SELECTIVE REACTIONS OF 14-MEMBERED MACROLIDES - A CONFORMATIONAL APPROACH USING MM2 CALCULATIONS

By

Edward George Neeland

B.Sc., The University of Waterloo, 1982
M.Sc., The University of Waterloo, 1984

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

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

November 1987

© Edward George Neeland, 1987
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Chemistry

The University of British Columbia
1956 Main Mall
Vancouver, Canada
V6T 1Y3

Date Jan 12, 1988
ABSTRACT

A number of 14-membered lactones, derived from \(42\) or \(43\), were used to investigate a series of alkylation, hydride reduction and hydrogenation reactions. These reactions yielded diastereoselective product distributions which were rationalized as proceeding through a [3434] conformation. A simple model for determining these low energy conformations was developed using MM2 calculations, energy trends of acyclic molecules, X-ray crystallography and NMR spectroscopy.

In order to unambiguously identify ring conformations, a method to generate polar maps of the large ring lactones was developed. These polar maps quickly differentiated complex ring conformations as well as identifying the symmetry elements of a conformation.

With the aid of polar maps, a new solid state conformation for 14-membered rings was discovered for two macrolides synthesized in this project. Furthermore, three additional unidentified examples of this conformation were recognized from the literature. Energy calculations showed this twisted conformation to be of very low energy. The discovery of the twist conformation led to an improved nomenclature for large rings which considers the number of bonds separating both corner and pseudo corner atoms. Under this proposed nomenclature, the twist conformation was designated the [34'3'4'] conformation.

During this investigation, a useful technique for assigning the stereochemistry of \(\mathcal{E}\) and \(\mathcal{Z}\)-trimethylsilyl (TMS) enol ethers was developed using \(^1\)H NMR nuclear Overhauser effect difference spectroscopy (NOEDS) experiments. One advantage of this technique over the widely used \(^{13}\)C NMR method is that only one isomer is required to accurately assign the \(\mathcal{E}\) or \(\mathcal{Z}\) stereochemistry.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>ii</td>
</tr>
<tr>
<td>List of Figures</td>
<td>vii</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>x</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>xi</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Results and Discussion</td>
<td>26</td>
</tr>
<tr>
<td>1.0 General</td>
<td>26</td>
</tr>
<tr>
<td>2.0 The Conformational Analysis of Cyclotetradecane</td>
<td>26</td>
</tr>
<tr>
<td>2.1 The Use of Polar Maps in Conformational Analysis</td>
<td>32</td>
</tr>
<tr>
<td>3.0 Simplifications in the Conformational Analysis of Large Ring Lactones</td>
<td>38</td>
</tr>
<tr>
<td>3.1 Substitution Patterns of Large Rings</td>
<td>38</td>
</tr>
<tr>
<td>3.1.1 The Corner and Pseudo Corner Positions</td>
<td>39</td>
</tr>
<tr>
<td>3.2 Energy Trends of Esters Applied to 14-Membered Lactones</td>
<td>41</td>
</tr>
<tr>
<td>3.3 A Summary of Restrictions for the Conformational Analysis of 14-Membered Lactones</td>
<td>42</td>
</tr>
</tbody>
</table>
| 4.0 

1H NMR Spectroscopy in the Conformational Analysis of Simple Tetradecanolides | 43   |
| 5.0 The Conformations and Reactivity of 14-Membered Lactones            | 48   |
| 5.1 The Preparation of 3-Oxo-13-Tetradecanolide                         | 48   |
| 5.1.1 C2 Methylation of 3-Oxo-13-Tetradecanolide                        | 50   |
| 5.1.2 Diastereoselective Reduction of 2-Methyl 3-Oxo-13-Tetradecanolide | 51   |
| 5.1.3 Chelation Control in the Reductions of the 3-Keto Lactone          | 54   |
| 5.1.4 X-ray Crystallographic Analysis of 

(2S*,3S*,13S*)-2-Methyl-3-Hydroxy-13-Tetradecanolide                      | 58   |
| 5.2 Additional Examples of the Twist Conformation                       | 60   |
| 5.3 Identifying Large Ring Conformations - A New System of Naming       | 63   |
5.4 The C2 Geminal Methylation of 3-Oxo-13-Tetradecanolide
5.4.1 The Reduction of 2,2-Dimethyl-3-Oxo-13-Tetradecanolide
5.4.2 The Crystal Structure and Conformational Analysis of (3S*,13S*)-2,2-Dimethyl-3-Hydroxy-13-Tetradecanolide
5.5 The Preparation and Reduction of 4-Methyl 3-Oxo-13-Tetradecanolide
5.6 The Preparation of 4,4-Dimethyl-3-Oxo-13-Tetradecanolide
5.7 Preparation and Hydrogenation of (E)-2-Methyl-2-Tetradecen-13-olide
5.8 The C2 Methylation of 13-Tetradecanolide
5.8.1 The Use of 1H NMR to Assign the Geometry of Trimethylsilyl Enol Ethers
5.9 The Preparation and Reduction of 2-Methylene-13-Tetradecanolide
6.0 Conclusion

Experimental
References
Appendices
Spectral Index
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The strain-free conformation of cyclotetradecane</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Rotation about a single bond producing a new conformation</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Baeyer's ring strain theory</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Sachse's rigid (A) and flexible (B) forms of cyclohexane.</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Sachse's interconversion of the monosubstituted rigid forms of cyclohexane</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>The structure of trans decalin according to the theories of Mohr and Baeyer</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>The structure of cis decalin according to the theories of Mohr and Baeyer</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Barton's view of the steroid skeleton</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>The strain-free conformation superimposed on the diamond lattice</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Enolate conformations of compound 6 and steric energies in kcal mol$^{-1}$</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>Diastereoselective alkylation as a function of lone methyl distance</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>Hydrogenation and Michael addition to 2-nonen-9-olides</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>Initially proposed and actual structure of gloeosporone (22)</td>
<td>17</td>
</tr>
<tr>
<td>14</td>
<td>The ring expansion of a cyclooctanone derivative to a 14-membered lactone</td>
<td>19</td>
</tr>
<tr>
<td>15</td>
<td>Synthesis of the unsaturated 16-membered lactone 30</td>
<td>21</td>
</tr>
<tr>
<td>16</td>
<td>Symmetry elements of the 14-membered strain free conformation</td>
<td>27</td>
</tr>
<tr>
<td>17</td>
<td>Magnitude of hydrogen interactions in the strain-free conformation of cyclotetradecane</td>
<td>28</td>
</tr>
<tr>
<td>18</td>
<td>Top and side views of the strain-free conformation of cyclotetradecane</td>
<td>28</td>
</tr>
<tr>
<td>19</td>
<td>The [3344] and [3335] non-diamond lattice conformations of cyclotetradecane</td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>Conformations of cyclotetradecane (relative strain energies in kcal mole$^{-1}$)</td>
<td>31</td>
</tr>
<tr>
<td>21</td>
<td>The polar map conventions</td>
<td>32</td>
</tr>
<tr>
<td>22</td>
<td>Rule for determining the sign of an anti torsional angle</td>
<td>34</td>
</tr>
<tr>
<td>Figure</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>23</td>
<td>Five lowest energy conformations of cyclotetradecane</td>
<td>37</td>
</tr>
<tr>
<td>24</td>
<td>Comparison of corner (top) and pseudo corner (bottom) atoms</td>
<td>40</td>
</tr>
<tr>
<td>25</td>
<td>Potential $s$-trans lactone sites within the preferred five conformations</td>
<td>42</td>
</tr>
<tr>
<td>26</td>
<td>Expansion of the six and eleven line patterns observed in the $^1$H NMR spectra</td>
<td>44</td>
</tr>
<tr>
<td>27</td>
<td>Low temperature 400 MHz $^1$H NMR analysis of 43 in CD$_3$OD</td>
<td>45</td>
</tr>
<tr>
<td>28</td>
<td>The origin of the eleven line multiplet observed in the $^1$H NMR spectrum</td>
<td>46</td>
</tr>
<tr>
<td>29</td>
<td>The origin of the six line multiplet observed in the $^1$H NMR spectrum</td>
<td>47</td>
</tr>
<tr>
<td>30</td>
<td>The total synthesis of starting 3-keto macrolide 43</td>
<td>49</td>
</tr>
<tr>
<td>31</td>
<td>Alkylation of 3-hydroxy esters</td>
<td>52</td>
</tr>
<tr>
<td>32</td>
<td>Proposed model for hydride reduction of macrolide 44</td>
<td>55</td>
</tr>
<tr>
<td>33</td>
<td>A summary of the reduction results for the mixture 44</td>
<td>56</td>
</tr>
<tr>
<td>34</td>
<td>ORTEP diagram showing top view of 49</td>
<td>59</td>
</tr>
<tr>
<td>35</td>
<td>ORTEP diagram showing side view of 49</td>
<td>59</td>
</tr>
<tr>
<td>36</td>
<td>Intermolecular hydrogen bond in the lattice of 49</td>
<td>60</td>
</tr>
<tr>
<td>37</td>
<td>Comparison of the twist conformation to the preferred [3434] conformation</td>
<td>60</td>
</tr>
<tr>
<td>38</td>
<td>Comparison of two twist conformations adopted by macrolides 49 and 51</td>
<td>61</td>
</tr>
<tr>
<td>39</td>
<td>Comparison of corner and pseudo corner in conformations D and C</td>
<td>64</td>
</tr>
<tr>
<td>40</td>
<td>Dale prime nomenclature for the twist conformation</td>
<td>65</td>
</tr>
<tr>
<td>41</td>
<td>Proposed mechanism for reduction of 54</td>
<td>68</td>
</tr>
<tr>
<td>42</td>
<td>Calculated lowest energy conformations of 55 and the X-ray conformations</td>
<td>69</td>
</tr>
<tr>
<td>43</td>
<td>ORTEP diagrams of 55 showing top view of the [3344] and</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>[3434] conformations</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>400 MHz NOEDS experiment of 55 by irradiating at 3.69 ppm in CDCl$_3$</td>
<td>73</td>
</tr>
<tr>
<td>45</td>
<td>The $^{13}$C NMR shift trend for distinguishing threo from erythro</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>stereochemistry</td>
<td></td>
</tr>
<tr>
<td>Figure</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>46</td>
<td>Application of the $^{13}$C NMR shift trend to compounds 58 and 59</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>and their acids</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Deoxygenation of macrolide 47</td>
<td>83</td>
</tr>
<tr>
<td>48</td>
<td>The NOEDS experiment on E and Z TMS enol ethers of 3-pentanone</td>
<td>86</td>
</tr>
<tr>
<td>49</td>
<td>NOEDS experiment proving the trans stereochemistry of macrolide 72</td>
<td>88</td>
</tr>
<tr>
<td>50</td>
<td>Conformational control in the selenoxide elimination to macrolide 74</td>
<td>90</td>
</tr>
<tr>
<td>51</td>
<td>The three lowest energy conformations for the enone 74</td>
<td>93</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

AIBN 2,2’-azobisisobutyronitrile
CD circular dichroism
Conf. conformation
CPU central processing unit
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC 1,3-dicyclohexylcarbodiimide
DMAP 4-dimethylaminopyridine
ether diethyl ether
glc gas-liquid chromatography
Harpoon base lithium 2,2,6,6-tetramethylpiperidide
HMPA hexamethylphosphoramidate
IR infra red
J coupling constant
LDA lithium diisopropyl amide
MCPBA meta-chloroperoxybenzoic acid
MM2 molecular mechanics
NMR nuclear magnetic resonance
ORTEP Oakridge Thermal Ellipsoid Plotting Program
THF tetrahydrofuran
tlc thin layer chromatography
Ts para-toluenesulfonyl
TMS trimethylsilyl
NOEDS nuclear Overhauser effect difference spectroscopy
Acknowledgements

First and foremost, I would like to thank my supervisor Dr. Larry Weiler for his guidance and advice during this project.

I am also very grateful to Dr. Steve Rettig for X-ray crystallographic analyses and helpful discussions.

Thanks are also due to Dr. John Scheffer and Clarice Moxham for the temporary use of their gas chromatography equipment.

The MACROMODEL program was generously provided by Dr. Cam Oehlschlager and is gratefully acknowledged.

In addition, a special thanks to Dr. Michael Fryzuk, Dr. Michael Blades, Dr. Melvin Comisarow, Dr. Gordon Bates, Dr. Bernard Shizgal and Dr. Chris Orvig for the use of their laserprinter while producing this thesis.

Finally, I would like to thank my wife, Lorie, for her encouragement, patience and devotion during the years of my graduate work.
As iron sharpens iron,
so one man sharpens another.

Proverbs 27:17, NIV Bible
INTRODUCTION

One of the most important factors in the development of organic chemistry has been conformational analysis. Its use, particularly in cyclohexane systems, has revolutionized the process of understanding and predicting the chemical outcome of reactions in cyclic systems. The purpose of this thesis is to investigate conformational effects on the reactivity of 14-membered lactones when treated simply as an extension of the chair cyclohexane form. It is well established\textsuperscript{1-4} that the most stable conformation of a fully saturated 14-membered ring is that shown in Figure 1. Within this conformation, the effects of unfavorable torsional and bond angles are minimized and in addition severe transannular interactions are absent. Accordingly, this conformation has been designated as the only "strain-free" conformation for a 14-membered ring.

![Figure 1. The strain-free conformation of cyclotetradecane.\textsuperscript{1-4}](image)

The initial goals of this work were to determine if this strain-free conformation was likewise preferred in modestly substituted 14-membered lactones and whether this conformation by itself was sufficient to account for the high diastereoselectivity in the reactions of these lactones. Ultimately, as the behavior of 14-membered lactones becomes better understood, both the structure and conformation(s) of large ring lactones will be used to confidently control regio- and diastereoselective reactions.

The concept of a conformation and its early refinements arose late in the 19\textsuperscript{th} century - the infancy of organic chemistry. The tetrahedral theory for carbon was independently reported by van't Hoff\textsuperscript{5} and LeBel\textsuperscript{6} in 1874. However van't Hoff further suggested that carbon atoms connected by a single bond could freely rotate and give rise to new arrangements of atoms in space. This was the genesis of conformational analysis.
Figure 2. Rotation about a single bond producing a new conformation.

The next development was the extension of van't Hoff's hypothesis to cyclic systems which culminated with Baeyer's ring strain theory in 1885. According to Baeyer, carbon atoms which make up a ring are co-planar and the preferred ring angle should be 109.5° in keeping with carbon's tetrahedral geometry. Internal ring angles which deviated from this ideal angle would introduce strain into the ring system. Baeyer therefore predicted that the ring strain energy would be greatest in cyclopropane (ring angle = 60°), gradually decrease to an energy minimum in cyclopentane (ring angle = 108°) and increase thereafter.

From the heats of combustion data, Baeyer's hypothesis was shown to be correct up to and including the cyclopentane molecule but the higher membered homologs possessed significantly less ring strain than expected. Even more remarkably, the cyclohexane molecule was shown to be strain-free. Baeyer, by restricting his ring systems to a series of rigid, planar, eclipsing CH₂ units, chose to ignore van't Hoff's theory of free rotation and this oversight led to the eventual breakdown of his theory. Nevertheless, the ring strain theory met with early widespread acceptance. It should be noted that the existence of a 14-membered ring was forbidden under Baeyer's theory because the tetrahedral ring angles would be overextended (theoretically to 154.3°).
The apparent anomaly of cyclohexane's strain-free state was resolved by Sachse\textsuperscript{10} in 1890. He rejected the planarity of cyclohexane and instead postulated that the cyclohexane molecule should exist in two forms which he named the rigid or symmetric form (A) and the flexible or asymmetric form (B).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{sachse_forms.png}
\caption{Sachse's rigid (A) and flexible (B) forms of cyclohexane.\textsuperscript{10} The hydrogen atoms have been omitted for clarity.}
\end{figure}

Sachse's model of cyclohexane conformed to the original ideas put forth by van't Hoff. This could be seen in the incorporation of both the tetrahedral carbon geometry and bond rotation to construct the rigid form which was in agreement with experimental results - i.e. strain-free. Sachse further recognized that two monosubstitution products of the rigid form were possible and that they could interconvert via a chair inversion.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{sachse_interconversion.png}
\caption{Sachse's interconversion of the monosubstituted rigid forms of cyclohexane.\textsuperscript{10}}
\end{figure}

Unquestionably, Sachse founded the concepts of chair and boat conformations, axial and equatorial substituents and their interconversion via chair flipping. Only fifteen years had elapsed from the theories of van't Hoff to the findings of Sachse yet these would continue to be overshadowed by Baeyer's planar ring theory until the early 20\textsuperscript{th} century.

Interest in Sachse's theory was revived in 1918 when Mohr\textsuperscript{11} pointed out with a stick and ball model that both Sachse's forms of the cyclohexane ring were interchangeable by rotation about single bonds. Furthermore, he predicted the existence of decalin as two fused chair isomers with the trans isomer predominating over the cis form. This directly
contradicted Baeyer's view of a planar decalin molecule which predicted the trans isomer should not exist or at best be very unstable relative to the more favoured cis decalin. However, such was the popularity of Baeyer's theory that the claims of Mohr were largely unheeded and the existence of trans decalin was doubted.

Figure 6. The structure of trans decalin according to the theories of Mohr and Baeyer. All but the bridgehead hydrogen atoms have been omitted for clarity.

Figure 7. The structure of cis decalin according to the theories of Mohr and Baeyer.

However in 1925, Hückel\textsuperscript{12} demonstrated that the decalin molecule indeed existed as an interconvertible mixture of trans and cis isomers, with the trans isomer in greater abundance. For the first time, conclusive evidence could be cited to support the Sachse-Mohr model. Unfortunately, further evidence supporting the chair form of cyclohexane was sporadic\textsuperscript{13--15} and it would be over a decade before the equatorial and axial bond distinction could be shown experimentally.\textsuperscript{16}

In 1950, Barton's work\textsuperscript{17} in the field of steroids provided the breakthrough necessary for the simultaneous acceptance of the chair form of cyclohexane and its use in conformational analysis. Undoubtedly influenced by Hückel's findings, Barton viewed the steroids as a series of fused Sachse-Mohr cyclohexane chair conformations.
His success in correctly explaining ester hydrolysis rates, eliminations and product ratios of the rigid steroid systems convinced the scientific community of the value of conformational analysis. The use of the cyclohexane chair conformation in Barton's work prompted investigations towards larger rings about which very little was known.

In 1918, Mohr first called attention to the diamond lattice as a template for constructing "tension" free molecules.\textsuperscript{11} The three dimensional carbon framework of the diamond molecule was considered a unique way of extending the ideal tetrahedral carbon bond lengths, bond angles and dihedral angles infinitely in a chairlike manner. Thus any ring system which was superimposable on the diamond lattice must retain a form of chair geometry and the lower strain energy which accompanies it (Figure 9). Of course, each ring would possess varying degrees of steric strain while occupying one of many diamond lattice arrangements and in the aforementioned conformation, strain effects due to unfavorable bond angles, torsional angles and strong transannular hydrogen interactions are minimized.
Mohr's hypothesis, although correct, was not followed up until the early 1960's when Dale used the diamond lattice to construct rings of low strain energy. Using models, Dale qualitatively investigated a series of even numbered saturated ring homologs from cyclohexane to the cyclic 30-membered ring in order to categorize all strain-free conformations and determine the effects of substitution therein. Dale concluded that all strain-free conformations were simply extended versions of the cyclohexane chair form and could be generated from the diamond lattice. In addition, severe transannular hydrogen interactions within the medium sized rings ensured cyclotetradecane to be the first large ring which could exist in a strain-free conformation (Figure 9). This important finding represented one of the first reasons for choosing to study 14-membered ring systems in this project. From here, Dale pioneered research in the field of large rings with the use of energy calculations to quantitatively compare conformational stabilities. Dale's energy calculations reaffirmed that the majority of the lowest energy conformations were derived from simple extensions of the chair form of cyclohexane. Dale's efforts were further developed by others using computer aided calculations to examine the conformations of more complex functionalized large rings.

Evidence to support Dale's findings concerning the diamond lattice conformations of 14-membered rings came from spectroscopy, CD studies and energy calculations but the most reliable and satisfying contribution was that of X-ray crystallography. X-ray analyses of cyclotetradecane and 1,8-diazacyclotetradecane dihydrobromide clearly showed that both molecules adopted the expected strain-free conformation in the solid state.

Dale's success in demonstrating that large rings could exist in fixed conformations aroused the interest of chemists eager to exploit the conformational bias of cyclic systems to selectively control synthetic reactions. Early studies employing stereocontrol in cyclic systems were first reported in germacranoidal rings as these proved to be more manageable in a predictive sense. Only a few noteworthy examples shall be discussed. To the best of our knowledge, the first conformationally controlled reaction of a macrolide was
reported in 1972 with the investigation of the cytotoxin liperfolide (1) by Doskotch and co-workers.26

\[
\text{\textbf{1}}\quad \text{OAc}\quad \text{O}
\]

The epoxidation of the intermediate epitulipinolide (2) was hoped to proceed through the conformation 2a shown below wherein only the re-re face of the olefin was open to attack. The expected 1,10-epoxide 3 was formed as the exclusive product and this compound was instrumental in assigning the stereochemistry of liperfolide (1) by comparison of spectral data.

\[
\text{\textbf{2}}\quad \text{OAc}\quad \text{O}\quad \text{MCPBA, Base}\quad \rightarrow\quad \text{\textbf{3}}\quad \text{OAc}\quad \text{O}
\]

In 1979, another use of conformational control was reported in Still's27 periplanone-B (4) synthesis. This unusually potent sex pheromone for cockroaches was tentatively identified as possessing a germacranoïd structure. Based on the conformational analysis of
ring intermediates, Still devised a synthesis of three of four possible diastereomers of the pheromone in order to assign its stereochemistry shown below.

In a key synthetic step, Still produced an intermediate diene 5 whose conformation shown below was expected to expose the si-si face of the conjugated enone for selective epoxidation. This reaction was indeed observed and ended with the first total synthesis of periplanone-B (4).

These examples demonstrated the usefulness of stereocontrol by medium sized rings but also highlighted the need for a reliable and simple method of predicting and explaining the conformations of medium rings. Early conformational analyses were made by simple inspection of molecular models which provided valuable insight to a reaction but this method was prone to error and subject to human wants and desires when extended to large rings.

In 1981, Still and Galynker addressed these shortcomings and demonstrated the use of Allinger's molecular mechanics (MM2) program (see appendix 3, page 141) in the identification of low energy conformations. Product distributions and intermediates from chemical reactions could now be predicted quantitatively using these calculations. Still
assumed that the distribution of products was related to the conformational energies of the starting material (early transition state) or product (late transition state). Accordingly, by calculating the strain energies of starting materials, intermediates or products, it was possible to predict the product ratios.

Still investigated three types of reactions on medium sized macrolides: kinetic deprotonation-alkylation of ketones, hydrogenation and Michael addition to α,β-unsaturated systems. Some examples will be described in detail to illustrate Still's use of MM2 calculations in conformational analysis.

The alkylation of 2-methylcyclooctanone (6) was carried out using lithium diisopropylamide followed by treatment with iodomethane at -60 °C. Trans-2,8-dimethylcyclooctanone (Z) was produced as the major diastereomer (95:5 mixture of trans:cis product).

Still assumed that this kinetic deprotonation-alkylation was best interpreted in terms of an early reactant-like transition state. Therefore likely conformations of the enolates of 2-methylcyclooctanone (6) were compared. As shown in Figure 10, alkylation through either (or both) of the two lowest energy enolates 9 or 12 would produce trans-2,8-dimethylcyclooctanone (Z) with the observed trans stereochemistry.
Figure 10. Enolate conformations\textsuperscript{28} of compound 6 and steric energies in kcal mol\textsuperscript{-1}.

Similar alkylations of 9 and 10-membered lactones were found to be equally selective and in the 10-membered case, a study was conducted to measure stereoselectivity as a function of distance from the lone methyl substituent. Not unexpectedly, it was found that diastereoselectivity diminishes with increasing methyl distance from the reacting center. This result was rationalized to an accurate degree using MM2 calculations on the enolates.
Figure 11. Diastereoselective alkylation as a function of lone methyl distance.²⁸

Cuprate additions to and hydrogenations of unsaturated lactones were also seen to consistently give high diastereoselectivities and interestingly in every case, opposite stereochemistries to each other.

Figure 12. Hydrogenation and Michael addition to 2-nonen-9-olides.²⁸
MM2 calculations of the starting material can provide insight into the observed complementary product stereochemistries. This was illustrated using 2-nonene-9-olide (13). The lowest energy conformation exhibiting a planar π system is diagrammed below. Peripheral attack of the conjugated olefin by hydrogen or a cuprate will occur from the same face and lead to products of opposite stereochemistry which is in agreement with experimental results.

Still extended these reactions to larger ring systems (up to 13-membered rings) and again found that the high diastereoselectivity was maintained. However, for these more complex molecules, no attempt was made to rationalize the results in terms of MM2 energies of conformations.

Still and Novack applied these reactivity trends towards the total synthesis\(^\text{29}\) of 3-deoxyrosaranolide (14), a derivative of the macrolide antibiotic rosaramycin. En route to the target molecule, 11 kinetic reactions were employed under conformational stereocontrol in establishing six of the eight asymmetric centers with excellent selectivity in the 16-membered ring.
The Wadsworth-Emmons ring closure of 15 led to the starting macrolide skeleton which was kinetically deprotonated with KN(Me3Si)2 and alkylated at C8 with iodomethane in greater than 20:1 diastereoselectivity. Hydrolysis of the thioketal to yield 16 was followed by an X-ray analysis to assign the product stereochemistry.

The introduction of a second methyl substituent at C6 was accomplished using LiN(Me3Si)2 and iodomethane. The methyl substituent was introduced both regioselectively (>20:1 over C4) and diastereoselectively (10:1 S configuration). Similar results were obtained on alkylation with a bromo-ester to give 17. The stereochemistry of compound 17 was again proven by X-ray crystallography.

Attempts to methylate C4 were successful but produced the wrong diastereomer. In order to circumvent this problem, the enolate was quenched with formaldehyde and the resulting hydroxymethyl ketone was eliminated via the mesylate to give the conjugated exocyclic methylene ketone. A Michael addition by thiophenolate followed by Raney nickel desulphurization gave the desired methyl substituent with the correct stereochemistry in greater than 25:1 selectivity. Alternatively, catalytic hydrogenation of the exocyclic double bond gave the identical product 18 but with reduced selectivity (9:1).
The tert-butyl ester moiety of 18 was hydrolyzed with trifluoroacetic acid and acylated using ethyl chloroformate to generate a mixed anhydride. Reduction with sodium borohydride led to 19 as a 5:1 mixture of \( \alpha: \beta \) alcohols respectively.
Allylic oxidation with manganese dioxide and epoxidation using meta-chloroperoxybenzoic acid led to the penultimate molecule in greater than 15:1 selectivity. This was oxidized with tristriphenylphosphine ruthenium dichloride to yield the desired target molecule 14, which was indistinguishable from the natural product. To better appreciate the effect of conformational control in this synthesis, those asymmetric centers which were generated using conformational stereocontrol are numbered in compound 14.
The synthesis of deoxyrosaranolide (14) elegantly demonstrated the use of conformational control in the reactions of large ring lactones. However, the absence of a simple model or MM2 calculations to explain the selectivities detracted from the overall synthesis. Indeed, the final generation of some asymmetric centers (e.g.: C₄ and C₅) appeared unpredictable because of supplementary reactions needed to generate the required chiral centers. The absence of energy calculations is commonly seen when dealing with the conformational analysis of the larger complex rings because of the greater number of conformations available to them. Further examples using conformational control to introduce asymmetric centers on medium and large rings have been reported³⁰-³² but again the explanation for the selectivities using conformational stabilities were not discussed except in Still's example. This general lack of conformational analyses using energy calculations among the higher membered macrolides further stirred our interest in this area.

A history of the chemistry of macrolides has been extensively detailed elsewhere³³ (1950 to 1984) and the following section is devoted to updating the literature (to November 1987).

The chemistry of large rings continues to be an actively pursued field. In general, current interests in macrolides can be divided into four closely linked areas. These concern: 1) the isolation and identification of new biologically active large rings; 2) construction of the aglycones of macrolide antibiotics; 3) the total synthesis of other natural product macrolides and 4) investigating and using the conformations of macrolides.

The discovery of additional natural products containing the large ring lactone only serves to reinforce the growing importance of this family. For example, Quinkert et al. have identified the lichen macrolide aspicilin (20) as an 18-membered lactone and this molecule represents only one of many newly discovered biologically active macrolides.³⁵,³⁶
Recently, Meyer et al.\textsuperscript{37} reported a revised structure for the fungicide gloeosporone. The original molecular structure, based on spectroscopic data, was proposed\textsuperscript{38} as compound 21. A subsequent X-ray analysis\textsuperscript{37} however showed that the original structure was in error and in fact gloeosporone was the 14-membered macrolide 22.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{Initially proposed and actual structure of gloeosporone (22).\textsuperscript{38}}
\end{figure}

If the number of recent publications concerning the syntheses of macrolide natural products and their derivatives can be used as an indicator of interest within this field then the structure and stereochemistries of the large macrolactones are still viewed as worthy challenges. For obvious reasons, these cannot be discussed in detail and only recent publications are given for interest.\textsuperscript{35,36} It should be emphasized that the majority of these syntheses used standard synthetic transformations and very few exploited the potential of conformational control.

If the macrolide skeleton can be formed during the early stages of a synthesis then the opportunity of introducing the asymmetric centers using conformational control can be
exploited sooner. Traditionally, the macrolide aglycones have been synthesized from long chain hydroxy-carboxylic acids, but this method suffers from competing intermolecular reactions during the cyclization process. For this reason, conditions which eliminate unwanted polymerization side reactions are under investigation. For example, Keck and Boden have successfully employed a DMAP-HCl catalyst in the presence of DCC to effect cyclization in good yields for 13-17-membered rings. The characteristic low yields (15-20%) of these cyclizations without DMAP-HCl have been attributed to a poor proton transfer and this catalyst was considered an efficient proton source. Using this improvement, yields of 14-membered macrolides were in the 75-80% range.

Deslongchamps and Brillon have investigated the effects of introducing cis and trans unsaturation in the cyclization of 14-membered acyclic chains. The yields of cyclized product were found to increase significantly at medium dilution when the chain contained cis olefins but were seen to decrease in the presence of trans and mixtures of cis-trans olefins relative to the saturated molecule. The two ends of the chain would be held in closer proximity in the cis instance and react faster whereas the presence of trans olefins in the long chain directs the ends of the chain away from each other and prevents cyclization.

Lipase enzymatic cyclizations of long chain hydroxy esters have very recently been reported. The lipases from Pseudomonas sp. and porcine pancreatic origin were most efficient at catalyzing these cyclizations and these enzymes have the advantage of producing optically active macrolides. Yields of optically pure 14-membered lactones were reported to be approximately 76-80% for the cyclization step.

A different strategy for the synthesis of large ring lactones employs ring expansion of medium ring precursors and this has also been reported to occur in good yields. Hesse and co-workers have used a simple intramolecular transesterification to yield 14-membered rings, eg. 23, via 12-membered precursors 24 and 25 which are derived from a cyclooctanone derivative 26.
Figure 14. The ring expansion of a cyclooctanone derivative to a 14-membered lactone.\textsuperscript{43}

A second example has been reported by Schreiber and Liew\textsuperscript{44} which utilizes a rearrangement of a hydroperoxy ketal to yield a 14-membered lactone. Ozonolysis of 27 produces the $\alpha$-hydroperoxytetrahydropyran 28 which when treated with cupric acetate and ferrous sulphate provided the macrolide 29.
Thus far, the use of conformational control has been limited to constructing target molecules with the same skeleton as the macrolide intermediate. That is: a simple 10-membered starting material using conformational control ultimately produces a more complex 10-membered product. However, a new development in the macrolide field introduces asymmetric centers via conformational control and subsequently transforms the macrolide into a different molecule which retains the asymmetry generated in the large ring intermediate but not the ring itself. In this way, selective reactions via conformational control are used to synthesize small rings or acyclic compounds stereoselectively. This strategy was first reported by Still et al. and Schreiber et al. and in both cases was used to synthesize an intermediate of the antibiotic monensin B. For reasons of brevity, only Still’s example will be discussed.

The triene 30 was constructed from the hydroxypentenoic ester 31 using a β-hydroxy ester dianion alkylation followed by ester enolate rearrangement, acid reduction and silyl protection to give 32 as shown below. Compound 32 was transformed to the acyclic precursor 33 of the macrolide triene using standard Claisen methodology and cyclized under Mukaiyama conditions to yield 30.
Treatment of the triene 30 with meta-chloroperoxybenzoic acid gave the tri-epoxide 34, whose structure was confirmed by X-ray analysis, in greater than 90% diastereoselectivity.
Saponification of 34 followed by acid catalyzed polycyclization led directly to the tris-tetrahydrofuranoid compound 35 which possesses the monensin polyether antibiotic skeleton. It should be pointed out however that this synthesis produced the threo stereochemistry at the C_{12}-C_{13} junction rather than the required erythro stereochemistry of monensin B.

Three interesting studies have been reported recently which are relevant to our methods for investigating the 14-membered rings. In these examples, the conformations of medium and large rings were investigated using molecular mechanics and/or X-ray crystallography. The first report deals with a bis 13-membered heterocycle joined by an aliphatic chain 36.
This compound provided a rare opportunity to examine an odd membered heterocycle which was not superimposable on the diamond lattice. Molecular mechanics calculations were performed on the 13-membered ring as its geminal-N-methyl derivative as a model for the parent molecule. The MM2 conformation of the gem-dimethyl derivative which exhibited the lowest strain energy was similar to the X-ray crystal structure of 36, however the considerable disorder in the crystal complicated the analysis.

A second study involved a thorough investigation of three cyclophanes 37. These chiral large rings are best known for their ability to interconvert enantiomers by a "skipping rope" process in which the aliphatic chain loops around to the opposite side of the naphthalene base. The three cyclophanes differed only in the length of the aliphatic chain (n=14-16) such that 20, 21 and 22-membered ring systems were investigated.

Unfortunately, as in the previous 13-membered example, attempts to solve the structures by X-ray crystallography were hampered by disorder in the crystals for the 20 and 21-membered cases. It was encouraging to discover that the lowest energy conformation of the 22-membered ring predicted by MM2 calculations was in full agreement with the solid state conformation determined subsequently by X-ray analysis. The 20 and 21-membered rings were studied using solid state $^{13}$C NMR. Previously, Möller et al. had shown that the $^{13}$C chemical shift of a methylene carbon is dependent on the conformation about the two bonds on either side of the methylene. Using Möller's method, Dougherty calculated the $^{13}$C shifts of the lowest energy conformations of the 20 and 21-membered rings and found that they were identical to those found experimentally.
Vedejs et al. have introduced an alternative method for rationalizing and predicting selective reactions of unsaturated medium rings. This approach eliminates the need for a full conformational analysis and instead concentrates on the immediate environment of the functionality which undergoes attack. This local conformer approach\(^{50}\) has proven valuable in rationalizing diastereoselective reactions and very recently has been applied to the epoxidations and osmylations of olefins in 12-membered lactones.\(^{51}\) For example, the epoxidation of the \(E\) alkene of the lactone 38 was predicted to go through the preferred local conformer 38a to give the epoxide 39 as a major product. This was experimentally observed.

However, the epoxidation of the isomeric \(Z\) alkene 40 gave macrolide 41 in a reduced 3:1 product ratio and this was rationalized as proceeding through the crownlike conformation 40a which displayed a pseudoequatorial substituent. The rationalization of the diastereoselectivities in these reactions did not require a detailed knowledge of the conformation of the entire ring, but only of the olefin and neighboring bonds.

![Chemical Structures](image)

Nevertheless, Vedejs submitted the starting lactones 38 and 40 as well as the products of these selective epoxidations to a conformational analysis using Still's MACROMODEL program (see appendix 2, page 139). For the \(Z\) alkenes, the MM2 calculations confirmed the local conformer approximation for rationalizing the epoxidations of unsaturated 12-membered lactones in terms of favoured ground state or product conformations. In contrast, the
epoxidation products derived from the E alkene could not be explained from a low energy starting material conformation but rather from preferred product stabilities. Therefore, the epoxidations of the Z alkenes were interpreted as proceeding through a transition state sufficiently advanced to experience this preference.

As demonstrated, a number of syntheses have relied on macrolide conformations to introduce asymmetric centers in the molecule but only sparse attempts have been made to analyze the conformations which govern the selectivity in large rings. Using MM2 calculations, researchers have rationalized these selectivities as proceeding through the lowest energy conformations of large rings. We were interested in using a knowledge of the low energy conformations of 14-membered rings to deduce regio and diastereoselectivity, but only after gaining a confident understanding of their conformational behavior. We realize that this approach may require future revisions in light of the Curtin-Hammett principle. However it represents a starting point to analyze macrolide reactivity.

The conformations of large rings are less well understood in comparison to the small and medium size rings. The three previously discussed examples involving conformational analyses of the 13-membered ring, the cyclophanes and Vedejs' local conformer effects represent a slowly growing trend. We therefore chose to study the chemistry and conformations of 14-membered lactones for the following reasons:

1) It has been well established, both from a theoretical and experimental standpoint, that 14-membered rings are the smallest rings which can occupy a strain-free conformation except the exhaustively studied cyclohexane ring. This requirement for a strain-free conformation should reduce the complexity of the conformational analysis.

2) A large number of the structurally interesting and biologically active natural products possess the 14-membered lactone skeleton.

3) The conformations of substituted 14-membered lactones have not been thoroughly examined using energy calculations and the conclusions resulting from these calculations should be verified by experimental data.
RESULTS AND DISCUSSION

1.0 General

In Dale's pioneering work\textsuperscript{1,2}, a series of homologous large rings [(CH\textsubscript{2})\textsubscript{8} to (CH\textsubscript{2})\textsubscript{30}] were investigated to determine the strain-free conformation(s) available to each ring. From an inspection of molecular models, Dale recognized a tendency for saturated large rings to adopt compact conformations consisting of two parallel methylene chains linked by bridges of minimum length. These rectangular shaped conformations were found to be more stable than those formed with a large hole in the ring interior and possessed less torsional and angle strain.

The same compact and stable conformations of large rings could be generated from the three dimensional framework of the diamond lattice. Dale realized that the network of carbon-carbon bonds within the diamond lattice represented an infinite extension of ideal tetrahedral carbon geometry. Conformations which were superimposable on the diamond lattice template must have ideal bond angles (109.5°) and favorable torsional angles of 60° or 180° to produce relatively stable arrangements of atoms.\textsuperscript{1}

![Diagram of a carbon lattice]

2.0 The Conformational Analysis of Cyclotetradecane

Only one conformation (see above) was possible for the 14-membered ring which was superimposable on the diamond lattice and strain-free, i.e.: free of bond angle strain, torsional angle strain and severe transannular hydrogen interactions. This conformation
shares certain similarities with the strain-free chair conformation of cyclohexane, but should not simply be dismissed as its 14-membered equivalent.

A closer comparison of both strain-free conformations immediately shows the large ring conformation to possess some important differences. The 14-membered strain-free conformation is less symmetric (C<sub>2h</sub> point group) and as such contains four diastereotopic methylene environments.

Monosubstitution of each diastereotopic methylene proton produces a total of eight conformations as opposed to two conformations for the cyclohexane chair. To further complicate matters, the 14-membered ring can accommodate both cis and trans double bonds compared to only cis double bonds in the 6-membered ring. Clearly, this creates greater complexity in the conformational analysis of large rings.

The four unique methylenes are numbered in Figure 17 which illustrates the relative magnitude of transannular interaction that internal hydrogen atoms experience while occupying the strain-free ring.
It is especially noteworthy that substituents on the C₃ atom experience the least interaction with the remainder of the ring. Dale named the atoms bearing these less hindered substituents, "corners", and designed the current system of conformational nomenclature upon them. The corner atom was recognized as the least sterically hindered ring position upon geminal substitution and was originally defined as an atom having two adjacent gauche dihedral angles each of which were followed by an anti dihedral angle. This definition, however, proved too simple and was later revised to include the concept of a torsional angle sign (see appendix 1, page 139). Dale defined the corner atom as having two adjoining gauche angles of equal sign each followed by an anti angle (e.g. 180°, -60°, -60°, 180°). A top view diagram of the 14-membered strain-free conformation immediately illustrates the corner position. Carbon atoms 3, 6, 10 and 13 are corner atoms.
Using a shorthand notation, Dale represented a large ring's conformation as the number of bonds between each corner atom. These numbers were then placed in square brackets using two rules: (1) The number of bonds between corner atoms are numbered in the order found in the conformation; (2) The smallest numbers were listed first within the square brackets without violating rule (1). Thus the 14-membered strain-free conformation was designated as the [3434] conformation (Figure 18).

Initially, Dale considered only those ring conformations which were superimposable on a diamond lattice. However, calculations on cyclotetradecane revealed two other low energy conformations which were not diamond lattice superimposable. These were designated the [3344] (1.1 kcal mole\(^{-1}\) higher than the [3434] base) and [3335] (2.4 kcal mole\(^{-1}\)) conformations and they were found to be lower in energy than every diamond lattice conformation with the exception of the [3434] arrangement (base value of 0.0 kcal mole\(^{-1}\)). The numbered atoms in Figure 19 are corner positions.

![Figure 19. The [3344] and [3335] non-diamond lattice conformations of cyclotetradecane.](image-url)
Dale briefly reported four additional higher energy 14-membered diamond lattice conformations\textsuperscript{20}, but it is doubtful whether he identified every possible diamond lattice derived conformation for the 14-membered ring. This task was left to Saunders, who reported that thirteen diamond lattice conformations were theoretically possible for a 14-membered ring using a ring-building computer program.\textsuperscript{54} Therefore, a total of fifteen possible conformations might be considered for the 14-membered ring and seemingly endless substitution patterns existed within each of the fifteen conformations. At this stage, the conformational analysis of 14-membered rings seemed overwhelming.

Saunders did not provide the diagrams of the thirteen diamond lattice derived conformations and we were forced to exhaustively identify and construct each of the conformations using molecular models. Together with the [3344] and [3335] conformations, these were subsequently submitted for MM2 calculations to determine the relative energies of each conformation.\textsuperscript{55}
Figure 20. Conformations of cyclotetradecane (relative strain energies in kcal mole\(^{-1}\)).

Fortunately, most conformations had significantly higher calculated energies than the lowest energy [3434] conformation. At this point, we arbitrarily decided to only consider the five lowest conformations as likely candidates for the 14-membered rings to occupy.

An alternative to this procedure uses the ring making facilities of Still's MACROMODEL program which has been well demonstrated in the medium sized rings\(^{32}\) (see appendix 2, page 139). Our attempts to apply this program\(^{55}\) to the 14-membered rings met with limited success for the simple hydrocarbon but the introduction of more complex 14-membered macrolides required large amounts of CPU time. For this reason, we adopted the present
strategy of concentrating our efforts on more favorable conformations. Still has warned that the limits of the MACROMODEL program are reached in 14-membered ring systems.32

2.1 The Use of Polar Maps in Conformational Analysis

During the above screening process, the identification and comparison of the many conformations was very time-consuming and prone to error. This task was simplified through the use of polar maps.56 A polar map is a circular graph which plots the sign and magnitude of the internal torsional angles of a ring vs. the bonds where they are found. The concentric circles of a polar map represent torsional angle values in ±60° increments and the straight lines which intersect the circles are the bonds (numbers 1-14) where the torsional angle is formed (Figure 21). Accordingly, a 14-membered ring produces 14 data points on a polar map. These points, when connected, generate a "star pattern" representing the conformation.

Figure 21. The polar map conventions.
Ogura first reported the use of polar maps in the conformation of an oleandomycin derivative and this was followed by a more detailed publication which summarized findings concerning several 14-membered diamond lattice conformations. In these publications, Ogura abandoned Dale's nomenclature system in favour of an alphabetical naming system. For example, under this system, the [3434] conformation was renamed as the A conformation. In addition, Ogura presented examples of several new diamond lattice conformations, B, C, D, E and F. Ogura's E and F conformations do not correspond to conformations E and F in Figure 20 above.

Ogura's conformations E and F were not mentioned by Dale nor found in our investigations of diamond lattice arrangements. Attempts to superimpose these two conformations on the diamond lattice were unsuccessful and it appears these conformations were incorrectly labelled as diamond lattice conformations. As shown by the dotted lines, the diamond lattice can not fully accommodate either conformation and our MM2 calculations indicated both conformations E and F to be of relatively high energy, 6.2 and 6.9 kcal mole\(^{-1}\) respectively higher than the [3434] reference.

In summary, both conformations E and F are not diamond lattice superimposable as Ogura reported and may be ignored when choosing preferred conformations of 14-membered rings. The problems associated with conformations E and F were in part identified through the use of polar maps.

Ogura's polar maps have the potential to greatly simplify the recognition of complex ring conformations. However, their usefulness is somewhat limited by the present methods of determining the signs of torsional angles. To date, polar maps report the smallest
torsional angles within a ring and this automatically determines the angle sign. However, as torsional angles approach 180°, this distinction becomes less clear cut and determining the torsional angle sign can become quite arbitrary.

\[ -180^\circ \text{ or } +180^\circ \]

As a consequence, polar maps of identical conformations may be generated which bear little resemblance to each other and this limits the usefulness of polar maps in the identification process.

We dealt with the difficulty in determining the signs of anti torsional angles in cyclic systems by consistently forming anti torsional angles within the ring and we further proposed\(^5^6\) that this be extended to all ring torsional angles (anti, gauche or otherwise) in order to standardize the construction of polar maps. This simple modification produces one unique polar map for each conformation.

Figure 22. Rule for determining the sign of an anti torsional angle.

MM2 and X-ray programs report torsional angles which are less than or equal to 180° whether formed inside or outside the ring and complications arose when this rule was applied to these torsional angles. Some resulting torsional angles were greater than 180° when
formed within the ring and could not be used to generate a polar map. This can be rectified by reversing the sign of the MM2/X-ray torsional angle and plotting this value instead. For example, a torsional angle of -175°, from X-ray data, is equivalent to a +185° angle when formed within the ring. Therefore, for convenience, the actual value used in the polar map became +175°. This convention introduces a small error in the value of the plotted torsional angle, but allows the polar map to be generated quickly and still retain the characteristic pattern.

These two modifications produce a single set of graph points which, when connected, generate a "star pattern" that is diagnostic for each conformation. Identical conformations yield identical patterns which usually can be compared at a glance.

The patterns of a polar map were further used to quickly indicate the presence and location of corner atoms within a conformation by recognizing the corner's characteristic anti-gauche-gauche-anti sequence of torsional angles. As well, the symmetry of the polar map mirrors the symmetry of the conformation. These last two points are almost impossible to determine without the aid of molecular models and even then may be time consuming. The symmetry elements of the [3434] conformation in Figure 16 are contained within the corresponding polar map. A brief glance at the polar map of the [3434] conformation immediately reveals the C2 rotation axis through bonds 4 and 11. In addition, the presence of the rotation-reflection axis can be seen by the enantiotopic relationship between torsional angles on either side of a line bisecting C1 and C8 shown on the following page. The center of inversion in the [3434] conformation can also be seen in the polar map. For example, the torsional angle of bond 4 is +180° and that of bond 11 is -180°; similarly bond 5 is -60° and bond 12 is +60°. Admittedly, the mirror plane and center of inversion are
less obvious but with a minimum of practice, the analysis of the polar map can completely reveal the symmetry elements of complex conformations with comparative ease.

The five lowest energy conformations of cyclotetradecane are fully described on the following page. The positions of the corner atoms on the conformations and polar maps are marked with an asterisk.
Figure 23. Five lowest energy conformations of cyclotetradecane.
3.0 Simplifications in the Conformational Analysis of Large Ring Lactones

The conformations in Figure 23 represent the five most favorable arrangements available to a 14-membered ring. However, the conformational analysis, while greatly simplified, is still complex because of the diversity of substitution which is possible within each of the five conformations. For example, the simple lactone 42 may adopt fourteen conformations within the [3434] framework alone.

It is obvious that within the five preferred conformations, a simple substitution pattern will produce a plethora of conformations. The MM2 energies of these conformations must then be individually calculated to determine their relative importance.

3.1 Substitution Patterns of Large Rings

The time required to calculate the relative energies of likely conformations can be significantly shortened by applying a few simple conformational restrictions. The substituents on a large ring can only occupy exterior positions since otherwise the transannular interactions become prohibitively large. The degree to which these unfavorable transannular interactions are relieved is dependent upon the position of substitution as demonstrated for the [3434] conformation. As noted in Figure 17, the C1 internal proton experiences the most severe transannular interactions in contrast to the C3 protons which experience none. Therefore, the reduction of strain in replacing an sp3 center with sp2 should proceed in the order C1>C4>C2>C3. Similarly, the introduction of a geminally substituted atom should force a large ring to adopt a conformation in which the fully
substituted atom occupies the C3 corner position in order to minimize strain. The corner positions within a conformation represent the sole position available for a geminally substituted atom which prevent the substituents from experiencing steric interactions within the ring interior.24

3.1.1 The Corner and Pseudo Corner Positions

During our studies of macrolides, we recognized a different corner position which we named the "pseudo corner". Substituents on this position also have significantly less interaction with the remainder of the ring and possessed an anti-gauche-gauche-anti torsional angle sequence about the pseudo corner atom. The pseudo corner could be distinguished from the true corner position through the sign differences in the torsional angle sequence. A ramification of forming all torsional angles within the ring is that the original definition of the corner atom can be expanded. Dale clarified the corner position by stipulating that both gauche angles flanking the corner atom must possess the same sign. No mention was made regarding the sign of the remaining 180° angles on either side of the gauche angles. Using our modification, these anti angles consistently possessed opposite signs of torsional angles relative to the gauche angles. The true corner (hereafter known as corner) position can now be fully described as an atom having two adjoining gauche angles of equal sign with the ensuing anti angles being both of opposite sign (eg. -180°, +60°, +60°, -180°). On the other hand, the pseudo corner existed with its anti-gauche-gauche-anti arrangement alternating in sign (eg. -180°, +60°, -60°, +180°).
Energy calculations on the geminal dimethyl derivatives of the C and D conformations showed the dimethyl substituted pseudo corner to be only 0.7 kcal mole$^{-1}$ less stable than the dimethyl substituted corner. The higher energy of a pseudo corner may stem from an extra internal 1,3 diaxial hydrogen interaction which is not present in a corner position. Predictably, the non-corner positions were very high in energy and disfavored for geminal substitution. Therefore, geminal substituents should be greatly favoured on the corner position over a non corner position. This result agrees with Dale's qualitative predictions. If the corner position is unavailable for substitution, for whatever reason, then the pseudo corner represents the next lowest energy state for occupation by a geminally substituted atom. It was at the completion of this work that we discovered a single publication by Dale briefly describing these "new" corners. Surprisingly, Dale too named these positions as pseudo corners.
3.2 Energy Trends of Esters Applied to 14-Membered Lactones

The above findings considerably simplify the conformational analysis of large rings but the conformational choices may be even further narrowed by applying well established energy trends of acyclic molecules. DesLongschamps has reported that the \textit{s-trans} geometry in esters is approximately 3.0 kcal mole\(^{-1}\) more stable than the \textit{s-cis} isomer.\(^{61}\) In fact, there is not a single example of an acyclic \textit{s-cis} ester.\(^{62}\) The 14-membered ring is large enough to accommodate an \textit{s-trans} linkage and therefore conformations containing the \textit{s-cis} lactones must be considered to be energetically disfavored.

![Diagram of s-Trans and s-Cis Esters]

Moreover, a very important empirical study of 1750 crystal structures of esters revealed a preference for the esters of secondary alcohols to exist in a conformation where the C-O-C-H torsional angle was limited to a 0-30° arc, i.e. a syn periplanar arrangement.\(^{62}\)

![Diagram of a 14-membered lactone]

It was anticipated that both of these effects involving the ester functionality would apply to large ring lactones and thereby drastically reduce the number of conformations which would need to be taken into account. Each of the five lowest energy conformations was examined for symmetry and the locations of all unique trans linkages were identified as sites for potential lactone substitution.
Figure 25. Potential s-trans lactone sites within the preferred five conformations.

Each trans linkage (Figure 25) has two possible orientations for lactone substitution while the stereochemistry of the C13 methyl group was fixed by the 0-30° C-O-C-H restriction. Under these guidelines, the number of possible conformations for each of the five lowest energy types dwindled to manageable levels. For example, only three of the fourteen possible [3434] conformations of lactone 42 need now be considered.

3.3 A Summary of Restrictions for the Conformational Analysis of 14-Membered Lactones

The following represents our approach to the conformational analysis of 14-membered lactones.

1) Ring substituents should occupy the exterior positions of a macrolide.
2) Geminally substituted atoms must occupy a corner position or barring its availability, a pseudo corner position.
3) The lactone linkage was assumed to exist in the s-trans geometry.
4) The lactone C-O-C-H torsional angle was restricted to a 0-30° range for secondary lactones.

5) MM2 calculations of the macrolides were limited to all combinations of the five lowest energy conformations which satisfied restrictions 1) - 4). Only these conformations were considered likely to be populated by the 14-membered rings.

4.0 $^1H$ NMR Spectroscopy in the Conformational Analysis of Simple Tetradecanolides

Prior to this work, the multiplet pattern of the ether methine proton of simple tetradecanolides was considered an indicator of the the rigidity of conformation. This potential 16 line pattern is the product of spin-spin coupling between the lactone methine proton ($H_x$) and five vicinal protons on the neighboring methyl and methylene groups.

![Conformational Diagram](image)

In the past, all $^1H$ NMR spectra of derivatives of **42** displayed either a six or an eleven line multiplet for the C$_{13}$ methine proton. The presence of the eleven line multiplet was considered to be derived from one conformation due to its sharply defined peaks as opposed to the very broad peaks found in the six line multiplet which were attributed to an average of several conformations.
Figure 26. Expansion of the six and eleven line patterns observed in the $^1$H NMR spectra.

However, this relationship was not supported by MM2 calculations nor by low temperature $^1$H NMR studies on many of the compounds reported in this thesis. Also during this work, macrolide derivatives with methine multiplets of twelve, thirteen and even sixteen lines were observed. For example, the 3-keto lactone 42 displayed the eleven line pattern for the methine proton and was thought to exist in one conformation. However, a temperature dependent $^1$H NMR study of 42 was not consistent with this. The room temperature $^1$H NMR spectrum, using either CDCl$_3$ or CD$_3$OD as solvent, displayed an AB quartet at ~3.6 ppm for the C$_2$ methylene protons. Using CD$_3$OD as solvent, the lowering of temperature was accompanied by the growth of a new singlet at 3.50 ppm which was initially considered to originate from the "freezing out" of one conformation from a mixture of rapidly equilibrating conformations. However, a closer examination of the room temperature $^1$H NMR spectrum already seemed to indicate the presence of this conformation. In addition, the lack of a coalescence temperature eliminated the freezing out hypothesis. Instead, the $^1$H NMR spectrum of macrolide 43 was interpreted as a mixture of at least two conformations which were undergoing slow exchange at room temperature. The lowering of temperature shifted the equilibrium towards the more stable conformation and could be seen by the growth of the 3.50 ppm singlet (Figure 27).
Figure 27. Low temperature 400 MHz $^1$H NMR analysis of 43 in CD$_3$OD.

We therefore concluded that macroclide 43 existed as a minimum of two conformations which nevertheless exhibited an eleven line pattern for the C$_{13}$ methine proton and this disproves the eleven line pattern as an indicator of one conformation. In fact, the origin of
both eleven and six line multiplets can be understood from an analysis of their coupling constants and their overlap.

As shown in Figure 28 above, the only requirement for an eleven line pattern is $J$ values in a ratio of 3:2:1 for the methine proton.

A similar analysis for the six line pattern revealed that $J$ values (or their cumulative average) in the ratio of 3:3:2 resulted in the broadened six line multiplet. Therefore, the existence of a dominant conformation may still be true for compounds displaying an eleven or six line pattern but this decision should not be based on the appearance of the methine multiplet in the $^1$H NMR spectrum.
Figure 29. The origin of the six line multiplet observed in the $^1H$ NMR spectrum.

One further clarification concerning $^1H$ NMR should be made at this point. The $^1H$ NMR coupling constants were not heavily relied upon to support a conformational preference unless the MM2 calculations indicated a predominance of one conformation. Physical measurements upon a solution mixture of conformations may produce data which often represents the time averaged contribution from different conformations. Ideally, the existence of a major conformation produces NMR data reflecting the electronic and geometrical environments within that conformation. Only in this case can coupling constants be used to verify a conformational preference. A minimum of 1.0 kcal mole$^{-1}$ energy difference between conformations is required before $^1H$ NMR coupling constants are useful in substantiating the existence of a major conformation. A possible solution to the problem of time averaged coupling constants has recently been reported by Font$^{63}$ who reports the use of a computer program which calculates $^1H$ NMR coupling constants from the relative
energies of conformations. In this way, the predicted average J values from a conformational equilibrium are generated which may be compared to the observed J values.

5.0 The Conformations and Reactivity of 14-Membered Lactones

5.1 The Preparation of 3-Oxo-13-Tetradecanolide

Throughout this thesis, two macrolides were used as starting materials for the conformation-reactivity analysis. The first large lactone 43 was prepared as shown on the following page.64
Figure 30. The total synthesis of starting 3-keto macrolide 43. i) Ac₂O, H₂SO₄, acetone; ii) AcCl, pyridine, CH₂Cl₂; iii) Hg(OAc)₂, CrO₃, H₂SO₄, acetone; iv) HgO, Br₂, CCl₄; v) NaBH₄, EtOH; vi) Reflux, THF; vii) 2 eq. LDA, 50 °C, THF.
5.1.1 Co Methylation of 3-Oxo-13-Tetradecanolide

Deprotonation of 43 with potassium t-butoxide followed by treatment with iodomethane gave a 2:1 mixture of diastereomeric (2R\textsuperscript{*},13R\textsuperscript{*} and 2S\textsuperscript{*},13R\textsuperscript{*}) lactones 44 of unassigned stereochemistry. The use of the star superscript indicates the presence of both enantiomers possessing the same relative chirality at the numbered atoms, e.g. 2R\textsuperscript{*},13R\textsuperscript{*} refers to an equal number of 2R,13R and 2S,13S stereoisomers.

\[
\text{\begin{center}
\begin{tikzpicture}
\node at (0,0) {$43$};
\node at (1.5,0) {$\overset{1a)}{\text{KO}^\text{Bu}}$};
\node at (4.5,0) {$\overset{b)}{\text{MeI}}$};
\node at (3,1.5) {$O$};
\node at (3,3) {$O$};
\node at (4.5,1.5) {$\sim$};
\node at (5.5,1.5) {$2:1$};
\node at (7,1.5) {$\sim$};
\node at (8,1.5) {$44$};
\end{tikzpicture}
\end{center}}
\]

MM2 calculations of possible enolate conformations suggested the predominance (98%) of the [3434] intermediate below. In this conformation, the interior of the ring significantly shields the inner re-re face of the olefin from electrophilic approach.

The enolate must be attacked from the ring periphery to initially produce the 2R\textsuperscript{*},13S\textsuperscript{*} diastereomer. MM2 calculations indicated that the lowest energy conformation placed the newly introduced methyl substituent at a corner position. Under the conditions employed, equilibration would produce a mixture of diastereomers at the corner position.
The equilibration of the 2-methyl-3-keto lactone was possible only because the sterically unhindered corner could freely accommodate both diastereomers in the [3434] conformation. If the methyl substituent was at a non-corner location, one diastereomer would force the C2 methyl group into the ring interior and generate significant transannular interactions. The observed 2:1 ratio shows that each diastereomer must have very similar energies.

5.1.2 Diastereoselective Reduction of 2-Methyl 3-Oxo-13-Tetradecanolide

Reduction of the 2:1 macrolide mixture 44 with sodium borohydride yielded all four possible diastereomeric 2-methyl-3-hydroxy lactones in a ratio of 13:3:2:1. It was obvious that one diastereomer of the 2:1 mixture reacted preferentially while the other was partially epimerized during the reduction.

Before beginning a conformational analysis, it was necessary to establish the relative stereochemistries of each diastereomer. Initially, this task seemed imposing, however the assignments were completed in the following manner. Sodium borohydride reduction of the starting 3-keto lactone 43 produced a 3:1 mixture of alcohols 45 and 46 whose relative
stereochemistries were previously determined\textsuperscript{65,66} by an X-ray analysis of their bromoacetate derivatives. The major 3-hydroxy lactone 45 (98% one diastereomer by glc) was separated from the minor 46 (96%) by chromatography.

Frater has demonstrated the highly stereoselective anti introduction of alkyl groups at the 2-position in 3-hydroxy esters\textsuperscript{67} (Figure 31).

![Diagram of alkylation reaction](image)

Figure 31. Alkylation of 3-hydroxy esters.\textsuperscript{67}

Alkylation of the major hydroxy lactone 45, under Frater's conditions, yielded a 9:1 mixture of products which based on the above open chain chelation product was predicted to be mainly the 2R\textsuperscript{*},3R\textsuperscript{*},13R\textsuperscript{*} diastereomer 47 accompanied by the minor 2S\textsuperscript{*},3R\textsuperscript{*},13R\textsuperscript{*} isomer 48. Glc co-injection of these purified lactones with the sodium borohydride reduction
mixture clearly identified the compounds present in 13 and 3 proportions as 47 and 48 respectively.

Similarly, the minor hydroxy lactone 46 yielded the products 49 and 50 but in more modest 3:1 ratio. The predicted stereochemistries were on less firm footing for these examples because of the lower diastereoselectivity. Nevertheless, glc analysis showed that 49 and 50 corresponded to the remaining diastereomers present in 2 and 1 amounts from the reduction of 44.

The reduction products of the 2-methyl-3-keto lactone 44 could now be fully assigned as shown on the following page.
5.1.3 Chelation Control in the Reductions of the 3-Keto Lactone

A simple conformational analysis of the 3-keto lactone 44 was unable to account for the observed product distributions. All low energy conformations of 44 from MM2 calculations indicated the si face of the carbonyl group as most accessible. Upon reduction, this would produce the $3S^*,13R^*$ stereochemistry in the major product and this was evidently the reverse of what was happening. Earlier results in our laboratory similarly demonstrated the failure of a simple conformational analysis to account for the reduction products of the unsubstituted 3-keto lactone 43.

These reduction results were rationalized by invoking chelation of the cation by the carbonyl oxygen atoms to expose the necessary re face for attack by hydride (Figure 32). Therefore, altering the degree of chelation by varying the counter-ion would be expected to affect the product ratio.
The reduction of the 2-methyl-3-keto lactone 44 using sodium borohydride produced a 5:1 ratio of $3R^*,13R^*$ to $3S^*,13R^*$ alcohols. This ratio increased to 49:1 in the presence of L-Selectride and fell to an almost statistical distribution of 1.6:1 when using tetrabutylammonium borohydride. These results were in good agreement with the proposed chelation hypothesis since the lithium counter-ion is a better chelating agent than sodium, whereas the tetrabutylammonium cation should not form a chelate. It is true that the use of any Selectride reducing agent should be expected to generate increased selectivity, therefore, a more rigorous test of this hypothesis was performed using tetrabutylammonium borohydride in the presence of lithium bromide. The resultant 60% increase of the major $3R^*,13R^*$ alcohol over the minor $3S^*,13R^*$ alcohol clearly supports the chelation hypothesis.
Figure 33. A summary of the reduction results for the mixture 44.

Of the four reduction products, 47, 48, 49 and 50, only the major 2R*-methyl-3R*-hydroxy-13R*-methyl lactone 47 could be isolated pure by chromatography for later use in chemical reactions. MM2 calculations for this lactone 47 indicated that the [3434] conformation shown on the following page represented the third lowest energy arrangement. However, the MM2 program does not include hydrogen bonding effects. Stabilizations of 2-6 kcal mol⁻¹ have been reported from hydrogen bonding effects and this would clearly stabilize this conformation.⁶⁹ We therefore assumed that this conformation was more highly populated than its MM2 energy suggested and possibly represented the predominant conformation. We have found similar intramolecular hydrogen bonding in the macrolide 45 lacking the C₂ methyl group.³³
Evidence in support the above conformation for $47$ could be found using $^{13}$C NMR and IR spectroscopy. Compound $47$ displayed a broad OH stretching band at $3335$ cm$^{-1}$ due to a hydrogen bonded hydroxyl group. A three fold solvent dilution produced no significant change in the IR spectrum and most importantly no free OH stretching band could be seen. In contrast, its C$_2$ epimer, $48$, displayed two bands from the presence of hydrogen bonded and free hydroxyl groups. Dilution as before produced exclusively the free OH stretching band (3650 cm$^{-1}$) at the expense of the hydrogen bonded band. The presence of internal hydrogen bonding might be expected to shift the major compound’s carbonyl carbon peak of the $^{13}$C NMR spectrum downfield relative to its C$_3$ epimer. The major compound $47$ displayed the carbonyl peak at $176.0$ ppm in comparison to $174.3$ ppm of its C$_3$ epimer. The dominance of this conformation in the starting material $45$ has been similarly analyzed and accounts for the good selectivity obtained in the Frater alkylation since the chelated intermediate could achieve planarity easily.

The low diastereoselectivity obtained in the 3-hydroxy lactone alkylation of $46$ was unanticipated. Typically, the Frater product distribution exhibits $\geq90\%$ anti selectivity.$^{67}$ In this example, a reduced 3:1 ratio was observed and this was the cause of some uncertainty in the identification of the product stereochemistries. The low selectivity was likely due to the unfavorable hydroxyl stereochemistry of the lactone $46$. Regardless of which conformation was populated in $46$, it would be very difficult for the alkoxide and carbonyl oxygen to chelate a counter-ion since this would involve a rather large deformation of the ring. This situation is illustrated on the following page using the [3434] conformation of the dianion intermediates of $46$ and $45$. 

![Diagram of compound 47]
The planar intermediate from 46 should not be attained easily and accordingly the alkylation was less selective.

5.1.4 X-ray Crystallographic Analysis of (2S*,3S*,13S*)-2-Methyl-3-Hydroxy-13-Tetradecanolide

The above two diastereomers 49 and 50 were very difficult to separate, for example they were barely resolved by glc. However, the major diastereomer selectively crystallized from a mixture of both diastereomers. The X-ray crystal structure of lactone 49 is shown in Figure 34. It was encouraging to see that the relative stereochemistries of the three centers were the same as we assigned above in spite of the low 3:1 selectivity. In addition, the lactone geometry was clearly in a s-trans relationship and the lactone C-O-C-H torsional angle was 22°. This X-ray analysis directly supported our previous assumptions 1) - 4). Namely, that the s-trans geometry and the 0-30° C-O-C-H angle limitation of esters of secondary alcohols were directly applicable to large ring lactones. Furthermore, compound 49 provided the first opportunity in our laboratory to observe a 14-membered solid state conformation of an underivatized alcohol. The only previous X-ray analyses were completed on two simpler bromoacetate diastereomers which might have distorted the ring from the favoured [3434] conformation. We also expected the solid state conformation to exist in one of the lower energy [3434] conformations since any conformation observed in a molecular crystal is not far from the solution structure.
However the X-ray crystallographic conformation turned out to be totally unexpected.

Surprisingly, compound 49 did not crystallize in any of the fifteen low energy conformations and, in fact, did not exist in an expected [3434] conformation. Examination of the unit cell packing diagram revealed an intermolecular hydrogen bond between the carbonyl oxygen of one molecule and the hydroxyl proton of another.
This hydrogen bonding was surmised to be holding the molecule in a high energy conformation, although all but three bonds had torsional angles similar to the [3434] conformation. Indeed, without the distortion at bonds 3, 4 and 5, it appeared that the solid state conformation may have adopted the [3434] arrangement.

5.2 Additional Examples of the Twist Conformation

Initially, the solid state conformation of 49 was dismissed as a renegade arrangement whose sole existence could be attributed to intermolecular hydrogen bond interactions. However, the twisted conformation was quickly resurrected with the synthesis of a second molecule 51 which also crystallized in a twist conformation. A comparison of the polar
maps of the two X-ray structures quickly showed the identity of the two conformations which was not immediately apparent from the ORTEP diagrams.

![Macrolide](image1)

![Polar map](image2)

![ORTEP diagram](image3)

Figure 38. Comparison of two twist conformations adopted by macrolides 49 and 51.

This additional example of a twist conformation also exhibited intermolecular hydrogen bonding in the solid state. We were willing to ascribe this second twist conformation to coincidence because the presence of hydrogen bonding implied another conformational distortion. However, during this work, Schreiber\textsuperscript{44} published the crystal structure of a 14-membered macrolide, (E)-5,9-dimethoxy-6-oxo-10-tridecen-13-olide, (52), and we also obtained unpublished crystallographic data on one of Woodward's\textsuperscript{71} 14-membered erythromycin precursors 53. From the ORTEP diagrams, we suspected both rings existed in the twist conformation and this was confirmed through an analysis of their polar maps. No
lattice packing data was given for these examples but hydrogen bonding could be ruled out as a factor in Schreiber's molecule.

The discovery of four twist conformations aroused our curiosity about this conformation. It is interesting to speculate on how long both Schreiber's and Woodward's twist conformations would have gone unnoticed without the aid of polar maps.

The calculated MM2 energy of the twist conformation of cyclotetradecane was only 3.4 kcal mole$^{-1}$ higher in energy than the [3434] conformation. In fact, this represented the fifth lowest energy conformation of a 14-membered ring and was lower in energy than eleven of the thirteen diamond lattice conformations. This calculation led us to redefine the ceiling on the conformational analysis of 14-membered rings to include six low energy conformations. During the preparation of this thesis, Hauske et al.$^{72}$ have reported an X-ray crystal structure of an erythromycin derivative which we also recognized as a fifth example of the twist conformation.

The next lowest energy conformation of cyclohexane, after the chair, is the twist boat which is $\sim$5.5 kcal mole$^{-1}$ higher in energy. Throughout this thesis, a comparison has been
made between the cyclohexane chair conformation and the corresponding 14-membered [3434] conformation. In light of the twist boat conformation and on a philosophical note, it is interesting to further speculate on whether the 14-membered twist conformation should not have been expected as a preferred conformation rather than being experimentally discovered.

An investigation of the twist conformation's polar maps indicated the presence of both corner and pseudo corner positions. The presence of these two positions within a conformation provides an opportunity to expand Dale's nomenclature system for ring conformations.

5.3 Identifying Large Ring Conformations - A New System of Naming

The present system for naming conformations is based on the number of bonds between corner atoms (see page 29 of this thesis). However, this system is unable to adequately describe a conformation which has only 1 or 2 corner positions. Others have recognized this and turned to an arbitrary system which designates each conformational type with a letter. But the use of the D,C or twist classifications for naming conformations is not a general one which could be applied to other ring systems.

Ogura reported the 14-membered D and C conformations which, under Dale's system, are classified as the [311] and [68] conformations respectively. Neither of these designations are as informative as, for example, the [3434] conformation, and as a possible solution, the pseudo corners could be taken into account to modify Dale's nomenclature. The D and C conformations are illustrated in Figure 39 using top view wedge diagrams where the + and - symbols describe the signs of the gauche torsional angles around pseudo corner and corner positions.
As shown above, the environment encountered by the corner atoms (flanked by a ++ gauche sequence) is not significantly different from that of the pseudo corner atoms (+- gauche sequence). Maintaining the spirit of Dale's nomenclature, we suggest that it be extended to include pseudo corners as the basis for naming conformations. Using polar maps, both corner and pseudo corner positions can be identified with ease. The number of bonds between a corner and pseudo corner atom or between two pseudo corner atoms shall be denoted with a primed number. As before, the smallest number of bonds should begin the sequence in the square brackets, but unprimed numbers shall have priority over any primed ones, i.e. if present, the starting value should represent the smallest number of bonds between two corner atoms. Hence, we propose the numbers in the square brackets as being reported: (corner-corner) > (corner-pseudo corner) > (pseudo corner-pseudo corner) In this way, the combination of unprimed and primed numbers will define a conformation in a more precise manner. As shown in the above Figure 39, the C conformation would be renamed the [3'3'4'4'] conformation and the D the [34'7'] conformation. The use of primed numbers also partitions the numbers in the square brackets and allows for a more immediate understanding.
of the conformation involved. For example, under Dale's system, the comprehension of the very abbreviated [68] notation may initially cause some confusion whereas the [3'3'4'4'] designation is more easily pictured and pleasing to the eye if not to the tongue.

Using Dale's system, the newly discovered twist conformation would be designated as the [311] conformation, which is the identical Dale name given to Ogura's D conformation. But under this newly proposed nomenclature, the twist is uniquely described as the [34'3'4'] conformation.

![Diagram of Dale prime nomenclature for the twist conformation.](image)

Carbons 13 and 10 = Corner atoms
Carbons 6 and 3 = Pseudo corner atoms

Figure 40. Dale prime nomenclature for the twist conformation.

In keeping with Dale's system, this new naming procedure remains descriptive and not dependent on memorizing a letter with a corresponding conformation. Undoubtedly, this system of naming could prove useful in other ring systems and shall be followed from this point on throughout the thesis.

5.4 The C2 Geminal Methylation of 3-Oxo-13-Tetradecanolide

The X-ray analysis of the [34'3'4'] conformation provided an opportunity to confirm most of our earlier assumptions concerning the conformations of simple macrolides. However, the theoretical preference for the dominance of the [3434] conformation was unproven and the sole occupation of a corner position by a geminally substituted atom was untested. We therefore turned our attention to the construction of a macrolide which could potentially test these predictions simultaneously.

The starting 3-keto lactone 43 was deprotonated with potassium t-butoxide and refluxed with an excess of iodomethane to produce the geminally substituted macrolide 54 in
very high yield and purity. MM2 calculations supported the existence of several equally low energy conformations outside the [3434] arrangement and since this compound was not crystalline, no definite conclusions concerning its conformation could be made.

5.4.1 The Reduction of 2,2-Dimethyl-3-Oxo-13-Tetradecanolide

The chemical reactivity of macrolide 54 was considered to be influenced by two competing factors. The geminal methyl group should occupy a corner position and this was verified by an inspection of molecular models and corresponding energy calculations.

The occupation of the corner position by a geminal methyl group essentially locked the remainder of the ring into a rigid arrangement and in every calculated conformation exposed the si face of the ketone for attack as in the case for the 2:1 mixture of 2-methyl 3-keto lactone 44.
However, as a caveat, we have shown that chelation in these molecules must also be considered as a strong influence on the conformations of the 3-keto macrolides. If the chelation effect overrides the corner requirement, then the re ketone face becomes more accessible and the geminal methyl group would be temporarily displaced from the corner position.

The reduction procedure used for compound 44 above was repeated for the geminally substituted 54. Thus treatment of 54 with L-Selectride produced two alcohols of undetermined stereochemistry in a ratio of 230:1. The stereochemical determinations from the previous reduction could now be taken advantage of to assign the stereochemistries in this instance.

Compound 47 from above was subjected to the Frater alkylation\textsuperscript{67} to afford the macrolide 55 in 97% yield. This compound was shown to be identical to the major reduction product from 54 by glc co-injection and $^1$H NMR spectra.
Apparently, the reduction was under chelation control and occurred from the re face of the ketone. As before, the replacement of the L-Selectride with tetrabutylammonium borohydride was predicted to decrease the proportion of the major alcohol 55. Not unexpectedly, the tetrabutylammonium borohydride product distribution decreased to a 1.6:1 ratio of 55 to 56. The practice of lithium bromide addition increased the selectivity in the tetrabutylammonium borohydride reduction to a 2.1:1 level. It seems that the chelation of the carbonyl oxygens overrides the tendency to have the geminal methyls occupy a corner position. If chelation was occurring from the [3434] conformation, then a slight twisting of the conformation, greatly aided by the metal chelation, would allow both geminal methyls to point away from the interior of the ring and produce a less strained arrangement.

Figure 41. Proposed mechanism for reduction of 54.

5.4.2 The Crystal Structure and Conformational Analysis of (3S*,13S*)-2,2-Dimethyl-3-Hydroxy-13-Tetradecanolide

MM2 calculations indicated the three lowest energy conformations for the major
alcohol 55 involved a [3434], [3344] and another [3434] conformation. Although both alcohols 55 and 56 were crystalline, only crystals from the major 55 could be grown which were suitable for X-ray analysis. The X-ray analysis indicated that 55 consisted of a 1:1 mixture of conformations in the solid state. The polar maps of the X-ray structures demonstrated that one was a [3344] conformation and the other a [3434] conformation. The solid state conformations corresponded to the second and third lowest energy conformations. This was verified by comparing the calculated conformations 55b and 55c to the observed solid state conformations.

![Figure 42. Calculated lowest energy conformations of 55 and the X-ray conformations. Most hydrogen atoms have been omitted for clarity.](image)

The geminal methyls occupied the corner positions in both the [3344] and [3434] conformations and these molecules represent one of the first examples confirming Dale’s
predictions that geminal methyl groups should occupy corner positions.\textsuperscript{73,74} In addition, both conformations contained the \textit{s-trans} lactone geometry. The C-O-C-H lactone angle was outside the range of 0-30° suggested from Dunitz's analysis (being 38° in both examples). This 8° deviation was not considered significant.

![Figure 43. ORTEP diagrams of 55 showing top view of the [3344] and [3434] conformations.](image)

The alcohol 55 was the last macrolide from which crystals could be grown which were suitable for an X-ray analysis. However, other 14-membered lactones produced within our laboratory were also analyzed by X-ray crystallography. From a total of 12 crystal structures and where applicable, assumptions 1) - 4) (page 42) were satisfied in every conformation. We were curious about the energies of the solid state conformations and used
the [3434], [3344], [3335], [34'7'], [3'3'4'4'] and [34'3'4'] conformations as low energy starting points for MM2 calculations. The structure of each crystalline macrolide was substituted into each of the six above conformations in accord with assumptions 1) - 4). This often resulted in a large number of conformations being generated for each separate macrolide. Nevertheless, in the absence of hydrogen bonding in the lattice, the solid state conformation was one of the calculated three lowest energy conformations. These three lowest energy conformations were consistently the [3434], [3344] and [3335] conformations and the remaining MM2 calculations reflected this trend.

Interestingly, although low energy [3344] and [3434] conformations 55b and 55c co-crystallized in the lattice, the MM2 energies suggested that in the absence of crystal lattice packing effects, the lowest energy [3434] conformation 55a should be the dominant conformation. The C3 methine proton of 55a existed in an anti:gauche relationship with the neighboring methylene protons and this was reflected in the observed coupling constants of 10.2 and 1.8 Hz. The only other remaining J value which could be obtained was the coupling of the C13 methine proton to the C12 methylene protons. The MM2 calculations indicated that the [3434] conformation 55a was more stable by 0.7 kcal mol\(^{-1}\) and should therefore be more highly populated to the extent that contribution from the minor species 55b should not significantly alter the J values expected for the major conformation. The observed J values of 9.3 and 2.5 Hz mainly represented the anti-gauche contribution from the [3434] geometry of 55a at C13 and C12.

Further supporting evidence for conformation 55a could be found from \(^1\)H NMR studies. Examining conformation 55a, one would predict that the anisotropy of the carbonyl group should influence the chemical shift of the geminal methyl groups differently. This could be seen in the two well separated methyl singlets at 1.22 and 1.11 ppm. In addition, long range "W" coupling from the C3 methine would be expected to broaden only the 2\(\alpha\) methyl group in this conformation. The \(^1\)H NMR spectrum showed the high field methyl singlet at 1.11 ppm as broader and less intense than its partner and we tentatively assigned the high field singlet as the 2\(\alpha\) methyl group.
Using the same analysis, a nuclear Overhauser effect difference spectroscopy (NOEDS) experiment involving the irradiation of the C₃ methine proton should selectively enhance the 2β methyl in 55a since the presumed 2α methyl (at 1.11 ppm) is in an anti arrangement. A NOEDS experiment confirmed this prediction with the specific enhancement of the methyl singlet at 1.22 ppm when the C₃ proton was irradiated.
Although X-ray crystallography provided a detailed look at the second and third lowest energy conformations available to compound 55, it seems that the $^1$H NMR analysis and MM2 calculations supported the existence of macrolide 55 in solution as the lowest energy [3434] conformation 55a.

### 5.5 The Preparation and Reduction of 4-Methyl 3-Oxo-13-Tetradecanolide

To this point, the effects of mono and geminal alkyl substitution had been investigated only at the C2 position of the starting 3-keto lactone 43. However, the corresponding
alkylations at the C4 position were considered to offer new challenges to our understanding concerning the conformational behavior of the large rings.

The dianion of the 3-keto lactone 43 was formed from the addition of two equivalents of lithium diisopropyl amide and was alkylated with one equivalent of iodomethane to produce the 4-methyl 3-keto lactone 57 as a single diastereomer.

Despite all efforts, this compound did not crystallize. Reduction of the ketone with sodium borohydride gave two alcohols in a ratio of 3:1. This ratio was the same as in the reduction of the unalkylated lactone 43. The chelation effect observed in the reduction of the 3-keto lactones has been established therefore it was assumed that the major product 58 exhibited the relative 3S*,13S* stereochemistry and the minor alcohol 59 possessed the 3R*,13S* stereochemistry.

After a time, both alcohols 58 and 59 crystallized but the crystals were disordered. Repeated crystallizations and derivatization of the alcohols invariably led to compounds which also gave disordered crystals. In an empirical study, Heathcock et al. demonstrated the use of 13C NMR shifts of α-methyl-β-hydroxy esters, acids and lactones to assign the erythro or
threo stereochemistry. The chemical shifts of the methine C2, carbinol C3 and the methyl group were all found at higher field in the erythro isomer compared to the threo. Heathcock's results were confirmed by two independent findings by Stothers\(^7\) and Whitesell\(^7\) in separate investigations on hydrocarbon systems which contained only methyl and hydroxyl substituents. All three groups concluded that these three carbons in an erythro environment would resonate upfield of the corresponding threo signals. These findings offered two methods to assign the stereochemistry of reduction products 58 and 59, both as their lactones and via their ring opened acids.

$$\text{Erythro}$$

$$\begin{align*}
\text{HO} & \quad \text{O} \\
\text{R}_1 & \quad \text{OR}_2 \\
\text{C}_1, \text{C}_2, \text{C}_3 \text{ at higher field}
\end{align*}$$

$$\text{Threo}$$

$$\begin{align*}
\text{HO} & \quad \text{O} \\
\text{R}_1 & \quad \text{OR}_2 \\
\text{C}_1, \text{C}_2, \text{C}_3 \text{ at lower field}
\end{align*}$$

Figure 45. The \(^{13}\text{C}\) NMR shift trend for distinguishing threo from erythro stereochemistry.

The resonances of the carbon atoms in question for the minor lactone 59 were consistently at higher field when compared to the major lactone 58. This immediately suggested an erythro relationship for the minor 59 and the threo stereochemistry for the major lactone 58. Both lactones 59 and 58 were hydrolysed with base to yield the corresponding hydroxy acids and their \(^{13}\text{C}\) NMR spectra were compared. The resulting hydroxy acid 61 of the minor compound again exhibited signals which were consistently at higher field than those for the major acid 60.
Figure 46. Application of the $^{13}$C NMR shift trend to compounds 58 and 59 and their acids.

The $^{13}$C NMR evidence and proposed reduction stereochemistry strongly pointed to the $3S^*,4S^*,13S^*$ as the major compound 58 and the $3R^*,4S^*,13S^*$ stereochemistry for the minor 59.

Therefore the starting keto lactone 57 possessed the $4S^*,13S^*$ stereochemistry and the C4 alkylation and subsequent reduction could now be examined in terms of possible conformational control. The geometries of the enolates were unknown but we postulated that
the dianion occupied a distorted \([3434]\) conformation \(62\) in which chelation of the metal ion was possible while also positioning the methyl group exterior to the ring. This conformation would expose the 3-re, 4-re face of the ketone enolate to the electrophile to exclusively produce the observed 4S\(^*\),13S\(^*\) stereochemistry upon alkylation.

![Diagram](image)

The methylated macrolide 57 also posed a less than straightforward conformational analysis. From 12 X-ray crystal structures, we have shown without exception, the validity of the \(s\)-trans lactone preference, a 0-40° lactone C-O-C-H torsional angle restriction and the preference for substituents to be out of the ring. Macrolide 57 represented one of very few examples in which assumptions 1) - 4) could not be accommodated in the preferred \([3434]\) conformation or in the second lowest \([3344]\) conformation. Only one \([3335]\) conformation could be constructed which positioned the 4S\(^*\),13S\(^*\) methyl substituents at exterior locations while simultaneously possessing the \(s\)-trans lactone geometry and a 0-40° C-O-C-H angle.

![Diagram](image)

This conformation also directed the carbonyl oxygen atoms for facile chelation of a metal cation which has been shown to be an important factor in the 3-keto macrolides. The reduction of the ketone from this conformation would produce the 3R\(^*\),4R\(^*\),13R\(^*\) stereochemistry as observed.
5.6 The Preparation of 4,4-Dimethyl-3-Oxo-13-Tetradecanolide

At this stage, our attention turned to synthesizing a geminally methylated macrolide at the C4 position. The synthesis of the 4,4-dimethyl-3-keto lactone 63 was first attempted using the lithium diisopropyl amide/iodomethane conditions which were proved successful for the monomethylation at the C4 position. However, the starting material was recovered in every instance. This was viewed in two ways. Either deprotonation of the C4 methine was not occurring or the dianion was forming but was unable to undergo electrophilic attack by the iodomethane. Treatment of 57 with lithium diisopropyl amide and a subsequent deuterium workup indicated no deuterium incorporation in the product as determined from the mass spectrum. Apparently the dianion of the methylated macrolide 57 was not forming with lithium diisopropyl amide. This was eventually solved through the use of the original procedure for generating a dianion. The introduction of sodium hydride/n-butyllithium as deprotonating agents yielded high levels of di-deuterated product upon deuterium workup and the similar treatment of 57 followed by the addition of iodomethane gave the geminally substituted macrolide 63. However, this reaction still required excess base and a long reaction time which reflected the difficulty in forming this molecule using this route.
Unfortunately, the resulting 4,4-dimethyl 3-keto macrolide $63$ was not crystalline but the conformational analysis of lactone $63$ was interpreted using the same [3335] conformation above. As in the mono methylated derivative, only one [3335] conformation could be populated in which the geminal dimethyl and lone methyl substituents were located exterior to the ring while retaining the s-trans lactone geometry and a 0-40° C-O-C-H angle. Within the macrolide ring, only the corner position can be geminally substituted in stable conformations.

The $\mathrm{C}_{13}$ to $\mathrm{C}_{12}$ proton couplings in $63$ suggested a gauche-gauche relationship and this was supported by observed J values of 2.9 and 7.0 Hz respectively.

5.7 Preparation and Hydrogenation of (E)-2-Methyl-2-Tetradecen-13-olide

A study of 14-membered $\alpha,\beta$-unsaturated macrolides represented a relatively unexplored area and promised new information concerning the conformational analyses and reactivity of these ring systems. The major product $47$, from the previous reduction of $44$, was tosylated and eliminated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to yield the
unsaturated lactone 64 as a single geometric isomer. The stereochemistry of this compound was determined through an NOEDS experiment. The irradiation of the vinylic C3 proton produced no enhancement of signal in the presumably distant C2-methyl protons which was only possible in the trans arrangement of these groups.

\[
\begin{align*}
\text{HO} & \\
\text{C} & \\
\text{O} & \\
1a) \text{TsCl/pyridine} & \\
b) \text{DBU} & \\
\end{align*}
\]

\[47 (2S^*,3S^*,13S^*) \]

\[64 \]

The production of one isomer is noteworthy because the macrolide rings are capable of incorporating both trans and cis double bonds within the ring. The elimination of the tosylate with a non-nucleophilic base (DBU) favors an anti geometry of the leaving group and abstracted proton but may occur via a syn geometry.\(^\text{79}\) The production of the \textit{E} stereochemistry in macrolide 64 can be understood in these terms as well as including conformational effects. A possible conformation for the tosylate of 47 is shown on the following page. The hydrogen atom which is parallel to the p orbitals of a carbonyl π bond will be abstracted preferentially by base.\(^\text{80}\) This conformation exists with the tosylate and adjacent C2 proton in a syn position. The C2 proton also occupies a sterically unhindered corner position in which it is parallel to the p orbitals of the carbonyl bond. These factors should enhance the likelihood of proton abstraction by the bulky DBU base. The elimination of the tosylate from this conformation would selectively generate the observed \textit{E} macrolide 64.
A similar macrolide 65 has been synthesized which only differed in the placement of the methyl substituent. This macrolide 65 was hydrogenated with platinum black to produce one diastereomer which was assigned the 3S*,13S* stereochemistry. Therefore it was hoped that the hydrogenation of the structurally similar 64 would produce a single product. However, hydrogenation of 64 with platinum black in ethanol produced a 1:1 mixture of diastereomers. These results contrasted with those of the 3-methyl diastereomer 65 and we turned to a conformational analysis and MM2 calculations of both unsaturated macrolides in order to rationalize the differences in selectivity between the two molecules.
The lowest energy conformation of the 3-methyl diastereomer 65 has been previously calculated as a distorted conformation\(^{33}\) in which only the 2-re, 3-si face of the olefin was available for hydrogenation. This prediction was in good agreement with the observed production of the cis product.

\[
\begin{align*}
\text{Pt} / \text{H}_2 & \rightarrow \\
\text{O} & \\
\text{H} & \\
\end{align*}
\]

The calculated lowest energy conformation of macrolide 64 indicated that the reduction of the olefin should produce only the 2S*, 13S* product. This prediction is not observed experimentally. We concluded that the platinum catalyst was able to freely attack either side of the enone and this led to the total lack of selectivity for the reduction.

5.8 The C\textsubscript{13} Methylation of 13-Tetradecanolide

We next turned our attention towards an investigation of the simple lactone 42.\(^{81-83}\) Treatment of 42 with lithium 2,2,6,6-tetramethylpiperidide (Harpoon base) followed by iodomethane led to a 13:1 mixture of diastereomers of undetermined stereochemistry. The kinetic nature of the product distribution was verified by base equilibration to an approximate 1:1 ratio using lithium diisopropyl amide.\(^{84}\)
Still has offered a \(^1\)H NMR chemical shift trend for assigning the stereochemistry of methylated lactones.\(^{28}\) In this rule, Still states that for the 2-methyl lactones of secondary alcohols, the chemical shift difference between the two methyl substituents in 9-12 membered lactones is always larger in the trans dimethyl case. From the observed NMR shifts of the corresponding methyls, this tentatively assigned the major 2-methyl lactone the trans or \(2S^*,13S^*\) stereochemistry and the minor as the cis or \(2R^*,13S^*\) stereochemistry. Still's rule was valid up to 12 membered lactones, but was untested on higher membered rings as in our case. We were not confident of Still's technique for assigning the stereochemistry in our molecules and hence, we sought to confirm the stereochemistry by a synthetic method.

The lactone \(47\) was deoxygenated under Barton's conditions\(^{85}\) to yield the \(2S^*,13S^*\) diastereomer \(66\) below.

![Deoxygenation of macrolide 47](image-url)
Glc co-injection studies with the 13:1 methylated diastereomers established that the minor methylated product was of 
\(2S^*,13S^*\) stereochemistry. The \(^1H\) NMR spectra of the deoxygenated product \(66\) and the minor methylated product showed no difference in the combined spectrum with that of the deoxygenated product alone. These results were substantiated by a further deoxygenation of a mixture of compound \(49\) and its diastereomer \(50\) to produce as a major product \(67\). Obviously, Still's chemical shift method does not extend to 14-membered lactones and justified our chemical approach for assigning stereochemistries of the methylated products \(67\) and \(66\).

\[\text{Major (13)} \quad \overset{67 (2R^*,13S^*)}{\sim} \]

\[\text{Minor (1)} \quad \overset{66 (2S^*,13S^*)}{\sim} \]

**5.8.1 The Use of \(^1H\) NMR to Assign the Geometry of Trimethylsilyl Enol Ethers**

The MM2 calculations of the enolate of \(42\) were expected to be less complicated than in previous alkylation studies because of the absence of chelation. Based on previous studies\(^{86}\), the \(E\)-enolate geometry was assumed. However, we desired a method to assign the enolate stereochemistry which was reliable and uncomplicated. Techniques to assign the stereochemistries of trapped enolates have been reported. For example, Heathcock et al. has shown that the allylic carbon \(C3\) of the \(E\)-trimethylsilyl enol ether isomer consistently resonates 5-6 ppm upfield from the \(Z\) isomer.\(^{86}\)
However, this method suffered from two shortcomings. First, the trapping of macrolide enolates as their trimethylsilyl (TMS) enol ethers frequently produces only one isomer (Z or E) and Heathcock's technique requires both isomers to assign the stereochemistry. Second, it may be challenging to identify the allylic carbon of interest in highly functionalized molecules. For these reasons we looked for a more flexible method for assigning the stereochemistries of TMS enol ethers. The nuclear Overhauser effect (NOE) has been used successfully to determine the geometries of methyl enol ethers.\textsuperscript{87} An analysis of molecular models of an E-TMS enol ether indicated that the vinylic and silyl methyl protons would overlap at closest approach and would be 2-3 Å apart at the maximum. These interatomic distances were sufficiently close that irradiation of either set of protons should exhibit an NOE enhancement.\textsuperscript{88} However, more meaningful NOE results would result if the TMS protons were chosen to be irradiated instead of the vinylic protons. The TMS protons will resonate at very high field (~0.0 ppm) away from the interference of other protons and this allows the use of greater irradiation power without the danger of "power leakage" to protons resonating nearby. Only one diastereomer would be required to assign the olefin stereochemistry in this method.

We prepared the TMS enol ethers \textsuperscript{68} and \textsuperscript{69} of cyclohexanone and propiophenone.\textsuperscript{86} Separate irradiation of the silyl protons in each molecule led to the selective enhancement of protons syn to the TMS protons. For the enol ether \textsuperscript{68}, only the vinylic and C\textsubscript{6} allylic protons showed enhanced signals. For \textsuperscript{69}, the ortho aromatic protons and the vinyl methyl protons were enhanced.
A 4:1 mixture of the $E$ and $Z$ isomers of 3-[(trimethylsilyl)oxy]-2-pentene$^8$, (Z0) and (Z1), provided a more rigorous test of this technique. The NMR spectrum of the vinyl protons is shown in Figure 48a; the major quartet being previously assigned to the $E$-TMS enol ether.$^8$ The simultaneous irradiation of the TMS protons of both isomers led to expected exclusive enhancement of the vinylic quartet of the major $E$ isomer (Figure 48b).
This method was extended to the trapped enolates of lactones.\textsuperscript{89} Thus the simple lactone 42 was deprotonated with lithium diisopropyl amide and quenched with trimethylsilyl chloride to give the desired ketene acetal 72 in 31\% yield. A major by-product (53\%) in this reaction was the C-silylated product 73 which is frequently observed in these reactions.\textsuperscript{90}

The stereochemistry of the ketene acetal 72 was shown to be trans by the sole enhancement of the vinylic quartet and canceling of all other signals in the $^1$H NMR NOEDS experiment (Figure 49).
The ketene acetal \( \text{72} \) was alkylated with chloromethyl phenyl sulfide in the presence of zinc dibromide followed by a Raney nickel desulphurization\(^{91} \) which gave a 3:1 mixture of \( \text{67} \) to \( \text{66} \). The reduced 3:1 selectivity seen in this reaction compared to the carbanion alkylation may be explained by the higher temperature of the former reaction as well as the use of a more reactive electrophile in the Lewis acid catalyzed alkylation. Nevertheless, the major product was identical to the Harpoon base/iodomethane reaction product and we concluded that electrophilic attack of the deprotonated lactone \( \text{42} \) involved an enolate with the same geometry as \( \text{72} \).
The 2 lowest energy conformations of this enolate are diagrammed below. Upon methylation, the lowest energy \[3434\] enolate would produce the \(2R^*,13S^*\) macrolide 67 in contrast with the \(2S^*,13S^*\) diastereomer 66 which would prevail from the alkylation of the second \[3335\] conformation.

The energy difference between the two conformations was 0.84 kcal/mole and this corresponds to the 90% dominance of compound 67 (at \(-78^\circ C\)) which is in good agreement with the observed 93% selectivity. The use of MM2 calculations in predicting the product distribution of reactions involving alkylations of intermediate enolates appears very useful in these cases.
5.9 The Preparation and Reduction of 2-Methylene-13-Tetradecanolide

The final area to be explored involved the effects of a 14-membered lactone on the reactivity of an exocyclic double bond. The exocyclic double bond was generated using standard selenium chemistry. The lactone 42 was treated with lithium diisopropyl amide and iodomethane. This product was further deprotonated with lithium diisopropyl amide and quenched with phenylselenenyl chloride. Oxidation to the selenoxide with hydrogen peroxide followed by elimination gave the \(\alpha,\beta\)-unsaturated large ring lactone 74. The importance of conformational effects were immediately apparent. If the sequence, methylation, selenation and oxidation was performed, then the desired conjugated olefin 74 was obtained in good yield. However, an initial selenation followed by methylation did not lead to the olefin upon oxidation. Each sequence produced a diastereomeric intermediate but only one diastereomer eliminated to produce the \(\alpha,\beta\)-unsaturated lactone.

![Figure 50. Conformational control in the selenoxide elimination to macrolide 74.](image)

We interpreted these results using the enolate stabilities calculated for the methylation series to establish the tentative stereochemistry of each diastereomeric
intermediate. This stereochemistry combined with a conformational analysis allows for a rationalization which can account for the lack of elimination in one of the diastereomers. An electrophilic addition to the lowest energy conformation of the enolate should produce 75. Base removal of the remaining C2 proton followed by a second addition would generate the geminally substituted conformation 76 where both substituents should occupy the corner position. The two diastereomers 76a and 76b are compared below.

The diastereomer 76a exists with the bulky phenyl selenyl group in the plane of the adjacent carbonyl group in contrast to conformation 76b which experiences no severe interactions. Upon oxidation, the phenyl selenoxide group of this second diastereomer 76b can freely rotate to a favorable position for abstraction of a C2 methyl proton. This leads to the elimination of selenic acid and produces the exocyclic α,β-unsaturated lactone 74. This elimination sequence is unlikely for the diastereomer 76a. In 76a, the rotation of the phenyl selenoxide produces a transition state in which severe steric and electronic interactions are generated. Thus the syn arrangement of the selenoxide and a methyl proton is conformationally blocked. This could account for the lack of elimination in the diastereomer 76a and provides another example of the influence of the macrolide ring on chemical reactivity.
Compound 74 underwent reduction in the presence of Raney nickel to yield a 4:1 mixture of 2-methylated lactones with the 2S*,13S* isomer predominating.

The MM2 calculations of the starting unsaturated lactone 74 revealed the lowest energy conformation as a [3434] conformation followed by two equally favoured [3344] and [3417] conformations.
Ordinarily, the ring shields one face of the olefin and selective reduction occurs from the ring periphery. This situation exists in the [3434] and [3344] conformations with only the si-si face of the exocyclic double bond open to reduction to give the observed 2S*,13S* major product. Clearly, the 2S*,13S* selectivity can be explained from an analysis of the unsaturated lactone's conformations. However, the origin of the minor 2R*,13S* diastereomer can be rationalized in two ways. Reduction of macrolide 74 may occur from the inner re-re face which is mainly shielded by the bulk of the ring. This argument has been traditionally used in the reactions of unsaturated cyclohexane systems to account for the existence of the minor reduction product. In this example, a different reasoning could involve the reduction occurring from the third lowest energy conformation.

Both olefin faces of the [34'7'] conformation are sterically unhindered at the C2 position. Indeed, from molecular models, the C2 atom is reminiscent of a corner atom. A comparison between the four torsional angles on either side of a corner atom and the C2 atom in the [34'7'] conformation above illustrates their similarity. The torsional angles about C2 in the [34'7'] conformation are (-)anti-(+)gauche-(+)gauche-(+)gauche. This compares favorably with a (-)anti-(+)gauche-(+)gauche-(+)anti sequence about a corner atom. Only the final torsional angle of (+)gauche in the [34'7'] conformation distinguishes C2 atom from a corner atom. Therefore, the re-re and si-si olefin faces at the C2 atom in the [34'7'] conformation would be more equally accessible and both diastereomers could be produced from this conformation.
6.0 Conclusion

We have shown that the reactions of 14-membered lactones often produce one major diastereomeric product. This diastereoselectivity may be explained by a dominant low energy conformation through which the reaction proceeds and frequently this conformation is the [3434] conformation which is derived from the diamond lattice. We have developed a simple model to determine low energy conformations which is based upon a number of well established acyclic energy trends and the large ring itself. As demonstrated for esters, the lactone functionality of the macrolides was fixed in an $s$-trans geometry and its C-O-C-H torsional angle was restricted to a 0-40° range. Furthermore, substituents upon the macrolide were placed outside the ring and geminally substituted atoms occupied the favoured corner position. These four restrictions have been verified by subsequent X-ray crystallographic analyses. In addition, despite the many possible conformations which seem to exist for a macrolide, our experimental results and MM2 calculations indicated that only the [3434], [3344] and [3335] conformations need to be considered for the conformational analysis of 14-membered lactones.

We have offered a rule which standardizes the construction of polar maps and thereby allows facile comparisons between conformations. This modification also allows all symmetry elements of a conformation to be determined from the polar map. The comparison of polar maps led directly to the recognition of a previously undiscovered low energy conformation for 14-membered rings. Two examples of this new conformation were found in this project and three examples from the literature. This new conformation, in turn, prompted an extension of the Dale nomenclature for the conformations of macrolides which employs the use of pseudo corner atoms. This modified nomenclature could differentiate conformations which were identical under Dale's naming system. This new nomenclature may be useful in other ring systems. Furthermore, a simple $^1$H NMR technique for assigning the geometry of trimethylsilyl (TMS) enol ethers was developed using the nuclear Overhauser
effect. This technique assigned the $E$ or $Z$ geometries of TMS enol ethers of single isomers. In contrast, current $^{13}$C NMR techniques require both isomers to assign these geometries.

In general, the diastereoselectivities exhibited in the products were predictable from an analysis of starting materials or intermediates. For example, a geminally substituted macrolide was observed to exist in two low energy conformations in which the quaternary carbon atom was in the corner position for both conformations. This represented one of the first examples of corner occupation in a geminally substituted ring as predicted by Dale. Even so, the behavior of the 14-membered lactones was sometimes difficult to explain using energy calculations. Reactions involving the 3-keto lactones were shown to be consistently controlled by conformations in which both carbonyl oxygens could chelate a metal ion. In one example, this chelation control outweighed the effects of having a geminal methyl group in the corner position. The hydrogenation of conjugated olefins in the macrolide ring represents another area into which further investigation is required because of the lack of understanding observed in the product distributions.

Often, the simple macrolides used in this project possessed a great deal of conformational freedom and this complicated the analysis. A possible solution to this problem would be the selective introduction of unsaturation to the acyclic precursor of the macrolide. Three advantages would result from this measure. First, the cyclization step to the macrolide should increase in yield. Second, the unsaturated macrolide, once formed, would be more rigid and have fewer available conformations. Third, the resonances of the NMR spectra of these macrolides would be better dispersed and could then be used to study the preferred conformation.

Obviously, there is opportunity for further research regarding the conformational analysis of 14-membered lactones. Ultimately, the conformational behavior of 14-membered lactones should culminate in the total syntheses of the macrolide antibiotics.
**EXPERIMENTAL**

**General**

**Reagents and equipment setup.** Dry solvents were prepared as follows: diethyl ether (ether), benzene, toluene and tetrahydrofuran (THF) were distilled into a collecting reservoir by heating at reflux over sodium benzophenone ketyl radical under a dry nitrogen (N₂) atmosphere. Using an oven dried syringe, these solvents were removed through a stopcock fitted on the reservoir. Methylene chloride and diisopropylamine were distilled from and stored over calcium hydride (CaH₂). Dimethylsulfoxide (DMSO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, t-butanol and hexamethylphosphoramide (HMPA) were distilled under reduced pressure from CaH₂ and stored over molecular sieves (3Å). Methanol was distilled from Mg(OMe)₂/l₂. Petroleum ether was of boiling range ~30-60 °C.

Unless otherwise specified all reactions were run at room temperature (~20-24 °C). Cold reaction temperatures were maintained using either an ice/water bath (0 °C) or an acetone or ethanol dry ice bath (-78 °C).

All reagents were supplied by the Aldrich Chemical Company and unless otherwise stated were used without further purification. Bottles of n-butyllithium (in hexanes) were equipped with used glc gas port septa wedged between the sure seal™ crown and twist cap. In this way, the n—butyllithium was stored in the open at room temperature with no significant changes in molarity for up to 9 months at a time. n—Butyllithium was standardized by titration against 2,2-diphenylacetic acid in THF at room temperature to the faintest appearence of a yellow colour. Sodium hydride (NaH) was weighed as a 60% dispersion in mineral oil and washed twice with THF to remove the oil prior to use.

Nitrogen was supplied by Union Carbide and prior to use was passed through two columns of indicating Drierite (CaSO₄ impregnated with CoCl₂).

Syringes and needles were oven dried at 120 °C for a minimum of 3-4 hours before use. For reactions requiring anhydrous conditions, the glassware (including the teflon coated magnetic stirring bar) was assembled hot from the oven. A nitrogen inlet was attached and the whole apparatus was flame-dried. Dry septa and teflon stop-cocks, if needed, were then
loosely fitted and the whole allowed to cool under nitrogen. For reactions involving less than 1 millimole of reagents, the starting material was weighed from a dry 2.5 mL (0.5 dram) vial equipped with a septum and later syringed into the reaction mixture.

The concentration or evaporation of solvents under reduced pressure refer to the use of a Büchi rotary evaporator.

**Products.** Reactions were monitored by thin layer chromatography (tlc) or gas liquid chromatography (glc). Analytical tlc was performed on commercial aluminum backed, pre-coated silica (SiO$_2$) gel plates (E. Merck, type 5554). The plates were visualized using short wave ultraviolet light or by spraying with a 3 M solution of sulfuric acid and heating with a heat gun. Analytical glc analyses were obtained on a Hewlett-Packard model 5880 gas chromatograph using either a 12 meter x 0.2 mm capillary Carbowax column or a 15 meter x 0.2 mm capillary DB-210 column. In all cases flame ionization detection was used with a helium carrier gas. All samples were made up in ether and injection volumes were 1-2 µL.

**Product Purification.** Reaction products were purified by flash chromatography using 230-400 mesh ASTM silica gel supplied by E. Merck Co. Solid samples were adsorbed onto the silica gel before chromatography. After column chromatography, the silica gel was routinely reclaimed so as to offset the high cost of replacement. This involved discarding the upper 2-4 cm of a column containing the most polar by-products and flushing the remaining silica gel with methanol (normally 500 mL) until clean. A hose connected to a water aspirator was attached to the column spigot and the silica gel sucked to dryness (powder dry). The silica gel was subsequently regenerated by oven heating for 8 hours at 120 °C. This purification procedure could be repeated 5-6 cycles before the silica gel turned a yellow colour whereupon it was discarded. This procedure greatly extended the normal usage of silica gel.

**Product Characterization.** Melting points were determined on a Koffler hot stage apparatus and are uncorrected.

Infrared (IR) spectra were recorded on a Perkin-Elmer model 710B or a Bomem Michelson 100 FT spectrophotometer as chloroform solutions between sodium chloride plates.
(0.2 mm thickness). Absorption positions are given in cm$^{-1}$ and are calibrated against the 1602 cm$^{-1}$ band of polystyrene. The abbreviations used in quoting the IR bands are: st = strong, m = medium, w = weak and br = broad.

Low resolution mass spectra were determined on a Varian MAT model CH4B or a Kratos-AEI model MS 50 spectrometer and are reported only for new compounds. The parent peak as well as major ions (10% of the base peak) are reported unless lower intensity peaks were structurally diagnostic. Exact masses were obtained by high resolution mass spectroscopy using a Kratos-AEI model MS 50 spectrometer. All instruments were operated at 70 eV.

Nuclear magnetic resonance (NMR) spectra were taken in deuterochloroform (CDCl$_3$), deuterobenzene (C$_6$D$_6$) or deuteromethanol (CD$_3$OD) solutions with signal positions given in parts per million (ppm) from the internal standards of tetramethylsilane (0.00 ppm) or chloroform [7.24 ppm (1H NMR) or 77.0 ppm (13C NMR)] on the $\delta$ scale. Proton nuclear magnetic resonance (1H NMR) spectra were recorded at 400 MHz on a Bruker WH-400 model spectrometer. Carbon (13C) NMR spectra were recorded on a Varian XL 300 MHz spectrometer using the Attached Proton Test (APT) program at 75.4 MHz or on the Bruker WH-400 spectrometer at 100.6 MHz. Integration ratios, signal multiplicities and where possible assignments and coupling constants (in hertz) are all indicated in parentheses. The abbreviations used in quoting the data are: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and J = coupling constant.

X-ray crystallographic analyses were carried out by Dr. Steve Rettig at the University of British Columbia.
A lithium diisopropylamide (LDA) solution was generated at 0 °C by stirring diisopropylamine (1.12 mL, 8.01 mmol) and t-BuLi (4.22 mL, 8.01 mmol) in 100 mL of THF under N₂ for 1 hour. This solution was cooled with a dry ice/acetone bath and the bromo-β-keto ester was added dropwise from an addition funnel. The reaction mixture was immediately placed in a hot water bath (55-60 °C) and warmed for 20 minutes. The solution was poured into aqueous NH₄Cl and extracted with ether (3 x 100 mL). The organic extracts were combined and evaporated under reduced pressure to afford a dark brown oil which was purified by passage through SiO₂ using a 1:7 ethyl acetate (EtOAc) : petroleum ether solvent mixture to give the macrolide 43 as a yellow oil (377.6 mg, 49%).

Compound (43). ¹³C NMR (100.6 MHz, CDCl₃) ppm: 202.1 (C₃, s), 166.7 (C₁, s), 71.9 (C₁₃, d), 50.8 (C₂, t), 40.6 (C₄, t), 35.2 (C₁₂, t), 20.3 (C₁₄, q), 26.3, 26.1, 26.0, 25.2, 24.7, 22.9, 21.0 (CH₂'s, t's). Other spectral data have been reported previously.³³

(2S*,13S*) and (2R*,13S*) 2-Methyl-3-oxo-13-tetradecanolides (44)
Freshly sublimed potassium \textit{t}-butoxide (178.0 mg, 1.59 mmol) was weighed into a dry flask equipped with a N\textsubscript{2} inlet and septum. Freshly distilled \textit{t}-butanol (3.0 mL) was injected and the macrolide 43 (315.0 mg, 1.31 mmol) (dissolved in 2.0 mL of \textit{t}-butanol) was added dropwise. After 30 minutes of refluxing, the reaction mixture was cooled to room temperature and Mel (0.09 mL, 1.44 mmol) was injected and further refluxed for 10 minutes. The reaction mixture was poured into aqueous NH\textsubscript{4}Cl and the aqueous layer extracted with ether (4 x 100 mL). The organic layers were reduced under vacuum. The crude oil was chromatographed using 1:19 EtOAc:petroleum ether to yield pure 44 (289.4 mg, 87\%) as a yellow oil. The \textit{gem}-dimethylated product 54 was isolated as a byproduct (11.4 mg, 3.2\%). Compound 44 was found to exist as a 2:1 mixture of diastereomers by NMR and glc.

Compound (\textit{Major 44}): IR (CHCl\textsubscript{3}) for major and minor: 1739, 1725, 1709, 1692 (C=O's, st) cm\textsuperscript{-1}; \textit{H NMR} (400 MHz, CDCl\textsubscript{3}) ppm: 5.00 (1H, m, C\textsubscript{13}-H, J = 7.2, 6.1, 4.5 Hz), 3.55 (1H, q, C\textsubscript{2}-H, J = 7.1 Hz), 2.68 (1H, ddd, C\textsubscript{4}-H, J = 18.0, 7.8, 7.0 Hz), 2.50 (1H, ddd, C\textsubscript{4}-H, J = 18.0, 8.0, 6.8 Hz), 1.89-1.12 (16H, m, CH\textsubscript{2}'s), 1.31 (3H, d, C\textsubscript{15}-H, J = 7.1 Hz), 1.24 (3H, d, C\textsubscript{14}-H, J = 6.4 Hz); \textit{13C NMR} (100.6 MHz, CDCl\textsubscript{3}) ppm: 205.5 (C\textsubscript{3}, s), 170.3 (C\textsubscript{1}, s), 71.9 (C\textsubscript{13}, d), 53.4 (C\textsubscript{2}, d), 39.0 (C\textsubscript{4}, t), 35.4 (C\textsubscript{12}, t), 20.4 (C\textsubscript{14}, q), 13.1 (C\textsubscript{15}, q), 26.1 24.8, 24.4, 24.2, 22.9, 22.8, 20.7 (CH\textsubscript{2}'s, t's); Mass spectrum of 4, m/e: 254 (M\textsuperscript{+}); Exact mass calc. for C\textsubscript{15}H\textsubscript{26}O\textsubscript{3}: 254.1882; Found: 254.1889.

Compound (\textit{Minor 44}): \textit{H NMR} (400 MHz, CDCl\textsubscript{3}) ppm: 4.94 (1H, m, C\textsubscript{13}-H, J = 6.4 Hz), 3.52 (1H, q, C\textsubscript{2}-H, J = 7.1 Hz), 2.82 (1H, ddd, C\textsubscript{4}-H, J = 18.7, 7.9, 6.8 Hz), 2.37 (1H, ddd, C\textsubscript{4}-H, J = 18.7, 7.9, 6.0 Hz), 1.89-1.12 (16H, m, CH\textsubscript{2}'s), 1.30 (3H, d, C\textsubscript{15}-H, J = 7.1 Hz), 1.21 (3H, d, C\textsubscript{14}-H, J = 6.1 Hz); \textit{13C NMR} (100.6 MHz, CDCl\textsubscript{3}) ppm: 204.5 (C\textsubscript{3}, s), 170.4 (C\textsubscript{1}, s), 71.6 (C\textsubscript{13}, d), 54.2 (C\textsubscript{2}, d), 39.4 (C\textsubscript{4}, t), 35.1 (C\textsubscript{12}, t), 20.0 (C\textsubscript{14}, q), 12.2 (C\textsubscript{15}, q), 25.9, 25.1, 24.64, 24.57, 24.52, 24.49, 23.0 (CH\textsubscript{2}'s, t's).
Reduction of 2-methyl-3-oxo-13-tetradecanolides (44)

Using NaBH₄

The macrolides 44 (105.0 mg, 0.413 mmol) were dissolved in ethanol (2.0 mL) and sodium borohydride (4.3 mg, 0.46 mmol) was added neat and stirred 1.5 hours. The addition of 8 drops of 1 M HCl was sufficient to quench the reaction. The reaction mixture was saturated with NaCl and extracted with ether (4 x 100 mL) to isolate the desired products. The crude product mixture was very clean (100.3 mg, 95%). Approximately 3% of starting material was detected by glc. The remainder of the product distribution was as follows: 47 (65.2%), 48 (16.3%) 49 (10.8%) and 50 (4.4%).

Compound (47): IR (CHCl₃): 3580-3100 (H-bonded OH, br), 1715 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 5.02 (1H, m, C₁₃-H, J = 6.8, 6.4, 4.2 Hz), 3.61 (1H, m, C₃-H, J = 7.6, 2.7 Hz), 2.85 (1H, d, O-H, J = 9.5 Hz), 2.67 (1H, dq, C₂-H, J = 7.1, 2.7 Hz), 1.63-1.16 (18H, m, CH₂'s), 1.27 (3H, d, C₁₅-H, J = 7.1 Hz), 1.20 (3H, d, C₁₄-H, J = 6.4 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 176.0 (C₁, s), 73.7 (C₁₃, d), 70.2 (C₃, d), 42.8 (C₂, d), 34.5 (C₁₂, t), 33.8 (C₄, t), 20.0 (C₁₄, q), 13.8 (C₁₅, q), 26.8, 25.9, 25.2, 24.2, 24.0, 22.8, 21.8 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 256 (M⁺, 1), 164 (14), 154 (29), 111 (12), 109 (24), 103 (87), 98 (21), 97 (25), 96 (13), 95 (37), 85 (40), 84 (15), 83 (37), 82 (20), 81 (34), 74 (77), 71 (15), 70 (21), 69 (48), 68 (20), 67 (41), 58 (12), 57 (65), 56 (47), 55 (100), 54 (12), 53 (16); Exact mass calc. for C₁₅H₂₉O₃: 256.2039 Found: 256.2041.
Compound (48): IR (CHCl₃): 3650 (free OH, w), 3550-3200 (H-bonded OH, br), 1725 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 4.92 (1H, m, C₁₃-H, J = 9.3, 6.4, 2.7 Hz), 3.58 (1H, m, C₃-H), 2.42 (1H, m, C₂-H, J = 9.0, 7.1 Hz), 1.67-1.10 (18H, m, CH₂'s), 1.23 (3H, d, C₁₅-H, J = 7.1 Hz), 1.18 (3H, d, C₁₄-H, J = 6.4 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 174.3 (Ci, s), 73.5 (C₁₃, d), 70.2 (C₃, d), 49.1 (C₂, d), 35.4 (C₁₂, t), 34.5 (C₄, t), 20.3 (C₁₄, q), 14.4 (C₁₅, q), 32.9, 26.4, 25.8, 25.5, 23.8, 23.4, 22.5 (CH₂'s, t's).

Compound (49): IR (CHCl₃): 3621 (free OH), 3590-3250 (H-bonded OH, br), 1724 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 5.02 (1H, m, C₁₃-H, J = 7.2, 6.3, 3.7 Hz), 3.66 (1H, m, C₃-H, J = 4.2, 3.1 Hz), 2.65 (1H, dq, C₂-H, J = 7.2, 3.1 Hz), 2.09-1.95 (1H, bs, O-H), 1.73-1.18 (18H, m, CH₂'s), 1.23 (3H, d, C₁₅-H, J = 7.2 Hz), 1.22 (3H, d, C₁₄-H, J = 6.3 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 173.9 (C₁, s), 73.0 (C₁₃, d), 71.1 (C₃, d), 46.9 (C₂, d), 35.6 (C₁₂, t), 32.3 (C₄, t), 20.4 (C₁₄, q), 12.5 (C₁₅, q), 26.5, 25.9, 25.5, 23.4, 22.8, 22.6, 22.4 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 256 (M⁺, 1), 165 (14), 164 (22), 109 (29), 103 (35), 98 (31), 97 (19), 96 (13), 95 (42), 85 (26), 83 (32), 82 (19), 81 (35), 74 (86), 71 (13), 70 (13); Exact mass calc. for C₁₅H₂₈O₃: 256.2039; Found: 256.2044; Mp: 68-69 °C.

Compound (50): ¹³C NMR (100.6 MHz, CDCl₃) ppm: 175.1 (C₁, s), 73.2 (C₁₃, d), 70.3 (C₃, d), 45.9 (C₂, d), 35.1 (C₁₂, t), 32.7 (C₄, t), 20.3 (C₁₄, q), 14.2 (C₁₅, q), 26.3, 26.0, 25.6, 24.1, 23.6, 22.5, 21.4 (CH₂'s, t's).

Using L-Selectride at -78 °C

L-Selectride in THF (3.58 mmol, 3.58 mL) was injected under N₂ to 2.0 mL of dry THF at -78 °C. The macrolides 44 (90.8 mg, 0.358 mmol) were injected in two 0.5 mL portions in THF and stirred for 11.5 hours at -78 °C. H₂O₂ (25 drops) and NaOH (15 mL, 1 M) were added. After 10 minutes, 1 M HCl was added dropwise until acidic to pH paper. The slightly acidic aqueous solution was saturated with NaCl and extracted three times with 100 mL of ether. Evaporation of the combined organic layers followed by passage through SiO₂ with a
1:7 EtOAc:petroleum ether solvent mixture yielded the 3 alcohols, 47, 48 and 49 (73.5 mg, 96% conversion, 84%). By glc, $^1$H and $^{13}$C, no trace of the 4th diastereomer 50 could be detected.

**Using L-Selectride at 0 °C**

L-Selectride (0.33 mL, 0.33 mmol) was injected into 1 mL of THF at 0 °C under N$_2$. Macrolides 44 (49.9 mg, 0.197 mmol) were injected in two 0.5 mL portions in THF and stirred for 2 hours. The ice-bath was removed and allowed to stir a further 9 hours. The addition of H$_2$O$_2$ (2 drops, 1.29 mmol) and NaOH (12 drops, 0.6 mmol) followed by NaCl and extractions with ether (3 x 80 mL) gave a yellow oil (58.5 mg). The crude oil consisted of 47 and 48 (97%) with only 3% of 49 and 50. The purified yield of the four alcohols was 41.1 mg (82%).

**Using n-Bu$_4$NBH$_4$**

The macrolides 44 (27.6 mg, 0.109 mmol) were dissolved in 1.5 mL EtOH and the n-Bu$_4$NBH$_4$ (50.3 mg, 0.196 mmol) was added in one portion. After stirring for 1 hour, 1 M HCl was added dropwise until H$_2$ evolution had ceased. The reaction mixture was saturated with NaCl and extracted with ether (3 x 50 mL). Chromatography with ether gave 29.3 mg of purified products in the ratios; 47 = 52.2%, 48 = 9.2%, 49 = 21.4%, 50 = 17.2%.

**Using n-Bu$_4$NBH$_4$ in the presence of LiBr**

The reduction procedure above was repeated using the same stoichiometries but included the addition of LiBr (80 mg, 10 eq). A yield of 25.4 mg of products was obtained from 23.4 mg of macrolides 44. The glc analysis indicated; 47 = 56.5%, 48 = 14.6%, 49 = 14.4%, 50 = 14.5%.
2-Methyl-3-hydroxy-13-tetradecanolides (47) and (48) via a methylation of (2S\(^*,13S^*\)-3-hydroxy-13-tetradecanolide) (45)

Equimolar amounts of diisopropylamine (0.19 mL, 1.4 mmol) and n-BuLi (0.90 mL, 1.4 mmol) were stirred in 1.5 mL of THF at 0 °C for 0.5 hour. The macrolide 45\(^{33}\) (160.1 mg, 0.63 mmol) was dissolved in THF and added dropwise to the LDA solution. After 2 hours of stirring at 0 °C, HMPA (0.44 mL, 2.5 mmol) and Mel (0.043 mL, 0.69 mmol) were injected with further stirring for 15 minutes. The ice bath was removed and stirring of the reaction was continued for 20 minutes. The mixture was poured into aqueous NH\(_4\)Cl and extracted with ether (4 x 100 mL). Concentration of the crude product under vacuum gave a yellow oil consisting of unreacted starting material (41.3\%), 47 (50.8\%), 48 (6.3\%), 49 and 50 (1.7\%). The ratio of 47 to its epimer 48 was 89:11.
2-Methyl-3-hydroxy-13-tetradecanolides (49) and (50) via a methylation of (2R*,13S*)-3-hydroxy-13-tetradecanolide (46)

LDA (2.6 mmol) was generated at 0 °C for 1 hour in 3.0 mL of THF from diisopropylamine (0.36 mL, 2.6 mmol) and n-BuLi (1.66 mL, 2.57 mmol). The macrolide 46 (163.0 mg, 0.64 mmol) was added dropwise in 1.5 mL of THF and stirred four hours at 0 °C. HMPA (0.45 mL, 2.6 mmol) and Mel (0.16 mL, 2.6 mmol) were added in quick succession with continued stirring for 30 minutes. Workup with aqueous NH₄Cl and ether extractions (2 x 80 mL) followed by CuSO₄ washings (2 x 80 mL) gave a yellow oil after concentration under vacuum. The oil was purified using column chromatography (1:7 EtOAc:petroleum ether solvent mixture) to give 16.3 mg of an unidentified non polar fraction, and 140.1 mg of diastereomeric α-methylated alcohols of which 3.4% was 47, 1.1% was 48, 64.8% was 49 and 21.8% was 50. In addition, 8.9% of starting material was recovered. The ratio of the desired epimers 49 and 50 was 3:1.
2.2-Dimethyl-3-oxo-13-tetradecanolide (54)

The macrolide 43 (87.7 mg, 0.365 mmol) was dissolved in 2.0 mL of dry 1-butanol and added dropwise to a homogeneous solution of potassium 1-butoxide (164.0 mg, 1.46 mmol) in 1-butanol (2.0 mL). The reaction was warmed with an 85-90 °C water bath for 10 minutes and stirred without the bath for an additional 50 minutes. Mel (0.23 mL, 3.65 mmol) was injected and further stirred at room temperature for 14.5 hours. The reaction was quenched with 1.5 mL of 1M HCl, saturated with NaCl and extracted with ether (4 x 60 mL). Purification through SiO2 and a 1:7 EtOAc:petroleum ether solvent mixture gave 54 as a yellow oil (95.8 mg, 98%).

Compound (54): IR (CHCl₃): 1724, 1708 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 4.94 (1H, m, C₁₃-H, J = 9.0, 6.1, 2.7 Hz), 2.51 (1H, ddd, C₄-H, J = 18.5, 9.6, 5.7 Hz), 2.41 (1H, ddd, C₄-H, J = 18.5, 9.4, 6.1 Hz), 2.74-1.12 (18H, m, CH₂'s), 1.33 (3H, s, C₁₅-H), 1.30 (3H, s, C₁₆-H), 1.17 (3H, d, C₁₄-H, J = 6.1 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 207.4 (C₃, s), 182.9 (C₁, s), 71.5 (C₁₃, d), 55.8 (C₂, s), 35.9 (C₄, t), 35.4 (C₁₂, t), 22.7, 21.7 (q's), 20.1 (C₁₄, q), 26.1, 25.8†, 24.1, 23.9, 22.6, 20.2 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 268 (M⁺, 1), 97(11), 88 (26), 83 (11), 81 (11), 70 (100), 69 (22), 67 (10), 55 (38); Exact mass calc. for C₁₆H₂₈O₃: 268.2039; Found: 268.2047.
Reduction of 2,2-dimethyl-3-oxo-13-tetradecanolide (54)

Using L-Selectride

To a 25 mL flask under N₂ at -78 °C was injected 2.0 mL THF and L-Selectride (2.02 mL, 2.02 mmol). To this mixture, the macrolide 54 (180.0 mg, 0.672 mmol) was injected (2 x 1.0 mL portions in THF) and was stirred 3 hours at -78 °C. The cooling bath was removed and stirred a further 2.5 hours whereupon H₂O₂ (14 drops, 6.1 mmol) and NaOH (6 mL, 6.1 mmol) was added while rapidly stirring the reaction mixture. The mixture was acidified with 1 M HCl, saturated with NaCl and extracted with ether (3 x 100 mL). Gas-liquid chromatography indicated a 231:1 ratio of 55 to its epimeric alcohol isomer 56. Column chromatography through SiO₂ using a 1:7 EtoAc:petroleum ether solvent gave 55 as white crystals (173.1 mg, 95%, MP = 65-66 °C).

Compound (55): IR (CHCl₃): 3629 (free OH, w), 3566-3347 (H-bonded OH, br), 1722 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 4.93 (1H, m, C₁₃-H, J = 9.3, 6.4, 2.5 Hz), 3.69 (1H, m, C₃-H, J = 10.2, 1.8 Hz), 1.68-1.13 (18H, m, CH₂’s), 1.22 (3H, s, C₁₅-H), 1.17 (3H, d, C₁₄-H, J = 6.4 Hz), 1.10 (3H, s, C₁₆-H); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 176.7 (C₁, s), 76.6 (C₁₃, d), 70.2 (C₃, d), 47.9 (C₂, s), 35.6 (C₁₂, t), 24.2, 17.9 (q’s), 20.3 (C₁₄, q), 30.9, 26.5, 26.3, 25.8, 24.3, 23.7, 23.6, 22.7 (CH₂’s, t’s); Mass spectrum, m/e (relative intensity): 270 (M⁺, 0.3) 117 (10), 88 (100), 70 (27), 69 (11),
108

67 (10), 57 (12), 55 (25); **Exact mass** calc. for C\(_{16}H_{30}O_3\): 270.2195; Found: 270.2203.

**Compound (56): IR** (CHCl\(_3\)): 3630 (free OH, w), 3600-3450 (H-bonded OH, br), 1725 (C=O, st) cm\(^{-1}\); **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) ppm: 5.03 (1H, m, C\(_{13}\)-H, J = 8.8, 6.3, 2.9 Hz), 3.38 (1H, dd, C\(_3\)-H, J = 10.6, 2.0 Hz), 2.10 (1H, bs, O-H), 1.85-1.11 (18H, m, CH\(_2\)'s), 1.22 (3H, s, C\(_{15}\)-H), 1.21 (3H, d, C\(_{14}\)-H, J = 6.3 Hz), 1.16 (3H, s, C\(_{16}\)-H); **\(^{13}\)C NMR** (100.6 MHz, CDCl\(_3\)) ppm: 176.4 (C1, s), 77.2 (C\(_{13}\), d), 70.6 (C\(_3\), d), 47.8 (C\(_2\), s), 35.6 (C\(_{12}\), t), 23.6, 21.0 (q's), 20.4 (C\(_{14}\), q), 30.6, 26.7, 25.7, 25.2, 23.0, 22.6, 22.5, 22.4, (CH\(_2\)'s, t's); **Mass spectrum**, m/e (relative intensity): 270 (M\(^+\), 1), 88 (100), 70 (30), 55 (19); **Exact mass** calc. for C\(_{16}H_{30}O_3\): 270.2195; Found: 270.2199; Mp: 64-66 °C.

**Using n-Bu\(_4\)NBH\(_4\)**

The macrolide 54 (26.3 mg, 0.098 mmol) was dissolved in 1.0 mL of EtOH at room temperature. The reducing agent (45.5 mg, 0.177 mmol) was added neat and stirred 1 hour. Further additions of n-Bu\(_4\)NBH\(_4\) (105.6 mg, 0.410 mmol) were necessary to complete the reaction in 12 hours. The glc analysis showed a 1.6 to 1.0 ratio of 55 and 56, respectively after a 1M HCl workup and ether extraction.

**Using n-Bu\(_4\)NBH\(_4\) in the presence of LiBr**

The macrolide 54 (41.5 mg, 0.155 mmol) was dissolved in 2 mL of EtOH at room temperature and LiBr (134.5 mg, 1.55 mmol) added. n-Bu\(_4\)NBH\(_4\) (71.7 mg, 0.279 mmol) was added in one portion and stirred 8 hours. Workup as above led to the isolation of 55 (11.4 mg, 27%) and 56 (15.6 mg, 37%) in the ratio of 67:33 respectively.
(3S*,13S*)-2,2-Dimethyl-3-hydroxy-13-tetradecanolide (55) via a methylation of (2S*,3S*,13S*)-2-methyl-3-hydroxy-13-tetradecanolide (47)

\[
\begin{align*}
\text{HO} \hspace{1cm} \text{O} \\
\text{\[47 (2S^*,3S^*,13S^*)\]}
\end{align*}
\]

LDA was generated from diisopropylamine (0.087 mL, 0.62 mmol) and n-BuLi (0.41 mL, 0.61 mmol) and stirred at 0 °C for 1 hour. The macrolide 47 (62.6 mg, 0.245 mmol) was injected in 2 x 0.5 mL portions in THF and the whole stirred 4 hours at 0 °C. HMPA (0.17 mL, 0.98 mmol) and Mel (0.076 mL, 1.2 mmol) were injected and further stirred for 15 minutes at 0 °C. The ice bath was removed and the reaction stirred 10 hours. The reaction mixture was pipetted into an aqueous NH₄Cl solution and extracted with ether (4 x 20 mL). The combined ethereal layers were further extracted with a saturated solution of CuSO₄, dried over MgSO₄ and evaporated. The crude macrolide 55 was passed through SiO₂ with CH₂Cl₂ to give 44.5 mg (67%) of pure product.

Studies on the dianion formation of 3-oxo-13-tetradecanolide (43)
The macrolide 43 (97.1 mg, 0.405 mmol) was injected to a suspension of NaH (11.7 mg, 0.49 mmol) in 0.5 mL THF and stirred for 1 hour at 0 °C. n-BuLi (0.28 mL, 0.45 mmol) was added and stirred for 18 minutes at this temperature followed by the injection of CF₃CO₂D in D₂O. The reaction mixture was saturated with NaCl and extracted with ether (3 x 50 mL). The combined organic layers were reduced under vacuum to yield 100.1 mg of highly pure product. The MS data showed the presence of equal amounts (relative peak intensities = 100) of mono and di-deuterated products with trace amounts of starting material (peak intensity = 5.8).

\[(4S^*,13S^*)-3\text{-Oxo-4-methyl-13-tetradecanolide}\] (57)

Diisopropylamine (0.39 mL, 2.8 mmol) and n-BuLi (1.6 mL, 2.8 mmol) were injected into 5.0 mL of THF under N₂ at 0 °C. After 30 minutes, the macrolide 43 (305.3 mg, 1.27 mmol), dissolved in 5.0 mL of THF, was added and stirred at 0 °C for 30 minutes. Mel (0.08 mL, 1.3 mmol) was injected and stirred a further 15 minutes. The anion was quenched by pouring the reaction into 250 mL of cold (0 °C) 1 M HCl. The solution was saturated with NaCl and extracted with ether (3 x 100 mL). The combined ethereal layers were concentrated under reduced pressure to give a red oil. Chromatography with CH₂Cl₂ yielded the methylated macrolide 57 as a light yellow oil. (259.3 mg, 81%). A frequent by-product 83 was identified as the 3-oxo-2,4,4-trimethyl-13-tetradecanolide in yields ranging from 5-15%.
Compound (57): IR (CHCl₃): 1725, 1709 cm⁻¹ (C=O, st); ¹H NMR (400 MHz, CDCl₃) ppm: 4.98 (1H, m, C₁₃-H, J = 8.1, 6.3, 2.9 Hz), 3.66 (1H, d, C₂-H, J = 13.9 Hz), 3.31 (1H, d, C₂-H, J = 13.9 Hz), 2.75 (1H, m, C₄-H, J = 7.4, 7.1, 5.2 Hz), 1.80 (1H, m, C₅-H) 1.65-1.17 (15H, m), 1.25 (3H, d, C₁₄-H, J = 6.3 Hz), 1.10 (3H, d, C₁₅-H, J = 7.1 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 205.8 (C₃, s), 166.4 (C₁, s), 72.6 (C₁₃, d), 48.7 (C₂, t), 45.8 (C₄, d), 34.7 (C₁₂, t), 20.2 (C₁₄, q), 16.4 (C₁₅, q), 31.1, 26.7, 26.1, 24.8, 23.3 (CH₂'s, t's), 25.9 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 254 (M⁺, 10), 117 (12), 116 (100), 98 (16), 97 (12), 83 (15), 69 (27), 56 (14), 55 (42), 43 (20), 42 (16), 41 (36), 29 (14); Exact mass calc. for C₁₅H₂₆O₃: 254.1882; Found: 254.1890.

Compound (83): IR (CHCl₃): 1726, 1708 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 4.99 (1H, m, C₁₃-H, J = 6.6, 6.4, 2.7 Hz), 3.95 (1H, q, C₂-H, J = 7.1 Hz), 1.66-1.14 (16H, m, CH₂'s), 1.34 (3H, d, C₁₅-H, J = 7.1 Hz), 1.25, 1.08 (3H, s's, C₄-CH₃'s), 1.20 (3H, d, C₁₃-H, J = 6.4 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 211.3 (C₃, s), 170.4 (C₁, s), 71.7 (C₁₃, d), 48.5 (C₄, s), 46.8 (C₂, d), 39.8 (C₅, t), 34.4 (C₁₂, t), 25.3 (q), 24.3 (q), 19.7 (C₁₅, q), 15.8 (q), 27.7, 26.8, 26.4, 25.0, 23.3, 22.6, (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 282 (M⁺, 9), 180 (35), 144 (19), 126 (11), 125 (31), 124 (27), 111 (45), 97 (55), 95 (11), 85 (16), 83 (57), 82 (19), 81 (12), 74 (56), 71 (14), 70 (11), 69 (100), 67 (14), 57 (38), 56 (30), 55 (63); Exact mass calc. for C₁₇H₃₀O₃: 282.2195; Found: 282.2194.

Reduction of (4S⁺,13S⁺)-3-oxo-4-methyl-13-tetradecanolide (57)
The macrolide 57 (305.5 mg, 1.20 mmol) was dissolved in 2.0 mL of ethanol followed by the addition of NaBH₄ (22.8 mg, 2.41 mmol) in one portion. After stirring for 1 hour, the reaction was quenched with 1 M HCl, saturated with NaCl and extracted with methylene chloride (5 x 100 mL). Evaporation of solvents followed by chromatography through SiO₂ with a 1:7 EtOAc:petroleum ether mixture gave pure product as a mixture of diastereomers 58 and 59 in a 3:1 ratio (264.2 mg, 86%).

Compound (58): IR (CHCl₃): 3621 (free OH, w), 3572-3300 (H-bonded OH, br), 1724 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 5.05 (1H, m, C₁₃-H, J = 9.0, 6.3, 2.9 Hz), 3.82 (1H, m, C₃-H, J = 6.1, 5.9, 3.7 Hz), 2.95-2.40 (1H, bs, O-H), 2.66 (1H, dd, C₂-H, J = 14.7, 6.1 Hz), 2.54 (1H, dd, C₂-H, J = 14.7, 3.7 Hz), 1.74-1.05 (16H, CH₂'s), 1.25 (3H, d, C₁₄-H, J = 6.3 Hz), 0.92 (3H, d, C₁₅-H, J = 6.6 Hz), 1.67 (1H, m, C₄-H, J = 9.3, 6.6, 5.9, 4.7 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 172.6 (C₁, s), 72.6 (C₁₃, d), 71.4 (C₃, d), 38.6 (C₂, t), 36.5 (C₄, d), 35.3 (C₁₂, t), 20.5 (C₁₄, q), 15.8 (C₁₅, q), 28.9, 26.1, 25.9, 25.0, 24.6, 24.1, 23.0 (CH₂'s, t's); Mass spectrum (m/e, relative intensity): 256 (M⁺, 2), 178 (10), 169 (17), 168 (98), 166 (20), 165 (12), 140 (16), 139 (16), 126 (19), 125 (26), 124 (21), 116 (15), 112 (24), 111 (43), 110 (22), 109 (17), 98 (31), 97 (76), 96 (39), 95 (29), 89 (96), 85 (24), 84 (39), 83 (69), 82 (41), 81 (36), 71 (28), 70 (54), 69 (81), 68 (23), 67 (30), 58 (15), 57 (44), 56 (58), 55 (100), 54 (12); Exact mass calc. for C₁₅H₂₈O₃: 256.2039; Found: 256.2055; Mp: 38-40 °C.

Compound (59): IR (CHCl₃): 3620 (free OH, w), 3544-3378 (H-bonded OH, br), 1723 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 5.05 (1H, m, C₁₃-H, J = 9.3, 6.4, 2.9 Hz), 3.92 (1H, m, C₃-H, J = 8.3, 4.2, 4.2 Hz), 2.63 (1H, dd, C₂-H, J = 13.7, 8.3 Hz), 2.51 (1H, dd, C₂-H, J = 13.7, 4.2 Hz), 2.00-1.80 (1H, bs, O-H), 1.74-1.15 (17H, m, CH₂'s), 1.23 (3H, d, C₁₄-H, J = 6.4 Hz), 0.94 (3H, d, C₁₅-H, J = 6.6 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 171.8 (C₁, s), 72.5 (C₁₃, d), 71.2 (C₃, d), 42.1 (C₂, t), 35.6 (C₄, t), 35.4 (C₁₂, t), 20.6 (C₁₄, q), 13.0 (C₁₅, q), 31.2, 26.3, 26.2, 24.7, 24.5, 23.6, 23.3, (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 256 (M⁺, 2), 196 (11), 168 (40), 165 (12), 140
To 1.0 mL of dry ether at 0 °C was added the macrolide 58 (68.9 mg, 0.269 mmol), N,N-dimethyl-4-aminopyridine (3.4 mg, 0.03 mmol) and pyridine (0.12 mL, 1.6 mmol) under N2. The slow addition of bromoacetyl bromide (0.094 mL, 1.08 mmol) resulted in the reaction mixture solidifying. Another 2.0 mL of ether was added and the whole allowed to sit for 8 hours (no stirring) at room temperature. The reaction was added to aqueous NH4Cl, saturated with NaCl and extracted with ether (3 x 50 mL). The combined ether layers were supplemented with 20 mL of toluene and evaporated under reduced pressure. The crude oil was purified via chromatography using a 1:7 EtOAc:petroleum ether solvent mixture to yield 82 as a yellow oil (78.1 mg, 77%). Distillation under a cold finger gave a clear and colourless oil (86 °C, 1 mm Hg).

**Compound (82):** IR (CHCl3): 1737, 1725 (C=O, st), 1283 (C-Br, st) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) ppm: 5.21 (1H, m, C₃-H, J = 5.9, 5.4, 5.3 Hz), 4.88 (1H, m, C₁₃-H, J = 7.0, 6.3, 4.7 Hz), 3.82, 3.81 (2H, ABq, C₁₆-H, J = 12.2 Hz), 2.65, 2.54 (2H, m, C₂-H, J = 15.5 5.9, 5.3 Hz), 2.03 (1H, m, C₄-H, J = 6.9, 5.4 Hz), 1.61-1.13 (16H, m, CH₂’s), 1.20...
(3H, d, C14-H, J = 6.3 Hz), 0.88 (3H, d, C17-H, J = 6.9 Hz); $^{13}$C NMR (100.6 MHz, CDCl$_3$)

ppm: 169.6 (C15, s), 166.6 (C1, s), 75.7 (C3, d), 72.5 (C13, d), 35.5 (C16, t), 34.7 (C2, t), 33.4 (C4, d), 29.4 (C12, t), 20.5 (C14, q), 14.9 (C17, q), 26.0, 25.9, 25.5, 24.8, 24.4, 23.8, 23.1 (CH$_2$'s, t's); Mass spectrum, m/e (relative intensity): 377 (M$^+$, 0.1), 238 (16), 179 (11), 178 (28), 168 (12), 165 (33), 149 (24), 140 (15), 139 (17), 138 (24), 137 (22), 136 (11), 125 (22), 124 (45), 123 (28), 122 (11), 121 (27), 114 (11), 112 (15), 111 (31), 110 (38), 109 (34), 108 (13), 107 (10), 98 (18), 97 (50), 96 (49), 95 (69), 94 (15), 93 (11), 89 (12), 85 (17), 84 (16), 83 (55), 82 (58), 81 (57), 79 (11), 71 (40), 70 (24), 69 (67), 68 (42), 67 (37), 57 (26), 56 (27), 55 (100), 54 (14); Exact mass calc. for C$_{17}$H$_{29}$O$_4$Br + H (C$_{17}$H$_{29}$O$_4$Br + H): 377.1327 (379.1307); Found: 377.1337 (379.1306).

$(3S^*,4S^*,13S^*)$-3-(4'-Toluenesulfonyloxy)-4-methyl-13-tetradecanolide

(78)

To a solution of macrolide 58 (61.1 mg, 0.239 mmol) and p-toluene sulfonyl chloride (182.1 mg, 0.955 mmol) was injected 2.0 mL of dry pyridine and stirred under N$_2$ for 160 hours at room temperature. The reaction was poured into 70 mL of 1 M HCl, saturated with NaCl and extracted with ether (4 x 50 mL). Toluene (20 mL) was added and the solvents reduced under vacuum to afford a dark yellow oil. Chromatography with a 1:7 EtOAc:petroleum ether solvent mixture gave pure product 78 (80.9 mg, 83%) as white crystals (Mp: 53-54 °C).
Compound (78): IR (CHCl₃): 1724 (C=O, st), 1358 (S=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 7.82 (2H, d, C₁⁷-H, J = 8.3 Hz), 7.35 (2H, d, C₁₆-H, J = 8.1 Hz), 5.06 (1H, m, C₃-H, J = 5.3, 6.6, 4.2 Hz), 4.89 (1H, m, C₁₃-H, J = 4.2, 6.1, 7.3 Hz), 2.65 (2H, dABq, C₂-H, J = 5.3, 6.6, 16.1 Hz), 2.45 (3H, s, C₁₈-H), 2.01 (1H, m, C₄-H), 1.66-1.11 (16H, m, CH₂'s), 1.23 (3H, d, C₁₄-H, J = 6.1 Hz), 0.85 (3H, d, C₂₀-H, J = 6.6 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 169.0 (C₁, s), 144.6 (C₁₅, s), 134.3 (C₁₈, s), 129.7, 127.7 (C₁₆, C₁₇, d's), 82.0 (C₃, d), 72.7 (C₁₃, d), 36.6 (C₂, t), 34.7 (C₄, d), 34.4 (C₁₃, t), 20.4 (C₁₄, C₁₈, q's), 14.6 (C₂₀, q) (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 410 (M⁺, 0.3), 239 (11), 238 (39), 178 (22), 168 (11), 167 (15), 166 (13), 165 (42), 154 (21), 140 (22), 139 (11), 138 (13), 137 (23), 136 (16), 135 (12), 126 (12), 125 (16), 124 (40), 123 (23), 122 (12), 121 (14), 114 (14), 112 (10), 111 (28), 110 (25), 109 (42), 108 (18), 107 (18), 100 (13), 99 (14), 98 (12), 97 (34), 96 (46), 95 (70), 94 (19), 93 (23), 92 (10), 91 (40), 85 (12), 84 (14), 83 (38), 82 (67), 81 (81), 80 (15), 79 (30), 77 (12), 71 (28), 70 (16), 69 (57), 68 (87), 66 (83), 66 (11), 65 (18), 57 (19), 56 (22), 55 (100), 54 (31), 53 (34); Exact mass calc. for C₂₂H₃₄SO₅: 410.2127; Found: 410.2111.

Base hydrolysis of (3S*, 4S*, 13S*)-3-hydroxy-4-methyl-13-tetradecanolide (58)

The macrolide 58 (38.7 mg, 0.151 mmol) was dissolved in a KOH solution [KOH (42.3 mg) in 1.5 mL of water] and 2.5 mL MeOH. The reaction mixture was refluxed for 43 hours.
and acidified with 1M HCl. Extraction with CH$_2$Cl$_2$/NaCl gave 31.9 mg of very pure product 60 needing no further purification (77%).

**Compound (60):** IR (CHCl$_3$): 3730-3066 (acid OH, st), 1719 (C=O, st); $^1$H NMR (400 MHz, CDCl$_3$) ppm: 5.09 (1H, bs, C$_1$-OH), 3.84 (1H, m, C$_3$-H, J = 9.4, 5.1, 2.8 Hz), 3.75 (1H, m, C$_{13}$-H), 2.46 (1H, dd, C$_2$-H, J = 2.8, 16.2 Hz), 2.38 (1H, dd, C$_2$-H, J = 9.4, 16.2 Hz), 1.57 (2H, m, C$_4$-H and C$_{12}$-H), 1.46-1.05 (15H, m, CH$_2$'s), 1.14 (3H, d, C$_{15}$-H, J = 6.1 Hz), 0.85 (3H, d, C$_{14}$-H, J = 6.8 Hz); $^{13}$C NMR (100.6 MHz, CDCl$_3$) ppm: 177.0 (C$_1$, s), 71.8 (C$_3$, d), 68.3 (C$_{13}$, d), 39.0 (C$_2$, t), 38.02 (C$_4$, d), 23.15 (C$_{14}$, q), 14.78 (C$_{15}$, q), 37.52, 32.14, 29.70, 29.49, 29.44, 29.36, 26.94, 25.61 (CH$_2$'s, t's); Mass spectrum, m/e (relative intensity): 257 [(M-OH)$^+$, 1], 256 [(M-H$_2$O)$^+$, 1] 168 (37), 152 (16), 125 (11), 124 (10), 114 (18), 112 (12), 111 (21), 110 (14), 109 (12), 107 (15), 98 (15), 97 (43), 96 (23), 95 (22), 89 (100), 85 (11), 84 (19), 83 (45), 82 (26), 81 (25), 72 (12), 71 (26), 70 (29), 69 (61), 68 (19), 67 (17), 57 (27), 56 (31), 55 (69).

**Base hydrolysis of** (3R*,4S*,13S*)-3-hydroxy-4-methyl-13-tetradecanolide (59)

![Base hydrolysis of (3R*,4S*,13S*)-3-hydroxy-4-methyl-13-tetradecanolide](image)

The macroide 59 (36.7 mg, 0.143 mmol) was dissolved in 2.5 mL of MeOH and a KOH (40.1 mg in 1.5 mL of water) solution added. The reaction was refluxed for 41 hours, acidified with 1M HCl and extracted with CH$_2$Cl$_2$/NaCl to yield 61 as a yellow oil of very high purity (29.2 mg, 74%).
Compound (61): IR (CHCl₃): 3674-3072 (acid OH st), 1725 (C=O, st); ¹H NMR (400 MHz, CDCl₃) ppm: 5.38 (1H, bs, C₁-OH), 3.90 (1H, m, C₃-H, J = 4.1 Hz), 3.76 (1H, m, C₁₃-H), 2.45 (2H, m, C₂-H), 1.55-1.05 (18H, m, CH₂'s), 1.15 (3H, d, C₁₄-H, J = 6.2 Hz), 0.87 (3H, d, C₁₅-H, J = 6.8 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 177.1 (C₁, s), 71.26 (C₃, d), 68.33 (C₁₃, d), 39.05 (C₂, t), 37.89 (C₄, d), 23.18 (C₁₄, q), 14.23 (C₁₅, q), 38.12, 32.52, 29.66, 29.48, 29.43, 29.34, 27.03, 25.59 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 257 [(M-OH)+, 1], 256 [(M-H₂O)+, 1], 168 (31), 152 (14), 125 (12), 124 (11), 114 (19), 112 (12), 111 (23), 110 (15), 109 (15), 107 (12), 98 (16), 97 (43), 96 (27), 95 (25), 89 (100), 84 (21), 83 (49), 82 (30), 81 (30), 72 (14), 71 (25), 70 (30), 69 (64), 68 (20), 67 (21), 57 (30), 56 (33), 55 (81).

Deprotonation Studies of (4S*,13S*)-3-oxo-4-methyl-13-tetradecanolide (57)

Using LDA

LDA (2.43 mmol) was generated as usual at 0 °C in 2.0 mL of dry THF for 30 minutes. The macrolide 57 (246.5 mg, 0.971 mmol) was added dropwise dissolved in 1.4 mL of THF and stirred at 0 °C for 30 minutes. D₂O (0.185 mL, 10.2 mmol) was injected and further stirred 30 minutes. A sample was withdrawn for MS both before and after the workup. The sample before workup exhibited peaks characteristic of both mono (m/e = 255, peak intensity = 54) and di deuterated product (m/e = 256, peak intensity = 2) but with the major m/e peak
as the starting material (m/e = 254, peak intensity = 100). The sample after workup showed no evidence of deuterated product.

**Using NaH/n-BuLi**

To a 25 mL flask under N$_2$ was added NaH (10.6 mg, 0.441 mmol) and washed with THF (2 x 0.5 mL portions). More THF (0.5 mL) was added and the macrolide 57 (93.4 mg, 0.368 mmol) dissolved in 2-0.5 mL portions of THF was injected. The reaction mixture was stirred for 40 minutes at 0 °C and n-BuLi (0.25 mL, 0.41 mmol) was injected. A further 15 minutes of stirring was followed by the addition of CF$_3$CO$_2$D/D$_2$O. The reaction mixture was saturated with NaCl, extracted with ether (3 x 50 mL) and the organic layers combined and evaporated to give a dark yellow oil. A crude sample was subjected to MS analysis which revealed a 100:8 ratio (via peak intensities) of the desired di deuterated product to starting material. Chromatography of the remaining crude oil gave pure product 81 as a faster moving band.

**Compound (81):** IR (CHCl$_3$): 1725, 1709 (C=O, st); $^1$H NMR (400 MHz, CDCl$_3$) ppm: 5.10 (1H, m, C$_{13}$-H, J = 7.8, 6.4, 3.4 Hz), 3.50 (2H, ABq, C$_2$-H, J = 14.7 Hz), 1.80 (1H, m, C$_{12}$-H), 1.65-1.15 (15H, m, CH$_2$'s), 1.24 (3H, d, C$_{14}$-H, J = 6.4 Hz), 1.11 (3H, s, C$_{15}$-H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) ppm: 206.3 (C$_3$, s), 167.3 (C$_1$, s), 71.8 (C$_{13}$, d), 48.8 (C$_2$, t), 34.4 (C$_{12}$, t), 20.1 (C$_{14}$, q), 16.5 (C$_{15}$, q), 30.8, 26.0, 25.8, 25.6, 25.5, 25.1 22.7 (CH$_2$'s, t's), C$_4$-D triplet not observed; **Mass spectrum,** m/e (relative intensity): 255 (M$^+$, 4), 87 (13), 118 (27), 117 (83), 116 (31), 112 (23), 111 (24), 105 (22), 99 (64), 98 (46), 97 (51), 96 (29), 95 (25), 87 (14), 85 (33), 84 (55), 83 (77), 82 (41), 81 (37), 77 (22), 73 (20), 72 (19), 71 (61), 70 (81), 69 (100) 68 (44), 67 (50) 58 (41), 57 (87) 56 (82), 55 (84) 54 (37), 53 (20); **Exact mass** calc. for C$_{15}$H$_{25}$DO$_3$: 255.1945; Found: 255.1949.
4,4-Dimethyl-3-oxo-13-tetradecanolide (63)

To a dry flask equipped with a septum and a nitrogen inlet was added NaH (69.4 mg, 2.28 mmol). Dry THF (2 x 1.0 mL) was used to wash away the mineral oil whereupon a further 2.0 mL of THF was added and the reaction vessel cooled to 0 °C. The macrolide 57 (290.5 mg, 1.14 mmol) was injected in two-1.0 mL portions in THF and stirred for 2 hours. n-BuLi (1.4 mL, 2.3 mmol) was injected and stirred at 0 °C. After 1 hour, Mel (0.09 mL, 1.37 mmol) was injected and stirred 30 minutes at 0 °C and 10 minutes with the ice bath removed. The reaction was quenched by pouring into 1 M HCL (25 mL), saturated with NaCl and extracted with ether (3 x 150 mL). Concentration of the organic solvents and passage of the crude oil through SiO₂ with a 1:15 hexanes:EtOAc eluant gave 63 as a yellow oil (233.9 mg, 77%). The product was shown to exist as a 10:1 mixture of product to starting material by ¹H NMR spectroscopy.

Compound (63): IR (CDCl₃): 1726, 1708 (C=O, st) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) ppm: 4.96 (1H, m, C₁₃-H, J = 6.4, 6.3, 2.9 Hz), 3.50 (2H, ABq, C₂-H, J = 15.9 Hz), 1.70-1.00 (16H, m, CH₂'s), 1.26 (3H, d, C₁₄-H, J = 6.3 Hz), 1.14 (3H, s, C₁₅-H), 1.10 (3H, s, C₁₆-H); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 207.6 (C₃, s), 167.1 (C₁, s), 72.9 (C₁₃, d), 48.5 (C₄, s), 44.5 (C₂, t), 40.4 (C₅, t), 24.5, 23.8 (q's ), 19.3 (C₁₄, q), 32.6, 27.4, 26.7, 26.6, 25.1, 23.6, 22.7 (CH₂'s, t's).
(2S*,3S*,13S*)-2-Methyl-3-(4'-toluenesulfonyloxy)-13-tetradecanolide (79)

p-Toluene sulfonyl chloride (477.9 mg, 2.5 mmol) was dissolved in 3.0 mL of freshly distilled pyridine under N₂. The macrolide 47 (157.1 mg, 0.614 mmol) was injected in two 0.5 mL portions in pyridine. After stirring at room temperature under N₂ for 94 hours, the tlc showed the reaction to be complete and the mixture was poured into 55 mL of 1 M HCl. Extraction with ether (5 x 50 mL), drying over MgSO₄ and evaporation of the combined organic solvents yielded the crude product as a yellow oil. The addition of toluene (50 mL) before removing the solvents ensured the complete azeotropic removal of water and pyridine. Chromatography with a 1:7 EtOAc:petroleum ether solvent mixture gave 79 as white crystals (233.7 mg, 91%, Mp=99-100 °C).

**Compound (79):** 1R (CHCl₃): 1725 (C=O, s), 1361 (S=O, s); ¹H NMR (400 MHz, CDCl₃) ppm: 7.81(2H, d, C₁₈-H, J = 8.2 Hz), 7.33 (2H, d, C₁₇-H, J = 8.2 Hz), 4.92 (1H, m, C₁₃-H, J = 9.5, 6.3, 2.7 Hz), 4.89 (1H, m, C₃-H, J = 10.7, 4.0, 1.5 Hz), 3.30 (1H, m, C₂-H, J = 6.8, 4.0 Hz), 2.43 (3H, s,C₂₀-H), 1.76-1.00 (18H, m, CH₂'s), 1.20 (3H, d, C₁₄-H, J = 6.3 Hz), 1.09 (3H, d, C₁₅-H, J = 6.8 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 171.9 (C₁, s), 144.8 (C₁₆, s), 133.8 (C₁₉, s), 129.8, 127.9 (C₁₇, C₁₈, d), 82.3 (C₃, d), 70.7 (C₁₃, d), 43.6 (C₂, d), 35.1 (C₁₂, t), 21.6 (C₂₀, q), 20.4 (C₁₄, q), 8.8 (C₁₅, q), 26.5, 25.9, 25.1, 25.0, 24.0, 22.7, 22.5, 22.2 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 410 (M⁺, ), 270 (12), 238 (20), 228 (14), 183 (12), 182 (15), 181 (15), 165 (20), 164 (20), 155 (35), 123 (10), 112 (12), 110 (12), 109 (22), 98 (41), 97 (13), 96 (23), 95 (32), 91
(62), 85 (13), 83 (19), 82 (25), 81 (30), 70 (11), 69 (24), 68 (35), 67 (27), 65 (11), 57 (20), 56 (100), 55 (43); Exact mass calc. for $C_{22}H_{34}SO_5$: 410.2127; Found: 410.2127.

(E)-2-methyl-2-tetradecen-13-olate (64)

The macrolide 79 (36.8 mg, 0.90 mmol) was dissolved in 1.0 mL of dry toluene at room temperature under N$_2$. DBU (0.04 mL, 0.27 mmol) was injected neat and the mixture stirred 6.5 hours. A further injection of base (0.08 mL, 0.54 mmol) followed by 11 hours of stirring was still not sufficient to complete the reaction. A final base addition (0.08 mL, 0.54 mmol) and stirring for 3 hours at room temperature completed the reaction. The reaction was quenched with 10 mL of 1M HCl and ether extraction (4 x 50 mL) of the aqueous layer gave the crude product. Chromatography with a 1:7 EtOAc:petroleum ether solvent mixture gave pure 64 as light coloured yellow oil (18.5 mg, 91%). This compound was found to isomerize to the deconjugated unsaturated lactone upon standing.

Compound (64): IR (CHCl$_3$): 1708 (C=O, st), 1600 (C=C, w) cm$^{-1}$; $^1$H NMR (400 MHz, CDC$_3$, ppm: 6.89 (1H, m, C$_3$-H, $J = 9.4$, 5.6, 1.4), 4.95 (1H, m, C$_{13}$-H, $J = 7.6$, 3.5, 6.3 Hz), 2.35 - 2.10 (2H, m, C$_4$H$_2$'s), 1.81 (3H, bs, C$_{15}$-H, $J = 1.4$ Hz), 1.68 - 1.15 (16H, m, CH$_2$'s), 1.24 (3H, d, C$_{14}$-H, $J = 6.3$ Hz); $^{13}$C NMR (100.6 MHz, CDCl$_3$, ppm: 168.1 (C$_1$, s), 143.7 (C$_3$, d), 127.7 (C$_2$, s), 71.3 (C$_{13}$, d), 34.4 (C$_{12}$, t), 20.2 (C$_{14}$, C$_{15}$, q's), 28.3, 27.4, 27.1, 26.9, 25.9, 25.6, 23.3 (CH$_2$'s, t's); Mass spectrum, m/e (relative intensity): 238 (M$^+$, 18), 205 (10), 194 (10), 167 (18), 165 (19), 164 (18), 152 (13),
Hydrogenation of (E)-2-methyl-2-tetradecen-13-olide (64)

PtO₂ (2.4 mg) in 1.5 mL of EtOH was stirred under a H₂ atmosphere for 20 minutes whereupon the Pt precipitated as black granules. The macrolide 64 (7.0 mg, 0.029 mmol) was injected to the solution dissolved in 2 x 1.0 mL portions of EtOH. After stirring for 2.75 hours at room temperature, the reaction was filtered through a cotton plug. This gave highly pure 67 and 66 (6.4 mg, 91%) in a 56:44 ratio by glc and \(^1\)H NMR spectroscopy.
Deoxygenation of \((2S^*,3S^*,13S^*)\)-2-methyl-3-hydroxy-13-tetradecanolide (47)

\[
\text{HO...}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

47 \((2S^*,3S^*,13S^*)\) ➔ 66 \((2S^*,13S^*)\)

To 0.75 mL THF at 0 °C under N\(_2\) was injected diisopropylamine (0.02 mL, 0.14 mmol) and n-BuLi (0.10 mL, 0.14 mmol) and stirred 40 minutes. The macrolide 47 (32.3 mg, 0.126 mmol) was injected in 1.0 mL of THF and stirred at 0 °C for 1 hour. Freshly distilled CS\(_2\) (0.08 mL, 1.3 mmol) was added and after 45 minutes of stirring, Mel (0.08 mL, 1.3 mmol) was injected. After 30 minutes of stirring, the ice bath was removed and the reaction was further stirred 4 hours. The reaction mixture was poured into aqueous NH\(_4\)Cl and extracted with ether (2 x 80 mL). The ether layers were dried over MgSO\(_4\) and concentrated to give 35.4 mg of a dark yellow oil which was carried directly to the next step.

The crude oil (35.4 mg, 0.10 mmol) was dissolved in 2.0 mL of dry toluene. AIBN (1.2 mg, 0.001 mmol) was added and immediately followed by the injection of the n-Bu\(_3\)SnH (0.07 mL, 0.26 mmol). The reaction mixture was refluxed under N\(_2\) for 24.5 hours. Chromatography using an eluant of 3% ether to 97% petroleum ether gave pure 66 as a colourless oil (12.6 mg, 51%).
Deoxygenation of (2S*,3R*,13S*) and (2R*,3R*,13S*)-2-methyl-3-hydroxy-13-tetradecanolides (49) and (50)

\[ \text{HO} - \text{O} \rightarrow \text{O} \]

\[ \sim 49 \text{ and } 50 \sim \rightarrow 67 (2R^*,13S^*) + 66 (2S^*,13S^*) \]

A 3:2 mixture of 49 and 50 (57.9 mg, 0.226 mmol) was dissolved in 1.0 mL of THF and added dropwise to a LDA solution (0.249 mmol) at 0 °C in 2.0 mL of THF. After 30 minutes, CS\(_2\) (0.14 mL, 2.26 mmol) was injected and stirred 1 hour. Mel (0.14 mL, 2.26 mmol) was injected and stirred at 0 °C for 15 minutes. The ice bath was removed and the reaction mixture was stirred 12 hours. The reaction mixture was saturated with NaCl and extracted with ether (2 x 80 mL) followed by drying over MgSO\(_4\) which gave a brown oil after solvent reduction. Chromatography (SiO\(_2\) and a 1:7 EtOAc:petroleum ether solvent mixture) gave pure products (44.8 mg, 57%). This mixture of xanthates was dissolved in 1.5 mL of toluene, AIBN (9.3 mg, 0.06 mmol) added and refluxed under N\(_2\) for 16 hours. The crude reaction products were extracted with KF (1 x 80 mL). After solvent removal, the crude oil was chromatographed using a 3% ether:97% petroleum ether mixture to yield 17.6 mg (32%) of a mixture of pure 67 (major) and 66 (minor).
13-Tetradecanolide (42)

The macrolide 42 was prepared according to literature.\textsuperscript{81-83}

Compound (42): IR (CHCl\textsubscript{3}): 1722 (C=O, st); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) ppm: 5.01 (1H, m, C\textsubscript{13}-H, J = 6.3, 6.1, 5.6 Hz), 2.42 (1H, ddd, C\textsubscript{2}-H, J = 14.3, 9.0, 3.5 Hz), 2.27 (1H, ddd, C\textsubscript{2}-H, J = 14.3, 8.4, 3.6 Hz), 1.76-1.18 (20H, m, CH\textsubscript{2}'s), 1.22 (3H, d, C\textsubscript{14}-H, J = 6.3 Hz); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) ppm: 173.6 (C\textsubscript{1}, s), 69.9 (C\textsubscript{13}, d), 35.0 (C\textsubscript{12, 1}), 34.5 (C\textsubscript{2, t}), 20.3 (C\textsubscript{14, q}), 26.3, 26.1, 25.8, 25.44, 25.41, 24.8, 23.8, 23.7, 22.0 (CH\textsubscript{2}'s, t's); Mass spectrum, m/e (relative intensity): 226 (M\textsuperscript{+}, 0.9), 111 (15), 98 (32), 97 (25), 96 (17), 95 (11), 84 (21), 83 (32), 82 (17), 81 (17), 71 (16), 70 (18), 69 (44), 68 (14), 67 (25), 58 (12), 57 (19), 56 (31), 55 (100), 54 (13), 53 (14).

Deprotonation of 13-tetradecanolide (42) with Harpoon Base
To a solution of 2,2,6,6-tetramethylpiperidine (0.317 mL, 1.88 mmol) in 3.0 mL of THF at room temperature was injected n-BuLi (0.94 mL, 1.50 mmol) and stirred 10 minutes. The solution was cooled to -78 °C and the macrolide 42 (170.0 mg, 0.752 mmol) dissolved in THF (3.0 mL) was added dropwise. After 1 hour of stirring at -78 °C, a solution of Mel (0.12 mL, 1.94 mmol) in HMPA (0.3 mL, 1.72 mmol) was injected and the reaction mixture was stirred 1 hour. The reaction was quenched with aqueous NH₄Cl and extracted with ether. Purification by column chromatography gave products 67 and 66 in a ratio of 13:1 (148.0 mg, 82%) as determined on a 50 m Carbowax glc capillary column. The column of choice to separate these diastereomers was found to be the 12 meter DB-210 column previously described. The 2,2-geminal methylated lactone byproduct ZZ was also isolated.

Compound (67): IR (CHCl₃): 1722 (C=O, st); ¹H NMR (400 MHz, CDCl₃) ppm: 4.91 (1H, m, C₁₃-H, J = 9.0, 6.1, 2.7 Hz), 2.39 (1H, m, C₂-H, J = 10.9, 6.8, 2.5 Hz), 1.67-1.10 (20H, m, CH₂'s), 1.17 (3H, d, C₁₄-H, J = 6.1 Hz), 1.12 (3H, d, C₁₅-H, J = 6.8 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 175.9 (C₁, s), 69.7 (C₁₃, d), 42.3 (C₂, d), 35.6 (C₁₂, t), 20.3 (C₁₄, q), 18.1 (C₁₅, q), 34.2, 26.5, 26.3, 25.9, 25.8, 25.0, 24.1, 23.5, 22.5 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 240 (M⁺, 2), 112 (10), 111 (21), 98 (16), 97 (34), 84 (12), 83 (37), 82 (10), 81 (11), 74 (48), 71 (13), 70 (28), 69 (61), 67 (21), 57 (31), 56 (47), 55 (100), 53 (11); Exact mass calc. for C₁₅H₂₈O₂: 240.2089; Found: 240.2085.

Compound (66): IR (CHCl₃): 1723 (C=O, st); ¹H NMR (400 MHz, CDCl₃) ppm: 5.02 (1H, m, C₁₃-H, J = 6.7, 6.3, 4.9 Hz), 2.52 (1H, m, C₂-H, J = 9.2, 6.8, 3.5 Hz), 1.67-1.15 (20H, m, CH₂'s), 1.19 (3H, d, C₁₄-H, J = 6.3 Hz), 1.10 (3H, d, C₁₅-H, J = 6.8 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 176.9 (C₁, s), 69.7 (C₁₃, d), 38.8 (C₂, d), 35.0 (C₁₂, t), 20.4 (C₁₄, q), 17.5 (C₁₅, q), 33.8, 26.4, 26.1, 25.7, 25.4, 24.3, 23.7, 22.1 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 240 (M⁺, 2), 112 (12), 111 (24), 98 (22), 97 (33), 95 (12), 84 (17), 83 (48), 82 (13), 81 (16), 74 (56), 71 (16), 70 (27), 69 (62), 68.
Exact mass calc. for C_{15}H_{28}O_2: 240.2089; Found: 240.2094.

Compound (Z7): IR (CDCl_3): 1721 (C=O, st) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) ppm:
- 4.93 (1H, m, C\(_{13}\)-H, J = 9.2, 6.3, 2.5 Hz), 1.75-1.10 (20H, m, CH\(_2\)'s), 1.19 (3H, d, C\(_{14}\)-H, J = 6.3 Hz), 1.17 (3H, s, C\(_{15}\)-H), 1.13 (3H, s, C\(_{16}\)-H).

13-Tetradecanolide (42) enolate formation and subsequent trapping with trimethylsilyl chloride.

\[ 
\begin{array}{ccc}
\text{OTMS} & \text{O} & \text{TMS} \\
\text{42} & \rightarrow & \text{72} \\
\end{array}
\]

Diisopropylamine (0.07 mL, 0.52 mmol) and n-BuLi (0.327 mL, 0.516 mmol) were injected into 1.0 mL of THF under N\(_2\) at 0 °C. After 15 minutes of stirring, the LDA solution was cooled to -78 °C and the macrolide 42 (105.9 mg, 0.469 mmol) was injected (2 x 0.5 mL portions in THF). The reaction mixture was stirred for 10 minutes at -78 °C and was followed by the injection of a trimethylsilyl chloride (0.10 mL, 0.80 mmol) and triethylamine (0.11 mL, 0.80 mmol) mixture dissolved in 0.75 mL of THF. After 10 minutes of stirring, the cooling bath was removed and the reaction mixture stirred 3.5 hours. The solvent was removed under high vacuum and 15.0 mL of dry hexanes were injected. The hexanes layer was filtered and evaporation of the organic layer gave a yellow oil (102.7 mg) containing a mixture of ketene acetal 72 (31%), C-silylated product 73 (53%) and the starting material.
42 (16%). The ketene acetal was not stable over a 4 hour time period and purification could not be achieved due to its instability.

Compound (72): $^1$H NMR (400 MHz, CDCl$_3$) ppm: 4.24 (1H, m, C$_{13}$-H, J = 6.3, 6.1, 3.3, Hz), 3.59 (1H, dd, C$_2$-H, J = 10.3, 5.1 Hz), 1.60-1.10 (20H, m, CH$_2$'s), 1.13 (3H, d, C$_{14}$-H, J = 6.1 Hz), 0.21 (9H, s, O-Si-C$_{15}$-H).

Compound (73): IR (CHCl$_3$): 1720 (C=O, st); $^1$H NMR (400 MHz, CDCl$_3$) ppm: 4.92 (1H, m, C$_{13}$-H), 1.87 (1H, dd, C$_2$-H, J = 12.8, 2.3 Hz), 1.75-1.10 (20H, m, CH$_2$'s), 0.05 (9H, s, Si-C$_{15}$-H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) ppm: 174.2 (C$_1$, s), 69.6 (C$_{13}$, d), 40.3 (C$_2$, d), 35.7 (C$_{12}$, t), 20.4 (C$_{14}$, q), 28.4, 27.1, 26.3, 26.0, 23.7 23.4, 23.3, 22.1 22.0 (CH$_2$'s, t's), TMS carbons not observed; Mass spectrum, m/e (relative intensity): 298 (M$^+$, 1), 227 (10), 208 (29), 199 (10), 167 (10), 166 (13), 155 (13), 126 (11), 112 (19), 111 (35), 110 (19), 109 (17), 101 (19), 98 (57), 97 (50), 96 (31), 95 (25), 91 (15), 85 (34), 82 (28), 71 (37), 69 (64), 67 (28), 57 (62), 56 (47), 55 (100); Exact mass calc. for C$_{17}$H$_{34}$SiO$_2$: 298.2328; Found: 298.2310.

2-(Phenylthiomethyl)-13-tetradecanolide (80)

LDA was generated from diisopropylamine (0.09 mL, 0.64 mmol) and n-BuLi (0.405 mL, 0.639 mmol) at 0 °C in 1.5 mL of THF for 10 minutes. The solution was cooled to -78 °C and the macrolide 42 (120.4 mg, 0.533 mmol) in 2 x 0.5 mL portions was syringed into the
reaction. After stirring for 0.75 hour, a trimethylsilyl chloride (0.10 mL, 0.800 mmol) and triethylamine (0.11 mL, 0.800 mmol) solution was injected and stirred an additional 15 minutes at -78 °C. The cooling bath was removed and stirring was continued for 3 hours during which time the reaction warmed to room temperature. The solvent was evaporated with a stream of N\textsubscript{2} gas. Dry CH\textsubscript{2}Cl\textsubscript{2} (2.0 mL) was used to transfer the ketene acetal to a separate flask containing PhSCH\textsubscript{2}SCl (0.086 mL, 0.64 mmol) and ZnBr\textsubscript{2} (2.4 mg, 0.01 mmol) at room temperature. This reaction mixture was stirred for 4 hours and filtered through a sintered glass funnel followed by chromatography (3% ether:97% petroleum ether) to give product \textit{80} (109.8 mg, 61%) as a mixture with the C-silylated product which was inseparable from the desired product.

Compound \textit{(80)}: Mass spectrum, m/e (relative intensity): 348 (M\textsuperscript{+}); Exact mass calc. for C\textsubscript{21}H\textsubscript{32}SO\textsubscript{4}: 348.2123; Found: 348.2130.

**Raney nickel reduction of 2-(phenylthiomethyl)-13-tetradecanolide (80)**

The impure sulfide \textit{80} (44.7 mg) was dissolved in 2.0 mL of an acetone:methanol (9:1) mixture and Raney-nickel (pH=10, aqueous W-2) was pipetted into the reaction at room temperature. After 2 hours, the tlc showed the reduction to be complete. The reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} and filtered through a 1/4 inch Celite bed. Evaporation of solvent under vacuum yielded products \textit{67} and \textit{66} in a 3:1 ratio by glc (21.4 mg, 67%).
Diisopropyl amine (0.21 mL, 1.5 mmol) was injected to a solution of n-BuLi (0.87 mL, 1.4 mmol) in 4.0 mL of THF at 0 °C and stirred for 10 minutes. The solution was cooled to -78 °C and a 13:1 mixture of macrolides 67 and 66 was injected in two one mL portions in THF and stirred one hour. Phenylselenenyi chloride (266.5 mg, 1.39 mmol) was dissolved in 2.0 mL of THF and injected to the reaction mixture. After 30 minutes of stirring, the solution was warmed to 0 °C and stirred another 30 minutes. The solution was quenched by pouring into cold 1M HCl, saturated with NaCl and extracted with ether (3 x 100 mL). The organic layer was evaporated under vacuum to yield a yellow oil. This crude phenylselenenyi adduct was dissolved in 6.0 mL of THF and cooled to 0 °C. Hydrogen peroxide (0.51 mL, 6.4 mmol) was added dropwise and stirred one hour. The reaction mixture was poured into an ammonium chloride/sodium chloride solution and extracted with ether (3 x 100 mL). The organic layers were concentrated under vacuum and passed through a SiO2 column using a 1:24 (EtOAc:hexanes) solvent mixture to yield 96.9 mg (64%) of the desired exocyclic a,ß-unsaturated lactone 74.

Compound (74): IR (CHCl3): 1709 (C=O, st), 1628 (C=C, w); 1H NMR (400 MHz, CDCl3) ppm: 6.02 (1H, d, C15-H, J = 1.90 Hz), 5.42 (1H, m, C15-H, J = 1.90, 1.0, 0.92 Hz), 5.22 (1H, m, C13-H, J = 7.3, 6.5, 2.9 Hz), 2.43 (1H, m, C3-H, J = 9.0, 1.0 Hz), 2.21
(1H, m, C₃-H, J = 9.0, 0.92 Hz), 1.65-1.10 (18H, m, CH₂'s), 1.24 (3H, d, C₁₄-H, J = 6.5 Hz); ¹³C NMR (100.6 MHz, CDCl₃) ppm: 167.5 (C₁, s), 141.5 (C₂, s), 124.8 (C₁₅, t), 70.6 (C₁₃, d), 34.5 (C₁₂, t), 33.0 (C₃, t), 19.9 (C₁₄, q), 26.6, 26.1, 26.0, 25.8, 25.2, 24.4, 23.9, 21.5 (CH₂'s, t's); Mass spectrum, m/e (relative intensity): 238 (M⁺, 12), 193 (13), 139 (11), 137 (11), 124 (18), 123 (24), 122 (22), 121 (13), 112 (13), 111 (22), 110 (33), 109 (41), 108 (13), 107 (11), 98 (16), 97 (27), 96 (42), 95 (62), 94 (23), 93 (16), 92 (40), 91 (100), 87 (14), 84 (14), 83 (32), 82 (44), 81 (73), 80 (13), 79 (23), 77 (15), 71 (12), 70 (15), 69 (57), 68 (36), 67 (70), 65 (29), 57 (19), 56 (22), 55 (92), 54 (30), 53 (22), 51 (13); Exact mass calc. for C₁₅H₂₆O₂: 238.1933; Found: 238.1934.

Raney nickel reduction of 2-(Methylene)-13-tetradecanolidde (74)

The macrolide 74 (34.4 mg, 0.15 mmol) was dissolved in a 9:1 acetone:water solvent mixture and cooled to 0 °C. Raney nickel (~0.1 mL as an aqueous suspension, W-2) was pipetted into the reaction mixture and the whole allowed to stir for 10 hours. The reaction was filtered through a cotton plug, saturated with NaCl and extracted with ether (4 x 15 mL). The evaporation of organic solvents under vacuum gave 34.2 mg (99%) of a 4:1 ratio of 6₆ to 6₇.
REFERENCES


(12) Hückel, W., Ann., 1925, 441, 1.


(18) It follows that any cyclic system having an odd number of atoms cannot fit on the diamond lattice and hence cannot have a strain-free conformation.


(55) All energy calculations were performed using the MM2 program which was supplied with MACROMODEL version 1.5 (1982). A three dimensional diamond lattice was constructed on a terminal screen by fusing chair cyclohexane units which were available from the MACROMODEL program. The desired 14-membered conformations were formed by deleting the bonds of the lattice not directly involved in making up the carbon skeleton of the ring. The energy of the resulting conformation was then calculated using the MM2 program. Using this lattice bond deletion method, a different part of the lattice was chosen to form the same conformation and the two energies were compared. The energies of identical conformations formed from two different parts of the lattice agreed to ± 0.1 kcal. The MACROMODEL program was kindly supplied by Dr. Cam Oehlschlager, Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada.


(70) This macrolide was synthesized by Thomas Hugo Keller, PhD thesis, University of British Columbia, 1988.


(84) First completed by Dr. J. Tercio B. Ferreira, Universidade Federal de Sao Carlos.
APPENDICES

1.0 The Torsional Angle

Within the n-butane molecule, the bonds labelled 1', 2' and 3' form the dihedral or torsional angle.

If the rear bond (3') is fixed, then the smallest angle required to superimpose the front bond (1') on the rear bond (3') determines the size of the torsional angle. If the front bond was rotated clockwise to achieve superimposition then the sign of the torsional angle is positive (+) and it is negative if anti-clockwise (-). Following these rules, the torsional angle sign and magnitude will be the same from whichever side is viewed (bond 1' or 3' as the front bond).

Clockwise = + angle  Anti clockwise = - angle

2.0 The MACROMODEL Program

Frequently, the process for determining low energy conformations of a cyclic system involves a two step process. Likely conformations of the ring are constructed using molecular models and the approximate co-ordinates of each conformation are used in an energy calculation program eg. Allinger's molecular mechanics (MM2) program. However, there are two limitations to this process. First, one cannot be assured that all likely conformations have been uncovered. Second, the crude starting co-ordinates supplied by the chemist will determine to some extent the resultant minimized energies. Different starting co-ordinates may yield different final energies for the same conformation. Still has written a program which eliminates the uncertainty involved in this process.
The MACROMODEL program operates in the following manner. One conformation of the ring is manually drawn on a terminal screen which is then minimized in terms of energy by the computer. From this minimized conformation, a bond is broken (chosen by the chemist) which is far removed from the presence of any functional groups (eg. esters or olefins). At this point, the computer regards the molecule as an acyclic chain. The program then attempts to join the two ends of the chain by random variation of torsional angles based on specified closure distances, bond angles, torsional angles and transannular contact which may be varied according to the precision required. Duplicate results are automatically eliminated and the remaining conformations provide the input to Allinger's MM2 program which minimizes the initial geometries and stores the results. This process has been demonstrated for cyclononane. From the manually drawn cyclononane in which a single bond was broken, the computer generated 7,962,624 conformations. Of course only a small percentage of these have the two ends of the chain within a reasonable bonding distance. If the constraints of a 1.2 Å closure distance and 100-120 ° closure bond angle are applied then only 2895 conformations remained. Nearly 66% of these were eliminated as duplicate conformations and the ~1000 conformations were minimized using MM2 calculations. Conformations within a set value (eg. 5 kcal mole\(^{-1}\)) of the lowest energy conformation were stored for further examination. This procedure generated the 4 known lowest energy conformations of cyclononane. The relative energies of the minimized conformations were found to be reproducible to within 0.1 kcal mole\(^{-1}\).

In general, this entire process can be completed within a 48 hour time period by an uninterrupted microvax or VAX computer. However the use of a personal VAX computer is uncommon to the organic chemist and instead a priority time sharing of these computers is normally found at most institutions. Therefore, the time required to generate the conformations, screen out unfavourable selections and calculate the energies may exceed reasonable lengths of time when dealing with large rings (≥ 14 membered).
3.0 The Molecular Mechanics (MM2) Program

The molecular mechanics (MM2) program was introduced by Allinger et al.\textsuperscript{21} as an alternative to the complicated \textit{ab initio} molecular orbital (MO) methods of calculating molecular energies. The energies calculated by the MM2 program are based on classical mechanics in which the equations used to calculate the energies are parameterized to best fit the experimental data. The MM2 program is much faster than the MO methods and produces very accurate values. In addition, the MM2 program is not restricted to the low atom limit for most MO methods. The energy calculated by the MM2 program is the sum of five different energy contributions.

The first energy term is associated with bond stretching. The MM2 program treats bond stretching as a modified Hooke's law equation. The remaining four terms include bending, torsional strain, Van der Waals interactions and electrostatic effects. Each is calculated by classical equations. This last term includes, for example, dipole-dipole interactions between carbonyl functionalities. However, electrostatic effects do not include the behavior of electrons. Therefore, stabilizing contributions from hydrogen bonding or the anomeric effect are not considered in the calculations. The sum of these five energy terms totals the "steric" energy of a molecule.

In order to minimize a molecule's energy, the MM2 program uses the steepest descent method. Thus the energy of a molecule is initially calculated from a given set of coordinates. One atom is moved to a new set of coordinates and the molecule's energy is recalculated. If the atom movement results in a lower molecular energy, then the atom is further moved in the same direction in increments reflecting the size of the energy change. This process is terminated when the energy difference is less than or equal to a preset default value. Although this process has been described using a single atom, in fact, every atom within the molecule is simultaneously subjected to this movement-calculation sequence until the energy of the system is minimized. Care must be exercised at this stage since an MM2 energy may
represent a false minimum and it is advisable to recalculate the energy using a different set of starting coordinates.
SPECTRAL INDEX
$\sim (2S^*, 3S^*, 13S^*)$

![Chemical structure diagram](image)
$49(2R^*,3R^*,13S^*)$
$61 \ (3R^*, 4S^*, 13S^*)$