SYNTHESIS AND REACTIVITY OF MACROCYCLIC LACTAMS AND DYNAMIC NMR STUDIES OF MACROCYCLIC AMINES AND A MACROCYCLIC KETONE

by

Leonard Lermer

B. Sc., University of Lethbridge, 1987

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

in
THE FACULTY OF GRADUATE STUDIES
(Department of Chemistry)

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The University of British Columbia
April 1999
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Department of Chemistry
The University of British Columbia
Vancouver, Canada

Date 15/04/99
Abstract

Conformationally controlled alkylation of lactams 65, 66, 67 and 68 were investigated. High stereoselectivity was obtained in the alkylation of the dianion of lactams 65, 66 and 67. The alkylation of 65 gave products 92 and 93 in a >99:1 ratio. Alkylation of 66 gave 94 and 95 in a 62:1 ratio, and alkylation of 67 gave 96 and 97 in a 10:1 ratio. The relative stereochemistry of the products from the alkylation of 67 was determined by X-ray crystallography, and by chemical correlation for the alkylation products from 65, 66.

The relative ratio of the products from the alkylation of the N-benzyl amide 68 was found to be solvent dependent. Alkylation of 68 in hexane resulted in a 5.7:1 ratio of 110 to 111, alkylation in THF resulted in a 2.3:1 ratio and in DMSO resulted in a 1:1.3 ratio. The relative stereochemistry of the two lactams 110 and 111 was determined by chemical correlation with the products 96 and 97 obtained from the dianion alkylation of lactam 67.
The observation of selective proton NOE enhancements upon irradiation of the NH proton and analysis of coupling constant values indicated that the amide regions of lactams 65-67 and 92-97 are conformationally similar and rigid, in the syn-periplanar and Z-amide conformation. Molecular mechanics calculations were able to correctly model the conformational rigidity of the amide region of the lactams and the stereochemistry of the products from the alkylation of lactams 65-67.

The conformational properties of 13-, 14- and 16-membered macrocyclic amines 120-122, N-methyl amines 123-125, N,N-dimethyl amines 126-128 and 
\((2R^*, 12S^*)\)-2,12-dimethylcyclocododecanone (98) were investigated using dynamic NMR (DNMR).
(2R*,12S*)-2,12-Dimethylcyclododecanone (98) was found to exist in two conformations from the $^{13}$C DNMR at -95 °C, a major unsymmetric conformation and a minor symmetric conformation. The major conformation was found to be 1.6 kcal/mol more stable than the minor conformation at -95 °C. Upon cooling to -115 °C, ketone 98 was found to exist only in the unsymmetric conformation. An energy barrier of $\Delta G^\ddagger = 8.6$ kcal/mol at -85 °C was measured for the process of ring inversion in the unsymmetric conformation. The observed chemical shift in the $^1$H and $^{13}$C DNMR were consistent with the unsymmetric [3333]-2-one and symmetric [2343] as the major and minor conformations respectively. The lowest energy conformation was found by molecular mechanics calculations to be the [3333]-2-one conformation (identical to the X-ray crystal structure) and the second lowest in energy was the [2343] conformation having a plane of symmetry, in agreement with the interpretation of the DNMR.

Azacyclotetradecane (121) was found to exist in two conformations from the $^1$H DNMR at -130 °C in a mixture of CHCl$_2$F and CHClF$_2$ (4:1), a major symmetric conformation and a minor unsymmetric conformation. The major conformation was found to be 0.21 kcal/mol more stable than the minor conformation at -130 °C. The barrier to ring inversion in the symmetric conformation was determined to be $\Delta G^\ddagger = 8.7$ kcal/mol at -90 °C. The barriers to ring inversion and pseudorotation in the
unsymmetric \([3434]\) conformation was determined to be \(\Delta G^\ddagger = 8.3-8.5\) kcal/mol at -90 °C and the activation energy for the process of local inversion between the two conformations was estimated to be in this same energy range. Azacyclotetradecane (121) was also found to exist in a major symmetric conformation and a minor unsymmetric conformation from the \(^{13}\)C DNMR at -110°C in \(d_8\)-toluene:CHCl\(_2\)F (1:3). The observed chemical shifts in the \(^1\)H and \(^{13}\)C DNMR were consistent with the symmetric \([3434]\) conformer 121-A and an unsymmetric \([3434]\) conformer 121-B as the major and minor conformations respectively.

![Diagram 121-A and 121-B](image)

N-Methylazacyclotetradecane (124) was found to exist in two conformations from the \(^1\)H DNMR at -110 °C in \(d_4\)-methanol:CHCl\(_2\)F (1:4), a major symmetric conformation and a minor unsymmetric conformation. The major conformation was found to be 0.30 kcal/mol more stable than the minor conformation at -110 °C. The barrier to ring inversion in the symmetric conformation was found to be \(\Delta G^\ddagger = 8.6\) kcal/mol at -90 °C. The barriers to ring inversion and pseudorotation in the unsymmetric conformation were measured to be \(\Delta G^\ddagger = 8.4\) kcal/mol at -95 °C and \(\Delta G^\ddagger = 8.2\) kcal/mol at -105 °C respectively. The observed chemical shifts in the \(^1\)H DNMR were consistent with the
symmetric [3434] conformer 124-A and an unsymmetric [3434] conformer 124-B as the major and minor conformations respectively.

\[
\begin{align*}
124-A & \\
124-B & 
\end{align*}
\]

N,N-Dimethyltrideca-1,13-diylammonium iodide (127) was found to have an energy barrier to ring inversion of \( \Delta G^\ddagger = 10.5 \text{ kcal/mol} \) at -48 °C in \( d_4 \)-methanol. The lowest energy conformation was found by molecular mechanics calculations to be the [3434] conformation having the geminal dimethyl group at a corner position identical to the X-ray crystal structure.

\[
\begin{align*}
127-A & 
\end{align*}
\]

Azacyclohexadecane (122) was found to exist in two conformations from the \(^1\text{H} \) DNMR at -120 °C in \( d_4 \)-methanol:CHCl\(_2\)F (1:3), a major symmetric conformation and a minor unsymmetric conformation. The major conformation was found to be 0.43 kcal/mol more stable than the minor conformation at -120 °C. The barrier to inversion in the symmetric [4444] conformation was measured as \( \Delta G^\ddagger = 7.8 \text{ kcal/mol} \) at
-110 °C. The observed chemical shifts in the $^1$H DNMR spectra were consistent with the symmetric [4444] conformer 122-A and an unsymmetric [4444] conformer 122-B as the major and minor conformations respectively.

N-Methylazacyclohexadecane (125) was found to exist in two conformations from the $^1$H DNMR at -120 °C in CHCl$_2$F, a major unsymmetric conformation and a minor symmetric conformation. The major conformation was found to be 0.33 kcal/mol more stable than the minor conformation at -120 °C. The slowing on the NMR time scale of the process of ring inversion in N-methylazacyclohexadecane (125) was observed prior to the separation of the two conformations upon cooling. The barrier to ring inversion in N-methylazacyclohexadecane (125) was measured as $\Delta G^\dagger = 9.0$ kcal/mol at -80 °C. The observed chemical shifts in the $^1$H DNMR were consistent with an unsymmetric [4444] conformer 125-C and the symmetric [4444] conformer 125-A as the major and minor conformations respectively.
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List of Compounds

65

66

67

68

72 $x = 1$

73 $x = 2$

74 $x = 4$

75 $x = 1$

76 $x = 2$

77 $x = 4$

78 $x = 1$

79 $x = 2$

80 $x = 4$

81 $x = 1$

82 $x = 2$

83 $x = 4$

84 $x = 1$

85 $x = 2$

86 $x = 4$

87

89

90

92 $x = 1$

94 $x = 2$

96 $x = 4$

93 $x = 1$

95 $x = 2$

97 $x = 4$
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMH</td>
<td>N,N-dimethylhydrazone</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethyl-N,N'-propylene urea</td>
</tr>
<tr>
<td>DNMR</td>
<td>dynamic nuclear magnetic resonance</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hours (s)</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
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<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
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<td>LAH</td>
<td>lithium aluminum hydride</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectroscopy</td>
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<td>L-Selectride</td>
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<td>multiplet</td>
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<tr>
<td>$^{1}$H NMR</td>
<td>nuclear magnetic resonance (proton)</td>
</tr>
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<td>phenyl</td>
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<tr>
<td>ppm</td>
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</tr>
<tr>
<td>Rf</td>
<td>in thin layer chromatography, ratio of distance traveled by the compound to the distance traveled by the solvent</td>
</tr>
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<td>s</td>
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</tr>
<tr>
<td>t</td>
<td>triplet</td>
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<td>TBDMS</td>
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</tr>
<tr>
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</tr>
<tr>
<td>TMS</td>
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<tr>
<td>Ts</td>
<td>tosyl</td>
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Acknowledgments

The research presented in this thesis would not be complete were it not for the contributions of a number of individuals whose efforts I would like to acknowledge.

First and foremost tremendous gratitude goes to Dr. L. Weiler, my research supervisor, for his guidance, advice, support, and patience throughout the course of this study.

I would like to express warm thanks to the NMR department, Liane Darge, and Marietta Austria, both for running numerous experiments on my behalf and for their instruction in the operation of the NMR equipment. Additionally I would like to thank Dr. Nick Burlinson for his insightful discussions regarding NMR experiments and processing techniques.

I am grateful to Steve Rettig for performing the X-ray crystallographic studies, Peter Borda who carried out the microanalysis and all the service personnel in the Mass Spectroscopy department.

I am particularly grateful to Dr. Colin Fyfe for reading my thesis and providing supportive advice and comments.

I would like to acknowledge the Natural Sciences and Engineering Research Council of Canada for providing financial assistance during the course of this study.

To my lab mates, who provided a challenging, dynamic and entertaining environment throughout my stay, I extend my thanks.

Finally, I would like to thank my family and friends for their support and encouragement throughout my graduate studies.
Chapter I

Introduction

The development of novel stereoselective reactions has been and remains one of the most intriguing challenges for synthetic organic chemists. The synthesis of the macrolide antibiotics with their multitude of asymmetric centers has proved to be a showcase for the power and ingenuity of many new synthetic techniques. The complex stereochemistry in the structure of erythromycin A (1) exemplifies the extent of stereocontrol required to synthesize such macrolides.

![Chemical structure](image)

A common approach to the synthesis of these macrolides involves the connection of subunits containing the correct absolute stereochemistry at each stereogenic center followed by a macrolactonization to form the ring. An example of this approach is illustrated by the retrosynthetic analysis of erythromycin A (1) shown in Scheme 1. This strategy was utilized by Woodward et al. in their successful synthesis of erythromycin A (1).^{1-3}
Scheme 1. The retrosynthetic analysis of erythromycin A (1) (from ref. 1-3).

A novel approach to the total synthesis of macrolides, which our group has been studying, involves formation of the macrocyclic ring early in the synthetic sequence, followed by the use of conformational effects to control both the stereochemistry and regiochemistry of reactions to incorporate further substituents on the large ring.\textsuperscript{4,5} The use of conformational controlled stereoselective reactions is common in small ring chemistry. The reduction of 4-t-butylcyclohexanone (6) by L-Selectride shown in Scheme 2 is an example of such control. This reduction occurs with a greater than 99:1 ratio of cis to trans products 7:8.\textsuperscript{6,7} In the ground state, 4-t-butylcyclohexanone (6) prefers the chair conformation in which the t-butyl group occupies an equatorial position. The high stereoselectivity obtained from the reduction indicates that this conformational preference in the ground state is reflected in the transition state.
Scheme 2. Stereoselective reduction of 4-t-butycyclohexanone (6).

To date, the analogous approach to control stereoselectivity in large ring compounds has seen very limited use. The lack of both experimental precedence and a good model to confidently predict the stereochemical outcome of a reaction based on the conformational analysis of large rings has prevented this methodology from being widely used in complex multistep syntheses. In an effort to assess the potential of this alternative approach in the synthesis of macrolides, our laboratory began a systematic study of less complex macrocyclic lactones.

The stereoselectivity in the reduction of 9-oxo-13-tetradecanolide (9) to 10 and 11 (9:1), shown in Scheme 3, demonstrates conformational control of a reaction in which the stereogenic centers are separated by a number of methylene units. High stereoselectivity has also been obtained for other reduction, alkylation, and hydroboration reactions in macrocyclic lactones.
Scheme 3. Stereoselective reduction of 9-oxo-13-tetradecanolide (9) (from ref. 8).

The two major experimental sections of this thesis, the alkylation of macrocyclic lactams and the dynamic NMR study of macrocyclic amines, were undertaken to expand the understanding of the conformational analysis of macrocycles and to study conformational effects in the control of the stereochemistry of reactions in such macrocyclic nitrogen derivatives. The first part of this thesis, discussed in Chapter II, involved a study of the alkylation reactions of 13-, 14- and 16-membered lactams. The results from these experiments were compared with previous results on the stereoselective alkylations of 14- and 16-membered lactones, to evaluate how the amide bond affects the stereoselectivity and the conformation of the ring. The second part of this thesis, discussed in Chapter III, involved a dynamic NMR study of macrocyclic amines to probe the conformational processes in these rings. Such conformational energy barriers are a measure of the conformational flexibility of the macrocyclic ring skeleton. As our understanding of the conformations of large ring increases, and our confidence to predict the stereochemical outcome of reactions controlled by the conformational bias of macrocyclic rings improves, the potential for
conformational control to be used in rational multistep syntheses of complex macrolides comes closer to being fully realized.

1.1 Structure and chemistry of macrolide antibiotics

The synthesis of medicinally important macrolide antibiotics is a long-term goal for the application of this research. In 1950 the first macrolide antibiotic, named pikromycin (12), was isolated from a strain of streptomyces. The antibacterial activity of this compound and its potential clinical value sparked a significant research effort into the isolation and structural determination of new macrolide antibiotics. These macrolide antibiotics characteristically contain a 12-, 14- or 16-membered lactone ring of a secondary alcohol, an array of hydroxyl and alkyl substituents and often one or more amino sugars attached to the ring.\(^\text{13}\) As new compounds which resembled the macrolide lactones were discovered the definition of the term macrolide was expanded, and now includes macrocyclic lactams, polyene macrolides and cyclic peptides. The original class of lactones has been renamed as the subclass, polyoxomacrolides.\(^\text{13,14}\)

\[
\begin{align*}
\text{R}^1 &= \text{desosaminy1} \\
\end{align*}
\]

In 1952, only two years after the discovery of pikromycin, erythromycin (1) was introduced to clinical medicine\(^\text{15}\) and today remains one of the most important macrolide
antibiotics. Erythromycin acts as an antibiotic by inhibiting critical protein synthesis in bacteria. The macrolide binds to the 50s subunit of the ribosome prior to the formation of the 70s ribosome in bacterial cells. Suppression of protein synthesis occurs as translocation of the macrolide-bound ribosome along the m-RNA strand is blocked. Macrolides generally have a low toxicity in humans as they have little affect on translocation along the larger 80s ribosome in mammalian cells. This combination of the macrolides' powerful antibiotic abilities and their low mammalian toxicities provide macrolides with their medicinal value.

1.2 Macrocyclic lactams

Recently two novel families of macrocyclic lactams have been discovered which also have medicinal potential. In 1991 the first naturally occurring macrolide lactams were isolated from the fermentation broth of actinomycetes. This series of compounds has been found to have both antifungal and antiviral properties. An example from this family of compounds is fluvirucin B1 (13). The second family of macrolactams was designed and synthesized to act as human renin inhibitors, in the modulation of blood pressure. These macrocyclic lactams were engineered to both increase bioavailability and to increase the inhibitor activity over known acyclic polypeptide inhibitors. Compound 14 is such an example. This 14-membered ring lactam was found to be as potent an inhibitor of human renin as any acyclic peptide inhibitor. Though no medicinally significant increase to the inhibition was observed, increased bioavailability was expected for these cyclic compounds since they showed significant resistance to cleavage by chymotrypsin.
1.3 The acyclic approach to the syntheses of the macrolides

The total synthesis of the macrolides posed significant challenges to synthetic chemists. The two major obstacles to the successful synthesis of the macrolides are the controlled construction of the carbon skeleton with the numerous stereogenic centers and the formation of the macrocyclic ring. In 1975, 25 years after the first macrolide was discovered, Masamune et al. published the first synthesis of a macrolide, the aglycone 18 of methymycin.\textsuperscript{23,24} The aglycone is a 12-membered lactone containing six stereogenic centers. The stereochemistry around the ring was set up by construction of an acyclic fragment 17 prepared from two subunits having the correct stereochemistry. One unit 15 containing ring carbons 9, 10 and 11 was prepared via the resolution of (±)-\textit{erythro}-2,3-dihydroxy-2-methylvaleric acid. The other unit, Prelog-Djerassi lactonic acid 16, was prepared as a racemic mixture from bicyclo[4.2.1.0]nonane-3,7-diene. A mixture of two diastereomers was obtained from a series of steps in which the two subunits were linked. Compound 17 was isolated from this mixture.
Scheme 4. Synthetic approach to the aglycone 18 of methymycin (from ref. 23 and 24).

The key step in the synthesis of 18 was the cyclization to the 12-membered ring. Previous studies of unsubstituted acyclic hydroxy acids had shown that the cyclization of 8- to 13-membered lactones is disfavoured. Both a large activation energy and unfavourable entropy must be overcome for the cyclization to occur. Masamune et al. speculated that the substitution pattern of the seco acid 17 might impart some rigidity to the acyclic compound and tend to bring the two ends together, thus lowering both the activation energy and entropy for cyclization. In practice the treatment of the seco acid 17 with trifluoroacetic anhydride in benzene afforded a 25% yield of the
cyclized aglycone 18.\textsuperscript{24} This significant accomplishment stimulated a number of synthetic studies towards the synthesis of other macrolides.\textsuperscript{27-29}

Within five years of the synthesis of methymycin, the syntheses of a large number of synthetically challenging macrolides were completed. Most of the synthetic routes followed a similar plan to that of Masamune et al. via a stereoselective construction of the acyclic precursor prior to cyclization to control the stereochemistry on the ring. The use of sugars as chiral starting materials,\textsuperscript{30-33} the use of six membered thiane rings to effect stereoselective reactions,\textsuperscript{1} and the use of chiral boron reagents to effect enantioselective aldol reactions\textsuperscript{34-40} are just three examples which illustrate the variety of synthetic methods developed to stereoselectively prepare the acyclic precursors of the macrolide antibiotics. Many of these macrolide syntheses were hampered by the inefficiency of the cyclization step late in the syntheses. The yield in the cyclization of the seco acids generally ranged from 23 to 41\%.\textsuperscript{24,35,36,41}

Two recent syntheses of macrolide compounds have improved the yield of the cyclization step by using bulky alcohol protecting groups to impose greater preorganization of the acyclic seco acid chain. Paterson et al. used an ethylidene and an acetal protecting group to promote the cyclization of the seco acid 19 in the synthesis of oleandomycin (21). A 78\% yield of the cyclized product 20 was obtained.\textsuperscript{40} The success of the cyclization was also found to be greatly dependent on the specific type of protecting group used. For example, the seco acid would not cyclize when the ethylidene was replaced with an acetonide, or if the epimeric ethylidene was used.
Scheme 5. Cyclic acetal promoted macrocyclization of oleandomycin precursor 19 (from ref. 40).

In the second example, Woodward et al. used a cyclic acetal and a cyclic carbamate as shown in Equation 1 to impose conformational rigidity in the acyclic precursor 22 in order to effect the cyclization of the seco acid 22 to 23 in 70% yield in the synthesis of erythromycin (1).\(^2\) In these two examples, cyclization was promoted by utilizing protecting groups to preorganize the seco acid. However the cyclization step remains a key challenge in the synthetic sequence of macrolide synthesis.\(^29\)
1.4 Remote asymmetric induction in medium and large rings

An alternative to this acyclic approach to the stereoselective synthesis of macrolides involves formation of the ring early in the reaction sequence followed by the use of the conformational bias of the macrocyclic ring to control the stereochemistry and regiochemistry of reactions which incorporate additional substituents on the ring.\textsuperscript{4,5,42} Still and Galynker were the first to demonstrate such conformational control of the stereochemistry involving reactions on medium and large rings.\textsuperscript{42} They found high stereoselectivity in alkylations, dimethylcuprate additions and hydrogenations of monosubstituted 8- to 12-membered macrocyclic ketones and lactones. Examples of these reactions on 9-membered lactones are shown in Figure 1.

<table>
<thead>
<tr>
<th>CIS : TRANS RATIO</th>
<th>Exp (yield)</th>
<th>Calc</th>
</tr>
</thead>
<tbody>
<tr>
<td>98:2 (&gt; 95%)</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>99:1 (89%)</td>
<td>97:3</td>
<td></td>
</tr>
<tr>
<td>6:94 (100%)</td>
<td>10:9</td>
<td></td>
</tr>
</tbody>
</table>

\textbf{Figure 1.} Remote asymmetric induction in reaction of 9-membered lactones (from ref. 42).
Conformational analysis aided by molecular mechanics calculations was used to rationalize the observed stereoselectivity. The product ratios for these kinetically controlled reactions are dependent on the relative energies of the transition states for each reaction. Unfortunately, molecular mechanics calculations can not be used to accurately calculate these energies at this time. In order to use molecular mechanics for the calculation of the product ratios of such reactions, it was assumed that the reaction pathway proceeds from the lowest energy conformation of the starting material or intermediate. The product ratios for kinetically controlled reactions having an early transition state may be predicted from the relative energies of the conformations of the starting material or intermediates.\textsuperscript{42,43} Thus the product ratios for the reactions in Figure 1 were calculated from the relative energies of the intermediate enolate for the alkylation reaction, and of the conjugated lactones for the reduction and the cuprate addition reactions. The results from these calculations are also given in Figure 1. The high correlation between the calculated ratios and the experimental results for this range of reactions and compounds indicates the usefulness of molecular mechanics calculations as an aid in the rationalization of the observed stereoselectivity. This correlation also supports the feasibility of using molecular modelling as a predictive tool in the future. The power and potential of macrocyclic conformational control was clearly illustrated in this seminal paper by Still and Galynker.\textsuperscript{42}

1.5 Conformational analysis of macrocyclic alkanes

Still and Galynker demonstrated that conformational effects control the stereochemical outcome of various reactions in medium sized rings. Our laboratory has been interested in the extension of such a study of the conformational properties
and reactivities in larger 14-, and 16-membered rings. The aim of these studies is to develop a model to predict the stereochemical outcome of conformational controlled reactions in macrocyclic rings.

Dale pioneered the study of the conformational properties of macrocyclic rings. He developed a conformational model of macrocyclic alkanes to explain the alternating pattern in the melting points and solid phase transition points in even- and odd-ring size cycloalkanes.\textsuperscript{44,45} For the 10- to 13-membered cycloalkanes, the even-membered rings have higher melting points and the odd-membered rings have lower melting points. This even/odd oscillation is also observed in the solid phase transition points in the 14- to 18-membered cycloalkanes. Dale postulated that a smaller change in the conformational entropy during a phase transition of even-membered rings produces the higher melting or solid-solid phase transition temperatures in the even-membered rings in comparison to the odd-membered rings. Dale’s model suggested that even-membered cycloalkanes have a single low energy conformation while odd-membered rings have several low energy conformations. The smaller change in conformational entropy during a phase change of even-membered rings results from the low energy conformation remaining predominant in the higher temperature phases.\textsuperscript{44}

At equilibrium $\Delta G_{eq} = 0$ and Equation 2 follows.

$$T_{eq} = \frac{\Delta H_{eq}}{\Delta S_{eq}}$$ (2)

The $\Delta H_{eq}$ term is expected to slowly and steadily increase with ring size, and the other forms of entropy which contribute to the $\Delta S_{eq}$, such as translational entropy, are not expected to vary significantly in the cycloalkane series.\textsuperscript{46}
This conformational rationalization of the observed oscillation in the temperature of the phase transitions for the cycloalkane series was developed using space filling molecular models constructed to model the low energy conformations of the larger rings. Along with the construction of this physical model, Dale developed a potential energy function based on the complete potential curve for the rotation around the central bond in n-butane (Figure 2) which was used to calculate the relative energies of the low energy conformations in these medium and large cycloalkane rings. The identification of the low energy conformation was found by minimizing the number of gauche butane torsional interactions in the ring.

![Dihedral angle of n-butane](image)

**Figure 2.** Dale's potential energy curve for butane (from ref. 45).

Dale pointed out that the lowest energy conformation determined by his model for each of the even-membered rings could be represented by tracing the carbon skeleton onto a diamond lattice framework. The lowest energy conformations of the 10-, 14- and 16-membered rings 30-32 are illustrated in Figure 3 (a) superimposed on the diamond lattice structure and (b) using Dale's wedge representation.45
Figure 3. (a) Diamond lattice conformation and (b) Dale's wedge representation of the lowest energy conformation of 30-32.
In order to facilitate the description of these macrocyclic conformations, Dale proposed a nomenclature system to describe the shape of each conformer. Using Dale's system, the diamond lattice conformation of cyclodecane (30), cyclotetradecane (31) and cyclohexadecane (32) are designated as the [2323], the [3434], and the [4444] conformations, respectively. These designations are shown under each of the top-view representations of the structures in Figure 3. Each number in the brackets represents the number of bonds along a "side" of the conformation. A corner atom, separating two adjacent sides occurs when two continuous gauche dihedral angles of the same sign are flanked by an anti dihedral angle on each side. By convention, the first number in the bracketed sequence has been selected to be the smallest number representing the shortest side, followed by the next smallest number and continuing around the ring in the same direction.

Diamond lattice structures have been found in the solid state by X-ray crystallography for the 10-, 12- and 14-membered rings. The solid state conformation of cyclotetradecane (31) closely fits the diamond lattice structure predicted by Dale's model. The X-ray structure of cyclododecane (33), illustrated in Figure 4, shows distortions in the bond lengths, bond angles and torsional angles from the ideal diamond lattice structure. The distortion of this 12-membered ring from the ideal diamond lattice structure is due to transannular hydrogen-hydrogen interactions. These hydrogen interactions were predicted by Dale's model to affect the diamond lattice conformation of rings smaller than 14-membered.
Figure 4. A comparison of the X-ray (from ref. 48) and diamond lattice conformations of cyclododecane (33). Bond lengths are shown in Ångstroms and torsional angles are underlined to distinguish them from bond angles.

The diamond lattice conformations of cyclododecane, cyclotetradecane and cyclohexadecane found in the solid state have also been observed in solution at low temperature by dynamic NMR. In the [3333] conformation of cyclododecane, illustrated in Figure 4, there are two types of carbons, non-corner and corner, in a ratio of 2:1. At -131 °C, the $^{13}$C spectrum of cyclododecane consists of two signals with an intensity ratio of 2:1, consistent with the [3333] conformation. The $^{13}$C NMR spectrum of cyclotetradecane at -132 °C comprises three lines with intensity ratios of approximately 4:1:2. Although the diamond lattice structure of cyclotetradecane (31) contains four types of carbons in relative ratios 2:2:2:1, Anet et al. suggested that the $^{13}$C NMR which contains only three signals still arises from the [3434] conformation in which the signals of two different carbon overlap. The $^{13}$C NMR spectrum of cyclohexadecane-1-$^{13}$C at -152 °C consists of three signals with relative ratios of 1:2:1.
in agreement with the number of carbon types and ratios found in the [4444] diamond lattice structure of cyclohexadecane (32).  

Unlike even-membered rings, the carbon framework of odd-membered rings cannot be traced on a diamond lattice. Low temperature NMR of the 11-, 13- and 15-membered rings indicated that in solution these molecules remained conformationally mobile at temperatures down to -135 °C. These observations agree with the proposal by Dale to rationalize the observed oscillation of the melting points and phase transition temperatures. Dale suggested that even-membered rings have a single low energy conformation while odd-membered rings have several low energy conformations.

The interpretation of infrared data of cyclic alkanes provides additional experimental evidence to support Dale's conformational proposal. The infrared spectra of cyclotetradecane (31) and cyclohexadecane (32), previously found to have the diamond lattice conformations in the solid state by X-ray crystallography, were determined in the low temperature (Lt)-solid phase, in the high temperature (Ht)-solid phase, and in the liquid phase. The infrared data of cyclotetradecane (31) were interpreted by Borgen and Dale to indicate that the molecule remains conformationally homogeneous in all three phases. More recently, Shannon et al. estimated from infrared data that 70 ±10% of the cyclotetradecane conformers in the Ht-solid phase and 60 ±10% of the conformers in the liquid phase near the 329 K melting point, remain in the [3434] conformation. From an analysis of the infrared data from cyclohexadecane (32), Borgen and Dale as well as Shannon et al. both concluded that a mixture of conformations occurs in the Ht-solid state and in the melt. Shannon et al. estimated that only 15% of the [4444] conformation exists in the melt at 343 K.
The infrared data for cyclotetradecane (31) clearly indicates that the conformational entropy change during the solid-solid transition is small since the [3434] conformation of cyclotetradecane remains the major populated conformation after the transition. The infrared data for cyclohexadecane (32) indicate that a greater increase in the conformational entropy occurs during the solid-solid transition of cyclohexadecane relative to cyclotetradecane. This interpretation is in agreement with the observed lower transition temperature for cyclohexadecane, 273 K for 32 versus 322 K for 31. Although the infrared analysis indicates that cyclohexadecane does not remain conformationally homogeneous, the conformational entropy change during the solid-solid phase transition of cyclohexadecane is significantly less than that of odd-membered rings, because the transition temperatures for the odd 13-, 15- and 17-membered rings are still considerably lower.

1.6 Conformational analysis of simple 14- and 16-membered macrocycles

Dale further developed his conformational model of macrocycles to include simple substituted macrocyclic compounds. Since the diamond lattice represents the minimum potential energy of 14- and 16-membered rings, Dale postulated that the ring of simple substituted 14- and 16-cycloalkanes would also maintain the diamond lattice structure. Thus only conformations in which the substituent differs in position on the diamond lattice structure need to be considered. With the introduction of a methyl substituent onto cyclotetradecane for example, five possible [3434] diamond lattice conformations may be drawn. These are illustrated in Figure 5. In each conformation the methyl substituent is in an exo position in order to avoid large transannular hydrogen
interactions. Dale suggested that the introduction of a single methyl group on cyclotetradecane should result in a mixture of these conformation.$^{53,55}$

![Diagram of methylcyclotetradecane conformations](image)

(a) \( \text{CH}_3 \)

(b) \( \text{CH}_3 \)

(c) \( \text{CH}_3 \)

(d) \( \text{CH}_3 \)

(e) \( \text{CH}_3 \)

Figure 5. Proposed [3434] diamond lattice conformations of methylcyclotetradecane (34).

In contrast, Dale proposed that the introduction of a gem-dimethyl group onto cyclotetradecane or cyclohexadecane should limit the number of low energy conformations because the gem-dimethyl substituted carbon must reside at a corner position in order to avoid large transannular hydrogen interactions.$^{55}$ Experimental evidence that the gem-dimethyl groups exist at a corner positions on the diamond lattice
has been obtained from the infrared spectra of the octamethylcyclotetradecane 35 and the octamethycyclohexadecane 36. The infrared spectra also indicate that both these compounds are conformationally homogeneous in the solid state and in solution.

The incorporation of ether oxygens and carbonyl groups has also been shown to restrict the number of low energy conformations. The ether oxygens of 1,5,9,13-tetraoxacyclohexadecane (37) were determined to occupy the positions β to two corner positions in the solid state by X-ray crystallography. Infrared spectroscopic analysis also confirmed that this conformation exists in the solid state and that 37 remains homogeneous in solution. Evidence from infrared spectroscopy indicates that the carbonyl groups of cyclotetradecane-1,8-dione (38) also occupy the position β to the two corner positions. Dale explained this positional preference in 37 and 38 as a result of stabilization due to the reduction of transannular hydrogen-hydrogen interactions.
The relative magnitude of the hydrogen interactions in the [3434] conformation of cyclotetradecane is illustrated in Figure 6.\textsuperscript{56} Using this graphical model, the location of the two carbonyls as shown in 38 should eliminate four gauche butane interactions and a 1,8-transannular hydrogen interaction. The position of the carbonyls in this conformation represents the maximum reduction of transannular interactions in the [3434] conformation. The position of the ethers in the [4444] conformation of 38 also maximizes the reduction of hydrogen interactions, by eliminating two gauche butane interactions for each oxygen.

![Figure 6. Magnitude of hydrogen interactions in the diamond lattice conformation of cyclotetradecane.](image)

The introduction of a lactone functionality into the 14- and 16-membered ring has also been found to reduce the possible conformations of these macrocyclic rings.\textsuperscript{57-59} In addition to a decrease in the number of transannular hydrogen interactions in the ring, the lactone functionality prefers the s-trans (Z) to the s-cis (E) geometry shown in Figure 7. This conformational preference was first established in acyclic esters. The energy difference between the two conformations in methyl formate (Figure 7, R=H, R'=CH$_3$) is
difficult to measure since very little of the E-isomer exists at room temperature. An estimate using matrix-isolation IR spectroscopy found the Z conformation was favoured by $\Delta H^o = 4.75 \pm 0.19$ kcal/mol. The average difference in the relative energy between these two conformations for acyclic esters is 3.0 kcal/mol.

![Ester conformational equilibrium](image)

**Figure 7.** Ester conformational equilibrium

The s-trans conformational preference of esters has also been observed in the X-ray crystal structure of tridecalactone (39). The X-ray crystal structure was found to closely resemble the diamond lattice conformation shown in structure 39.

![X-ray crystal structure of tridecalactone](image)

An acyclic conformational preference of esters of secondary alcohols has also been shown to influence the conformation of macrocyclic lactones. This effect is important in the conformational analysis of the macrolide antibiotics since many of the macrolides are lactones of secondary alcohols. In an empirical study of 1750 crystal structures of acyclic esters of secondary alcohols, Schweizer and Dunitz found that the
C(O)-O-C-H dihedral angles of many of these esters are close to planar as illustrated in Figure 8.62

![Figure 8](image)

**Figure 8.** Syn-periplanar arrangement of C(O)-O-C-H group of esters of secondary alcohols.

The C(O)-O-C-H angles of over 85% of the cases studied were observed to lie between 0° and 40°. Most of the remaining cases were found to have dihedral angles between 40° and 60° degrees.62 In a series of nine X-ray crystal structures of macrocyclic lactones of secondary alcohols both the preferred s-trans geometry of esters and the syn periplanar arrangement of esters of secondary alcohols were observed in every structure.56 Though these acyclic and macrocyclic studies are based on the conformations of the molecules in their crystal structures, Dunitz has stated that the preferred conformation of an isolated molecule closely resembles that of the crystal structure.63

The conformational analysis of secondary lactones may be significantly simplified by applying these acyclic preferences to macrocyclic systems. For example, the initial conformational analysis of 13-tetradecanolide (40) was limited to the consideration of the three conformations shown in Figure 9 (a).57,58 These three conformers represented the only possible [3434] conformations of the molecule having both the s-trans geometry and the syn-periplanar C(O)-O-C-H arrangement of the lactone on the [3434]
frame. Applying these same principles to 15-hexadecanolide (41), the conformational analysis of this molecule may be limited to two conformers shown in Figure 9 (b).

![Figure 9](image)

**Figure 9.** Possible diamond lattice conformations for (a) 13-tetradecanolide (40), and (b) 15-hexadecanolide (41) with an s-trans lactone geometry and a syn-periplanar C(O)-O-C-H orientation.

1.7 Syntheses of macrolides using macrocyclic conformational control

The conformational analysis and the study of stereoselectivity of reactions of lactones of secondary alcohols have been extended by our research group to lactones containing additional functionality. These efforts have concentrated on the study of the 3-, 5-, 7-, 9-, and 11-oxo-13-tetradecanolides. These locations of the ketone in each of these lactones were selected because they represent oxygenated positions in the polyoxy macrolides. Our interest is in a systematic development of a conformational model based on these more manageable compounds as a prelude to the study of more complex macrocyclic molecules.
Even without a well developed model to predict the stereochemical outcome of reactions on macrocyclic rings, the potential of such transformations has attracted a number of groups to explore the use of conformational bias in large rings to control the stereochemical and regiochemical outcomes of key reactions in the synthesis of naturally occurring macrolides. In a seminal paper by Still and Novack, six new chiral centers in (±)-3-deoxyrosaranolide (43) were stereoselectively created under conformational control from the cyclic precursor 42 containing just two chiral centers.\textsuperscript{64}

The methylation of 42 at C8 to provide 44, shown in Scheme 6, was obtained with greater than 20:1 stereoselectivity. After hydrolysis of the thioketal, kinetic deprotonation of 45 at C6 followed by alkylation gave 46 with greater than 20:1 selectivity over alkylation at C4. This alkylation also occurred with a 10:1 stereoselectivity, with the major isomer having the correct R stereochemistry at C6.
Scheme 6. The synthesis of (±)-3-deoxyrosaranolide (43) (from ref. 64)

Methylation of 46 at C4 occurred with high stereoselectivity (>40:1), however this produced the incorrect 4R diastereomer. An alternative multistep procedure was required to obtain the product with the correct stereochemistry. Quenching of the enolate of 46 with formaldehyde and subsequent dehydration via the mesylate afforded
the exocyclic methylene ketone 47. Michael addition of thiophenolate to 47 followed by
desulphurization afforded compound 48 with a greater than 25:1 stereoselectivity with
the correct 4S stereochemistry.

Reduction of 48 with NaBH₄-CeCl₃ lead to the unnatural 5S alcohol with a >20:1
stereoselectivity. The 5R alcohol was obtained with 5:1 stereoselectivity by converting
48 to a mixed anhydride followed by NaBH₄ reduction. Allylic oxidation of 49, followed
by an epoxidation provided 50 with 15:1 stereoselectivity. This was the final
conformationally controlled reaction. Oxidation of the primary alcohol with
(Ph₃P)₃RuCl₂ completed the synthesis of (±)-3-deoxyrosaranolide (43). This paper by
Still and Novack was the first to demonstrate the power of macrocyclic stereocontrol in
the synthesis of macrolides.⁶⁴

In a second example of a synthesis using a combination of acyclic and macrocyclic
stereocontrol, Paterson and Rawson successfully prepared (+)-(9S)-dihydro-
erythronolide (56) shown in Scheme 7.⁶⁵ Two subunits, 51 and 52, containing seven
stereocenters were used to synthesize the macrocyclic lactone 53. Macro cyclic
conformational control was responsible for the essentially 100% stereoselectivity
obtained in the osmylation of the silyl enol ether in 53, the reduction of the C5 ketone in
54, and the osmylation of the alkene in 55 to complete the synthesis of
(+)-(9S)-dihydroerythronolide (56).
Scheme 7. Conformational controlled synthesis of (+)-(9S)-dihydroerythronolide (56) (from ref. 65).
Paterson and Rawson were able to tentatively predict the stereoselective outcomes of the osmylations, based on the experimental precedence from the previous work on (±)-3-deoxyrosaranolide (43) by Still and Novack\textsuperscript{64} and molecular mechanics computer modelling. The molecular mechanics model of the ground state conformation of 53 clearly predicted the stereochemical outcome of the osmylation reaction at the C11-C12 alkene. This same model indicated that a greater conformational flexibility exists around the C5-C6 alkene region, providing less confidence in the prediction of the selectivity for the osmylation of the C5-C6 double bond in 53.\textsuperscript{65}

The conformational bias of macrocyclic rings has also been used to carry out stereoselective synthesis of non-macrocyclic compounds. For example, Still and Romero used a conformational controlled epoxidation in an attempt to prepare six new stereocenters of an 18-carbon subunit of monensin B (57) in a single step.\textsuperscript{66}

The triepoxide 59 with six new stereocenters, shown in Scheme 8, was isolated from the stereoselective epoxidation of the cyclic triene 58. After saponification of 59, spontaneous cyclization of the seco acid occurred to yield the 18-carbon unit 60 resembling that of the C9 to C23 segment of monensin B (57). Unfortunately, the
stereocenters at C20 and C21 of the polyether 60 are epimeric with the natural product. Still and Romero commented that the computer power in 1986 made the conformational analysis of 58 impractical to confidently predict the outcome of the epoxidation of this relatively simple compound.66 Although the wrong diastereomer was obtained to use 60 as a precursor in the synthesis of monensin B (57), the epoxidation of 58 still demonstrated the effectiveness of conformational control in producing high stereoselectivity in the reactions of macrocyclic rings.

![Scheme 8. Conformational controlled epoxidation of macrolide 58 (from ref. 66).](image)

These three examples of the use of macrocyclic conformational control all involved macrocyclic lactones. More recently, the conformational bias of a macrocyclic lactam was used to prepare the aglycon 62 of the macrocyclic lactam fluvirucin B1 (13).20,67 The 14-membered lactam 61 was prepared from an acyclic diene via a metathesis
reaction. Greater than 95% diastereoselectivity was obtained in the hydrogenation of 60 due to the conformation of the macrocyclic lactam.

All four of these syntheses illustrate the high stereoselectivity that the conformational bias of macrocycles can impose on reactions of large rings. Although these examples demonstrated the use of macrocyclic stereocontrol to provide a high degree of stereoefficiency in synthesis, this methodology has seen only limited use. The incorrect diastereomer from the methylation of 46 obtained during the synthesis of (±)-3-deoxyrosaranolide (43) demonstrates the inability to confidently predict the stereochemical outcome of these reactions. Still and Novak stated that, “Our next goal is to find a reliable way to predict macrocyclic diastereoselection so that macrocyclic stereocontrol strategies may be used rationally in complex synthesis and so that the mechanism of the stereoselection may be elucidated.” Due to the complexity of the conformational behaviour of macrocyclic compounds this goal still remains elusive today.

1.8 Development of a “reliable” model

Much of the work done in our laboratory to develop a “reliable” model to predict macrocyclic stereoselection has involved the study of reactions of simple substituted
lactones. Conformational analysis aided by molecular mechanics calculations were used to rationalize the observed stereoselectivity. These results have provided valuable information. To expand our understanding of the conformations and chemistry of macrocycles, we have begun to study reactions of simple substituted 13-, 14- and 16-membered lactams. The aim of this study is to investigate the effect of the amide bond on the conformation of the rings and on the stereoselectivity of reactions of these macrocyclic lactams.

1.9 Introduction to the study of dynamic processes by NMR spectroscopy

Recently we have begun to utilize dynamic NMR to probe the conformational energy barriers in macrocyclic ethers and amines. Dynamic NMR provides an opportunity to determine the energy barriers between conformations, the relative energies of these conformations and information about the structures of the conformations in solution.

Dynamic conformational processes occurring in ring systems have interested chemists ever since Hassel first demonstrated the existence of the two chair conformations for chlorocyclohexane (63) by electron diffraction.\textsuperscript{68}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure10}
\caption{Conformational equilibrium of chlorocyclohexane (63).}
\end{figure}
Though the two conformations of 63 shown in Figure 10 were observed by electron diffraction, the rate of the ring inversion process which interconverts these two conformations proved to be too slow for detection by electron diffraction or other spectroscopic techniques that existed at that time.

The development of NMR spectroscopy furnished a technique to experimentally probe conformational processes which have energy barriers between 5 and 25 kcal/mol.\textsuperscript{69} Within the operating temperature of an NMR spectrometer, the rates of isomerization for processes having such energy barriers can be slowed to the same magnitude as the rate of relaxation of NMR signals. For example, the interconversion of the chair conformations of cyclohexane has an energy barrier of 10.3 kcal/mol. As a result these conformers undergo rapid exchange at room temperature on the NMR time scale. During the slow nuclear spin relaxation, the protons in cyclohexane are rapidly interconverting between the axial and equatorial positions. This results in a single NMR signal for the two geminal protons due to the averaging of these two different magnetic environments. On cooling the sample, the rate of ring inversion can be slowed to the point where the probability of an inversion occurring during the transition time of a nuclear spin is small. At this temperature the two signals due to the axial and equatorial protons begin to separate.\textsuperscript{70} This process is illustrated in Figure 11 for a theoretical noncoupled system.
The rate constant at the coalescence temperature ($K_c$) for the chemical exchange, shown in Figure 11, can be approximated from the difference in frequency ($\Delta \nu$) using the equation:

$$K_c = \pi \cdot \Delta \nu \div \sqrt{2}$$  \hspace{1cm} (3)

The free energy of activation ($\Delta G^\ddagger$) for the process can then be calculated using this rate constant $K_c$, in the Eyring Equation:

$$K_c = (k_B T_c / h) \exp(-\Delta G^\ddagger / RT_c)$$  \hspace{1cm} (4)

where $k_B$ = Boltzmann's constant, $h$ = Planck's constant, $R$ = gas constant and $T_c$ = coalescence temperature.
1.10 Conformational processes in cyclic molecules

There are three distinct conformational processes in cyclic molecules that may be studied by NMR. These processes are ring inversion, pseudorotation and local inversion. The distinction between these three processes, is illustrated in Figure 12 for azacyclooctane (64). Ring inversion, represented by the exchange between the boat-chair conformations A and A', is analogous to the chair-chair inversion in cyclohexane. This process averages the geminal protons on each carbon without changing the positional sites of the nitrogen and carbon atoms.

The process of pseudorotation was initially defined as the rapid rotation of the "envelope flap" around the cyclopentane ring due to the low energy barrier for this process. This definition has been expanded to describe the positional exchange of atoms around any ring conformation, irrespective of the height of the energy barrier for the process. For azacyclooctane, pseudorotation exchanges the positional sites of the nitrogen and carbon atoms around the boat-chair conformation (ring skeleton) of the 8-membered ring. In conformation A (Figure 12) a plane of symmetry exists which makes the protons on opposite sides of the plane such as H1 and H1' equivalent. Conformation B is unsymmetrical. At room temperature, rapid pseudorotation between conformations B and B' maintains a time averaged plane of symmetry between H1 and H1'.

The third process, local inversion is illustrated in Figure 12 by the conversion of azacyclooctane from the boat-chair conformation A to the crown conformation C. This involves the change of sign of two dihedral angles, while the other angles remain unchanged. Both ring inversion and pseudorotational process can occur among the
crown conformations of azacyclooctane as previously described for the boat-chair conformations.

Figure 12. Conformational process in azacyclooctane (64).

These three processes may be distinguished by dynamic NMR due to their different effects on the $^1$H and $^{13}$C spectra, as the temperature is lowered.$^{72}$ At room temperature a single signal is observed for the alpha protons of azacyclooctane. All three conformations A, B and C, shown in Figure 12, as well as other higher energy conformations are significantly populated and contribute to the NMR signals at this temperature. Ring inversion, pseudorotation and local inversion all occur rapidly,
averaging the magnetic environments of the four alpha protons from all of the populated conformations.

Below -118 °C, the α-proton signal separates into two equally intense and symmetrically shifted signals, without any affect on the $^{13}$C spectrum. This observation is characteristic of the slowing of ring inversion. The proton signal separates as the interconversion of the geminal protons is slowed. The $^{13}$C spectrum is not affected when ring inversion is slowed because no change in the positional sites of the carbon atoms occurs during a ring inversion process. The free energy of activation $\Delta G^\ddagger = 7.3 \pm 0.2$ kcal/mol was calculated for this ring inversion from the observed coalescence of these two alpha proton signals at -118 °C.\textsuperscript{72}

No evidence for the slowing of a pseudorotational process in azacyclooctane was observed. Effects on in both the $^1$H and $^{13}$C spectra would be expected to occur upon slowing pseudorotation. The two signals for the alpha protons did not change on cooling to -180 °C. There are two possible explanations for this observation. The first possibility is that pseudorotation has stopped completely and the molecules are frozen exclusively in the symmetric boat-chair conformation A (Figure 12). The second possibility is that pseudorotation between the low energy boat-chair conformations A and B remains rapid. This rapid pseudorotation between conformation A and B provides a pathway for the rapid pseudorotation between conformations B and B'' to continue thus maintaining the time averaged plane of symmetry between the H1 and H1' alpha protons.

Molecular mechanics calculations support this second possibility. These calculations indicate that conformation B, having the nitrogen atom at position 3 on the boat-chair cyclooctane skeleton, is close in energy to that of the lowest energy
conformation A due to relief of the large non-bonded transannular repulsions. Thus, at low temperature, conformations A and B are expected to be significantly populated and to contribute to the NMR signals. In this case rapid pseudorotation between conformations A and B as well as pseudorotation between B and its mirror image B” must continue to maintain the signal averaging observed in the $^1$H NMR spectra.$^{72}$

The freezing out of a local inversion process in azacyclooctane was indicated by the observation of a second set of minor signals just above the baseline in the $^{13}$C spectrum at -130 °C. The minor conformation producing these small signals was suggested to be the crown conformation C based on previous studies of cyclooctane. The barrier for the interconversion between the boat-chair and the crown conformation of azacyclooctane was determined to be $\Delta G^\ddagger = 10.5 \pm 0.2$ kcal/mol with a free energy difference between the two conformations of $\Delta G^0 = 1.2 \pm 0.1$ kcal/mol.$^{72}$

1.11 Dynamic processes in macrocyclic alkanes

In 1972, Anet et al. demonstrated that large ring cycloalkanes had conformational energy barriers high enough for a similar NMR study.$^{51}$ The $^1$H and $^{13}$C NMR study of cyclononane and subsequent studies on the 10-, 12-, 14- and 16-membered cyclic alkanes showed that these rings exhibited conformational barriers between 5 and 8 kcal/mol. Only estimates for the rate constants could be obtained from the $^1$H NMR spectra. Changes in the spectra, at lower temperatures, indicated that some conformational processes had slowed, however the lack of separation between the signals prevented the determination of the chemical shift differences and coupling constants.$^{51}$
Two isotopomers of cyclododecane with different deuterium substitution patterns, cyclododecane-d_{18}-trans-1,2-trans-5,6-trans-9,10-h\textsubscript{6} and cyclododecane-d_{20}-1,1,3,3-h\textsubscript{4}, were prepared to simplify the low temperature spectra of cyclododecane.\textsuperscript{73} Overlapping signals remained a problem even with these isotopically labeled compounds, however coupling constants and chemical shifts could be determined from line shape analysis aided by computer simulations. The energy barriers were then calculated from the $^1$H spectra using these values.\textsuperscript{73}

In comparison to the $^1$H spectra, the changes in the $^{13}$C spectra of these rings were less complex. The $^{13}$C spectrum of cyclotetradecane separated from a single signal at room temperature into three peaks at -132 °C with intensity ratios of approximately 4:1:2. This corresponds to the slowing of the pseudorotational process in the calculated lowest energy \([3434]\) conformation of cyclotetradecane in which two of the four types of carbons are overlapping. The spectrum of the $^{13}$C enriched cyclohexadecane separated into three peaks with ratios of 1:2:1 consistent with the calculated global minimum \([4444]\) conformation. Free energy barriers for the conformational changes obtained from the $^{13}$C NMR spectra for these and other ring sizes were found to correspond with those estimated from the $^1$H spectra. The values for the conformational barriers determined by $^{13}$C NMR are listed in Table 1.
Table 1. Energy barriers to pseudorotation in cycloalkanes as determined by \(^{13}\text{C}\) NMR.

<table>
<thead>
<tr>
<th>Cycloalkane</th>
<th>(\Delta G^\ddagger) (kcal/mol)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclononane</td>
<td>6.0</td>
<td>74</td>
</tr>
<tr>
<td>cyclodecane</td>
<td>6.0</td>
<td>74</td>
</tr>
<tr>
<td>cyclododecane</td>
<td>7.3</td>
<td>51</td>
</tr>
<tr>
<td>cyclotetradecane</td>
<td>7.0</td>
<td>51</td>
</tr>
<tr>
<td>cyclohexadecane</td>
<td>6.7</td>
<td>52</td>
</tr>
</tbody>
</table>

1.12 Dynamic NMR studies of macrocyclic ethers and amines

We have begun a series of dynamic NMR studies to examine the conformational properties in solution of macrocyclic ethers and amines. The incorporation of a heteroatom into the macrocyclic rings was expected to increase the chemical shift separation for the proton signals, and hence to simplify the analysis of the low temperature proton spectra. The aim of this project is to investigate the structure, the relative thermodynamic populations, and the dynamic processes that occur in macrocyclic ethers and amines.
Chapter II

Stereoselective Alkylations in Macrocyclic Lactams

As discussed earlier, our laboratory has been interested in the study of the conformational properties and reactivity in 14- and 16-membered rings. The aim of these studies is to develop a model to predict the stereochemical outcomes of conformationally-controlled reactions in macrocyclic rings. The present study of the conformational properties and alkylations to 13-, 14- and 16-membered lactams, compounds 65, 66, 67 and 68, was undertaken to evaluate how the amide bond might affect the conformation of the ring and the selectivity of simple alkylations. The relative stereochemistry of the products from the alkylation of 67 were determined by X-ray crystallography, and by chemical correlation for the alkylation products from 65, 66 and 68. Conformational analysis aided by molecular mechanics calculations of the starting lactams, enolate intermediates and the corresponding cyclic hydrocarbons were used to evaluate how the amide bond affects the conformation of the ring and contributes to the observed stereoselectivity.
2.1 Preparation of macrocyclic methyl lactams 65-67

The syntheses of the 13-, 14- and 16-membered lactams 65, 66 and 67 is outlined in Scheme 9. The key step in this synthetic sequence was the use of a Beckmann reaction (step vii) to prepare the macrocyclic lactams from the 2-methyl oximes 81-83. This rearrangement avoids a macrocyclization step, which often proceeds in low yield due to the inherent competition between the intermolecular and intramolecular reactions.

2.1.1 Preparation of 2-methyl 12-, 13- and 15-membered cyclic ketones 78-80

A one-pot multi-step sequence was used to prepare the 2-methyl macrocyclic ketones 78-80 from the commercially available unsubstituted macrocyclic ketones 69-71. Previous work in our laboratory found that the deprotonation of cyclopentadecanone using LDA in THF and alkylation with Mel produced a significant amount of dimethylated products. The separation of the dimethyl ketones from the desired monomethyl ketone proved to be difficult. The clean monoalkylated ketones were obtained via the alkylation of the corresponding dimethylhydrazone followed by acid hydrolysis. Deprotonation of the hydrazone with n-BuLi and acid hydrolysis workup rather than the previously reported use of LDA and oxidative cleavage using NaIO₄ provided a significant increase in the overall yield and a simplification of the procedure for the preparation of the 2-methyl ketones 78-80.
Scheme 9. Syntheses of 13-, 14- and 16-membered lactams: (i) H$_2$NNMe$_2$; (ii) n-BuLi, THF, 0 °C; then Mel, 0 °C; (iv) 20% H$_2$SO$_4$ (aq); (v) NH$_2$OH · HCl, NaOAc, MeOH; (vi) TsCl, Pyr, CH$_2$Cl$_2$; (vii) SiO$_2$, Et$_2$O.

2.1.2 Preparation of 2-methylcyclotridecanone (79) via a ring expansion

An alternative single carbon ring expansion developed by Taguchi et al. was also investigated to prepare the monoalkylated 13-membered ring ketone 79 from the inexpensive 12-membered ring ketone 69. The two-step ring expansion followed by
alkylation was simplified to a one-pot procedure in which the intermediate enolate from the ring expansion was directly alkylated by the addition of methyl iodide and HMPA. The monoalkylated ketone 79 was isolated in 50% yield via this route.

Scheme 10. Preparation of 2-methylcyclotridecanone (79) via a ring expansion: (i) Et$_2$O, CH$_2$Br$_2$; then LiTMP, THF; (ii) 2-eq n-BuLi, THF; then CH$_3$I, HMPA.

2.1.3 Preparation of lactams 65-67 and 84-86 via Beckmann rearrangement

The preparation of the macrocyclic oximes 81-83 from the corresponding ketones 78-80 (step iv, Scheme 9) afforded both the syn and anti isomers. The major product of each reaction was assigned as the anti isomer based on $^{13}$C chemical shift data. The $^{13}$C chemical shifts of the C=N and $\alpha$-methyl substituent of more hindered syn oximes are found upfield relative to the corresponding signals of the anti isomer. In the NMR spectrum of 81 (Figure 13) the smaller upfield C=N and methyl $^{13}$C signals (162.4 and 17.8 ppm) were assigned to the minor syn isomer and the larger downfield signals (163.7 and 20.7 ppm) were assigned to the major anti isomer.
Figure 13. 50 MHz $^{13}$C spectrum of the mixture of anti (major) and syn (minor) isomers of oxime 81.

Similar chemical shift correlations were also observed in the $^1$H NMR of 81-83. As shown in Scheme 11, the methyl signal of the minor syn isomer for oxime 81 was found 0.06 ppm upfield of the methyl signal for the anti isomer and the methine signal was found 0.94 ppm downfield of the methine signal in the anti isomer. These chemical shift correlations were also observed in the $^1$H spectra of 82 and 83. The syn:anti isomeric ratios of oximes 81-83 were measured from the $^1$H NMR spectra and found to be 1:3 for
the 12-membered ring oxime 81, 1:7 for the 13-membered ring 82 and 1:3.5 for the 15-membered ring 83.

Scheme 11. $^1$H and $^{13}$C (in parenthesis) chemical shift assignments of the syn and anti isomers of 2-methylcyclooctadecane oxime (81).

Because we were unable to separate these isomers by normal or reverse phase chromatography the mixture of syn and anti oximes was used in the syntheses of the lactams. The Beckmann rearrangement (steps vi and vii, Scheme 9) was carried out using a procedure developed by Olson et al. $^{82}$ This procedure involves the formation of the oxime tosylate followed by loading the tosylate onto a silica gel column that catalyzes the Beckmann rearrangement. The two isomeric lactams obtained from this reaction were easily separated by flash chromatography on the same silica gel column. The regioisomers were identified from their NMR spectra. The NMR spectrum of 84 contains one signal at 2.20 ppm assigned to the methine $\alpha$-proton and two signals at 2.94 and 3.60 ppm assigned to the two protons $\alpha$ to the nitrogen whereas the NMR spectrum of 85 contains two signals at 2.08 and 2.25 ppm for the $\alpha$-protons and one signal at 4.08 ppm for the proton $\alpha$ to the nitrogen.
The relative product ratio of the lactam regioisomers was found to be equal to the ratio of the two oximes in the starting material. This indicates that no equilibration of the syn and anti oximes occurs under these reaction conditions and that the major product of the oxime formation was the anti diastereomer, as suggested above.

2.1.4 Preparation of N-benzyl 16-membered macrocyclic lactam 68

The 16-membered lactam 67 was protected with a benzyl group in order to investigate the effect of this protecting group on the conformation of the 16-membered lactam, and on the stereoselectivity of ring alkylation. Deprotonation of lactam 67 with 2 eq of n-BuLi and addition of 3 eq of benzyl bromide afforded the N-benzyl lactam 68 in 53% yield.

The \textsuperscript{1}H NMR indicated that 68 exists as a 1.2:1 mixture of the two amide conformers. The Z-amide was assigned as the major isomer based on the \textsuperscript{13}C chemical shift of the benzylic carbon and the carbon \( \alpha \) to the nitrogen. The \textsuperscript{13}C chemical shift of the carbon anti to the carbonyl in a series of N,N-dialkylamides was observed downfield of the syn carbon.\textsuperscript{83} This trend was followed by the signals for the benzylic carbons in
E- and Z-isomers of N-benzyl macrocyclic polylactams and of acyclic N-benzylamide compounds.\(^4\) The \(^1\)H and \(^{13}\)C chemical shifts for the major and minor isomers of lactam 68, listed in Table 2, were assigned with the aid of COSY and HMQC experiments.

<table>
<thead>
<tr>
<th>Position</th>
<th>Major Z-Isomer</th>
<th>Minor E-Isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(^1)H (ppm)(^a)</td>
<td>(^{13})C (ppm)(^b)</td>
</tr>
<tr>
<td>Me</td>
<td>1.01</td>
<td>19.40</td>
</tr>
<tr>
<td>(\alpha) to C=O</td>
<td>2.07, 2.30</td>
<td>33.89</td>
</tr>
<tr>
<td>(\alpha) to N</td>
<td>4.97</td>
<td>48.96</td>
</tr>
<tr>
<td>Ph-CH(_2)</td>
<td>4.35, 4.56</td>
<td>46.11</td>
</tr>
<tr>
<td>C=O</td>
<td>174.79</td>
<td>173.79</td>
</tr>
</tbody>
</table>

\(^{a}\) 400 MHz NMR in CDCl\(_3\)
\(^{b}\) 125 MHz NMR in CDCl\(_3\)

2.2 Study of dianion generation in macrocyclic lactams

Alkylation of lactams 65, 66 and 67 was carried out via the dianion. Generation of the dianion of macrocyclic lactams was first investigated using the commercially available azacyclotridecan-2-one (88). Takahata et al. have shown that the formation of the dianion of valerolactam can be achieved using n-BuLi/HMPA in THF.\(^5\) Under the same conditions dianion formation from 88 was not obtained, as shown in Table 3. None of the C-methylated product 84 was produced and only a small amount of the N-methylated product 89 was detected.
Table 3. Summary of the reaction conditions tested to generate the dianion of 88.

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Electrophile</th>
<th>% C-alkylation</th>
<th>% N-alkylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 eq n-BuLi/HMPA</td>
<td>THF</td>
<td>1 eq CH₃I</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>2.2 eq n-BuLi</td>
<td>THF</td>
<td>1 eq CH₃I</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3 eq n-BuLi/LiCl</td>
<td>THF</td>
<td>3 eq CH₃I</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>2.6 eq n-BuLi/t-BuOK</td>
<td>THF</td>
<td>1.2 eq CH₃I</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>2.2 eq t-BuLi</td>
<td>THF</td>
<td>1 eq CH₃I</td>
<td>9ᵃ</td>
<td>21</td>
</tr>
</tbody>
</table>

ᵃ 1,3-Dimethyl-1-azacyclotridecan-2-one (90)

Dianion formation was unable to be obtained under all the conditions shown in Table 3. It was thought that the incomplete dianion formation in THF might be due to reaction of the alkyl lithium with the solvent. The enolate 91 has been shown to form quantitatively in THF upon the addition of n-BuLi at 25 °C, and upon the addition of t-BuLi at -78 °C.⁸⁶

![Diagram](image)

To investigate this proposal, dianion formation of 88 was investigated in THF, Et₂O and hexane using D₂O as the electrophile. The significant increase in deuterium substitution of the α-protons in Et₂O and hexane suggests that the generation of the dianion is solvent dependent.
Table 4. Solvent dependence of the dianion generation of 88.

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Electrophile</th>
<th>% C-deuterated</th>
<th>% N-deuterated</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 eq t-BuLi</td>
<td>THF</td>
<td>D$_2$O</td>
<td>13</td>
<td>64</td>
</tr>
<tr>
<td>4.0 eq t-BuLi</td>
<td>Et$_2$O</td>
<td>D$_2$O</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>2.2 eq t-BuLi</td>
<td>hexane</td>
<td>D$_2$O</td>
<td>54</td>
<td>67</td>
</tr>
</tbody>
</table>

Once generation of the dianion of 88 in Et$_2$O and hexane was proven, alkylation of the dianion in these solvents was investigated. Table 5 contains a summary of the reaction conditions to test alkylation with Mel. A greater yield of C-alkylated product was obtained in hexane. 1-Azacyclotridecan-2-one (88) is insoluble in hexane at room temperature, however upon addition of the 2.2 eq t-BuLi, the lactam slowly dissolved. After addition of 1 eq of methyl iodide the solution remained homogeneous. Upon quenching of the reaction with water a white precipitate was obtained which was found to be the desired C-alkylated lactam 84.

\[
\begin{align*}
&\text{88} &\rightarrow &\text{84} + \text{89} + \text{90} \\
&1. \text{see Table 5} \\
\end{align*}
\]

Even with the addition of a large excess of methyl iodide to the dianion of 88 no precipitate was observed prior to quenching the reaction with water and only the C-methyl product 84 was obtained. None of the N-methyl or dimethylated products 89
and 90 were detected. This suggests that the monoanion of lactam 84 was unreactive toward excess methyl iodide.

Table 5. Alkylation of the dianion of 88.

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Electrophile</th>
<th>% C-alkylation 84</th>
<th>% N-alkylation 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7 eq t-BuLi</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>1.2 eq CH&lt;sub&gt;3&lt;/sub&gt;I</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>2.2 eq t-BuLi</td>
<td>hexane</td>
<td>1 eq CH&lt;sub&gt;3&lt;/sub&gt;I</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>5 eq t-BuLi</td>
<td>hexane</td>
<td>4 eq CH&lt;sub&gt;3&lt;/sub&gt;I</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>3 eq t-BuLi</td>
<td>hexane</td>
<td>4 eq CH&lt;sub&gt;3&lt;/sub&gt;I</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>4 eq t-BuLi</td>
<td>hexane/HMPA</td>
<td>6 eq CH&lt;sub&gt;3&lt;/sub&gt;I</td>
<td>69</td>
<td>27&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1,3-Dimethyl-1-azacyclotridecan-2-one (90)

This apparent lack of reactivity of the monoanion was further investigated. The dianion of 88 was first generated with 4 eq of t-BuLi in hexane. After the addition of a large excess of Mel (6 equivalents), a small portion of the reaction was worked up. C-alkylation was shown to have occurred exclusively. HMPA was then added to the remaining alkylation reaction. After workup a 27% yield of dimethyl product 90 was obtained. These observations demonstrate that the dianion of 88 was generated in hexane and that the monoanion of 3-methyl-1-azacyclotridecan-2-one (84) was unreactive towards methyl iodide in hexane under these conditions.

2.3 Alkylation of the dianion of macrocyclic lactams 65, 66 and 67

Alkylation of lactams 65, 66 and 67 was carried out using an excess of t-BuLi to generate the dianion, followed by the addition of a larger excess of methyl iodide, taking advantage of the previous observed lack of reactivity of the lactam monoanion with
methyl iodide. In all three cases no dimethyl or N-methyl products were detected. High stereoselectivity and high chemical yields were obtained for the alkylation of the lactams (Table 6).

![Reaction Scheme]

**Table 6.** Stereoselective alkylation of lactams 65, 66, 67.

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Starting Material</th>
<th>Products (R,S)* : (S,S)*</th>
<th>Yield</th>
<th>Ratiosa,b (R,S)* : (S,S)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>65</td>
<td>92 : 93</td>
<td>98%</td>
<td>&gt; 99:1</td>
</tr>
<tr>
<td>14</td>
<td>66</td>
<td>94 : 95</td>
<td>89%</td>
<td>62:1</td>
</tr>
<tr>
<td>16</td>
<td>67</td>
<td>96 : 97</td>
<td>94%</td>
<td>10:1</td>
</tr>
</tbody>
</table>

a Determined by GC
b See section 2.3 for determination of product stereochemistry

### 2.3.1 Determination of the relative stereochemistry of 96

The relative stereochemistry of the major product obtained from the alkylation of the 16-membered lactam 67 was determined to have the (3S*,16R*) configuration by X-ray crystallography. The disordered crystal structure of 96 shown in Figure 14 was determined to be composed of two conformations in a 2:1 ratio in which the bonds in the major conformer are represented by solid lines and the minor conformer distorted from
C16 to C11 by unfilled double lines. Thus the minor isomer 97 in the alkylation of 67 must have the (3S*,16S*) stereochemistry.

Figure 14. X-ray crystal structure of (3S*,16R*)-3,16-dimethyl-1-azacyclohexadecan-2-one (96).

2.3.2 Determination of the relative stereochemistry of the products from the alkylation of lactams 65 and 66

We were unable to obtain suitable crystals of the 13- and 14-membered lactams 92, 94 and 95 for an X-ray crystallographic study. Thus chemical correlations were used to determine the relative stereochemistry in these lactams.
Alkylation of the 2-methyl ketone 78 afforded the 2,2'-dimethyl ketones 98 and 99 in a 5.8:1 ratio and alkylation of 2-methyl ketone 79 afforded 100 and 101 in a 2.4:1 ratio.

![Chemical structures](image)

1. LDA, THF
2. Mel, DMPU

After chromatographic separation, the configuration of the ketones 98-101 was determined as follows. LiAlH₄ reduction of the major ketone 98 yielded two alcohols 102 and 103 in a 6:1 ratio, whereas the minor ketone 99 gave a single alcohol 104. Thus the major ketone 98 must have the (R*,S*) stereochemistry and the minor ketone 99 must have the (R*,R*) stereochemistry. Reduction of the minor 13-membered ketone 101 also yielded a single product 105, proving that 101 is the (R*,R*) isomer.
The X-ray crystal structure of dimethyl ketone 98 is shown in Figure 16. The stereochemistry in the X-ray crystal structure of 98 was found to be the same as that determined by chemical correlation.
Figure 16. X-ray crystal structure of (2R*,12S*)-2,12-dimethylcyclododecanone (98).

Formation of the oximes of these ketones proved to be a challenge. All attempts to prepare the oximes from the ketones 98-101 with retention of the stereochemistry failed. This was believed to be a result of the steric crowding around the ketone. No oxime product was obtained from the dimethyl ketone 98 using the previous methodology for the formation of the less hindered oximes 81-83. Other standard methods also failed.\textsuperscript{87,88} A low yield was obtained using the original conditions for the formation of oximes 81-83 except the reaction was run under a pressure of 1000 psi. A low yield were also obtained by treating the ketone with the potassium salt of N,O-bistrimethylsilyl hydroxylamine.\textsuperscript{89,90}

Two methods were used to obtain the 2,12-dimethyl oximes in high yield (Figure 17). The first procedure involving the methylation of the dianion of the 2-methyl
oxime 81. This alkylation was highly stereoselective. The second method followed a procedure coined the "lethargic reaction" by Pearson and Keaton. These authors obtained quantitative yield of highly hindered oximes by generating the dianion of hydroxyl amine in a strongly basic solution and allowing this dianion to react with a ketone. The reactions required 32 to 450 days for completion. Though requiring a shorter reaction time much lower yield were obtained at reflux temperatures, due to decomposition of the hydroxyl amine.

To shorten the reaction time, we used refluxing temperatures for the preparation of the oximes 106-109. The preparation of the oximes from 98 or 100 was not stereoselective due to equilibration of the methyl group under these basic reaction conditions.

Figure 17. Syntheses of the oximes 106-109: (i) 2eq LDA, THF; (ii) Mel; (iii) 2eq t-BuOK, t-amyl alcohol, H₂NOH·HCl.
After separation by silica gel column chromatography, the relative stereochemistry of the oximes 106-109 was determined by oxidative cleavage back to the dimethyl ketones 98-101. The relative stereochemistry of the carbons α to the ketone was retained under these oxidation conditions.

The X-ray crystal structures of the dimethyl oximes 107 and 109 are shown in Figure 18 and Figure 19, respectively. The (R*,R*) stereochemistry found in the X-ray crystal structures of 107 and 109 was the same as that determined using the chemical correlation above.
**Figure 18.** The X-ray crystal structure of \((2R^*,12R^*)\)-2,12-dimethylcyclododecanone oxime (107).

**Figure 19.** The X-ray crystal structure of \((2S^*,13S^*)\)-2,13-dimethylcyclotridecanone oxime (109).
Large $^1\text{H}$ NMR chemical shift differences between the isomeric (R*,S*) and (R*,R*) oximes were observed. For example, 0.20 and 0.14 ppm $^1\text{H}$ chemical shift differences were observed between the signals for the methyl groups on the 12- and 13-membered (R*,S*) oximes 106 and 108. Much smaller 0.04 and 0.01 ppm differences were observed in the 12- and 13-membered (R*,R*) oximes 107 and 109.

The (R*,S*) and (R*,R*) isomers of the dimethyl lactams 92-95 were prepared from the corresponding oximes 106-109 via the same Beckmann conditions described previously for the preparation of the methyl lactams 65-67. Under these conditions the reaction of oximes 106-109 was stereospecific. The identification of the relative stereochemistry of the products from the alkylation of lactams 65 and 66 was then determined by comparison of their GC and NMR spectra with those of lactams 92-95 of known stereochemistry.
2.3.3 Alkylation of the N-benzyl lactam 68

The alkylation of the N-benzyl lactam 68 was carried out to investigate the effect of a nitrogen-protecting group on the stereoselectivity of the alkylation. Alkylations were carried out in three different solvents. The reaction conditions and the relative ratio of the (R*,S*) to (S*,S*) products are listed in Table 7. In all three solvents only two products 110 and 111 were obtained. Methylation of the benzylic position was not detected as previously found for the alkylation of the unsubstituted 13-membered N-benzyl lactam. 95

![Chemical structure](image)

**Table 7. Alkylation of N-benzyl lactam 68.**

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>(R*,S*) : (S*,S*)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-BuLi</td>
<td>Hexane</td>
<td>-78</td>
<td>5.67 : 1</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>THF</td>
<td>-78</td>
<td>2.29 : 1</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>THF</td>
<td>0</td>
<td>1.38 : 1</td>
</tr>
<tr>
<td>NaH</td>
<td>DMSO</td>
<td>RT</td>
<td>1 : 1.31</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC.
A sample of the alkylated lactam 110 was isolated by flash chromatography. However, we were unable to isolate a pure sample of lactam 111 due to difficulty in the chromatographic separation. The relative stereochemistry of the two lactams 110 and 111 was determined by chemical correlation. The N-benzyl lactam 110 was deprotected with Li/NH$_3$ to give a single product which was shown to be identical to lactam 96 synthesized earlier. In addition, reductive cleavage of the mixture of lactams 110 and 111 gave 96 and 97. The GC ratio of products 96 and 97 was the same as that of the starting materials 110 and 111 demonstrating that epimerization does not occur during the Li/NH$_3$ reduction.
2.3.4 \( ^1 \)H Chemical shift difference correlations with the relative stereochemistry of dimethyl lactams 92-97

Previously Still and Galynker observed that the \( ^1 \)H NMR chemical shift differences between the two methyl groups of 2-methyl macrocyclic lactones of secondary alcohols were larger for the diastereomer having the (S*,S*) configuration in 9- to 11-membered lactones.\(^{42}\) This trend was observed to hold in the 14- and 16-membered lactones.\(^{75,97}\) For example, the (2S*,15S*)-2-methyl-15-hexadecanolide (115) was found to have a 0.03 ppm greater \( ^1 \)H chemical shift difference between the methyl groups than the (2R*,15S*) diastereomer 114.\(^{75}\) A similar difference was observed between the 14-membered lactones (2S*,13S*)-113 and (2R*,13S*)-112.

As shown in Table 8, the difference in the \( ^1 \)H NMR chemical shift between the two methyl groups in the 14- and 16-membered lactams is 0.01 ppm larger in the corresponding (S*,S*) than in the (R*,S*) diastereomer, following the trend observed in the lactones. However, the difference in the \( ^1 \)H NMR chemical shift between the two methyl groups in the 13-membered (R*,S*) and (S*,S*) lactam diastereomer is much smaller and does not follow this trend.
### Table 8. Comparison of the $^1$H chemical shifts for the methyl α to the carbonyl and the methyl α to the heteroatom in some macrocyclic lactams and lactones.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Ring Size</th>
<th>$\delta$-Me's$^a$ (ppm)</th>
<th>$\Delta\delta$-Me's (ppm)</th>
<th>$\Delta\delta(S^<em>,S^</em>)-\Delta\delta(R^<em>,S^</em>)$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactams</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-92</td>
<td>13</td>
<td>1.12, 1.10</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-93</td>
<td>13</td>
<td>1.10, 1.09</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-94</td>
<td>14</td>
<td>1.11, 1.11</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-95</td>
<td>14</td>
<td>1.11, 1.10</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-96</td>
<td>16</td>
<td>1.11, 1.10</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-97</td>
<td>16</td>
<td>1.11, 1.08</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td><strong>Lactones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-112</td>
<td>14</td>
<td>1.17, 1.12</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-113</td>
<td>14</td>
<td>1.19, 1.10</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-114</td>
<td>16</td>
<td>1.21, 1.15</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-115</td>
<td>16</td>
<td>1.19, 1.10</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ 400 MHz NMR in CDCl$_3$

However, a chemical shift correlation with the stereochemistry in the lactam series is observed in the shifts of the protons α to the carbonyl. The $^1$H chemical shifts of these α-protons of the lactams and corresponding lactones are listed in Table 9. The $^1$H signal for the α-proton in the (R$^*$,S$^*$) diastereomer of the 16-membered lactam 96 is 0.53 ppm downfield of the α-proton in the (S$^*$,S$^*$) diastereomer 97. The α-proton in the (R$^*$,S$^*$) diastereomers of the 13- and 14-membered lactams are also found downfield of their corresponding (S$^*$,R$^*$) diastereomers. This trend holds in the 16-membered lactone, but is reversed for the 14-membered lactone.
Table 9. Comparison of the $^1$H chemical shifts for the proton $\alpha$ to the carbonyl in some macrocyclic lactams and lactones.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Ring Size</th>
<th>$\delta \alpha$-proton$^a$ (ppm)</th>
<th>$\delta(S^<em>,S^</em>) - \delta(R^<em>,S^</em>)$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactams</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-92</td>
<td>13</td>
<td>2.39</td>
<td>-0.25</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-93</td>
<td>13</td>
<td>2.14</td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-94</td>
<td>14</td>
<td>2.39</td>
<td>-0.30</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-95</td>
<td>14</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-96</td>
<td>16</td>
<td>2.37</td>
<td>-0.53</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-97</td>
<td>16</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td><strong>Lactones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-112</td>
<td>14</td>
<td>2.39</td>
<td>+0.13</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-113</td>
<td>14</td>
<td>2.52</td>
<td></td>
</tr>
<tr>
<td>(R$^<em>$,S$^</em>$)-114</td>
<td>16</td>
<td>2.43</td>
<td>-0.03</td>
</tr>
<tr>
<td>(S$^<em>$,S$^</em>$)-115</td>
<td>16</td>
<td>2.40</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ 400 MHz NMR in CDCl$_3$

2.4 Conformational analysis of lactams 65-67

The combination of the structural characteristic of esters and the conformational principles of macrocyclic hydrocarbon rings was previously used to simplify the conformational analysis of macrocyclic lactones, as discussed in Section 1.6. In a similar manner, a simplified picture of the conformational analysis of macrocyclic lactams may be developed.

Secondary amides have a preference for the Z (s-trans) arrangement. For example, the Z conformations of N-methylformamide and N-methylacetamide are more stable than the E conformations by 1.4-1.6 and 2.1-2.5 kcal/mol, respectively.98
The differences in energy between the Z and E conformations of N-methylformamide and N-methylacetamide are smaller than for corresponding esters. For example, methyl formate was found to favour the Z conformer by 4.75 kcal/mol.\textsuperscript{99,100} The preference for the Z-conformer in esters is a result of both steric and charge interactions\textsuperscript{101,102} as well as n-\(\sigma^*\) overlap,\textsuperscript{103} similar to the anomeric effect. The preference of the Z conformation in amides is only a result of steric factors and charge interactions.\textsuperscript{101,104}

However it should be noted that the barrier to E/Z interconversion is higher in amides than in esters. Methyl formate was found to have a barrier of rotation of 10-13 kcal/mol.\textsuperscript{105} N-Methylformamide and N-methylacetamide were found to have much larger barriers in the range of 18-22 kcal/mol.\textsuperscript{106} As a result the two amide conformers can be observed at room temperature by NMR.

The preference for the Z arrangement of acyclic amides has also been observed in large membered rings. Using infrared spectroscopy, it was found that five- to eight-membered lactams have the E conformation and that 10-membered and larger lactams have the Z conformation.\textsuperscript{84,107,108} Williamson and Roberts using NMR spectroscopy demonstrated that the nine-membered lactam exists as an equilibrium mixture of equally populated E and Z conformers having a free energy of activation for the interconversion of \(\Delta G^\ddagger = 17\) kcal/mol.\textsuperscript{109}
The preference for the syn-periplanar arrangement in esters of secondary alcohols has also been shown to occur in the corresponding amides having two alkyl substituents on the carbon \( \alpha \) to the N as illustrated below. A survey of X-ray crystal structures of such amides showed that the C(O)-N-C-H angle of these amides was found to lie between 0° and 40° in 74% of the cases in the data set, and 88% of the structures were found to have values of this angle between 0° and 50° degrees. If this constraint applies to in macrocyclic lactams the C(O)-N-C-H torsional angle should be small, in the range of 0° to 50°.

Based on the combination of these two structural constraints of amides and the conformational preferences of macrocyclic alkane rings, three possible conformations of the 14-membered methyl lactam 66 and the two possible conformations of the 16-membered methyl lactam 67 may be drawn (Figure 20).
2.4.1 The preference for the Z amide geometry in lactams 65-67

The preference for the amide in the lactams 65-67 to exist in the Z (s-trans) conformation was suggested by the observation of an NOE enhancement\textsuperscript{111,112} of the proton $\alpha$ to the carbonyl in lactams 65-67 upon irradiation of the NH proton (Table 10).

Table 10. NOE\textsuperscript{s} of the $\alpha$-protons in methyl lactams 65-67 upon irradiation of the NH proton

<table>
<thead>
<tr>
<th>Lactams</th>
<th>Ring Size</th>
<th>$\alpha$-Protons (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NOE enhancement observed</td>
</tr>
<tr>
<td>65</td>
<td>13</td>
<td>2.07</td>
</tr>
<tr>
<td>66</td>
<td>14</td>
<td>2.04</td>
</tr>
<tr>
<td>67</td>
<td>16</td>
<td>1.96</td>
</tr>
</tbody>
</table>
A selective NOE enhancement of one of the two diastereomeric \( \alpha \)-protons in lactams 65-67 was observed. Only the high field \( \alpha \)-proton was found to have a strong (5-10\%) NOE enhancement upon irradiation of the NH proton. NOE enhancements of this magnitude were suggested by Bell and Saunders to represent internuclear distances of 2.8 to 3.4 Å.\(^{113}\) These distances were determined for protons which are relaxed solely by a single proton or methyl group, and thus represent maximum values for the distances of protons relaxed by more than one proton. The lower field \( \alpha \)-proton was found to have no enhancement.

The selective NOE enhancement of a single \( \alpha \)-proton suggests that the N-C(0)-C-C angle is in a rigid gauche arrangement. In the gauche arrangement only proton \( H_a \) is close enough to the NH proton to experience an NOE enhancement of the magnitude observed. In the anti arrangement both protons \( H_a \) and \( H_b \) should experience similar NOE effects when the NH proton is irradiated.
The selective NOE effect indicates that the gauche N-C(O)-C-C angle is rigid since rapid conformational averaging would be expected to eliminate the selectivity and most likely significantly reduce or eliminate the observation of an NOE enhancement of either proton.\textsuperscript{111,113} The magnitude of a NOE enhancement is dependent upon the distance between nuclei. The conformationally averaged distance of the two \( \alpha \)-protons from the NH proton would be greater than the NH-H\( \alpha \) distance in the rigid gauche conformation.\textsuperscript{113} This rationalization that rotational averaging of the N-C(O)-C-C torsion is frozen is further supported by the large chemical shift difference of 0.12-0.2 ppm observed between the two \( \alpha \)-protons.\textsuperscript{114} The gauche N-C(O)-C-C torsional angle suggested by this chemical shift difference and the NOE effects are consistent with two of the three conformations of the 66 (V and X) and one of the two conformations of 67 (Y) shown in Figure 20.

\subsection*{2.4.2 The preference of the syn-periplanar arrangement in lactams 65-67}

Evidence for the preference for the syn-periplanar arrangement in amides was also found from the large \( ^3J_{\text{NHCH}} \) vicinal coupling constants in the lactams 65-67 (Table 11). These values were determined with the aid of a series of decoupling experiments to simplify the coupling patterns. The numbering system used is illustrated for lactam 66. Protons that are cis (as drawn) to the methyl group are denoted as "a" and the protons that are trans to the methyl group are denoted as "b".
Table 11. $^3J$ Coupling constants (Hz) of lactams 65-67.

<table>
<thead>
<tr>
<th></th>
<th>65 n=13</th>
<th>66 n=14</th>
<th>67 n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vicinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n-1)a - n</td>
<td>9.6</td>
<td>9.3</td>
<td>8.0</td>
</tr>
<tr>
<td>(n-1)b - n</td>
<td>2.4</td>
<td>3.0</td>
<td>3.8</td>
</tr>
<tr>
<td>NH - n</td>
<td>9.4</td>
<td>9.0</td>
<td>9.5</td>
</tr>
<tr>
<td>(n-1)b - (n-2)a</td>
<td></td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>(n-1)b - (n-2)b</td>
<td></td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>3a - 4a</td>
<td>3.1</td>
<td>3.0</td>
<td>4.6</td>
</tr>
<tr>
<td>3a - 4b</td>
<td>9.7</td>
<td>10.6</td>
<td>10.1</td>
</tr>
<tr>
<td>3b - 4a</td>
<td>8.2</td>
<td>7.2</td>
<td>6.1</td>
</tr>
<tr>
<td>3b - 4b</td>
<td>3.5</td>
<td>3.0</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Geminal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a - 3b</td>
<td>13.7</td>
<td>13.7</td>
<td>13.7</td>
</tr>
</tbody>
</table>

The large $^3J_{\text{NHCH}}$ values for the NH-H$_n$ coupling indicate that the C$_{(n-1)}$-C$_n$-N-C(O) torsional angle is rigid. The relationship between the $^3J_{\text{NHCH}}$ coupling constant and the
dihedral angle $\phi$ between the NH and CH proton $\alpha$ to the nitrogen has been described by the Karplus-like $^{115,116}$ equation $^5$. $^{117,118}$ This equation was developed from the coupling constants in peptides. $^{117-119}$

$$^{3}J_{\text{NHCH}} = 9.8 \cos^2 \phi - 1.1 \cos \phi + 0.4 \sin^2 \phi$$

Using this equation the $^{3}J$ values for the coupling constants correspond to a H-N-C$_n$-H$_n$ dihedral angle $\phi$ of 157°, 154° and 158° for the lactams 65, 66 and 67, respectively. These angles are intermediary between the 120° H-N-C-H dihedral angles $\phi$ of a diamond lattice conformation and the 180° dihedral angle of amides in the syn-periplanar arrangement. This compromise may be a result of a static system in which the H-N-C$_n$-H$_n$ dihedral angle $\phi$ is held at $\sim$ 150° or a dynamic system in which conformational averaging between major populated conformations having the syn-periplanar configuration and minor populated conformations having the diamond lattice configurations occurs.
2.4.3 Conformational rigidity of the amide region in lactams 65-67

Analysis of the remaining coupling constants in Table 11 indicates that the amide region from \( C(n-2) \)-\( C(n-1) \) bond to the \( C_3-C_4 \) bond of lactams 65-67 is conformationally rigid and has a similar geometry in all three of the lactams.

The large difference in the \( ^3J \) values for the \( H(n)-H(n-1a) \) (8.8 - 9.1 Hz) and the \( H_n-H(n-1b) \) (2.4 - 3.8 Hz) indicates that the \( C(n-2)-C(n-1)-C_n-N \) torsional angle is rigid and suggests that this torsional angle is gauche.

![Diagram of lactam structure](image)

The selective NOE enhancements and the large chemical shift difference between the two protons \( \alpha \) to the carbonyl discussed earlier, indicated that the \( N-C(O)-C_3-C_4 \) torsional angle is also in a rigid gauche conformation. The magnitude of the geminal coupling also supports this proposal. A correlation between the geminal coupling constants of \( \alpha \)-protons next to a carbonyl group and the \( X-C(O)-C-C \) torsional angle has been shown to occur in peptides\(^{118,120,121}\) and in other carbonyl compounds.\(^{118,122}\) An equation to describe this relationship was developed by Barfield and Grant.\(^{123}\) The magnitude of the H-C-H geminal coupling constant for these \( \alpha \)-protons was found to
range from 10 to 19 Hz.\textsuperscript{118,122} The value of 13.7 Hz measured for the geminal coupling constant in all three lactams corresponds to an N-C(O)-C\textsubscript{3}-C\textsubscript{4} torsion angle of 60 ± 20° or 125 ± 20°.\textsuperscript{118,122} The relatively small geminal coupling constant thus indicates that the N-C(O)-C\textsubscript{(n)}-C\textsubscript{(n-1)} torsion is not in an anti conformation. This agrees with the previous rationalization from the NOE data that the N-C(O)-C\textsubscript{3}-C\textsubscript{4} torsion is approximately 60°.

The next torsional angle around the lactam, the C(O)-C\textsubscript{3}-C\textsubscript{4}-C\textsubscript{5} also appears to be rigid. Among the four protons on the central carbons of the C(O)-C\textsubscript{3}-C\textsubscript{4}-C\textsubscript{5} unit there are two small, one medium and one large $^{3}J$ coupling constants. The large and small $^{3}J$ values indicate that the torsional angle is rigid. The medium $^{3}J$ value for the H\textsubscript{3b}-H\textsubscript{4a} vicinal coupling constant indicates that this particular coupling constant is probably affected by the electronegative amide group.\textsuperscript{124,125} The amide influences the A value in the Karplus equation ($J^{3} = A\cos^{2}\phi + C$),\textsuperscript{115,116} complicating the direct use of the equation in such systems.\textsuperscript{125-127} Although the Karplus equation may not be used to directly determine the four torsional angles between such adjacent methylene groups, the vicinal coupling constants may be related to the C(O)-C-C-C torsional angle independent of electronegative effects, using the R-value ratio method developed by Lambert.\textsuperscript{126,127}
The ratio, \( R = J_{\text{trans}}/J_{\text{cis}} = [JH_{3a}H_{4b}+JH_{3b}H_{4a}]/(JH_{3a}H_{4a}+JH_{3b}H_{4b}) \) uses four coupling values that are assumed to have the same dependency on electronegativity. Thus the R-value does not depend on the electronegativity but only on the conformation. The R value is related to the C(O)-C\(_3\)-C\(_4\)-C\(_5\) torsional angle \( \phi \) by Equation 6.\(^{126,127}\)

\[
\cos \phi = \left[ \frac{3}{2+4R} \right]^{1/2}
\]

The R-values for the 13-, 14- and 16-membered lactam were found to be 2.72, 2.96, and 1.72 which correspond to \( \phi \) angles of 61.2°, 62.3° and 54.4°, respectively, and are consistent with the gauche arrangement for the C(O)-C\(_3\)-C\(_4\)-C\(_5\) angle. The determination that the C(O)-C\(_3\)-C\(_4\)-C\(_5\) and the N-C(O)-C\(_3\)-C\(_4\) torsion are both predominantly gauche indicates that the C\(_n\) carbon is located at a corner position.

Further conformational analysis of the remaining hydrocarbon section of the lactam rings was hindered by overlap of the proton signals. However, measurement of the coupling constants of the H\(_{(n-1)b}\) proton with the C\(_{(n-2)}\) protons in the 14-membered
lactam could be determined. Decoupling the H<sub>3</sub> proton resulted in the collapse of the H<sub>(n-1)b</sub> signal to a doublet (J = 14 Hz) due to geminal coupling and a triplet (J = 7.7 Hz). The observation that the J<sub>(n-1)b,(n-2)a</sub> and J<sub>(n-1)b,(n-2)b</sub> vicinal coupling constants are similar and averaged suggests that this C<sub>n</sub>-C<sub>(n-1)</sub>-C<sub>(n-2)</sub>-C<sub>(n-3)</sub> unit and the remainder of the ring in 66 are conformationally mobile.

In summary, the preferences for the Z (s-trans) and the syn-periplanar conformations in amides were both found to extend to the lactams 65-67. Analysis of the NOE<sup>15</sup> and the coupling constants indicate that the amide regions of lactams 65-67 from the C<sub>(n-2)</sub>-C<sub>(n-1)</sub> torsion to the C<sub>3</sub>-C<sub>4</sub> torsion are similar and conformationally rigid.

2.5 Conformational analysis of lactams 92-97

A comparison of the vicinal coupling constants of the dimethyl lactams 92-97 listed in Table 12 with those of the monomethyl lactams 65-67, indicates that the conformations of the amide regions of each pair of lactams are similar. Previously, it was proposed that the C<sub>3</sub> carbon is predominantly located at a corner position in the methyl lactams 65-67. Since the coupling constants for the protons on C<sub>3</sub> and C<sub>4</sub> of the dimethyl lactams 92-97 are similar to the coupling constants in the corresponding monomethyl lactams 65-67, it would suggest that the C<sub>3</sub> carbon is predominantly located at a corner position in lactams 92-97 also.
Table 12. Vicinal coupling constants (Hz) of lactams 92-97 compared to lactams 65-67.

<table>
<thead>
<tr>
<th></th>
<th>65</th>
<th>92</th>
<th>93</th>
<th>66</th>
<th>94</th>
<th>95</th>
<th>67</th>
<th>96</th>
<th>97</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>n - (n-1)a</td>
<td>9.6</td>
<td>10.1</td>
<td>8.9</td>
<td>9.3</td>
<td>9.3</td>
<td>9.3</td>
<td>8.0</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>n - (n-1)b</td>
<td>2.4</td>
<td>2.4</td>
<td>2.8</td>
<td>3.0</td>
<td>3.1</td>
<td>2.7</td>
<td>3.8</td>
<td>3.7</td>
<td>3.2</td>
</tr>
<tr>
<td>n • NH</td>
<td>9.4</td>
<td>9.5</td>
<td>9.5</td>
<td>9.0</td>
<td>9.0</td>
<td>9.1</td>
<td>9.5</td>
<td>8.5</td>
<td>9.0</td>
</tr>
<tr>
<td>3a - 4a</td>
<td>3.1</td>
<td>-</td>
<td>3.4</td>
<td>3.0</td>
<td>-</td>
<td>2.4</td>
<td>4.6</td>
<td>-</td>
<td>4.2</td>
</tr>
<tr>
<td>3a - 4b</td>
<td>9.7</td>
<td>-</td>
<td>9.8</td>
<td>10.6</td>
<td>-</td>
<td>10.6</td>
<td>10.1</td>
<td>-</td>
<td>10.2</td>
</tr>
<tr>
<td>3b - 4a</td>
<td>8.2</td>
<td>10.0</td>
<td>-</td>
<td>7.2</td>
<td>10.3</td>
<td>-</td>
<td>6.1</td>
<td>10.1</td>
<td>-</td>
</tr>
<tr>
<td>3b - 4b</td>
<td>3.5</td>
<td>4.0</td>
<td>-</td>
<td>3.0</td>
<td>3.7</td>
<td>-</td>
<td>4.8</td>
<td>5.2</td>
<td>-</td>
</tr>
</tbody>
</table>

The $^3J_{NHCH}$ coupling values for lactams 92-97 were found to be similar to the values found for the monomethyl lactams 65-67. Using Equation 5, the $^3J_{NHCH}$ value of 8.5 Hz for lactam 96 corresponds to a H-N-C$_n$-H$_n$ dihedral angle of 149°. As discussed earlier, the calculation of a value > 120° indicates that the C$_{(n-1)}$-C$_n$-N-C(O) torsion is influenced by the preference of amides to adopt a syn-periplanar arrangement. This preference is evident in the two conformers of lactam 96 found in the solid state, shown in Figure 14 (Section 2.3.1). In both the major and minor conformers the C$_{(n-1)}$-C$_n$-N-C(O) torsion is found to be at a non-diamond lattice angle of 130°, with H$_n$-C$_n$-N-H dihedral angles 173° and 157°, respectively.

Irradiation of the NH proton resulted in a NOE enhancement of the $\alpha$-proton of lactams 93, 95 and 97 having the (S*,S*) stereochemistry and no enhancement of the $\alpha$-proton of lactams 92, 94 and 96 having the (R*,S*) stereochemistry, as listed in Table 13. This NOE correlation agrees with the previous proposal from the coupling constants that the conformation of this region around the amide is similar to that in lactams 65-67.
and not affected significantly by methyl substitution of an $\alpha$-proton. As discussed earlier, the chemical shifts of the $\alpha$-proton in the (S*,S*) diastereomers are found upfield of the $\alpha$-proton in the (R*,S*) diastereomer (Table 9). The selective NOE enhancement of the $\alpha$-proton of the (S*,S*) lactams on NH irradiation corresponds to the observation of the selective NOE effect for the upfield H$_{3a}$-proton in the monomethyl lactams 65-67. The NOE enhancement of the H$_3$ proton in the (S*,S*) dimethyl lactams indicates a preference for the Z conformation of the amide and the gauche conformation of the N-C(O)-C$_3$-C$_4$ torsional angle in these rings similar to that found in the monomethyl lactams 65-67.

Table 13. NOE$^\dagger$ of the protons $\alpha$- to the carbonyl group in dimethyl lactams 92-97 on irradiation of the NH proton.$^a$

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Ring Size</th>
<th>Effect on $\alpha$-Proton (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R*,S*)-92</td>
<td>13</td>
<td>Strong NOE 2.39</td>
</tr>
<tr>
<td>(S*,S*)-93</td>
<td>13</td>
<td>No NOE 2.14</td>
</tr>
<tr>
<td>(R*,S*)-94</td>
<td>14</td>
<td>Strong NOE 2.39</td>
</tr>
<tr>
<td>(S*,S*)-95</td>
<td>14</td>
<td>No NOE 2.09</td>
</tr>
<tr>
<td>(R*,S*)-96</td>
<td>16</td>
<td>Strong NOE 2.37</td>
</tr>
<tr>
<td>(S*,S*)-97</td>
<td>16</td>
<td>No NOE 1.84</td>
</tr>
</tbody>
</table>

$^a$ 400 MHz NMR in CDCl$_3$

The lack of an observed NOE enhancement of the H(n)b proton is negative evidence that the Z preference and gauche conformation of the N-C(O)-C$_3$-C$_4$ torsional angle also are preferred in the (R*,S*) dimethyl lactams. The similarity in the chemical shift difference between the H$_b$ proton in the (R*,S*) dimethyl lactams relative to the H$_a$
proton α- to the carbonyl in the (S*,S*) lactams, and the difference between the 
Hb-proton relative to the Ha-proton α to the carbonyl of the methyl lactams, indicates 
that the conformation of the N-C(O)-C3-C4 angle in the (S*,S*) as well as the (R*,S*) 
dimethyl lactams is gauche as found in the methyl lactams. Thus the chemical shift 
difference, NOE effects and coupling constants all indicate that the local conformation of 
the amide region in the methyl lactams 65-67 and dimethyl lactams 92-97 are all similar 
and rigid.

2.6 Molecular mechanics conformational search of lactams 65-67

A series of conformational searches of the MM2* energy surface 
("Born-Oppenheimer surface")\textsuperscript{128-130} for the low energy conformers of the 13-, 14- and 
16-membered lactams 65-67 were carried out. A conformational search of the low 
energy conformations of the corresponding macrocyclic hydrocarbons was also carried 
out to compare with the lactams in order to determine the effect of the amide group and 
methyl substituent on the ring conformations.

The searches were performed using the Monte Carlo method\textsuperscript{131} available in the 
molecular modelling program MACROMODEL.\textsuperscript{132} This Monte Carlo method\textsuperscript{131} probes 
the energy surface by disconnecting a carbon-carbon bond in the ring, then randomly 
rotates the remaining torsional bonds. When the two free ends of the chain come within 
a preset distance of each other (2 bond lengths), the algorithm reforms the bond and 
carries out a minimization of the intermediate structure on the MM2* energy surface 
using the Polak-Ribiere conjugate gradient (PRCG) method.\textsuperscript{132}

The conformational sets of low energy conformers for the 13-, 14- and 
16-membered hydrocarbon rings obtained using the MACROMODEL program
correlated well with both the structures and relative conformational energies found using previous reported methods for searching the conformational space of the cycloalkanes.\textsuperscript{11,133-137}

A summary of the number of low energy conformations found within 1, 2 and 3 kcal/mol above the global minimum of both the cyclic hydrocarbons and the lactams is given in Table 14.

**Table 14. A comparison of the number of low energy conformations of lactams 65-67 and the corresponding cyclic hydrocarbons.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>$\Delta E$ (kcal/mol)</th>
<th>cyclo-tridecane</th>
<th>lactam 65</th>
<th>cyclo-tetradecane</th>
<th>lactam 66</th>
<th>cyclo-hexadecane</th>
<th>lactam 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>28</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>30</td>
<td>5</td>
<td>81</td>
<td>8</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Using the conformational search and MM2* force field in MACROMODEL.

The conformational searches yielded 17 conformations within 3 kcal/mol of the global minimum for cyclo-tridecane, compared to 30 conformations within the same energy range for the 13-membered lactam 65. Similar calculations on cyclo-tetradecane gave 5 conformations within 3 kcal/mol of the global minimum, compared to 81 for the 14-membered lactam 66. The calculations on cyclo-hexadecane lead to 8 conformations within 3 kcal/mol of the global minimum, whereas the lactam 67 has more than 100 conformations in this energy range. Hence these calculations suggest that the conformational analysis of these lactams are more complex than those of their corresponding hydrocarbons.
It is interesting however to compare the calculated global minimum conformations of the lactams 65-67 with those of the corresponding hydrocarbons. The global minimum conformers for the lactams and hydrocarbons are illustrated in Figure 21 using the polar map notation. A description of the polar map notation may be found in Appendix I. The amide C₃-C(O)-N-Cₙ torsional angle is set as number 1 in these polar maps. The numbering of the torsion angles around the ring follows the direction of the numbering of the atoms, for example number 2 is the C₄-C₃-C(O)-N angle.

Figure 21. The global minimum conformations of (a) macrocyclic hydrocarbons 116, 31 and 32, and (b) lactams 65-67.
The global minimum conformation of cyclotridecane (116) was found to be a non-diamond lattice conformation. The global minimum conformations of the 14- and 16-membered hydrocarbons were found to be in the [3434] and [4444] diamond lattice conformations, respectively. Comparison of the polar maps suggests that the 13-membered lactam 65 has the same global minimum conformation as cyclotridecane (116). The global minimum conformation of the 14-membered ring lactam 66 closely resembles that of the [3434] of the cyclic hydrocarbon except for the C(O)-N-C_n-C_{n-1} torsional angle \( \phi \) (torsion n) that is found to be 150\(^\circ\), half way between the diamond lattice angle of 180\(^\circ\) found in the hydrocarbon and the 120\(^\circ\) C(O)-N-C-C angle expected for syn-periplanar amides. This calculated angle of 150\(^\circ\) agrees with the previous determination of the C(O)-N-C\(_n\)-C\(_{n-1}\) torsional angle \( \phi \) in methyl lactam 66 of 146\(^\circ\) from the \(^3\)J\(_{\text{NH,Hn}}\) coupling constant (Table 11 and below). Thus the global minimum conformation of 66 represents a compromise between the preference of the ring to adopt a diamond lattice conformation and the preference of the amide to adopt a syn-periplanar arrangement.

\[
\begin{align*}
\text{calculated from} \\
^3J \text{ value (NH-H}_n\text{)} \\
\phi &= 154^\circ \\
\varphi &= 146^\circ
\end{align*}
\]
The global minimum conformation of the 16-membered ring lactam 67 does not resemble a diamond lattice conformation. The C(O)-N-C-C torsional angle is 127° and the C(O)-N-C-H angle is 7° (syn-periplanar). The larger 16-membered ring distorts significantly from the [4444] diamond lattice found for the hydrocarbon to relieve the strain due to the preference of the C(O)-N-C-H angle to be syn-periplanar. The second lowest energy conformation found 0.1 kcal/mol above the global minimum conformation shown below resembles the [4444] diamond lattice conformation in which the C(O)-N-C-C is 153° (torsion 16 below). This is similar to the distortion of the diamond lattice found in the global minimum conformation of the 14-membered lactam 66.

![Polar map of the second lowest energy conformation of 67.](image)

**Figure 22.** Polar map of the second lowest energy conformation of 67.

The global minimum conformation of the 13-membered hydrocarbon must be non-diamond lattice. It contains a torsional angle of 99.5°. Thus the global minimum conformation is able to accommodate the syn-periplanar C(O)-N-C-C torsional angle. The corresponding C(O)-N-C-C torsional angle in the global minimum conformation of
the 13-lactam is 114°. The incorporation of the lactam and the addition of the methyl substituent onto the 13-membered ring have little effect on the global minimum conformation, as evidenced by the close similarity of the polar maps of the global minimum conformations of 65 and 116 in Figure 21.

The preference for the C(O)-N-C-H for a syn-periplanar arrangement raises the relative energy of the [3434] and [4444] diamond lattice conformations in the 14- and 16-membered lactams and lowers the energy of the conformers which are able to accommodate the C(O)-N-C-C torsional angle of 120°. This reduces the energy difference between the global minimum conformation and higher energy conformations, increasing the number of conformations within 2 kcal/mol of the global minimum, and thus increasing the complexity of the conformational analysis of these lactams relative to that of their corresponding hydrocarbons.

2.6.1 Rigidity of the amide region in the low energy conformations of lactams 66-67

Although a large number of conformations were found within 2 kcal/mol of the global minimum conformation for the methyl lactams 66 and 67 by the MM2* calculations, the amide regions of lactams 65-67 were found to have the same local conformation in these conformations. This agrees with the previous analysis of the amide region based on NOE effects and coupling constants.

This local amide conformation in the methyl lactams 66 is in agreement with the calculated averaged vicinal coupling constants for the low energy conformations of methyl lactam 66 and the experimentally measured values shown in Table 15. The calculation of the coupling constants for lactam 66 are based on the Boltzmann
weighted average of the coupling constants from the 28 lowest energy conformations that are within 2 kcal/mol of the global minimum. Except for the values for $J_{3a,4b}$ and $J_{3b,4a}$, the measured and calculated coupling constants are in reasonable agreement. The poor correlation of the $J_{3a,4b}$ and $J_{3b,4a}$ suggests that the Altona method\textsuperscript{125} does not accurately model vicinal coupling constants for protons $\alpha$- to an amide. Using the R-value ratio method which removes the effects of electronegativity a value of 61° for the C(O)-C$_3$-C$_4$-C$_5$ torsional angle was determined from the calculated values for the vicinal coupling constants of the $\alpha$-protons. This closely agrees with the 62° value determined from the measured vicinal coupling constants. The close agreement of the two values using the R-value method, supports the proposal that the medium values for the $J_{3a,4b}$ and $J_{3b,4a}$ are due to the amide rather than conformational averaging effects. The consistency between the calculated and experimental values for the coupling constants indicates that the molecular mechanics calculation is able to correctly model the conformational stability of the amide region of these lactams.
Table 15. Experimental and calculated coupling constants of the conformations within 2 kcal/mol of the global minimum conformation of lactam 66.

<table>
<thead>
<tr>
<th>Vicinal Coupling Constants</th>
<th>Observed (Hz)</th>
<th>Calculated $^{a,b}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n-1)a - n</td>
<td>9.1</td>
<td>10.6</td>
</tr>
<tr>
<td>(n-1)b - n</td>
<td>3.2</td>
<td>2.9</td>
</tr>
<tr>
<td>NH - n</td>
<td>9.0</td>
<td>-</td>
</tr>
<tr>
<td>(n-1)b-(n-2)a</td>
<td>7.7</td>
<td>6.4</td>
</tr>
<tr>
<td>(n-1)b-(n-2)b</td>
<td>7.7</td>
<td>9.9</td>
</tr>
<tr>
<td>3a - 4a</td>
<td>3.0</td>
<td>2.3</td>
</tr>
<tr>
<td>3a - 4b</td>
<td>10.6</td>
<td>5.9</td>
</tr>
<tr>
<td>3b - 4a</td>
<td>7.2</td>
<td>12.0</td>
</tr>
<tr>
<td>3b - 4b</td>
<td>3.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

$^a$ Using the Altona modification of the Karplus equation from ref. 125.

$^b$ Averaged values for 28 lowest energy conformations.
2.7 Molecular mechanics conformational searches of dimethyl lactams 92-97

A series of conformational searches of the MM2* energy surface\textsuperscript{128-130} using the Monte Carlo method\textsuperscript{131} available in the MACROMODEL\textsuperscript{132} program for the low energy conformers of the 13-, 14- and 16-membered (R*,S*) and (S*,S*) dimethyl lactams 92-97 was carried out. A summary of the number of low energy conformations found within 1, 2 and 3 kcal/mol above the global minimum conformations of the lactams is given in Table 16.

<table>
<thead>
<tr>
<th>(\Delta E) (kcal/mol)</th>
<th>(R*,S*) Lactam 92</th>
<th>(S*,S*) Lactam 93</th>
<th>(R*,S*) Lactam 94</th>
<th>(S*,S*) Lactam 95</th>
<th>(R*,S*) Lactam 96</th>
<th>(S*,S*) Lactam 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>6</td>
<td>23</td>
<td>20</td>
<td>47</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>48</td>
<td>53</td>
<td>77</td>
<td>136</td>
<td>222</td>
</tr>
</tbody>
</table>

The similar number of low energy conformations found in the (R*,S*) and (S*,S*) dimethyl lactams 92-97 in comparison with the number of low energy conformation found previously for the methyl lactam of the same ring size 65-67 (Table 14) suggests that substitution of one of the hydrogens \(\alpha\) to the carbonyl with a methyl group does not increase the conformational complexity. This suggestion agrees with the previous proposal based on the coupling constants and NOE observations that the conformation of the amide region is not greatly affected by methyl substitution of an \(\alpha\)-proton and that the C\(_3\) carbon is at a corner position.
Polar maps of the global minimum conformations for the lactams 92-97 are given in Figure 23.

Figure 23. Polar maps of the global minimum conformation of (a) (R*,S*)-dimethyl lactams 92, 94 and 96, and (b) (S*,S*)-dimethyl lactams 93, 95 and 97.

Comparison of the polar maps indicates that the global minimum conformations of the dimethyl lactams 92, 93, 94 and 96 have the same local conformation around the amide region from torsional angle (n-2) through to torsional angle 4 (n = ring size), shown with the asterisks (*) in Figure 23. The conformation in this region is similar to the conformation about the amide in the global minimum conformation of the monomethyl lactams 65-67, and agrees with the conformation proposed from the NOE and coupling constant data. This local amide conformation was also found in the major
and minor conformers of the X-ray crystal of the lactam 96 (Figure 14). The polar maps of these two conformations are shown in Figure 24, for comparison of the amide region. It happens that these conformers were the third and fourth lowest energy conformations, 0.19 and 0.39 kcal/mol higher in energy relative to the global minimum conformer. Their calculated relative energies are consistent with the relative ratio of 2:1 from the X-ray data.

Figure 24. Polar map representation of the major and minor conformations found in the X-ray crystal structure of lactam 96.

The global minimum conformations of the 13-membered lactams 92 and 93 and the (R*,S*) lactam 96 were also found to have the same ring conformation in the remainder of the ring as the global minimum conformation of the corresponding monomethyl lactam.

The amide region in the global minimum conformation of the (S*,S*) lactams 95 and 97 does not have the same local conformation as the other lactams. Although the (n-1) and (n) torsional angles in the global minimum conformations of these rings are distorted from the amide conformation discussed above, this local amide conformation (shown by the * in Figure 23) is found in the majority of the other low energy
conformations of lactams 95 and 97. For example this local conformation of the amide is found in the second lowest conformation for the (S*,S*) rings in 95 and 97, as illustrated in their corresponding polar maps shown in Figure 25.

Figure 25. Polar map representation of the the second lowest calculated conformation for the (S*,S*) lactams 95 and 97.

A comparison of the solid state conformation of the 14-membered lactam 94 or 95 rings with that of their calculated global minimum conformations has unable to be presented as X-ray quality crystals of these lactams have not been obtained to date. The solid state structure of the p-BrC₆H₄SO₂⁻ derivative of the naturally occurring 14-membered lactam 13¹³⁸ shown in Figure 26 was found to have the same [3434] ring conformation as the global minimum conformation of 95 (Figure 23), however the values for the C-C-C(O)-N and C(O)-N-C-C torsions (2 and 14) are reversed. The difference in the local amide region is likely due to the influence of the substituents on the ring conformation.
2.8 Rationalization of the relative stereoselectivity in lactone alkylations

The rationalization of the stereoselectivity of the methylation of the 14- and 16-membered ring lactones 40 and 41 was aided by molecular mechanics calculations on the Z-enolate of these lactones, shown in Figure 27, and was based on three assumptions.\(^\text{42,75}\) The first assumption was that the transition state is modelled by the enolate (a characteristic of a reaction having an early transition state), secondly, that the electrophile would approach the enolate from the peripheral (outside) face, and thirdly that the Z-enolate was generated exclusively.

---

Figure 26. (a) Ball and stick (from ref. 138) and (b) polar map representations of the X-ray structure of the p-BrC\(_6\)H\(_4\)SO\(_2\)- derivative of fluvirucin B\(_1\) 13.
Figure 27. The local conformation of the Z-enolate of macrocyclic lactones (from ref. 42 and 75).

The first two assumptions were considered reasonable since the incoming electrophile, methyl iodide, is small and reactive and the ring should have sufficient flexibility to minimize transannular effects during rehybridization. The third assumption is based on the exclusive formation of the Z-enolate upon kinetic deprotonation in acyclic esters\textsuperscript{139} and in 14-membered lactones.\textsuperscript{57} The predicted stereoselectivity in these alkylations compared favourably with the experimental results for the 14-membered ring and less so for the 16-membered ring, as summarized in Table 17.
Table 17. Observed and calculated stereoselectivity in the alkylation of 14- and 16-membered lactones 40 and 41.

<table>
<thead>
<tr>
<th>Lactones</th>
<th>Products</th>
<th>Calculated ratio</th>
<th>Observed ratio</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>112:113</td>
<td>9:1</td>
<td>13:1</td>
<td>57</td>
</tr>
<tr>
<td>41</td>
<td>114:115</td>
<td>24:1</td>
<td>4:1</td>
<td>11,75</td>
</tr>
</tbody>
</table>

2.9 Rationalization of the relative stereoselectivity in lactam alkylations

Based on the same assumptions used in the prediction of the stereoselectivity in lactone alkylations, an attempt to rationalize the stereoselectivity in the alkylation of the dianion of lactams 65-67 was developed based on the conformational analysis of the intermediate dianions. The enolate of the lactam (Figure 28) is assumed to have the
E geometry, having the same configuration with respect to the ring atoms as the Z-enolate of the lactone (Figure 27).

Figure 28. The local conformation of the E-enolate of macrocyclic lactams.

Molecular modelling of the E-enolates of lactams 65-67 was carried out using a Monte Carlo searching technique and the PRCG minimization method with the MM2* force field. A summary of the number of conformations found within 1, 2 and 3 kcal/mol of the global minima are shown in Table 18.

<table>
<thead>
<tr>
<th>( \Delta E ) (kcal/mol)</th>
<th>lactam 65</th>
<th>dianion of 65</th>
<th>lactam 66</th>
<th>dianion of 66</th>
<th>lactam 67</th>
<th>dianion of 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>18</td>
<td>28</td>
<td>12</td>
<td>74</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>&gt;166</td>
<td>81</td>
<td>40</td>
<td>&gt;100</td>
<td>56</td>
</tr>
</tbody>
</table>

In spite of the very large number of calculated conformations for each dianion, all of the enolate conformations within 3 kcal/mol of the global minimum conformation of the dianions of 65, 66 and 67 were found to have a similar local conformation of the
amide region, namely the E geometry with the methyl group as shown in X (Figure 29). The Y geometry was not found in any of the calculated conformations within 3 kcal/mol of the global minimum conformation.

![Figure 29. Local conformation of the E-enolate of macrocyclic lactams 65-67.]

Thus, the molecular modelling calculations for the alkylation of lactams 65-67 suggest that under kinetic conditions exclusive formation of the (R*,S*) product should occur in all three rings. The very high selectivity that occurred in the alkylation of the 13- and 14-membered ring lactams 65 and 66 correlates well with the calculations. This was not the case in the 16-membered ring lactam 67 (Table 6). The correlation between the experimental and calculated results was also poorer for the alkylation of the 16-membered lactone 41, as seen in Table 17.

The poorer correlation between the calculated and experimental results for the stereoselective alkylations of the 16-membered lactam 67 may be due to errors in the
two assumptions used in the model. Although the local geometry of the dianion of the lactam is expected to be quite rigid, the exclusive attack from the exo face of the enolate of this larger 16-membered ring may not be complete. The incoming nucleophile may be able to attack from the endo face of some of the conformations in which this face is more open. In the [4444] conformation the endo face is quite hindered since it is perpendicular to the plane of the ring. However in a few of the higher energy conformers, the endo face is not perpendicular to the plane of the ring and thus is more open to nucleophilic attack.

The second assumption that the E-enolate was formed exclusively may also fail here. The model of the enolates of the lactams suggests that the (R*,S*) product is obtained from the E-enolate, and the (S*,S*) product is obtained from the Z-enolate. The decrease stereoselectivity in the alkylation may result from a reduced stereoselectivity in the formation of the enolate.

The large solvent effect on the stereoselectivity of the alkylation of the benzyl lactam 68 noted in Table 7, indicates that there may be a solvent effect on the selectivity of enolate formation. Higher selectivity (5.7:1) was obtained when the reaction was run in hexane, a non-polar solvent, and the opposite selectivity (1:1.3) was obtained in DMSO, a more polar solvent. In a previous study by Ireland et al., these workers observed a similar solvent effect in the formation of the E and Z enolates of esters. For example, formation of the enolate of methyl butanoate (117) with LDA in THF followed by trapping with t-BuMe₂SiCl resulted in a 91:9 ratio of 118 to 119. Formation of the enolate of 117 with LDA in a THF-HMPA solution however gave a 16:84 ratio of 118 to 119. The increased polarity of the THF-HMPA solvent system resulted in the opposite stereoselectivity in enolate formation.
To model the formation of the E-and Z-enolates in our macrocyclic lactams, the calculated conformers of lactams 65-67 were reexamined. We assumed that the deprotonation of the lactams should involve the loss of the α-proton which has the C-H bond closest to being perpendicular to the carbonyl. Assuming that the E-enolate leads to the (R*,S*) lactam and that the Z-enolate leads to the (S*,S*) lactam, calculated values of 39:1, 9:1, and 4.5:1 were obtained for the (R*,S*) to (S*,S*) ratios of the 13-, 14- and 16-membered lactams 65-67, respectively. Although these values are all lower than the experimental results, the trend of diminishing stereoselectivity with increased ring size follows the actual experimental results for these lactams. This suggests that the reduced selectivity in the formation of the E-enolate may be the reason for the difference between the calculated and the observed stereoselectivities for the alkylations of lactams 65-67.

Table 19. Observed and calculate stereoselectivity in the alkylation of 13-, 14- and 16-membered lactams.

<table>
<thead>
<tr>
<th>Lactams</th>
<th>Products (R*,S*):(S*,S*)</th>
<th>Observed ratio</th>
<th>Calculated ratio based on exclusive Z enolate formation (R*,S*):(S*,S*)</th>
<th>Calculated ratio based on E:Z ratio (R*,S*):(S*,S*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>92:93</td>
<td>&gt; 99:1</td>
<td>1:0</td>
<td>39:1</td>
</tr>
<tr>
<td>66</td>
<td>94:95</td>
<td>62:1</td>
<td>1:0</td>
<td>9:1</td>
</tr>
<tr>
<td>67</td>
<td>96:97</td>
<td>10:1</td>
<td>1:0</td>
<td>4.5:1</td>
</tr>
</tbody>
</table>
Chapter III

Dynamic NMR Studies of Macrocyclic Amines and a Ketone

A series of dynamic NMR (DNMR) studies of 13-, 14- and 16-membered macrocyclic amines 120-122, N-methyl amines 123-125, N,N-dimethyl amines 126-128 and (2R*,12S*)-2,12-dimethylcyclooctadecanone (98) were carried out to further our understanding of the conformational properties of these macrocyclic rings.

The conformations, the relative thermodynamic populations and the dynamic processes (ring inversion, pseudorotation and local inversion)\(^{71}\) that occur in these macrocyclic rings were determined from the spectroscopic data. A combination of molecular mechanics calculations,\(^{129}\) entropy effects\(^ {54}\) and transition state theory\(^{141}\) was used to aid in the interpretation of the observed conformational effects in the dynamic NMR spectra.

The results of the \(^1\)H and \(^13\)C dynamic study of (2R*,12S*)-2,12-dimethylcyclooctadecanone (98) are presented first. The observations of the slowing of conformational processes in both the \(^1\)H and \(^13\)C dynamic spectra of ketone 98
simplified the interpretation of the dynamic effects. The understanding of the dynamic effects in (2R*,12S*)-2,12-dimethylcycloclododecanone (98) could be related to earlier data on macrocyclic ketones and aided the interpretation of the effects observed in the 1H DNMR spectra of the amines 120-128.

3.1 Dynamic study of (2R*,12S*)-2,12-dimethylcycloclododecanone (98)

It has previously been determined that in solution at low temperature the 13C NMR spectrum of unsubstituted cyclododecanone was consistent with the [3333]-2-one\(^\dagger\) conformation,\(^{142,143}\) which was also found in the solid state by X-ray crystallography.\(^{144}\) From the 1H and 13C dynamic NMR spectra of cyclododecanone-d\(_{16}\)-2,2,12,12-h\(_4\) Rawdah calculated that the low energy [3333]-2-one conformation has an energy barrier for ring inversion and pseudorotation of 7.5 kcal/mol.\(^{145}\) (2R*,12S*)-2,12-Di-

methylcycloclododecanone (98) was also found to have the square [3333]-2-one conformation in the solid state (Figure 15). The 1H and 13C DNMR spectra of 98 were studied to examine the effect of the (2R*,12S*)-dimethyl substitution on the conformation and the energy barrier to pseudorotation in the 12-membered ring.

The 13C DNMR spectra of 98 in a mixture of CHCl\(_2\)F and CHClF\(_2\) (4:1) are shown in Figure 30. The 13C spectrum at -50 °C contains seven signals, indicating that rapid pseudorotation and local inversions among populated conformations were occurring to produce the time averaged symmetry. The signal for the carbonyl was not observed. At -115 °C thirteen sharp signals are observed. The 13 signals are of similar height, indicating that a single non-pseudorotating unsymmetric conformation is present at low

\(\dagger\) In this conformational nomenclature the corner position nearest the ketone is labelled carbon one and the position of the ketone then follows.
temperature. The signals at 49.1 and 46.7 ppm are due to the carbons \( \alpha \) to the carbonyl in this conformation.

The analysis of the \(^{13}\text{C} \) spectrum at -95 °C is more complex due to line broadening and signal overlap. The spectrum seems to be a composition of overlapping \(^{13}\text{C} \) signals from the spectra observed at -50 °C and -115 °C. At -95 °C three \( \alpha \)-carbon signals 49.1, 48.0 and 46.7 ppm are observed in the ratios 1.5:1:1.5. This pattern indicates that both the symmetric and the non-pseudorotating unsymmetric conformations are populated in a 1:3 ratio and that interconversion between these two conformations has slowed.

Upon cooling below -95 °C the \( \alpha \)-carbon signals of the unsymmetric conformation at 49.1 and 46.7 ppm sharpen, and the \( \alpha \)-carbon signal at 48.0 ppm diminishes. Below -105 °C the \( \alpha \)-carbon signal at 48.0 ppm is no longer observed. This indicates that upon cooling the relative population of the symmetric conformation diminishes and is no longer populated below -105 °C.
Figure 30. $^{13}$C DNMR spectra (75 MHz) of (2R*,12S*)-2,12-dimethylcyclo- dodecanone (98).
The energy barrier for pseudorotation in the unsymmetric conformation was calculated from the difference in frequency between the two $^{13}$C $\alpha$-signals, $\Delta v = 180$ Hz at -115 °C, and the coalescence temperature of -85 °C to give $\Delta G^\ddagger = 8.6$ kcal/mol. The (R*,S*)-dimethyl substitution $\alpha$ to the carbonyl has increased the barrier to pseudorotation by ~1 kcal/mol compared to pseudorotation in the unsubstituted 12-membered ring ketone. The difference in energy between the symmetric and unsymmetric conformations was calculated to be 1.6 kcal/mol from the measured 1:3 ratio of the $^{13}$C $\alpha$-signals at -95 °C.

The $^1$H DNMR spectra of 98 are shown in Figure 31. The separation of the symmetric and the non-pseudorotating unsymmetric conformations is first observed in the $^1$H DNMR at -95 °C. Two signals at 1.98, 1.79 ppm and an upfield signal at 0.67 ppm from the non-pseudorotating unsymmetric conformation become evident. The signal at 2.1 ppm in the DNMR spectra is an impurity believed to be acetone.

The shift in the relative population of the symmetric and unsymmetric conformations observed in the $^{13}$C DNMR spectra is also observed in the $^1$H DNMR spectra upon cooling. The two signals at 1.98 and 1.79 ppm due to the hydrogens $\beta$ to the carbonyl and the upfield signal at 0.67 ppm of the unsymmetric conformation increase in intensity as the signal of the symmetric conformation at 1.61 ppm disappears. At -115 °C the relative integration of the $\beta$-proton signals to the $\alpha$-proton signals indicate that the signals at 1.98 and 1.79 ppm represent two of the four $\beta$-protons of the unsymmetric non-pseudorotating conformation. The other two $\beta$-proton signals are shifted upfield under the other methylene signals.
Figure 31. $^1$H DNMR spectra (300 MHz) of (2R*,12S*)-2,12-dimethyl-Cyclododecanone (98).
In contrast to the shifts observed for the β-proton signals, the separation of the α-proton signal of the unsymmetric and symmetric conformation was not observed at -95 °C. Overlap of the α-proton signals of the unsymmetric conformation with the signal from the symmetric conformation is believed to mask the separation. At -115 °C the population of the symmetric conformation decreases and the α-proton signals separate into two equally intense peaks at 3.03 and 2.89 ppm, assigned to a non-pseudorotating unsymmetric conformation.

The value of $\Delta G^\ddagger = 8.1$ kcal/mol was calculated from the $\Delta v = 42$ Hz for the separation of the α-protons at -115 °C and the coalescence temperature of -105 °C. This $\Delta G^\ddagger$ value calculated from the $^1$H shifts was found to be lower than the value obtained from the $^{13}$C spectrum. Errors in the determination of $\Delta G^\ddagger$ from the $^1$H DNMR spectra may result from an error in detection of the coalescence temperature due to overlap of the α-proton signals of the unsymmetric conformation with the signals of the symmetric conformation. Less significant errors may be introduced by neglect of the coupling of the α-proton to the methyl and β-protons. A value of $\Delta G^\ddagger = 8.6$ kcal/mol which is similar to the value calculated from the $^{13}$C DNMR spectra for example would be obtained using a coalescence temperature of -96 °C instead of -105 °C. Chemical substitution of the methyl and β-protons with deuterium would eliminate any error due to neglect of coupling, however signal overlap with the α-protons of the symmetric conformation would still be a problem.
3.1.1 Rationalization of the $^1$H and $^{13}$C chemical shifts in 98

Previously the chemical shifts in the $^{13}$C DNMR spectra of cyclododecanone$^{51}$ were found to be consistent with the [3333]-2-one conformation, the same conformation found in the X-ray crystal structure.$^{144}$ Although the structure of the unsymmetric conformation of 98 can not be definitively determined from the DNMR data, shielding effects of the carbonyl$^{81,147}$ and shielding effects due to steric compression between transannular hydrogens$^{148-151}$ can be used to correlate chemical shifts observed in the $^1$H and $^{13}$C DNMR spectra with the conformation of cyclic ketones in solution. The effects of anisotropy,$^{147,152,153}$ electric-field$^{154}$ and steric interactions$^{148,155,156}$ have been used to correlate $^1$H and $^{13}$C chemical shifts with conformation.$^{127,157-161}$

The shielding and deshielding areas around a carbonyl bond due to diamagnetic anisotropy is illustrated in Figure 32 for acetophenone.$^{81}$

![Figure 32](image)

Figure 32. Shielding (+) and deshielding (-) zones in acetophenone (from ref. 81).

The shielding effects resulting from steric compression of protons have been observed in a number of rigid compounds.$^{148}$ An example of this shielding effect is evident in the hindered cage systems, shown in Figure 33.$^{149}$ Steric compression repels the electron density from $H_b$ toward the carbon, deshielding $H_b$ and shielding $H_a$.$^{149}$ This effect was termed an "intramolecular van der Waals shift".$^{155}$
Although the macrocyclic rings are not rigid molecules, upon slowing ring inversion the non-bonded transannular hydrogen interactions result in chemical shift differences between the endo and exo protons and between the corner and non-corner carbons. For example, slowing pseudorotation in cyclododecane (33) at low temperature, leads to steric compression of the endo protons shown in Figure 34.\(^{51,73}\) As a result the endo protons are deshielded (1.39 ppm) and the exo protons are shielded (1.18 ppm).\(^{51,73,145}\) In addition, the non-corner carbons (A) in the [3333] conformation are shielded (21.8 ppm) relative to the corner carbons (B) (26.6 ppm) at -130 °C.\(^{51,145}\)

**Figure 33.** Deshielding effect due to van der Waals repulsion (from ref. 155).

**Figure 34.** 1,4-Gauche butane interactions and low temperature $^{13}$C chemical shift assignment in the [3333] conformation of cyclododecane (33).
The $^1$H and $^{13}$C chemical shifts expected in the [3333]-2-one conformation of 98 due to the proximity to the carbonyl and steric compression are consistent with the shifts observed in the DNMR spectra at -115 °C. Steric compression of the H$_2$-endo proton due to two gauche butane interactions between the H$_2$-endo proton with the H$_5$- and H$_3'$-endo protons shown in Figure 35, should result in a deshielding of the H$_2$-proton and a shielding of the C$_2$-methyl group. Following this proposal, the downfield $\alpha$-proton signal at 3.03 ppm was assigned to the H$_2$-endo proton while the signal at 2.89 ppm was assigned to the H$_2'$ proton. The upfield $\alpha$-carbon $^{13}$C signal at 46.7 ppm was assigned to the C$_2$ carbon while the signal at 49.1 ppm was assigned to C$_2'$. The upfield $^{13}$C signal at 18.5 ppm was assigned to the methyl group attached to the C$_2$ carbon and the signal at 24.4 ppm was assigned to the methyl group attached to C$_2'$. This separation of 2.4 ppm between the two $\alpha$-carbon signals is consistent with the [3333]-2-one conformation. This shift difference is similar to that observed between the corner and adjacent carbon signals (4.8 ppm) in the [3333] conformation of cyclododecane.$^{51}$

![Figure 35. 1,4-Gauche butane interactions in the [3333]-2-one conformation of 98.](image-url)
The peak width at half height of the proton signal at 3.03 ppm is approximately 38.8 Hz while that for the peak at 2.89 ppm is approximately 30.8 Hz. In the [3333]-2-one conformation the H_2'-proton would experience two small gauche couplings to the β-protons while the H_2-endo proton would experience a small gauche and a larger anti coupling.¹¹⁵ Correlation of the observed greater peak width for the downfield α-proton signal (3.03 ppm) with the larger vicinal couplings expected for the endo (non-corner) α-proton in the non-pseudorotating [3333]-2-one conformation supports the above chemical shift assignments.

The two downfield β-protons signals at 1.98 ppm and 1.79 ppm were assigned to the H_3'-endo proton and the H_3a corner proton in the [3333]-2-one conformation shown in Figure 35. H_3' is expected to be deshielded due to steric compression by two 1,4-gauche butane interactions. Although the corner H_3a proton does not experience steric compression, this proton is deshielded due to its proximity to the deshielding region of the carbonyl. The other two β-proton signals are under the methylene envelope.

The only other signal observed outside the large overlapping methylene envelope is an upfield signal at 0.67 ppm corresponding to a single proton. This signal was assigned to the H_4'-endo proton. Although this proton is deshielded by steric compression with the H_7-endo proton, it was assigned to the upfield signal since it lies directly in the shielding region of the carbonyl shown below in the [3333]-2-one conformation of 98.
These rationalizations of the observed chemical shifts supports the existence of the [3333]-2-one conformation, the conformation found in the solid state, as the conformation at low temperature in solution.

3.1.2 Modelling of the dynamic processes in 98

A model of the conformational and the dynamic processes in (2R*,12S*)-2,12-dimethylcyclooctadecane (98) comprised of molecular mechanics calculations and transition state theory was developed to compare with the above analysis of the DNMR spectra. The first step in the model was to carry out a Monte Carlo conformational search\textsuperscript{131} over the MM2* energy surface\textsuperscript{128} for the low energy conformers of 98 using the MACROMODEL program.\textsuperscript{132} The five lowest energy conformations and their relative energies are shown in Figure 36. The lowest energy conformation was found to be the [3333]-2-one conformer, identical to the X-ray crystal structure shown in Figure 15.
Figure 36. Five lowest energy (MM2*) conformers of \((2R^*,12S^*)\)-2,12-dimethyl-cyclododecanone (98).
The relative MM2* energies\textsuperscript{128} of these conformations, and their populations at various temperatures are listed in Table 20. The relative MM2* energies correlate with enthalpy differences. The concentration of each conformer was calculated from the Gibbs free energy ($\Delta G^0 = \Delta H^0 - T\Delta S^0$) which includes the enthalpy term from the MM2* calculations and an entropy factor which accounts for the entropy of symmetry and the entropy of mixing.\textsuperscript{54}

The inclusion of the entropy of mixing and the entropy of symmetry was used by Shannon et al. to improve the correlation between infrared data of cyclotetradecane and cyclohexadecane at various temperatures with the molecular mechanics calculations of the relative conformational populations.\textsuperscript{54} The entropy of mixing accounts for the increase in entropy for a chiral molecule by a factor of Rln(2) above that of an achiral molecule since the enantiomeric pair have degenerate energy levels.\textsuperscript{54} The entropy of symmetry is given by $\Delta S_{\text{sym}} = -R \ln \sigma$ where $\sigma$ is the symmetry number of the point group of the conformer.\textsuperscript{54} Conformations with higher symmetry have less entropy.

Table 20. The five lowest energy conformers of 98 found by molecular mechanics calculations.

<table>
<thead>
<tr>
<th>Conformer number</th>
<th>Ring Skeleton</th>
<th>MM2* Relative</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta H^0$</td>
<td>$\Delta S^0$</td>
<td>22 °C</td>
</tr>
<tr>
<td>1</td>
<td>[3333] 0 R ln2</td>
<td>43.8</td>
<td>56.1</td>
</tr>
<tr>
<td>2</td>
<td>[2343] 0.19 0</td>
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</tr>
<tr>
<td>4</td>
<td>[2334] 1.05 R ln2</td>
<td>7.2</td>
<td>5.2</td>
</tr>
<tr>
<td>5</td>
<td>[1344] 1.26 R ln2</td>
<td>5.1</td>
<td>3.2</td>
</tr>
</tbody>
</table>
The lowest energy conformation from the MM2* calculations was the unsymmetric [3333]-2-one conformer and the second lowest in energy was the [2343] conformation having a plane of symmetry. This agrees with the previous interpretation of the DNMR data for 98 that the [3333]-2-one conformation predominates at low temperature and at higher temperatures a symmetric conformation becomes significantly populated. The disappearance of the NMR signals from the symmetric conformation below -105 °C suggest that the energy difference between these two conformations is greater than the value calculated by MM2*.

3.1.3 Transition state model of the dynamic processes in 98

A qualitative transition state model to describe the shifts observed in the $^1$H and $^{13}$C DNMR spectra due to dynamic processes that occur among these low energy conformations was developed. This model was based on the mechanism proposed by Dale for pseudorotation in macrocyclic cycloalkanes.$^{141}$

From an analysis of the interconversions in the C$_9$-C$_{16}$ cycloalkanes, Dale proposed that the most favourable mechanism for conformational interconversions in macrocyclic rings involves a migration of a single corner position. He suggested that other mechanisms would require two or more coincidental changes to the ring, resulting in a large increase in the potential energy. The lowest energy pathway to effect a single corner movement occurs via a transition state having a single $0^\circ$ torsional angle. A series of multiple single corner movements are able to account for pseudorotational and ring inversion processes in cyclododecane. The [12334] transition state for the local inversion of the [3333] to the [2334] conformation is illustrated in Figure 37. In Dale's
notation for naming transition state conformations the first digit is underlined to distinguish these transition states from energy minima conformers.\textsuperscript{141}

\textbf{Figure 37.} Multiple corner movements (pseudorotation) in cyclododecane (33) (from ref. 141).

The five low energy conformations determined by molecular mechanics can be interconverted by single corner movements as illustrated in Scheme 12.
Scheme 12. Single corner movements among the five lowest energy conformations of (2R*,12S*)-2,12-dimethylcyclooctadecanone (98).

Based on Dale's single corner movement mechanism the interconversion of the unsymmetric lowest energy conformation 1 to the symmetric second lowest energy conformation 2 requires the molecule to pass through a transition state involving the movement of the corner methyl group, shown as transition B in Scheme 12 and illustrated as Y in Figure 38. The energy barrier for transition B is greater than the other transitions due to an increase in the steric repulsions as the methyl group passes through an eclipsed conformation with a hydrogen on the adjacent carbon.
The conformations in Scheme 12 may be classified into two sets. The first set is composed of the [3333] conformer 1 and both of the [2334] conformers 3 and 4. These conformations all have one methyl group at a corner and the other methyl group on a carbon adjacent to a corner. Interconversion among the conformations in this set may occur via a lower energy corner movement that involves only the eclipsing of hydrogens (transition state X in Figure 38). The second set is composed of conformers [2343] and [1343], 2 and 5 in Scheme 12, that have both methyl groups on the carbons adjacent to the corner carbons of the ring. Again interconversion of these two conformers may occur via a transition state that has only hydrogen-hydrogen eclipsing. However, interconversion between the two sets must occur via a transition state that has a methyl-hydrogen eclipsing (transition state Y in Figure 38) and hence is of higher energy.

In order for pseudorotational averaging of the NMR signals in the unsymmetric conformers to occur via single corner movements, the corner methyl group must move to an adjacent position and the adjacent methyl group must move to a corner position. These positional changes require passage through the same higher energy transition
state required for the interconversion between the unsymmetric and symmetric
conformations. Thus conformational model agrees with the observed simultaneous
slowing of pseudorotation in the unsymmetric conformations in the $^{13}$C spectrum at
-95°C and the interconversion between the unsymmetric and symmetric conformer sets.

The MM2* calculations indicate that at -95°C at least three of the lowest energy
conformations are significantly populated. The broad line shape of the $^{13}$C signals at
-95°C suggests that the peaks are a result of signals from multiple conformations in
which interconversion has begun to slow on the NMR time scale, however separation of
the signals has not occurred yet.

The energy difference between the two conformational sets was calculated from
the relative populations between set one containing conformers 1, 2 and 4, and set 2
containing conformers 2 and 5 at -95°C. The calculated value of $\Delta G^\circ = 1.8$ kcal/mol is
close to the measured value of $\Delta G^\circ = 1.6$ kcal/mol. Further separation of the $^{13}$C
signals on cooling is not observed since the populations of the higher energy
conformers in each set become less significant at lower temperatures.

In summary, the separation of signals, the sharpening of signals, and the loss of
signals observed in the $^{13}$C dynamic NMR spectra of 98 are all described by this model
consisting of molecular mechanics calculations, entropy effects and transition state
theory. The value of this model as an aid in the interpretation of dynamic processes in
macrocyclic rings is supported by the good qualitative and to a lesser extent quantitative
ability of the model to describe the dynamic processes and conformers in the DNMR of
$(2R^*,12S^*)$-2,12-dimethyl-cyclododecanone (98).
3.2 Dynamic NMR studies of amines 120-128

The DNMR studies of amines 120-128 were carried out to investigate the conformational properties of macrocyclic amines in solution. Previous analyses of the $^1$H DNMR spectra of in the 14- and 16-membered hydrocarbon rings was complicated by signal overlap.$^{51,52}$ The incorporation of a nitrogen atom into the ring shifts the signals for the $\alpha$- and $\beta$-protons downfield, out from under the methylene envelope. This shift was expected to contribute to a simplification of the dynamic NMR spectral analysis and facilitate the determination of both the relative thermodynamic populations of the low energy conformations, and the dynamic energy barriers for ring inversion, pseudorotation and local inversion$^{71}$ occurring in these macrocyclic rings.

The introduction of the nitrogen atom into the ring also provides an opportunity to prepare macrocyclic N-methyl cyclic amines and their quaternary ammonium salts. The DNMR spectra of these compounds was also investigated to study the effects of methyl and gem-dimethyl substituents on the conformational properties of these 14- and 16-membered heterocyclic rings.

3.2.1 Preparation of amines 120-128

The macrocyclic amines 120-122 were prepared by reduction of the corresponding unsubstituted lactams. The 13-membered ring lactam 88 was commercially available. The 14- and 16-membered ring lactams were prepared, from the macrocyclic ketones, as shown in Scheme 13.
Scheme 13. Syntheses of 14- and 16-membered lactams 131 and 133.

The preparation of amines 120-122, N-methyl amines 123-125, and iodo-N,N-dimethylamine salts 133-135 as well as the hydrochloride salts of 136-137 is illustrated in Scheme 14.

3.3 Dynamic NMR study of azacyclotetradecane (121)

$^{13}$C DNMR studies of cyclotetradecane showed that the 14-membered ring existed in the symmetric [3434] conformation in solution at -132 °C$^{51}$ and in the solid state at -98 °C.$^{162}$ An energy barrier to pseudorotation of $\Delta G^\ddagger = 7.3$ kcal/mol was determined from the $^{13}$C DNMR spectra in solution.$^{51}$ A similar value was estimated from the shifts in the $^1$H DNMR spectra. Line broadening of the proton signals occurred at -100 °C and separation at -120 °C, however analysis of the spectra was hindered by signal overlap and complexity.$^{51}$ The incorporation of a ketone into the fourteen membered ring affected both the conformations and the energy barriers observed by DNMR. The $^{13}$C DNMR spectra of cyclotetradecanone indicated that two conformations were present in a 3:2 ratio at -160 °C.$^{143}$ The energy barrier to their interconversion was estimated to be 5.9 kcal/mol.$^{143}$ DNMR studies of azacyclotetradecane were undertaken to determine the effect of the substitution of a nitrogen in the ring on the conformations and dynamic properties of the 14-membered ring.

The $^1$H DNMR spectra of azacyclotetradecane (121) in a mixture of CHCl$_2$F and CHCIF$_2$ (4:1) are shown in Figure 39. The proton spectrum at -50 °C contains 7 signals with ratios 4:4:4:4:8:2:1. At -70 °C, the line broadening suggests that conformational process have already begun to slow. The peak for the NH proton (0.80 ppm at -50 °C) is not observed upon cooling. The disappearance of the NH signal was previously observed in the DNMR studies of azacyclooctane (64), and is believed to be a result of line broadening caused by quadrapolar relaxation and a slower rate of proton exchange at low temperature.$^{72,163}$

At -90 °C a number of new signals are observed, a high field signal at 0.38 ppm and two additional signals due to the $\alpha$-protons at 1.88 and 2.60 ppm. These new
signals indicate that a number of conformational processes have slowed at this temperature.

At -130 °C, the two developing minor $\alpha$-peaks have both sharpened and increased in intensity and the major $\alpha$-peak has separated into two signals. These four peaks for the $\alpha$-hydrogens at 2.60, 2.36, 2.23 and 1.88 ppm have relative intensities of approximately 1:7:5:1.
Figure 39. The $^1$H DNMR spectra (500 MHz) of azacyclotetradecane (121) in a mixture of CHCl$_2$F and CHClF$_2$ (4:1).
3.3.1 Interpretation of the $^1$H DNMR spectra of 121 at low temperature

The pattern observed for the $\alpha$-proton signals at -130 °C was interpreted as resulting from the overlap of signals from a symmetric and an unsymmetric conformation. This analysis is illustrated in Figure 40. The peak at 2.23 ppm and an equally intense peak at 2.36 ppm are characteristic of $\alpha$-proton signals in the symmetric conformation shown in Figure 41 with slow ring inversion. The signal at 2.60 ppm, the remainder of the signal at 2.36 ppm and the peak at 1.88 ppm having relative intensities of 1:2:1 represent the four different $\alpha$-protons of an unsymmetric conformation in which the rate of ring inversion and pseudorotation have slowed on the NMR time scale.

![Symmetric and Unsymmetric Conformations](image)

**Figure 40.** Separation of the $\alpha$-proton NMR signals of 121 at -130 °C.

![Symmetric [3434] Conformer](image)

**Figure 41.** The symmetric [3434] conformer of azacyclotetradecane (121).
The high field signal at 0.38 ppm is the only other signal outside the broad methylene envelope from which further conformational information may be derived. The first observation of this signal at -90 °C coincides with the observed slowing of ring inversion, pseudorotation and conformational interconversion. The relative integration of this upfield signal at 0.38 ppm is equivalent to the sum of 1/2 of the signal at 2.23 ppm plus the signal at 2.60 ppm. This relative intensity suggests that the signal at 0.38 ppm represents one proton from the symmetric conformation plus one proton from the non-pseudorotating unsymmetric conformation.

The chemical shift of this proton was rationalized using a combination of shielding effects due to steric interactions and bond anisotropies. The integration of the high field signal indicates that the proton from the symmetric conformation (Figure 41) which contributes to the upfield signal results from one of the protons on the unique carbon in this conformation. Two transannular gauche butane interactions in this conformation are shown in Figure 42. These van der Waals repulsions would lead to an upfield shift for the 8-exo proton.

![Figure 42. Gauche butane interactions in the [3434] symmetric conformer of azacyclotetradecane (121).]
Steric compression alone can not account for the high field shift of the $H_8$-exo proton in the symmetric [3434] conformation since a number of other endo protons, such as the endo $H_5$ and $H_5'$ experience similar steric compression, yet their corresponding exo protons are not shielded to the same extent. A second effect must further shield the $H_8$-exo proton relative to the $H_5/H_5'$-exo protons in the symmetric [3434] conformation of azacyclotetradecane. The shielding effects of the magnetic anisotropy of C-C bonds are believed to account for the increase shielding of the $H_8$-exo proton.

Magnetic anisotropy in C-C bonds results in a deshielding cone along the C-C axis. In cyclohexane, illustrated in Figure 43, the $C_1$ equatorial proton lies in the deshielding region of the $C_2$-$C_3$ and $C_2'$-$C_3'$ bonds and the $C_1$ axial proton lies in the shielding region. The difference in chemical shift between the axial and equatorial protons $\delta_{ae}$ in cyclohexane was found to be 0.4-0.5 ppm. The geometry in cyclohexane is similar to that found in portions of 121.

![Deshielding of equatorial protons in cyclohexane due to C-C bond anisotropy (from ref. 81).](image)

**Figure 43.** Deshielding of equatorial protons in cyclohexane due to C-C bond anisotropy (from ref. 81).
In the symmetric [3434] conformation of azacyclotetradecane, shown in Figure 44, the H₈-exo proton is in an pseudo-axial position and is shielded by the anisotropic cones of the C₆'-C₇' and the C₆-C₇ bonds. In comparison the H₅'-exo proton in the symmetric [3434] conformer of 121 is in a pseudo-axial orientation relative to the C₃'-C₄' bond (shielded), however this proton is pseudo-equatorial relative to the C₆'-C₇' bond (deshielded). The two interactions counteract each other, resulting in a smaller shift upfield for the H₅'-exo proton compared to the H₈-exo proton in the symmetric [3434] conformation. The four exo protons on the 4, 4', 5 and 5' carbons were tentatively assigned to the signal at 0.78 ppm in the ¹H DNMR spectrum of azacyclotetradecane at -130 °C. The H₇-exo protons are not expected to be shifted upfield relative to the H₅-exo protons since the H₇-endo protons experience only a single transannular 1,4-gauche butane interaction.

Figure 44. The pseudo-axial orientation of the H₈-exo proton relative to the C₆'-C₇' bond (shielding) in the symmetric [3434] conformer of 121.

This rationalization of the upfield shift of the H₈-exo proton in the symmetric [3434] conformation of azacyclotetradecane is based on steric and C-C bond anisotropy arguments that do not involve the nitrogen. This suggests that a similar chemical shift
should occur in the low temperature $^1$H DNMR spectra of cyclotetradecane. Anet et al. determined from $^{13}$C DNMR studies that cyclotetradecane existed in the symmetric [3434] conformation in solution at -132 °C. Although the $^1$H NMR spectrum remained complex at -141 °C, an upfield peak was observed with an approximate ratio of 1:13 relative to the other signals. The ratio suggests that the high-field peak is due to the two exo protons on the carbons located in middle positions in the [3434] conformation of cyclotetradecane, as shown below. If other protons in the [3434] conformation were responsible for the upfield shift the integration of the peak would be in a 1:6 ratio, which is clearly not the case. The observation of the upfield chemical shift for the exo proton on the middle carbon in the [3434] conformation of cyclotetradecane supports the proposed steric and C-C bond anisotropy arguments used above to explain a similar upfield chemical shift in the symmetric conformation of azacyclotetradecane (121).

The contribution to the high field signal from the unsymmetric conformation of azacyclotetradecane (121) was rationalized in terms of steric and C-C bond anisotropy arguments as well. Unfortunately the observed chemical shifts do not provide definitive evidence as to which unsymmetric conformation is involved. One possible unsymmetric [3434] conformation, shown in Figure 45, was selected to illustrate how steric and C-C
anisotropy shielding effects may result in a single proton of a non-pseudorotating unsymmetric conformation might contribute to the high field signal at 0.42 ppm. Other possible unsymmetric conformations could contain similar unique protons.

In the unsymmetric [3434] conformation shown in Figure 45, the C7'-carbon is located at a "middle" position. The H7'-endo proton would experience three large transannular interactions resulting in shielding of the H7'-exo protons as well as two anisotropy shielding effects due to the C6'-C6' and C7'-C8 bonds.

Figure 45. A possible unsymmetric [3434] conformation of 121.

The observation of the high field signal integrating to one proton from the unsymmetric conformation supports the proposition that pseudorotation is frozen in the unsymmetric conformation at this temperature. If rapid pseudorotational averaging occurred a high field signal from the unsymmetric conformations would be unlikely since the H7'-exo proton at the middle position and the H7 proton on a corner carbon would have an average chemical shift which should be at lower field. Secondly, if the
high field signal was from a rapidly pseudorotating unsymmetric conformation then the upfield signal should integrate for two protons.

3.3.2 Measurement of the barriers to ring inversion and pseudorotation in 121

A Gibbs free energy difference between the major and minor conformations of 0.21 kcal/mol at -130 °C was calculated from the relative integration (1:2.1) between the unsymmetric and symmetric α-proton signals.

The slowing of the local inversion between the symmetric and unsymmetric conformations, as well as ring inversion in the symmetric conformation, and ring inversion and pseudorotation in the unsymmetric conformation are all first observed to occur at -90 °C. The difference in frequency of the α-protons in the symmetric conformation is $\Delta v = 65$ Hz at -130 °C. Using equations 3 and 4, a value of $\Delta G^\ddagger = 8.7$ kcal/mol was calculated for ring inversion in the symmetric conformation at -90 °C.

The energy barriers for ring inversion and pseudorotation were also estimated for the minor conformation. If pseudorotation and ring inversion in the minor conformation are independent of each other, a chemical shift tree illustrated in Scheme 15 can be drawn. The peak at 2.30 ppm represents the averaged signal for the α-protons of the minor conformation due to rapid ring inversion and pseudorotation distinct from that of the α-proton signals for the major conformation.
Scheme 15. Determination of the chemical shift separation of the $\alpha$–protons in azacyclotetradecane (121) caused by freezing of pseudorotation and ring inversion of an unsymmetric conformation.

A $\Delta G^\ddagger$ value of 8.4 kcal/mol at -90 °C was calculated for process 1 in the unsymmetric conformation using the $\Delta v$ of 180 Hz shown in Scheme 15 and a value of $\Delta G^\ddagger = 8.3 - 8.5$ kcal/mol at -90 °C was calculated using the two values for the $\Delta v$ of 120 and 240 Hz for process 2 shown in Scheme 15. However, we are unable to determine which of these two processes is ring inversion and which is pseudorotation from these data.

Equation 3, used to calculate the above energy barriers, is a simplification based on the assumption that the chemical exchange occurs between equally populated non-coupled nuclei. This is not the case for local inversion between the symmetric and unsymmetric conformations. However the energy barrier between the symmetric and unsymmetric conformers can be estimated as $\Delta G^\ddagger = 8.3 - 8.5$ kcal/mol from the observation that the coalescence temperature is the same for the symmetric and unsymmetric conformations. The $\Delta v$ difference for the two processes does not
significantly affect the calculation. The observation that the slowing of local inversion between the symmetric and unsymmetric conformations and that the slowing of pseudorotation in the unsymmetric conformation occur at the same temperature suggests that these two processes may share the same transition state.

The observation of two conformations at low temperature for azacyclotetradecane parallels the observation of two conformations for cyclotetradecanone. The energy barriers to ring inversion and pseudorotation in azacyclotetradecane were found to be 1.3-1.5 kcal/mol greater than the barrier to pseudorotation in cyclotetradecane, in contrast to the lower energy barriers for the same dynamic processes in cyclotetradecanone relative to cyclotetradecane.

3.3.3 $^{13}$C DNMR spectra of azacyclotetradecane (121)

The low solubility of 121 in CHCl$_2$:CHCIF$_2$ (4:1) at temperatures below -90 °C produced a poor signal to noise ratio in the $^{13}$C spectrum and thus prevented a direct comparison of the $^{13}$C DNMR and $^1$H DNMR spectra of 121. A number of alternative solvents were examined to overcome the solubility problem. An improvement in the $^{13}$C signal to noise ratio was obtained using a 1:3 mixture of d$_8$-toluene and CHCl$_2$F. The $^1$H and $^{13}$C DNMR spectra of azacyclotetradecane (121) in a 1:3 d$_8$-toluene:CHCl$_2$F mixture are shown in Figure 46 and 47, respectively.

The coalescence temperatures, general pattern in the $^1$H spectra and relative populations between the symmetric and unsymmetric conformation at low temperature obtained in the d$_8$-toluene:CHFCI$_2$ mixture are similar to the previous data in the CHFCI$_2$:CFCl$_3$ mixture. The $^{13}$C spectrum is significantly improved over the CHFCI$_2$:CFCl$_3$ spectrum as a result of the increased solubility of azacyclotetradecane in
d$_8$-toluene:CHFCl$_2$. There are some chemical shift differences in the $^1$H spectrum of azacyclotetradecane in Figure 46 due to the change in solvent. A greater overlap of the $\alpha$-proton signals of the symmetric conformer at -120 °C and a separation of the high field signals from the two conformations are observed.
Figure 46. $^1$H DNMR spectra (500 MHz) of azacyclotetradecane (121) in a mixture of d$_8$-toluene:CHCl$_2$F (1:3).
Figure 47. $^{13}$C DNMR spectra (125 MHz) of azacyclotetradecane (121) in a mixture of $d_8$-toluene:CHCl$_2$F (1:3).
Seven signals are observed for the $^{13}$C spectrum of 121 (Figure 47) in the d$_8$-toluene:CHFCl$_2$ solvent mixture at -50 °C. This spectrum is similar to that obtained in CDCl$_3$ at room temperature. The assignment of the room temperature spectrum in CDCl$_3$ is given in Scheme 16. The assignment of the $^{13}$C signals, for carbons 2, 3, 4 and 5 were determined from an HMBC experiment. The assignment of carbon 8 was based on the relative integration of the $^{13}$C peaks. The observed upfield shift of the γ-carbon to the nitrogen is believed to be a result of the effect of increased electronegativity on γ-carbon shielding.$^{167,168}$

![Diagram](image)

**Scheme 16.** Assignment of the $^{13}$C (125 MHz) of azacyclotetradecane (121) in CDCl$_3$ at room temperature.

Upon cooling below -70 °C the seven signals broaden into multiple envelopes of signals. Significant sharpening of these signals occurs at -110 °C due to a lowering of the populations of higher energy conformers, as previously observed in the dynamic $^{13}$C spectrum of (2R*,12S*)-2,12-dimethylcyclododecanone (98).
Three peaks are observed at -110 °C for the α-carbons, two equally intense signals at 46.3 and 40.0 ppm and a much larger peak at 45.5 ppm. The high field carbon signals have also sharpened, however the deconvolution of these signals into conformational sets is hampered by signal overlap, poor signal to noise, and the shifting of signals upfield under the large toluene signals.

The large $^{13}$C peak at 45.5 ppm for the α-carbons is consistent with the $^1$H data indicating that the major set of signals results from the symmetric [3434] conformation. The two minor signals for the α-carbons may result from a single unsymmetric conformation in which pseudorotation has slowed or from two equally populated unsymmetric conformations in which pseudorotation remains rapid. The large chemical shift difference between the two α-carbon signals of the minor conformation (6.3 ppm) is similar to the chemical shift difference between the adjacent carbon on the three bond side and the corner carbon in the non-pseudorotating [3434] conformation of the cyclotetradecane in solution at -130 °C$^{51,52}$ and in the solid state at -98 °C (Scheme 17).$^{162}$ The large $^{13}$C chemical shift range for the α-carbons in 121 thus indicates that pseudorotational averaging is frozen, supporting the previous proposal that the minor set of α-proton signals is a result of a single non-pseudorotating unsymmetric conformation.
It is interesting to note that although the exo protons on the middle carbons in the [3434] conformation of cyclotetradecane are at the highest field in the low temperature $^1$H DMR spectra, the $^{13}$C signal of this carbon is not the furthest upfield in the low temperature $^{13}$C DNR spectrum in solution or in the solid state. The adjacent carbons of the three bond side of the [3434] conformation are the highest field signals in the $^{13}$C spectrum of cyclotetradecane in the solid state$^{162}$ and in solution$^{52}$ at low temperature and hence experience the greatest shielding. These chemical shifts were rationalized using gauche and vicinal-gauche shielding effects. These effects were quantified by Cantow and coworkers from the $^{13}$C shifts observed between the anti and gauche conformations of methyl substituted n-butane and n-pentane derivatives at low temperature.$^{169,170}$
3.3.4 Molecular mechanics modelling of the conformations of azacyclotetradecane (121)

The above analysis of the experimental data provided a great deal of information about the number of conformations and the conformational processes that occur in 121. The structure of the unsymmetric conformer remains a question, which could not, however, be answered by the DNMR data. Molecular modelling of azacyclotetradecane was used to find possible low energy conformations.

A Monte Carlo search\textsuperscript{131} for the low energy conformations on the MM2$^*$ energy surface\textsuperscript{128} of azacyclotetradecane was carried out using the MACROMODEL program. The three lowest energy conformations are shown in Figure 48.

![Figure 48](image)

Figure 48. The three lowest energy conformations of azacyclotetradecane (121).

The nine lowest energy conformers and their relative populations at various temperatures are listed in Table 21. Higher energy conformations are not listed since their populations were considered to be insignificant at these temperatures.
Table 21. The nine lowest energy conformations of azacyclotetradecane (121).

<table>
<thead>
<tr>
<th>Conformer</th>
<th>MM2* $\Delta H^\circ$ (kcal/mol)</th>
<th>Relative $\Delta S^\circ$ (kcal/mol*K)</th>
<th>Concentration (%)</th>
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<td>47.5</td>
</tr>
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<td>121-B</td>
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</tr>
<tr>
<td>121-C</td>
<td>1.09</td>
<td>R ln2</td>
<td>14.9</td>
</tr>
<tr>
<td>121-D</td>
<td>1.41</td>
<td>R ln2</td>
<td>8.6</td>
</tr>
<tr>
<td>121-E</td>
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<td>3.7</td>
</tr>
<tr>
<td>121-F</td>
<td>1.90</td>
<td>R ln2</td>
<td>3.8</td>
</tr>
<tr>
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<td>1.98</td>
<td>R ln2</td>
<td>3.2</td>
</tr>
<tr>
<td>121-H</td>
<td>2.27</td>
<td>R ln2</td>
<td>2.0</td>
</tr>
<tr>
<td>121-I</td>
<td>2.41</td>
<td>R ln2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

These molecular mechanics calculations suggest 90% of azacyclotetradecane at -130 °C is in the symmetric [3434] conformation 121-A. This calculated value is higher than the measured ratio of 2.1:1 between the symmetric [3434] conformation 121-A and an unsymmetric conformation.

Two unsymmetric conformations are calculated to be close enough in energy to the symmetric global minimum conformation to be observed by NMR. They are the [3434] conformation 121-B and the [3344] conformation 121-C, illustrated in Figure 48. Both are 1.1 kcal/mol above the global minimum conformation 121-A. This calculation does not agree with the proposal from the dynamic NMR spectra that a single unsymmetric conformation exists at low temperature.

3.3.5 Chemical shift correlations in conformers 121-B and 121-C

The transannular steric interactions with the $\alpha$-protons of conformations 121-(A-C) are illustrated in Figure 49. In 121-C there is little change in the local environments of
the α-protons and carbons compared to the local environments of the α-protons and carbons in conformation 121-A. A small change due to the C-C anisotropic shielding effects on the protons should occur with this conformational change. The repulsion between the H2 and the H5-endo protons is slightly lower and the repulsion between the H2' and the H5'-endo protons is slightly greater in conformer 121-C relative to the interactions between the H5 and H2-endo protons in conformation 121-A. However, these interactions are not expected to result in the large observed chemical shift differences for the α-protons and carbon signals.

In contrast a significant difference in the local environments of the two α-carbons in conformation 121-B exists in comparison to the α-carbons in conformation 121-A. In conformation 121-A the H2-endo proton experiences one 1,4-gauche interaction with the endo proton on carbon 5. In the conformation 121-B the H2-endo proton experiences two 1,4-gauche interactions with the endo protons on carbons 5 and 3'. This should result in an increase in the shielding of C2 carbon and the attached H2-exo proton relative to the C2-carbon and H2-exo proton in conformation 121-A. Neither of the α-protons on the C2' corner atom in 121-B experience any transannular proton interactions. As a result the α-carbon in 121-A is expected to be more shielded than the corner carbon C2' in conformation 121-B. Based on these arguments the α-carbon signal at 40.0 ppm was assigned to the adjacent α-carbon and the signal at 46.9 was assigned to the corner α-carbon in the unsymmetric conformation 121-B. As discussed earlier the large chemical shift difference of 6.3 ppm observed is consistent with the chemical shift difference of 4.8 ppm for the carbon signals from the corresponding positions in the [3434] conformation of cyclotetradecane.
Figure 49. Transannular endo hydrogen-hydrogen interactions in the lowest energy conformers (A, B, C) of 121.

These chemical shift arguments can also be applied to the four $^1$H signals assigned to the $\alpha$-protons in the unsymmetric conformation. The signal at 1.88 ppm and one of the signals at 2.36 ppm can be assigned to the exo and endo protons on $C_2$ of conformer 121-B. The other signal at 2.36 ppm and the signal at 2.60 can be
assigned to the two protons on the corner C₂' carbon since these protons experience no transannular interactions. The different orientations of the two corner protons relative to the lone pair of the nitrogen are believed to result in the observed 0.24 ppm chemical shift difference for these two protons.\textsuperscript{127,161,171} A proton trans-coplanar to the lone pair of a nitrogen experiences an increased shielding of this magnitude.\textsuperscript{171} Although rapid nitrogen inversion of the lone pair may still occur, conformations with the lone pair exo to the ring are not highly populated. The signal at 2.36 ppm was assigned to the H₂' proton anti to the nitrogen lone pair and the signal at 2.60 to the H₂' proton gauche to the lone pair. Thus the chemical shifts observed in both the \textsuperscript{13}C and \textsuperscript{1}H spectra are more consistent with conformation 121-B than with conformation 121-C.

Although these chemical shift arguments for conformation 121-B are consistent with the observed \textsuperscript{1}H and \textsuperscript{13}C shifts for the minor unsymmetric conformation, this is not conclusive evidence. Other possible conformations may not be totally discounted at this time. For example, the chemical shift data may also be rationalized using the unsymmetric [3434] conformation, shown in Figure 45. The observed large upfield shift of one of the α-protons is actually more consistent with this conformer than with conformation 121-B. The H₂-exo proton in this conformation is located in the shielded "middle" position. A third steric interaction of the H₂-endo proton with the H₇' transannular hydrogen occurs in this conformation. This interaction may also account for the chemical shift of the H₇'-exo proton in the unsymmetric conformation upfield of the H₈-exo proton in the DNMR of azacyclotetradecane in d₈-toluene:CHFCl₂.
3.3.6 Model of the dynamic processes in azacyclotetradecane (121)

To further aid in the interpretation of the chemical shifts observed in the DNMR spectra, a model of the energy barriers for the ring inversion, pseudorotation and the local inversion processes in azacyclotetradecane was developed. This model was based on the same lowest energy single corner atom movement mechanism proposed by Dale for the interconversions of large ring cycloalkanes.\textsuperscript{141}

A web of [3434], [3344] and [3335] conformations of azacyclotetradecane (121) which interconvert via multiple single corner atom movements is illustrated in Scheme 18 and outlines possible conformational pathways to effect local inversion, pseudorotation and ring inversion.
Mirror Image Conformations

Scheme 18. Single corner movements in azacyclotetradecane (121).
Each of the single corner movements represents a local inversion.

Pseudorotational averaging of the conformations shown in Scheme 18 may occur via C$_2$- or C$_s$-pseudorotation. The distinction between these two types of pseudorotation is illustrated in Scheme 19 for conformation 121-B. C$_2$- pseudorotation occurs via a pathway of multiple single corner atom movements through either of the [3344] conformations Y or Z. Rapid C$_2$-pseudorotation interconverts the protons labeled H$_1$ with H$_2'$ and H$_2$ with H$_1'$ in Scheme 19. C$_s$-pseudorotation occurs via the movement through either the [3335] conformers N or M, or the symmetric [3434] conformation 121-A. Rapid C$_s$-pseudorotation exchanges H$_1$ with H$_1'$ and H$_2$ with H$_2'$. Averaging of the geminal proton NMR signals due to ring inversion (H$_1$=H$_2$, H$_1'$=H$_2'$) occurs only if both C$_2$- and C$_s$-pseudorotation occur rapidly.

Scheme 19. Effects of the C$_2$- and C$_s$-pseudorotations on the α-protons of the [3434] conformation 121-B of azacyclotetradecane (121).
The transition states which interconvert the \([3434]\) with the \([3344]\) conformer and the \([3344]\) with the \([3335]\) conformer of cyclotetradecane (31) were described by Dale as \([13343]\) and the \([13334]\), respectively.\(^{141}\) These transition states have a single torsional angle of \(0^\circ\) and are illustrated in Scheme 20.

![Scheme 20. Interconversion in cyclotetradecane via the \([13343]\) and the \([13334]\) transition states (from ref. 141)](image)

The incorporation of the nitrogen in the cyclotetradecane ring framework complicates the transition state analysis. Based on Dale's mechanism there are 14 possible \([13343]\) transition states and 14 possible \([13334]\) transition states. The interconversions through one of these transition states represent one of the local inversions between the conformations illustrated in Scheme 18.

A search for the structure and relative energies of the fourteen possible \([13343]\) and the fourteen \([13334]\) transition states structures which interconvert the conformations of azacyclotetradecane described by the web was undertaken using
MACROMODEL following a previous methodology developed by Anet\textsuperscript{51} for the study of the transition states in cyclododecane. The transition state pathway between two conformers representing a single bond movement was mapped out via 5° incremental torsional movements of a gauche corner bond through the eclipsed state to a gauche bond of the opposite sign. After each incremental torsional movement the structure was minimized on the MM2* surface. Mapping of the saddle points on the MM2* energy surface between the two conformations was carried out by this incremental bond movement method in both directions. The energy values shown on the conformational web in Scheme 18 each represent the energy of the transition state structure ($\Delta G^\ddagger$) occurring at the saddle point on the MM2* energy surface between the two conformations. These values are relative to the energy of the global minimum conformation 121-A.

Evaluation of the transition state energies required to effect ring inversion in the [3434] conformer 121-A (C\textsubscript{2}-pseudorotation) on Scheme 18 indicates that two distinct steps are involved. These two steps are designated by the lines drawn across Scheme 18 and involve the movement of the nitrogen atom. The transition states between the conformations shown in Scheme 18 may be classified into three sets. The first set is comprised of transition states in which the four ring atoms of the single 0° torsional angle occurring during a corner atom movement are all carbon atoms, as illustrated in Figure 50 as transition X. The second set is comprised of transition states in which the nitrogen is a non-central atom of the 0° torsional angle, transition Y. These transition states represent the movement of the nitrogen from a middle (β to a corner position) to a position adjacent to a corner. The final set is comprised of transition states in which the nitrogen is one of the central atoms of the 0° torsional angle, transition Z. These
transition states represent the movement of the nitrogen atom from a position adjacent to a corner position.

![Chemical structures](image)

**Figure 50.** Single corner movement transition states in azacyclotetradecane (121).

The Y transition states were found to have energy values of 9 - 10 kcal/mol except for the transition state between conformer 121-C and conformer M (Scheme 18). The Z transition states were found to have energy values of 11 - 12 kcal/mol. The increase in the transition state energies involving the movement of nitrogen can not be attributed to a difference in the C-N and C-C rotational energy barriers. The rotational barriers about sp\(^3\)-sp\(^3\) carbon-carbon single bonds and that about carbon-nitrogen single bonds are similar in energy. For example the torsional barriers of propane and dimethyl amine are 3.3 kcal/mol\(^{172,173}\) and 3.28 kcal/mol\(^{174}\), respectively. In substituted n-butanes the rotational barrier of the C-N bond was actually found to be lower than the C-C bond. 2-Dimethyl-3-methyl-butane has a rotational barrier of 6.9 kcal/mol at -134 °C\(^{175}\) and the corresponding barrier in t-butyl dimethyl amine has a value of 6.0 kcal/mol at -153 °C.\(^{176}\)

The energies of the X transition states were found to be dependent on the position of the nitrogen in the ring. The X transition states in which the nitrogen is located at a middle position have energy values of 7 - 8 kcal/mol, the X transition states in which the nitrogen is located at an adjacent position have energy values similar to that of Y
transition states (9 - 10 kcal/mol) and the X transition states in which the nitrogen is located at a corner position have energy values similar to those of Z transition states (10 - 11 kcal/mol). This relationship indicates that the increase in energy of the transition states as the nitrogen moves from the middle to the adjacent position and then to the corner position is a reflection of the increased energy of the ground state conformations which is due to greater transannular strain. When the nitrogen is located at a middle position as in the conformer 121-A shown in Figure 45, there is a maximum reduction of hydrogen interactions in the [3434] conformation, two gauche and one 1,8 transannular interactions, as illustrated in Figure 6 of Section 1.6. When the lone pair is located at an adjacent position as in conformer 121-B a reduction of two gauche interactions occurs and when the lone pair is located in the corner position as in conformer 121-C there is no reduction of transannular hydrogen interactions.

The interconversion of conformations 121-A and 121-B has a calculated energy barrier of 9.4 kcal/mol. C₅-pseudorotation in conformer 121-B and local inversion between 121-B and the symmetric conformation 121-A have the same transition state in the conformational web. The observation that both these processes are frozen out at the same temperature agrees with the single corner movement mechanism. This also supports the previous proposal that the energy barrier between the major and minor conformations is the same as the energy barrier for pseudorotation in the minor unsymmetric conformation (8.2 - 8.5 kcal/mol).

The measured barrier to ring inversion in the unsymmetric 121-B (8.7 kcal/mol) was found to be lower than the energy to ring inversion in conformation 121-A (8.2-8.5 kcal/mol) by approximately the value of the difference in energy (0.21 kcal/mol) between the two conformations. This agrees with the indication from the conformational
web in Scheme 18 that $C_2$-pseudorotation in conformations 121-A and 121-B occurs via the same limiting transition state.

According to the calculated transition state energies on the conformational web, the slowing of ring inversion ($\Delta G^\dagger = 10.8$ kcal/mol) should be observed prior to the slowing of local inversion ($\Delta G^\dagger = 9.4$ kcal/mol) between the major and minor conformations. The slowing of these two processes was observed to occur at the same temperature, suggesting that the value calculated for ring inversion may be high. The measured values for ring inversion in the symmetric and unsymmetric conformations may also be low. As was previously observed in the DNMR spectra of $(2R^*,12S^*)$-2,12-dimethylcyclododecane, the energy barrier to ring inversion in the $^1$H spectra was determined to be 0.5 kcal/mol lower than the value determined from the $^{13}$C spectrum. It was suggested that this was a result of signal overlap due to rapid $C_s$-pseudorotation and local inversion among the populated conformations, and to proton coupling. Both these processes may also have an affect on the measurement of the coalescence temperature in the $^1$H DNMR spectra of azacyclotetradecane.

Although the calculated values for ring inversion and pseudorotation are 1 to 2.1 kcal/mol above the experimental values, the trends observed in this model provide a reasonable and consistent description of the conformations and the processes that occur in the DNMR of azacyclotetradecane (121). The model also illustrates some of the complexity and potential errors in the analysis of DNMR spectra involving multiconformational systems.
3.4 The $^1$H DNMR study of N-methylazacyclotetradecane (124)

The $^1$H DNMR spectra of N-methylazacyclotetradecane (124) in d$_4$-methanol:CHCl$_2$F (1:4), shown in Figure 51, was investigated to study the effects of the substitution of the N-methyl group on the conformations and the dynamic processes that occur in the 14-membered ring.

At -70 °C N-methylazacyclotetradecane (124) was observed to undergo rapid local inversion, pseudorotation and ring inversion. The four $\alpha$-protons are averaged to a single peak at 2.50 ppm. The N-methyl signal is at 2.27 ppm and the remaining protons on the ring form a large methylene envelope of overlapping signals.

At -110 °C the N-methyl peak has separated into three unequal signals at 2.30, 2.18, and 2.04 ppm. The presence of these three peaks indicates that three non-interconverting conformations exist in the spectra of N-methylazacyclotetradecane (124) at low temperature.
Figure 51. The $^1$H DNMR spectra (500 MHz) of N-methylazacyclotetradecane (124) in a mixture of $d_4$-methanol:CHCl$_2$F (1:4).
The presence of two of these three conformations is also evident in the pattern observed for the $\alpha$-protons. Two sets of $\alpha$-proton signals are observed, three smaller signals of equal intensity at 3.04, 2.98 and 2.81 ppm and a larger signal at 2.55 ppm. Integration indicated that an $\alpha$-proton signal equal in intensity to the peak at 2.55 ppm and a signal equal in intensity to the peak at 2.81 ppm overlap with the N-methyl peaks.

The lineshape of the signal at 2.30 ppm suggests that the downfield shoulder is the overlapping upfield $\alpha$-proton signal equal in intensity to the peak at 2.55 ppm. The ratio of the signal at 2.55 ppm with the peak at 2.30 ppm is 2:5. Accounting for the integration of the overlapping $\alpha$-proton signal, the N-methyl signal at 2.30 ppm is in a 3:2 ratio with the peak at 2.55 ppm. These integrations indicate the shoulder and the peak at 2.55 ppm each represent two protons of the major conformation, as expected for a symmetric conformation. The 1:3 ratios of each of the minor set of $\alpha$-protons signals to the N-methyl signal at 2.18 ppm suggest that these peaks each represent a single proton in an unsymmetric conformation in which pseudorotation has slowed. Thus the pattern and relative integrations of the $\alpha$-proton signals suggests that a major symmetric conformation and a minor non-pseudorotation unsymmetric conformation are present at -110 °C, similar to the conformations proposed to be present in the low temperature spectrum of azacyclotetradecane.

The proposal that two conformations of 124 exist at -110 °C is further supported by the relative integration of the upfield signal at 0.66 ppm. This signal is equal to 1/2 the signal at 2.55 ppm plus the signal at 2.81 ppm. Thus the signal at 0.66 ppm represents one proton of the symmetric conformer and one proton of the non-pseudorotating unsymmetric conformation, as was previously observed in the DNMR spectrum of azacyclotetradecane (121).
The relative ratio of the major and minor conformations was best determined from the ratio of the integrations of the peaks at 3.04 and 2.98 ppm for the minor conformation with that of the signal at 2.55 ppm for the major conformer, since these signals have the least overlap with other peaks. This relative ratio is 2:1 and corresponds to a $\Delta G^\circ = 0.30$ kcal/mol at -110 °C for the two conformers.

The two signals for the symmetric conformation at 2.55 ppm and the shoulder at 2.38 ppm ($\Delta v = 85$ Hz) at -110 °C were observed to separate at -90 °C. The energy barrier to ring inversion for the symmetric conformer was calculated using equations 3 and 4 as $\Delta G^\ddagger = 8.6$ kcal/mol at the coalescence temperature of -90 °C.

The determination of the energy barriers in the unsymmetric conformation is difficult due to signal overlap. A chemical shift diagram similar to Scheme 15 for azacyclotetradecane (121) cannot be drawn since only three of the four $\alpha$-proton signals are observed. The signals for the unsymmetric conformation were first observed at -90 °C. The developing broad signal at 2.88 ppm is the first indication that slowing of the interconversion between the major and the minor conformations has occurred. The separation of this signal into two signals at 3.01 and 2.83 ppm in a 2:1 ratio at -100 °C indicates that ring inversion in the minor conformation has slowed. The relative integration of these signals indicates that pseudorotation has slowed since the fourth signal for the unsymmetric conformation has shifted upfield at this temperature. Upon cooling the signals sharpen and the larger downfield signal separates into two signals at 3.04 and 2.98 ppm at -110 °C. The barrier to ring inversion in the minor conformation was estimated as $\Delta G^\ddagger = 8.4$ kcal/mol at -95 °C. This value was calculated using equations 3 and 4 from the separation of the two signals at 3.01 and 2.83 ppm at -110 °C ($\Delta v = 90$) and the coalescence of these signals observed at -95 °C. The barrier
to $C_s$-pseudorotation in the unsymmetric conformation was determined to be
$\Delta G^\ddagger = 8.2$ kcal/mol from the separation of the two signals at 3.04 and 2.98 ppm and the
observed coalescence of these signals at -105 °C.

Comparison of the $^1$H DNMR spectra of N-methylazacyclotetradecane (124) and
azacyclotetradecane (121) shows that N-methylation does not greatly affect the
conformations nor the energy barriers between these conformations. The relative
populations of the symmetric and unsymmetric conformation of azacyclotetradecane
(121) and N-methylazacyclotetradecane (124) were both observed to be 2:1. The
barrier to ring inversion between the symmetric conformations was found to be
8.6 - 8.7 kcal/mol at -90 °C in both compounds and the energy barriers to $C_s$- and
$C_2$-pseudorotation in the unsymmetric conformations were determined to be similar as
well (8.2 - 8.5 kcal/mol). The torsional barrier in trimethylamine was found to be
1.1 kcal/mol greater than the torsional barrier in dimethylamine.$^{177,178}$ Thus the
increased torsional barrier of the C-N bond due to the substitution of the methyl group
does not seem to affect the energy barrier to ring inversion. This suggests that the
influence of the transannular interactions on the transition states in
azacyclotetradecane (121) is greater than any increased rotational barrier about the
C-N bond in 124.

3.4.1 Molecular modelling of the low energy conformations of 124

A Monte-Carlo search of the MM2* energy surface found three conformations to
be significantly populated at low temperature, consistent with the observation of three
conformations in the low temperature NMR spectra of
N-methylazacyclotetradecane (124). These three low energy conformations shown in
Figure 52 were found to have the same ring skeleton as the low energy conformer of the unsubstituted azacyclotetradecane (121).

![Diagram of conformers](image)

**Figure 52.** The three lowest energy conformations of N-methylazacyclotetradecane (124).

The eight lowest energy conformations along with their relative populations at various temperatures are listed in Table 22.

**Table 22.** The eight lowest energy conformers of N-methylazacyclotetradecane (124).

<table>
<thead>
<tr>
<th>Conformer</th>
<th>MM2*</th>
<th>Relative</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ H°</td>
<td>Δ S°</td>
<td>20 °C</td>
</tr>
<tr>
<td>124-A</td>
<td>0.0</td>
<td>0</td>
<td>24.1</td>
</tr>
<tr>
<td>124-B</td>
<td>0.1</td>
<td>R ln2</td>
<td>42.2</td>
</tr>
<tr>
<td>124-C</td>
<td>0.7</td>
<td>R ln2</td>
<td>15.6</td>
</tr>
<tr>
<td>124-D</td>
<td>1.0</td>
<td>R ln2</td>
<td>9.3</td>
</tr>
<tr>
<td>124-E</td>
<td>1.4</td>
<td>R ln2</td>
<td>4.4</td>
</tr>
<tr>
<td>124-F</td>
<td>1.8</td>
<td>R ln2</td>
<td>2.3</td>
</tr>
<tr>
<td>124-G</td>
<td>2.1</td>
<td>R ln2</td>
<td>1.3</td>
</tr>
<tr>
<td>124-H</td>
<td>2.3</td>
<td>R ln2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

The MM2 calculation of three significantly populated conformations agrees with the observation of three N-methyl signals below -110 °C. However the calculated
populations do not agree with the observed relative ratios of the conformers in the \( ^1\)H NMR. The symmetric conformer 124-A was the major observed conformation. The MM2* calculations suggested that this conformation is the global minimum conformer. However, upon addition of the entropy factors the relative population of the unsymmetric conformer 124-B was calculated to be greater. This inconsistency suggests that the calculated \( \Delta H^\circ \) difference may be too small or the entropy factor too large in these calculations.

The \( ^1\)H chemical shifts observed for the \( \alpha \)-proton signals of the minor conformation are consistent with the shifts expected for conformer 124-B upon slowing of ring inversion and pseudorotation. The assignment of the \( \alpha \)-proton signals of the unsymmetric conformation was based on the same steric compression arguments discussed for the shifts in conformer 121-B of azacyclotetradecane. The \( H_2 \)-endo proton was assigned to the signal at 2.98 ppm and the \( H_2 \)-exo proton was assigned to the upfield signal of the unsymmetric conformation hidden under the N-methyl peaks due to the steric compression effects of the two 1,4-gauche interactions. The two corner \( \alpha \)-protons were assigned to the signals at 3.04 and 2.81 ppm. The chemical shift difference (0.23 ppm) between the two corner protons results from additional shielding of the corner proton which is anti to the nitrogen lone pair.
The upfield shift of the N-methyl signal of the minor conformation 124-B relative to the major conformation 124-A can not be explained by the transannular steric compression and C-C bond anisotropy shielding arguments. For azacyclotetradecane (121) the exo hydrogen at the middle position of the symmetric conformer 121-A was upfield of the exo hydrogens in adjacent positions. This would suggest that the N-methyl group in the symmetric conformation 124-A should be upfield of the N-methyl group in the unsymmetric conformation 124-B, but this is not the case. 1,3-Diaxial interactions between the methyl and hydrogen can deshield the N-methyl signals due to steric compression. The N-methyl group in 124-A experiences two such 1,3 diaxial H-CH$_3$ interactions and hence its signal is expected to be downfield of that of the N-methyl group in the 124-B conformation which experiences only one such interaction (Figure 53).

![Figure 53](image)

**Figure 53.** 1,3 H-CH$_3$ diaxial interactions in the conformations 124-A and 124-B of N-methylazacyclotetradecane (124).
3.5 X-ray structure and $^1$H DNMR study of N,N-dimethyltrideca-1,13-diylammonium iodide (127)

In conformational studies of the fourteen membered rings, Dale proposed that a gem-dimethyl group should occupy a corner position of the [3434] skeleton. The determination of the X-ray crystal structure of N,N-dimethyltrideca-1,13-diylammonium iodide (127), shown in Figure 54, showed that Dale's predicted low energy structure exists in the solid state.

![Figure 54. The X-ray crystal structure of N,N-dimethyltrideca-1,13-diylammonium iodide (127).](image)

The $^1$H DNMR of the N,N-dimethyltrideca-1,13-diylammonium iodide (127) in $d_4$-methanol, shown in Figure 55, reveals that the gem dimethyl group greatly increases the energy barrier to ring inversion relative to the barrier in azacyclotetradecane (121).
and N-methylazacyclotetradecane (124). At room temperature the proton spectrum of N,N-dimethyltrideca-1,13-diylammonium iodide (127) consists of six signals at 3.35, 3.14, 1.66, 1.49, 1.46, and 1.38 ppm in the ratios 4:6:4:8:2:8. Separation of the α-signal at 3.35 ppm was first observed below -48 °C. Upon cooling to -68 °C the signal for the four α-protons at 3.35 ppm separated into two signals 145 Hz apart, with relative intensities of 1:1. This Δν corresponds to an energy barrier for ring inversion of 10.5 kcal/mol at the coalescence temperature of -48 °C.
Figure 55. The $^1$H DNMR spectra (500 MHz) of N,N-dimethyltrideca-1,13-diylammonium iodide (127) in $d_4$-methanol.
The slowing of the ring inversion is also marked by the separation of the
β-protons, and the appearance of two peaks upfield from the methylene envelope. The
relative intensities of each of the two α-signals at 3.54 and 3.25 ppm, each of the two
β-signals at 1.72 and 1.61 ppm and each of the two upfield signals at 1.27 and 1.10
ppm corresponds to two equivalent protons of a single conformation. This indicates that
pseudorotation is rapid at -68 °C. The low solubility of the iodo salt below this
temperature prevented studies at lower temperatures where pseudorotation might be
frozen out.

3.5.1 Molecular mechanics calculations of 127

The five lowest energy conformations of 127 found by MM2* calculations are listed
in Table 23. Conformation 127-A, the global minimum conformation, was also predicted
by Dale’s model to be the lowest energy conformation. In addition this was the
conformation found in the solid state by X-ray crystallography.

Table 23. The five lowest energy conformations of 127.

<table>
<thead>
<tr>
<th>Conformers</th>
<th>MM2* Δ H° kcal/mol</th>
<th>Relative Δ S° kcal/mol*K</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>127-A</td>
<td>0.00</td>
<td>0</td>
<td>53.3</td>
</tr>
<tr>
<td>127-B</td>
<td>0.95</td>
<td>R ln2</td>
<td>21.1</td>
</tr>
<tr>
<td>127-C</td>
<td>0.99</td>
<td>R ln2</td>
<td>19.7</td>
</tr>
<tr>
<td>127-D</td>
<td>2.03</td>
<td>R ln2</td>
<td>3.3</td>
</tr>
<tr>
<td>127-E</td>
<td>2.20</td>
<td>R ln2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

In order for C₅-pseudorotational averaging of the protons in conformation 127-A
via the single bond movement mechanism to occur, a low energy pathway similar to
that described in the conformational web for azacyclotetradecane (Scheme 18) must
exist. The intermediates in this movement require one of the methyl groups to occupy an endo position when the nitrogen shifts from the corner position. The large increase in transannular strain during such a transition would account for the increase in the energy barrier to ring inversion.\textsuperscript{71,141}

Continued rapid C\textsubscript{2}-pseudorotation in 127 may occur via two single corner movement local inversions not involving the movement of the nitrogen atom from the corner position as shown in Figure 56. The observation of the single sharp peak at 3.14 ppm for the geminal N,N-dimethyl group at temperatures below -48 °C at which geminal averaging of the \(\alpha\)- and \(\beta\)-protons has slowed is consistent with this mechanism. In the two intermediate [3344] structures of the C\textsubscript{2}-pseudorotation of conformation 127-A, the geminal methyl groups are averaged even though the geminal \(\alpha\)- and \(\beta\)-protons are no longer averaged.

![Figure 56. C\textsubscript{2}-Pseudorotation in conformation 127.](image)
The second, third and fourth low energy conformations are all able to interconvert with conformation 127-A via a single corner movement in which the nitrogen atom remains at the corner position. These conformations 127-B to 127-D may exist and contribute to the averaged NMR signals. The energy barrier for these local inversions is expected to be similar to the energy barrier of 7.3 kcal/mol for the pseudorotation in cyclotetradecane (31). In theory, a transition barrier of this energy could be measured upon cooling; however below -68 °C the N,N-dimethyltrideca-1,13-diylammonium iodide (127) precipitates out of the methanol solution.

3.6 Dynamic NMR study of azacyclohexadecane (122)

In a previous 1H DNMR study of cyclohexadecane (32), the conformation and dynamic processes could not be evaluated from the 1H spectra. Line broadening of the signal occurred at temperatures below -100 °C indicating that conformational processes had slowed at this temperature; however clear separation of the signals did not occur. The slowing of pseudorotation was observed in the 13C DNMR. An energy barrier for pseudorotation of 6.7±0.2 kcal/mol at the coalescence temperature of -124 °C was determined from the 13C DNMR spectra of cyclohexadecane-1-13C. The 1H DNMR spectra of azacyclohexadecane (122) were investigated in order to determine the conformations and conformational processes that occur in the 16-membered nitrogen-containing ring. The incorporation of the nitrogen into the 16-membered ring is expected to raise the conformational energy barriers in the ring and to provide sufficient increase in chemical shift differences to aid in the detection and identification of the conformational processes by 1H DNMR.
A series of low temperature $^1$H NMR spectra of azacyclohexadecane (122) in a 1:3 mixture of d$_4$-methanol and CHCl$_2$F are presented in Figure 57. At -70 °C the $\alpha$- and $\beta$-proton signals are found at 2.61 ppm and 1.55 ppm, respectively. The remaining proton signals form a large overlapping envelope between 1.4 and 1.15 ppm. Little change to the spectrum is observed until below -100 °C. Separation of the $\alpha$-signals was first observed at -110 °C. At -120 °C the $\alpha$-proton signal has divided into a sharper peak 2.55 ppm and a broad signal at 2.67 ppm having a shoulder at 2.77 ppm. The signal at 2.67 ppm including the shoulder and peak at 2.55 ppm are in a 2.4:1 ratio.

The relative integration and the pattern of the $\alpha$-proton signals indicates that two conformations are present, a major symmetric conformation associated with the signal at 2.55 ppm and part of the signal at 2.67 ppm, and a minor conformation associated with the remainder of the signal at 2.67 and the shoulder at 2.77 ppm. The two conformations are in a 2:1.4 ratio. If pseudorotation in the minor conformation was frozen out, the $\alpha$-proton signals at 2.77 ppm would be expected to have separated into additional peaks as was observed in the 14-membered ring analog 121. Since this was not observed, pseudorotation in the minor conformation of 122 must be rapid even at -120 °C.

A $\beta$-proton signal is observed at 1.85 ppm. Because the integration of this signal is too small for it to come from the major symmetric conformation it is assigned to the minor conformation. The integration of this $\beta$-proton signal at 1.85 ppm is in a 1:4 ratio with the integration of the $\alpha$-signals of the minor conformation. There are two possibilities for this observation.

First, the signal at 1.85 ppm may represent two $\beta$-protons of a minor conformation that continues to undergo rapid pseudorotation. This explanation suggests that the
α-proton signals are a result of three conformations, a major symmetric conformation and two equivalent rapidly pseudorotating minor conformations in a 1:1 ratio.

A second explanation for the relative integration of the signal at 1.85 ppm may be that this signal represents a single β-proton of the minor conformation in which pseudorotation has slowed. This would contradict the above proposal that pseudorotation remains rapid in the unsymmetric conformation based on the absence of chemical shift separation in the α-proton signals. The observation of the slowing of pseudorotation in β-protons and other high field signals prior to the separation of the α-proton signals however was previously observed in the 1H DNMR spectra of (2R*,12S*)-2,12-dimethylcycloketetradecanone (98). This may be a result of a smaller signal separation for the α-proton signals in 122 compared to the other proton signals.

According to equation 3, for two sets of nuclei, which are interconverting at the same rate, the separation of the resonances having the greater chemical shift difference will be observed at a higher temperature.

The broad upfield signal at about 0.70 ppm is first observed at -110 °C. This signal sharpens and separates into two peaks at 0.70 and 0.62 ppm at -120 °C. The two signals are in a 1:1 relative ratio. Combined they are in a 1:1.7 ratio with the total integration of the α-proton signals. The integration of these two upfield signals at 0.70 and 0.62 ppm supports the proposal that pseudorotation has slowed in the minor conformation.
Figure 57. $^1$H DNNMR spectra (500 MHz) of azacyclohexadecane (122) in a mixture of $d_4$-methanol:CHCl$_2$F (1:3).
In the symmetric [4444] conformation 122-A, illustrated in Figure 58, three carbons and the nitrogen reside at middle positions. The three exo protons on these middle carbons are believed to contribute to the upfield signals. As proposed for azacyclotetradecane (121), the upfield shift of the exo protons on the middle carbons is due to shielding effects resulting from the steric compression of the endo protons (two 1,4-gauche interactions) and C-C bond anisotropy. The $H_5, H_5'$-exo protons were tentatively assigned to the signal at 0.70 ppm and the $H_6$-exo proton to part of the signal at 0.62 ppm.

The remainder of the signal at 0.62 ppm not accounted for is in a 1:2 ratio with the minor $\alpha$-proton signals. As proposed for azacyclotetradecane (121), the observation of an upfield signal due to a minor conformation indicates that pseudorotation has slowed in the minor conformation. If pseudorotation had not slowed continued signal averaging would have resulted in a lower field signal due to averaging.
The unsymmetric [4444] conformation 122-B shown in Figure 58 is a possibility for the minor conformation. In conformation 122-B four exo protons are situated on carbons in the middle position. Only the \( \text{H}_6 \) and \( \text{H}_6' \)-exo protons are believed to be upfield. Shielding of the \( \text{H}_4 \)-exo proton would be less than the shielding of the \( \text{H}_8 \)-exo and \( \text{H}_8' \)-exo protons due to reduced steric compression of the \( \text{H}_4 \)-endo proton. The \( \text{H}_4 \)-endo proton experiences one 1,4-gauche butane interaction with the nitrogen lone pair and one 1,4-gauche butane interaction with a hydrogen rather than two 1,4-gauche butane interactions with hydrogens that the \( \text{H}_8 \)-endo and \( \text{H}_8' \)-endo protons experience.

Further separation of the \( \alpha \)-proton signals upon cooling below -120 °C could not be observed since azacyclohexadecane (122) precipitated out of solution in \( \text{d}_4 \)-methanol:CHCl\(_2\)F. Numerous mixed solvent systems were tried in an attempt to study azacyclohexadecane at temperatures below -120 °C, but none was successful.

Based on this model that two conformations are present, a free energy difference \( \Delta G^\circ = 0.43 \text{ kcal/mol} \) was calculated from the relative intensities of the \( \alpha \)-proton signals at -120 °C. An energy barrier for ring inversion (\( \text{C}_2 \)-pseudorotation) in the symmetric conformer 122-A was calculated as \( \Delta G^\ddagger = 7.8 \text{ kcal/mol} \) at the coalescence temperature of -110 °C from the \( \Delta v \) between the peak at 2.55 ppm and 2.67 ppm at -120 °C. This barrier for ring inversion in conformation 122-A of azacyclohexadecane is 1.1 kcal/mol greater than the energy barrier to pseudorotation in the [4444] conformation of cyclohexadecane-1-\( ^{13} \text{C} \).\(^{52} \) The energy barriers to ring inversions and pseudorotation in the unsymmetric conformation could not be determined due to signal overlap.
3.6.1 Molecular mechanics modelling of azacyclohexadecane (122).

Two low energy conformations were found using a Monte Carlo search\textsuperscript{131} with the MM2\textsuperscript{*} force field. They were the [4444] conformers 122-A and 122-B, in agreement with the above spectral analysis. The calculated relative ratio of 4:1 for these two conformers at -120 °C is higher than the experimental ratio of 1.4:1.

Table 24. The seven lowest energy conformations of azacyclohexadecane (122).

<table>
<thead>
<tr>
<th>Conformer</th>
<th>MM2\textsuperscript{*}</th>
<th>Relative</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta H^\circ$</td>
<td>$\Delta S^\circ$</td>
<td>-50 °C</td>
</tr>
<tr>
<td>122-A</td>
<td>0.00</td>
<td>0</td>
<td>59.33</td>
</tr>
<tr>
<td>122-B</td>
<td>0.65</td>
<td>R ln2</td>
<td>27.46</td>
</tr>
<tr>
<td>122-C</td>
<td>1.43</td>
<td>R ln2</td>
<td>4.76</td>
</tr>
<tr>
<td>122-D</td>
<td>1.61</td>
<td>R ln2</td>
<td>3.12</td>
</tr>
<tr>
<td>122-E</td>
<td>1.80</td>
<td>R ln2</td>
<td>2.04</td>
</tr>
<tr>
<td>122-F</td>
<td>1.83</td>
<td>R ln2</td>
<td>1.90</td>
</tr>
<tr>
<td>122-G</td>
<td>1.97</td>
<td>R ln2</td>
<td>1.39</td>
</tr>
</tbody>
</table>

3.6.2 Transition state model of azacyclohexadecane (122)

Based on Dale’s single corner movement theory, transition pathways to interconvert the lowest three energy conformations are shown in Scheme 21. The interconversions W, X, Y and Z all represent multiple single corner movements (local inversions). Interconversions W and X represent $C_6$-pseudorotation. Interconversions Y and Z represent $C_2$-pseudorotation.

The two MM2 calculated low energy conformations are 122-A and 122-B. The separation of the $\alpha$-protons into two sets of signals indicates that the local inversion between 122-A and 122-B, transition W, has slowed. In addition, the observation of the
α-proton signals assigned to the symmetric conformation 122-A indicates that C2-pseudorotation in this conformation has slowed. The 1.1 kcal/mol increase in activation energy for C2-pseudorotation (ring inversion) in 122-A compared to the activation energy of pseudorotation in cyclohexadecane (32) may be a reflection of the increase in transannular strain as the nitrogen moves from a middle position one adjacent to the corner on the [4444] conformer, as previously discussed for azacyclotetradecane. The observation of high field signals and the single β-signal indicates that C2- and Cs-pseudorotation, interconversions W, X and Z in Scheme 21, in conformation 122-B have slowed.

The incorporation of the nitrogen into the 16-membered ring of 122 has increased both the chemical shifts separation compared to cyclohexadecane (32) and the measured energy barriers relative to the barrier to pseudorotation in cyclohexadecane (32). Overlap of the α-proton signals continues to hinder the full analysis of the conformational and the dynamic processes that occur in 122. However interpretation of the observed shifts by the conformational model developed in the previous DNMR studies suggests that a major symmetric conformation (122-A) and the minor non-pseudorotating unsymmetric conformation (122-B) are present at -120 °C.

3.7 The 1H DNMR study of N-methylazacyclohexadecane (125)

The DNMR spectra of N-methylazacyclohexadecane (125) in CHCl2F are presented in Figure 59. This study was conducted to determine the effect of the methylation of the nitrogen atom on the conformations and conformational properties of the sixteen membered nitrogen ring.
At -70 °C, N-methylazacyclohexadecane is undergoing rapid ring inversion, pseudorotation and local inversion. The signals for the α-, β- and N-methyl protons are all downfield of a large signal due to the remaining methylene protons in the ring. Upon cooling, the α-proton signal at 2.31 ppm broadens. Below -85 °C the signal separates into two peaks, one at 2.44 ppm and the other buried under the N-methyl signals. The separation of these α-signals indicates that the process of ring inversion (C\textsubscript{2}-pseudorotation) has slowed while C\textsubscript{s}-pseudorotation and other local inversions remain rapid.

![Diagram of N-methylazacyclohexadecane](image)
Figure 59. The $^1$H DNMR spectra (500 MHz) of N-methylazacyclohexadecane (125) in CHCl$_2$F.
The chemical shift separation used to calculate the energy barrier for ring inversion was determined by doubling the chemical shift difference between the downfield peak 2.44 ppm and the averaged signal at 2.31 ppm. Using this value of $\Delta \nu = 130$ Hz, an energy barrier of $\Delta G^\ddagger = 9.0$ kcal/mol at the coalescence temperature of $-80 \, ^\circ C$ was calculated for ring inversion. This represents a significant increase in the energy barrier for ring inversion, compared to ring inversion in azacyclohexadecane (122) and in cyclohexadecane (32).

The increase in the energy barrier to C$_2$-pseudorotation and an increase in the chemical shift differences of the $\alpha$-protons$^{161,171}$ in 125 compared to 122 and 32 both contribute to freezing the C$_2$-pseudorotation at $-80 \, ^\circ C$. The freezing of C$_2$-pseudorotation at a higher temperature than the freezing of C$_s$-pseudorotation and local inversion was not observed in the other DNMR spectra.

At $-110 \, ^\circ C$ the $\alpha$-proton signals broaden. Upon further cooling to $-130 \, ^\circ C$ four $\alpha$-protons signals at 2.79, 2.55, 2.45 and 2.30 ppm are observed. Two new upfield signals at 0.75 and 0.65 ppm also appear at these temperatures. The N-methyl signal remains a single peak although line broadening and an upfield shift to 2.10 ppm occurs.

The chemical shift separations observed for the $\alpha$-proton signals are similar to those observed in the low temperature spectrum of N-methylazacyclotetradecane (124). The chemical shifts in 124 resulted from a symmetric and an unsymmetric conformation in which pseudorotation had slowed. The similar chemical shifts in the low temperature spectrum of N-methylazacyclohexadecane (125) suggest that similar conformations exist.
In the 14-membered ring of 124 three of the signals for the α-protons from the unsymmetric conformation and one of the signals from the symmetric conformation were observed. Similarly, the signals at 2.79, 2.55 and 2.45 ppm in Figure 59 may represent three α-proton signals from an unsymmetric non-pseudorotating conformation of 125. The fourth signal at 2.30 ppm can be assigned to the downfield α-proton signal of the symmetric conformation. The relative integration of these four α-signals with the N-methyl signal suggests that an α-proton signal from the unsymmetric conformation and an α-proton signal equal to two protons of the symmetric conformation are buried under the N-methyl peak.

A downfield shift of the weighted average of all the α-signals from the high temperature signal at 2.31 ppm is also observed. This suggests that the population of the unsymmetric conformation increases as the temperature is lowered. This shift in population is also indicated by the decreased intensity of the signal at 2.30 ppm for the symmetric conformation upon cooling from -120 to -130 °C.

The observation of the two high field signals at 0.75 and 0.65 also agrees with the proposal that two conformations exist at low temperature. The signal at 0.75 ppm is too small to represent a single proton of the unsymmetric conformation. Thus this signal must result from protons of the minor symmetric conformation and the signal at 0.65 ppm represents two protons of the unsymmetric conformation. Based on the observations of the upfield signals for the symmetric conformation in the 1H DNMR spectra of azacyclohexadecane (122), a signal having half the intensity of the peak at 0.75 ppm should exist further upfield perhaps under the signal at 0.65 ppm.

The signal at 1.71 ppm for one of the β-protons of the unsymmetric conformation increases in intensity below -120 °C which suggest that local inversion between the
symmetric and unsymmetric conformation, and pseudorotation in the unsymmetric conformation have slowed. This agrees with the proposal that in azacyclohexadecane (122) pseudorotation of the minor unsymmetric conformation was frozen out at −120 °C.

The determination of the relative populations of the major and minor conformations was complicated by signal overlap of the α-proton signals and the N-methyl signals. The total integration of the α-carbons and the N-methyl signals was determined from the integration of the signals ranging from 2.9 to 1.9 ppm. The contribution of the N-methyl signals to this total integration was calculated as 3/7 of the total integration. The contribution of the α-protons signals from the major unsymmetric conformation to the total integration was calculated as 4 times the integration of the peak at 2.79 ppm, the only distinct α-proton signal. The contribution of the α-protons signals from the minor unsymmetric conformation to the total integration was calculated as the remainder. A ratio of 3:1 was determined by comparing these calculated integrations of the α-protons signals. This ratio corresponds to an energy difference of

$$\Delta G^\circ = 0.33 \text{ kcal/mol}$$

between the two conformations.
3.7.1 Molecular mechanics modelling of 125

The eight lowest energy conformations of N-methylazacyclohexadecane (125) from molecular mechanics calculations are listed in Table 25.

Table 25. The calculated eight lowest energy conformers of 125.

<table>
<thead>
<tr>
<th>Conformer</th>
<th>( \Delta H^\circ (\text{MM2}^*) ) (kcal/mol)</th>
<th>( \Delta S^\circ ) (kcal/mol*K)</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125-A</td>
<td>0.00</td>
<td>0</td>
<td>24.4</td>
</tr>
<tr>
<td>125-B</td>
<td>0.16</td>
<td>0</td>
<td>18.7</td>
</tr>
<tr>
<td>125-C</td>
<td>0.20</td>
<td>R ln2</td>
<td>34.7</td>
</tr>
<tr>
<td>125-D</td>
<td>1.06</td>
<td>R ln2</td>
<td>7.9</td>
</tr>
<tr>
<td>125-E</td>
<td>1.38</td>
<td>R ln2</td>
<td>4.6</td>
</tr>
<tr>
<td>125-F</td>
<td>1.43</td>
<td>R ln2</td>
<td>4.2</td>
</tr>
<tr>
<td>125-G</td>
<td>1.56</td>
<td>R ln2</td>
<td>3.4</td>
</tr>
<tr>
<td>125-H</td>
<td>1.87</td>
<td>R ln2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

The MM2* calculations suggest that three conformations are populated at low temperature. These three conformations are illustrated in Figure 60. All have the [4444] conformation, but differ in the position of the nitrogen. The number of populated low energy conformations found by the MM2* calculations does not agree with the above proposal that only two conformations exist in the low temperature \(^1\)H DNMR spectra of 125. Conformation 125-B was eliminated from consideration as contributing to the observed shifts.
This suggestion that conformer 125-B is not populated at low temperature is based on analysis of the multiple single corner movement mechanism for interconversions in 125. The conformational processes which interconvert these three [4444] conformations are illustrated in Scheme 22. The interconversions W, X, Y and Z each represent multiple single corner movements. The observation of the separation of the α-proton signals into equally intense signals at -100 °C indicates that ring inversion of the populated conformations is frozen while local inversion and C₅-pseudorotation (H₁ = H₁', and H₂ = H₂') among the populated conformations continues. The interconversion between conformation 125-A and 125-B either via interconversion Y or through the combination of interconversion W and Z in Scheme 22 represents the process of ring inversion in conformer 125-A (C₂-pseudorotation, H₁' = H₂ and H₂' = H₁). Thus rapid interconversion between 125-A and 125-B must have slowed at -100 °C. If 125-B was populated then two sets of two α-proton signals for the two non-interconverting conformations would be observed upon slowing of ring inversion at -100 °C. Since only one set of two α-proton signals is observed, conformer 125-B must not be significantly populated.
Scheme 22. Conformational processes in the low energy [4444] conformations of N-methylazacyclohexadecane (125).
In conformation \textbf{125-C}, the H$_2$'-endo protons experience a transannular van der Waals repulsion with the H$_5$' and H$_3$-endo protons, shown below. This interaction would deshield the H$_2$'-endo proton and shield the H$_2$'-exo proton. The upfield signal under the N-methyl signal was therefore tentatively assigned to the H$_2$'-exo proton and the signal at 2.45 ppm was assigned to the H$_2$'-endo proton. The two corner protons H$_{2a}$ and H$_{2b}$ were assigned to the signals at 2.55 and 2.79 ppm, respectively. The chemical shift difference of these two corner protons is believed to result from increased shielding of the H$_{2a}$ proton relative to the H$_{2b}$ proton due to its trans-coplanar orientation to the nitrogen lone pair.$^{127,161,171}$ In agreement with these assignments the signal at 2.45 ppm is more broad than the signal at 2.55 ppm as the H$_2$'-endo proton experiences a large anti coupling of with a β-proton and with the NH proton where as the H$_{2a}$ proton experiences only small gauche couplings with both β-protons and the NH proton.

The signal at 2.30 ppm was assigned to the α-endo protons of the symmetric \textbf{125-A} conformation. This signal diminishes upon cooling from -120 °C to -130 °C as the other signals for the unsymmetric conformation \textbf{125-C} increase.
These chemical shift assignments are tentative and were aided by the chemical shift model developed from the observed shifts in the other DNMR spectra. Signal overlap hinders the accurate determination of the integration of each of the signals.

3.8 X-ray structure of N,N-dimethylpentadeca-1,15-diylammonium iodide (128)

The X-ray crystal structure of N,N-dimethylpentadeca-1,15-diylammonium iodide (128) is shown in Figure 61. This sixteen membered ring exists in the [4444] diamond lattice structure in which the methyl substituents are at a corner position. This same conformation was observed for the X-ray crystal structure of the N-methylpentadeca-1,15-diylammonium chloride monohydrate (138) shown in Figure 62. The strong preference for the geminal carbon to reside at a corner position predicted by Dale,53,55 is also seen in Figure 61 and was also found by the molecular mechanics conformational search of the N,N-dimethylpentadeca-1,15-diylammonium ion. There is a large energy difference between the global minimum conformation 128-A and the next lowest energy conformation 128-B (Table 26), consistent with Dale’s prediction.

The study of the conformations of N,N-dimethylpentadeca-1,15-diylammonium iodide (128) in solution by DNMR could not to be carried out since the quaternary salt was found to be insoluble in d₄-methanol and other NMR solvents with low freezing points.
Table 26. The calculated six lowest energy conformations of N,N-dimethylpentadeca-1,15-diylammonium iodide (128)

<table>
<thead>
<tr>
<th>Conformer</th>
<th>MM2*</th>
<th>Δ H° (kcal/mol)</th>
<th>Δ S° (kcal/mol*K)</th>
<th>Concentration (%) 22 °C</th>
<th>Concentration (%) -90 °C</th>
<th>Concentration (%) -120 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>128-A</td>
<td>0.00</td>
<td>0</td>
<td>77.7</td>
<td>96.5</td>
<td>98.7</td>
<td></td>
</tr>
<tr>
<td>128-B</td>
<td>1.80</td>
<td>0</td>
<td>7.2</td>
<td>1.4</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>128-C</td>
<td>1.86</td>
<td>R ln2</td>
<td>6.5</td>
<td>1.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>128-D</td>
<td>2.21</td>
<td>R ln2</td>
<td>3.6</td>
<td>0.4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>128-E</td>
<td>2.24</td>
<td>R ln2</td>
<td>3.4</td>
<td>0.4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>128-F</td>
<td>2.69</td>
<td>R ln2</td>
<td>1.6</td>
<td>0.1</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 61. The X-ray crystal structure of N,N-dimethylpentadeca-1,15-diylammonium iodide (128).
3.9 Study of the $^1$H DNMR of azacyclotridecane (120)

Dale predicted that the odd membered ring cyclotridecane should exist in a number of conformations, since it is unable to adopt a single low energy diamond lattice conformation.\textsuperscript{44,45} This was also found in the MM2* calculations of the low energy conformation of cyclotridecane itself discussed in section 2.6 (Table 14).

The DNMR spectra of azacyclotridecane (120) are shown in Figure 63. Line broadening is observed at temperatures below -80 °C. At -120 °C some separation of the $\alpha$–signal is beginning however no conclusions can be drawn from this spectrum since the signals overlap badly.
Figure 63. $^1$H DNMR spectra (500 MHz) of azacyclotridecane (120) in CHCl$_2$F.
3.10 X-ray crystal study of N,N-dimethyldodeca-1,12-diylammonium iodide (126)

Geminal dimethyl substitution was found by DNMR studies to increase the conformational stability of the 14-membered amine ring. Unfortunately, the low solubility of 126 prevented us from studying its DNMR. However, the X-ray crystal structure of N,N-dimethyldodeca-1,12-diylammonium iodide (126) is shown in Figure 64. The ring skeleton has the [13333] conformation with the gem-dimethyl group situated at a corner position. This conformer was also calculated to be the global minimum energy conformation (Table 27).\textsuperscript{55,133}

\textbf{Figure 64.} The X-ray structure of N,N-dimethyldodeca-1,12-diylammonium iodide (126).
Table 27. The calculated eight lowest energy conformers of N,N-dimethyldodeca-1,12-diyl-ammonium iodide (126).

<table>
<thead>
<tr>
<th>Conformer</th>
<th>MM2* Δ H° (kcal/mol)</th>
<th>Δ S° kcal/mol*K</th>
<th>Relative Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>126-A</td>
<td>0.00</td>
<td>0</td>
<td>49.04 65.36 71.74</td>
</tr>
<tr>
<td>126-B</td>
<td>0.38</td>
<td>0</td>
<td>25.74 23.13 20.71</td>
</tr>
<tr>
<td>126-C</td>
<td>0.79</td>
<td>0</td>
<td>12.70 7.41 5.31</td>
</tr>
<tr>
<td>126-D</td>
<td>1.15</td>
<td>0</td>
<td>6.89 2.76 1.63</td>
</tr>
<tr>
<td>126-E</td>
<td>1.57</td>
<td>0</td>
<td>3.39 0.88 0.42</td>
</tr>
<tr>
<td>126-F</td>
<td>1.81</td>
<td>0</td>
<td>2.24 0.45 0.19</td>
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</table>

The torsional angles of the solid state structure of 126 and the global minimum conformation determined by MM2* and by Rubin et al.\textsuperscript{179} using Boyd's iterative program Molbuild are listed in Table 28. The close agreement of the measured and calculated torsional angles suggests that both these force fields accurately model the cyclic ammonium salt.
<table>
<thead>
<tr>
<th>Torsional angles (°)</th>
<th>126</th>
<th>N,N-dimethyldodeca-1,12-diylammonium</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>X-ray structure</td>
<td>MM2*</td>
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<tr>
<td>C1-C2-C3-C4</td>
<td>75</td>
<td>71</td>
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<td>C2-C3-C4-C5</td>
<td>72</td>
<td>73</td>
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<tr>
<td>C3-C4-C5-C6</td>
<td>-169</td>
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<td>C4-C5-C6-C7</td>
<td>68</td>
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<td>C5-C6-C7-C8</td>
<td>80</td>
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<td>C6-C7-C8-C9</td>
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<td>C7-C8-C9-C10</td>
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<td>C8-C9-C10-C11</td>
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<td>C9-C10-C11-C12</td>
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<td>C10-C11-C12-N1</td>
<td>174</td>
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<td>C11-C12-N1-C1</td>
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<td>C12-N1-C1-C2</td>
<td>55</td>
<td>58</td>
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<tr>
<td>N1-C1-C2-C3</td>
<td>-167</td>
<td>-168</td>
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</table>

a From ref. 179
Chapter IV

Summary and Conclusion

High stereoselectivity was obtained in the alkylation of the dianions of the methyl lactams 65, 66 and 67. These alkylations afforded the (3R*,nS*) and (3S*,nS*) products (n = ring size) in a >99:1, 62:1 and 10:1 ratios, respectively. The relative ratio of the products from the alkylation of the N-benzyl lactam 68 was found to be solvent dependent. For example alkylation of 68 resulted in products (3R*,16S*) 110 and (3S*,16S*) 111 in a 5.7:1 ratio in hexane, a 2.3:1 ratio in THF and a 1:1.3 ratio in DMSO. The relative stereochemistry of the products from the alkylation of 67 was determined by X-ray crystallography, and by chemical correlation for the alkylation products from 65, 66 and 68.

![Chemical structures of lactams 65-68](image)

Observations of NOE enhancements upon irradiation of the NH proton and analysis of coupling constant values indicated that the amide regions of lactams 65-67 and 92-97 are conformationally rigid and similar, in the syn-periplanar and Z-amide conformation. Molecular mechanics calculations were able to correctly model the conformational rigidity of the amide region of these lactams and the stereochemistry of
the products from the alkylation of lactams 65-67. This study of the conformational properties and alkylations to 13-, 14- and 16-membered lactams, compounds 65, 66, 67 and 68, added to our understanding of the effect of the amide bond on the conformation of the large rings and the selectivity of simple alkylations.

Conformational properties of 13-, 14- and 16-membered macrocyclic amines 120-122, N-methyl amines 124-125, N,N-dimethyl ammonium salt 127 and (2R*,12S*)-2,12-dimethylcyclododecanone (98) were determined from DNMR studies. A model comprised of molecular mechanics calculations, theoretical entropy effects and transition state theory aided in the interpretation of the observed conformational effects in the DNMR spectra.
(2R*,12S*)-2,12-Dimethylcyclododecanone (98) was found to exist in a major unsymmetric conformation and a minor symmetric conformation ($\Delta G = 1.6$ kcal/mol) from the $^{13}$C DNMR at -95 °C. Upon cooling to -115 °C, ketone 98 was found to exist only in the unsymmetric conformation. An energy barrier of $\Delta G^\ddagger = 8.6$ kcal/mol at -85 °C was measured for the process of ring inversion in the unsymmetric conformation. The observed chemical shifts in the $^1$H and $^{13}$C DNMR spectra were consistent with the unsymmetric [3333]-2-one and symmetric [2343] as the major and minor conformations, respectively. The lowest energy conformation was found by molecular mechanics calculations to be the [3333]-2-one conformation (identical to the X-ray crystal structure) and the second lowest in energy was the [2343] conformation having a plane of symmetry, in agreement with the interpretation of the DNMR spectra.

Azacyclotetradecane (121) was found to exist in a major symmetric and a minor unsymmetric conformation ($\Delta G = 0.21$ kcal/mol) from the $^1$H DNMR spectrum at -130 °C in a mixture of CHCl$_2$F and CHCIF$_2$ (4:1). The barrier to ring inversion in the symmetric conformation was determined to be $\Delta G^\ddagger = 8.7$ kcal/mol at -90 °C. An energy barrier of $\Delta G^\ddagger = 8.3-8.5$ kcal/mol at -90 °C, for the processes of ring inversion and pseudorotation in the unsymmetric [3434] conformation were determined. The process of local
inversion between the two conformations was estimated as being in this same energy range. In agreement with the interpretation of the $^1$H DNMR spectra, azacyclotetradecane (121) was also found to exist in a major symmetric conformation and a minor unsymmetric conformation in its $^{13}$C DNMR spectra at -110°C in $d_8$-toluene:CHCl$_2$F (1:3). The observed chemical shifts in the $^1$H and $^{13}$C DNMR spectra were consistent with the symmetric [3434] conformer 121-A and an unsymmetric [3434] conformer 121-B as the major and minor conformations, respectively.

N-methylazacyclotetradecane (124) was found to exist in a major symmetric conformation and a minor unsymmetric conformation from its $^1$H DNMR spectrum at -110 °C in $d_4$-methanol:CHCl$_2$F (1:4). The major conformation was found to be 0.30 kcal/mol more stable than the minor conformation at -110 °C. The barrier to ring inversion in the symmetric conformation was measured as $\Delta G^\ddagger = 8.6$ kcal/mol at -90 °C. The barrier to ring inversion and pseudorotation in the unsymmetric conformation were found to be $\Delta G^\ddagger = 8.4$ kcal/mol at -95 °C and $\Delta G^\ddagger = 8.2$ kcal/mol at -105 °C, respectively. The observed chemical shifts in the $^1$H DNMR spectra were consistent
with the symmetric [3434] conformer 124-A and an unsymmetric [3434] conformer 124-B as the major and minor conformations, respectively.

N,N-Dimethyltrideca-1,13-diylammonium iodide (127) was found to have an energy barrier to ring inversion of $\Delta G^\ddagger = 10.5$ kcal/mol at -48 °C in $d_4$-methanol. The lowest energy conformation was found by molecular mechanics calculations to be the [3434] conformation having the geminal dimethyl group at a corner position identical to the X-ray crystal structure.

\[ \text{127-A} \]
Azacyclohexadecane (122) was found to exist in a major symmetric and a minor unsymmetric conformation from its $^1$H DNMR spectra at -120 °C in d$_4$-methanol:CHCl$_2$F (1:3). The major conformation was found to be 0.43 kcal/mol more stable than the minor conformation at -120 °C. The barrier to inversion in the symmetric [4444] conformation was measured as $\Delta G^\ddagger = 7.8$ kcal/mol at -110 °C. The observed chemical shifts in the $^1$H DNMR spectra were consistent with the symmetric [4444] conformer 122-A and an unsymmetric [4444] conformer 122-B as the major and minor conformations, respectively.

N-methylazacyclohexadecane (125) was found to exist in two conformations in CHCl$_2$F; a major unsymmetric conformation and a minor symmetric conformation. The major conformation was found to be 0.33 kcal/mol more stable than the minor conformation at -120 °C. The slowing on the NMR time scale of the process of ring inversion in N-methylazacyclohexadecane (125) was observed prior to the separation of the two conformations upon cooling. The barrier to ring inversion in N-methylazacyclohexadecane (125) was measured as $\Delta G^\ddagger = 9.0$ kcal/mol at -80 °C.
The observed chemical shifts in the $^1$H DNMR spectra were consistent with an unsymmetric [4444] conformer 125-C and the symmetric [4444] conformer 125-A as the major and minor conformations, respectively.

The results of these studies of the macrocyclic ketone, amines, and lactams all contribute to our understanding of the conformational properties of macrocyclic rings and to the development of a general conformational model for the prediction of the stereoselective outcome of macrocyclic conformationally controlled reactions. Confidence in the ability to predict the stereochemical outcome of reactions on macrocyclic rings furthers the development of this approach towards the total syntheses of biologically-active macrolides.
Chapter V

Experimental

General

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware, unless otherwise stated. Anhydrous reagents and solvents were prepared according to procedures in the literature. Alkylithiums (n-BuLi and t-BuLi) obtained from Aldrich Chemical Co. were standardized by titration against 2,2-diphenylacetic acid in THF.

Analytical gas chromatography (GC) was performed on a Hewlett-Packard model 5880A instrument, fitted with a split mode capillary injector, a 0.22 mm DB210 column of approximately 12 meters in length and a flame-ionization detector. Helium was used as the carrier gas. Where indicated the DB210 column was replaced with an OV101 column of approximately 12 meters in length.

Flash chromatography was carried out using Silica gel 60, 230–400 mesh, supplied by E. Merck Co. Silica gel 60 F254 on aluminum sheets (E. Merk, type 5554) was used for TLC analysis.

Uncorrected melting points were obtained on a Fisher-Johns hot stage melting point apparatus. For compounds purified by Kugelrohr distillation, boiling points are given as oven temperature. The boiling points are uncorrected.
$^1$H and $^{13}$C nuclear magnetic resonance spectra were obtained on a Varian XL-300, Bruker AC-200, Bruker WH-400 or a Bruker AMX-500 instrument. Solvent, signal multiplicity, coupling constants, and integration ratios are indicated in parentheses. The $^1$H DNMR spectra were on the Bruker AMX-500 with a 45° flip angle, a 3s acquisition time, a sweep width of 10,000 Hz and a 32K block size. The carbon $^{13}$C DNMR spectra were obtained on the Bruker AMX-500 with a 40° flip angle, a 1s acquisition time, a sweep width of 29412 Hz and a 64K block size.

A Bomen FT-IR Michelson-100 was used to obtain the infrared (IR) spectra. The spectra were collected and processed using Bomen Spectra Calc program on an IBM compatible computer. The spectra were obtained either in CHCl$_3$ solution using a 0.2 mm thick NaCl cell, or as a solid in KBr.

Low-resolution mass spectra (LRMS) were obtained on a Kratos-AEI model MS-50 or model MS-9 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Kratos-AEI model MS-50 spectrometer. All spectra were obtained using an ionization energy of 70 eV.

Microanalyses were carried out on a Carlo Erba Elemental Analyzer 1106 or a Fisons CHN-O Elemental Analyzer Model 1108 in the Microanalytical Laboratory at UBC.
13-methyl-1-azacyclotridecan-2-one (65) and 3-methyl-1-azacyclotridecan-2-one (84)

Pyridine (0.73 mL, 9.06 mmol) was added to a solution of oximes 81 (0.9570g, 4.53 mmol) in 50 mL of dry CH$_2$Cl$_2$ at 0 °C. Tosyl chloride was then added as a dry powder and the reaction was stirred overnight at room temperature. After removal of the solvent under reduced pressure 30 mL of Et$_2$O and 5 mL of SiO$_2$ were added. The white slurry was stirred for 30 minutes. The solvent was then removed under reduced pressure and the white powder was loaded on to the top of a silica column. Flash chromatography eluting with pet. ether/Et$_2$O (1:1) afforded the Beckmann rearranged product 84 (0.1877 g, 0.89 mmol, 19.6 %) followed by 65 (0.6962 g, 3.30 mmol, 72.8 %). The crude 65 was recrystallized from EtOH/H$_2$O to afford 65 (0.6603 g, 3.13 mmol) in an 69.0% yield as white needles.

**Compound 65**

Mp: 152.5-153 °C;

IR (CHCl$_3$): 3435, 3336, 2930, 2859, 1656, 1506, 1455 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.10 (d, J = 6.7 Hz, 3H), 1.18-1.40 (m, 14H), 1.40-1.60 (m, 2H), 1.65-1.85 (m, 2H), 2.08 (ddd, J = 3.1, 9.7, 13.6 Hz, 1H), 2.25 (ddd, J
\[ = 3.5, 8.2, 13.6 \text{ Hz}, 1\text{H}), 4.08 \text{ (qddd, } J = 6.7, 2.4, 9.4, 9.6 \text{ Hz}, 1\text{H}), 5.20 \text{ (d, } J = 9.4 \text{ Hz}, 1\text{H});\]

\[^{13}\text{C NMR (50 MHz, CDCl}_3\text{) ppm: 172.4, 44.7, 36.8, 36.0, 26.6, 26.2, 25.8, 25.3, 25.0, 25.0, 24.5, 22.7, 21.6;}\]

LRMS (El) m/z (relative intensity): 211(4), 196(4), 182(3), 168(3), 44(100);

HRMS (El) m/z calcd for \( \text{C}_{13}\text{H}_{25}\text{NO: 211.1936; found: 211.1933;}\)

Anal. calcd for \( \text{C}_{13}\text{H}_{25}\text{NO: C, 73.88; H, 11.92; N, 6.63;}\)

\[ \text{Found: C, 74.04; H, 11.68; N, 6.59.}\]

Compound 84

Mp: 151-151.2 \text{ °C};

IR (CHCl\textsubscript{3}): 3668, 3451, 3336, 2931, 2859, 1663, 1511, 1457 cm\textsuperscript{-1};

\(^1\text{H NMR (400 MHz, CDCl}_3\text{) ppm: 1.10 \text{ (d, } J= 6.84 \text{ Hz}, 3\text{H}), 1.20-1.40 \text{ (m, 15H), 1.46 (m, 1H), 1.5-1.7 (m, 2H), 2.20 \text{ (qdd, } J = 6.7, 3.4, 10.1 \text{ Hz}, 1\text{H}), 2.94 \text{ (dddd, } J = 2.1, 4.6, 7.9, 13.4 \text{ Hz}, 1\text{H), 3.60 \text{ (tdd, } J = 7.6, 2.7, 13.7 \text{ Hz}, 1\text{H), 5.46 \text{ (bs, 1H);}}\]

\[^{13}\text{C NMR (50 MHz, CDCl}_3\text{) ppm: 176.4, 41.9, 40.0, 34.4, 28.4, 26.8, 26.4, 25.8, 25.0, 24.7, 24.3, 23.8, 18.2;}\]

LRMS (El) m/z (relative intensity): 212(17), 211(84), 196(8), 182(28), 170(12), 168(29), 55(100);

HRMS (El) m/z calcd for \( \text{C}_{13}\text{H}_{25}\text{NO: 211.1936; found: 211.1943;}\)

Anal. calcd for \( \text{C}_{13}\text{H}_{25}\text{NO: C, 73.88; H, 11.92; N, 6.63;}\)

\[ \text{Found: C 74.10; H, 11.92; N, 6.68.}\]
14-methyl-1-azacyclotetradecan-2-one (66)

Following the procedure for the preparation of lactams 65 and 84, tosyl chloride (0.1720 g, 0.904 mmol) was added to a solution of oximes 82 (0.1565 g, 0.695 mmol) and pyridine (0.118 mL, 1.06 mmol) in 25 mL of CH$_2$Cl$_2$. After work-up, flash chromatography afforded the Beckmann rearranged product 66 (0.1057 g, 0.469 mmol) in 67.5 % yield. Lactam 66 was recrystallized from EtOH/H$_2$O co-solvent system to afford 66 (0.0845 g, 54 %) as white needles.

IR (CHCl$_3$): 3436, 3317, 2932, 2860, 1659, 1507, 1456 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.09 (d, J = 6.7 Hz, 3H), 1.1-1.5 (m, 18H), 1.57 (m, 1H), 1.75-1.86 (m, 1H), 2.04 (ddd, J = 3.1, 10.6, 13.7 Hz, 1H), 2.26 (ddd, J = 3.5, 7.2, 13.7 Hz, 1H), 4.08 (qddd, J = 6.7, 3.0, 9.0, 9.3 Hz, 1H), 5.30 (d, J = 9.0 Hz, 1H);

$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 172.54, 44.20, 36.56, 35.97, 26.34, 25.95, 25.61, 25.50, 25.27, 25.27, 23.58, 23.52, 22.38, 21.54;

LRMS (EI) m/z (relative intensity): 225(12), 210(6), 196(5), 182(4) 168(2), 44(100);

HRMS (EI) m/z calcd for C$_{14}$H$_{27}$NO: 225.2093; found: 225.2092;

Anal. calcd for C$_{14}$H$_{27}$NO: C, 74.61; H, 12.08; N, 6.21;

Found: C, 74.60; H, 12.10; N, 6.14.
16-methyl-1-azacyclohexadecan-2-one (67) and 3-methyl-1-azacyclohexadecan-2-one (86)

Following the procedure for the preparation of lactam 65 and 84, tosyl chloride (0.7424 g, 3.89 mmol) was added as a solid to a solution of oximes 83 (0.6255 g, 2.47 mmol) and pyridine (0.40 mL, 4.9 mmol) in 30 mL of CH₂Cl₂. After work-up, flash chromatography afforded the Beckmann rearranged product 86 (0.1251 g, 0.49 mmol, 20.0%) followed by 67 (0.4754 g, 1.87 mmol, 76.0%). Lactam 67 was recrystallized in an EtOH/H₂O co-solvent system to afford 67 (0.4545 g, 72.7%), as white needles.

Compound 67

IR (CHCl₃): 3438, 3322, 2930, 2857, 1660, 1508, 1457 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.09 (d, J = 6.7 Hz, 3H), 1.13-1.55 (m, 23H), 1.72-1.84 (m, 1H), 1.87 (ddd, J = 4.6, 10.0, 13.7 Hz, 1H), 2.29 (ddd, J = 4.8, 6.1, 13.7 Hz, 1H), 4.06 (qddd, 6.7, 3.8, 8.0, 9.5 Hz, 1H), 5.22 (d, J = 9.5 Hz, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 172.6, 45.0, 37.1, 37.0, 28.0, 27.7, 27.7, 27.3, 27.1, 26.2, 26.0, 25.8, 25.5, 25.3, 24.9, 21.7;

LRMS (EI) m/z (relative intensity): 254(4), 235(21), 238(8), 224(13), 210(8), 44(100);

HRMS (EI) m/z calcd for C₁₆H₃₁NO: 253.2406; found: 253.2398;

Anal. calcd for C₁₆H₃₁NO: C, 75.83; H, 12.33; N, 5.53;

Found: C, 75.90; H, 12.27; N, 5.51.
Compound 86

Mp: 117.8-118°C;

IR (CHCl₃): 3451, 3337, 2995, 2857, 1663, 1513, 1459 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.10 (d, J = 6.7 Hz, 3H), 1.15-1.48 (m, 22H), 1.52 (m, 1H), 1.64 (m, 1H), 2.12 (m, 1H), 2.91 (m, 1H), 3.68 (m, 1H), 5.45 (bs, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 175.5, 42.1, 39.0, 34.9, 29.4, 28.1, 27.3, 27.3, 27.1, 27.0, 26.4, 25.6, 25.6, 25.5, 25.3, 18.2;

LRMS (El) m/z (relative intensity): 254(17), 253(79), 238(10), 224(32), 210(38), 196(26), 55(100);

HRMS (El) m/z calcd for C₁₆H₃₁NO: 253.2406; found: 253.2400;

Anal. calcd for C₁₆H₃₁NO: C, 75.83; H, 12.33; N, 5.53;

Found: C, 76.00; H, 12.24; N, 5.57.

1-Benzyl-16-methyl-1-azacyclohexadecan-2-one (68)

n-BuLi (0.65 mL, 1.43 M, 0.929 mmol) was added to a solution of lactam 67 (0.1176 g, 0.491 mmol) and a crystal of 1,10-phenanthroline in 10 mL THF at -78 °C. After one hour the red solution was warmed to 0 °C for one hour then recooled to -78 °C prior to the addition of benzyl bromide (0.17 mL, 1.4 mmol). The solution remained red
after two hours. The solution was allowed to warm to room temperature and stirring was continued overnight for 10 hours. The solution had turned yellow overnight. The reaction was quenched with H$_2$O. The aqueous layer was extracted with Et$_2$O. The combined organic layers were dried with MgSO$_4$, filtered and concentrated under reduced pressure to afford an yellow oil. Flash chromatography eluted with pet. ether afforded N-benzyl lactam 68 (0.1115 g, 0.325 mmol) in 53 % yield as a clear yellow oil, followed by recovered lactam starting material 67 (0.0610 g, 0.241 mmol) after flushing the column with Et$_2$O. The benzyl lactam was Kugelrohr distilled (155 °C/0.2 mm Hg) to afford 68 (0.1026 g, 49%) as a clear colourless liquid.

Bp: 155 °C at 0.2 mm Hg;

IR (CHCl$_3$): 2529, 2856, 1728, 1640, 1495, 1456 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: (1:1.3 ratio of two conformations) 1.01 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.15-1.62 (m, 45H), 1.70 (m, 1H), 1.80 (m, 2H), 2.08 (m, 1H), 2.33 (m, 2H), 2.62 (m, 1H), 4.02 (m, 1H), 4.32-4.58 (m, 4H), 4.96 (bs, 1H), 7.1-7.4 (m, 10H);

$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 139.9, 139.0, 128.6, 128.6, 128.2, 128.2, 127.3, 127.3, 127.0, 126.5, 125.9, 125.9, 53.3, 49.0, 46.2, 44.0, 35.0, 35.0, 33.9, 33.1, 28.3, 27.9, 27.7, 27.6, 27.6, 27.6, 27.1, 27.0, 26.9, 26.5, 26.2, 26.2, 26.1, 26.0, 25.9, 25.8, 25.8, 25.8, 25.6, 25.5, 25.2, 24.7, 19.9, 19.4;

LRMS (El) m/z (relative intensity): 344(16), 343(57), 328(10), 314(7), 253(16), 252(84);

HRMS (El) m/z calcd for C$_{23}$H$_{37}$NO: 343.2875; found: 343.2874;

Anal. calcd for C$_{23}$H$_{37}$NO: C, 80.41; H, 10.86; N, 4.08;

Found: C, 80.29; H, 10.79; N, 4.15.
Cyclododecanone-N,N-dimethylhydrazone (72)

A solution of cyclododecanone (69) (5.7004 g, 3.13 mmol) and N,N-dimethylhydrazine (12.0 mL, 158 mmol) was stirred for 24 hours at 50 °C. Anhydrous benzene (30 mL) was then added and an azeotropic distillation was carried out. After 12 hours, the benzene and excess N,N-dimethylhydrazine were removed under reduced pressure to afford 72 (6.8758 g, 3.06 mmol, 98%) as yellow crystalline solid. Recrystallization from hexane produced white rhombic crystals (5.8444 g, 2.60 mmol) in 83% overall yield.

Mp: 33.5 - 34.0 °C;
IR (CHCl₃): 2935, 2859, 2775, 1627, 1467 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.3-1.5 (m, 14H), 1.58 (tt J = 6.7, 6.7, 2H), 1.64 (tt, J = 6.2, 6.2 Hz, 2H), 2.24 (t, J = 6.9 Hz, 2H), 2.29 (s, 6H), 2.47 (t, J = 6.9 Hz, 2H);
¹³C NMR (50 MHz, CDCl₃) ppm: 172.0, 47.5, 47.5, 31.8, 27.7, 25.5, 24.9, 24.4, 24.2, 24.2, 23.3, 23.1, 23.9, 22.5;
LRMS(EI) m/z (relative intensity): 224[M⁺](18), 180(19), 113(5), 100(41), 60(100);
HRMS (EI) m/z calcd for C₁₄H₂₈N₂: 224.2252; found: 224.2253;
Anal. Calcd for C₁₄H₂₈N₂: C, 74.94; H, 12.48; N, 12.58;
Found: C, 74.83; H, 12.50; N, 12.54.
Cyclopentadecanone-\(N,N\)-dimethylhydrazone (74)

The \(N,N\)-dimethylhydrazone 74 of cyclopentadecanone (71) was prepared following the same procedure to prepare 72. A solution of 1.0549 g (4.70 mmol) cyclopentadecanone (71) in \(N,N\)-dimethylhydrazine (17.8 mL, 23.5 mmol) was stirred at 50 °C for 12 hours. The azeotropic distillation was carried out for 12 hours after the addition of benzene (25 mL). Removal of the benzene and excess dimethylhydrazine afforded 1.235 g of a clear yellow oil determined to be 98.9% 74 and 1.1% cyclopentadecanone (71) by GC. The oil could not be crystallized from hexane as previously done for 72. Attempts to purify 74 on a silica column and by distillation both were hampered by hydrolysis of the hydrazone. The IR and \(^1\)H NMR spectra were consistent with those reported in the literature.\(^{75}\)

IR (CHCl\(_3\)): 2925, 2851, 2813, 2769, 1711, 1630, 1453 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) ppm: 1.20-1.46 (m, 20H), 1.54 (m, 4H), 2.20 (m, 2H), 2.39 (s, 6H), 2.40 (t, \(J =7.2\) Hz, 2H).
2-Methylcyclododecanone (78)

Compound 78 was prepared in a multistep sequence from cyclododecanone (69). A solution of cyclododecanone (69) (4.8933 g, 26.8 mmol) in N,N-dimethylhydrazine (10.0 mL, 131.6 mmol) was stirred for 2 hours at 50 °C. Anhydrous benzene (100 mL) was then added and an azeotropic distillation was carried out. After 20 hours, the benzene and excess N,N-dimethylhydrazine were removed under reduced pressure to afford a pale yellow solid containing 99% 72 by GC. The hydrazone 72 was redissolved in 100 mL of anhydrous THF. The solution was cooled to -78 °C prior to the addition of n-BuLi in hexanes (24.4 mL, 32.3 mmol). After 1 hour the solution was warmed to 0 °C for 10 minutes and recooled to -78 °C. Upon addition of Mel (3.34 mL, 53.5 mmol) a white precipitate occurred immediately. The reaction was allowed to slowly warm to RT. After continued stirring for 30 minutes at RT the reaction was quenched with water. Acid hydrolysis of hydrazone 75 was then carried out by the addition of 50 mL of H₂SO₄ (2.8 M). Upon addition of the acid the solution slowly turned yellow. After stirring vigorously for 4 hours, the organic layer was diluted with ether, washed once with H₂O, twice with NaHCO₃, once with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using pet. ether/EtOAc (30:1) as the eluent yielded 78 (4.290 g, 81%) as a pale yellow oil.
Bp: 100 °C at 0.3 mm Hg;

IR (CHCl₃): 2931, 2863, 1708, 1466 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.08 (d, J = 6.9 Hz, 3H), 1.14-1.45 (m, 14H), 1.53 (dtd, J = 13.4, 7.8, 3.5 Hz, 1H), 1.62-1.75 (m, 3H), 2.38 (ddd, J = 16.2, 7.4, 5.3 Hz, 1H), 2.67 (ddd, J = 16.2, 6.8, 5.1 Hz, 1H), 2.72 (qdd, J = 6.9, 8.8, 3.6 Hz, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 215.8, 45.5, 37.0, 31.5, 25.8, 25.4, 24.1, 24.0, 23.8, 22.7, 22.3, 22.1, 16.7;

LRMS(EI) m/z (relative intensity): 196[M⁺](21), 167(8), 149(9), 139(19), 55(100);

HRMS (EI) m/z calcd for C₁₃H₂₄O: 196.1827; found: 196.1821;

Anal. Calcd for C₁₃H₂₄O: C, 79.53; H, 12.32;

    Found: C, 79.70; H, 12.36.

2-Methylcyclotridecanone (79)

Compound 79 was prepared using the same methodology used to prepare 78. A solution of cyclotridecanone (70) (1.7121 g, 8.73 mmol) and N,N-dimethylhydrazine (12.0 mL, 158 mmol) was stirred for 1.5 hours at 50 °C. Anhydrous benzene (40 mL) was then added and an azeotropically distillation was carried out. After 12 hours, the benzene and excess N,N-dimethylhydrazine were removed under reduced pressure to afford a pale yellow solid containing 98% 73 by GC. The solid was dissolved in 25 mL
of THF and cooled to -78 °C prior to the addition of n-BuLi in hexane (8.41 mL, 11.4 mmol). The solution was stirred at -78 °C for 30 minutes and then warmed to 0 °C for 10 minutes. Mel (1.09 mL, 17.4 mmol) was added after recooling the solution to -78 °C. A white precipitate formed immediately. The solution was stirred for 10 minutes at -78 °C and then warmed to 0 °C for an additional 10 minutes before quenching with H₂O. Acid hydrolysis of the hydrazone was then carried out by the addition of 10 mL of a H₂SO₄ (2.8 M). After rapid stirring for 10 minutes, the aqueous layer was extracted with ether and the combined extracts with the organic layer were washed twice with a NaHCO₃ solution, dried over MgSO₄, and filtered. Concentration of the organic layer yielded a yellow oil. Purification by flash chromatography on silica gel using pet. ether / EtOAc (30:1) as the eluent yielded 2-methylcyclotridecane (79) as a pale yellow solid. Recrystallized in hexane afforded 79 (1.6785 g, 7.99 mmol) in 92% overall yield as a white crystalline solid. A 0.0476 g sample was further purified by sublimation at 30 °C/0.04 mm Hg onto a cold finger maintained at 0 °C to yield 79 (0.0366 g, 77%) as a white powder.

Mp: 31-31.5 °C;
Bp: 90 °C at 1 mm Hg;
IR (CHCl₃): 2928, 2859, 1709, 1459, 1408, 1371 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.06 (d, J = 6.7 Hz, 3H), 1.20-1.50 (m, 17H), 1.45-1.55 (m, 1H), 1.60-1.70 (m, 1H), 1.70-1.85 (m, 1H) 2.32 (ddd, J = 16.6, 7.5, 4.1 Hz, 1H), 2.62 (ddd, J = 16.6, 9.4, 3.6 Hz, 1H), 2.65 (m, 1H);
¹³C NMR (50 MHz, CDCl₃) ppm: 215.6, 46.2, 40.2, 32.9, 26.6, 26.3, 26.1, 25.6, 25.2, 24.9, 24.3, 24.3, 22.6, 17.0;
LRMS (El) m/z (relative intensity): 210(26), 181(13), 163(13), 139(16), 55(100);  
HRMS (El) m/z calcd for C_{14}H_{26}O: 210.1983; found: 210.1981;  
Anal. calcd for C_{14}H_{26}O: C, 79.94; H, 12.46;  
    Found: C, 80.05; H, 12.41.

2-Methylcyclopentadecanone (80)

2-Methylcyclopentadecanone (80) was prepared using the same procedure described for the preparation of ketones 78 and 79. A solution of cyclopentadecanone (71) (1.0224 g, 4.5 mmol) and N,N-dimethylhydrazine (1.7 mL, 22.8 mmol) was warmed to 50 °C. Azeotropic distillation for 12 hours after the addition of benzene (10 mL), followed by the removal of the benzene and excess N,N-dimethylhydrazine under reduced pressure afforded a yellow oil. A sample of the oil taken for GC analysis indicated that >99% of the ketone 71 was converted to the hydrazone 74. The oil was redissolved in 10 mL THF, cooled to -78 °C, and a solution of n-BuLi in hexane (3.6 mL, 5.0 mmol) was added. After stirring at -78 °C for 6 hours Mel (0.37 mL, 5.9 mmol) was added. The reaction was stirred at -78 °C for 30 minutes, then allowed to warm to RT. GC analysis of a sample at this time showed that the alkylation had occurred in 87% yield and the two isomers of the methyl hydrazone 77 were present in a 3.47:1
ratio. The hydrolysis of the hydrazone 77 was then carried out with the addition of 10 mL of a H₂SO₄ (2.8 M). A yellow oil was obtained after work up as described previously for the preparation of 78 and 79. Purification by flash chromatography on silica gel eluted with pet. ether / EtOAc (30:1) followed by Kugelrohr distillation (110 °C/ 0.2 mm Hg), yielded 2-methylcyclopentadecanone (80) (0.8752 g, 3.67 mmol) as a clear colourless oil in 81% yield.

Bp: 110 °C at 0.2 mm Hg;

IR (CHCl₃): 2925, 2857, 1710, 1457, 1368 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.06 (d, J = 6.27 Hz, 3H), 1.15-1.50 (m, 21H), 1.50-1.62 (m, 1H), 1.62-1.78 (m, 2H), 2.38 (dt, J = 11.2, 6.8 Hz, 1H), 2.51 (dt, J = 11.2, 6.8 Hz, 1H), 2.62 (m, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 215.6, 46.0, 40.5, 33.1, 27.5, 27.3, 26.9, 26.7, 26.5, 26.5, 26.3, 26.3, 26.2, 26.1, 22.8, 16.7;

LRMS (EI) m/z (relative intensity): 238(40), 209(18), 191(12), 181(11), 72(100);

HRMS (EI) m/z calcd for C₁₆H₃₀O: 238.2297; found: 238.2304;

Anal. calcd for C₁₆H₃₀O: C, 80.60; H, 12.68;

Found: C, 80.81; H, 12.97.
2-Methylcyclododecanone oximes (81)

Hydroxylamine hydrochloride (0.689 g, 9.91 mmol) and sodium acetate (0.862 g, 10.5 mmol) were added to a solution of 2-methylcyclododecanone (78) (1.287 g, 6.57 mmol) in 50 mL of methanol. The reaction mixture was stirred for 10 hours. After removal of the methanol under reduced pressure, the remaining white powder was suspended in H₂O and extracted three times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered and the solvent was removed under reduced pressure to afford 81 (1.36 g, 98%) as a white powder. The crude product was recrystallized from hexane to yield 81 (1.206 g, 87%) as white needles.

Mp: 105-106 °C;

IR (CHCl₃): 3588(s), 3266(b), 2927, 2861, 1654, 1468, 1456 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 0.99 (d, J = 7.0 Hz, 0.75H), 1.02 (d, J = 6.7 Hz, 2.25H), 1.15-1.6 (m, 17H), 1.75-1.86 (m, 0.75H), 1.86-2.00 (m, 0.25H), 2.00-2.05 (m, 0.75H), 2.05-2.14 (m, 0.25H), 2.33 (ddd, J = 4.0, 12.0, 16.5 Hz, 0.25H), 2.49 (qdd, J = 6.7, 4.0, 10.7 Hz, 0.75H), 2.81 (ddd, J = 4.6, 10.7, 13.1 Hz, 0.75H), 3.45 (qdd, J = 7.0, 3.4, 11.6 Hz, 0.25H), 9.0 (bs, 1H);
\(^{13}\)C NMR (50 MHz, CDCl\(_3\)) ppm: (major isomer) 163.7, 35.3, 32.6, 26.1, 25.8, 25.0, 24.6, 24.3, 23.7, 23.7, 22.8, 22.6, 20.8, (minor isomer) 162.4, 32.7, 31.2, 26.6, 25.9, 25.5, 23.6, 23.6, 23.5, 23.2, 22.6, 22.4, 17.8;

LRMS (El) m/z (relative intensity): 211(8), 194(11), 182(14), 168(3), 87(100);

HRMS (El) m/z calcd for C\(_{13}\)H\(_{25}\)NO: 211.1936; found: 211.1931;

Anal. calcd for C\(_{13}\)H\(_{25}\)NO: C, 73.88; H, 11.92; N, 6.63;

Found: C, 73.83; H, 11.92; N, 6.58.

2-Methylcyclotridecanone oximes (82)

Following the same procedure used for the preparation of 81, the addition of hydroxylamine hydrochloride (0.0884g, 1.27 mmol) and sodium acetate (0.1113g, 1.36 mmol) to 2-methylcyclotridecanone (79) (0.178g, 0.848 mmol) in 20 mL of methanol afforded after work up 82 (0.1833 g, 0.81 mmol) as a white powder in 96 % yield. The crude white powder was recrystallized from hexane to yield 82 (0.1281 g, 70%) as white needles.

Mp: 88-88.2 °C;
IR (CHCl₃): 3587, 3220, 2931, 2859, 1460 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.05 (d, J = 7.0, 0.3H), 1.06 (d, J = 7.0, 2.7H), 1.15-1.55 (m, 17H), 1.55-1.75 (m, 2H), 1.775-1.88 (m, 1H), 2.02 (td, J = 7.0, 12.8 Hz, 0.88H), 2.34 (qt, J = 7.0, 6.7 Hz, 0.88H), 2.58 (td, J = 7.0, 12.8 Hz, 0.88H), 3.26 (m, 0.22H), 8.3 (bs, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: (major isomer) 165.3, 38.9, 32.7, 27.3, 27.1, 26.0, 26.0, 25.5, 25.3, 25.3, 24.7, 24.6, 24.4, 19.1;

LRMS (EI) m/z (relative intensity): 226[M+1]+(20), 225[M+](100), 208(54), 196(53), 178(10), 166(11);

HRMS (EI) m/z calcd for C₁₄H₂₇NO: 225.2093; found: 225.2091;

Anal. calcd for C₁₄H₂₇NO: C, 74.61; H, 12.08; N, 6.21;

    Found: C, 74.60; H, 11.97; N, 6.10.

2-Methylcyclopentadecanone oximes (83)

Following the same procedure used for the preparation of 81, the addition of hydroxylamine hydrochloride (0.1311g, 1.89 mmol) and sodium acetate (0.1885g, 2.30 mmol) to 2-methylcyclopentadecanone (80) (0.2913g, 1.22 mmol) in 30 mL of methanol afforded after work up a white solid 83 (0.2911 g, 1.14 mmol) in a 94 % yield. The
crude white powder was recrystallized from hexane to afford 83 (0.2470 g, 80%) as white needles.

**Mp:** 65.4-66.0 °C;
**IR (CHCl₃):** 3589, 3266, 2930, 2858, 1653, 1459 cm⁻¹;
**¹H NMR (400 MHz, CDCl₃) ppm:** 1.04 (d, J = 7.0 Hz, 0.5H), 1.06 (d, J = 7.0 Hz, 2H), 1.18-1.48 (m, 21H), 1.48-1.58 (m, 1H), 1.58-1.75 (m, 2H), 2.08 (ddd, J = 6.4, 8.2, 14.7 Hz, 0.17H), 2.23 (ddd, J = 6.1, 9.2, 12.8 Hz, 1H), 2.33 (m, 1.67H), 3.26 (m, 0.17H), 8.9 (bs, 1H);
**¹³C NMR (50 MHz, CDCl₃) ppm:** (major isomer) 165.2, 38.9, 33.3, 28.2, 27.2, 26.8, 26.8, 26.8, 26.4, 26.3, 26.1, 26.1, 25.9, 24.7, 18.6;
**LRMS (El) m/z (relative intensity):** 253(9), 236(11), 224(22), 87(100);
**HRMS (El) m/z calcd for C₁₆H₃₁NO: 253.2406; found: 253.2405;
**Anal. calcd for C₁₆H₃₁NO: C, 75.83; H, 12.33; N, 5.53; Found: C, 75.78; H, 12.30; N, 5.45.**

**1-Dibromomethylcyclododecanol (87)**

![1-Dibromomethylcyclododecanol (87)](image)

To a stirring solution of TMP (6.6 mL, 39.1 mmol) in 40 mL THF at 0 °C was added n-BuLi in hexane (27.4 mL, 1.41 M, 39.5 mmol). After 10 minutes this solution
was added dropwise via a cannula to a solution of cyclododecanone (69) (3.268 g, 17.9 mmol) and CH₂Br₂ (2.77 mL, 39.5 mmol) in 100 mL dry Et₂O at -100 °C and stirred for one hour. After quenching the reaction with saturated aqueous NH₄Cl solution, the aqueous layer was extracted with Et₂O and the combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to yield a yellow oil. Purification by flash chromatography on silica gel eluting with pet. ether/EtOAc (2:1) yielded 87 as a pale yellow solid. The solid was recrystallized from hexane cooled to 0 °C to afford 87 (5.0768 g, 14.2 mmol) in 79.4% overall yield as a white crystalline solid. Concentration of the mother liquor and recrystallization afforded additional 87 (1.015 g, 2.9 mmol) as a white crystalline solid for a combined yield of 95%.

Mp: 62.3 °C;
IR (CHCl₃): 3567, 3550, 2932, 2859, 1470, 1447 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.25-1.55 (m, 18H), 1.62 (dt, J = 4, 11 Hz, 2H), 1.88 (dt, J = 3.7, 14 Hz, 2H), 2.00 (s, 1H), 5.72 (s, 1H);
LRMS (Ei) m/z (relative intensity): 356(0.2), 341(2), 339(4), 337(2), 277(5), 275(5), 95(100);
Anal. calcd for C₁₃H₂₄OBr₂: C, 43.84; H, 6.79; Br, 44.87;
Found: C, 43.84; H, 6.90; Br, 44.81.

Preparation of ketone 79 by ring expansion of 87

To a stirred solution of alcohol 87 (0.9240 g, 2.59 mmol) in 10 mL THF at -78 °C was slowly added n-BuLi (3.54 mL, 1.54 M, 5.45 mmol) using a syringe pump set at 0.07 mL/min. After the addition of n-BuLi, the reaction was stirred for 30 minutes at
-78 °C, warmed to 0 °C for 10 minutes and recooled to -78 °C prior to the addition of HMPA (1 mL) and MeI (0.48 mL, 7.8 mmol). The reaction was stirred at -78 °C for 30 minutes then allowed to warm to room temperature and stirred for 2 hours prior to quenching with 1N HCl (4 mL). The solution was diluted with Et₂O, washed 4 times with saturated aqueous CuSO₄, once with H₂O, dried with MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography eluting with pet. ether/EtOAc (40:1) afforded ketone 79 (0.2635 g, mmol) as a clear yellow oil in 48% yield having the same spectroscopic properties as described above.

1-Methyl-1-azacyclotridecan-2-one (89)

Upon cooling to -78 °C, lactam 88 (1.07 g, 5.42 mmol) in 50 mL THF precipitated out of solution. The lactam rapidly redissolved upon addition of n-BuLi (4.30 mL, 1.52 M, 6.54 mmol) to the suspension. After stirring for 2 hour at -78 °C MeI was added (0.44 mL, 7.1 mmol). The solution was allowed to warm to room temperature and stirring was continued overnight for 10 hours. The reaction was quenched with H₂O. The aqueous layer was extracted (3X) with Et₂O. The combined organic layers were dried with MgSO₄, filtered and the solvent was removed under reduced pressure to afford an dark yellow oil. Kugelrohr distillation of the oil (135 °C/1.2 mm Hg) afforded 89 (1.07 g, 5.06 mmol) in 93% yield as clear light yellow oil.
Bp: 135 °C at 1.2 mm Hg;

IR (CHCl$_3$): 2926, 2859, 1643, 1455, 1401 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: (two conformations in an approx. 0.8:1.1 ratio) 1.10-1.44 (m, 13.0H), 1.44-1.60 (m, 0.8H), 1.60-1.68 (m, 1.6H), 1.68-1.79 (m, 1.3H), 2.10 (ddd, J = 2.4, 9.8, 13.7 Hz, 0.8H), 2.31 (t, J = 7.6 Hz, 1.1H), 2.48 (td, J = 4.0, 13.4 Hz, 0.8H), 2.62 (ddd, J = 2.4, 9.2, 13.7 Hz, 0.8H), 2.88 (s, 1.7H), 2.99 (s, 1.3H), 3.25 (t, J = 7.6 Hz, 1.1H), 4.45 (ddd, J = 2.4, 10.9, 13.1 Hz, 0.8H);

$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 173.4, 173.0, 48.0, 46.2, 35.5, 33.3, 33.0, 31.6, 26.4, 26.4, 25.9, 25.5, 25.4, 25.2, 25.2, 25.0, 24.8, 24.7, 24.7, 24.6, 24.4, 24.0, 24.0, 23.6, 23.3, 23.2;

LRMS (EI) m/z (relative intensity): 211(100), 196(39), 182(9), 170(24), 154(11);

HRMS (EI) m/z calcd for C$_{13}$H$_{25}$NO: 211.1936; found: 211.1933

Anal. calcd for C$_{13}$H$_{25}$NO: C, 73.88; H, 11.92; N, 6.63;

Found: C, 74.02; H, 12.06; N, 6.88.

1,3-dimethyl-1-azacyclotridecan-2-one (90)

![Chemical structure](image)

An excess of t-BuLi (1.106 mL, 1.914 mmol) was added to a fine suspension of 1-aza-cyclotridecan-2-one (88) (0.0944 g, 0.478 mmol) in 10 mL of hexane at room temperature. The suspended lactam was completely dissolved within 2 hours. Excess
Mel (0.18 mL, 2.9 mmol) was added after 12 hours. The reaction mixture remained clear and colourless. After stirring for 10 minutes a 1 mL test sample was removed. After standard work up of the test sample the product was found to be 3-methyl-1-azacyclotridecan-2-one (84) by TLC and GC comparison with an authentic sample. The reaction was continued for one hour. HMPA (0.5 mL) was then added. A white precipitate formed almost immediately. The reaction was quenched with water and diluted with EtOAc. The organic layer was washed four times with saturated CuSO₄ (to remove HMPA), once with H₂O, once with brine, dried with MgSO₄, and filtered. After concentration under reduced pressure a yellow solid (0.0888g) was obtained containing a mixture of 84 and 90. Flash chromatography using pet. ether/Et₂O (1:1) afforded 0.0486g (0.23 mmol, 48%) of a white solid which was identical to compound 84 obtained from the Beckmann rearrangement of 81, and 0.0285g (0.13 mmol, 26%) of 90 as a yellow oil. Kugelrohr distillation of the oil afforded 0.0260g of 90 (0.116 mmol, 24%) as a clear colourless oil.

IR (CDCl₃): 2932.2, 2861.6, 1626.56, 1445.5, 1408.2 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.05 (d, J = 6.71 Hz, 1.5H), 1.06 (d, J = 6.72 Hz, 1.5H), 1.11-1.53 (m, 15.5H), 1.53-1.74 (m, 2H), 1.94 (m, 0.5H) 2.47 (ddd, J = 3.1, 5.5, 13.6 Hz, 0.5H), 2.71-2.84 (m, 1H), 2.89 (s, 1.5H), 3.01 (s, 1.5H), 3.12 (dt, J = 14.1, 7.02 Hz, 0.5H), 3.48 (dt, J = 14.3, 7.02 Hz, 0.5H), 4.44 (ddd, J = 3.05, 10.07, 13.43 Hz, 0.5H);

¹³C NMR (50 MHz, CDCl₃) ppm: 203.1, 48.2, 47.0, 35.8, 35.4, 34.0, 34.0, 33.7, 32.4, 26.7, 26.5, 26.5, 26.3, 26.3, 26.0, 25.8, 25.3, 25.3, 25.3, 24.8, 24.3, 24.1, 24.0, 24.0, 23.5, 17.7, 17.6;

LRMS (EI) m/z (relative intensity): 225(100), 210(7), 196(64), 184(14), 168(7), 154(7);
HRMS (EI) m/z calcd for C$_{14}$H$_{27}$NO: 225.2093; found: 225.2092;  
Anal. calcd for C$_{14}$H$_{27}$NO: C, 74.61; H, 12.08; N, 6.21;  
    Found: C, 74.58; H, 12.04; N, 6.16.

(3R*,13S*)-3,13-dimethyl-1-azacyclotridecan-2-one (92)

To a fine suspension of lactam 65 (0.1179 g, 0.557 mmol) in 60 mL of hexane at room temperature was added $t$-BuLi in hexane (1.31 mL, 2.23 mmol). The suspended lactam slowly dissolved within 2 hours. After stirring for 10 hours, Mel (0.17 mL, 2.8 mmol) was added to the solution. No precipitation was observed. The reaction was quenched with water after 3 hours. A white precipitate was observed immediately upon addition of water. EtOAc was added to redissolve the precipitate. The organic layer was washed with H$_2$O, once with brine, dried with MgSO$_4$, and filtered. After the removal of the solvent under reduced pressure a white solid was obtained containing lactam 92 (0.1240 g, 0.55 mmol) in 98% yield. The white solid was recrystallized in acetone to afford 92 (0.0737 g) as small white needles.

Mp: 202.5-203 °C  
IR (CHCl$_3$): 3435, 2932, 2861, 1652, 1511, 1457 cm$^{-1}$;
$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.10 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 7.3 Hz, 3H),
1.18-1.48 (m, 16H), 1.52 (m, 1H), 1.69 (tdd, J = 7.9, 2.4, 14.3 Hz, 1H), 2.37
(qdd, J = 7.3, 4.0, 10.0, 1H), 4.01 (qddd, J = 6.7, 2.4, 9.5, 10.1 Hz, 1H), 5.18
(d, J = 9.5 Hz, 1H);
$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 175.8, 45.1, 43.1, 36.5, 34.9, 27.0, 26.9, 25.0, 24.3,
24.2, 24.0, 22.9, 21.9, 18.8;
LRMS (El) m/z (relative intensity): 226[M+1]$^+$ (10), 225[M]$^+$ (55), 210(14), 196(17),
182(13), 44(100);
HRMS (El) m/z calcd for C$_{14}$H$_{27}$NO: 225.2093; found: 225.2092;
Anal. calcd for C$_{14}$H$_{27}$NO: C, 74.61; H, 12.08; N, 6.21;
Found: C, 74.54; H, 12.06; N, 6.18.

$^{(3S^*,13S^*)}$-3,13-dimethyl-1-azacyclotridecan-2-one (93)

Following the procedure for the preparation of lactam 65, tosyl chloride (0.0247 g,
0.129 mmol) was added as a solid to a solution of oxime 107 (0.0211 g, 0.0936 mmol)
and pyridine (16 μL, 0.197 mmol) in 5 mL of CH$_2$Cl$_2$. After work-up, flash
chromatography afforded the Beckmann rearranged product 93 (0.0204 g, 0.0905
mmol, 97 %). Crude lactam 93 was recrystallized from EtOH/H$_2$O to afford 93
(0.0185 g, 88 %), as white needles.
IR (CHCl₃): 3435, 3328, 2931, 2860, 1660, 1503, 1455 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.09 (d, J = 6.7 Hz, 3H) 1.10 (d, J = 6.7 Hz, 3H), 1.15-1.50 (m, 16H), 1.62 (m, 1H), 1.70 (tdd, J = 8.4, 2.8, 14.0 Hz, 1H), 2.13 (qdd, J = 6.7, 3.4, 9.8 Hz, 1H), 4.06 (qddd, J = 6.7, 2.8, 8.9, 9.5 Hz, 1H), 5.14 (d, J = 9.5 Hz, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 175.6, 44.6, 41.4, 35.9, 34.1, 26.8, 26.3, 26.1, 25.0, 25.0, 24.6, 22.7, 21.6, 18.1;

LRMS (El) m/z (relative intensity): 225(100), 210(27), 196(27), 182(27);

HRMS (El) m/z calcd for C₁₄H₂₇NO: 225.2093; found: 225.2092;

Anal. calcd for C₁₄H₂₇NO: C, 74.61; H, 12.08; N, 6.21;

Found: C, 74.51; H, 12.08; N, 6.18.

(3R*,14S*)-3,14-dimethyl-1-azacyclotetradecan-2-one (94) and
(3S*,14S*)-3,14-dimethyl-1-azacyclotetradecan-2-one (95)

Following the same procedure for the preparation of 92, t-BuLi in hexane (0.63 mL, 0.76 mmol) was added to a fine suspension of lactam 66 (0.0430 g, 0.191 mmol) in 30 mL of hexane at room temperature. The suspended lactam slowly dissolved within 2 hours. After stirring for 10 hours, Mel (0.059 mL, 0.96 mmol) was added to the
solution. The reaction was quenched with water after 3 hours. After standard work up a white solid was obtained containing lactams 66, 94 and 95 in a 9:62:1 ratio by GC. Flash chromatography on silica gel eluting with pet. ether/Et₂O (1:1) afforded lactam 95 (0.0010 g, 0.004 mmol, 2%), 66 (0.0030 g, 0.013 mmol, 7%), and 94 (0.0291 g, 0.122 mmol, 64%), as white solids.

Compound 94
IR (CDCl₃): 3444, 2933, 2860, 1654, 1513, 1450 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.11 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 7.3 Hz, 3H), 1.15-1.48 (m, 18H), 1.54-1.65 (m, 2H), 2.39 (qdd, J = 7.3, 3.7, 10.3 Hz, 1H), 4.02 (qddd, J = 6.7, 3.1, 9.0, 9.3 Hz, 1H), 5.12 (d, J = 9.0 Hz, 1H);
LRMS (El) m/z (relative intensity): 240(5), 239(60), 224(10), 210(16), 196(10), 44(100);
HRMS (El) m/z calcd for C₁₅H₂₉NO: 239.2249; found: 239.2247;
Anal. calcd for C₁₅H₂₉NO: C, 75.26; H, 12.21; N, 5.85;
    Found: C, 75.04; H, 12.24; N, 5.76.

Compound 95
IR (CDCl₃): 3435, 2932, 2860, 1662, 1508, 1451 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.10 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.15-1.50 (m, 18H), 1.58 (tdd, J = 8.1, 13.0, 2.8 Hz, 1H) 1.68 (m, 1H), 2.09 (qdd, J = 6.7, 2.4, 10.6 Hz, 1H), 4.12 (qddd, J = 6.7, 2.7, 9.1, 9.3 Hz, 1H), 5.09 (d, J = 9.1 Hz, 1H);
¹³C NMR (75 MHz, CDCl₃) ppm: 175.7, 44.2, 41.8, 36.3, 34.5, 26.6, 26.0, 25.9, 25.3, 25.2, 23.6, 23.5, 22.5, 21.9, 18.7;
LRMS (El) m/z (relative intensity): 240(10), 239(52), 224(12), 210(19), 196(11), 182(7), 44(100); 

HRMS (El) m/z calcd for C_{15}H_{29}NO: 239.2249; found: 239.2247; 
Anal. calcd for C_{15}H_{29}NO: C, 75.26; H, 12.21; N 5.85; 

Found: C, 75.14; H, 12.22; N 5.74.

(3R*,16S*)-3,16-dimethyl-1-azacyclohexadecan-2-one (96) and (3S*,16S*)-3,16-dimethyl-1-azacyclohexadecan-2-one (97)

Following the same procedure for the preparation of 92, t-BuLi in hexane (2.1 mL, 1.48 M, 3.2 mmol) was added to a fine suspension of lactam 67 (0.1609 g, 0.635 mmol) in hexane (100 mL) at room temperature. After stirring for 10 hours, Mel (0.25 mL, 3.9 mmol) was added to the solution. The reaction was quenched with water after 3 hours. Following standard work up a white solid (0.1680 g) was obtained containing lactams 96 and 97 in a 1:9.8 ratio by GC. Flash chromatography on silica gel eluting with pet.
ether/Et_{2}O (1:1) afforded lactam 97 (0.0057 g, 0.021 mmol) a mixture of lactam 96 and 97 (0.0472 g) followed by lactam 96 (0.1100 g, 0.41 mmol) in an overall yield of 94%.
Lactam 96 was recrystallized from mixed solvent system of EtOH and H₂O to afford lactam 96 (0.0968 g, 88%) as white needles.

**Compound 96**

IR (CHCl₃): 3443, 2927, 2858, 1652, 1506, 1458 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.10 (d, J = 6.4 Hz, 3H), 1.02 (d, J = 7.3 Hz, 3H), 1.15-1.43 (m, 22H), 1.44-1.62 (m, 2H), 2.37 (qddd, J = 7.3, 5.2, 10.1 Hz, 1H), 3.99 (qddd, J = 6.4, 3.7, 8.3, 8.5 Hz, 1H), 5.16 (d, 8.5 Hz, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 175.5, 45.0, 42.1, 36.7, 35.1, 27.8, 27.7, 27.2, 27.1, 26.2, 26.0, 25.9, 25.7, 25.7, 25.1, 21.5, 17.9;

LRMS (El) m/z (relative intensity): 268[M⁺](16), 267[M⁺](88), 252(22), 238(44), 224(26), 210(11), 44(100);

HRMS (El) m/z calcd for C₁₇H₃₃NO: 267.2562; found: 267.2560;

Anal. calcd for C₁₇H₃₃NO: C, 76.34; H, 12.44; N, 5.24;

Found: C, 76.67; H, 12.41; N, 5.05.

**Compound 97**

IR (CHCl₃): 3445, 2931, 2860, 1660, 1508, 1455 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.09 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.14-1.45 (m, 21H), 1.50 (m, 1H), 1.65 (m, 2H), 2.03 (qddd, J = 6.7, 4.2, 10.2, 1H), 4.09 (qddd, J = 6.7, 3.2, 8.3, 9.0 Hz, 1H), 5.14 (d, 9.0 Hz, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 175.3, 45.6, 42.5, 37.1, 34.9, 28.2, 27.8, 27.4, 27.3, 27.2, 26.2, 25.8, 25.3, 25.2, 24.9, 21.8, 18.4;

LRMS (El) m/z (relative intensity): 268[M⁺](8), 267[M⁺](82), 252(20), 238(32), 224(18), 210(10), 44(100);
HRMS (El) m/z calcd for C_{17}H_{33}NO: 267.2562; found: 267.2560;

(2R*,12S*)-2,12 Dimethylcyclododecanone (98) and
(2S*,12S*)-2,12 dimethylcyclododecanone (99)

\[ \text{98} + \text{99} \]

\[ n-\text{BuLi in hexane (1.14 mL, 8.15 mmol) was added to a solution of diisopropyl amine (5.7 mL, 7.6 mmol) in 20 mL of THF at -78 °C. After stirring for 10 minutes at -78 °C, warming the solution to 0 °C for 10 minutes and recooling to -78 °C, the solution was transferred via a cannula into a solution of ketone 78 (1.2049 g, 6.13 mmol) and one crystal of 1,10 phenanthroline in 30 mL of THF at -78 °C. The solution turned dark red immediately. After 5.5 hours, Mel (0.63 mL, 10 mmol) followed by 5 mL of DMPU were injected. No colour change was observed within 1 hour. The reaction was maintained at -78 °C overnight (11 hours) at which time the solution became clear and pale yellow. The reaction was then warmed to room temperature, and quenched with 1 mL of water. After the removal of THF under reduced pressure the oil was taken up in Et₂O and washed twice with water. The organic layer was then dried with MgSO₄, filtered and concentrated under reduced pressure to afford a mixture of 98 and 99 (1.24 g, 96%) in a 6:1 ratio by GC analysis. Flash chromatography eluting with CH₂Cl₂ afforded three fractions containing ketone 99 (0.129 g, 0.61 mmol) as white solid, a} \]
mixture of 98 and 99 (0.075 g, 0.35 mmol) as an oil and compound 98 (0.990 g, 0.47 mmol) as white solid, in a 91 % overall yield.

Compound 98
Mp: 44.5-45 °C;
IR (CHCl₃): 2935, 2867, 1703, 1462 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.02 (d, J = 6.4 Hz, 6H), 1.05-1.17 (m, 2H), 1.17-1.4 (m, 12H), 1.48-1.58 (m, 2H), 1.66-1.78 (m, 2H), 2.91-2.99 (m, 2H);
¹³C NMR (CDCl₃, 50 MHz) ppm: 73.4, 42.7, 31.0, 25.4, 24.9, 22.3, 22.0, 16.9;
LRMS (EI) m/z (relative intensity): 211(5), 210(30), 181(5), 168(3), 153(15), 112(31), 86(100);
HRMS (EI) m/z calcd for C₁₄H₂₆O: 210.1984; found: 210.1984;
Anal. calcd for C₁₄H₂₆O: C, 79.94; H, 12.46;
    Found: C, 80.00; H, 12.41.

Compound 99
Mp: 25-25.2 °C;
IR (CHCl₃): 2932, 2862, 1694, 1461 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.08 (d, J = 6.9 Hz, 6H), 1.15-1.47 (m, 16H) 1.82-1.92 (m, 2H), 2.74 (qdd, J = 6.9, 9.7, 4.2 Hz, 2H);
¹³C NMR (CDCl₃, 50 MHz) ppm: 219.5, 43.0, 32.7, 25.3, 24.5, 24.1, 23.3, 18.8;
LRMS (EI) m/z (relative intensity): 211(4), 210(30), 181(5), 168(3), 153(15);
HRMS (EI) m/z calcd for C₁₄H₂₆O: 210.1984; found: 210.1984;
Anal. calcd for C₁₄H₂₆O: C, 79.94; H, 12.46;
    Found: C, 80.00; H, 12.53.
Following the same procedure for the preparation of 98 and 99, ketone 79 (0.4091g 1.9 mmol) was deprotonated with LDA previously prepared from 2.6 mL (2.9 mmol) of n-BuLi and 0.425 mL (3.1 mmol) of diisopropyl amine. The lithium enolate was then alkylated with 0.242 mL (3.89 mmol) of Mel. After work up and separation on a silica column eluting with pet. ether/Et₂O (6:1), 0.3096g (71%) of 100 as a white solid, and 0.1018g (23%) of 101 as a yellow oil were obtained. Recrystallization of the solid from EtOH/H₂O afforded 0.3001g (67%)100 as white needles. Kugelrohr distillation (100 °C/0.1 mm Hg) of the oil afforded 0.0943g (21%) of 101 as a clear colourless oil.

Compound 100

IR (CHCl₃): 2929, 2861, 1704, 1459, 1375 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.02 (d, J = 7.8 Hz, 6 H) 1.15-1.45 (m, 18 H) 1.68-1.80 (m, 2 H), 2.68-2.78 (m, 2H);

¹³C NMR (CDCl₃, 50 MHz) ppm: 218.8, 45.5, 32.6, 25.7, 25.5, 25.2, 23.4, 17.4;

LRMS (EI) m/z (relative intensity): 225 (M+1⁺, 10) 224 (M⁺, 47), 210(2), 195(6), 177(3) 86(100);

HRMS (EI) m/z calcd for C₁₅H₂₈O: 224.2140; found: 224.2143;
Anal. calcd for $\text{C}_{15}\text{H}_{28}\text{O}$: C, 80.29; H, 12.58;

Found: C, 80.07; H, 12.57.

**Compound 101**

IR (CHCl$_3$): 2929, 2861, 1696, 1459, 1374 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.04 (d, $J = 6.8$ Hz, 6H), 1.2-1.35 (m, 14H), 1.35-1.48 (m, 4H), 1.60-1.76 (m, 2H), 2.65 (m, 2H);

$^{13}$C NMR (CDCl$_3$, 50 MHz) ppm: 219.0, 43.6, 32.8, 26.3, 25.5, 25.3, 25.0, 17.0;

LRMS (El) m/z (relative intensity): 225 (M$^{+}$, 6), 224 (M$^{+}$, 32), 210 (2), 195 (5), 86(100);

HRMS (El) m/z calcd for $\text{C}_{15}\text{H}_{28}\text{O}$: 224.2140; found: 224.2143;

Anal. calcd for $\text{C}_{13}\text{H}_{28}\text{O}$: C, 80.29 H, 12.58;

Found: C, 80.11; H, 12.57.

(2R*,12S*)-2,12-Dimethylcyclododecan-1β-ol (102) and
(2R*,12S*)-2,12-dimethylcyclododecan-1α-ol (103)

Ketone 98 (0.3984 g, 1.89 mmol) dissolved in 10 mL of THF was injected dropwise into a solution of lithium aluminum hydride (0.036 g, 0.95 mmol) in 10 mL THF at 0 °C.

After 70 minutes the reaction was quenched by the addition of a few crystals of
Na$_2$SO$_4$·10H$_2$O followed by 10 mL of water. The products were extracted using Et$_2$O, which was then dried (MgSO$_4$), filtered and concentrated under reduced pressure. Flash chromatography on a silica gel eluting with CH$_2$Cl$_2$ afforded 0.3166 g (78.8%) alcohol 102 and 0.0537g (13.4%) alcohol 103.

**Compound 102**

Mp: 28.7-29 °C;

IR (CHCl$_3$): 3625, 3450, 2910, 1458, 1064, 969 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 0.96 (d, J = 6.9, 6H), 1.04 (m, 2H), 1.16-1.34 (m, 8H) 1.39-1.68 (m, 10H), 3.35 (t, J = 3.35 Hz, 1H);

$^{13}$C NMR (CDCl$_3$, 50 MHz) ppm: 81.0, 37.9, 28.7, 25.3, 25.3, 24.5, 23.8, 19.9;

LRMS (El) m/z (relative intensity): 212(M$^+$, 23), 194(3), 179(2), 170(5), 58(100);

Anal. calcd for C$_{14}$H$_{28}$O: C, 79.18; H, 13.29;

    Found: C, 79.37; H, 13.36.

**Compound 103**

Mp: 77-78 °C

IR (CHCl$_3$): 3630, 3611, 2931, 2867, 2852, 1462 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 0.90 (d, J = 6.9 Hz, 6H), 1.20-1.50 (m, 18H), 1.75-1.85 (m, 2H), 3.54 (t, J = 5.68 Hz, 1H);

$^{13}$C NMR (CDCl$_3$, 50 MHz) ppm: 74.0, 32.7, 30.8, 24.8, 24.0, 22.7, 20.1, 14.5;

LRMS (El) m/z (relative intensity): 212(M$^+$, 22), 194(3), 179(2), 170(5), 154(17), 58(100);

Anal. calcd for C$_{14}$H$_{28}$O: C, 79.18; H, 13.29;

    Found: C, 79.25; H, 13.32.
Following the procedure for the reduction of 98, ketone 99 (0.0716 g, 0.34 mmol) in 10 mL THF at 0°C was reduced with 0.0075 g (0.19 mmol) of lithium aluminum hydride to produce 0.0607 g (84%) of 104 as a white powder. The powder was recrystallized from EtOH/H₂O to yield 0.0519 g (72%) of 104 as a white crystalline solid.

Mp: 87.5-88.0 °C;

IR (CHCl₃): 3624, 3601, 2931, 2862, 1466 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 0.80 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 1.0 (m, 1H), 1.17-1.70 (m, 18H), 1.80-1.90 (m, 1H), 3.11 (dd, J = 1.2, 10 Hz, 1H);


LRMS (EI) m/z (relative intensity): 212 (M⁺, 27), 194(3), 179(1), 170(7), 154(15), 58(100);

HRMS (EI) m/z calcd for C₁₄H₂₈O: 212.2140; found: 212.2148;

Anal. calcd for C₁₄H₂₈O: C, 79.18; H, 13.29;

   Found: C, 79.42; H, 13.49.
Following the procedure for the reduction of 98, ketone 101 (0.0322 g, 0.14 mmol) was reduced with 0.0027 g (0.0718 mmol) of lithium aluminum hydride to produce 0.0300 g (90%) of 105 as a clear pale yellow oil. Kugelrohr distillation of the oil afforded 0.0276g (85%) 105 of a clear colourless oil which crystallized.

Mp: 77-78.2 °C;

IR (CHCl₃): 3624, 3602, 2929, 2861, 1459 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 0.85-1.05 (m, 2H), 0.96 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 1.05-1.52 (m, 19H), 1.52-1.64 (m, 1H), 1.74-1.85 (m, 1H), 3.1 (dd, J = 2, 8 Hz, 1H);

¹³C NMR (CDCl₃, 50 MHz) ppm: 81.4, 35.5, 33.1, 30.2, 26.5, 26.1, 25.8, 25.6, 25.6, 25.4, 24.7, 24.7, 17.7, 16.6;

LRMS (El) m/z (relative intensity): 226(M⁺, 29), 208(4), 184(4), 168(12), 152(4), 58(100);

HRMS (El) m/z calcd for C₁₄H₂₈O: 212.2140; found: 226.22997;

Anal. calcd for C₁₄H₂₈O: C, 79.18; H, 13.29;

   Found: C, 79.28; H, 13.33.
(2R*,12S*)-2,12-Dimethycyclododecanone oxime (106) and (2S*,12S*)-2,12-dimethycyclododecanone oxime (107)

Ketone 98 (0.3742 g, 1.78 mmol) was added as a powder to a solution of 0.6399 g (5.70 mmol) of t-BuOK and 0.1610 g (2.32 mmol) NH₂OH·HCl in 25 mL of t-amyl alcohol. The reaction was then refluxed for 12 hours. After cooling to room temperature solution was concentrated under reduced pressure. The residue was taken up in 20 mL of 1M ammonium chloride and extracted with Et₂O. The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure. Separation on a silica column eluting with pet. ether/EtOAc (20:1) afforded 0.1940 g (48 %) of oxime 107, 0.0532 g (13%) of oxime 106 and 0.1615g (28%) of recovered ketone 98.

Compound 106
Mp: 108.5-109 °C;
IR (KBr): 3274, 2927, 2856, 1728, 1661, 1466, 1445 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.09 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.18-1.55 (m, 17H), 1.62 (m, 1H), 2.37 (m, 1H), 2.45 (m, 1H), 8.1 (bs, 1H);
¹³C NMR (50 MHz, CDCl₃) ppm: 164.9, 39.8, 39.0, 33.9, 32.5, 27.9, 26.9, 26.6, 26.0, 25.8, 22.4, 21.9, 19.3, 18.2;
LRMS (EI) m/z (relative intensity): 225(10), 208(13), 196(9), 192(7);
HRMS (El) m/z calcd for C_{14}H_{27}NO: 225.2093; found: 225.2091;
Anal. calcd for C_{14}H_{27}NO: C, 74.61; H, 12.08; N 6.21;

Found: C, 74.52; H, 12.06; N, 6.18.

Compound 107

Mp: 122-122.2 °C;
IR (KBr): 3266, 2926, 2852, 1657, 1467, 1438 cm^{-1};
$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.08 (d, J = 7.1 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H),
1.15-1.40 (m, 13H), 1.45 (m, 2H), 1.68 (m, 1H), 1.83 (m, 1H), 2.50 (qdd, J = 6.7, 10.8, 4.1 Hz, 1H), 3.45 (m, 1H), 8.5 (bs, 1H);
$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 167.0, 34.5, 33.2, 32.8, 31.0, 26.8, 26.1, 25.0, 24.6,
24.4, 23.2, 23.2, 23.0, 19.0;
LRMS (El) m/z (relative intensity): 225(23), 208(24), 196(17), 182(7);
HRMS (El) m/z calcd for C_{14}H_{27}NO: 225.2092; found: 225.2095;
Anal. calcd for C_{14}H_{27}NO: C, 74.61; H, 12.08; N, 6.21;

Found: C, 74.48; H, 12.00; N, 6.15.

(2R*,13S*)-2,13-Dimethylcyclotridecanone oxime (108) and
(2R*,13S*)-2,13-dimethylcyclotridecanone oxime (109)
Following the procedure for the preparation of 106 and 107, ketone 100 0.0849 g (0.38 mmol) was added to 0.526 g (0.758 mmol) of NH₂OH·HCl and 0.170 g (1.51 mmol) of t-BuOK in 15 mL t-amyl alcohol. After work up, separation on a silica column eluting with pet. ether/Et₂O (20:1) afforded 0.0387 g (43%) of oxime 109, 0.0240 g (26%) of oxime 108 and 0.0095 g (10%) of recovered ketone 100.

Compound 108
Mp: 119-119.2 °C;
IR (KBr): 3244, 2926, 2855, 1673, 1452 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.08 (d, J = 6.8 Hz, 3H), 1.00-1.15 (m, 1H), 1.22-1.42 (m, 15H), 1.41 (d, J = 7.01 Hz, 3H), 1.52 (m, 1H), 1.59 (m, 1H), 1.80 (m, 1H), 2.01 (m, 1H), 2.18-2.30 (m, 2H), 7.85 (s, 1H);
¹³C NMR (CDCl₃, 50 MHz) ppm: 166.8, 40.4, 39.4, 32.5, 31.6, 26.3, 25.6, 25.3, 25.3, 25.1, 24.5, 23.4, 18.3, 16.9;
LRMS (El) m/z (relative intensity): 239(10), 222(12), 210(10), 114(18), 101(100);
HRMS (El) m/z calcd for C₁₅H₂₉NO: 239.2249; found: 239.2255;
Anal. calcd for C₁₅H₂₉NO: C, 75.26; H, 12.21;
           Found: C, 75.37; H, 12.12.

Compound 109
Mp: 107.2-107.5 °C;
IR (KBr): 3266, 29217, 2853, 1657, 1457 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 1.08 (d, J = 7.0 Hz, 3H), 1.09 (d, J = 7.1 Hz, 3H), 1.20-1.48 (m, 18H), 1.48-1.75 (m, 2H), 2.30-2.45 (m, 1H), 3.06-3.29 (m, 1H), 7.87 (s, 1H);
\[^{13}\text{C}\] NMR (CDCl\textsubscript{3}, 50 MHz) ppm: 167.9, 35.1, 35.1, 33.7, 31.8, 27.0, 26.7, 26.3, 25.9, 25.7, 25.4, 25.3, 25.0, 21.3, 17.6;

LRMS (EI) m/z (relative intensity): 239(40), 224(10), 222(27), 210(3), 196(24), 115(100);

HRMS (EI) m/z calcd for C\textsubscript{15}H\textsubscript{29}NO: 239.2249; found: 239.2252;

Anal. calcd for C\textsubscript{15}H\textsubscript{29}NO: C, 75.26; H, 12.21; N, 5.85;

Found: C, 75.27; H, 12.21; N, 5.65.

**Beckmann rearrangement of 106-108**

**Lactam 92**

Following the procedure for the preparation of lactam 65, tosyl chloride (0.010 g, 0.52 mmol) was added as a solid to a solution of oxime 106 (0.0087 g, 0.038 mmol) and pyridine (6.2 \(\mu\)L, 0.077 mmol) in 5 mL of CH\(_2\)Cl\(_2\). After work-up, flash chromatography afforded the Beckmann rearranged product 92 (0.0071 g, 0.032 mmol, 82 %) as a white solid. GC and \(^1\text{H}\) NMR are consistent with previously prepared sample 92.

**Lactam 94**

Following the procedure for the preparation of lactam 65, tosyl chloride (0.0086 g, 0.045 mmol) was added as a solid to a solution of oxime 108 (0.0062 g, 0.026 mmol) and pyridine (3 \(\mu\)L, 0.037 mmol) in 5 mL of CH\(_2\)Cl\(_2\). After work-up, flash chromatography afforded the Beckmann rearranged product 94 (0.0040 g, 0.017 mmol, 65 %) as a white solid. GC and \(^1\text{H}\) NMR are consistent with previously prepared sample 94.
Lactam 95

Following the procedure for the preparation of lactam 65, tosyl chloride (0.019 g, 0.10 mmol) was added as a solid to a solution of oxime 109 (0.0161 g, 0.0382 mmol) and pyridine (11 μL, 0.13 mmol) in 5 mL of CH₂Cl₂. After work-up, flash chromatography afforded the Beckmann 95 (0.0148 g, 0.062 mmol, 92 %) as a white solid. GC and ¹H NMR are consistent with previously prepared sample 95.

(3R*,16S*)-1-Benzyl-3,16-dimethyl-1-azacyclohexadecan-2-one (110) and (3S*,16S*)-1-benzyl-3,16-dimethyl-1-azacyclohexadecan-2-one (111)

Method 1

To a solution of benzyl lactam 68 (0.0553 g, 0.16 mmol) in THF (9 mL) at -78 °C was added t-BuLi in hexane (0.13 mL, 1.48 M, 0.19 mmol). The solution was stirred for 10 minutes then Mel (0.040 mL, 0.64 mmol) was added. After 15 minutes the reaction was allowed to warm to room temperature, then quenched with water. The aqueous layer was extracted with Et₂O. The organic extracts were combined, dried with MgSO₄, and filtered. Removal of the solvent under reduced pressure afforded 0.0570 g of a mixture of lactams 110, 111 and 68 in a ratio of 1.65:1:0.6 as yellow oil. Flash chromatography eluting with pet. ether afforded 110 (0.0098 g, 0.0275 mmol), a
mixture of lactams 110 and 111 (0.0365 g, 0.1022 mmol) and recovered starting material lactam 68 (0.0092 g, 0.0268 mmol).

**Method 2**

DMSO (3 mL) was added to NaH (1.4 g, 60% NaH in oil, 0.35 mmol). The mixture was warmed to 80 °C for 2 hours and cooled to RT. Benzyl lactam 68 (0.0092 g, 0.026 mmol) in 2 mL of DMSO was added via a cannula to the reaction vessel. After stirring overnight at RT, MeI (0.0064 mL, 0.1 mmol) was added. Following standard work up lactams 110, 111 and 68 were obtained in 1:1.31:1 ratio by GC. Flash chromatography afforded a 1:1.31 mixture of lactams 110 and 111 (0.0041g) as an oil.

**Compound 110**

IR (CHCl₃): 2936, 2859, 1634, 1501, 1451 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.11 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.0-1.45 (m, 22H), 1.45-60 (m, 1H), 1.75-1.90 (m, 1H), 2.82-2.95 (m, 1H), 4.05-4.15 (m, 1H), 4.45 (d, J = 14.9 Hz, 1H), 4.54 (d, J = 14.9 Hz, 1H), 7.1-7.4 (m, 5H);

¹³C NMR (50 MHz, CDCl₃) ppm: 177.6, 140.2, 128.2, 127.2, 126.4, 53.4, 43.9, 35.8, 35.3, 33.8, 28.0, 28.0, 27.2, 26.9, 26.6, 26.1, 25.9, 25.8, 25.0, 25.0, 20.5, 19.2;

LRMS (El) m/z (relative intensity): 358(13), 357(49), 342(7), 328(11), 314(4), 267(17), 266(80), 91(100);

HRMS (El) m/z calcd for C₂₄H₉₉NO: 357.3031; found: 357.3034.
Deprotection of 110 to 96

NH₃ (10 mL) was condensed into a flask, dried over Na and redistilled (5 mL) into the reaction flask at -78 °C. The NH₃ solution turned blue upon the addition of lithium (0.010 g, 1.44 mmol). After stirring for 10 minutes benzyl lactam 110 (0.0098 g, 0.027 mmol) in THF (1 mL) was added to the reaction vessel at -78 °C. The reaction was quenched with EtOH after 15 minutes. The solvent was removed under reduced pressure. The white solid was taken up in Et₂O and washed twice with H₂O. The organic layer was dried with MgSO₄, filtered and the solvent removed under reduced pressure to afford lactam 96 (0.0073 g, 0.027 mmol) in 100 % yield. Both the GC retention time and ¹H NMR were identical to those previously reported for lactam 96.

Deprotection of a mixture of 110 and 111 to 96 and 97
Following the same procedure used for the reduction of 110, a 1:1 mixture of benzyl lactams 110 and 111 (0.0084 g, 0.024 mmol) in 1 mL THF was added to a solution of Li (0.0090 g, 1.3 mmol) in NH₃ (10 mL) to afford after work up a 1:1 mixture (by GC) of dialkylated lactams 96 and 97 (0.0064 g, 0.024 mmol) in 100 % yield as a white solid. Both the GC retention times and \(^1\)H NMR spectra were identical to those previously reported for lactams 96 and 97.

Azacyclotridecane (120)

A solution of 1-azacyclotridecan-2-one (88) (0.1902 g, 0.901 mmol) in POCl₃ (0.924 mL, 9.9 mmol) was stirred at room temperature for 2 hours. Excess POCl₃ was removed at 0.2 mm Hg for one hour to give a clear faintly yellow oil. This oil was then dissolved in 20 mL of DME and 0.102 g (2.7 mmol) of NaBH₄ was added. The evolution of a gas occurred immediately. After stirring for four hours the solution had become dark yellow and contained a white precipitate. After removal of DME under reduced pressure, the residue was taken up in 20 mL of H₂O, to which 10 mL of 1 M HCl was added dropwise. The acidic solution was refluxed for 30 minutes, cooled to room temperature, washed twice with Et₂O, and then NaOH (3 M) was added until the solution was strongly basic. The basic solution was extracted with Et₂O. The combined organic fractions were dried with MgSO₄, filtered and concentrated under reduced
pressure to afford 0.1477 g (83%) of 120 as a clear pale yellow oil. This oil was distilled
(90 °C/0.2 mm Hg) in a Kugelrohr apparatus to yield 0.1438 g (81%) of 120 as a clear
colourless oil.

IR (neat): 3550-3250(b), 2922, 2854, 2808, 1452 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) ppm: 0.94 (bs, 1H), 1.28-1.42 (m, 16H), 1.42-1.50 (m, 4H),
2.61 (t, J = 5.4 Hz, 4H);
¹³C NMR (50 MHz, CDCl₃) ppm: 47.9, 27.9, 26.5, 26.0, 25.4, 24.6;
LRMS (El) m/z (relative intensity): 183(31), 154(11) 142(20), 140(22), 126(18), 112(27),
44(97), 30(100);
HRMS (El) m/z calcd for C₁₂H₂₅N: 183.1987; found: 183.1984;
Anal. calcd for C₁₂H₂₅N: C, 78.62; H, 13.74; N, 7.64;
Found: C, 78.79; H, 13.72; N, 7.86.

Azacyclotetradecane (121)

Following the same procedure for the preparation of amine 120, a solution of
1-azacyclotetradecan-2-one (131) (0.2423 g, 1.14 mmol) in POCI₃ (1.17 mL, 12.6 mmol)
was stirred at room temperature for 2 hours. Excess POCI₃ was removed at 0.2 mm Hg
for one hour to give a clear faintly yellow oil. This oil was then dissolved in 20 mL of DME and NaBH$_4$ (0.1304 g, 3.44 mmol) was added. After stirring for four hours the solution was concentrated under reduced pressure and the residue was taken up in 20 mL of H$_2$O, to which 10 mL of 1 M HCl was added dropwise. The acidic solution was refluxed for 30 minutes, cooled to room temperature and extracted twice with Et$_2$O. Concentration of the organic fraction under reduced pressure afforded unreacted lactam 120 (0.0074 g, 3.1%). NaOH (3 M) was added to the aqueous acidic fraction until the solution was strongly basic. The basic solution was then extracted with Et$_2$O to afford amine 121 (0.204 g, 90%) as a white solid. The solid was sublimed at 90 °C (0.22 mm Hg) in a Kugelrohr apparatus to yield 0.1841 g (81%) of 121 as a white solid.

DSC Solid-Solid Transition 31.0 °C, Mp: 41.1 °C;

IR (CHCl$_3$): 2929, 2858, 1602, 1461 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 0.98 (bs, 1H), 1.20-1.44 (m, 18H), 1.44-1.60 (m, 4H), 2.61 (t, J = 6.0 Hz, 4H);

$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 46.1, 27.2, 26.0, 25.1, 24.2, 23.8, 23.2;

LRMS (El) m/z (relative intensity): 198(17), 197(100), 196(26), 182(13) 168(39), 156(86), 154(89);

HRMS (El) m/z calcd for C$_{13}$H$_{27}$N: 197.2143; found: 197.2143;

Anal. calcd for C$_{13}$H$_{27}$N: C 79.11; H 13.79; N 7.097

Found: C79.05; H 13.78; N 7.098.
Azacyclohexadecane (122)

Following the same procedure as for the preparation of amine 120, a solution of 1-azacyclopentadecan-2-one (132) (0.6219 g, 2.60 mmol) in POCI₃ (2.66 mL, 28.6 mmol) of was stirred at room temperature for 2 hours. Excess POCI₃ was removed at 0.2 mm Hg for one hour to give a clear faintly yellow oil. This oil was then dissolved in 40 mL of DME and NaBH₄ (0.2949 g, 7.79 mmol) was added. After stirring for four hours the solution was concentrated under reduced pressure and the residue was taken up in 20 mL of H₂O, to which 10 mL of 1 M HCl was added dropwise. The acidic solution was refluxed for 30 minutes, cooled to room temperature and extracted twice with Et₂O. NaOH (3 M) was added to the aqueous acidic fraction until the solution was strongly basic. The basic solution was then extracted with Et₂O to afford amine 122 (0.503 g, 86%) as a white solid. The solid was sublimed at 90 °C (0.22 mm Hg) in a Kugelrohr apparatus to yield 0.4390 g (75%) 122 as a white solid.

DSC solid-solid transition: -19.6 °C, Mp: 48.5 °C;

IR (KBr): 2926, 2853, 1456, 1354 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.2-1.4 (m, 23H), 1.48 (tt, J = 6.1, 6.1 Hz, 4H), 2.61 (t, J = 6.1Hz, 4H);

¹³C NMR (50 MHz, CDCl₃) ppm: 47.6, 28.1, 26.9, 26.8, 26.6, 26.5, 26.5, 25.2;
LRMS (El) m/z (relative intensity): 225(17), 210(8), 196(9), 182(17), 168(12);
HRMS (El) m/z calcd for C_{15}H_{31}N: 225.2456; found: 225.2451;
Anal. calcd for C_{15}H_{31}N: C 79.92; H 13.86; N 6.21;
    Found: C 79.93, H 13.82; N 6.17.

**N-Methylazacyclotridecane (123)**

![Structure of N-Methylazacyclotridecane (123)](image)

Formaldehyde (0.250 mL, 2.73 mmol) was added to a solution of amine 120 (0.1160 g, 0.62 mmol) in 2 mL of CH$_3$CN. A white precipitate formed immediately, then redissolved after a few seconds. The disappearance of the precipitate coincided with the appearance of an oil. NaCNBH$_3$ (0.0585 g, 0.93 mmol) was added as a solid. After 30 minutes a clear oil insoluble in the CH$_3$CN was observed. The reaction was quenched with the addition of a drop of acetic acid. After the addition of H$_2$O the solution was extracted with Et$_2$O. The combined organic extracts were dried with MgSO$_4$, filtered and concentrated under reduced pressure to afford amine 123 (0.1121 g, 0.569 mmol) in 92% yield as a clear yellow oil. Kugelrohr distillation at 70 - 85 °C (0.2 mm Hg) afforded amine 123 as a clear colourless oil.

IR (neat): 2925, 2854, 2783, 1457, 1350 cm$^{-1}$;
**N-Methylazacyclotetradecane (124)**

Following the procedure for the preparation of amine 120, formaldehyde (0.225 mL, 2.81 mmol) was added to a solution of amine 121 (0.1107 g, 0.56 mmol) in 2 mL of CH$_3$CN. NaCNBH$_3$ (0.0564 g, 0.90 mmol) was added as a solid. After 30 minutes the reaction was quenched with the addition of a drop of acetic acid. Following work up amine 124 (0.1103 g, 0.52 mmol) was obtained in 93% yield as a clear yellow oil. Kugelrohr distillation at 90 °C (0.1 mm Hg) afforded 0.1047 g of amine 124 (88%) as a clear colourless oil.

IR (neat): 2918, 2858, 2789, 1459 cm$^{-1}$;
\[^1\text{H}\text{ NMR}\ (400 \text{ MHz, CDCl}_3) \text{ ppm: 1.2-1.4 (m, 18H), 1.43 (tt, J = 5.8, 5.8 \text{ Hz, 4H}), 2.10 (s, 3H), 2.28 (t, J = 5.8 \text{ Hz, 4H});}\]

\[^{13}\text{C}\text{ NMR}\ (50 \text{ MHz, CDCl}_3) \text{ ppm: 55.1, 42.1, 25.8, 25.5, 25.1, 24.8, 24.0, 24.0;}\]

LRMS (EI) m/z (relative intensity): 211(40), 210(16), 182(12), 168(30), 154(20), 140(19), 58(100);

HRMS (EI) m/z calcd for C\textsubscript{14}H\textsubscript{29}N: 211.2300; found: 211.2303;

Anal. calcd for C\textsubscript{14}H\textsubscript{29}N: C 79.55; H 13.83; N 6.63;

Found: C 79.56; H 13.69; N 6.84.

\textbf{N-Methylazacyclohexadecane (125)}

![Chemical Structure](image)

Following the procedure for the preparation of amine \textbf{120}, formaldehyde (0.208 mL, 2.58 mmol) was added to a solution of amine \textbf{121} (0.1160 g, 0.52 mmol) in 2 mL of CH\textsubscript{3}CN. NaCNBH\textsubscript{3} (0.0518 g, 0.82 mmol) was added as a solid. After 30 minutes the reaction was quenched with the addition of a drop of acetic acid. Following work up amine 125 (0.1142 g, 0.52 mmol) was obtained in 94% yield as a clear yellow oil. Kugelrohr distillation at 60 °C (0.2 mm Hg) afforded 0.1102 g of amine \textbf{124} (89%) as a clear colourless oil.

IR (neat): 2928, 2855, 2785, 1459 cm\textsuperscript{-1};
\( ^1H \) NMR (400 MHz, CDCl\(_3\)) ppm: 1.24-1.37 (m, 22H), 1.42 (tt, J = 6.5, 6.5 Hz, 4H), 2.17 (s, 3H), 2.27 (t, J = 6.56 Hz, 4H);

\( ^13C \) NMR (50 MHz, CDCl\(_3\)) ppm: 56.2, 43.2, 27.3, 26.9, 26.5, 26.4, 26.4, 26.4, 25.6;

LRMS (El) m/z (relative intensity): 239(24), 224(6), 210(6), 196(15), 182(9), 44(100);

HRMS (El) m/z calcd for C\(_{16}\)H\(_{33}\)N: 239.2613; found: 239.2611;

Anal. calcd for C\(_{16}\)H\(_{33}\)N: C 80.26; H 13.89; N 5.85;

Found: C 80.08; H 13.81; N 6.00.

N,N-Dimethyldodeca-1,12-diylammonium iodide (126)

To a suspension of KHCO\(_3\) (0.30 g, 3.0 mmol) and amine 120 (0.0469 g, 0.256 mmol) in 6 mL of MeOH was added Mel (0.30 mL, 5 mmol). After 14 hours the solvent was removed under reduced pressure. CHCl\(_3\) (10 mL) was added and the suspension was stirred for 30 minutes. The suspension was filtered and concentrated under reduced pressure to afford a white solid. The solid was washed twice with dry Et\(_2\)O to afford of 126 (0.0804 g, 0.23 mmol) in 93 % yield as a white powder.

IR (KBr): 2937, 2864, 1484, 1465 cm\(^{-1}\);
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) ppm: 1.30-1.40 (m, 12H), 1.40-1.50 (m, 4H), 1.67-1.80 (m, 4H), 3.45 (s, 6H), 3.4-3.5 (m, 4H);

\textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}) ppm: 62.0, 53.0, 26.4, 25.3, 24.8, 24.4, 20.0;

LRMS (El) m/z (relative intensity): 339(1), 212(20), 198(15), 144(30), 58(100)

Anal. calcd for C\textsubscript{14}H\textsubscript{30}NI: C 49.56; H 8.91; N 4.13;

Found: C 49.58; H 8.83; N 4.13.

\textbf{N,N-Dimethyltrideca-1,13-diyammonium iodide (127)}

\begin{center}
\begin{tikzpicture}
\node (n) at (0,0) [draw, shape=circle, fill=white] {I-};
\node (a) at (-0.5,0.5) [draw, shape=circle, fill=white] {CH\textsubscript{3}};
\node (b) at (-0.5,-0.5) [draw, shape=circle, fill=white] {CH\textsubscript{3}};
\node (c) at (0.5,0.5) [draw, shape=circle, fill=white] {N+};
\end{tikzpicture}
\end{center}

Mel (0.152 mL, 2.4 mmol) was added to a suspension of KHCO\textsubscript{3} (0.152 g, 1.5 mmol) and amine 121 (0.0301 g, 0.15 mmol) in 5 mL of MeOH. After 14 hours the solvent was removed under reduced pressure. CHCl\textsubscript{3} (10 mL) was added to the remaining solid and the suspension was stirred for 30 minutes, filtered, and concentrated under reduced pressure. The remaining white solid was washed twice with dry Et\textsubscript{2}O to afford 0.0378g (95%) of 127 as white powder.

IR (KBr): 2936, 2863, 1464 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) ppm: 1.24-1.34 (m, 8H), 1.34-1.53 (m, 10H), 1.58-1.70 (m, 4H), 3.40-3.50 (m, 4H), 3.48 (s, 6H);
$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 61.7, 53.1, 26.0, 25.4, 23.6, 23.2, 22.7, 19.3

LRMS (El) m/z (relative intensity): 353(1), 226(4), 211(22), 182(97), 168(15), 58(100);

HRMS (El) m/z calcd for C$_{15}$H$_{32}$NI: 353.1579; found: 353.1581;

Anal. calcd for C$_{15}$H$_{32}$NI: C 50.99; H 9.13; N 3.96;

Found: C 50.99; H 9.16; N 3.89.

N,N-Dimethylpentadeca-1,15-diylammonium iodide (128)

![Diagram of N,N-Dimethylpentadeca-1,15-diylammonium iodide (128)](image)

To a suspension of KHC$_3$O$_3$ (0.164 g, 1.64 mmol) and amine 122 (0.0370 g, 0.16 mmol) in 6 mL of MeOH was added Mel (0.163 mL, 2.6 mmol). After 14 hours the solvent was removed under reduced pressure. CHCl$_3$ (10 mL) was added to the solid and the suspension was stirred for 30 minutes. The suspension was filtered and the solvent was removed under reduced pressure to provide a white powder. The powder was washed twice with dry Et$_2$O and recrystallized from nitromethane to afford 0.0343 g (74 %) of 128 as white rhombohedral crystals.

IR (KBr): 2994, 2927, 2857, 1487, 1465, 1439 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.18-1.26 (m, 4H), 1.26-1.37 (m, 9H), 1.38-1.50 (m, 9H), 1.58-1.72 (m, 4H), 3.35-3.55 (m, 4H), 3.48 (s, 6H);
$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 62.3, 52.9, 26.6, 26.4, 26.3, 26.2, 25.4, 23.6, 21.3;

LRMS (El) m/z (relative intensity): 381(0.3), 254(1), 239(8), 210(2), 196(5), 142(12), 58(100);

HRMS (El) m/z calcd for C$_{17}$H$_{36}$N: 381.1894; found: 381.1892;

Anal. calcd for C$_{17}$H$_{36}$N: C 53.54; H 9.51; N 3.67;

Found: C 53.65; H 9.75; N 3.67.

**Cyclotridecanone oxime (129)**

Following the same procedure for the preparation of oxime 81, sodium acetate (0.4281 g, 5.21 mmol) and (0.3474 g, 4.99) of NH$_2$OH·HCl were added as solids to a solution of cyclotridecanone (70) (0.6173 g, 4.99 mmol) in 10 mL of methanol. After work up the crude product was recrystallized from EtOH/H$_2$O to yield 0.6378 g (96%) of 129 as white needles.

Mp: 107.8-108 °C;

IR (CHCl$_3$): 3242, 2930, 2858, 1668, 1461, 1439 cm$^{-1}$;
1H NMR (400 MHz, CDCl₃) ppm: 1.26-1.46 (m, 16H), 1.57 (tt, J = 7.1, 7.1 Hz, 2H), 1.60 (tt, J = 7.1, 7.1 Hz, 2H), 2.21 (t, J = 7.1 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 8.45 (bs, 1H);

13C NMR (50 MHz, CDCl₃) ppm: 161.7, 33.6, 27.4, 27.3, 26.5, 26.0, 25.7, 25.5, 25.3, 25.2, 25.0, 24.3, 24.0;

LRMS (El) m/z (relative intensity): 211(4), 194(12), 178(5), 168(3), 154(3), 73(100);

HRMS (El) m/z calcd for C₁₃H₂₅NO: 211.1936; found: 211.1937;

Anal. calcd for C₁₃H₂₅NO: C 73.88; H 11.92; N 66.6;

Found: C 74.00; H 12.00; N 6.59.

Cyclopentadecanone oxime (130)

Following the same procedure for the preparation of oxime 81, sodium acetate (0.8459 g, 10.3 mmol) and NH₂OH•HCl were added as solids to a solution of cyclopentadecanone (71) (1.394 g, 6.2 mmol) in 30 mL of methanol. After work up the crude product was recrystallized from EtOH/H₂O to yield 1.4720 g (99%) of 130 as white needles.

Mp: 78.5-78.9 °C;
IR (KBr): 3272, 2972, 2855, 1654, 1454 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) ppm: 1.26-1.44 (m, 20H), 1.55 (m, 4H), 2.16 (t, J = 7.6 Hz, 2H), 2.32 (t, J = 7.6 Hz, 2H), 7.92 (bs, 1H);

\(^13\)C NMR (50 MHz, CDCl\(_3\)) ppm: 162.5, 34.3, 27.9, 27.3, 27.3, 26.7, 26.5, 26.4, 26.4, 26.4, 26.3, 26.3, 25.2, 24.4;

LRMS (EI) m/z (relative intensity): 239(11), 222(16), 206(4), 73(100);

HRMS (EI) m/z calcd for C\(_{15}\)H\(_{29}\)NO: 239.2249; found: 239.2251;

Anal. calcd for C\(_{15}\)H\(_{29}\)NO: C 75.26; H 12.21; N 5.85;

  Found: C 75.08; H12.33; N 5.76.

1-Azacyclotetradecan-2-one (131)

Following the same procedure as for the preparation of lactam 65, pyridine (0.34 mL, 4.1 mmol) and tosyl chloride (0.5144 g, 2.69 mmol) were added to oxime 129 (0.4386 g, 2.07 mmol) in 25 mL of CH\(_2\)Cl\(_2\). After concentration of the solution under reduced pressure, flash chromatography on silica eluting with Et\(_2\)O afforded the Beckmann rearranged product. The crude lactam was recrystallized from EtOH/H\(_2\)O to afford 0.3169 g of lactam 131 in 72 % yield, as white needles.

Mp: 157-157.2 °C;
IR (CHCl₃): 3322, 3072, 2855, 1640, 1544, 1459, 1438 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.20-1.47 (m, 4H), 1.27-1.42 (m, 12H), 1.45 (m, 2H), 1.64 (m, 2H), 2.20(m, 2H), 3.30 (dt, J = 5.8, 5.8 Hz, 2H), 5.58 (bs, 1H);

¹³C NMR δ 173.1, 38.5, 36.2, 28.3, 26.5, 25.8, 25.8, 25.7, 25.4, 25.3, 24.0, 23.8, 23.2;

LRMS (El) m/z (relative intensity): 212(17), 211(100), 210(5), 196(7), 182(16), 170(20), 168(28);

HRMS (El) m/z calcd for C₁₃H₂₅NO: 211.1936; found: 211.1936;

Anal. calcd for C₁₃H₂₅NO: C 73.88; H 11.92; N 6.63;

Found: C 73.90; H 12.04; N 6.60.

1-Azacyclohexadecan-2-one (132)

Following the same procedure as for the preparation of lactam 65, pyridine (0.756 mL, 9.34 mmol) and tosyl chloride (1.159 g, 6.08 mmol) were added to oxime 130 (1.1198 g, 4.67 mmol) in 50 mL of CH₂Cl₂. After concentration of the solution under reduced pressure, flash chromatography on silica gel eluting with Et₂O afforded the Beckmann rearranged product. The crude lactam was recrystallized from EtOH/H₂O to afford 0.9638 g of lactam 132 in an 86% yield as white needles.

IR (CDCl₃): cm⁻¹: 3452, 3325, 2931, 2858, 1663, 1518;
\[ ^1H \text{NMR (400 MHz, CDCl}_3 \text{)} \text{ppm: 1.15-1.39 (m, 20H), 1.39-1.50 (m, 2H), 1.55-1.65 (m, 2H), 2.14 (t, J = 6.5 Hz, 2H), 3.26 (dt, J = 5.8, 5.8 Hz, 2H), 5.72 (bs, 1H);} \]
\[ ^1H \text{NMR (50 MHz, CDCl}_3 \text{)} \text{ppm: 173.2, 39.0, 36.8, 29.3, 27.9, 27.7, 27.3, 27.1, 27.1, 26.4, 25.9, 25.8, 25.6, 25.5, 25.5;} \]
\[ \text{LRMS (El) m/z (relative intensity): 240(10), 239(100), 210(20), 196(25), 182(14);} \]
\[ \text{HRMS (El) m/z calcd for C}_{15}\text{H}_{29}\text{NO: 239.2249; found: 239.2249;} \]
\[ \text{Anal. calcd for C}_{15}\text{H}_{29}\text{NO: C 75.26; H 12.21; N 5.85; Found: C 74.98; H 12.10; N 5.80.} \]

**Dodeca-1,12-diylammonium chloride (133)**

HCl was bubbled through a solution of amine 120 (0.1150 g, 0.63 mmol) in 20 mL of Et\(_2\)O for approximately 1 minute. A white precipitate formed immediately which redissolved upon continued bubbling of HCl. Concentration of the solution under reduced pressure afforded an oil. Dry Et\(_2\)O was added to the oil and a precipitation occurred. The precipitate was rinsed with Et\(_2\)O to afford 0.1237g (90 %) of 133 as a white solid. The solid was recrystallized from EtOAc with two drops of EtOH to afford 133 (0.1183 g, 86%) as small white hydroscopic needles.

IR (KBr): 2934, 2860, 2787(b), 1580, 1459 cm\(^{-1}\);
$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.30-1.44 (m, 12H), 1.45-1.56 (m, 4H), 1.83 (tt, J = 7.1, 7.1 Hz, 4H), 3.02 (t, J = 7.1 Hz, 4H), 9.35 (bs, 2H);

$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 44.2, 25.5, 23.3, 25.1, 24.1, 23.3;

LRMS (El) m/z (relative intensity): 183(M$^+$-HCl, 19), 142(12), 140(14), 126(11), 112(17), 44(88), 30(100);

Anal. calcd for C$_{12}$H$_{26}$NCl: C 65.57; H 11.92; N 6.37; Found: C 65.26; H 12.03; N 6.17.

Trideca-1,13-diylammonium chloride (134)

Following the same procedure as for the preparation of 133, amine 121 (0.0513 g, 0.26 mmol) was treated with HCl to give 134. The solid was recrystallized from EtOAc with two drops of EtOH to afford 134 (0.0494 g, 81%) as small white needles.

IR (CHC$\equiv$H): 2934, 2860, 2900-2400, 1580, 1472, 1458 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.20-1.48 (m, 14H), 1.50 (tt, J = 6.4, 6.4 Hz, 4H), 1.79 (tt, J = 7.5, 7.5 Hz, 4H), 2.97 (m, 4H), 9.42 (bm, 2H);

$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 42.9, 25.2, 25.0, 24.6, 24.2, 23.2, 21.7;

LRMS (El) m/z (relative intensity): 198(14), 197(M$^+$-HCl, 100), 196(19), 182(10), 180(13), 168(28);

HRMS (El) m/z calcd C$_{13}$H$_{27}$N: 197.2143, found 197.2452;
Anal. calcd for C\textsubscript{13}H\textsubscript{28}NCl: C 66.78; H 12.07; N 5.99;

Found: C 66.63; H 12.03; N 5.87.

**Pentadeca-1,15-diylammonium chloride (135)**

Following the same procedure as for the preparation of 133, amine 122 (0.1003 g, 0.44 mmol) was treated with HCl to give 135. The solid was recrystallized from EtOAc to afford 135 (0.0958 g, 82%) as small white needles.

Mp: 182-183 °C;

IR (KBr): 2933, 2858, 2900-2400, 1588, 1462 cm\(^{-1}\);

\(^1\)H NMR (500 MHz, CDCl\(_3\)) ppm: 1.20-1.36 (m, 18H), 1.42 (tt, J = 6.5, 6.5 Hz, 4H), 1.76 (tt, J = 7.4, 7.4 Hz, 4H), 2.95 (m, 4H), 9.4 (bs, 2H);

\(^13\)C NMR (50 MHz, CDCl\(_3\)) ppm: 44.2, 26.5, 26.4, 26.4, 26.4, 26.2, 24.5, 23.1;

LRMS (El) m/z (relative intensity): 225(M\(^{+}\)-HCl, 20), 210(8), 196(10), 184(13) 182(19), 168(12), 44(100);

HRMS (El) m/z calcd for C\textsubscript{15}H\textsubscript{31}N (M\(^{+}\)-HCl): 225.2456; found: 225.2456

Anal. calcd for C\textsubscript{15}H\textsubscript{32}NCl: C 68.80; H 12.32; N 5.35;

Found: C 68.69; H 12.27; N 5.40.
Following the same procedure as for the preparation of 133, amine 123 (0.0502 g, 0.25 mmol) was treated with HCl to give 136. The solid was recrystallized from EtOAc to afford 136 (0.0550 g, 92%) as small white needles.

IR (KBr): 2925, 2858, 2498, 2800-2050, 1459 cm$^{-1}$;  
$^1$H NMR (400 MHz, CDCl$_3$) ppm: 1.2-1.45 (m, 14H), 1.45-1.58 (m, 2H), 1.65-2.00 (m, 4H), 2.71 (d, J = 5.08 Hz, 3H), 2.84-3.00 (m, 2H), 3.00-3.18 (m, 2H), 12.1 (bs, 1H);  
$^{13}$C NMR (50 MHz, CDCl$_3$) ppm: 52.7, 41.9, 25.8, 24.8, 24.7, 24.4, 20.5;  
LRMS (EI) m/z (relative intensity): 197(M$^+$-HCl, 30), 196(10), 182(7), 154(16), 140(14), 126(14), 58(100);  
HRMS (EI) m/z calcd for C$_{16}$H$_{33}$N (M$^+$-HCl): 197.2143; found: 197.2452;  
Anal. calcd for C$_{13}$H$_{28}$NCl: C 66.78; H 12.07; N 5.99;  
Found: C 66.93; H 12.12; N 5.83.
N-Methyltetradeca-1,13-diylammonium chloride (137)

Following the same procedure as for the preparation of 133, amine 124 (0.1130 g, 0.54 mmol) was treated with HCl to give 137. The solid was recrystallized from EtOAc with two drops of EtOH to afford 137 (0.1275 g, 96%) as small white needles.

IR (KBr): 3438, 2929, 2858, 2620, 1634, 1469 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDC\(_3\)) ppm: 1.1-1.35 (m, 8H), 1.35-1.50 (m, 10H), 1.50-1.60 (m, 2H), 1.60-1.80 (m, 2H), 2.70 (s, 3H), 2.70-2.90 (m, 2H), 3.00-3.20 (m, 2H), 12.35 (bs, 1H);

\(^{13}\)C NMR (50 MHz, CDC\(_3\)) ppm: 54.5, 41.6, 25.9, 25.2, 24.0, 23.5, 23.2, 18.9;

LRMS (El) m/z (relative intensity): 212(12), 211(M\(^+\)-HCl, 62), 210(29), 196(12), 182(21), 168(48), 84(100);

Anal. calcd for C\(_{14}\)H\(_{30}\)NCI: C 67.84; H 12.20; N 5.65;

Found: C 67.67; H 12.12; N 5.60.
N-Methylpentadeca-1,15-diylammonium chloride (138)

Following the same procedure as for the preparation of 133, amine 125 (0.0351 g, 0.15 mmol) was treated with HCl to give 138. The solid was recrystallized from EtOAc with two drops of EtOH to afford 138 (0.0381 g, 94%) as small white needles.

IR (KBr): 2934, 2859, 2800-2200, 1463 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) ppm: 1.1-1.50 (m, 22H), 1.60-1.72 (m, 2H), 1.72-1.85 (m, 2H), 2.72 (d, J = 4.88 Hz, 3H), 2.89 (ddd, J = 5.03, 12.7, 12.7 Hz, 2H), 3.08 (ddd, J = 4.9, 12.5, 12.5 Hz, 2H), 12.37 (bs, 1H);

¹³C NMR (50 MHz, CDCl₃) ppm: 52.6, 41.5, 26.5, 26.4, 26.4, 26.3, 25.9, 24.3, 21.0;

LRMS (EI) m/z (relative intensity): 239(M⁺-HCl, 22), 210(5), 196(18), 182(10), 168(10), 154(8), 140(12), 44(100);

Anal. calcd for C₁₆H₃₄NCl: C, 69.65; H, 12.42; N, 5.08;

Found: C, 69.68; H, 12.18; N, 5.06.
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Appendix I

Polar maps were introduced by Ogura and coworkers as a method to represent the three dimensional conformations of rings on a two dimensional pattern. Polar maps are generated by plotting the endocyclic torsional angles on a graph consisting of concentric circles representing the torsional angles of $0^\circ$, $\pm 60^\circ$, $\pm 120^\circ$, and $\pm 180^\circ$. The sign of a dihedral angles is positive when the direction of rotation from the front plane to the back plane is clockwise, as illustrated in the Newman projection in Figure 26.

Figure 26. Newman projection of a positive torsional angle.

The polar maps illustrated below for the global minimum conformation of cyclotetradecane and in Figures 21-24 in Chapter II use the Fyles and Gandour convention, in which the circles represent the angles of $0^\circ$, $+60^\circ$, $+120^\circ$, $180^\circ$, $-120^\circ$, $-60^\circ$, $0^\circ$ from the center outward. This modification of earlier conventions reduces the ambiguity of the anti torsional angles ($+175^\circ$ vs. $-175^\circ$).
Polar map representations of the torsional angles exhibit a unique pattern for each conformation. This greatly aids in the identification and comparison of conformations.
Spectral Appendix
Wave number (cm$^{-1}$)

% Transmittance

4000 3200 2400 1600 800

0 10 20 30 40 50 60 70 80 90 100
Wavenumbers (cm$^{-1}$)

% Transmittance

4000 3200 2400 1600 800

Wavenumbers (cm$^{-1}$)