SYNTHESIS AND CONFORMATIONAL STUDIES OF 10,10-DIMETHYLTRIDECANOLIDE

By

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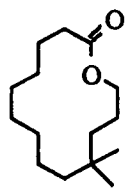
ABSTRACT

The synthesis of 10,10-dimethyltridecanolide (42) was achieved via a fifteen-step sequence in 9% overall yield.

The hydrolysis of macrolides 42, 35, and ester 109 was used to probe the conformational behavior of macrolide 42. The results of this study were rationalized through molecular mechanics (MM2) calculations of conformations for macrolide 42.

MM2 studies confirmed initial conformational analyses that macrolide 42 should exist predominantly in the [3434] conformation 42a. More importantly, they also revealed the existence of a [3344] conformation 42f.

Hydrolysis studies showed that macrolides 42 and 35 hydrolyzed more slowly than ester 109 due to the steric effect of the intermediates. They also suggested that the minor conformation 42f very likely controlled the hydrolysis process of macrolide 42.



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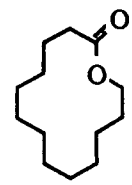

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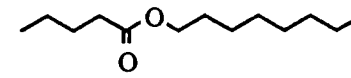

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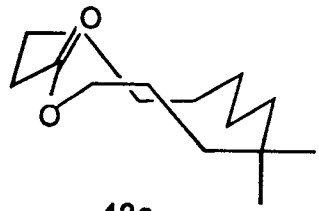

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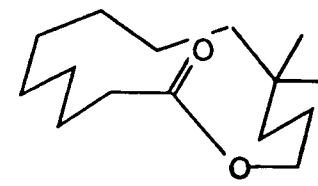

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List of Abbreviations

AcO	acetoxyl
Ac_2O	acetic anhydride
CD	circular dichroism
DCC	1,3-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
ether	diethyl ether
glc	gas-liquid chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
IR	infrared
min	minute(s)
MCPBA	meta-chloroperoxybenzoic acid
MS	mass spectrometry
NMR	nuclear magnetic resonance
PPTs	pyridinium p-toluenesulphonate
TEA	triethylamine
THF	tetrahydrofuran
THP	tetrahydropyran
tlc	thin layer chromatography
TBDMS	tert-butyldimethylsilyl
TMS	trimethylsilyl

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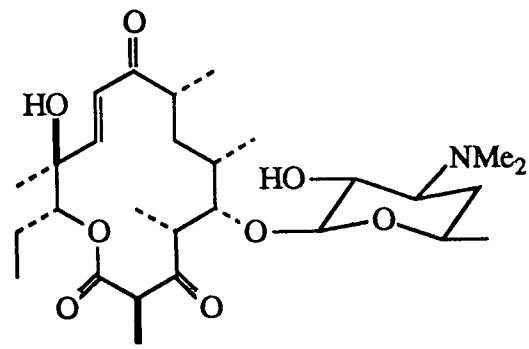
This thesis is dedicated to my parents.

CHAPTER ONE

Introduction

Perhaps one of the most significant breakthroughs in the development of natural product chemistry was the isolation of pikromycin (1) by Brockmann and Henkel in 1950.[1] It was the first macrolide antibiotic isolated from a bacterial source. Soon afterwards, several other microbially produced antibiotics were discovered which were thought to be structurally related to pikromycin. By the end of 1957, chemical degradation studies led to the revelation of the gross structures of methymycin (2), erythromycin A (3) and B (4) and carbomycin A (5) (Figure 1).[2-5] Each of these antibiotics shared a common feature - a lactone incorporated in a medium or large-ring system. This was the genesis of macrolide chemistry.



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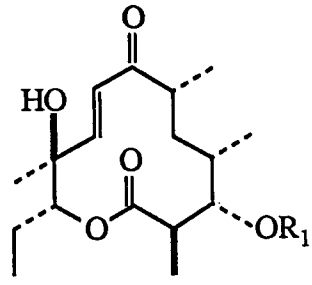
The term "macrolide" originally referred to the above antibiotics but, as time passed, it has gradually been used in a broader sense to define all organic compounds with a large lactone ring (12 or more atoms).



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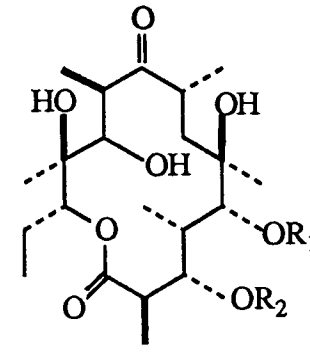

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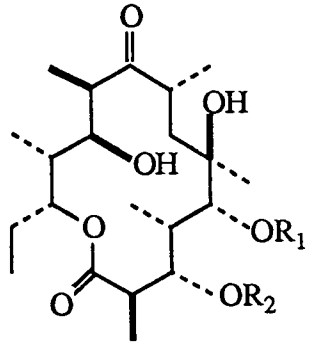

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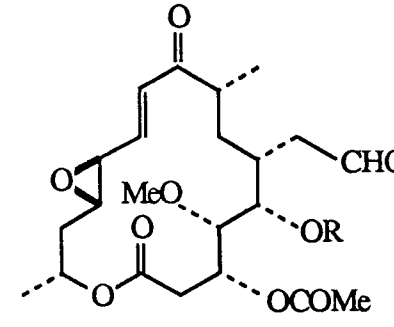

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Figure 1. Structures of macrolide antibiotics isolated in the 1950's, R, R_1 and R_2 represent different carbohydrates.

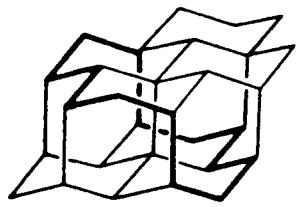
Over the next 20 years, the field of macrolide chemistry was firmly established with the isolation of more than 100 large ring lactone natural products possessing diverse biological activities.[6] Approximately one-half of these natural products are classified as "polyoxo"

macrolides, which normally contain 12, 14 or 16-membered lactone rings with numerous ring substituents including one to three glycoside units.

An interesting structural feature of the macrolide antibiotics, which may be related to their biological activities, is the relative conformational rigidity of the molecules in solution. These molecules often exist in one identical conformation whether in solution or in the solid state.[7] Presumably, the high degree of substitution on the macrolide plays an important role in this rigidity in that the accommodation of many steric and electronic factors leads to a single minimum energy conformation for any particular macrolide.

The conformations of complex 14-membered macrolide antibiotics have aroused considerable interest among chemists and a number of models have been proposed to explain the conformations of various macrolides. One of the most studied conformations is that of erythronolide B, the aglycone of erythromycin B.

In 1963, Dale introduced a minimum energy diamond-lattice conformation 6 (bold line) for cyclotetradecane.[8] A model for the preferred conformer of erythronolide B (7) was advanced by Celmer in 1965.[9] Although Celmer's model was in close agreement with the ^1H NMR data, it did not agree with X-ray crystallographic data. Celmer's conformation was also very strained because of transannular hydrogen interactions and a 1,3-diaxial methyl interaction. A second diamond-lattice conformation 8 was proposed for erythronolide B (9) from NMR and CD spectra data. This eventually led to the Perun model 10.[10] The Perun model was favourably compared to the solid state conformation of erythromycin A[10] and is now widely used as a basis for assigning stereochemistries of substituents in 14-membered macrolide antibiotics.



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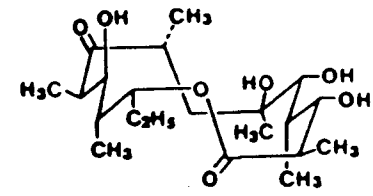

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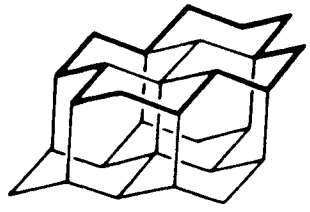

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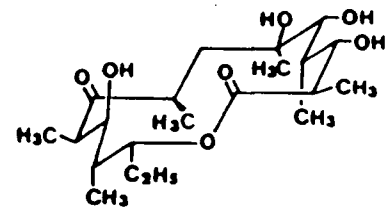

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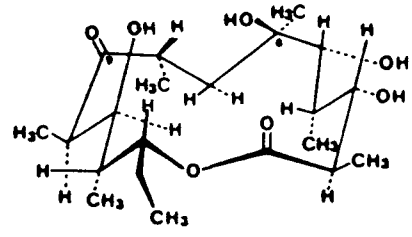

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Figure 2. Conformation models for cyclotetradecane and erythronolide B.

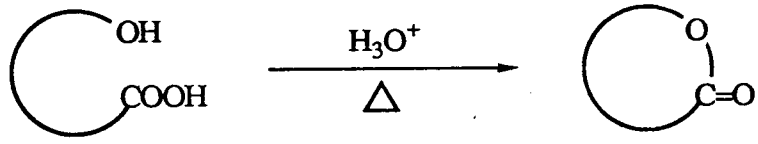
Although a considerable number of conformational studies of macrolide antibiotics have been carried out over the past 30 years, the total synthesis of macrolide antibiotics has been slow to develop. There were two major problems associated with the synthesis of macrolide antibiotics: one was the construction of a medium or large-size lactone and the other involved the introduction of numerous chiral centres into the molecule. Efficient lactone ring construction procedures are now available due to the development of new synthetic methodology and advanced experimental techniques. However, selective introduction of chiral centres on a large ring remains challenging and still demands creativity and imagination for its satisfactory completion.

1.1 Lactonization of Long-Chain Hydroxy Acids

The first problem associated with the synthesis of a macrolide antibiotic is the construction of the lactone functionality. Although many methods to generate lactones have been developed over the past 30 years,[11-19] lactonization of long-chain hydroxy acids is by far the most common. This stems from the ready availability of the acyclic precursors and from the belief that the biosynthesis of a macrolide antibiotic very likely proceeds through a final lactonization stage to form the aglycone.

However, the employment of the lactonization procedure, while conceptually simple, is not always an easy task to accomplish. Ring closure of a long-chain precursor is disfavoured due to an entropy loss as the two distant chain ends approach each other. As a result, intermolecular rather than intramolecular cyclization often occurs. Nevertheless, efforts to develop highly effective lactonization procedures have proven to be successful over the years.

The first lactonization of long-chain hydroxy acids 11 was carried out by Stoll and Rouve in 1934.[20] In their studies, the use of dilute solutions (e.g. 2.0 - 8.0 x 10^{-4} M) and catalysts such as p-toluenesulfonic acid were found to be essential.



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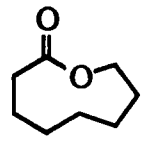
The synthesis of lactones has been conducted in this manner with yields ranging from approximately 1% for nonanolide (12) to 87% for hexadecanolide (13).[20] However, this method suffers from the awkward high dilution conditions needed to effect lactonizations and from the resulting poor yields of the lactones.



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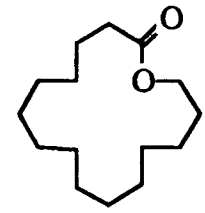

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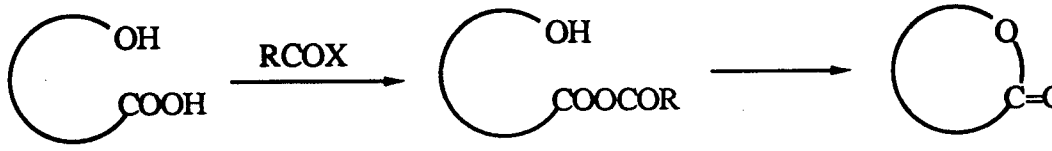
The desire to perform cyclizations under milder conditions and with higher yields led to a strategy which activated the carboxylic acid before the lactonization. It was anticipated that the intramolecular attack of the free hydroxyl functionality on the newly activated carboxylic acid would occur under relatively mild conditions. The reaction of hydroxy acids with phosgene-triethylamine or with trifluoroacetic anhydride has successfully produced lactones through the formation of a mixed anhydride 14.



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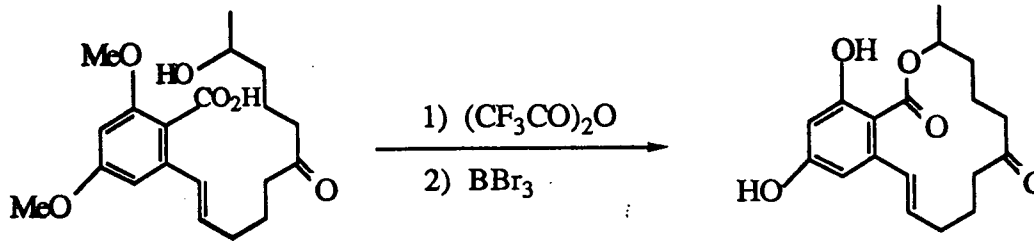
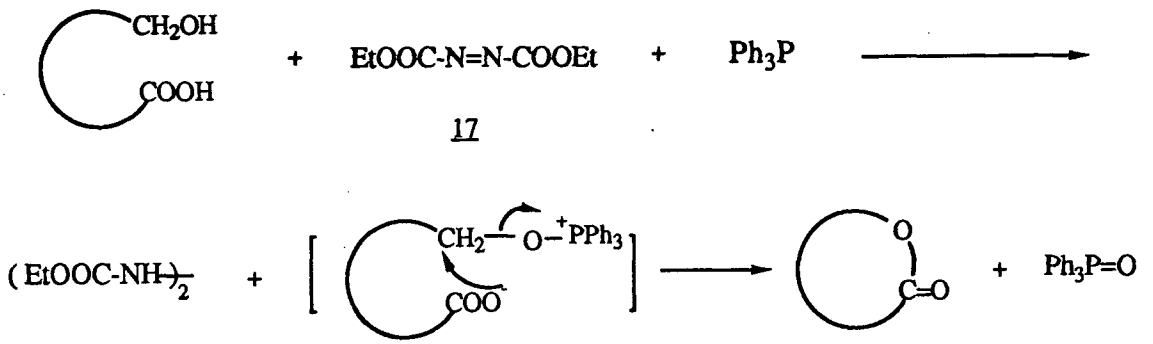
For example, treatment of the hydroxy acid 15 with trifluoroacetic anhydride followed by cleavage of the methoxyl ethers gave zearalenone (16) in moderate yield.[21]



15 16

A different strategy for the cyclization of hydroxy acids has also been reported by Kurihara et al., wherein the hydroxyl function was activated and the carboxylate anion acted as the nucleophile.[22] In this way, the reaction of the hydroxy acids with triphenylphosphine and diethyl azodicarboxylate (17) at room temperature effected ring closures via an alkoxyphosphonium carboxylate 18.



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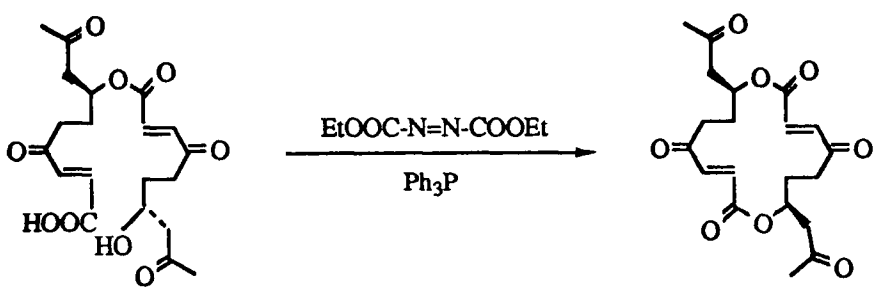
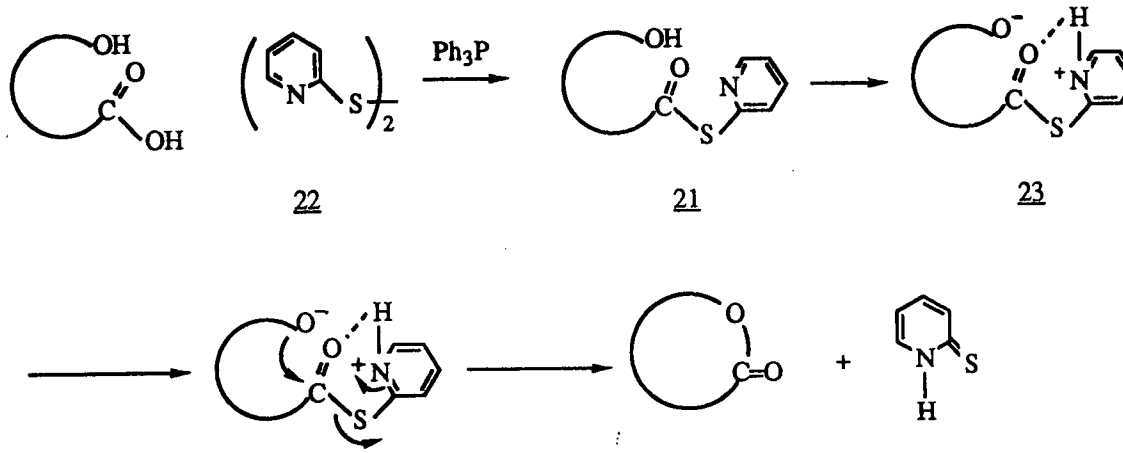
This procedure has been employed by White and co-workers in their synthesis of vermiculine (19).[23] Cyclization of the hydroxy acid 20 with triphenylphosphine and diethyl azodicarboxylate produced vermiculine (19) in 15% yield. This process also resulted in an inversion of the stereochemistry of the original alcohol.[23]



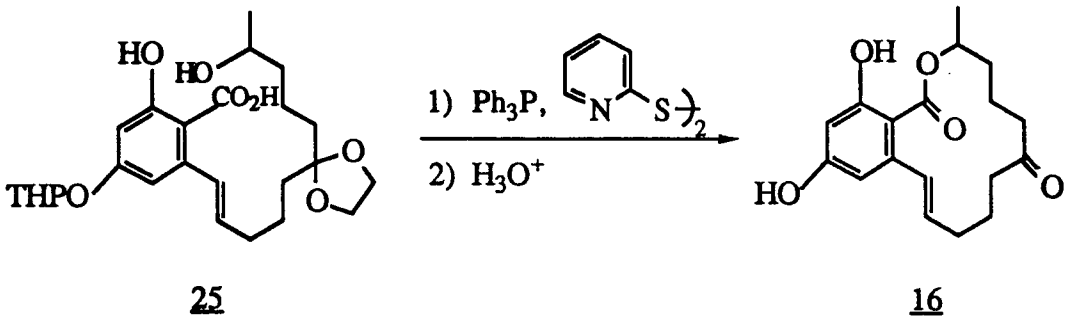
20 19

The advantage of activating the carboxylic acid or hydroxyl function prior to the esterification step was obvious. An even more expedient procedure involved simultaneously

activating both the hydroxyl and carboxylic acid groups. Corey and Nicolaou[24] envisioned a "double activation" through a carboxylic derivative that was able to transfer a proton from the hydroxyl to the carboxylic oxygen. One such derivative was the 2-pyridinethiol ester 21 prepared from the reaction of a hydroxy acid and di(2-pyridyl)disulfide (22) in the presence of triphenylphosphine.[25] The proton transfer from the hydroxyl to carbonyl oxygen in 21 was greatly facilitated by the basic nitrogen of the pyridine ring. The zwitterionic intermediate 23 thus generated underwent a facile cyclization to eventually yield the desired lactone 24.



Corey and co-workers have successfully applied this methodology in the synthesis of several complex macrolides.[24] In their synthesis of zearalenone (16), the key lactonization step was accomplished by heating the hydroxy acid 25 with di(2-pyridyl)disulfide and triphenylphosphine in benzene. Subsequent hydrolysis of the ketal and tetrahydropyranyl ether protecting groups produced zearalenone (16) in 75% yield overall.[24]



Recently, a modification of Corey's double activation method was reported by Gerlach and Thalmann[26] who found that the presence of silver ions ($AgClO_4$ or $AgBF_4$) complexed with 2-pyridinethiol esters as shown in 26 which then were able to undergo a rapid cyclization at room temperature.

26a 26b

A problem associated with Corey's double activation method is that the reaction products must be separated from thiopyridone, triphenylphosphine oxide, dipyridyl sulfide, and in the case of Ag-activation, from excess silver thiolate. To circumvent this problem, another simple and highly effective cyclization method has been developed by Schmidt and Dietsche.[27] In this method, 1-phenyl-2-tetrazoline-5-thione and tert-butylisocyanide were used for the double activation of the hydroxy acids to produce 16, 17, 18, and 20-membered lactones in over 90% yield. The purification of lactones so produced was uncomplicated.

Previously, our laboratory has used a modified form of Corey's double activation method for the construction of 14-membered lactones of interest. Although the lactonization reactions proceeded smoothly with moderate to good yields, the difficulties in purifying the final products remained. In this project, Schmidt and Dietsche's method was applied to the cyclization step in the synthesis of 10,10-dimethyltridecanolide, a strategically dimethylated 14-membered lactone.

1.2 Remote Asymmetric Induction Via Conformational Control

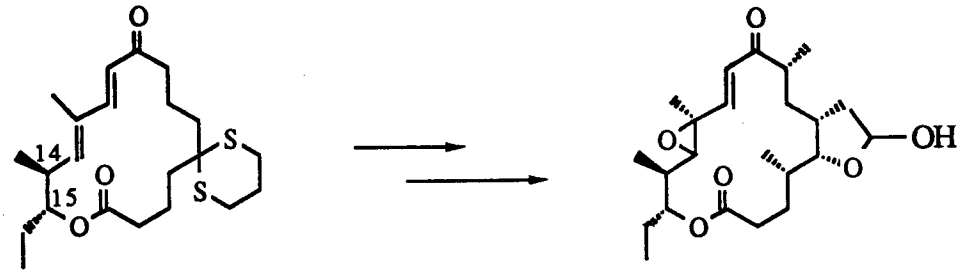
The second problem encountered in the synthesis of macrolide antibiotics was the establishment of the relative stereochemistry of numerous asymmetric centres on an acyclic precursor. This is a problem that continues to challenge synthetic chemists.

There are a variety of synthetic methods available to establish vicinal or 1,2-stereochemical relationships using reactions that proceed with high internal or relative asymmetric induction, and to set up 1,3 and a few 1,4-relationships using reactions based on well understood 5 and 6-membered ring conformations.

However, the establishment of correct stereochemical relationships between widely separated or remote asymmetric centres usually requires some form of absolute stereochemical control. Each set of remote asymmetric centres can only be prepared from an enantiomerically pure starting material or by a reaction proceeding with high enantioselectivity.

Traditionally, the large number of asymmetric centres are introduced into the acyclic precursors of the macrolides using enantiomerically pure starting materials, but this strategy is very difficult to accomplish.

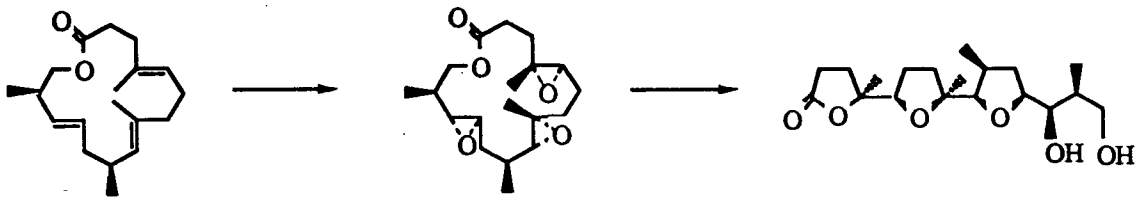
A new strategy for the establishment of remote stereochemical relationships in macrolide synthesis has been developed by Still and co-workers[28,29] who exploited the conformations of medium or large-membered lactones as a source of stereocontrol in generating new asymmetric centres. In their synthesis of 3-deoxyrosaranolide (27),[29] the simple 16-membered lactone 28 was first constructed. The other six asymmetric centres in the target molecule 27 were then established with excellent diastereoselectivity using the two asymmetric centres at C_{14} and C_{15}, and the conformational preference of the 16-membered lactone.



28 27

Although the conformation ultimately responsible for the success of this stereoselectivity was not determined, this synthesis clearly illustrated the concept of remote asymmetric induction via conformational control: the pre-existing asymmetric centre(s) in a large-membered lactone caused the molecule to adopt a particular conformation or conformations which then directed the stereochemical outcome of the reaction (e.g. by allowing the attack of a reagent to occur from only one face of the molecule).

Interestingly, Still has also extended this conformational stereocontrol strategy to the preparation of stereochemically complex acyclic compounds. This strategy entails the synthesis of a medium or large-membered lactone, elaboration of the desired stereochemistry via conformational control and cleavage of the lactone ring. For example, in the synthesis of the tris(tetrahydrofuranoid) compound 29,[30] a 16-membered lactone 30 was first constructed. Treatment of the lactone 30 with meta-chloroperoxybenzoic acid gave the triepoxide 31, in greater than 90% diastereoselectivity. Saponification of 31 followed by acid catalyzed polycyclization led directly to the desired product 29.



30 31 29

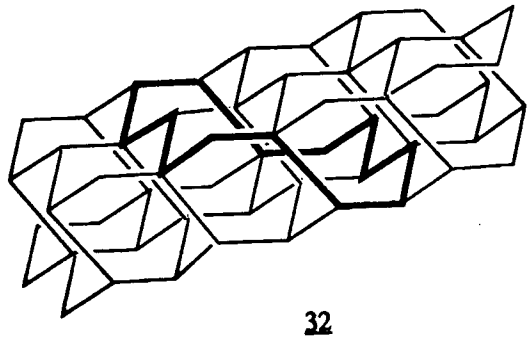
Unfortunately, the conformation of the reacting lactone was not determined. However, it is clear that the use of conformational control in the introduction of asymmetric centres will eventually provide easy access to a large number of complex macrolide antibiotics and some acyclic natural products which otherwise may have been difficult to synthesize.

Obviously, in order to accelerate and extend the application of this new strategy, an understanding of the conformational behavior of large lactone rings and the factors controlling their conformational preferences is important. This knowledge can aid in predicting and controlling the stereochemical outcome of a reaction involving in the lactone ring.

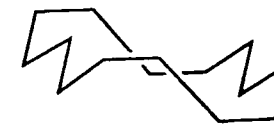
As a contribution to the development of this conformational control strategy, our laboratory has been involved in the studies of the conformational behavior of 14-membered lactones and the fundamental principles governing the stereochemistry of reactions of these compounds. The 14-membered lactones were chosen as our primary targets because many macrolide antibiotics contain such a lactone skeleton and also 14-membered rings are the next ring size after cyclohexane which can adopt a strain-free conformation.[31]

1.3 Conformational Behavior of 14-Membered Lactones

The simplest 14-membered ring is the hydrocarbon cyclotetradecane whose conformation has been described in detail by Dale.[8,31] From an inspection of space-filling models, Dale recognized a tendency for saturated large rings to adopt compact conformations consisting of two parallel methylene chains linked by bridges of minimum length. These rectangularly shaped conformations could be generated from the three-dimensional framework of a diamond-lattice 32 where the ideal tetrahedral carbon geometry and the favorable torsional angles of 60° or 180° were obtained.[8] Dale predicted a strain-free (i.e. free of bond angle strain, torsional angle strain and severe transannular hydrogen interactions), lowest-energy conformation 33 for cyclotetradecane and named it as the [3434] conformation.[32] The numbers within the square brackets represent the number of carbon-carbon bonds between atoms having two adjoining gauche angles of equal sign each followed by an anti angle.[32,33] Dale's prediction was later confirmed by X-ray analysis of cyclotetradecane in the solid state.[34]



32



33

At first glance, Dale's [3434] conformation of cyclotetradecane shares many similarities with the well-known chair conformation of cyclohexane. However, a close comparison of both strain-free conformations reveals an important difference between them. The 14-membered strain-free conformation is less symmetric and as such contains four diastereotopic methylene environments. The four unique methylenes are numbered in Figure 3

which also illustrates the relative magnitude of transannular interactions that internal hydrogen atoms experience in this conformation.

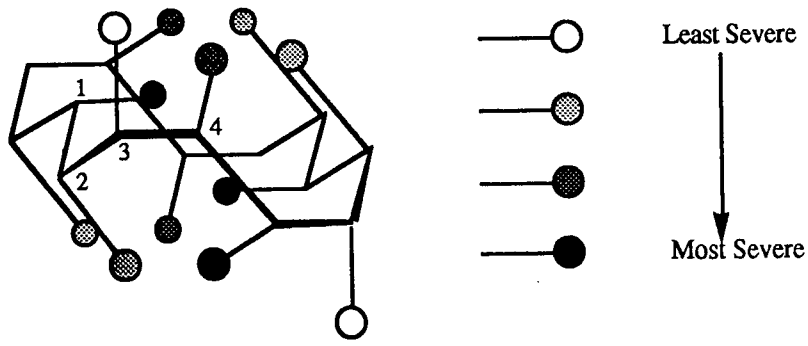


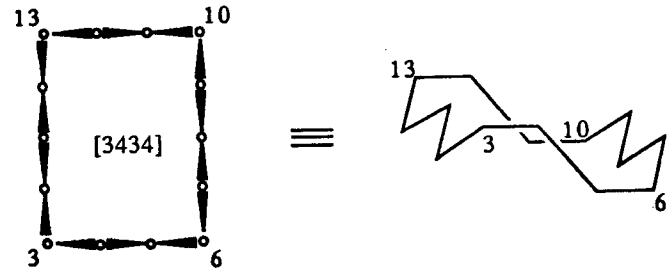
Figure 3. Magnitude of hydrogen interactions in the [3434] conformation of cyclotetradecane.

The different magnitude of the hydrogen interactions has a profound effect on the preferences for substitution of a ring carbon atom as well as substitution of the hydrogen atoms. Since replacement of an sp^3 carbon atom in the ring with an oxygen or with an sp^2 carbon atom will reduce the transannular hydrogen repulsions, the preference for such a substitution should therefore follow the order $C_1 > C_4 > C_2 > C_3$. For hydrogen replacement, two different substitution patterns exist: a single substitution or a geminal disubstitution. A single substituent attached to any of the carbon atoms can only occupy exterior positions. Otherwise the transannular interactions would be prohibitively large.[33,34] This will lead to a mixture of four conformers which differ from one another only in the choice of the substituent position.

The two geminal substituents, however, will be restricted to a corner position C_3 since it is only at this position that the substituents experience little transannular interactions. Dale defined the corner atom as having two adjoining gauche angles of equal sign each followed by an anti angle (e.g. 180°, -60°, -60°, 180°).[32] A corner position represents the sole position

available for geminal disubstitution in that substituents on this position experience the least amount of steric interaction from the ring.[33,34]

A top view diagram of the [3434] strain-free conformation 34 immediately reveals the corner positions as carbon atoms 3, 6, 10 and 13.



34

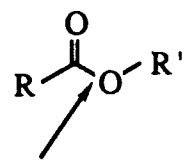
Figure 4. Top and side views of the [3434] conformation of cyclotetradecane.

The ring system which is of primary interest in this project, the 14-membered lactone, can now be considered. The introduction of an ester linkage into the cyclotetradecane ring should not distort the [3434] conformation of the ring itself, since no new angular strain is introduced. Dale's strain-free [3434] conformation for cyclotetradecane can also be reasonably expected to be the lowest-energy conformation for most of the 14-membered lactones, except for highly substituted ones with demanding steric and geometric requirements. One such exception is erythronolide B (10) where the Perun model must be adopted in order to explain experimental results.

For reasons of brevity, only 14-membered lactones which we expect to adopt the [3434] conformation will be discussed in detail and publications concerning those with conformations other than [3434] are given for interest.[35,36] It should be emphasized that most simple 14-membered lactones seem to adopt the [3434] conformation as demonstrated by our laboratory through detailed conformational analyses using X-ray crystallography, NMR spectroscopy and molecular mechanics (MM2) calculations.[37-39]

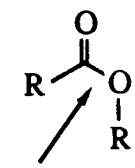
Even if our analysis is restricted to the [3434] conformation, the simplest 14-membered lactone tridecanolide (35) can still be expected to exist in seven different conformers.

However, the preference of a planar s-trans geometry for esters immediately eliminates four of the possible conformers. It has been reported by Deslongchamps[40] that the planar s-trans geometry in ester 36 is approximately 3.0 kcal/mole more stable than the planar s-cis isomer 37. In fact, there is not a single example of an acyclic s-cis ester.[41]



s - trans

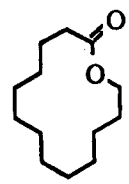
36



s - cis

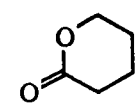
37

The 14-membered ring is large enough to accommodate a planar s-trans linkage as confirmed by dipole moment measurements.[42,43] Tridecanolide (35) has a dipole moment of 1.86 Debyes,[42] similar to those of acyclic esters which range from 1.6 to 2.0 Debyes.[43] On the other hand, δ-valerolactone (38) where the lactone group is held rigidly in the s-cis linkage has a dipole moment of 4.22 Debyes.



s - trans

35

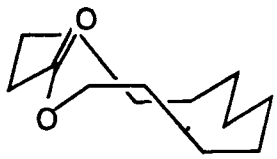


s - cis

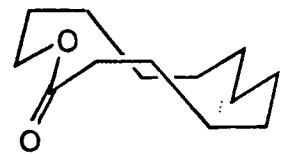
38

For tridecanolide only three [3434] conformations 35a, 35b and 35c can accommodate a planar s-trans lactone. The relative steric energies of these conformations have been found to be 0.2 kcal/mole, 0.0 kcal/mole and 0.1 kcal/mole, respectively, by MM2 calculations.[44] In

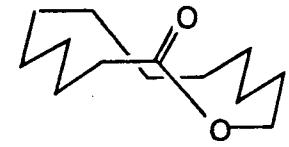
contrast, the relative steric energies of the four conformers with s-cis lactone linkages have been found to be 7.2 kcal/mole, 7.8 kcal/mole, 7.9 kcal/mole and 8.2 kcal/mole.[44] Accordingly, conformations possessing s-trans lactones should predominate and tridecanolide (35) should exist as a mixture of conformers 35a, 35b and 35c in nearly equal amounts.



35a



35b

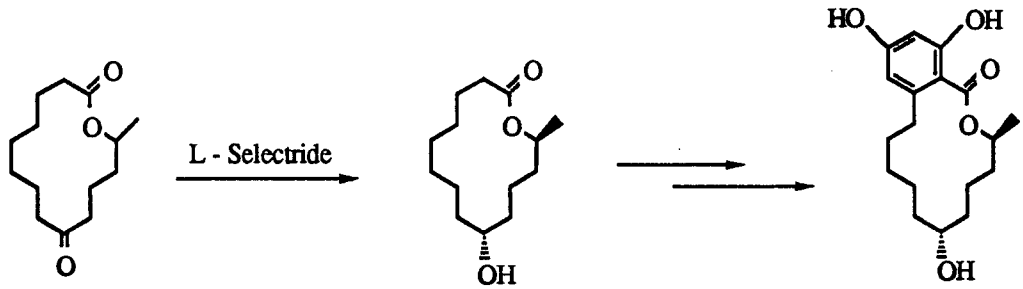


35c

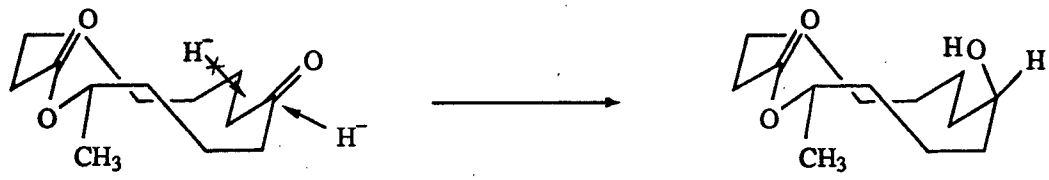
Obviously, in order to exploit the conformations of 14-membered lactones as a source of stereocontrol, the number of low-energy reacting conformations must be reduced to a minimum. This can be achieved by introducing rigidity to the lactone rings through appropriate substitutions and/or functionalizations.

Based on the simple conformational analyses of 14-membered lactones discussed above, our laboratory has been able to plan the synthesis of conformationally rigid 14-membered lactones and take advantage of their expected [3434] conformations to successfully control diastereoselective reactions.

For example, en route to the synthesis of zeranol (39), the required $9R^*$, $13S^*$ stereochemistry was established via a [3434] conformationally controlled diastereoselective reduction reaction. The preference of a planar s-trans lactone linkage and the preferred occupation of a carbonyl at a non-corner position resulted in a single [3434] conformation 40a for macrolide 40. When this macrolide was treated with L-Selectride, reduction occurred from the more open exocyclic face, leading to the desired product 41 with excellent diastereoselectivity.



40 41 39



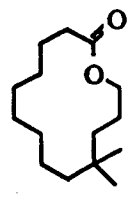
40a 41

1.4 Restricting the Low-Energy Conformations of 14-Membered Lactones by Geminal Disubstitution

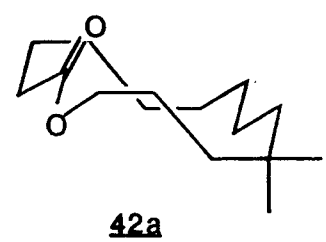
It is clear that 14-membered lactones are potentially useful as three-dimensional templates for the introduction of asymmetric centres. In our laboratory, various 14-membered lactones have been synthesized and investigated for conformationally controlled reactions over the past few years. During the course of these studies, one common problem arose: often, the 14-membered lactone under investigation possessed more than one stable low-energy conformation which complicated the analysis and reduced the utility of the results obtained. It was felt that a synthesis and study of a lactone with one stable conformation would provide valuable insight into the conformational and chemical behavior of 14-membered lactones. The total synthesis of 10,10-dimethyltridecanolide (42) was conducted with this goal in mind.

One of the many efficient ways to introduce rigidity into the lactone rings, and therefore reduce the number of conformations available, is by geminal disubstitution. The geminal substituents should force a 14-membered lactone to adopt a conformation in which the quaternary carbon atom occupies a corner position.

10,10-Dimethyltridecanolide (42) could be expected to exist predominantly in a single rigid [3434] conformation 42a in which the geminal dimethyl group occupies the corner position and the lactone function has a planar s-trans geometry. Conformational and reactivity studies of this compound should lead to a better understanding of the conformational and chemical behavior of 14-membered lactones.



42



42a

CHAPTER TWO

Results and Discussion

This chapter consists of four sections: (1) the synthesis of the target molecule 10,10-dimethyltridecanolide (42); (2) hydrolysis studies of two macrolides 42, 35, and an ester 109; (3) MM2 calculations of conformations for macrolide 42 and (4) conclusions from these investigations and future considerations.

2.1 Synthesis of 10,10-Dimethyltridecanolide (42)

The synthetic route to 10,10-dimethyltridecanolide (42) was devised using the following considerations. A geminal dimethyl group was to be introduced prior to the construction of the lactone ring so that it could serve to reduce the number of conformations available to the remainder of the ring. The lactone ring, on the other hand, was to be constructed via the lactonization of a long chain hydroxy acid precursor. Thus, the penultimate target for the synthesis became the ω-hydroxy acid 43 with a geminal dimethyl group δ to the hydroxyl function (Figure 5).

Since the geminal dimethyl group was an isolated one, direct alkylation was not feasible. Nevertheless, it could be generated from a keto functionality via a series of chemical transformations. The carboxylic acid functionality in 43 could be prepared from the oxidation of a pre-existing hydroxyl group. Hence, the synthetic problem was further reduced to the preparation of the γ-hydroxy ketone 44. Further disconnection of the synthetic intermediate 44 was made in view of the fact that the most logical precursor of a γ-hydroxy ketone derivative was γ-butyrolactone (45) coupled with the corresponding Grignard reagent 46. The Grignard reagent 46 could be prepared from the commercially available 1,9-nonanediol (47). This completed our retrosynthetic analysis and it suggested an efficient approach to the synthesis of macrolide 42.

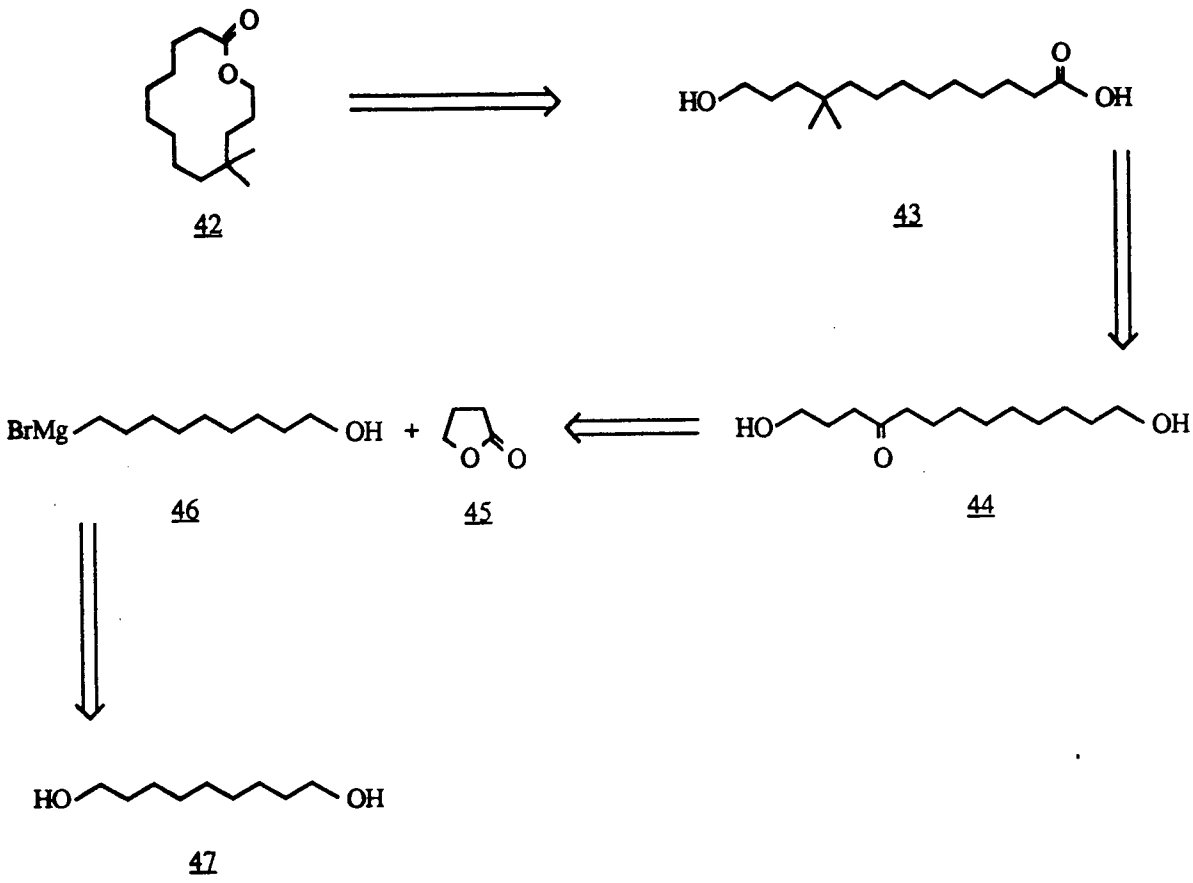
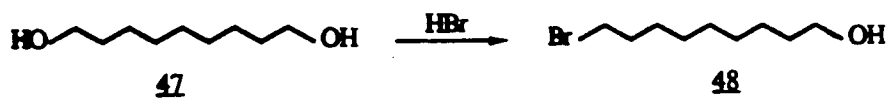
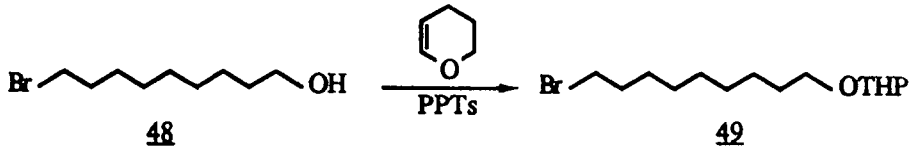


Figure 5. Retrosynthetic analysis of macrolide 42.

Based on the synthetic scheme outlined above, our synthesis was initiated with the monobromination of 1,9-nonanediol (47). This reaction was achieved by continuously extracting a mixture of the diol and aqueous hydrobromic acid with heptane. The yield obtained after column chromatographic purification was 84%. The infrared (IR) spectrum of the bromo alcohol 48 showed a hydroxyl stretching absorption at 3337 cm^{-1}. The ^1H NMR spectrum of 48 exhibited two sets of triplets at δ 3.42 and δ 3.66 which were attributed to the α-methylene protons of the bromo and hydroxyl groups respectively.



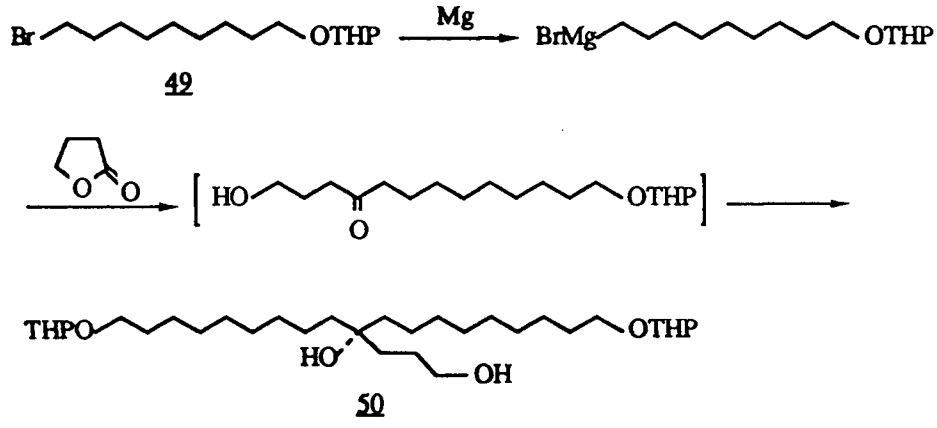
Protection of the hydroxyl group of the bromo alcohol 48 was carried out by treatment of this material with dihydropyran in the presence of pyridinium p-toluenesulphonate (PPTs). The reaction proceeded smoothly to give the tetrahydropyranyl ether 49 in 91% yield. Absence of a hydroxyl absorption in the IR spectrum of 49 indicated a successful reaction. A triplet at δ 4.60 in the ^{1}H NMR spectrum of 49 confirmed the presence of the acetal methine proton.



48 49

The next step in the synthesis was to convert compound 49 into a nucleophile and prepare a γ-hydroxy ketone derivative via a nucleophilic addition to γ-butyrolactone.

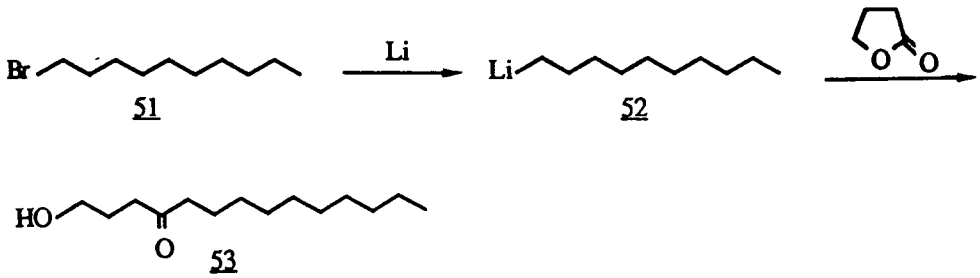
When the bromide 49 was treated with magnesium and the resulting Grignard reagent added slowly to γ-butyrolactone, the desired γ-hydroxy ketone could not be detected. Instead, we isolated the diol 50 which was the product of the addition of two equivalents of Grignard reagent to the lactone. It appeared that the second Grignard addition to the ring opened compound was faster than addition to the γ-butyrolactone.

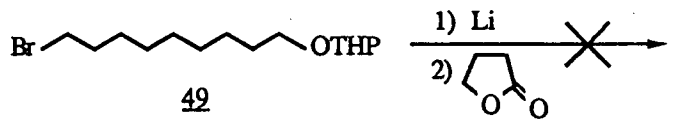


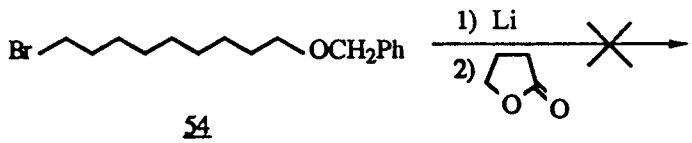
49 50

In another attempt to prepare the desired γ-hydroxy ketone, organolithium reagents were investigated. The simple alkyl bromide 51 reacted with lithium to give the organolithium reagent 52 which successfully opened γ-butyrolactone to give the γ-hydroxy ketone 53 in 56%

yield. Surprisingly, when the tetrahydropyranyloxy bromide 49 and the benzyloxy bromide 54 were subjected to this procedure, no reaction was observed and the starting bromides were recovered.

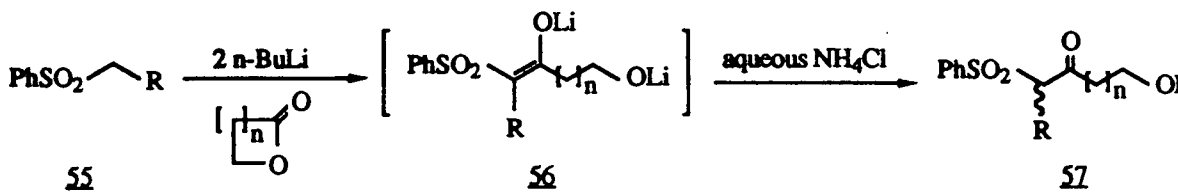






At this point, we were forced to search for alternate conditions for this reaction. Our attention turned to the use of sulfone chemistry.

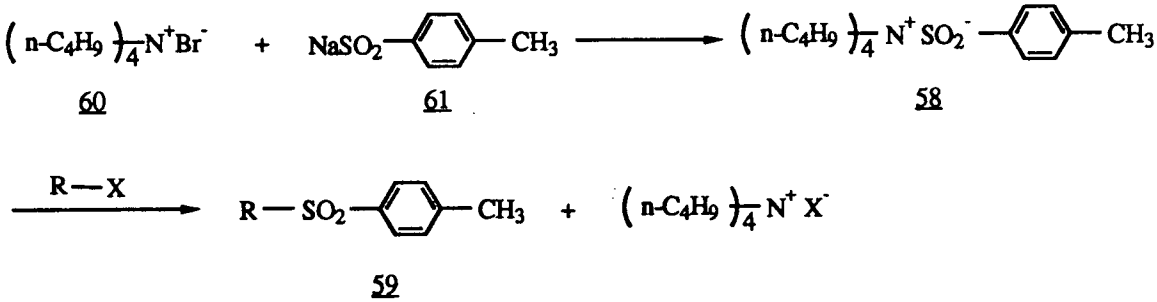
It had been reported by Covicchioli et al.[45] that α,α-dilithio derivatives of alkyl phenyl sulfones react with small and medium-size lactones to give the corresponding hydroxy ketones. The α,α-dilithio derivatives of alkyl phenyl sulfones were prepared by treatment of the sulfones 55 with two equivalents of n-butyllithium. The attack of lactones by these gem-dimetallic compounds afforded intermediate enolates 56 which upon workup gave the single addition products 57. The formation of diols by a second organometallic addition was therefore avoided.



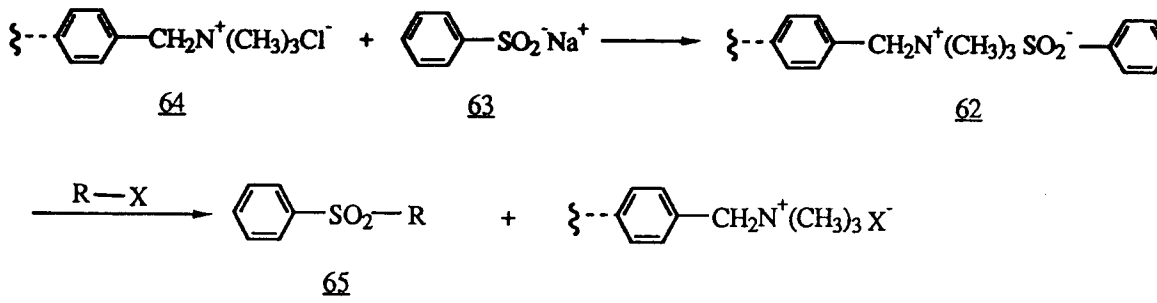
To apply Covicchioli's method in our synthesis, the bromide 49 must first be converted into its corresponding phenyl sulfone. Several methods are available for such a conversion.

Direct alkylation of alkali metal salts of benzene sulphinic acids is a widely used procedure.[46] The reaction is usually performed in refluxing alcohol or in dimethylformamide at room temperature, but it proceeds slowly and often gives only moderate yields of sulfones.

An improved synthesis of sulfones has been reported by Veenstra and Zwanenburg[47] who used tetrabutylammonium p-toluenesulphonate (58) as the nucleophile in reactions with alkyl halides to give the corresponding sulfones 59 in good yields. Compound 58 was prepared by extraction of a concentrated aqueous solution of tetrabutylammonium bromide (60) and sodium p-toluenesulphinate (61) with methylene chloride.

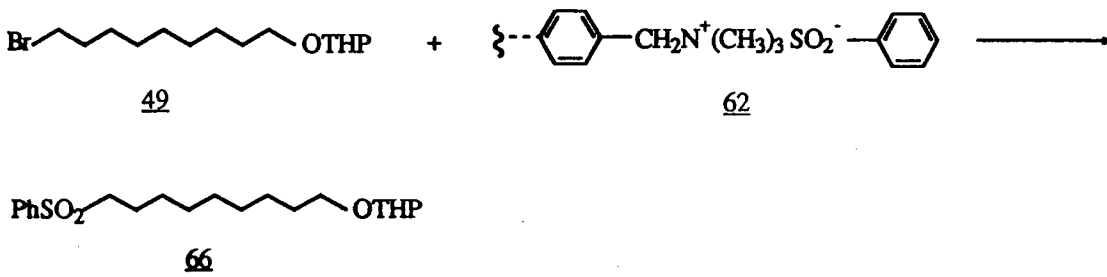


Recently, a versatile procedure for the preparation of phenyl sulfones has also been published by Manescalchi et al.[48] This method involved the alkylation of benzenesulphinate anion supported on Amberlyst A-26, a macroreticular anion exchange resin containing a quaternary ammonium group. The Amberlyst A-26 supported benzenesulphinate anion 62 was prepared by the exchange reaction of sodium benzenesulphinate (63) with the resin in chloride form 64. The alkylation reaction was achieved by stirring 62 with alkyl halides in refluxing benzene. The phenyl sulfones 65 thus produced were isolated simply by filtering the resin and removing the solvent under reduced pressure. The yields with primary alkyl halides were reproducibly above 90% and the unpurified products showed very low levels of by-products by spectral analysis.[48]

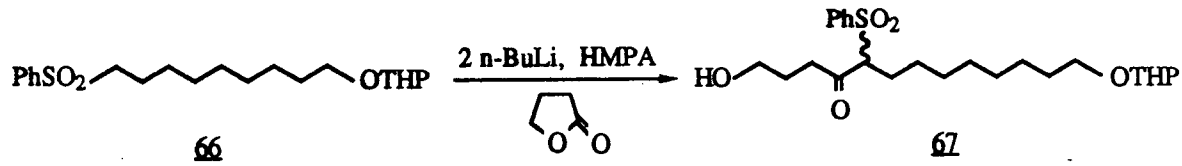


≀··· = polymer

Although each of these three methods discussed above could be applied to our synthesis, we favoured Manescalchi's procedure in view of its superior yields and relatively straightforward workup. Using this procedure, the phenyl sulfone 66 was prepared from the bromide 49 in 94% yield. The ^{1}H NMR spectrum of 66 exhibited a multiplet at δ 7.52-7.92 for five aromatic protons and a triplet at δ 3.08 for the α-methylene protons of the benzenesulfonyl group. In addition, the mass spectrum of 66 showed the expected parent peak at m/e 368.



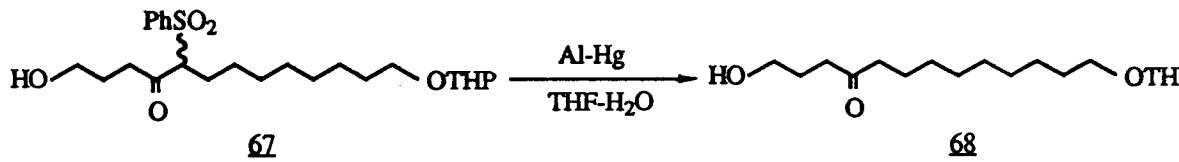
Having obtained the phenyl sulfone in high yield, we set out to perform the alkylation reaction again. The sulfone 66 was first treated with two equivalents of n-butyllithium to give the α,α-dilithio species which was then stablized with a small amount of HMPA and allowed to react with γ-butyrolactone. The reaction proceeded smoothly and rapidly to afford the γ-hydroxy ketone 67 in 81% yield.



66 67

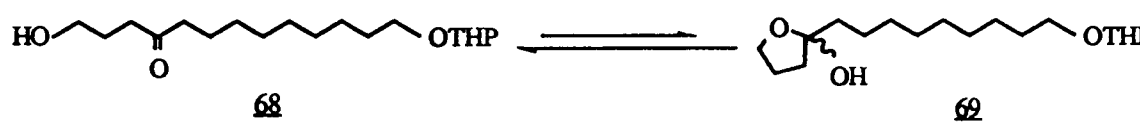
The IR spectrum of 67 showed absorptions at 3440 cm^{-1} and at 1720 cm^{-1}, indicating the presence of a hydroxyl and a carbonyl group respectively. In addition, the diastereotopic methylene protons, α to the carbonyl group, gave rise to two sets of triplets at δ 2.64-2.78 and δ 2.98-3.10 in the ^1H NMR spectrum of 67.

Reductive desulfonation of 67 to the hydroxy ketone 68 was smoothly accomplished in 79% yield by means of aluminum amalgam in refluxing aqueous tetrahydrofuran.[49] The ^1H NMR spectrum of 68 supported the desulfonated structure of this product.



67 68

The desulfonated product 68 exhibited two spots by tlc after purification. The less polar fraction was identified as the hemiketal 69 which was in equilibrium with the γ-hydroxy ketone 68. This equilibrium was not observed in compound 67, possibly due to the steric effect of the benzenesulfonyl group.

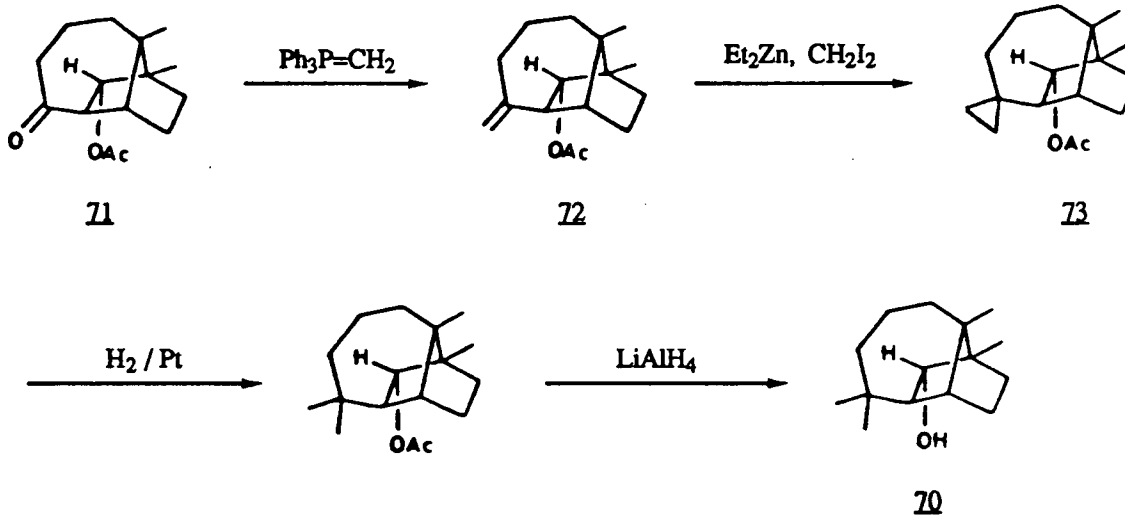


68 69

The presence of 69 was not expected to interfere with our synthetic scheme since differences in reactivity between the primary and tertiary alcohols or the carbonyl functionality could be used to shift the equilibrium to the desired acyclic form 68. However, reaction of 68 might proceed slowly due to the existence of the less reactive hemiketal 69. This was indeed found to be the case in subsequent steps.

With the carbon framework of the 14-membered lactone constructed, continuation of the synthesis next required the introduction of the geminal dimethyl group. The replacement of a ketone by two methyl groups is an attractive strategy and a number of methods for such a transformation have been reported.

One of the most popular methods uses a three-step sequence.[50,51] A Wittig olefination of a ketone produces an alkene which is then transformed into a cyclopropane via a Simmons-Smith reaction. The cyclopropane ring thus obtained can be hydrogenated to give a geminal dimethyl group. Money and co-workers[50] have reported this procedure in the synthesis of (+)-longiborneol (70). The ketone 71 was first treated with methylenetriphenylphosphorane to give the alkene 72 which was then subjected to the cyclopropanation reaction. Subsequent hydrogenation of the cyclopropane ring in 73 and reduction of the acetoxyl group furnished (+)-longiborneol (70).

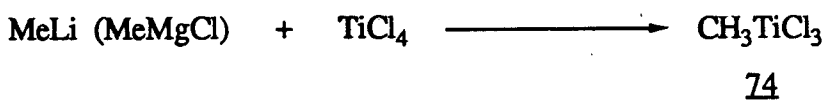


71 72 73

70

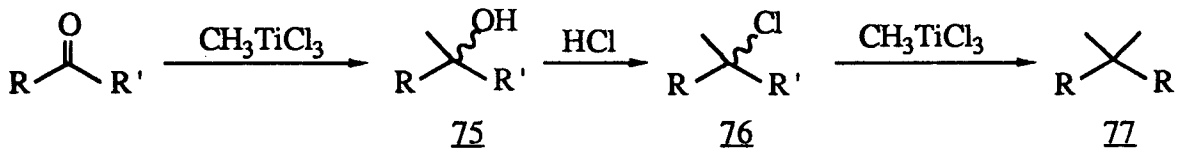
However, certain problems accompany the use of this procedure: (1) Wittig reactions are very sensitive to the steric environment around the carbonyl group undergoing reaction.[52] (2) The basic character of the ylide reagent is often incompatible with easily enolizable ketones.[53] (3) Cyclopropanation reactions frequently give low yields due to the interference of other functional groups with the cyclopropanating reagents.[54]

In 1980, Reetz et al.[55] reported a different approach to the preparation of a geminal dimethyl group from a carbonyl function. This method involved the use of methyltitanium trichloride (74) which was prepared quantitatively by treatment of methyllithium or methylmagnesium chloride with titanium tetrachloride.



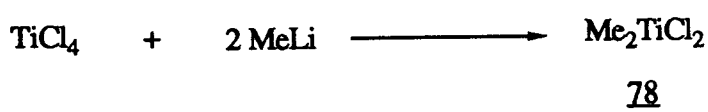
74

Methyltitanium trichloride (74) is a non-basic reagent and reacts chemo- and stereoselectively with carbonyl compounds. Thus, the reaction of the titanium reagent with a ketone produces a tertiary alcohol 75 which can be readily converted into the tertiary chloride 76. The addition of another equivalent of 74 produces the geminal dimethyl compound 77.

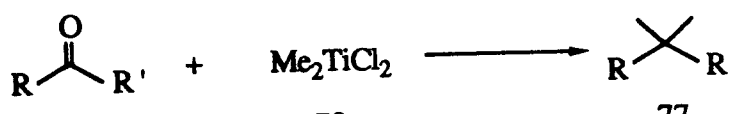


75 76 77

One year later, Reetz et al.[56] reported that dimethyltitaniumdichloride (78), from the reaction of titanium tetrachloride with two equivalents of methyllithium, exhaustively methylated ketones to form geminal dimethyl compounds 77.



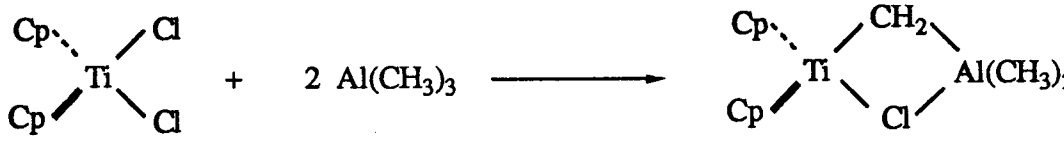
78



78 77

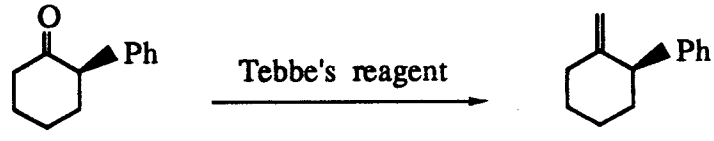
Interestingly, another titanium reagent 79 has also been reported capable of directly dimethylating a ketone. This reagent was first synthesized by Tebbe et al. in 1978[57] and has become known as Tebbe's reagent. It was prepared by treatment of titanocene dichloride (80)

with two equivalents of trimethylaluminum (81). The reagent was soon made commercially available due to its versatile applications in organic synthesis.



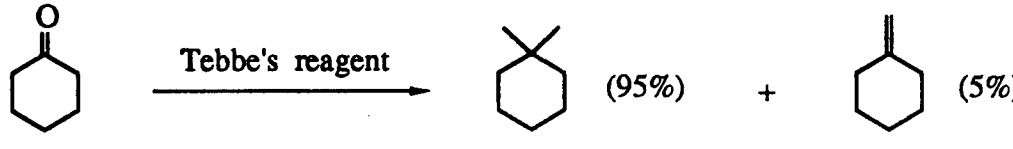
80 81 79

One of the most useful properties of Tebbe's reagent is its superiority in methylenating carbonyl compounds. It can methylenate aldehydes, ketones, and the carbonyl groups of carboxylic acid derivatives.[58] It does not appear to enolize ketones as Wittig reagents sometimes do. Thus, the optically active ketone 82 can be converted to the corresponding methylene product 83 in 93% yield without racemization.[58]



82 83

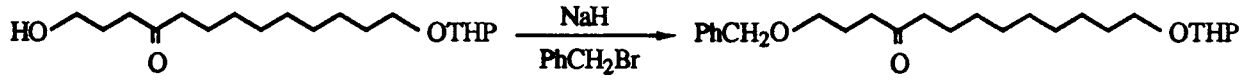
In 1983, Grubbs et al.[58] reported that the conversion of a ketone to a geminal dimethyl group could, in some cases, be achieved by using two equivalents of Tebbe's reagent. These authors cited a single example - this being the dimethylation of cyclohexanone 84. In this reaction, a small amount of methylenated product 85 was also isolated.[58]



84 85

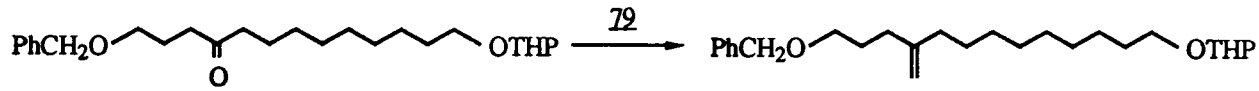
In light of these results, it seemed worthwhile to investigate the use of the titanium reagents in our synthesis. We first chose to explore the possibility of direct dimethylation of

our molecule using Tebbe's reagent. Thus, the hydroxyl group in compound 68 was first benzylated to give the keto compound 86 in 75% yield.



68 86

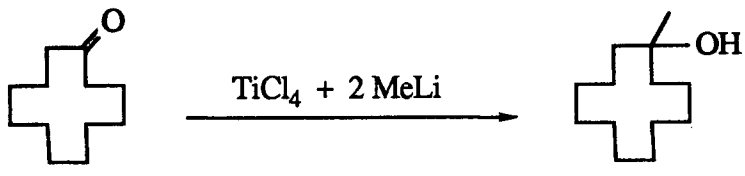
When the keto compound 86 was treated with 2.4 equivalents of Tebbe's reagent using Grubbs' procedure,[58] only the methylenated product 87 was isolated. Attempts to effect the dimethylation reaction were then carried out with varying equivalents of Tebbe's reagents using different reaction conditions. Unfortunately, in no case was any dimethylated product detected. However, the methylenation reaction did proceed rapidly in yields of greater than 80%.



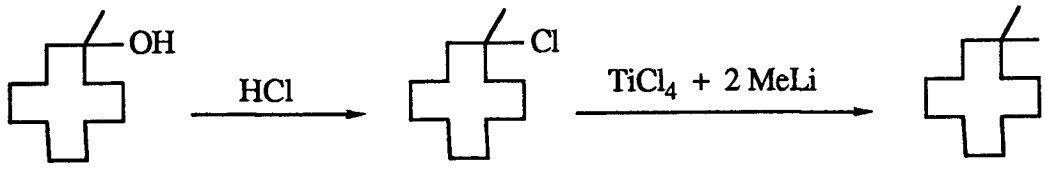
86 87

Although Tebbe's reagent proved to be a powerful methylenating reagent in our studies, its high cost detracted from its use in a large scale synthesis. Our attention next turned to the reagent described by Reetz and co-workers.[56]

Titanium tetrachloride was treated with two equivalents of methyllithium according to Reetz's procedure.[56] The resulting titanium reagent was then allowed to react with one-half equivalent of cyclododecanone (88) which was used as a model. The reaction proceeded smoothly to give 1-methylcyclododecanol (89) instead of the desired 1,1-dimethylcyclododecane (90). Efforts to effect the direct dimethylation reaction under a variety of conditions again proved to be fruitless. However, the dimethylated product 90 was obtained by conversion of the tertiary alcohol 89 into the chloride 91 and subsequent treatment of 91 with the titanium reagent again.



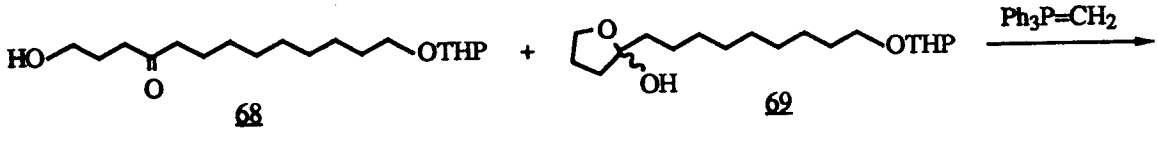
88 89



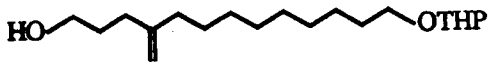
89 91 90

The strong acidic conditions required for the conversion of 89 to 91 and its low yield presumably due to the competing dehydration reaction also made this route impractical in our synthesis. This method was, therefore, abandoned.

The failure of direct dimethylation with titanium reagents led us to return to the more classical procedures of converting a ketone group into a geminal dimethyl group. The first step was a Wittig olefination reaction. Thus, the γ-hydroxy ketone 68 and its cyclic form 69 were allowed to react with three equivalents of methylenetriphenylphosphorane. As expected, the reaction proceeded slowly due to the presence of the unreactive hemiketal 69. However, a prolonged reaction time of 80 h gave the alkene 92 in 80% yield. The absence of the carbonyl absorption and appearance of an olefinic absorption at 1644 cm^{-1} in the IR spectrum of compound 92 indicated a successful Wittig reaction. The absorption at δ 4.75 in its ^1H NMR spectrum was ascribed to the terminal vinyl protons.

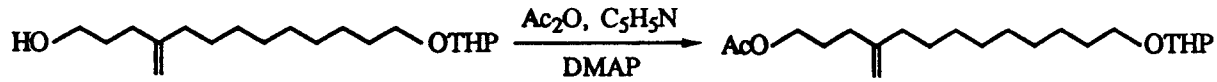


68 69



92

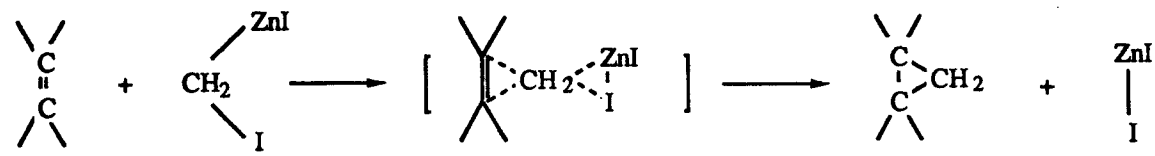
At this stage, it was necessary to protect the hydroxyl group in compound 92. An acetate protecting group was chosen, since it would survive the subsequent oxidation reaction. Treatment of the alcohol 92 with acetic anhydride and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) gave the desired ester 93 in 94% yield.



92 93

The IR spectrum of 93 showed a carbonyl stretching band at 1743 cm^{-1}. The ^1H NMR spectrum of 93 exhibited a sharp singlet at δ 2.08 attributed to the methyl protons of the acetate and a triplet at δ 4.08 ascribable to the methylene protons α to the acetoxyl group. In addition, the mass spectrum of 93 showed a molecular ion peak at m/e 354.

The next step in the synthesis was to convert the alkene into a cyclopropyl ring. One of the first effective syntheses of a cyclopropane unit from an alkene was performed in 1958 by Simmons and Smith[59] who treated an olefin with methylene iodide in the presence of zinc-copper couple. These authors proposed that methylene iodide reacted with zinc-copper to form an intermediate iodomethylzinc iodide (94), the carbon atom of which was electrophilic and thus attacked the double bond to give cyclopropane 96 through the transition state 95.[59]

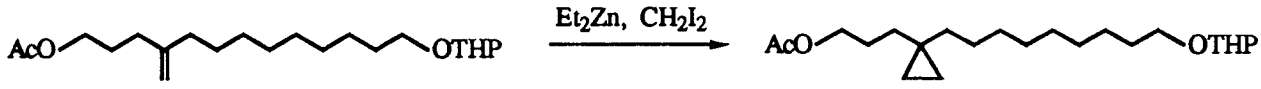


94 95 96

In 1968, Furukawa and co-workers[60] published a paper concerning the cyclopropanation of alkenes using diethylzinc and methylene iodide. These authors showed that cyclopropanes could be obtained more easily with this new cyclopropanating reagent. Since

then, the Furukawa modification of the Simmons-Smith cyclopropanation procedure has been used in organic synthesis with considerable success.[61]

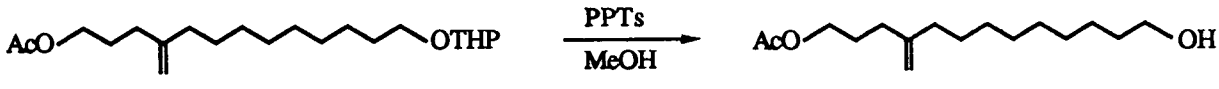
When the olefin 93 was heated with diethylzinc-methylene iodide in toluene at 60 °C , the corresponding cyclopropane compound 97 was produced, but in low yield (about 25-30%). Capillary glc analysis of the crude reaction mixture indicated the presence of more polar by-products. Although these by-products were not isolated and characterized, it seemed likely that they were formed by reaction of the tetrahydropyranyl ether in compound 93 with the cyclopropanating reagents.



93 97

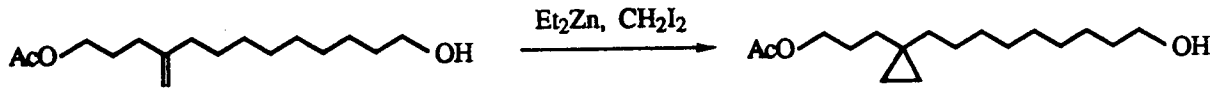
Clearly, the low yield of this reaction warranted alternative plans for the preparation of compound 97. Specifically, it was felt that the alcohol 98 obtained by the cleavage of the tetrahydropyranyl ether in 93 might be a better substrate for the cyclopropanation reaction.

Treatment of 93 with pyridium p-toluenesulfonate afforded the hydroxy alkene 98 in 90% yield.



93 98

When the hydroxy olefin 98 was subjected to the modified Simmons-Smith reaction, the corresponding cyclopropyl compound 99 was produced in 41% yield. This yield was higher than the one obtained earlier, but still left much to be desired.



98 99

At this point, we were encouraged by the improved yield and decided to investigate the reaction by further modifying the substrate by protecting the alcohol 98 as a tert-butyldimethylsilyl (TBDMS) ether.

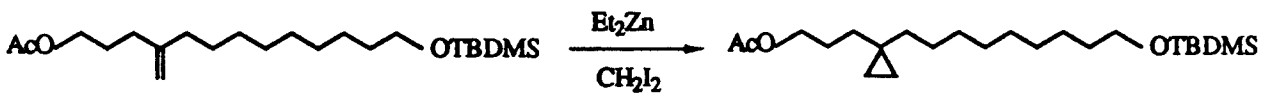
Silyl ether derivatives of alcohols have a number of useful properties. The volatility of trimethylsilyl ethers makes them suitable for separation and structure elucidation by a combination of gas chromatography and mass spectrometry.[62] On the other hand, their lability to mild conditions limits their use as protecting groups.[63] However, the stability of TBDMS ethers to a wide range of reaction conditions makes them particularly effective protecting groups for the hydroxyl function.[64] This stability results from the fact that most of their reactions proceed by nucleophilic attack at silicon, which is, therefore, sensitive to steric hindrance.

Reaction of the alcohol 98 with triethylamine (TEA), tert-butyldimethylsilyl chloride and a catalytic amount of 4-dimethylaminopyridine gave the silyl ether 100 in 95% yield.

98 100

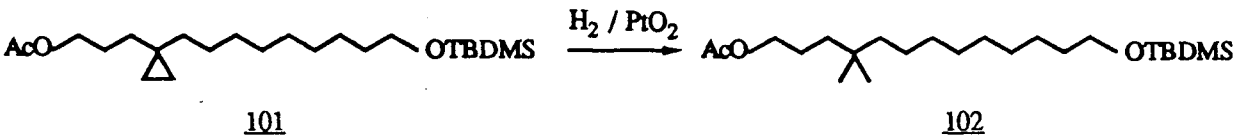
The ^{1}H NMR spectrum of compound 100 exhibited a six-proton singlet at δ 0.06 due to the silyl methyl protons, while a second singlet ascribable to the tert-butyl methyl protons appeared at δ 0.90.

To our satisfaction, the cyclopropanation reaction of the silyl ether alkene 100 proceeded cleanly, under the conditions used earlier, to give the cyclopropyl compound 101 in 88% yield. The IR spectrum of 101 showed a cyclopropyl-hydrogen stretching absorption at 3065 cm^{-1}. In addition, the cyclopropyl protons of 101 gave rise to a doublet at δ 0.22 in the ^{1}H NMR spectrum.

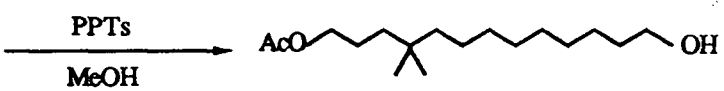


100 101

Hydrogenolysis of the least hindered cyclopropyl bond[65] of compound 101 was accomplished by treatment of a solution of 101 in glacial acetic acid with a catalytic amount of platinum oxide under hydrogen. The geminal dimethyl silyl ether 102 thus produced (in 79% yield) was hydrolyzed to the corresponding alcohol 103 in 87% yield by treatment of 102 with pyridinium p-toluenesulfonate.



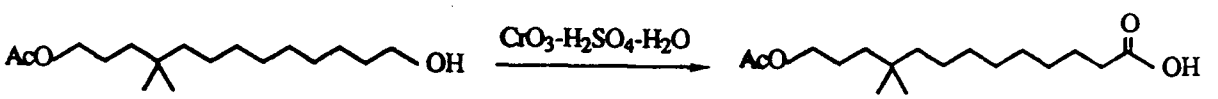
101 102



103

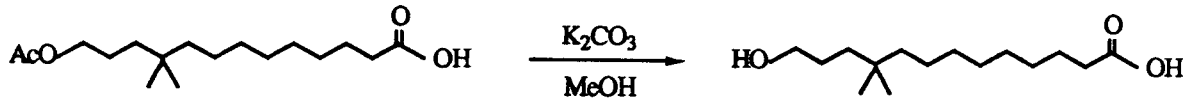
The IR spectrum of 103 showed a hydroxyl absorption at 3560-3204 cm^{-1}. The ^1H NMR spectrum exhibited a sharp singlet at δ 0.84 which was attributed to the six protons of the geminal dimethyl group in the molecule.

The next two steps in the synthesis were rather straightforward. Oxidation[66] of alcohol 103 gave the carboxylic acid 104 in 77% yield. The IR spectrum of 104 showed the acid absorptions at 3480-3014 cm^{-1} and 1712 cm^{-1}. In addition, the ^1H NMR spectrum of 104 exhibited a triplet at δ 2.36 which was ascribable to the α-methylene protons of the carboxylic acid function.



103 104

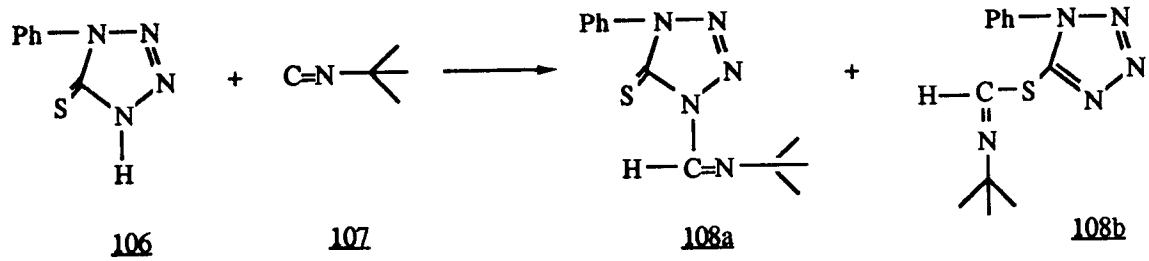
The acetate protecting group in compound 104 was hydrolyzed with potassium carbonate in methanol. The ω-hydroxy acid 105 thus produced (in 98% yield) was highly pure and was carried directly to the lactonization reaction.



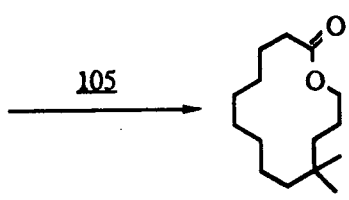
104 105

With ample quantities of the hydroxy acid 105 in hand, we were ready to perform the final cyclization step in our synthesis. The literature records an extensive list of methods for effecting the lactonizations of hydroxy acids, and many of these have been discussed in the Introduction. Among the several existing methods, Schmidt and Dietsche's procedure has proven reliable.[27] Our lactonization reaction was therefore carried out using this procedure.

Treatment of 1-phenyl-2-tetrazoline-5-thione (106) with one equivalent of tert-butylisocyanide (107) in toluene at room temperature gave compound 108a and 108b which upon addition of 0.8 equivalent of the ω-hydroxy acid 105 afforded the 14-membered lactone 42 in 66% yield.



106 107 108a 108b



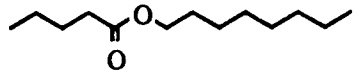
42

The IR spectrum of macrolide 42 showed a lactone carbonyl absorption at 1718 cm^{-1}. The ^1H NMR spectrum of 42 was readily assignable. The six methyl protons gave rise to a sharp

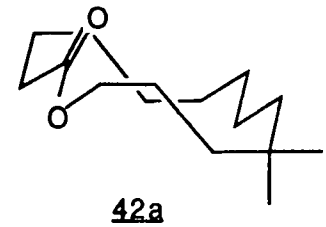
singlet at δ 0.84. The α-methylene protons of the lactone oxygen and the α-methylene protons of the carbonyl group resulted in two sets of multiplets at δ 4.18 and δ 2.40 respectively. In addition, the mass spectrum exhibited a molecular ion peak at m/e 240. Thus, the synthesis of 10,10-dimethyltridecanolide (42) was completed.

2.2 Hydrolysis of 10,10-Dimethyltridecanolide (42), Tridecanolide (35) and n-Octyl Pentanoate (109)

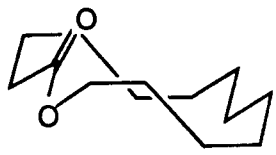
To investigate the conformational behavior of the macrolide synthesized in this project, the hydrolysis of 10,10-dimethyltridecanolide (42), tridecanolide (35) and n-octyl pentanoate (109) was performed. From simple conformational analyses, macrolide 42 was expected to exist predominantly in conformation 42a. On the other hand, tridecanolide (35) was known to exist as a mixture of conformers 35a, 35b and 35c in nearly equal amounts.[44]



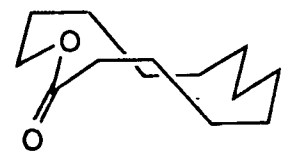
109



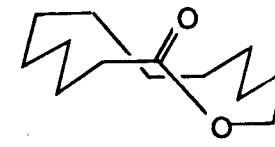
42a



35a



35b



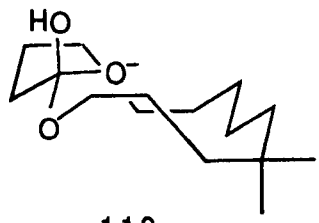
35c

Examination of the environments surrounding the lactone functionality in each of the above conformations revealed that 42a and 35a directed the lactone carbonyl towards the sterically more hindered interior of the ring.

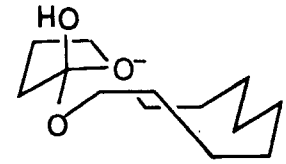
Consideration of the steric interactions of the tetrahedral intermediates in the base catalyzed hydrolysis reaction led to an initial prediction that hydrolysis of conformers 42a and 35a would be slower than that of conformer 35b or 35c. Since macrolide 35 exists as a mixture of 35a, 35b and 35c, it should hydrolyze faster than macrolide 42 which exists predominantly in conformation 42a.

The intermediates involved in the hydrolysis of 42a and 35a are 110 and 111 where the oxyanion is forced into a sterically crowded environment. The intermediates encountered in the

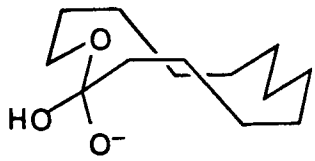
hydrolysis of 35b and 35c (112 and 113 respectively) are less steric hindered. All of these intermediates are assumed to maintain the [3434] ring conformations of the starting materials.



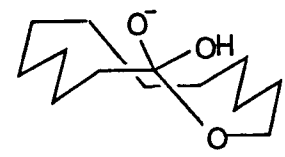
110



111



112

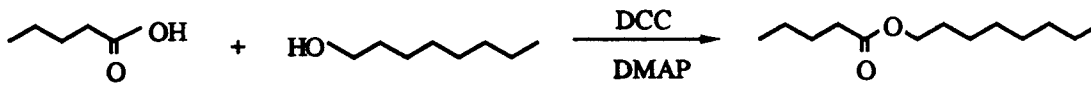


113

In addition to studying the hydrolysis of macrolides 42 and 35, the hydrolysis of a 13-carbon ester was also conducted. It was expected that the ester would hydrolyze faster than either of the macrolides.

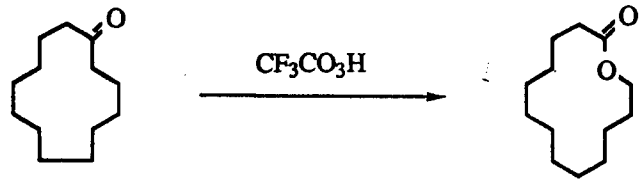
The synthesis of macrolide 42 has been detailed in Section 2.1. The other two compounds used for hydrolysis studies were prepared as follows:

Ester 109 was prepared by treatment of 1-octanol (114) and valeric acid (115) with dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP). The esterification reaction proceeded smoothly to give the desired product 109 in 94% yield.



115 114 109

Macrolide 35 was synthesized using a modified Baeyer Villiger reaction.[67] Treatment of cyclotridecanone (116) with peroxytrifluoroacetic acid gave the desired product 35 in 67% yield.



116 35

Hydrolysis of macrolides 42 and 35, and ester 109 with potassium carbonate in methanol was first carried out at room temperature. The relative rates of hydrolysis were determined by monitoring a reaction mixture which contained the hydrocarbon dodecane as an internal standard and following the disappearance of the ester and the macrolides by gas-liquid chromatography (glc). The data obtained from this reaction are plotted in Figure 6 as relative intensities of the hydrolysis compounds to the internal standard versus reaction time.

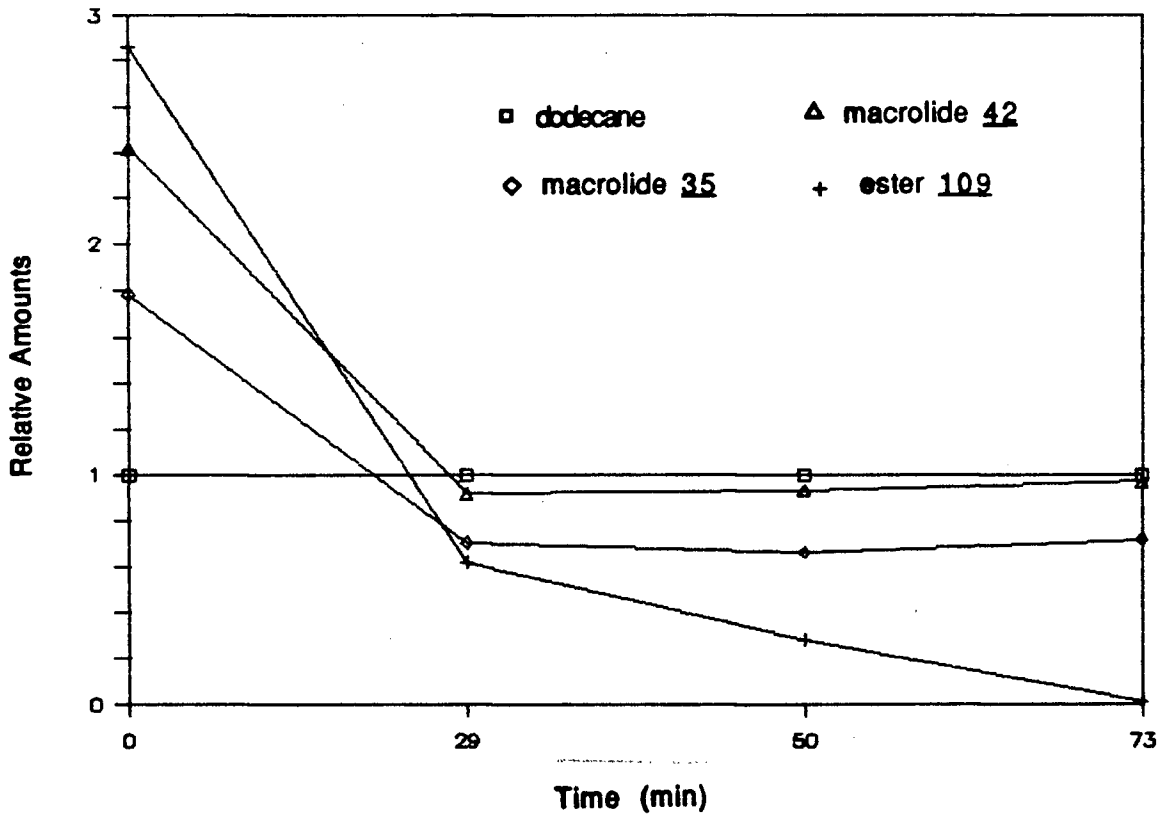


Figure 6. Plot of the rates of the hydrolysis of 42, 35 and 109 at room temperature.

Figure 6 shows that ester 109 hydrolyzed faster than the macrolides under these conditions. This result could be explained in terms of the steric hindrance of the intermediates involved in the reaction. Attack on the macrolides by the hydroxyl anion would force the oxyanion into a sterically crowded environment regardless of their conformations. On the other hand, attack on a long-chain ester by the hydroxyl anion would be free of any steric interaction. One would therefore anticipate a much more rapid hydrolysis of the ester than the macrolides.

However, the observation that both macrolides hydrolyzed at the same rate was surprising. If macrolide 42 existed in a single [3434] conformation 42a and the hydrolysis of these macrolides proceeded through intermediates maintaining the [3434] conformations, macrolide 42 should hydrolyze more slowly than macrolide 35. Hydrolysis of macrolides 42 and 35, and ester 109 at low temperatures (0 °C and -20 °C) also gave similar results to those shown in Figure 6.

To interpret the hydrolysis results and understand the conformational preferences of macrolide 42 from a theoretical point of view, we next undertook the molecular mechanics (MM2) calculations[38,39] of conformations for macrolide 42.

2.3 Molecular Mechanics Calculations of Conformations for 10,10-Dimethyltridecanolide (42)

One of the goals of this project was to construct and investigate a 14-membered macrolide which should exist predominantly in one conformation. The structural requirements we used to predict a single conformation for macrolide 42 were the preference for a planar s-trans lactone linkage and the occupation of a geminal dimethyl group at the corner position in the [3434] conformation of the 14-membered lactone.

Our theoretical approach to studying the conformational preferences of this system was to calculate the steric energies of all likely conformations of macrolide 42 and from these energies to determine their approximate Boltzmann distributions. The calculation of these conformational energies was performed using the molecular mechanics (MM2) program.[38,39]

Molecular mechanics calculations have been gaining popularity in the past few years as researchers try to interpret their results and formulate synthetic plans based on conformational analyses. The MM2 program was introduced by Allinger and co-workers[38,39] as an alternative to the complicated ab initio molecular orbital (MO) methods of calculating molecular energies. The energies calculated by the MM2 program are based on classical mechanics in which the equations used to calculate the energies are parameterized to best fit the experimental data. Molecules are represented as though constructed from balls and springs with a series of potential energy functions to express the "steric" energy of a molecule.

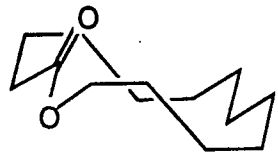
The "steric" energy of a molecule is the sum of five different energies. The first energy term is associated with bond stretching which the MM2 program treats as a modified Hooke's law equation. The remaining four terms include angle bending, torsional strain, dipole and Van der Waals interactions.

To calculate the minimum energy conformation of a molecule, the MM2 program employs the steepest-descent method. A likely conformation of a molecule is first constructed using molecular models and its approximate co-ordinates are determined. These are provided as an

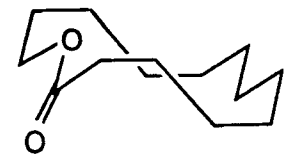
input file to the MM2 computer program and the steric energy is calculated from this given set of co-ordinates. The computer then moves one atom to a new set of co-ordinates and recalculates the energy. If the atom movement results in a lower energy, then the atom is further moved in the same direction until the energy difference is less than or equal to a preset value. Although this process has been described using a single atom, in fact, every atom within the molecule is simultaneously subjected to this movement-calculation sequence until the energy of the system is minimized.

The resulting steric energy of a certain conformation is an energy relative to a hypothetical, strain-free, reference system. The difference in energy between conformations of a molecule is given by direct comparison of the calculated steric energies. However, if a comparison between different molecules is required, steric energies should not be used; an alternative for this type of comparison is to use the heats of formation, which can also be calculated by the MM2 program.

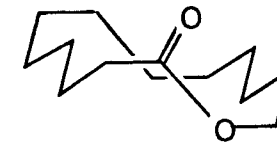
The conformations of macrolide 42 to be investigated arose from the conformational analyses of simple 14-membered lactones. As described previously, the low-energy conformations for tridecanolide (35) are 35a, 35b and 35c.[44] These three conformers were taken as the basic framework to generate conformers 42a, 42b and 42c for macrolide 42. Their relative steric energies were determined by MM2 calculations. In addition, the relative steric energy of conformer 42d which had a geminal dimethyl group at the corner position but a lactone linkage at a position different from that of conformer 42a was also calculated.



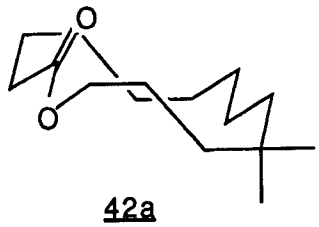
35a



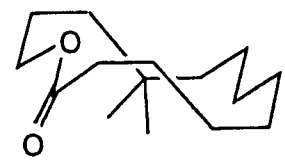
35b



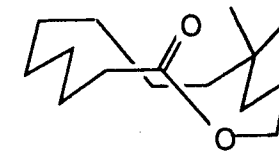
35c



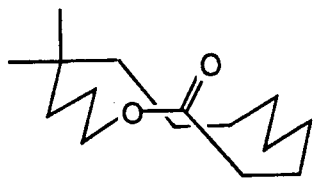
42a



42b



42c



42d

Figure 7 shows the computer plots of the side and top views of conformations 42a, 42b, 42c and 42d, and their relative steric energies.

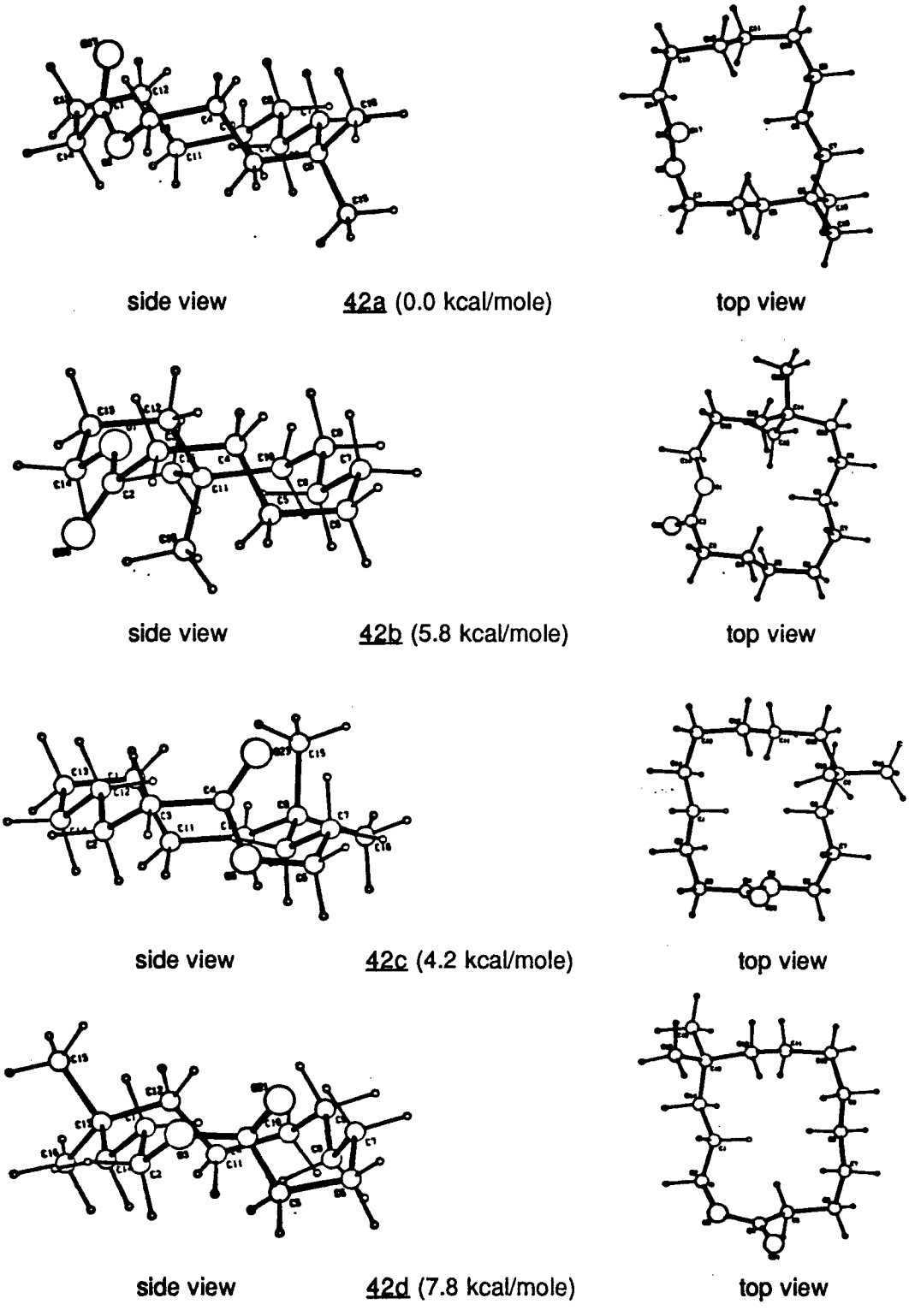


Figure 7. Computer plots of the [3434] conformations for macrolide 42.

MM2 calculations showed that the energy of conformer 42a was the lowest. Accordingly, the steric interactions in this conformation should be the least. This was in agreement with our simple conformational analysis. The non-corner geminal dimethyl groups in 42b and 42c introduced steric interaction in the rings and therefore raised their steric energies. Conformer 42b had a higher energy than conformer 42c. This was due to the fact that the dimethyl group in 42b was at a sterically more hindered position. As expected, conformer 42d, containing the s-cis lactone linkage, was destabilized and resulted in a relatively high energy state.

Although the diagrams shown in Figure 7 demonstrated the [3434] character of the conformations and their structures, it was difficult to recognize the symmetry of the conformations or to easily compare one conformation with another. It was also difficult to determine if any deviation from the ideal [3434] conformation had occurred. Fortunately, these difficulties could be solved through the use of polar maps.[68]

A polar map is a circular graph which plotting the sign and magnitude of the internal torsional angles of a ring vs. the bonds along which they are found. The concentric circles of a polar map represent values of the torsional angle in $\pm$ 60° increments and the straight lines which intersect the circles are the bonds (numbers 1-14) where the torsional angle is formed (Figure 8). Accordingly, a 14-membered ring produces 14 data points on a polar map. These points, when connected, generate a "star pattern" representing the conformation.

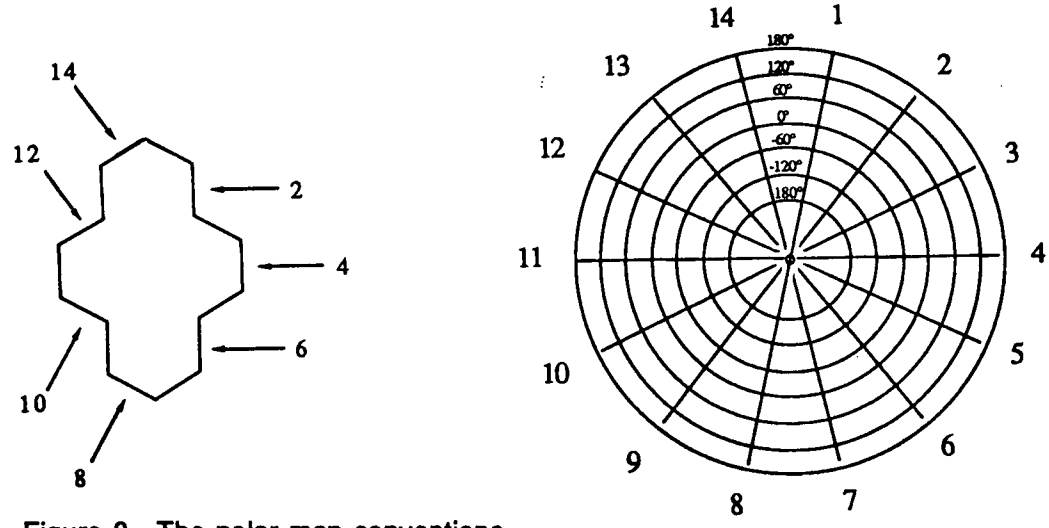


Figure 8. The polar map conventions.

The value of polar maps is that the complete set of torsional angles formed by the ring atoms will always uniquely define the conformation. The torsional angles may be obtained from MM2 calculations, from X-ray data or from an inspection of a molecular model. Recent developments in the determination of the signs of torsional angles have also enhanced the general use of polar maps.[35,69]

The polar map of the [3434] conformation of cyclotetradecane is shown in Figure 9. The polar map clearly illustrates the C_2 rotation axis through bonds 4 and 11. In addition, the patterns of the polar map can be used to quickly indicate the presence and location of corner atoms within a conformation by recognizing the corner's characteristic anti-gauche-gauche-anti sequence of torsional angles.[35] The position of the corner atoms on the conformations and polar maps are marked with an asterisk.

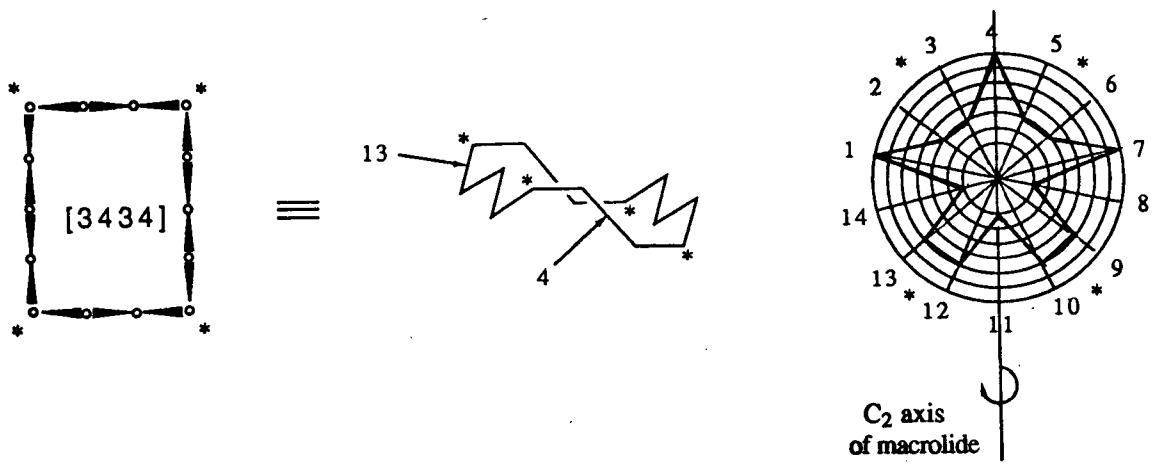


Figure 9. The [3434] conformation of cyclotetradecane and the polar map of its torsional angles.

With the aid of polar maps, conformations can be unambiguously identified and examined. This is facilitated if the ideal conformation, for example, the ideal [3434] conformation, is simultaneously plotted on the same map with the one under examination. The polar maps of the four conformations determined by MM2 calculations (Figure 7) are given in Figure 10 which also shows the ideal [3434] conformation in broken lines.

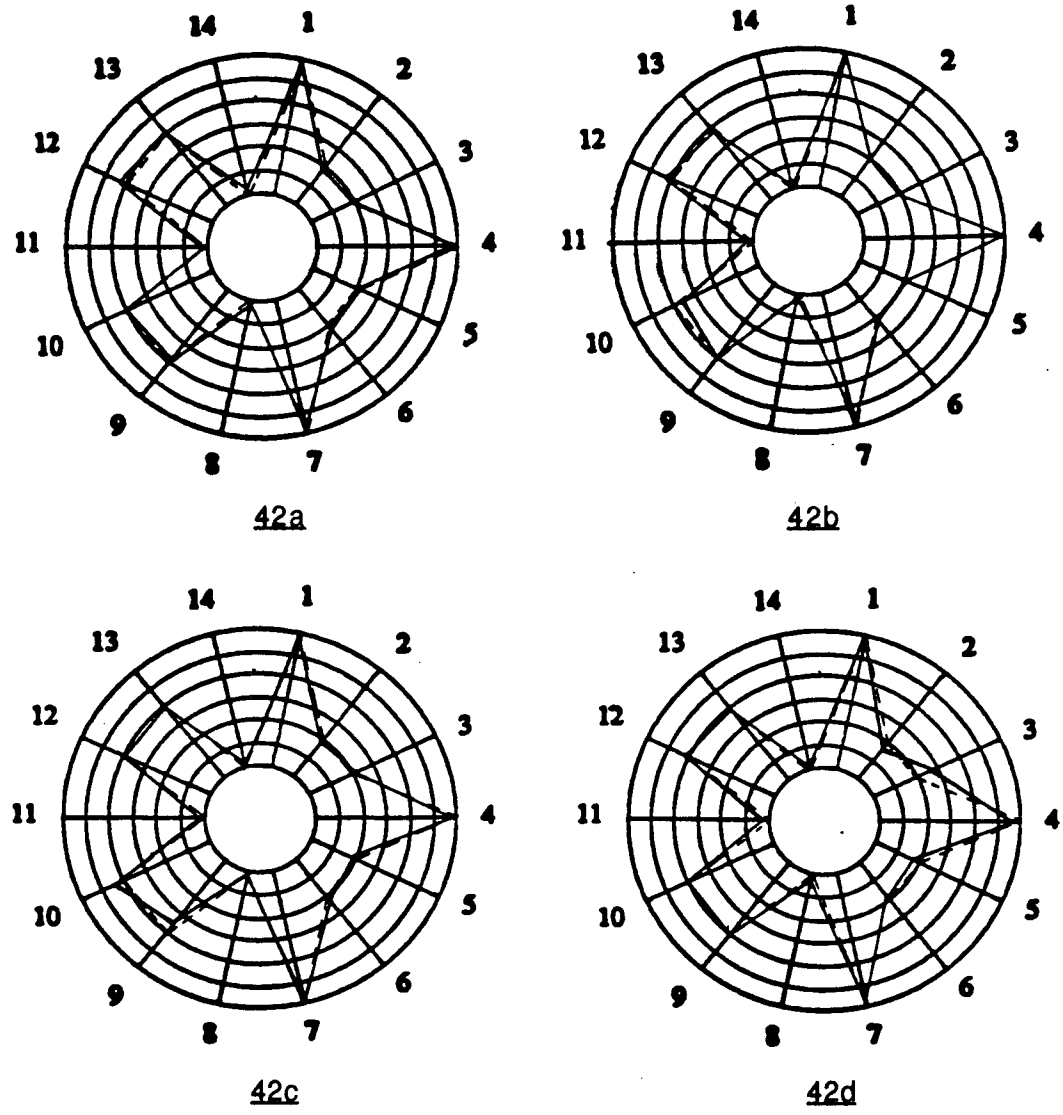


Figure 10. Superposition of the polar maps of the ideal [3434] conformation (broken lines) and the [3434] conformations of macrolide 42.

The polar maps in Figure 10 show that conformer 42a closely approximated the ideal [3434] conformation. This was in agreement with our prediction that a geminal dimethyl group at the corner position would not introduce severe transannular interactions into the ring and would therefore not significantly distort the [3434] ring framework.

On the other hand, the polar maps of conformers 42b and 42c showed a small but significant deviation from the ideal [3434] conformation at bonds 10 and 9, respectively. These are the bonds that contain the non-corner dimethyl substituted carbon. The steric hindrance introduced by the dimethyl group has forced the ring to change its conformation. It is interesting to note that the strain appears to be concentrated at a few bonds rather than distributes over many bonds and the main portion of the ring still adheres to the [3434] framework. Similarly, the main portion of the ring is [3434] like for conformer 42d with deviation occurring at bond 3 which contains the s-cis lactone group.

Early in our project, we were only concerned with the [3434] conformations for macrolide 42. However, recent work in our laboratory revealed several other low-energy conformations for certain macrolides.[35,36] Among them were two non-diamond lattice conformations described by Dale.[32]

In his pioneering work on conformations of cyclic alkanes, Dale considered only those ring conformations which were superimposable on a diamond lattice. However, calculations on cyclotetradecane later revealed two low-energy conformations which were not diamond lattice superimposable. These were designated the [3344] (1.1 kcal/mole higher than the [3434] base) and [3335] (2.2 kcal/mole) conformations (Figure 11).[32] These conformations were found to be lower in energy than every diamond lattice conformation with the exception of the [3434] arrangement (base value of 0.0 kcal/mole). The position of the corner atoms of the conformations in Figure 11 is marked with an asterisk.

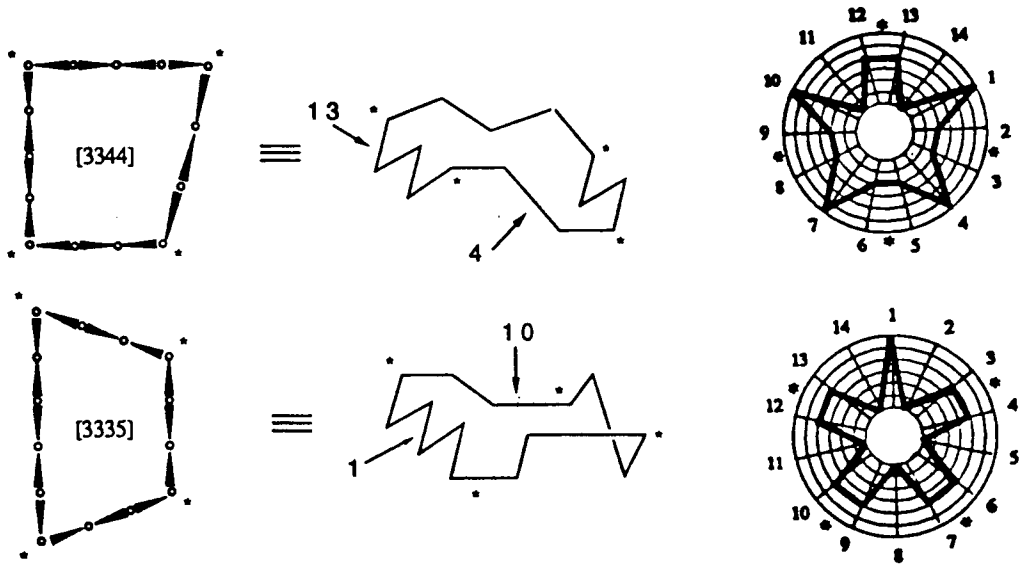
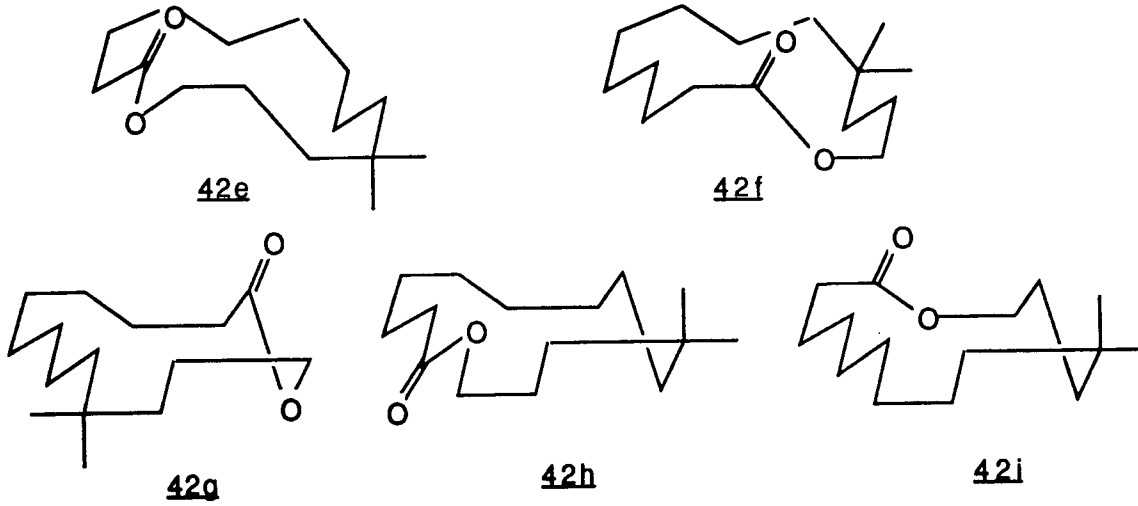
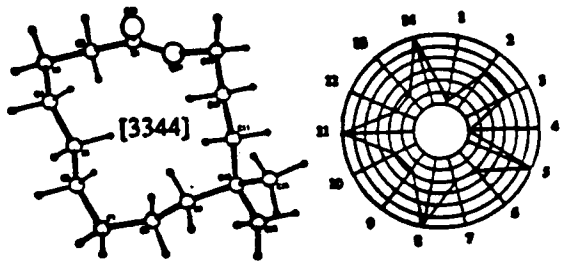


Figure 11. The [3344] and [3335] conformations of cyclotetradecane and their polar maps.

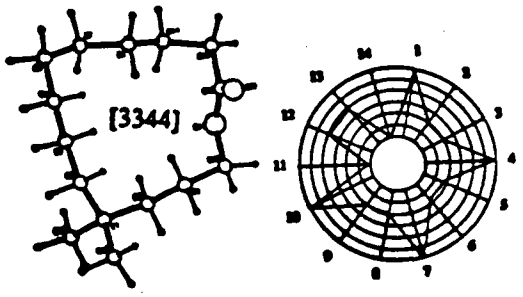
We were prompted to investigate these two conformations for macrolide 42 by MM2 calculations and we restricted our calculations to those conformations containing an s-trans lactone linkage and a geminal dimethyl group at the corner position. Since the [3344] and [3335] arrangements were less symmetric than the [3434], two [3344] conformations 42e and 42f, and three [3335] conformations 42g, 42h and 42i were possible for macrolide 42. Their calculated steric energies relative to 42a, computer plots and polar maps are given in Figure 12.





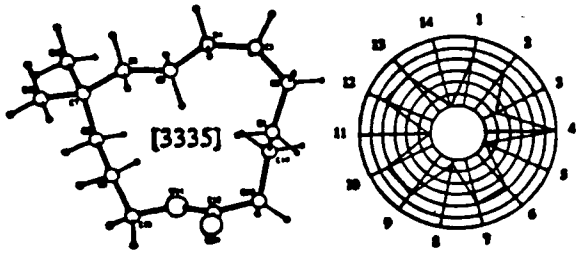
top view polar map

42e (1.2 kcal/mole)



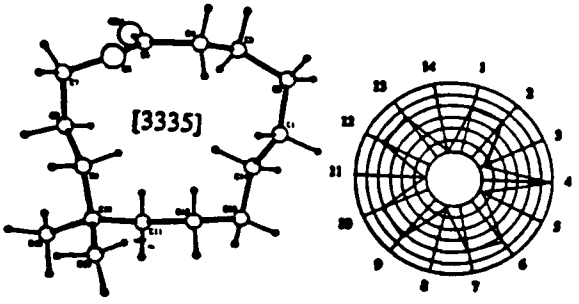
top view polar map

42f (1.3 kcal/mole)



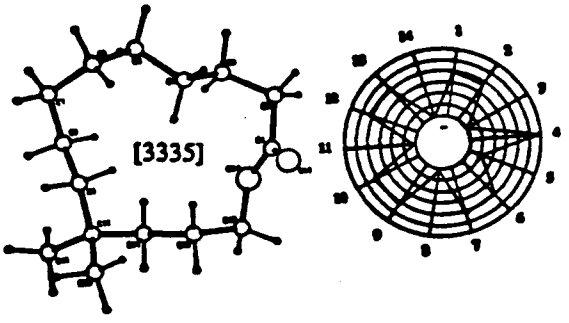
top view polar map

42g (1.9 kcal/mole)



top view polar map

42h (4.8 kcal/mole)



top view polar map

42i (3.5 kcal/mole)

Figure 12. Computer plots and polar maps of the [3344] and [3335] conformations for macrolide 42 (relative steric energy in kcal/mole).

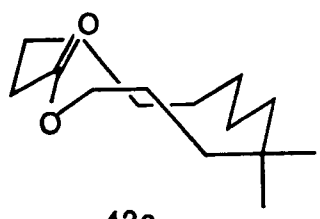
With the steric energies of all likely conformations calculated, the proportions of different conformations for macrolide 42 could now be estimated using the Boltzmann distribution equation. For two isomers A and B in equilibrium, the equilibrium constant K (the ratio of the number of A molecules, N_A, to the number of B molecules, N_B) is given by equation 1. E_A and E_B are the energies of two isomers, R is the gas constant and T is the absolute temperature.

$$K = \frac{N_A}{N_B} = \exp\left[- \frac{(E_A - E_B)}{RT} \right] \qquad (1)$$

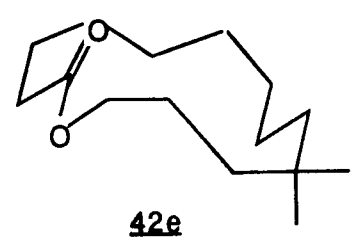
Using the calculated relative steric energies of the above conformations, an estimate of their distribution can be obtained. For example, consider conformers 42a and 42c at 25 °C, equation 1 becomes

$$\frac{N_{42a}}{N_{42c}} = \exp\left[- \frac{(0.0 - 4.2) \times 10^3 \text{ cal/mole}}{1.986 \text{ cal/K mole} \times 298 \text{ K}} \right] = 1.2 \times 10^3$$

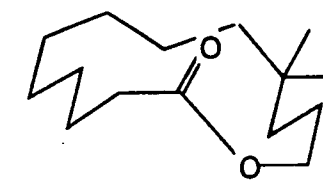
Conformation 42c is not significantly populated at room temperature and for practical purposes it can be ignored. Similarly, conformations 42b, 42d, 42g, 42h and 42i need not be considered as possible conformers for macrolide 42. Our attention could therefore be concentrated on one [3434] conformation 42a and two [3344] conformations 42e and 42f. The Boltzmann distribution of these conformations is; 42a : 42e : 42f = 80 : 11 : 9. Accordingly, macrolide 42a should exist as a mixture of these three conformations.



42a



42e



42f

Among these three conformations 42e is identical with 42a in the region of the molecule containing the lactone functionality. The chemistry of 42e should be similar to that of 42a and it would be sufficient to describe macrolide 42 in terms of conformations 42a and 42f.

The lactone groups of 42a and 42f are in different environments. Conformer 42a has the lactone carbonyl group directed toward a sterically more hindered ring interior than conformer 42f. The tetrahedral intermediate from hydrolysis of 42f should be sterically less hindered than that of 42a and the hydrolysis of 42f should therefore be faster than 42a.

The results of the hydrolysis studies could now be interpreted. A possible explanation for our observation of the similar rates of the hydrolysis of the two macrolides is that the [3434] ring conformations were not maintained in the hydrolysis intermediates. The steric hindrance introduced by the hydrolysis intermediates may have led to a change of the [3434] conformation such that the difference of the lactone carbonyl environment in the ground state conformations was not reflected in the reaction.

Another explanation for the hydrolysis studies is that macrolide 42 exists as an equilibrium mixture of conformations 42a/e and 42f. The rates of conformational change between these conformers are much faster than that of the hydrolysis reaction and conformer 42f is expected to hydrolyze more easily than conformer 42a. According to the Curtin-Hammett principle,[70] the ratio of the conformations of macrolide 42 would not be reflected in the hydrolysis process. From Le Chatelier's principle, the selective hydrolysis of conformer 42f would shift the equilibrium from conformer 42a to 42f. Therefore the minor conformer 42f was the one that controlled the hydrolysis process and not the predominant conformer 42a. Consequently, the hydrolysis of macrolide 42 was observed to be faster than expected in comparison to macrolide 35.

2.4 Conclusion

The synthesis of 10,10-dimethyltridecanolide (42) was accomplished via a fifteen-step sequence in 9% overall yield. During the synthesis, it was found that direct Grignard attack of γ-butyrolactone failed to produce the corresponding γ-hydroxy ketone. However, this was solved by the use of sulfone chemistry. Conversion of the keto functionality into a geminal dimethyl group in our molecule was achieved by a three-step sequence (Wittig olefination, Simmons-Smith reaction and hydrogenation).

MM2 studies confirmed the conformational analysis that macrolide 42 should exist predominantly in the [3434] conformation 42a which possessed a planar s-trans lactone linkage and the geminal dimethyl group at a corner position. However, more importantly, MM2 studies also revealed the existence of a [3344] conformation 42f which evidently was controlling the rate of hydrolysis of macrolide 42.

In the beginning, we restricted the conformational analysis to the [3434] conformation. But during this project, it was found that the [3434] conformation was not sufficient to explain the hydrolysis results. Base catalysed hydrolysis of macrolides 42 and 35 appears complex for detailed conformational analysis. It can be expected that further elaboration of the lactone ring, for example, introduction of additional geminal dimethyl groups, should favour the existence of only one conformation and therefore simplify conformational analysis.

Obviously, there is much work that can and should be done on constructions of 14-membered lactones with defined conformation(s) and on chemical reactions of such macrolides. Ultimately, the conformational behavior of 14-membered lactones could culminate in the total synthesis of the macrolide antibiotics and the application of conformational control in synthetic chemistry as a whole.

CHAPTER THREE

Experimental

General

Solvents, reagents and equipment setup. Solvents were dried as follows: diethyl ether (ether), benzene, toluene and tetrahydrofuran (THF) were distilled into a collecting reservoir by heating at reflux over sodium benzophenone ketyl radical under a dry nitrogen (N_2) atmosphere. Methylene chloride (CH_2Cl_2) and triethylamine (TEA) were distilled from calcium hydride and methanol (MeOH) from magnesium methoxide. Using an oven dried syringe, an anhydrous solvent was removed through a stopcock fitted on the reservoir.

Unless otherwise specified, all reagents were supplied by the Aldrich Chemical Company and used without further purification. Bottles of n-butyllithium (in hexanes) and diethylzinc (in toluene) were equipped with used glc gas port septa wedged between the Sure/Seal crown and the twist cap. In this way, they were stored with no significant changes in molarity for up to nine months. n-Butyllithium was standardized by titration against 2,2-diphenylacetic acid in THF at room temperature to the faintest appearance of a yellow color.

Acetic anhydride and 3,4-dihydro-2H-pyran were distilled over calcium hydride. γ-Butyrolactone, pyridine, and hexamethylphosphoramide (HMPA) were distilled under reduced pressure from calcium hydride and stored over molecular sieves (3 °A). Methylene iodide was distilled under reduced pressure and stored over tin metal.

Nitrogen was supplied by Union Carbide and prior to use was passed through two columns of indicating Drierite ($CaSO_4$ impregnated with $CoCl_2$).

Syringes and needles were oven-dried at 120 °C for a minimum of 3-4 hours and stored in a desiccator. Unless stated otherwise, all reactions were carried out under an atmosphere of dry nitrogen. The glassware (including the Teflon coated magnetic stirring bar) was assembled and connected to the vacuum pump and flame-dried. After the glassware had cooled, dry nitrogen was introduced to the system.

Cold temperatures were maintained using either an ice/water bath (0 °C) or an acetone/dry ice bath (-78 °C).

The concentration or evaporation of solvents under vacuum refers to the use of a Buchi rotary evaporator. Petroleum ether refers to the fraction boiling between 30-60 °C.

Reaction monitoring. All reactions were monitored by thin layer chromatography (tlc) and/or gas-liquid chromatography (glc). Analytical tlc was performed on aluminum backed, precoated silica (SiO_2) gel plates (E. Merck, type 5554). The plates were visualized by ultraviolet fluorescence or by heating the plates after spraying them with 3M sulfuric acid. Analytical glc was performed on a Hewlett Packard model 5880A gas chromatography using a 12 m x 0.2 mm capillary Carbowax column or a 15 m x 0.2 mm capillary DB-210 column. In both cases, flame ionization detection was used with a helium carrier gas. All samples were made up in ether and injection volumes were 2 µl.

Product purification. Unless otherwise stated, all reaction products were purified by flash chromatography using 230-400 mesh ASTM silica gel supplied by E. Merck Co. In most cases, the silica gel was reclaimed after column chromatography. This involved discarding the upper 2-4 cm of silica gel in the column and flushing the remaining silica gel with methanol until clean. A hose connected to a water aspirator was attached to the column spigot and the silica gel sucked to dryness (powder dry). The silica gel was subsequently regenerated by oven heating for 6-8 hours at 120 °C. This recycling procedure could be repeated 3-4 times before the silica gel turned a yellow color whereupon it was discarded. This procedure greatly extended the general usage of silica gel column chromatography.

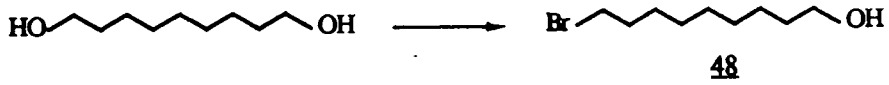
Product characterization. Infrared (IR) spectra were recorded on a Bomem Michelson 100 FT spectrophotometer. Samples were dissolved in chloroform and the spectrum was taken and subsequently subtracted from a spectrum of pure chloroform. In some cases, a neat sample was directly employed. Absorption positions are given in cm^{-1} and abbreviations used in quoting the IR bands are: st=strong, m=medium, w=weak and br=broad.

Low resolution mass spectra were determined on a Varian MAT model CH4B or a Kratos-AEI model MS 50 spectrometer. The parent peak as well as major ion fragmentations are reported as percentages of the base peak. Exact masses were obtained by high resolution mass spectroscopy using a Kratos-AEI model MS 50 spectrometer. All instruments were operated at 70 ev.

Nuclear magnetic resonance (NMR) spectra were taken in deuterochloroform ($CDCl_3$) solution with signal positions given in parts per million (ppm) from the internal standard of tetramethylsilane (0.00 ppm) on the δ scale. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz on a Varian XL-300 or at 400 MHz on a Bruker WH-400 spectrometer and are reported in the form: chemical shift (number of protons, signal multiplicities). The abbreviations used in quoting the data are: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

3.1 Preparation of 10,10-Dimethyltridecanolide (42)

9-Bromo-1-nonanol (48)



48

A suspension of 1,9-nonanediol (35.1 g, 219 mmol) in 50 mL of 48% HBr was prepared in an 1 L liquid-liquid continuous extractor. The suspension was heated to 90 °C and was extracted with 400 mL of heptane at this temperature for 72 h. The extract was cooled, washed twice with saturated aqueous sodium bicarbonate and once with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude oil was purified by column chromatography using a mixture of petroleum ether : ethyl acetate (3 : 1) as eluent to give the monobrominated product 48 (40.8 g, 84%) as colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.66 (2H, t), 3.42 (2H, t), 1.92-1.28 (15H, m);

IR ($CHCl_3$, cm^{-1}): 3337 (free OH, st), 1260 (C-Br, m);

MS (m/e, relative intensity): 206 (^{81}Br: M^+ - H_2O, 9), 204 (^{79}Br: M^+ - H_2O, 9), 178 (9), 176 (9), 164 (13), 162 (13), 150 (19), 148 (19), 137 (32), 135 (34), 97 (58), 83 (44), 82 (21), 81 (14), 70 (13), 69 (85), 68 (20), 67 (17), 57 (14), 56 (17), 55 (100), 54 (12).

1-Bromo-9-[(tetrahydro-2H-pyran-2-yl)oxy]-nonane (49)

49

Pyridinium p-toluenesulfonate (PPTs) (1.50 g, 5.97 mmol) was added into 120 mL of dry CH_2Cl_2 at room temperature under N_2. 9-Bromo-1-nonanol (13.8 g, 61.9 mmol) was dissolved in 20 mL of dry CH_2Cl_2 and injected. The mixture was cooled to 0 °C with an ice bath and freshly distilled dihydropyran (8.17 mL, 89.6 mmol) was added dropwise. After the addition, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with ether, washed twice with cold 1N HCl and once with brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude yellow oil was chromatographed on a silica gel column using a mixture of petroleum ether : ethyl acetate (3 : 1) to give the desired product 49 (17.3 g, 91%) as a colorless oil.

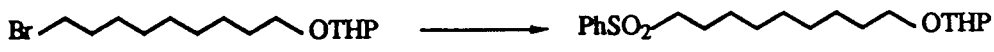
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.60 (1H, t), 3.94-3.36 (6H, m), 1.92-1.26 (20H, m);

IR (cm^{-1}): 1260 (C-Br, m), 1128 (C-O, m);

MS (m/e, relative intensity): 307 (^{81}Br: M^+ - 1, 7), 305 (^{79}Br: M^+ - 1, 9), 85 (100), 84 (10), 83 (13), 69 (22), 67 (12), 57 (21), 56 (28), 55 (34), 43 (18), 41 (38), 40 (13), 32 (27), 29 (20), 28 (27);

Exact mass calc. for $C_{14}H_{26}{}^{81}BrO_2$: 307.1097; Found: 307.1107; calc. for $C_{14}H_{26}{}^{79}BrO_2$: 305.1117; Found: 305.1115.

1-Phenylsulfonyl-9-[(tetrahydro-2H-pyran-2-yl)oxy]-nonane (66)



66

A 0.1 M aqueous solution of sodium benzenesulfinate was slowly percolated through a column filled with Amberlyst A-26 (Rohm and Haas) in the chloride form until a negative test for chloride ion in the eluate was obtained. The resin was successively washed with water, acetone, ether and dried under vacuum at 50 °C for 5 h to give Amberlyst A-26 in benzenesulfinate form. This resin (47.5 g, 158 meq.) was added into a solution of bromide 49 (40.5 g, 132 mmol) in 300 mL of dry benzene. The mixture was vigorously stirred at reflux for 48 h. The resin was filtered and washed with CH_2Cl_2. The filtrate was concentrated under vacuum and the crude oil was chromatographed on a silica gel column using a mixture of petroleum ether : ethyl acetate (4 : 1) as eluent to recover bromide 49 (3.80 g, 8.4%) and to give sulfone 66 (41.3 g, 94%) as a light yellow oil.

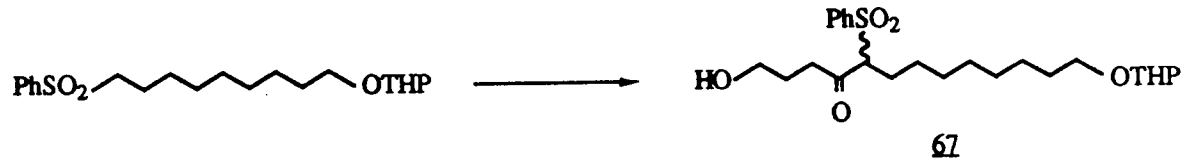
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (2H, d), 7.70-7.52 (3H, m), 4.58 (1H, t), 3.92-3.04 (6H, m), 1.90-1.20 (20H, m);

IR (cm^{-1}): 3062 (phenyl C-H, w), 1310 (S=O, st);

MS (m/e, relative intensity): 368 (M^+, 2), 367 (M^+ - 1, 7), 339 (13), 285 (40), 284 (13), 283 (43), 268 (12), 267 (51), 255 (23), 254(11), 251 (20), 239 (12), 143 (56), 125 (37), 124 (14), 101 (38), 100 (10), 85 (100), 84 (19), 83 (24), 69 (47), 67 (13), 57 (17), 56 (10), 55 (36).

Exact mass calc. for $C_{20}H_{32}SO_4$: 368.2023; Found: 368.2017.

1-Hydroxy-5-phenylsulfonyl-13-[(tetrahydro-2H-pyran-2-yl)oxy]-tridecan-4-one (67)



67

n-Butyllithium (6.8 mL, 11 mmol) was injected at 0 °C into a well-stirred solution of sulfone 66 (2.0 g, 5.4 mmol) in 60 mL of dry THF under N_2. After stirring for 30 minutes the reaction was cooled to -78 °C and freshly distilled HMPA (0.6 mL, 3 mmol) and γ-butyrolactone (0.44 mL, 5.4 mmol) were added. The mixture was stirred for 3 h and allowed to warm to room temperature. It was then quenched with aqueous NH_4Cl and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed twice with saturated aqueous cupric sulfate and once with brine, dried over $MgSO_4$ and evaporated under vacuum. The crude product was chromatographed on a silica gel column using a mixture of petroleum ether : ethyl acetate (1 : 1) as eluent to give the γ-hydroxy keto compound 67 (1.64 g, 81%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.80 (2H, d), 7.74-7.54 (3H, m), 4.58 (1H, t), 4.18-4.08 (1H, m), 3.92-3.32 (6H, m), 3.10-2.66 (2H, m), 1.92-1.14 (21H, m);

IR (cm^{-1}): 3556-3328 (H-bonded OH, br), 3062 (phenyl C-H, w), 1718 (C=O, st), 1310 (S=O st);

MS (m/e, relative intensity): 367 (M^+ - $C_4H_7O_2$, 23), 353 (16), 352 (17), 351 (18), 350 (17), 340 (11), 339 (45), 313 (33), 309 (12), 285 (14), 283 (17), 267 (21), 211 (11), 144 (14), 143 (51), 142 (20), 126 (21), 211 (11), 144 (14), 143 (51), 142 (20), 126 (21), 125 (100), 124 (45), 101 (58), 100 (30), 97 (21), 96 (15), 95 (12), 86(50), 85 (49), 84 (73), 83 (85), 82 (18), 81 (22), 79 (12), 78 (22), 77 (37), 71 (14), 70 (13), 69 (53), 68 (18), 67 (47), 57 (63), 56 (53), 55 (86), 54 (14), 43 (56), 42 (57), 41 (83), 39 (17).

1-Hydroxy-13-[(tetrahydro-2H-pyran-2-yl)oxy]-tridecan-4-one (68)

68

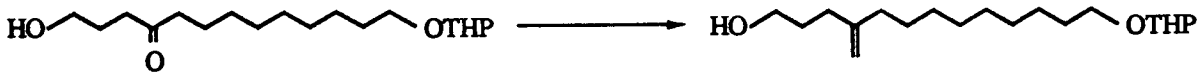
Aluminum foil (813 mg, 0.15 mmol) was cut into strips approximately 5 cm x 0.5 cm and immersed into a 2% aqueous mercuric chloride solution for 15-25 seconds. The aluminum strips were rinsed with methanol and ether, cut into pieces approximately 0.5 cm^2 and added immediately to a solution of sulfone 67 (909 mg, 2.01 mmol) in 60 mL of 10% aqueous THF. The mixture was stirred at reflux for 8 h, cooled and filtered. The solid phase was washed with THF and the filtrate evaporated under vacuum to remove most of the solvent. The residue was extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by column chromatography using a mixture of petroleum ether : ethyl acetate (1 : 1) as eluent gave compound 68 (495 mg, 79%) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.58 (1H, t), 3.92-3.32 (6H, m), 2.58 (2H, t), 2.44 (2H, t), 1.90-1.22 (21H, m);

IR (cm^{-1}): 3441 (free OH, st), 1710 (C=O, st);

MS (m/e, relative intensity): 296 (M^+ - H_2O, 18), 211 (21), 101 (16), 97 (88), 95 (13), 85 (100), 84 (49), 81 (14), 71 (13), 69 (18), 67 (22), 57 (13), 56 (15), 55 (60), 43 (19), 41 (25).

4-[9-(Tetrahydro-2H-pyran-2-yl)oxynonyl]-pent-4-ene-1-ol (92)



92

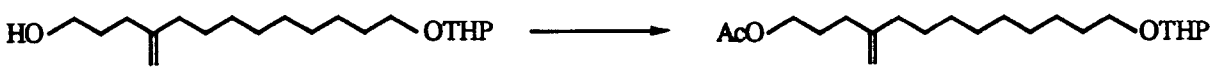
n-Butyllithium (3.13 mL, 5.0 mmol) was injected into 50 mL of dry ether at room temperature under N_2. Triphenylmethylphosphonium bromide (1.79 g, 5.0 mmol) was cautiously added in portions and the resulting orange solution was stirred vigorously at room temperature for 4 h. The keto compound 68 (628 mg, 2.0 mmol) was dissolved in 15 mL of dry ether and added dropwise to the reaction via an addition funnel, upon which the orange color discharged and a white precipitate formed. The mixture was stirred at reflux for 80 h, cooled and filtered. The ether filtrate was washed with 1N HCl and brine, dried over $MgSO_4$ and concentrated under vacuum. The crude oil was chromatographed on a silica gel column using a mixture of petroleum ether : ethyl acetate (6 : 1) as eluent to give the alkene compound 92 (499 mg, 80%) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (2H, s), 4.58 (1H, t), 3.92-3.32 (6H, m), 2.12 (2H, t), 2.04 (2H, t), 1.90-1.22 (21H, m);

IR (cm^{-1}): 3536-3252 (H-bonded OH, br), 3076 (=C-H, w), 1644 (C=C, m);

MS (m/e, relative intensity): 311 (M^+ - 1, 3), 210 (M^+ -THPOH, 7), 109 (15), 101 (48), 97 (20), 96 (10), 95 (38), 86 (22), 85 (70), 84 (53), 83 (37), 82 (27), 81 (40), 69 (68), 68 (24), 67 (81), 57 (50), 56 (51), 55 (100), 43 (55), 42 (13), 41 (87), 39 (23);

2-[(3-Acetoxy)-propyl]-11-[(tetrahydro-2H-pyran-2-yl)oxy]-undec-1-ene (93)



93

Freshly distilled acetic anhydride (0.99 mL, 10 mmol) and pyridine (0.85 mL, 10 mmol) were injected into 125 mL of anhydrous ether at room temperature under N_2. A catalytic amount of 4-dimethylaminopyridine (DMAP) was added. The alcohol 92 (2.18 g, 7.0 mmol) was dissolved in 20 mL of dry ether and added dropwise to the mixture via an addition funnel. The reaction was stirred at room temperature for 4 h. The mixture was diluted with ether and washed three times with brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by column chromatography using a mixture of petroleum ether : ethyl acetate (3 : 1) as eluent gave the acylated compound 93 (2.41 g, 94%) as a yellow oil.

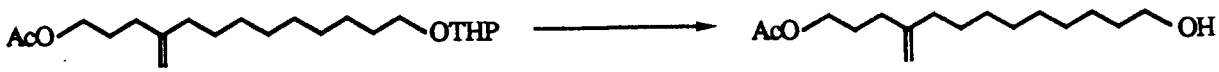
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (2H, d), 4.58 (1H, t), 4.08 (2H, t), 3.92-3.34 (4H, m), 2.12-1.98 (7H, m), 1.90-1.22 (20H, m);

IR (cm^{-1}): 3076 (=C-H, w), 1743 (C=O, st), 1646 (C=C, m);

MS (m/e, relative intensity): 354 (M^+, 4), 353 (M^+ - H, 3), 210 (18), 123 (15), 121 (13), 111 (10), 110 (15), 109 (21), 108 (16), 107 (10), 101 (17), 97 (18), 96 (22), 95 (62), 94 (13), 93 (21), 85 (79), 84 (39), 83 (39), 82 (88), 81 (54), 80 (13), 79 (27), 69 (42), 68 (30), 67 (100), 57 (24), 56 (37), 55 (90), 54 (26), 53 (21), 42 (88), 41 (67);

Exact mass calc. for $C_{21}H_{38}O_4$: 354.2771; Found: 354.2769.

10-[(3-Acetoxy)-propyl]-undec-10-ene-1-ol (98)



98

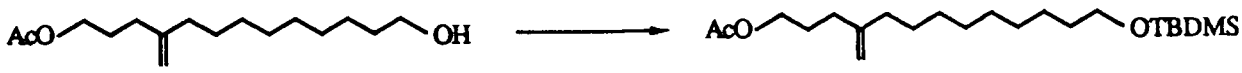
The THP ether 93 (4.17, 11.8 mmol) was dissolved in 30 mL of dry MeOH and injected into 120 mL of dry MeOH at room temperature under N_2. Pyridinium p-toluenesulfonate (306 mg, 1.18 mmol) was added and the mixture was stirred at room temperature for 48 h. The solvent was evaporated under vacuum and the residue was taken up in ether, washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by column chromatography using a mixture of petroleum ether : ethyl acetate (3 : 1) as eluent gave the alcohol 98 (2.85 g, 90%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (2H, d), 4.08 (2H, t), 3.64 (2H, t), 2.12-1.98 (7H, m), 1.86-1.22 (17H, m);

IR (cm^{-1}): 3534-3220 (H-bonded, OH, br), 3076 (=C-H, w), 1743 (C=O, st), 1646 (C=C, m);

MS (m/e, relative intensity): 252 (M^+ - H_2O, 7), 210 (M^+ -AcOH, 4), 110 (10), 109 (12), 108 (11), 97 (10), 96 (13), 95 (51), 83 (18), 82 (100), 81 (18), 79 (12), 69 (23), 68 (19), 67 (92), 57 (10), 56 (14), 55 (32), 43 (42), 41 (22).

2-[(3-Acetoxy)-propyl]-11-tert-butyldimethylsiloxyundec-1-ene (100)



100

To 40 mL of dry CH_2Cl_2 at room temperature was added successively the alcohol 98 (540 mg, 2.0 mmol) in 5 mL of dry CH_2Cl_2, triethylamine (0.56 mL, 4.0 mmol), DMAP (49 mg, 0.4 mmol) and tert-butyldimethylsilyl chloride (452 mg, 3.0 mmol) under N_2. The mixture was vigorously stirred at room temperature for 4 h, quenched with 1N HCl and extracted with ether. The organic layer was washed with saturated aqueous bicarbonate, brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography using a mixture of petroleum ether : ethyl acetate (6 : 1) as eluent to give the protected TBDMS ether 100 (730 mg, 95%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (2H, d), 4.08 (2H, t), 3.60 (2H, t), 2.12-1.98 (7H, m), 1.84-1.22 (16H, m), 0.90 (9H, s), 0.06 (6H, s);

IR (cm^{-1}): 3076 (=C-H, w), 1743 (C=O, st), 1646 (C=C, m), 1100 (Si-O, st);

MS (m/e, relative intensity): 327 ($M^+ - C_4H_9$, 23), 118 (10), 117 (100), 109 (13), 95 (20), 83 (12), 81 (22), 75 (37), 73 (11), 69 (20), 67 (21), 55 (22), 43 (18), 41 (14).

1-[(3-Acetoxy)-propyl]-1-[(9-tert-butyldimethylsiloxy)-nonyl]-cyclopropane (101)

101

To a well-stirred, heated (55 °C) solution of the alkene 100 (450 mg, 0.96 mmol) in 20 mL of dry toluene was injected a solution of diethyl zinc (Et_2Zn) in toluene (1.75 mL, 1.92 mmol) and freshly distilled methylene iodide (CH_2I_2) (0.30 mL, 3.8 mmol) under N_2. The mixture was stirred at 55 °C for 22 h. A further injection of CH_2I_2 (0.15 mL, 1.9 mmol) and Et_2Zn (0.88 mL in toluene, 0.96 mmol) followed by 11 hours of stirring was still not sufficient to complete the reaction. Two further additions of CH_2I_2 (0.15 mL, 1.9 mmol) and Et_2Zn (0.88 mL, 0.96 mmol) and a further stirring for 20 h completed the reaction. The mixture was cooled to room temperature and quenched with 10 mL of 1N HCl. The layers were separated and the aqueous layer extracted with ether. The combined organic phases were washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by column chromatography using a mixture of petroleum ether : ethyl acetate (9 : 1) gave the cyclopropyl compound 101 (410 mg, 88%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.08 (2H, t), 3.60 (2H, t), 2.06 (3H, s), 1.74-1.22 (20H, m), 0.90 (9H, s), 0.22 (4H, d), 0.06 (6H, s);

IR (cm^{-1}): 3065 (cyclopropyl C-H, w), 1743 (C=O, st), 1100 (Si-O, st);

MS (m/e, relative intensity): 341 ($M^+ - C_4H_9$, 23), 118 (10), 117 (100), 109 (13), 95 (20), 83 (12), 81 (22), 75 (37), 73 (11), 69 (19), 67 (19), 55 (20), 43 (13), 41 (10).

1-Acetoxy-4,4-dimethyl-13-tert-butyldimethylsiloxytridecane (102)

102

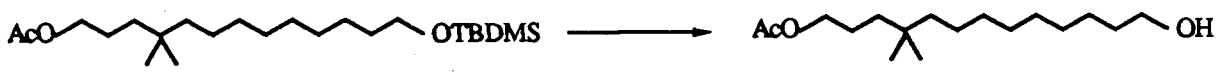
To a solution of the cyclopropyl compound 101 (580 mg, 1.46 mmol) in 5 mL of glacial acetic acid was added PtO_2 (99 mg). The resultant suspension was stirred under an H_2 atmosphere (3.5 atm.) for 24 h. Saturated aqueous sodium bicarbonate was added to the mixture with stirring until it became basic. The resultant aqueous slurry was extracted with ether (4 x 20 mL). The combined ether extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was chromatographed on a silica gel column using a mixture of petroleum ether : ethyl acetate (9 : 1) as eluent to give the hydrogenation product 102 (110 mg) as a yellow oil and the dimethyl alcohol 103 (218 mg) as a colorless oil. The hydrogenation reaction yield was 79% based on the yield of the next reaction.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.04 (2H, t), 3.60 (2H, t), 2.06 (3H, s), 1.60-1.16 (20H, m), 0.90 (9H, s), 0.84 (6H, s), 0.06 (6H, s);

IR (cm^{-1}): 1743 (C=O, st), 1100 (Si-O, st);

MS (m/e, relative intensity): 343 ($M^+ - C_4H_9$, 48), 300 (10), 299 (35), 283 (10), 255 (11), 135 (18), 118 (10), 117 (100), 111 (16), 97 (25), 83 (43), 75 (27), 73 (11), 71 (11), 69 (31), 57 (13), 55 (23), 43 (13).

13-Acetoxy-10,10-dimethyltridecan-1-ol (103)



103

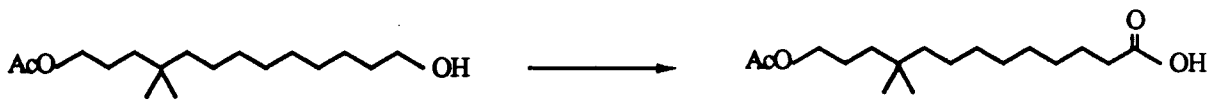
The TBDMS ether 102 (220 mg, 0.55 mmol) was dissolved in 5 mL of dry MeOH and injected into 20 mL of MeOH at room temperature under N_2. PPTs (15.6 mg, 0.06 mmol) was added and the mixture was stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the residue was taken up in ether, washed twice with saturated aqueous sodium bicarbonate and once with brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by column chromatography using a mixture of petroleum ether : ethyl acetate (3 : 1) as eluent gave alcohol 103 (136 mg, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.04 (2H, t), 3.64 (2H, t), 2.06 (3H, s), 1.62-1.14 (21H, m), 0.84 (6H, s);

IR (cm^{-1}): 3560-3204 (H-bonded, OH, br), 1743 (C=O, st);

MS (m/e, relative intensity): 268 (M^+ - H_2O, 0.2), 226 (M^+ - AcOH, 5), 211 (18), 111 (28), 109 (16), 101 (14), 97 (43), 96 (11), 95 (22), 85 (16), 84 (20), 83 (71), 82 (28), 81 (23), 71 (18), 70 (13), 69 (70), 67 (21), 61 (29), 57 (29), 56 (18), t5 (100), 43 (56), 42 (11), 41 (32).

13-Acetoxy-10,10-dimethyltridecanoic acid (104)



104

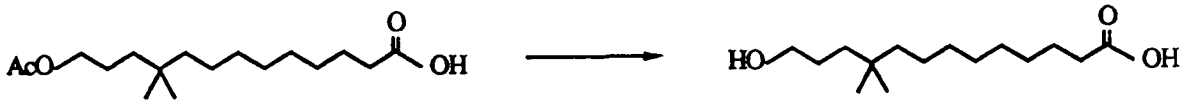
Alcohol 103 (270 mg, 0.94 mmol) was dissolved in 5 mL of acetone and cooled to 0 °C with an ice bath. Jones reagent was added dropwise via a small syringe under N_2 until the solution stayed dark-brown (like the Jones reagent itself). The mixture was stirred at 0 °C for 20 minutes. 2-Propanol was added slowly until the solution became clear with a blue precipitate being formed. The solid was filtered and washed with acetone. The filtrate was concentrated under vacuum and the residue taken up in ether. Aqueous 15% NaOH was added and the layers separated. The aqueous phase was acidified with 1N HCl and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by column chromatography using a mixture of petroleum ether : ethyl acetate (3 : 1) and approximately 1% acetic acid as eluent gave acid 104 (105 mg, 77%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.04 (2H, t), 2.36 (2H, t), 2.06 (3H, s), 1.68-1.14 (19H, m), 0.84 (6H, s);

IR (cm^{-1}): 3480-3014 (acid OH, br), 1743 (ester C=O, st), 1712 (acid C=O, st);

MS (m/e, relative intensity): 240 (M^+ - AcOH, 3), 225 (13), 212 (34), 199 (12), 181 (10), 97 (12), 84 (12), 83 (100), 82 (11), 69 (18), 61 (13), 57 (12), 56 (10), 55 (37), 43 (28), 41 (16).

10,10-Dimethyl-13-hydroxytridecanoic acid (105)



105

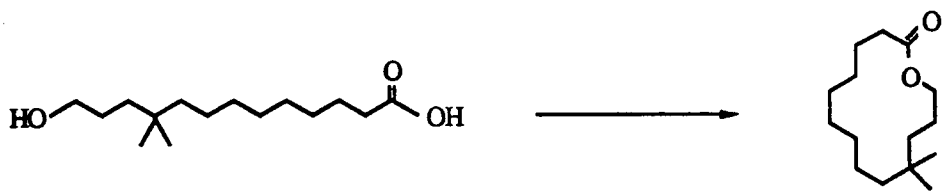
Acetate 104 (100 mg, 0.33 mmol) was dissolved in 5 mL of dry MeOH. Pulverized potassium carbonate (101 mg, 0.73 mmol) was added under N_2 and the mixture was vigorously stirred at room temperature for 5 h. The solvent was evaporated under vacuum and the residue was taken up in ether, washed twice with 1N HCl and once with brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum to give the clean ω-hydroxy acid 105 (84 mg, 98%) which was carried directly to the next reaction.

^{1}H NMR (300 MHz, $CDCl_4$) δ: 3.62 (2H, t), 2.36 (2H, t), 1.68-1.14 (20H, m), 0.84 (6H, s);

IR (cm^{-1}): 3564-3014 (alcohol OH, acid OH, br), 1712 (acid C=O, st);

MS (m/e, relative intensity): 240 (M^+ - H_2O, 1), 199 (12), 181 (17), 163 (13), 125 (10), 111 (12), 101 (30), 99 (10), 97 (22), 95 (10), 85 (10), 84 (12), 83 (100), 82 (10), 81 (28), 71 (17), 70 (10), 69 (37), 67 (11), 57 (26), 56 (18), 55 (71), 43 (33), 41 (31).

10,10-Dimethyltridecanolide (42)



42

1-Phenyl-2-tetrazoline-5-thione (71 mg, 0.40 mmol) and tert-butylisocyanide (0.05 mL, 0.4 mmol) were added to 3 mL of dry toluene at room temperature under N_2. After 10 minutes of stirring the homogeneous solution was added to a solution of the hydroxy acid 105 (80 mg, 0.31 mmol) in 6 mL of dry toluene under N_2. The mixture was diluted with 60 mL of dry toluene and stirred at reflux for 4 h. The mixture was cooled, evaporated under vacuum to a volume of approximately 4 mL. This concentrated solution was filtered through a short silica gel column using benzene as eluent to give macrolide 42 (49 mg, 66%) as a light yellow solid. The dimer by-product (12 mg, 20%) was also isolated, which could be hydrolyzed back to acid 105.

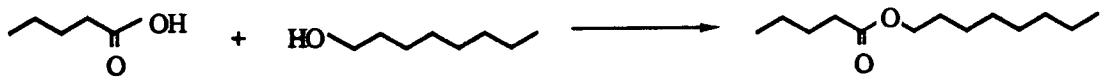
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.22-4.14 (2H, m), 2.44-2.36 (2H, m), 1.74-1.12 (18H, m), 0.84 (6H, s);

IR (cm^{-1}): 1718 (C=O, st);

MS (m/e, relative intensity): 240 (M^+, 11), 225 (M^+ - CH_3, 14), 212 (47), 84 (13), 83 (100), 82 (22), 69 (22), 67 (10), 56 (13), 55 (43), 43 (10), 41 (20);

Exact mass calc. for $C_{15}H_{28}O_2$: 240.2090; Found: 240.2085.

3.2 Preparation of n-Octyl Pentanoate (109)



109

To a well-stirred, ice cooled solution of 1-octanol (390 mg, 3.0 mmol) and valeric acid (367 mg, 3.6 mmol) in 30 mL of dry CH_2Cl_2 was added slowly a solution of dicyclohexylcarbodiimide (DCC) (655 mg, 3.2 mmol) in 5 mL of CH_2Cl_2 and a catalytic amount of DMAP. The mixture was stirred at room temperature overnight. The urea was filtered off by suction filtration. The filtrate was diluted with CH_2Cl_2 and washed twice with 1N HCl, saturated sodium bicarbonate and brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude oil was purified by column chromatography using a mixture of petroleum ether : ethyl acetate (6 : 1) as eluent to give ester 109 (604 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.25 (2H, t), 2.50 (2H, t), 1.85-1.05 (22H, m);

IR (cm^{-1}): 1722 (C=O, st), 1173 (C-O, m);

MS (m/e, relative intensity): 214 (M^+, 4), 172 (7), 158 (12), 157 (22), 112 (40), 103 (100), 85 (87), 84 (41), 83 (38), 71 (23), 70 (56), 69 (30), 61 (13), 60 (10), 57 (97), 56 (51), 55 (43), 44 (13), 43 (53), 42 (27), 41 (62), 39 (13);

Exact mass calc. for $C_{13}H_{26}O_2$: 214.1934; Found: 214.1934.

3.3 Preparation of tridecanolide (35)

35

Trifluoroacetic anhydride (0.68 mL, 4.8 mmol) was added slowly to a solution of 90% hydrogen peroxide (0.14 mL, 4.0 mmol) in 4 mL of CH_2Cl_2 at 0 °C under N_2. The solution was stirred at 0 °C for 25 min and at room temperature for 10 min. The resulting peroxytrifluoroacetic acid was added slowly to a well-stirred mixture of cyclotridecanone (393 mg, 2.0 mmol) and disodium hydrogen phosphate in 30 mL of CH_2Cl_2 at 0 °C. After the addition, the mixture was stirred at reflux for 2 h. The mixture was cooled to room temperature and poured into water. The organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$ and concentrated under vacuum. The crude oil was purified by column chromatography using toluene as eluent to give macrolide 35 (246 mg, 63%) as a colorless oil.

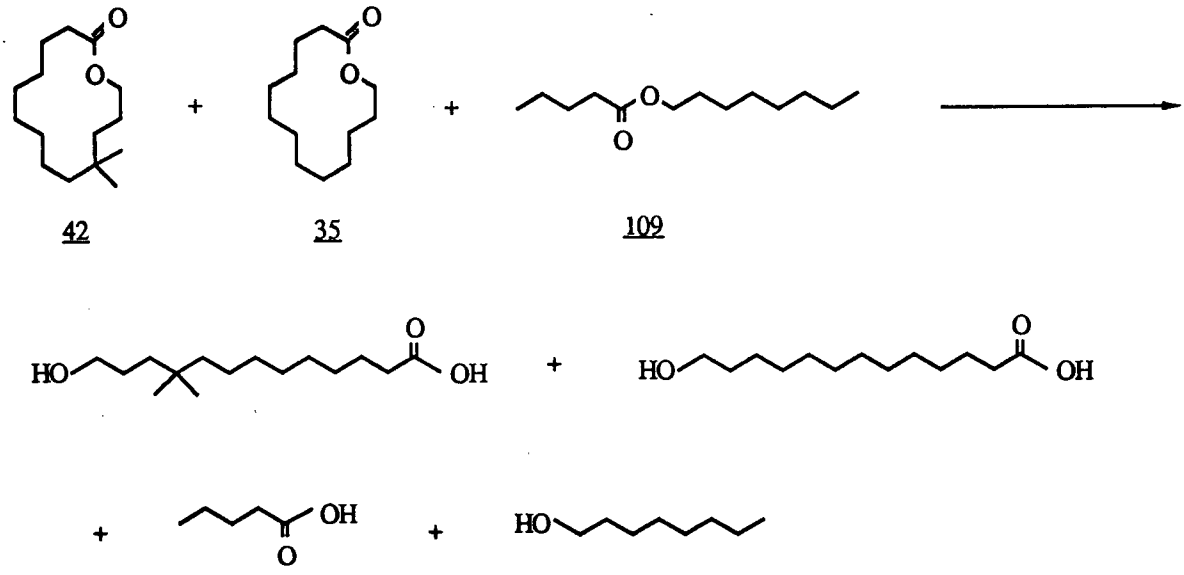
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.35 (2H, m), 2.58 (2H, m), 1.90-1.40 (20H, m);

IR (cm^{-1}): 1720 (C=O, st), 1144 (C-O, m);

MS (m/e, relative intensity): 212 (M^+, 12), 194 (14), 176 (11), 169 (8), 111 (15), 110 (21), 98 (33), 97 (30), 96 (34), 95 (17), 84 (31), 83 (42), 82 (41), 81 (22), 73 (16), 71 (13), 70 (22), 69 (58), 68 (32), 67 (27), 60 (10), 57 (18), 56 (28), 55 (100), 54 (13), 43 (32), 42 (21), 41 (59);

Exact mass calc. for $C_{13}H_{24}O_2$: 212.1777; Found: 212.1775.

3.4 Hydrolysis of 10,10-Dimethyltridecanolide (42), Tridecanolide (35) and n-Octyl Pentanoate (109)



42 35 109

Macrolide 42 (5 mg, 0.02 mmol), macrolide 35 (4 mg, 0.02 mmol), ester 109 (7 mg, 0.03 mmol) and dodecane (3 mg, 0.02 mmol) were dissolved in 1 mL of MeOH. Pulverized potassium carbonate (20 mg, 0.15 mmol) was added and the mixture was stirred at room temperature. The reaction was monitored by gas-liquid chromatography (glc). The relative intensities of the hydrolysis compounds to the dodecane internal standard were recorded. The hydrolysis reaction was also carried out at 0 °C and -20 °C under the same procedure as described above.

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Appendix 1

MM2 calculations

The strain energies of different conformations for macrolide 42 were calculated using Allinger's MM2 computer program.[38b] The force field used in molecular mechanics calculations consists of a set of equations derived from classical mechanics, which contain adjustable parameters that are optimized to obtain the best fit of the calculated and experimental properties of the molecules. The MM2 program is much faster than quantum mechanical calculations and produces very reliable values. In addition, the MM2 program allows rapid calculations of considerably large molecules, since the equations used are sufficiently simple to be rapidly solved by modern computers.

The quality of a molecular mechanics force field, and hence the reliability of its predictions, is critically dependant on the parameters used. For the calculations in this thesis, the parameters of Allinger's 1982 MM2 force field were employed.

All the calculations were performed on the Amdohl computer in the Computing Centre of the University of British Columbia. The time required to generate the conformations, screen out unfavorable selections and calculate the energies were usually 5 to 10 min.

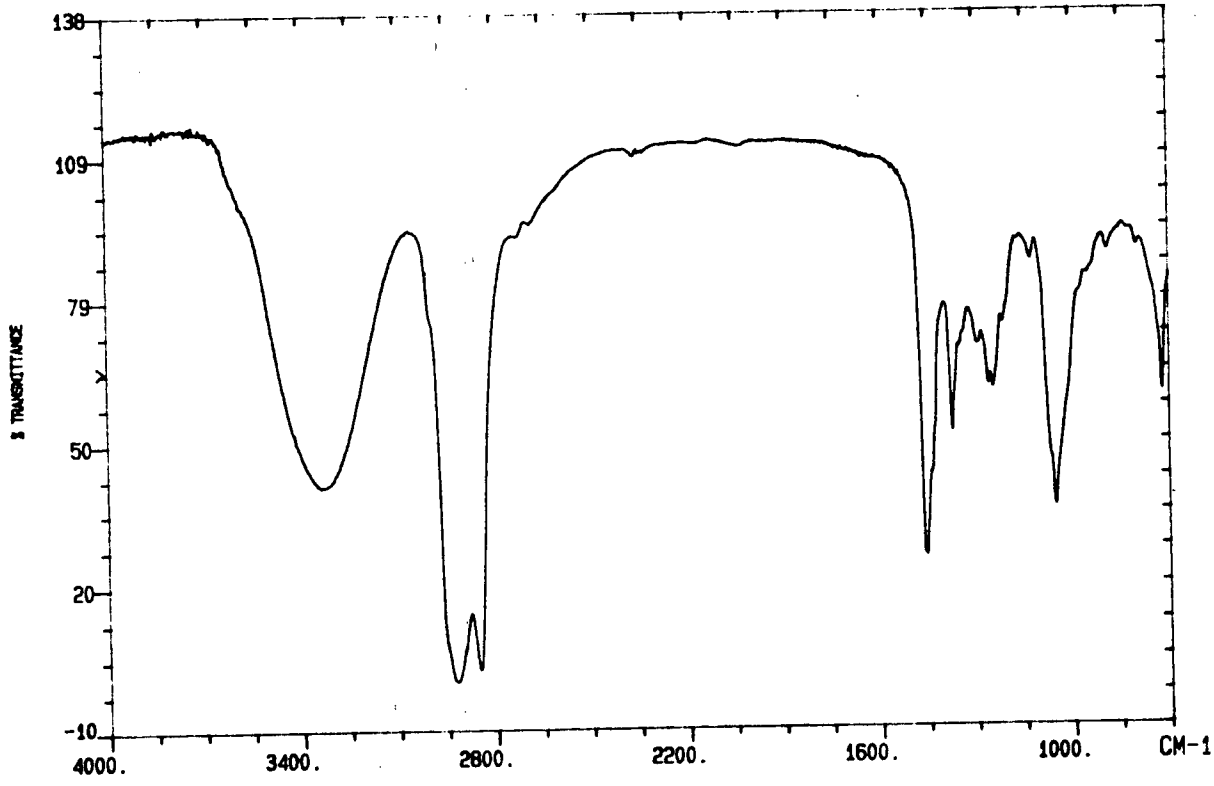
Appendix 2

NMR and IR spectra

Br
OH

48

5
4
3
2
1
0 PPM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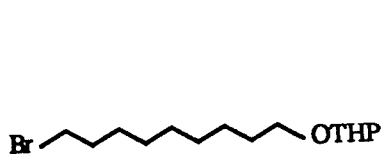
1600.
1000.
CM-1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OTHP

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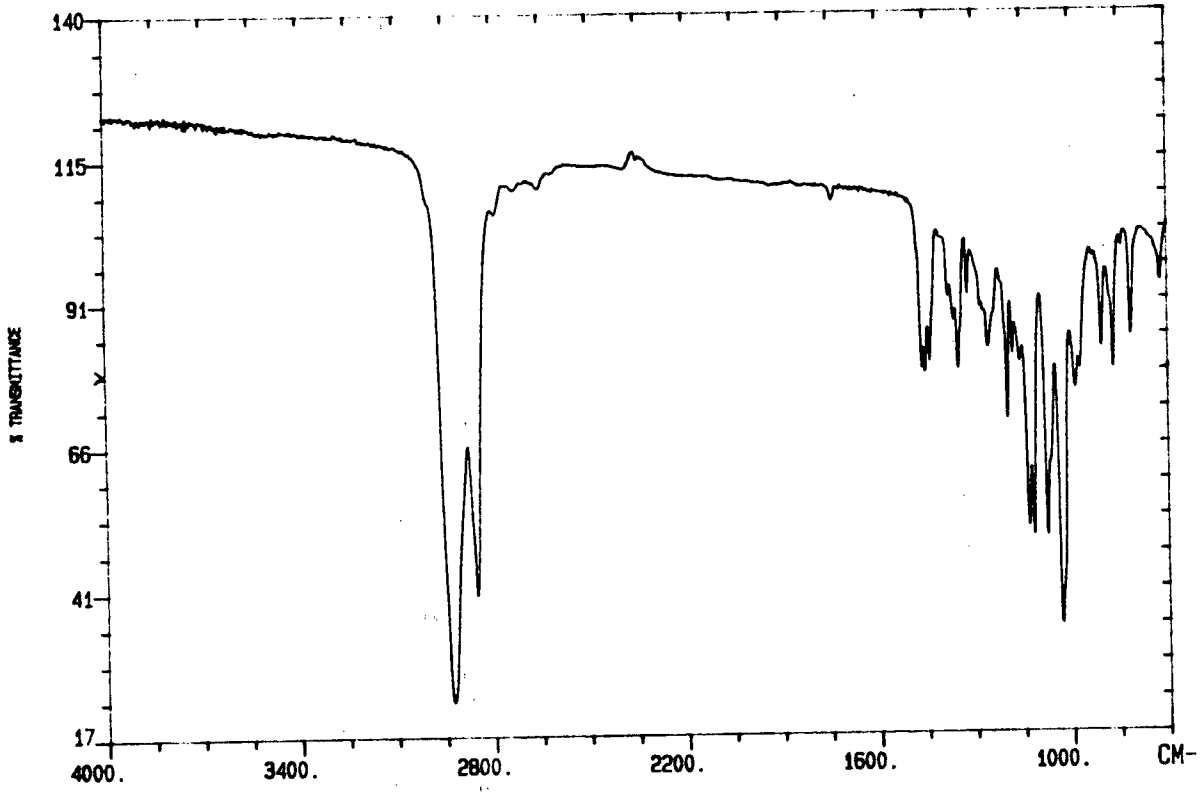
0 PPM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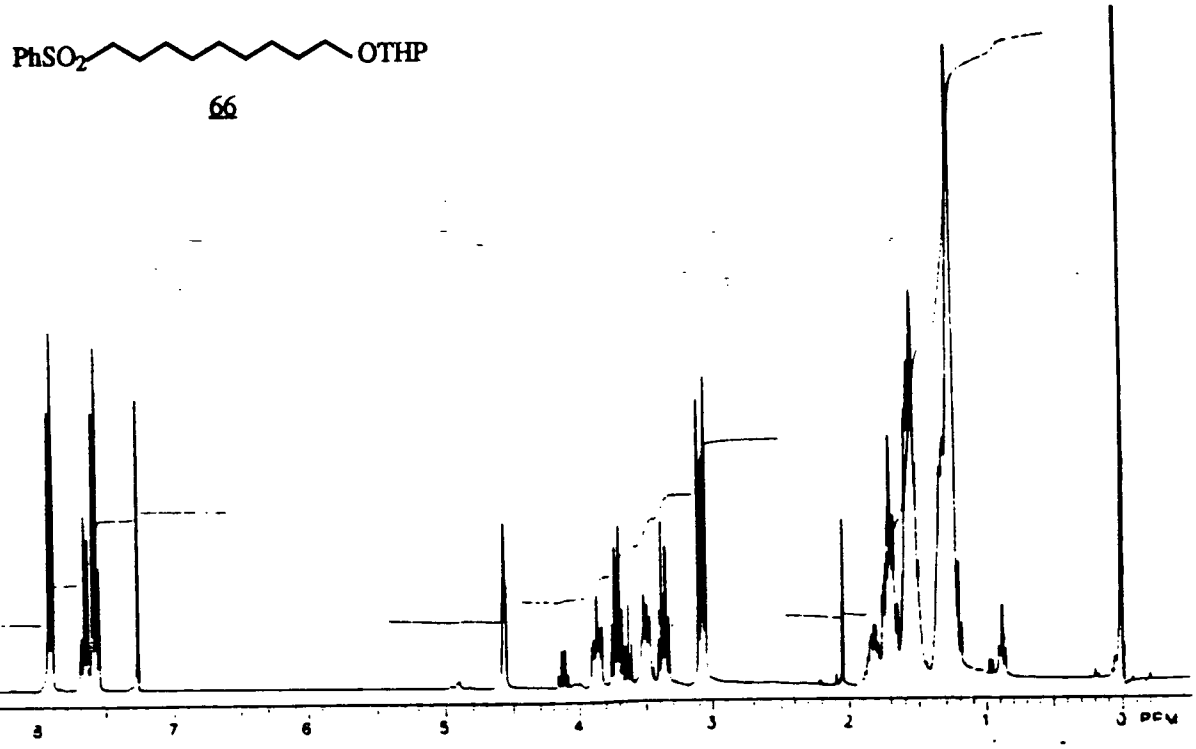
CM-1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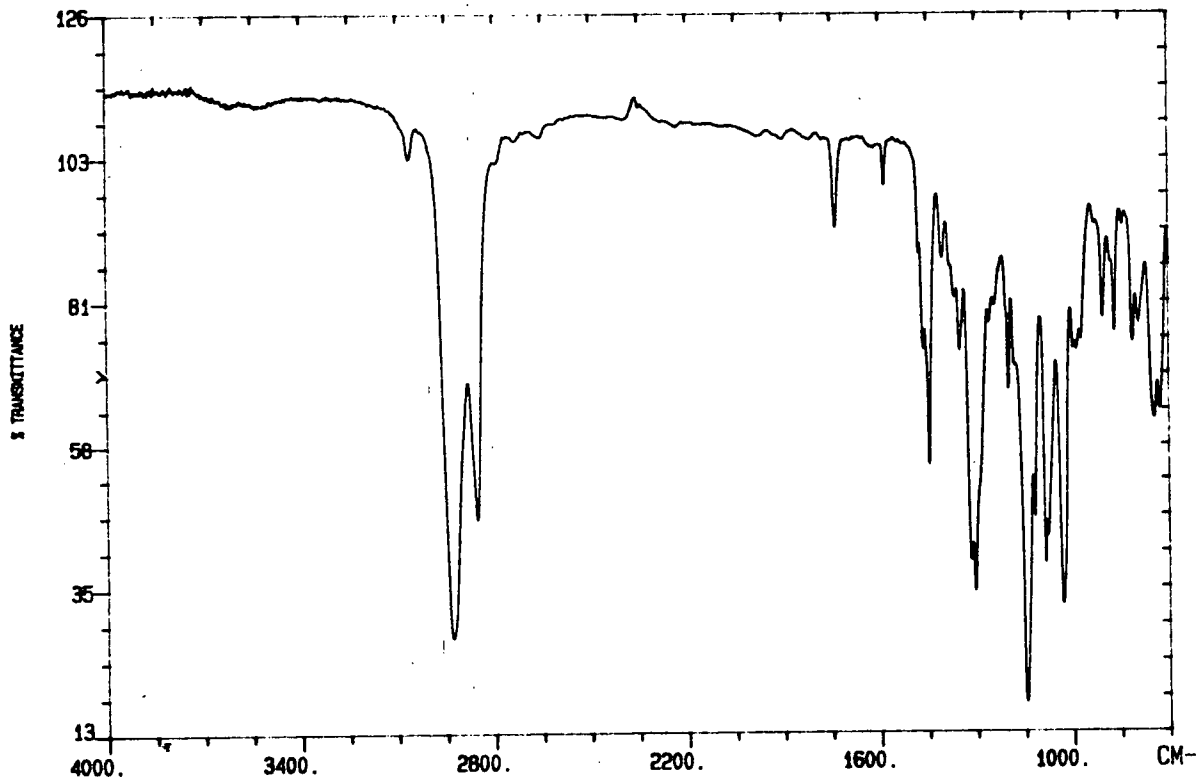
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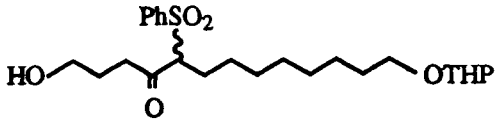
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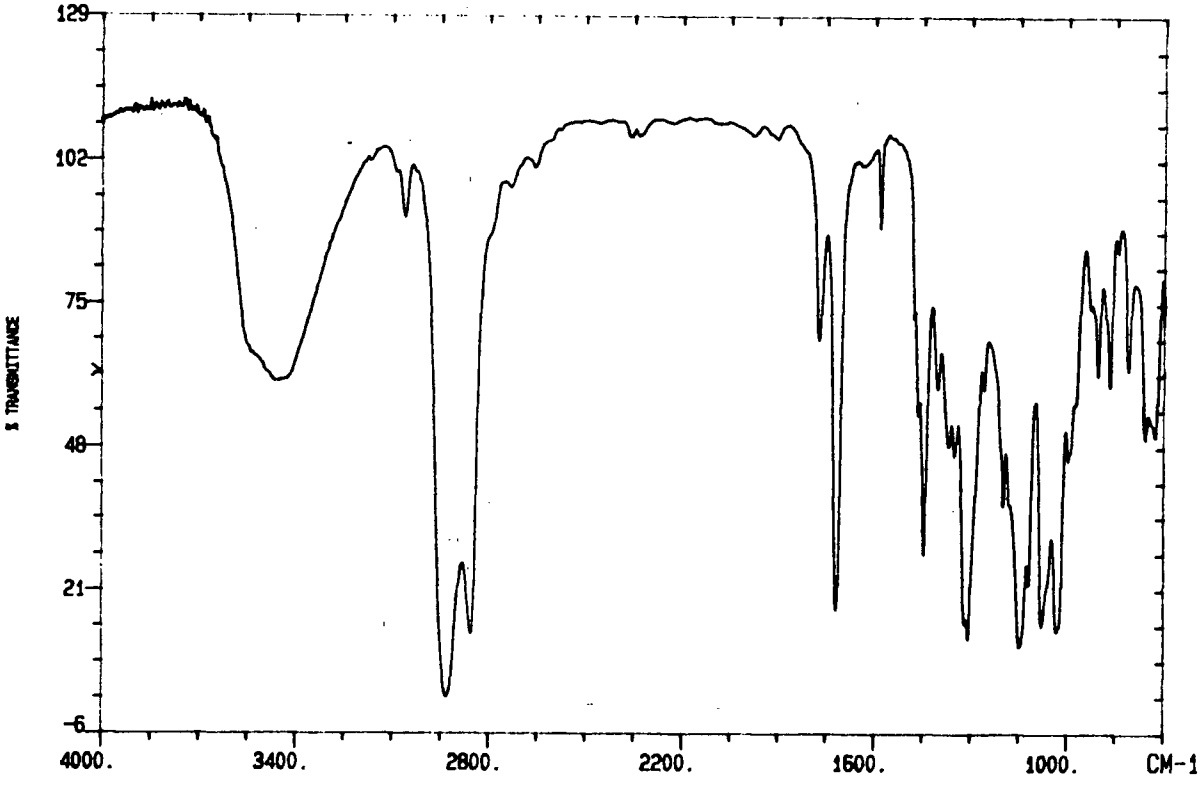
67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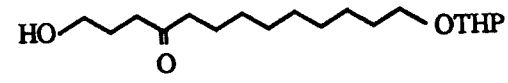
HO
O
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68

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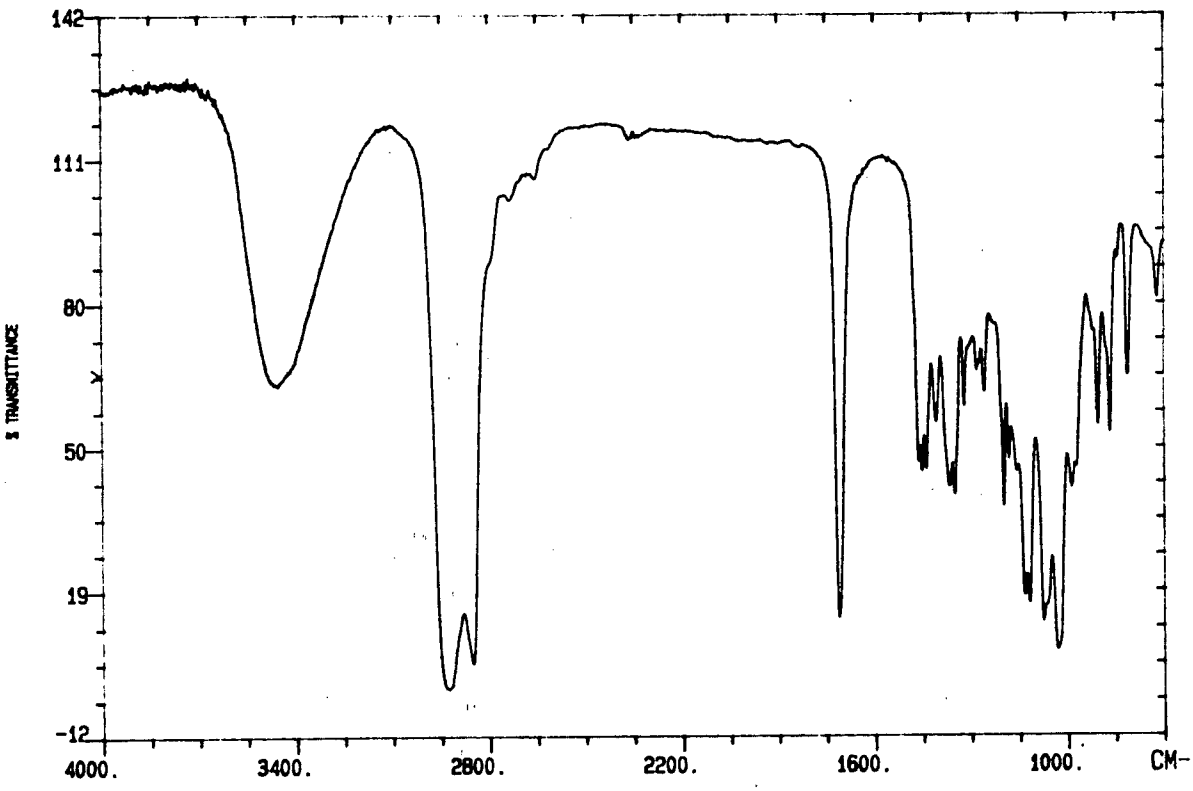
4
3
2
1
0 PPM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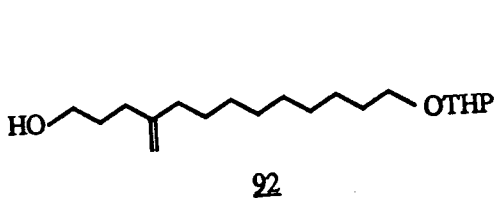
CM-1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OTHP

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3
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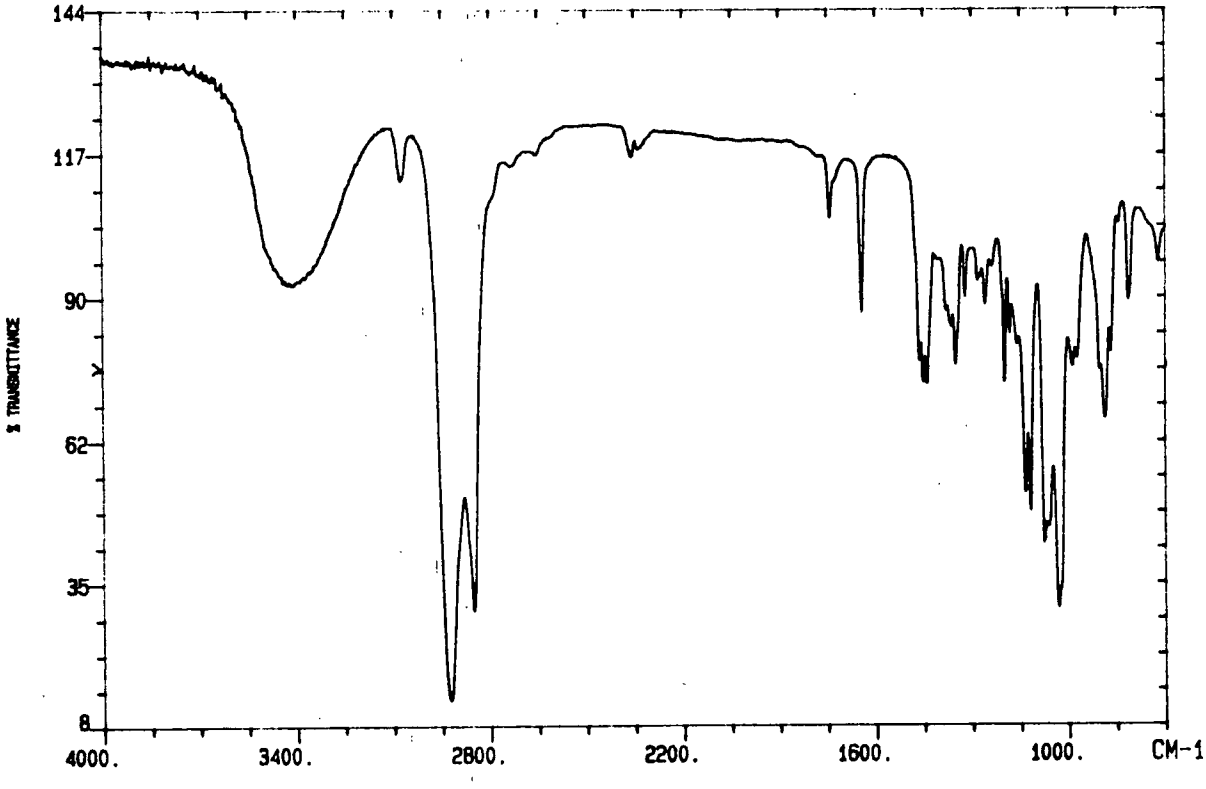
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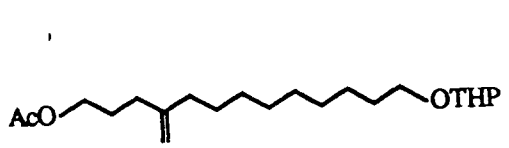
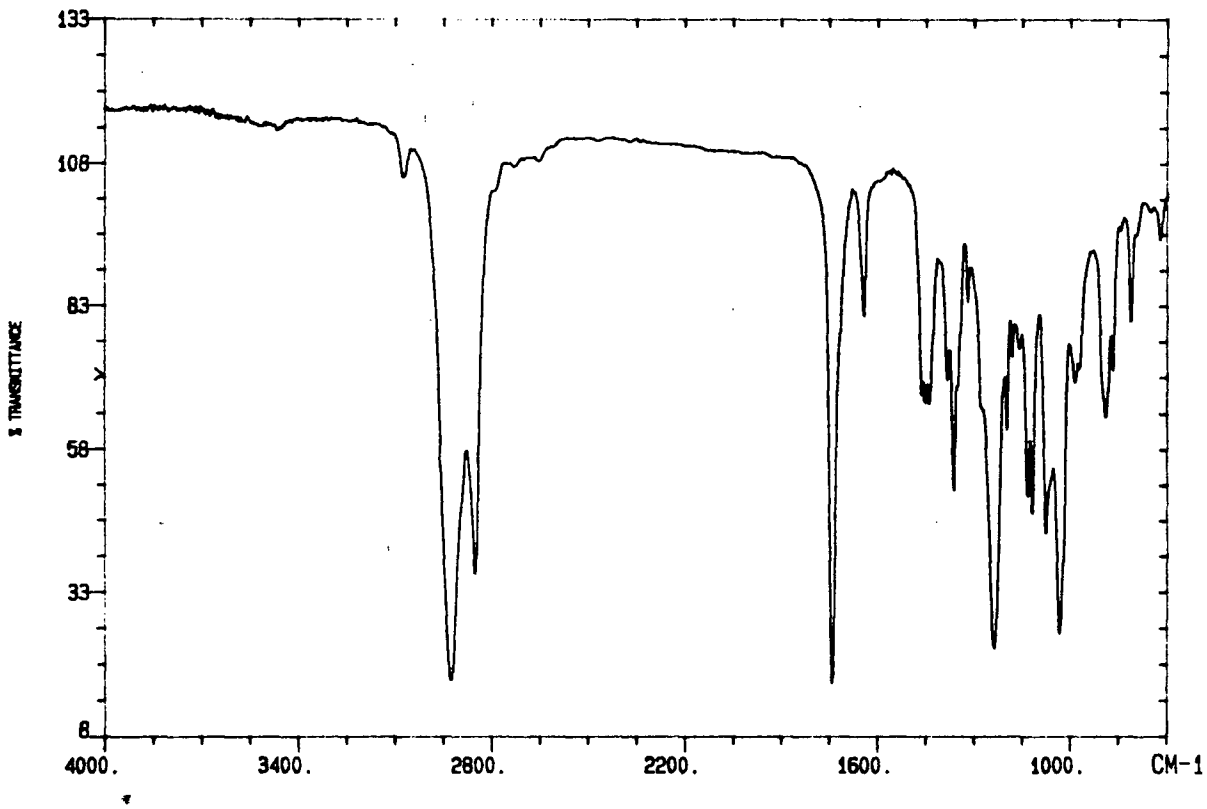
CM-1


AcO
OTHP

93

5
4
3
2
1
0 PPM


133
108
83
58
33
8
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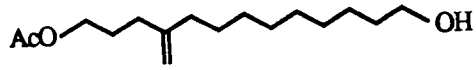
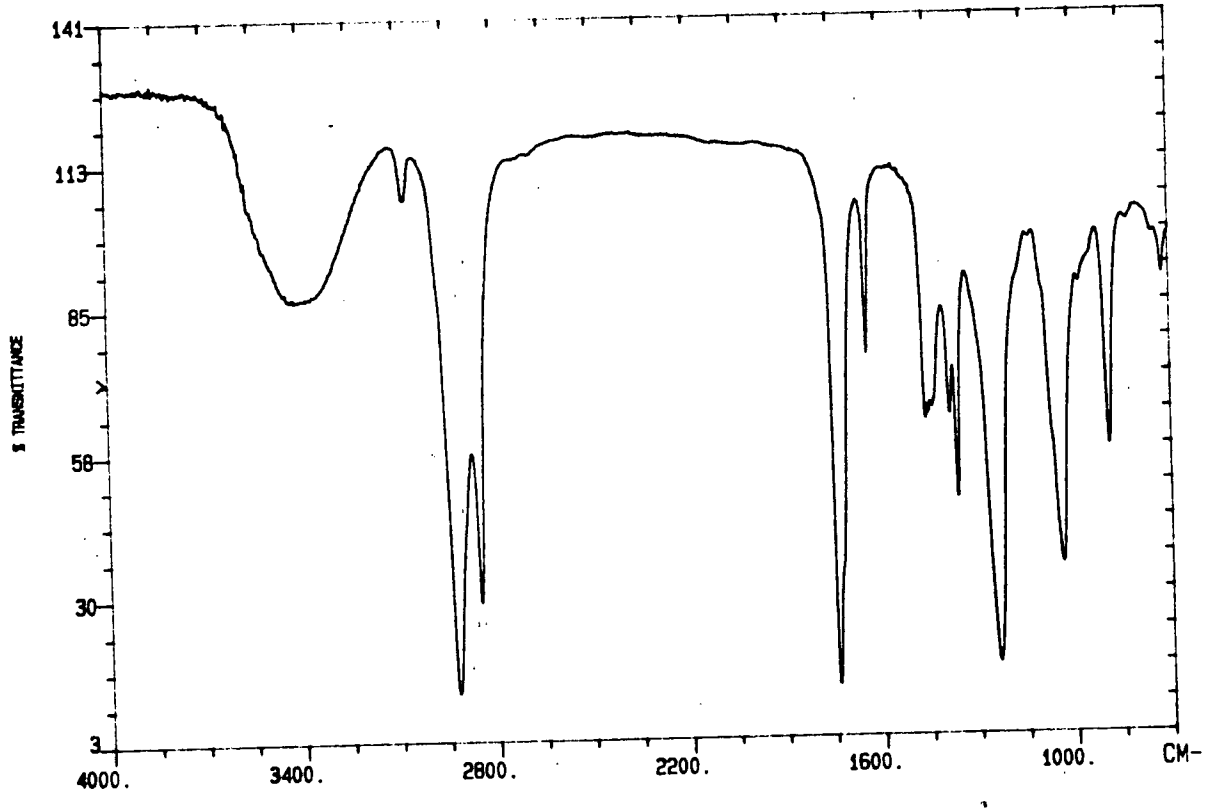
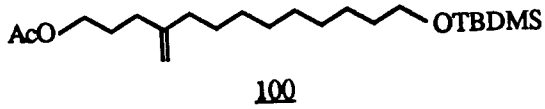
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


AcO
OH

98

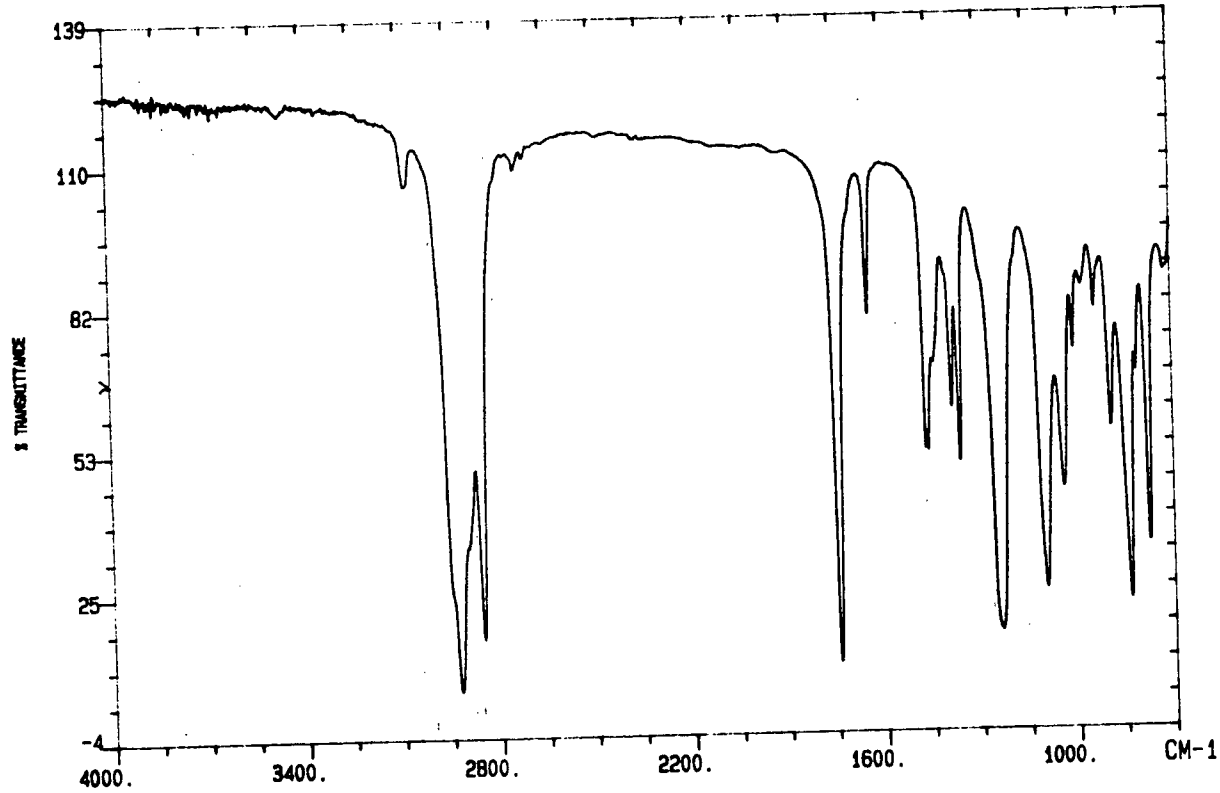
5
4
3
2
1
0 PPM

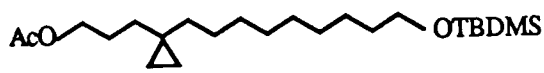

141
113
85
58
30
3
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


AcO
OTBDMS

100

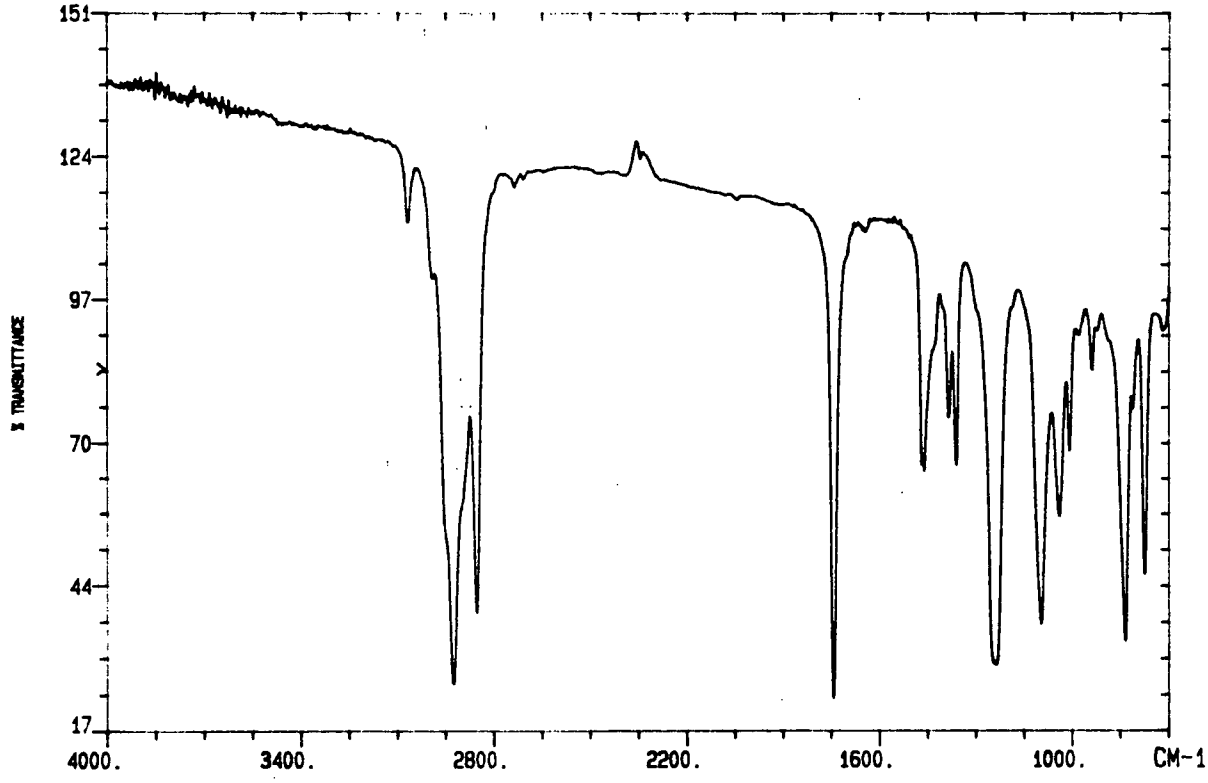
5
4
3
2
1
0 PPM

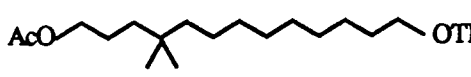

139
110
82
53
25
-4
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


AcO
OTBDMS

101

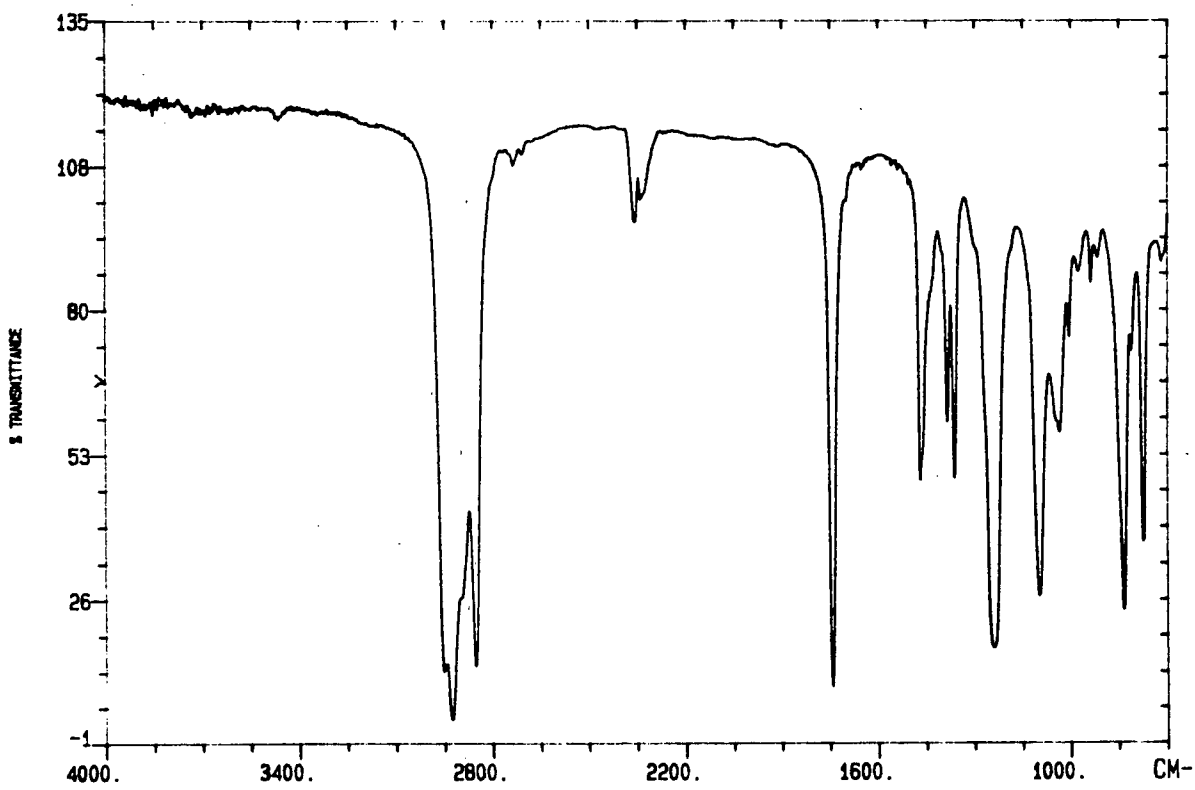
5
4
3
2
1
0 PPM

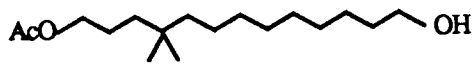

151
124
97
70
44
17
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


AcO
OTBDMS

102

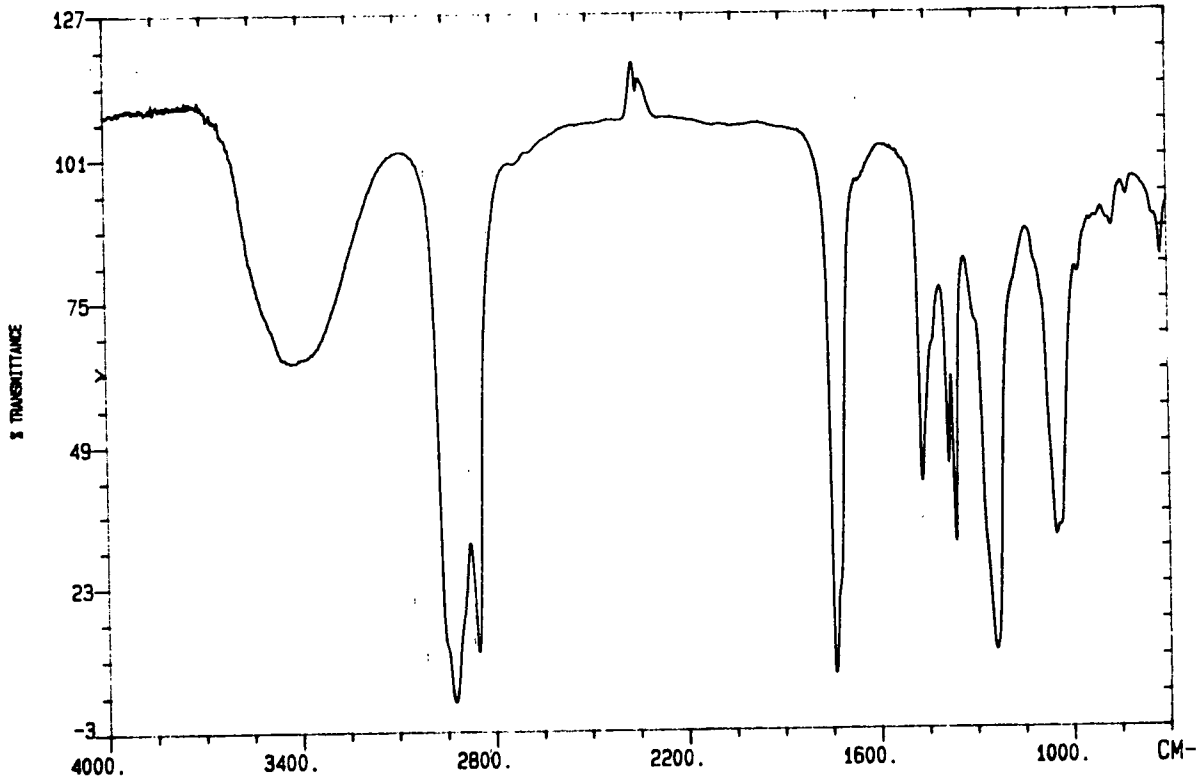
5
4
3
2
1
0 PPM

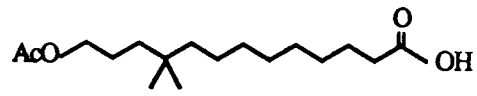

135
108
80
53
26
-1
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


AcO
OH

103

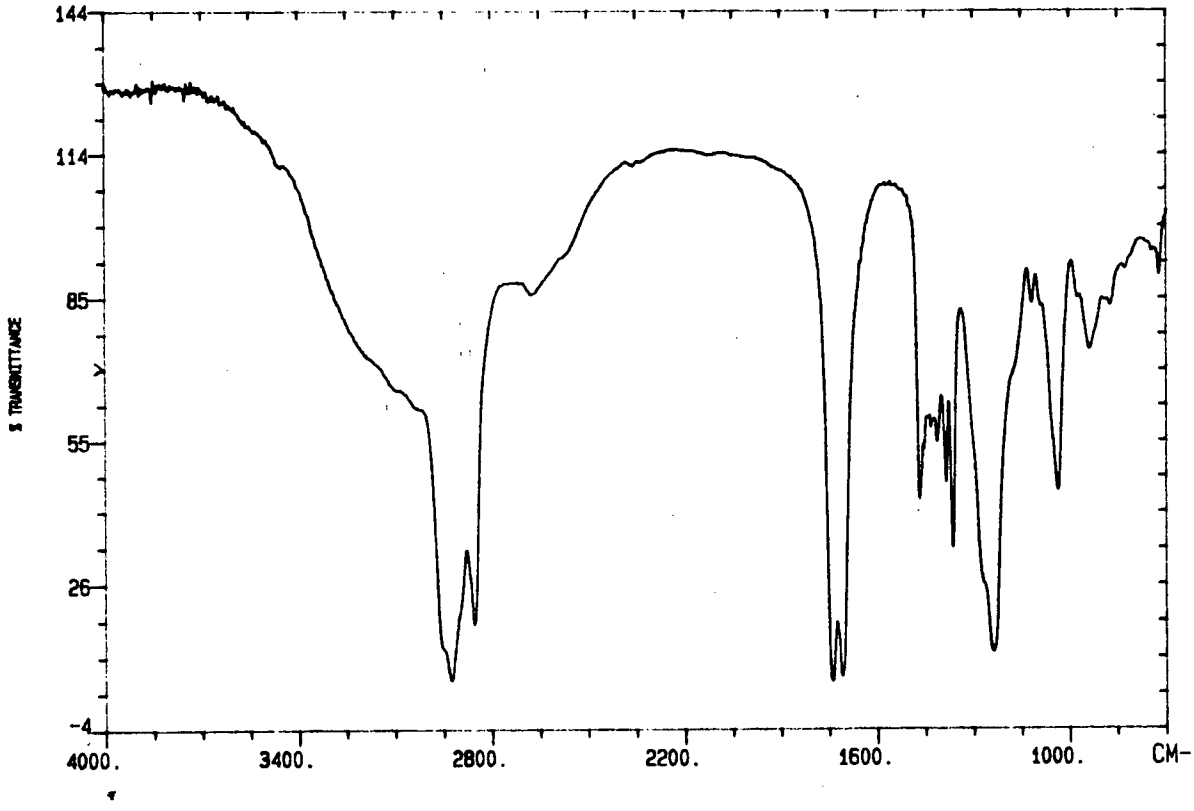
5
4
3
2
1
0 PPM

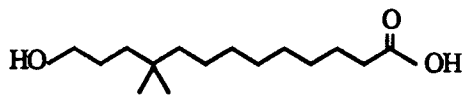

127
101
75
49
23
-3
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


AcO
O
OH

104

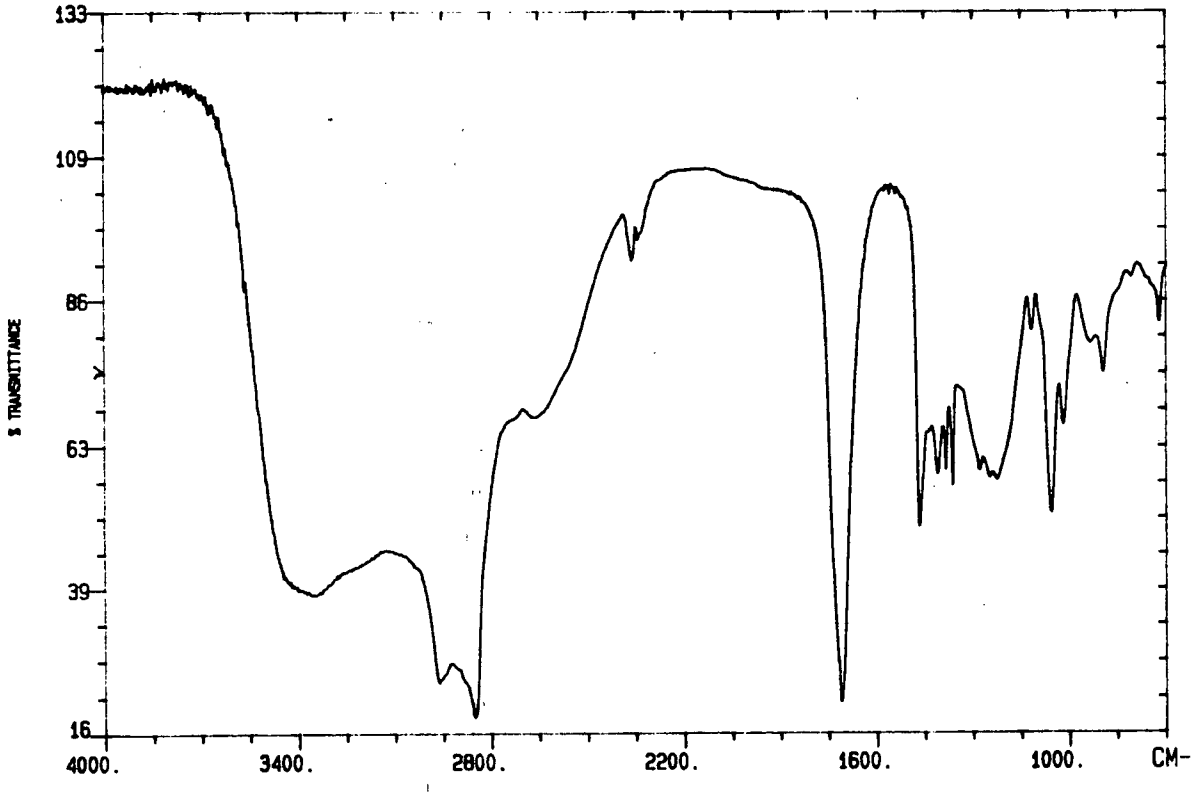
5
4
3
2
1
0 PPM


144
114
85
55
26
-4
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


HO
O
OH

105

4
3
2
1
0 PPM


133
109
86
63
39
16
% TRANSMITTANCE
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3400.
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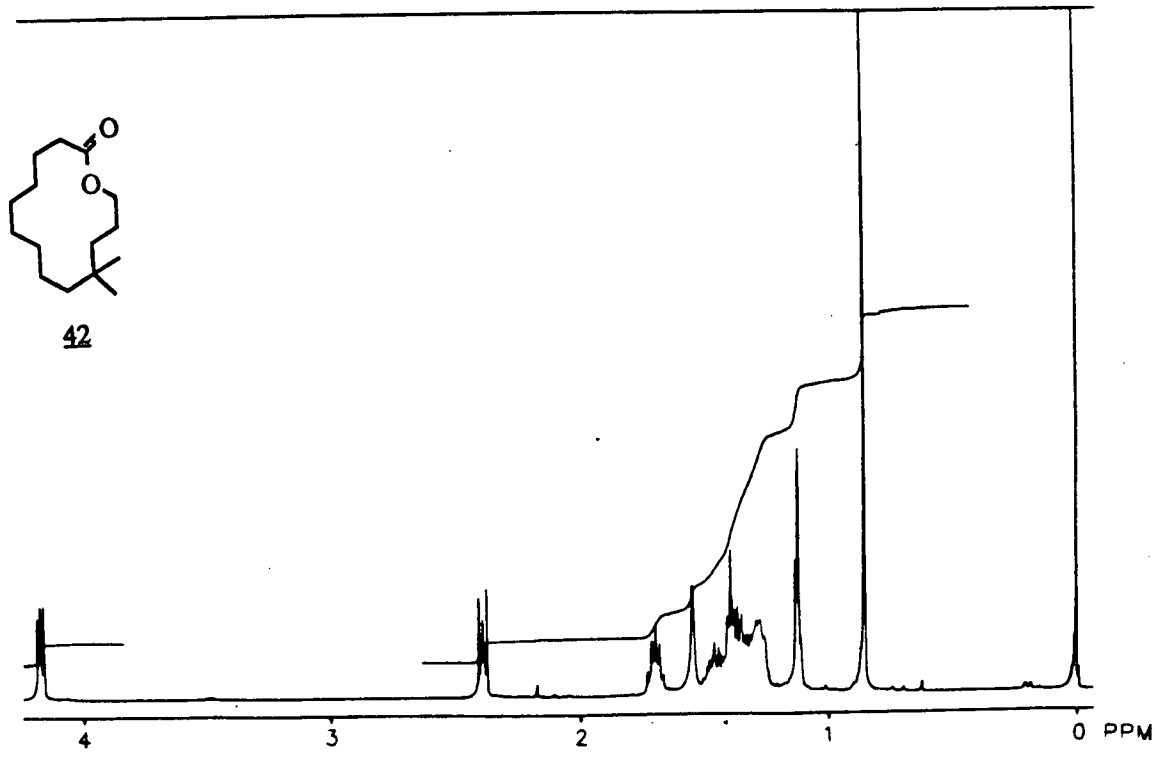
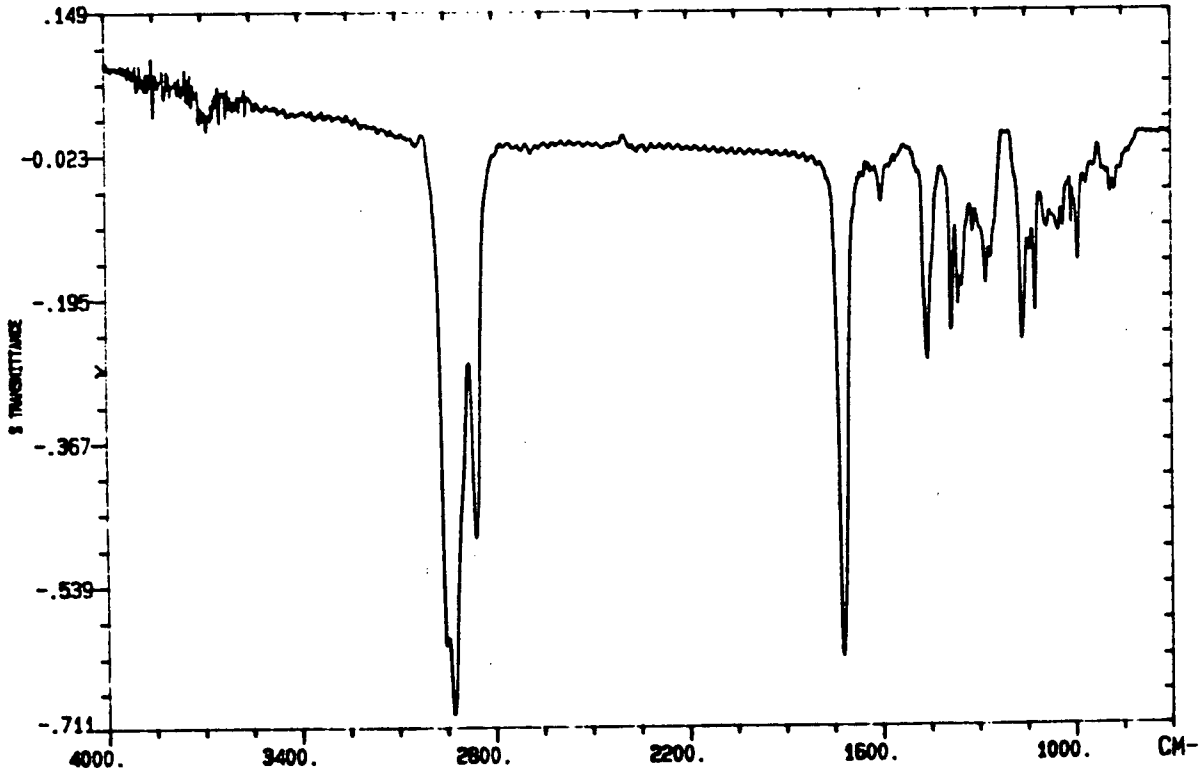
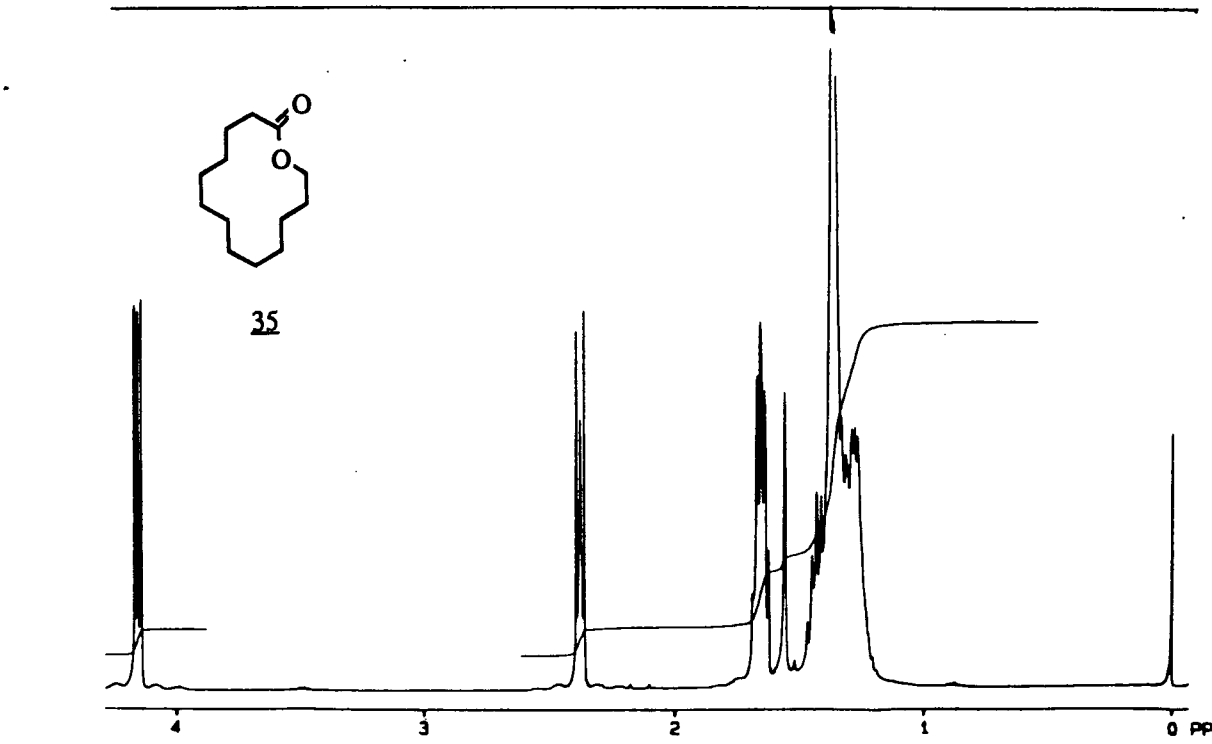
2200.
1600.
1000.
CM-1

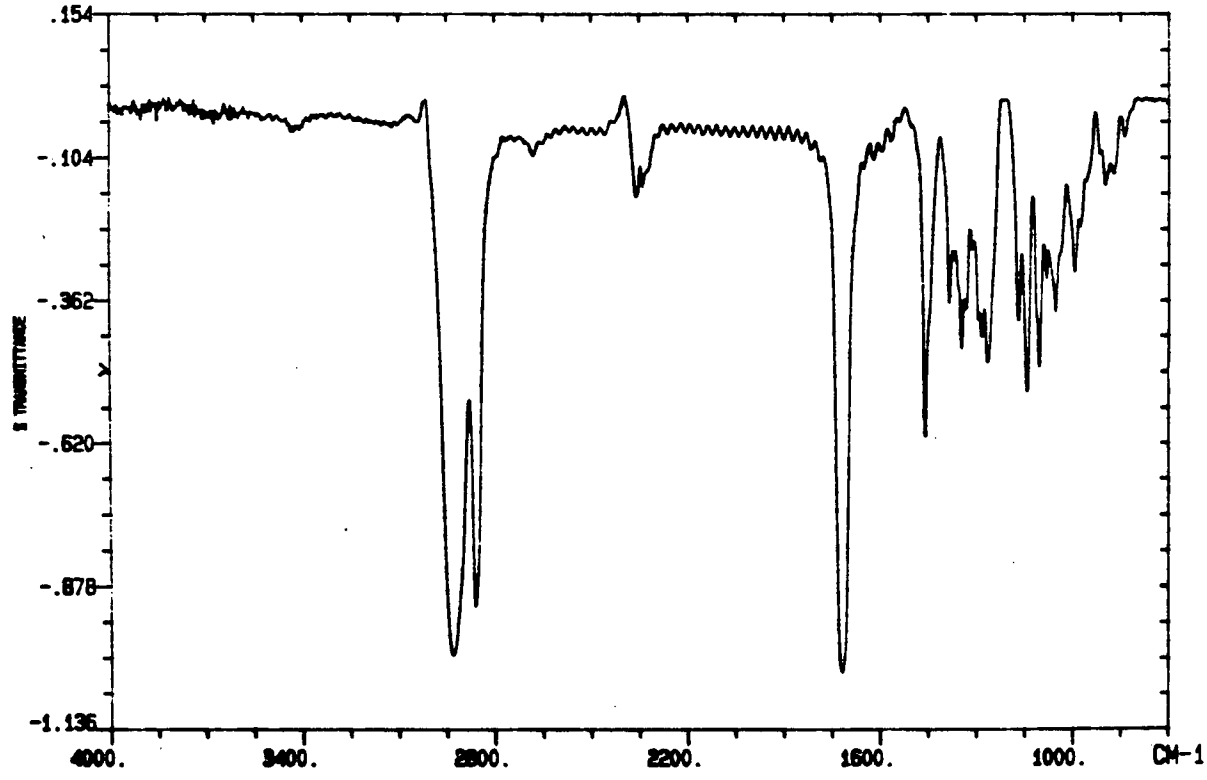

O
O
4
3
2
1
0 PPM

42


.149
-0.023
-.195
-.367
-.539
-.711
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


O
O
4
3
2
1
0 PPM

35


.154
-.104
-.362
-.620
-.878
-1.136
% TRANSMITTANCE
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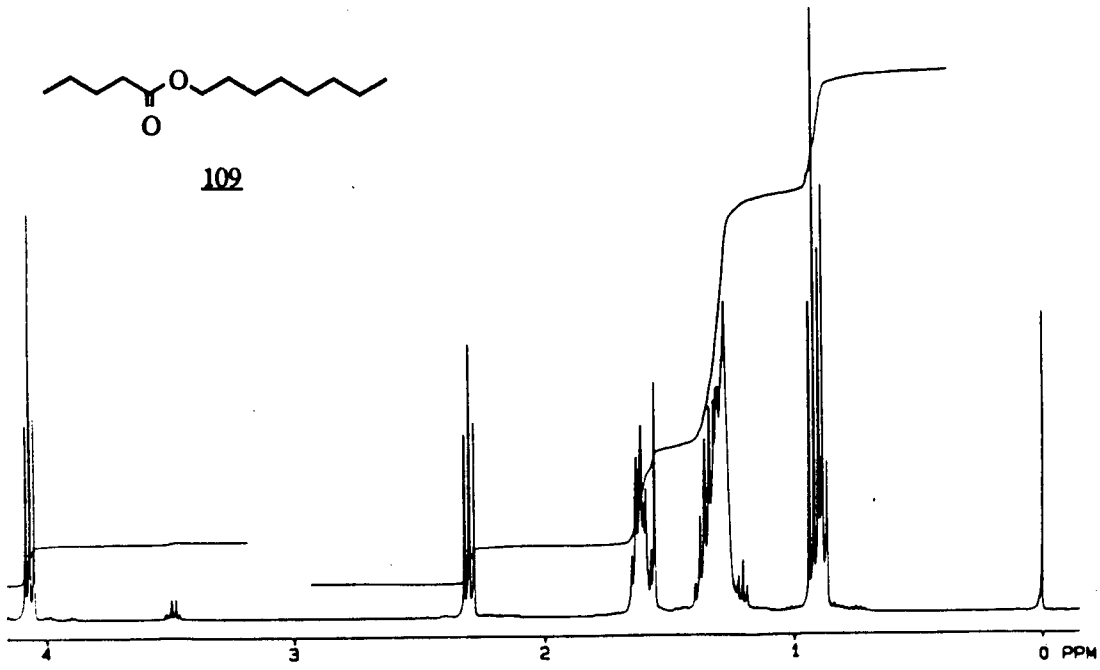
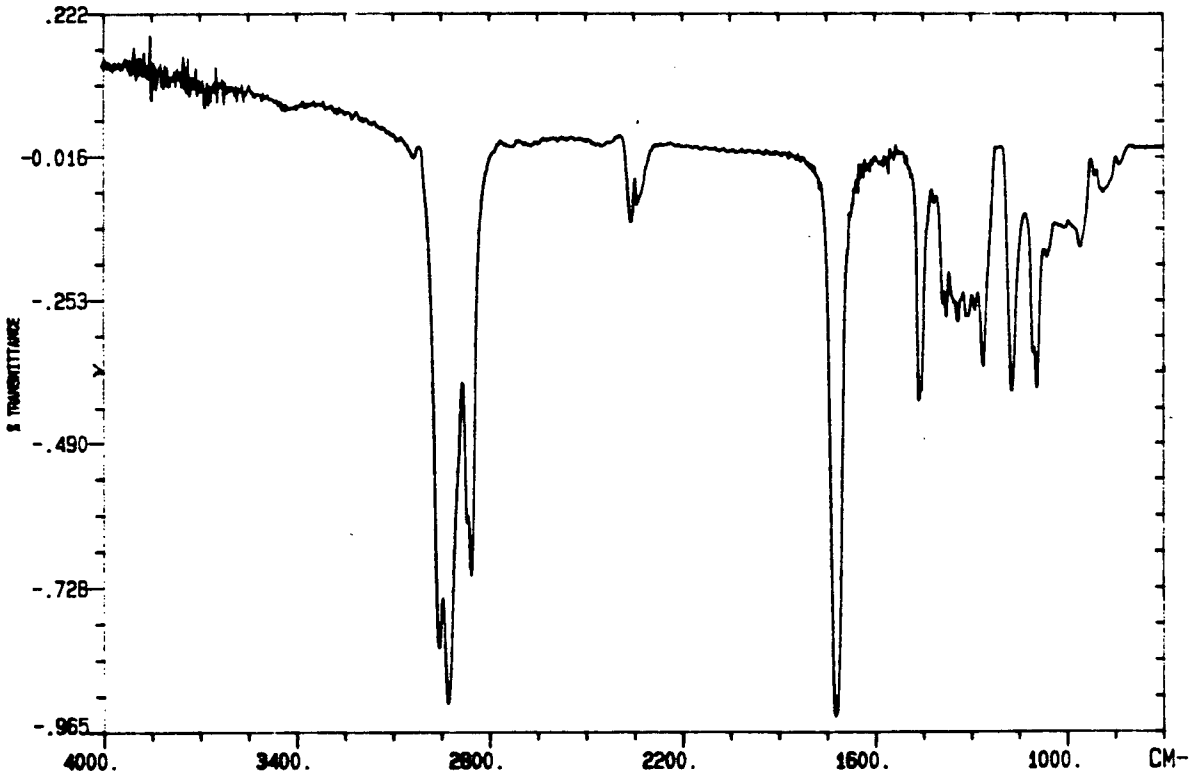
3400.
2800.
2200.
1600.
1000.
CM-1


O
O
4
3
2
1
0 PPM

109


.222
-0.016
-.253
-.490
-.728
-.965
% TRANSMITTANCE
4000.
3400.
2800.
2200.
1600.
1000.
CM-1