CONFORMATIONALLY CONTROLLED REACTIONS IN 14-MEMBERED MACROLIDES

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ABSTRACT

The conformationally controlled reactions of macrolides $42$, $43$, $72$ and $74$ were investigated. Treatment of these 14-membered lactones with hydride reducing agents and organocopper reagents led to diastereoselective product formation. The product distributions could be rationalized using low energy starting material or product conformations. A detailed conformational analysis involving MM2/MMP2 calculations and X-ray crystallographic studies led to a simple model for determining these low energy conformations.

In order to simplify the identification of ring conformations, an improved procedure for the generation of polar maps was developed. With the aid of polar maps, a previously unknown low energy conformation for 14-membered rings was discovered. The discovery of this new conformation led to an improved nomenclature system for large rings, which considers the number of bonds separating both corner and pseudo corner atoms. Under this proposed nomenclature, the newly discovered conformation is designated the $[34'3'4']$ conformation.

The work described in this thesis also led to a useful method for assigning the stereochemistry of trimethylsilyl enol ethers. Nuclear Overhauser effect difference spectroscopy (NOEDS) was used to unambiguously distinguish between E and Z trimethylsilyl enol ethers. One advantage of this technique over the widely used $^{13}$C NMR method is that only one isomer is required to accurately assign the E or Z geometry.

\[
\begin{align*}
42 & \quad R = H \\
43 & \quad R = \text{CH}_3 \\
72 & \quad R = H \\
74 & \quad R = \text{CH}_3
\end{align*}
\]
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>BHT</td>
<td>3,5-di-tert-butyl-4-hydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
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<tr>
<td>calcld.</td>
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<tr>
<td>CD</td>
<td>circular dichroism</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>double doublet</td>
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<tr>
<td>DCC</td>
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<tr>
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<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<td>DEAD</td>
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<td>DMAP</td>
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</tr>
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<td>N,N-dimethylformamide</td>
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<tr>
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</tr>
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<td>Et</td>
<td>ethyl</td>
</tr>
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<td>ether</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>eV</td>
<td>electron volts</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour (s)</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
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<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
<td>LRMS</td>
<td>low resolution mass spectroscopy</td>
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<tr>
<td>m</td>
<td>multiplet</td>
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<td>MCPBA</td>
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</tr>
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<td>ORTEP</td>
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<td>N,N,N',N'-tetramethylethylene diamine</td>
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<td>TMS</td>
<td>trimethylsilyl</td>
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This thesis is dedicated to my parents.
CHAPTER I

Introduction

Ever since Hassell and Barton demonstrated the importance of conformation to chemical reactivity, conformational analysis has become one of the most important branches of organic chemistry. Today the concepts and ideas of conformational analysis are widely used in the interpretation of steric and electronic effects in organic compounds, and of chemical transformations and reaction mechanisms.

1.1 CONFORMATIONAL ANALYSIS OF SIX-MEMBERED RINGS

The foundations of modern stereochemistry were laid in 1874 when van’t Hoff and Le Bel independently introduced the concept of the tetrahedral carbon atom. Although their ideas were not accepted by all chemists at the time, the three-dimensional nature of molecules slowly gained supporters. During a time when most chemists still believed that cyclohexane was a coplanar regular hexagon and that eclipsed conformations were more stable than staggered forms, Sachse suggested in 1890, that cyclohexane exists in two puckered arrangements later termed "chair" and "boat" conformations. Sachse's theory was rejected for nearly 30 years, until Mohr pointed out that the existence of numerous bicyclic and tricyclic systems were inexplicable on the basis of planar structures, while such molecules were easily constructed using the chair form of six-membered rings. Experimental evidence supporting Sachse's and Mohr's hypothesis was provided by Huckel and co-workers in 1923. They synthesized the two isomers of decahydronaphthalene whose existence had been predicted by Mohr in his pioneering work. From this point on progress in conformational analysis slowly gained momentum with significant contributions from Boeseken and van Giffen (cyclic diols), and Mizushima and Higasi (spectroscopic studies of substituted ethanes). Still there remained considerable resistance to these new concepts, until Hassel published his electron diffraction studies on
chlorocyclohexane. In an article entitled "The Cyclohexane Problem", Hassel showed that: (1) chlorocyclohexane existed largely in the chair form, (2) there was a rapid ring inversion which allowed the substituents to occupy either the axial or the equatorial position and (3) that the more stable chair conformation had the substituent in the equatorial position (Figure 1). These results were not widely known until after World War II when several of his articles appeared in the English language.

![Figure 1. The two different chair conformations of chlorocyclohexane.](image)

However, the real breakthrough in this field did not come until 1950, when Barton published his paper on the conformational analysis of cyclohexanes including the steroid nucleus. By applying Hassel's ideas to polysubstituted cyclohexanes, Barton was able to explain results of organic reactions which had puzzled chemists for years. In the case of neomenthol (1) and menthol (2), he suggested that the differences in rates of esterification were due to the different steric environments of the two reacting substituents (Figure 2). The hydroxyl group in menthol (2) occupies an equatorial position, whereas the alcohol in neomenthol (1) occupies an axial position. Barton reasoned that since axial substituents are more hindered due to transannular interactions with other axial bonds, the equatorial hydroxyl group should be more easily esterified, which is in accordance with experimental results. In Barton's paper there are numerous examples which demonstrate the importance of conformational analysis in explaining the differences of stability or reactivity of stereoisomers.
Figure 2. Esterification of neomenthol (1) and menthol (2) (R = i-Pr).

An important limitation of Barton's work was his intentional choice of compounds that exist largely in one conformation. An illustration of the complexities that can arise in conformationally mobile systems was given in 1953 by Eliel. He pointed out that neomenthol (1) is esterified at one-third the rate of neoisomenthol (3). This can only be explained if the two molecules react from the less stable conformations 1a and 2a, since in conformation 3 there is a more severe crowding of the axial hydroxyl group than in 1 (Figure 3). Qualitative conformational analysis predicts that the equilibrium constant for 1 and 1a is smaller than for 3 and 3a, since in the former, two alkyl groups must occupy axial positions. Assuming that both 1a and 3a are of the same reactivity, Eliel concluded that 3a should be esterified more readily than 1a, because of its higher equilibrium concentration. This was one of the few examples in which ground state conformational preferences could not be used to predict reaction rates.
Figure 3. Conformational equilibrium for neomenthol (1) and neoisomenthol (3) (R = i-Pr).

This relationship between ground-state conformations of a reactant and the product distribution was clarified by Curtin one year later. The Curtin-Hammett Principle states that "in a chemical reaction that yields one product from one conformation and a different product from another conformational isomer (and provided these two isomers are rapidly interconvertible relative to the rate of product formation) the product composition is related to the relative concentrations of the conformational isomers and the respective rate constants of their reactions."12

The ideas and conclusions of these pioneers have led to a new and fundamental understanding of organic chemistry, and assisted in many of the subsequent developments in organic synthesis and physical organic chemistry. For example, the conformational analysis of heterocyclic systems has helped to explain the chemistry of important natural products such as carbohydrates.13 The chair conformation of six-membered rings has also helped to advance the chemistry of open chain compounds. The use of a chair transition state to rationalize the diastereoselectivity of aldol reactions has been very successful,14 and more recently, spiroketalts have been used as intermediates for the stereospecific synthesis of complex aliphatic compounds (Figure 4).15 In these systems the desired relative stereochemistry is induced during an
equilibrium controlled spiroketalization, which takes advantage of conformational preferences in six-membered rings along with the anomeric effect.\textsuperscript{15c}

\begin{center}
\includegraphics[width=\textwidth]{figure4.png}
\end{center}

\textbf{Figure 4.} Spiroketalts as intermediates for the diastereoselective preparation of acyclic molecules.\textsuperscript{15}

\section*{1.2 CONFORMATIONAL ANALYSIS OF MEDIUM AND LARGE RINGS}

The first macrocyclic compounds were discovered by Ruzicka in 1926, while investigating the constituents of musk oil.\textsuperscript{16} He isolated muscone (4) and civetone (5) which exhibited the highly coveted musk scent. The structure elucidation of these two compounds proved to be very difficult, since only chemical methods were available and muscone, for example, contained only one functional group. However, careful chemical degradation and comparison of the fragments with known compounds finally revealed the structures of these novel compounds.
Ruzicka's work on macrocyclic compounds was carried out with two motives, one practical - the preparation of artificial, musk-like perfumes - and one theoretical - the investigation of the physical and chemical properties of large rings. At that time, the second goal of his research seemed rather uninteresting, since according to popular belief, the chemistry of large ring cycloalkanes should not have differed greatly from that of cyclohexane.

Relying mainly on the acyloin condensation to prepare their compounds, Ruzicka and Prelog investigated the chemical properties of medium and large ring hydrocarbons, alcohols and ketones. They found, for example, that the curve of melting point versus ring size did not steadily rise as with aliphatic hydrocarbons. In fact, all physical and chemical properties of these many membered rings showed an interesting and unexpected dependence on ring size.

The understanding of conformational details controlling these phenomena was lacking until 1961 when Dunitz et al. demonstrated by X-ray diffraction that a variety of substituted cyclodecanes crystallized in essentially the same conformation (Figure 5). This was rather surprising at the time since the cyclodecane ring was thought to be very flexible and to exist in many different conformations. Although an explanation for these results could not be found, Dunitz et al. concluded that the conformation of the ring skeleton common to these different molecules must represent a potential energy minimum.
The conformation of cis-1,6-diaminocyclodecane dihydrochloride.\textsuperscript{19}

In the absence of a detailed knowledge of the energies of different conformations, it was difficult to judge the significance of these findings. In 1963, Dale pointed out that the solid state conformation of the above cyclodecane derivatives closely followed the diamond lattice, as did the chair conformation of cyclohexane (Figure 6).\textsuperscript{20} This was a major breakthrough in the conformational analysis of medium and large rings. Since the diamond lattice is an extended network of ideal carbon-carbon bond lengths and tetrahedral angles, any conformation superimposable on the diamond lattice should exhibit a minimum in the angle and torsional strain.

By studying the models of various cycloalkanes, Dale came to two important conclusions:\textsuperscript{20}

1. Strain-free conformations for cycloalkanes with an odd number of carbons atoms are impossible since they cannot be superimposed on the diamond lattice.
2. No ring size between cyclohexane and cyclotetradecane can have a strain-free conformation since a diamond lattice conformation for those compounds involves too close an approach between some of the internal hydrogens. Even though the conformation of the cyclodecane derivatives follows the diamond lattice quite closely, these compounds clearly show a compromise between angle strain, torsional energy, and transannular hydrogen repulsion.

The latter conclusion suggested an explanation for experimental results obtained in the preparation of cyclic imino-nitriles. Ziegler et al.21 had reported that the yield in the cyclization of α,ω-bisnitriles dramatically decreased for the seven- to 13-membered rings before recovering to over 70% for 14-membered cyclic imino-nitriles.

Using these principles, Dale proposed low energy conformations for all even-membered carbon rings from C₆ to C₁₆. X-ray crystallography and theoretical calculations have subsequently shown that those predictions were very accurate. For example, the solid state conformation of cyclotetradecane22 and the structurally equivalent 1,8-diazacyclotetradecane dihydrobromide23 were very similar to the strain-free conformations derived from the diamond lattice (Figure 7).

Figure 7. The strain-free diamond lattice conformation of cyclotetradecane (* corner position).
Another interesting feature of medium and large rings is illustrated in Figure 7 using the strain-free conformation of cyclotetradecane. If the molecule is viewed from the top, four "corners" can be easily identified, each consisting of one corner atom which is unique in that it is flanked by two gauche bonds. Dale recognized that the hydrogens attached to a corner atom are directed away from the ring and concluded that this should be the only position in a macrocycle that can easily accommodate two geminal substituents without causing severe transannular interactions (Figure 8). Evidence to support this prediction has come from a crystal structure of 1,1,9,9-tetramethylcyclohexadecane which indeed showed the geminal methyl groups occupying the corner positions.24

![Diagram showing internal hydrogen interactions in cyclotetradecane](image)

**Figure 8.** Internal hydrogen interactions in cyclotetradecane (*corner position*).

Initially the corner position was defined as having two contiguous gauche dihedral angles followed on each side by an anti dihedral angle.20 This definition was later modified when examinations of molecular models led to the conclusion that the lowest energy arrangement of dihedral angles about a corner atom is a sequence of two gauche bonds of the same sign. A corner position therefore has two contiguous gauche dihedral angles of the same sign flanked on either side by an anti dihedral angle (Figure 9).25
The recognition of corner atoms also led to a naming system for the individual conformations of macrocyclic rings. This shorthand notation consists of a series of numbers within brackets, each number representing the number of bonds between two corner atoms. The direction around the ring is chosen so that the smallest number of bonds between corner atoms begins the sequence in the square brackets, followed by the next smallest possible number. Therefore the strain-free diamond lattice conformation for cyclotetradecane is designated as a [3434] conformation.

The qualitative recognition of the low energy diamond lattice conformation was followed by exploratory calculations of strain energies in medium and large rings. Using the potential energy curve for butane, Dale manually minimized conformations constructed with Dreiding models by trying to maximize the number of anti dihedral angles and avoid eclipsed bonds. The calculated strain energies were rather crude; however, the energy trends obtained in this study
have proven to be remarkably reliable. More accurate values became available a few years later when Anet et al. reported the use of molecular mechanics calculations to determine the strain energies of medium and large rings.\textsuperscript{26a} Cyclotetradecane, for example, was calculated to exist largely in the \([3434]\) conformation. The calculations also revealed two low energy conformations which were not superimposable on the diamond lattice. These were the \([3344]\) - strain energy relative to the \([3434]\) conformation of 1.1 kcal/mol\textsuperscript{26b} - and the \([3335]\) conformation (2.4 kcal/mol)\textsuperscript{26b} (Table I).

Table I. The three lowest energy conformations of cyclotetradecane

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Top view</th>
<th>Side view</th>
<th>Strain energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>([3434])</td>
<td><img src="image1" alt="Top view" /></td>
<td><img src="image2" alt="Side view" /></td>
<td>0 kcal/mol</td>
</tr>
<tr>
<td>([3344])</td>
<td><img src="image3" alt="Top view" /></td>
<td><img src="image4" alt="Side view" /></td>
<td>1.1 kcal/mol</td>
</tr>
<tr>
<td>([3335])</td>
<td><img src="image5" alt="Top view" /></td>
<td><img src="image6" alt="Side view" /></td>
<td>2.4 kcal/mol</td>
</tr>
</tbody>
</table>

* corner position
The [3344] and [3335] conformations were also found to be intermediates in the pseudorotation of the [3434] conformer. The calculated energy barriers were all between 7 and 8 kcal/mol.\textsuperscript{26b} This was in agreement with results obtained from low temperature \textsuperscript{1}H and \textsuperscript{13}C NMR by Anet et al.\textsuperscript{27} At -132 °C cyclotetradecane exists predominantly in a [3434] conformation and line shape studies pointed to an activation energy for pseudorotation of approximately 7 kcal/mol.

The introduction of functional groups on the cycloalkane ring was thought to have little effect on the preferred conformation.\textsuperscript{20} In medium rings, the introduction of an sp\textsuperscript{2} carbon or an ether group should reduce transannular interactions and, therefore, have a stabilizing effect on the diamond lattice conformation. In larger rings these effects should be small, since transannular interactions in these systems are less severe or non existent.

1.3 REMOTE ASYMMETRIC INDUCTION IN MEDIUM RINGS

The creation of new stereocenters with a high level of control is one of the central problems in natural product synthesis. While the control of vicinal asymmetric centers and 1,3 asymmetric induction is well established, the most commonly used solution to the problem of more remote asymmetric induction involves the coupling of two fragments with the correct absolute stereochemistry. A new and very elegant alternative to absolute stereocontrol for the construction of remote asymmetric centers was reported in 1981 by Still and Galynker.\textsuperscript{28} The work by Dale, Dunitz, Anet and others clearly suggested that medium and large rings existed in well defined conformations. Still and Galynker proposed that, as in six membered rings, substituents in these various conformations should prefer to occupy pseudoequatorial positions, except in corner positions, where the energy difference between a pseudoaxial and a pseudoequatorial substituent should be very small. Another very interesting property of medium and large rings stems from their conformational properties. In contrast to cyclohexane derivatives, sp\textsuperscript{2} centers in macrocycles often are perpendicular to the plane of the ring. This
results in the two diastereotopic faces being very different in these systems. This point is illustrated by comparing the structures of cis-cyclohexene and trans-cyclotetradecene (Figure 10). While the two faces (A and B) of the double bond in cyclohexene are equivalent, face B of cyclotetradecene is severely hindered by the carbon atoms of the macrocycle and by transannular hydrogen interactions. Therefore reagents should approach the \( \pi \) system of a macrocyclic alkene largely or perhaps exclusively from the peripheral face A.

![Diastereofacial selectivity in cyclohexene and cyclotetradecene.](image)

**Figure 10.** Diastereofacial selectivity in cyclohexene and cyclotetradecene.

In order to predict and explain the stereochemical outcome of some chemical reactions of medium and large-ring systems, Still and co-workers\(^{28,29}\) used molecular mechanics (MM2) calculations (Appendix I).\(^{30}\) These studies led to a simple model to estimate product distributions. Using the Hammond postulate,\(^{31}\) they assumed that product ratios were closely related to the conformational energies of starting materials (early transition state) or products (late transition state). By calculating the steric energies of starting materials, intermediates and products, it was possible to quantitatively predict product distributions. Some illustrative examples will be described here.
The kinetic deprotonation of 3-methylcyclooctanone (6) with lithium diisopropylamide followed by alkylation of the lithium enolate with iodomethane afforded the cis-dimethylated product 7 with 98% selectivity. To gain some insight into the stereoselectivity of this reaction, the strain energies of possible enolate intermediates and products were calculated (Figure 11). An examination of the low energy conformations revealed that the 98% selectivity could not be explained by the enolate energies alone, since alkylation of 6d, which is very similar in energy to 6a and 6c, from the peripheral face would lead to trans-2,7-dimethylcyclooctanone. However, the observed product ratio follows a Boltzmann distribution of the calculated strain energies of the products. Kinetic alkylation of nine- and ten-membered lactones and ketones proceeded with equally high stereoselectivity, and the same approach was successfully used to rationalize the product distributions in these systems. Not unexpectedly, these studies showed that the stereoselectivity diminishes with increasing distance between the enolate and the controlling asymmetric center on the ring.

\[
\begin{align*}
\text{O} & \quad \text{1a) LDA} \\
7 & \quad \text{b) MeI} \quad > 98 \% \text{ cis}
\end{align*}
\]
The addition of lithium dimethylcopper(I) to 8-methyl-2-cycloocten-1-one (8) led to the exclusive formation of trans-2,7-dimethylcyclooctane (9) which is diastereomeric with 7. This result was explained by considering the two lowest energy conformations of the starting material. Peripheral attack on either 8a or 8b will lead to low energy enolate intermediates and eventually to the observed trans-dimethyl ketone 2 (Figure 12).
Figure 12. Cuprate addition to the low energy conformations of 8.\textsuperscript{28}

More recently, a slightly different approach was used to predict the diastereoselective reactions of cyclododecenes. Vedejs and co-workers\textsuperscript{32} eliminated the need for a full conformational analysis of the starting material or product by concentrating only on the immediate environment of the functional group. This local conformer approach has been very successful in rationalizing conformationally controlled epoxidations and osmylations. For example, epoxidation of (E)-3-methylcyclooctadecene (10) was predicted to produce epoxide 11 by peripheral attack on local conformer 10a. Indeed treatment of 10 with MCPBA afforded a 6:1 mixture of diastereomeric epoxides, the major isomer 11 having the predicted relative stereochemistry (Figure 13).
1.4 MACROLIDES

Pikromycin (12), the first macrolide antibiotic, was isolated from an *Actinomycetes* culture by Brockmann and Henkel in 1950. Since then a large number of macrolides possessing interesting biological activities have been isolated, and many have proven to be of considerable importance clinically, as preservatives, and as supplements to animal feed. This commercial importance and the synthetic challenge that these very complex natural products present, have led to intense activity in the field of macrolide chemistry. The synthesis of macrolides has been reviewed extensively and will not be specifically discussed at this point.

Macrolide antibiotics share several characteristic features, as can be seen from the structures of pikromycin (12), erythromycin A (13) - probably commercially the most important member of this family - , oleandomycin (14), and lankamycin (15):

1. They all contain a 12-, 14-, or 16-membered lactone of a secondary alcohol.
2. An array of hydroxyl and alkyl substituents is characteristically distributed on the ring.

Figure 13. Local conformer approach to the diastereoselective epoxidation of (E)-3-methylcyclododecene (10).
3. Sugars, very often amino sugars, are attached to one or more of the secondary hydroxyl groups on the lactone ring.

Conformational analysis has been an essential tool in understanding the interesting chemical behavior of these complex natural products and undoubtedly the conformations of these molecules also have an important bearing on the structure-activity relationship of the antibiotics.\textsuperscript{34b} A combination of spectroscopic methods and X-ray crystallography have been utilized to solve this problem.
The first attempt to predict the three dimensional structure of a macrolide appeared in 1965, when Celmer\textsuperscript{35} advanced a model for a preferred conformer of erythronolide B, the aglycone of erythromycin B (16). Basically patterned after the diamond lattice conformation of cyclotetradecane earlier proposed by Dale, the Celmer model (Figure 14) was in reasonable agreement with \textsuperscript{1}H NMR data.\textsuperscript{36} However, further consideration revealed several discrepancies which suggested that this proposed conformation was not a favoured low energy conformation. Egan et al.\textsuperscript{37} showed that the CD data could not be explained using the Celmer conformation, which also included unfavorable steric interaction between the 4- and 6-methyl groups, and the 12-methyl group and lactone carbonyl functionality. Furthermore, it was concluded that the \textsuperscript{1}H NMR data suggested that the macrolide ring was rigid and therefore should correspond more closely to the solid state conformation\textsuperscript{38} of erythromycin A. A critical reexamination of all the available data, led to the proposal of the Perun conformation for erythromycin B (Figure 14).\textsuperscript{37}\textsuperscript{a} This non-diamond lattice conformation can account for all \textsuperscript{1}H NMR coupling constants and leads to a predicted negative Cotton effect, in agreement with experimental results.\textsuperscript{37}\textsuperscript{a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure14.png}
\caption{Possible conformations for the aglycone of erythromycin B.}
\end{figure}

An investigation of the conformational behavior of erythromycin derivatives by \textsuperscript{13}C NMR showed that those macrolides had limited conformational flexibility, and that the
experimental data again could best be explained using the Perun conformation. Similar studies on several different macrolide antibiotics confirmed the Perun conformation and yielded evidence that oleandomycin (14) and lankamycin (15) occur in the same low energy conformation as the erythromycins.

The conformational picture is somewhat different for the macrolide antibiotics containing an \( \alpha,\beta \)-unsaturated ketone. Ogura and co-workers studied the three-dimensional structure of p-bromobenzoylpikromycin and kromycin using a combination of X-ray crystallography, CD, and NMR spectroscopy. These researchers found that these compounds existed in previously unknown diamond lattice conformations. Since Dale's nomenclature system was inconvenient for the naming of these new conformations, they turned to an arbitrary system which designates each conformation with a letter. For example, Dale's [3434] conformation was renamed the A conformation. On the basis of the X-ray analysis of kromycin, a dehydrated aglycone of pikromycin, Ogura et al. proposed the diamond lattice conformation model C\textsuperscript{41a} and subsequently showed that this conformation could most easily account for the experimentally observed CD and NMR data (Figure 15).

Furthermore, an X-ray crystal structure of p-bromobenzoylpikromycin revealed that this 14-membered macrolide ring closely resembled the diamond lattice conformation model D (Figure 16).\textsuperscript{41c,d}
In general these macrolide antibiotics proved to be fairly rigid molecules with the preferred conformation in solution being essentially the same as that in the solid state. Several researchers have concluded that X-ray crystallography is an essential tool in studying the conformations of these compounds.34b,37,41

1.5 THE SYNTHESIS OF NATURAL PRODUCTS USING CONFORMATIONALLY CONTROLLED REACTIONS IN MACROCYCLES

The preparation of large ring natural products is an important and active field in synthetic organic chemistry today. Several groups have used the conformational bias in medium or large rings to control the stereochemical outcome of key reactions in the synthesis of macrolide natural products.43 However the vast majority of researchers still prefer to assemble the stereochemical centers with the help of aldol or related alicyclic reactions before the macrocyclic ring is formed. The immense potential of remote stereochemical induction in the synthesis of complex natural products is illustrated in three recent examples.

Still and Novak have reported the total synthesis of 3-deoxyrosaranolide (17),44 a derivative of the aglycone of the macrolide antibiotic rosaramycin. In this synthesis, six asymmetric centers were introduced with conformational stereocontrol of the macrolide, using the substituents at C14 and C15 to induce the desired relative stereochemistry. Naturally, this
approach is more elegant and involves fewer chemical transformations than the traditional strategies involving absolute stereocontrol to establish the relative stereochemistry.

Compound 18, with the desired relative stereochemistry at carbon atoms 14 and 15 was cyclized using Wadsworth-Emmons conditions to give the starting macrolide 19. The first conformationally controlled reaction involved kinetic deprotonation with potassium bis(trimethylsilyl)amide followed by alkylation at C8 with iodomethane in 70% yield and with greater than 20:1 diastereoselection. The kinetic nature of this and the following reactions was proven by base equilibration of the product to a 1:1 diastereomeric mixture at the newly established asymmetric center. Deprotection of the ketone moiety afforded 20 which was shown to have the desired 8α-configuration by X-ray crystallography.
The next step involved functionalization of the macrolide at C6. Usually, alkylations of ketones with secondary carbon atoms on either side proceed with very poor regioselectivity; however, the conformational preferences in this particular 16-membered ring allowed the introduction of an acetate group with remarkable selectivity. Treatment of 20 with lithium bis(trimethylsilyl)amide and alkylation with tert-butyl bromoacetate proceeded with 20:1 regioselectivity and 6:1 stereoselectivity to yield 21. The stereochemistry of the major compound was again established using X-ray crystallography.

Introduction of the C4 methyl group by alkylation of 21 again proceeded with very high diastereoselectivity, but unfortunately produced the unnatural 4β-isomer. Since earlier experiments had indicated that alkylations and hydrogenations afford complementary results, the lithium enolate of ketone 21 was reacted with formaldehyde, followed by dehydration of the resulting hydroxy ketone via the mesylate to give the enone 22. Catalytic hydrogenation of the methylene ketone 22 produced the desired compound 23 with 9:1 stereoselectivity. Hydrolysis of the tert-butyl ester functionality and reaction of the acid with ethyl chloroformate produced a mixed anhydride which was reduced with sodium borohydride to afford 24 as a 5:1 mixture of 5α/5β alcohols. The synthesis was completed by oxidation of the allylic alcohol 24 with manganese dioxide, followed by epoxidation of the trisubstituted olefin, which led to diastereomer 25 in greater than 15:1 selectivity. This compound was further oxidized to afford the desired 16-membered macrolide (17).
21

\[ \text{LiN(SiMe}_3\text{)}_2 \]

\[ \text{HCHO} \]

\[ \text{MsCl/Base} \]

\[ \text{H}_2/(\text{Ph}_3\text{P})_3\text{RhCl} \]

22

\[ \text{CF}_3\text{COOH} \]

\[ \text{Et}_3\text{N, ClCOOEt} \]

\[ \text{NaBH}_4 \]

\[ \text{MnO}_2 \]

\[ \text{MCPBA, Base} \]

23

24

25
Still and Novak pointed out that the high stereoselectivities of these reactions must be due to the conformational preferences of the reaction transition states. However, they were unable to explain their results since MM2 calculations are unreliable with large rings having 16 or more members.29

One year later, Still and co-workers reported the synthesis of thromboxane A2 (26).45 Even though this acid-labile natural product does not contain a macrocyclic ring the conformational preferences of macrolides was applied to effect a key reaction in the synthesis of 26.

The synthesis started with commercially available thromboxane B2 (27, TXB2) which was transformed in several steps to the 10-bromo-TXB2 methyl ester 28. Treatment of compound 28 under modified Mitsunobu conditions afforded oxetane 29 in 20% yield accompanied by 25% starting material.
Removal of the bromine substituent however proved to be difficult, since the radical produced at C10 took part in an undesired side reaction. All attempts at free-radical debromination of 29 yielded only traces of the desired reduction product, and instead produced a compound which showed spectroscopic data in accord with structure 30.

![Chemical structure](image)

\[ \text{31 (R = C}_5\text{H}_{11}) \]

This problem was solved by forming a macrocyclic lactone and thereby restricting the approach between the radical at C10 and the C14 olefinic carbon. The macrocyclic lactone 31 was produced from TXB2 (27) via the thiopyridyl ester in good yield, followed by smooth transformation to compound 32. A modified Mitsunobu cyclization afforded the 10-bromo TXA derivative 33 which was treated with polymer bound tin hydride to smoothly produce the key
intermediate 34 in 85% yield. The X-ray structure of 34 clearly illustrates that the conformation of the macrocyclic lactone inhibits the approach between the two reactive centers (Figure 17). Saponification of 34 afforded the sodium salt of target molecule Thromboxane A2.

Figure 17. Solid state conformation of 34 from X-ray crystallography.45

Monensin B (35) is an important member of the polyether antibiotics which, because of their interesting biological activity, and unusual structures, have attracted considerable attention from organic chemists. Cane et al.46 have proposed a polyepoxide cyclization for the biosynthesis of these compounds (Figure 18) and recently several groups have investigated
the feasibility of a biomimetic approach based on this cyclization in the synthesis of polyether antibiotics. The most difficult step in such a strategy concerns the preparation of the polyepoxide precursor, e.g. 36. Schreiber and Still have independently reported a very elegant solution to this problem, taking advantage of conformational preferences and stereoselective reactions of macrocycles.

Schreiber and co-workers started their synthesis with 37 which was treated with Meldrum’s acid and diazomethane followed by allylic oxidation and acetylation to yield 38. Macrocyclization of this keto ester using tetrakis(triphenylphosphine)palladium(0) afforded the required 12-membered macrolide 39. Again, the relative stereochemistry was determined by X-ray crystallography. Decarboxylation of 39 and oxidation with MCPBA yielded the bisepoxide 40 with 9.5:1 selectivity. The stereochemistry of the major component 40 was rationalized by peripheral attack on the lowest energy conformation of 39. Saponification followed by acetonization led to the stereospecific formation of monensin B subunit 41.
These three examples clearly show the utility and potential of conformational preferences and stereoselective reactions in macrocycles. These syntheses also illustrate the most difficult part of this approach, establishing the relative stereochemistry of remote asymmetric centers. While molecular modeling can be used to predict the outcome of kinetically as well as equilibrium controlled reactions, the task of conclusively proving the configuration at the newly established center can be very challenging. If an X-ray crystallographic analysis is impossible, chiral synthesis of the product or transformation to a compound with known stereochemistry are the only alternatives.
CHAPTER II

Results and Discussion

The work by Still, Vedejs, Schreiber and others described in the introduction clearly established that conformational preferences in medium and large rings could be used for the selective introduction of substituents. However, while the preferred conformations of medium-size rings were determined and their behavior in chemical reactions thoroughly investigated, the possible conformations of large rings and therefore the source of the diastereoselective reactions in these systems is not well understood. Very recently, Masek et al.\textsuperscript{48} have analyzed the conformations of 20-, 21- and 22-membered cyclophanes and Rubin et al.\textsuperscript{49} have reported an investigation of the conformational behavior of a 13-membered ammonium salt.

In view of the biological importance of macrolide antibiotics, we decided to investigate this problem by studying the chemistry of simple 14-membered lactones. The aim of this project was to develop a better understanding of the conformations of 14-membered macrolides with the hope that this insight could be applied to the synthesis of more complex molecules. Furthermore, a more detailed knowledge of the conformational behavior of these macrolides might also help to understand the interesting biological activity of some of the naturally-occurring members of this family. Another actively pursued branch of macrolide chemistry that would profit from a better understanding of 14-membered ring chemistry involves the preparation of aglycone derivatives of erythromycin A, for example in a search for improved biological activity.\textsuperscript{50}

MM2 calculations have been used extensively to rationalize the outcome of diastereoselective reactions in medium rings. This method involves the calculation of the strain energies of starting materials, intermediates and products, and then rationalizing the selectivities as proceeding through the lowest energy conformations of one of these species. It is understood, in light of the Curtin-Hammett principle, that this method might in some cases be unable to
account for product compositions. However, since this approach was successfully used by Still and others, we were encouraged to apply it to our 14-membered macrolides.

The most promising starting point for our investigation seemed to be a keto lactone, since the prochiral carbonyl functionality can be utilized in a number of different ways to introduce a new stereochemical center. Because all the 14-membered ring macrolide antibiotics contain a ketone at C9, 9-oxo-13-tetradecanolide (42) seemed to be an ideal molecule for our investigations. We anticipated that 42 might be conformationally mobile, and therefore chose to prepare a second, more rigid macrolide - 10,10-dimethyl-9-oxo-13-tetradecanolide (43). This would not only give us the opportunity to compare the behavior of these two closely related compounds, but we would also have a chance to investigate whether geminally substituted carbon atoms indeed prefer to occupy corner positions, as suggested by Dale (Chapter 1.2).

During their work with 10-membered lactones, Still and Galynker²⁸ had observed that the stereoselectivity of kinetic alkylations decreases as the distance between the enolate and the controlling asymmetric center increases (Chapter 1.3). In both keto lactones 42 and 43, the carbonyl group is three carbons removed from the controlling center (C₁₃), and it would be interesting to see whether the methyl group at C₁₃ can efficiently control the stereochemistry of reactions at C₇, C₈ and C₉.
2.1 SYNTHESIS OF 9-OXO-13-TETRADECANOLIDE (42) AND 10,10-DIMETHYL-9-OXO-13-TETRADECANOLIDE (43)

Our plan for the synthesis of the two keto lactones \(42\) and \(43\) is outlined in Figure 19. Since a large quantity of macrolide was desired, simple and inexpensive starting materials were chosen.

The synthetic scheme is rather straightforward, the most troublesome step being the formation of the lactone ring. A number of methods for the cyclization of \(\omega\)-hydroxy acids are available, but our experience has shown that the yields of these lactonizations are variable. Since the macrocyclization would be the last or second last step in our synthesis, an efficient method with reproducible yields was desired. The most promising alternative seemed to be an intramolecular Wadsworth-Emmons reaction. Nicolaou and co-workers\(^5\) have shown that the internal reaction between a keto phosphonate and an aldehyde proceeds in excellent yield, using potassium carbonate and a crown ether in dilute toluene solution.\(^5\) A second disconnection at the ester linkage leads to the protected hydroxy acid \(44\) and the keto phosphonates \(45\) and \(46\) as potential starting materials. Dauben et al.\(^5\) had previously shown that compounds similar to \(45\) and \(46\) could easily be prepared by treatment of methyl esters with the lithium salt of dimethyl methylphosphonate.
Figure 19. Retrosynthetic analysis of macrocycles 42 and 43.
2.1.1 Synthesis of 7-benzylxyloxyheptanoic acid (44)

Three different methods to prepare 7-hydroxyheptanoic acid were investigated, all involving oxidative cleavage of the readily available cycloheptanone (47). Taub et al.\textsuperscript{54} had used potassium persulfate in the presence of sulfuric acid as the oxidizing agent to produce methyl 7-hydroxyheptanoate (48). In our hands this procedure led to a variety of products, with 48 being produced reproducibly in only 40-50\% yield.

\[
\begin{align*}
\text{47} & \xrightarrow{\text{K}_2\text{SO}_5, \text{CH}_3\text{OH}} \quad \text{48} \\
\text{49} & \xrightarrow{1. \text{O}_3, 2. \text{NaBH}_4} \quad \text{50} \\
\text{47} & \xrightarrow{\text{CF}_3\text{CO}_2\text{H}, \text{Na}_2\text{HPO}_4} \quad \text{51}
\end{align*}
\]

A second possible route to 44 takes advantage of a well known reaction between enol acetates and ozone.\textsuperscript{55} 1-Acetoxyheptene (49) was prepared in 76\% yield by treatment of cycloheptanone with acetic anhydride in the presence of toluenesulfonic acid. The enol acetate was then dissolved in a mixture of methylene chloride and methanol, and treated with excess
ozone to afford, after reductive workup with sodium borohydride, 7-hydroxyheptanoic acid \((50)\) in 85% yield. Even though the desired compound was produced in good yield, this two step procedure was abandoned, since large scale ozonolyses are known to be hazardous and cumbersome.\(^{56}\)

The method of choice for the preparation of 44 involved a Baeyer-Villiger oxidation of 47 followed by treatment of the crude lactone mixture with potassium hydroxide and benzyl bromide in refluxing toluene. The intermediate lactone \(51\) was obtained by slow addition of trifluoroperacetic acid to cycloheptanone.\(^{28}\) If desired, the crude product could be distilled yielding heptanolide \((51)\) in 70% yield. However, it is known that this reaction produces oligomeric and polymeric esters as side products, and it was therefore desirable to subject the unpurified product directly to the benzylation procedure. This gave 7-benzyloxyheptanoic acid (44) in an overall yield of 81%.

2.1.2 Preparation of keto phosphonates 45 and 46

A Michael addition of methyl acetoacetate to either ethyl or methyl acrylate in the presence of a catalytic amount of sodium ethoxide at 95-100 °C resulted in the formation of keto ester \(52\) in 75-80% yield.\(^{57}\) In our initial approach, we planned to use hydroxy ester \(53\) as an intermediate for the synthesis of the keto phosphonate 45. Accordingly, \(52\) was decarboxylated under Krapcho conditions\(^{58}\) to produce ethyl 5-oxohexanoate in excellent yield followed by the low temperature reduction of the ketone with sodium borohydride. The sodium borohydride reduction\(^{59}\) proved to be rather sensitive to the reaction conditions. Good yields of methyl 5-
hydroxyhexanoate (53) could only be obtained if the reaction was quenched at low temperature with dilute HCl. Normal workup - acidification at room temperature - invariably led to cyclization of 53 affording 5-hexanolid (54) in 65% yield.

The phosphonate was introduced by reacting two equivalents of lithium dimethyl methylphosphonate with methyl 5-benzyloxyhexanoate (55). The crude reaction product was then hydrogenated in the presence of palladium on carbon to provide the desired 2-[(dimethylphosphono)methyl]-2-hydroxy-6-methyltetrahydropyran (45) in 70% yield. Spectroscopic analysis revealed that 45 existed in two isomeric forms with the cyclic phosphonate predominating. Integration of the C1 doublets in the 1H NMR spectrum of 45 at δ 2.15 ppm (cyclic form 45b) and δ 3.1 (acyclic form 45a) indicated an isomer ratio of 5.7:1. The predominance of the cyclic isomer allowed us to design a much simpler synthesis for compound 45. Treatment of the crude keto ester 52 with dilute H2SO4 led to the formation of 5-oxo-hexanoic acid (56) in 86% overall yield. The keto acid was then dissolved in water and reduced with sodium borohydride to afford, after acidic workup, 5-hexanolid (54).
The phosphonate 45 could then be obtained by reacting two equivalents of lithium dimethyl methylphosphonate with 5-hexanolid (54). Not surprisingly, this method led to the same equilibrium mixture of 45a and 45b as determined previously.

Since geminal dimethylation of 54 proved to be difficult, we decided to prepare lactone 57 by reduction of the known keto acid 58. Accordingly, reaction of 3-methyl-2-butanone with methyl vinyl ketone yielded 3,6,6-trimethyl-2-cyclohexenone (59), which was oxidatively cleaved in 80% yield to afford 2,2-dimethyl-5-oxohexanoic acid (58). The method used for the
cleavage of $5_9$ was recently published by Cella.\textsuperscript{56} As previously mentioned, large scale ozonolysis can be hazardous if the ozonides accumulate in the system or are incompletely destroyed during the workup. Cella has developed a two-phase procedure which uses aqueous hydroperoxide in conjunction with a phase transfer catalyst to continuously decompose the hazardous ozonide during the reaction.

Reduction of the keto acid $5_9$ followed by acidic workup led to the formation of 2,2-dimethyl-5-hexanolide ($5_7$) in 83% yield. The phosphonate could then be introduced following the above protocol to afford 2-[(dimethylphosphonoo)methyl]-2-hydroxy-3,3,6-trimethyltetrahydropyran ($4_6$).
2.1.3 Preparation of macrolides 42 and 43

Initial attempts to condense\(^7\)-benzyloxyheptanoic acid (44) and 2-[(dimethylphosphono)methyl]-2-hydroxy-6-methyltetrahydropyran (45) using DCC and DMAP in methylene chloride afforded [6'-((dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-benzyloxyheptanoate (60) in only 25% yield.

![Chemical structure](image)

A major by-product was isolated and identified as compound 61. The formation of this compound was rather surprising since we had expected that the hydroxyl group in 45b would react very slowly and therefore allow preferential formation of 60. However, Neises and Steglich\(^62\) have shown that even sterically hindered esters are readily formed under these reaction conditions.

![Chemical structure](image)

61
To solve this problem we investigated the use of a more polar solvent for the esterification reaction. The phosphonate 46 exists almost exclusively as 46b in deuterochloroform (Figure 20). When 46 was dissolved in dimethyl sulfoxide-d6 a 1:1 mixture of cyclic form 46b and hydroxy ketone 46a was obtained (Figure 20).

Figure 20. $^1$H NMR (400 MHz) spectrum of 46 in CDCl3 (upper) and DMSO-d6 (lower).
Dimethyl sulfoxide is not suitable as a solvent for this esterification reaction, since it would lead to oxidation of the secondary hydroxyl group. However, the use of DMF had previously been reported for the esterification of very polar carboxylic acids. When 44 and 45 were dissolved in DMF and treated with DCC and a catalytic amount of DMAP, 63% of the desired ester 60 was obtained. Further optimization of the reaction conditions (see Experimental) eventually provided 60 in yields of 80-85% reproducibly. The same procedure was used for the coupling of compounds 44 and 46 to provide [4',4'-dimethyl-6'-(dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-benzyloxyheptanoate (62) in 51% yield.

Deprotection of the terminal alcohol in 60 and 62 was accomplished using standard hydrogenolysis conditions.

![Chemical Structures](image)

Surprisingly, the attempted oxidation of alcohol 63 with a DMSO-acetic anhydride mixture led to the exclusive formation of compound 64. Methylthiomethyl ethers, which are formed by nucleophilic attack of the alcohol 63 on sulfonium salt 65, are common side
products in DMSO-acetic anhydride oxidations;\textsuperscript{63,64} however, the exclusive formation of \textbf{64} under these reaction conditions was unexpected.

\[
\begin{align*}
\text{S} & \quad \text{O} \\
\text{O} & \quad \text{C} \quad \text{O} \\
\text{PO(OMe)2} & \quad \\
\end{align*}
\]

\textbf{64}

\[
\begin{align*}
\text{S} & \quad \text{=} \\
\text{+} & \\
\end{align*}
\]

\textbf{65}

An alternative procedure for the oxidation of alcohols uses DCC as a substitute for the acetic anhydride. This closely related Moffatt oxidation\textsuperscript{64} has been widely used in organic chemistry and proven to be simple and reliable. Indeed, when \textbf{63} was treated with DCC and dichloroacetic acid in DMSO, a 73\% yield of the desired aldehyde \textbf{66} was produced. Methylthiomethyl ether \textbf{64} was still a major by-product, accounting for 20\% of the products.

\[
\begin{align*}
\text{HO} & \quad \text{C} \quad \text{O} \\
\text{O} & \quad \text{C} \quad \text{O} \\
\text{PO(OMe)2} & \quad \\
\end{align*}
\]

\textbf{63} \quad R = \text{H} \\
\textbf{70} \quad R = \text{CH\textsubscript{3}}

\[
\begin{align*}
\text{DMSO, DCC, Cl\textsubscript{2}CHCO\textsubscript{2}H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{C} \quad \text{O} \\
\text{O} & \quad \text{C} \quad \text{O} \\
\text{PO(OMe)2} & \quad \\
\end{align*}
\]

\textbf{66} \quad R = \text{H} \\
\textbf{71} \quad R = \text{CH\textsubscript{3}}
A third method was explored to further improve the yield of this oxidation. The Swern oxidation\textsuperscript{65} has recently become a preferred method for the oxidation of hydroxyl groups, due to the easy workup and the consistently higher yields compared to the Moffatt oxidation. However, when \(6'-(\text{dimethylphosphono})-1\'-\text{methyl}-5'\'-\text{oxohexyl}\)-7-hydroxyheptanoate (63) was treated with oxalyl chloride, DMSO and triethylamine, the desired aldehyde \(6_6\) was isolated in only 17% yield, accompanied by an unknown by-product. This product contained two chlorine atoms and an aldehyde functionality while the \(^1\)H NMR spectrum clearly showed that the protons at \(C_6\) were lost. Using this data, we proposed structure 67 for this unexpected reaction product. Dow and Evans\textsuperscript{66} observed the formation of a dichloro ketone 69 during the Swern oxidation of model compound 68.

![Chemical structure 67](image)

Very recently, Smith et al.\textsuperscript{67} have reported that the Swern oxidation of alcohols can lead to the formation of \(\alpha\)-chloro ketones. The source of the positive chlorine which can react with the enol is thought to be the initially formed complex between DMSO and oxalyl chloride or one of its decomposition products. Since previous work in our laboratory had suggested that chromium based reagents generally oxidize very polar alcohols in only moderate yields, we
decided to use the Moffatt oxidation for the synthesis of 42 and 43. Treatment of alcohol 70 with DCC and dichloroacetic acid in DMSO afforded the aldehyde 71 in 77% yield. Both 66 and 71 proved to be unstable and, therefore, were immediately converted to the corresponding macrolides.

Intramolecular Wadsworth-Emmons reaction of aldehyde 66 smoothly provided a 15:1 mixture of (7E)-9-oxo-7-tetradecen-13-olide (72) and the corresponding Z isomer 73. The yield was consistently in the 63-70% range, which is very satisfactory for such a macrocyclic cyclization. The large amount of crown ether required for an efficient cyclization is a slight drawback. Nicolaou and co-workers\(^5\) used 12 equivalents of 18-crown-6 for the formation of the 16-membered ring in their O-mycinosyltylonolide synthesis. Our results showed that a reasonable compromise between yield and reaction time could be reached by using six equivalents of the expensive crown ether.

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{PO(OMe)}_2 \\
\end{align*}
\]

\(66\)

\[\text{K}_2\text{CO}_3, 18\text{-crown-6}\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\(73\)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\(72\)
Similarly, (7E)-10,10-dimethyl-7-tetradecen-13-olide (74) was obtained in 64% yield by treating aldehyde 71 with finely pulverized potassium carbonate and 18-crown-6 in toluene. The E isomer of 74 was formed exclusively in this cyclization.

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{P} & \quad \text{O} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{K}_2\text{CO}_3, \ 18\text{-crown-6}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{K}_2\text{CO}_3, \ 18\text{-crown-6}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2 & \quad \text{Pd/C}
\end{align*}
\]

Hydrogenation of the \(\alpha,\beta\)-unsaturated ketones afforded the macrolides 42 and 43.
2.2 CONFORMATIONAL ANALYSIS OF 14-MEMBERED MACROLIDES

2.2.1 Conformational analysis of cyclotetradecane

Still and co-workers have developed a computer program (MACROMODEL), which greatly simplifies the conformational analysis of medium and large ring systems. This program attempts to generate all possible conformations of a medium or large ring by random variation of torsional angles in an acyclic molecule that is generated by breaking a bond in the desired macrocycle. The conformations with chain endings within a certain closure distance are then subjected to MM2 calculations. Unfortunately, the computer time required to generate and minimize thousands of conformations was not available, and we therefore chose a different approach to this problem.

Dale's conformational analysis of cyclotetradecane has already been discussed. His calculations showed that the [3434], [3344] and [3335] were the three lowest energy conformations for a 14-membered ring (Figure 21). However, we were uncertain whether these strain energies calculated over ten years ago were reliable and especially whether these three conformations would be sufficient to account for the stereoselectivities in our macrolides. We therefore decided to undertake a detailed conformational analysis of cyclotetradecane.
Figure 21. Dale's three lowest energy conformations of cyclotetradecane and calculated relative strain energies.26

Saunders68 used a ring-building computer program to determine that thirteen diamond lattice conformations are theoretically possible for cyclotetradecane. At this point the conformational analysis of our macrolides seemed to be overwhelmingly complex since one had to consider at least fifteen different conformations (including the two non-diamond lattice [3344] and [3335] conformations) for every molecule. Unfortunately, Saunders did not provide the structures of the thirteen diamond lattice conformations and we were forced to exhaustively construct each of the conformations with molecular models. The fifteen different arrangements of atoms for cyclotetradecane were then subjected to MM2 calculations30 to determine the relative strain energy for each conformation (Figure 22).

As expected most diamond lattice conformations possessed severe transannular interactions and had therefore significantly higher strain energies than the lowest energy [3434] conformation. Unfortunately Dale's nomenclature system cannot be applied to most of these conformations, so that we turned to an arbitrary naming system for the more exotic diamond lattice conformations (Ogura had previously proposed this approach for conformations B, C and D).41 It was anticipated that the intrinsically high strain energy of most of these conformations would make them unimportant for the conformational analysis of 14-membered rings.
2.2.2 Polar maps

During the initial stages of our work, the identification of conformations was very
difficult and time consuming. To illustrate this problem, consider 75 and 76 which are ORTEP
diagrams of two related macrolides. It is very difficult to decide from these diagrams if the two
conformations are related or indeed in which of the many possible conformations these two
molecules exist. Originally, we used a set of molecular models to solve this problem; however, this procedure was very tedious and prone to error.

This task was greatly simplified by using polar maps. Polar maps are circular graphs which plot the magnitude and sign of the endocyclic dihedral angles of a cyclic molecule versus the bond number (Figure 23). Since the dihedral angles uniquely determine the three-dimensional structure of a molecule, a polar map will lead to a characteristic pattern for each.
conformation. The concentric circles represent the dihedral angles which for convenience show only the circles for dihedral angles of 0°, ±60°, ±120° and ±180°.

Ogura introduced the use of polar maps during his work on the solid state conformation of oleandomycin. This simple tool proved to be very useful for depicting the three-dimensional structure of several macrolides, and Ogura eventually reported a compilation of polar maps for several 14-membered diamond lattice conformations. Even though polar maps have great potential in the conformational analysis of medium and large rings, researchers have not readily accepted this method to represent the three-dimensional structure of a molecule.

The usefulness of polar maps is somewhat limited by Ogura’s procedure to describe dihedral angles. Ogura’s polar maps utilize the smallest dihedral angle within the ring and this automatically determines the sign. However, as dihedral angles approach 180° this procedure to determine the sign of a dihedral angle becomes quite arbitrary.

![Figure 24. The ambiguity arising for anti dihedral angles.](image)

This can lead to a situation where the polar maps of identical conformations may be generated which bear little resemblance to each other. For example, compounds 75 and 76 crystallized in the same conformation, but the patterns of dihedral angles (taken from the X-ray crystallographic analysis) for the two molecules look very different.
To resolve this difficulty in determining the signs of the anti dihedral angles in cyclic systems, we propose that only the endocyclic anti dihedral angles be used for the generation of the polar map (Figure 25).69

![Diagram of anti dihedral angles](image)

*Figure 25. Rule for determining the sign of the anti dihedral angle.*

Since MM2 programs or X-ray crystallographic data report dihedral angles which are less than or equal to 180° only, complications arose when we attempted to apply this rule. Some of the resulting torsional angles were greater than 180° and could not be used for the construction of a polar map. This problem can be solved by simply reversing the sign of the angle derived from the X-ray/MM2 data and plotting this value instead. We realize that this introduces a slight error in the plotted dihedral angle, e.g. a value of -175° formed outside the ring becomes for convenience +175 when in fact it should be +185°. However this approximation permits the quick generation of a polar map and produces a characteristic pattern for each conformation.
If these two rules are applied to the macrolides 75 and 76, two similar polar maps are produced which prove that both molecules crystallized in almost identical [3434] conformations.

The polar maps for the five lowest energy conformations of cyclotetradecane are shown in Figure 26. This analysis should greatly facilitate the identification of different conformations.
Figure 26. Polar maps for the five lowest energy conformations of cyclotetradecane.
2.2.3 The corner and pseudo corner positions

A polar map can also be used to quickly locate the corner positions of a conformation by recognizing its characteristic sequence of dihedral angles. As discussed previously, the corner position was initially defined as an atom having two contiguous gauche dihedral angles each followed by an anti dihedral angle. By studying our polar maps we noticed that, for example, the polar map of the C conformation (Figure 27) contains two different types of atoms that satisfy this definition. The classical corner atom, which was recognized in 1973 by Dale, is flanked by two gauche angles of the same sign (e.g. 180, +60, +60, 180). A second possible corner position (pseudo corner) has the two gauche angles with different signs (e.g. 180, -60, +60, 180). Later we found that Dale had observed the pseudo corner in the crystal structures of 1,4,8,11-tetraoxacyclotetradecane; however, this arrangement of atoms was only thought to be possible due to a stabilizing 1,4-interaction between the ether oxygens and hydrogen atoms.

![Figure 27. Comparison of the two corner positions within the C conformation of cyclotetradecane.](image)

If the previously discussed convention (Chapter 2.2.2) to determine the sign of the anti dihedral angles is used, one can extend the definitions for the corner and the pseudo corner positions (Figure 28):

1. A corner position has two contiguous gauche angles of equal sign followed on each side by an anti dihedral angle with the opposite sign (e.g. -180°, +60°, +60°, -180°).
2. A pseudo corner atom is defined as having an anti-gauche-gauche-anti arrangement with alternating signs (e.g. -180°, +60°, -60°, +180°).

![Figure 28. The corner (above) and pseudo corner position (below).](image)

As discussed in the introduction, the corner position can accommodate a geminally substituted atom with the least amount of steric crowding within the macrolide. Using MM2 calculations, we investigated the effect of geminal methyl substitution on these two types of corner positions and compared the results with substitution at a non-corner position. Calculations on both the C and D conformations show that geminal substitution of the corner to be of lowest energy, followed by substitution at the pseudo corner. Geminal substitution at a pseudo corner introduces one additional 1,3 diaxial interaction (0.6 kcal/mol) compared to a corner position. Predictably, geminal substitution of the non-corner position was a high energy situation and disfavored. Therefore, in geminally substituted systems, the quaternary carbon atom should greatly favour the corner position over a non corner position. This result agrees
with Dale's qualitative prediction. However, if the corner position cannot be geminally substituted, for whatever reasons, then geminal substitution at the pseudo corner position should be the next lowest energy situation.

2.2.4 The lactone linkage

The previously discussed calculations (Figure 22) should considerably simplify the conformational analysis of our macrolides. A further reduction in the number of conformations to be considered should be possible, since the key functionality in our molecules is a lactone group.

It is well known that the s-trans geometry of esters is more stable than the corresponding s-cis arrangement. Deslongchamps has estimated the energy difference between the two ester conformations to be 3.0 kcal/mol, which explains why open chain esters occur in the s-trans form.

Since the 14-membered ring is large enough to easily accommodate an s-trans lactone functionality, any conformation containing an s-cis lactone can therefore be discounted in our conformational analysis. Furthermore, Dunitz and Schweizer have studied the conformational preferences of carboxylic esters with particular emphasis on the conformations of the substituents attached to the ether oxygen. The experimental information, which was taken from the Cambridge Structural Database, and included 1750 compounds with a C-CO-O-C fragment, showed that esters of secondary alcohols invariably contain a C-O-C-H dihedral angle in the range of 0-60°, and in over 85% of the cases the angle is in the range of 0-40°.
We felt fairly confident that this trend could be applied to simple lactones of secondary alcohols and therefore help to limit the number of conformations that have to be calculated. As an example, applying these restrictions we would only have to consider the following three [3434] conformations for 13-tetradecanolide (Figure 29).

![Conformations of 13-tetradecanolide](image)

**Figure 29.** The three possible substitution patterns for 13-tetradecanolide with an s-trans lactone geometry and a C-O-C-H dihedral angle of less than 60°.

2.3 THE SOLID STATE CONFORMATIONS OF COMPOUNDS 42, 43, 72 and 74

One of the most commonly used methods for the conformational analysis of macrocycles involves the determination of solid state structures. The complexity of $^1$H NMR spectra and the limited amount of information that can be obtained from other spectroscopic methods have made X-ray crystallography the method of choice for the determination of conformational preferences in macrolides (Chapter 1.4).

One might contend that structures observed in the crystalline lattice do not necessarily represent low energy conformations; however, Dunitz has concluded that "any conformation
observed in a molecular crystal cannot be far from an equilibrium structure of the isolated molecule. X-ray analysis thus provides information about the preferred conformations of molecules although it has nothing to say about the energy differences between them. "

To aid in the conformational analysis of our macrolides, the X-ray crystal structures of compounds 42, 43, 72 and 74 were determined. We were interested in determining whether the conformational preferences calculated by Dale could be applied to our modestly substituted lactones. Furthermore, this was an opportunity to investigate if the Schweizer-Dunitz observation can be extended to lactones, namely that in s-trans lactones of secondary alcohols the C-O-C-H angle is limited to 0-40°, and to test the suggestion that substituents will prefer to be outside the ring and geminally substituted carbon atoms will occur only at corner positions.

The stereodiagrams for the four macrocyclic ketones are shown in Figure 30. The conformational assignments proved to be very easy, since with the help of polar maps (Table II), all molecules could be unambiguously assigned to one of the five conformational groups shown in Figure 26.
Figure 30. Stereodiagrams for the crystal structures of macroolides 42, 43, 72 and 74.
Table II. The solid state conformations of macrolides 42, 43, 72 and 74

<table>
<thead>
<tr>
<th>Macrolide</th>
<th>Side view</th>
<th>Polar map</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td><img src="image" alt="Side View" /></td>
<td><img src="image" alt="Polar Map" /></td>
<td>[3434]$^*$</td>
</tr>
<tr>
<td>43</td>
<td><img src="image" alt="Side View" /></td>
<td><img src="image" alt="Polar Map" /></td>
<td>[3344]</td>
</tr>
<tr>
<td>74a</td>
<td><img src="image" alt="Side View" /></td>
<td><img src="image" alt="Polar Map" /></td>
<td>[3434]$^*$</td>
</tr>
<tr>
<td>74b</td>
<td><img src="image" alt="Side View" /></td>
<td><img src="image" alt="Polar Map" /></td>
<td>[3335]</td>
</tr>
<tr>
<td>72</td>
<td><img src="image" alt="Side View" /></td>
<td><img src="image" alt="Polar Map" /></td>
<td>[C]$^*$</td>
</tr>
</tbody>
</table>

* Diamond lattice conformation
The variety of observed conformations was somewhat surprising, since Dale's calculations had suggested that substituted 14-membered rings prefer to exist in the strain-free [3434] diamond lattice conformation. It was uncertain at this point whether the presence of a [3344], [3335] and especially the [C] conformation implied that our compounds had crystallized in high energy conformations, or rather, that the conformational analysis of these macrolides was more complex than expected. 10,10-Dimethyl-9-oxo-13-tetradecanolide (43) was found to be conformationally disordered, crystallizing in both [3434] and [3335] conformations.

Not unexpectedly, the geometry of the lactone linkage was s-trans in every molecule. In addition, the C-O-C-H dihedral angles were consistently within the 0-40° range (Appendix II) reported for the open chain esters.73

Weak C-H···O interactions involving the carbonyl oxygen atom may be at least partially responsible for the stability of this particular conformation of the lactone linkage. Details of the geometry of these interactions in compounds 42, 43, 72 and 74 are summarized in Appendix II.

In structures 43 and 74, the geminal methyls were found to occupy the corner positions, and these compounds represent one of the first examples confirming Dale's prediction that geminally substituted carbon atoms would occupy a corner position.

2.4 LOW ENERGY CONFORMATIONS OF MACROLIDES 42, 43, 72 AND 74

It is well known that minimum energy geometries found by molecular mechanics calculations depend largely on the starting conformation of the molecule (local minimum problem).30 This means that if there is more than one potential energy well for a molecule, a systematic study of all feasible structures has to be carried out to determine the global minimum conformation of a particular molecule.

Since we were interested in determining the lowest energy conformations, we subjected our macrolides to a detailed conformational analysis using MM2 and for the unsaturated ketones
MMP2 calculations. This would also provide some insight into whether our macrolides had crystallized in low energy conformations.

Because of the high inherent strain energy of most conformations, we decided to focus on the five structures in Figure 26. To avoid any bias towards the X-ray crystal structures, we used the coordinates of the carbon skeletons in Figure 26 as starting points with the appropriate functional groups and substituents. To reduce the number of calculations required, the previously discussed criteria were used:

1. Substituents should occupy only exterior positions on the macrolide.
2. Quaternary carbon atoms must occupy a corner position or if unavailable a pseudo corner position.
3. The lactone linkage must have the s-trans geometry.
4. The C-O-C-H dihedral angle is restricted to a 0-60° range.

The three lowest energy conformations for macrolide 42 are shown in Table III. Surprisingly, the global minimum is a [3344] conformation followed by the expected low energy [3434] structures. As expected, the conformational analysis of this particular macrolide was very complex, with seven conformations within 1.8 kcal/mol of the global minimum. An investigation of the $^1$H NMR spectrum of 42 shows that the coupling constants are all in the neighborhood of 6 and 7 Hz which is indicative of a conformationally mobile system. Egan et al. had shown that extreme values for vicinal coupling constants (10-12 Hz and 0-2 Hz) are indicative of macrolides which occur largely in one conformation, while in conformationally mobile ring systems the coupling constants are time averaged to intermediate values. Dunitz has suggested that X-ray analysis provides information about the low energy conformations of molecules. Indeed macrolide 42 crystallized in a conformation only 1 kcal/mol removed from the global minimum with all dihedral angles practically identical to those obtained from the MM2 calculation.
Table III. The three lowest energy conformations of 42

<table>
<thead>
<tr>
<th>Low Energy Conformations</th>
<th>Solid State Structure</th>
<th>Strain Energy*</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>42a</td>
<td>![42a diagram]</td>
<td>0 kcal/mol</td>
<td>[3344]</td>
</tr>
<tr>
<td>42b</td>
<td>![42b diagram]</td>
<td>1.0 kcal/mol</td>
<td>[3434]*</td>
</tr>
<tr>
<td>42c</td>
<td>![42c diagram]</td>
<td>1.3 kcal/mol</td>
<td>[3434]*</td>
</tr>
</tbody>
</table>

* Strain energy is reported relative to the lowest energy conformation.
* Diamond lattice conformation.

At first glance, the introduction of a geminal methyl group at C10 does not lead to a much simpler conformational behavior of 43 (Table IV). However, an inspection of the polar maps of 43a-43c reveals an interesting similarity. In contrast to 42a and 42c, for example, which contain functional groups in completely different steric environments, all three conformations 43a-43c share the same local conformation 77. While this relationship can be established using molecular models, polar maps are much more convenient, since sequences of dihedral angles common to all conformations can easily be identified (Figure 31).
### Table IV. The three lowest energy conformations of 43

<table>
<thead>
<tr>
<th>Low Energy Conformations</th>
<th>Solid State Structure</th>
<th>Strain Energy$^a$</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>43a</td>
<td><img src="image" alt="43a Structure" /></td>
<td>0 kcal/mol</td>
<td>[3344]</td>
</tr>
<tr>
<td>43b</td>
<td><img src="image" alt="43b Structure" /></td>
<td>1.0 kcal/mol</td>
<td>[3434]*</td>
</tr>
<tr>
<td>43c</td>
<td><img src="image" alt="43c Structure" /></td>
<td>1.5 kcal/mol</td>
<td>[3344]</td>
</tr>
</tbody>
</table>

$^a$ Strain energy is reported relative to the lowest energy conformation.

$^*$ Diamond lattice conformation.

**Figure 31.** The local conformation common to the three lowest energy conformations of 43.
As in the case of macrolide 42, the lowest energy conformation of 10,10-dimethyl-9-oxo-13-tetradecanolide (43) is a [3344] conformation, which is 1 kcal/mol lower in energy than the [3434] conformation 43b. Conformation 43b would have been expected to exhibit the lowest energy following Dale's work on cyclotetradecane. Again X-ray crystallographic analysis proved to be a very useful tool for finding low energy conformations, in this case actually providing the global minimum structure.

Ogura had found (Chapter 1.4) that macrolides containing \(\alpha,\beta\)-unsaturated ketones show different conformational preferences from saturated ketones. We observed the same trends, namely that the [3434] and the [3344] conformations become less important relative to the [3335] and [C] conformations (Table V). The presence of a double bond in these molecules presumably removes unfavorable transannular interactions, thereby lowering the strain energy of the [C]

<table>
<thead>
<tr>
<th>Low Energy Conformations</th>
<th>Solid State Structure</th>
<th>Strain Energy*</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>72a</td>
<td><img src="image" alt="72a" /></td>
<td>0 kcal/mol</td>
<td>[3335]</td>
</tr>
<tr>
<td>72b</td>
<td><img src="image" alt="72b" /></td>
<td>0.1 kcal/mol</td>
<td>[twist]</td>
</tr>
<tr>
<td>72c</td>
<td><img src="image" alt="72c" /></td>
<td>0.7 kcal/mol</td>
<td>[C]*</td>
</tr>
</tbody>
</table>

* Strain energy is reported relative to the lowest energy conformation.

* Diamond lattice conformation.
and [3335] conformers. The unsaturated macrolide 72 has six conformations within 1.5 kcal/mol of the global minimum [3335] conformation 72a, including conformations with the s-cis (e.g. 72a) or the s-trans (e.g. 72c) enone geometry. The IR spectrum of 72 in chloroform solution suggests the presence of more than one conformer. Instead of the expected three absorptions for the two carbonyl groups and the double bond, the solution spectrum contains four bands between 1600 and 1730 cm\(^{-1}\) (Figure 32). Since Fermi resonance can be excluded (no band at half the wavenumber), and the IR spectrum in the solid state (C conformation) exhibits the expected three absorptions (Figure 32), we would suggest that the additional signal must stem from a second conformation present in solution. During his investigation of dimethylated cyclohexadecanes, Dale had observed a difference between the IR spectra in solution and in the solid state and concluded that the complexity in the solution spectrum was also caused by a mixture of conformers.75

![Figure 32. The solution and solid state IR of macrolide 72.](image-url)
Again the introduction of two methyl groups at C10 leads to a simplification of the conformational picture, with all conformers of 74 within 5 kcal/mol of the global minimum structure sharing a similar local conformation 78 (Table VI).

Table VI. The three lowest energy conformation of 74

<table>
<thead>
<tr>
<th>Low Energy Conformations</th>
<th>Solid State Structure</th>
<th>Strain Energy*</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>74a</td>
<td></td>
<td>0 kcal/mol</td>
<td>[3335]</td>
</tr>
<tr>
<td>74b</td>
<td></td>
<td>0.5 kcal/mol</td>
<td>[twist]</td>
</tr>
<tr>
<td>74c</td>
<td></td>
<td>1.0 kcal/mol</td>
<td>[3434]*</td>
</tr>
</tbody>
</table>

* Strain energy is reported relative to the lowest energy conformation.
* Diamond lattice conformation.

It is important to point out that, even though the MM2 calculations indicate that the crystal structures may not always correspond to the lowest energy conformation, our results show that X-ray crystallography is very useful in finding low energy structures. In all four cases, the solid
state structure was one of the three lowest energy conformers - never more than 1 kcal/mol above the global minimum. Even when two conformations co-crystallized in the unit cell, as seen in macrolide 74, both conformations were within 1.0 kcal/mol of the global minimum conformation.

2.5 DIASTEREOSELECTIVE REDUCTION OF (7E)-9-OXO-7-TETRADECEN-13-OLIDE (72) AND (7E)-10,10-DIMETHYL-9-OXO-7-TETRADECEN-13-OLIDE (74)

Reduction of 72 with sodium borohydride in the presence of cerium chloride\(^7\) at -78°C afforded a 63:37 mixture of two diastereomeric alcohols 79 and 80 of undetermined stereochemistry. Initially the separation of the two diastereoisomers by gas chromatography was unsuccessful. This problem was overcome by reacting the crude mixture of the two alcohols 79 and 80 with trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine. The resulting trimethylsilyl ethers 81 and 82 could then easily be separated either by gas chromatography or flash column chromatography. If desired, the alcohols could be liberated by treating the trimethylsilyl ethers with tetrabutylammonium fluoride followed by standard workup. Unfortunately all attempts to crystallize the two diastereomeric alcohols were unsuccessful.

![Diagram](https://via.placeholder.com/150)
Hydrogenation of an 86:14 mixture of 79 and 80 in the presence of palladium on charcoal produced a mixture of two diastereomeric alcohols which upon chromatography afforded the samples of pure 9-hydroxy-13-tetradecanolides 83 and 84. The minor isomer 84 crystallized as platelets suitable for structure determination.

\[ \begin{align*}
79 : 80 \\
(86 : 14)
\end{align*} \]

\[ \begin{align*}
83 & \quad 9R^*,13S^* \\
& \quad 86 \% \\
84 & \quad 9S^*,13S^* \\
& \quad 14 \%
\end{align*} \]

X-ray crystallographic analysis revealed the relative stereochemistry of the two substituents in 84 as 9S*,13S* (Figure 33). Therefore, the minor isomer of the allylic alcohols had the 9R*,13S* configuration as shown in 80. The asterisk indicates that both enantiomers are present in the compound.

\[ \text{Figure 33. The X-ray crystal structure of macrolide 84.} \]
The diastereoselectivity of the sodium borohydride reduction was disappointing, leading only to a small predominance of the 9S*,13S* isomer. Therefore we turned our attention to reducing agents that promised higher stereoselectivities.

Treatment of 72 with lithium tri-(tert-butoxy)aluminium hydride\textsuperscript{77} at -50 °C for 3 hours did not produce any allylic alcohol. If the temperature was raised to -25 °C, slow reduction occurred, leading to a 63:37 mixture of 79 and 80. We also decided to investigate the use of the bulky Selectride reducing agents which have been widely used for the stereoselective reductions of ketones.\textsuperscript{78} There was, however, a potential pitfall since these reducing agents are known to give either 1,2- or 1,4-reduction of α,β-unsaturated ketones depending on the steric environment of the enone.\textsuperscript{79}

Reaction of 72 with K-Selectride (potassium tri-sec-butylborohydride) in tetrahydrofuran at -78 °C led to smooth 1,2 reduction in 93% yield. The crude alcohols were converted into their trimethylsilyl ethers and analyzed by capillary gas chromatography. The diastereoselectivity had improved providing 79 and 80 in an 83:17 ratio.

L-Selectride (lithium tri-sec-butylborohydride) led to a mixture of 1,2 and 1,4 reduction products in which only 44% of macrolides 79 and 80 were isolated together with 53% of the saturated ketone 42. Again the reduction of the ketone proceeded with respectable selectivity, leading to a 86:14 mixture of diastereomeric allylic alcohols 79 and 80.

The even bulkier LS-Selectride (lithium trisiamylborohydride) gave the best results, reducing (7E)-9-oxo-7-tetradecen-13-olide (72) in 89:11 selectivity and 76% yield. A summary of the reduction results for macrolide 72 is given in Table VII. Surprisingly, with this last reagent, conjugate reduction only occurred as a minor side reaction, accounting for 10% of the reaction products. The reason for the varying amounts of conjugate reduction products provided by the three Selectride reducing agents is unknown.
Table VII. Reduction of (7E)-9-oxo-7-tetradecen-13-olide (72) with various reducing agents

<table>
<thead>
<tr>
<th>Reducing reagents</th>
<th>Temperature</th>
<th>Stereoselectivity</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$S^<em>S^</em>$</td>
<td>$S^<em>R^</em>$</td>
</tr>
<tr>
<td>NaBH₄, CeCl₃</td>
<td>0 °C</td>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>Li(t-BuO)₂AlH</td>
<td>-25 °C</td>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>K-Selectride</td>
<td>-78 °C</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>-78 °C</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>LS-Selectride</td>
<td>-78 °C</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td>Predicted selectivity (MM2)</td>
<td>-78 °C</td>
<td>94</td>
<td>6</td>
</tr>
</tbody>
</table>

To rationalize these interesting results, we carried out an examination of the low energy conformations of the starting material and products. It is apparent (Figure 34) that the predominant formation of 79 cannot be adequately explained using the strain energies of the allylic alcohols, since the two lowest energy conformations of 79 (79a and 80a respectively) have strain energies separated by only 0.1 kcal/mol. This is not surprising, since Wu et al.⁸⁰ have demonstrated that only early transition states can satisfactorily account for the selectivities observed in nucleophilic additions to cyclohexenones.

Still and co-workers⁹⁸ have demonstrated (Chapter 1.3) that reagents approach the π-system of a macrocyclic compound largely or perhaps exclusively from the peripheral face. This can be expected to occur selectively in conformations 72a and 72b (Figure 34), since the carbonyl group is perpendicular to the plane of the macrocyclic ring and therefore the re face of the carbonyl group in 72a and 72b is blocked by the carbon atoms in the macrocyclic ring. A complication arises because conformation 72c has the ketone in a corner position where attack from both faces is allowed. In fact, the steric environments of the si and the re faces in 72c are almost identical, so that 72c presumably would give rise to an equal mixture of diastereoisomers.
However, peripheral attack on the local conformation common to 72a and 72b clearly should produce the 9S*,13S* allylic alcohol 79 predominantly.

**Figure 34.** Conformation of 72 and the corresponding reduction products.
In addition, Still and co-workers\textsuperscript{28} have used Boltzmann distributions of the relevant conformations to predict the selectivity of a reaction. This approach is more complicated for the 14-membered macrolides under consideration, since it is difficult to estimate the reactivity of conformations with the ketone group in a corner position (e.g. 72c). However, an attempt was made to apply Still’s approach to our macrolides.

Using the calculated steric energies (Figure 34) of 72a, 72b and 72c, the Boltzmann distribution at -78 °C was calculated. The ratio of the three conformations 72a:72b:72c is 50:39:11 which, if exclusive peripheral attack is assumed for 72a and 72b, leads to a predicted selectivity of approximately (9S*,13S*):(9R*,13S*) = 94:6.

This is in surprisingly good agreement with the diastereoselectivity observed in the reduction with LS-Selectride. Since the ratio between allylic alcohols 79 and 80 seems to be strongly dependent on the steric demand of the reducing agents, the concept of exclusive peripheral attack on conformations 72a and 72b by small reducing agents should be reevaluated. We conclude that sodium borohydride poorly distinguishes between the re and the si face of 72a and 72b, while more bulky reducing agents like LS-Selectride react almost exclusively at the peripheral si face of those two low energy conformations.

Unfortunately, treatment of 74 with the Selectride reducing agents followed by work up with a mixture of chlorotrimethylsilane and triethylamine provided only trimethylsilyl enol ethers (vide infra). This limited our investigation of 1,2-reductions to the sodium borohydride/cerium chloride system which had been only moderately successful with 72. Even though it was suspected that sodium borohydride does not show good diastereofacial selectivity in 14-membered macrolides, we anticipated that the conformational homogeneity of 74 would lead to an improved selectivity in the reduction reaction. Indeed, when 74 was treated with sodium borohydride and cerium chloride, an 87:13 mixture of alcohols 85 and 86 was produced.
To establish the relative stereochemistry at the two chiral centers, the two isomers were separated by column chromatography. While the minor isomer remained as an oil, the major alcohol 85 could be crystallized for X-ray analysis. Figure 35 shows the ORTEP-diagram for macrolide 85 which shows that the major alcohol was formed with the 9R*,13S* stereochemistry.

The conformational analysis of 74 is straightforward since all conformations within 4 kcal/mol of the global minimum contain the same local conformation 78. The C conformation 74d which had been important for the conformational analysis of 72 is now 4.6 kcal/mol higher
in strain energy than the lowest energy [3335] conformation, due to transannular interactions introduced by the two substituents at C_{10}. Peripheral attack of a reducing agent on 78 should lead predominantly to (9R^{*},13S^{*})-(7E)-10,10-dimethyl-9-hydroxy-7-tetradecen-13-olide (85) in agreement with experimental results.

Even though the MM2 calculations again predict the relative stereochemistry of the major diastereomer in the reduction of 74, the stereoselectivity observed in this reduction is much lower than expected from the conformational analysis. This supports the earlier suggestion that sodium borohydride shows poor diastereofacial selectivity in the reduction of 14-membered macrolides.

2.6 REDUCTION OF 9-OXO-13-TETRADECANOLIDE (42) AND 10,10-DIMETHYL-9-OXO-13-TETRADECANOLIDE (43)

Treatment of 42 with sodium borohydride in methanol at -78 °C produced an equal mixture of the two diastereomeric alcohols 83 and 84 in 89% yield. The two compounds could be separated using column chromatography. As previously discussed, the relative stereochemistry of the two isomers was established by X-ray crystallography.
As before, the use of Selectride reducing agents led to improved stereoselectivities. Reduction of 42 with K-Selectride at -78 °C led to an 89% yield of 83 and 84 with 78:22 selectivity. Similar reductions with L-Selectride and LS-Selectride at -78 °C provided the two diastereomeric macrolides with still greater selectivity. Both reactions proceeded in over 85% yields furnishing 83 and 84 in a ratio of 89:11 and 90:10, respectively. If the temperature of the L-Selectride reduction was raised to 0 °C, the diastereoselectivity fell to 80:20. A summary of the results is presented in Table VIII.

![Chemical Structures](image)

Table VIII. Reduction of 9-oxo-13-tetradecanolide (42) with various reducing agents

<table>
<thead>
<tr>
<th>Reducing reagents</th>
<th>Temperature</th>
<th>Stereoselectivity</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>-78 °C</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>K-Selectride</td>
<td>-78 °C</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>0 °C</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>-78 °C</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td>LS-Selectride</td>
<td>-78 °C</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>Predicted selectivity (MM2)</td>
<td>-78 °C</td>
<td>94</td>
<td>6</td>
</tr>
</tbody>
</table>
The behavior of the three lowest energy conformations of 42 towards nucleophilic attack is outlined in Figure 36. As mentioned above these reactions do not appear to be governed by product strain energies. Compound 42 has three conformations 42c, 42d and 42e which have the keto carbonyl group in a corner position and hence could be attacked from either the re or si face (e.g. 42c in Figure 36). Nevertheless the two lowest energy conformations 42a and 42b should both lead to (9R*,13S*)-9-hydroxy-13-tetradecanolide (83) on peripheral attack, and a Boltzmann distribution at -78°C actually predicts a ratio of 94:6, in good agreement with the experimental result from the LS-Selectride reduction of 90:10.
Figure 36. Conformations of macrolide 42 and its reduction products.
The stereoselectivity of the sodium borohydride reduction of 43 once again proved to be unsatisfactory, yielding two alcohols with a 60:40 selectivity. When 43 was treated with L-Selectride at -78 °C, no reduction product could be isolated even after several hours reaction time. Indeed it was necessary to raise the temperature to 0 °C, before the reduction proceeded with an acceptable rate, yielding two diastereomeric alcohols in a ratio of 89:11.

\[
\begin{align*}
\text{43} & \quad \rightarrow \quad 87 \quad 89\% \\
& \quad + \quad 88 \quad 11\%
\end{align*}
\]

The relative stereochemistry of the minor isomer 88 was established by catalytic reduction of the previously prepared macrolide 86.

\[
\begin{align*}
\text{86} & \quad \xrightarrow{\text{H}_2/\text{Pd/C}} \quad \text{88}
\end{align*}
\]

The geminal dimethyl group in 43 destabilizes conformations with the carbonyl group in a corner position. The steric energies of these conformations is more than 4 kcal/mol above the global minimum structure. The local conformation that is common to all low energy
conformations is shown in Figure 37 and peripheral attack on the si face of the ketone should lead to formation of the (9R*,13S*)-10,10-dimethyl-9-hydroxy-13-tetradecanolide (87). The MM2 calculations therefore correctly predict the relative stereochemistry of the major isomer from the L-Selectride reduction.

![Diagram](diagram.png)

**Figure 37.** Peripheral hydride attack on the preferred local conformation of 42.

Although the observed selectivities fell short of the predicted values, it was gratifying to note that the reduction of 9-oxo-13-tetradecanolide (42) and 10,10-dimethyl-9-oxo-13-tetradecanolide (43) with suitable reducing agents proceeded with reasonable stereoselectivity, and with the predicted relative stereochemistry (MM2). The introduction of a geminal dimethyl group at C10 simplified the conformational analysis and, as expected, led to improved stereoselectivity. Sodium borohydride proved to be an unsuitable reducing agent for the stereoselective reductions of our simple 14-membered macrolides. Similar results that further support the hypothesis that sodium borohydride can reduce a carbonyl group from the inside of a tetradecanolide ring have been reported elsewhere. 82
2.7 X-RAY CRYSTALLOGRAPHIC ANALYSIS OF (9S*,13S*)-9-HYDROXY-13-TETRADECANOLIDE (84) AND (9R*,13S*)-(7E)-10,10-DIMETHYL-9-HYDROXY-7-TETRADECEN-13-OLIDE (85)

The crystal structures of alcohols 84 and 85 proved to be very interesting (Figure 38). It was encouraging to see that the solid state conformation of 84 supported the previously discussed assumptions, exhibiting an s-trans lactone linkage, a C-O-C-H dihedral angle of 6.5 °, and the hydroxyl group occupying an exterior position. However, hydroxy lactone 85 violated two of Dale's basic principles, namely that geminally disubstituted atoms can only occupy corner positions and that substituents pointing into the ring would cause severe transannular interactions.

Figure 38. Polar maps of the solid state conformations of macrolide 84 and 85
Furthermore, the polar maps (Figure 38) clearly show that both macrolides crystallized in conformations that are very different from the expected low energy conformations discussed previously (Figure 26).

Examination of the unit cell packing diagram revealed intermolecular hydrogen bonds between the carbonyl oxygens and the hydroxyl groups in both molecules. It is well known that hydrogen bonding can stabilize high energy conformations by several kcal/mol and we therefore suggest that both those solid state conformations are stabilized in the crystalline lattice by the intermolecular hydrogen bonds.

MM2 calculations suggest a rather high strain energy for the solid state conformation of 85. Comparison of the polar map of 85 with the polar maps of the higher energy conformations in Figure 22 identified the solid state structure of 85 as a B conformation (Figure 39). Note the ease in identifying these two conformations from a comparison of their polar maps. The carbon atoms of a B conformation fit on a diamond lattice; however, molecular mechanics calculations suggest that the high strain energy makes this conformation unimportant in solution or the gas phase.

![Figure 39. Polar map of diamond lattice conformation B.](image)

The B conformation has previously been proposed, to account for the spectroscopic data of erythronolide B; however, to the best of our knowledge, this is the first report of crystallographic data supporting the existence of this diamond lattice conformation.
The twisted solid state conformation of macrolide 84 turned out to be only 1.7 kcal/mol higher than the global minimum. Furthermore, a second macrolide 82 prepared in our laboratory also crystallized in a twist conformation and a comparison of the polar maps quickly showed the similarity of the two conformations. This similarity was not immediately apparent from the ORTEP diagrams and it illustrates the value of polar maps. This second example of a twist conformation also exhibited an intermolecular hydrogen bond.

During this work, Schreiber and Liew published the crystal structure of a 14-membered macrolide, (10E)-5,9-dimethoxy-6-oxo-10-tridecen-13-olide (90), and we also obtained unpublished crystallographic data on one of the intermediates 91 in the Woodward synthesis of erythromycin. From the ORTEP diagrams, we suspected that both macrolides crystallized in the same twist conformation as 84 and 89 and this was confirmed by a comparison of their polar maps. Recently Hauske et al. have reported the solid state conformation of an erythromycin derivative which we recognized as existing in the same twisted conformation. It is

![Diagram of compounds 84 and 90](image-url)
important to point out that without polar maps this conformational similarity would have been very difficult to detect. Having found several examples, we were curious to determine whether this new conformation might be a low energy conformation for cyclotetradecane.

The strain energy calculated for this new twist conformation of cyclotetradecane was only 3.4 kcal/mol higher than the [3434] structure. Indeed, if this value is compared to the strain energies of the other conformations in Figure 26, the twist conformation emerges as the fifth lowest energy conformation for a 14-membered ring, being lower in energy than all diamond lattice conformations except the [3434] and the D conformers.

Polar maps also revealed a very close resemblance of the dihedral angle pattern of the Perun conformation and the twist conformation (Figure 40). The only significant differences between the two polar maps occur around carbon-carbon bond 6. Since Egan et al. have reported that the aglycone ring of erythromycin is flexible between bond 5 and bond 8 depending on the nature and position of the ring substituents, it is interesting to speculate that the Perun conformation may be a slightly distorted twist conformation.
Initially, the newly discovered conformation was named the twist conformation, since it bore a resemblance to the twist-boat conformation of cyclohexane. Using Dale's naming system, the newly discovered twist conformation and Ogura's D conformation (Chapter 1.4) would both be designated as the [311] conformation. Note that these conformations are 3-11 conformations not 3-1-1 conformations. The sum of the numbers in the square brackets must equal the number of bonds in the ring.

Dale's system for naming conformations is based on the number of bonds between corner atoms, and is unable to describe a conformation adequately which has only one or two corner positions. Ogura recognized this and turned to an arbitrary system which designates each conformational type with a letter. However, the use of the A, B, C or D classifications for naming conformations is not a general one which could be applied to other ring systems. Ogura designated two of the 14-membered conformations as the C and D conformations which, under Dale's system, are classified as the [68] and [311] conformations, respectively. Neither of these designations is as informative as, for example, the [3434] conformation. A possible solution to
this problem, would be to include the pseudo corners in the analysis. 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 primed ones, i.e. the starting value should represent the smallest number of bonds between two corner atoms, if possible. Under this new nomenclature the C conformation would be renamed the [3'3'4'4'] conformation, the D the [34'7'] conformation, and the twist conformation is uniquely described as the [34'3'4'] conformation.

Even though the proposed nomenclature system appears complex at first, the combination of unprimed and primed numbers provides a more informative description of a conformation and still adheres to Dale's original proposal.
2.8 CONJUGATE REDUCTION OF MACROLIDES 72 AND 74

Several research groups have demonstrated that alkylations in macrocyclic systems usually proceed with very high stereoselectivity. In this reaction the enolate is formed by treating a ketone or lactone with an appropriate base, followed by trapping of the intermediate enolate with an electrophile. The importance of enolate geometries for acyclic stereoselection has been investigated by Heathcock et al., who have demonstrated that in aldol reactions, for example, there is a good correlation between the geometry of the enolate intermediate and the stereochemistry of the resulting aldol product. In large ring enolates a similar correlation should be possible since electrophilic attack at only one face of the enolate should be preferred. It is reasonable to assume that the stereoselective alkylation of a large ring compound is preceded by selective formation of one enolate. Indeed Still and co-workers have used the steric energies of enolates to rationalize the outcome of methylations and results from our laboratory have also been successfully explained using this approach.

In order to understand the factors controlling the diastereoselective alkylations and to eventually develop a model which could be used to predict the outcome of these types of reactions, it would be desirable to study the intermediate enolates and correlate the experimental results with strain energies calculated by the MM2 program. As a preliminary step, we decided to investigate the stereoselective formation of enolates and enol ethers in our macrocyclic ketones 42, 43, 72 and 74. It was anticipated that trapping of the enolate intermediates could be achieved using either chlorotrimethylsilane or trimethylsilyl trifluoromethanesulfonate furnishing trimethylsilyl enol ethers which could be isolated and characterized. However, it is well known that the determination of the enol ether geometry is challenging and that trimethylsilyl enol ethers are quite labile.

When 72 was reduced with L-Selectride at -78 °C, followed by treatment of the intermediates with a filtered mixture of chlorotrimethylsilane and triethylamine, a 50% yield of enol ethers 92 and 93 was obtained, accompanied by 44% of the 1,2 reduction products 81 and 82 (Chapter 2.5). The ratio of 92 and 93 was determined to be 97:3 by capillary gas
chromatography and $^1$H NMR spectroscopy. The characterization of the enol ethers proved to be challenging, since storage for more than one day usually led to partial decomposition. Purification could routinely be achieved by filtering the crude reaction products through a 10-cm silica gel column, followed by removal of residual solvents and other volatile impurities under vacuum. This procedure did not lead to hydrolysis or isomerization of the enol ethers.

The major isomer 92 of the conjugate reduction had the E geometry as determined by both NOE experiments and $^{13}$C NMR spectroscopy (Chapter 2.9). The high stereoselectivity of the hydride addition of L-Selectride to the enone system was gratifying; however, the low yield was disappointing. The tendency of L-Selectride to reduce some $\alpha,\beta$-unsaturated ketones to allylic alcohols encouraged us to look for other reagents which might effect the desired reaction.

\[
\begin{align*}
\text{L-Selectride, TMSCl} & \quad -78^\circ\text{C} \quad 97 \\
\text{Et}_3\text{SiH, Wilkinson's catalyst} & \quad 25^\circ\text{C} \quad 90 \\
\text{Predicted selectivity (MM2)} & \quad -78^\circ\text{C} \quad >99 \\
\end{align*}
\]

Semmelhack and co-workers\(^{88}\) have used copper(I) bromide and sodium bis(2-methoxyethoxy)aluminium hydride for the conjugate reduction of enones. Treatment of 72 with this heterogeneous hydrido-copper species afforded a very good yield of ketone 42. However, all attempts to trap the intermediate enolate with chlorotrimethylsilane failed.
A much more promising method involved the preparation of triethylsilyl enol ethers by rhodium-catalyzed hydrosilation of α,β-unsaturated ketones. Treatment of 72 with Wilkinson's catalyst in triethylsilane at 60 °C produced two isomeric enol ethers 94 and 95 in a ratio of 79:21. The double bond geometry of the two products was determined by 13C NMR spectroscopy (Chapter 2.9) which proved to be rather tedious, but eventually revealed that the major isomer 94 was the E enol ether. The stereoselectivity was improved by performing the reaction at room temperature, giving 94 and 95 in 92% yield and 90:10 selectivity.

To rationalize the predominant formation of the E enol ethers we used a method that Still and co-workers had successfully used to rationalize the outcome of conjugate additions of copper reagents to α,β-unsaturated carbonyl compounds. This approach is based on several assumptions:

1. Ground-state conformational preferences of enones are reflected in the resulting enolates.
2. Enone conformations are in equilibrium.
3. Transition state geometries are reflected by the enolate geometries (late transition state).
4. Enolate formation is the rate determining step in the reaction.

Chamberlin and Reich have shown, that experimental results obtained for the conjugate addition of L-Selectride to α,β-unsaturated ketones are consistent with the first assumption. In this thesis, all conjugate additions are modeled this way – first by determining all low energy conformations of the α,β-unsaturated ketone within 4-5 kcal/mol of the global minimum structure, then by transforming the enone conformations into the requisite product enolate. Calculation of the Boltzmann distribution of those product enolates will then lead to the prediction of the stereoselectivity of the conjugate addition. It is not clear that this approach will be useful to rationalize the stereoselectivity of the rhodium catalyzed conjugate reduction. However our MM2 calculations show that while the conformations of the starting material 72 or the products 92 and 93 cannot account for the experimental result, the strain energies of the enolates correctly predict the stereoselectivity of the rhodium catalyzed conjugate reduction.
Figure 41 shows the conformations of the four lowest energy states for the conjugate reduction of 72.

Figure 41. Conformations of 72 and the enolates obtained on conjugate reductions.
The strong preference for the E enol ether can be explained if, as discussed above, the strain energies of the product enolates are considered. In fact, a Boltzmann distribution of the four reaction intermediates predicts a product ratio of >99:1 E:Z, in good agreement with the experimental results. The observed product ratio cannot be explained using the starting enone conformations, since a Boltzmann distribution of these conformations based on their strain energies would predict a large predominance of the Z enol ethers.

The reaction of L-Selectride (-78 °C) with 74 and trapping of the enolate results in the clean formation of (8Z)-10,10-dimethyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide (26) in 90% yield. Only traces of the corresponding E enol ether (97) could be detected. Treatment of 74 with triethylsilane in the presence of Wilkinson's catalyst provided two isomeric triethylsilyl enol ethers 28 and 22 in 94% yield and 91:9 selectivity. Comparison of the 1H NMR and 13C NMR spectra with known enol ethers established the Z geometry of the major isomer.

MM2 calculations on the enolates formed as intermediates in the conjugate reduction of 74 show that all E enolates exhibit very high strain energies due to unfavorable transannular interactions (Figure 42). A Boltzmann distribution of the enolate strain energies predicts a greater than 99% selectivity for the Z enol ethers in excellent agreement with the experimental results.
Figure 42. Conformations of 74 and the enolates obtained on conjugate reduction.
2.9 DETERMINATION OF THE GEOMETRIES OF TRIMETHYLSILYL ENOL ETHERS USING THE NUCLEAR OVERHAUSER EFFECT

$^1$H NMR spectroscopy has been used to determine the geometry of silyl enol ethers for several years. House and co-workers$^{90}$ have pointed out that the vinyl proton in an E enol ether generally resonates downfield from the corresponding proton in the Z diastereomer. However, several exceptions to this empirical observation are known.$^{87}$ This has led to the development of a method based on $^{13}$C NMR spectroscopy. Heathcock et al. have demonstrated that the allylic carbon (C3 in 92) of an E trimethylsilyl enol ether resonates 5-6 ppm upfield from the Z isomer.$^{87}$

![Diagram 92]

However this method suffers from two shortcomings: first, both isomers must be available to assign the geometry with confidence;$^{91}$ second, in highly functionalized molecules, it can be challenging to identify the allylic carbon of interest.

The nuclear Overhauser effect (NOE)$^{92}$ has been used successfully to uniquely determine the geometries of methyl enol ethers.$^{93}$ Selective irradiation of the methyl group leads to enhancement of the vinyl proton in E methyl enol ethers, while the corresponding Z isomers show no enhancement. Analysis of molecular models of an E trimethylsilyl enol ether such as 101 indicates that the vinylic proton and the protons of the methyl groups attached to the silicon atom are sufficiently close that irradiation of either set of protons should produce a NOE enhancement in the other. This enhancement is not expected in Z enol ethers such as 100.

To test this hypothesis, we prepared the trimethylsilyl enol ethers 100 and 101 from cyclohexanone and propiophenone. Propiophenone is known to give mainly the Z enol ether upon treatment with LDA and chlorotrimethylsilane.$^{87}$ Separate irradiation of the silyl methyl
protons in each isomer led to the selective enhancement of protons syn to the TMS protons in the difference NOE experiment. For the enol ether 101, only the vinylic and the allylic C6 protons showed enhancement. For 100, the ortho aromatic protons and the vinyl methyl protons were enhanced.

A 4:1 mixture of the E and Z isomers of 3-(trimethylsilyloxy)-2-pentene (102a, 102b) provided an even more convincing example of the usefulness of this technique. The NMR spectrum of the vinyl protons in the mixture is shown in Figure 43 (upper). Two quartets are readily visible at δ 4.50 and δ 4.58, with the major isomer at lower field. This isomer had previously been assigned the E geometry by 13C NMR spectroscopy. The simultaneous irradiation of the silyl methyl protons of both isomers led to exclusive enhancement of the vinylic quartet of the major isomer which confirmed the E geometry of the double bond (Figure 43, lower).
Figure 43. The $^1$H NMR and NOE difference spectrum (irradiation of the TMS protons) of the vinyl protons of a 4:1 mixture of 102a and 102b.

The application of this difference NOE procedure to the macrocyclic trimethylsilyl enol ethers 92 and 93 gave unambiguous and quick results which subsequently were confirmed by $^{13}$C NMR studies on both isomers. On irradiation of the trimethylsilyl protons at $\delta$ 0.16 in the major isomer 92, only the vinyl signal at $\delta$ 4.45 was enhanced, whereas irradiation of the trimethylsilyl protons at $\delta$ 0.15 in 93 gave enhanced NOE's in the signals at $\delta$ 2.05 and 2.25 and
no enhancement of the vinyl signal at δ 4.43. These results clearly proved that the major isomer 92 has the E geometry (Figure 44) and that 93 has the Z geometry.

Figure 44. NOEDS experiment of macrolide 92.
2.10 PREPARATION OF ENOL ETHERS UNDER EQUILIBRIUM CONTROL

MM2 calculations on the enol ethers of macrolide 42 indicated that under equilibrium conditions, it should be possible to selectively form one of the four possible enol ethers. This would be an extremely interesting demonstration of conformational control, since it is usually nearly impossible to generate selective enolates or enol ethers from ketones which have secondary carbon atoms on each side.

Initially we tried to study this problem using enol acetates. The MM2 calculations indicated that they would behave similarly to enol ethers and enol acetates are more stable than enol ethers. Treatment of 42 with isopropenyl acetate and toluenesulfonic acid provided a 91% yield of four isomeric enol acetates in a ratio of 27:15:24:34. However, attempted equilibration of this mixture with perchloric acid and acetic anhydride led to decomposition of the macrolides.

As a result we turned our attention to a study of the trimethylsilyl enol ethers. Several methods are available for the preparation of silyl enol ether mixtures under equilibrium control, however, many of these procedures involve rather harsh conditions. Emde et al. have reported that trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine is an excellent silylating agent for a variety of compounds and is especially convenient for the preparation of trimethylsilyl enol ethers in high yield. These workers also noted that equilibrium
controlled mixtures of enol ethers could be obtained if only 0.8 equivalent of triethylamine is used.

Accordingly, treatment of 42 with one equivalent of trimethylsilyl trifluoromethanesulfonate and 0.8 equivalent of triethylamine afforded four isomeric enol ethers in a ratio of 5:85:4:6.
The identification of the trimethylsilyl enol ethers was straightforward, since 92 and 93 had previously been prepared. Gas chromatographic co-injection of the reaction mixture with the two isomers 92 and 93 obtained from the conjugate reduction of 72, proved that the major isomer from the trimethylsilyl trifluoromethanesulfonate reaction was identical with the minor isomer 93 of the 1,4-reduction. The identity of the two remaining unknown compounds was established using the usual spectroscopic methods, and the double bond geometry was determined by NOE difference spectroscopy.

Although MM2 calculations provide strain enthalpies (ΔH), Still and co-workers29 have successfully used the results of these calculations to rationalize the outcome of equilibrium controlled reactions in cyclic compounds. The minimum energy conformations of the four possible trimethylsilyl enol ethers from 42 are shown in Figure 45. (8Z)-9-(trimethylsilyloxy)-8-

![Figure 45. The lowest energy conformations for the four possible enol ethers from 42.](image-url)
tetradecen-13-olide (92) exhibits the lowest strain energy and is at least 1.7 kcal/mol lower than the lowest energy conformations of the three other possible enol ethers (Figure 45). Calculation of the Boltzmann distribution at 25 °C leads to a predicted ratio of 92:93:103:104 = 5:90:<1:4 in good agreement with the experimental result.

The result of this reaction illustrates the usefulness and potential of conformational control in the reactions of macrocyclic molecules. By taking advantage of the conformational preferences of our 14-membered lactone, we were able to prepare one out of four possible enol ethers from 42 in 85% selectivity. This result was easily rationalized from the MM2 calculations shown in Figure 45. It is interesting to note that the conjugate reduction of 72 (trapping of the enolates with chlorotrimethylsilane) and the reaction of trimethylsilyl trifluoromethanesulfonate with 42 are complementary, providing access to either silyl enol ether 92 and 93.

Treatment of 43 with trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine, produced (8Z)-10,10-dimethyl-9-(trimethylsilyloxy)-8-cyclotetradecen-13-olide (96) as the only product.
The two low energy conformations of the geminal dimethyl trimethylsilyl enol ethers derived from 43 are shown in Figure 46. The energy difference between the two molecules leads to the prediction that equilibration conditions should lead to the exclusive formation of 96, in excellent agreement with the experimental result.

![Diagram of enol ethers 26 and 97]

**Figure 46.** The low energy conformations for enol ethers 26 and 97.

2.11. CONJUGATE ADDITION OF ORGANOCOPPER (CUPRATE) REAGENTS TO ENONES 72 AND 74

Treatment of 72 with lithium dimethylcopper(I) at -20 °C afforded a 70% yield of conjugate adducts 105 and 106 of unknown stereochemistry, accompanied by several polar side products. The ratio of 105 and 106 was determined by capillary gas chromatography as 55:45. While column chromatography led to the isolation and identification of one of the reaction by-products 107, all attempts to separate the two diastereomeric ketones 105 and 106 by repeated column chromatography were unsuccessful. Characterization of 107 showed that the organocopper reagent had attacked the lactone moiety leading to ring opening. The selectivity of this conjugate addition was unsatisfactory; however, attempts to improve the performance of this
reaction failed, since at lower temperature the conjugate addition was very slow, and any increase in the reaction temperature led progressively to increased amounts of the polar side products.

To improve the selectivity of the conjugate addition we turned our attention to the higher order organocopper reagents. Lipshutz and co-workers\(^96\) have found that these reagents, react rapidly with \(\alpha,\beta\)-unsaturated ketones affording the conjugate addition products in high yields. In our hands, the performance of the reagent generated \textit{in situ} from lithium (2-thienyl)(cyano)cupper(II)\(^96a\) and methyllithium was rather disappointing. Although the conjugate addition occurred at \(-78^\circ C\), a small amount of polar by-products was still formed, and the stereoselectivity improved only marginally to 60:40.

Several researchers have used additives to improve the regio- and stereoselectivities of organocopper reactions. Boron trifluoride etherate\(^28\) and especially chlorotrimethylsilane\(^97\) are
reported to accelerate the conjugate addition and inhibit side reactions. Treatment of 72 with lithium dimethylcopper(I) in the presence of boron trifluoride etherate at -78 °C indeed provided a 76:24 mixture of the two diastereomeric ketones 105 and 106. This result was encouraging, since the stereoselectivity had increased and the usual side products were completely absent.

The combination of lithium dimethylcopper(I) and chlorotrimethylsilane was especially attractive, since it enabled us to trap the enolate intermediates and, therefore, gain further insight into the selectivity of the conjugate addition. Reaction of 72 with lithium dimethylcopper(I) and chlorotrimethylsilane in THF at -78 °C gave a mixture of three enol ethers in a ratio of 71:23:6.

\[ \text{72} \xrightarrow{(\text{CH}_3)_2\text{CuLi}} \text{105*106} \]
The two major compounds 108 and 109 could be isolated by column chromatography and NOE difference spectroscopy revealed the E geometry of the two enol ethers. Unfortunately all attempts to separate the third enol ether 110 from the two major compounds failed and therefore the relative stereochemistry of the two substituents in 110 could only be inferred.

Hydrolysis of 108 with tetrabutylammonium fluoride afforded pure 105, which was recrystallized from hexanes and submitted for X-ray crystallographic analysis. The ORTEP diagram of 105 is shown in Figure 47 establishing the 7S*,13S* stereochemistry. Similarly hydrolysis of 109 afforded 106.

![ORTEP diagram of macrolide 105.](image)

Figure 47. ORTEP diagram of macrolide 105.

The best selectivity was achieved using a mixture of methylcopper(I), tetramethylethylenediamine and chlorotrimethylsilane in THF at -78 °C. This heterogeneous reagent mixture led to the formation of 108:109:110 in a ratio of 82:11:7. As with the lithium dimethylcopper(I)-chlorotrimethylsilane conjugate addition the reaction is very fast (10-15 min) and clean. The product mixture was not separated in this case (co-injection with the previously isolated enol ethers unambiguously established the identity of these compounds). Direct hydrolysis with tetrabutylammonium fluoride afforded an 89:11 mixture of 105 and 106. This result suggests that 110 has the same relative stereochemistry as 105 but has a Z double bond. The results for the reaction of 72 with organocopper reagents are summarized in Table IX.
Table IX. Reaction of (7E)-9-oxo-7-tetradecen-13-olide (72) with organocopper reagents

<table>
<thead>
<tr>
<th>Organocopper reagents</th>
<th>Temperature</th>
<th>Stereoselectivity</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>105 S* S*</td>
<td>106 S<em>R</em></td>
</tr>
<tr>
<td>Me₂CuLi</td>
<td>-20 °C</td>
<td>55 : 45</td>
<td></td>
</tr>
<tr>
<td>Me(2-Th)(CN)CuLi₂</td>
<td>-78 °C</td>
<td>60 : 40</td>
<td></td>
</tr>
<tr>
<td>Me₂CuLi/BF₃Et₂O</td>
<td>-78 °C</td>
<td>76 : 24</td>
<td></td>
</tr>
<tr>
<td>Me₂CuLi/TMSCl</td>
<td>-78 °C</td>
<td>77 : 23</td>
<td>71 : 23</td>
</tr>
<tr>
<td>MeCu/TMEDA/TMSCl</td>
<td>-78 °C</td>
<td>89 : 11</td>
<td>82 : 11</td>
</tr>
<tr>
<td>Predicted selectivity (MM2)</td>
<td>-78 °C</td>
<td>&gt;99 : &lt;1</td>
<td>&gt;99 : &lt;1</td>
</tr>
</tbody>
</table>

The stereochemistry of the reaction products can be rationalized using the strain energies of the enolate reaction intermediates (Chapter 2.8). Starting material energies are obviously not directly related to the stereochemistry of the products, since peripheral cuprate addition to the most stable conformation 72a of the α,β-unsaturated ketone would yield (7S*,13S*)-(8Z)-7-methyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide (110), which is only a minor reaction product.

![Chemical structures](image)

The lowest energy conformations for the three enolates are shown in Figure 48. The lowest energy conformation for the fourth possible enolate has a very high strain energy and therefore does not have to be considered. A Boltzmann distribution using the strain energies of
the enolates correctly predicts the relative stereochemistry and the double bond geometry of the observed products. For example, the MM2 calculations predict that the major reaction product should be \((7S^*,13S^*)-(8E)\)-7-methyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide \((108)\) in agreement with our experimental results.
Even though the stereoselectivities were again smaller than expected from the MM2 calculations, it is remarkable that both the geometry of the double bond as well as the relative stereochemistry of the major reaction product could have been predicted using this method. Interestingly, our experimental results also suggest that each of the reaction products (108, 109, and 110) is formed by peripheral attack of the organocopper reagent on a different conformation; for example the major isomer 108 is produced by peripheral attack on 72e.

Reaction of 74 with lithium dimethylcopper(I) in the presence of chlorotrimethylsilane produced only two silyl enol ethers 111 and 112 in a ratio of 85:15. The reaction mixture of
methylcopper(I), tetramethylethylenediamine and chlorotrimethylsilane led to an even higher selectivity yielding 111 and 112 in a ratio of 93:7. The enol ether geometry of the two reaction products was again established by NOE difference spectroscopy, 111 having the Z geometry, while 112 was assigned the E geometry. Both enol ethers were hydrolyzed with tetrabutylammonium fluoride to provide the alkylated ketones 113 and 114 respectively. The relative stereochemistry of the substituents of the major isomer 113 was again established by X-ray crystallography (Figure 49).

**Figure 49.** X-ray crystal structure of macrolide 113.

MM2 calculations predict that peripheral attack of organocopper reagents on the local conformation common to all low energy conformations of 74 should lead to the formation of enolate 115 which upon reaction with chlorotrimethylsilane produces (7S*,13S*)-(8Z)-7,10,10-trimethyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide (111).
Again, the experimentally observed stereoselectivity was slightly less than predicted from the MM2 calculations. Nonetheless, using a Boltzmann distribution of strain energies of the enolate intermediates, the relative stereochemistry and the double bond geometry of the reaction products could be correctly predicted.

2.12 SOLID STATE CONFORMATION OF MACROLIDES 105 AND 113

Macrolides 105 and 113 crystallized in almost identical [3344] conformations. Polar maps again proved to be very useful for the identification of the solid state conformation of 113 (Figure 50). Unfortunately, the dihedral angles for the X-ray crystal structure of 105 were not available at the time this thesis was submitted; however, careful inspection of the ORTEP diagrams revealed the similarity of the two conformations.

![Figure 50. Polar map of the solid state conformation of macrolide 113.](image)

Again, both solid state conformations had an s-trans lactone linkage, a C-O-C-H dihedral angle between 0 and 40°, and all substituents occupied corner positions. A table summarizing the crystallographic details for the lactone linkage can be found in Appendix II.
In order to gain further insight into the conformational preferences of 14-membered keto lactones, the strain energies of the important conformations of 105 and 113 were calculated. Table X and Table XI show the three lowest energy conformations for 105 and 113 respectively. In both cases the global minimum structure was identical with the solid state conformation.

Table X. The three lowest energy conformations of 105

<table>
<thead>
<tr>
<th>Low Energy Conformations</th>
<th>Solid State Structure</th>
<th>Strain Energy(a)</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>105a</td>
<td><img src="105a.png" alt="Image" /></td>
<td>0 kcal/mol</td>
<td>[3344]</td>
</tr>
<tr>
<td>105b</td>
<td><img src="105b.png" alt="Image" /></td>
<td>0.4 kcal/mol</td>
<td>[3434]*</td>
</tr>
<tr>
<td>105c</td>
<td><img src="105c.png" alt="Image" /></td>
<td>0.6 kcal/mol</td>
<td>[3434]*</td>
</tr>
</tbody>
</table>

\(a\) Strain energy is reported relative to the lowest energy conformation.

* Diamond lattice conformation.
Table XI. The three lowest energy conformations of 113

<table>
<thead>
<tr>
<th>Low Energy Conformations</th>
<th>Solid State Structure</th>
<th>Strain Energy*</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>113a</td>
<td><img src="image" alt="113a Structure" /></td>
<td>0 kcal/mol</td>
<td>[3344]</td>
</tr>
<tr>
<td>113b</td>
<td><img src="image" alt="113b Structure" /></td>
<td>1.2 kcal/mol</td>
<td>[3434]*</td>
</tr>
<tr>
<td>113c</td>
<td><img src="image" alt="113c Structure" /></td>
<td>1.5 kcal/mol</td>
<td>[3344]</td>
</tr>
</tbody>
</table>

* Strain energy is reported relative to the lowest energy conformation.
* Diamond lattice conformation.

It is very interesting that all keto lactones (42, 43, 105 and 113) examined in this thesis share the same global minimum conformation 116. This particular [3344] conformation is consistently lower in energy than all possible [3434] conformers. MM2 calculations suggest that 116 experiences less transannular strain compared to the [3434] conformations.
2.13 CONCLUSION

The conformational behavior of 14-membered lactones proved to be rather complex. In contrast to cyclotetradecane, the energy trend \([3434]<[3344]<[3335]\) is not maintained. The X-ray crystallographic data show that the conformational analysis of macrolides can be considerably simplified by applying two principles which are well known for open chain esters: namely, lactone functionalities exist in the s-trans form and the C-O-C-H dihedral angle of the secondary lactone is restricted to a 0-40° arc. Furthermore, sterically bulky substituents prefer to occupy exterior positions on the macrocycle, while geminally substituted atoms are generally situated in corner positions.

In order to unambiguously identify conformations, an improved procedure for the generation of polar maps was developed. Polar maps have proven to be very useful, and this simple tool for the identification of conformation should find widespread use in macrocyclic chemistry. With the aid of polar maps, a new conformation for 14-membered rings was discovered. MM2 calculations showed that this twisted conformation exhibited a low strain energy and should therefore be considered for future work in this area. The discovery of this new conformation also led to a modification of the Dale nomenclature system for macrocycles.

A number of 14-membered lactones with a ketone at C9 were used to investigate conformationally controlled hydride reductions and conjugate additions. The diastereoselectivities of all reactions could be successfully rationalized using Boltzmann distributions of the strain energies of starting materials or products. This method provides very accurate results; however, it is rather complex and necessitates extensive MM2 calculations. A much simpler approach takes advantage of the fact that most low energy conformations share the same local energy conformations. These local energy conformations can then be used as a simple model to predict the outcome of reactions as was first proposed by Vedejs and co-workers.

During our work with trimethylsilyl enol ethers, a useful technique for assigning the geometry of the enol ether double bond was developed using \(^1\)H NMR nuclear Overhauser effect
difference spectroscopy. One advantage of this technique over the widely used $^{13}$C NMR method is that only one isomer is required to accurately assign the E or Z stereochemistry.
CHAPTER III

Experimental

3.1 GENERAL

Unless otherwise stated, all reactions were performed under nitrogen using oven-dried glassware. Cold temperature baths were prepared as follows: -78 °C (dry ice - acetone), -50 to -20 °C (dry ice - aqueous CaCl₂), and 0 °C (ice - water).

Anhydrous reagents and solvents were prepared according to the procedure given in the literature. Alkylithiums were standardized by titration against diphenylacetic acid in THF and were obtained from Aldrich Chemical Co. Copper(I) iodide (Aldrich) was purified by dissolving 13.6 g of copper(I) iodide and 120 g of KI in 100 mL of distilled water. The resulting mixture was stirred for 2 h with 2 g of activated charcoal, followed by filtration over Celite and precipitation of the copper(I) iodide with 600 mL of water.

Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard model 5880A, equipped with a split mode capillary injection system and a flame ionization detector, using 0.22 mm columns of OV-101, Carbowax-20M, SE-30 or DB-210. The columns were purchased from J.W. Scientific Co. Helium was used as the carrier gas in all cases.

Preparative flash column chromatography was performed using silica gel 60, 230-240 mesh, supplied by E. Merck Co. Usually a 60 to 1 ratio of silica gel to compound was used.

Melting points were performed on a Reichert microscope hot stage melting apparatus, and are uncorrected. In the cases where a Kugelrohr distillation was performed, boiling points are given as the oven temperature. Boiling points are uncorrected.

Infrared (IR) spectra were recorded on a Perkin-Elmer model 710B spectrophotometer or on a BOMEM FT-IR Michaelson-100 connected to an IBM compatible microcomputer. IR spectra were taken in a chloroform solution using NaCl cells of 0.2 mm thickness and were calibrated.
with the 1601 cm\(^{-1}\) band of polystyrene except for those spectra recorded on the BOMEM FT-IR instrument.

Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded in deuterochloroform or deuterobenzene (NOE) solutions on a Bruker WP-80 (80 MHz), Varian XL-300 (300 MHz), or a Bruker WH-400 (400 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) on the \(\delta\) scale versus tetramethylsilane (\(\delta 0\) ppm) or chloroform (\(\delta 7.27\) ppm) as internal standards. Signal multiplicity, coupling constants, and integration ratios are indicated in parentheses. Carbon-13 NMR (\(^{13}\)C NMR) spectra were recorded on a Varian XL-300 (75 MHz) instrument using the Attached Proton Test pulse sequence to assign the signals.

Low resolution mass spectra (LRMS) were recorded on either a Varian MAT model CH4B or a Kratos-AEI model MS 50 spectrometer. Only peaks with greater than 20% relative intensity or those which were analytically useful are reported. High resolution mass spectra (HRMS) were carried out on a Kratos-AEI model MS 50 instrument. An ionization potential of 70 eV was used in all measurements.

Microanalyses were carried out at the microanalytical laboratory at the University of British Columbia using a Carlo Erba Elemental Analyzer 1106.

Experimental procedures are reported for the preparation of all new compounds, and for known substances for which no detailed information had been published or where procedures were modified. High resolution mass spectral data or microanalyses were obtained only for previously unknown compounds.
3.2 7-BENZYOXYHEPTANOIC ACID (44)

Crude heptanolide 51 (11 g, 0.086 mol) was dissolved in 250 mL of toluene and refluxed overnight in the presence of 51 g of benzyl bromide (0.30 mol) and 28 g of potassium hydroxide (0.50 mol). The heterogeneous reaction mixture was then treated with 400 mL of water and stirred for 30 min. The aqueous layer was separated, acidified with concentrated HCl, and extracted with ether. The organic layer was dried (MgSO₄), filtered, the solvent evaporated and the resulting oil distilled (158 °C / 2 mm Hg) to afford 19 g (80%) of 44.

**IR** (CHCl₃, cm⁻¹) 3400-2400, 3040, 2950, 2870, 1720, 1460, 1420, 1290, 1200.

**¹H NMR** (CDCl₃, 80 MHz) δ 1.2-1.7 (m, 8H), 2.23 (t, J = 7 Hz, 2H), 3.38 (t, J = 6 Hz, 2H), 4.40 (s, 2H), 7.35 (s, 5H), 11.4 (s, 1H).

**LRMS** (m/z) 236 (2, M⁺), 108 (11), 107 (68), 92 (28), 91 (100), 79 (11), 65 (12).
3.3 7-HEPTANOLIDE (51)

Anhydrous Na$_2$HPO$_4$ (35.5 g, 0.25 mol) was added to a mechanically stirred solution of 4.5 g of cycloheptanone (0.04 mol) in 40 mL of methylene chloride. To the resulting ice cooled suspension was added slowly a solution of 35 mL of trifluoroperacetic acid (3.1 M, 0.11 mol) in methylene chloride. The reaction mixture was stirred overnight, and then poured into water. The organic layer was separated, washed with saturated NaHCO$_3$ solution, dried (MgSO$_4$), and filtered. Evaporation of the solvent followed by distillation (62 °C / 7 mm Hg) afforded 3.5 g (69%) of 51.

**IR** (CHCl$_3$, cm$^{-1}$) 2950, 2880, 1730, 1450, 1360, 1300, 1230, 1130, 1100, 1000.

**$^1$H NMR** (CDCl$_3$, 80 MHz) δ 1.5-2.0 (m, 8H), 2.55 (t, J = 7 Hz, 2H), 4.38 (t, J = 7 Hz, 2H).

**LRMS** (m/z) 128 (2.8, M$^+$), 100 (27), 98 (35), 80 (17), 70 (29), 69 (47), 56 (41), 55 (100), 42 (55), 41 (61), 39 (30).
3.4 METHYL 5-HYDROXYHEXANOATE (53)

A mixture of 30.3 g of methyl 5-oxohexanoate\textsuperscript{57} (0.21 mol) and 50 mL of methanol was slowly added to a stirred solution of 36 g of NaBH\textsubscript{4} (0.95 mol) in 440 mL of methanol, at -23 °C. After 50 min the resulting reaction mixture was treated with 1N HCl at -23 °C, until the solution reached pH 2. The methanol was then evaporated (temperature < 20 °C) and the residual aqueous phase was extracted with ethyl acetate. The organic phase was washed with saturated NaHCO\textsubscript{3} solution, saturated NaCl solution, dried (MgSO\textsubscript{4}) and filtered. Evaporation of the solvent and distillation (80 °C / 2 mm Hg) afforded 26 g (81%) of 53.

IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}) 3800-3300, 3640, 2970, 2890, 1725, 1440, 1380, 1230, 1180, 1070, 1020.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 80 MHz) \( \delta \) 1.17 (d, J = 6 Hz, 3H), 1.50 (m, 4H), 2.32 (t, J = 6 Hz, 2H), 3.65 (s, 3H), 3.77 (m, 1H).

LRMS (m/z) 146 (0.1, M\textsuperscript{+}), 102 (44), 99 (28), 74 (100), 71 (24), 69 (20), 59 (20), 45 (55), 43 (83), 42 (26), 41 (28), 28 (73).
The following reaction was performed in an open two-neck flask fitted with an addition funnel. 2,2-Dimethyl-5-oxohexanoic acid (58) (10 g, 0.063 mol) was dissolved in 100 mL of water and the solution neutralized (phenolphthalein) by addition of 10 % sodium hydroxide solution. The resulting red solution was stirred at room temperature and a mixture of 3.7 g of NaBH₄ (0.10 mol) in 50 mL of water added at such a rate that the temperature remained between 20-30 °C. The reaction mixture was stirred a further 2 h, the excess of borohydride decomposed with concentrated HCl (ice cooling required), and the resulting reaction mixture extracted six times with ethyl acetate. The combined organic layers were dried (MgSO₄), filtered and the solvent evaporated. Distillation (72 °C / 2 mm Hg) afforded 7.4 g (83%) of 57 as a colorless sweet smelling oil.

**IR** (CHCl₃, cm⁻¹) 2990, 2940, 2880, 1720, 1380, 1280, 1150, 1130, 1070.

**¹H NMR** (CDCl₃, 80 MHz) δ 1.30 (s, 6H), 1.36 (d, J = 6 Hz, 3H), 1.6-2.0 (m, 4H), 4.5 (m, 1H).

**LRMS** (m/z) 142 (6, M⁺), 99 (6), 98 (20), 70 (37), 69 (19), 56 (100).
3.6 2,2-DIMETHYL-5-OXOHEXANOIC ACID (58)

3,3,6-Trimethyl-2-cyclohexenone61 (12 g, 138.3 mol) was dissolved in 200 mL of methylene chloride and mixed vigorously with 5.0 g of sodium hydroxide (0.12 mol) and 15 g of 30% hydrogen peroxide. A phase transfer catalyst (Adogen, 0.2 g, 0.5 mmol) was added and the two phase mixture cooled to -5 °C. Ozone was bubbled through the heterogeneous reaction mixture until GC analysis indicated that all the starting material in the organic layer had been consumed. The suspension was then diluted with 30 mL of H2O and the aqueous layer separated. Acidification with concentrated HCl (with ice cooling) produced an oily substance which was extracted with ethyl acetate. The organic layer was dried (MgSO4), filtered, the solvent evaporated and the residue distilled (93 °C / 0.2 mm Hg) to afford 11.0 g (80%) of 2,2-dimethyl-5-oxohexanoic acid (58).

IR (CHCl3, cm⁻¹) 3600-2400, 2980, 2950, 2880, 1710, 1390, 1380, 1110.

¹H NMR (CDCl3, 80 MHz) δ 1.22 (s, 6H), 1.85 (m, 2H), 2.17 (s, 3H), 2.45 (m, 2H), 11.4 (s, 1H).

LRMS (m/z) 158 (14, M⁺), 140 (11), 134 (12), 131 (11), 118 (25), 98 (18), 97 (36), 91 (36), 88 (34), 77 (20), 71 (30), 70 (100), 69 (57), 56 (29), 55 (57).
3.7 2-[(DIMETHYLPHOSPHONO)METHYL]-2-HYDROXY-6-METHYL TETRAHYDRO-PYRAN (45)

\[ \text{HO} \quad \text{PO(OMe)}_2 \]

\[ \text{HO} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{PO(OMe)}_2 \]

\[ 45a \quad 45b \]

a. Reaction of 5-hexanolide with lithium dimethyl methylphosphonate

A solution of 24.8 g of dimethyl methylphosphonate (0.2 mol) in 600 mL of THF at \(-78 \, ^\circ\text{C}\) was treated with 133 mL of \text{n}-butyllithium (1.50 M, 0.2 mol) over a 10 min period. The resulting suspension was stirred for 30 min at \(-78 \, ^\circ\text{C}\) and then treated with a solution of 11.4 g of 5-hexanolide (0.1 mol) in 60 mL of THF. The yellow suspension was allowed to warm up to room temperature and stirred for an additional 3 h before being cooled to 0 \, ^\circ\text{C}\) and quenched with 10 mL glacial acetic acid. The reaction mixture was partitioned between saturated NaCl solution and ether, and the organic layer was washed with NaHCO\(_3\) solution, saturated NaCl solution, dried (MgSO\(_4\)), and filtered. After removal of the solvents, column chromatography with ethyl acetate as eluant afforded 18 g (78\%) of 45.

\text{IR (CHCl}_3, \text{cm}\text{\(^{-1}\})} \quad \text{3550 - 3300, 2990, 2940, 1720, 1440, 1460, 1210, 1030, 990.}

\text{\(^1\text{H NMR for 45a (CDCl}_3, \text{80MHz)})} \delta 1.20 \, (d, \text{J = 6 Hz, 3H}), 1.25-2.0 \, (m, 4H), 2.68 \, (t, \text{J = 7 Hz}, 2H), 3.12 \, (d, \text{J = 22 Hz, 2H}), 3.7 \, (d, \text{J = 12 Hz, 6H}), 4.1 \, (m, 1H).

\text{\(^1\text{H NMR for 45b (CDCl}_3, \text{80MHz)})} \delta 1.16 \, (d, \text{J = 6 Hz, 3H}), 1.25-2.0 \, (m, 6H), 2.17 \, (d, \text{J = 18 Hz, 2H}), 3.61 \, (d, \text{J = 12 Hz, 3H}), 3.85 \, (d, \text{J = 12 Hz, 3H}), 4.1 \, (m, 1H).

\text{LRMS (m/z) 238 (0.11, M\text{\(^+\)}), 220 (9.9), 166 (53.6), 151 (100), 124 (70.9), 111 (21.8), 110 (26.1), 109 (51.1), 95 (20.8), 94 (55.8).}

\text{HRMS calcd for C}_9\text{H}_{19}\text{O}_5\text{P : 238.0970 ; found : 238.0972.}
b. Reaction of methyl 5-benzyloxyhexanoate with lithium dimethyl methylphosphonate

A solution of 1.1 g of dimethyl methylphosphonate (9.3 mmol) in 20 mL of THF at -78°C was treated with 4.2 mL of n-butyllithium (2 M) over a 10 min period. The resulting suspension was stirred for 30 min at -78°C and then treated with a solution of 1.0 g of methyl 5-benzyloxyhexanoate (4.2 mmol) in 10 mL of THF. The yellow suspension was allowed to warm to room temperature and stirred for an additional 3 h before being cooled to 0°C and quenched with 10 mL of water. The reaction mixture was partitioned between 5% NH₄Cl and ether. The organic layer was separated and the aqueous phase was acidified with 1 M HCl and extracted with ether. The combined organic extracts were dried (MgSO₄) and filtered. Evaporation of the solvents afforded 1.5 g of a yellow oil which was dissolved in 50 mL ethanol and hydrogenated at room temperature in the presence of 50 mg of 10% Pd/C. After the uptake of one equivalent of hydrogen the reaction mixture was filtered and the solvent evaporated to afford 0.7 g (70%) of 45.

Characterization of 45 see 3.7a.

3.8 2-[(DIMETHYLPHOSPHONO)METHYL]-2-HYDROXY-3,3,6-TRIMETHYLTETRAHYDROPYRAN (46)

Lithium dimethyl methylphosphonate, prepared from 53 mL of n-butyllithium (0.08 mol) and 11.2 g of dimethyl methylphosphonate (0.09 mol), was reacted with 6.0 g of 2,2-dimethyl-5-hexanolide (57) (0.042 mol) following the same procedure as in the preparation of 2-
[(dimethylphosphono)methyl]-2-hydroxy-6-methyltetrahydropyran (45). After removal of the solvents, column chromatography with ethyl acetate - petroleum ether (4:1) as eluant afforded 11 g of 46 (94%).

IR (CHCl₃, cm⁻¹) 3600-3200, 2960, 1725, 1450, 1380, 1220, 1020, 980.

¹H NMR (CDCl₃) δ 1.95 (s, 3H), 2.0 (s, 3H), 1.23 (d, J = 6 Hz, 3H), 1.0-2.0 (m, 4H), 2.13 (d, J = 20 Hz, 2H), 3.70 (d, J = 12 Hz, 3H), 3.82 (d, J = 12 Hz, 3H), 4.1 (m, 1H).

LRMS (m/z) 266 (0.14, M⁺) 248 (2.8), 194 (29), 169 (46), 153 (45), 151 (80), 125 (25), 124 (100), 110 (20), 109 (43), 95 (20), 94 (64), 82 (23), 79 (43), 69 (29), 56 (40), 55 (51).

HRMS calcd for C₁₁H₂₃O₅P: 266.1283; found: 266.1270.

3.9 16'-[(DIMETHYLPHOSPHONO)-1'-METHYL-5'-OXOHEXYL]-7-BENZYL-OXOHEPTANOATE (60)

![Chemical structure image]

To a stirred, ice cooled solution of 4.7 g of 7-benzyloxyheptanoic acid (44) (0.020 mol), 0.2 g of DMAP (1.6 mmol) and 5.7 g of 2-[(dimethylphosphono)methyl]-2-hydroxy-6-methyltetrahydropyran (45) (0.024 mol) was slowly added a solution of 4.5 g of DCC (0.022
mol) in 10 mL of DMF. After 3 h, the urea was filtered off by suction filtration and the filtrate was diluted with methylene chloride. The resulting yellow solution was washed twice with 1 M HCl followed by NaHCO₃ and saturated NaCl solution. The organic layer was dried (MgSO₄), filtered and the solvents evaporated to yield a yellow oil. Column chromatography with ethyl acetate as eluant afforded 6.9 g (75%) of 60 and 1.1 g (13%) of 61.

**Data for 60.**

IR (CHCl₃, cm⁻¹) 2990, 2940, 2860, 1720, 1450, 1370, 1250, 1030.

¹H NMR (CDCl₃, 80 MHz) δ 1.2 (d, J = 6 Hz, 3H), 1.1-1.8 (m, 12H), 2.25 (t, J = 7 Hz, 2H), 2.6 (t, J = 7 Hz, 2H), 3.05 (d, J = 22 Hz, 2H), 3.45 (t, J = 6 Hz, 2H), 3.7 (d, J = 11 Hz, 6H), 4.5 (s, 2H), 4.88 (m, 1H), 7.33 (s, 5H).

LRMS (m/z) 456 (0.22, M⁺), 222 (20), 221 (100), 220 (36), 166 (21), 151 (59), 91 (56).


**Data for 61.**

IR (CHCl₃, cm⁻¹) 3020, 2960, 2870, 1725, 1460, 1385, 1220, 1040.

¹H NMR (CDCl₃, 80 MHz) δ 1.1 (d, J = 6 Hz, 3H), 1.1 - 1.6 (m, 14H), 1.88 (d, J = 18 Hz, 2H), 2.17 (t, J = 7 Hz, 2H), 3.35 (t, J = 6 Hz, 2H), 3.64 (d, J = 11 Hz, 6H), 4.4 (s, 2H), 4.83 (m, 1H), 7.19 (s, 5H).

LRMS (m/z) 456 (2.3, M⁺), 390 (7.3), 261 (54), 260 (34), 221 (70), 209 (72), 151 (40), 124 (24), 107 (39), 95 (31), 91 (100), 55 (26).

3.10  [4',4'-DIMETHYL-6'- (DIMETHYLPHOSPHONO)-1'-METHYL-5'-OXOHEXYL]-7-
BENZYLOXYHEPTANOATE (62)

7-Benzylxyheptanoic acid (44) (1.0 g, 4.2 mmol) was treated with 1.2 g of 2-
[(dimethylphosphono)-methyl]-2-hydroxy-3,3,6-trimethyltetrahydropyran (46) (4.6 mmol)
following the same procedure as in the preparation of [6'-(dimethylphosphono)-1'-methyl-5'-
oxohexyl]-7-benzylxyheptanoate (60). After removal of the solvents, chromatography with
ethyl acetate - petroleum ether (4:1) as eluant afforded 1.0 g (51%) of 62.

**IR (CHCl₃, cm⁻¹)** 2990, 2940, 2860, 1720, 1450, 1360, 1230, 1020.

**¹H NMR (CDCl₃, 300 MHz)** δ 1.13 (s, 6H), 1.18 (d, J = 6 Hz, 3H), 1.3-1.7 (m, 12H), 2.26
(t, J = 7 Hz, 2H), 3.13 (d, J = 22 Hz, 2H), 3.45 (t, J = 7 Hz, 2H), 3.78 (d, J = 12 Hz,
6H), 4.5 (s, 2H), 5.85 (m, 1H); 7.33 (s, 5H).

**LRMS (m/z)** 485 (0.35, M+1), 484 (0.31, M⁺), 250 (20), 249 (100), 194 (21), 151 (71), 125
(22), 124 (55), 121 (44), 97 (32), 91 (70).

**HRMS** calcd for C₂₅H₄₁O₇P : 484.2590; found : 484.2590.
3.11 [6'-DIMETHYLPHOSPHONO]-1'-METHYL-5'-OXOHEXYL]-7-HYDOXY-HEPTANOATE (63)

![Chemical Structure](image)

A mixture of 9.0 g of [6'-((dimethylphosphono)-1'-methyl-5'-oxoheptyl]-7-benzyloxyheptanoate (60) (0.019 mol) and 1.0 g palladium on carbon in 300 mL ethanol was hydrogenated at room temperature and atmospheric pressure. After the uptake of 1 equivalent of hydrogen, the mixture was filtered and the solvent evaporated to afford 7.1 g (97%) of 63.

**IR (CHCl3, cm⁻¹)** 3650-3300, 2990, 2940, 2860, 1715, 1450, 1370, 1220, 1020.

**¹H NMR** (CDCl₃, 80 MHz) δ 1.09 (d, J = 6 Hz, 3H), 1.1-1.9 (m, 12H), 2.15 (t, J = 7 Hz, 2H), 2.6 (t, J = 7 Hz, 2H), 3.08 (d, J = 22 Hz, 2H), 3.6 (t, J = 7 Hz, 2H), 3.81 (d, J = 12 Hz, 6H), 4.9 (m, 1H).

**LRMS** m/z 367 (1.7, M+1), 348 (1, M-H₂O), 221 (100), 220 (85), 166 (64), 151 (89), 124 (56), 109 (31), 94 (22), 55 (25).

**HRMS** calcd for C₁₆H₃₂O₇P: 367.1885; found: 367.1883.

Calcd for C₁₆H₂₉O₇P: 348.1700; found: 348.1686.
3.12 \[4',4'-\text{DIMETHYL-6'}-(\text{DIMETHYLPHOSPHONO})-1'-\text{METHYL-5'}-\text{OXOHEXYL}]-7-\text{HYDROXYHEPTANOATE (70)}

A mixture of 5.0 g of \[4',4'-\text{dimethyl-6'}-(\text{dimethylphosphono})-1'-\text{methyl-5'}-\text{oxohexyl}]-7-\text{benzyloxyheptanoate (62)}\ (0.010 mol) and 0.5 g palladium on carbon in 200 mL ethanol was hydrogenated at room temperature and atmospheric pressure. After the uptake of 1 equivalent of hydrogen, the mixture was filtered and the solvent evaporated to afford 3.2 g (84%) of 70.

**IR** (CHCl₃, cm⁻¹) 3600-3300, 2990, 2940, 2850, 1715, 1450, 1360, 1220, 1010.

**¹H NMR** (CDCl₃, 300 MHz) δ 1.13 (s, 6H), 1.2 (d, J = 6 Hz, 3H), 1.3-1.7 (m, 12H), 2.3 (t, J = 7 Hz, 2H), 3.16 (d, J = 22 Hz, 2H), 3.62 (t, J = 7 Hz, 2H), 3.81 (d, J = 12 Hz, 6H), 4.86 (m, 1H).

**LRMS** (m/z) 395 (0.7, M+1), 249 (50), 194 (35), 169 (22), 151 (84), 125 (37), 124 (100), 121 (29), 109 (22), 97 (54), 94 (33), 55 (56).

**HRMS** calcd for C₁₆H₃₆O₇P : 395.2199; found : 395.2204.
A mixture of 0.35 g of [6'- (dimethylphosphono)- 1'-methyl- 5'- oxohexyl]- 7- hydroxyheptanoate (72) (1.0 mmol), 3 mL of DMSO and 2 mL of acetic anhydride was stirred at room temperature for 24 h. The reaction mixture was then diluted with 20 mL chloroform and washed with saturated NaHCO₃ solution and saturated NaCl solution. Drying (MgSO₄), filtration and evaporation of the solvents followed by column chromatography with ethyl acetate as eluant afforded 0.23 g (66%) of 64.

IR (CHCl₃, cm⁻¹) 2990, 2940, 2860, 1720, 1460, 1380, 1240, 1040.

¹H NMR (CDCl₃, 80 MHz) δ 1.13 (d, J = 6 Hz, 3H), 1.1-1.8 (m, 12H), 2.06 (s, 3H), 2.20 (t, J = 7 Hz, 2H), 2.55 (t, J = 7 Hz, 2H), 3.00 (d, J = 23 Hz, 2H), 3.42 (t, J = 6 Hz, 2H), 3.68 (d, J = 11 Hz, 6H), 4.52 (s, 2H), 4.77 (m, 1H).

LRMS (m/z) 411 (18, M-15), 379 (42), 349 (29), 222 (10), 221 (100), 166 (14), 151 (40), 124 (12), 109 (9), 61 (12), 55 (7).

HRMS calcd for C₁₇H₃₂O₇PS : 411.1606 ; found : 411.1599.
Dichloroacetic acid (0.18 mL, 2.2 mmol) was added slowly to a stirred solution of 1.6 g of [6'(dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-hydroxyheptanoate (63) (4.5 mmol) and 2.8 g of DCC (13 mmol) in 15 mL DMSO. After 2 h, the excess carbodiimide was destroyed by the addition of 1.1 g of oxalic acid dihydrate (9.0 mmol) in 10 mL methanol. The resulting mixture was diluted with 200 mL ethyl acetate and the urea filtered off. The filtrate was washed with NaHCO₃ and saturated NaCl solution, and dried with MgSO₄. Before the drying agent was filtered off, the suspension was stored overnight in the freezer (precipitation of residual urea). Evaporation of the solvents, followed by column chromatography with ethyl acetate as eluant afforded 1.2 g (73%) of 66 and 0.4 g (20%) of by-product 64.

**IR** (CHCl₃, cm⁻¹) 2990, 2950, 2850, 2730, 1720, 1460, 1370, 1250, 1030.

**¹H NMR** (CDCl₃, 80 MHz) δ 1.23 (d, J = 6 Hz, 3H), 1.2-2.0 (m, 10H), 2.3 (t, J = 7 Hz, 2H), 2.46 (m, J = 7, 2 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 3.1 (d, J = 23 Hz, 2H), 3.83 (d, J = 12 Hz, 6H), 4.88 (m, 1H), 9.78 (t, J = 2 Hz, 1H).

Due to its instability, this compound was not further characterized.

Characterization of 64 see 3.13.
3.15 [4',4'-DIMETHYL-6'-(DIMETHYLPHOSPHONO)-1'-METHYL-5'-OXOHEXYL]-7-
OXOHEPTANOATE (71)

![Chemical Structure of 71]

[4',4'-Dimethyl-6'-(dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-hydroxyheptanoate (70) (3.0 g, 7.6 mmol) was oxidized with 4.7 g of DCC (22.8 mmol) in 20 mL of DMSO following the same procedure as in the preparation [6'-(dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-oxoheptanoate (66). Removal of the solvents and column chromatography with ethyl acetate as eluant afforded 2.3 g (77%) of 71.

**IR** (CHCl₃, cm⁻¹) 2990, 2950, 2860, 2740, 1720, 1460, 1380, 1230, 1125.

**¹H NMR** (CDCl₃, 300 MHz) δ 1.05 (s, 6H), 1.1 (d, J = 6, 3H), 1.2-1.7 (m, 10H), 2.2 (t, J = 7 Hz, 2H), 2.37 (t, J = 7 Hz, 2H), 3.07 (d, J = 22 Hz, 2H), 3.7 (d, J = 12 Hz, 6H), 5.74 (m, 1H), 9.69 (s, 1H).

Due to its instability, this compound was not further characterized.
3.16 (7E)-9-OXO-7-TETRADECEN-13-OLIDE (72)

[6'-(Dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-oxoheptanoate (66) (0.35 g, 0.96 mmol), 1.5 g of 18-crown-6 (5.8 mmol), and 0.40 g of anhydrous, finely pulverized K2CO3 (2.9 mmol) were stirred vigorously in 400 mL toluene. After 12 h at 70-75 °C, the reaction mixture was cooled to room temperature, washed with water, saturated NaCl solution, dried (MgSO4) and filtered. Evaporation of the solvent and column chromatography with petroleum ether - ethyl acetate (9:1) as eluant afforded 150 mg 72 and 10 mg 73 (overall 63%).

Data for 72.

mp 65-66 °C (hexane).

IR (CHCl3, cm⁻¹) 2970, 2900, 1725, 1695, 1670, 1630, 1460, 1250, 1130, 990.

1H NMR (CDCl3, 400 MHz) δ 1.2 (d, J = 6 Hz, 3H), 1.25-1.8 (m, 10H), 2.18-2.6 (m, 6H), 5.01 (m, J = 6, 2.4, 7.1 Hz, 1H), 6.03 (d, J = 16 Hz, 1H), 6.56 (m, J = 7.5, 16 Hz, 1H).

13C NMR (CDCl3) δ 19.8 (CH3), 22.3 (CH2), 24.4 (CH2), 26.4 (CH2), 26.7 (CH2), 31.0 (CH2), 34.6 (CH2), 41.1 (CH2), 69.8 (CH), 130.3 (CH), 147.5 (CH), 173.1 (C=O), 201.7 (C=O).

LRMS (m/z) 238 (27, M⁺), 151 (53), 124 (22), 123 (100), 122 (29), 112 (28), 95 (25), 82 (29), 81 (73), 80 (35), 55 (35), 53 (20).

Data for 73.

IR (CHCl₃, cm⁻¹) 2950, 2875, 1720, 1690, 1660, 1620, 1460, 1260, 1130.

¹H NMR (CDCl₃, 400 MHz) δ 1.2 (d, J = 6 Hz, 3H), 1.3–1.8 (m, 10H), 2.1–2.7 (m, 6H), 5.05 (m, 1H), 5.9 (m, 6, 11 Hz, 1H), 6.17 (d, 11 Hz, 1H).

¹³C NMR (CDCl₃) δ 19.2 (CH₃), 25.1 (CH₂), 27.5 (CH₂), 27.6 (CH₂), 27.8 (CH₂), 33.9 (CH₂), 34.1 (CH₂), 35.2 (CH₂), 42.3 (CH₂), 69.2 (CH), 129.7 (CH), 145.0 (CH), 173.3 (C=O), 203.6 (C=O).

LRMS (m/z) 238 (19, M⁺), 151 (60), 124 (20), 123 (30), 115 (23), 97 (21), 95 (63), 81 (100), 69 (29), 68 (35), 67 (35), 55 (93), 54 (21), 53 (35), 43 (33), 41 (63).

HRMS calcd for C₁₄H₂₂O₃ : 238.1569 ; found : 238.1567.

3.17 (7E)-10,10-DIMETHYL-9-OXO-7-TETRADECEN-13-OLIDE (74)

[4',4'-Dimethyl-6'-(dimethylphosphono)-1'-methyl-5'-oxohexyl]-7-oxoheptanoate (71) was cyclized with 2.3 g of potassium carbonate (17 mmol) and 8.9 g of 18-crown-6 (34 mmol) following the same procedure as in the preparation of (7E)-9-oxo-7-tetradecen-13-olide (72). Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (5:95) as eluant afforded 0.95 g of 74 (64%).
mp 92-94 °C (hexane).

**IR** (CHCl₃, cm⁻¹) 2990, 2940, 2870, 1720, 1685, 1625, 1460, 1345, 1250, 1135, 980.

**¹H NMR** (CDCl₃, 400 MHz) δ 1.10 (s, 3H), 1.15 (s, 3H), 1.13 (d, J = 6.5 Hz, 3H), 1.20-1.85 (m, 10H), 2.20-2.45 (m, 4H), 5.05 (m, J = 3, 5, 6.5 Hz, 1H), 6.54 (d, J = 15 Hz, 1H), 6.79 (m, J = 6, 8, 15 Hz, 1H).

**¹³C NMR** (CDCl₃) δ 18.9 (CH₃), 23.1 (CH₃), 24.7 (CH₃), 23.9 (CH₂), 26.0 (CH₂), 26.1 (CH₂), 30.3 (CH₂), 30.8 (CH₂), 34.0 (CH₂), 35.3 (CH₂), 69.5 (CH), 126.0 (CH), 145.8 (CH), 46.1 (C), 172.7 (C=O), 214.1 (C=O).

**LRMS** (m/z) 266 (6.1, M⁺), 123 (14), 97 (59), 96 (35), 81 (37), 69 (16), 67 (13), 55 (100), 53 (21).

**HRMS** calcd for C₁₆H₂₆O₃ : 266.1881 ; found : 266.1879.

### 3.18 9-OXO-13-TETRADECANOLIDE (42)

A mixture of 100 mg of (7E)-9-oxo-7-tetradecen-13-olide (72) (0.42 mmol) and 50 mg of palladium on carbon in 10 mL of ethanol was hydrogenated at room temperature and atmospheric pressure. After the uptake of one equivalent of hydrogen, the mixture was filtered and the solvent evaporated to afford 85 mg (84%) of 42.
mp 42-43 °C (hexane).

IR (CHCl₃, cm⁻¹) 2980, 2900, 1725, 1720, 1470, 1375, 1260, 1140, 1010.

¹H NMR (CDCl₃, 400 MHz) δ 1.16 (d, J = 6.4 Hz, 3H), 1.2-2.0 (m, 14H), 2.16-2.46 (m, 6H), 4.95 (m, J = 6.4, 3.7, 7.3 Hz, 1H).

¹³C NMR (CDCl₃) δ 20.1 (CH₃), 20.5 (CH₂), 22.9 (CH₂), 24.5 (CH₂), 26.0 (CH₂), 30.0 (CH₂), 34.4 (CH₂), 35.0 (CH₂), 40.5, (CH₂) 42.2 (CH₂), 69.9 (CH), 173.2 (C=O), 211.6 (C=O).

LRMS (m/z) 240 (48, M⁺), 222 (34), 171 (69), 125 (58), 115 (64), 112 (100).

Anal. Calcd. for C₁₄H₂₄O₃ : C, 69.95 ; H, 10.07. Found : C, 70.00 ; H, 10.04.

3.19 10,10-DIMETHYL-9-OXO-13-TETRADECANOLIDE (43)

A mixture of 400 mg of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide (74) (1.5 mmol), 40 mg of palladium on carbon and 20 mL of ethanol was hydrogenated at room temperature and atmospheric pressure. After the uptake of one equivalent of hydrogen, the mixture was filtered and the solvent evaporated to afford 410 mg (100%) of 43.

mp 86-88 °C (hexane).

IR (CHCl₃, cm⁻¹) 2990, 2950, 2870, 1725, 1705, 1460, 1370, 1130, 1040.
**1H NMR** (CDCl$_3$, 400 MHz) $\delta$ 1.07 (s, 3H), 1.14 (s, 3H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.2-1.8 (m, 14H), 2.25 (m, $J = 6.8, 9.9, 16$ Hz, 1H), 2.28 (m, $J = 4, 7.1, 14.8$ Hz, 1H), 2.40 (m, $J = 4, 9.9, 14.8$ Hz, 1H), 2.57 (m, $J = 6.8, 9.6, 16.0$ Hz, 1H), 5.05 (m, $J = 2, 6, 6.4$ Hz, 1H).

**13C NMR** (CDCl$_3$) $\delta$ 19.1 (CH$_3$), 23.1 (CH$_3$), 24.8 (CH$_3$), 21.3 (CH$_2$), 24.2 (CH$_2$), 24.7 (CH$_2$), 25.8 (CH$_2$), 26.1 (CH$_2$), 30.9 (CH$_2$), 33.5 (CH$_2$), 33.6 (CH$_2$), 34.2 (CH$_2$), 69.7 (CH), 47.6 (C), 173.1 (C=O), 215.3 (C=O).

**LRMS** (m/z) 268 (5.2, M$^+$), 171 (28), 125 (21), 98 (25), 97 (100), 96 (22), 69 (36).

**HRMS** calcd for C$_{16}$H$_{28}$O$_3$ : 268.2033 ; found : 268.2036.

3.20 **9-HYDROXY-13-TETRADECANOLIDE (83, 84)**

![Diagram of 9-hydroxy-13-tetradecanolide](image)

83 84

**a. Reduction of 9-oxo-13-tetradecanolide with L-Selectride**

A solution of 70 mg of 9-oxo-13-tetradecanolide (42) (0.29 mmol) in 1 mL THF was added slowly to a mixture of 0.58 mL of L-Selectride (1 M, 0.58 mmol) and 5 mL of THF at -78 °C. After 3 h at -78 °C, the cooling bath was removed and the reaction was quenched with 2 drops of 1 M HCl and 2 drops of 30% H$_2$O$_2$. The reaction mixture was stirred for 10 min and then diluted with ethyl acetate. The organic phase was washed with NaHCO$_3$ solution, saturated
NaCl solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with chloroform - methanol (95:5) as eluant afforded 58 mg 83 and 7 mg 84 (92%).

**Data for 83.**

mp 47-48 °C (hexane).

IR (CHCl₃, cm⁻¹) 3620, 2930, 2860, 1460, 1250, 1100, 900.

**¹H NMR** (CDCl₃) δ 1.24 (d, J = 6.3 Hz, 3H), 1.2-1.75 (m, 18H), 2.28 (m, J = 5, 8, 15.5 Hz, 1H), 2.42 (m, J = 5, 8, 15.5 Hz, 1H), 3.85 (m, 1H), 4.99 (m, J = 6.3, 3.5, 8.2 Hz, 1H).

**¹³C NMR** (CDCl₃) δ 18.4 (CH₃), 20.0 (CH₂), 20.5 (CH₂), 24.8 (CH₂), 25.6 (CH₂), 25.8 (CH₂), 25.9 (CH₂), 32.1 (CH₂), 33.6 (CH₂), 34.9 (CH₂), 35.3 (CH₂), 69.8 (CH), 70.6 (CH), 173.6 (C=O).

**LRMS** (m/z) 241 (0.2, M-1), 155 (71), 115 (22), 109 (32), 99 (100), 83 (22), 81 (77), 69 (23), 67 (38), 57 (43), 55 (92).

**Anal. Calcd.** for C₁₄H₂₆O₃: C, 69.38; H, 10.81. **Found:** C, 69.47; H, 10.87.

**Data for 84.**

mp 57-59 °C (hexane).

IR (CHCl₃, cm⁻¹) 3620, 2930, 2860, 1460, 1250, 1100, 900.

**¹H NMR** δ (CDCl₃) δ 1.20 (d, J = 6.5 Hz, 3H), 1.2-1.75 (m, 18H), 2.24 (m, J = 4, 9, 14 Hz, 1H), 2.39 (m, J = 4, 9, 14 Hz, 1H), 3.75 (m, 1H), 5.00 (m, 5.3, 5.6, 6.5 Hz, 1H).

**¹³C NMR** (CDCl₃) δ 17.4 (CH₃), 20.0 (CH₂), 21.0 (CH₂), 24.7 (CH₂), 25.2 (CH₂), 25.8 (CH₂), 26.2 (CH₂), 32.6 (CH₂), 34.1 (CH₂), 34.6 (CH₂), 35.1 (CH₂), 69.6 (CH), 70.5 (CH), 173.5 (C=O).

**LRMS** (m/z) 241 (0.2, M-1), 155 (83), 115 (24), 109 (36), 99 (100), 98 (24), 83 (24), 81 (78), 70 (22), 69 (24), 67 (41), 57 (47), 55 (98).

b. Reduction of 9-oxo-13-tetradecanolide with K-Selectride

9-Oxo-13-tetradecanolide (42) (20 mg, 0.084 mol) was reduced with 84 μL of K-Selectride (1 M, 0.084 mmol) following the same procedure as in the reduction of 9-oxo-13-tetradecanolide with L-Selectride. After 2 h at -78 °C, thin layer chromatography indicated that the reduction was complete. To determine the diastereoselectivity, the two alcohols were silylated by addition of 28 μL of triethylamine (0.20 mmol) and 25 μL of chlorotrimethylsilane (0.2 mmol). The cooling bath was then removed and the reaction mixture stirred for a further 30 min. The resulting solution was washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents afforded 25 mg (93%) of a 78:22 mixture of silylated 83 and 84. The ratio of isomers was determined by GC (DB-210 column, 150 °C).

c. Reduction of 9-oxo-13-tetradecanolide with LS-Selectride

9-Oxo-13-tetradecanolide (42) (50 mg, 0.21 mol) was reduced with 420 μL of LS-Selectride (1 M, 0.42 mmol) following the same procedure as in the reduction of 9-oxo-13-tetradecanolide with L-Selectride. After 3 h at -78 °C, the reaction was quenched with 2 drops of 1 M HCl and 2 drops of 30% H₂O₂. The reaction mixture was stirred for 10 min and then diluted with ethyl acetate, washed with NaHCO₃ solution, saturated NaCl solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with chloroform-methanol (95:5) as eluant afforded 40 mg 83 and 4.5 mg 84 (85%).
d. Reduction of 9-oxo-13-tetradecanolide with sodium borohydride

9-Oxo-13-tetradecanolide (42) (20 mg, 0.084 mmol) was dissolved in 2 mL methanol and cooled to -78 °C. NaBH₄ (3.3 mg, 0.087 mmol) was added to the reaction mixture in one portion. After 1 h, the reaction was quenched with 1 M HCl, diluted with ethyl acetate, washed with saturated NaCl solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with chloroform - methanol (95:5) as eluant afforded 18 mg (89%) of a 50:50 (¹H NMR) mixture of 83 and 84.

e. Hydrogenation of (7E)-9-hydroxy-7-tetradecen-13-olide

(7E)-9-Hydroxy-7-tetradecen-13-olide (25 mg, 0.10 mmol) (86:14 = 79:80 mixture of diastereomers) was dissolved in 5 mL ethanol. After the addition of 20 mg palladium on carbon the resulting mixture was hydrogenated until one equivalent of hydrogen had been consumed. Filtration and evaporation of the solvent afforded 21 mg (86%) of 9-hydroxy-13-tetradecanolide (83:84 = 86:14).
a. Reduction of 10,10-dimethyl-9-oxo-13-tetradecanolidewith L-Selectride

10,10-Dimethyl-9-oxo-13-tetradecanolid (43) (20 mg, 0.075 mmol) dissolved in 1 mL THF was added dropwise into a stirred solution of 140 μL of L-Selectride (1 M, 0.14 mmol) in 3 mL THF at 0 °C. The mixture was stirred for 1 h and quenched with 2 drops of 1 M HCl and 2 drops of H2O2. The reaction mixture was diluted with 10 mL of ethyl acetate, washed with NaHCO3 solution, saturated NaCl solution, dried (MgSO4) and filtered. Evaporation of the solvents gave 18 mg (90%) of an 89:11 (1H NMR) mixture of 87 and 88.

Data for 87.

IR (CHCl3, cm−1) 3640, 2950, 2890, 1720, 1450, 1360, 1060.

1H NMR (CDCl3, 400 MHz) δ 0.85 (s, 3H), 0.93 (s, 3H), 1.22 (d, J = 6 Hz, 3H), 1.2-1.7 (m, 16H), 2.36 (m, 2H), 3.38 (dd, J = 7.5, 2 Hz, 1H), 4.88 (m, J = 6, 2.5, 9 Hz, 1H).

13C NMR (CDCl3) δ 20.8 (CH3), 22.2 (CH3), 25.5 (CH3), 23.6 (CH2), 24.1 (CH2), 25.1 (CH2), 25.3 (CH2), 26.0 (CH2), 29.4 (CH2), 30.6 (CH2), 32.7 (CH2), 33.8 (CH2), 71.4 (CH), 77.2 (CH), 35.6 (C), 172.9 (C=O).
LRMS (m/z) 255 (0.5, M-CH₃), 252 (0.5), 173 (30), 155 (100), 127 (12), 109 (18), 105 (11), 98 (26), 97 (24), 83 (13), 70 (18).


calcd for C₁₆H₂₈O₂ : 252.2089 ; found : 252.2091.

b. Hydrogenation of (7E)-10,10-dimethyl-9-hydroxy-7-tetradecen-13-olide

(9S*,13S*)-(7E)-10,10-Dimethyl-9-hydroxy-7-tetradecen-13-olide (86) (25 mg, 0.10 mmol) was dissolved in 5 mL of ethanol. After the addition of 10 mg of palladium on carbon, the resulting mixture was hydrogenated until one equivalent of hydrogen had been consumed. The reduction was very slow, taking 24 h for completion. Filtration and evaporation of the solvent followed by column chromatography with ethyl acetate - petroleum ether (1:4) as eluant afforded 23 mg (92%) of (S*,S*)-10,10-dimethyl-9-hydroxy-13-tetradecanolide (88).

Data for 88.

IR (CHCl₃, cm⁻¹) 3630, 2931, 2860, 1714, 1459, 1369, 1100.

¹H NMR (CDCl₃, 400 MHz) δ 0.86 (s, 3H), 0.96 (s, 3H), 1.19 (d, J = 6 Hz, 3H), 1.2-1.7 (m, 15H), 1.90 (m, 1H), 2.30 (m, J = 4, 6, 15.5 Hz, 1H), 2.43 (m, J = 4, 12, 15.5 Hz, 1H), 3.32 (d, J = 8.5 Hz, 1H), 5.23 (m, J = 6, 4, 8 Hz, 1H).

¹³C NMR (CDCl₃) δ 18.0 (CH₃), 21.7 (CH₃), 24.9 (CH₃), 23.7 (CH₂), 24.3 (CH₂), 24.8 (CH₂), 25.1 (CH₂), 36.4 (CH₂), 28.3 (CH₂), 32.9 (CH₂), 33.0 (CH₂), 69.4 (CH), 77.2 (CH), 36.9 (C), 173.6 (C=O).

LRMS (m/z) 270 (M⁺), 255 (0.5, M⁺-CH₃), 252 (0.5), 173 (26), 155 (81), 127 (13), 109 (26), 105 (11), 98 (30), 97 (33), 83 (17), 70 (29), 67 (73), 56 (100), 55 (81), 43 (62), 41 (56).

HRMS calcd for C₁₆H₃₀O₃ : 270.2195 ; found : 270.2197.
c. Reduction of 9-oxo-13-tetradecanolide with sodium borohydride

9-Oxo-13-tetradecanolide (42) (20 mg, 0.074 mmol) was dissolved in 2 mL of methanol and cooled to -78 °C. A 3 mg sample of NaBH₄ (0.079 mmol) was added to the reaction mixture in one portion. After 1 h, the reaction was quenched with 1 M HCl, diluted with ethyl acetate, washed with saturated NaCl solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with chloroform - methanol (95:5) as eluant afforded 17 mg (85%) of a 60:40 mixture of 87 and 88.

3.22 (7E)-9-(TRIMETHYLSILYLOXY)-7-TETRADECEN-13-OLIDE (81, 82)

![Image of compounds 81 and 82]

a. Reduction of (7E)-9-oxo-7-tetradecen-13-olide with sodium borohydride in the presence of cerium chloride

NaBH₄ (3.2 mg, 0.084 mmol) was added to a stirred mixture of 32 mg of cerium chloride heptahydrate (0.084 mmol) and 20 mg of (7E)-9-oxo-7-tetradecen-13-olide (72) (0.084 mmol) in 4 mL methanol at -78 °C. The resulting solution was stirred at -78 °C for 30 min and then quenched with 2 drops of 1 M HCl. The methanol was evaporated and the residue was dissolved in 30 mL ether. The organic phase was washed with saturated NaHCO₃ solution and dried with MgSO₄. The two diastereomeric products could be separated by column
chromatography if the alcohols were silylated. The solution was filtered and the solvent was evaporated. The residue was dissolved in 5 mL of THF and 100 μL triethylamine and 40 μL trimethylsilyl trifluoromethanesulfonate were added. After 15 min, the reaction mixture was diluted with 20 mL of ether, washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (2:98) as eluant afforded 15 mg 81 and 8.9 mg 82 (92%).

Data for 81.

IR (CHCl₃, cm⁻¹) 2940, 2870, 1720, 1460, 1380, 1260, 900, 860.

¹H NMR (CDCl₃, 400 MHz) δ 0.07 (s, 9H), 1.19 (d, J = 6 Hz, 3H), 1.2-1.75 (m, 12H), 1.19 (m, 1H), 2.16 (m, 1H), 2.29 (m, 2H), 4.12 (m, J = 7, 8, 4 Hz, 1H), 5.02 (m, J = 2.5, 6, 8 Hz, 1H), 5.31 (dd, J = 7, 15.5 Hz, 1H), 5.47 (m, J = 6, 8, 15.5 Hz, 1H).

¹³C NMR (CDCl₃) δ 0.32 (CH₃), 20.8 (CH₃) 20.6 (CH₂), 25.1 (CH₂), 26.7 (CH₂), 27.6 (CH₂), 31.2 (CH₂), 35.1 (CH₂), 35.4 (CH₂), 36.9 (CH₂), 69.9 (CH), 73.1 (CH), 130.7 (CH), 134.6 (CH), 173.6 (C=O).

LRMS (m/z) 312 (15, M⁺), 222 (12), 197 (98), 169 (21), 155 (82), 129 (18), 75 (43), 73 (100), 55 (21).

HRMS calcd for C₁₇H₃₂O₃Si: 312.2121; found: 312.2129.

Data for 82.

IR (CHCl₃, cm⁻¹) 2940, 2870, 1720, 1460, 1380, 1260, 900, 860.

¹H NMR (CDCl₃, 400 MHz) δ 0.06 (s, 9H), 1.17 (d, J = 6 Hz, 3H), 1.2-1.8 (m, 12H), 1.92 (m, 1H), 2.15 (m, 1H), 2.26 (m, 2H), 3.94 (m, 4, 9, 7.5 Hz, 1H), 5.00 (m, 1H), 5.24 (dd, J = 7.5, 15.5 Hz, 1H), 5.33 (m, J = 4, 9, 15.5 Hz, 1H).

¹³C NMR (CDCl₃) δ 20.6 (CH₃) 20.6 (CH₂), 25.2 (CH₂), 26.9 (CH₂), 27.9 (CH₂), 31.4 (CH₂), 35.1 (CH₂), 36.0 (CH₂), 37.9 (CH₂), 34.1 (CH₂), 34.6 (CH₂), 35.1 (CH₂), 70.2 (CH), 74.7 (CH), 132.0 (CH), 134.8 (CH), 173.5 (C=O).
$. LRMS (m/z) 312 (13, M$^+$), 222 (10), 197 (100), 169 (20), 155 (78), 129 (19), 75 (41), 73 (93), 55 (20).

HRMS calcd for C$_{17}$H$_{32}$O$_3$S: 312.2121; found: 312.2122.

b. Reduction of (7E)-9-oxo-7-tetradecen-13-olide with K-Selectride

(7E)-9-Oxo-7-tetradecen-13-olide (72) (20 mg, 0.084 mmol) was dissolved in 5 mL of THF and cooled to -78 °C. To this solution was added 84 μL of K-Selectride (1 M, 0.084 mmol) and the mixture was stirred at -78 °C for 15 min. A filtered mixture of 20 mg of triethylamine (0.20 mmol), 20 mg of chlorotrimethylsilane (0.19 mmol) and 1 mL of THF was then added, and the cooling bath was removed. The resulting solution was stirred at room temperature for 30 min followed by evaporation of the solvents and filtration through a silica gel column with ethyl acetate - petroleum ether (1:9) as eluant affording 24 mg of 81 and 82 (93%). Capillary GC (DB-1 column, 140 °C) was used to determine the diastereoselectivity (81:82 = 83:17).

c. Reduction of (7E)-9-oxo-7-tetradecen-13-olide with L-Selectride

(7E)-9-Oxo-7-tetradecen-13-olide (72) (20 mg, 0.084 mmol) was reduced with 84 μL of L-Selectride (1 M, 0.084 mmol) following the same procedure as in the reduction of (7E)-9-oxo-7-tetradecen-13-olide (72) with K-Selectride. Evaporation of the solvents followed by column chromatography with ethyl acetate - hexane (1:9) as eluant afforded 29 mg of a 86:14 (DB-1 column, 140 °C) mixture of 81 and 82 and 33 mg (95% overall) of the enol ethers 92 and 93 (E:Z = 97:3; SE-30 column, 170 °C).

Data for 92.

IR (CHCl$_3$, cm$^{-1}$) 2980, 2910, 1720, 1665, 1460, 1250, 1100, 860.
**1H NMR** (CDCl₃, 400 MHz) δ 0.19 (s, 9H), 1.23 (d, J = 6 Hz, 3H), 1.2-2.50 (m, 18H), 4.48 (dd, J = 6, 11 Hz, 1H), 4.93 (m, 1H).

**13C NMR** (CDCl₃) δ 0.4 (CH₃), 20.3 (CH₃), 22.6 (CH₂), 24.4 (CH₂), 25.5 (CH₂), 25.6 (CH₂), 26.1 (CH₂), 26.9 (CH₂), 28.2 (CH₂), 30.6 (CH₂), 35.2 (CH₂), 35.8 (CH₂), 69.2 (CH), 107.4 (CH), 152.0 (C), 173.7 (C=O).

**LRMS** (m/z) 312 (20, M⁺), 197 (39), 184 (24), 169 (35), 155 (30), 143 (23), 130 (23), 75 (41), 73 (100), 55 (32).

**HRMS** calcd for C₁₇H₃₂O₃S: 312.2121; found: 312.2119.

Data for 23 see 3.25.

d. Reduction of (7E)-9-oxo-7-tetradecen-13-olide with LS-Selectride

(7E)-9-oxo-7-tetradecen-13-olide (22) (20 mg, 0.084 mmol) was reduced with 84 μL LS-Selectride (1 M, 0.084 mmol) following the same procedure as in the reduction of (7E)-9-oxo-7-tetradecen-13-olide (22) with K-Selectride. Evaporation of the solvents followed by column chromatography with ethyl acetate - hexane (1:9) eluant afforded 20 mg of an 89:11 mixture (DB-1 column, 140 °C) of 81 and 82 and 2.6 mg (86% overall) of the 1,4-reduction products.

e. Reduction of (7E)-9-oxo-7-tetradecen-13-olide with lithium tri-(tert-butoxy)aluminium hydride

tert-Butanol (38 mg, 0.51 mmol) was added to a suspension of 6.5 mg of lithium aluminium hydride (0.17 mmol) in 5 mL of THF at 0 °C. After 30 min, the resulting solution was cooled to -50 °C and treated with a mixture of 20 mg of (7E)-9-oxo-7-tetradecen-13-olide (22) (0.085 mmol) in 1 mL THF. The colorless solution was stirred for 3 h at -50 °C and 2 h at -25 °C, quenched with 1 M HCl, diluted with ethyl acetate, washed with NaHCO₃ solution,
saturated NaCl solution, dried (MgSO₄) and filtered. Evaporation of the solvents afforded 17 mg (84%) of an 63:37 mixture (¹H NMR) of 8₁ and 8₂.

3.23 (7E)-10,10-DIMETHYL-9-HYDROXY-7-TETRADECEN-13-OLIDE (8₅, 8₆)

NaBH₄ (3.0 mg, 0.075 mmol) was added to a stirred solution of 28 mg of cerium chloride heptahydrate (0.075 mmol) and 20 mg of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide (7₄) (0.075 mmol) in 3 mL of methanol at -78 °C. The resulting solution was kept at -78 °C for 2 h, and then quenched with 2 drops of 1 M HCl. The methanol was evaporated and the residue was dissolved in 20 mL ethyl acetate. The organic phase was washed with saturated NaHCO₃ solution, dried with MgSO₄ and filtered. Evaporation of the solvent and column chromatography with chloroform as eluant afforded 16 mg 8₅ and 2.4 mg 8₆ (89% overall).

Data for 8₅.

mp 92 - 94 °C (hexane).

IR (CHCl₃, cm⁻¹) 3619, 2930, 2860, 1715, 1460, 1365, 1260, 1127, 980.
1H NMR (CDCl₃, 400 MHz) δ 0.95 (s, 3H), 0.97 (s, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.1-1.73 (m, 10H), 2.05 (m, 1H), 2.17 (m, 1H), 2.3 (m, 2H), 3.87 (d, J = 6 Hz, 1H), 4.94 (m, J = 3, 6.2, 8 Hz, 1H), 5.51 (m, 2H).

13C NMR (CDCl₃) δ 21.7 (CH₃), 23.1 (CH₃), 24.2 (CH₃), 25.1 (CH₂), 27.2 (CH₂), 27.9 (CH₂), 30.1 (CH₂), 32.0 (CH₂), 34.3 (CH₂), 34.7 (CH₂), 71.7 (CH), 79.6 (CH), 131.1 (CH), 132.3 (CH), 37.5 (C), 173.9 (C=O).

LRMS (m/z) 268 (0.6, M⁺), 253 (0.5), 250 (0.5), 171 (13), 153 (28), 97 (100), 96 (23), 81 (21), 69 (25), 55 (72).

Anal. Calcd. for C₁₆H₂₈O₃ : C, 71.60 ; H, 10.52. Found : C, 71.80 ; H, 10.60.

Data for 86.

IR (CHCl₃, cm⁻¹) 3619, 2930, 2860, 1715, 1460, 1365, 1260, 1127, 980 cm⁻¹.

1H NMR (CDCl₃, 400 MHz) δ 0.89 (s, 3H), 0.98 (s, 3H), 1.23 (d, J = 6 Hz, 3H), 1.1-1.7 (m, 10H), 2.0 (m, 1H), 2.22 (m, 1H), 2.3 (m, 2H), 3.63 (d, J = 7 Hz, 1H), 4.98 (m, J = 6, 6, 4 Hz, 1H), 5.45 (m, J = 8, 16 Hz, 1H), 5.53 (m, J = 4, 9, 16 Hz, 1H).

13C NMR (CDCl₃) δ 18.8 (CH₃), 21.0 (CH₃), 24.3 (CH₃), 25.7 (CH₂), 27.9 (CH₂), 28.4 (CH₂), 30.2 (CH₂), 31.8 (CH₂), 35.2 (CH₂), 36.1 (CH₂), 71.2 (CH), 81.7 (CH), 131.0 (CH), 134.7 (CH), 173.5 (C=O).

LRMS m/z 268 (0.7, M⁺), 253 (0.3), 250 (0.3), 171 (18), 153 (39), 125 (24), 97 (96), 83 (21), 70 (24), 69 (41), 55 (100).

HRMS calcd for C₁₆H₂₈O₃ : 268.2038 ; found : 268.2038.
9-Oxo-13-tetradecanolide (42) (50 mg, 0.21 mmol) was mixed with 3 mL of isopropyl acetate and 4 mg of toluenesulfonic acid (0.02 mmol) and the resulting reaction mixture was refluxed for 72 h. A mixture of acetone and isopropyl acetate was very slowly distilled from the reaction which made it necessary to replace the isopropyl acetate in the reaction flask every 10 h. After 72 h, evaporation of the solvent and column chromatography with ethyl acetate - petroleum ether (2:8) as eluant afforded 53 mg of a 27:15:24:34 mixture of 4 isomeric enol acetates (91%).

**IR** (CHCl₃, cm⁻¹) 2970, 2890, 1727, 1720, 1460, 1370, 1230.

**¹H NMR** (CDCl₃, 400 MHz) δ 1.20 (d, J = 7 Hz, 3H), 1.23 (d, J = 7 Hz, 3H), 1.24 (d, J = 7 Hz, 3H), 1.26 (d, J = 7 Hz, 3H), 1.2-2.5 (m, 72H), 2.1 (s, 3H), 2.12 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 4.9-5.2 (m, 8H).

**¹³C NMR** (CDCl₃) δ 15.1 (CH₃), 18.4 (CH₃), 19.3 (CH₃), 19.6 (CH₃), 20.1 (CH₃), 20.5 (CH₃), 20.6 (CH₃), 20.8 (CH₃), 20.9 (CH₂), 21.2 (CH₂), 21.3 (CH₂), 22.3 (CH₂), 23.7 (CH₂), 24.0 (CH₂), 24.1 (CH₂), 24.3 (CH₂), 24.4 (CH₂), 25.2 (CH₂), 25.4 (CH₂), 26.2 (CH₂), 26.4 (CH₂), 26.5 (CH₂), 26.8 (CH₂), 27.3 (CH₂), 27.5 (CH₂), 28.1 (CH₂), 28.3 (CH₂), 31.0 (CH₂), 31.8 (CH₂), 32.7 (CH₂), 33.2 (CH₂), 33.4 (CH₂), 34.0 (CH₂), 34.9 (CH₂), 35.7 (CH₂), 35.9 (CH₂), 65.6 (CH), 68.5 (CH), 69.2 (CH), 71.3 (CH), 116.4 (CH), 116.5 (CH), 117.7 (CH), 117.9 (CH), 146.3 (C), 148.2
(C), 149.3 (C), 149.8 (C), 168.6 (C=O), 168.9 (C=O), 169.4 (C=O), 169.5 (C=O), 172.6 (C=O), 172.8 (C=O), 173.2 (C=O), 173.6 (C=O).

**LRMS** (m/z) 282 (4, M+), 240 (27), 238 (17), 222 (32), 125 (39), 112 (100), 97 (54), 83 (32), 55 (83).

**HRMS** calcd for C_{16}H_{26}O_{4} : 282.1831 ; found : 282.1828.

### 3.25 (8Z)-9-(TRIMETHYLSILYLOXY)-8-TETRADECEN-13-OLIDE (93)

![Chemical Structure](attachment:image)

Trimethylsilyl trifluoromethanesulfonate (94 mg, 0.42 mmol) was added dropwise to a solution of 100 mg of 9-oxo-13-tetradecanolide (42) (0.42 mmol) and 34 mg of triethylamine (0.33 mmol) in 2 mL of dry ether at 0 °C. The reaction mixture was stirred overnight at room temperature and then was diluted with ether, washed with NH₄Cl solution, dried (MgSO₄), filtered, and the solvent evaporated. The crude product was filtered through a silica gel column with ethyl acetate - petroleum ether (5:95) as eluant to afford 97 mg of four isomeric silyl enol ethers in a ratio of 5:85:4:6 (92:93:103:104).

Data for 92 see 3.22c.
Data for 23.

IR (CHCl₃, cm⁻¹) 2940, 2860, 1720, 1665, 1460, 1250, 840.

¹H NMR (CDCl₃, 400 MHz) δ 0.15 (s, 9H), 1.17 (d, J = 6.5 Hz, 3H), 1.2-2.10 (m, 16H), 2.25 (m, 2H), 4.40 (t, J = 8 Hz, 1H), 5.05 (m, J= 3.5, 6.5, 7.0, 1H).

¹³C NMR (CDCl₃) δ 0.6 (CH₃), 13.7 (CH₃), 21.0 (CH₂), 24.5 (CH₂), 24.6 (CH₂), 27.3 (CH₂), 28.4 (CH₂), 28.6 (CH₂), 33.3 (CH₂), 34.4 (CH₂), 34.7 (CH₂), 69.2 (CH), 109.7 (CH), 149.8 (C), 173.9 (C=O).

LRMS (m/z) 312 (28 M⁺), 197 (37), 184 (28), 169 (40), 155 (31), 143 (23), 130 (29), 75 (35), 73 (100), 55 (29).

HRMS calcd for C₁₇H₃₂O₃Si : 312.2121 ; found : 312.2119.

Data for 103.

IR (CHCl₃, cm⁻¹) 2940, 2860, 1720, 1665, 1460, 1250, 840.

¹H NMR (CDCl₃, 400 MHz) δ 0.14 (s, 9H), 1.18 (d, J = 6.5 Hz, 3H), 1.2-2.46 (m, 18H), 4.52 (dd, J = 9, 16 Hz, 1H), 5.05 (m, 1H).

¹³C NMR (CDCl₃) δ 0.7 (CH₃), 19.5 (CH₃), 21.3 (CH₂), 24.0 (CH₂), 24.9 (CH₂), 27.8 (CH₂), 29.4 (CH₂), 29.5 (CH₂), 33.4 (CH₂), 34.7 (CH₂), 35.2 (CH₂), 70.2 (CH), 108.9 (CH), 150.2 (C), 172.6 (C=O).

LRMS (m/z) 312 (27, M⁺), 184 (26), 169 (44), 155 (25), 143 (21), 130 (24), 75 (46), 73 (100), 55 (40).

HRMS calcd for C₁₇H₃₂O₃Si : 312.2121 ; found : 312.2117.

Data for 104.

IR (CHCl₃, cm⁻¹) 2940, 2860, 1720, 1665, 1460, 1250, 840.

¹H NMR (CDCl₃) δ 0.13 (s, 9H), 1.16 (d, J = 6.5 Hz, 3H), 1.2-2.45 (m, 18H), 4.62 (t, J = 8 Hz, 1H), 4.98 (m, 1H).
\[^{13}\text{C NMR} \ (\text{CDCl}_3) \delta 0.6 \ (\text{CH}_3), \ 19.5 \ (\text{CH}_3), \ 21.2 \ (\text{CH}_2), \ 24.7 \ (\text{CH}_2), \ 24.8 \ (\text{CH}_2), \ 26.5 \ (\text{CH}_2), \ 28.5 \ (\text{CH}_2), \ 28.9 \ (\text{CH}_2), \ 34.1 \ (\text{CH}_2), \ 34.4 \ (\text{CH}_2), \ 34.6 \ (\text{CH}_2), \ 69.5 \ (\text{CH}), \ 109.9 \ (\text{CH}), \ 150.5 \ (\text{C}), \ 173.5 \ (\text{C}=\text{O}).\]

LRMS (m/z) 312 (28 M\(^+\)), 197 (24), 184 (20), 169 (32), 155 (20), 143 (17), 130 (17), 75 (39), 73 (100), 55 (18).

HRMS calcd for C\(_{17}\)H\(_{32}\)O\(_3\)Si : 312.2121; found : 312.2125.

3.26 (8E)-9-(TRIETHYLSILYLOXY)-8-TETRADECEN-13-OLIDE (94)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Si(CH}_2\text{CH}_3)_3 & \\
\end{align*}
\]

This reaction was performed in an NMR tube. To a solution of 50 mg of (7E)-9-oxo-7-tetradecen-13-olide (72) (0.21 mmol) in 1 mL of triethylsilane was added 1 mg of tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst). The resulting suspension was sonicated for 12 h at 20 °C. The reaction mixture was diluted with 10 mL of hexane and filtered through a Celite pad. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:9) as eluant afforded 69 mg (92%) of a 89:11 mixture of 94 and 95 (Carbowax-20M column, 190 °C).
Data for 24.

IR (CHCl₃, cm⁻¹) 2960, 2880, 1725, 1670, 1470, 1380, 1240, 1110, 920.

¹H NMR (CDCl₃, 400 MHz) δ 0.66 (q, J = 8 Hz, 6H), 0.97 (t, J = 8 Hz, 9H), 1.24 (d, J = 6 Hz, 3H), 1.2-2.5 (m, 18H), 4.45 (dd, J = 6, 11 Hz, 1H), 4.92 (m, 1H).

¹³C NMR (CDCl₃) δ 6.8 (CH₃), 20.3 (CH₃), 5.1 (CH₂), 22.8 (CH₂), 24.5 (CH₂), 25.5 (CH₂), 26.2 (CH₂), 26.9 (CH₂), 28.3 (CH₂), 30.7 (CH₂), 35.3 (CH₂), 35.8 (CH₂), 69.3 (CH), 106.5 (CH), 152.1 (C), 173.7 (C=O).

LRMS (m/z) 354 (31, M⁺), 253 (23), 239 (94), 226 (95), 211 (82), 197 (78), 157 (64), 103 (69), 87 (100), 75 (96).

HRMS calcd for C₂₀H₃₈O₃Si : 354.2590 ; found : 354.2593.

Data for 25.

IR (CHCl₃, cm⁻¹) 2960, 2880, 1725, 1670, 1470, 1380, 1240, 1110, 920.

¹H NMR (CDCl₃, 400 MHz) δ 0.64 (q, J = 8 Hz, 6H), 0.98 (t, J = 8 Hz, 9H), 1.19 (d, J = 6 Hz, 3H), 1.2-2.5 (m, 18H), 4.38 (t, J = 7 Hz, 1H), 5.08 (m, 1H).

¹³C NMR (CDCl₃) δ 6.7 (CH₃), 18.6 (CH₃), 5.5 (CH₂), 21.1 (CH₂), 24.3 (CH₂), 24.6 (CH₂), 26.2 (CH₂), 27.3 (CH₂), 28.5 (CH₂), 33.3 (CH₂), 35.3 (CH₂), 35.8 (CH₂), 69.3 (CH), 109.1 (CH), 150.0 (C), 173.8 (C=O).

LRMS (m/z) 354 (32, M⁺), 253 (19), 239 (89), 226 (100), 211 (88), 197 (72), 157 (67), 103 (79), 87 (97), 75 (97), 59 (78).

HRMS calcd for C₂₀H₃₈O₃Si : 354.2590 ; found : 354.2585.
a. Reaction of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide with L-Selectride

(7E)-10,10-Dimethyl-9-oxo-7-tetradecen-13-olide (74) (20 mg, 0.075 mmol) was dissolved in 5 mL of THF and cooled to -78 °C. To this solution was added 80 µL of L-Selectride (1 M, 0.080 mmol) and the resulting reaction mixture stirred at -78 °C for 15 min. A filtered mixture of 15 mg triethylamine (0.15 mmol), 16 mg chlorotrimethylsilane (0.15 mmol) and 1 mL of THF was then added and the cooling bath was removed. The resulting solution was stirred at room temperature for 30 min. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (3:97) as eluant afforded 23 mg (90%) of 96.

IR (CHCl₃, cm⁻¹) 2920, 2875, 1720, 1657, 1456, 1358, 1126, 855.

¹H NMR (CDCl₃, 400 MHz) δ 0.19 (s, 9H), 0.96 (s, 3H), 1.02 (s, 3H), 1.17 (d, J = 6 Hz, 3H), 1.2-1.85 (m, 12H), 1.97 (m, 1H), 2.05 (m, 1H), 2.28 (m, 2H), 4.44 (dd, J = 6, 8 Hz, 1H), 5.05 (m, 1H).

¹³C NMR (CDCl₃) δ 1.3 (CH₃), 18.9 (CH₃), 26.5 (CH₃), 28.0 (CH₃), 25.2 (CH₂), 25.5 (CH₂), 27.6 (CH₂), 28.3 (CH₂), 29.3 (CH₂), 31.7 (CH₂), 34.4 (CH₂), 36.3 (CH₂), 70.6 (CH), 106.0 (CH), 39.8 (C), 156.6 (C), 171.7 (C=O).
LRMS (m/z) 340 (13, M⁺), 286 (24), 196 (30), 171 (20), 158 (68), 143 (35), 97 (30), 75 (41), 82 (53), 75 (48), 73 (100), 69 (22), 55 (52).


b. Reaction of 10,10-dimethyl-9-oxo-13-tetradecanolide with trimethylsilyl trifluoromethanesulfonate

Trimethylsilyl trifluoromethanesulfonate (41 mg, 0.19 mmol) was added dropwise to a solution of 50 mg of 10,10-dimethyl-9-oxo-13-tetradecanolide (43) (0.19 mmol) and 15 mg of triethylamine (0.15 mmol) in 2 mL ether at 0 °C. The reaction mixture was stirred for 5 h at room temperature and then diluted with ethyl acetate, washed with NaHCO₃ solution, dried (MgSO₄), filtered and the solvent evaporated. The crude product was chromatographed with ethyl acetate - petroleum ether (5:95) as eluant to afford 35 mg of 96 (55%) and 18 mg of 43 (starting material).

3.28 (8Z)-10,10-DIMETHYL-9-(TRIETHYLSILYLOXY)-8-TETRADECEN-13-OLIDE (98)

To a solution of 20 mg of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide (74) (0.075 mmol) in 1 mL triethylsilane was added 1 mg of tris(triphenylphosphine)rhodium(I) chloride
(Wilkinson's catalyst). The resulting suspension was stirred for 2 h at 20 °C. Then the reaction mixture was diluted with 10 mL of hexane and filtered through a Celite pad. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:9) as eluant afforded 25 mg (94%) of a 91:9 mixture of \( \text{28} \) and \( \text{22} \) (DB-210 column, 150 °C).

Data for \( \text{28} \).

IR (CHCl\(_3\), cm\(^{-1}\)) 2960, 2940, 2860, 1725, 1670, 1470, 1380, 1240, 1110, 920.

\( ^1\text{H} \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 0.70 (q, \( J = 8 \text{ Hz}, 6\text{H} \)), 0.98 (s, 3H), 1.00 (t, \( J = 8 \text{ Hz}, 9\text{H} \)), 1.03 (s, 3H), 1.18 (d, \( J = 6 \text{ Hz}, 3\text{H} \)), 1.0-1.85 (m, 12H), 2.00 (m, 1H), 2.17 (m, 3H), 4.43 (dd, \( J = 6, 8.5 \text{ Hz}, 1\text{H} \)), 5.18 (m, 1H).

\( ^{13}\text{C} \) NMR (CDCl\(_3\)) \( \delta \) 7.5 (CH\(_3\)), 19.0 (CH\(_3\)), 26.7 (CH\(_3\)), 28.0 (CH\(_3\)), 6.6 (CH\(_2\)), 25.2 (CH\(_2\)), 25.7 (CH\(_2\)), 27.8 (CH\(_2\)), 28.4 (CH\(_2\)), 29.4 (CH\(_2\)), 31.8 (CH\(_2\)), 34.5 (CH\(_2\)), 36.6 (CH\(_2\)), 70.7 (CH), 105.6 (CH), 39.9 (C), 156.6 (C), 172.5 (C=O).

LRMS (m/z) 382 (73, M\(^+\)), 267 (38), 213 (21), 200 (53), 171 (25), 157 (49), 115 (42), 103 (69), 87 (100), 75 (66).

HRMS calcd for C\(_{22}\)H\(_{42}\)O\(_3\)Si : 382.2903 ; found : 382.2883.

Data for \( \text{22} \).

IR (CHCl\(_3\), cm\(^{-1}\)) 2960, 2940, 2850, 1725, 1670, 1470, 1380, 1240, 1110, 920.

\( ^1\text{H} \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 0.71 (q, \( J = 8 \text{ Hz}, 6\text{H} \)), 0.98 (s, 3H), 1.00 (t, \( J = 8 \text{ Hz}, 9\text{H} \)), 1.03 (s, 3H), 1.20 (d, \( J = 6 \text{ Hz}, 3\text{H} \)), 1.1-1.9 (m, 12H), 1.96 (m 1H), 2.29 (m, 3H), 4.50 (dd, \( J = 7, 8.5 \text{ Hz}, 1\text{H} \)), 5.05 (m, 1H).

\( ^{13}\text{C} \) NMR (CDCl\(_3\)) \( \delta \) 6.7 (CH\(_3\)), 18.6 (CH\(_3\)), 5.5 (CH\(_2\)), 21.1 (CH\(_2\)), 24.3 (CH\(_2\)), 24.6 (CH\(_2\)), 26.2 (CH\(_2\)), 27.3 (CH\(_2\)), 28.5 (CH\(_2\)), 33.3 (CH\(_2\)), 35.3 (CH\(_2\)), 35.8 (CH\(_2\)), 69.3 (CH), 109.1 (CH), 150.0 (C), 173.8 (C=O).

LRMS (m/z) 382 (52, M\(^+\)), 281 (23), 269 (21), 200 (39), 171 (23), 157 (49), 103 (82), 87 (73), 75 (100), 59 (33).
HRMS calcd for C_{22}H_{42}O_{3}Si: 382.2903; found: 382.2907.

3.29 7-METHYL-9-(TRIMETHYLSILYLOXY)-8-TETRADECEN-13-OLIDE (108, 109)

![Diagram of 7-METHYL-9-(TRIMETHYLSILYLOXY)-8-TETRADECEN-13-OLIDE (108, 109)]

108 109

a. Reaction of (7E)-9-oxo-7-tetradecen-13-olide with lithium dimethylcopper(I) in the presence of chlorotrimethylsilane

Copper(I) iodide (102 mg, 0.54 mmol) was suspended in 2 mL of THF and cooled to 0 °C. Methylithium (1.4 M, 0.72 mL, 1.0 mmol) was added dropwise and the resulting colorless solution stirred at 0 °C for 20 min. The solution was cooled to -78 °C and then treated with 76 μL of chlorotrimethylsilane (0.6 mmol), followed by 100 mg of (7E)-9-oxo-7-tetradecen-13-olide (72) (0.42 mmol) dissolved in 1 mL THF. After 1 h, the reaction mixture was quenched with NH₄Cl solution. The organic phase was diluted with ethyl acetate, washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:8) as eluant afforded 96.2 mg of 108 and 31 mg 109 (93%). A small amount of 110 was formed during the reaction, however this compound could not be isolated.
Data for 108.

IR (CHCl₃, cm⁻¹) 2950, 2870, 1720, 1660, 1470, 1380, 1240, 980, 840.

¹H NMR (C₆D₆, 400 MHz) δ 0.16 (s, 9H), 0.89 (d, J = 7 Hz, 3H), 1.19 (d, J = 6 Hz, 3H), 1.2-2.5 (m, 17H), 4.19 (d, J = 9.5 Hz, 1H), 5.03 (m, 1H).

¹³C NMR (CDCl₃) δ 0.7(CH₃), 18.4 (CH₃), 22.4 (CH₃), 23.0 (CH₂), 25.1 (CH₂), 27.1 (CH₂), 29.1 (CH₂), 33.6 (CH₂), 34.1 (CH₂), 35.6 (CH₂), 38.3 (CH₂), 29.5 (CH), 70.2 (CH), 115.4 (CH), 150.0 (C), 173.8 (C=O).

LRMS (m/z) 326 (18, M⁺), 211 (25), 184 (30), 168 (75), 139 (14), 75 (42), 73 (100), 69 (30), 55 (34), 44 (31), 41 (21).

HRMS calcd for C₁₈H₃₄O₃S: 326.2277; found: 326.2274.

Data for 109.

IR (CHCl₃, cm⁻¹) 2960, 2880, 1725, 1670, 1460, 1380, 1240, 980, 840.

¹H NMR (CDCl₃) δ 0.18 (2, 9H), 0.92 (d, J = 6 Hz, 3H), 1.24 (d, J = 6 Hz, 3H), 1.2-2.5 (m, 17H), 4.24 (d, J = 10 Hz, 1H), 4.97 (m, 1H).

¹³C NMR (CDCl₃) δ 0.5 (CH₃), 20.5 (CH₃), 23.2 (CH₃), 25.0 (CH₂), 26.3 (CH₂), 27.1 (CH₂), 28.4 (CH₂), 32.7 (CH₂), 35.1 (CH₂), 36.3 (CH₂), 37.5 (CH₂), 30.6 (CH), 71.2 (CH), 113.4 (CH), 151.4 (C), 173.5 (C=O).

LRMS (m/z) 326 (17, M⁺), 211 (20), 169 (46), 168 (23), 211 (82), 143 (13), 139 (13), 81 (10), 75 (49), 73 (100), 69 (32), 55 (43).

HRMS calcd for C₁₈H₃₄O₃Si: 326.2277; found: 326.2276.

b. Reaction of (7E)-9-oxo-7-tetradecen-13-olide with methylcopper in the presence of TMEDA and chlorotrimethylsilane

A dry flask was charged with 122 mg of N,N,N',N'-tetramethylethylenediamine (1.05 mmol), 92 mg of copper(I) iodide (0.48 mmol) and 4 mL of THF. After stirring for 10 min a
black-brown solution had formed, which was cooled to 0 °C. Methyllithium (1.3 M, 369 μL, 0.48 mmol) was added dropwise and the resulting yellow solution was stirred at 0 °C for 10 min. The solution was cooled to -78 °C and, after 20 min, 146 mg of chlorotrimethylsilane (1.34 mmol) was added, followed by 83 mg (7E)-9-oxo-7-tetradecen-13-olide (42) (0.35 mmol) in 1 mL of THF. After 20 min, the reaction mixture was quenched with NH₄Cl solution. The organic phase was diluted with ethyl acetate, washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:8) as eluant afforded 102 mg of a 82:11:7 mixture of 108 and 109 and 110 (89%).

3.30 7-METHYL-9-OXO-13-TETRADECANOLIDE (105, 106)

\[ \text{106} \quad \text{105} \]

a. Hydrolysis of trimethylsilyl enol ether 108 with tetrabutylammonium fluoride

(7S*,13S*)-(8E)-7-methyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide (108) (20 mg, 0.061 mmol) dissolved in 5 mL THF was treated with 0.5 mL of tetrabutylammonium fluoride (1 M). The resulting yellow reaction mixture was stirred at room temperature for 20 min, washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents followed by
column chromatography with ethyl acetate - petroleum ether (1:8) as eluant afforded 14 mg (90%) of **105**.

**IR** (CHCl₃, cm⁻¹) 2960, 2900, 1715, 1470, 1260, 1125.

**¹H NMR** (CDCl₃, 400 MHz) δ 0.90 (d, J = 7 Hz, 3H), 1.21 (d, J = 6 Hz, 3H), 1.2-2.53 (m, 18H), 2.57 (dd, J = 5.5, 12 Hz, 1H), 5.00 (m, J = 6, 6.2, 4.5 Hz, 1H).

**¹³C NMR** (CDCl₃) δ 20.2 (CH₃), 21.0 (CH₃), 24.1 (CH₂), 24.4 (CH₂), 24.8 (CH₂), 26.4 (CH₂), 34.1 (CH₂), 34.6 (CH₂), 35.0 (CH₂), 41.5 (CH₂), 47.9 (CH₂), 29.1 (CH), 69.5 (CH), 173.3 (C=O), 209.6 (C=O).

**LRMS** (m/z) 254 (8, M⁺), 236 (7), 139 (52), 115 (34), 112 (100), 97 (54), 83 (33), 69 (33), 55 (45).


**b. Hydrolysis of trimethylsilyl enol ether 109 with tetrabutylammonium fluoride**

(7R*,13S*)-(8E)-7-methyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide **109** (15 mg, 0.046 mmol) dissolved in 5 mL of THF was treated with 0.5 mL of tetrabutylammonium fluoride (1 M). The resulting yellow reaction mixture was stirred at room temperature for 20 min, washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents followed by column chromatography with ethyl acetate - petroleum ether (1:8) afforded 11 mg (87%) of **106**.

**IR** (CHCl₃, cm⁻¹) 2950, 2880, 1712, 1470, 1260, 1130.

**¹H NMR** (CDCl₃, 400 MHz) δ 0.95 (d, J = 6.5 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.2-2.5 (m, 18H), 2.55 (dd, J = 6.5, 12 Hz, 1H), 4.95 (m, 1H).

**¹³C NMR** (CDCl₃) δ 20.2 (CH₃), 21.3 (CH₃), 24.2 (CH₂), 24.4 (CH₂), 25.0 (CH₂), 28.5 (CH₂), 34.5 (CH₂), 35.0 (CH₂), 35.4 (CH₂), 42.7 (CH₂), 48.3 (CH₂), 70.3 (CH), 173.2 (C=O), 211.6 (C=O).

**LRMS** (m/z) 254 (11, M⁺), 236 (8.4), 185 (18), 139 (52), 125 (15), 113 (42), 112 (100), 97 (45), 83 (25), 69 (29), 55 (39).
HRMS calcd for C_{15}H_{26}O_{3} : 254.1881 ; found : 254.1882.

c. Reaction of (7E)-9-oxo-7-tetradecen-13-olide with lithium dimethylcopper(I)

Copper(I) iodide (50 mg, 0.25 mmol) was suspended in 5 mL of ether and cooled to 0 °C. Methylthium (1.2 M, 0.42 mL, 0.50 mmol) was added dropwise and the resulting colorless solution stirred at 0 °C for 20 min. The solution was further cooled to -20 °C and then treated with 50 mg (7E)-9-oxo-7-tetradecen-13-olide (72) (0.21 mmol) dissolved in 1 mL of THF. After 2 h at -20 °C the reaction mixture was quenched with NH_{4}Cl solution, the organic phase diluted with ether, washed with saturated NaCl solution, dried (MgSO_{4}) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:8) as eluant afforded 37 mg (70%) of a 55:45 mixture of 105 and 106 (SE-30 column, 140 °C).

1,4 Additions of cuprate reagents without chlorotrimethylsilane or boron trifluoride etherate yielded varying amounts of polar material. One of the by-products was isolated and characterized as compound 107.

\[
\begin{align*}
\text{IR (CHCl}_{3}, \text{ cm}^{-1}) & : 3680 - 3300, 3608, 2960, 2930, 2860, 1710, 1459, 1374, 1130, 890. \\
{^1}H \text{ NMR (CDCl}_{3}, \text{ 400 MHz}) & : \delta 0.88 (d, J = 6 \text{ Hz}, 3\text{H}), 1.18 (d, J = 6 \text{ Hz}, 3\text{H}), 1.1-1.75 (m, 14\text{H}), 1.20 (s, 6\text{H}), 2.0 (m, 1\text{H}), 2.19 (dd, J = 8, 15 \text{ Hz}, 1\text{H}), 2.38 (dd, J = 6, 15 \text{ Hz}, 1\text{H}), 2.42 (m, 2\text{H}), 3.76 (m, 1\text{H}).
\end{align*}
\]
LRMS (m/z) 268 (11, M-H2O), 253 (43), 157 (28), 139 (84), 130 (51), 112 (76), 97 (66), 83 (47), 69 (100), 55 (70).

HRMS calcd for C17H32O2 : 268.2400 ; found : 268.2402.

d. Reaction of (7E)-9-oxo-7-tetradecen-13-olide with lithium dimethylcopper(I) and boron trifluoride etherate

A 59 mg sample of copper(I) iodide (0.31 mmol) was suspended in 1 mL of ether and cooled to 0 °C. Methylithium (1.4 M, 0.39 mL, 0.55 mmol) was added dropwise and the resulting solution stirred at 0 °C for 20 min. The solution was cooled to -78 °C and then treated with 70 mg of boron trifluoride etherate (0.5 mmol), followed by 50 mg of (7E)-9-oxo-7-tetradecen-13-olide (22) (0.21 mmol) dissolved in 0.5 mL of ether. After 2 h at -78 °C, the reaction mixture was quenched with NH4Cl solution, the organic phase diluted with ethyl acetate, washed with saturated NaCl solution, dried (MgSO4) and filtered. Evaporation of the solvents and column chromatography with chloroform - methanol (99:1) as eluant afforded 45 mg (84%) of a 76:24 mixture of 105 and 106 (SE-30 column, 140 °C).

e. Reaction of 9-oxo-7-tetradecen-13-olide with a higher order organocopper reagent

Thiophene (51 mg, 0.6 mmol) in 4 mL THF was treated with 375 μL of n-butyllithium (1.6 M, 0.6 mmol) at -78 °C. The mixture was stirred for 15 min at -78 °C, then 30 min at -20 °C. The resulting solution was transferred via a cannula into a slurry of 54 mg of copper(I) cyanide (0.6 mmol) in 1 mL of THF at -78 °C. The mixture was warmed to - 30 °C, giving a clear tan solution which was cooled again to -78 °C and treated with 428 μL of methyllithium (1.4 M, 0.6 mmol). This solution was stirred at -78 °C for 30 min and then treated with 50 mg of (7E)-9-oxo-7-tetradecen-13-olide (22) (0.21 mmol) dissolved in 1 mL of THF). After 2 h the reaction mixture was quenched with NH4Cl solution, the organic phase was diluted with ether,
washed with saturated NaCl solution, dried (MgSO₄) and filtered. Evaporation of the solvents followed by column chromatography with ethyl acetate - petroleum ether (1:9) as eluant afforded 34 mg (63%) of a 60:40 mixture of 105 and 106 (SE-30 column, 140 °C).

### 3.31 7,10,10-TRIMETHYL-9-(TRIMETHYLSILYLOXY)-8-TETRADECEN-13-OLIDE (111, 112)

a. Reaction of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide with lithium dimethylcopper(I) in the presence of chlorotrimethylsilane

Copper(I) iodide (198 mg, 1.04 mmol) was suspended in 2 mL of THF and cooled to 0 °C. Methyllithium (1.4 M, 1.35 mL, 1.9 mmol) was added dropwise and the resulting colorless solution was stirred at 0 °C for 20 min. The solution was cooled to -78 °C and treated with 206 mg of chlorotrimethylsilane (1.9 mmol), followed by 70 mg of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide (74) (70 mg, 0.26 mmol) dissolved in 1 mL of THF. After 1 h, the reaction mixture was quenched with NH₄Cl, the organic phase was washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (5:95) as eluant afforded 74 mg 111 and 13 mg 112 (85%).
Data for 111.

IR (CHCl₃, cm⁻¹) 2950, 2940, 2870, 1725, 1665, 1460, 1350, 1220, 850.

¹H NMR (CDCl₃, 400 MHz) δ 0.23 (s, 9H), 0.95 (s, 3H), 0.96 (s, 3H), 0.99 (d, J = 7.5 Hz, 3H), 1.11 (d, J = 6 Hz, 3H), 1.15-2.6 (m, 15H), 4.26 (d, J = 10 Hz, 1H), 5.12 (m, 1H).

¹³C NMR (CDCl₃) δ 1.3 (CH₃), 19.1 (CH₃), 23.1 (CH₃), 27.0 (CH₃), 27.4 (CH₃), 25.8 (CH₂), 28.1 (CH₂), 29.9 (CH₂), 32.0 (CH₂), 34.9 (CH₂), 37.2 (CH₂), 39.6 (CH₂), 30.5 (CH), 71.4 (CH), 112.6 (CH), 43.3 (C), 155.6 (C), 173.1 (C=O).

LRMS (m/z) 354 (29, M⁺), 253 (23), 239 (26), 223 (21), 211 (13), 158 (24), 143 (20), 73 (100).

HRMS calcd for C₂ₐH₃₈O₃Si : 354.2590 ; found : 354.2614.

Data for 112.

IR (CHCl₃, cm⁻¹) 2960, 2935, 2880, 1725, 1670, 1460, 1360, 1240, 840.

¹H NMR (CDCl₃, 400 MHz) δ 0.18 (s, 9H), 0.95 (s, 3H), 0.96 (s, 3H), 1.01 (d, J = 7.5 Hz, 3H), 1.06 (d, J = 6 Hz, 3H), 1.15-2.6 (m, 15H), 4.23 (d, J = 10 Hz, 1H), 5.32 (m, 1H).

¹³C NMR (CDCl₃) δ 1.3 (CH₃), 18.2 (CH₃), 23.1 (CH₃), 27.0 (CH₃), 27.4 (CH₃), 25.7 (CH₂), 29.2 (CH₂), 31.2 (CH₂), 31.9 (CH₂), 33.6 (CH₂), 34.8 (CH₂), 39.8 (CH₂), 28.6 (CH), 68.9 (CH), 113.6 (CH), 42.8 (C), 155.8 (C), 173.1 (C=O).

LRMS (m/z) 354 (39, M⁺), 339 (19), 239 (29), 223 (38), 183 (22), 158 (33), 143 (30), 73 (100).

HRMS calcd for C₂₀H₃₈O₃Si : 354.2590 ; found : 354.2588.
b. Reaction of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide with methylcopper in the presence of TMEDA and chlorotrimethylsilane

A dry flask was charged with 26 mg of N,N,N',N'-tetramethylethylenediamine (0.22 mmol), 18.5 mg of copper(I) iodide (0.098 mmol) and 4 mL of THF. After stirring for 10 min, a black-brown solution had formed which was cooled to 0 °C. Methylthiium (1.3 M, 75 μL, 0.098 mmol) was added dropwise and the resulting yellow solution was stirred at 0 °C for 10 min. Then the solution was cooled to -78 °C, and after 20 min, was treated with 25 mg of chlorotrimethylsilane (0.22 mmol), followed by 20 mg of (7E)-10,10-dimethyl-9-oxo-7-tetradecen-13-olide (74) (0.075 mmol) dissolved in 1 mL of THF. After 20 min, the reaction mixture was quenched with NH₄Cl, the organic phase washed with NaHCO₃ solution, dried (MgSO₄) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:8) as eluant afforded 24 mg of a 93 : 7 mixture of 111 and 112 (89%).
3.32 7,10,10-TRIMETHYL-9-OXO-13-TETRADECANOLIDE (113, 114)

a. Hydrolysis of trimethylsilyl enol ether 111 with tetrabutylammonium fluoride

(7S*,13S*)-(8Z>7J0,10-unmethyl-9^111 (31 mg, 0.090 mmol) dissolved in 5 mL of THF was treated with 0.5 mL of tetrabutylammonium fluoride (1 M). The resulting yellow reaction mixture was stirred at room temperature for 20 min, washed with NaHCO3 solution, dried (MgSO4) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:9) as eluant afforded 20 mg (82%) of 113.

Data for 113.

mp 76 - 78 °C (hexane).

IR (CHCl3, cm⁻¹) 2950, 2860, 1720, 1705, 1470, 1375, 1260, 1045.

1H NMR (CDCl3, 400 MHz) δ 0.94 (d, J = 7.5 Hz, 3H), 1.02 (s, 3H), 1.18 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H), 1.2-1.7 (m, 11H), 1.83 (m, 1H), 1.86 (dd, J = 8, 17 Hz), 2.05 (m, 1H), 2.29 (m, J = 4, 6.5, 14.5 Hz, 1H), 2.42 (m, 3.5, 11, 14.5 Hz, 1H), 2.85 (dd, J = 5.5, 17 Hz, 1H), 5.10 (m, J = 6.5, 4, 3 Hz, 1H).
\[^{13}\text{C}\text{ NMR (CDCl}_3\text{) }\delta 18.8\text{ (CH}_3\text{), 21.1\text{ (CH}_3\text{), 22.1\text{ (CH}_3\text{), 25.7\text{ (CH}_3\text{), 23.2\text{ (CH}_2\text{), 25.1\text{ (CH}_2\text{, 26.7\text{ (CH}_2\text{, 30.2\text{ (CH}_2\text{, 33.2\text{ (CH}_2\text{, 33.6\text{ (CH}_2\text{, 35.1\text{ (CH}_2\text{, 40.9\text{ (CH}_2\text{, 26.7\text{ (CH}, 69.3\text{ (CH}, 48.5\text{ (C, 172.2\text{ (C=O), 214.0\text{ (C=O).}})}}

\text{LRMS (m/z) 282 (3, M\text{ }^+\text{), 185 (17), 167 (7), 139 (9), 97 (100), 86 (28), 84 (43), 55 (61).}}

\text{HRMS calcd for C}_{17}\text{H}_{30}\text{O}_3 : 282.2195 \text{; found : 282.2187.}}

b. \text{ Hydrolysis of trimethylsilyl enol ether 112 with tetrabutylammonium fluoride}}

\((7R^*,13S^*)\text{-}(8E)-7,10,10\text{-trimethyl-9-(trimethylsilyloxy)-8-tetradecen-13-olide (112)}\)

(11 mg, 0.030 mmol) dissolved in 5 mL of THF was treated with 0.5 mL of tetrabutylammonium fluoride (1 M). The resulting yellow reaction mixture was stirred at room temperature for 20 min, washed with NaHCO\text{3 solution, dried (MgSO}_4\text{) and filtered. Evaporation of the solvents and column chromatography with ethyl acetate - petroleum ether (1:8) as eluant afforded 8 mg (88%) of 114.}

\text{Data for 114.}}

\text{IR (CHCl\text{3, cm}^{-1}) 2960, 2860, 1720, 1710, 1470, 1375, 1260, 1040.}

\text{\[^{1}\text{H NMR (CDCl}_3\text{, 400 MHz) }\delta 0.99\text{ (d, J = 7 Hz, 3H), 1.03 (s, 3H), 1.14 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H), 1.2-2.1 (m, 14H), 2.25-2.50 (m, 2H), 2.79 (dd, J = 4, 15.5 Hz, 1H), 4.88 (m, 1H).}}

\text{\[^{13}\text{C NMR (CDCl}_3\text{) }\delta 19.2\text{ (CH}_3\text{), 20.3\text{ (CH}_3\text{), 22.5\text{ (CH}_3\text{), 24.6\text{ (CH}_3\text{, 22.8\text{ (CH}_2\text{, 25.4\text{ (CH}_2\text{, 25.9\text{ (CH}_2\text{, 31.0\text{ (CH}_2\text{, 33.5\text{ (CH}_2\text{, 34.6\text{ (CH}_2\text{, 34.8\text{ (CH}_2\text{, 41.5\text{ (CH}_2\text{, 27.2\text{ (CH}, 70.5\text{ (CH}, 47.3\text{ (C, 173.0\text{ (C=O), 213.3 (C=O).}})

\text{LRMS m/z 282 (3, M\text{ }^+\text{), 185 (17), 167 (7), 139 (9), 97 (100), 86 (28), 84 (43), 55 (61).}}

\text{HRMS calcd for C}_{17}\text{H}_{30}\text{O}_3 : 282.2195 \text{; found : 282.2195.}}\)
REFERENCES


(2) Barton, D.H.R. *Experientia* 1950, 6, 316.


(10) Eliel, E.L. *Experientia* 1953, 9, 91.


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APPENDIX I

MM2/MMP2

The strain energies were calculated using Allinger's MM2 and MMP2 (for compounds with conjugated \( \pi \)-systems) computer programs.\(^{30}\) The force field used in molecular mechanics calculations consists of a set of equations derived from classical mechanics, which contain adjustable parameters that are optimized to obtain the best fit with calculated and experimental properties of molecules. The MM2/MMP2 program is much faster than quantum mechanical calculations and produces very accurate values. In addition, the MM2/MMP2 program allows rapid calculations of even very large molecules, since the equations used are sufficiently simple to be rapidly solved with modern computers.

The final strain energy is the sum of five different energy contributions, namely bond stretching, angle bending, torsional strain, van der Waals interactions and electrostatic effects. This last term includes, for example, dipole-dipole interactions between carbonyl functionalities.

In order to minimize a molecule's energy, the MM2/MMP2 program uses the steepest descent method. The energy of a molecule is calculated for a given set of coordinates (input coordinates). One atom is moved to a new set of coordinates and the molecule's energy is recalculated. If the movement results in a lower 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.

The quality of a molecular mechanics force field, and hence the reliability of its predictions, is critically dependant on the parameters used. For the calculations in this thesis, the parameters of the 1982 MM2 force field were used with the exception of the recently published values for ketones\(^{102}\) and enolates.\(^{103}\)
APPENDIX II

The geometry of the lactone linkage

<table>
<thead>
<tr>
<th>Compounds</th>
<th>O'•••H (Å)</th>
<th>C-H•••O °</th>
<th>C=O'•••H °</th>
<th>C-O-C-H °</th>
<th>C•••O' (Å)</th>
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<td>42</td>
<td>2.40</td>
<td>96</td>
<td>80</td>
<td>37.5</td>
<td>2.686(2)</td>
</tr>
<tr>
<td>43</td>
<td>2.28</td>
<td>104</td>
<td>82</td>
<td>14.1</td>
<td>2.696(7)</td>
</tr>
<tr>
<td>72</td>
<td>2.31</td>
<td>105</td>
<td>82</td>
<td>6.3</td>
<td>2.727(4)</td>
</tr>
<tr>
<td>74a</td>
<td>2.30</td>
<td>104</td>
<td>80</td>
<td>4.2</td>
<td>2.716(9)</td>
</tr>
<tr>
<td>74b</td>
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<td>84</td>
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<td>4.5</td>
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<td>105</td>
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<td>20.0</td>
<td>2.678(5)</td>
</tr>
</tbody>
</table>

\(^a\) O(3), C(14), O(1), C(2), H(2) for 42, 72 and 85; O(2), C(2), O(1), C(14), H(14) for 43, 74, 84 and 113.
SPECTRAL APPENDIX
400 MHz

FREQUENCY (CM⁻¹)

PERCENT TRANSMISSION

MICROMETERS (µm)

4000 3400 2300 2900 3400 2000 1600 1400 1300 1200 1100 1000 800 600 400

4000 3400 2300 2900 3400 2000 1600 1400 1300 1200 1100 1000 800 600 400
400 MHz

72
400 MHz

74