CONFORMATIONALLY CONTROLLED REACTIONS OF UNSATURATED MACROCYCLIC LACTONES AND KETO LACTONES

by

ERIK FENSTER

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Department of ___Chemistry___

The University of British Columbia
Vancouver, Canada

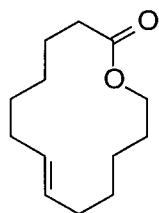Date ___June 28, 2000___

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ABSTRACT

As part of a study of the chemistry of macrocyclic compounds in our laboratory, the 14-membered unsaturated lactones **29** and **30** were synthesized with high stereoselectivity (>16:1 *E/Z*) via the ring closing olefin metathesis (RCM) reaction of the open chain diene esters. The configuration of the double bond in these unsaturated lactones was determined by ^{1}H homonuclear decoupling NMR experiments. Equilibrium studies demonstrated that the RCM reaction proceeds under thermodynamic control in the cases of **29** and **30**. The keto lactones **67** and **68** were synthesized via the hydroboration of **30** followed by TPAP oxidation of the hydroxy lactone products.
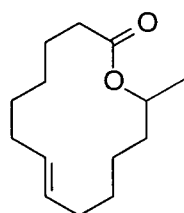
The conformationally controlled reactions of the macrocyclic lactones **29**, **30**, **67** and **68** were investigated. Treatment of the unsaturated lactone **29** with borane tetrahydrofuran complex, disiamylborane and 9BBN led to the formation of the hydroxy lactones **47** and **48** in a 1:1 regioisomeric ratio. Treatment of the unsaturated lactone **30** with the same hydroborating reagents led to the formation of the hydroxy lactones **51**, **52**, **53** and **54** in a 1:1 regioisomeric ratio but with good π-face selectivity (>7:1 using 9BBN). The epoxidation of **30** using MCPBA and methyl(trifluoromethyl)dioxirane, leading to epoxides **63** and **64** also showed moderate π-face selectivity (>3:1 using MCPBA at -78 °C). Treatment of keto lactones **67** and **68** with $NaBH_4$ and K-Selectride under a variety of reaction conditions led to the formation of hydroxy lactones **52**, **53** and **51**, **54**, respectively. The hydroxy lactones were obtained in good stereoselectivity (>10:1 using K-Selectride at -78 °C) in the case of **67**, and in low stereoselectivity (1:1.5 using K-Selectride at -78 °C) in the case of **68**.

In general, the stereoselectivity exhibited in the reactions of these macrocyclic lactones could be rationalized from the conformational analysis of the starting materials or the products. The relative stereochemistry of the stereogenic centers within the compounds synthesized during the course of the
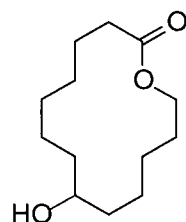
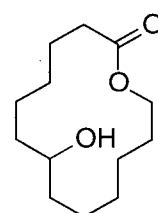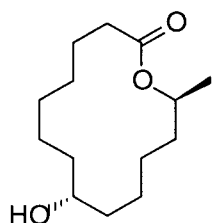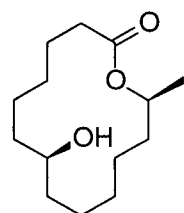project were successfully assigned with the use of chemical correlations and X-ray analysis.

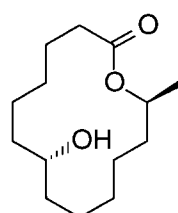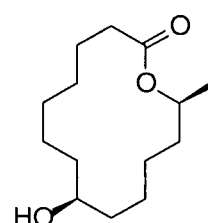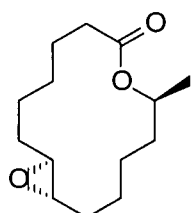| **29** | **30** | **47** | **48** |

| **51** | **52** | **53** | **54** |

| **63** | **64** | **67** | **68** |
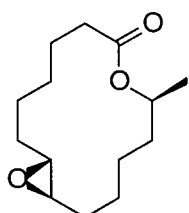
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LIST OF ABBREVIATIONS

AIBN	azobis(isobutyronitrile)
9BBN	9-borabicyclo[3.3.1]nonane
bp	boiling point
Bu	butyl
C_x	carbon (where x represents the number of the carbon atom)
calcd	calculated
CI	chemical ionization
conc.	concentrated
d	doublet
δ	chemical shift
DCC	1,3-dicyclohexylcarbodiimide
DCI	desorption chemical ionization
DHP	dihydropyran
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
EI	electron ionization
Et	ethyl
EtOAc	ethyl acetate
FT	Fourier transform
GC	gas chromatography
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum or spectroscopy
IR	infrared (spectroscopy)
J	coupling constant
Kcal	kilocalorie
K-Selectride	potassium tri- *sec*-butylborohydride

LRMS	low resolution mass spectrum or spectroscopy
m	multiplet
M	moles per litre (concentration)
M^+	parent mass (mass spectra)
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MM	molecular mechanics
mp	melting point
Ms	methylsulfonyl
m/z	mass-to-charge ratio
NMO	4-methylmorpholine *N*-oxide
^{1}H NMR	nuclear magnetic resonance (proton)
^{13}C NMR	nuclear magnetic resonance (carbon)
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
RCM	ring closing olefin metathesis
R_f	retention factor or ratio to front
rt	room temperature
s	singlet
Sia_2BH	disiamylborane
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl

ACKNOWLEDGEMENTS

To my aunt, uncle, and grandparents

CHAPTER 1

INTRODUCTION

Ever since the demonstration of the importance of conformation to chemical reactivity by Hassel[1,2] and Barton,[3] conformational analysis has become an integral part of organic chemistry. Today, conformational analysis is widely used in the interpretation of steric and electronic effects in organic compounds, and of chemical transformations and mechanisms.

1.1   Early Conformational Analysis Studies of Small Ring Systems

In the late 19th century, the concept of conformation in organic molecules began to develop. This originated with the tetrahedral geometry theory for the carbon atom independently reported by van't Hoff[4] and Lebel[5] in 1874. Baeyer further extended this hypothesis to cyclic systems in 1885.[6] In his ring strain theory, carbon atoms which make up a ring are coplanar and the preferred ring angle should be 109.5° in accordance with carbon's tetrahedral geometry. Therefore, internal ring angles which deviated from this ideal angle would introduce strain into the ring system. Cyclopentane was then expected to have the least amount of ring strain (ring angle 108°), whereas smaller as well as larger rings would progressively have an increasing amount of ring strain. Heats of combustion data[7] confirmed Baeyer's theory for cyclopropane up to and including cyclopentane, but larger ring systems possessed less ring strain than expected, and cyclohexane, remarkably, showed no ring strain. In addition to the concept of the tetrahedral arrangement for carbon, van't Hoff further suggested that carbon atoms connected by a single bond could freely rotate and give rise to new arrangements in space.[4] Baeyer chose to ignore this theory of free rotation,

and the oversight led to the eventual breakdown of his theory. However, the ring strain theory was widely accepted early on.
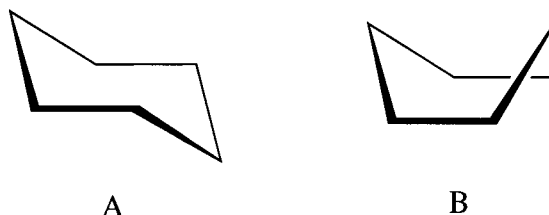
Figure 1. Sachse's rigid (A) and flexible (B) conformations of cyclohexane.[8,9]

The apparent inconsistency of cyclohexane's strain-free state was resolved by Sachse in 1890. Rejecting Baeyer's planar model, Sachse postulated that cyclohexane existed in two conformations.[8,9] These were named the rigid or symmetric form and the flexible or asymmetric form (Figure 1). This postulation incorporated the ideas of the tetrahedral carbon geometry as well as bond rotation put forth by van't Hoff. Sachse further believed that two monosubstituted forms of the rigid conformation were possible and that they could be interconverted (Figure 2).
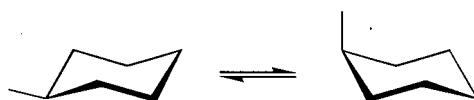
Figure 2. Interconversion of the monosubstituted rigid forms of cyclohexane, as proposed by Sachse.

In 1918, Mohr[10] demonstrated that the Sachse conformations for cyclohexane were interchangeable by rotation about single bonds. Mohr further predicted the existence of decalin as two fused chair isomers, with the *trans* isomer predominating over the *cis* form (Figure 3). This again was in contradiction with Baeyer's theory since two planar 6-membered rings can only
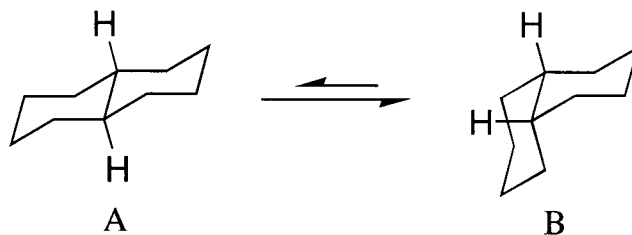
Figure 3. The structures of *trans*-decalin (A) and *cis*-decalin (B) according to Mohr.[10] All but the bridgehead hydrogen atoms have been omitted for clarity.

be fused *cis* and, consequently, a planar *trans*-decalin molecule was not expected to exist or at the least be less favored than the *cis* isomer.

The Baeyer strain theory was nevertheless well accepted until Hückel demonstrated in 1925 the existence of the decalin molecule as an interconvertible mixture of *cis* and *trans* isomers.[11] Two decades later Hassel showed experimentally the distinction between the axial and equatorial bonds.[1]

However, it was Barton's work in 1950 on the conformational analysis of cyclohexanes, including the steroid nucleus, which lead to the widespread acceptance of the chair form of cyclohexane and its use in conformational analysis.[3] Barton in fact viewed the steroids as a series of fused Sachse-Mohr cyclohexane chair conformations in order to correctly explain ester hydrolysis rates, eliminations and product ratios in such systems. He was also able to explain results of reactions involving polysubstituted cyclohexanes. For example, in the case of neomenthol (**1**) and menthol (**2**), Barton suggested that the difference in rates of esterification was due to the difference in steric environment of the two reacting substituents (Figure 4). The hydroxyl substituent in neomenthol (**1**) occupies an axial position whereas the hydroxyl in menthol (**2**) occupies an equatorial position. Barton correctly predicted that since axial substituents are more hindered due to transannular interactions with other axial bonds, the equatorial hydroxyl should be more easily esterified.
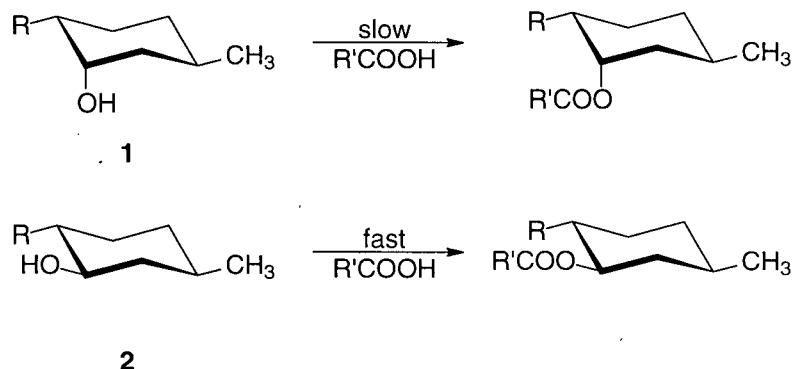
Figure 4. Esterification of neomenthol (**1**) and menthol (**2**) (R = i-Pr).

However, Barton's work was limited to compounds that exist predominantly in one conformation. In 1953, Eliel demonstrated the complexities that can arise in conformationally mobile systems (Figure 5).[12] He noted that neoisomenthol (**3**) undergoes esterification at three times the rate of neomenthol (**1**). This rate difference can only be explained if the reaction occurs with the less stable conformations **1a** and **3a**. This is expected due to the severe crowding of the axial hydroxyl group of **3** compared to that of **1**. The equilibrium constant for **3** and **3a** is expected to be larger than for **1** and **1a** since the conformational analysis reveals two alkyl groups which must occupy axial positions in **3**. Assuming **1a** and **3a** have the same reactivity, Eliel then reasoned that **3a** is esterified faster than **1a** because of its larger equilibrium concentration. This
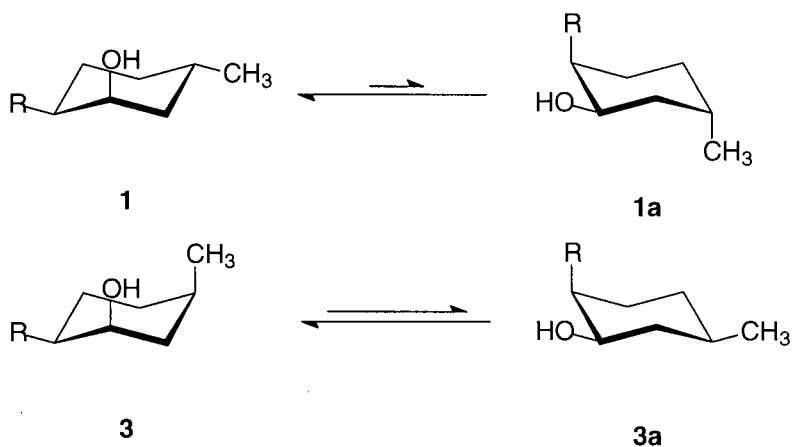
Figure 5. Conformational equilibrium for neomenthol (**1**) and neoisomenthol (**3**) (R = i-Pr).

example demonstrated that the preferred ground state conformations cannot always be used to predicted reaction rates.

The relationship between ground state conformation of the reactant and the product distribution was established by Curtin a year later.[13] The Curtin-Hammett Principle dictates that in a reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and providing that these two isomers are rapidly interconvertible) the product composition is not solely dependent on the relative proportions of the conformational isomers in the substrate; it is controlled by the difference in the standard Gibbs free energies of the respective transition states.

These early conformational studies did not take into account ring systems larger than cyclohexane since most chemists believed such larger systems behaved more closely to linear alkanes. However, the work performed by Barton, Eliel and others has allowed for a profound understanding of not only cyclic and heterocyclic chemistry, but also of chemical reactivity in general.

1.2 **Conformational Analysis of Medium and Large Ring Compounds**

The first macrocyclic compounds were discovered by Ruzicka in 1926, while investigating the components of musk oil.[14,15] Civetone **4** and Muscone **5** were isolated and their structures elucidated by careful chemical degradation and comparison of the fragments with known compounds.

4

5
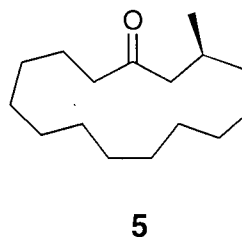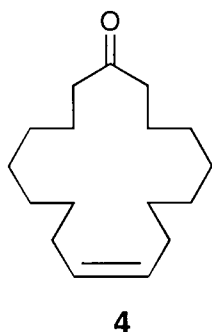
The discovery of these compounds further revealed the inadequacies of the Baeyer strain theory,[6] since it predicted that large ring compounds would be too unstable to exist due to overextension of internal bond angles.

The research into these musk oil components was of twofold importance. First, these compounds were of high commercial value in the fragrance industry, and second, little was known about the chemical and physical properties of these large ring compounds. Research into macrocyclic compounds continued through the efforts of Ruzicka[16,17] and Prelog,[18] who synthesized and investigated the properties of large ring hydrocarbons, alcohols and ketones. This research revealed an unexpected and interesting dependency of the physical and chemical properties of macrocyclic compounds on ring size. For example, the curve of melting point versus ring size did not increase steadily as for aliphatic acyclic hydrocarbons.[16-18]

It was not until 1961 when Dunitz and co-workers[19] provided some understanding of the conformational details that control these phenomena. X-ray diffraction of a variety of cyclodecane derivatives showed that these compounds all crystallized in a common conformation (Figure 6). This was a surprising result since it was believed that the cyclodecane ring system was highly flexible and that it existed in many conformations. Dunitz concluded that this common conformation of the ring skeleton must represent a potential energy minimum.
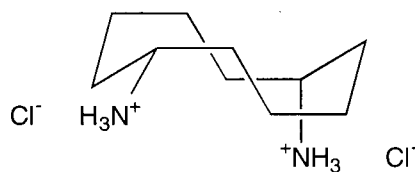
Figure 6. The conformation of cis-1,6-diaminocyclodecane dihydrochloride.[19]

Two years later, Dale noticed that the solid state conformation of the cyclodecane system was superimposable on the diamond lattice (Figure 7).[20,21] This diamond lattice represents a network of ideal bond lengths and bond angles.

It follows that any conformation that is superimposable on the diamond lattice exhibits a minimum in the angle and torsion strain.
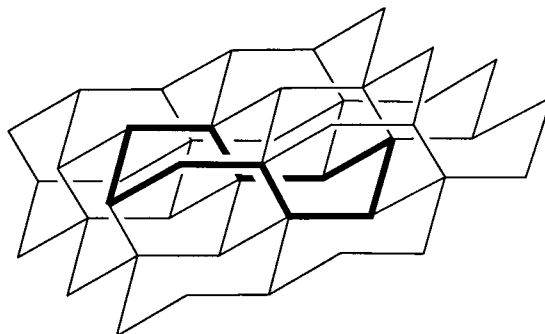
Figure 7. The diamond lattice conformation of cyclodecane.

Using molecular models, Dale was able to predict the low energy conformations of all even-membered cycloalkanes C_6 to C_{16}. In doing so, Dale arrived at two important conclusions:

1) Cycloalkanes containing an odd number of carbon ring atoms do not possess strain-free energy conformations since these cannot be superimposed on the diamond lattice.

2) Cycloalkanes possessing between 7 and 13 carbon ring atoms cannot have a strain-free conformation since a diamond lattice conformation for these systems results in too close an approach between internal hydrogens. Even though the conformation of cyclodecane was shown by Dunitz to follow the diamond lattice quite closely, it clearly demonstrated a compromise between angle strain, torsional energy, and transannular hydrogen repulsion.

Subsequently, theoretical calculations and X-ray crystallography showed Dale's predictions to be accurate. For example, the strain-free conformation derived from the diamond lattice has been found experimentally to be similar to the solid state conformation for cyclotetradecane (Figure 8).[22,23]

side view   top view
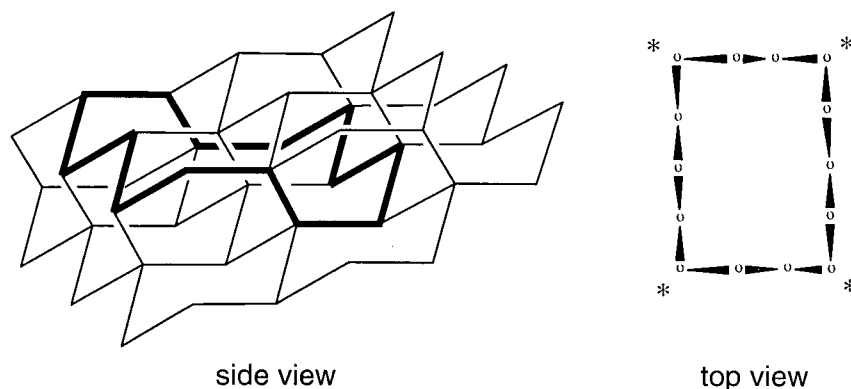
Figure 8. The strain-free diamond lattice conformation of
cyclotetradecane (* denotes corner position).

Dale further noticed that these low energy macrocyclic conformations exhibit a common feature. When viewed from the top, as illustrated for cyclotetradecane in Figure 8, four "corners" of a rectangular contour can be distinguished. Dale recognized that the hydrogens bonded to these corner atoms are directed away from the ring and suffer the least number of steric interactions (Figure 9). These are the only positions on the ring which can therefore accommodate two geminal substituents without causing severe transannular interactions.[24]

number of transannular
interactions

——○   1

——◎   2

——●   3
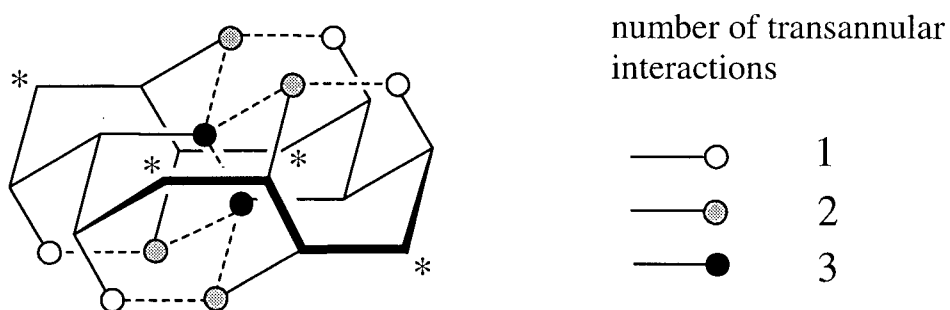
Figure 9. Transannular hydrogen interactions in cyclotetradecane
(* denotes corner position).

A corner position in a macrocycle was defined as having 2 adjoining gauche dihedral angles of the same sign flanked on either side by an antidihedral angle (Figure 10).[20,25]
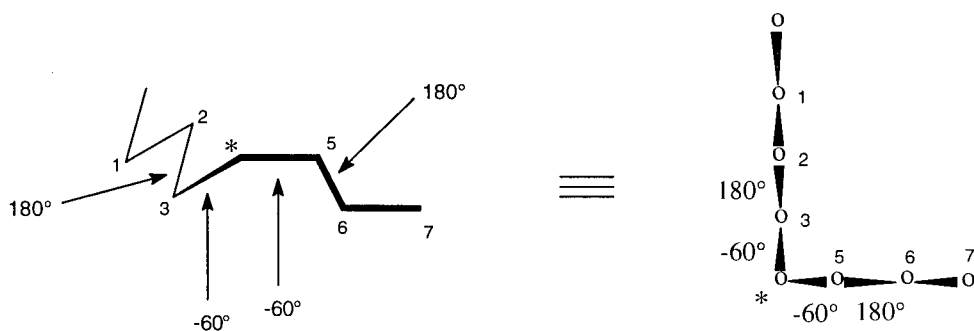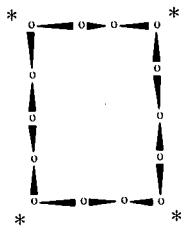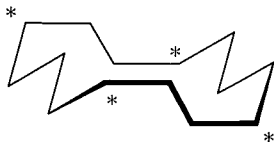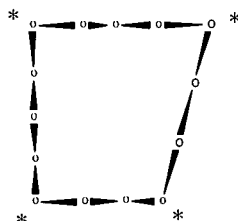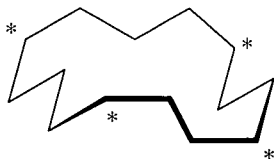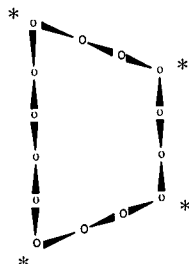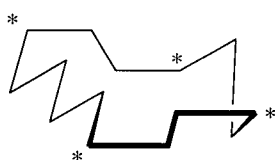
Figure 10. The definition of a corner position in a macrocyclic system (∗ denotes corner position).

From these observations, Dale also devised a nomenclature system to describe macrocyclic conformations.[25] He used a set of brackets with a series of numbers, in which the numbers indicate the number of bonds between each corner position. The ring is named such that the smallest number is listed first within the brackets. Therefore, the diamond lattice conformation for cyclotetradecane is named [3434] (Table1).

Initially, Dale considered only those ring conformations which were superimposable on a diamond lattice. However, calculations on cyclotetradecane, first using modified Dreiding models on a semi-quantitative scale[25] and then molecular mechanics,[26] revealed two additional low energy conformations which were not superimposable on the diamond lattice.[27] These were designated the [3344] and [3335] conformations (Table 1) and were calculated to have strain energies of 1.1 kcal/mol and 2.4 kcal/mol respectively, relative to the [3434] conformation.

Table 1. The Three Lowest Energy Conformations of Cyclotetradecane.[27]

Conformation	Top View	Side View	Strain Energy (kcal/mol)[a]
[3434]			0.0
[3344]			1.1
[3335]			2.4

[a] Strain energy is reported relative to the lowest energy conformation.

1.3   Remote Asymmetric Induction in Medium and Large Rings

The control of newly generated stereocenters remains an interesting and challenging subject of organic chemistry. While the control of vicinal and 1,3-asymmetric induction is well known, the stereocontrol of more remote centers often presents a greater challenge. The work of Barton[3] and Eliel[12] introduced

the aspects of conformationally controlled reactions in cyclohexane systems. With the realization that medium and large ring compounds also exist in well defined conformations, research into the conformationally controlled reactions of macrocycles has progressed over the last twenty years.

The use of conformational control in the construction of remote asymmetric centers in medium and large rings was first studied by Still and Galynker in the early nineteen-eighties.[28] With the aid of molecular mechanics calculations,[29] a simple model was established to estimate product distributions. Using the Hammond postulate,[30] product ratios were assumed to be closely related to the conformational energies of starting materials (early transition state) or products (late transition state). By calculating the conformational energy of the starting materials, intermediates and products, it was possible to quantitatively predict product distributions.

An example of Still and Galynker's work is the alkylation of 3-methylcyclooctanone (6).[28] Deprotonation with lithium diisopropylamide followed by addition of methyl iodide afforded the *cis* dimethylated product 7 with 98% selectivity over the *trans* product. This selectivity could not be explained by the strain energies of the enolate intermediate conformations since 6d, which yields the *trans* product, is similar in energy to 6a and 6c, which yield the *cis* product (Figure 11). However a Boltzman distribution for the product conformations yields a result which agrees with the observed selectivity.

6   1) LDA   2) MeI   7   98 % *cis*
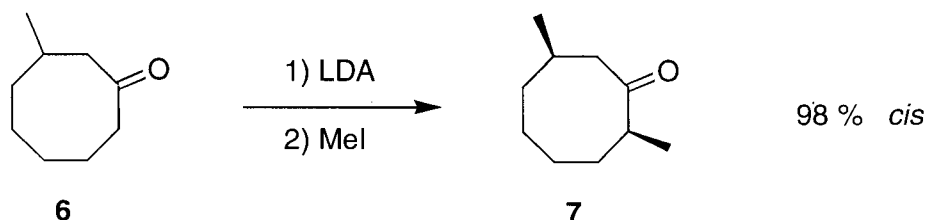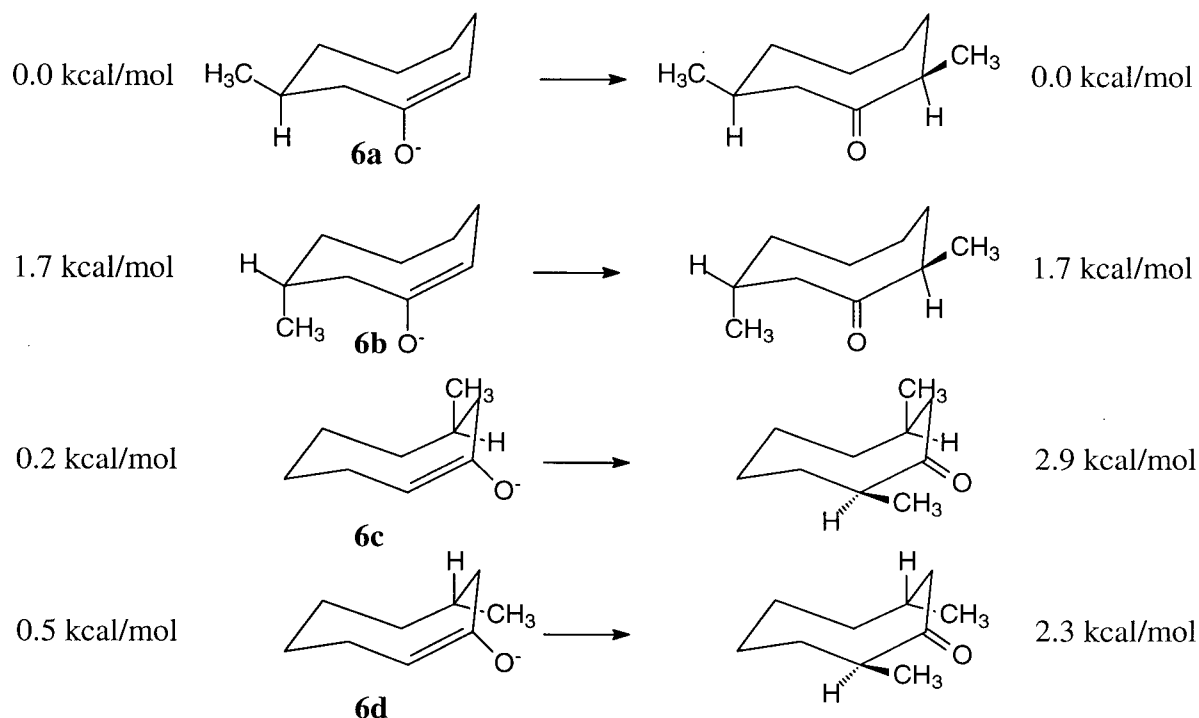
Figure 11. Conformations of 2,7-dimethylcyclooctanone and of the enolates of 3-methylcyclooctanone.

Another interesting and more recent example of conformational controlled reactions involving medium rings is the epoxidation of the unsaturated lactone **8** with MCPBA, which produced **9** as a single diastereomer in 81% yield.[31] The calculated low energy conformation of **8** shows that the MCPBA reagent preferentially attacks from one face of the olefinic function (Figure 12).
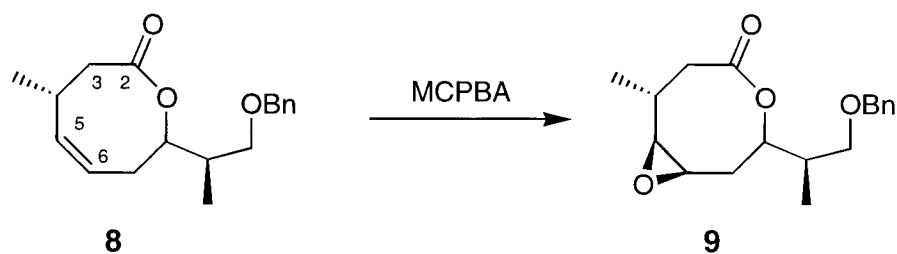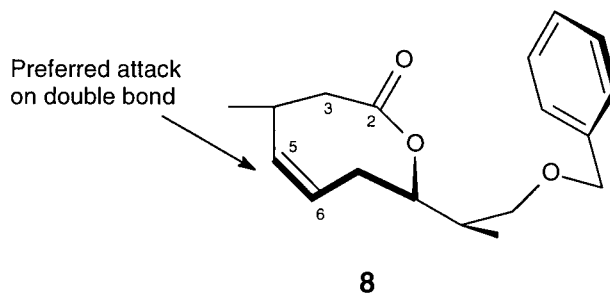
Figure 12. Epoxidation of the low energy conformation of the unsaturated lactone **8**.

This result demonstrates an interesting aspect of olefinic functions in medium and large ring compounds. In contrast to cyclohexene, larger ring molecules contain sp^2 centers which are usually perpendicular to the ring. This arrangement provides two diastereospecific faces which are highly different. An examination of Figure 13 illustrates that the two faces of the double bond in *cis*-cyclohexene are equivalent. On the other hand, the diamond lattice conformation of cyclotetradecene reveals that face **B** is severely hindered by the transannular hydrogen interactions and the carbon atoms of the ring. Therefore, Still realized that reagents should approach the π system of a macrocyclic alkene largely or perhaps exclusively from the periphery of the ring.[28]
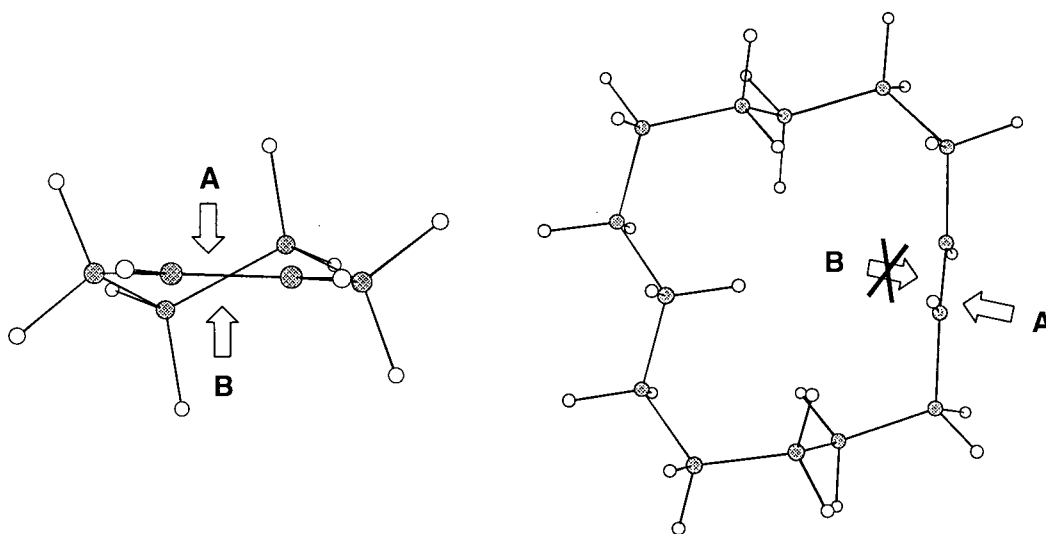
Figure 13. Diastereofacial selectivity in cyclohexene and cyclotetradecene.

Following the work of Stills and Galynker, Vedejs and coworkers developed a modified approach in order to predict diastereoselective reactions of macrocycles containing olefinic functions.[32,33] The local ring segment containing the alkene tends to adopt only certain conformations which control the stereochemical outcome of the reaction. Epoxidation and osmylation studies have shown this approach to be very successful.[32,33] An example of this local conformer approach developed by Vedejs and coworkers is the epoxidation of (E)-3-methylcyclodecene (10).[32] The local conformer prediction on 10a by peripheral attack of the reagent would produce epoxide 11. In fact, a 6:1 mixture of epoxides was obtained experimentally upon treatment of 10 with MCPBA, the major isomer 11 having the predicted relative stereochemistry (Figure 14).
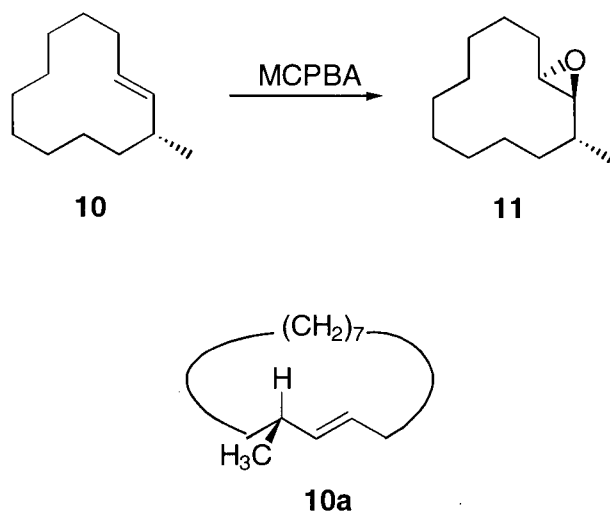
Figure 14. Local conformer effect in the epoxidation of (E)-3-methylcyclodecene (10).

Our own laboratory has been studying the conformationally controlled reactions in simple 14- and 16-membered macrocyclic systems. Notably, high diastereoselectivity has been obtained for hydride reduction,[34-37] alkylation,[34,38,39] and hydroboration[40] reactions of macrocyclic lactones and lactams. For example, the diastereoselectivity obtained in the hydride reduction of 9-oxo-13-

tetradecanolide (**12**), yielding a 9:1 product mixture of **13** and **14**, respectively, demonstrates the conformational control of a macrocyclic system in which the reacting center is remote from the stereogenic center.[35]
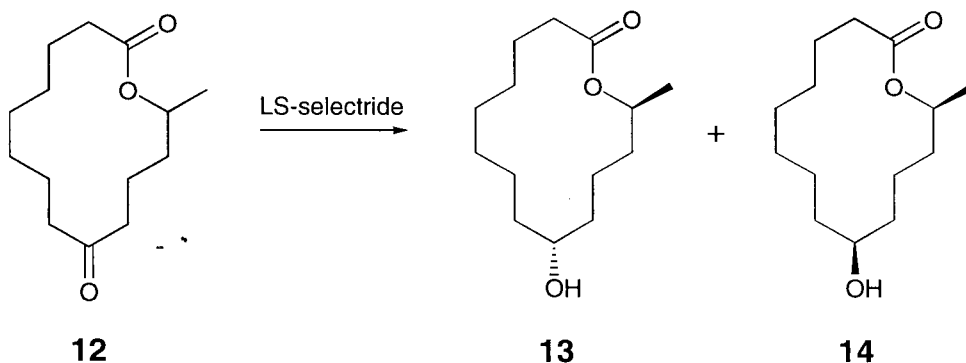
1.4   Conformationally Controlled Reactions in Macrolide Synthesis

The first macrolide antibiotic to be discovered, pikromycin (**15**) was isolated in 1950 from a strain of streptomyces.[41] Since this discovery, a number of macrolide compounds which have medicinal properties have been isolated. With the realization of the importance of macrolide antibiotics to the pharmaceutical industry, much attention has been focussed on the isolation and synthesis of macrolides in the past fifty years.[42]

R = desosaminyl

15
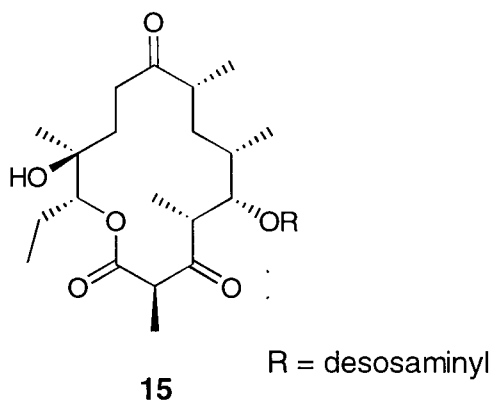
One important sub-group of macrolide antibiotics is the polyoxo-macrolides. These are structurally characterized by a 12, 14 or 16 membered lactone ring with one or more deoxy-sugars attached and up to 12 asymmetric centers incorporated into the aglycone. The large number of stereocenters has remained a formidable challenge in the total synthesis of these molecules.[43-47] However, a number of research groups have explored the use of conformational bias in large rings to control the stereochemical and regiochemical outcome in the synthesis of macrolides. Still and Novack were the first to display the use of macrocyclic stereocontrol in their synthesis of 3-deoxyrosaranolide (16) (Scheme 1).[48]

The 16-membered ring of the target structure was first prepared by a Horner-Emmons cyclization to give the keto-macrolide 17, containing two stereogenic centers. The six remaining stereocenters necessary to achieve the target 16 were created using conformationally controlled reactions. Kinetic deprotonation of 17 at C_8 followed by methylation gave 18 with better than 95% stereoselectivity. The C_6 side chain was then introduced by alkylation of the kinetically generated enolate to give 20 with better than 95% regioselectivity and 85% stereoselectivity. Initially, an attempt to introduce the methyl substituent at C_4 yielded the incorrect 4R diastereoisomer, although with high stereoselectivity (>97%). Alternatively, the enolate of 20 was quenched with formaldehyde, followed by dehydration via the mesolate to afford the exocyclic methylene ketone 21.

Conjugate addition of thiophenolate to 21 followed by desulphurization afforded compound 22 with better than 95% stereoselectivity. Ester hydrolysis and sodium borohydride reduction of the derived mixed anhydride then gave the desired C_5 alcohol 23 with 83% stereoselectivity. Finally, oxidation at C_9, epoxidation of the alkene at C_{12}/C_{13} (83% stereoselectivity) and selective oxidation of the primary hydroxyl group gave 3-deoxyrosaranolide (16).
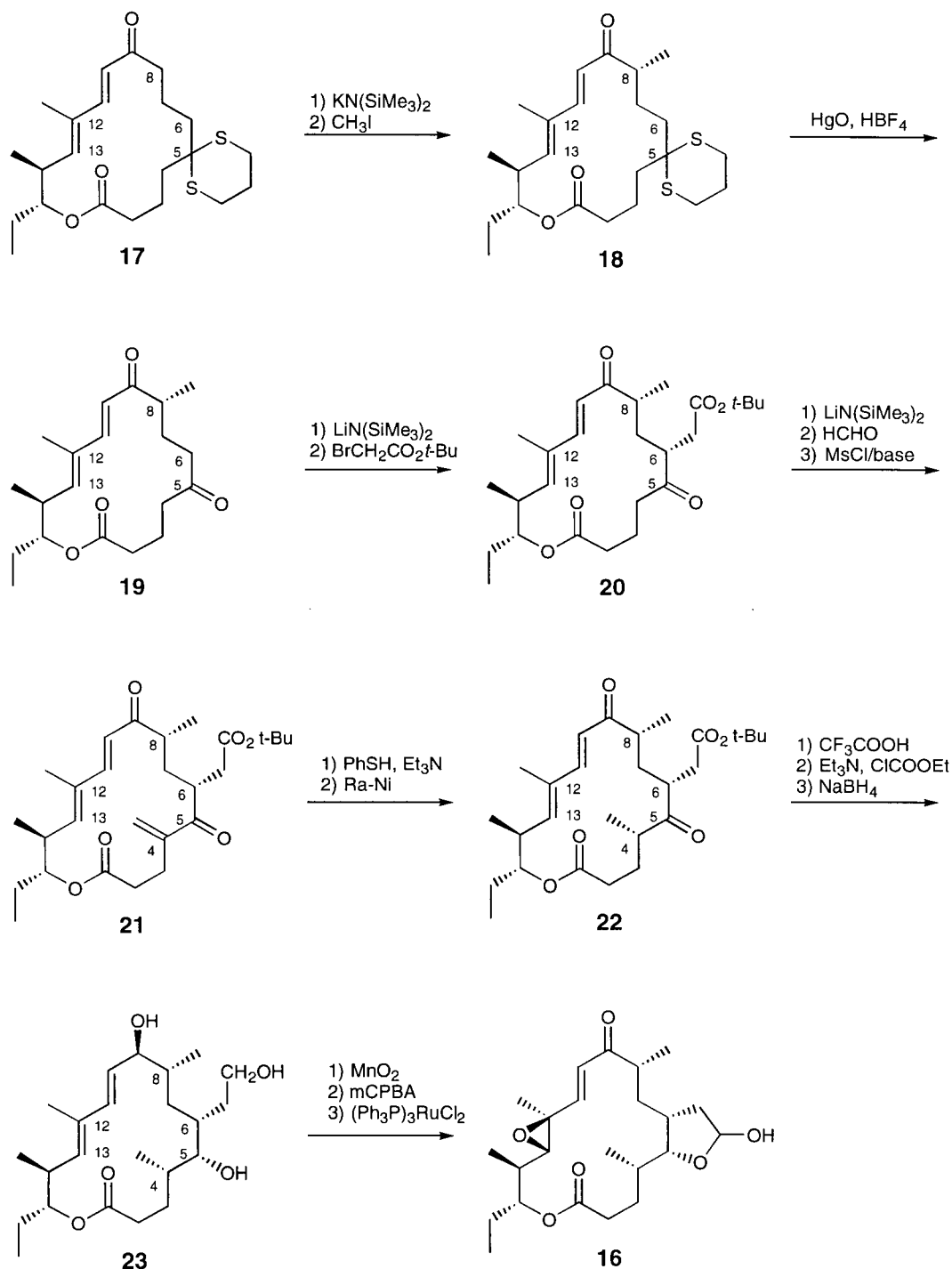
Scheme 1. The synthesis of 3-deoxyrosaranolide using macrocyclic stereocontrol.[48]

In a second example, Paterson and Rawson successfully prepared (+)-(9*S*)-dihydroerythronolide (**24**) using a combination of acyclic and macrocyclic stereocontrol.[49] Scheme 2 demonstrates how four of the ten stereocenters were introduced using the conformational bias of the ring.
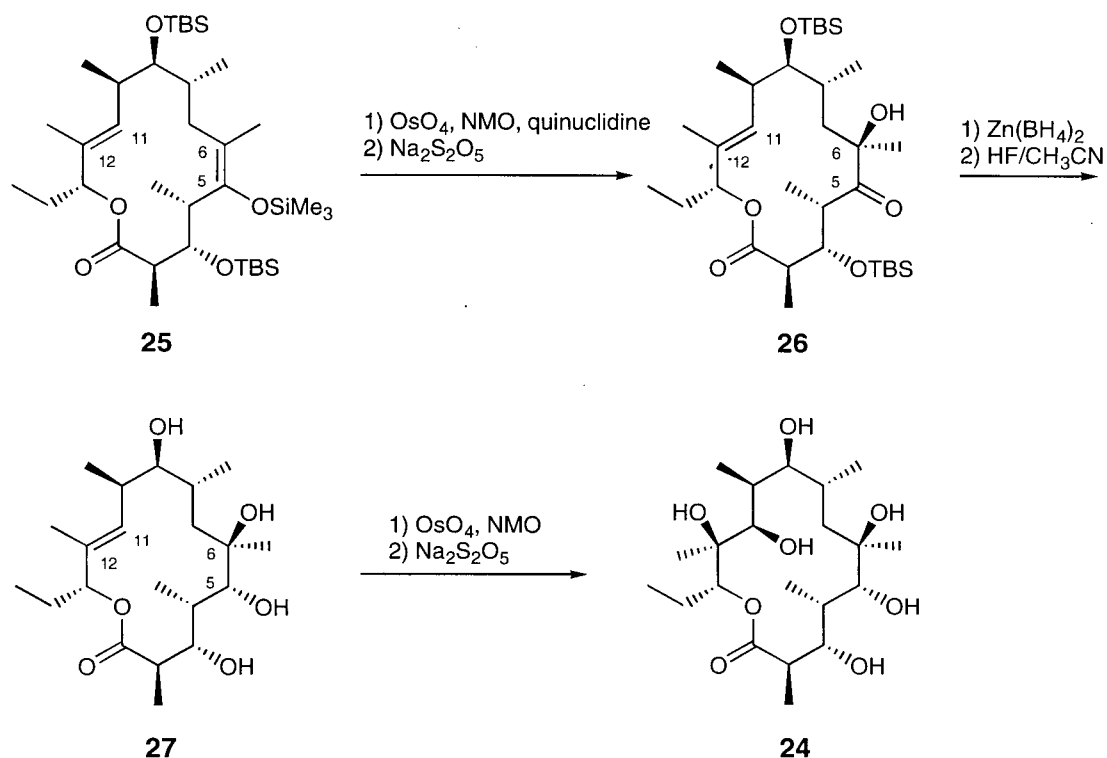
Scheme 2. Conformationally controlled reactions in the synthesis of dihydroerythronolide (**24**).[49]

Osmylation of the intermediate **25** occurred with 100% π-face selectivity to yield **26**. This was followed by reduction of the C_5 ketone and deprotection of the silyl ethers to yield **27** as a single product. A final osmylation to complete the synthesis gave **24**, again with high selectivity.

Although the complexity of the conformational behavior of macrocycles limits its use in synthesis, the literature contains a number of examples in which the conformational bias of large ring systems is employed in the assembling of natural products.[50-55] In many of these recent examples, molecular mechanics calculations have been used to rationalize the outcome of the conformationally controlled reactions.

1.5   Ring Closing Olefin Metathesis

The formation of C-C bonds is an integral part of organic synthesis. This is especially true if the C-C bond formation in a synthesis involves a cyclization to form the ring structure of the target molecule. There exists a variety of ring forming reactions for macrocycles.[56] However, the yields are often disappointing due to the entropy factor of the reaction.

One C-C bond forming cyclization reaction which has gained much interest in recent years, although examples have been reported since the early 1980's,[57,58] is the ring closing olefin metathesis reaction (RCM).[59-61] This reaction takes a pair of intramolecular alkenes and couples them in the presence of a transition metal alkylidene catalyst suited for such a cyclization. Although the mechanism is not completely understood, the catalytic species is known to be a metal alkylidene and there is evidence for the involvement of metallacyclobutanes.[62] The overall reaction mechanism thus effectively involves a series of alternating [2+2] cycloaddition and cycloreversions between metal alkylidene and metallacyclobutane species (Scheme 3).

Early uses of ring closing olefin metathesis involved transition metal alkylidene catalyst which had moderate or poor functional group tolerance, were sensitive to air, moisture or trace solvent impurities, and were thermally unstable on storage. The recent interest in ring closing olefin metathesis owes its recognition to the development of the bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride catalyst 28 by Grubbs and coworkers.[63] This catalyst is easy to prepare, air stable and catalytically active without rigorous water and oxygen exclusion from the reaction system. It is also tolerant of most functional groups, which makes it attractive in the synthesis of complex natural products.

23
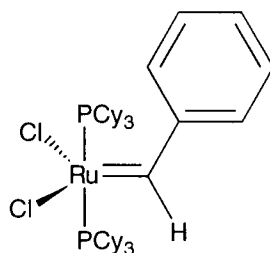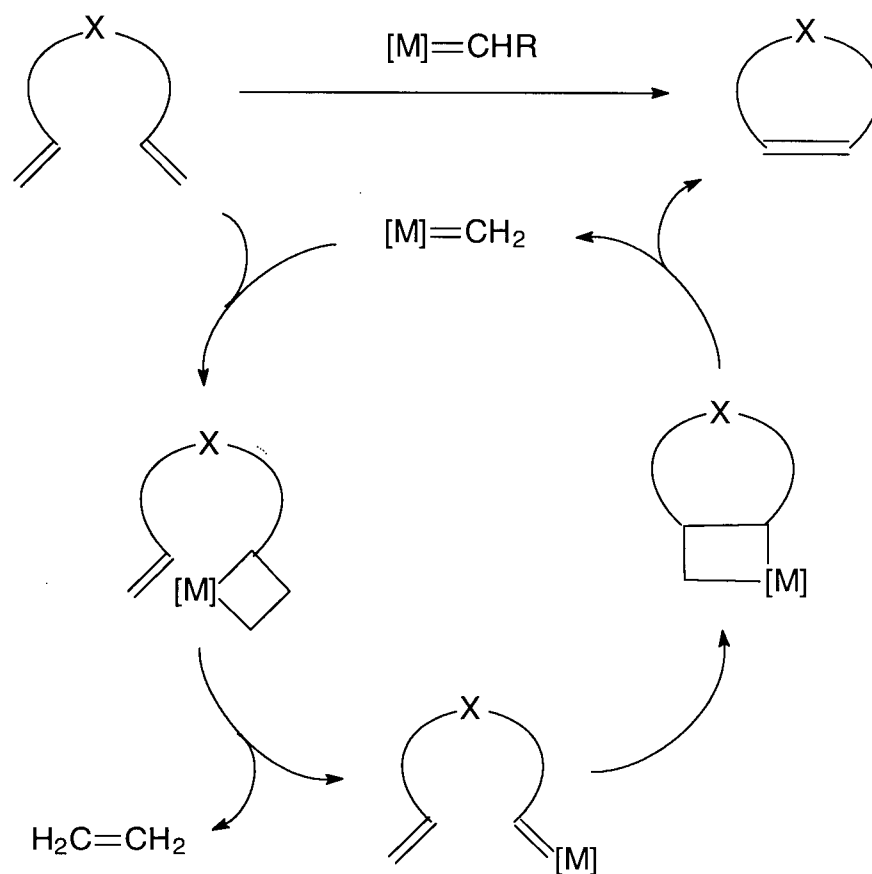
Scheme 3. Mechanism for the ring closing olefin metathesis reaction ([M]=CHR is a transition metal benzylidene catalyst).

A problem with the ring closing olefin metathesis reaction is that stereocontrol of the resulting olefin function is difficult to predict and the reaction often proceeds to yield a mixture of *E* and *Z* isomers. Previous research in our laboratory[64] has demonstrated the use of molecular mechanics calculations to predict the ratios of *E* and *Z* isomers obtained in the formation of a series of unsaturated 14-membered lactones and lactams. It has also been observed that lower yields are obtained if the forming olefinic function is located in the proximity of the carbonyl oxygen or the heteroatom in these macrocyclic lactones and lactams. This may be a result of metal-substrate chelation.[65] It is believed that the carbonyl oxygen of esters or amides acts as a relay for the evolving carbene which assembles the reacting sites within the coordination sphere of the metal

(complex **A** in Figure 15). However, if such relays form 5- or 6-membered ring systems (complex **B** or **C** in Figure 15), the resulting complex may be too stable and the cyclization will not proceed.
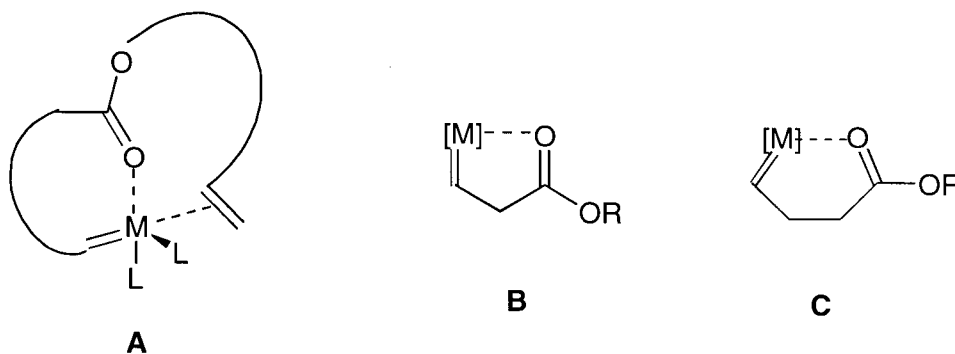
Figure 15. Relay assembling of the reactive sites (**A**) and sources of unproductive complexes (**B** and **C**) in ring closing olefin metathesis.

CHAPTER 2

RESULTS AND DISCUSSION

Chapter 1 provided an introduction to the methods whereby the conformation of macrocyclic rings can be used to control the stereochemistry of newly formed stereogenic centers. In this thesis, the reactivity and conformational rigidity of 14-membered lactones were investigated through a study of the selectivities obtained in the reactions of such ring systems.

The macrocyclic lactones used in this work were chosen such that they contained the functional group of interest remote from the lactone linkage and any stereogenic centers in the molecule. This would ensure that any observed selectivity would be due primarily to conformational effects. Thus, the regioselectivity in the hydroboration reactions of unsaturated lactone **29** was investigated as well as the regio- and stereoselectivity in the hydroboration reactions of unsaturated lactone **30**. We were also interested in comparing the regioselectivity differences, if any, between the hydroborations of **29** and **30**. The stereoselectivity of the hydride reduction of keto lactones **67** and **68** was also examined.

Subsequently, through X-ray analysis and chemical correlations, the relative stereochemistry of the newly formed stereocenters in the reaction products were determined. Molecular mechanics calculations were then carried out and correlations were drawn between these calculations and the experimental results.

29   **30**   **67**   **68**
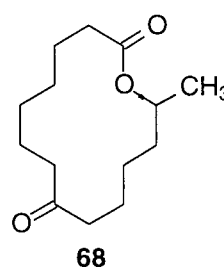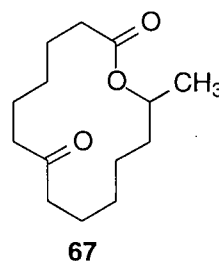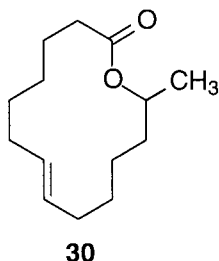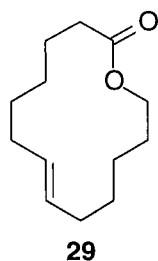
2.1   Synthesis of (7E)-13-Tridec-7-enolide (29) and (7E)-13-Tetradec-7-enolide (30)

Our retrosynthetic plan for the syntheses of the two unsaturated lactones **29** and **30** is outlined in Scheme 4. Since a relatively large quantity of macrolide was desired in both cases, simple and inexpensive starting materials were chosen. Due to the similarities in structure between lactones **29** and **30**, we decided to use intermediates that were common in the synthesis of both lactones.

The greatest challenge in the syntheses would be to introduce the olefin function exclusively with *E* stereochemistry. Also, the cyclization step would be an important component of our syntheses, as the cyclization of macrocycles usually proceeds with poor to moderate yields.[56] Thus, we decided to handle both concerns in one step. Previous work in our laboratory[64] has demonstrated that the ring closing olefin metathesis (RCM) to form **29** proceeds in good yield and with better than 99:1 *E:Z* ratio from the diene ester **31**. Due to the structural similarities to **29**, we believed that the RCM to form lactone **30** would also proceed in good yield and with good stereoselectivity from the diene ester **32**.

Another disconnection at the ester linkage in **31** and **32** leads to alcohols **34** and **35**, respectively, and the common acid **33**. Both acid **33** and alcohol **35** lead retrosynthetically to the alcohol **34**, through a one-carbon chain extension.[66] Thus, the precursor to the three intermediates **33**, **34** and **35** is the inexpensive 1,6-hexanediol (**36**).
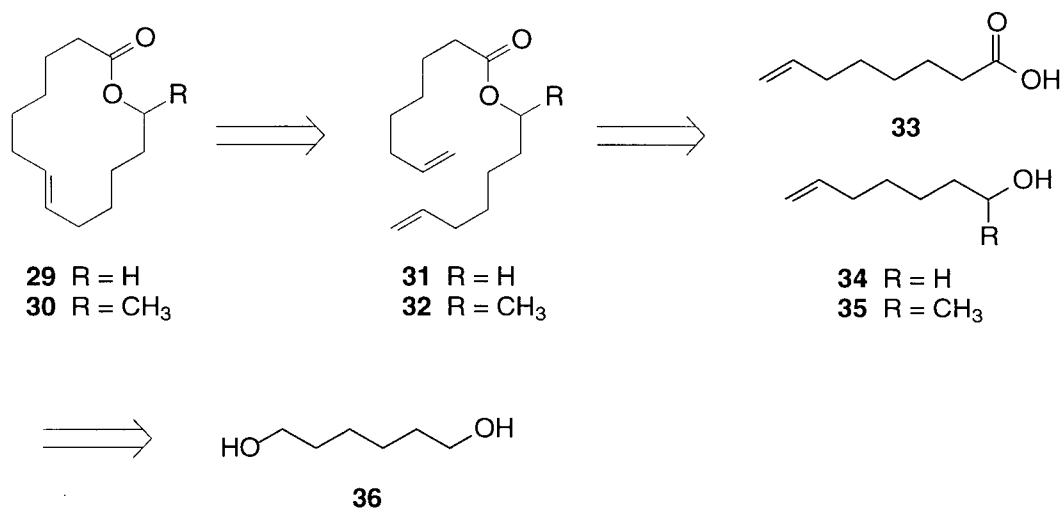
Scheme 4. Retrosynthetic analysis of (7*E*)-13-tridec-7-enolide (**29**) and (7*E*)-13-tetradec-7-enolide (**30**)

2.1.1 Synthesis of 6-Hepten-1-ol (34)

The synthesis of 6-hepten-1-ol (**34**) is outlined in Scheme 5. The commercially available 1,6-hexanediol (**36**) was monoprotected[67] as its THP ether **37**, and the unprotected primary hydroxyl function was subsequently oxidized under the Swern conditions[68] to yield aldehyde **38**. Wittig olefination[69] of **38** with the anion of methyltriphenylphosphonium bromide gave the olefin **39**. Finally, removal of the THP protecting group with a catalytic amount of PPTS in methanol provided the target intermediate **34** in 44% overall yield from **36**.
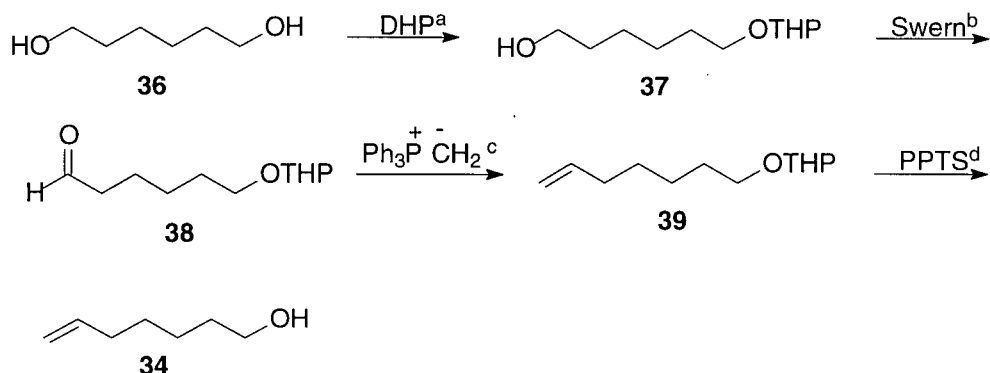
Key: (a) DHP, H$^+$ resin, toluene, rt, 70%; (b) (COCl)$_2$, DMSO, Et$_3$N,
CH$_2$Cl$_2$, -78 °C, 80%; (c) Ph$_3$P$^+$CH$_3$Br$^-$, n-BuLi, THF, 0 °C, 86%;
(d) PPTS, CH$_3$OH, rt, 91%.

Scheme 5. Synthesis of 6-hepten-1-ol (**34**).

2.1.2 Synthesis of 7-Octenoic acid (33)

7-Octenoic acid (**33**) was synthesized from 6-hepten-1-ol (**34**) using a one-
carbon chain extension method (Scheme 6). The toluenesulfonate derivative **40**
was formed from alcohol **34**, and the tosylated substituent was displaced by
cyanide anion to extend the hydrocarbon chain by one carbon unit, yielding **41**.
Nitrile **41** was then hydrolyzed to produce the desired acid **33** in an overall yield
of 57% from **34**.
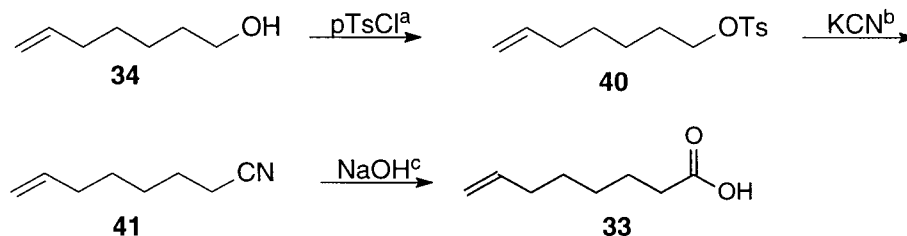
Key: (a) p-MeC$_6$H$_4$SO$_2$Cl, pyridine, 0 °C→rt, 85%; (b) KCN, MeCN, 82
°C, 70%; (c) NaOH, ethylene glycol, 150 °C, then conc. HCl,
95%.

Scheme 6. Synthesis of 7-octenoic acid (**33**).

2.1.3 Synthesis of 7-Octen-2-ol (35)

The secondary alcohol **35** was also synthesized from 6-hepten-1-ol (**34**). The synthesis of the 7-octen-2-ol intermediate (**35**) is outlined in Scheme 7. Oxidation of alcohol **34** under the Swern conditions[68] yielded aldehyde **42**. Addition of methyllithium to **42** then produced the secondary alcohol **35** in 45% overall yield from **34**.
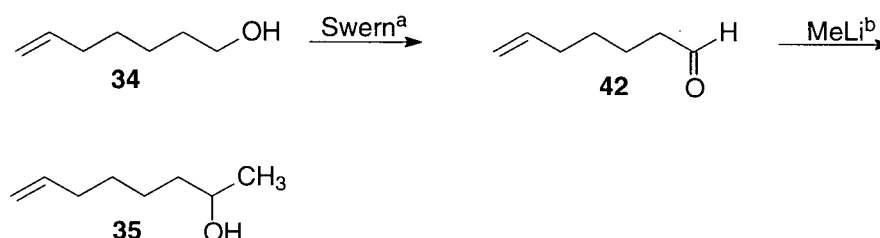
Key: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 77%; (b) MeLi, THF, 0 °C, then NH_4Cl, 59%.

Scheme 7. Synthesis of 7-octen-2-ol (**35**).

2.1.4 Ring Closing Olefin Metathesis (RCM) of 6-Heptenyl-7'-Octenoate (31) and 1-Methyl-6-Heptenyl-7'-Octenoate (32)

From this point on in the syntheses of lactones **29** and **30**, the procedure developed previously in our laboratory[64] for the synthesis of **29** was followed. Accordingly, acid **33** and alcohol **34** were coupled using DCC and DMAP to form diene ester **31** (Scheme 8). This was followed by the RCM of **31**, using the bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride catalyst **28**,[63] to produce lactone **29** in an overall yield of 75% for the two steps. In the same manner, acid **33** and alcohol **35** were coupled to yield diene ester **32**, followed by ring closing olefin metathesis to produce lactone **30** in an overall yield of 72% for the two steps.
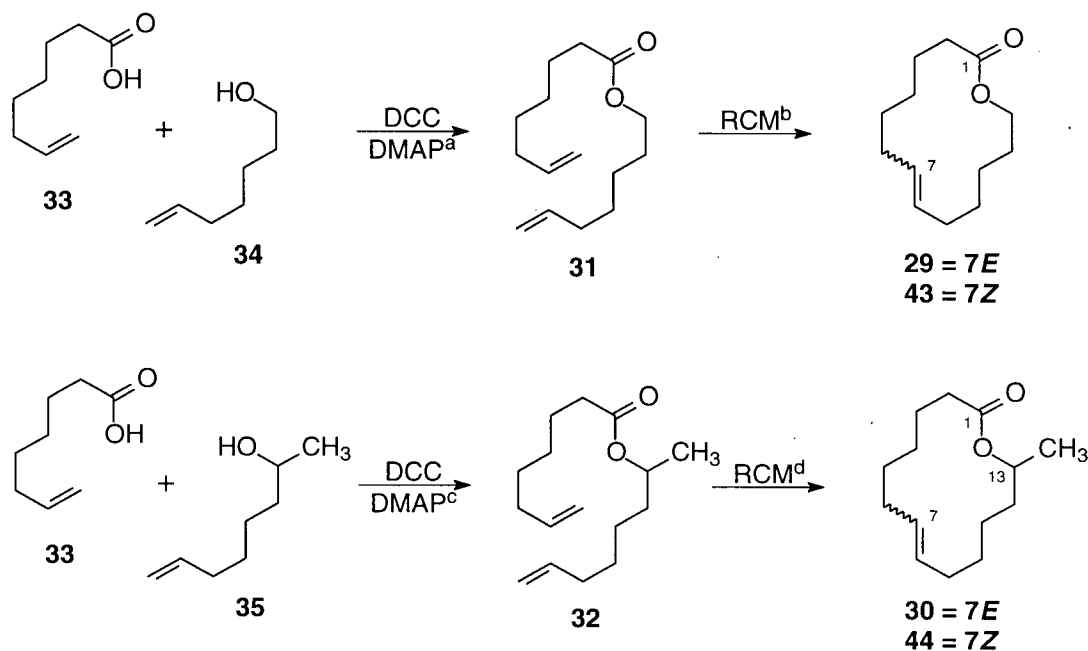
Key: (a) DCC, DMAP, CH$_2$Cl$_2$, rt, 87%; (b) 2 mol% **28**, CH$_2$Cl$_2$, rt, 86%; (c) DCC, DMAP, CH$_2$Cl$_2$, rt, 85%; (d) 2 mol% **28**, CH$_2$Cl$_2$, rt, 85%.

Scheme 8. Synthesis of (7*E*)-13-tridec-7-enolide (**29**) and (7*E*)-13-tetradec-7-enolide (**30**).

Evidence for the formation of **29** and **30** via the ring closing metathesis reaction can be obtained from ^{13}C NMR spectroscopy. Four olefinic carbon peaks are apparent in the spectra of diene esters **31** (δ 138.81, 138.71, 114.46, 113.30 ppm) and **32** (δ 138.81, 138.73, 114.37, 113.27 ppm). However, the spectra of **29** (δ 131.80, 131.49 ppm) and **30** (δ 131.80, 131.49 ppm) reveal the presence of only the two downfield olefinic carbon peaks, which are indicative of internal alkene carbons.

The RCM of diene esters **31** and **32** proceeded to yield mixtures of *E* and *Z* isomers. The yields of the two reactions and the *E/Z* ratios were found to be very similar (Table 2). The *E* isomers were the major products in both cases with an *E/Z* ratio of 95:5 for the reaction of **31** and 94:6 for the reaction of **32**. In both

cases, the *E* and *Z* isomers were not separable by thin layer chromatography, and radial chromatography under a variety of eluant conditions allowed for only small amounts of the major isomers (**29** and **30**) to be isolated from the *E* and *Z* mixtures. However, repeated flash column chromatography with silver nitrate impregnated TLC grade silica gel[70,71] yielded adequate amounts of the isolated *E* isomers **29** and **30**, along with a small amount of mixtures of *E* and *Z* isomers. The *E* and *Z* isomer ratios in both cases were measured by gas chromatography.

Table 2. The Ring Closing Olefin Metathesis of Diene Esters **31** and **32**.

Substrate	products	Yield (%)	*E/Z*	Calculated[74] *E/Z*
31	**29, 43**	86	95:5	96:4
32	**30, 44**	85	94:6	96:4

The olefin configurations of unsaturated lactones **29** and **30** were determined by the coupling constants between the vinyl protons. This was obtained from ^{1}H homonuclear decoupling NMR experiments on lactones **29** and **30**. The coupling constant for olefinic protons of a *trans* double bond is usually found to be 12-18 Hz, whereas for a *cis* double bond this value is typically found to be in the 6-12 Hz range.[72] From the ^{1}H NMR decoupling experiments it was determined that the olefinic protons of the major isomer **29** had a coupling constant of 15.0 Hz, and the double bond was correspondingly assigned the *E* configuration. In the same manner, the double bond of the major isomer **30** was assigned the *E* configuration based on a coupling constant of 15.4 Hz between the olefinic protons.

The IR spectra of **29** and **30** were in agreement with the analysis from the ^{1}H homonuclear decoupling NMR experiments. In order for a molecular vibration to give rise to an IR absorption, the molecular motion must result in a change of the dipole moment of the molecule. The IR spectra of *cis* alkenes typically show moderate absorptions for the carbon-carbon double bond stretching frequency. On the other hand, the corresponding absorption in the *trans* isomer is weaker or sometimes not visible.[73] The changes in dipole moment of the carbon-carbon double bond of **29** and **30** are either very small or zero, and therefore no carbon-carbon stretch band for the double bond is visible in the IR spectra at 1640-1670 cm^{-1} region in either case. This can only be rationalized with the assignment of the *E* configuration for both unsaturated lactones **29** and **30**.

The *E/Z* ratio observed in the RCM of diene ester **32** was first rationalized in the same manner as for **31** previously reported in our laboratory.[64] In the reported study of RCM reactions yielding unsaturated 14-membered lactones and lactams, including the reaction of **31**, it was suggested that the relative transition state energies in the formation of the *E* and *Z* isomers were reflected in the strain energies of the products.[64] However, the global minimum energy conformation[75] of tridecanolide (**45**) shown in Figure 16 was considered for the unsaturated lactone series. The *E/Z* ratios correlated well to the dihedral angles of structure **45** at the corresponding double bond position for each lactone investigated. This suggested that the conformation of the transition state for ring formation is similar to that of **45** and this controls the stereochemistry of the resulting double bond. This model then predicts a predominant formation of the *E* isomer in the metathesis of diene ester **31**. The global minimum energy conformation[75] of 13-tetradecanolide (**46**) is also shown in Figure 16. The dihedral angle at the double bond position in the conformation **46** also predicts the predominance of the *E* isomer in the metathesis reaction of **32**.

45   **46**
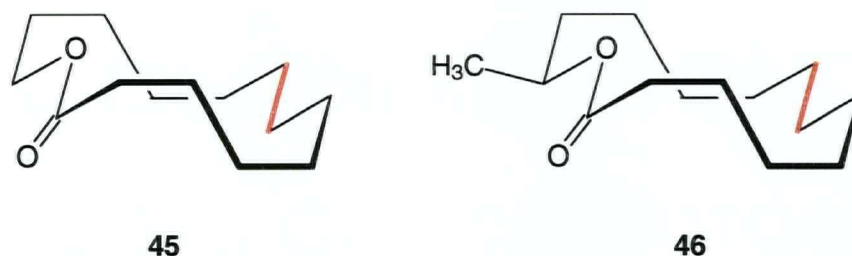
Figure 16. The global minimum energy conformations[75] of tridecanolide
(**45**) and 13-tetradecanolide (**46**). The corresponding double
bond positions for **29** and **30** are highlighted in red.

The structural resemblance of the global energy minimum of 13-tetradecanolide (**46**) to that of tridecanolide (**45**) might then explain the comparable E/Z ratios obtained in the metathesis reactions for **31** and **32**. The above analysis for the RCM reaction of diene esters **31** and **32** suggests that the relative energies of the transition state structures for each reaction might be reflected in the global minimum energy structure of the saturated ring systems **45** and **46**. However, MM3* calculations[74] were performed on each of the macrocyclic lactone products in the two RCM cases. The calculated E/Z ratios were comparable to the observed E/Z ratios for the metathesis reactions (Table 2).

We were interested in determining whether the catalytic alkylidene species involved in the RCM reaction of **31** and **32** was capable of the ring opening, and subsequent equilibration of the products. Therefore, in order to determine the factors that control the E/Z ratios obtained in the metathesis reactions, equilibrium studies were performed on the E isomers **29** and **30**. This was achieved using the active form of the metathesis catalyst **28**, $Cl_2(PCy_3)_2Ru=CH_2$. In both cases the unsaturated lactones isomerized in near quantitative yields to an E/Z ratio that was similar to that obtained in the metathesis reactions (Table 3). A 64:36 mixture of **30** and **44** also isomerized to a ratio that was similar to

that obtained from the metathesis reaction. The calculated E/Z ratios agree closely with the equilibrium values.

Table 3. Equilibrium Studies on Unsaturated Lactones **29** and **30**.

Substrate	Products	Yield (%)	Equilibrium E/Z	Metathesis E/Z	Calculated[74] E/Z
29	**29, 43**	98	96:4	95:5	96:4
30	**30, 44**	96	95:5	94:6	96:4
30, 44 (64:36)	**24, 44**	---	94:6	94:6	96:4

The equilibrium studies tentatively suggest that the metathesis reactions of diene esters **31** and **32** occur under thermodynamic control. These results also demonstrate the validity of molecular mechanics calculations as a predictive tool for the preferred stereochemistry of the alkene products.

2.2 Regio- and Stereoselectivity Studies on (7E)-13-Tridec-7-enolide (29) and (7E)-13-Tetradec-7-enolide (30)

With the unsaturated macrocyclic lactones **29** and **30** in hand, an investigation of the conformational effects of the ring systems on the addition reactions to the double bond could be executed. Hydroboration reactions were performed on **29** and **30**, and the regio- and stereoselectivity of these reactions were examined. The effect of the 13-methyl substituent in **30** was also investigated in the regioselectivity of the hydroboration reactions. In addition, epoxidation reactions were performed on **30**, and the diastereoselectivity was examined.

2.2.1 Hydroboration Studies on (7E)-13-Tridec-7-enolide (29)

Our primary objective was to isolate and characterize each of the two regioisomeric hydroboration products from **29** before performing hydroboration studies under a variety of conditions. Lactone **29** was therefore initially treated with borane tetrahydrofuran complex to give, after an oxidative work-up, a mixture of hydroxy lactones **47** and **48** (Scheme 9).
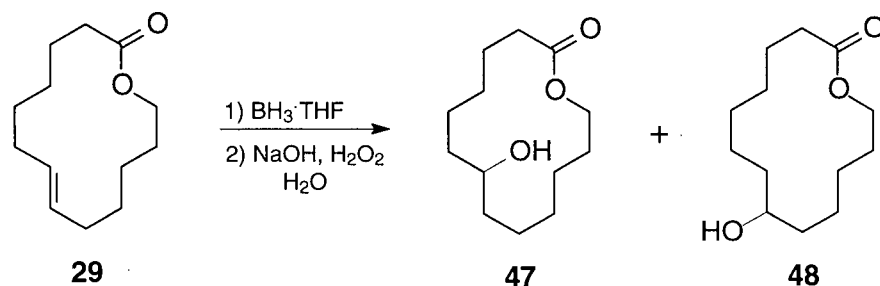
Scheme 9. Hydroboration of (7E)-13-tridec-7-enolide (**29**).

The hydroxy lactones **47** and **48** were not separable by flash column, radial or gas chromatography under a variety of conditions. In order to separate the hydroxy lactones for characterization purposes, as well as for the determination of the regioisomeric ratio, the corresponding trimethylsilyl ethers were formed (Scheme 10). This strategy has previously been employed in our laboratory[40] in order to separate isomeric hydroxy lactones. The silyl derivatives **49** and **50** were separable by gas chromatography and the analysis revealed a regioisomeric ratio of 49:51 for the hydroboration using borane tetrahydrofuran complex. The silyl ether derivatives were structurally identified by comparing the GC retention times with that of an authentic sample of **49** previously synthesized in our laboratory.[76] The silyl derivatives were also separable by radial chromatography. The separated silyl ethers **49** and **50** were then desilylated using tetrabutylammonium fluoride to yield the hydroxy lactones **47** and **48**.
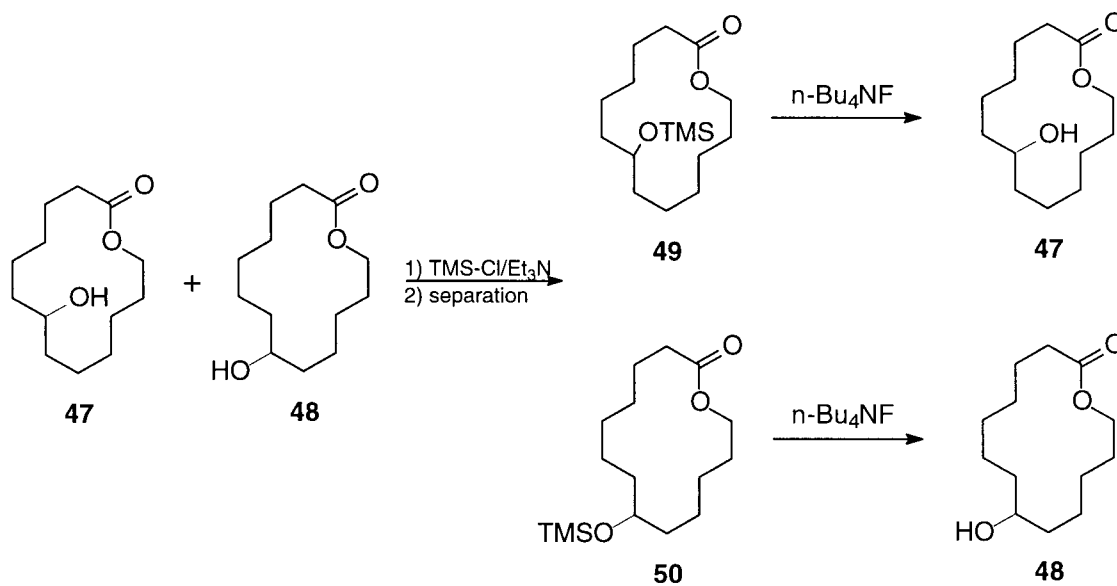
Scheme 10. Separation of hydroxy lactones **47** and **48**

The initial isolation and characterization of the hydroxy lactones **47** and **48** revealed that the addition of borane tetrahydrofuran complex to **29** proceeded with no regioselectivity. This was followed by investigating the effect of temperature on the selectivity of the hydroboration. The reaction of **29** with borane tetrahydrofuran at -78 °C proceeded with no selectivity, according to the analysis of the silylated derivatives (50:50). We then turned our attention to bulkier hydroborating agents in an effort to increase selectivity. Treatment of **29** with disiamylborane proceeded to yield a 50:50 mixture of hydroxy lactones, and with 9BBN gave negligible regioselectivity, producing a 46:54 mixture of **47** and **48**. The results for the hydroborations performed on **29** are summarized in Table 4.

Table 4. Hydroboration Study on (7E)-13-Tridec-7-enolide (**29**).
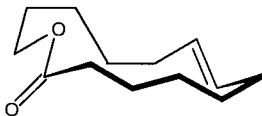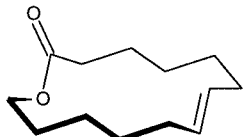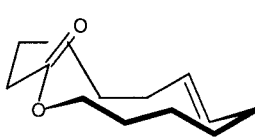
Hydroborating agent	Temperature	Selectivity		Yield (%)
		47	**48**	
BH$_3$THF	22 °C	49	51	88
BH$_3$THF	-78 °C	50	50	90
Sia$_2$BH	22 °C	50	50	86
9BBN	22 °C	46	54	93
Calculated[74]	22 °C	50	50	---

2.2.2 Conformational Analysis of (7E)-13-Tridec-7-enolide (29)

In order to rationalize the hydroboration results of macrocycle **29**, we turned our attention to molecular modeling. The unsaturated macrocyclic lactone **29** was subjected to a detailed conformational analysis using MM3* calculations.[74] Ab initio calculations[77] performed for the reaction of alkenes with various hydroborating agents support the presence of a relatively early transition state along the reaction coordinate. Applying Hammond's postulate,[30] the low energy conformations of the unsaturated lactone **29** were assumed to be good approximations for the transition states in the reaction of **29** with the various hydroborating agents.

The conformational analysis, however, proved to be quite complex. Thirty-four conformations were found within 2 kcal/mol of the global minimum. The introduction of a double bond into the ring system of a macrocycle makes the adoption of a diamond lattice conformation impossible,[20] thereby increasing the conformational mobility of the ring system in **29**. The three lowest energy conformations of unsaturated lactone **29** are shown in Table 5.

Table 5. The Three Lowest Energy Conformations of **29**.

Low Energy Conformation		Strain Energy[a] (kcal/mol)	Conformation
29a		0.00	[3344]
29b		0.02	[3434]
29c		0.09	[3344]

[a] Strain energy is reported relative to the lowest energy conformation.

29

29a 29b 29c
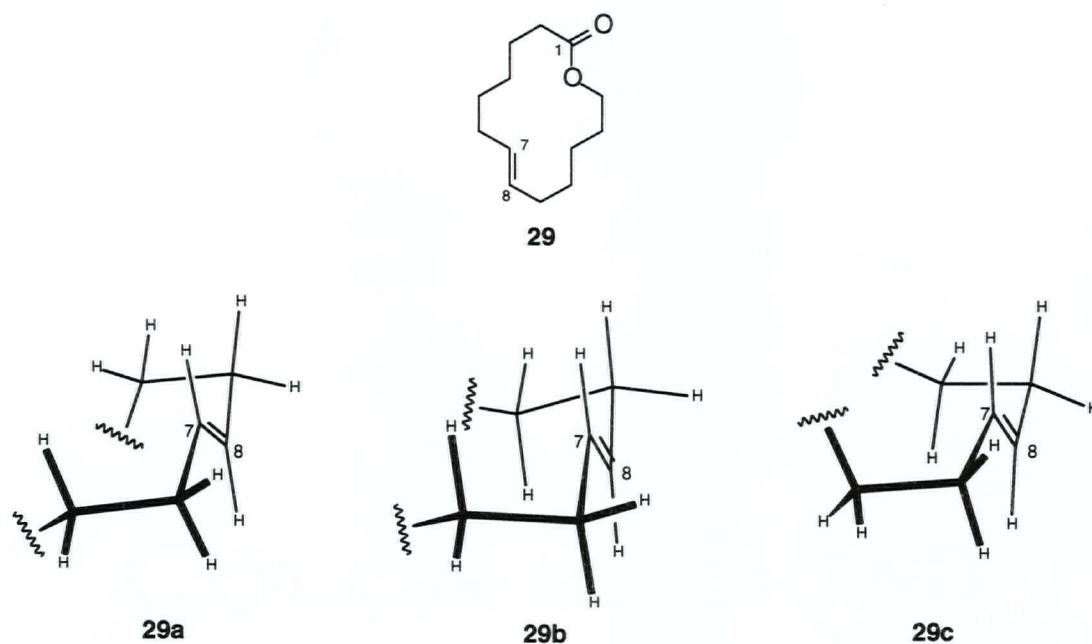
Figure 17. Local conformations around the double bond in (7E)-13-tridec-7-enolide (**29**).

The three lowest energy conformations for **29** listed in Table 5 all reveal the same local conformation around the double bond (Figure 17). This is also evident from an examination of their polar maps (Figure 18).

29

29a 29b 29c
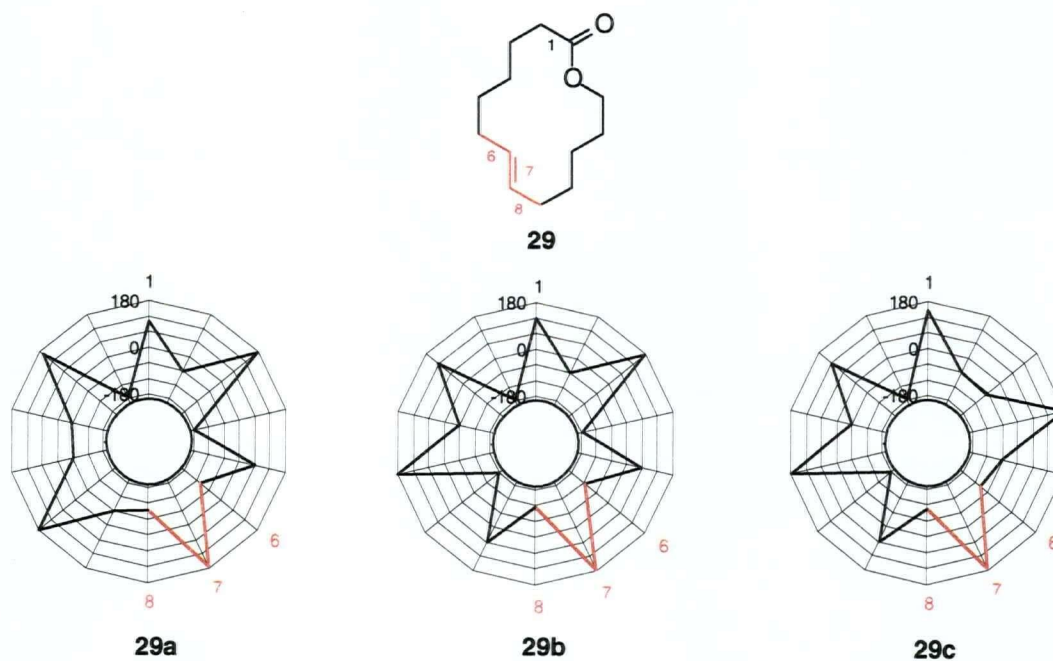
Figure 18. Polar maps of the three lowest energy conformations of (7E)-13-tridec-7-enolide (**29**).

Microwave spectroscopy[78,79] and ab initio calculations[80,81] have shown that the preferred conformation of unsaturated hydrocarbon chains is that in which the allylic hydrogens are eclipsed with the center of the double bond. The calculated local conformations around the double bond in the three lowest energy conformations of **29** (Figure 17) agree with this preferred conformation. These conformations show C6, C7, C8 and C9, along with a hydrogen bonded to each carbon, in the same plane. In fact, all of the conformations obtained from the MM3* search within 2 kcal/mol of the global minimum reveal the same local conformation around the olefin function. Consequently, this arrangement provides for similar steric environments at C7 and C8. Accordingly, it can be expected that the boron of the hydroborating agent cannot distinguish between these two positions. The model based on the conformational search performed on **29** thus illustrates that the reaction would provide an equal amount of the two possible products. This calculated result is in agreement with the experimentally obtained ratios of regioisomers in the hydroboration reaction of **29**.

2.2.3 Hydroboration Studies on (7*E*)-13-Tetradec-7-enolide (30)

As with the hydroboration of **29**, our primary objective was to isolate and characterize each of the stereoisomeric products from the hydroboration of **30** before performing hydroboration studies under a variety of conditions. Lactone **30** was therefore initially hydroborated with borane tetrahydrofuran complex to give, after an oxidative work-up, a mixture of hydroxy lactones **51**, **52**, **53**, and **54** (Scheme 11).
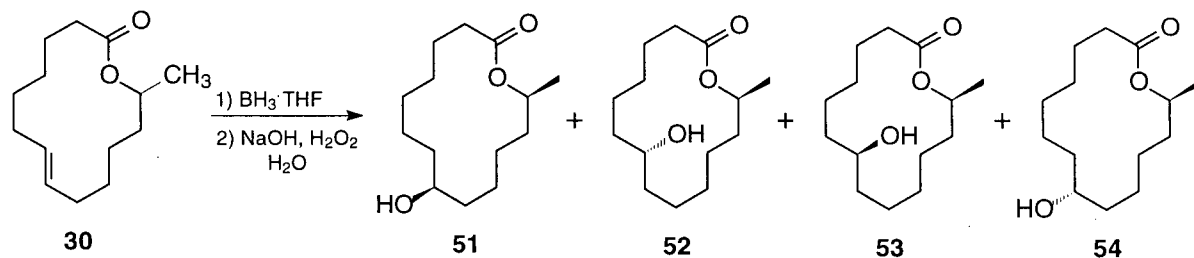
Scheme 11. Hydroboration of (7*E*)-13-tetradec-7-enolide (**30**).

The hydroxy lactones **51**, **52**, **53**, and **54** were not separable by flash column, radial or gas chromatography under a variety of conditions. In order to separate the hydroxy lactones for characterization purposes, as well as to determine the isomeric ratios, the respective trimethylsilyl ethers were formed in the same manner as the trimethylsilyl ethers of the hydroboration products of **29**. This produced a reaction mixture of four products which separated as two spots by TLC, and as three peaks by GC. The formation of the triethylsilyl and of the tert-butyldimethylsilyl derivatives did not provide for better separations. The application of flash column chromatography using TLC grade silica gel on each of the various silylated reaction mixtures resulted in the isolation of two fractions, each of which contained two isomeric products.

We decided to turn our attention to other types of derivatives in an attempt to separate the four isomeric products resulting from the hydroboration of **30**. The formation of carbamate derivatives has previously been described in the separation of stereoisomeric mixtures of alcohols.[82,83] The reaction of phenyl isocyanate with the product mixture from the hydroboration of **30** gave a quantitative yield of carbamates **55**, **56**, **57**, and **58** (Scheme 12).
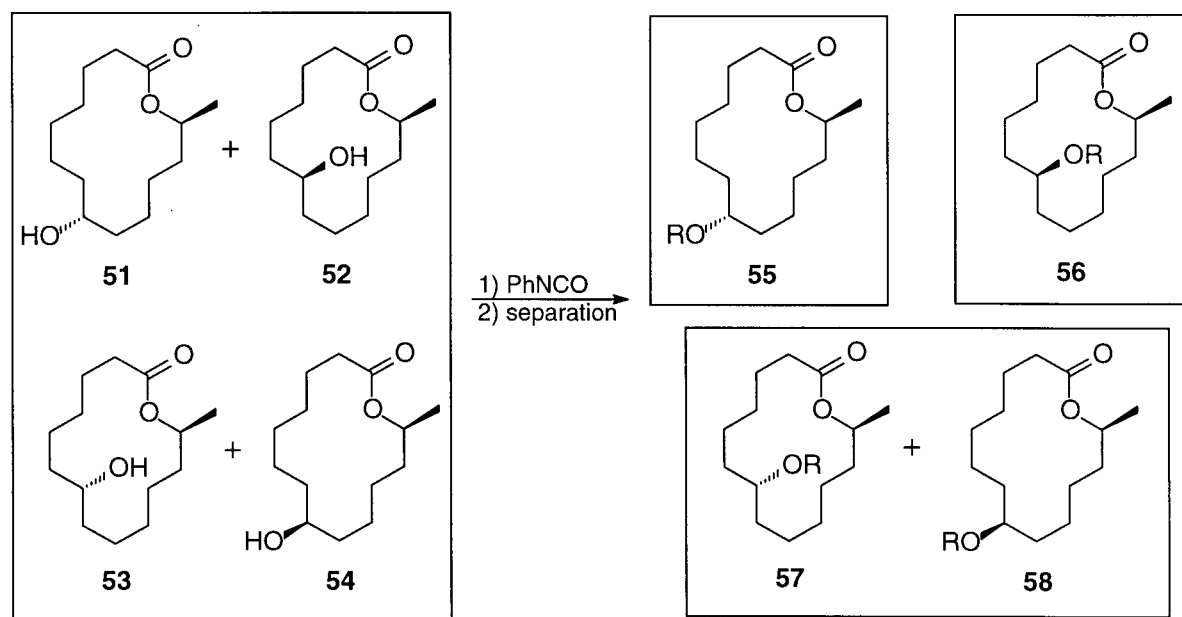
Scheme 12. Separation of hydroxy lactones **51**, **52**, **53**, and **54**

The phenyl carbamates could not be resolved by gas chromatography. However, the phenyl chromophore in the carbamate derivatives allowed for the relative amounts of the derivatives to be quantified using HPLC in conjunction with a UV detector. Four resolved peaks were observed from the HPLC analysis in a 37:18:31:14 ratio. Flash column chromatography using TLC grade silica gel provided pure samples of the phenyl carbamates **55** and **56**. Unfortunately, the carbamates **57** and **58** were not separable by this method.

We then set out to structurally identify the four isomers obtained. Each of the two sets of regioisomers was identified first in the following manner. The hydroboration of a 64:36 mixture of E/Z unsaturated lactones **59** and **60**, previously synthesized in our laboratory,[64] yielded four isomeric hydroxy lactones which were subsequently transformed to the phenyl carbamate derivatives. The HPLC chromatograph of the derivatives **56, 57, 61** and **62** was compared to that of the carbamate derivatives from the hydroboration of **30** (Scheme 13). This comparison revealed two peaks common to both of the HPLC traces, which had the same retention times. The stereoisomers **56** and **57** were assigned to these two peaks, which make up one of the two sets of regioisomers from the hydroboration of **30**. Consequently, stereoisomers **55** and **58** were assigned as the second set of regioisomers.

In order to identify the set of isomers resulting from the hydroboration on the same face of the double bond, we again utilized a chemical correlation approach. In their demonstration of local conformer control in the epoxidation and osmylation of unsaturated lactones and cyclic olefins, Vedejs and coworkers[32,84] correlated the epoxidation products to known alcohols using nucleophilic hydride ring opening of the epoxides. Based on this work, we used a modified approach to identify the two sets of π-face isomers (Scheme 13).
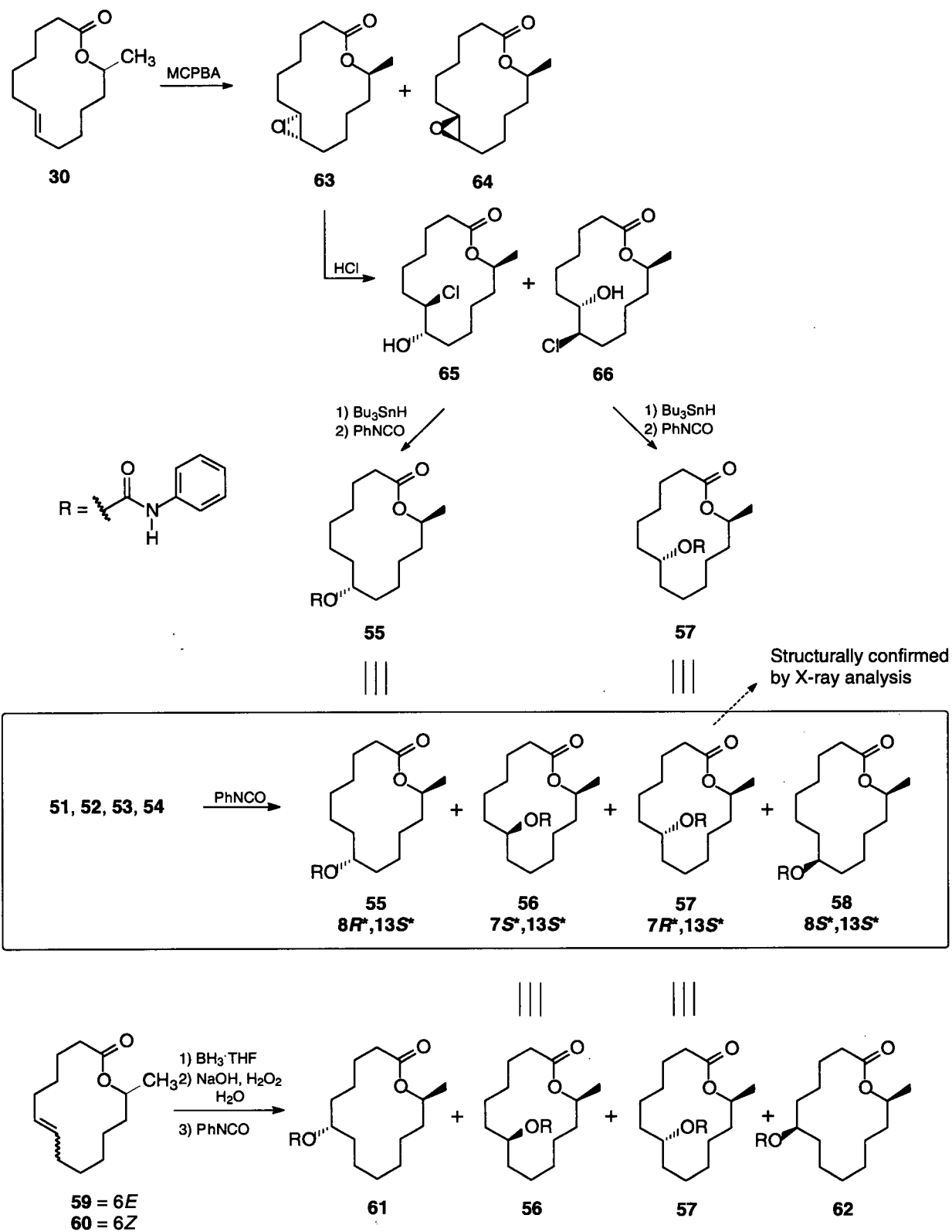
Scheme 13. Chemical correlations used in the structural identification of carbamate derivatives **55, 56, 57** and **58** (triple lines represent chemical correlations).

Epoxidation of **30** with *m*-chloroperbenzoic acid at 22 °C yielded two diastereomers, **63** and **64**, in a 67:33 ratio and 98% total yield. The lactone functionality prevented the epoxide ring opening using lithium aluminum hydride to obtain the hydroxy lactones directly. Alternatively, hydrochloric acid cleavage of the epoxide[85] followed by the dehalogenation of the chlorohydrin[86] was performed on the major diastereomer of the epoxidation (Scheme 13). Thus addition of hydrochloric acid to epoxide **63** yielded a mixture of regioisomeric chlorohydrins **65** and **66** in 94% yield. The two regioisomers were separated by radial chromatography, and the isolation revealed a 48:52 ratio of **65** and **66** for the hydrochloric acid addition.

Chlorohydrins **65** and **66** were reduced with tributyltin hydride to yield the corresponding hydroxy lactones. Finally, the HPLC chromatographs of the carbamate derivatives **55** and **57** were compared to the HPLC trace for the carbamate derivatives from the hydroboration of **30**. Since it is well known that alkene epoxidations with peracids occur via *syn* addition, we were confident that derivatives **55** and **57** contained the carbamate group on the same face of the ring system. Consequently, derivatives **56** and **58** both contained the carbamate group on the opposite face.

At this point, the set of π-face isomers, **55/57** and **56/58**, had been elucidated, as well as the two sets of regioisomers **56/57** and **55/58**. We could not conclusively assign the structure for each compound within these sets since it was not possible to establish the structure of the major isomer obtained from the epoxidation of **30**. However, crystals suitable for an X-ray analysis were obtained for the phenyl carbamate **57** (Figure 19). This confirmed the 7*R**,13*S** relative stereochemistry for **57**.

The phenyl carbamate derivative **56** was then assigned the 7*S**,13*S** stereochemistry since the results from the hydroboration of **59** and **60** revealed that carbamate **56** was the diastereomer of **57**. Also, the epoxidation of unsaturated lactone **30** revealed that carbamate **55** was the regioisomer of **57**, and hence **55** was assigned the 8*R**,13*S** stereochemistry. Finally, carbamate **58** was assigned the 8*S**,13*S** stereochemistry. The use of the star superscript

(*) indicates the presence of both enantiomers possessing the same relative stereochemistry at the numbered atoms, e.g. 7R*,13S* refers to an equal amount of 7R,13S and 7S,13R stereoisomers. This star notation is used throughout this thesis.
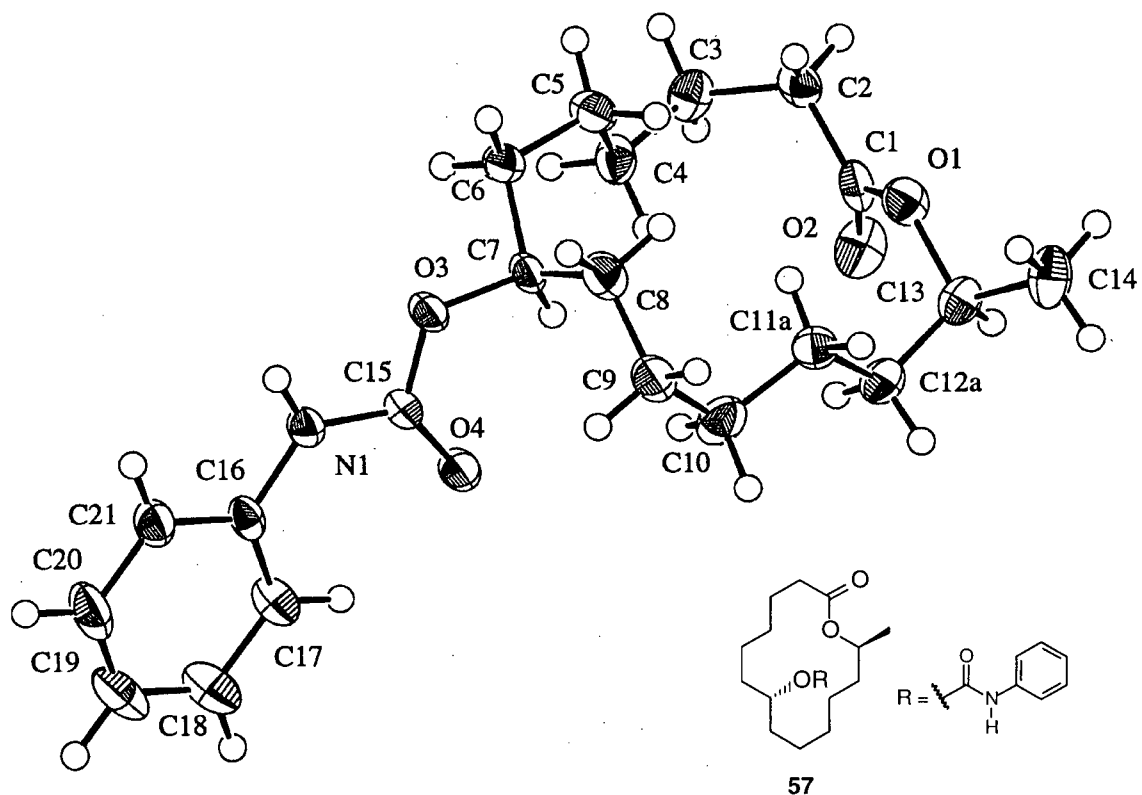
Figure 19. ORTEP representation of (7R*, 13S*)-7-(N-phenylcarbamoyl)oxy-13-tetradecanolide (**57**), showing 50% probability ellipsoids and hydrogen atoms with arbitrary thermal parameters for clarity.

The initial isolation and characterization of the hydroxy lactones revealed that the addition of the borane tetrahydrofuran complex to the unsaturated lactone **30** at 22 °C proceeded to yield a 37:18:31:14 ratio of the four isomeric products **51**, **52**, **53**, and **54**, respectively. This roughly correlates to a 2:1 π-face selectivity. However, this also revealed no regioselectivity in the hydroboration of

30. The effect of lower temperature on the selectivity of the hydroboration was also investigated. The reaction of **30** with borane tetrahydrofuran at -78 °C proceeded with no regioselectivity, according to the HPLC analysis of the carbamate derivatives (50:50), but did provide for slightly better π-face selectivity (3:1 ratio for **51/53** and **52/54**). We then turned our attention to bulkier hydroborating agents in the hope of obtaining increased selectivity. Hydroboration of **30** with disiamylborane proceeded with no regioselectivity and slightly lower π-face selectivity than with borane tetrahydrofuran at -78 °C. The lower selectivity obtained with disiamylborane may be a result of the higher reaction temperature required. The hydroboration of **30** with 9BBN also gave no regioselectivity, but resulted in the greatest π-face selectivity (7:1 ratio for **51/53** and **52/54**). The results for the hydroborations performed on **30** are summarized in Table 6.

Table 6. Hydroboration Study on (7*E*)-13-Tetradec-7-enolide (**30**).

Hydroborating agent	Temperature	Selectivity				π-Face selectivity		Yield (%)
		51	**52**	**53**	**54**	**51/53**	**52/54**	
BH₃·THF	22 °C	37	18	31	14	68	32	90
BH₃·THF	-78 °C	42	17	33	8	75	25	93
Sia₂BH	22 °C	41	18	31	10	72	28	85
9BBN	22 °C	45	8	43	4	88	12	92
Calculated[74]	22 °C	42	8	42	8	84	16	---

2.2.4 Epoxidation Studies on (7*E*)-13-Tetradec-7-enolide (30)

The epoxidation of the unsaturated lactone **30** with MCPBA, used to determine the stereochemistry of the hydroxy lactones, showed moderate diastereoselectivity and we therefore decided to explore this further. The hydroxy lactones **55** and **57** obtained from the major epoxidation isomer had the 8*R**,13*S** and the 7*R**,13*S** stereochemistry respectively. We therefore concluded that the major isomer **63** from the epoxidation of **30** must have the 7*S**,8*S**,13*S** stereochemistry. The epoxidation at 22 °C yielded a 2:1 ratio of diastereomers **63** and **64**. We decided to perform this reaction a lower temperature in order to increase the selectivity. The same reaction at 0 °C gave a 2.2:1 ratio, and at -78 °C the reaction was found to be the most selective with a 3.3:1 ratio. The epoxidation was also performed using methyl(trifluoromethyl)dioxirane[87] at 0 °C, since this reagent had previously demonstrated increased selectivity when compared to MCPBA and other epoxidizing agents.[88] However, the use of the dioxirane epoxidation agent gave a similar diastereoselectivity as MCPBA. The results for the epoxidations performed on **30** are summarized in Table 7.
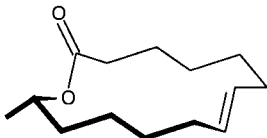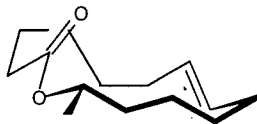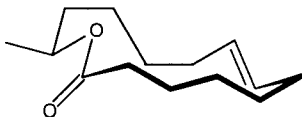
Table 7. Epoxidation Study on (7*E*)-13-Tetradec-7-enolide (**30**).

Epoxidation agent	Temperature	Selectivity 63	Selectivity 64	Yield (%)
MCPBA	22 °C	67	33	98
MCPBA	0 °C	69	31	91
MCPBA	-78 °C	77	23	100
Methyl(trifluoromethyl) dioxirane	0 °C	70	30	98
Calculated[74]	-78 °C	90	10	---

2.2.5 Conformational Analysis of (7*E*)-13-Tetradec-7-enolide (30)

In order to rationalize the hydroboration and epoxidation results of macrocycle **30**, we again turned our attention to molecular modeling. The unsaturated lactone **30** was subjected to a detailed conformational analysis using MM3* calculations.[74] In accordance with ab initio calculations[77] and Hammond's postulate,[30] it was again assumed that the transition state structure for the hydroboration resembles the low energy conformations of **30**. The epoxidation of alkenes have also been determined from ab initio calculations[89,90] to proceed through relatively early transition states along the reaction coordinate. Accordingly, the low energy conformations of **30** were used in the same manner to approximate the transition state structure for the epoxidation reaction.

Table 8. The Three Lowest Energy Conformations of **30**.

Low Energy Conformation	Strain Energy[a] (kcal/mol)	Conformation
30a	0.00	[3434]
30b	0.02	[3344]
30c	0.32	[3344]

[a] Strain energy is reported relative to the lowest energy conformation.

30

30a   30b   30c
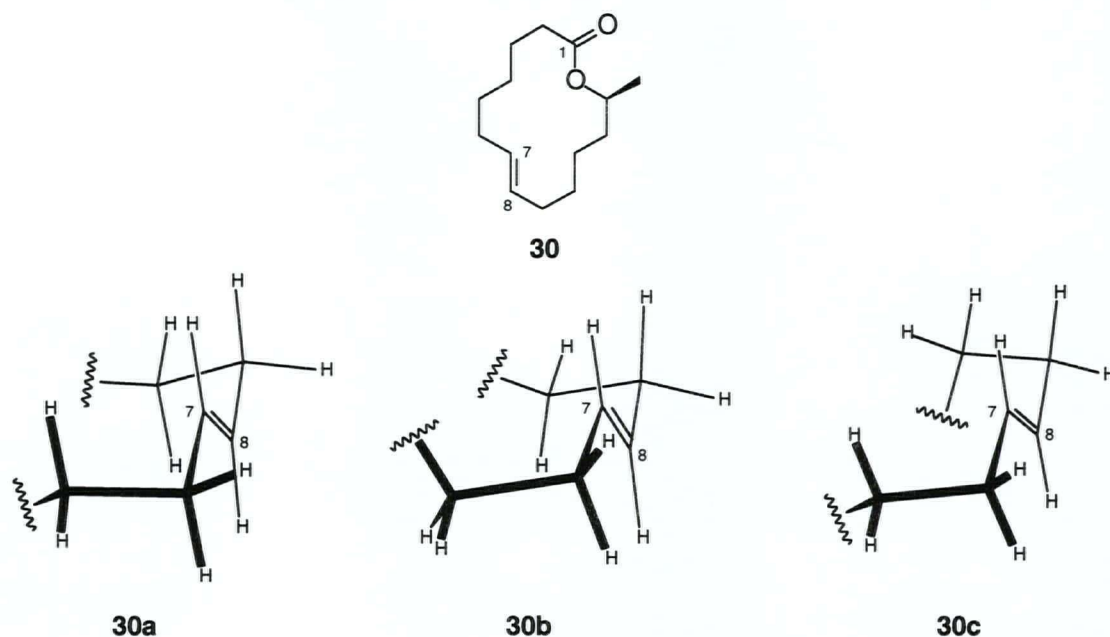
Figure 20. Local conformations around the olefinic double bond in (7*E*)-13-tetradec-7-enolide (**30**).

As with the unsaturated lactone **29**, the conformational analysis for **30** proved to be quite complex. Twenty-four conformations were found within 2 kcal/mol of the global minimum. The three lowest energy conformations of unsaturated lactone **30** are shown in Table 8.

30

30a   30b   30c
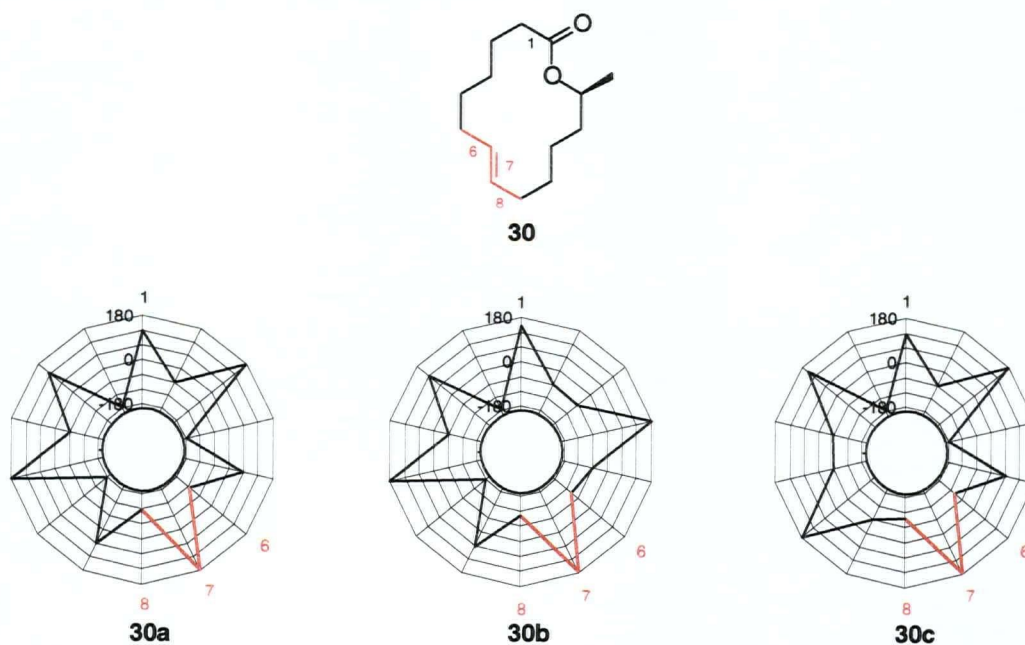
Figure 21. Polar maps of the three lowest energy conformations of (7*E*)-13-tetradec-7-enolide (**30**).

The three lowest energy conformations for **30** listed in Table 8 all reveal the same local conformation around the double bond (Figure 20). This is also evident from an examination of their polar maps (Figure 21).

The three lowest energy conformations of **30** show the same eclipsed conformation around the double bond as does the unsaturated lactone **29**. In fact, all the conformations obtained from the MM3* search within 2 kcal/mol of the global minimum exhibit the same local conformation around the olefinic function. Hence, the steric environments at C7 and C8 are similar and, as with unsaturated lactone **29**, the model based on the conformational search illustrates that the reaction would provide equal amounts of the two products. This calculated result is in agreement with the 50:50 ratios of regioisomers observed in the hydroboration reactions of **30**.

To rationalize the π-face selectivities observed in the hydroborations and epoxidations, a more detailed examination of the low energy conformations of **30** was carried out (Figure 22). Still and Gallynker[28] have demonstrated that reagents approach the π system of a macrocyclic compound largely or perhaps exclusively from the peripheral face. This can be expected to occur in each of the three lowest energy conformations of **30** (**30a**, **30b**, **30c**), illustrated in Figure 21, to yield the hydroboration products with the $8R^*,13S^*$ and $7R^*,13S^*$ stereochemistries (**51** and **53**). In fact, the five lowest energy conformations (up to 0.70 kcal/mol above the global minimum) are predicted to yield the $8R^*,13S^*$ and $7R^*,13S^*$ products. The sixth and seventh lowest energy conformations (**30d**, **30e**) are expected to yield products with the $8S^*,13S^*$ and $7S^*,13S^*$ stereochemistries (**52** and **54**). This analysis was expanded to the 24 conformations within 2 kcal/mol of the global minimum. A total of 18 of these conformations would give rise to the $8R^*,13S^*$ and $7R^*,13S^*$ products, whereas only six conformations would lead to the $8S^*,13S^*$ and $7S^*,13S^*$ products. This analysis suggests that **51** and **53** would be the major diastereomers resulting from the hydroboration of **30**.

Figure 22. Low energy conformations of (7*E*)-13-tetradec-7-enolide (**30**) and the corresponding predicted hydroboration products.
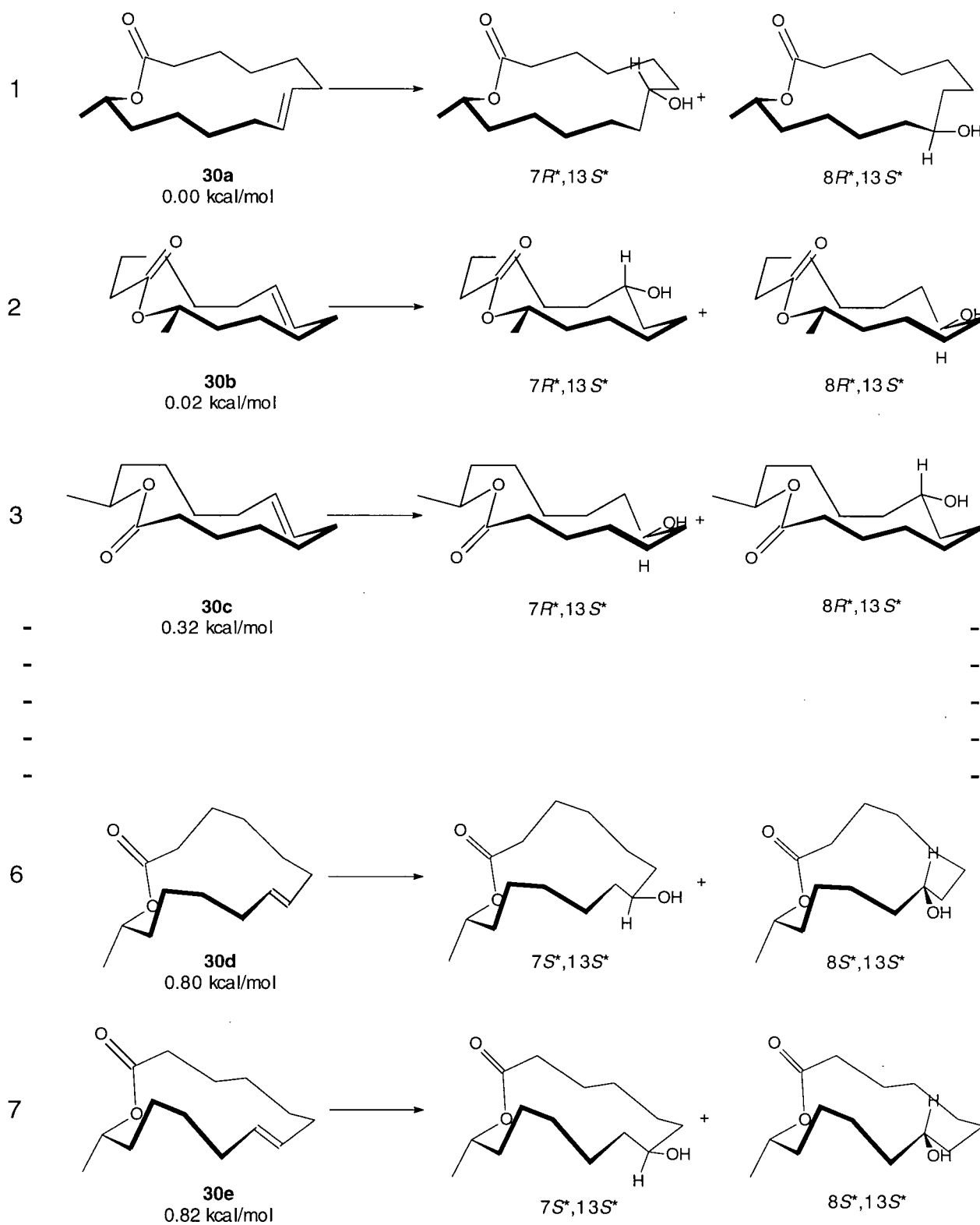
An attempt to calculate the π-face selectivity was performed. Still and Gallynker[28] have used Boltzmann distributions of the low energy conformations to rationalize the selectivity of a variety of reaction types. The population fraction (p_i) of conformations which lead to products **51** and **53** was calculated by introducing the energy contribution for each of these conformations (n_i), along with the energy contribution associated with all conformations (N), into a Boltzmann distribution equation:[91]

$$p_i = \frac{n_i}{N} = \frac{e^{-\varepsilon_i/kT}}{\sum_j e^{-\varepsilon_j/kT}}$$

where ε_i is the energy of the molecular conformation, k is the Boltzmann constant (1.38066×10^{-23} JK^{-1}) and T is the temperature.

This revealed a population ratio of 84:16 at 22 °C in favor of the conformations which lead to **51** and **53** over those which give rise to **52** and **54**. Since the hydroboration of **30** is predicted to yield a 50:50 ratio of regioisomers based on the conformational analysis performed earlier, each of the π-face isomers should contain an equal number of regioisomers. Hence, the ratio of the products **51**, **52**, **53** and **54** is calculated to be 42:8:42:8. This is in agreement with the experimental results (Table 6).

In the same manner, the calculations applied to the epoxidation of the unsaturated lactone **30** suggests a 90:10 ratio of diastereomers **63** and **64** at -78 °C. Although the calculated result for the epoxidation is in general agreement with the experimental result (Table 7), the epoxidations were found to be less selective than for when the bulkier hydroborating agents were employed. Thus, the π-face selectivity using MCPBA as well as methyl(trifluoromethyl)dioxirane appears to be similar to that of the borane-tetrahydrofuran complex.

Although the presence of the additional methyl substituent in the structure of **30** provided for a less conformationally mobile ring system than that of **29**, this did not improve the regioselectivity in the hydroboration reactions. The source of the poor regioselectivity appears to be the stable eclipsed conformation around the double bond, which is present in all the low energy conformations of unsaturated lactones **29** and **30**.

2.3 Stereoselectivity Studies on 7-Oxo-13-Tetradecanolide (67) and 8-Oxo-13-Tetradecanolide (68)

With the hydroxy lactones **51**, **52**, **53** and **54** from the hydroboration study in hand, the corresponding keto lactones for the hydride reduction study were obtained via oxidation of the alcohol function. These compounds allowed for further investigations into conformationally controlled reactions of these ring systems.

Keto lactones **67** and **68** were synthesized using the TPAP oxidation of a 37:18:31:14 mixture of **51**, **52**, **53** and **54** (Scheme 14). The two resulting keto lactones, formed in a 1:1 ratio, were separated by flash column chromatography using TLC grade silica gel.

Reduction reactions were then performed on of the keto lactones **67** and **68**, using a variety of hydride reducing agents. The ratios of the resulting hydroxy lactones were then determined from the HPLC retention times of the carbamate derivatives, permitting a study of the stereoselectivity of the reduction reactions.
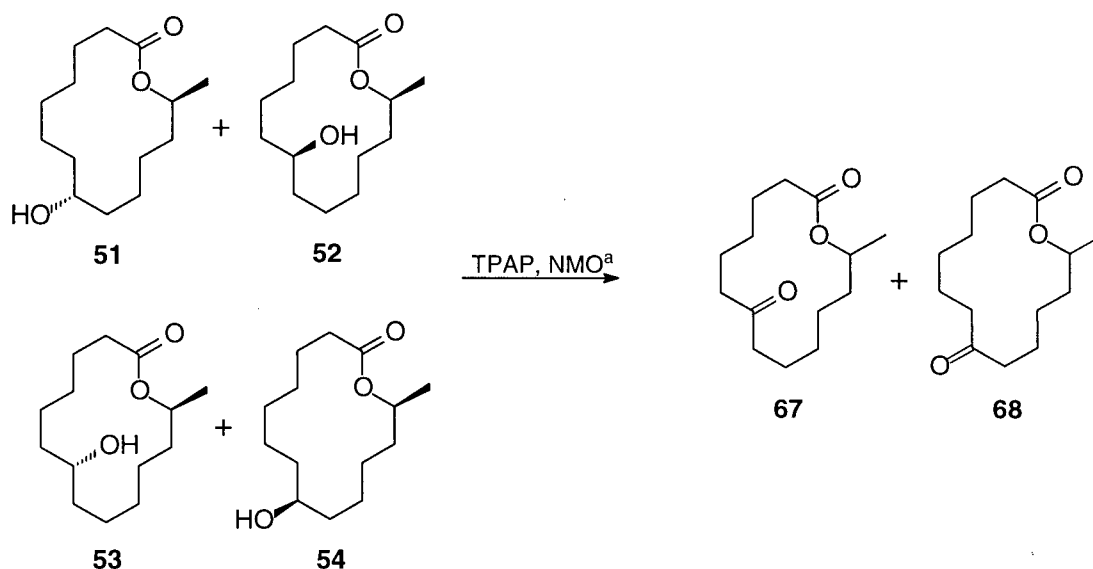
Key: (a) 10 mol% TPAP, NMO, 3 Å molecular sieves, CH_2Cl_2, rt, 86%.

Scheme 14. Synthesis of 7-oxo-13-tetradecanolide (**67**) and 8-oxo-13-tetradecanolide (**68**).

2.3.1 Hydride Reduction Studies on 7-Oxo-13-Tetradecanolide (67)

The 7-oxo-13-tetradecanolide (**67**) was subjected to a variety of hydride reducing agents and reaction conditions. The $NaBH_4$ reduction was first performed at low temperature (-78 °C), yielding a 1:1 ratio of the two diastereomeric products. The products were identified from the HPLC comparison of the phenyl carbamate derivatives with those from the hydroboration study of **30**. The reduction of **67** with $NaBH_4$ under Luche conditions[92] (cerium chloride additive) gave only slight selectivity. We then turned our attention to the bulkier reducing reagent K-Selectride.[93] The reaction of keto lactone **67** with K-Selectride in THF at -15 °C provided good selectivity with a better than 6.5:1 ratio for **52:53**. The ease with which this reaction proceeded led us to believe that this same reaction could be performed at even lower temperature in order to further improve selectivity. Thus, the same reaction at -78 °C produced the two hydroxy lactones **52** and **53** with better than 10:1 selectivity. The results for the hydride reductions performed on **67** are summarized in Table 9.

Table 9. Hydride Reduction Study on 7-Oxo-13-Tetradecanolide (**67**).

Reducing agent	Temperature	Selectivity 52	53	Yield (%)
$NaBH_4$	-78 °C	50	50	80
$NaBH_4$, $CeCl_3$	-78 °C	55	45	86
K-Selectride	-15 °C	87	13	83
K-Selectride	-78 °C	91	9	91
Calculated[74]	-78 °C	92	8	---

2.3.2 Hydride Reduction Studies on 8-Oxo-13-Tetradecanolide (68)

The 8-oxo-13-tetradecanolide (68) was subjected to the same variety of hydride reducing agents as were used with the keto lactone 67. The NaBH$_4$ reduction was first performed at low temperature (-78 °C), yielding a 1:1 ratio of diastereomeric products 51 and 54. The two products were also identified from the HPLC comparison of the phenyl carbamate derivatives with those from the hydroboration study of 30. The reduction of 68 with NaBH$_4$ under Luche conditions[92] (cerium chloride additive) did not provide significant selectivity, nor did the reaction with the bulkier reagent K-Selectride[93] at -15 °C. The reaction of keto lactone 68 with K-Selectride in THF at -78 °C produced the two hydroxy lactones 51 and 54 with low selectivity, yielding a 1:1.5 ratio, respectively. The results for the hydride reductions performed on 68 are summarized in Table 10.

Table 10. Hydride Reduction Study on 8-Oxo-13-Tetradecanolide (68).
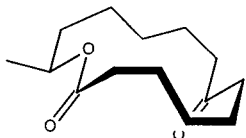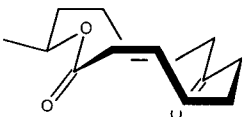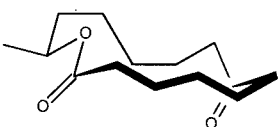
Reducing agent	Temperature	Selectivity		Yield (%)
		51	54	
NaBH$_4$	-78 °C	50	50	83
NaBH$_4$, CeCl$_3$	-78 °C	56	44	87
K-Selectride	-15 °C	47	53	90
K-Selectride	-78 °C	40	60	89
Calculated[74]	-78 °C	8	92	---

2.3.3 Conformational Analysis of 7-Oxo-13-Tetradecanolide (67) and of 8-Oxo-13-Tetradecanolide (68)

In order to rationalize the hydride reduction results for the keto lactones, we again turned our attention to molecular modeling. The keto lactones **67** and **68** were subjected to a detailed conformational analysis using MM3* calculations.[74] Previous ab initio calculations[94-96] have revealed that the transition state for ketone reduction lies early along the reaction coordinate. As previously in the hydroboration and epoxidation studies, it was assumed that the transition state structure for the reductions resembles the low energy conformations of the respective keto lactone. This method has previously been used in our laboratory,[35,36] with the aid of the MM2* force field parameters,[29] for the hydride reduction of a series of keto lactones.
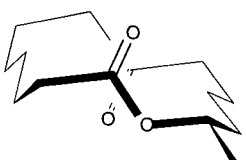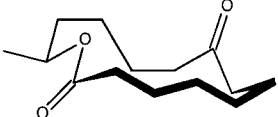
The conformational analysis for **67** and **68** proved to be quite complex. Twenty-two conformations for **67**, and twenty-three conformations for **68**, were found within 2 kcal/mol of the global minimum in each system. The three lowest conformations of keto lactones **67** and **68** are shown in Table 11 and Table 12, respectively.

Table 11. The Three Lowest Energy Conformations of **67**.

Low Energy Conformation	Strain Energy[a] (kcal/mol)	Conformation
67a	0.00	[3344]
67b	0.16	[3434]
67c	0.24	[3344]

[a] Strain energy is reported relative to the lowest energy conformation.

Table 12. The Three Lowest Energy Conformations of **68**.

Low Energy Conformation	Strain Energy[a] (kcal/mol)	Conformation
68a	0.00	[3434]
68b	0.52	[3344]
68c	0.78	[3335]

[a] Strain energy is reported relative to the lowest energy conformation.

The calculated selectivities were determined using the peripheral attack assumption[28] of the hydride reducing reagents on the ring systems of **67** and **68**. The three lowest energy conformations of **67** provide for the exclusive formation of the 7S^*,13S^* product (hydroxy lactone **52**) (Figure 23). A total of 17 conformations within 2 kcal/mol of the global minimum were found which lead to the formation of the 7S^*,13S^* product (**52**). Only 5 conformations lead to the formation of the 7R^*,13S^* product (**53**).

67a
0.00 kcal/mol
"H⁻"
7S^*,13S^*

67b
0.16 kcal/mol
"H⁻"
7S^*,13S^*

67c
0.24 kcal/mol
"H⁻"
7S^*,13S^*

Figure 23. Low energy conformations of 7-oxo-13-tetradecanolide (**67**) and the corresponding predicted reduction products.

A Boltzmann distribution[91] of the conformations within 2 kcal/mol of the global minimum reveals a population ratio of 92:8 at -78 °C in favor of the conformations which lead to **52** over those which give **53**. This is in good agreement with the experimentally obtained ratio of 91:9 observed in the

reduction of **67** with K-Selectride at -78 °C (Table 11). It is interesting to note the lack of stereoselectivity of the reduction using $NaBH_4$. This suggests that $NaBH_4$ may be able to reduce a carbonyl group from the inside as well as from the periphery of the ring system. Similar results using $NaBH_4$ in the reduction of tetradecanolide keto lactones have been reported elsewere.[97,98]

A similar prediction was performed for the keto lactone **68**. The three lowest energy conformations provide for the exclusive formation of the $8S^*,13S^*$ product (hydroxy lactone **54**) (Figure 24). A total of 17 conformations within 2 kcal/mol of the global minimum were found which lead to the formation of the $8S^*,13S^*$ product (**54**) whereas 6 conformations lead to the formation of the $8R^*,13S^*$ product (**51**).
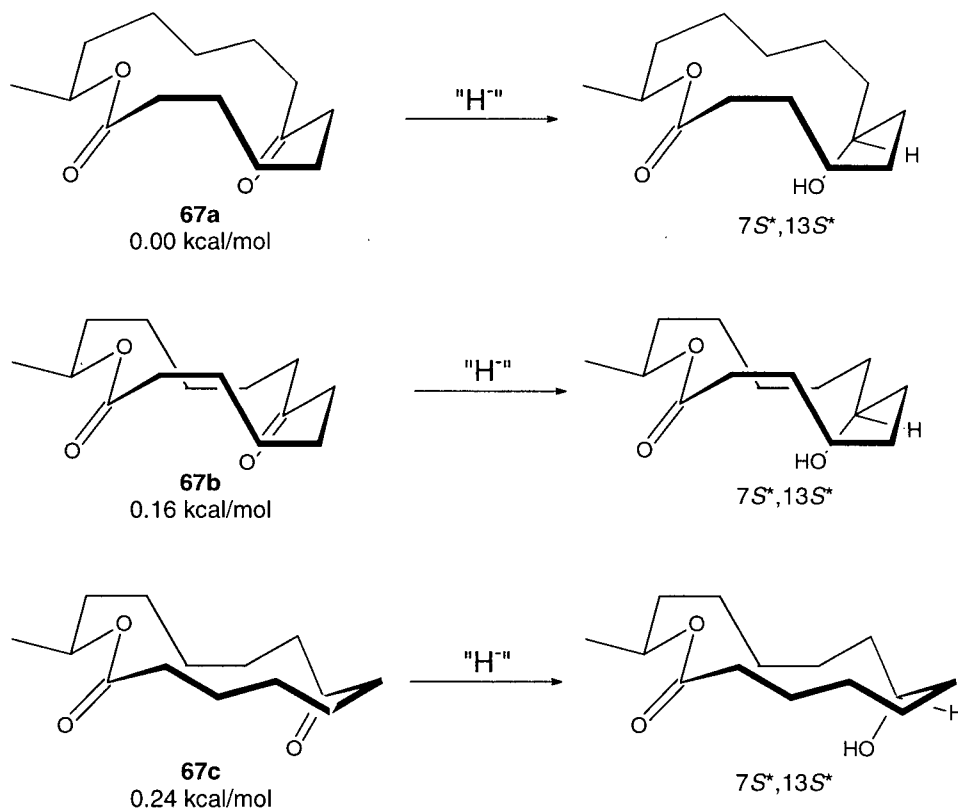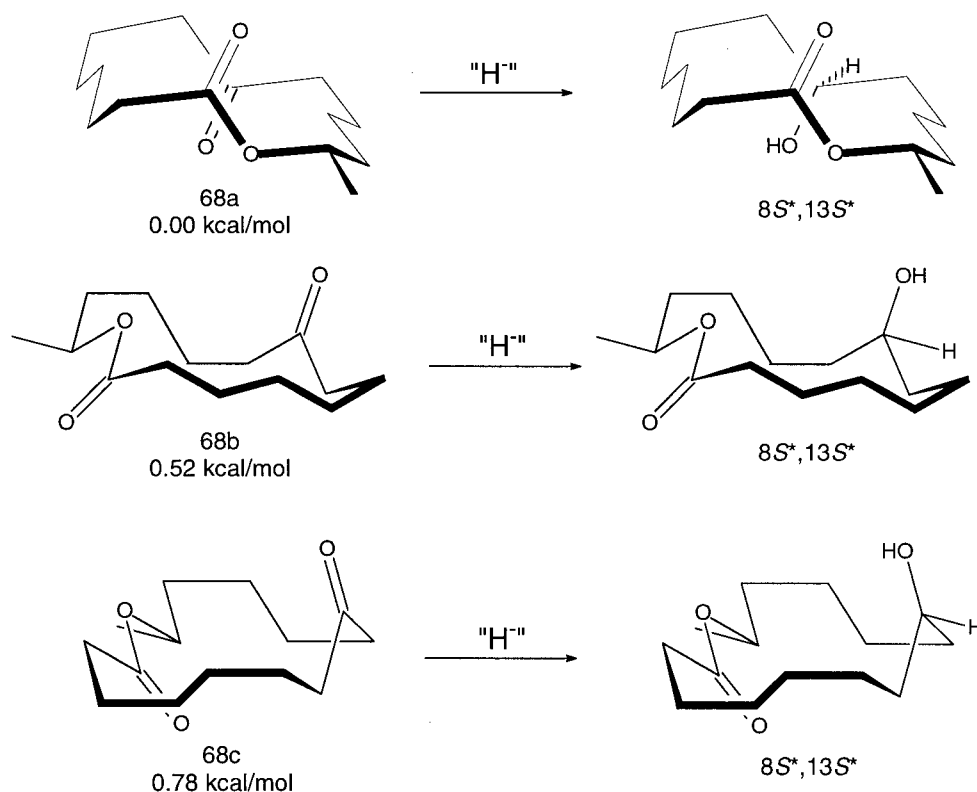

Figure 24. Low energy conformations of 8-oxo-13-tetradecanolide (**68**) and the corresponding predicted reduction products.

A Boltzmann distribution[91] of the conformations within 2 kcal/mol of the global minimum reveals a population ratio of 92:8 at -78 °C in favor of the conformations which lead to **54** over those which give **51**. This calculated selectivity was not observed experimentally. The greatest selectivity observed in the reduction of **68** was 1:1.5 for **51** and **54** respectively in the reduction with K-Selectride at -78 °C. However, the conformations obtained via MM3* calculations do predict the observed major diastereomer **54**.

We decided to investigate whether the transition state for the reduction lies later along the reaction coordinate, in order to explain the lack of agreement between the calculated and the experimentally observed ratios. The hydroxy lactone products **51**, **52**, **53** and **54** were each subjected to a detailed conformational analysis using MM3* calculations. A Boltzmann distribution of the conformations of **51** and **54** was calculated and revealed a population ratio of 60:40 in favor of the conformations for **51** over of those for **54**. In fact, this predicts the opposite major diastereomer as that which was observed experimentally for the reduction of **68**. The Boltzmann distribution calculation for **52** and **53** reveals a ratio of 67:33 in the reduction of **67**. This also predicts the opposite major diastereomer as that observed experimentally. Thus, the previous assumption of an early transition state appears more valid.

However, the calculated results for the reduction of **67** do not agree as closely with the observed experimental ratios as for the reduction of **68**. Further studies may be required in order to determine the source of this anomaly.

2.4 Conclusion

The conformational behavior of unsaturated 14-membered lactones and keto lactones proved to be rather complex. In general, the selectivity exhibited in the reactions of the macrocyclic lactones was rationalized from the conformational analysis of starting materials.

The hydroboration results demonstrated that the additions to the double bond proceed with low regioselectivity but with high π-face selectivity. Conformational analysis of the unsaturated macrocyclic lactones illustrated the lack of differentiation between the alkene carbons, thus explaining the lack of regioselectivity observed. High π-face selectivity was also evident in the epoxidation studies. The keto lactone hydride reduction results demonstrated that these reactions also proceed with moderate to high diastereoselectivity.

The relative stereochemistries associated with the stereogenic centers of the macrocyclic lactones created throughout the thesis were successfully assigned with the use of chemical correlations and X-ray analysis. The molecular model calculations have proved useful in the rationalization of experimentally obtained product distributions. These calculations appear to have predictive value as a semiquantative tool for the stereochemical outcome of reactions to these compounds.

CHAPTER 3

EXPERIMENTAL

3.1 General

All reactions were performed under a nitrogen atmosphere in flame- or oven-dried glassware. Elevated temperature reactions were performed in either a silicone oil bath or with a Glas-Col heating mantle at the desired temperature. Low temperature reactions were performed in a dry ice/acetone (-78 °C), a dry ice/ethylene glycol (-15 °C), or an ice water (0 °C) bath.

Anhydrous solvents were obtained by distillation. Diethyl ether, tetrahydrofuran and toluene were distilled from sodium. Methylene chloride and triethylamine were distilled from calcium hydride. Methanol was distilled from magnesium methoxide. Dimethyl sulfoxide and pyridine were distilled at reduced pressure from calcium hydride. The low boiling fraction of petroleum ether (bp 35-60 °C) was used. In the case of olefin metathesis reactions, methylene chloride was deoxygenated by sparging with nitrogen for 60 min. Otherwise, the solvents were used as received from the supplier.

Reagents were purified according to the procedures given in the literature.[99] Unless otherwise noted, reagents were purchased from the Aldrich Chemical Co. Alkyllithium reagents were standardized by titration with diphenylacetic acid in THF at 0 °C. The bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride (Grubbs' catalyst) reagent **28** was prepared according to the method of Schwab, Grubbs, and Ziller.[100] The bis(tricyclohexylphosphine)methylidine ruthenium (IV) dichloride catalyst (the active form of the catalyst **28**), was prepared by Mr. Andre Hodder[64] according to the method of Schwab, Grubbs, and Ziller.[100]

The concentration or removal of solvents under reduced pressure refers to the use of a Bucchi rotary evaporator. A brine solution refers to a saturated sodium chloride solution. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated aluminium plates (0.2 mm thickness). A 1% *p*-anisaldehyde spray or irradiation with ultraviolet light (254 nm) were used in the visualization of TLC plates. Flash column chromatography[101] was performed using silica gel 60, 230-400 mesh, supplied by E. Merck Co. TLC grade column chromatography refers to flash column chromatography with silica gel type H (10-40μ) supplied by Aldrich Chemical Co. Radial chromatography was performed using a Harrison Chromatotron model 8924. The adsorbant used was silica gel 60, PF_{254} with gypsum binder supplied by EM Science. Silver nitrate impregnated silica gel was prepared according to the procedure of de Vries.[70,71] Solvent systems used in liquid chromatography techniques were usually chosen such that the desired product had an R_f of approximately 0.20-0.30 on TLC.

Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard model 5880A gas chromatograph, equipped with a split mode capillary injection system and a flame ionization detector. The stationary phase consisted of an OV-101 capillary column of dimensions 0.20 mm x 12 m, and helium was used as the carrier gas. High performance liquid chromatography (HPLC) was carried out using a Waters silica Radial-Pak cartridge in a RCM 8 x 10 compression module containing Nova-Pak silica. Solvents were delivered through the column with the aid of a Waters 600E multisolvent delivery system, and a Waters 994 programmable photodiode array detector set at 250 to 400 nm was used.

Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. In the cases where Kugelrohr distillations were performed, boiling points are given as the oven temperature and are uncorrected. Infrared (IR) spectra were obtained using either a Bomem Michelson 100 FT-IR spectrophotometer or a Perkin Elmer 1710 FT-IR spectrophotometer. IR spectra were obtained as a neat sample of the liquid or as a deuteriochloroform solution held between two NaCl plates.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuteriochloroform solutions using either a Bruker AC-200 (200 MHz), Bruker WH-400 (400 MHz), or a Bruker AMX-500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) with proton decoupling spectra were recorded in deuteriochloroform solutions using a Bruker AC-200 (50 MHz). Chemical shifts for all spectra are reported in parts per million (ppm) on the δ scale and are referenced to chloroform (δ 7.24 ^{1}H NMR; δ 77.0 ^{13}C NMR) as an internal standard.

Low resolution mass spectra (LRMS) in electron ionization (EI) mode were recorded on a Kratos-AEI model MS 50 spectrometer. LRMS in chemical ionization (CI) mode were recorded on either a Kratos MD 80 spectrometer or a Kratos Concept II HQ spectrometer. LRMS in desorption chemical ionization (DCI) mode were recorded on a Delsi Nermag R10-10 C spectrometer. Only peaks with relative intensities greater than 20% or those of analytical importance are reported. High resolution mass spectra (HRMS) in EI mode were recorded on a kratos-AEI mode MS 50 spectrometer. HRMS in CI mode were recorded on either a Kratos MS 80 spectrometer or a Kratos Cocept II HQ spectrometer.

Microanalyses were performed by Mr. Peter Borda in the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a fisions CHN-O Elemental Analyzer Model 1108.

3.2   <u>Conformational Analysis Methods</u>

BATCHMIN, a part of MACROMODEL molecular modelling program developed by Still and coworkers[75] was used to calculate the global minimum conformations of the macrocyclic lactones studied in this work. The MM3* force field, based on the MM3 parameters developed by Allinger and coworkers,[74] was used to minimize structures in conjunction with the Monte Carlo Multiple Minimum Search (MCMM) in order to find the global minimum conformations.

3.3   Chemical Methods

3.3.1   2-(6'-Hydroxyl hexoxyl) tetrahydropyran (37)[102]
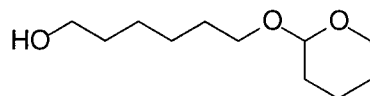
Dowex 50W x 12 acidic resin (30.0 g) was added to a solution of 1,6-hexanediol (22.00 g, 186.2 mmol) and 3,4-dihydropyran (15.66 g, 186.2 mmol) in toluene (350 mL). The solution was stirred at rt for 4 hours and the resin was removed by vacuum filtration.   The filtrate was sequentially washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The dried solution was filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% ethyl acetate in petroleum ether as eluant afforded alcohol **37** (26.37 g, 130.3 mmol) in 70% yield as a clear colourless oil.

IR (neat): 3392, 2935, 2863, 1454, 1351, 1121, 1072, 1030, 904 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$): 4.54 (t, J = 3.5 Hz, 1H), 3.26-3.93 (m, 6H), 1.29-1.94 (m, 15H);
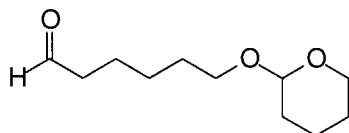
^{13}C NMR (50 MHz, CDCl$_3$): δ 98.86, 67.54, 62.60, 62.35, 32.65, 30.74, 29.66, 26.03, 25.55, 25.47, 19.61;

LRMS (EI) *m/z* (relative intensity): 201 (4), 101 (18), 85 (100), 55 (39);

HRMS (EI) *m/z* calculated for C$_{11}$H$_{21}$O$_3$: 201.14907, found: 201.14947;

Analysis calculated for C$_{11}$H$_{22}$O$_3$: C, 65.31; H, 10.96. Found: C, 65.09; H, 10.97.

3.3.2 2-(6'-Oxohexoxyl) Tetrahydropyran (38)[102]

A solution of dimethylsulfoxide (22.1 mL, 311 mmol) in CH_2Cl_2 (100 mL) was added via cannula to a solution of oxalyl chloride (12.4 mL, 143 mmol) in CH_2Cl_2 (300 mL) at -78 °C. The solution was stirred for 5 minutes and alcohol **37** (26.20 g, 129.5 mmol) in CH_2Cl_2 (100 mL) was added via cannula. This mixture was stirred for 15 minutes at -78°C. Triethylamine (84.8 mL, 609 mmol) was added, the mixture was stirred for 5 minutes, and warmed to rt. The reaction was quenched with water, the organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, sequentially washed with 1N HCl solution, water, 5% Na_2CO_3 solution, and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 25% ethyl acetate in petroleum ether as eluant afforded aldehyde **38** (20.63 g, 103.0 mmol) in 80% yield as a clear colourless oil.

IR (neat): 2937, 2864, 1727, 1450, 1356, 1265, 1129, 1077,1030, 869 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.71 (s, 1H), 4.50 (s, 1H), 3.21-3.90 (m, 4H), 2.39 (t, J = 7.2 Hz, 2H), 1.23-1.88 (m, 12H);
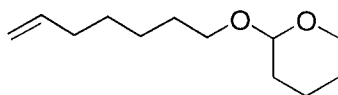
^{13}C NMR (50 MHz, $CDCl_3$): δ 202.64, 98.90, 67.25, 62.36, 43.83, 30.76, 29.50 25.91, 25.49, 21.93, 19.68;

LRMS (EI) m/z (relative intensity): 200 (M$^+$, 3), 199 (8), 101 (75), 99 (50), 85 (100), 81 (26);

HRMS (EI) m/z calculated for $C_{11}H_{20}O_3$ (M$^+$-1): 199.13352, found: 199.13342;

Analysis calculated for $C_{11}H_{19}O_3$: C, 65.97; H, 10.07. Found: C, 66.02; H, 10.14.

3.3.3 2-(6'-Hexenoxyl) Tetrahydropyran (39)[102]

n-Butyllithium in hexane (1.7 M, 118.9 mL, 202.2 mmol) was added via syringe over 15 minutes to a solution of methyltriphenylphosphonium bromide (72.24 g, 202.2 mmol) in THF (500 mL) at 0°C. Aldehyde **38** (20.25 g, 101.1 mmol) in THF (50 mL) was added dropwise via cannula and the reaction was stirred at 0°C for 90 minutes. Water was added to the reaction, the organic layer was collected, and the aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with brine, and dried over anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 15% diethyl ether in petroleum ether as eluant afforded alkene **39** (17.26 g, 87.04 mmol) in 86% yield as a clear colourless oil.

IR (neat): cm^{-1}: 3076, 2934, 2863, 1641, 1448, 1351, 1322, 1261, 1201, 1129, 1076, 1031, 870, 815 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$): 5.68-5.92 (m, 1H), 4.86-5.06 (m, 2H), 4.56 (t, J = 2.9 Hz, 1H), 3.28 - 3.94 (m, 4 H), 2.04 (m, 2H), 1.25-1.92 (m, 12H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 138.79, 114.19, 98.69, 67.42, 62.12, 33.65, 30.70, 29.53, 28.69, 25.69, 25.47, 19.58;

LRMS (EI) m/z (relative intensity): 198 (M$^+$, 2), 197 (6), 101 (41), 85 (100);

HRMS (EI) m/z calculated for C$_{12}$H$_{21}$O$_2$ (M$^+$-1): 197.15416, found: 197.15456;

Analysis calculated for C$_{11}$H$_{22}$O$_3$: C, 72.68; H, 11.18. Found: C, 72.68; H, 11.22.

3.3.4 6-Hepten-1-ol (34)[102]
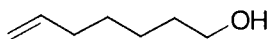
Pyridinium *p*-toluenesulfonate (1.29 g, 5.14 mmol) was added to a solution of alkene **39** (17.00 g, 85.73 mmol) in methanol, and the reaction was stirred at rt for 48 hours. The solvent was removed by rotary evaporation and the residue was dissolved in diethyl ether. The ether solution was washed sequentially with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The dried solution was filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% diethyl ether in petroleum ether as eluant, followed by distillation of the resulting oil afforded alcohol **34** (8.93 g, 78.2 mmol) in 91% yield as a clear colourless oil.

bp: 80 °C / 25 mm Hg;

IR (neat): 3338, 3077, 2930, 2860, 1640, 1442, 1054, 994, 910 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.68-5.89 (m, 1H), 4.90-5.02 (m, 2H), 3.61 (t, J = 6.5 Hz, 2H), 2.04 (m, 2H), 1.52 (m, 3H), 1.37 (m 4H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 138.85, 113.90, 62.86, 33.69, 32.57, 28.66, 25.21;

LRMS (EI) *m/z* (relative intensity): 114 (M$^+$, 10), 97 (20), 96 (70), 95 (25), 81 (100), 68 (68), 67 (81), 55 (66), 54 (51), 53 (20);

HRMS (EI) *m/z* calculated for $C_7H_{14}O$: 114.10447, found: 114.10431;

3.3.5 6-Heptenyltosylate (40)
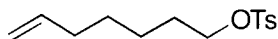
Alcohol **34** (4.10 g, 35.9 mmol) was added to a solution of *p*-toluenesulfonyl chloride (8.90 g, 46.7 mmol) in pyridine (12 mL) at 0°C. The reaction was stirred for 60 minutes at 0°C, warmed to rt, and stirred for 3 hours at

rt. Water was added to the reaction, the organic layer was collected, and the aqueous layer was extracted with diethyl ether. The organic layers were combined, and sequentially washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% diethyl ether in petroleum ether as eluant afforded tosylate **40** (8.15 g, 30.4 mmol) in 85% yield as a clear pale yellow oil.

IR (neat): 2931, 28.60, 1640, 15.99, 1455, 1360, 1307, 1189, 1177, 1098, 937, 820 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.30 Hz, 2H), 5.62-5.83 (m, 1H), 4.86-5.00 (m, 2H), 4.00 (t, J = 6.5, 2H), 2.43 (s, 3H), 1.97 (q, 2H), 1.61 (m, 2H), 1.30 (m, 4H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 144.77, 138.56, 133.36, 129.92, 127.99, 114.72, 70.67, 35.55, 28.78, 28.25, 24.91, 21.73;

LRMS (CI(+), ammonia) *m/z* (relative intensity): 286 (M$^+$+18, 100), 155 (5);

HRMS (CI(+), ammonia) *m/z* calculated for $C_{14}H_{24}NO_3S$: 286.14771, found: 286.14780;

Analysis calculated for $C_{14}H_{20}SO_3$: C, 62.66; H, 7.51; S, 11.95. Found: C, 62.86; H, 7.59; S, 11.80.

3.3.6 6-Heptenylcyanide (41)
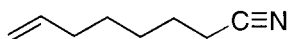
Oven dried potassium cyanide (2.91 g, 44.7 mmol) was added to a solution of tosylate **40** (8.00 g, 29.8 mmol) and 18-crown-6 (0.027 g) in acetonitrile (35 mL) and the solution was heated at reflux for 24 hours. CH_2Cl_2 was added, the solution was filtered by vacuum filtration and the solvent was

removed under reduced pressure. Distillation of the resulting oil afforded nitrile **41** (2.57 g, 20.9 mmol) in 70% yield as a clear colourless oil.

bp: 108 °C / 23 mm Hg;

IR (neat): 3077, 2932, 2861, 2246, 1641, 1428, 996, 913 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$): δ 5.64-5.86 (m, 1H), 4.85-5.04 (m, 2H), 2.31 (t, J = 6.5 Hz, 2H), 2.05 (q, 2H), 1.60 (m, 2H), 1.40 (m, 4H);
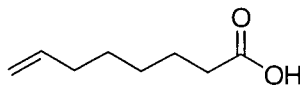
^{13}C NMR (50 MHz, CDCl$_3$): δ 138.37, 119.84, 114.92, 33.44, 28.17, 28.08, 25.33, 21.59, 17.18;

LRMS (EI) *m/z* (relative intensity): 123 (M$^+$, 10), 122 (59), 95 (30), 94 (100), 82 (22), 80 (25), 55 (44);

HRMS (EI) *m/z* calculated for C$_8$H$_{12}$N: 122.09697, found: 122.09707;

Analysis calculated for C$_{11}$H$_{22}$O$_3$: C, 65.97; H, 10.07. Found: C, 66.02; H, 10.14.

3.3.7 7-Octenoic acid (33)[103]

Potassium hydroxide (4.34 g, 77.3 mmol) was added to a solution of nitrile **41** (2.38 g, 19.3 mmol) in ethylene glycol (25 mL) and the reaction was stirred at 150 °C for 6 hours. A second portion of potassium hydroxide (4.34 g, 77.3 mmol) was added and the reaction was stirred at 150 °C for 12 hours. Water was added and the reaction solution was washed with diethyl ether. The aqueous solution was acidified with concentrated HCl and extracted with diethyl ether. The organic layers were combined, washed with brine and dried over anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Distillation of the resulting oil afforded acid **33** (2.61 g, 18.3 mmol) in 95% yield as a clear pale yellow oil.

bp: 135 °C / 9 mm Hg;

IR (neat): 2979, 2865, 1711, 1641, 1425, 1282, 1231, 994, 913 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$): δ 11.10 (s, w, 1H), 5.67-5.89 (m, 1H), 4.86-5.06 (m, 1H), 2.34 (t, J = 7.38 Hz, 2H), 2.03 (q, 2H), 1.63 (m, 2H), 1.63 (m, 2H), 1.37 (m, 4H);
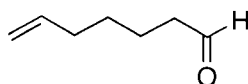
^{13}C NMR (50 MHz, CDCl$_3$): δ 180.33, 138.71, 114.45, 34.02, 33.49, 28.47 (2), 24.48;

LRMS (EI) *m/z* (relative intensity): 142 (M$^+$, 5), 124 (91), 100 (25), 96 (49), 83 (37), 82 (73), 67 (29), 60 (42), 55 (100);

HRMS (EI) *m/z* calculated for C$_8$H$_{14}$O$_2$: 142.09938, found: 142.09912;

Analysis calculated for C$_8$H$_{14}$O$_2$: C, 67.57; H, 9.92. Found: C, 67.63; H, 9.96.

3.3.8 6-Heptenal (42)

A solution of dimethylsulfoxide (1.93 mL, 48.3 mmol) in CH$_2$Cl$_2$ (15 mL) was added via cannula to a solution of oxalyl chloride (1.93 mL, 22.2 mmol) in CH$_2$Cl$_2$ (50 mL) at -78 °C. The solution was stirred for 5 minutes and alcohol **34** (2.30 g, 20.1 mmol) in CH$_2$Cl$_2$ (15 mL) was added via cannula. This mixture was stirred for 15 minutes at -78 °C. Triethylamine (13.2 mL, 94.7 mmol) was added, the mixture was stirred for 5 minutes, and warmed to rt. The reaction was quenched with water, the organic layer was collected, and the aqueous layer was extracted with CH$_2$Cl$_2$. The organic layers were combined, sequentially washed with 1N HCl solution, water, 5% Na$_2$CO$_3$ solution, and brine, and dried over anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Distillation of the resulting oil afforded aldehyde **42** (1.92 g, 17.1 mmol) in 77% yield as a clear colourless oil.

bp: 80°C / 30 mm Hg;

IR (neat): 3077, 2930, 2721, 1725, 1641, 1425, 996, 913 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$): δ 9.75 (s, 1H), 5.65-5.91 (m, 1H), 4.86-5.08 (m, 2H),

2.43 (t, J = 7.2 Hz, 2H), 2.06 (q, 2H), 1.20-1.79 (m, 4H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 202.47, 138.17, 114.76, 43.64, 33.35, 28.27, 21.44;

LRMS (EI) *m/z* (relative intensity): 112 (M$^+$, 1) 94 (26), 79 (32), 69 (20), 68 (100),

67 (40), 57 (27), 56 (23), 55 (48);

HRMS (EI) *m/z* calculated for C$_7$H$_{12}$O: 112.08882, found: 112.08833.

3.3.9 7-Octen-2-ol (35)
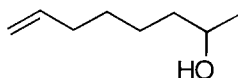
Methyllithium in diethyl ether (1.25 M, 15.7 mL, 19.6 mmol) was added dropwise to a solution of aldehyde **42** (1.83 g, 16.3 mmol) in THF (80 mL) at 0 °C. The reaction was stirred at 0 °C for 30 minutes, after which saturated NH$_4$Cl solution was added and the mixture was stirred a further 15 min at 0 °C. The reaction was diluted with diethyl ether, the organic layer was collected and the aqueous layer was extracted with diethyl ether. The organic layers were combined, and sequentially washed with water and brine, and dried over anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% diethyl ether in petroleum ether as eluant, followed by distillation of the resulting oil afforded alcohol **35** (1.48 g, 11.6 mmol) in 59% yield as a clear colourless oil.

bp: 72 °C / 10 mm Hg;

IR (neat): 3349, 3078, 2969, 2931, 2858, 1642, 1462, 1374, 1122, 991, 911 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$): δ 5.65-5.92 (m, 1H), 4.84-5.06 (m, 2H), 3.77 (m, 1H),

1.94-2.13 (m, 2H), 1.24-1.55 (m, 7H), 1.17 (d, J = 3.1 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 139.02, 114.51, 68.22, 39.30, 33.85, 29.02, 25.36,

23.61;

LRMS (CI(+), ammonia) *m/z* (relative intensity): 146 (M$^+$+18, 100), 144 (M$^+$+16), 128 (3);

HRMS (CI(+), ammonia/methane) *m/z* calculated for $C_8H_{16}O$: 146.15450, found: 146.15458.

3.3.10 6-Heptenyl-7'-Octenoate (31)[102]
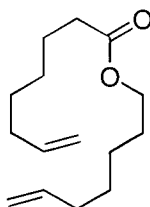
1,3-Dicyclohexylcarbodiimide (2.36 g, 11.4 mmol) was added to a solution of alcohol **34** (1.09 g, 9.53 mmol), acid **33** (1.36 g, 9.53 mmol) and 4-(dimethylamino)pyridine (140 mg, 1.14 mmol, 12 mol%) in dichloromethane (50 mL), and the reaction was stirred for 24 hours. The solvent was removed under reduced pressure, and column chromatography of the residue with 10% diethyl ether in petroleum ether as eluant followed by distillation of the resulting oil afforded diene ester **31** (1.98 g, 8.31 mmol) in 87% yield as a clear colourless oil.

bp: 140 °C / 9 mm Hg;

IR (neat): 3077, 2931, 2858, 1737, 1641, 1453, 1178, 994, 911 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.78 (m, 4H), 4.96 (m, 1H), 4.94 (m, 1H), 4.04 (t, J = 6.7 Hz, 2H), 2.27 (t, J = 7.6 Hz, 2H), 1.85-2.08 (m, 4H), 1.57-1.64 (m, 4H), 1.27-1.44 (m, 8H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.87, 138.81, 138.71, 114.46, 113.30, 64.28, 34.31, 33.58, 33.54, 28.70, 28.59, 28.48, 25.39, 24.83;

LRMS (EI) *m/z* (relative intensity): 238 (M$^+$, 12), 125 (35), 124 (68), 97 (38), 96 (60), 83 (59), 82 (74), 81 (71), 68 (28), 67 (100), 54 (95), 53 (45);

HRMS (EI) *m/z* calculated for $C_{15}H_{26}O_2$: 238.19328, found: 238.19250.

Analysis calculated for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.66: H, 11.07.

3.3.10 1-Methyl-6-Heptenyl-7'-Octenoate (32)
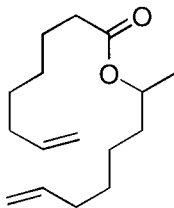
1,3-Dicyclohexylcarbodiimide (2.11 g, 10.2 mmol) was added to a solution of alcohol **35** (1.09 g, 8.51 mmol), acid **33** (1.21 g, 8.51 mmol) and 4-(dimethylamino)pyridine (125 mg, 1.02 mmol, 12 mol%) in dichloromethane (50 mL), and the reaction was stirred for 24 hours. The solvent was removed under reduced pressure, and column chromatography of the residue with 10% diethyl ether in petroleum ether as eluant followed by distillation of the resulting oil afforded diene ester **32** (1.82 g, 7.21 mmol) in 85% yield as a clear colourless oil.

bp: 140 °C / 7 mm Hg;

IR (neat): 3077, 2932, 2859, 1734, 1641, 1462, 1178, 994, 911 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.77 (m, 2H), 4.83-5.01 (m, 5H), 2.25 (t, J = 7.5 Hz, 2H), 2.02 (m, 4H), 1.23-1.64 (m, 12H), 1.17 (d, J = 6.3 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.44, 138.81, 138.73, 114.37, 113.27, 70.65, 35.77, 34.67, 33.60, 33.56, 28.67, 28.59, 28.53, 24.92, 24.85, 20.01;

LRMS (EI) m/z (relative intensity): 252 (M$^+$, 2), 142, (21), 125 (53), 124 (41),111 (27), 110 (36), 107 (25), 96 (25), 95 (25), 83 (21), 82 (61), 81 (60), 69 (98), 68 (65), 67 (30), 55 (100), 54 (27);

HRMS (EI) m/z calculated for C$_{16}$H$_{28}$O$_2$: 252.20893, found: 252.20834;

Analysis calculated for C$_{16}$H$_{28}$O$_2$: C, 76.14; H, 11.18. Found: C, 75.98: H, 11.38.

3.3.11 (7*E*)-13-Tridec-7-enolide (29)[102]
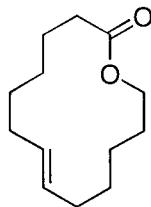
a) <u>Ring closing olefin metathesis of 31 using the Grubbs catalyst 28</u>

A deoxygenated solution of Grubbs' catalyst **28** (137 mg, 0.166 mmol, 2 mol%) in CH_2Cl_2 (100 mL) was added via cannula over 30 minutes to a deoxygenated solution of diene ester **31** (1.98 g, 8.31 mmol) in CH_2Cl_2 (3.9 L). The reaction was then stirred for 90 minutes and the reaction was quenched with 10 drops of triethylamine. The solvent was removed under reduced pressure and column chromatography of the residue with 10% diethyl ether in petroleum ether afforded a mixture of unsaturated lactones **29** and **43** (1.50 g, 7.15 mmol) in 86% yield. A GC analysis of the residue prior to chromatographic separation revealed a 95:5 *E:Z* composition. Further separation by silver nitrate impregnated TLC grade silica gel afforded the pure *E* isomer **29** (1.16g).

mp: 34-35 °C;

IR (neat): 2931, 2856, 1719, 1255, 976 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (m, 2H), 4.12 (t, J = 5.2 Hz, 1H), 2.29 (t, J = 6.1 Hz, 2H), 1.99 (m, 4H), 1.55 (m, 4H), 1.25-1.41 (m, 8H);

^{1}H DECOUPLED NMR (500 MHz, $CDCl_3$): Irradiation at δ 1.99, simplification of signal at 5.24 (d, J = 15.0 Hz, 1H) and at 5.21 (d, J = 15.0 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 173.85, 131.49, 131.14, 63.24, 34.65, 31.47, 31.03, 28.05, 27.99, 27.24, 26.68, 25.12, 23.34;

LRMS (EI) *m/z* (relative intensity): 210 (M$^+$,100), 82 (23);

HRMS (EI) *m/z* calculated for $C_{13}H_{22}O_2$: 210.16198, found: 210.16274;

Analysis calculated for $C_{13}H_{22}O_2$: C,74.24; H, 10.54. Found: C, 74.46: H, 10.68.

b) <u>Metathesis equilibrium study of **29** using Cl$_2$(PCy$_3$)$_2$Ru=CH$_2$</u>

A deoxygenated solution of bis(tricyclohexylphosphine)methylidine ruthenium (IV) dichloride catalyst (2.0 mg, 0.0024 mmol, 2 mol%) in CH$_2$Cl$_2$ (5 mL) was added via cannula to a deoxygenated solution of unsaturated lactone **29** (25.0 mg, 0.119 mmol) in CH$_2$Cl$_2$ (55 mL). The reaction was then stirred for 3 hours and the reaction was quenched with 1 drop of triethylamine. The solvent was removed under reduced pressure and column chromatography of the residue with 10% diethyl ether in petroleum ether afforded a mixture of unsaturated lactones **29** and **43** (24.4 mg, 0.116 mmol) in 98% yield. A GC analysis of the residue prior to chromatographic separation revealed a 96:4 *E:Z* composition.

3.3.12 *(7E)*-13-Tetradec-7-enolide (30)
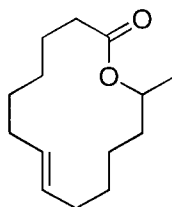
a) <u>Ring closing olefin metathesis of **32** using the Grubbs catalyst **28**</u>

A deoxygenated solution of Grubbs' catalyst **28** (112 mg, 0.136 mmol, 2 mol%) in CH$_2$Cl$_2$ (100 mL) was added via cannula over 30 min to a deoxygenated solution of diene ester **32** (1.72 g, 6.81 mmol) in CH$_2$Cl$_2$ (3.3 L). The reaction was then stirred for 90 minutes and the reaction was quenched with 10 drops of triethylamine. The solvent was removed under reduced pressure and column chromatography of the residue with 10% diethyl ether in petroleum ether afforded unsaturated lactones **30** and **44** (1.30 g, 5.79 mmol) in 85% yield. A GC analysis of the residue prior to chromatographic separation showed a 94:6 *E:Z* composition. Further purification by silver nitrate impregnated TLC grade silica gel afforded the pure *E* isomer **30** (1.06 g).

IR (neat): 2928, 2854, 1729, 1446, 1334, 1248, 1207, 1132, 1095, 970 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.21 (m, 2H), 5.00 (m, 1H), 2.27 (t, J = 5.35 Hz, 2H), 2.07-1.91 (m, 4H), 1.67-1.18 (m, 12H), 1.17 (d, J = 5.4 Hz, 3H);

^{1}H DECOUPLED NMR (500 MHz, CDCl$_3$): Irradiation at δ 1.99, simplification of signal at 5.22 (d, J = 15.4 Hz, 1H) and at 5.19 (d, J = 15.4 Hz, 1H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.88, 131.80, 131.49, 70.15, 35.76, 35.14, 31.64, 28.51, 28.14, 27.79, 27.06, 25.32, 23.60, 20.83;

LRMS (EI) *m/z* (relative intensity): 224(M$^+$,37), 110 (28), 109 (33), 108 (24), 96 (86), 95 (67), 94 (69), 93 (20), 82 (76), 81 (89), 80 (24), 79 (36), 69 (23), 68 (60), 67 (100), 55 (53), 54 (40);

HRMS (EI) *m/z* calculated for C$_{14}$H$_{24}$O$_4$: 224.17763, found: 224.17737;

Analysis calculated for C$_{14}$H$_{24}$O$_2$: C, 74.95; H, 10.78. Found: C, 74.82; H,10.95.

b) Metathesis equilibrium study of 30 using Cl$_2$(PCy$_3$)$_2$Ru=CH$_2$

A deoxygenated solution of bis(tricyclohexylphosphine)methylidine ruthenium (IV) dichloride catalyst (1.8 mg, 0.0022 mmol, 2 mol%) in CH$_2$Cl$_2$ (5 mL) was added via cannula to a deoxygenated solution of unsaturated lactone 30 (25.0 mg, 0.111 mmol) in CH$_2$Cl$_2$ (50 mL). The reaction was then stirred for 3 hours and the reaction was quenched with 1 drop of triethylamine. The solvent was removed under reduced pressure and column chromatography of the residue with 10% diethyl ether in petroleum ether afforded a mixture of unsaturated lactones 30 and 44 (24.1 mg, 0.107 mmol) in 96% yield. A GC analysis of the residue prior to chromatographic separation revealed a 95:5 *E:Z* composition.

c) Metathesis equilibrium study of 30 and 44 using Cl$_2$(PCy$_3$)$_2$Ru=CH$_2$

A deoxygenated solution of bis(tricyclohexylphosphine)methylidine ruthenium (IV) dichloride catalyst (0.4 mg, 0.0005 mmol, 2 mol%) in CH$_2$Cl$_2$ (1 mL) was added via cannula to a deoxygenated solution of a 64:36 mixture of unsaturated lactones 30 and 44 (5.0 mg, 0.022 mmol) in CH$_2$Cl$_2$ (10 mL). The reaction was then stirred for 3 hours and the reaction was quenched with 1 drop

of triethylamine. A GC analysis of the reaction mixture revealed a 94:6 *E:Z* composition.

3.3.13 7-Hydroxy-13-Tridecanolide (47)[101] and 8-Hydroxy-13-Tridecanolide (48)

47   48
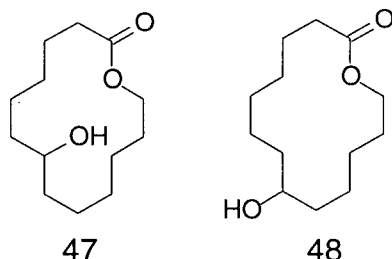
a) Hydroboration of **29** with borane-THF at rt

A solution of borane-THF complex in THF (1 M, 950 µL, 0.950 mmol) was added dropwise to a stirred solution of lactone **29** (100.2 mg, 0.4764 mmol) in THF (5 mL). The reaction was stirred for 4 hours and then cooled to 0 °C. 3N NaOH (400 µL) and 30% H_2O_2 (800 µL) were added sequentially and the reaction was warmed to rt and stirred for 30 minutes at rt. Water was added and the reaction solution was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH_2Cl_2 as eluant afforded a mixture of hydroxy lactones **47** and **48** (95.4 mg, 0.418 mmol) in 88% yield as a clear pale yellow oil.

To a solution of hydroxy lactones **47** and **48** (95.4 mg, 0.418 mmol) and triethylamine (117 µL, 836 mmol) in THF (5mL) was added chlorotrimethylsilane (106 µL, 836 mmol) dropwise. The reaction was stirred for 24 hours and then diluted with diethyl ether, washed with $NaHCO_3$, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Radial chromatography of the residue with 10% ethyl acetate in hexanes afforded separated silyl ethers **49** (57.8 mg, 0.192 mmol) and **50** (57.5

mg, 0.191 mmol) as a clear pale yellow oils in a total yield of 92% for **49** and **50**. A GC analysis of the residue prior to chromatographic separation revealed a 50:50 composition of silyl ethers **49** and **50**.

A solution of tetrabutylammonium fluoride in THF (1 M, 384 μL, 0.384 mmol) was added to a solution of silyl ether **49** (57.8 mg, 0.192 mmol) in THF (5 mL) and the reaction was stirred for 2 hours. Water was added and the reaction mixture was extracted with diethyl ether. The organic layers were combined and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH_2Cl_2 as eluant afforded hydroxy lactone **47** (44.2 mg, 0.182 mmol) in 95% yield as a clear colourless oil.

The same procedure for silyl ether **50** (57.5 mg, 0.191 mmol) afforded hydroxy lactone **48** (43.6 mg, 0.180 mmol) in 94% yield as a white solid.

47

IR (neat): 3403, 2942, 2861, 1733, 1461, 1347, 1250, 1147, 1106, 996, 918 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.28 (m, 1H), 3.95 (m, 1H), 3.69 (m, 1H), 2.42 (m, 1H), 2.24 (m, 1H), 1.10-1.82 (m, 19H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.64, 68.02, 63.26, 35.51, 33.96, 32.28, 27.56, 26.42, 24.96, 24.69, 23.89, 23.08, 22.54;

LRMS (EI) *m/z* (relative intensity): 228 (M$^+$,1), 127 (100), 117 (30), 113 (25), 99 (24), 98 (41), 95 (50), 81 (47), 69 (20), 55 (38);

HRMS (EI) *m/z* calculated for C$_{14}$H$_{24}$O$_4$: 228.17254, found: 228.17218;

48

mp: 79-80 °C;

IR (KBr): 3382, 2942, 2864, 1724, 1463, 1255, 1149, 1098, 1028, 995 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.28 (m, 1H), 3.96 (m, 1H), 3.69 (m, 1H), 2.43 (m, 1H), 2.26 (m, 1H), 1.11-1.88 (m, 19H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.79, 68.56, 63.00, 35.50, 34.34, 32.08, 27.54, 26.02, 25.77, 24.55, 23.50, 23.24, 22.59;

LRMS (EI) *m/z* (relative intensity): 228 (M$^+$,1), 127 (100), 117 (30), 113 (25), 99
(24), 98 (41), 95 (50), 81 (47), 26 (73), 69 (34), 56 (24), 55 (32);

HRMS (EI) *m/z* calculated for $C_{14}H_{24}O_4$: 228.17254, found: 228.17264;

Analysis calculated for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.82; H, 10.95.

b) Hydroboration of 29 with borane-THF at -78 °C

A solution of borane-THF complex in THF (271 μL, 0.271 mmol) was
added dropwise to a stirred solution of lactone **29** (28.5 mg, 0.136 mmol) in THF
(2 mL) at -78 °C and the reaction was stirred for 20 hours. Standard work-up and
purification, as outlined in method (a), gave hydroxy lactones **47** and **48** (27.8
mg, 0.122 mmol) in 90% yield and in a ratio of 50:50 (GC analysis of TMS
ethers) as a clear pale yellow oil.

c) Hydroboration of 29 with disiamylborane

A solution of disiamylborane in THF (260 μL, 0.260 mmol) was added
dropwise to a stirred solution of lactone **29** (27.3 mg, 0.130 mmol) in THF (2 mL)
and the reaction was stirred at rt for 24 hours. Standard work-up and purification,
as outlined in method (a), yielded hydroxy lactones **47** and **48** (25.5 mg, 0.112
mmol) in 86% yield and in a ratio of 50:50 (GC analysis of TMS ethers) as a clear
pale yellow oil.

d) Hydroboration of 29 with 9BBN

A solution of lactone **29** (25.1 mg, 0.119 mmol) in THF (0.5 mL) was
added dropwise to a solution of 9BBN dimer (29.8 mg, 0.122 mmol) dissolved in
THF (1.5 mL) and the reaction was stirred at rt for 13 hours. Standard work-up,
as outlined in method (a), and purification yielded hydroxy lactones **47** and **48**
(25.3 g, 0.111 mmol) in 93% yield and in a ratio of 46:54 (GC analysis of TMS
ethers) as a clear pale yellow oil.

3.3.14 (8*R**, 13*S**)-8-(*N*-Phenylcarbamoyl)oxy-13-Tetradecanolide (55), (7*S**, 13*S**)-7-(*N*-Phenylcarbamoyl)oxy-13-Tetradecanolide (56), (7*R**, 13*S**)-7-(*N*-Phenylcarbamoyl)oxy-13-Tetradecanolide (57) and (8*S**, 13*S**)-8-(*N*-Phenylcarbamoyl)oxy-13-Tetradecanolide (58)
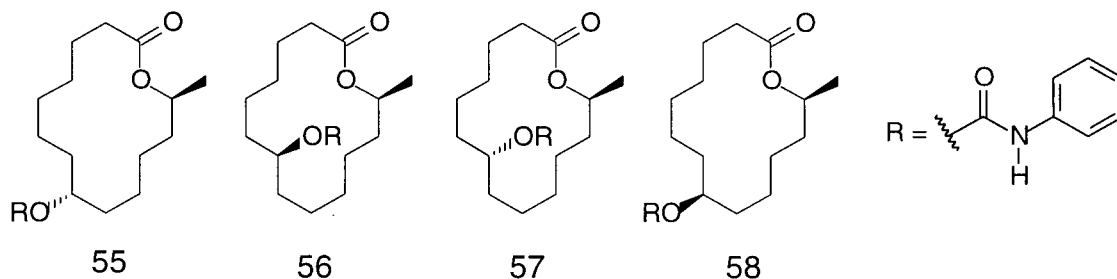
a) Hydroboration of **30** with borane-THF at rt

A solution of borane-THF complex in THF (1.25 mL, 1.25 mmol) was added dropwise to a stirred solution of lactone **30** (140.3 mg, 0.6254 mmol) in THF (6 mL). The reaction was stirred for 4 hours and cooled to 0 °C. 3N NaOH (525 µL) and 30% H_2O_2 (950 µL) were added sequentially and the reaction was warmed to rt and stirred for 30 minutes at rt. Water was added and the reaction solution was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH_2Cl_2 as eluant afforded a mixture of hydroxy lactones **51**, **52**, **53** and **54** (136.3 mg, 0.5629 mmol) in 90% yield as a clear colourless oil.

Phenyl isocyanate (612 µL, 5.63 mmol) was added to a solution of hydroxy lactones **51**, **52**, **53** and **54** (136.3 mg, 0.5629 mmol) in pyridine at 0°C. The reaction was stirred at rt for 30 minutes and the solvent was removed under reduced pressure. The residue was taken up in diethyl ether and water was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic extracts were combined, washed with brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. TLC grade column chromatography of the

residue with 20% ethyl acetate in hexanes afforded separated carbamate derived hydroxy lactones **55** (75.2 mg, 0.208 mmol) as a white solid and **56** (36.2 mg, 0.100 mmol) as a white solid, and an inseparable mixture of carbamate derived hydroxy lactones **57** and **58** (91.6 mg, 0.253 mmol) as a white solid in a total yield of 100% for **55**, **56**, **57** and **58**. An HPLC analysis of the residue prior to chromatographic separation showed a 37:18:31:14 composition of **55**, **56**, **57** and **58**.

55

mp: 80-82 °C;

IR (KBr): 3337, 2928, 2861, 1724, 1713, 1601, 1545, 1503, 1445, 1331, 1314, 1227, 1137, 1083, 1054, 1031 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35 (d, J = 7.9 Hz, 2H), 7.27 (td, J = 7.9, 2.0 Hz, 2H), 7.01 (tt, J =7.3, 1.2 Hz, 1H), 6.53 (s, 1H), 5.01 (m, 1H), 4.86 (m, 1H), 2.21-2.48 (m, 2H), 1.17-1.84 (m, 21H), 1.20 (d, J = 8.4 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.50, 153.55, 138.11, 128.95, 123.13, 118.47, 72.68, 69.34, 34.91, 34.44, 32.94, 29.40, 25.93, 25.39, 24.60, 23.99, 23.08, 22.41, 20.11;

LRMS (CI(+), ammonia) m/z (relative intensity): 379 (M$^+$+18, 41), 363 (M$^+$+2, 22), 362 (M$^+$+1, 98), 361 (M$^+$, 52), 260 (85), 242 (43), 225 (47), 207 (22), 158 (21), 155 (20), 119 (78), 95 (24), 94 (34), 93 (100);

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{21}$H$_{32}$NO$_4$: 362.23312, found: 362.23292;

56

mp: 124-125 °C;

IR (KBr): 3318, 2943, 2863, 1729, 1693, 1600, 1544, 1503, 1444, 1315, 1235, 1195, 1164, 1098, 1052, 1027 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.37 (d, J = 7.9 Hz, 2H), 7.28 (td, J = 7.9, 2.0 Hz, 2H), 7.02 (tt, J =7.3, 1.2 Hz, 1H), 6.58 (s, 1H), 5.03 (m, 1H), 4.94 (m, 1H), 2.22-2.48 (m, 2H), 1.15-1.83 (m, 21H), 1.21 (d, J = 6.4 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.90, 153.41, 138.16, 128.98, 123.14, 118.47, 73.34, 70.74, 34.91, 34.44, 32.94, 29.40, 25.93, 25.39, 24.60, 23.99, 23.08, 22.41, 20.11;

LRMS (CI(+), ammonia) m/z (relative intensity): 379 (M$^+$+18, 29), 363 (M$^+$+2, 16), 362 (M$^+$+1, 73), 361 (M$^+$, 44), 260 (48), 242 (35), 225 (52), 207 (20), 155 (21), 119 (72), 94 (31), 93 (100);

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{21}$H$_{32}$NO$_4$: 362.23312, found: 362.23385;

57

mp: 148.149 °C;

IR (KBr): 3341, 2927, 2857, 1725, 1708, 1600, 1543, 1501, 1444, 1315, 1226, 1084, 1052, 1029 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 (d, J = 7.9 Hz, 2H), 7.27 (td, J = 7.9, 2.0 Hz, 2H), 7.01 (tt, J =7.3, 1.2 Hz, 1H), 6.53 (s, 1H), 5.01 (m, 1H), 4.86 (m, 1H), 2.22-2.46 (m, 2H), 1.15-1.86 (m, 21H), 1.20 (d, J = 6.4 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.00, 153.38, 138.12, 128.98, 123.13, 118.46, 72.97, 69.80, 34.44, 33.94, 32.77, 29.49, 26.34, 25.63, 24.91, 24.05, 22.96, 21.76, 19.88;

LRMS (CI(+), ammonia) m/z (relative intensity): 379 (M$^+$+18, 29), 362 (M$^+$+1, 46), 361 (M$^+$, 19), 260 (22), 225 (31), 119 (73), 94 (35), 93 (100);

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{21}$H$_{32}$NO$_4$: 362.23312, found: 362.23335;

57 and 58

mp: 135-137 °C;

IR (CDCl$_3$): 3440, 2931, 2859, 1727, 1708, 1600, 1543, 1502, 1444, 1314, 1226, 1132, 1084, 1053, 1029 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35 (m, 2H), 7.27 (m, J = 7.9, 2H), 7.01 (m, 1H), 6.59 (s, 1H), 5.01 (m, 1H), 4.88 (m, 1H), 2.21-2.48 (m, 2H), 1.17-1.87 (m, 21H), 1.20 (m, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.70, 173.02, 153.42, 153.38, 138.18, 138.15, 129.01, 128.95, 123.17, 123.08, 118.52, 118.41, 72.98, 70.74, 69.84, 69.78, 35.50, 35.07, 34.48, 33.97, 33.91, 32.82, 31.85, 29.53, 26.59, 26.44, 26.31, 25.56, 24.95, 24.77, 24.11, 24.03, 23.00, 22.92, 21.79, 21.33, 19.92, 19.77;

LRMS (CI(+), ammonia) *m/z* (relative intensity): 379 (M$^+$+18, 9), 362 (M$^+$+1, 21), 361 (M$^+$, 10), 260 (81), 242 (24), 225 (48), 119 (100), 94 (26), 93 (44);

HRMS (CI(+), ammonia/methane) *m/z* calculated for C$_{21}$H$_{32}$NO$_4$: 362.23312, found: 362.23336;

b) Hydroboration of **30** with borane-THF at -78 °C

A solution of borane-THF complex in THF (248 μL, 0.248 mmol) was added dropwise to a stirred solution of lactone **30** (30.0 mg, 0.124 mmol) in THF (2 mL) at -78 °C and the reaction was stirred for 24 hours. Standard work-up and purification, as outlined in method (a), yielded hydroxy lactones **51**, **52**, **53** and **54** (27.9 mg, 0.115 mmol) in 93% yield and in a ratio of 42:17:33:8 (HPLC analysis of carbamates) as a clear colourless oil.

c) Hydroboration of **30** with disiamylborane

A solution of disiamylborane in THF (290 μL, 0.290 mmol) was added dropwise to a stirred solution of lactone **30** (32.5 mg, 0.145 mmol) in THF (2 mL) and the reaction was stirred at rt for 24 hours. Standard work-up and purification, as outlined in method (a), yielded hydroxy lactones **51**, **52**, **53** and **54** (29.7 mg, 0.123 mmol) in 85% yield and in a ratio of 41:18:31:10 (HPLC analysis of carbamates) as a clear colourless oil.

d) Hydroboration of **30** with 9BBN

A solution of lactone **30** (33.4 mg, 0.149 mmol) in THF (0.5 mL) was added dropwise to a solution of 9BBN dimer (36.4 mg, 0.149 mmol) dissolved in THF (1.5 mL) and the reaction was stirred at rt for 12 hours. Standard work-up and purification, as outlined in method (a), yielded hydroxy lactones **51**, **52**, **53**

and **54** (33.3 mg, 0.137 mmol) in 92% yield and in a ratio of 45:8:43:4 (HPLC analysis of carbamates) as a clear colourless oil.

e) Dehalogenation of **65** with n-tributyltin hydride

n-Tributyltin hydride (33 µL, 0.12 mmol) was added to a solution of chlorohydroxy lactone **65** (31.1 mg, 0.112 mmol) and 2,2'-azobisisobutyronitrile (3 mg, 0.02 mmol, 16 mol%) in toluene (0.5 mL). The reaction was stirred at 85^0C for 1 hour and then diluted with diethyl ether. The reaction was washed with water and the organic layer was dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Radial chromatography using 2% methanol in CH_2Cl_2 as eluant afforded hydroxy lactone **51** (25.5 mg, 0.105 mmol) in 94% yield as a clear colourless oil.

f) Dehalogenation of **66** with n-tributyltin hydride

n-Tributyltin hydride (36 µL, 0.13 mmol)) was added to a solution of chlorohydroxy lactone **66** (33.7 mg, 0.122 mmol) and 2,2'-azobisisobutyronitrile (3 mg, 0.02 mmol, 15 mol%) in toluene (0.5 mL). The reaction was stirred at 85^0C for 1 hour and then diluted with diethyl ether. The reaction was washed with water and the organic layer was dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Radial chromatography using 2% methanol in CH_2Cl_2 as eluant afforded hydroxy lactone **53** (27.7 mg, 0.114 mmol) as a clear colourless oil.

g) Reduction of **67** with sodium borohydride at -78 °C

Sodium borohydride (3.8 mg, 0.10 mmol) was added in one portion to a solution of keto lactone **67** (20.0 mg, 0.0832 mmol) in methanol (2 mL) at -78 °C. The reaction was stirred at -78 °C for 1 hour and then quenched with 2 drops of 1N HCl solution. The reaction mixture was diluted with ethyl acetate, washed with brine and the organic layer was dried over anhydrous $MgSO_4$. The organic layer was filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH_2Cl_2 chloride as eluant

afforded a mixture of hydroxy lactones **52** and **53** (16.7 mg, 0.0689 mmol) in 80% yield and in a ratio of 50:50 (HPLC analysis of carbamates) as a clear colourless oil.

h) Reduction of **68** with sodium borohydride at -78 °C

Sodium borohydride (3.5 mg, 0.09 mmol) was added in one portion to a solution of keto lactone **68** (19.8 mg, 0.0823 mmol) in methanol (2 mL) at -78 °C. The reaction was stirred at -78 °C for 1 hour and then quenched with 2 drops of 1N HCl solution. Standard work-up and purification, as outlined in method (g), yielded hydroxy lactones **51** and **54** (33.3 mg, 0.137 mmol) in 83% yield and in a ratio of 50:50 (HPLC analysis of carbamates) as a clear colourless oil.

i) Reduction of **67** with sodium borohydride in the presence of cerium chloride at -78 °C

Sodium borohydride (4.6 mg, 0.12 mmol) was added in one portion to a solution of cerium chloride heptahydrate (36.2 mg, 0.120 mmol), and keto lactone **67** (25.4 mg, 0.106 mmol) in methanol (2 mL) at -78 °C. The reaction was stirred at -78 °C for 1 hour and then quenched with 2 drops of 1N HCl solution. The solvent was removed under reduced pressure and the residue was dissolved in diethyl ether and washed with saturated $NaHCO_3$ solution. The organic layer was separated and dried over anhydrous $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH_2Cl_2 as eluant afforded a mixture of hydroxy lactones **52** and **53** (22.3 mg, 0.0920 mmol) in 86% yield and in a ratio of 55:45 (HPLC analysis of carbamates) as a clear colourless oil.

j) Reduction of **68** with sodium borohydride in the presence of cerium chloride at -78 °C

Sodium borohydride (4.1 mg, 0.11 mmol) was added in one portion to a solution of cerium chloride heptahydrate (33.2 mg, 0.110 mmol), and keto lactone **68** (21.8 mg, 0.0907 mmol) in methanol (2 mL) at -78 °C. The reaction was

stirred at -78 °C for 1 hour and then quenched with 2 drops of 1N HCl solution. Standard work-up and purification, as outlined in method (i), yielded hydroxy lactones **51** and **54** (18.9 mg, 0.0780 mmol) in 87% yield and in a ratio of 56:44 (HPLC analysis of carbamates) as a clear colourless oil.

k) Reduction of **67** with K-Selectride at -15 °C

A solution of K-Selectride in THF (1M, 215 µL, 0.215 mmol) was added to a solution of keto lactone **67** (25.8 mg, 0.107 mmol) in THF (3 mL) at -15 °C. The reaction was stirred at -15 °C for 30 minutes and then 1N HCl solution (100 µL) and 30% H_2O_2 (100 µL) were added sequentially. The reaction was warmed to rt, diluted with diethyl ether, and washed with $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$, the extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH_2Cl_2 as eluant afforded a mixture of hydroxy lactones **52** and **53** (23.3 mg, 0.0961 mmol) in 83% yield and in a ratio of 87:13 (HPLC analysis of carbamates) as a clear colourless oil.

l) Reduction of **68** with K-Selectride at -15 °C

A solution of K-Selectride in THF (1M, 235 µL, 0.235 mmol) was added to a solution of keto lactone **68** (28.2 mg, 0.117 mmol) in THF (3 mL) at -15°C. The reaction was stirred at -15°C for 30 minutes and then 1N HCl solution (100 µL) and 30% H_2O_2 (100 µL) were added sequentially. Standard work-up and purification, as outlined in method (k), yielded hydroxy lactones **51** and **54** (23.5 mg, 0.0970 mmol) in 90% yield and in a ratio of 47:53 (HPLC analysis of carbamates) as a clear colourless oil.

m) Reduction of **67** with K-Selectride at -78 °C

A solution of K-Selectride in THF (1M, 184 µL, 0.184 mmol) was added to a solution of keto lactone **67** (22.1 mg, 0.0920 mmol) in THF (3 mL) at -78 °C. The reaction was stirred at -78 °C for 30 minutes and then 1N HCl solution (100

μL) and 30% H_2O_2 (100 μL) were added sequentially. Standard work-up and purification, as outlined in method (k), yielded a mixture of hydroxy lactones **52** and **53** (20.5 mg, 0.0846 mmol) in 91% yield and in a ratio of 91:9 (HPLC analysis of carbamates) as a clear colourless oil.

n) Reduction of **68** with K-Selectride at -78 °C

A solution of K-Selectride in THF (1M, 208 μL, 0.208 mmol) was added to a solution of keto lactone **68** (25.0 mg, 0.104 mmol) in THF (3 mL) at -78 °C. The reaction was stirred at -78 °C for 30 minutes and then 1N HCl solution (100 μL) and 30% H_2O_2 (100 μL) were added sequentially. Standard work-up and purification, as outlined in method (k), yielded hydroxy lactones **21** and **22** (23.4 mg, 0.0966 mmol) in 89% yield and in a ratio of 40:60 (HPLC analysis of carbamates) as a clear colourless oil.

3.3.15 6-(*N*-Phenylcarbamoyl)oxy-13-Tetradecanolide (61, 62) and 7-(*N*-Phenylcarbamoyl)oxy-13-Tetradecanolide (56, 57)

56   61   57   62
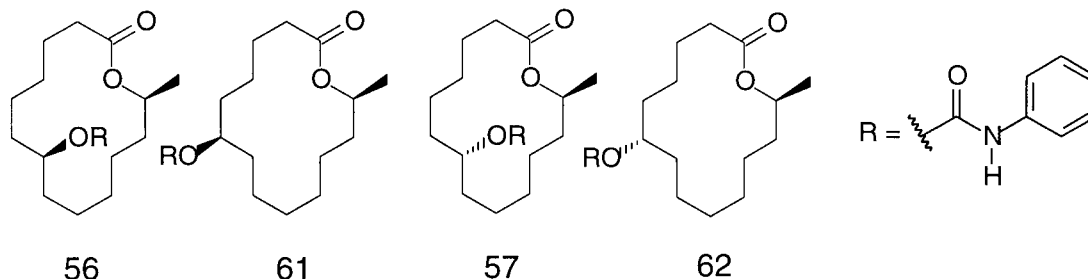
A solution of borane-THF complex in THF (1M, 0.180 μL, 0.180 mmol) was added dropwise to a stirred solution of a 64:36 mixture of unsaturated lactones **59** and **60** (20.2 mg, 0.0900 mmol) in THF (2 mL). The reaction was stirred for 4 hours and cooled to 0 °C. 3N NaOH (75 μL) and 30% H_2O_2 (150 μL) were sequentially added and the reaction was warmed to rt and stirred for 30 minutes. Water was added and the reaction solution was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, and dried over

anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 3% methanol in CH$_2$Cl$_2$ as eluant afforded a mixture of hydroxy lactones (18.6 mg, 0.0767 mmol) in 85% yield as a clear colourless oil.

Phenyl isocyanate (84 μL, 0.77 mmol) was added to the mixture of hydroxy lactones (18.6 mg, 0.0767 mmol) in pyridine at 0 °C. The reaction was stirred at rt for 30 minutes and the solvent was removed under reduced pressure. The residue was taken up in diethyl ether and water was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic extracts were combined, washed with brine, and dried over anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 20% ethyl acetate in hexanes afforded a mixture of carbamate derived hydroxylactones **56**, **61**, **57** and **62** (27.5 mg, 0.0761 mmol) in 99% yield as a yellow oil. An HPLC analysis of the residue prior to chromatographic separation showed a 10:25:49:16 composition.

56, **61**, **57** and **62**

IR (CDCl$_3$): 3333, 2943, 2864, 1727, 1708, 1600, 1543, 1443, 1315, 1226, 1051, 1027 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35 (m, 2H), 7.27 (m, 2H), 7.02 (m, 1H), 6.52 (m, 1H), 5.01 (m, 1H), 4.87 (m, 1H), 2.22-2.47 (m, 2H), 1.17-1.85 (m, 21H);

LRMS (EI) *m/z* (relative intensity): 379 (M$^+$+18, 31), 362 (M$^+$+1, 65), 361 (M$^+$, 31), 260 (38), 242 (20), 225 (57), 119 (52), 94 (25), 93 (100);

HRMS (EI) *m/z* calculated for C$_{14}$H$_{24}$O$_4$: 362.23312, found: 362.23225;

3.3.17 (7S*, 8S*, 13S*)-7,8-Epoxy-13-Tetradecanolide (63) and (7R*, 8R*, 13S*)-7,8-Epoxy-13-Tetradecanolide (64)

63   64
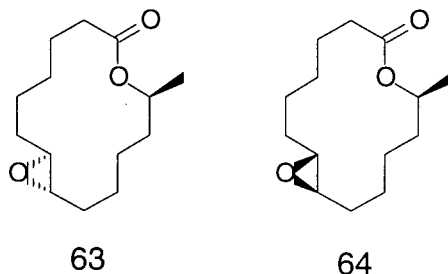
a) <u>Epoxidation of **30** with MCPBA at rt</u>

57-86% MCPBA (375 mg, 1.22-1.90 mmol), was added to a solution of lactone **30** (250 mg, 1.12 mmol) in CH_2Cl_2 (13 mL) at 0 °C. The reaction was stirred for 30 minutes at rt, and then washed with NaOH solution, water and dried over anhydrous $MgSO_4$. The organic layer was filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% diethyl ether in petroleum ether as eluant afforded a mixture of epoxy lactones **63** and **64** (264 mg, 1.10 mmol) in 98% yield as a clear colourless oil. A GC analysis of the oil revealed a 67:33 composition of **63** and **64.** Further purification by TLC grade column chromatography afforded pure samples of **63** (66 mg) as a clear pale yellow oil and **64** (6 mg) as a clear pale yellow oil.

63

IR (neat): 2932, 2859, 1729, 1461, 1365, 1338, 1288, 1253, 1162, 1120, 1006, 914, 816, 778 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.00 (m, 1H), 2.59 (m, 1H), 2.32 (m, 1H), 2.04-2.31 (m, 2H), 0.87-1.87 (m, 16H), 1.20 (d, J = 6.4 Hz, 3H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 173.66, 69.80, 59.12, 59.07, 36.51, 34.25, 32.26, 32.16, 28.08, 25.88, 25.86, 25.54, 25.41, 20.87;

LRMS (EI) m/z (relative intensity): 240 (M$^+$, 4), 112 (22), 98 (28), 97 (52), 96 (35), 95 (36), 83 (20), 81 (65), 69 (29), 68 (33), 67 (43), 55 (100);

HRMS (EI) m/z calculated for $C_{14}H_{24}O_4$: 240.17254, found: 240.17191;

64

IR (neat): 2932, 2860, 1729, 1458, 1362, 1336, 1290, 1254, 1163, 1131, 1108, 1019, 1003, 913, 821, 768 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.02 (m, 1H), 2.58 (m, 1H), 2.21 (m, 1H), 2.23-2.46 (m, 2H), 0.78-1.72 (m, 16H), 1.19 (d, J = 6.3 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.20, 69.11, 59.44, 59.30, 35.76, 35.03, 31.89, 31.57, 28.65, 25.48, 25.09, 24.57, 24.50, 20.72;

LRMS (EI) *m/z* (relative intensity): 240 (M^{+}, 4), 112 (22), 98 (29), 97 (53), 96 (34), 95 (36), 83 (20), 81 (65), 69 (30), 68 (33), 67 (43), 55 (100);

HRMS (EI) *m/z* calculated for C$_{14}$H$_{24}$O$_4$: 240.17254, found: 240.17324;

b) Epoxidation of **30** with MCPBA at 0 °C

57-86% MCPBA (75.0 mg, 0.244-0.381 mmol), was added to a solution of lactone **30** (50.0 mg, 0.223 mmol) in CH$_2$Cl$_2$ (3 mL) at 0 °C, and the reaction was stirred for 3 hours at 0 °C. Standard work-up and purification, as outlined in method (a), yielded epoxy lactones **63** and **64** (48.8 mg, 0.203 mmol) in 91% yield and in a ratio of 69:31 (GC analysis) as a clear pale yellow oil.

c) Epoxidation of **30** with MCPBA at -78 °C

57-86% MCPBA (75.0 mg, 0.244-0.381 mmol), was added to a solution of lactone **30** (50.3 mg, 0.224 mmol) in CH$_2$Cl$_2$ (3 mL) at -78 °C, and the reaction was stirred for 22 hours at -78°C. Standard work-up and purification, as outlined in method (a), yielded epoxy lactones **63** and **64** (53.2 mg, 0.224 mmol) in 100% yield and in a ratio of 77:23 (GC analysis) as a clear pale yellow oil.

c) Epoxidation of **30** with methyl(trifluoromethyl)dioxirane[87] at 0 °C

An aqueous solution of Na$_2$EDTA (0.0004 M, 2.2 mL, 0.0008 mmol) was added to a solution of lactone **30** (102.1 mg, 0.4551 mmol) in acetonitrile (3.5 mL) and the reaction mixture was cooled to 0 °C. Excess 1,1,1-trifluoroacetone (0.45 mL) was added followed by a portionwise addition of Oxone (1.301 g, 2.276

mmol) and NaHCO$_3$ (325.1 mg, 3.641 mmol), and the reaction was stirred for 1.5 hours at 0°C. Excess dimethyl sulfide (1 mL) was added and the reaction was extracted with CH$_2$Cl$_2$ and dried over anhydrous MgSO$_4$. The organic layer was filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% diethyl ether in petroleum ether as eluant yielded epoxy lactones **63** and **64** (107.2 mg, 0.446 mmol) in 98% yield and in a ratio of 70:30 (GC analysis) as a clear pale yellow oil.

3.3.18 (7R^*, 8S^*, 13S^*)-7-Chloro-8-Hydroxy-13-Tetradecanolide (65) and (7S^*, 8R^*, 13S^*)-8-Chloro-7-Hydroxy-13-Tetradecanolide (66)

67   68
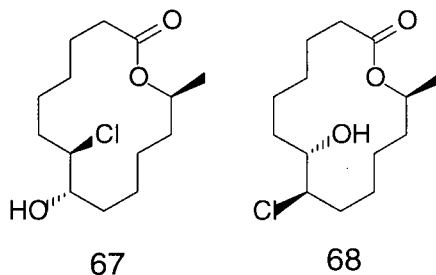
Concentrated HCl (32 µL, 0.37 mmol) was added to a solution of epoxy lactone **63** (60.0 mg, 0.250 mmol) in THF (2 mL) at 0 °C and the reaction was stirred at rt for 3 hours. Water was added and the solution was extracted with diethyl ether. The ether extracts were dried over anhydrous MgSO$_4$. The extracts were filtered and the solvent was removed under reduced pressure. Radial chromatography using 2% methanol in CH$_2$Cl$_2$ as eluant afforded separated chlorohydroxy lactone **65** (31.1 mg, 0.112 mmol) as a clear yellow oil, and chlorohydroxy lactone **66** (33.7 mg, 0.122 mmol) as a clear yellow oil in a total yield of 94%.

65

IR (CDCl$_3$): 3442, 2947, 2863, 1728, 1458, 1376, 1245, 1209, 1169, 1050, 988, 957, 732, 678 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.06 (m, 1H), 4.20 (m, 1H), 3.89 (m, 1H), 2.13-2.47 (m, 2H), 1.11-2.00 (m, 17H) 1.19 (d, J = 6.4 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.10, 70.34, 69.79, 68.01, 35.33, 33.16, 29.35, 27.21, 27.15, 24.35, 23.88, 23.73, 23.63, 19.36;

LRMS (CI(+), ammonia) m/z (relative intensity): 296 (M$^+$+2, 27), 294 (M$^+$, 81), 258 (100), 241 (38), 223 (32), 126 (23), 113 (39), 95 (18);

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{14}$H$_{29}$O$_3$N^{37}Cl: 296.18063, found: 296.18103;

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{14}$H$_{29}$O$_3$N^{35}Cl: 294.18359, found: 294.18339;

66

IR (CDCl$_3$): 3397, 2931, 2857, 1729, 1463, 1376, 1330, 1254, 1213, 1137, 1037, 998, 932, 714, 685 cm^{-1};

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.84 (m, 1H), 4.17 (m, 1H), 3.83 (m, 1H), 2.13-2.49 (m, 2H), 1.07-2.02 (m, 17H) 1.21 (d, J = 6.1 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 173.41, 70.71, 69.98, 68.33, 35.24, 34.46, 28.72, 28.66, 26.69, 25.19, 24.39, 24.23, 23.23, 20.82;

LRMS (CI(+), ammonia) m/z (relative intensity): 296 (M$^+$+2, 19), 294 (M$^+$, 57), 258 (100), 241 (21), 223 (16);

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{14}$H$_{29}$O$_3$N^{37}Cl: 296.18063, found: 296.17951;

HRMS (CI(+), ammonia/methane) m/z calculated for C$_{14}$H$_{29}$O$_3$N^{35}Cl: 294.18359, found: 294.18311;

3.3.16 7-Oxo-13-Tetradecanolide (67) and 8-oxo-13-Tetradecanolide (68)

67   68
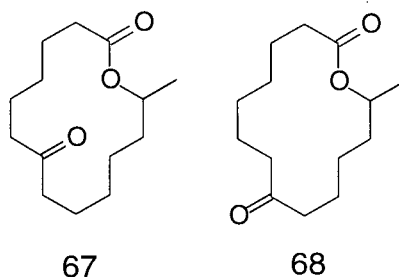
Tetrapropylammonium perruthenate (0.103 mmol, 36.2 mg, 10 mol%) was added to a solution of 4-Methylmorpholine N-oxide (181 mg, 1.55 mmol), 3Å molecular sieves (30 mg), and a mixture of approximately a 37:18:31:14 ratio of hydroxy lactones **51**, **52**, **53** and **54** (0.250 mg, 1.03 mmol), in CH_2Cl_2 (15 mL). The reaction was stirred for 1 hour and filtered through Celite. The solvent was removed under reduced pressure and column chromatography of the residue with 15% ethyl acetate in hexanes afforded a mixture of keto lactones **67** and **68** (214 mg, 0.890 mmol) as a clear pale yellow oil. Further purification by TLC grade column chromatography afforded separated keto lactone **67** (106 mg, 0.445 mmol) in 86% yield as a clear pale yellow oil, and keto lactone **68** (104 mg, 0.441 mmol) as a clear pale yellow oil.

67

IR ($CDCl_3$): 2937, 2862, 1729, 1713, 1460, 1366, 1252, 1132, 1094, 1001 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (m, 1H), 2.17-2.65 (m, 6H), 1.04-1.98 (m, 14H), 1.17 (d, J = 6.1 Hz, 3H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 211.54, 173.42, 69.68, 42.22, 40.66, 35.72, 35.01, 27.76, 27.42, 26.99, 24.89, 24.21, 23.78, 20.13;

LRMS (EI) m/z (relative intensity): 240 (M$^+$,33), 153 (26), 143 (39), 140 (95), 126 (28), 125 (52), 112 (33), 111 (41), 99 (26), 98 (100), 97 (67), 84 (24), 83 (27), 82 (64), 81 (27), 71 (27), 69 (43), 67 (24), 55 (85);

HRMS (EI) m/z calculated for $C_{14}H_{24}O_3$: 240.17254, found: 240.17263;

32

IR (CDCl$_3$): 2933, 2861, 1729, 1713, 1460, 1371, 1253, 1132, 1094, 990 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.97 (m, 1H), 2.13-2.64 (m, 6H), 1.03-1.97 (m, 14H), 1.17 (d, J = 6.4 Hz, 3H);

^{13}C NMR (50 MHz, CDCl$_3$): δ 210.80, 172.97, 70.32, 41.94, 40.52, 35.24, 34.04, 27.06, 26.72, 24.97, 24.65, 24.12, 22.15, 20.49;

LRMS (EI) *m/z* (relative intensity): 240 (M$^+$,15), 157 (22), 139 (32), 129 (21), 126 (100), 111 (50), 97 (30), 84 (36), 83 (44), 69 (47), 68 (23), 56 (20), 55 (51);

HRMS (EI) *m/z* calculated for C$_{14}$H$_{24}$O$_3$: 240.17254, found: 240.17271;

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APPENDICES

Appendix I.   <u>Description of Polar Maps</u>

In order to simplify the identification and comparison of the conformations of oleandomycin, Ogura and coworkers[104] introduced the use of polar maps.[105] These plots have since been used to describe the three dimensional conformation of a variety of large rings in terms of a two dimensional pattern. Polar maps are essentially circular graphs that plot the magnitude and sign of the endocyclic torsional angles versus the bond number (Figure 25). These values are determined using a Newman projection along the torsional bond with the lower numbered atom closest to the observer. The sign of the torsional angle is positive if the direction of rotation is clockwise and negative if counterclockwise.
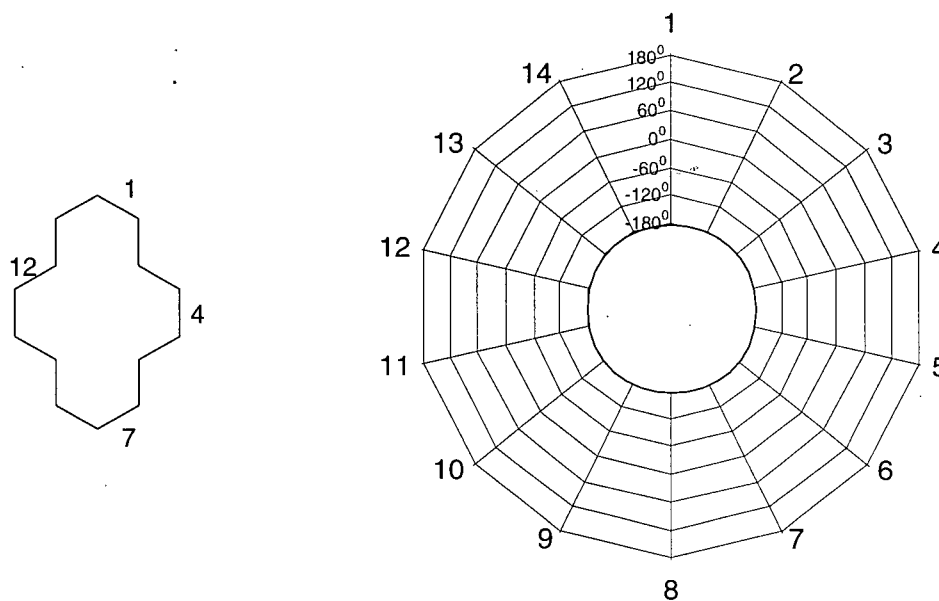
Figure 25. The polar map convention for a 14-membered macrocycle

The torsional angles may be obtained from an examination of molecular models, X-ray crystallographic data or molecular mechanics calculations. However, complications arise when the torsional angles are obtained from X-ray crystallographic data or molecular mechanics calculations since these report angles less than 180° whether they are exocyclic or endocyclic. A simple solution to overcome this is to reverse the sign of the angle obtained and plot this value instead. Thus an exocyclic torsional angle of -175° would become +175°, when in fact it is +185°. Although this does introduce a slight error, it allows for the rapid and reproducible generation of polar maps.

Appendix II.   Representative Chromatograms

31

$\xrightarrow{\text{2 mol\% 28}}$

29 = 7E
43 = 7Z

oven temp 150°c
column 10101
helium 30.0 psi
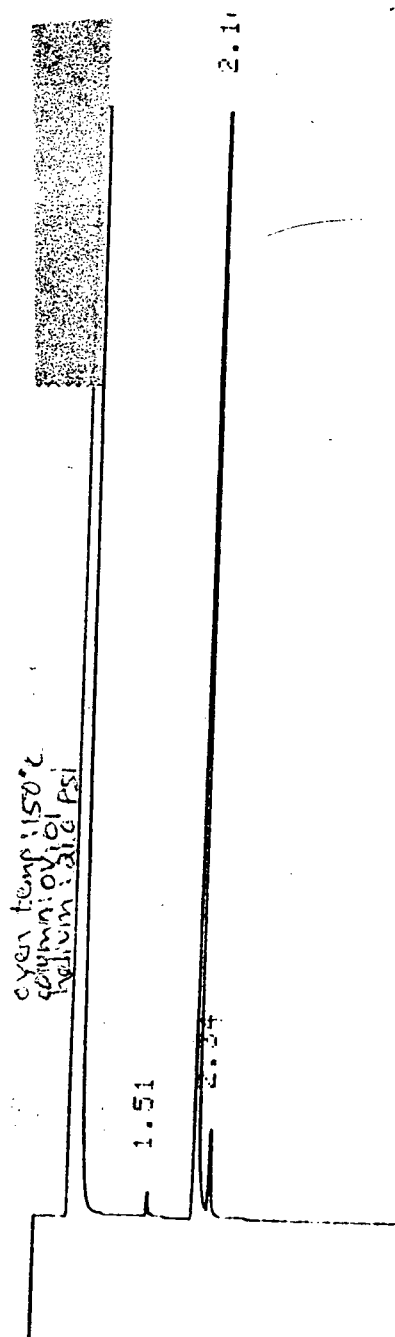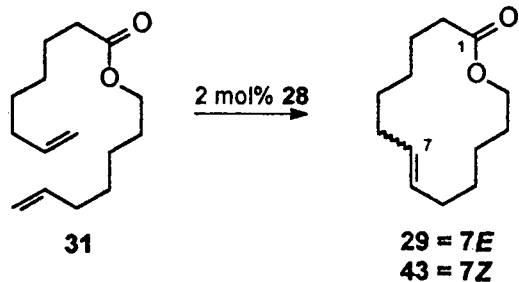
Hp 5880A MANUAL INJECTION @ 14:45   JAN 6, 1980
AREA %

RT	AREA	TYPE	AREA %
1.51	9.72	C BV	1.117
2.16	815.50	C BV	93.685
2.34	45.25	C VB	5.198

TOTAL AREA = 870.47
MULTIPLIER = 1

32 → **30 = 7E**, **44 = 7Z**

2 mol% **28**

TOTAL AREA = 51356600.00
MULTIPLIER = 1
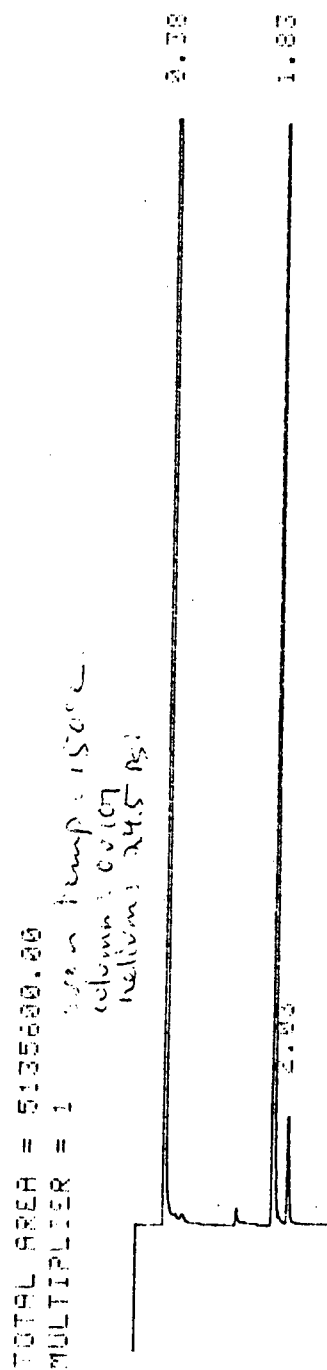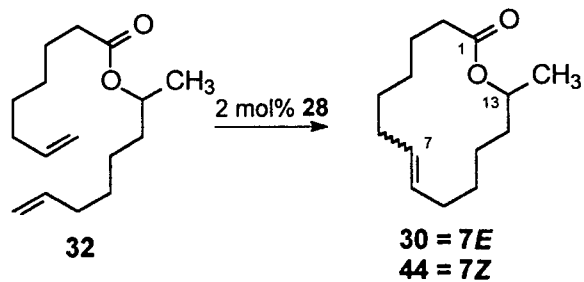
[HP] 5880A MANUAL INJECTION @ 13:14 MAR. 25, 1999

RT	AREA	TYPE	AREA %
1.83	296.69	0 BB	93.905
2.03	21.63	0 DB	6.095
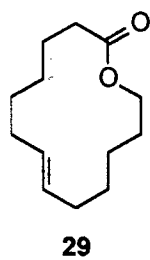
1) BH₃·THF, RT
2) NaOH, H₂O₂
   H₂O
3) TMS-Cl/Et₃N

OTMS

+

TMSO

29   **49**   **50**

AREA %

48.546
51.454

AREA TYPE

RT

TOTAL AREA = 121.33
MULTIPLIER = 1

Reaction scheme: **30** → 1) BH₃·THF, RT 2) NaOH, H₂O₂, H₂O 3) PhNCO → **55** + **56** + **57** + **58**

$R = $ (phenyl carbamate: CH₂–C(=O)–NH–C₆H₅)
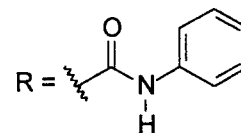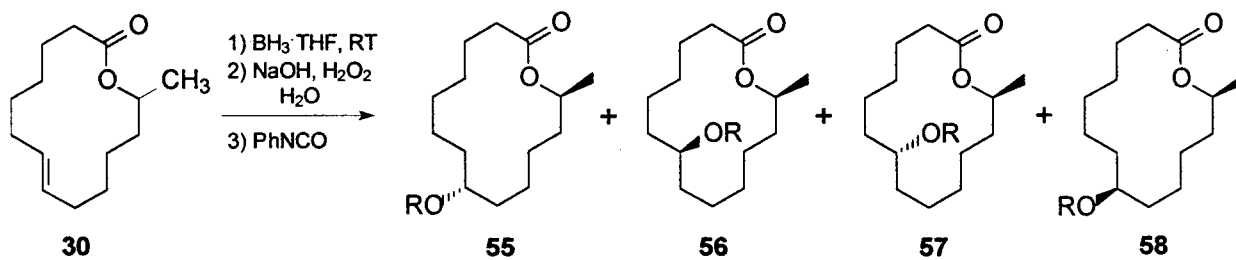

```
Waters 994    INTEGRATOR                           STOP : 30.04 min
Date        : Nov/11/99 01:38:02  FILE NAME  : ERIK
Wavelength  : M1
Time Range  : 5.00 --- 30.04 min  Smothing      : 15         points
Interval    : FAST               Minimum area  : 1.0E-05     AU•min
Time double : 30          min    Slope         : 0.01        AU/min
Minus peak  : OFF               Drift         : 0.01        AU/min
Paper speed : 5.0      mm/min    Height        : 0.01        AU/min
Maserine correct OFF            Width         : 0.01         min
Sample name : EFC99B            Packing material: Si
Column      : 8.0mmID• 10.0cm   Mobile phase  : 96/4 Hexanes/EtOAc
Flow rate   : 3.00     ml/min    Pressure      : 400.0       PSI
Temperature : 25.0        °C     Injection volume: 90         µl
Flow cell   : 10          mm
```
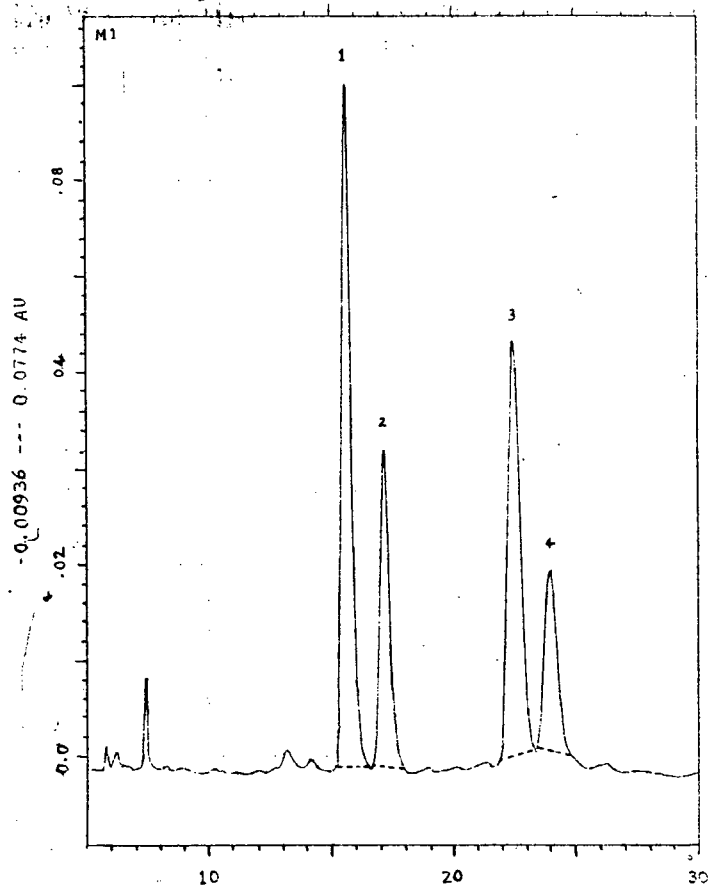
No.	Retention [Min]	Height [AU]	Left [Min]	Right [Min]	Area [AU•Min]	Area [%]	Mark
1	15.59	0.07026	15.27	16.51	3.127E-02	37.2	1
2	17.15	0.03091	16.68	17.98	1.544E-02	18.4	1
3	22.46	0.04365	21.90	23.36	2.583E-02	30.8	1
4	23.96	0.01875	23.42	24.83	1.142E-02	13.6	1
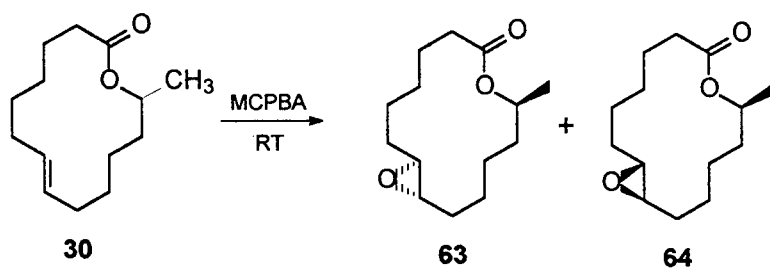
30   63   64

Appendix III.   <u>Spectral Appendix</u>

37

38

39

Integral
1.0000 1.9893 0.9858 4.0017 14.496

(ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.

% Transmittance

Wave number (cm−1)
3200 2400 1600 800

OH

34

40

1.9980 2.0104 1.0000 1.9961 2.0007 3.0836 2.0108 2.0252 4.0025

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

(ppm)

% Transmittance

100 90 80 70 60 50 40 30 20 10 0

3200 2400 1600 800

Wave number (cm-1)

41

Integral

1.0000
1.9957
1.9882
2.0028
6.0028

(ppm)

% Transmittance

Wave number (cm—1)

33

42

35

OH

Int egral

0.9991
2.0000
0.9969
1.9998
10.602

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

(ppm)

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3600 3100 2600 2100 1600 1100 600

Wavenumber (cm-1)

31

Integral

1.9075　3.7916　2.0000　2.0003　3.9336　12.167

（ppm）
7.5　7.0　6.5　6.0　5.5　5.0　4.5　4.0　3.5　3.0　2.5　2.0　1.5　1.0　0.

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

Wave number（cm−1）
3200　2400　1600　800

32

29

Integral

2.0000 2.0005 2.0027 4.0033 12.388

(ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

Wave number (cm—1)
3200 2400 1600 800

30

Integral

1.9718 1.0000 2.0108 4.0122 15.157

(ppm)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3500 3000 2500 2000 1500 1000 500

Wavenumber (cm-1)

47

Integral

1.0000 1.0010 1.0023 2.0021 20.217

(ppm)

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

% Transmittance

100 90 80 70 60 50 40 30 20 10 0

3500 3000 2500 2000 1500 1000 500

Wavenumber (cm-1)

48

55

R =

56

R = structure with amide linked to phenyl group

57

R =

Int egral: 4.0623 0.9873 0.9433 2.0000 2.0300 21.941

(ppm)

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

% Transmittance

100 90 80 70 60 50 40 30 20 10 0

3500 3000 2500 2000 1500 1000 500

Wavenumber (cm-1)

57 + 58

R = (structure with amide linked to phenyl)

NMR spectrum (ppm scale 7.5 to 0.5):
- 5.0261
- 0.9439
- 2.0000
- 1.9986
- 21.268

IR spectrum: % Transmittance vs Wavenumber (cm-1), 3500 to 500

63

64

65

(ppm)

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

Integral

1.0000   0.9970   0.9874   2.0708   19.930

% Transmittance

Wavenumber (cm-1)

3500 3000 2500 2000 1500 1000 500

66

Int egral

0.9204 0.9182 1.0000 2.0249 20.673

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

% Transmittance

3500 3000 2500 2000 1500 1000 500
Wavenumber (cm-1)

67

68