -24.4° (c = 0.54, chloroform) (lit. (97) mp 42°C; [α]D²⁵ -20.0° (c = 0.54 chloroform). The protected aminoalcohol (40a) was obtained as described in Method A, mp 55-56°C, [α]D²⁵ +10.5° (c = 0.5, chloroform). The ¹H NMR and IR data are
summarized in Tables 6 and 7.

(S)-N-(Benzyloxycarbonyl)-3-aminobutanol (40b)

Benzylichloroformate (3.4 g, 0.002 mol) was added to a mixture of the crude residue of the hydrochloride of aminoester 39 (R = H) (0.002 mol), water (20 mL) and Na₂CO₃ (2 g) at 0°C. After the addition, the mixture was stirred at room temperature for 3 h and extracted with ethyl acetate (3 x 100 mL) and dried. The solvent was evaporated to leave an oil which was crystallized from ethyl acetate - petroleum ether to give ester (29b) in 65% yield, mp 53-54°C. The ester was reduced with DIBAL at 0°C to give the alcohol 40b (50%); IR (KBr): 3326, 2968, 1695, 1536, 1260, 1050 cm⁻¹; ¹H NMR: 1.17 (d, 3H, J = 7 Hz), 1.67 (m, 2H), 3.10 (m, 1H), 3.4-4.13 (m, 3H), 5.03 (s with broad shoulder, 3H), 7.03 (s, 5H).

(S)-N-(Butyloxycarbonyl)-3-aminobutyl bromide (41a)

This compound was prepared in 50% yield using the same procedure as for 37b, mp 55-58°C; [α]D²⁵ +8.2 (c = 0.5, chloroform) (lit. (97) mp 55°C; IR (KBr): 3328, 2974, 2935, 1702, 1688, 1680, 1520, 1078 cm⁻¹; ¹H NMR: 1.25 (d, 3H, J = 6 Hz), 1.4 (s, 9H), 1.8 (m, 2H), 3.0 (m, 1H), 3.56 (dd, 2H), 3.90 (m, 1H), 4.33 (m, 1H).

(S)-N-(Benzyloxycarbonyl)-3-aminobutyl bromide (41b)

The procedure used was the same as that for the preparation of 37a. The product was obtained in 85% yield. The ¹H NMR and IR data are summarized in Tables 6 and 7.
S-(+)

Method A

The bromide 41b (2 g, 0.007 mol) was added to the anion prepared from sodium (0.017 g, 0.0075 mol) in dry ethanol (3 mL) and diethyl malonate (1.28 g, 0.008 mol). The reaction mixture was stirred overnight, poured on ice and extracted with methylene chloride (3 x 100 mL). The organic layer was dried, the solvent removed and the residue chromatographed on silica gel using ethyl acetate - hexane as eluant to give the diester 42 as a colorless oil (70%). The 1H NMR and IR data are given in Tables 6 and 7.

Diester 42 (4 g) in ethanol (30 mL) was reduced overnight with hydrogen over 10% palladium on carbon. The solvent was removed and water (2 mL), NaCl (0.4 g) and DMF (5 mL) was added to the residue and refluxed overnight. The mixture was extracted with methylene chloride (2 x 25 mL), dried and the solvent removed to give a residue which crystallized from ethyl acetate - petroleum ether.

Method-B

Ester 29a (10 g, 0.046 mol) in ether or toluene (100 mL) was cooled to -78°C and reduced with Dibal-H (90 mL of 1.5 M solution in toluene). The reaction was quenched at the same temperature by adding 6.5 mL of methanol. The solution was poured into a saturated solution of Rochelle salt (65 mL) and water (400 mL) at 0°C. After stirring for one hour at this temperature, the mixture was filtered, the filtrate extracted with ether (2 x 100 mL) and the residue also extracted with ether (4 x 75 mL). The
combined filtrates were dried and evaporated to give the aldehyde derived from 39a which was used directly as follows. The residue in THF solution (50 mL) was added to a -78° C solution of the Wittig reagent prepared from BuLi (28.6 mL of 2.5 M solution) and triethyl phosphonoacetate (13.6 g, 0.06 mol) in THF (250 mL). After stirring for 2 h, the reaction was quenched with water, extracted with ethyl acetate (3 x 100 mL) and dried. The solvents were removed and the residue chromatographed on silica gel using petroleum ether - ethyl acetate (9:1) as eluant to give the olefinic ester 46 which was immediately reduced with hydrogen in the presence of 10% palladium on carbon. Filtration and evaporation of the solvent was followed by treatment of the residue with 1:1 trifluoroacetic acid in methylene chloride at 0° C for 30 min to remove the 1BOC protecting group. Triethyl amine (1.1 equiv) in methylene chloride was added and, after removal of the solvent the residue was heated at 180° C for 1 h. Distillation under reduced pressure gave the lactam 28 which immediately solidified; mp 80-81° C; [α]D<sup>25</sup> +25.6° (c = 2.04, water) (lit. (48) [α]D<sup>25</sup> +27.8° (c = 2.03, water); <sup>1</sup>H NMR 7.30-6.80 (bs, 1H), 3.67-3.05 (m, 1H), 2.40-2.05 (m, 2H), 2.00-1.25 (m, 4H), 1.20-1.15 (d, 3H, J = 8 Hz).

(S)-N-(4-carbethoxybutyl)-6-methyl-2-piperidinone (48)

This was prepared in the same manner as described for 69b using 43. The product was obtained as a colorless oil in 60% yield, bp 116-118° C (0.2 mm). The <sup>1</sup>H NMR, IR and <sup>13</sup>C NMR data are summarized in Tables 6, 7 and 8.

Anal. Calcd. for C<sub>13</sub>H<sub>23</sub>NO<sub>3</sub>: C, 64.73; H, 9.54; N, 5.81. Found: C, 65.01;
H, 9.50; N, 5.67.

(S)-4-methyl-Δ^5,10-dehydroquinolizinium perchlorate (49).

This compound was obtained in 45% yield using the same procedure as outlined for 18; mp 249-250° C (dec). The ^1H NMR, IR and ^13C NMR data are summarized in Tables 6, 7 and 8. This compound has been reported in the racemic form previously. (98)

(S)-10-cyano-4-methylquinolizidine (50)

Nitrile 50 was obtained in the same manner as described for 19 (70% yield). The ^1H NMR and IR data are given in Tables 6 and 7.

(4S,9aR) and (4S,9aS)-9a-(4-phenoxycbutyl)-4-methylquinolizidine (51)

This was prepared from 50 using a procedure described in the literature. (42) Compound 47 was obtained as a colorless oil in 40% yield. The ^1H NMR and IR data are given in Tables 6 and 7.

This material was not purified further but carried on directly to the cyclization reaction.

2-methyl-1-azoniatricyclo[4.4.3.0^1,6]tridecane bromide (6).

This was prepared by the usual procedure described in the literature. (42) The ether 20 (0.25 g) was converted to the bromide 21 using concentrated hydrobromic acid and the crude material, without any purification was cyclized using silver oxide in water to give the hydroxide salt which was neutralized with hydrobromic acid to give pure product (0.085 g) after recrystallization from methanol; mp >300° C; [α]_D^{25} -22.5° (c = 1.0, methanol). Spectroscopic data for the trifluoroacetate salt are
given in Tables 1 and 2. The sample did not give acceptable carbon analysis, possibly due to presence of extraneous ionic material or to the extremely compact nature of the tricyclic system which is known to affect the carbon analyses as they are usually performed by microanalytical laboratories. (99) However, the field desorption mass spectrum gave a single peak at the expected m/z = 194, the 13C NMR showed the correct number of absorptions and the 1H NMR was entirely consistent with the assigned structure.

*Anal.* Calcd. for C15H24NBr: C, 56.93; H, 8.82; N, 5.11. Found: C, 55.70; H, 9.02; N, 4.93.

2-Methyl-1-azoniatricycl[4.4.4.01,6]tetradecane iodide (7).

In a similar manner, the iodide 7 (X = I) was obtained in 20% yield from 51; mp >300°C C15H24NBr. 
$\alpha$ D -14.9° (c = 0.5, methanol). Spectroscopic data for the hydroxide salt are given in Tables 2 and 3 and are identical to the previously prepared racemic material. (42) The FDMS gave a single peak at m/z = 208.

**General Procedure for the Phase-Transfer Cyclopropanation Reactions.**

To a mixture of toluene (20 mL) and 1 mL of 9.5 M aqueous sodium hydroxide was added, the catalyst (20 mg). The system was purged with nitrogen and cooled to 0°C in an ice-bath. To this solution was added 0.01 mol of the α,β-unsaturated carbonyl compound at 0°C with good stirring. The addition required 10 min and stirring was continued for 1 h at 0°C and a further 2 h at ambient temperature. The solution was diluted
with water (20 mL), the layers separated and the organic phase dried. The mixture was filtered, the solvent evaporated and the catalyst removed by the addition of anhydrous ether and filtration of the turbid solution. The ether was evaporated and the residue chromatographed on silica gel with ether - hexane as eluant. The products had spectra identical to those of authentic material. (73)

Ethyl 2-oxocyclohexanecarboxylate

This was prepared from cyclohexanone using the literature procedure for the preparation of the corresponding methyl ester. (74) The product was obtained in 75% yield. $^1$H NMR: 12.03 (s, 0.2H), 4.20 (q, 2H, $J = 7$ Hz), 3.37 (t, 0.5H, $J = 7$ Hz), 2.23 (m, 4H), 1.20 (m, 4H), 1.27 (t, 3H, $J = 7$ Hz).

General procedure for Phase-Transfer Alkylation Reactions.

A solution of ethyl 2-oxocyclohexanecarboxylate (0.005 mol) in toluene (20 mL) which contained 0.005 mol of the alkylating agent and the catalyst (15 mg) was stirred vigorously in the presence of 4.5 mL of aqueous 2.5 M sodium hydroxide solution at room temperature overnight. The organic phase was separated and washed with water, and then brine. The dried solution was filtered, evaporated and the residue chromatographed over silica gel using ether - hexane as eluant. The products had spectra identical to those of authentic material. (25a)
6-chlorohexene (65)

The ring opening of 2-chloromethyltetrahydropyran as outlined for the synthesis of 4-penten-1-ol (100) gave unsatisfactory yields. Therefore the following procedure was used.

2-Chloromethyltetrahydropyran (101) (26.0 g, 0.17 mol) was dissolved in 75 mL of liquid ammonia in a three-necked flask equipped with a Claisen condenser. Ether (100 mL) was added and small pieces of sodium (7.9 g, 0.34 mol) were added over a period of about 6 h. The mixture which contained a blueish-white precipitate was poured into a beaker and decomposed with ice water and saturated ammonium chloride solution. The organic layer was separated and dried, the solvent was removed and the residue distilled at atmospheric pressure to give 10.6 g (61%) of 5-hexene-1-ol as a colorless liquid; bp 77-80°C; IR (neat): 3520 (broad), 3080, 2980, 2940, 2860, 1635, 1450, 1430, 1410, 1110, 980, 900, 630 cm⁻¹; ¹H NMR: 6.20-5.50 (m, 1H), 5.23-4.90 (m, 2H), 3.77-3.47 (t, 2H, J = 7 Hz), 2.33 (m, 7H).

The alcohol was converted to chloride 65 in 52% yield according to the literature procedure for 5-chloro-1-pentene (42), bp 133-134°C (lit.(102) 132-134°C).

N-(5-hexenyl)-6-methyl-2-piperidinone (66)

A solution of 8.8 g (0.08 mol) of racemic 6-methyl-2-piperidinone and 10.4 g (0.1 mol) of 5-chloropentene (42) in 30 mL of dry THF was added to a suspension of pulverized KOH (5.04 g, 0.09 mol) and 5.31 g (0.016 mol) of
tetrabutyl ammonium bromide in 50 mL of THF. The addition required 1 h. The mixture was stirred vigorously and then refluxed for 12 h. The precipitate was filtered and the filtrate evaporated in vacuo to leave an oil. Methylene chloride was added to the residue, the solution was washed with water, then saturated brine and dried. Evaporation gave an oil which upon distillation gave 8.0 g (58%) of the product; bp 127-131°C (1.7 mm). The ¹H NMR and IR spectra are given in Tables 9 and 10; ¹³C NMR: 169.9, 138.2, 115.6, 115.0, 52.3, 44.8, 32.4, 31.4, 30.5, 27.1, 20.1.

N-(4-carboxybutyl)-6-methyl-2-piperidinone (67).

To a vigorously stirred cold solution of 6.23 g (0.04 Mol) of KMnO₄ in 100 mL of water was added a solution of 3.6 g (0.04 mol) of the racemic lactam 28 in 15 mL of acetic acid over 30 min. The mixture was stirred at ambient temperature for 12 h, cooled in an ice bath and 3 g of sodium sulfite was added followed by enough 6M hydrochloric acid to bring the pH to 1. The solution was extracted with methylene chloride (4 x 25 mL), the organic extracts washed with cold water and dried. Evaporation and trituration with ether gave the acid 67 in 45% yield. The ¹H NMR and IR spectra are summarized in Tables 9 and 10; ¹³C NMR: 177.0, 170.8, 84.0, 52.2, 45.0, 34.0, 31.8, 30.2, 27.2, 22.5, 19.9, 17.3.

N-(4-carbethoxybutyl)-2-piperidinone (69b)

Potassium hydride [20 g of 35% by weight in mineral oil (0.16 mol)] was washed three times with pentane and dried under nitrogen. Dry DME (100 mL) was added followed by the dropwise addition of 2-piperidinone (0.15 mol)
mol) in 50 mL of DME. The mixture was stirred at room temperature for about 3 h. Ethyl 5-bromovalerate (17 g, 0.15 mol) in 50 mL of DME was added slowly and the mixture was stirred at room temperature for 8 h. The reaction was quenched with ethanol followed by a small amount of water and then filtered. The filtrate was concentrated and methylene chloride (100 mL) and water (50 mL) were added. The aqueous layer was separated and the organic layer was washed with brine and dried. Removal of the solvent and distillation gave 69b in 70% yield; bp 115-118 °C (1 mm). The 1H NMR and IR data are summarized in Tables 9 and 10.

N-(4-carboxybutyl)-2-pyrrolidinone (69a)

This compound was prepared in the same manner as described for 69b using 2-pyrrolidinone. The product was obtained as a colorless oil in 65% yield. bp. 108-109 °C (1.2 mm). The 1H NMR and IR data are summarized in Tables 9 and 10.

Δ 1,9- and/or Δ 8,9-Dihydroindolizidine and its perchlorate (70a)

This was obtained as a colorless oil in 45% yield using the general procedure for soda lime pyrolsysis previously outlined. The NMR and IR (1675 cm⁻¹) spectra were identical to those reported (103) for the mixture of isomers.

The perchlorate was prepared in the usual manner (as described for 18) in 65% yield. The spectra were identical to those reported (103) for authentic material.
D1,10-Dehydroquinolizidine and its perchlorate (70b)

Using the general procedure for soda lime pyrolyses previously given, compound 70a was prepared. The spectra were identical to those reported (104) for an authentic sample.

N-(4-pentenyl)-hexahydroazepin-2-one (71).

Compound 71 was prepared using the same procedure described for 66 using hexahydroazepine-2-one (ε-caprolactam) and 5-chloro-1-pentene. (42) The product was obtained as a colorless oil in 62% yield; bp 95-98°C (0.7 mm). The 1H NMR and IR spectra are given in Tables 9 and 10; 13C NMR: 175.6, 138.0, 114.9, 49.7, 48.0, 37.4, 31.2, 30.1, 28.9, 27.5, 23.5.

N-(ω-carboxybutyl)-hexahydroazepin-2-one (72).

This compound was prepared using the same procedure as given for 67. The product was obtained in 45% yield; mp 74-75°C. The 1H NMR and IR spectra are given in Tables 9 and 10. 13C NMR: 176.8, 176.4, 49.9, 47.8, 36.9, 31.5, 29.9, 28.5, 23.3.

Anal. Calcd. for C_{10}H_{17}NO_3: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.17; H, 8.60; N, 7.16.

Dehydro-1-azabicyclo[5.3.0]decane (73)

This was prepared by the pyrolysis of 72 over soda lime in the usual manner (49% yield). (85a) Although the perchlorate could not be isolated, treatment of the acidic reaction solution with saturated aqueous KCN gave the nitrile whose IR spectrum showed the expected absorption at 2250 cm⁻¹.
for a nitrile. The $^1H$ NMR spectrum was completely unresolved. $^{13}C$ NMR:

115.8, 65.5, 54.9, 51.1, 40.4, 38.1, 27.0, 25.9, 23.9, 21.3.
Infrared and NMR spectra of new compounds prepared
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shift (in ppm from TMS)</th>
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<td>10</td>
<td>1.4-2.6 (m, 4 H), 3.13-4.06 (m, 3 H), 3.86 (br s, 1 H), 7.63 (s, 1 H)</td>
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<td>13</td>
<td>1.6-2.53 (m, 4H), 3.23 (d, 2H, J = 6 Hz), 3.43-4.03 (m, 1H), 7.5 (br s, 1H).</td>
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<td>15</td>
<td>1.17 (d, 3H, J = 7 Hz), 1.67 (m, 1H), 2.27 (m, 3H), 3.76 (m, 1H), 7.76 (br s, 1H).</td>
</tr>
<tr>
<td>16</td>
<td>1.20 (d, 3H, J = 7 Hz), 1.26 (t, 3H, J = 7 Hz). 1.56 (m, 5H), 2.23 (m, 5H), 2.93 (m, 1H), 3.6 (m, 2H), 4.13 (q, 2H).</td>
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<td>1.46 (d, 3H, J = 7 Hz), 1.50-1.99 (m, 2H), 2.46-2.49 (m, 2H), 2.51-2.84 (m, 2H), 2.85-3.14 (m, 2H), 3.60 (m, 2H), 4.50 (m, 2H).</td>
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<td>1.12 (d, 3H, J = 6.1 Hz), 1.2-1.8 (m, 8H), 1.95-2.20 (m, 4H), 2.62 (m, 1H), 3.15 (bd, 1H, J = 10.5 Hz).</td>
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<tr>
<td>28</td>
<td>1.15 (d, 3H, J = 7 Hz), 1.26-2.00 (m, 4H), 2.01-2.43 (m, 2H), 3.07-3.67 (m, 1H), 6.87-7.33 (m, 5H).</td>
</tr>
</tbody>
</table>
36  
1.17 (d, 3H, J = 7 Hz), 1.67 (m, 2H), 3.1 (m, 1H), 3.14-4.13 (m, 3H), 5.03 (br s, 3H), 7.3 (s, 5H).

37a  
1.7 (d, 2H, J = 7 Hz), 2.42 (s, 2H), 3.4-4.13 (m, 3H), 5.03 (br, 3H), 7.33 (s, 5H), 7.56 (m, 4H).

37c  
1.17 (d, 3H, J = 7 Hz), 3.43 (bd, 2H, J = 4 Hz), 3.7-4.27 (m, 1H), 5.03 (br, 3H), 7.37 (s, 5H).

38  
1.17 (d, 3H, J = 7 Hz), 2.43 (AB quartet, 2H), 3.90 (m, 1H), 5.03 (s, 2H), 5.63 (bd, 1H), 7.30 (s, 5H).

40a  
1.17 (d, 3H, J = 7 Hz), 1.67 (m, 2H), 3.1 (m, 1H), 3.4-4.13 (m, 3H), 5.03 (s with broad shoulder, 3H).

41b  
1.13 (d, 3H, J = 7 Hz), 1.93 (q, 2H, J = 7 Hz), 3.33 (t, 2H, J = 7 Hz), 3.53-4.27 (m, 1H), 5.03 (singlet with broad shoulder, 3H), 7.30 (s, 5H).

42  
1.13 (d, 3H, J = 7 Hz), 1.23 (t, 6H, J = 7 Hz), 1.43-2.33 (m, 3H), 3.33 (t, 1H, J = 7 Hz), 3.77 (m, 1H), 4.2 (q, 4H, J = 7 Hz), 5.03 (s, with broad shoulder, 3H).

48  
1.2 (d, 3H, J = 7 Hz), 1.23 (t, 3H, J = 7 Hz), 1.43-2.1 (m, 8H), 2.1-2.53 (m, 4H), 2.67-3.17 (m, 1H), 3.27-3.57 (m, 2H), 4.13 (q, 2H, J = 7 Hz).
49 1.5 (d, 3H, J = 7 Hz), 1.93 (m, 8H), 2.80 (m, 4H), 3.77 (m, 3H).
50 1.05 (d, 3H, J = 7 Hz), 1.0-1.80 (m, 12H), 2.15 (t, 1H), 2.35 (m, 1H), 3.12 bd, 1H).
51 1.00-2.10 (m, 20H), 2.05-2.75 (m, 4H), 3.50 (t, 2H, J = 6 Hz), 6.75-7.50 (m, 5H).
Table 7.

IR Spectra of Compounds Prepared in Part I

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorptions (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>3240, 2967, 2931, 1690, 1423, 1378, 1277.</td>
</tr>
<tr>
<td>16</td>
<td>2967, 2934, 2870, 1733, 1687, 1417, 1375, 1251, 1184, 1156, 1098.</td>
</tr>
<tr>
<td>18</td>
<td>1700</td>
</tr>
<tr>
<td>19</td>
<td>2200.</td>
</tr>
<tr>
<td>20</td>
<td>3010, 2930, 1600, 1585, 1490, 1465, 1450, 1290.</td>
</tr>
<tr>
<td>25</td>
<td>3000, 2960, 2920, 1730, 1450, 1420, 1375, 1200, 1100, 1070, 1035.</td>
</tr>
<tr>
<td>28</td>
<td>3200, 2960, 2890, 1675, 1480, 1400, 1384, 800.</td>
</tr>
<tr>
<td>35</td>
<td>3349, 2964, 2911, 1595, 1461, 1372, 1059.</td>
</tr>
<tr>
<td>36</td>
<td>3453, 3322, 1678, 1665, 1548, 1255, 964.</td>
</tr>
<tr>
<td>37a</td>
<td>3380, 1671, 1565, 1548, 1350, 1256, 749.</td>
</tr>
<tr>
<td>37c</td>
<td>3337, 1686, 1254.</td>
</tr>
<tr>
<td>38</td>
<td>3333, 2254, 1689, 1536, 1270, 1062.</td>
</tr>
<tr>
<td>40a</td>
<td>3326, 2968, 1695, 1536, 1260, 1050.</td>
</tr>
<tr>
<td>41b</td>
<td>3356, 2974, 2936, 1688, 1529, 1366, 1174.</td>
</tr>
<tr>
<td>48</td>
<td>3048, 2943, 2872, 1733, 1634, 1472, 1375, 1248, 1182.</td>
</tr>
</tbody>
</table>
49 1670.
50 2940, 2860, 2820, 2360, 1438, 1425, 1355, 1320, 1238, 1070, 1020, 985, 770
51 3010, 2936, 2864, 1600, 1585, 1497, 1468, 1455, 1245, 1171
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shift (in ppm from TMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>178.4, 50.1, 30.6, 29.0, 22.0</td>
</tr>
<tr>
<td>18</td>
<td>190.4, 68.9, 45.7, 37.4, 27.8, 26.5, 20.0, 17.8, 16.3</td>
</tr>
<tr>
<td>19</td>
<td>99.7, 98.0, 57.0, 45.7, 35.3, 34.6, 34.5, 28.9, 24.6, 21.4</td>
</tr>
<tr>
<td>20</td>
<td>160.3, 129.5, 120.7, 114.8, 67.9, 49.2, 35.5, 26.0, 20.5, 20.2</td>
</tr>
<tr>
<td>28</td>
<td>172.0, 48.5, 30.9, 30.3, 22.5, 19.7</td>
</tr>
<tr>
<td>48</td>
<td>178.2, 169.5, 59.9, 51.8, 44.3, 33.7, 30.1, 27.0, 22.2, 19.8, 17.3, -14.0</td>
</tr>
<tr>
<td>49</td>
<td>188.1, 115.7, 57.0, 52.4, 32.9, 27.4, 20.8, 18.4, 16.8, 134.6</td>
</tr>
<tr>
<td>50</td>
<td>118.5, 61.3, 54.6, 47.0, 37.6, 34.6, 25.5, 21.4, 20.7</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical shift (in ppm from TMS)</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>66</td>
<td>6.09-5.85 (m, 1H), 5.10-4.90 (m, 2H), 3.95-3.28 (m, 2H), 3.08-2.55 (m, 1H), 2.50-1.38 (m, 10H), 1.18-0.13 (d, 3H).</td>
</tr>
<tr>
<td>67</td>
<td>9.03 (s, 1H), 4.03-3.32 (m, 2H), 3.32-2.80 (m, 1H), 2.67-2.10 (m, 4H), 2.08-1.36 (m, 6H), 1.25 (d, 3H, J = 7 Hz).</td>
</tr>
<tr>
<td>69a</td>
<td>4.13 (q, 2H, J = 7 Hz), 3.67-3.01 (m, 4H), 2.6-1.26 (m, 9H), 1.25 (t, 3H, J = 7 Hz).</td>
</tr>
<tr>
<td>69b</td>
<td>4.06 (q, 2H, J = 7 Hz), 3.67-3.06 (m, 4H), 2.56-2.1 (m, 4H), 2.1-1.43 (m, 9H), 1.21 (t, 3H, J = 7 Hz).</td>
</tr>
<tr>
<td>71</td>
<td>6.0-5.33 (m, 1H), 5.05-4.55 (m, 2H), 3.30-3.08 (m, 4H), 2.48-2.13 (m, 2H), 2.10-1.80 (bt, 2H, J = 8 Hz), 1.78-1.20 (m, 8H).</td>
</tr>
<tr>
<td>72</td>
<td>9.3 (s, 1H), 3.5 (m, 4H), 2.5 (m, 4H), 2.0 (bs, 8H).</td>
</tr>
<tr>
<td>Compound</td>
<td>Absorptions (cm(^{-1}))</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>66</td>
<td>3090, 2980, 2870, 1640, 1465, 1415, 1330, 1185, 990, 910.</td>
</tr>
<tr>
<td>67</td>
<td>3350 - 2450 (broad), 1770, 1615, 1450, 1400, 1330, 1200, 1170.</td>
</tr>
<tr>
<td>69a</td>
<td>1702.</td>
</tr>
<tr>
<td>69b</td>
<td>1700.</td>
</tr>
<tr>
<td>71</td>
<td>3080, 2950, 2855, 1660, 1635, 1470, 1430, 1350, 975, 900.</td>
</tr>
<tr>
<td>72</td>
<td>3300 - 2600 (broad), 1730, 1610, 1495, 1440, 1380, 1210.</td>
</tr>
</tbody>
</table>
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