SYNTHESIS AND REACTIVITY OF 14-MEMBERED KETO LACTONES

by

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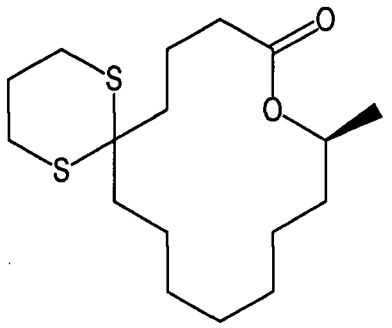
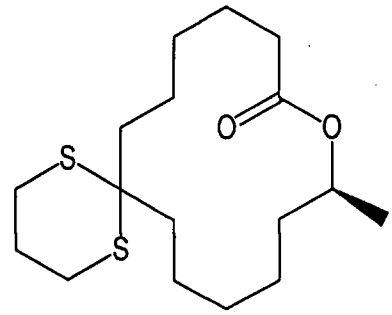
DE-6 (2/88)

Abstract

A convergent synthesis using dithiane alkylations to produce a long chain hydroxy acid, and subsequent macrolactonization of the latter, yielded the 14-membered macrolides **47** and **58**.

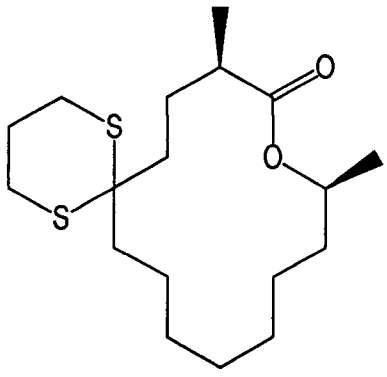


47

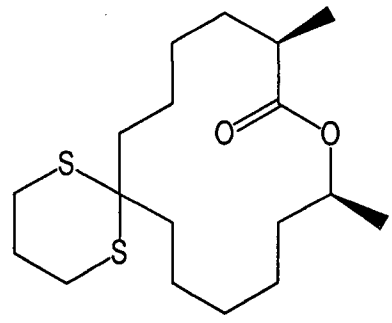


58

Alkylation of **47** with methyl iodide gave a diastereomeric product mixture of α-methylated lactones with the major product having the 2R*,13S* stereochemistry (**71**). The product ratio was explained by using low energy starting material conformations combined with MM2 calculations. Alkylation of **58** in the same manner also yielded a mixture with the major product having the 2R*,13S* stereochemistry (**77a**).

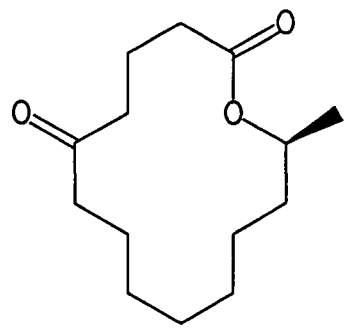


71
2R*,13S*

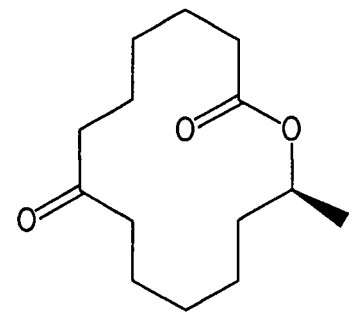


77a
2R*,13S*

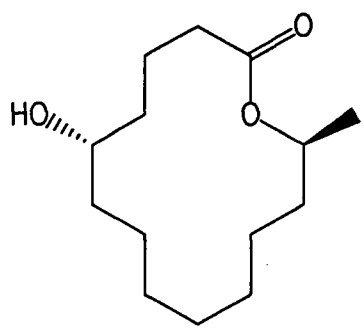
Hydrolysis of the dithiane ring on **47** and **58** gave the keto lactones **28** and **29** respectively. Reduction of the ketone in **28** yielded a mixture of diastereomeric hydroxy lactones of which the major product had the 5S*,13S* stereochemistry (**61**); this stereochemistry was confirmed by the X-ray crystallographic structure of the *p*-bromobenzene sulfonate derivative. Reduction of the ketone in **29** also yielded a diastereomeric mixture of hydroxy lactones; the 7S*,13S* stereochemistry of the major product **67** was suggested by MM2 calculations.



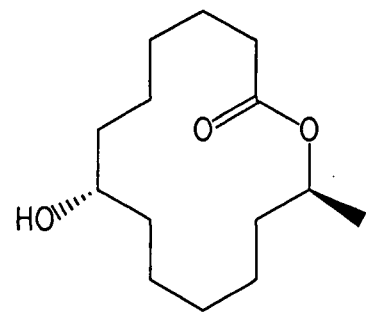
28



29



61
5S*,13S*



67
7S*,13S*

Treatment of both **28** and **29** with trimethylsilyl trifluoromethanesulfonate and *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of triethylamine gave rise to mixtures of isomeric enol ethers; the product distribution could be partly explained by MM2 calculations based on product conformations.

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List of abbreviations

Å	angstrom
ANAL	elemental analysis
calcd	calculated
CD	circular dichroism
COSY	correlation spectroscopy
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
eV	electron volts
FT	Fourier transform
GC	gas chromatography
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared
J	coupling constant
LDA	lithium di-isopropylamide
LRMS	low resolution mass spectroscopy
m	meta
m	multiplet
MAD	methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)
Me	methyl

MM	molecular mechanics
mp	melting point
n	normal
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOEDS	nuclear Overhauser effect difference spectroscopy
p	para
Ra-Ni	Raney nickel
R_f	in thin layer chromatography, ratio of distance traveled by the compound to the distance traveled by the solvent
R_t	retention time
s	singlet
t	triplet
TBDMS	*tert*-butyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl

Acknowledgements

First, I would like to thank Dr. Weiler for his encouragement and his patience during my studies in his group.

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

Finally, I would like to thank my colleagues in the Weiler group for making the laboratory an enjoyable, if not downright looney, working environment.

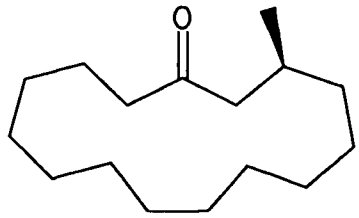
CHAPTER I

Introduction

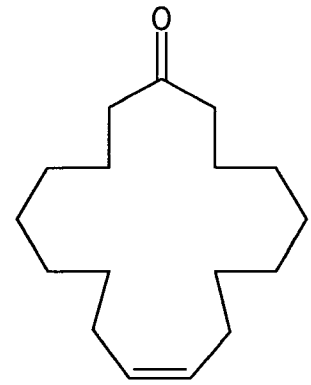
In the last 50 years, the laboratory synthesis of complex natural products has presented a formidable challenge to the organic chemist. The complexity and the cyclic nature of many of these natural products have led chemists to a better understanding of the importance of conformation to chemical reactivity.[1,2] Today, the concepts and ideas of conformational analysis have a prevalent place in the rationalization of reaction mechanisms and chemical transformations.[3]

1.1 Structure and chemistry of large rings

Muscone (**1**) and civetone (**2**), components of musk oil, were the first macrocyclic natural products ever isolated, by Ruzicka in 1926.[4]



1

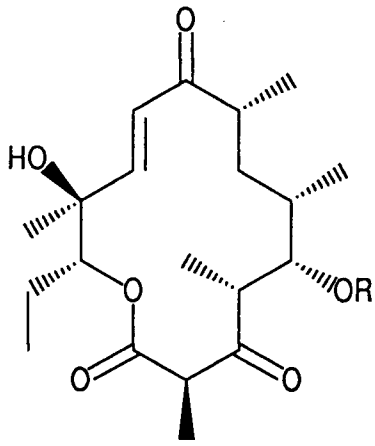


2

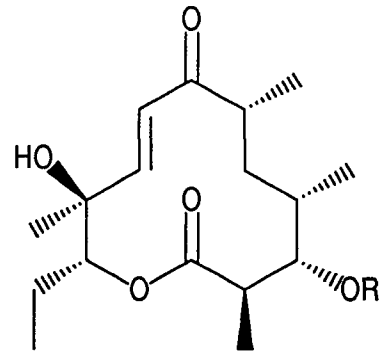
With no modern spectroscopic methods available, he was able to ascertain the macrocyclic nature of these two compounds by chemical degradation (not an easy task as muscone, for example, had but one functional group). The actual conformations of muscone and civetone were not known at the time; the general belief was that large rings existed in a multitude of conformations and that their chemistry should not differ much from that of cyclohexane.

After Ruzicka's work, more macrocyclic compounds were isolated, identified, and

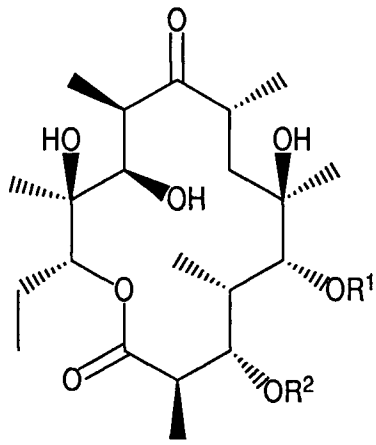
synthesized. An interesting class of macrocyclic compounds, due to their diverse biological properties, is the one known as "poly-oxo" macrolides. Poly-oxo macrolides consist of a lactone ring, normally 12-, 14-, or 16-membered. Other features include: (1) an array of substituents uniquely and systematically distributed around the ring and (2) the linkage of one or more sugar residues, very often containing nitrogen. Representative examples are pikromycin (**3**) (first one ever isolated, by Brockmann and Henkel in 1950),[5] methymycin (**4**), erythromycin A (**5**), and carbomycin A (**6**).



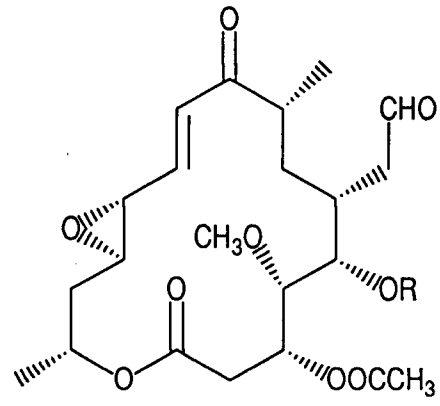
3, R= desosaminyl



4, R= desosaminyl



5, R^1= desosaminyl
R^2= cladinosyl



6, R= (isovaleryl)-mycarosyl-mycaminosyl

Because of their interesting properties, chemists have tried for many years to synthesize these macrolides. However, it was not until the late 1970's that major synthetic accomplishments

were made in this field. There were two reasons for this: one was the difficulty in constructing a medium- or large-ring lactone and the other was the challenge of introducing chiral centers on a straight chain aliphatic acid. Today, numerous methods for macrolactonization are available and have been extensively reviewed.[6] Also, introduction of chiral centers with good stereoselectivity has been achieved for a variety of transformations such as carbonyl reductions, additions to carbon-carbon double bonds, alkylations, and aldol condensations.

However, in addition to the above transformations (achieved, in the great majority of cases, with the help of chiral auxiliaries), another methodology has been gaining popularity, and this factor is the effect of a molecule's conformation on the stereoselectivity of its reactions.

1.2 Conformational analysis of large rings

Following up on his work on large ring compounds, Ruzicka and co-workers, along with Prelog, noted that the plot of melting point versus ring size for cyclic aliphatic hydrocarbons showed an unexpected dependency on ring size.[7,8] This phenomenon was left unexplained until Huber-Buser et al., in 1961, showed that large ring molecules could exist in one of many possible conformations; X-ray crystallographic structures of many substituted cyclodecanes showed that these compounds all crystallized in the same conformation, implying that these compounds all existed in the same potential energy minimum well.[9]

A few years later, Dale pointed out that the conformations of the above substituted cyclodecanes were easily superimposed on a diamond lattice (Figure 1).[10]

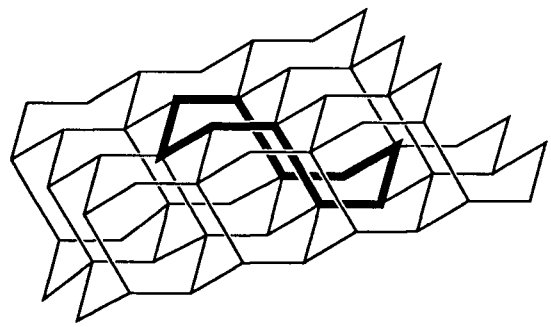


Figure 1. The diamond lattice conformation of cyclodecane.

The diamond lattice is an array of carbon atoms with bond lengths of 1.54 Å, C-C-C bond angles of 109.5°, and gauche or trans torsional angles; any conformation which can be superimposed on this lattice must represent a potential energy minimum.

Dale asserted two important facts: 1) that a ring with an odd number of atoms cannot be superimposed on the diamond lattice and hence cannot exist in a strain free conformation, and 2) that 7- to 13-membered ring compounds cannot exist in a diamond lattice conformation because of the severe transannular hydrogen interactions.[10] That the cyclodecane derivatives exist in a diamond lattice conformation clearly shows a compromise between angle strain, torsional energy, and transannular hydrogen repulsions in these compounds. Dale then proposed low energy conformations for all even-numbered rings from C_6 to C_{16}. All of these predictions have proved fairly accurate by X-ray crystallography and theoretical calculations of model compounds. An example of this is the conformation of cyclotetradecane (Figure 2).[11]

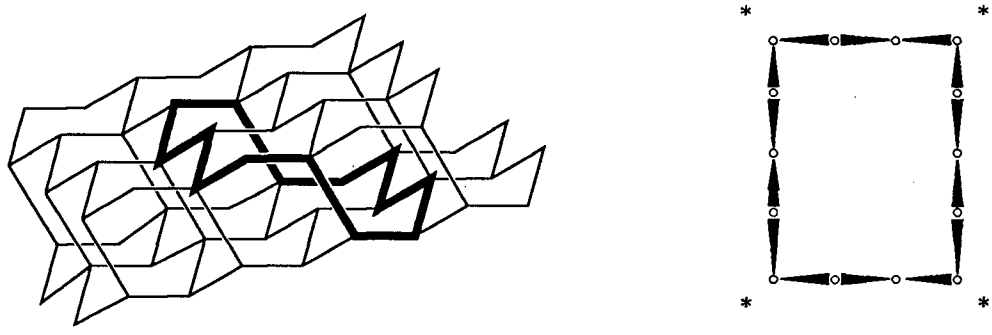


Figure 2. Diamond lattice conformation of cyclotetradecane (* corner position).

If one views the strain free conformation of cyclotetradecane from the "top", an interesting feature can be seen: some carbon atoms have both hydrogens pointing outside of the ring, whereas the other carbon atoms have at least one hydrogen pointing inside the ring. The hydrogens pointing outside the ring don't experience any transannular repulsions (Figure 3) and their parent carbons are said to occupy a "corner" position. Dale concluded that these corner atoms should be the only carbons capable of accomodating geminal disubstitution without transannular interactions.

Number of internal hydrogen interactions

A: 1
B: 2
C: 3

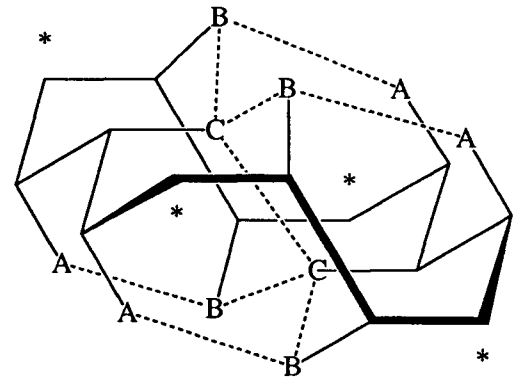


Figure 3. Intramolecular hydrogen interactions in cyclotetradecane (* corner position).

Examination of molecular models led to the definition of a corner position as a sequence of two contiguous gauche dihedral angles of the same sign flanked on either side by an anti dihedral angle.[12] We noticed two different types of corner positions. One, the classical corner position as defined by Dale, is flanked by two gauche angles of the same sign (e.g. 180°, +60°, +60°, 180°).[10] Another corner position, which we called a pseudo-corner, has two contiguous gauche angles of opposite signs (e.g. 180°, -60°, +60°, 180°). This pseudo-corner was also recognized by Borgen et al. in crystal structures of 1,4,8,11-tetraoxacyclotetradecane.[10]

We formulated the following definitions for the corner and pseudo-corner positions (Figure 4):

1. A corner position has two contiguous gauche angles of the same sign flanked on either side by an anti dihedral angle of opposite sign (e.g. -180°, +60°, +60°, -180°).

2. A pseudo-corner position has two contiguous gauche angles flanked on either side by an anti dihedral angle, with alternating signs (e.g. -180°, +60°, -60°, +180°).

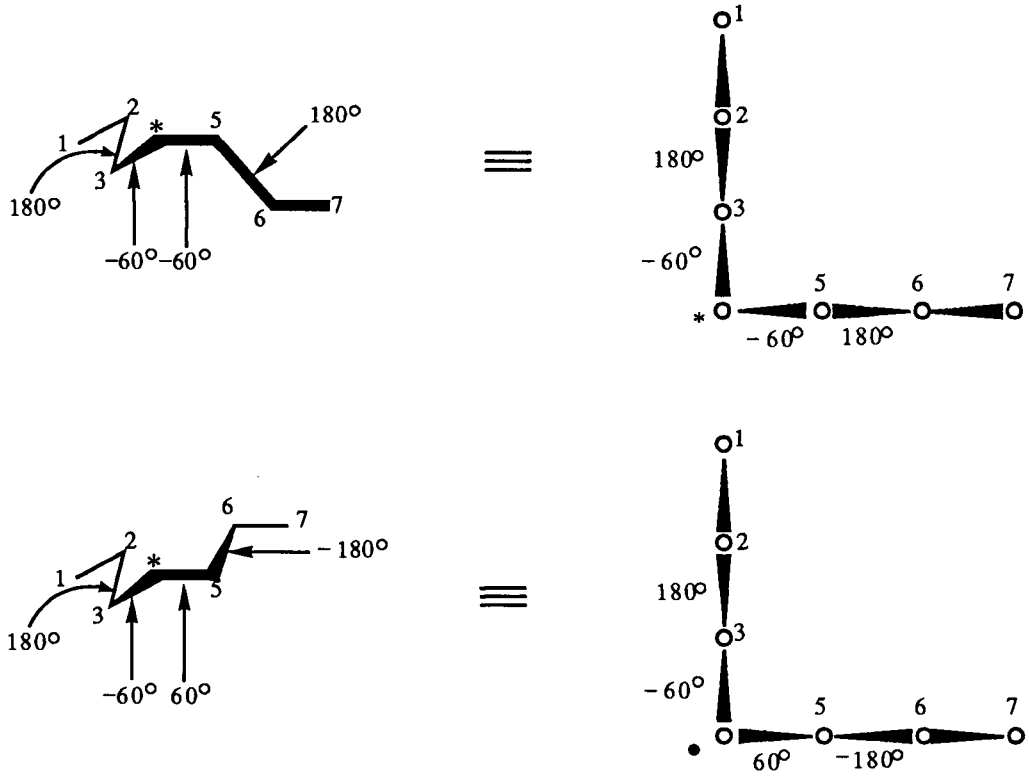
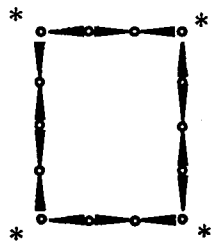
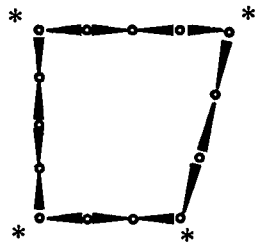
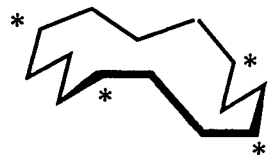
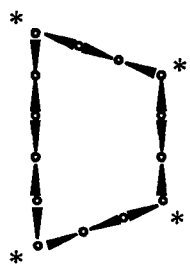
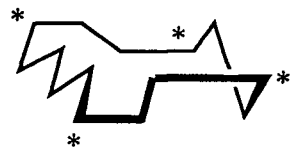


Figure 4. The corner (above) and pseudo-corner (below) position.

Dale used the corner positions to establish a simple nomenclature for macrocycles.[12] This nomenclature consists of a series of numbers in brackets, each number representing the number of bonds between consecutive corner atoms. Thus the lowest energy conformation for cyclotetradecane is a [3434] conformation (see Table I).

Dale then proceeded to calculate the strain energy of different diamond lattice conformations, using the potential energy curve of butane. The calculated strain energies were crude but the energy trends proved very reliable.[12] Later, with the advent of molecular mechanics calculations, Anet and Cheng obtained more accurate strain energies which showed that cyclotetradecane should exist predominantly in the [3434] conformation.[13] In addition, two non-diamond lattice conformations were discovered: the [3344] (with a strain energy of 1.1 kcal/mol relative to the [3434] conformation) and the [3335] (relative strain energy of 2.4 kcal/mol).

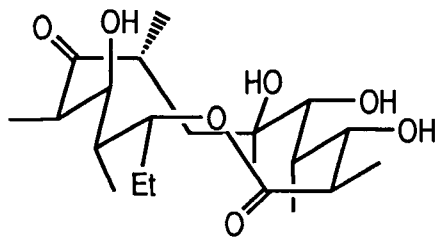
Table I. The three lowest energy conformations of cyclotetradecane

Conformation	Top view	Side view	Strain energy
[3434]			0 kcal/mol
[3344]			1.1 kcal/mol
[3335]			2.4 kcal/mol

* corner position

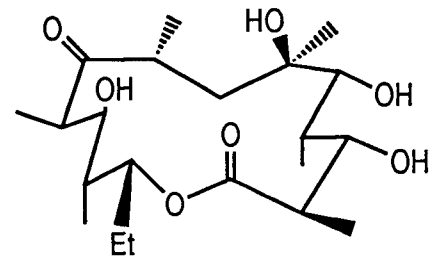
The [3344] and [3335] conformations were found to be rotamers in the pseudo-rotation of the [3434] conformation. Calculated pseudo-rotational barriers of 7-8 kcal/mol agreed with the low temperature ^{1}H NMR and ^{13}C NMR studies by Anet et al., who found a pseudo-rotational barrier of 7 kcal/mol by using line shape techniques.[13]

Following the results of these conformational analyses, researchers began to investigate the conformations of the natural macrolides. The first model for the three-dimensional structure of a macrolide was advanced by Celmer in 1965.[14] He proposed a structure for the preferred conformer of erythronolide B (**8**), the aglycone of erythromycin B. Patterned after Dale's [3434] conformation, the Celmer model was in reasonable agreement with the ^{1}H NMR data (Figure 5).[15]



8

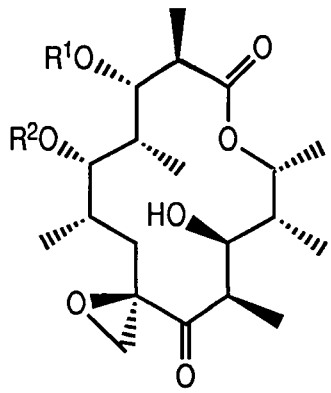
Celmer Conformation[15]



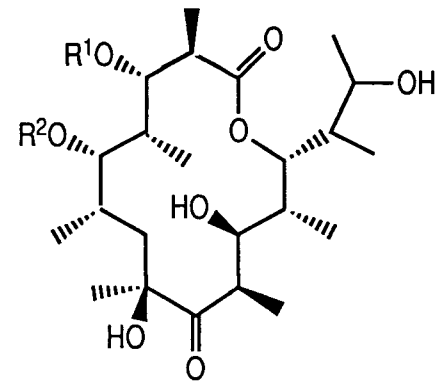
Perun Conformation[16]

Figure 5. Celmer and Perun conformation for aglycone of erythromycin B.

However, some discrepancies with other data led to the belief that this was not the most favored, low-energy conformation: disagreement with the CD data, unfavorable steric interactions between the 4- and 6-methyl groups, and the 12-methyl group and lactone functionality.[16] Close re-examination of all data led to the Perun conformation for erythronolide B (Figure 5), which agreed with all experimental data.[16] The Perun conformation could best explain the experimental results on several erythromycin derivatives.[17] Similar studies on different macrolide antibiotics confirmed the Perun conformation and showed that oleandomycin (**9**) and lankamycin (**10**) occurred in the same low energy conformation as the erythromycins.[18]



9, R^1= oleandrosyl
R^2= desosaminyl



10, R^1= aracnosyl
R^2= chalcosyl

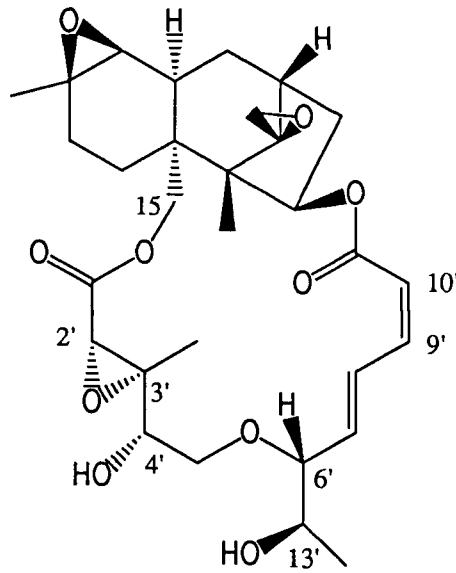
There has been some controversial evidence regarding the conformational equilibrium of

these macrocyclic rings in the solid and liquid states. In recent studies, Shannon et al. showed that cyclotetradecane existed in the [3434] conformation to an extent of 60% at 340 K.[19] This is at odds with calculations by Dale which indicated that cyclotetradecane existed almost entirely in the [3434] conformation in the liquid state.[20] Clearly, the conformational behavior of large rings is not clear cut and caution needs to be exerted in the conformational analysis of these compounds.

1.3 Conformational control in synthesis of macrocyclic natural products

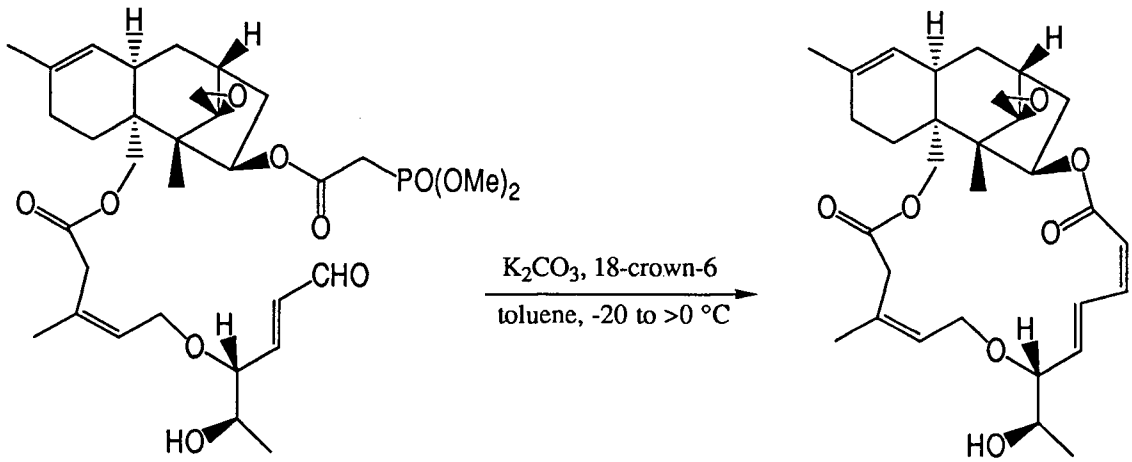
The stereoselective synthesis of complex macrocyclic natural products has been one of the major goals of organic chemistry. The majority of researchers prefer to attack such a synthesis by synthesizing parts of the molecule with stereocontrolled reactions on acyclic chains, giving fragments with the correct relative stereochemistry, then joining these parts together to give the final product with the correct absolute stereochemistry. However, some groups have shown a preference for the more elegant method of conformational control to introduce new chiral centers.[21] Following are three examples on the application of this method.

Still, one of the pioneers in the application of conformational control in synthesis, and co-workers used this approach in the final stages of his synthesis of baccharin B5 (**11**), a highly oxygenated trichothecanoid with anti-leukemic properties.[22]

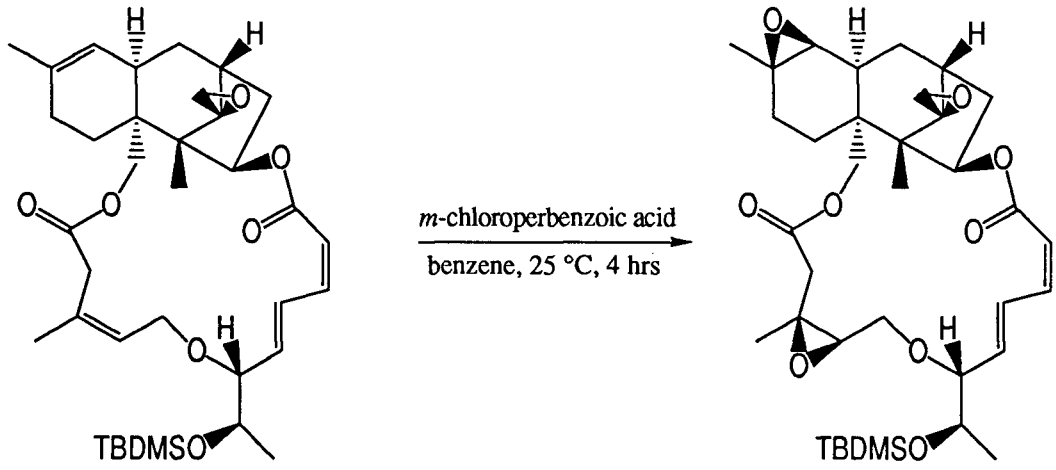


Still's synthetic plan toward baccharin B5 involved the use of D-xylose as a source of the C6' and C13' asymmetric centers and conformational control for the selectivity in the macrocyclization and for the introduction of the C2' and C4' chiral centers. The α,β-unsaturated aldehyde **12**, the macrolide precursor, was obtained from the corresponding phosphonoester in 65% yield as a 4:1 E:Z mixture, of which the E-precursor was easily separated by column chromatography. This aldehyde was then cyclized using K_2CO_3 and 18-crown-6 in toluene (-20 to 0 °C) to yield a 1.5:1 mixture of (E,Z)- and (E,E)-macrolides in 75% yield. Flash column chromatography afforded the pure (E,Z)-macrolide (**13**) in 45% yield.

Still was now ready to use his conformational control approach to complete the synthesis of baccharin B5. The hydroxyl group at C13' was protected as its *tert*-butyldimethylsilyl ether to give compound **14**. Next came the key reaction: treatment of **14** with *m*-chloroperbenzoic acid in benzene afforded a single triepoxide **15** in 70% yield.



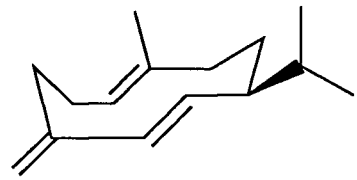
12 **13**



14 **15**

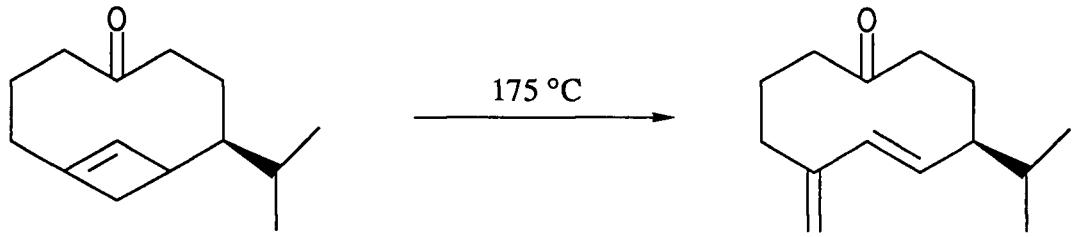
The stereoselectivity of the reaction, as measured by response calibrated HPLC, appeared to be >15:1 for both the cyclohexane epoxide and the macrocyclic epoxide at C2'-C3', with the latter stereochemistry controlled by the conformation of the ring. This triepoxide was then carried through to the final product, baccharin B5 (**11**).

Later, Schreiber and Hawley used the conformational control of enolate geometry in a synthesis of germacrene-D (**16**), a terpenoid compound which mimics the action of a sex pheromone of the American cockroach *Periplaneta Americana*.[23]



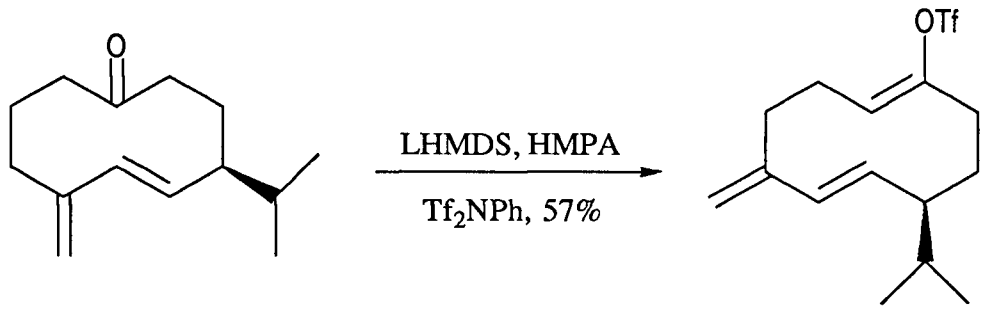
16

The intermediate **18** was obtained by thermal isomerization of the cyclobutene **17** in 92% yield.



17 **18**

The plan was to generate the enolate derivative **19** and submit it to a cuprate coupling to obtain the final product **16**. Results of enolization with lithium diisopropylamide to give the required enol triflate were unsatisfactory. However, lithium hexamethyldisilazide in a mixture of THF and HMPA provided the high regioselectivity required for the enolization, and afforded a 10:1 mixture of enol triflates with the major product having structure **19**.



18 **19**

The stereochemical assignment of the enol triflate **19** was based on its conversion to germacrene-D (**16**). Reaction of **19** with lithium dimethylcuprate gave a 10:1 mixture of germacrene-D and an inseparable isomer.

Schreiber and Hawley rationalized the site- and stereoselectivity of the enolization reaction by considering the conformational properties of the ketone **18**. The boat-chair conformation **18'** is consistent with the results of COSY 2D NMR and NOEDS experiments.[24] Enolization could occur in two possible directions. However, one needs only to compare the dihedral angles of the carbons involved in the enolization to see the selectivity that would occur (Figure 6).

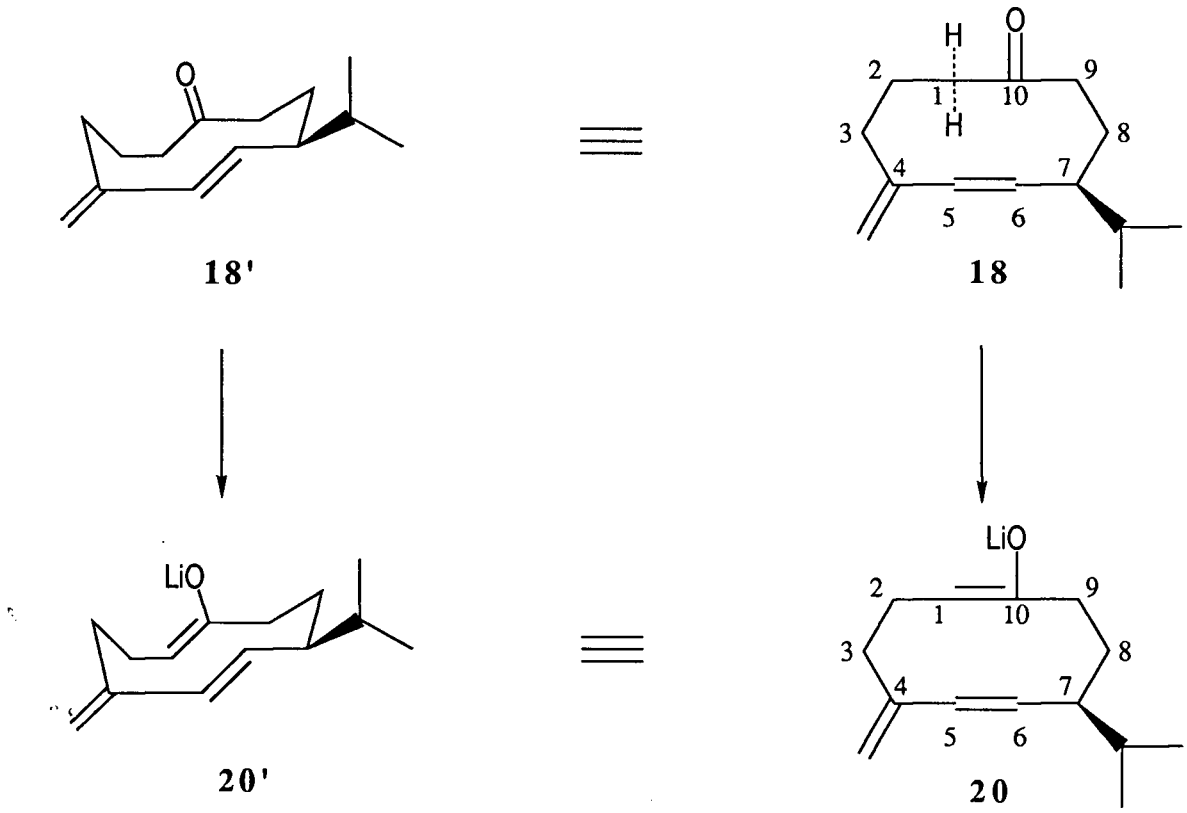
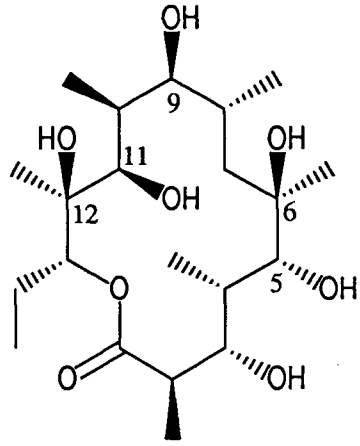


Figure 6. Site selectivity in enolization of **18**.

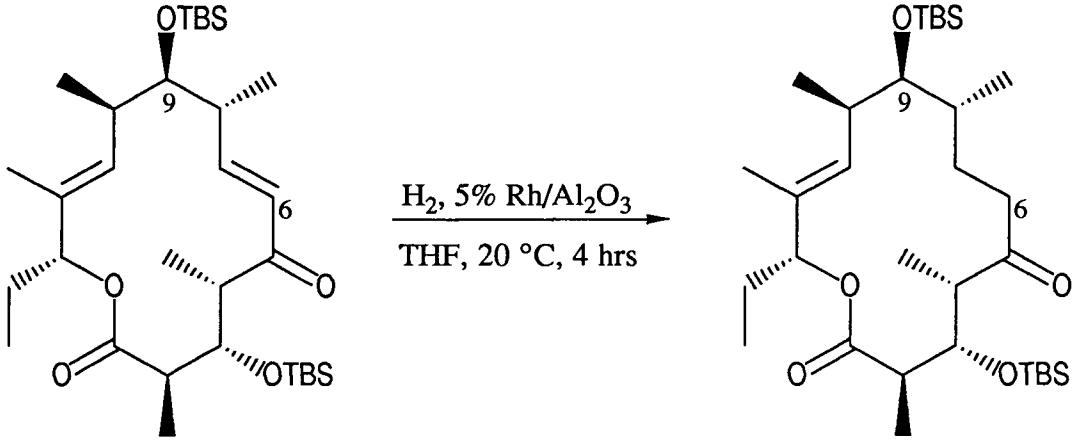
The four-carbon fragment C2-C1-C10-C9 has a dihedral angle of 180° (anti) in both **18'** and **20'**, thus negating the need for conformational reorganization after proton abstraction from C1. On the other hand, the four-carbon fragment C1-C10-C9-C8, having a dihedral angle of 120° in **20'**, would require, upon proton abstraction from C9, major conformational reorganization to avoid the formation of a non-planar enolate and is clearly disfavored. Trapping of the enolate **20'** would give the observed enol triflate **19**. The results of the enolization shown above to give the final product corroborated and showed the usefulness of conformational analysis of medium rings.

Our final example of macrocyclic control comes from a synthesis of (+)-(9S)-dihydroerythronolide A (**21**) performed by Paterson's group in Cambridge.[25]



21

The substituted macrolide **22** was obtained from its seco-acid precursor via a macrolactonization by the Yamaguchi method[26] in 91-96% yield.

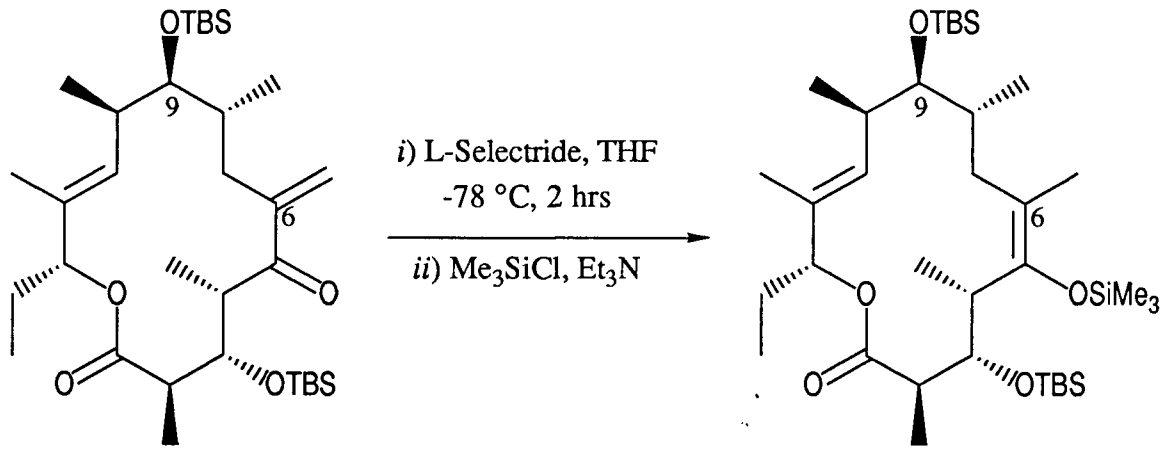


22 **23**

The enone **22** was selectively hydrogenated with 5% Rh/Al_2O_3 to give the ketone **23** in 92% yield. Deprotonation of **23** by LDA in THF occurred exclusively at C6 to give a single enolate stereoisomer as shown by quenching with trimethylsilyl chloride. Reaction of the enolate with formaldehyde gave a 57:43 mixture of hydroxymethylated isomers which underwent mesylation and *in situ* elimination with DBU to give the α-methylene ketone **24.**

MM2 calculations on the enone **24** showed a preference for the s-cis conformation over the

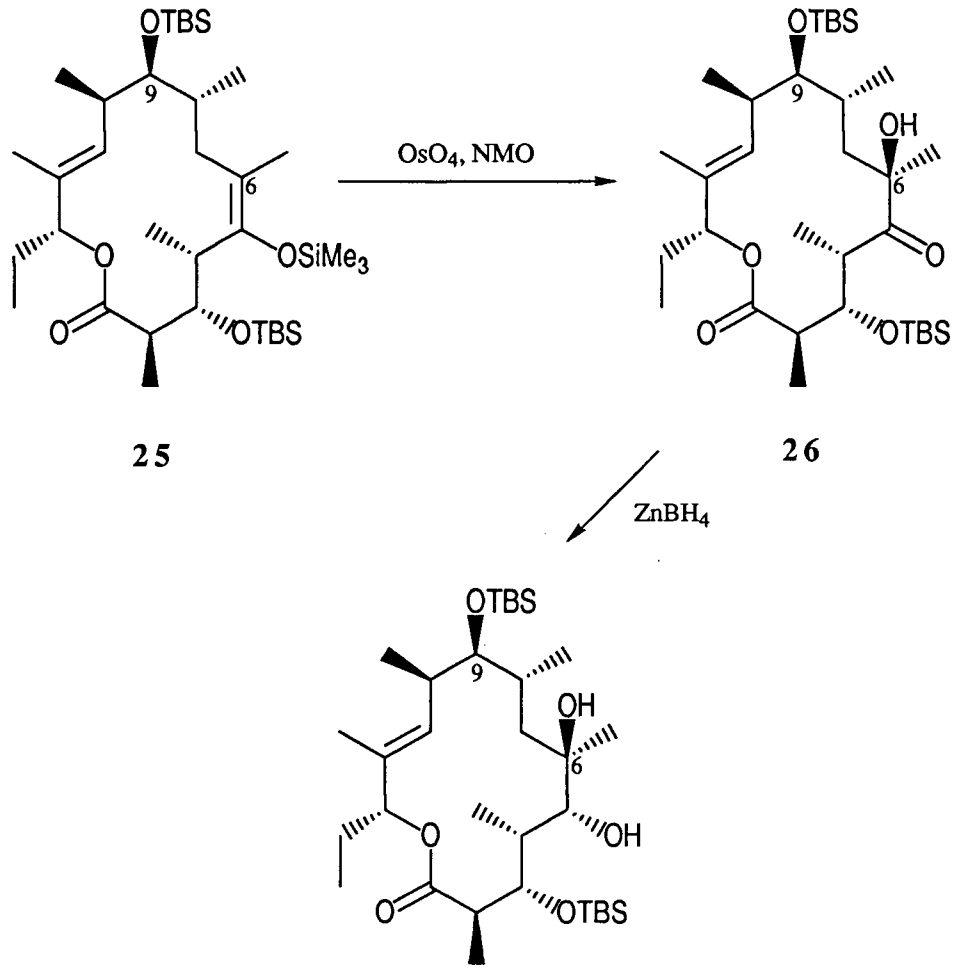
s-trans by greater than 4 kcal/mol and therefore was predicted to give the required E-enolate upon 1,4-addition of a suitable reagent.[27] Indeed, reaction of **24** with Li-Selectride in THF at -78 °C gave, after quenching with trimethylsilyl chloride, 93% of a single enol ether **25** with the E geometry (the Z-isomer is more strained by greater than 12 kcal/mol by MM2 calculations).



24 **25**

En route to the final product, the enol ether **25** was osmylated to cleanly give a single α-hydroxyketone **26** in 85% yield. Reduction of **26** (with macrocyclic stereocontrol and chelation by the hydroxyl group at C6) using zinc borohydride gave a single diol product **27** in 70% yield.

Deprotection of the hydroxyl groups and osmylation at C11-C12 gave the final product (+)-(9S)-dihydroerythronolide A (**21**). The usefulness of the conformational control approach is best described by Paterson himself:



25 **26** **27**

"By postponing the introduction of the stereochemistry and hydroxylation patterns at C5, C6, C11, and C12 until after macrocycle formation, the synthesis has the following advantages: (*i*) flexibility in the manipulation of the silyl enol ether and (less reactive) C11-C12 double bond in **24**; (*ii*) brevity due to the limited use of protecting groups (ca. 20 steps = 2 steps/chiral center); (*iii*) a high yielding macrolactonization (91-96%), as there are fewer transannular and vicinal interactions and the sp^2 carbon skeleton imparts extra conformational rigidity, thus favoring cyclization; (*iv*) highly stereoselective reactions are obtained due to the conformational preferences of the macrolide intermediates."[25]

Everything said by Paterson regarding the latter synthesis can be applied to the synthesis of many macrocyclic compounds and the elegance of the conformational approach for generation of

chiral centers will soon take its rightful place in the arsenal of the synthetic chemist.

1.4 Conformational analysis of 14-membered macrolides

The computer program MACROMODEL, developed by Still and co-workers,[28] was used to determine the low energy conformations of the macrolides studied in this work. The program generates all possible conformations of a medium or large ring by random variation of torsional angles in an acyclic molecule created by breaking a bond in the ring. The conformations with chain termini within a ring closure distance are then submitted to MM2 calculations. Previously, our group could not afford the extensive computer time required for such an operation and used a different approach; a brief synopsis of that approach is presented here.[29]

1.4.1 Conformational analysis of cyclotetradecane

After Dale's conformational analysis of cyclotetradecane[30] (in which he showed that the [3434], [3344], and [3335] were the three lowest energy conformations), Saunders[31] calculated that there were thirteen possible diamond lattice conformations for cyclotetradecane. Our group constructed a model of each conformation and submitted them to MM2 calculations.[32] The conformations exhibited a relative strain energy in the range of 0-12 kcal/mol, consistent with severe transannular interactions within the carbon framework of the cyclotetradecane (Figure 7). As Dale's nomenclature could not be used for the majority of these conformations, an arbitrary naming system was used (Ogura and co-workers had previously proposed this for conformations B, C, and D).[33]

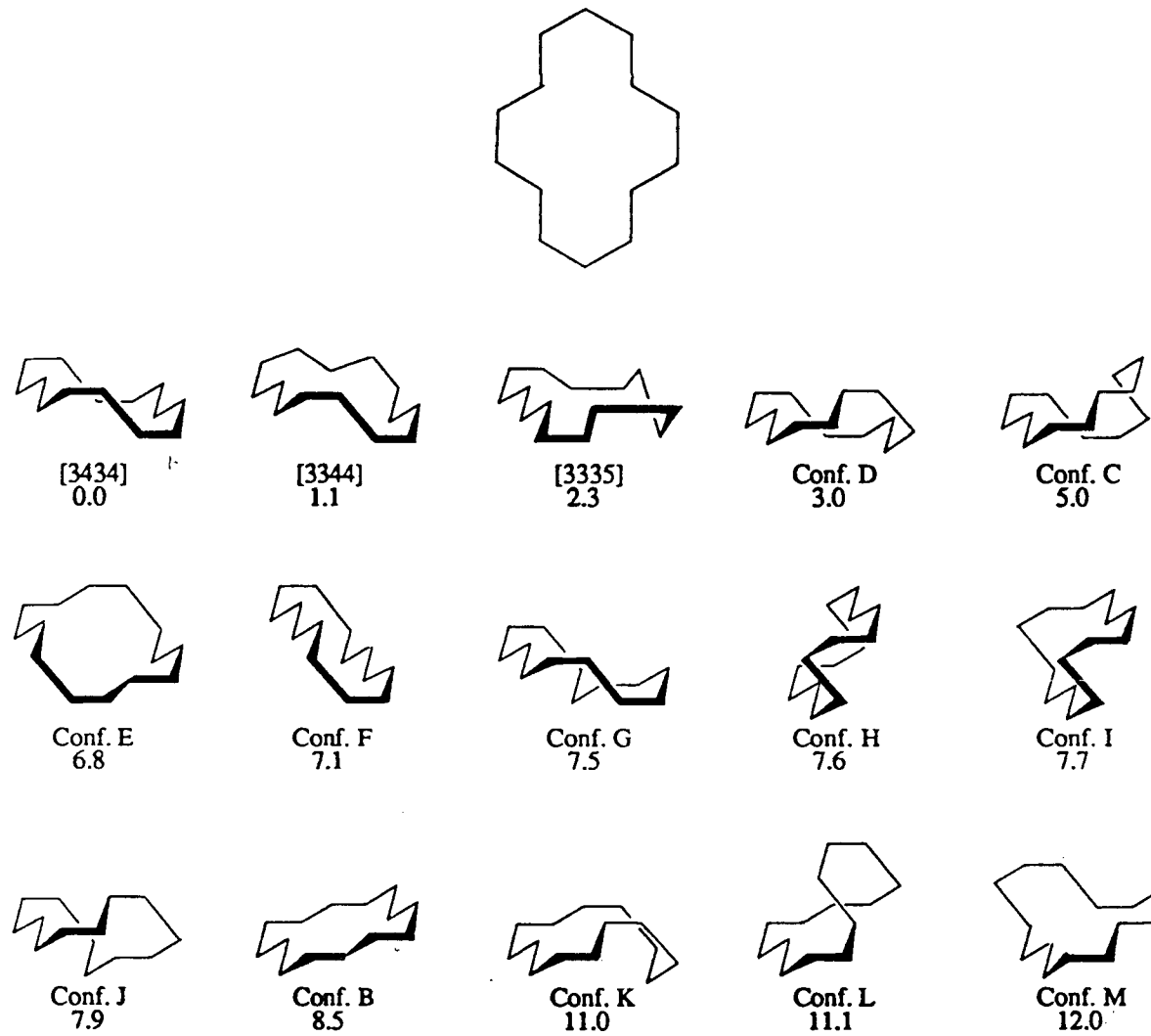


Figure 7. Conformations of cyclotetradecane and relative strain energies in kcal/mol (MM2).

1.4.2 Polar maps

When looking at the conformational similarities between two different macrolides, one can be faced with a tremendous problem (particularly if the macrolides are highly substituted). Conformational similarities are not always apparent and the use of molecular models is tedious and prone to error.

A method used by our group,[34] and introduced by Ogura et al. in his oleandomycin studies,[35] is the use of polar maps. A polar map is a circular graph showing the magnitude and sign of the endocyclic dihedral angle of a cyclic molecule in relation to the bond number (Figure 8).

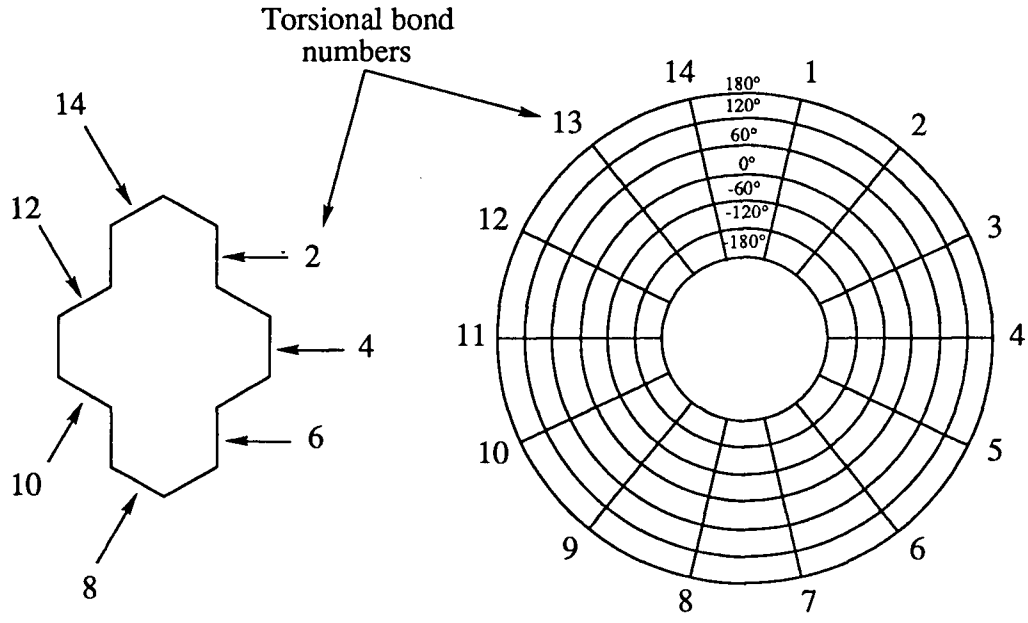


Figure 8. Construction of a polar map.

The dihedral angles uniquely describe the conformation of a molecule and a polar map will exhibit a characteristic pattern for each conformation. The concentric circles represent the magnitude and sign of the dihedral angle. Ogura used the smallest endocyclic dihedral angle within the ring to determine the sign of the angle and as the angle approaches 180°, the determination becomes quite arbitrary as we can choose a 180° angle to be either positive or negative. This can lead to a situation where two compounds crystallizing in the same conformation may have different polar maps because of an erroneous determination in the sign of an anti dihedral angle.

To solve this problem, we proposed that only dihedral angles within the ring be used for the generation of polar maps.[34] If the direction of rotation for a dihedral angle within the ring is clockwise from C1 to C4 in C1-C2-C3-C4, then the dihedral angle sign is positive. Otherwise, the sign is negative (Figure 9: drawing **A** is used to determine the sign of the angle, not drawing **B**).

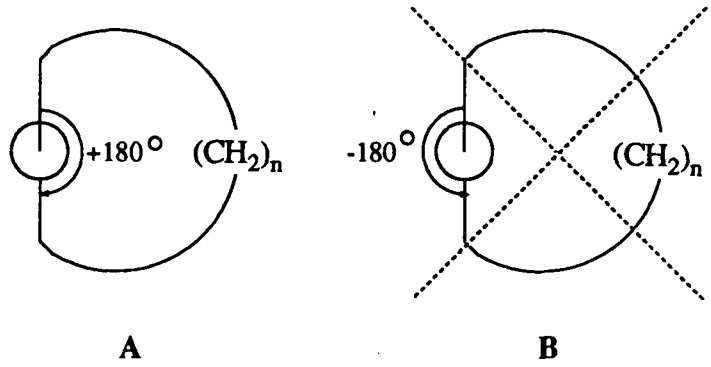


Figure 9. Rule for determining the sign for an anti dihedral angle.

The polar maps for the five lowest energy conformations of cyclotetradecane are shown in Figure 10. Polar maps have proven themselves to be a very useful tool for comparison of conformations.

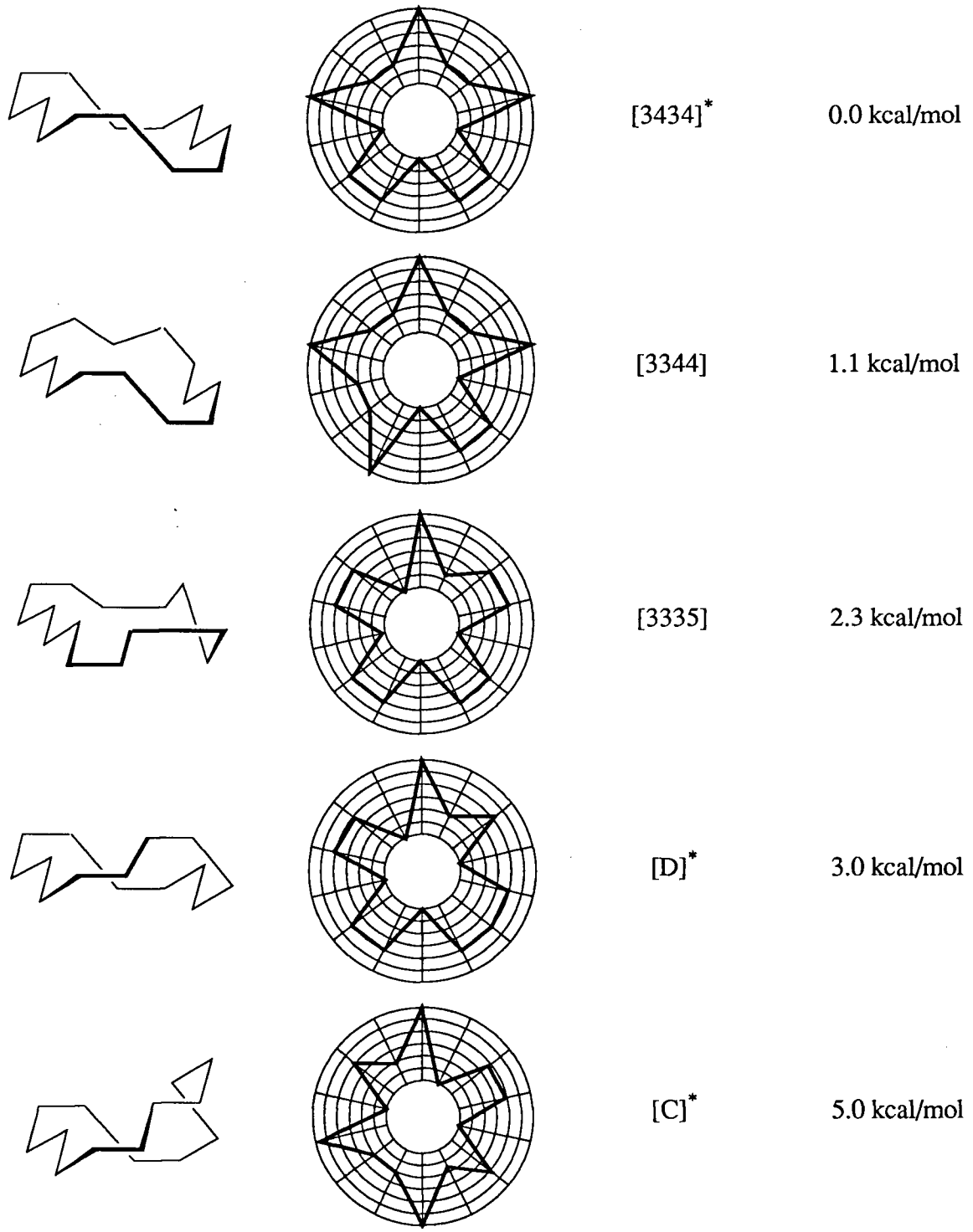


Figure 10. Polar maps for the five lowest energy conformations of cyclotetradecane (* diamond lattice conformation; strain energy relative to lowest energy conformation).

1.4.3 The corner and pseudo-corner positions

A polar map enables us to quickly determine where the corner and pseudo-corner positions can be found in a conformation by recognizing the characteristic sequence of dihedral angles at a corner and pseudo-corner (see Figure 4 for the definition of a corner and a pseudo-corner position). In observing the polar map for the C conformation (Figure 11), we can see the two different types of corner positions.

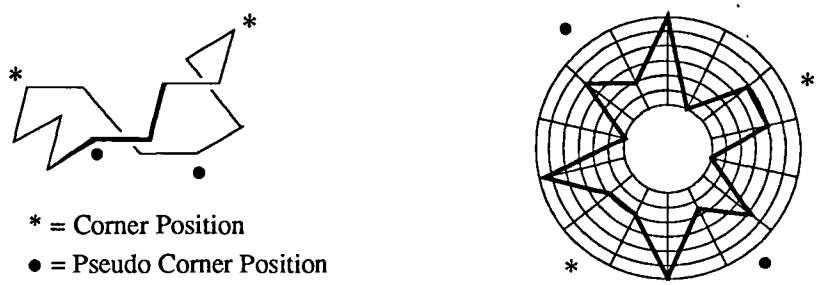


Figure 11. Comparison of the two corner positions in the C conformation of cyclotetradecane.

Geminal substitution at a corner or pseudo-corner position, according to MM2 calculations, would occur in the following sequence:

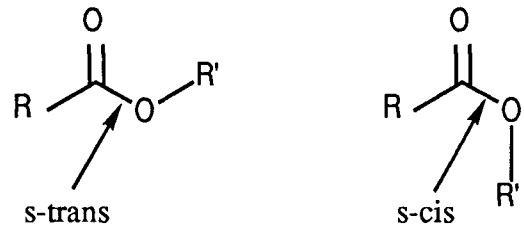
1. Geminal substitution at a corner atom.
2. Geminal substitution at a pseudo-corner position (introduction of an additional 1,3-diaxial interaction, raising the energy by 0.6 kcal/mol relative to a corner position).
3. Geminal substitution at a non-corner atom.

These results agreed with Dale's qualitative prediction.[10]

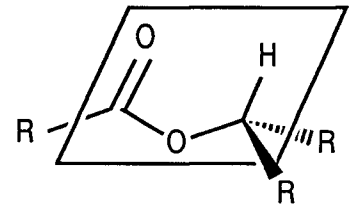
1.4.4 The lactone linkage

A further reduction in the number of conformations which need to be considered (Figure 7) is possible as a result of the lactone functionality in our macrolides.

Deslongchamps[36] has estimated the energy difference between the s-trans and s-cis ester conformations to be of the order of 3.0 kcal/mol, thus explaining why open chain esters occur in the s-trans form.



Because a 14-membered ring is large enough to accomodate an s-trans lactone, conformations with an s-cis lactone linkage can be ignored in our conformational analysis. In addition, studies by Dunitz and Schweizer[37] on over 1750 esters of secondary alcohols showed that these contain a C-O-C-H dihedral angle in the range 0-60°, with 85% of the cases in the 0-40° range.



Applying this trend to lactones of secondary alcohols, and using these restrictions on the [3434] conformation, we are left with only three possible conformations of 13-tetradecanolide to consider (Figure 12).

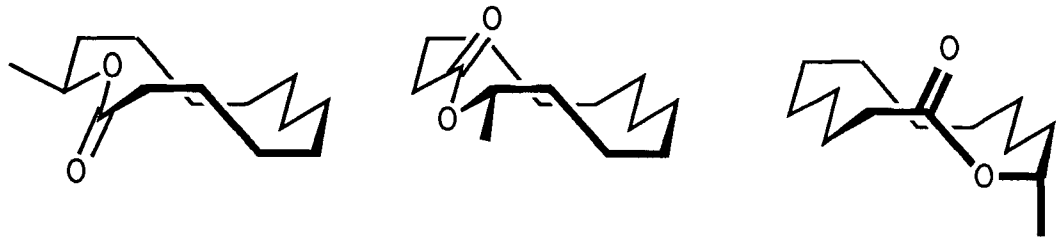


Figure 12. The three possible substitution patterns for 13-tetradecanolide with an s-trans lactone geometry and a C-O-C-H dihedral angle of less than 60° in a [3434] conformation.

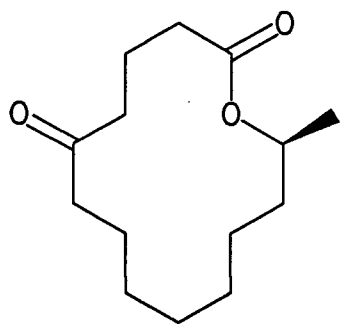
CHAPTER II

Results and discussion

Still, Schreiber, and Paterson's syntheses, described in the introduction, show that conformational control of large rings can be a powerful tool in organic synthesis. With the increasing interest by pharmaceutical companies toward the laboratory manufacture of complex drugs based on macrocyclic rings (one example is the synthesis of FK-506, a potent immunosuppressant),[38] their work now comes under a new light.

We have chosen to study the conformational control of 14-membered keto lactones. There are various reasons for this decision. Many macrolide antibiotics contain a 14-membered lactone ring, and the effect of the conformation of the ring on their chemical properties needed closer scrutiny. Knowledge of the effect of the conformation of the ring on its chemical reactivity might lead us to a better understanding of their biological mode of action. Also, the knowledge gained about 14-membered lactones might be applied to other macrolides.

Because many poly-oxo macrolides contain oxygen functionalities at C-5 and C-7, we chose to concentrate our studies on 5-oxo-13-tetradecanolide (**28**) and 7-oxo-13-tetradecanolide (**29**). The usefulness of the ketone group in introducing various functionalities in a molecule was also a powerful motivator in the choice of these two macrolides.



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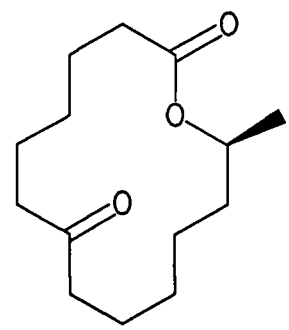


29

In addition, the presence of an asymmetric center at C-13 in both macrolides would enable us to study the effect of a remote asymmetric center on the stereoselectivity of the reactions performed on the ring. Still and Galynker,[39] during their work on 10-membered lactones, found that the stereoselectivity of kinetic alkylations decreased with increasing distance from the asymmetric center. In both our macrolides, the ketone group is five atoms removed from the asymmetric center. We can expect this difference in the position of the ketone group, relative to both the asymmetric center and the lactone functionality, to have an effect on the conformation of the macrolides, which will translate into an effect on the stereoselectivity of the various reactions performed on these two macrolides.

2.1 Synthesis of 5-oxo-13-tetradecanolide (28)

The retrosynthetic scheme for our synthesis of 5-oxo-13-tetradecanolide is shown in Figure 13. As should be the case in all syntheses, starting materials were inexpensive and commercially available, as large amounts of the macrolide would be required.

The plan consisted of synthesizing the molecule in two parts, coupling these and cyclizing the resulting long-chain hydroxy acid to give the lactone ring. Of all the reactions involved in the synthesis, the lactonisation was thought to be the most troublesome step. However, Corey et al.,[40] as well as Masamune et al.,[41] have perfected many high-yielding cyclization methods, called "double activation" methods, by converting the carboxylic acid terminus of the hydroxy acid precursor to 2-pyridinethiol esters and t-butylthiol esters respectively. A modification of these methods was used in our synthesis.[42]

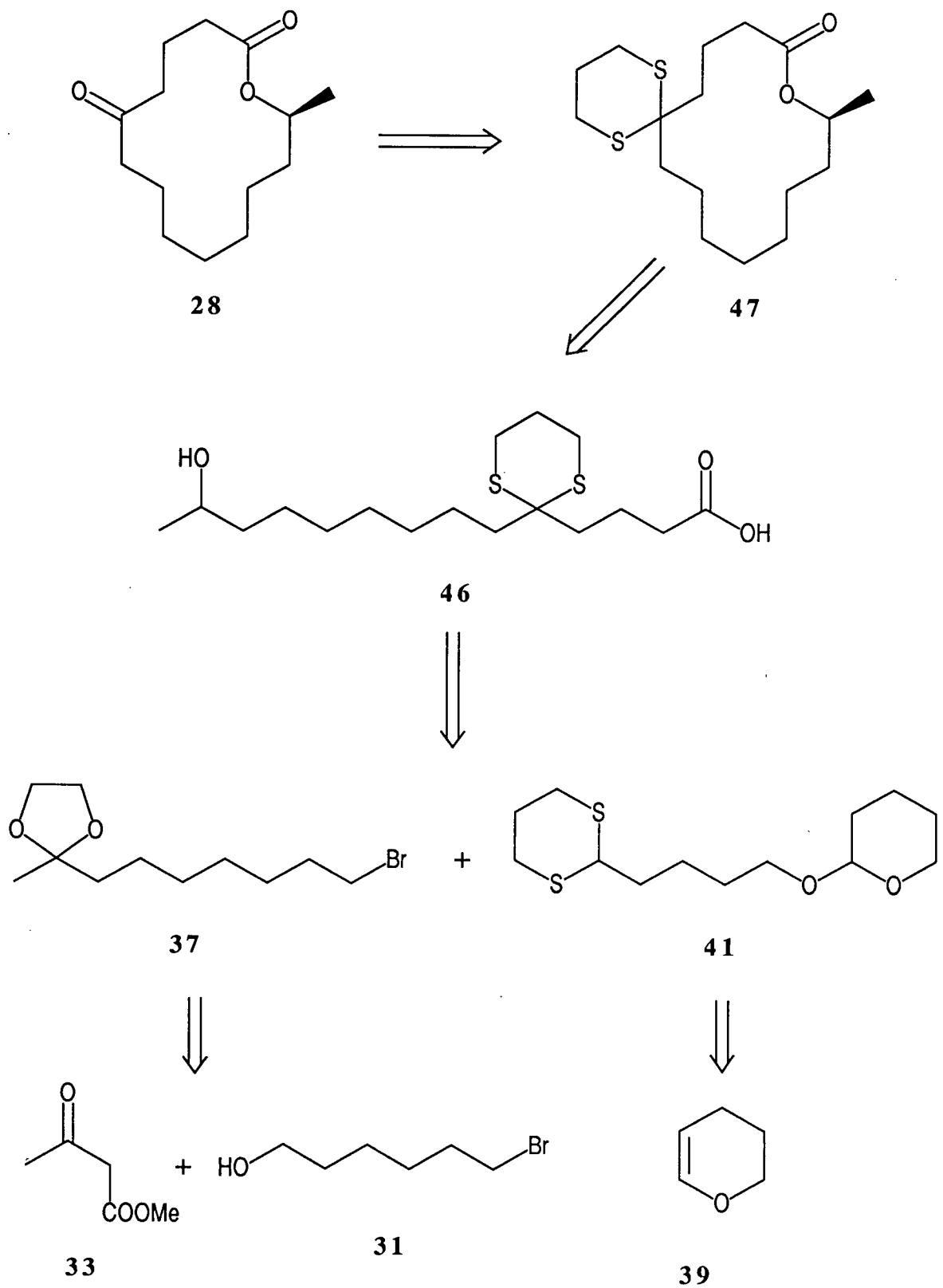
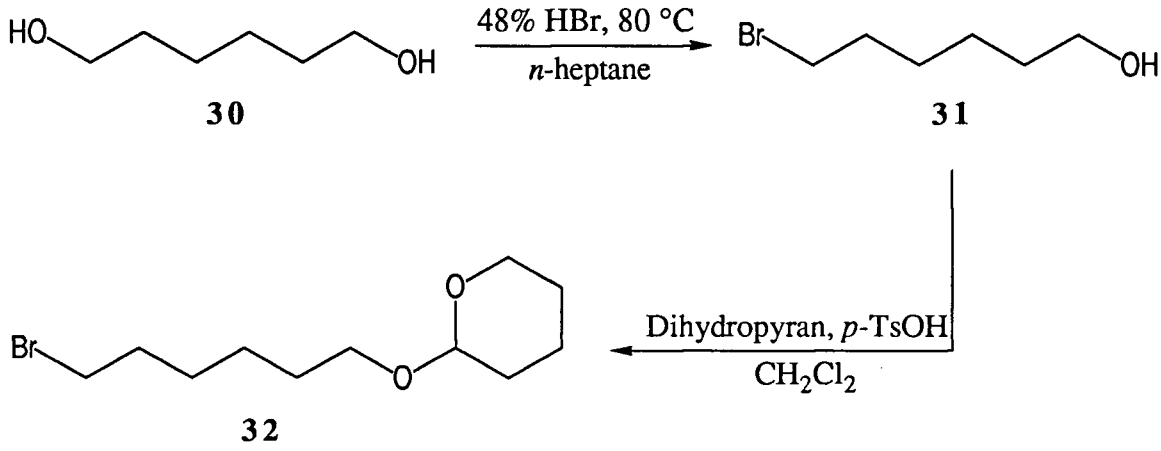


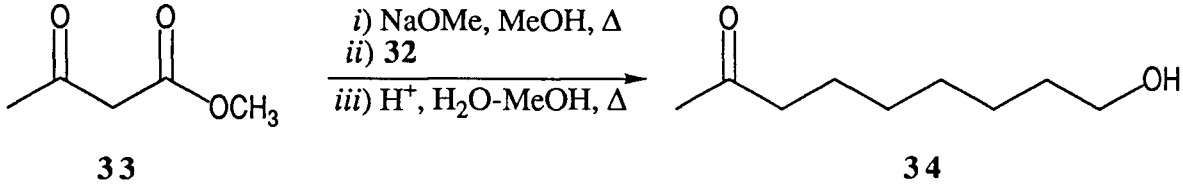
Figure 13. Retrosynthetic analysis of 5-oxo-13-tetradecanolide (**28**).

2.1.1 Synthesis of 9-bromo-2-(2-tetrahydropyranyloxy)nonane (37)

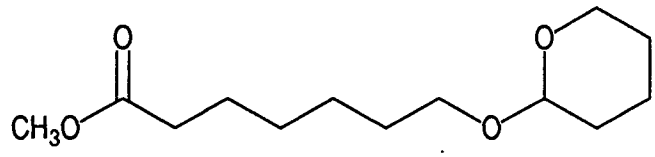
1,6-Hexanediol (**30**) was treated with aqueous HBr under continuous liquid-liquid extraction with *n*-heptane to give 6-bromo-1-hexanol (**31**) in yields ranging from 70-85%.[43] The bromo alcohol was then protected as its tetrahydropyranyl ether **32** by reacting it with dihydropyran in presence of a catalytic amount of *p*-toluenesulfonic acid.[44]



We now needed to add three carbons to **32** to obtain the nine-carbon chain required for the first part of our molecule. One method of choice for such a transformation is the acetoacetic acid synthesis, where the alkyl halide reacts with the anion of methyl acetoacetate to give, through nucleophilic substitution, the long-chain β-keto ester. Decarboxylation, in basic or acidic conditions, gives the long-chain ketone. Thus, the anion of methyl acetoacetate (**33**), generated with sodium methoxide in methanol, was treated with the protected bromo alcohol **32**, the intermediate β-keto ester immediately decarboxylated in acidic conditions to give 9-hydroxy-2-nonanone (**34**).[45]

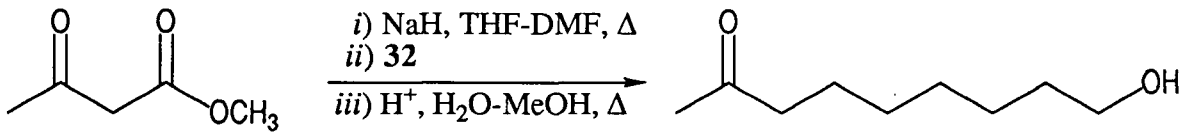


The yields, however, were poor and examination of the alkylation product, prior to decarboxylation, showed it to be mainly the ester **35**, obtained by a retro Claisen reaction through attack of sodium methoxide on the intermediate β-keto ester.



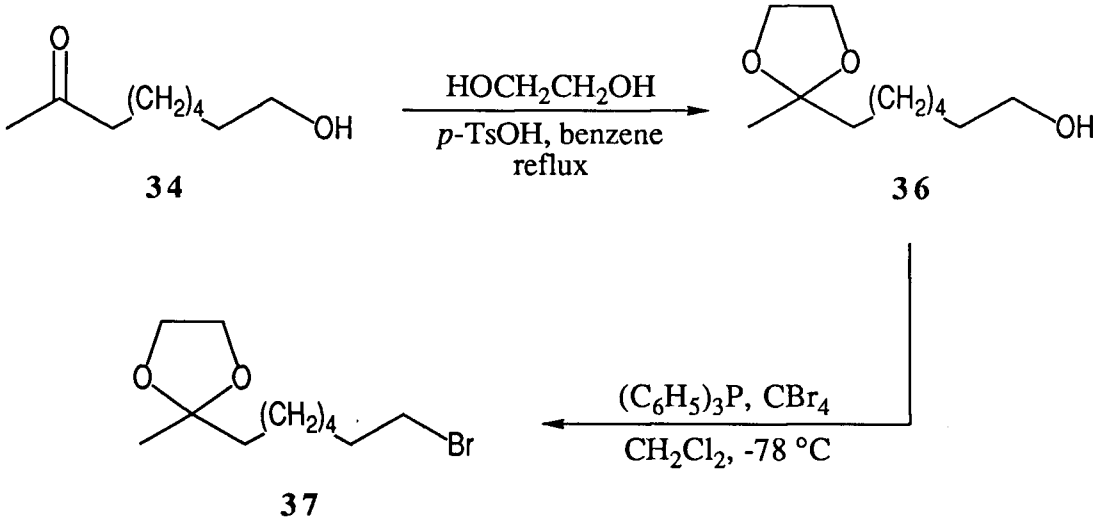
35

The hydroxy ketone **34** was finally obtained in good yield (79%) by using NaH as a base in a mixture of THF and DMF, followed by decarboxylation in acidic conditions.[46]



33 **34**

9-Hydroxy-2-nonanone ethylene acetal (**36**) was obtained in 91% yield by allowing **34** to react with 1,2-ethanediol and a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water.[47] The alcohol **36** was then converted into the bromide **37** with triphenylphosphine and carbon tetrabromide at -78 °C in dichloromethane in 88% yield.[48]

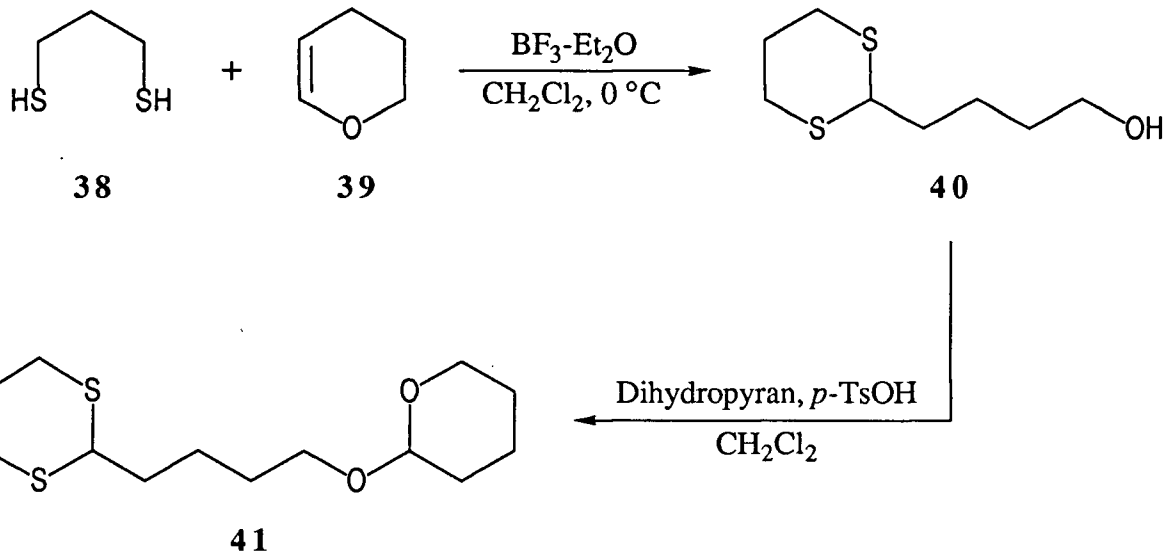


34 **36**

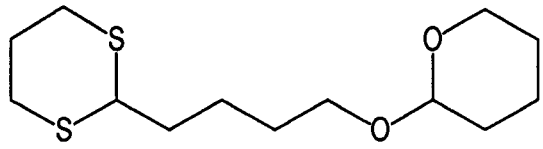
37

2.1.2 Synthesis and cyclization of hydroxy acid **46**

With the first part of our molecule in hand, namely the protected keto bromide **37**, we were now ready to proceed with the synthesis of the second portion. We first had to synthesize the protected hydroxy dithiane **41**. The unprotected hydroxy dithiane **40** had been synthesized by reaction between 1,3-propanedithiol (**38**) and 5-hydroxypentanal in the presence of boron trifluoride etherate.[47] 5-Hydroxypentanal can be obtained by hydration of dihydropyran (**39**),[49] but is difficult to isolate. It was thought that we could carry out a one-step reaction by using 1,3-propanedithiol (**38**) and dihydropyran (**39**). Thus, a mixture of 1,3-propanedithiol (**38**) and dihydropyran (**39**) was treated with boron trifluoride etherate in CH_2Cl_2. The crude hydroxy dithiane **40** contained some protected hydroxy dithiane **41**. This crude product was then treated with dihydropyran to give **41** in 72% yield.[44]

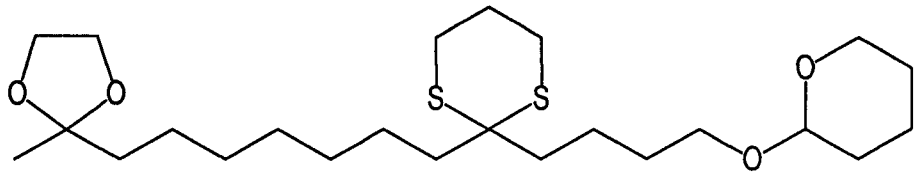


The protected tetradecane **42** was obtained in 88% yield by coupling the anion of the dithiane **41**, generated with *n*-butyllithium in THF at -20 °C, with the protected keto bromide **37**.[47] The tetradecane derivative **42** was then deprotected in a mixture of acetone, methanol, and water at 55 °C, using *p*-toluenesulfonic acid as a catalyst, to give the hydroxytetradecanone **43** in 97% yield.



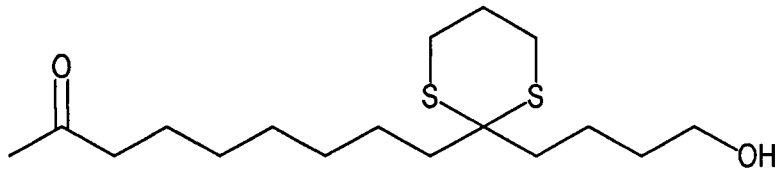
41

i) *n*-BuLi, THF, -20 °C
ii) **37**



42

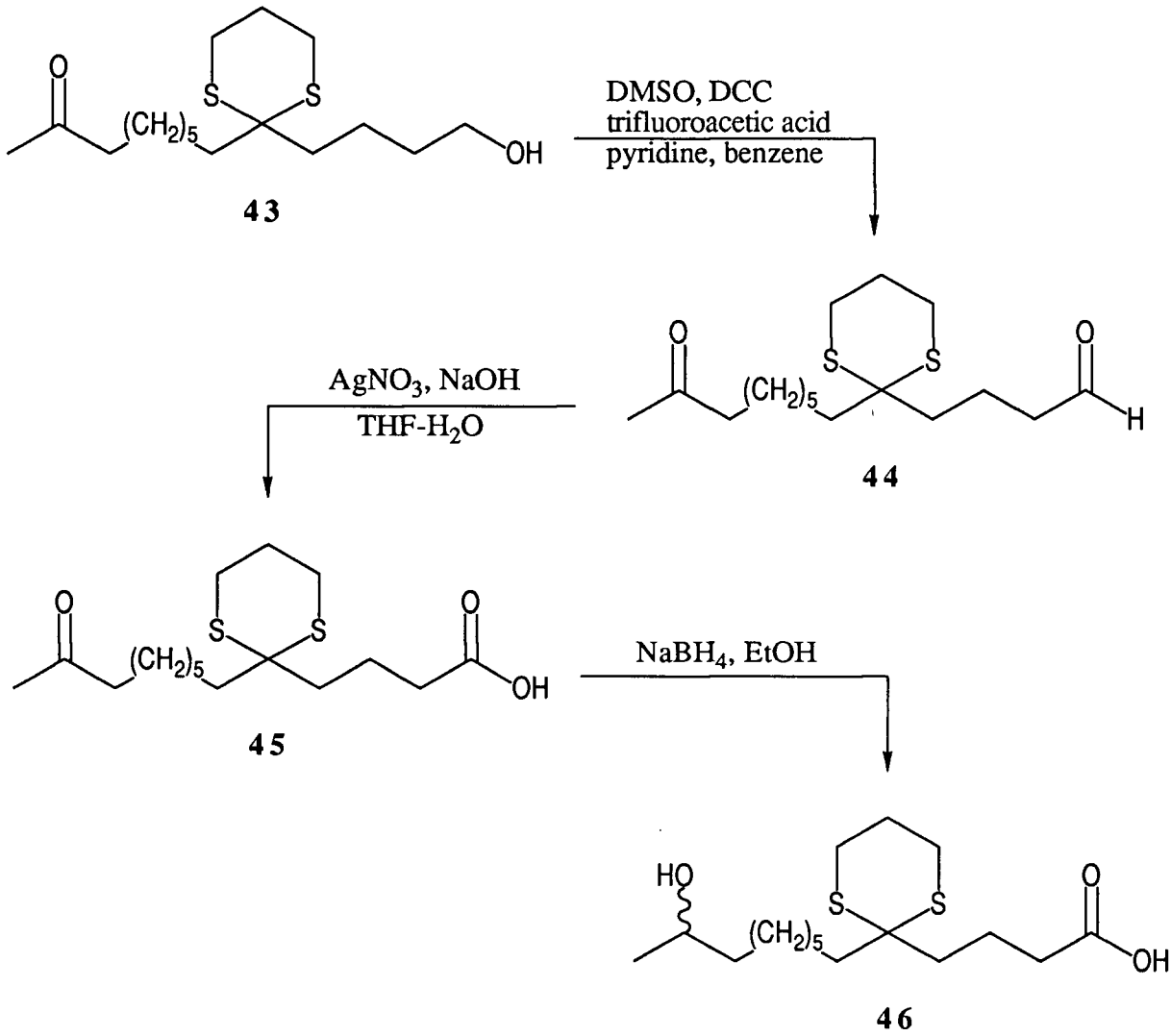
Acetone/methanol/water
p-TsOH, Δ



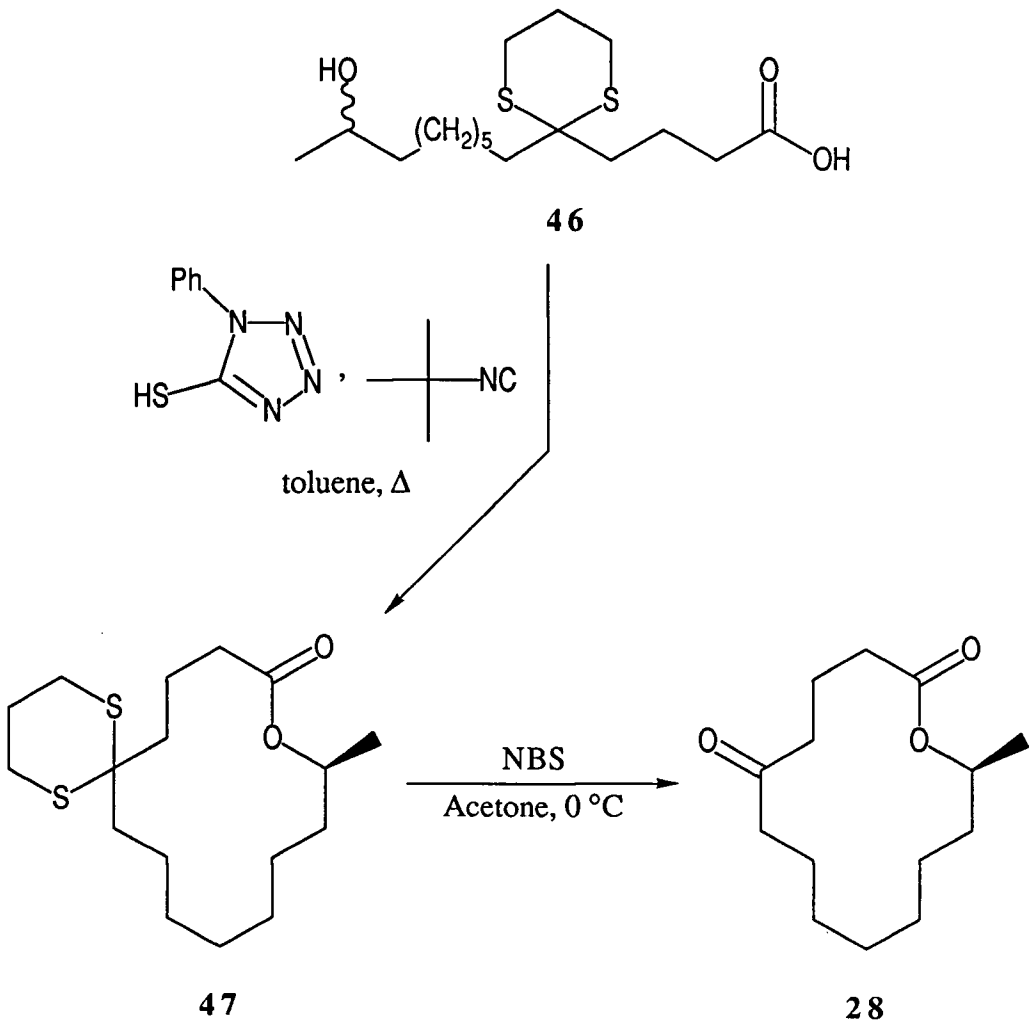
43

Before proceeding with the cyclization it was necessary to oxidize the alcohol to an acid group and reduce the ketone to an alcohol to give the long-chain hydroxy acid **46**. Unfortunately, this oxidation turned out to be the major challenge in our synthesis. Our initial attempts with Jones' reagent[50] and Corey's pyridinium dichromate reagent[51] ended with decomposition of the starting material **43**. We then decided to carry out the oxidation in two steps. First, we would oxidize the terminal alcohol to an aldehyde, then convert the aldehyde to the carboxylic acid. Here again, we ran into some problems. The Swern oxidation,[52] as well as Corey's pyridinium chlorochromate or dichromate reagents[51] and the Dess-Martin reagent,[53] also gave decomposition of the starting material. Finally, we found that the Pfitzner-Moffat oxidation[54] allowed us to smoothly oxidize the alcohol to the aldehyde **44** in 70% yield. The aldehyde was converted to the

acid **45** by a silver oxide oxidation, the silver oxide generated *in situ* from silver nitrate and sodium hydroxyde, in 97% yield.[55] The hydroxy acid **46** was then obtained by sodium borohydride reduction of the ketone in 100% yield.



With the long-chain hydroxy acid in hand, we were now able to study the macrolactonization. A mixture of *tert*-butyl isocyanide and 1-phenyl-*1H*-tetrazole-5-thiol in toluene was added to a solution of **46** in toluene and the resulting solution refluxed to yield the protected keto lactone **47** in a very good yield of 78%.[42] The keto lactone **28** was obtained in 86% yield (17% overall) from the protected keto lactone **47** by oxidative hydrolysis of the dithiane using N-bromosuccinimide (NBS) in acetone.[56]



2.2 Synthesis of 7-oxo-13-tetradecanolide (29)

As for the synthesis of 5-oxo-13-tetradecanolide (**28**), starting materials for the synthesis of 7-oxo-13-tetradecanolide (**29**) were inexpensive and commercially available. The retrosynthetic analysis for 7-oxo-13-tetradecanolide (**29**) is shown in Figure 14.

The plan here was also to synthesize the molecule in two parts, couple these, and cyclize the resulting hydroxy acid to the 14-membered lactone. Our plan called for the same 6-carbon starting material for each fragment.

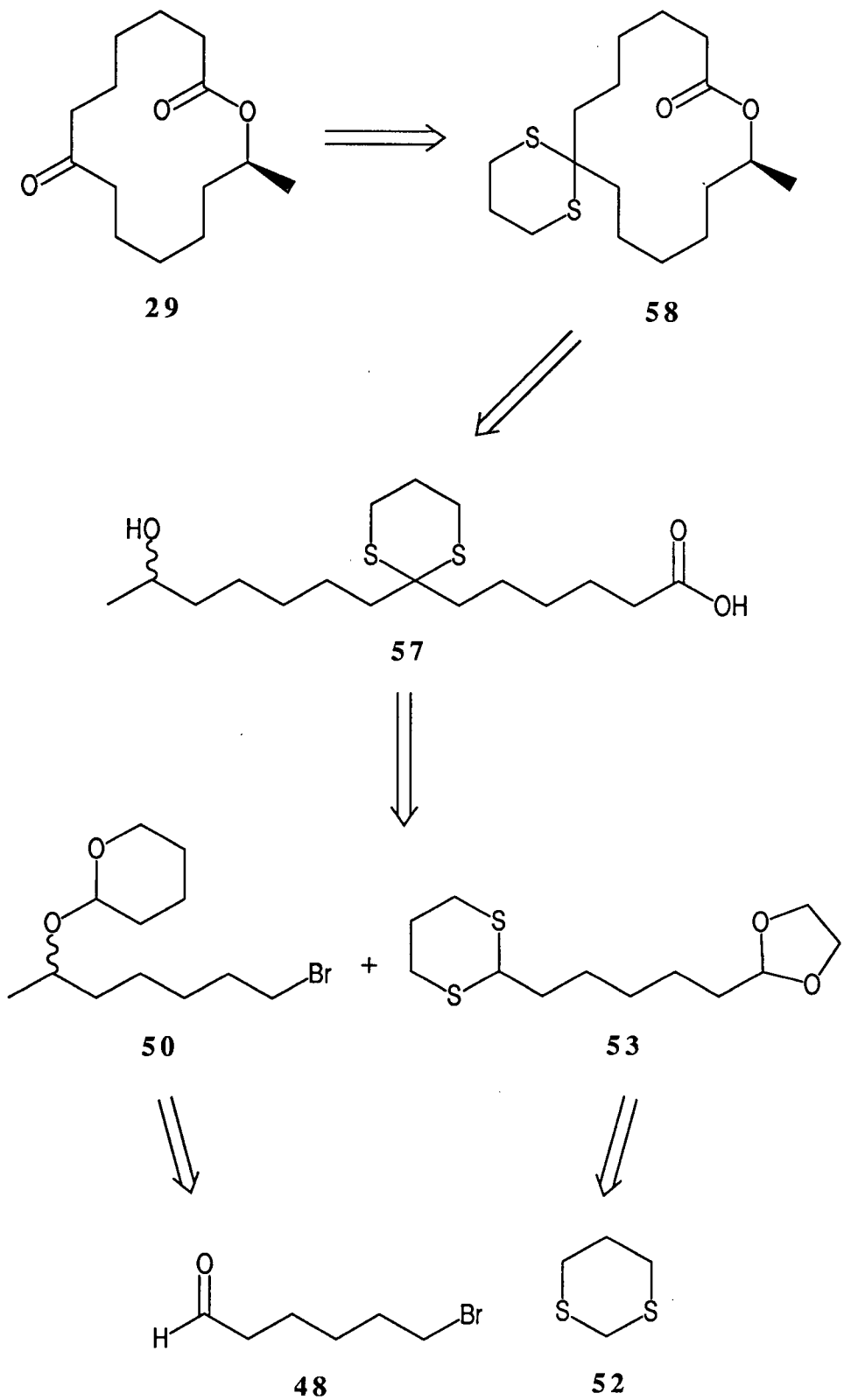
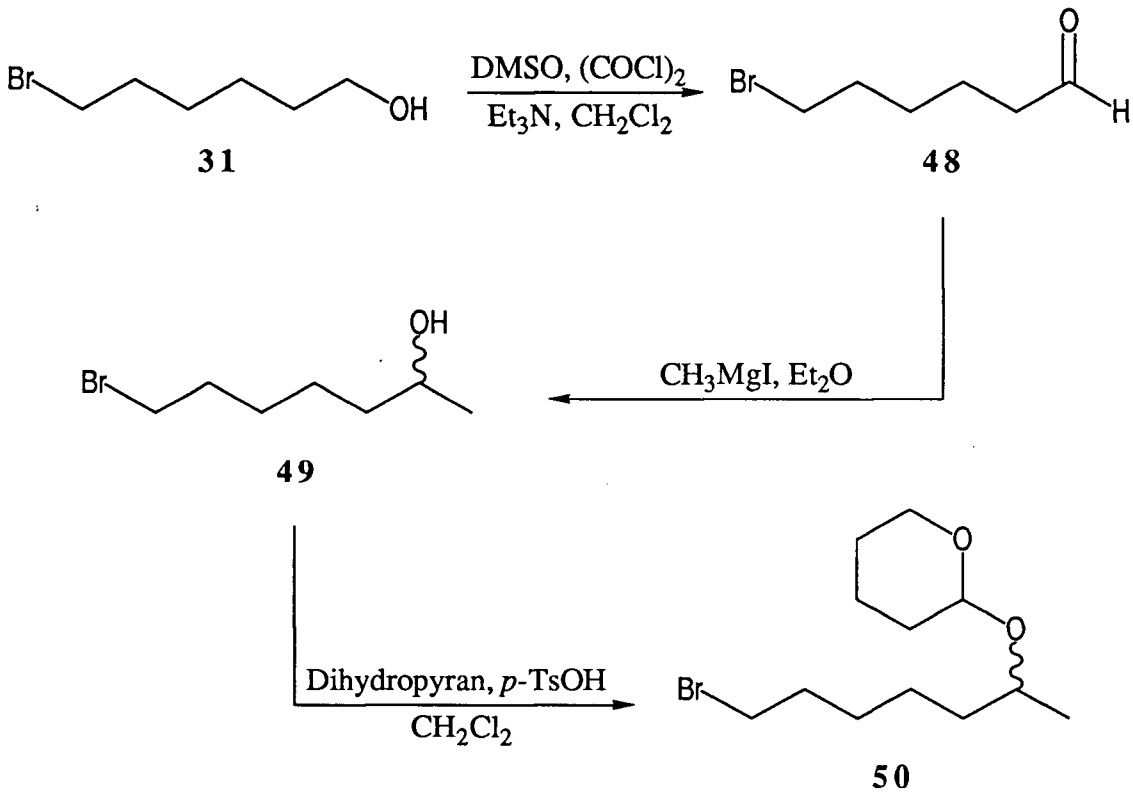


Figure 14. Retrosynthetic analysis of 7-oxo-13-tetradecanolide (**29**).

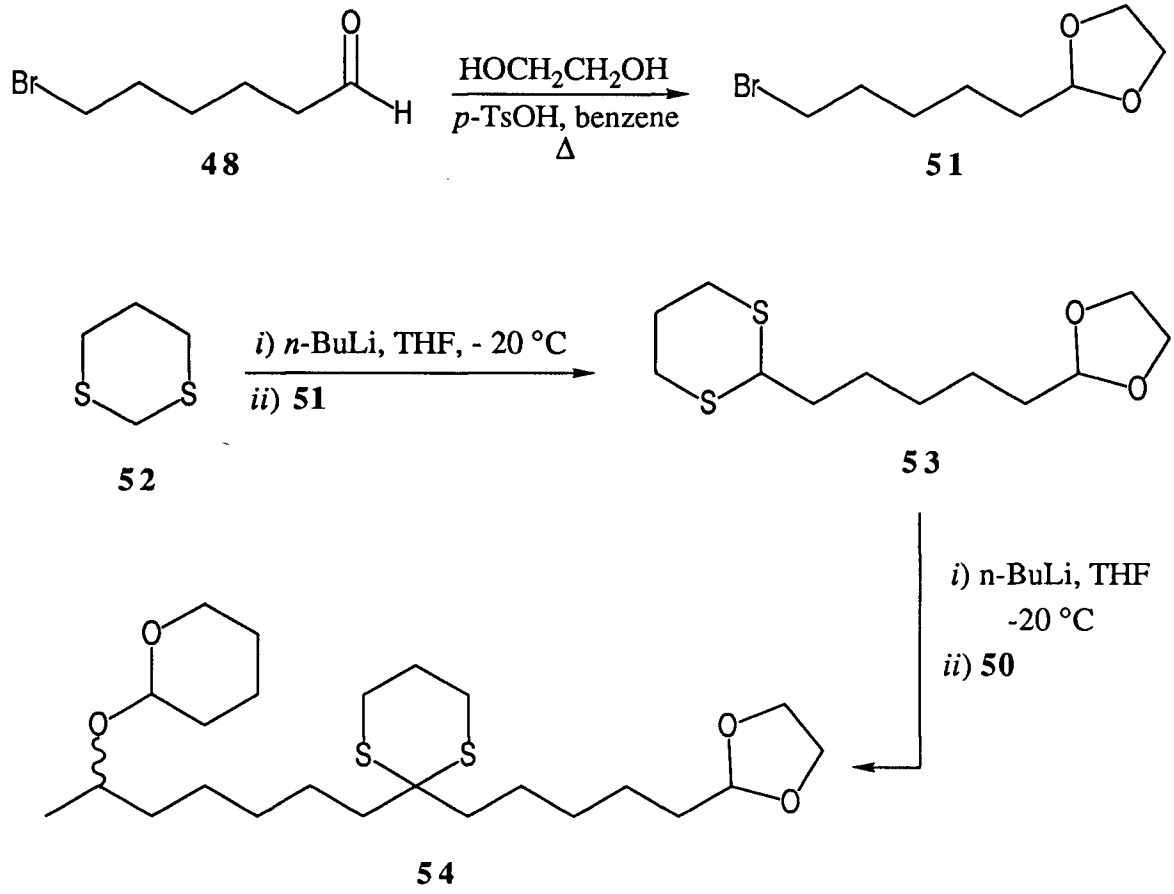
2.2.1 Synthesis of 7-bromo-2-(2-tetrahydropyranyloxy)heptane (48)

6-Bromohexanal (**48**) was obtained in 82% yield from 6-bromo-1-hexanol (**31**) using a Swern oxidation.[52] Conversion of **48** into 7-bromo-2-heptanal (**49**) was effected by the Grignard reaction of **48** with methylmagnesium iodide (79% yield). The secondary alcohol **49** was then protected as its tetrahydropyranyl ether **50** in 98% yield in the usual fashion.[44]

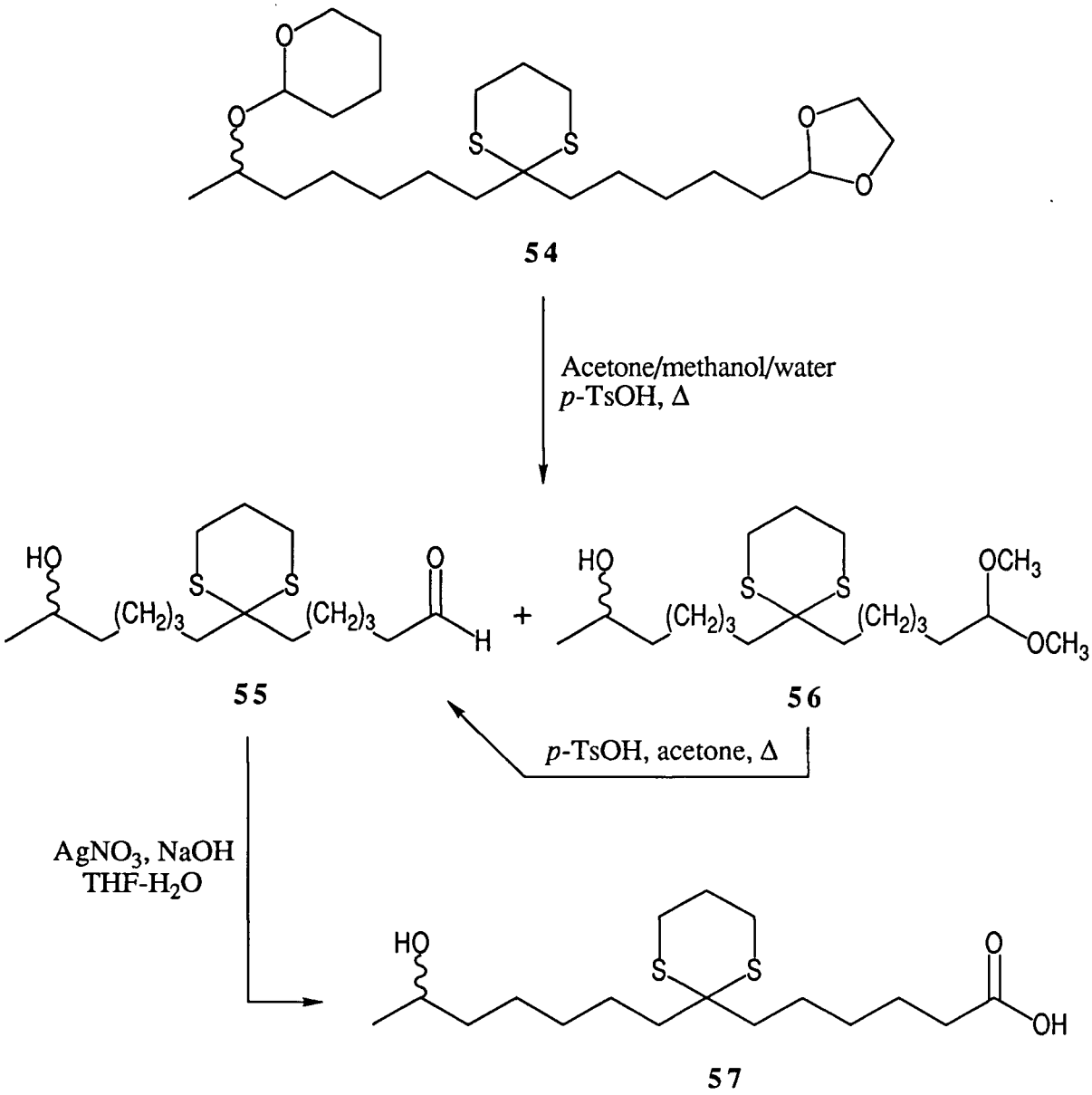


2.2.2 Synthesis and cyclization of hydroxy acid 57

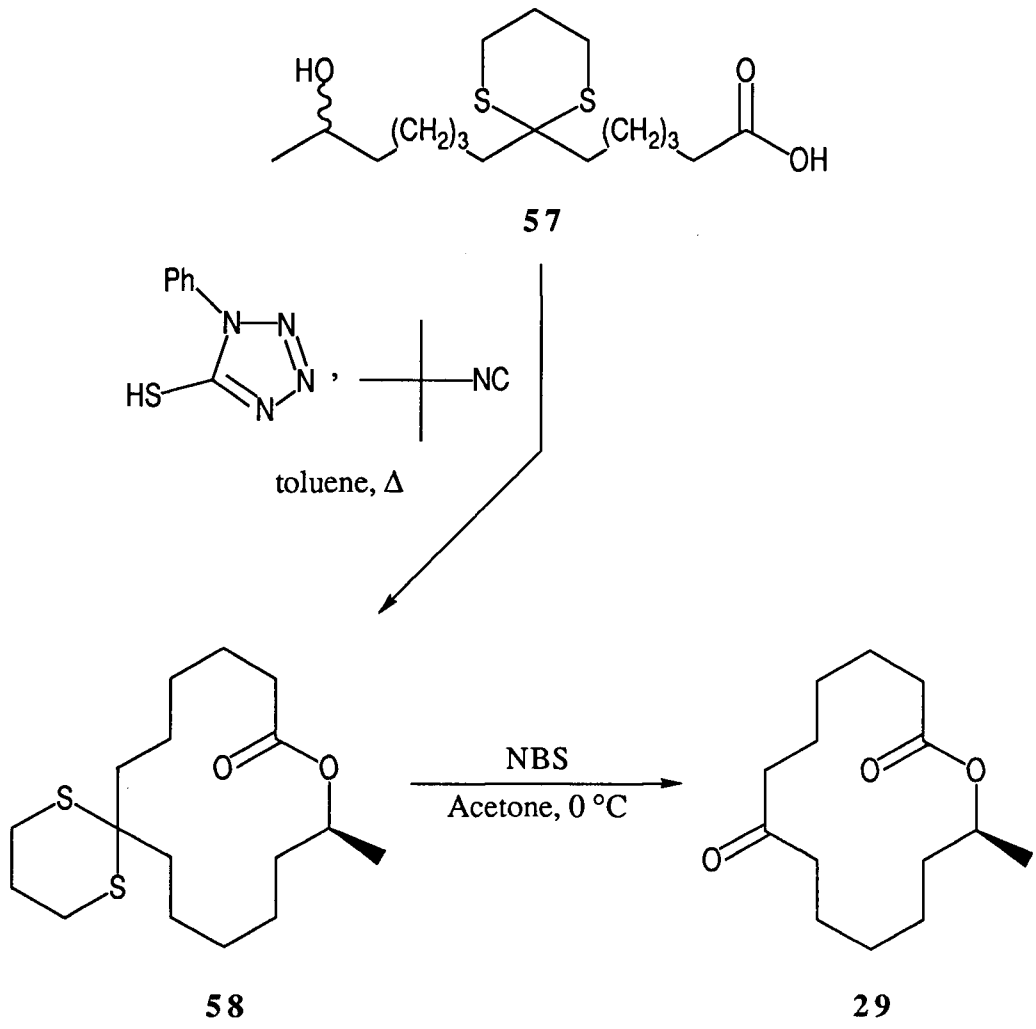
6-Bromohexanal (**48**) was protected as its ethylene acetal **51** in 96% yield.[47] The bromo acetal **51** was then coupled with the anion of 1,3-dithiane (**52**), generated with *n*-butyllithium in THF, to give the dithianylacetal **53** in 84% yield, which was subsequently coupled, in the same fashion, to the protected bromo alcohol **50** to give the tetradecane derivative **54** with a yield of 82%.



The tetradecane derivative **54** was treated with pyridinium *p*-toluenesulfonate in a mixture of acetone, methanol, and water to give the hydroxy tetradecanal **55** in 33% yield.[57] A by-product of the reaction, the dimethyl acetal **56**, was also converted to **55** with *p*-toluenesulfonic acid in acetone in 100% yield. Compound **55** was then converted to the carboxylic acid **57** using a silver oxide oxidation.[55]



Cyclization of the hydroxy acid **57** to the lactone **58** was accomplished in 55% yield by the method described previously using *tert*-butyl isocyanide and 1-phenyl-*1H*-tetrazole-5-thiol.[42] The keto lactone **29** was then obtained in 66% yield (9% overall) by oxidative cleavage of the dithiane in **58** using N-bromosuccinimide in acetone.[56]



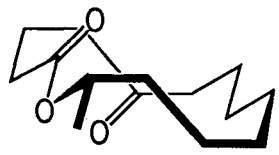
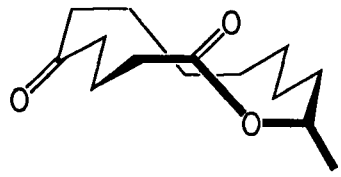
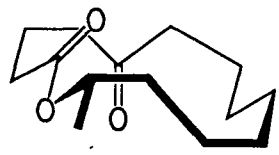
2.3 Low energy conformations of macrolides **28** and **29**

Minimum energy geometries found by molecular mechanics calculations often depend on the starting conformation of the molecule (local minimum problem).[32] To calculate the low energy conformations of 14-membered lactones, previously our group used as starting conformations the five low energy conformations shown in Figure 10 -the [3434], [3344], [3335], D, and C conformations- along with the following criteria:

1. The lactone linkage should have the s-trans geometry.
2. The C-O-C-H dihedral angle in the lactone linkage should be in the 0-60° range.
3. Substituents should occupy exterior positions on the macrolide ring, and geminally disubstituted carbons occupy either a corner, or pseudo-corner, position.

However, the use of the MACROMODEL program, developed by Still and co-workers,[28] greatly simplified our calculations. The latest version of MACROMODEL has a conformational search routine in it. After providing a starting structure for a given molecule, the program provided us with a list of conformers for the molecule, in order of increasing energy. The conformational search was thus expanded to include conformations other than the five low energy conformations mentioned earlier.

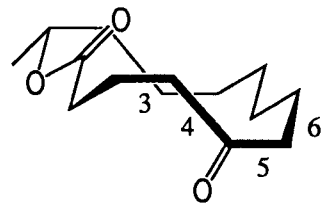
Table II. The three lowest energy conformations of 28.

Low energy conformations		Strain energy[a]	Conformation
28a		0.00 kcal/mol	[3434]*
28b		0.26 kcal/mol	[3434]*
28c		0.35 kcal/mol	[3344]

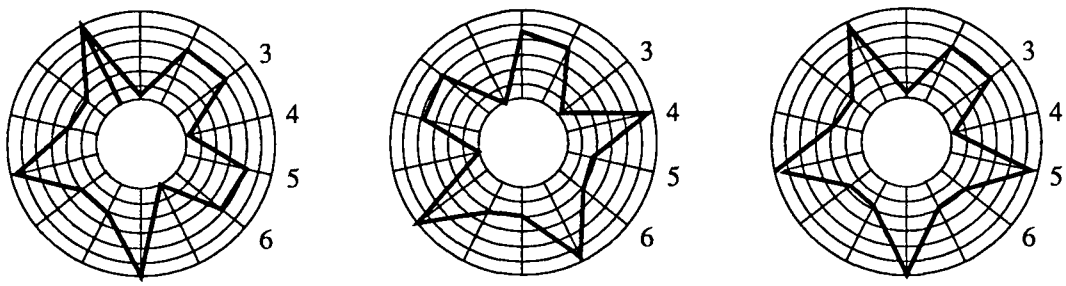
[a] Strain energy is reported relative to the lowest energy conformation.
* Diamond lattice conformation.

The three lowest energy conformations for the macrolide **28**, obtained from the MACROMODEL program, are shown in Table II. The conformational analysis of **28** was quite complex, with five conformations being within 0.4 kcal/mol of the global minimum. The two lowest energy conformations turned out to have the [3434] geometry while the third lowest had the

[3344] conformation. Conformations **28a** and **28c** had the same local conformation at the ketone group.



28a



28a **28b** **28c**

Figure 15. Polar maps of the three lowest energy conformations of **28.**

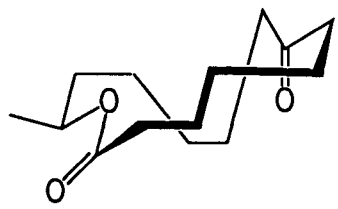
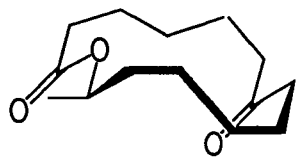
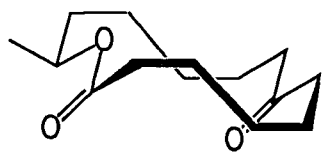
All three conformations had their C-O-C-H dihedral angle well inside the 0-60° range established as our criterion (43° for **28a**, 46° for **28b**, and 40° for **28c**). Unfortunately, we were unable to obtain an X-ray crystallographic structure for **28** (obtained as an oil), which could have provided some insight into our findings.

Examination of the ^{1}H NMR spectrum of **28** seemed to confirm the fact that the three lowest energy conformations (if not more) co-existed in solution. Egan et al.[16] had shown that extreme values for vicinal coupling constants (10-12 Hz and 0-2 Hz) indicated that the molecule existed largely in one conformation while intermediate coupling constants (6-7 Hz) were found in conformationally mobile systems. The methine proton in **28** exhibited an eleven-line pattern with coupling constants of 4,6, and 8 Hz, which would indicate a conformationally mobile molecule, in

agreement with the fact that five low energy conformations were found for **28** within 0.4 kcal/mol of the global minimum.

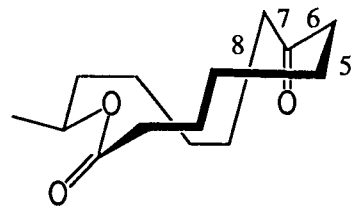
Another surprise awaited us as we proceeded with the conformational analysis of the macrolide **29**. As shown in Table III, the lowest energy conformation **29a** appeared to be a twist conformation, then a [3344] conformation, and finally a [3434] conformation although it should be noted that all three conformations are exceedingly close in energy. The three conformations all had a C-O-C-H dihedral angle within the 0-60° range, in accordance to Schweizer and Dunitz's findings.[37] The polar maps for the three conformations are shown in Figure 16. Again, we were unable to obtain a X-ray crystallographic structure to evaluate these results as **29** was obtained as an oil which refused to crystallize.

Table III. The three lowest energy conformations of 29.

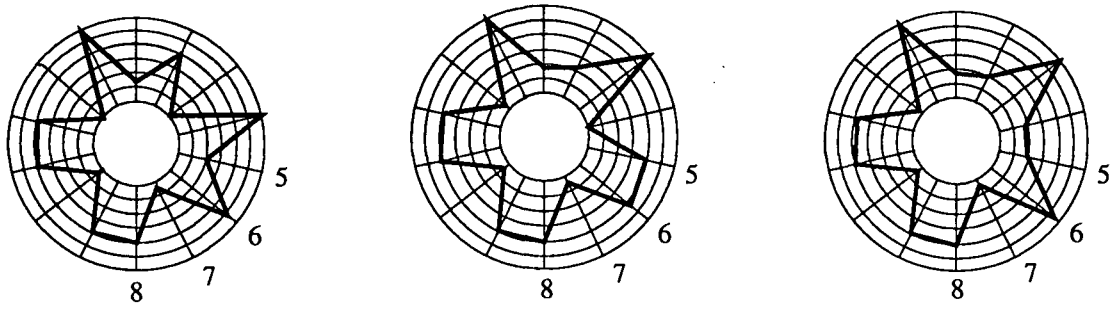
Low energy conformations		Strain energy[a]	Conformation
29a		0.0 kcal/mol	twist
29b		0.05 kcal/mol	[3344]
29c		0.09 kcal/mol	[3434]*

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

Although one might be surprised to see a [3344] conformation lower in energy than the usually more stable [3434], the occurrence is not uncommon. Our group has observed such results before; a few macrolides synthesized in our laboratory crystallized in a [3344] conformation.[59]



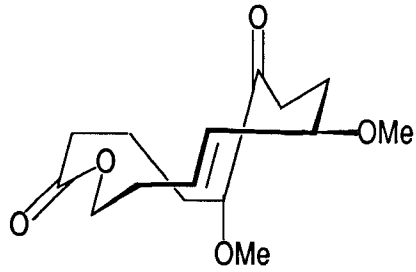
29a

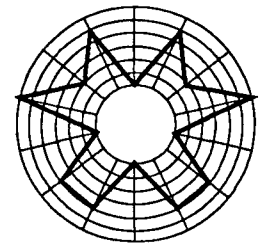


29a **29b** **29c**

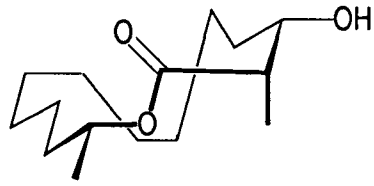
Figure 16. Polar maps of the three lowest energy conformations of **29.**

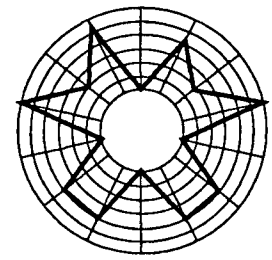
So named because of its resemblance to the twist-boat conformation of cyclohexane, the twist conformation was first reported by Shreiber and Liew[58] in a report on the crystal structure of (10E)-5,9-dimethoxy-6-oxo-10-tridecen-13-olide (**59**), a 14-membered macrolide. Our group also confirmed the existence of this twist conformation; the hydroxy lactone **60**, obtained by reduction of the corresponding keto lactone, crystallized in a twist conformation.[59] MM2 calculations on the twist conformation of cyclotetradecane showed it to be the fifth lowest energy conformation for a 14-membered ring, with a relative strain energy of 3.4 kcal/mol.





59





60

If one used Dale's nomenclature to name the twist and Ogura's D conformations, both would be designated as [311] conformations, *i.e.* there are 3 and 11 carbon-carbon bonds between successive corner positions. Because of this ambiguity, our group proposed to extend Dale's nomenclature system to include the pseudo-corners in the analysis; the number of bonds between a corner and a pseudo-corner, or between two pseudo-corners, shall be indicated by a primed number. With this new nomenclature, the D and twist conformations can be designated as [34'7'] and [3'4'3'4'] conformations.

Examination of the ^{1}H NMR of **29** gave rise to the same finding as for macrolide **28**; namely the methine proton in **29** also exhibited an eleven-line pattern, with coupling constants of 3, 6, and 9.5 Hz, supporting the fact that the molecule is conformationally mobile.[17]

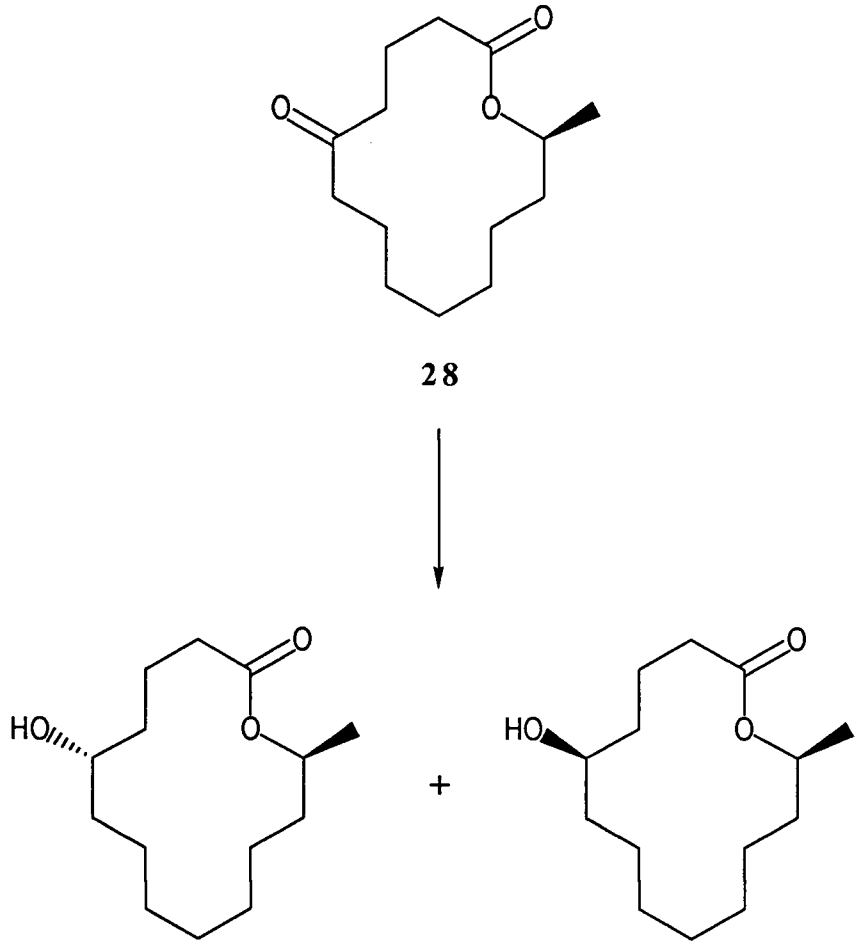
2.4 Diastereoselective reduction of 28 and 29

With both of our macrolides containing a ketone group, we were interested in evaluating the effect of the conformation of the ring on the reduction of the ketone group by various reducing

agents. It was hoped that the possible diastereoselectivity of these reductions could be rationalized and/or predicted by molecular mechanics calculations.

2.4.1 Diastereoselective reduction of **28**

From previous research in our laboratory, it was found that the reduction of 14-membered keto lactones with sodium borohydride proceeded with little or no selectivity.[29] Similarly, reduction of **28** using sodium borohydride gave a 100% yield of a 43:57 mixture (GC: the response factor for the two isomers was assumed to be identical) of two diastereomeric alcohols **61** and **62** of undetermined stereochemistry. Changing the borohydride counter ion to tetramethylammonium gave a mixture of alcohols **61** and **62** in a ratio of 41:59



28

61
5S*,13S*

62
5R*,13S*

(98% yield), a very little change in the selectivity. At this stage, we were unable to separate the two alcohols by column chromatography and their relative stereochemistry was still unknown.

Having had little success in achieving stereoselectivity with simple borohydride reduction, we decided to turn our attention to bulkier reducing agents, in the hope that they would provide increased selectivity. Thus reduction of **28** using L-Selectride (lithium tri-*sec*-butylborohydride) in THF at -78 °C proceeded smoothly to give a 73:27 mixture (by GC analysis) of the two diastereomeric alcohols **61** and **62** (97% yield). Fortunately, when **28** was treated with excess L-Selectride, alcohol **61** was isolated as pure colourless crystals in 52% yield. However these crystals of **61** were not adequate for structure determination. Therefore we prepared the *p*-bromobenzenesulfonate derivative **63** (obtained as colourless prisms) for an X-ray crystallographic analysis , which showed the relative stereochemistry of its substituents to be 5S*,13S* (Figure 17). Hence the major isomer of the diastereomeric alcohols had the 5S*,13S* stereochemistry. The asterisks indicate that both enantiomers of the compound are present.

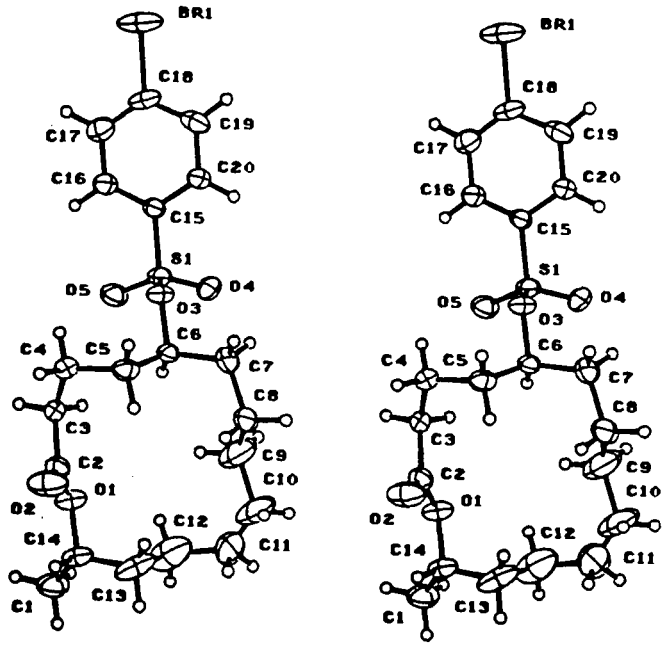


Figure 17. Stereodiagram for macrolide **63**.

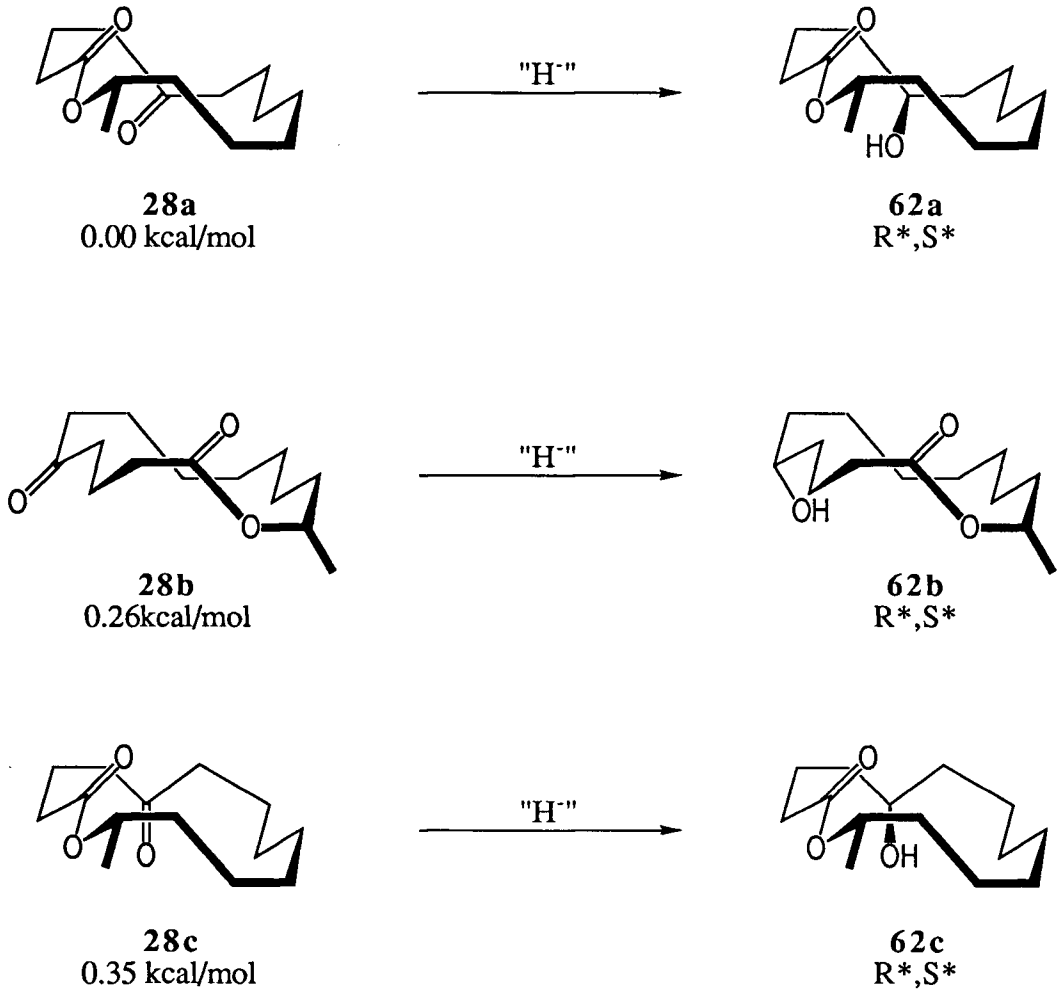
Reduction of **28** with K-Selectride gave a 58% yield of the same diastereomeric alcohols **61** and **62** in an 84:16 ratio respectively. This reduction was very sluggish and the 84:16 ratio is not the initial ratio as the reaction invariably proceeded with decomposition of products, which produced an increase in the ratio of **61** to **62**. Addition of excess reducing agent did not improve the yield of the reaction; it merely increased the yield of decomposition products.

The reductions with L-Selectride and K-Selectride gave the alcohol **61** as the major product. We wondered if the selectivity could be reversed, *i.e.* if we could form alcohol **62** predominantly. A method for reducing carbonyl groups with the reverse selectivity of that achieved by the Selectride reagents has been developed by Yamamoto et al..[60] Using a bulky organoaluminium reagent such as methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (**64**) (MAD) to complex the carbonyl group from the more open face, this allowed delivery of the hydride from the more hindered face, thus giving the opposite selectivity to the Selectride reagents (which reduce the carbonyl from the more open face). Thus, reduction of **28** with MAD and *tert*-butylmagnesium chloride gave a 93% yield of a 20:80 mixture of alcohols **61** and **62** respectively, a selectivity superior to that achieved by the Selectride reagents. The results for the various reductions performed on **28** are summarized in Table IV.

Table IV. Reduction of 5-oxo-13-tetradecanolide (28) with various reducing agents.

Reducing agents	Temperature	Stereoselectivity		Yield %
		61 (S*,S*)	**62** (S*,R*)	
$NaBH_4$	-78 °C	43	57	100
Me_4NBH_4	-78 °C	41	59	98
L-Selectride	-78 °C	73	27	97
K-Selectride	-78 °C	84	16	58
MAD/*tert*-BuMgCl	-78 °C	20	80	93
Predicted selectivity (MM2)	-78 °C	0	100	

Still and Galynker[31] had demonstrated that reagents attack the π-system of a macrocyclic ring almost exclusively from the periphery of the ring, or the more open face. Our group has previously used this rationale to explain results obtained in our laboratory. We therefore decided to examine the results of peripheral attack by the reducing agents on the three lowest energy conformations of **28** (Figure 18).



28a
0.00 kcal/mol

62a
R*,S*

28b
0.26kcal/mol

62b
R*,S*

28c
0.35 kcal/mol

62c
R*,S*

Figure 18. Investigation of peripheral attack on the three lowest energy conformations of **28**.

As one can see, the product expected from peripheral attack on the ketone group is the same for all three starting conformation, namely the 5R*,13S* alcohol. This is in contradiction with our experimental results which show a mixture of **61** and **62** in the case of all the reductions

performed, regardless of the reducing agent. Indeed, the major product in the case of the Selectride reductions is the 5S*,13S* alcohol, as opposed to the predicted 5R*,13S*.

Wu and Houk have shown that reduction of cyclic ketones occur so that there is minimal torsional strain introduced as the newly formed C-O bond rotates inside or outside of the ring.[61] Close examination of the conformations **28a**, **28b**, and **28c** revealed that upon reduction from peripheral attack, the newly formed C-O bond has to rotate past a C-C bond and this process is energetically disfavored. It seems therefore that reduction of **28** does not occur from the ground state conformations **28a**, **28b**, and **28c** and that other conformations, of higher energy, must be involved.

The fact that both unsubstituted borohydride reductions gave little or no selectivity simply confirmed that tetrahydridoborate is not a bulky group, and therefore can approach the carbonyl group from both faces more easily than do the substituted borohydride reagents.

The difference in yield and isomer ratio between the Li-Selectride and K-Selectride reductions may be explained by the fact that the K-Selectride reduction gave some decomposition product. A higher decomposition rate for the minor isomer **62** would explain the higher **61:62** ratio.

The most rewarding result in the various reductions performed was the reverse selectivity obtained with the Yamamoto reagent. The combination of MAD and *tert*-butylmagnesium chloride gave us a selectivity of 20:80 for **61** and **62** respectively, a total reversal of the Selectride selectivity, as expected. A mechanism which may explain this result is shown in Figure 19. No stereochemical correlation between the product obtained in the figure and our results is implied: we are simply showing the manner of operation of the reduction process using MAD and *tert*-butylmagnesium chloride.

It is interesting to note that the stereoselectivity in the MAD reduction was not only the reverse of that of the Selectride reagents, but also slightly better. The higher stereoselectivity for the Yamamoto reduction can possibly be explained by a greater steric requirement for the organoaluminium in its complexation of the ketone in **28**.

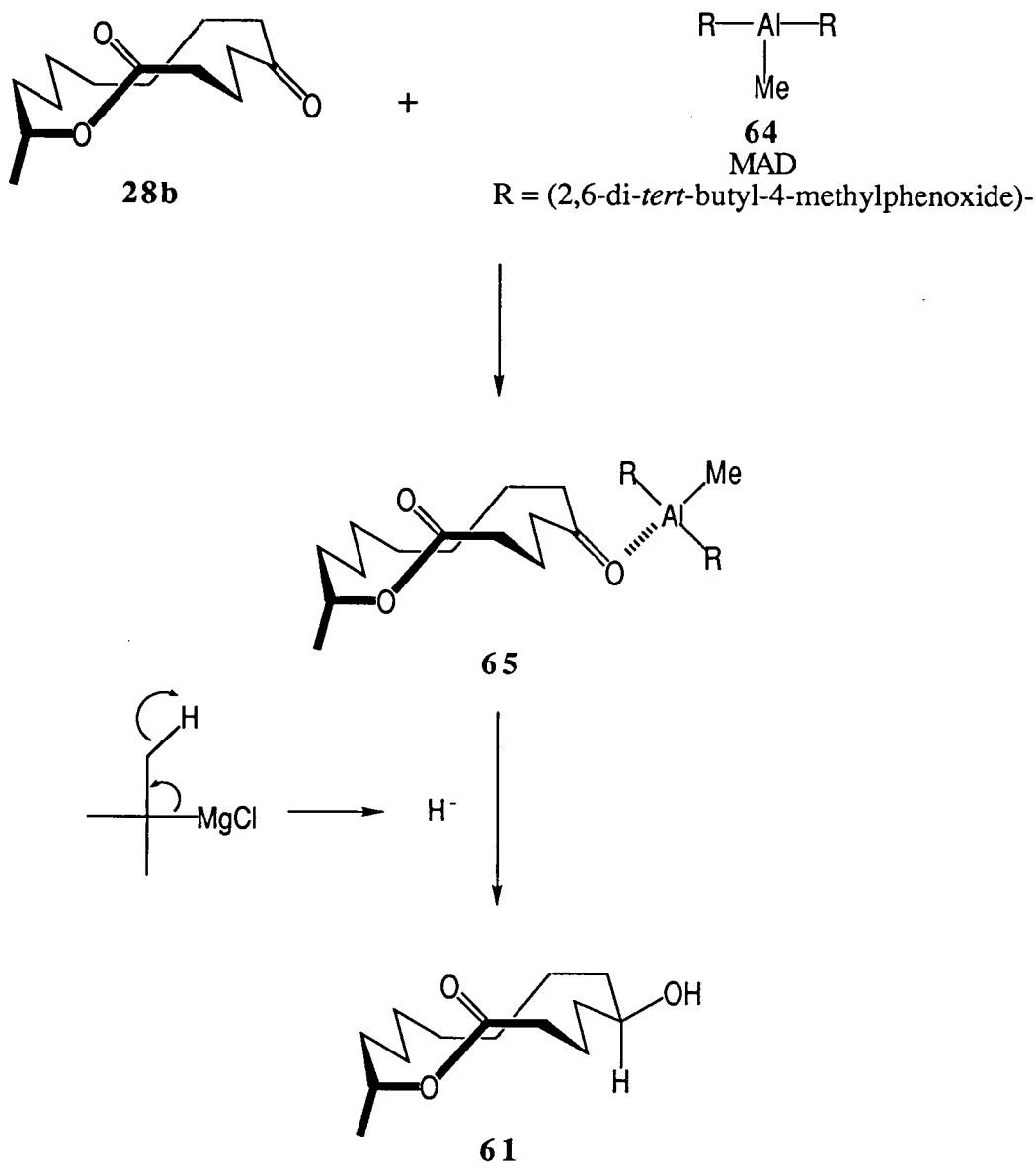
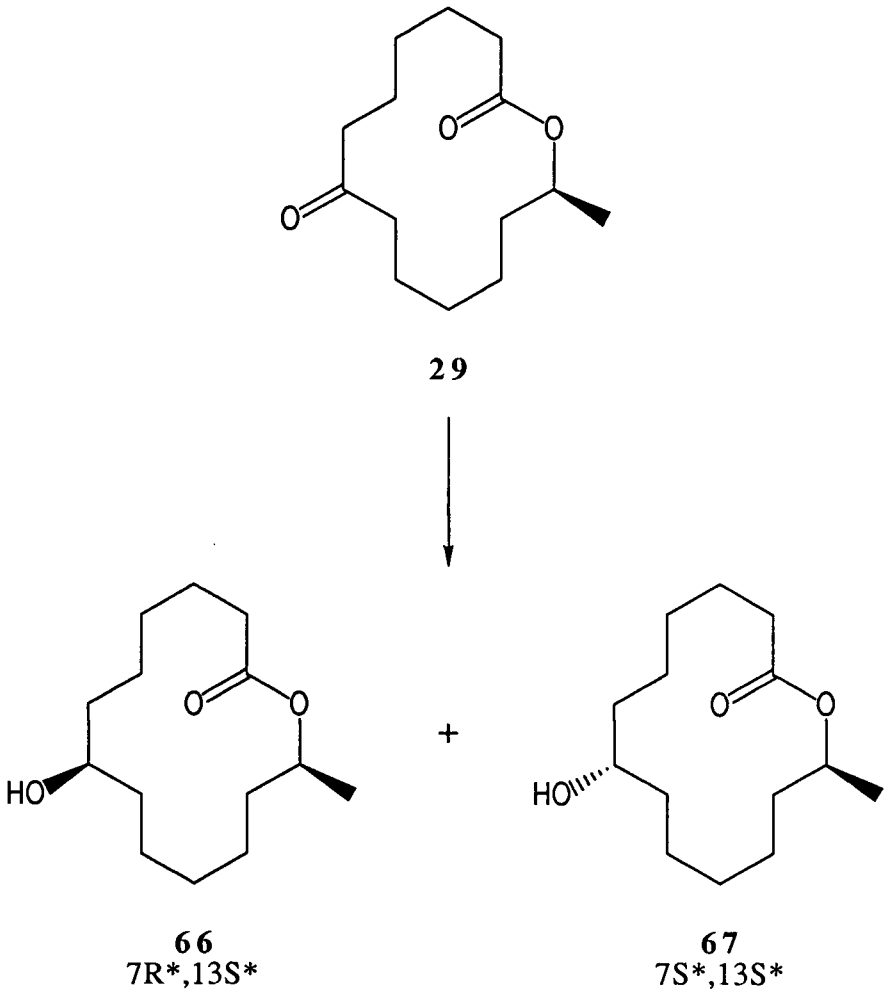


Figure 19. Possible mechanism for the reduction of **28** with MAD and *tert*-butylmagnesium chloride.

2.4.2 Diastereoselective reduction of **29**.

Reductions on **29** were carried out with the same reagents as for **28**. Thus, reduction of **29** with L-Selectride in THF at -78 °C gave a 100% yield of a 9:1 mixture of two diastereomeric alcohols of undetermined stereochemistry. This ratio was determined by NMR as we could not separate the diastereomers by GC. We were also unable to separate the two diastereomers by column chromatography.



Reduction of **29** with K-Selectride at -78 °C in THF gave an 83% yield of a mixture of alcohols in a slightly decreased selectivity of 80:20 compared to L-Selectride. This reduction proceeded much more smoothly than the same one performed on macrolide **28**, with much less decomposition products.

The sodium borohydride reduction of **29** gave, as for macrolide **28**, little or no selectivity: a 1:1 ratio of alcohols in 91% yield. This confirmed again the inability of borohydride to differentiate between the *si* and *re* faces of the carbonyl group because of its small size.

The Yamamoto reduction of **29**, with MAD and *tert*-butylmagnesium chloride, also yielded poor results; a 74% yield of a 1:1 mixture of diastereomeric alcohols, with the same major product being predominant as was found in the Selectride reductions. The fact that the desired reverse selectivity (as compared to the Selectride reagents) was not achieved is unexplained at the moment. A summary of the results obtained is shown in Table V.

Table V. Reduction of 7-oxo-13-tetradecanolide (29) with various reducing agents.

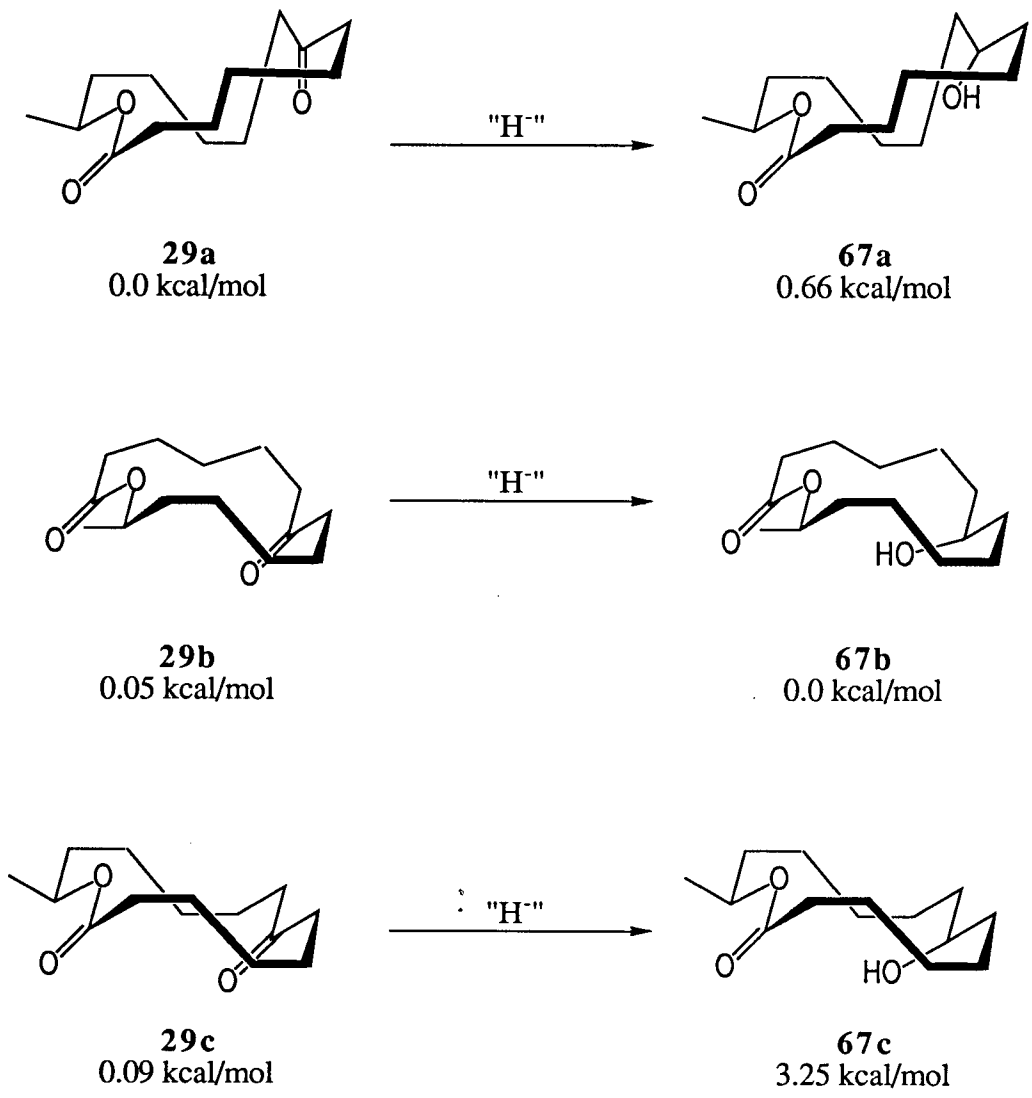
Reducing reagents	Temperature	Stereoselectivity		Yield %
		67 (S*,S*)	**66** (R*,S*)	
$NaBH_4$	-78 °C	50	50	91
L-Selectride	-78 °C	90	10	100
K-Selectride	-78 °C	80	20	83
MAD/*tert*-BuMgCl	-78 °C	50	50	74
Predicted selectivity (MM2)	-78 °C	100		

We were now faced with a major problem: the determination of the relative stereochemistry of the two products in the reduction of **29**. We could not obtain adequate crystals of **29**, or of its *p*-bromobenzenesulfonate derivative, for a structure determination. We had to search for other means of determining the stereochemistry of the products.

One possibility available to us was ^{1}H NMR. If the product existed largely in one major conformation, then we could possibly correlate the coupling constants of the alcohol methine proton with the coupling constants on low energy conformations obtained from a MACROMODEL search for both diastereomeric alcohols. As it turned out, the coupling constants for the alcohol methine proton were 8.5, 4, and 4 Hz, i.e. coupling constants consistent with a conformationally mobile molecule.[17] This was not surprising in light of the report by Shannon et al. that cyclotetradecane itself existed in several different conformations in the liquid state.[19] From these results, it was apparent we could not use ^{1}H NMR to ascertain the relative stereochemistry of the two alcohol products.

With no physical means of assigning the stereochemistry of the products, we found ourselves restricted to the use of molecular mechanics calculations as a possible way of predicting the stereochemistry of the major reduction product. The results of peripheral hydride attack on macrolide **29**'s three lowest energy conformations are depicted in Figure 20.

From our calculations, the three lowest energy conformations of **29** would all give rise to the same product upon peripheral hydride attack, namely the 7S*,13S* alcohol (**67b** is actually the enantiomer of **67a** and **67c**). It turned out that the five lowest energy conformations of **29** give the 7S*,13S* alcohol from peripheral hydride attack. MM2 calculations therefore suggest that the major product obtained from our reductions with the bulky Selectride reagents might be the 7S*,13S* alcohol **67**, and the minor product the 7R*,13S* alcohol **66**. Caution must be emphasized here because of the results obtained in the reduction of **28**.



29a
0.0 kcal/mol

67a
0.66 kcal/mol

29b
0.05 kcal/mol

67b
0.0 kcal/mol

29c
0.09 kcal/mol

67c
3.25 kcal/mol

Figure 20. Investigation of peripheral hydride attack on the three lowest energy conformations of **29**.

With the predicted ratio of 100:0 in favor of the 7S*,13S* over the 7R*,13S*, it was gratifying that the Selectride reagents again gave high facial selectivity toward the carbonyl's *si* and *re* faces. Once again, the sodium borohydride reduction displayed poor diastereoselectivity. The surprising result was the poor diastereoselectivity exhibited by MAD and *tert*-butylmagnesium chloride as opposed to the excellent selectivity in the reduction of keto lactone **28**. At first it was thought that the MAD reagent had failed to complex with the ketone; however, upon addition of the MAD reagent to the keto lactone, the yellow colour indicative of successful complexation appeared instantly. Since complexation was occurring, there had to be another reason for the lack of selectivity. The rationale for this lack of selectivity is still unknown at this time.

2.5 Alkylation of 5-(1',3'-dithian-2'-yl)-13-tetradecanolide (47) and 7-(1',3'-dithian-2'-yl)-13-tetradecanolide (58)

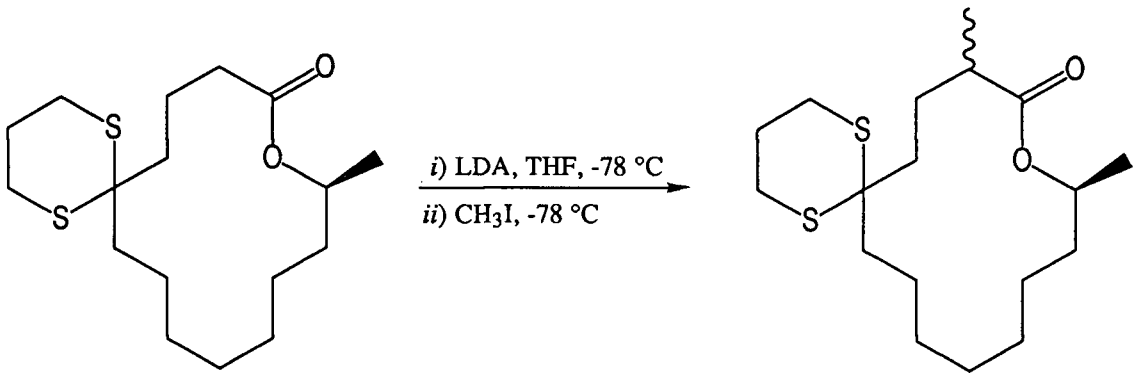
Diastereoselective carbon-carbon bond formation has figured predominantly in organic synthesis. Control of the diastereoselectivity has been achieved mostly through the use of chiral auxiliaries such as Evans' chiral amide and imide enolates,[62] Masamune's optically active mandelic acid derivatives,[63] and Meyers' chiral enamines and oxazolines.[64]

We were interested in seeing whether the conformational preferences of our two macrolides would induce diastereoselectivity in a-alkylation of the ketone and lactone groups.

2.5.1 Alkylation of 5-(1',3'-dithian-2'-yl)-13-tetradecanolide (47)

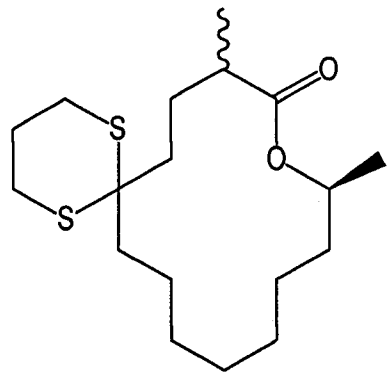
Our first attempts involved alkylation of 5-oxo-13-tetradecanolide (**28**). Treatment of **28** with lithium di-isopropylamide, followed by addition of methyl iodide, gave only decomposition products with some recovered starting material. The result was the same using either lithium tetramethylpiperidide or lithium hexamethyldisilazide as bases.

With the lack of success in alkylation of **28**, we turned to the alkylation of 5-(1',3'-dithian-2'-yl)-13-tetradecanolide (**47**). Treatment of **47** with lithium di-isopropylamide at -78 °C, followed by addition of methyl iodide, gave a 95% yield of an 85:15 mixture (GC: the response factor is assumed to be the same for both isomers) of diastereomeric α-methylated lactones **68**. No dialkylated product was observed. We were unable to separate the diastereomers by column chromatography.

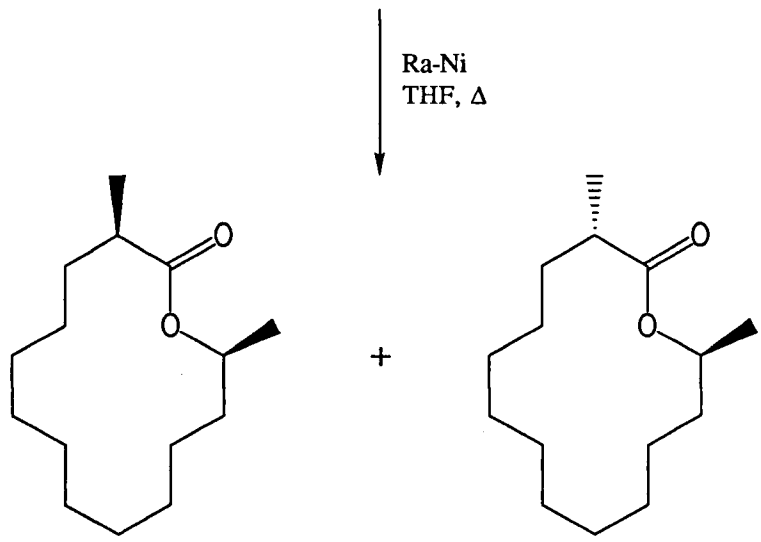


47 **68**
85:15

To determine the relative stereochemistry of the products, **68** was desulfurized with Ra-Ni in THF; work-up and co-injection with authentic materials for GC identification established that the major product was (2R*,13S*)-2-methyl-13-tetradecanolide (**69**) and the minor product (2S*,13S*)-2-methyl-13-tetradecanolide (**70**).[65]



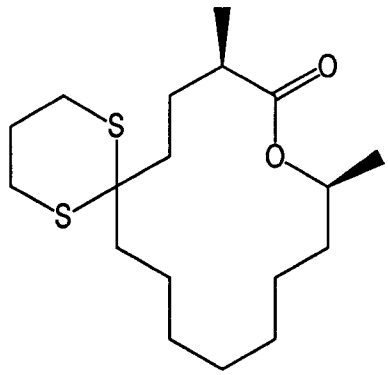
68



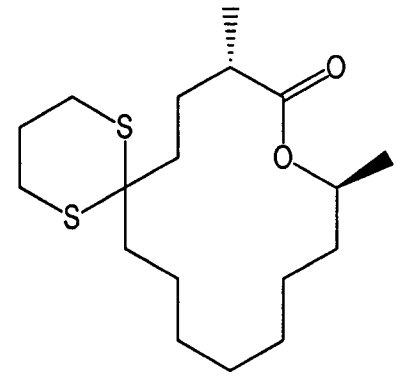
69
2R*,13S*

70
2S*,13S*

Therefore the major product from the alkylation of **47** was (2R*,13S*)-2-methyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide (**71**) and the minor product (2S*,13S*)-2-methyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide (**72**). The kinetic nature of the reaction was confirmed by base equilibration of the 85:15 mixture of **71:72** to a ratio of 49:51.



71
2R*,13S*



72
2S*,13S*

A MACROMODEL search showed that the three lowest energy conformations of **47** are, in order of increasing energy, a [3434] (**47a**), a [3434] (**47b**), and a [3344] (**47c**) conformation. Interestingly, the two [3434] conformations are the same, the only difference being in the orientation of the dithiane ring relative to the macrocycle. All three conformations have an s-trans dihedral angle at the lactone group. In accordance with Dale's prediction on gem-disubstituted 14-membered rings, the dithiane ring occupied a corner position (Figure 21).[10]

Deprotonation of **47** should involve loss of the hydrogen which is the closest to being parallel to the *p* orbitals of the π bond of the carbonyl group (stereoelectronic control approach).[66] This results in **73a**, **73b**, and **73c** as possible conformations for the enolate (Figure 21).

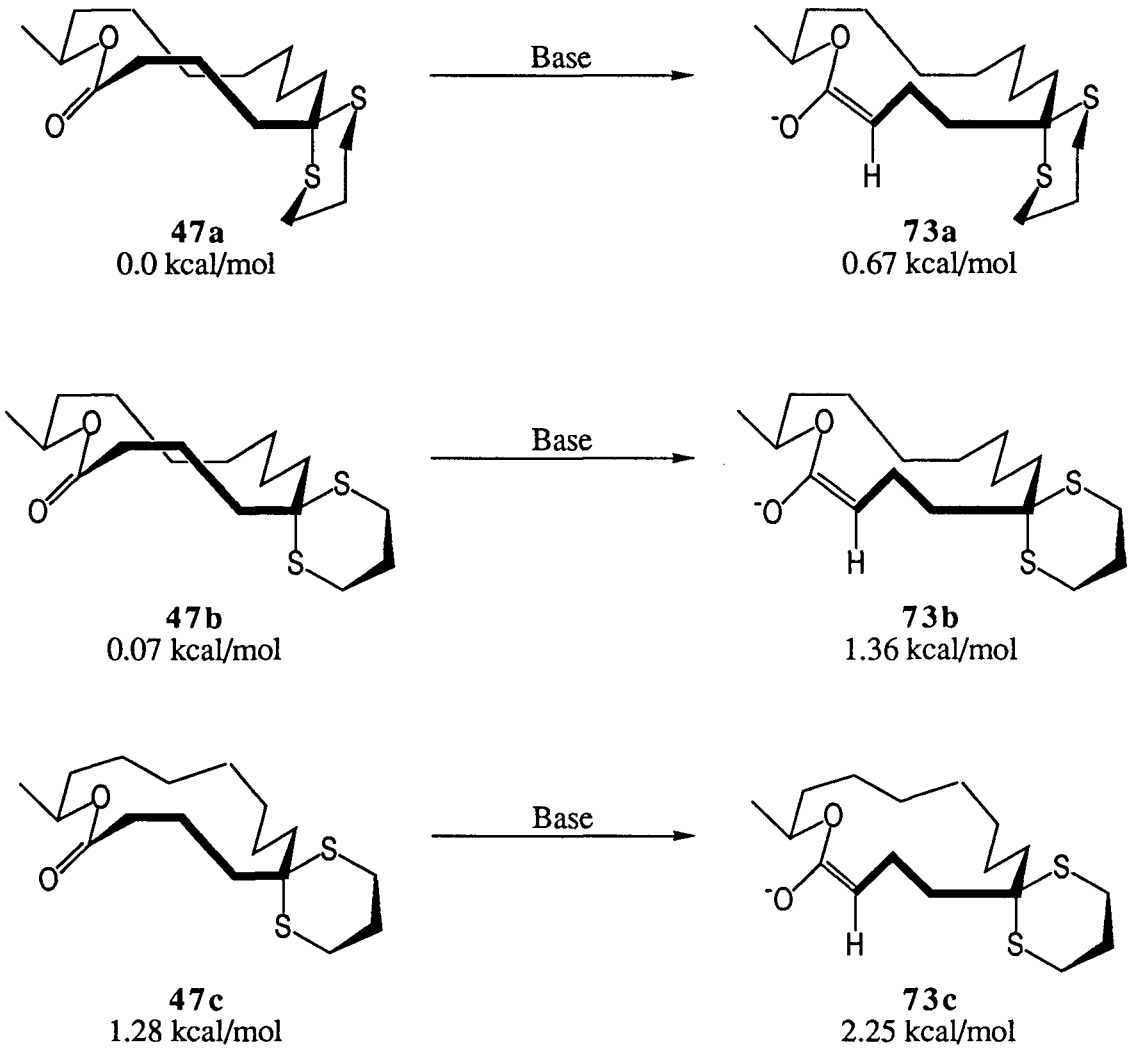
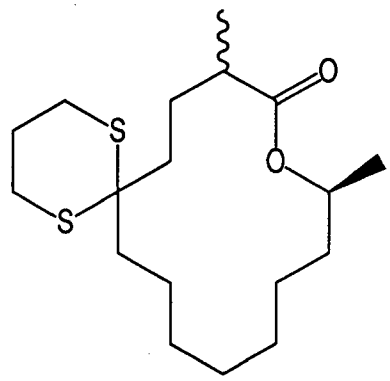


Figure 21. Proton abstraction of the three lowest energy conformations of **47**: strain energies for enolates relative to lowest energy enolate **73e**.

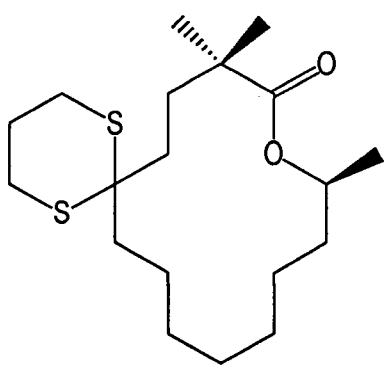
Alkylation of the three conformations **73a**, **73b**, and **73c** should occur from the same direction as the deprotonation. This would then lead to formation of the 2R*,13S* isomer from the three conformations as the sole product of the reaction. This is in reasonable agreement with our results, in which we saw an 85:15 ratio of products in favor of the 2R*,13S* isomer over the 2S*,13S* isomer.

We were curious to see whether the gem-dimethylated compound obtained from alkylation of either **71** or **72** would adopt a conformation in which the two gem-disubstituted carbons would occupy corner positions. Accordingly, the original 85:15 mixture of **68** was treated with lithium di-isopropylamide in THF at -78 °C. Subsequent addition of methyl iodide gave an 87% yield of an 85:15 mixture of 2,2-dimethyl-5-(1',3'-

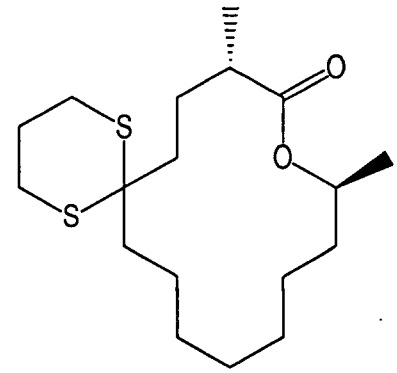


68
85:15

i) LDA, THF, -78 °C
ii) CH_3I, -78 °C



+

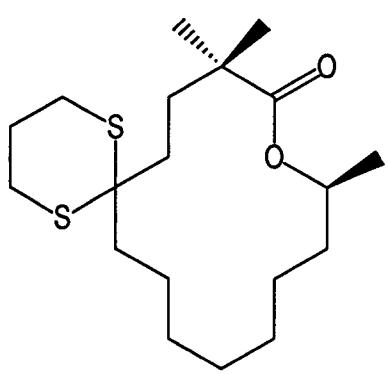


74

72
2S*,13S*

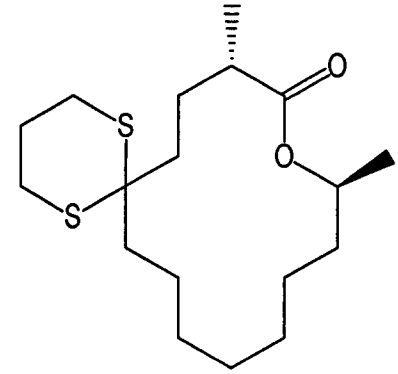
dithian-2'-yl)-13-tetradecanolide (**74**) and (2S*,13S*)-2-methyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide (**72**). Again the mixture proved very difficult to separate. We decided to hydrolyze the dithiane ring in the hope that the resulting product mixture would be easier to separate. Thus, the 85:15 mixture of **74** and **72** was treated with N-bromosuccinimide in aqueous acetone at 0 °C to give an 85:15 mixture of 2,2-dimethyl-5-oxo-13-tetradecanolide (**75**) and (2S*,13S*)-2-methyl-5-oxo-13-tetradecanolide (**76**).

Even this mixture proved quite difficult to separate, but very careful column chromatography enabled us to obtain a small quantity of pure **75** as an oil. Although it would have been interesting to get a structure determination for **75** to study its conformation, we were unable to crystallize the oil.



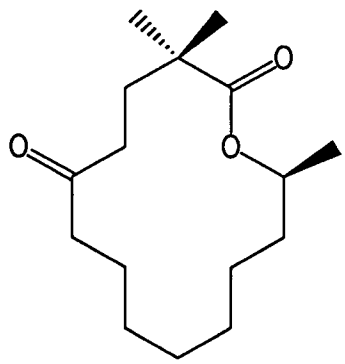
74

+



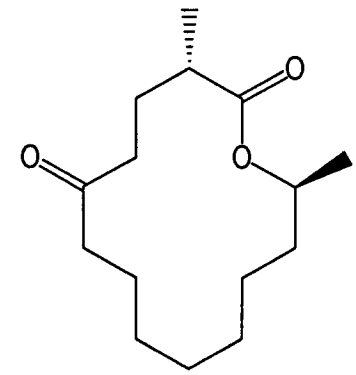
72
2S*,13S*

NBS, aqueous acetone
0 °C



75

+



76
2S*,13S*

Pure 2,2-dimethyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide (**74**) was obtained in 89% yield as colourless crystals by treating **75** with propanedithiol (**38**) in the presence of boron trifluoride-etherate in dichloromethane at 0 °C. Fortunately, crystals suitable for structure determination were obtained for **74**. The stereodiagram for **74** is shown in Figure 22.

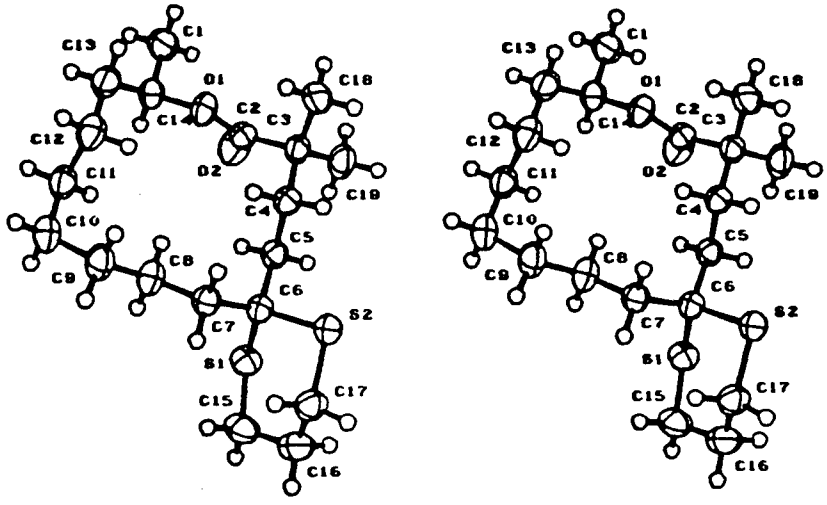
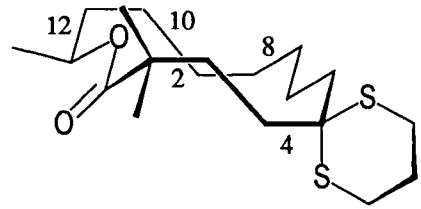
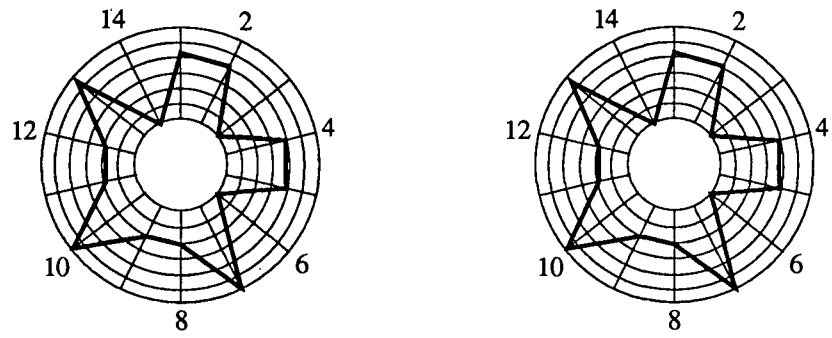


Figure 22. Stereodiagram for macrolide **74**.

As can be seen quite clearly on the stereodiagram, **74** exists in a low energy [3434] conformation, with an s-trans dihedral angle at the lactone group, a C-O-C-H angle of 43°, and with both gem-disubstituted carbons occupying corner positions, as predicted by Dale.[10] In addition, a MACROMODEL search of compound **74** showed that the lowest energy conformation was a [3434] conformation identical to the one shown in the stereodiagram of **74**, as can be seen on the polar maps (Figure 23): a very satisfying result.



74



A **B**

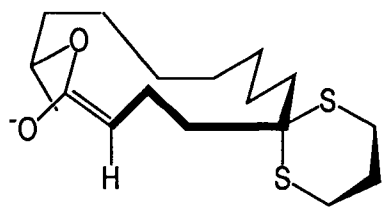
Figure 23. Polar maps for macrolide **74** from crystal structure (**A**), and from MM2 calculation (**B**).

The polar map of the lowest energy conformation from MM2 calculation (**B**) is actually the mirror image of the one obtained by plotting the torsional angles read from the crystal structure (**A**); for purpose of comparison, the signs of the torsional angles in (**B**) have been reversed..

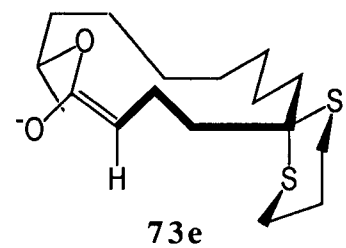
Something puzzled us in the alkylation of **68** to the dimethyl compound **74**, and that was that compound **72** did not react to give compound **74**. One possible explanation for this was that the lactone's remaining α-hydrogen in **72** might not be parallel to the *p* orbitals of the π bond of the carbonyl group, thus rendering its abstraction by base more difficult. It was immediately apparent that if **72** was the trans isomer and adopted a conformation similar to one of the starting low energy conformations **47a**, **47b**, and **47c**,

the methyl group would be sitting in a corner position; this would then give us a product in which the lactone's remaining α-hydrogen is in a good position for abstraction by base and compound **72** should then react to give **74**. However, competitive protonation of such an enolate (the protonated base being the proton source) may give back compound **72**.

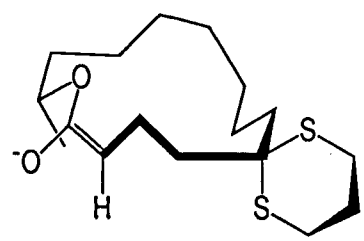
A MACROMODEL conformational search performed on the intermediate enolate **73** revealed that the three lowest energy conformations, **73d**, **73e**, and **73f** all had the methyl group in a pseudo-axial position, presumably to relieve interaction between the methyl group and the oxygen anion in the enolate. Alkylation from the more open face would then give as a product the (2R*,13R*)-dimethylated lactone **72**. Thus the 85:15 ratio of **71**:**72** might be explained by alkylation of the enolates **73a**-**73f** in unequal amounts.



73d
0.73 kcal/mol



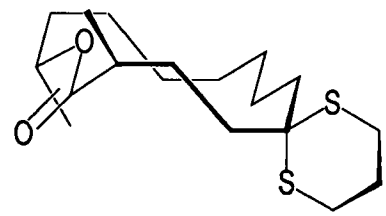
73e
0.0 kcal/mol



73f
0.77 kcal/mol

If compound **72** exists in conformation **72a**, then the lactone's remaining α-hydrogen would be in a position where its abstraction by base under stereoelectronic

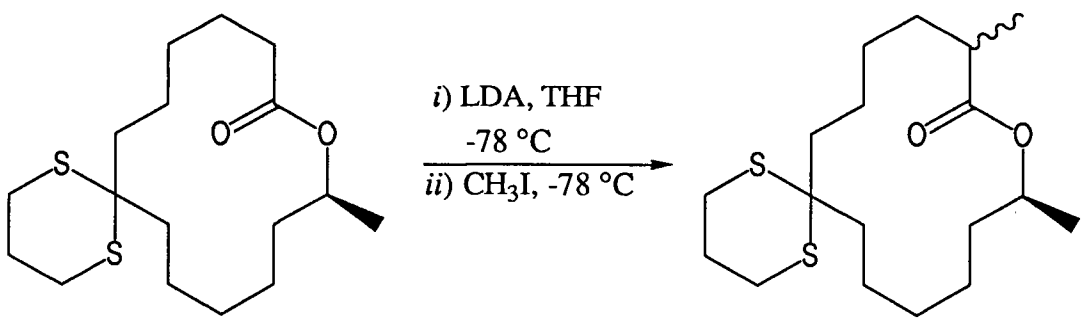
control is much less likely, thus preventing **72** from reacting to form **74**. This is another possible explanation for the lack of reaction of **72**.



72a

2.5.2 Alkylation of 7-(1',3'-dithian-2'-yl)-13-tetradecanolide (58)

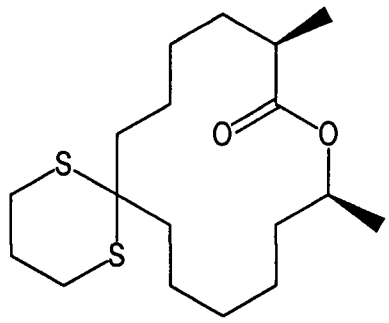
Treatment of **58** with lithium di-isopropylamide in THF at -78 °C, followed by addition of methyl iodide, gave a 100% yield of a 75:25 mixture (GC: the response factor is assumed to be the same for both isomers) of diastereomeric α-methylated lactones **77**. No dialkylated product was observed.



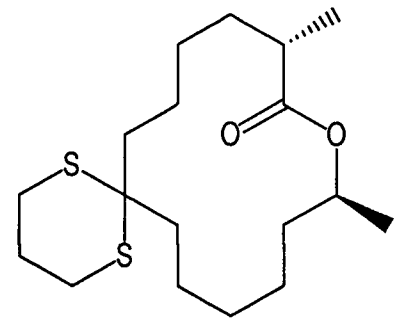
58 **77a,b**

To determine the relative stereochemistry of the products, **77** was desulfurized with Ra-Ni in THF; work-up and co-injection with authentic materials for GC identification established that the major product was (2R*,13S*)-2-methyl-13-tetradecanolide (**69**) and the minor product (2S*,13S*)-2-methyl-13-tetradecanolide (**70**).[65] Therefore the major product from the alkylation of 7-(1',3'-dithian-2'-yl)-13-tetradecanolide (**58**) was

(2R*,13S*)-2-methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (**77a**) and the minor product (2S*,13S*)-2-methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (**77b**).



77a
2R*,13S*
major



77b
2S*,13S*
minor

Fortunately, we obtained further confirmation on the stereochemistry of the products as the major isomer **77a** crystallized out of the oily product mixture in crystals suitable for a structure determination. As one can see in the stereodiagram (Figure 24), the stereochemistry is clearly 2R*,13S*. In addition, the lactone group is in the s-trans arrangement and the C-O-C-H dihedral angle has a value of 22°. Both facts agree with the restrictions previously used for 14-membered lactone rings. Comparison of the polar map of the crystal structure of **77a** with that of the lowest energy conformation obtained in a MACROMODEL search showed the two to be quite similar. The conformation is the same but for a difference of a few degrees in some of the torsional angles (Figure 25): the only noticeable difference is for torsional angle 12. Once again, the polar maps are mirror images of each other; the sign of the torsional angles in (**B**) have been reversed for ease of comparison.

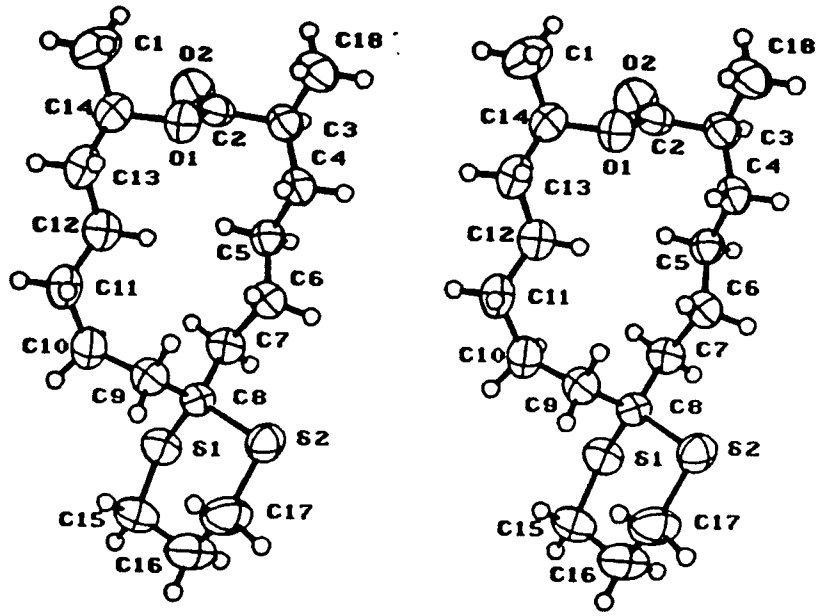


Figure 24. Stereodiagram for macrolide **77a**.

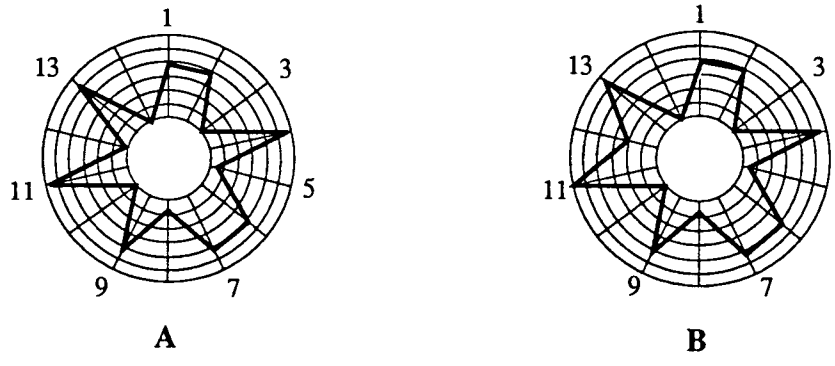
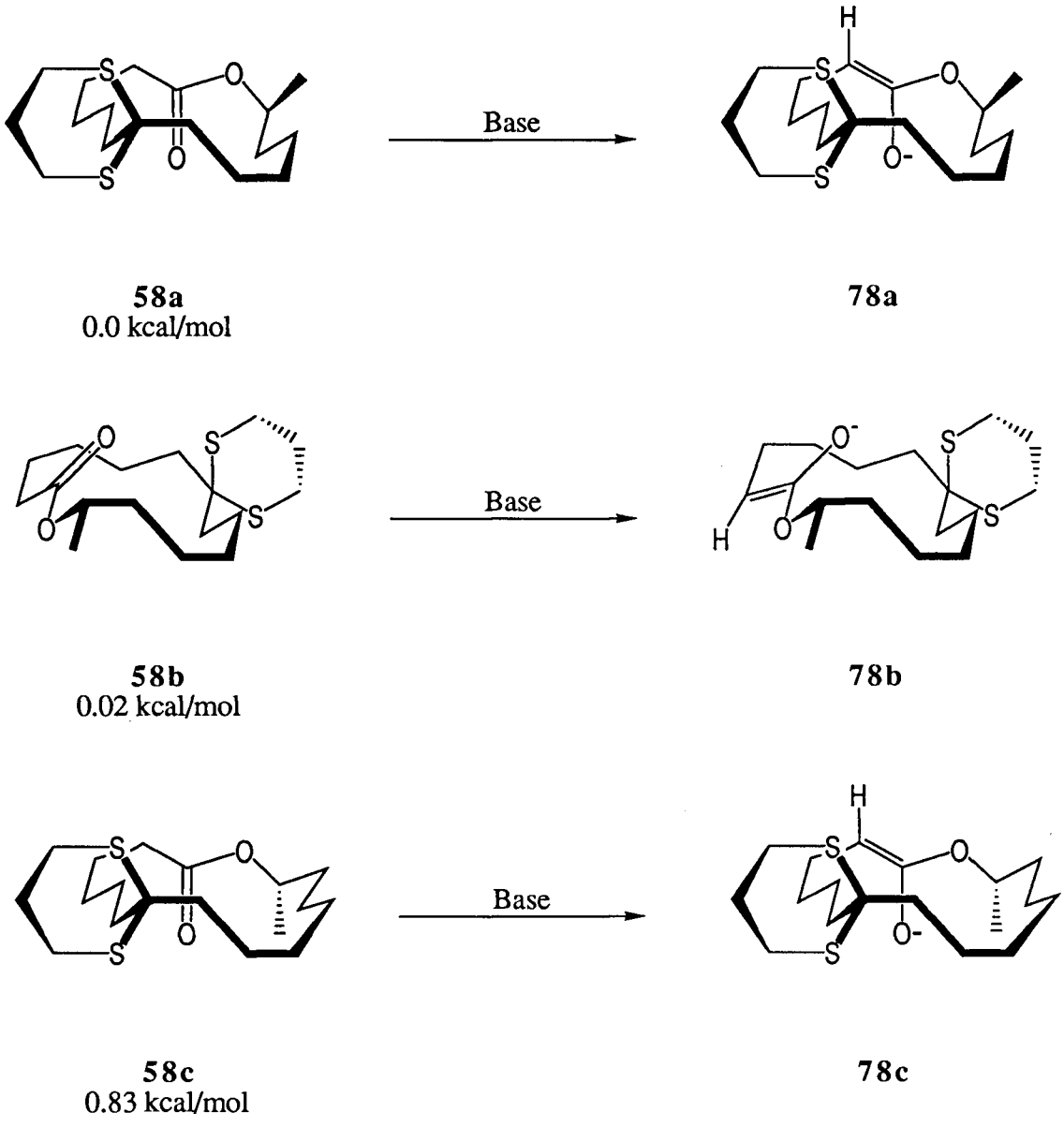


Figure 25. Polar maps for **77a** from crystal structure (**A**) and MM2 calculation (**B**).

The stereoelectronic control approach was used again to rationalize the results of alkylation of **58**. However, these results are not as satisfactory as for the alkylation of **47**. The three lowest energy conformations for **58**, obtained in a MACROMODEL search (Figure 26), were all [3344] conformations; two of them, **58b** and **58c**, are epimers. The Boltzmann distribution for these three conformations at -78 °C was calculated to be 37:37:26 for **58a**:**58b**:**58c**.

Abstraction of the proton closest to being parallel to the *p* orbital of the π bond of the carbonyl group would give rise to the enolates **78a**, **78b**, and **78c**.[66] Alkylation from the same direction as proton abstraction should then give (2S*,13S*)-2-methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (**77b**) from **78a** and **78b**, and (2S*,13R*)-2-methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (**77a**) from **78c**. Using the Boltzmann distribution obtained for the starting conformations, the calculated product ratio was 74:26 in favor of **77b** over **77a**; this was at odds with our experimental ratio of 80:20 in favor of **77a** over **77b**.



58a
0.0 kcal/mol

78a

58b
0.02 kcal/mol

78b

58c
0.83 kcal/mol

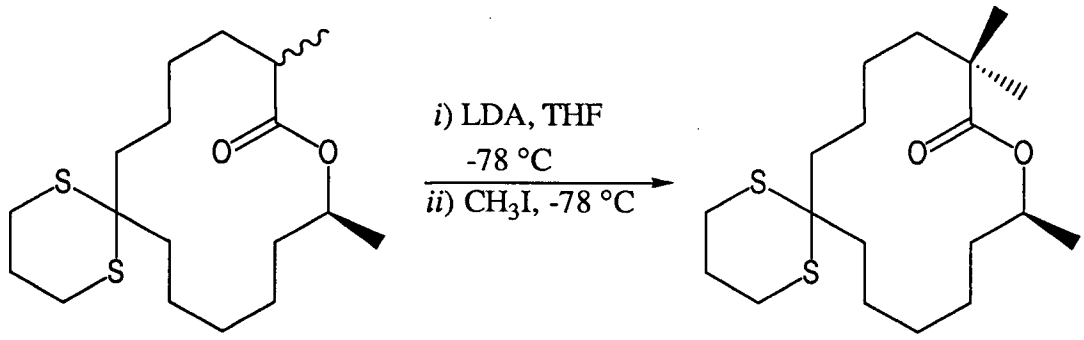
78c

Figure 26. Proton abstraction of the three lowest energy conformations of **58**.

Thus we considered the possibility that the intermediate enolate **78** might undergo a conformational change. A MACROMODEL search on the intermediate enolate **78** showed that the three lowest energy conformations would yield **77b** as final product. After this

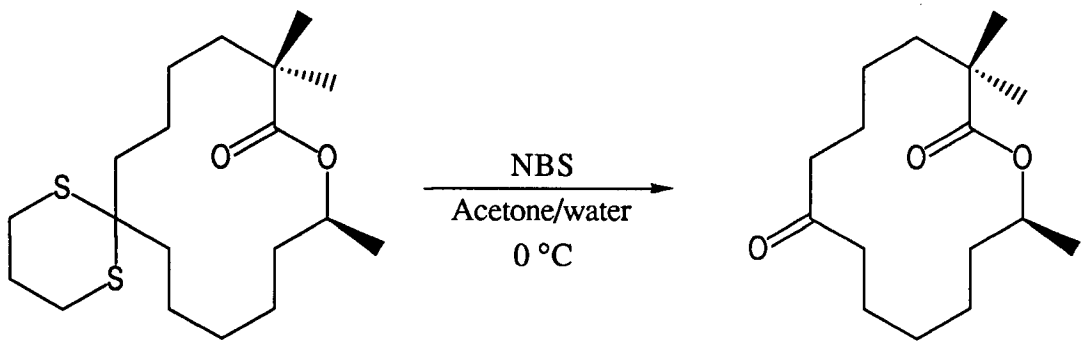
negative result, we were at a loss as to finding an adequate explanation for the stereochemical outcome of the alkylation of **58**, and this stereoselectivity remains unexplained.

Once again, we decided to verify whether gem-disubstitution would occur at a corner position, as predicted by Dale.[10] Thus, the mixture of **77a** and **77b** was treated with lithium di-isopropylamide in THF at -78 °C to give a 33% yield of 2,2-dimethyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (**79**) as an oil. We were unable to obtain suitable crystals of **79** for a structure determination, which would have enabled us to further corroborate Dale's prediction.



77a,b **79**

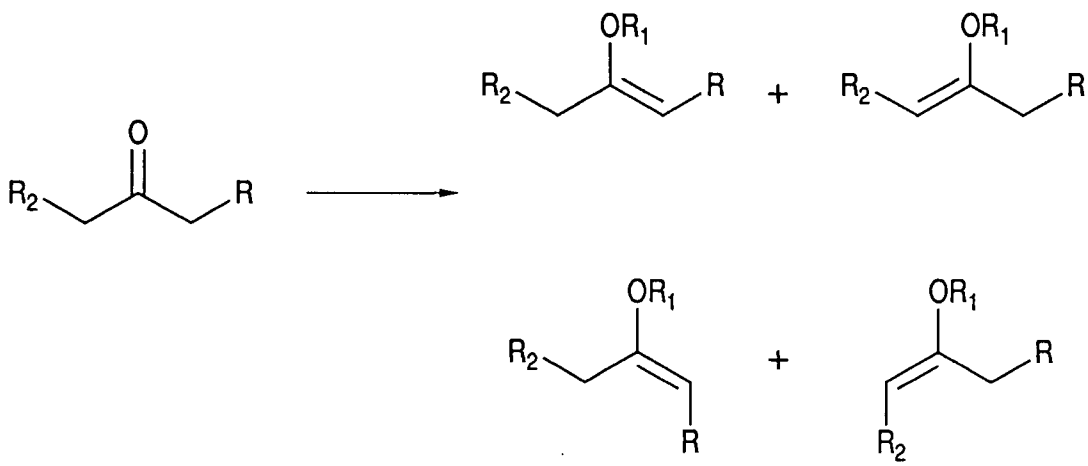
We also prepared 2,2-dimethyl-7-oxo-13-tetradecanolide (**80**), which was obtained by oxidative hydrolysis of the dithiane group in **79** by N-bromosuccinimide. Although **80** was obtained as white crystals, they were inadequate for an X-ray structure determination.



79 **80**

2.6 Preparation of enol ethers from **28** and **29**

Enol ethers are very useful synthetic intermediates. We decided to see whether we could selectively form one of the four possible enol ethers obtainable from **28** and **29**. As selective generation of enol ethers is quite difficult from ketones having a secondary carbon atom on each side, success in this matter on our part would be a step forward for conformational control.



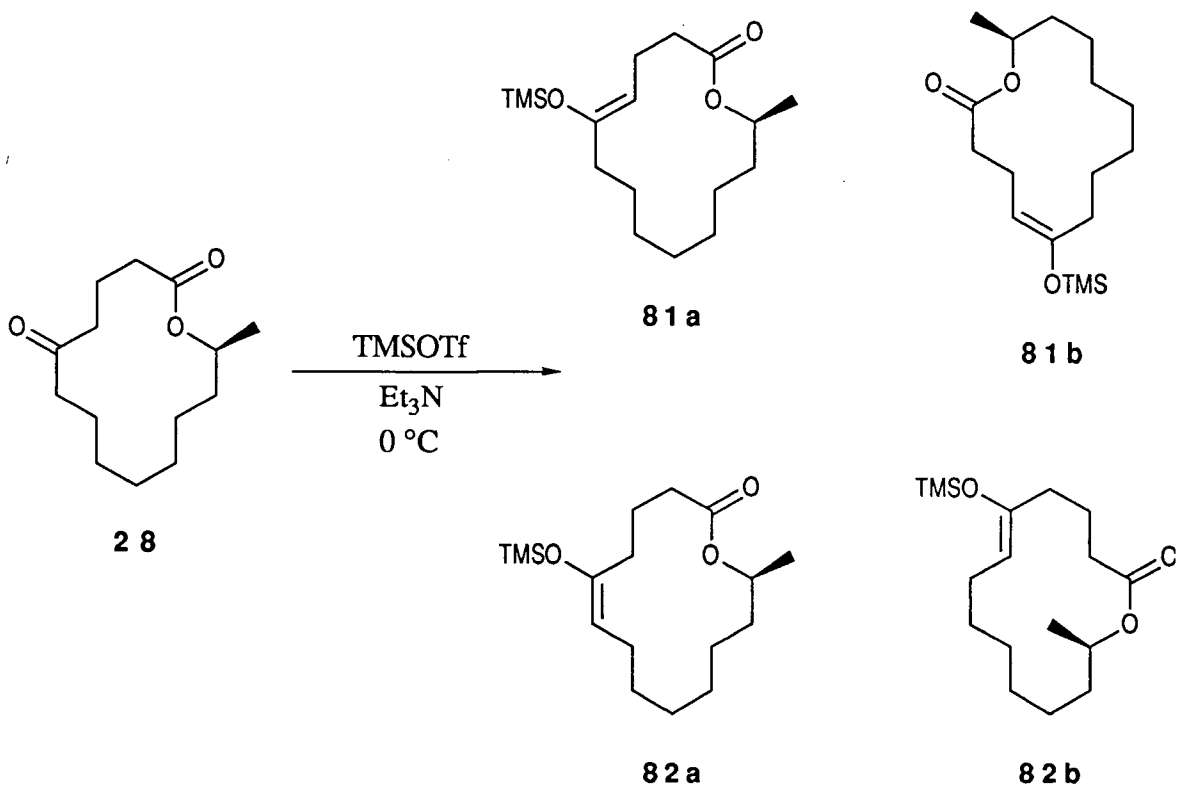
Many methods for formation of enol ethers are available in the literature.[67] Most involve vigorous conditions; however, Emde et al. have reported that the use of silyl trifluoromethanesulfonates in the presence of triethylamine is mild and convenient for the preparation of enol ethers.[67c,d] They also noted that the use of only 0.8 equivalents of

triethylamine led to an equilibrium controlled mixture of enol ethers. We used this method on both our macrolides, **28** and **29**.

2.6.1 Enol ether generation from **28**

We decided to generate two different kinds of enol ethers from macrolide **28**, namely the trimethylsilyl and *tert*-butyldimethylsilyl enol ethers.

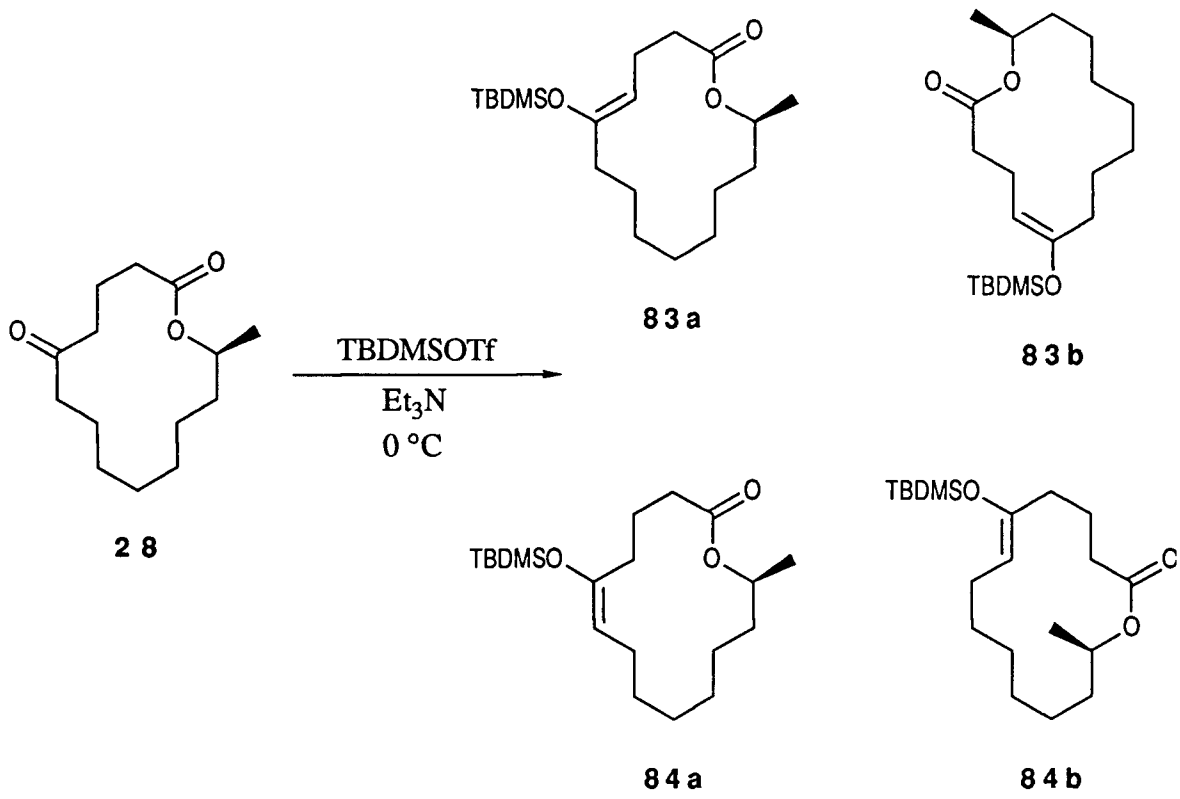
Initial treatment of **28** with 1 equivalent of trimethylsilyl trifluoromethanesulfonate and 0.8 equivalent of triethylamine gave us no product. We had to increase the amount of reagents to 1.5 equivalents of trimethylsilyl trifluoromethanesulfonate and 2 equivalents of triethylamine before we were able to isolate a mixture of three isomeric enol ethers in a ratio of 14:72:14 (GC).



28 **81a** **81b** **82a** **82b**

The three isomeric enol ethers were unseparable, and we could not determine their structure. Still and co-workers had previously used the results of MM2 calculations to rationalize the results of equilibrium controlled reactions in cyclic compounds.[29] We therefore conducted a MACROMODEL search in order to find the lowest energy conformations for each of the possible products. The Boltzmann distribution at 0 °C for the lowest energy conformations of all four possible enol ethers gave a 98:1.5:0.5 ratio for **81a**:**82b**:**81b** respectively; that ratio was quite different from the experimental ratio, which could imply that the reaction did not proceed under strict equilibrium control. If we compare the calculated ratio to our experimental ratio of 14:72:14, one might conclude that the enol ether **81a**, the 4Z isomer, was the major product of the reaction, with the remainder composed of **82b** (the 5Z isomer) and **81b** (the 4E isomer). Regardless of the true structure of the product, an experimental ratio of 14:72:14 represents an acceptable example of conformational control, especially in such a mobile system.

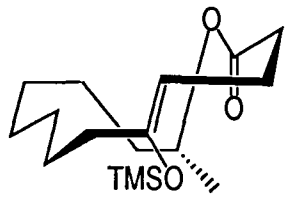
It was thought that the use of a bulkier silylating reagent might result in a greater selectivity in enol ether formation from **28**. Thus, we turned toward *tert*-butyldimethylsilyl trifluoromethanesulfonate as a silylating agent. Treatment of **28** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine yielded a mixture of three isomeric enol ethers, again unseparable, in a ratio of 19:70:11.



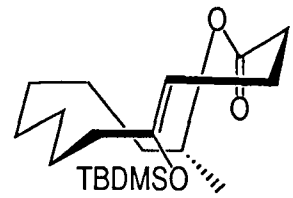
28 **83a** **83b** **84a** **84b**

This was a rather disappointing result. One would have thought that the size of the *tert*-butyldimethylsilyl group would have induced a higher selectivity than that obtained. Once again, a MACROMODEL search was carried out on all four possible enol ethers, and a Boltzmann distribution calculated at 0 °C. The resulting calculated ratio of 80:19.5:0.5 for **83a**:**83b**:**84b** respectively was closer to the experimental result of 19:70:11 than in the TMS enol ether formation. From a comparison of the calculated and experimental ratios, one might conclude that the major product in the formation of the TBDMS enol ethers from **28** was compound **83a**.

An interesting point was the fact that in both reactions, the product with the lowest energy conformation was the 4Z isomer for both the TMS and the TBDMS enol ethers. In addition, the lowest energy conformations for **83a** (the TMS enol ether) and **85a** (the TBDMS enol ether) were the same; both had the twist conformation (Figure 27).



81a



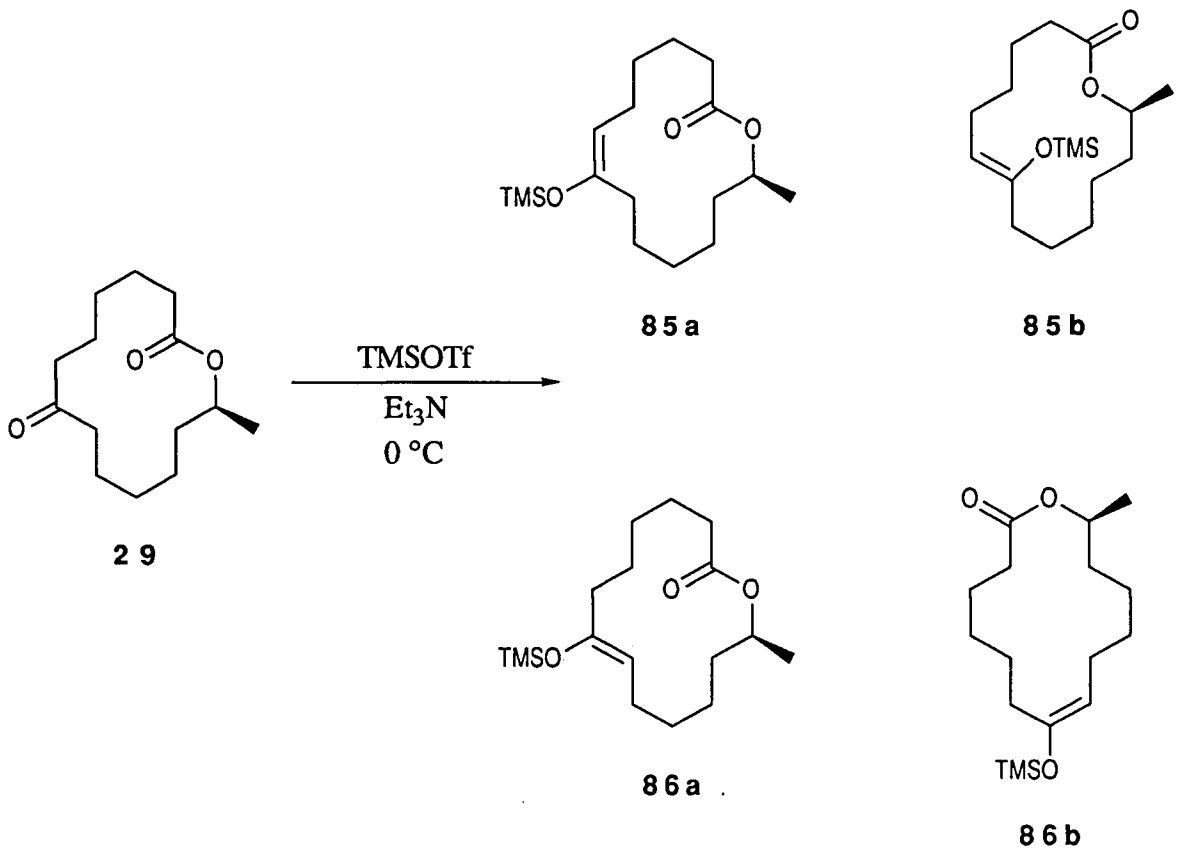
83a

Figure 27. Lowest energy conformations (MM2) of **81a** and **83a**.

2.6.2 Enol ether generation from **29**

Treatment of **29** with trimethylsilyl trifluoromethanesulfonate and triethylamine yielded a mixture of four isomeric enol ethers in a ratio of 74:12:6:8.

We searched, with the help of MACROMODEL, for the lowest energy conformations for the four possible products. A Boltzmann distribution at 0 °C gave a ratio of 98.2:1.7:0.1 for **86a**:**85b**:**86b** respectively. This calculated ratio and the experimental one are quite different again, as for the TMS enol ether formation from **28**.

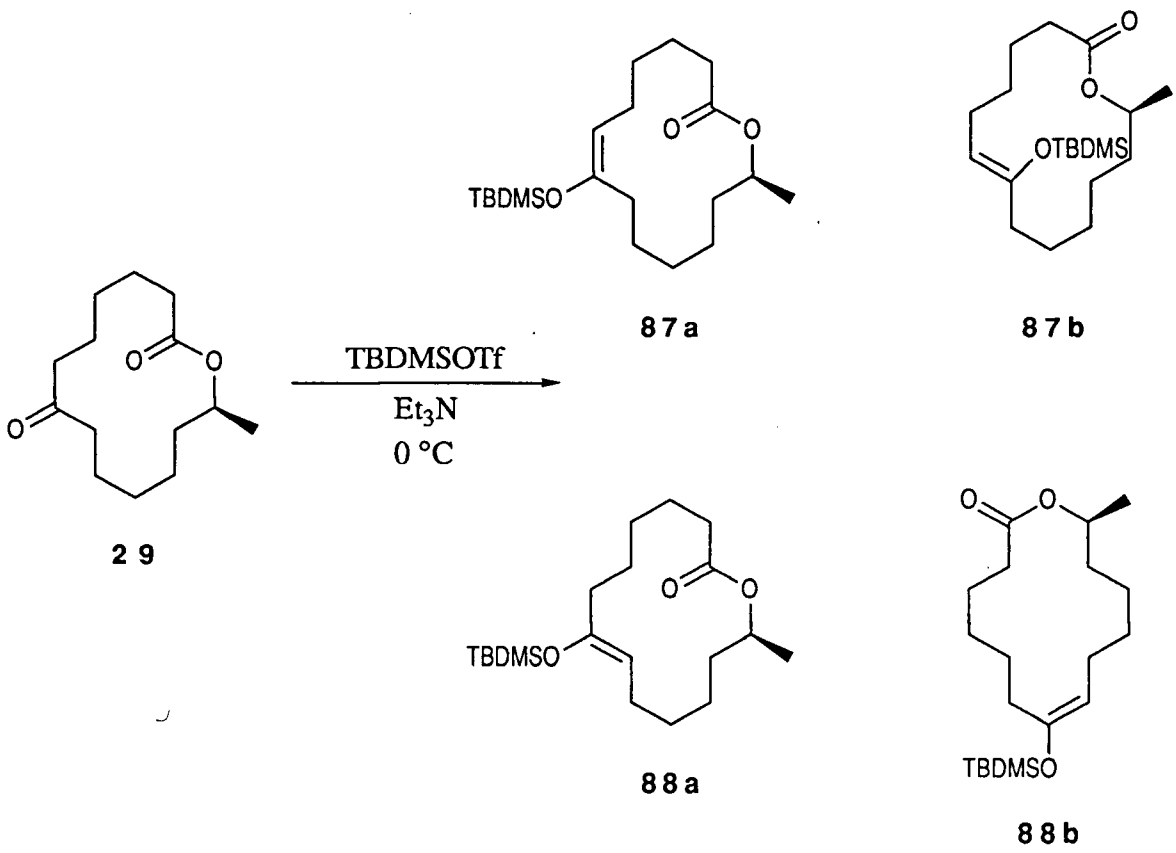


As for the previous enol ether formations, the difference between the calculated and the experimental ratios could possibly be explained by incomplete equilibration of the product mixture.

To compare the selectivity of the TMS enol ether formation with that of a bulkier silylating agent, **29** was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine at 0 °C to give a mixture of isomeric enol ethers in a ratio of 69:6:16:9. Again, we were disappointed with the fact that selectivity did not increase with the bulkier silylating agent.

A MACROMODEL search gave us the lowest energy conformations of each isomeric product and the calculated Boltzmann distribution turned out to be 83:17 for **88a** and **87b** respectively. This is much closer to the experimental ratio than was the case in the

TMS enol ether formation. Of course, as we could not assign any structures to the product obtained because they were unseparable, we could only assume that the two major products of the reaction were **88a** and **87b**.

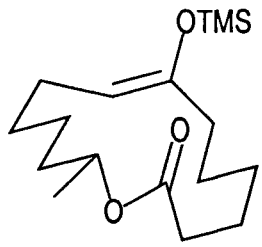


87a **87b**

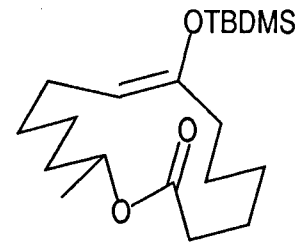
29

88a **88b**

The product with the lowest energy conformation was the 7Z isomer for both the TMS and the TBDMS enol ethers of **29**. Both products, **86a** and **88a**, had the same low energy conformation; recall that this was also the case in the formation of enol ethers from **28**, where both products, the TMS and the TBDMS enol ethers, had the 4Z geometry (Figure 28).



86a



88a

Figure 28. Lowest energy conformations (MM2) for **86a** and **88a**.

2.7 Conclusion

We have found that the conformational behavior of 14-membered lactones can be complex; in particular, we showed, in the case of lactone **28** for example, that the lowest energy conformations obtained from a MACROMODEL search need not necessarily be involved in reduction reactions.

We performed a number of reactions on 14-membered lactones with a ketone group either at C_5 (compound **28**) or C_7 (compound **29**) to investigate the conformational control due to large rings, particularly in hydride reductions, alkylations, and enol ether formations. The diastereoselectivity of some reactions could be rationalized with the aid of Boltzmann distributions of the conformations of starting materials; some results, on the other hand, were left unexplained. This rationalization based on extensive modeling had the disadvantage of requiring large amounts of computer time for the conformational searches used in MACROMODEL. The results of the conformational searches carried out, in combination with other arguments such as increase of torsional strain in the ketone reductions, showed that one cannot use only ground state conformations to explain product formation in various reactions.

CHAPTER III

Experimental

3.1 General

Unless otherwise stated, all reactions were performed under N_2 in flame-dried glassware. The cold temperature baths used were: dry ice-acetone (-78 °C), dry ice-chloroform (-60 °C), dry ice-carbon tetrachloride (-20 °C) and ice-water (0 °C).

Anhydrous reagents and solvents were prepared according to the procedure given in the literature.[68] Alkyllithium reagents (Aldrich Chemical Co.) were standardized against diphenylacetic acid in THF, a faint yellow color being indicative of the end-point.

Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard model 5880A, equipped with a split mode capillary injector and a flame ionization detector, using either a 0.22 mm diameter DB-210 column of 12 m in length or a 0.22 mm diameter SE-30 column of 12 m in length. Helium was the carrier gas. Retention times (R_t) are reported as follows: R_t (column type, initial temperature/time at initial temperature/rate of temperature increase/final temperature, carrier gas pressure).

Silica gel 60, 230-400 mesh, supplied by E. Merck Co., was used for preparative flash column chromatography. Thin layer chromatography was performed on aluminium-backed plates of silica gel 60 (2 mm thickness), also supplied by E. Merck Co.

Melting points were performed on a Fisher-Johns hot stage melting point apparatus and are corrected.

Infra-Red (IR) spectra were recorded on a BOMEM FT-IR Michaelson-100 connected to an IBM compatible computer. IR spectra were taken neat on NaCl plates or in chloroform solution using NaCl cells of 0.2 mm thickness. The spectrometer is internally calibrated by a HeNe laser to a resolution of 4 cm^{-1}.

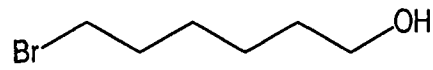
Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in deuterochloroform solutions on a Bruker AC-200 (200 MHz), Varian XL-300 (300 MHz), or a Bruker WH-400 (400

MHz). Chemical shifts are given in parts per million (ppm) on the δ scale versus tetramethylsilane (δ 0 ppm) or chloroform (δ 7.27 ppm) as internal standards. Signal multiplicity, coupling constants, and integration ratios are given in parentheses.

Low resolution mass spectra (LRMS) were recorded on a Kratos-AEI model MS 50 or model MS 9 spectrometer. Only peaks with greater than 20% relative intensity or those which were analytically useful are reported. High resolution mass spectra (HRMS) were obtained from a Kratos-AEI model MS 50 spectrometer. An ionization potential of 70 eV was used in all measurements.

Microanalyses were done at the microanalytical laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer 1106.

3.2 6-Bromo-1-hexanol



31

A suspension of 1,6-hexanediol (17.1 g, 0.144 mol) and 48% aqueous hydrobromic acid (8.9 M, 40 mL, 0.36 mol) was added to a liquid-liquid extractor. The mixture was heated at 80 °C under continuous extraction with *n*-heptane. After 44 hours, the two layers were separated. The aqueous layer was saturated with NaCl and extracted with diethyl ether. The combined organic phases were washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of solvents afforded a golden oil which was purified by column chromatography with 3:1 petroleum ether-ethyl acetate as eluant to give 20.7 g (79%) of **31** as a colourless oil.

R_t (SE-30, 80 °C/2 min/20 °C min^{-1}/200 °C, 10 psi) 3.22 min.

IR (neat) 3340, 2980, 2845, 1448, 1260, 1055 cm^{-1}.

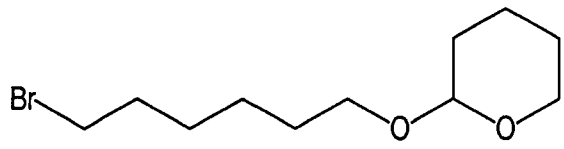
^1H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.53 (m, 5H), 1.58 (m, J = 7 Hz, 2H), 1.87 (m, J = 6.5 Hz, 2H), 3.40 (t, J = 7 Hz, 2H), 3.63 (t, J = 6.5 Hz, 2H).

LRMS (m/z) 164 (^{81}Br, M^+ - H_2O, 1), 162 (^{79}Br, M^+ - H_2O, 2), 136 (8), 134 (9), 83 (54), 55 (100).

HRMS calcd for $C_6H_{11}{}^{81}Br$ (M^+ - H_2O): 164.0025; found: 164.0022.

calcd for $C_6H_{11}{}^{79}Br$ (M^+ - H_2O): 162.0045; found: 162.0037.

3.3 6-Bromo-1-(2-tetrahydropyranyloxy)hexane



32

To a solution of 6-bromo-1-hexanol (10.0 g, 55 mmol) in CH_2Cl_2 (300 mL) was added 3,4-dihydro-2*H*-pyran (6.0 mL, 66 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate. The resulting mixture was stirred at room temperature for 1.5 hours, after which time it was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (12:1 petroleum ether-ethyl acetate as eluant) yielded 13.2 g (90%) of **32** as a clear, colourless oil.

R_t (SE-30, 80 °C/2 min/20 °C min^{-1}/200 °C, 10 psi) 8.01 min.

IR (neat) 2936, 2862, 1448, 1352, 1200, 1030, 985 cm^{-1}.

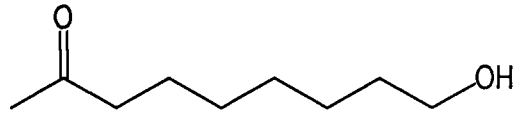
^1H NMR ($CDCl_3$, 400 MHz) δ 1.34-1.76 (m, 12H), 1.87 (m, J = 7 Hz, 2H), 3.34-3.45 (m, 3H), 3.50 (m, 1H), 3.73 (dt, J = 7, 10 Hz, 1H), 3.86 (m, 1H), 4.56 (t, J = 4 Hz, 1H).

LRMS (m/z) 265 (^{81}Br, M^+ - 1, 2), 263 (^{79}Br, M^+ - 1, 2), 185 (1), 85 (100), 56 (38), 55 (48), 41 (44).

HRMS calcd for $C_{11}H_{20}O_2{}^{81}Br$ (M^+ - 1): 265.0628; found: 265.0634.

calcd for $C_{11}H_{20}O_2{}^{79}Br$ (M^+ - 1): 263.0647; found: 263.0651.

3.4 9-Hydroxy-2-nonanone



34

Methyl acetoacetate (7.5 mL, 70 mmol) was slowly added to a suspension of NaH (2.8 g of a 60% suspension in mineral oil, 70 mmol) in THF (150 mL) and DMF (50 mL). After the effervescence had sudsided, 6-bromo-1-(2-tetrahydropyranyloxy)hexane (9.2 g, 35 mmol) in THF (50 mL) was added dropwise over 15 minutes and the resulting solution was refluxed for 44 hours. The mixture was then quenched with NH_4Cl, diluted with diethyl ether and washed with water, followed by saturated NaCl solution. The solvent was removed and the golden oil obtained was refluxed in 3M HCl (100 mL) and methanol (35 mL) for 1.5 hours. The mixture was then extracted with CH_2Cl_2. The organic phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of the solvent and column chromatography (3:1 petroleum ether-ethyl acetate as eluant) gave 4.3 g (79%) of **34** as a colourless oil.

R_t (SE-30, 80 °C/2 min/20 °C min^{-1}/200 °C, 10 psi) 4.30 min.

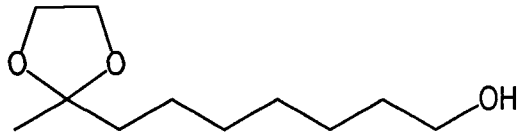
IR ($CHCl_3$) 3621, 2933, 2875, 1710, 1363, 1042 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.45 (m, 6H), 1.58 (m, 4H), 2.14 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H).

LRMS (m/z) 158 (M^+, 2), 140 (3), 100 (26), 97 (35), 83 (56), 82 (100), 71 (59), 58 (66), 55 (21).

HRMS calcd for $C_9H_{18}O_2$: 158.1306; found: 158.1311.

3.5 9-Hydroxy-2-nonanone ethylene acetal



36

To a solution of 9-hydroxy-2-nonanone (12.4 g, 78 mmol) in benzene (200 mL) was added ethanediol (13.1 mL, 0.23 mol) and a catalytic amount of pyridinium *p*-toluenesulfonate. The mixture was refluxed with water separation by a Dean-Stark trap for 4 hours. The solvent was removed and the oil obtained was dissolved in diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of the solvent afforded 14.4 g (91%) of **36** as a colourless oil.

R_t (SE-30, 80 °C/2 min/20 °C min^{-1}/200 °C, 10 psi) 5.67 min.

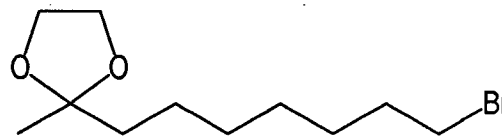
IR ($CHCl_3$) 3685, 2935, 2870, 1477, 1428, 1216, 1023, 928 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.32-1.42 (m, 8H), 1.55 (m, 2H), 1.63 (m, 2H), 2.33 (br s, 1H), 3.61 (t, J = 6 Hz, 2H), 3.93 (m, 4H).

LRMS (m/z) 187 (M^+ - CH_3, 13), 87 (100), 43 (28).

HRMS calcd for $C_{10}H_{19}O_3$ (M^+ - CH_3): 187.1334; found: 187.1334.

3.6 9-Bromo-2-nonanone ethylene acetal



37

A solution of 9-hydroxy-2-nonanone ethylene acetal (14.4 g, 91 mmol) in CH_2Cl_2 (350 mL) was cooled to -78 °C. Triphenylphosphine (25.2 g, 96 mmol) was added in one portion, followed by carbon tetrabromide (31.8 g, 96 mmol). The reaction mixture was stirred at -78 °C for 1.5 hours and the cooling bath removed. After stirring at room temperature for 1 hour, petroleum ether was added and the precipitated triphenylphosphine oxide was filtered off. Solvents were removed and the oil dissolved in 1:1 petroleum ether-diethyl ether to again precipitate, and filter off, the triphenylphosphine oxide. Solvent evaporation and column chromatography (9:1 petroleum ether-ethyl acetate eluant) gave 16.7 g (88%) of **37** as a colourless oil.

R_t (SE-30, 80 °C/2 min/20 °C min^{-1}/200 °C, 10 psi) 5.62 min.

IR (neat) 2934, 2863, 1454, 1375, 1229, 1060, 947, 856 cm^{-1}.

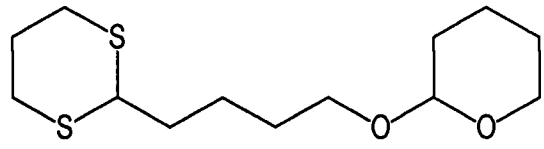
^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 1.30-1.50 (m, 8H), 1.85 (m, J = 9 Hz, 2H), 3.41 (t, J = 9 Hz, 2H), 3.95 (m, 4H).

LRMS (m/z) 251 (^{81}Br, M^+ - CH_3, 8), 249 (^{79}Br, M^+ - CH_3, 8), 87 (100).

HRMS calcd for $C_{10}H_{18}O_2{}^{81}Br$ (M^+ - CH_3): 251.0470; found: 251.0470.

calcd for $C_{10}H_{18}O_2{}^{79}Br$ (M^+ - CH_3): 249.0490; found: 249.0494.

3.7 5-(1',3'-Dithian-2'-yl)-1-(2-tetrahydropyranyloxy)pentane



41

1,3-Propanedithiol (13 mL, 0.18 mol) and 3,4-dihydro-2*H*-pyran (25 mL, 0.28 mol) were dissolved in CH_2Cl_2 (300 mL) and the solution cooled to 0 °C. Boron trifluoride etherate (27 mL, 0.22 mol) was added dropwise over 30 minutes and the mixture was stirred overnight. After quenching with water, the organic phase was washed successively with 3N NaOH solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. To the dry organic layer was then added 3,4-dihydro-2H-pyran (20 mL, 0.22 mol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate. The resulting solution was stirred for 2 hours at room temperature after which time it was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of the solvent followed by column chromatography (6:1 petroleum ether-ethyl acetate eluant) yielded 26 g (72%) of **41** as a slightly yellow oil.

R_t (SE-30, 80 °C/2 min/20 °C min^{-1}/200 °C, 10 psi) 9.62 min.

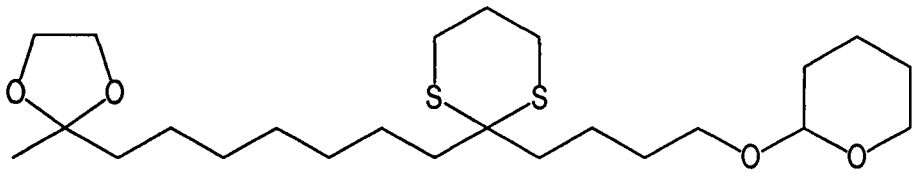
IR ($CHCl_3$) 2943, 2869, 1454, 1352, 1277, 1135, 1030 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.95 (m, 14H), 2.86 (m, 4H), 3.40 (dt, J = 6.5, 10 Hz, 1H), 3.51 (m, 1H), 3.75 (dt, J = 6.5, 10 Hz, 1H), 3.86 (m, 1H), 4.06 (t, J = 7 Hz, 1H), 4.58 (t, J = 3.5 Hz, 1H).

LRMS (m/z) 276 (M^+, 2), 191 (100), 119 (45), 85 (59).

HRMS calcd for $C_{13}H_{24}O_2S_2$: 276.1217; found: 276.1210.

3.8 10-(1',3'-Dithian-2'-yl)-14-(2-tetrahydropyranyloxy)-2-tetradecanone ethylene acetal



42

A solution of 5-(1',3'-dithian-2'-yl)-1-(2-tetrahydropyranyloxy)pentane (3.7 g, 14 mmol) in THF (70 mL) was cooled to -20 °C and *n*-butyllithium (1.6 M in hexane,8.8 mL, 14 mmol) added dropwise over 15 minutes. After stirring for 2 hours, a solution of 9-bromo-2-nonanone ethylene acetal (3.3 g, 12 mmol) in THF (30 mL) was added dropwise and the resulting mixture was stirred for 1 hour at -20 °C. The cooling bath was removed and, after stirring at room temperature for 1 hour, the reaction was quenched with saturated NH_4Cl solution. The mixture was washed successively with water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of solvent gave a yellow sirupy oil which was subjected to column chromatography (12:1 petroleum ether-ethyl acetate eluant) to provide 5.0 g (88%) of **42** as a slightly yellow oil.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.37.

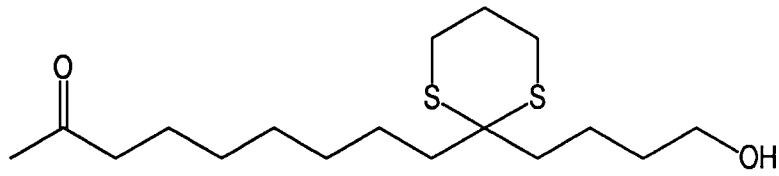
IR (neat) 2934, 2865, 1451, 1374, 1201, 1137, 1034 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.30-2.00 (m, 8H), 2.81 (m, 4H), 3.42 (dt, J = 7, 10 Hz, 1H) 3.51 (m, 1H), 3.77 (dt, J = 7, 10 Hz, 1H), 3.83-3.97 (m, 5H), 4.58 (t, J = 3.5 Hz, 1H).

LRMS (m/z) 460 (M^+, 3), 376 (3), 361 (2), 303 (6), 191 (12), 87 (100), 85 (33), 55 (29), 43 (56).

HRMS calcd for $C_{24}H_{44}O_4S_2$: 460.2681; found: 460.2683.

3.9 10-(1',3'-Dithian-2'-yl)-14-hydroxy-2-tetradecanone



43

10-(1',3'-Dithian-2'-yl)-14-(2-tetrahydropyranyloxy)-2-tetradecanone ethylene acetal (5.4 g, 12 mmol) was dissolved in a mixture of acetone (60 mL), water (60 mL), and methanol (120 mL), followed by the addition of a catalytic amount of pyridinium *p*-toluenesulfonate. The solution was heated to 55 °C and stirred for 2 hours. The solvents were evaporated and the residue dissolved in diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 3.8 g (97%) of **43** as a colourless oil.

R_f (1:1 petroleum ether-ethyl acetate eluant) 0.25.

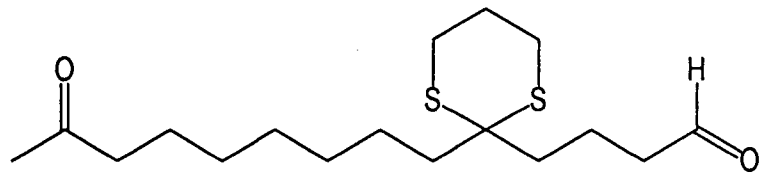
IR ($CHCl_3$) 3687, 3620, 2937, 2858, 1710, 1458, 1362, 1246, 1052 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 1.20-1.70 (m, 14H), 1.82-2.00 (m, 6H), 2.14 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 5.5 Hz, 2H), 2.82 (t, J = 5.5 Hz, 2H), 3.68 (t, J = 6.5 Hz, 2H).

LRMS (m/z) 332 (M^+, 9), 259 (48), 225 (27), 191 (62), 98 (66), 55 (72), 43 (100).

HRMS calcd for $C_{17}H_{32}O_2S_2$: 332.1845; found: 332.1845.

3.10 5-(1',3'-Dithian-2'-yl)-13-oxotetradecanal



44

To a solution of 10-(1',3'-dithian-2'-yl)-14-hydroxy-2-tetradecanone (3.9 g, 12 mmol) in benzene (100 mL) was added successively: DMSO (9.0 mL, 120 mmol), dichloroacetic acid (0.50 mL, 6.0 mmol), and 1,3-dicyclohexylcarbodiimide (DCC) (7.4 g, 36 mmol). The reaction mixture was stirred overnight, then diluted with ethyl acetate and the excess DCC destroyed by slow addition of a solution of oxalic acid dihydrate (3.6 g, 29 mmol) in methanol (25 mL). The resulting suspension was poured into saturated NaCl solution and the mixture filtered to remove the urea precipitate. The layers were separated and the organic phase was washed successively with water and saturated NaCl (more urea precipitated, removed again by fitration), then dried ($MgSO_4$) and filtered. Removal of solvents and column chromatography (6:1 petroleum ether-ethyl acetate eluant) afforded 2.7 g (70%) of **44** as a yellowish oil.

R_f (5:3 petroleum ether-ethyl acetate eluant) 0.38.

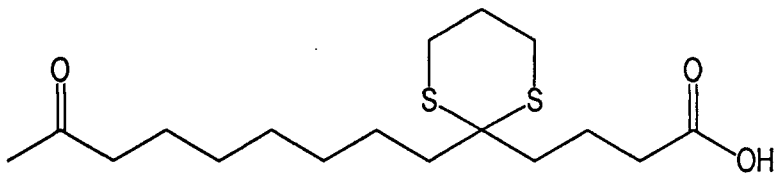
IR ($CHCl_3$) 2935, 2857, 2725, 1714, 1419, 1358, 1275 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (m, 6H), 1.44 (m, 2H), 1.58 (m, 2H), 1.73-2.00 (m, 8H), 2.14 (s, 3H), 2.43 (t, J = 8 Hz, 2H), 2.49 (m, J = 7, 2 Hz, 2H), 2.82 (m, 4H), 9.1 (t, J = 2 Hz, 1H).

LRMS (m/z) 330 (M^+, 7), 259 (22), 189 (28), 145 (25), 55 (55), 43 (100).

HRMS calcd for $C_{17}H_{30}O_2S_2$: 330.1687; found: 330.1687.

3.11 5-(1',3'-Dithian-2'-yl)-13-oxotetradecanoic acid



45

5-(1',3'-dithian-2'-yl)-13-oxotetradecanal (2.7 g, 8.1 mmol) was dissolved in THF (75 mL) and water (47 mL). Silver nitrate (6.9 g, 41 mmol) was added to this solution, followed by 3M NaOH (28 mL, 81 mmol). After stirring for 2 hours, the black precipitate was removed by filtration through a pad of Celite® and the Celite® washed with diethyl ether and 3M NaOH. The aqueous phase was separated and acidified with 3M HCl, then extracted with chloroform. The chloroform phase was washed with saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of the solvent provided 2.7 g (96%) of pure **45** as a viscous oil.

R_f (9:1 chloroform-methanol eluant with one drop of acetic acid) 0.38.

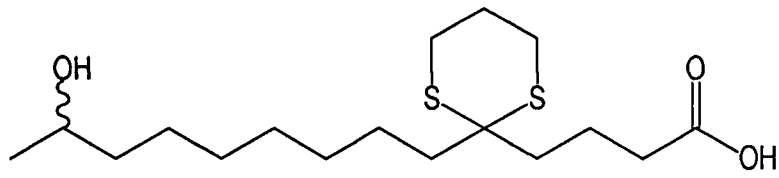
IR ($CHCl_3$) 3200, 2989, 2939, 2860, 1711, 1455, 1360 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (m, 6H), 1.45 (m, 2H), 1.85 (m, 4H), 1.95 (m, 4H), 2.18 (s, 3H), 2.45 (m, 4H), 2.85 (m, 4H).

LRMS (m/z) 346 (M^+, 8), 259 (44), 205 (74), 145 (43), 107 (32), 97 (35), 79 (50), 71 (53), 67 (51), 55 (69), 45 (51), 43 (100), 41 (78).

HRMS calcd for $C_{17}H_{30}O_3S_2$: 346.1636; found: 346.1639.

3.12 5-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanoic acid



46

5-(1',3'-Dithian-2'-yl)-13-oxotetradecanoic acid (2.2 g, 6.4 mmol) was dissolved in ethanol (50 mL) and the solution was cooled to 0 °C. Sodium borohydride (0.49 g, 13 mmol) was added slowly and the reaction mixture was stirred at 0 °C for 1 hour. The excess borohydride was destroyed with 1M HCl, the solution was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent gave 2.2 g (100%) of **46** as a viscous colourless oil.

R_f (9:1 chloroform-methanol eluant with one drop of acetic acid) 0.30.

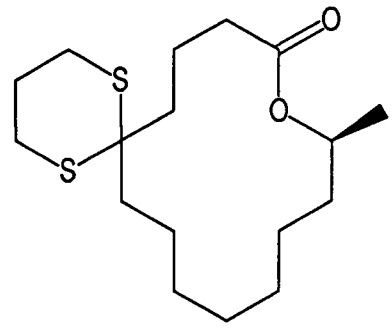
IR ($CHCl_3$) 3684, 2933, 1747, 1715, 1425, 1217, 1021, 928 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, J = 6 Hz, 3H), 1.25-1.55 (m, 12H), 1.82 (m, 4H), 1.97 (m, 4H), 2.41 (t, J = 7 Hz, 2H), 2.82 (m, 4H), 3.82 (m, J = 6 Hz, 2H).

LRMS (m/z) 348 (M^+, 17), 261 (35), 205 (100), 145 (32), 107 (24).

HRMS calcd for $C_{17}H_{30}O_3S_2$: 348.1793; found: 348.1789.

3.13 5-(1',3'-Dithian-2'-yl)-13-tetradecanolide



47

1-Phenyl-1*H*-tetrazole-5-thiol (0.61 g, 3.4 mmol) was suspended in toluene (25 mL). *tert*-Butyl isocyanide (0.39 mL, 3.4 mmol) was added and the solution was stirred until homogeneous. 5-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanoic acid (990 mg, 2.84 mmol) in toluene (25 mL) was added. This solution was diluted with toluene (825 mL) and refluxed for 1 hour. The toluene was removed to give a dark golden oil which was submitted to column chromatography (9:1 petroleum ether-ethyl acetate eluant) to yield 736 mg (78%) of **47** as a yellowish oil.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.47.

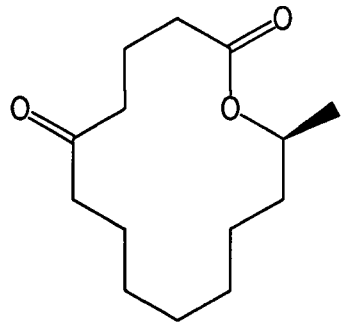
IR ($CHCl_3$) 2936, 2860, 1718, 1458, 1371, 1258, 1167, 1100 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 6 Hz, 3H), 1.25-1.75 (m, 12H), 1.80-2.20 (m, 8H), 2.53 (m, J = 12, 6.5, 3 Hz, 1H), 2.81 (m, 5H), 4.94 (m, J = 6, 10, 2 Hz, 1H).

LRMS (m/z) 330 (M^+, 62), 315 (4), 255 (21), 203 (49), 169 (22), 145 (65), 135 (23), 106 (62), 79 (33), 67 (47), 55 (53), 41 (100).

HRMS calcd for $C_{17}H_{30}O_2S_2$: 330.1688; found: 330.1686.

3.14 5-Oxo-13-tetradecanolide



28

N-bromosuccinimide (3.0 g, 17 mmol) was dissolved in a mixture of acetone (45 mL) and water (5 mL). The solution was cooled to 0 °C and 5-(1',3'-dithian-2'-yl)-13-tetradecanolide (621 mg, 1.9 mmol) in acetone (15 mL) was added slowly with stirring. After 10 minutes, the solution was shaken with a mixture of saturated Na_2SO_3 solution and 1:1 CH_2Cl_2-hexane. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents and column chromatography (12:1 petroleum ether-ethyl actetate eluant) gave 390 mg (86%) of **28** as a colourless oil.

R_t (DB-210, 140 °C, 20 psi) 9.10 min.

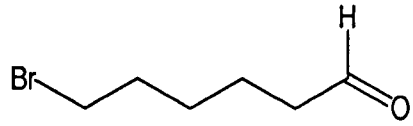
IR (CHCl3) 2936, 2862, 1727, 1710, 1458, 1374, 1262, 1132 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, J = 6 Hz, 3H), 1.20-1.40 (m, 8H), 1.45-1.70 (m, 4H), 1.90 (m, 2H), 2.20 (m, J = 14, 7, 5 Hz, 1H), 2.28-2.55 (m, 4H), 2.79 (m, J = 17, 8, 7 Hz, 1H), 5.02 (m, J = 6, 8, 4 Hz, 1H).

LRMS (m/z) 240 (M^+, 6), 225 (6), 130 (42), 125 (29), 115 (100), 112 (95), 97 (38), 87 (42), 84 (50), 69 (61), 67 (25), 55 (62), 43 (36), 41 (64).

HRMS calcd for $C_{14}H_{24}O_3$: 240.1725; found, 240.1723.

3.15 6-Bromohexanal



48

Oxalyl chloride (9.1 mL, 0.10 mol) was dissolved in CH_2Cl_2 (200 mL) and the solution was cooled to -60 °C. DMSO (16 mL, 0.23 mol) in CH_2Cl_2 (40 mL) was added and the mixture was stirred for 15 minutes. A solution of 6-bromo-1-hexanol (15.7 g, 87 mmol) in CH_2Cl_2 (80 mL) was added dropwise over 15 minutes and the reaction mixture was stirred at -60 °C for 30 minutes, after which time triethylamine (61 mL, 0.44 mol) was added. After 10 minutes stirring, the cold bath was removed and water added. The organic phase was washed successively with water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents gave a yellow oil which was purified by column chromatography (9:1 petroleum ether-ethyl acetate eluant) to give 12.7 g (82%) of **48** as a colourless oil.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.52.

IR (neat) 2931, 2857, 2719, 1724, 1460, 1390, 1253 cm^{-1}.

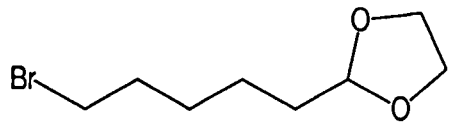
^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (m, 2H), 1.65 (m ,J = 7 Hz, 2H), 1.95 (m, J = 7.5 Hz, 2H), 2.45 (m, J = 7, 2 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H), 9.75 (t, J = 2 Hz, 1H).

LRMS (m/z) 181 (^{81}Br, M^+ + 1, 1), 179 (^{79}Br, M^+ + 1, 1), 81 (46), 57 (20), 55 (42), 45 (25), 44 (100), 41 (35).

HRMS calcd for $C_5H_{11}{}^{81}Br$ (M^+ - CO): 152.0025; found: 152.0040.

calcd for $C_6H_{10}O^{79}Br$ (M^+ - 1): 176.9916; found: 176.9914.

3.16 6-Bromohexanal ethylene acetal



51

To a solution of 6-bromohexanal (6.5 g, 36 mmol) in benzene (180 mL) was added ethanediol (10.1 mL, 181 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate. The mixture was refluxed with water separation by a Dean-Stark trap for 3.5 hours. The solvent was removed and the oil obtained was dissolved in diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of the solvent yielded 7.8 g (96%) of **51** as a colourless oil.

R_f (3:1 petroleum ether-acetone eluant) 0.54.

IR ($CHCl_3$) 2945, 2879, 1461, 1401, 1132, 1044, 950 cm^{-1}.

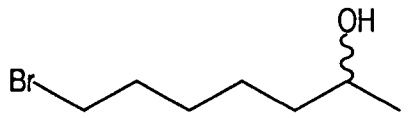
^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (m, 4H), 1.67 (m, 2H), 1.89 (m, J = 7 Hz, 2H), 3.42 (t, J = 7 Hz, 2H), 3.86 (m, 2H), 3.97 (m, 2H), 4.86 (t, J = 5 Hz, 1H).

LRMS (m/z) 223 (^{81}Br, M^+ - 1, 1), 221 (^{79}Br, M^+ - 1, 1), 73 (100), 45 (17).

HRMS calcd for $C_8H_{14}O_2{}^{81}Br$ (M^+ - 1): 223.0158; found: 223.0158.

calcd for $C_8H_{14}O_2{}^{79}Br$ (M^+ - 1): 221.0177; found: 221.0186.

3.17 7-Bromo-2-heptanol



49

Magnesium turnings (0.52 g, 21 mmol) were suspended in diethyl ether (50 mL), along with a few crystals of iodine. Iodomethane (1.3 mL, 21 mmol) was added and the mixture was gently refluxed for 30 minutes. The reaction mixture was then cooled to 0 °C and a solution of 6-bromohexanal (3.5 g, 19 mmol) in diethyl ether (40 mL) was added dropwise over 15 minutes. The resulting solution was stirred for 30 minutes, after which time the cooling bath was removed and the reaction mixture was quenched with saturated NH_4Cl solution. The organic phase was separated, washed successively with water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of the solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 3.0 g (79%) of **49** as a colourless oil.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.29.

IR ($CHCl_3$) 3613, 2934, 2861, 1458, 1380, 1069 cm^{-1}.

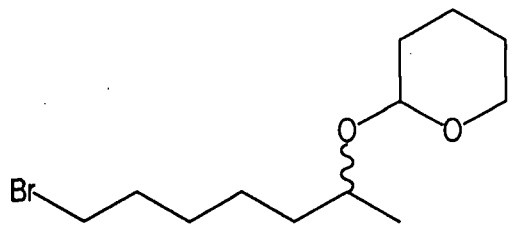
^1H NMR ($CDCl_3$, 200 MHz) δ 1.15 (d, J = 6 Hz, 3H), 1.40 (m, 6H), 1.70 (s, 1H), 1.85 (m, J = 6 Hz, 2H), 3.40 (t, J = 6 Hz, 2H), 3.75 (m, J = 6 Hz, 1H).

LRMS (m/z) 195 (^{81}Br, M^+ - 1, 0.1), 193 (^{79}Br, M^+ - 1, 0.2), 181 (2), 179 (2), 97 (17), 45 (100).

HRMS calcd for $C_7H_{14}O^{81}Br$ (M^+ - 1): 195.0209; found: 195.0180.

calcd for $C_7H_{14}O^{79}Br$ (M^+ - 1): 193.0228; found: 193.0229.

3.18 7-Bromo-2-(2-tetrahydropyranyloxy)heptane



50

To a solution of 7-bromo-2-heptanol (10.1 g, 52 mmol) in CH_2Cl_2 (300 mL) was added 3,4-dihydro-2*H*-pyran (5.7 mL, 62 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate. The resulting mixture was stirred at room temperature for 3 hours, after which time it was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (12:1 petroleum ether-ethyl acetate eluant) yielded 14.1 g (98%) of **50** (a clear, colourless oil) as a mixture of diastereomers.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.69.

IR ($CHCl_3$) 2939, 2860, 1454, 1377, 1125, 1074, 1027, 981 cm^{-1}.

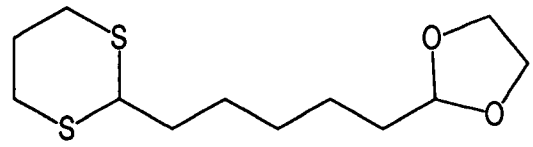
^1H NMR ($CDCl_3$, 400 Mhz) δ 1.12, 1.24 (2t, J = 6 Hz, 3H), 1.30-2.00 (m, 14H), 3.41, 3.42 (2t, J = 7 Hz, 2H), 3.50 (m, 1H), 3.74, 3.80 (2m, J = 6 Hz, 1H), 3.91 (m, 1H), 4.64, 4.70 (2t, J = 5 Hz, 1H).

LRMS (m/z) 236 (^{81}Br, M^+ - C_2H_4O, 4.4), 234 (^{79}Br, M^+ - C_2H_4O, 4.5), 179 (38), 177 (38), 103 (25), 102 (36), 101 (68), 97 (53), 57 (50), 56 (64), 55 (60), 43 (54).

HRMS calcd for $C_{12}H_{22}O_2{}^{81}Br$ (M^+ - 1): 279.0784; found: 279.0812.

calcd for $C_{12}H_{22}O_2{}^{79}Br$ (M^+ - 1): 277.0804; found: 277.0803.

3.19 7-(1',3'-Dithian-2'-yl)heptanal ethylene acetal



53

1,3-Dithiane (4.6 g, 38 mmol) was dissolved in THF (75 mL) and the solution was cooled to -20 °C. *n*-Butyllithium (1.6 M in hexane, 24 mL, 38 mmol) was added over 15 minutes and the solution was stirred for 2 hours. 6-Bromohexanal ethylene acetal (7.7 g, 34 mmol) in THF (100 mL) was then added and the reaction mixture stirred for 1 hour, after which time the cooling bath was removed. After stirring for an additional hour, the reaction was quenched with saturated NH_4Cl solution. The mixture was washed successively with water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of solvent gave a yellow oil which was subjected to column chromatography (9:1 petroleum ether-acetone eluant) to provide 7.5 g (84%) of **53** as a colourless oil.

R_f (3:1 petroleum ether-acetone eluant) 0.49.

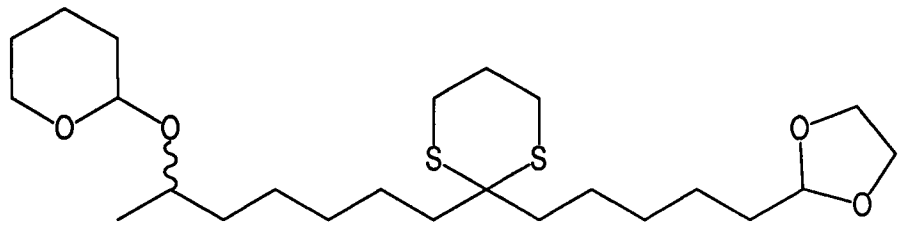
IR ($CHCl_3$) 2982, 2940, 2861, 1461, 1363, 1277, 1135, 1037 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.50 (m, 4H), 1.54 (m, J = 7.5 Hz, 2H), 1.67 (m,2H), 1.77 (m, J = 8 Hz, 2H), 1.88 (m, 2H), 2.85 (m, 4H), 3.85 (m, 2H), 3.97 (m, 2H), 4.04 (t, J = 7 Hz, 1H), 4.85 (t, J = 5 Hz, 1H).

LRMS (m/z) 262 (M^+, 20), 119 (49), 73 (100), 45 (20).

HRMS calcd for $C_{12}H_{22}O_2S_2$: 262.1061; found: 262.1058.

3.20 7-(1',3'-Dithian-2'-yl)-13-(2-tetrahydropyranyloxy)tetradecanal ethylene acetal



54

7-(1',3'-Dithian-2'-yl)heptanal ethylene acetal (7.4 g, 28 mmoles) was dissolved in THF (100 mL), the mixture cooled to -20 °C and *n*-butyllithium (1.6 M in hexane, 18 mL, 29 mmol) was added. After 2 hours stirring, a solution of 7-bromo-2-(tetrahydropyranyloxy)heptane (8.7 g, 31 mmol) was added and the reaction mixture was stirred for 1 hour, after which time the cooling bath was removed. Stirring was continued for another hour, then the reaction was quenched with saturated NH_4Cl solution. The organic phase was washed successively with water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (12:1 petroleum ether-acetone eluant) gave 10.6 g (82%) of **54** (a pale yellow oil) as a mixture of diastereomers.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.39.

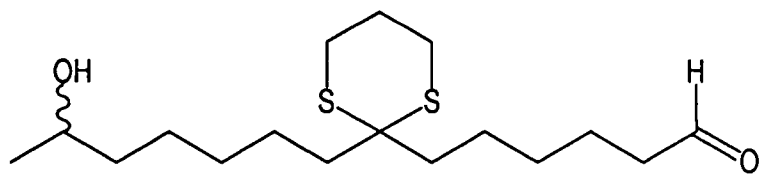
IR ($CHCl_3$) 2940, 2861, 1433, 1276, 1132, 1074, 1028 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.12, 1.23 (2d, J = 6 Hz, 3H), 1.30-1.75 (m, 22H), 1.85 (m, 4H), 1.96 (m, 2H), 2.82 (m, 4H), 3.50 (m, 1H), 3.72, 3.78 (2m, J = 6 Hz, 1H),3.84-4.00 (m, 5H), 4.64, 4.71 (2t, J = 3.5 Hz, 1H), 4.86 (2 overlapping triplets, J = 5 Hz, 1H).

LRMS (m/z) 460 (M^+, 4), 376 (7), 359 (1), 261 (20), 119 (20), 85 (37), 73 (100), 67 (20), 55 (41), 45 (26), 41 (33).

HRMS calcd for $C_{24}H_{44}O_2S_2$: 460.2681; found: 460.2684.

3.21 7-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanal



55

a. From 7-(1',3'-dithian-2'-yl)-13-(2-tetrahydropyranyloxy)tetradecanal ethylene acetal

7-(1',3'-dithian-2'-yl)-13-(2-tetrahydropyranyloxy)tetradecanal ethylene acetal (10.2 g, 22 mmol) was dissolved in a mixture of acetone (75mL), methanol (150 mL) and water (75 mL), followed by the addition of a catalytic amount of pyridinium *p*-toluenesulfonate. The solution was heated to 55 °C and stirred for 4 hours. The solvents were evaporated and the residue dissolved in diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (6:1 petroleum ether-ethyl acetate eluant) gave 2.4 g (33%) of **55** as a colourless oil. The major product was 7-(1',3'-dithian-2'-yl)-13-hydroxytetradecanal dimethyl acetal **56** (2.99 g, 36%).

Data for 7-(1',3'-dithian-2'-yl)-13-hydroxytetradecanal (**55**)

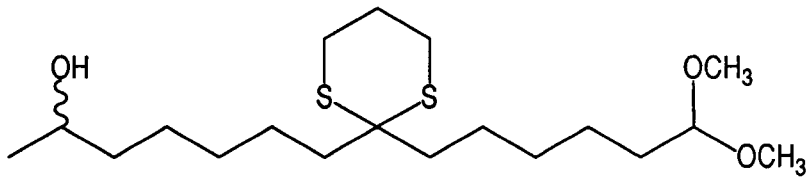
R_f (3:1 petroleum ether-ethyl acetate eluant) 0.17.

IR ($CHCl_3$) 3612, 2937, 2860, 2725, 1723, 1439, 1275, 1083 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6 Hz, 3H), 1.30-1.55 (m, 12H), 1.68 (m, J = 7 Hz, 2H), 1.88 (m, 4H), 1.94 (m, 2H), 2.44 (m, J = 7, 2 Hz, 2H), 2.81, 2.82 (2t, J = 5.5 Hz, 4H), 3.81 (m, J = 6 Hz, 1H), 9.78 (t, J = 2 Hz, 1H).

LRMS (m/z) 332 (M^+, 25), 233 (56), 219 (20), 217 (100), 145 (32), 119 (46), 109 (26), 95 (29), 81 (42), 79 (29), 67 (32), 55 (37), 43 (38), 41 (41).

HRMS calcd for $C_{17}H_{32}O_2S_2$: 332.1844; found: 332.1845.



56

Data for 7-(1',3'-dithian-2'-yl)-13-hydroxytetradecanal dimethyl acetal (**56**)

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.31.

IR ($CHCl_3$) 3613, 2938, 2860, 1444, 1275, 1127, 1057 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, J = 6 Hz, 3H), 1.30-1.50 (m, 14H), 1.61 (m, 2H), 1.86 (m, 4H), 1.95 (m, 2H), 2.81, 2.82 (2t, J = 5.5 Hz, 4H), 3.32 (s, 6H), 3.80 (m, J = 6 Hz, 1H), 4.36 (t, J = 7 Hz, 1H).

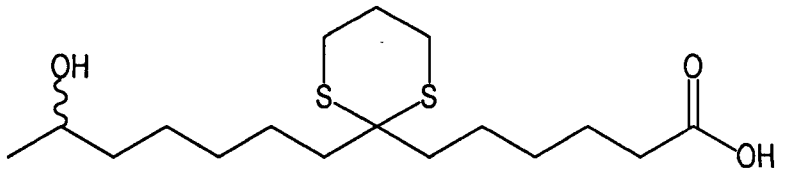
LRMS (m/z) 378 (M^+, 13), 346 (11), 249 (45), 233 (49), 231 (38), 145 (29), 137 (29), 125 (26), 106 (40), 97 (79), 81 (58), 79 (44), 75 (87), 71 (64), 67 (63), 55 (58), 45 (44), 43 (46), 41 (100).

HRMS calcd for $C_{19}H_{38}O_3S_2$: 378.2263; found: 378.2256.

b. From 7-(1',3'-dithian-2'-yl)-13-hydroxytetradecanal dimethyl acetal

7-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanal dimethyl acetal (2.9 g, 7.7 mmol) was dissolved in acetone (60 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate was added. The solution was stirred at 55 °C for 3 hours. The solution was concentrated to 20 mL and the residue dissolved in diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent afforded 2.6 g (100%) of **55**.

3.22 7-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanoic acid



57

7-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanal (2.6 g, 7.8 mmol) was dissolved in THF (75 mL) and water (16 mL). Silver nitrate (15.1 g, 89 mmol) was added to this solution, followed by 3M NaOH (59 mL, 177 mmol). After stirring for 2 hours, the black precipitate was removed by filtration through a pad of Celite® and the Celite® washed with diethyl ether and 3M NaOH. The aqueous phase was separated and acidified with 3M HCl, then extracted with chloroform. The chloroform phase was washed with saturated NaCl solution, then dried ($MgSO_4$) and filtered. Evaporation of the solvent provided 2.2 g (81%) of pure (NMR) **57** as a viscous oil.

R_f (9:1 chloroform-methanol eluant with one drop of acetic acid) 0.22.

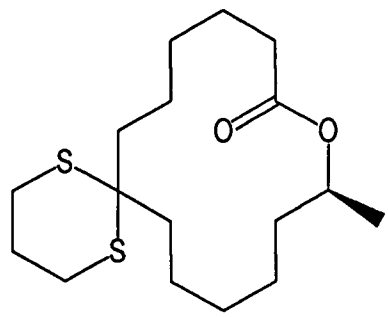
IR ($CHCl_3$) 3618, 2975, 2838, 2864, 1746, 1716, 1455, 1388, 1263, 1047 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6 Hz, 3H), 1.30-1.55 (m, 12H), 1.68 (m, J = 7 Hz, 2H), 1.85 (m, 4H), 1.96 (m, 2H), 2.36 (m, J = 7 Hz, 2H), 2.81, 2.82 (2t, J = 5.5 Hz, 4H), 3.81 (m, J = 6 Hz, 1H).

LRMS (m/z) 348 (M^+, 10), 330 (3.1), 233 (100), 145 (19), 107 (27), 106 (26), 81 (21).

HRMS calcd for $C_{17}H_{32}O_3S_2$: 348.1793; found: 348.1799.

3.23 7-(1',3'-Dithian-2'-yl)-13-tetradecanolide



58

1-Phenyl-1*H*-tetrazole-5-thiol (0.90 g, 5.1 mmol) was suspended in toluene (25 mL). *tert*-Butyl isocyanide (0.54 mL, 5.1 mmol) was added and the solution was stirred until homogeneous. 7-(1',3'-Dithian-2'-yl)-13-hydroxytetradecanoic acid (1.18 g, 2.33 mmol) in toluene (25 mL) was added and the solution was diluted with toluene (900 mL) and refluxed for 1 hour. The toluene was removed to give a dark golden oil which was submitted to column chromatography (12:1 petroleum ether-ethyl acetate eluant) to yield 614 mg (55%) of **58** as colourless crystals.

R_t (DB-210, 200 °C, 20 psi) 7.38 min.

mp 74.5-75.5 °C (hexane).

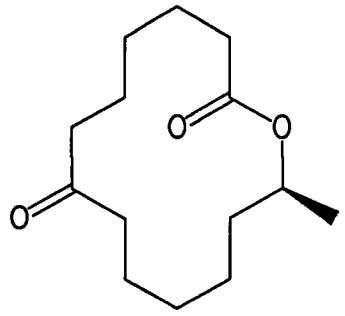
IR ($CHCl_3$) 2941, 2861, 1719, 1441, 1337, 1228, 1159 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, J = 6 Hz, 3H), 1.30-1.64 (m, 12H), 1.71 (m, 2H), 1.95 (m, 4H), 2.07 (m, 2H), 2.36 (m, 2H), 2.80 (m, 4H), 5.14 (m, 1H).

LRMS (m/z) 331 (M^+ + 1, 20), 330 (M^+, 100), 255 (49), 231 (87), 223 (33), 214 (32), 145 (66), 106 (61), 105 (37), 95 (39), 81 (66), 79 (45), 67 (60), 55 (98), 41 (99).

HRMS calcd for $C_{17}H_{30}O_2S_2$: 330.1687; found: 330.1690.

3.24 7-Oxo-13-tetradecanolide



29

N-bromosuccinimide (1.5 g, 8.3 mmol) was dissolved in a mixture of acetone (20 mL) and water (5 mL). The solution was cooled to 0 °C and 7-(1',3'-dithian-2'-yl)-13-tetradecanolide (306 mg, 0.93 mmol) in acetone (10 mL) was added slowly with stirring. After 10 minutes, the solution was shaken with a mixture of saturated Na_2SO_3 solution and 1:1 CH_2Cl_2-hexane. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents and column chromatography (12:1 petroleum ether-ethyl actetate eluant) gave 147 mg (66%) of **29** as a colourless oil.

R_t (DB-210, 160 °C, 20 psi) 5.47 min.

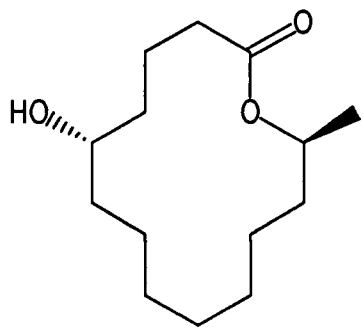
IR ($CHCl_3$) 2939, 2863, 1719, 1712, 1439, 1362, 1257, 1127 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, J = 5 Hz, 3H), 1.10-1.45 (m, 4H), 1.50-1.75 (m, 6H), 1.79 (m, 2H), 1.91 (m, 2H), 2.20-2.42 (m, 4H), 2.50-2.62 (m, 2H), 4.88 (m, J = 6, 9.5, 3 Hz, 1H).

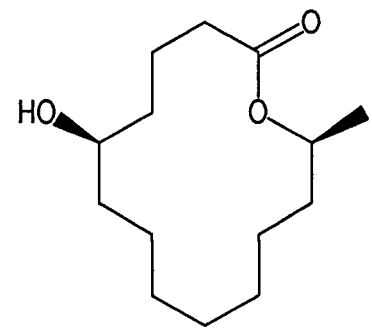
LRMS (m/z) 240 (M^+, 6), 140 (42), 125 (35), 98 (40), 97 (42), 82 (27), 69 (31), 55 (100), 43 (29), 42 (29), 41 (48).

HRMS calcd for $C_{14}H_{24}O_3$: 240.1725; found: 240.1731.

3.25 5-Hydroxy-13-tetradecanolide



61



62

a. Reduction of 5-oxo-13-tetradecanolide with excess Li-Selectride

5-Oxo-13-tetradecanolide (54 mg, 0.23 mmol) was dissolved in THF (5 mL) at -78 °C. Li-Selectride (1M in THF, 0.68 mL, 0.68 mmol) was added in one portion. The solution was stirred for 3 hours and then quenched by addition of 30% H_2O_2 (2 mL), followed by 3M NaOH (2 mL). The solution was diluted with water, then extracted with diethyl ether. The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 28 mg (52%) of **61** as colourless crystals.

R_t (DB-210, 140 °C, 20 psi) 7.11 (**62**), 8.03 (**61**) min.

mp 47-49 °C (hexane).

IR ($CHCl_3$) 3611, 2935, 2882, 1718, 1455, 1374, 1259, 1132, 1056, 974 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, J = 6 Hz, 3H), 1.25-2.00 (m, 18H), 2.30 (m, J = 15, 8.5, 4 Hz, 1H), 2.51 (m, J = 15, 9.5, 3.5 Hz, 1H), 3.77 (m, 1H), 5.02 (m, J = 6.5 Hz, 1H).

LRMS (m/z) 242 (M^+, 1), 224 (6), 117 (55), 99 (100), 95 (28), 81 (34), 71 (21), 69 (29), 67 (21), 55 (39), 41 (35).

HRMS calcd for $C_{14}H_{26}O_3$: 242.1882; found: 242.1876.

ANAL calcd: C, 69.38; H, 10.85 %

found: C, 69.48; H, 10.85 %.

b. Reduction of 5-oxo-13-tetradecanolide with Li-Selectride

5-Oxo-13-tetradecanolide (60 mg, 0.25 mmol) was dissolved in THF (5 mL) at -78 °C. Li-Selectride (1M in THF, 0.26 mL, 0.26 mmol) was added over 15 minutes. The solution was stirred for 30 minutes and then quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). The solution was diluted with water, then extracted with diethyl ether. The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 59 mg (97%) of a 73:27 mixture (GC) of **61** and **62** as colourless crystals.

c. Reduction of 5-oxo-13-tetradecanolide with K-Selectride

5-Oxo-13-tetradecanolide (45 mg, 0.19 mmol) was dissolved in THF (5 mL) at -78 °C. K-Selectride (1M in THF, 0.21 mL, 0.21 mmol) was added over 15 minutes. The solution was stirred for 30 minutes, and then quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). The solution was diluted with water, then extracted with diethyl ether. The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 13 mg of 5-oxo-13-tetradecanolide and 26 mg (58%) of a 84:16 mixture (GC) of **61** and **62** as colourless crystals.

d. Reduction of 5-oxo-13-tetradecanolide with sodium borohydride

5-Oxo-13-tetradecanolide (37 mg, 0.15 mmol) was dissolved in methanol at -78 °C and $NaBH_4$ (2mg, 0.05 mmol) added. The solution was stirred for 6 hours, with addition of $NaBH_4$ (4 mg) each hour. The mixture was then quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). The solution was diluted with water, then extracted with diethyl ether. The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 36 mg (100%) of a 43:57 mixture (GC) of **61** and **62** as colourless crystals.

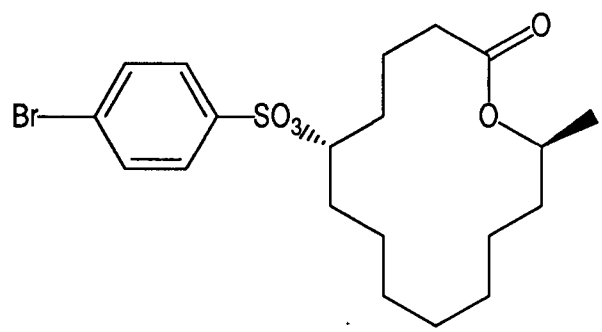
e. Reduction of 5-oxo-13-tetradecanolide with tetramethylammonium borohydride

5-Oxo-13-tetradecanolide (57 mg, 0.24 mmol) was dissolved in methanol (5 mL) and tetramethylammonium borohydride (62 mg, 0.24 mmol) added at -78 °C with stirring. After 2 hours more reducing agent (64 mg, 0.24 mmol) was added. After 3 hours, the mixture was then quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). The solution was diluted with water, then extracted with diethyl ether. The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) gave 56 mg (98%) of a 41:59 mixture (GC) of **61** and **62** as colourless crystals.

f. Reduction of 5-oxo-13-tetradecanolide with methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) and *tert*-butylmagnesium chloride

5-Oxo-13-tetradecanolide (43 mg, 0.18 mmol) was dissolved in a solution of MAD (0.26M in toluene, 4.2 mL, 1.1 mmol). The solution was cooled to -78 °C and *tert*-butylmagnesium chloride (2M in THF, 0.54 mL, 1.1 mmol) added in one portion. After 45 minutes stirring, the reaction mixture was quenched by the addition of 3M HCl and diluted with diethyl ether. It was washed successively with water and saturated NaCl solution, then dried (MgSO4) and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl acetate eluant) yielded 40 mg (93%) of a 20:80 mixture (GC) of **61** and **62** as colourless crystals.

3.26 (5S*,13S*)-5-(*p*-Bromobenzenesulfonyloxy)-13-tetradecanolide



63

To a solution of (5S*,13S*)-5-hydroxy-13-tetradecanolide (28 mg, 0.12 mmol) in pyridine (3 mL) was added *p*-bromobenzenesulfonyl chloride (0.18 g, 0.70 mmol). The solution was stirred at room temperature overnight, then poured into 1M HCl. The aqueous solution was then extracted with CH_2Cl_2. The organic phase was washed successively with saturated NaHCO3 solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. After removal of solvent, the residue was submitted to column chromatography (19:1 petroleum ether-ethyl acetate eluant) to give 49 mg (92%) of **63** as colourless crystals.

R_f (3:1 petroleum ether-ethyl acetate) 0.58.

mp 78.5-80.5 °C (hexane).

IR ($CHCl_3$) 2935, 2861, 1720, 1620, 1578, 1446, 1356, 1257, 1186, 1176, 1070, 824 cm^{-1}.

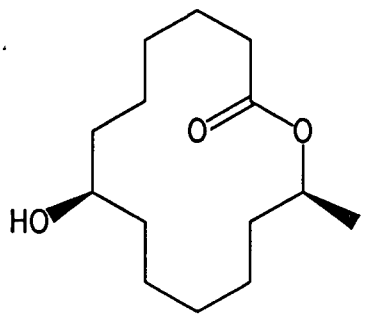
^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6 Hz, 3H), 1.20-1.48 (m, 10H), 1.56 (m, 6H), 1.78 (m, 2H), 2.24 (m, 1H), 2.42 (m, 1H), 4.72 (m, 1H), 5.02 (m, J = 6, 8.5, 3.5 Hz, 1H), 7.70 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H).

LRMS (m/z) 447 (^{81}Br, M^+ - CH_3, 0.4), 445 (^{79}Br, M^+ - CH_3, 0.5), 241 (22), 238 (38), 236 (36), 224 (75), 174 (22), 164 (30), 155 (32), 110 (38), 109 (36), 99 (97), 95 (64), 82 (81), 81 (100), 68 (70), 67 (84), 55 (79), 41 (69).

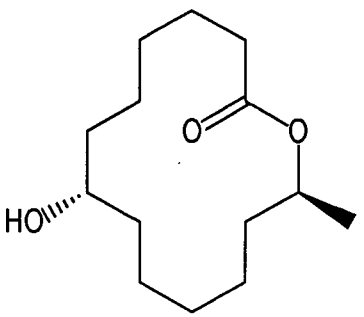
HRMS calcd for $C_{19}H_{26}O_5S^{81}Br$ (M^+ - CH_3): 447.0665; found: 447.0675
calcd for $C_{19}H_{26}O_5S^{79}Br$ (M^+ - CH_3): 445.0684; found: 445.0685.

ANAL calcd: C, 52.06; H, 6.33; S, 6.95 %
found: C, 52.22; H, 6.31; S, 7.00 %.

3.27 7-Hydroxy-13-tetradecanolide



66



67

a. Reduction of 7-oxo-13-tetradecanolide with Li-Selectride

7-Oxo-13-tetradecanolide (63 mg, 0.26 mmol) was dissolved in THF (5 mL) and the solution was cooled to -78 °C. Li-Selectride (1M in THF, 0.29 mL, 0.29 mmol) was added in one portion and the mixture was stirred for 30 minutes. The cooling bath was removed and the reaction was quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). Water (15 mL) was added and the resulting mixture was extracted with diethyl ether. The ether phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent gave 64 mg (100%) of a 9:1 mixture (NMR) of **67** and **66** as colourless crystals.

Data for **67**

R_t (DB-210, 160 °C, 20 psi) 3.97 min.

mp 77-78 °C (hexane).

IR ($CHCl_3$) 3611, 2936, 2863, 1715, 1447, 1331, 1254, 1149 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, J = 6 Hz, 3H), 1.25-1.75 (m, 18H), 2.20-2.40 (m, 2H), 3.78 (m, J = 8.5, 4, 4.5 Hz, 1H), 5.02 (m, J = 8.5, 6, 2.5 Hz, 1H).

LRMS (m/z) 242 (M^+, 0.1), 224 (10), 145 (20), 127 (100), 116 (49), 109 (72), 98 (40), 81 (61), 67 (35), 55 (35).

HRMS calcd for $C_{14}H_{26}O_3$: 242.1882; found: 242.1880.

b. Reduction of 7-oxo-13-tetradecanolide with K-Selectride

7-Oxo-13-tetradecanolide (48 mg, 0.20 mmol) was dissolved in THF (5 mL) and the solution was cooled to -78 °C. K-Selectride (1M in THF, 0.22 mL, 0.22 mmol) was added in one portion and the mixture was stirred for 45 minutes. Then, more K-Selectride (0.22 mL, 0.22 mmol) was added and the mixture was stirred for an additional 45 minutes. The cooling bath was removed and the reaction was quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). Water (15 mL) was added and the resulting mixture was extracted with diethyl ether. The ether phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography gave 40 mg (83%) of an 80:20 mixture (NMR) of **67** and **66** as colourless crystals.

c. Reduction of 7-oxo-13-tetradecanolide with sodium borohydride

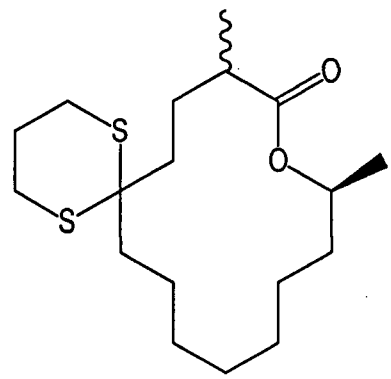
7-Oxo-13-tetradecanolide (30 mg, 0.13 mmol) was dissolved in methanol (5 mL) at 0 °C. $NaBH_4$ (5 mg, 0.13 mmol) was added in one portion and the mixture stirred for 2 hours. More $NaBH_4$ (5 mg, 0.13 mmol) was added and stirring was continued for 1 hour. The cooling bath was removed and the mixture was then quenched by addition of 30% H_2O_2 (1 mL), followed by 3M NaOH (1 mL). The solution was diluted with water and extracted with diethyl ether. The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered. Removal of solvent and column chromatography (6:1 petroleum ether-ethyl acetate eluant) gave 27 mg (91%) of a 50:50 mixture (NMR) of **67** and **66** as colourless crystals.

d. Reduction of 7-oxo-13-tetradecanolide with methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) and *tert*-butylmagnesium chloride

7-Oxo-13-tetradecanolide (39 mg, 0.16 mmol) was dissolved in a solution of MAD in toluene (0.13M, 3.7 mL, 0.49 mmol). The solution was cooled to -78 °C and *tert*-butylmagnesium chloride (2M in THF, 0.24 mL, 0.49 mmol) was added in one portion. After 1.5 hours stirring, the reaction mixture was quenched by the addition of 3M HCl and diluted with diethyl ether. It was washed successively with water and saturated NaCl solution, then dried (MgSO4) and filtered. Removal of solvent and column chromatography (3:1 petroleum ether-ethyl

acetate eluant) yielded 29 mg (74%) of a 50:50 mixture (NMR) of **67** and **66** as colourless crystals.

3.28 5-(1',3'-Dithian-2'-yl)-2-methyl-13-tetradecanolide



68

Diisopropylamine (0.46 mL, 3.3 mmol) was dissolved in THF (5 mL) at -78 °C. *n*-Butyllithium (1.68M in THF, 2.0 mL, 3.3 mmol) was added and the solution was stirred for 10 minutes. A solution of 5-(1',3'-dithian-2'-yl)-13-tetradecanolide (725 mg, 2.2 mmol) in THF (10 mL) was added and the mixture was stirred at -78 °C for 1 hour. Methyl iodide (0.68 mL, 11 mmol) was added and stirring was continued for 1 hour, after which time the cooling bath was removed. The reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents gave 721 mg (95%) of **68** (an oily yellowish solid) as an 85:15 mixture (GC) of diastereomers.

R_t (DB-210, 200 °C, 20 psi) 4.89 (minor product, **72**), 5.60 (major product, **71**) min.

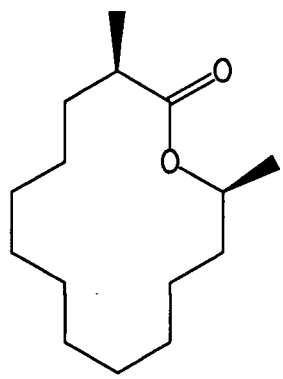
IR ($CHCl_3$) 2937, 2863, 1714, 1455, 1275, 1251, 1190, 1077 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (m, 6H), 1.36-2.20 (m, 20H), 2.37, 2.65 (2m, 1H each), 2.82 (m, 4H), 4.93 (m, 1H).

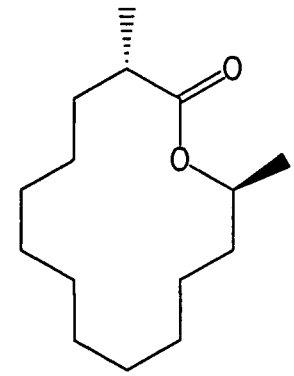
LRMS (m/z) 344 (M^+, 53), 269 (24), 217 (26), 145 (100), 106 (51), 95 (29), 81 (41), 79 (32), 55 (60), 41 (94).

HRMS calcd for $C_{18}H_{32}O_2S_2$: 344.1844; found: 344.1850.

3.29 2-Methyl-13-tetradecanolide



69

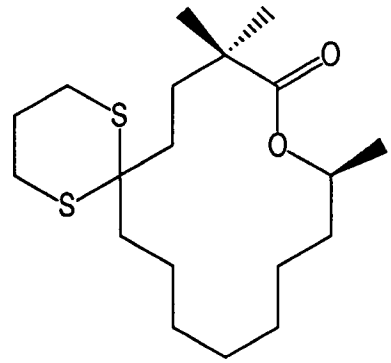


70

5-(1',3'-Dithian-2'-yl)-2-methyl-13-tetradecanolide (from experiment 3.28, 78 mg, 0.23 mmol) was dissolved in THF (10 mL) and Raney nickel (W-2 in aqueous solution of pH=10, 1.5 g) was added. The suspension was refluxed for 2 hours, then cooled to room temperature and diluted with diethyl ether. It was washed successively with water and saturated NaCl solution, then dried and filtered. Evaporation of solvents gave 38 mg (70%) of an 85:15 mixture (GC) of **69** and **70** by comparison with authentic materials.[65]

$\mathbf{R_t}$ (DB-210, 130 °C/2 min/2 °C min^{-1}/140 °C, 20 psi) 5.56 (**70**), 6.25 (**69**) min.

3.30 2,2-Dimethyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide



74

a. From alkylation of 2-methyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide with methyl iodide

Diisopropylamine (0.41 mL, 2.9 mmol) was dissolved in THF (5 mL) at -78 °C. *n*-Butyllithium (1.68M in THF, 1.7 mL, 2.9 mmol) was added and the solution was stirred for 10 minutes. A solution of 2-methyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide (from experiment 3.28, 666 mg, 1.9 mmol) in THF (5 mL) was added and the mixture was stirred at -78 °C for 1.5 hour. Methyl iodide (0.60 mL, 9.7 mmol) was added and stirring was continued for 1 hour, after which time the cooling bath was removed. The reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents and column chromatography (19:1 petroleum ether-ethyl acetate as eluant) gave 601 mg (87%) of an 85:15 mixture (GC) of **74** and **72**. The mixture was used without further purification or characterization.

b. From reaction of 2,2-dimethyl-5-oxo-13-tetradecanolide with 1,3-propanedithiol

1,3-Propanedithiol (10 μL, 0.10 mmol) and 2,2-dimethyl-5-oxo-13-tetradecanolide (21 mg, 0.08 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. Boron trifluoride etherate (20 μL, 0.16 mmol) was added and the solution was stirred for 4 hours. After quenching with water, the organic phase was washed successively with 3N NaOH solution, water

and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (19:1 petroleum ether-ethyl acetate as eluant) gave 25 mg (89%) of **74** as colourless crystals.

Rf (3:1 petroleum ether-ethyl acetate eluant) 0.60.

mp 87-89 °C (hexane).

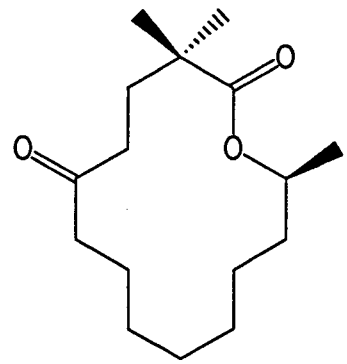
IR ($CHCl_3$) 2937, 2863, 1714, 1451, 1277, 1202, 1153, 1121, 1046 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 3H), 1.20 (d, J = 6 Hz, 3H), 1.22 (s, 3H), 1.40-1.70 (m, 16H), 1.97 (m, 3H), 2.11 (m, J = 14, 5 Hz, 1H), 2.80 (m, 4H), 4.89 (m, J = 6, 10, 2 Hz, 1H).

LRMS (m/z) 358 (M^+, 33), 145 (89), 107 (47), 106 (31), 95 (26), 81 (31), 79 (25), 69 (36), 67 (37), 55 (64), 43 (47), 41 (100).

HRMS calcd for $C_{19}H_{34}O_2S_2$: 358.2000; found: 358.1998.

3.31 2,2-Dimethyl-5-oxo-13-tetradecanolide



75

N-bromosuccinimide (2.7 g, 15 mmol) was dissolved in a mixture of acetone (36 mL) and water (4 mL). The solution was cooled to 0 °C and 2,2-dimethyl-5-(1',3'-dithian-2'-yl)-13-tetradecanolide (from experiment 3.30, 593 mg, 1.7 mmol) in acetone (15 mL) was added slowly with stirring. After 10 minutes, the solution was shaken with a mixture of saturated Na_2SO_3 solution and 1:1 CH_2Cl_2-hexane. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents and careful column chromatography (24:1 petroleum ether-ethyl acetate as eluant) gave 24 mg (5%) of **75** as colourless crystals and 311 mg of a mixture of **75** and **76**.

R_t (DB-210, 140 °C, 20 psi) 13.80 min.

mp 57-59 °C (hexane).

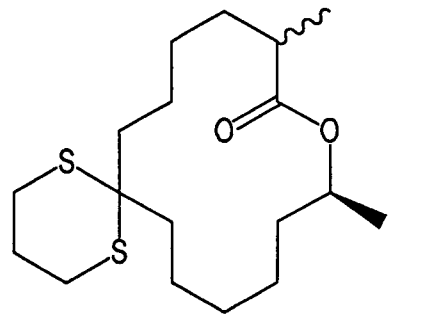
IR ($CHCl_3$) 2936, 2864, 1709, 1447, 1264, 1187, 1124 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 3H), 1.22 (d, J = 6 Hz, 3H), 1.27 (s, 3H), 1.30-1.45 (m, 7H), 1.50-1.75 (m, 6H), 1.93 (m, J = 13.5, 3.5 Hz, 1H), 2.22 (m, J = 14, 10.5, 5 Hz, 1H), 2.34 (m, J = 18, 12.5, 5.5 Hz, 1H), 2.50 (m, 2H), 4.96 (m, 1H).

LRMS (m/z) 268 (M^+, 6), 181 (19), 143 (30), 140 (31), 125 (34), 115(82), 97 (75), 88 (35), 70 (52), 69 (71), 56 (31), 55 (75), 43 (50), 41 (100).

HRMS calcd for $C_{16}H_{28}O_3$: 268.2039; found: 268.2034.

3.32 7-(1',3'-Dithian-2'-yl)-2-methyl-13-tetradecanolide



77

Diisopropylamine (71 μL, 0.51 mmol) was dissolved in THF (5 mL) at -78 °C. *n*-Butyllithium (1.56M in THF, 0.33 mL, 0.51 mmol) was added and the solution was stirred for 10 minutes. A solution of 7-(1',3'-dithian-2'-yl)-13-tetradecanolide (111 mg, 0.34 mmol) in THF (5 mL) was added and the mixture was stirred at -78 °C for 1 hour. Methyl iodide (0.11 mL, 1.7 mmol) was added and stirring was continued for 1 hour, after which time the cooling bath was removed. The reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents gave 116 mg (100%) of **77** (an oily yellowish solid) as a 75:25 mixture (GC) of diastereomers.

R_t (DB-210, 200 °C, 20 psi) 7.02 (minor product, **77b**), 8.18 (major product, **77a**) min.

IR ($CHCl_3$) 2939, 2860, 1721, 1711, 1446, 1243, 1194 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (m, 3H), 1.22 (m, 3H), 1.20-1.75 (m, 14H), 1.80-2.10 (m, 6H), 2.40-2.60 (m, 1H), 2.78 (m, 4H), 4.95 (m, 1H).

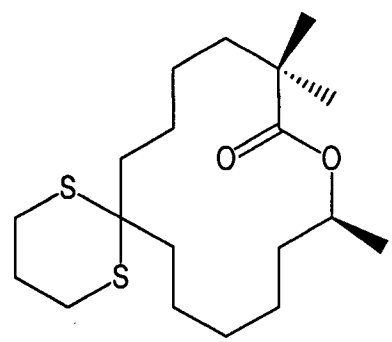
LRMS (m/z) 344 (M^+, 54), 269 (24), 231 (31), 145 (40), 107 (34), 106 (32), 95 (73), 81 (38), 79 (25), 67 (44), 55 (65), 43 (30), 41 (100).

HRMS calcd for $C_{18}H_{32}O_2S_2$: 344.1844; found: 344.1889.

3.33 2-Methyl-13-tetradecanolide (69,70) from 2-methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (77)

2-Methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (from experiment 3.32, 53 mg, 0.15 mmol) was dissolved in acetone (10 mL) and Raney nickel (W-2 in aqueous solution of pH=10, 1.5 g) was added. The suspension was refluxed for 2 hours, then cooled to room temperature and diluted with diethyl ether. It was washed successively with water and saturated NaCl solution, then dried and filtered. Evaporation of solvents gave 33 mg (89%) of a 75:25 mixture (GC) of **69** and **70** by comparison with authentic materials.[65]

3.34 2,2-Dimethyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide



79

Diisopropylamine (93 μL, 0.66 mmol) was dissolved in THF (5 mL) at 0 °C. *n*-Butyllithium (1.57M in THF, 0.42 mL, 0.66 mmol) was added and the solution was stirred for 10 minutes. A solution of 2-methyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (from experiment 3.32, 77 mg, 0.22 mmol) in THF (5 mL) was added and the mixture was stirred at 0 °C for 1 hour. Methyl iodide (0.14 mL, 2.2 mmol) was added and stirring was continued for 1 hour, after which time the cooling bath was removed. The reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents and column chromatography (24:1 petroleum ether-ethyl acetate as eluant) gave 26 mg

(33%) of **79** as a colourless oil.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.67.

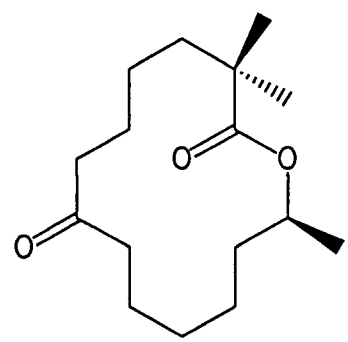
IR ($CHCl_3$) 2941, 2862, 1712, 1441, 1244, 1182, 1126 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 3H), 1.17 (s, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.20-1.80 (m, 14H), 1.85-2.18 (m, 6H), 2.76 (m, 4H), 5.07 (m, 1H).

LRMS (m/z) 358 (M^+, 72), 283 (27), 231 (48), 214 (30), 145 (37), 132 (30), 107 (36), 106 (35), 81 (43), 69 (31), 67 (46), 55 (80), 43 (41), 41 (100).

HRMS calcd for $C_{19}H_{34}O_2S_2$: 358.2000; found: 358.1995.

3.35 2,2-Dimethyl-7-oxo-13-tetradecanolide



80

N-bromosuccinimide (77 mg, 0.44 mmol) was dissolved in a mixture of acetone (9 mL) and water (1 mL). The solution was cooled to 0 °C and 2,2-dimethyl-7-(1',3'-dithian-2'-yl)-13-tetradecanolide (26 mg, 0.07 mmol) in acetone (5 mL) was added slowly with stirring. After 10 minutes, the solution was shaken with a mixture of saturated Na_2SO_3 solution and 1:1 CH_2Cl_2-hexane. The organic phase was washed successively with saturated $NaHCO_3$ solution, water and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvents and careful column chromatography (24:1 petroleum ether-ethyl acetate as eluant) gave 7 mg (37%) of

80 as colourless crystals.

R_f (3:1 petroleum ether-ethyl acetate eluant) 0.56.

mp 47-49 °C (hexane).

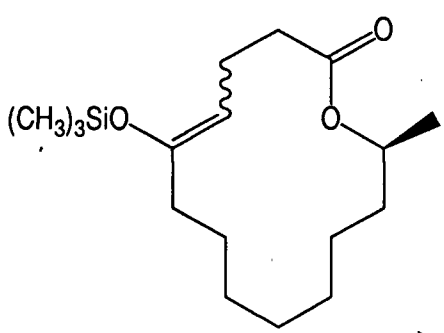
IR ($CHCl_3$) 2940, 2867, 1715, 1459, 1376, 1255, 1121, 908 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 3H), 1.16 (d, J = 6 Hz, 3H), 1.17 (s, 3H), 1.15-1.28 (m, 5H), 1.3-1.6 (m, 8H), 1.71 (m, J = 13, 4 Hz, 1H), 1.86 (m, 1H), 1.97 (m, 1H), 2.28 (m, 1H), 2.59 (m, 1H), 4.80 (m, J = 6, 10, 3 Hz, 1H).

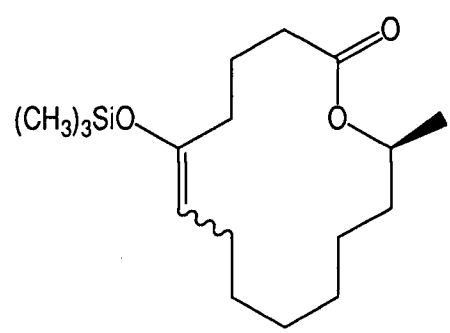
LRMS (m/z) 268 (M^+, 5), 181 (20), 97 (24), 83 (30), 82 (65), 69 (26), 67 (27), 55 (100), 42 (20), 41 (70), 39 (22).

HRMS calcd for $C_{16}H_{28}O_3$: 268.2039; found: 268.2039.

3.36 5-(Trimethylsilyloxy)-4-tetradecen-13-olide and 5-(trimethylsilyloxy)-5-tetradecen-13-olide



81



82

5-Oxo-13-tetradecanolide (40 mg, 0.17 mmol) and triethylamine (46 μL, 0.33 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (48 μL, 0.25 mmol) was added and the reaction mixture was stirred at 0°C for 1 hour, after which time the cooling bath was removed. After an additional hour, the reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The ether phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (19:1 petroleum

ether-ethyl acetate as eluant) gave 45 mg (87%) of a 14:72:14 mixture (GC) of isomeric enol ethers as a clear oil.

R_t (DB-210, 160 °C, 10 psi) 3.91, 4.51, 4.69 min.

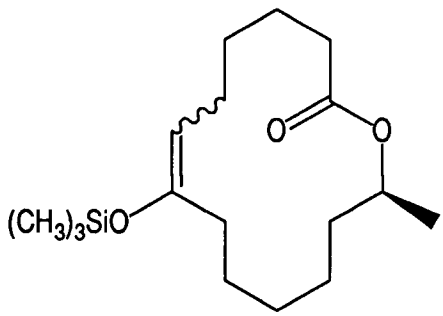
IR ($CHCl_3$) 2937, 2858, 1720, 1712, 1665, 1602, 1442, 1375, 1254, 1144, 844 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.16-0.20 (3s, 9H total), 1.21 (m, 3H), 1.25-2.10 (m, 16H), 2.20- 2.50 (m, 2H), 4.48-4.65 (3m, 1H total), 4.95-5.10 (2m, 1H total).

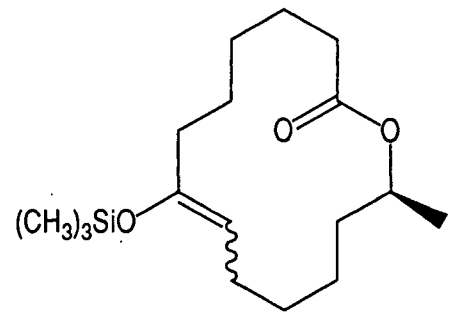
LRMS (m/z) 312 (M^+, 7), 297 (2), 222 (1), 143 (39), 130 (35), 113 (22), 75 (51), 73 (100), 55 (24), 45 (26), 41 (26).

HRMS calcd for $C_{17}H_{32}SiO_3$: 312.2121; found: 312.2129.

3.37 7-(Trimethylsilyloxy)-6-tetradecen-13-olide and 7-(trimethylsilyloxy)-7-tetradecen-13-olide



85



86

7-Oxo-13-tetradecanolide (44 mg, 0.18 mmol) and triethylamine (51 μL, 0.37 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (53 μL, 0.28 mmol) was added and the reaction mixture stirred at 0°C for 1 hour, after which time the cooling bath was removed. After an additional hour, the reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The ether phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (19:1 petroleum ether-ethyl acetate as eluant) gave 50 mg (88%) of a 74:12:6:8 mixture (GC) of isomeric enol ethers as a clear oil.

R_t (DB-210, 160 °C, 10 psi) 4.49, 4.85, 5.10, 5.55 min.

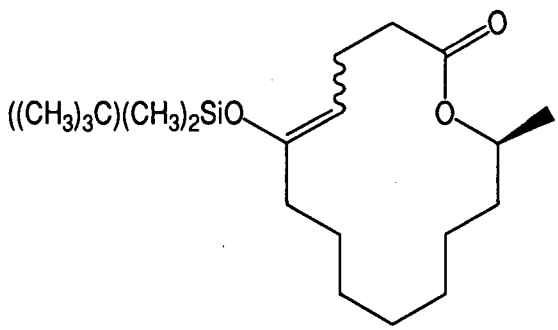
IR ($CHCl_3$) 2939, 2858, 1720, 1711, 1671, 1602, 1442, 1359, 1254, 844 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.15-0.20 (4s, 9H total), 1.20-1.70 (m, 16H), 1.85-2.10 (m, 3H), 2.30 (m, 2H), 4.30-4.70 (4m, 1H total), 5.00 (m, 1H).

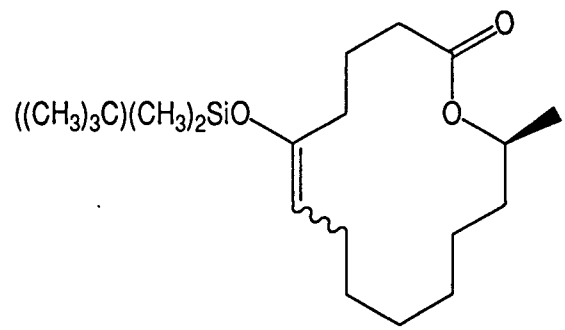
LRMS (m/z) 312 (M^+, 12), 143 (26), 130 (62), 75 (50), 73 (100), 55 (20), 43 (20).

HRMS calcd for $C_{17}H_{32}SiO_3$: 312.2121; found: 312.2114.

3.38 5-(*tert*-Butyldimethylsilyloxy)-4-tetradecen-13-olide and 5-(*tert*-butyldimethylsilyloxy)-5-tetradecen-13-olide



83



84

5-Oxo-13-tetradecanolide (52 mg, 0.22 mmol) and triethylamine (60 μL, 0.43 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (75 μL, 0.33 mmol) was added and the reaction mixture was stirred at 0°C for 1 hour, after which time the cooling bath was removed. After an additional hour, the reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The ether phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (19:1 petroleum ether-ethyl acetate as eluant) gave 70 mg (90%) of a 19:70:11 mixture (GC) of isomeric enol ethers as a clear oil.

R_t (DB-210, 160 °C, 10 psi) 8.63, 9.79, 10.11 min.

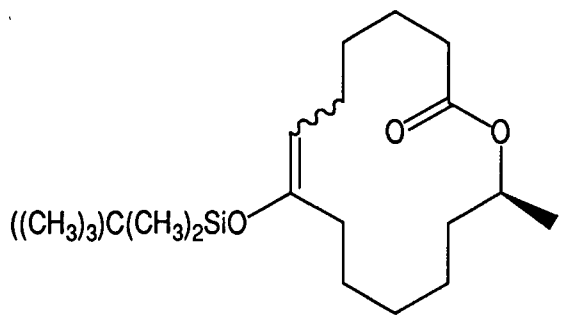
IR ($CHCl_3$) 2936, 2858, 1720, 1712, 1669, 1608, 1364, 1256, 1148, 1039, 839 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.10-0.16 (3s, 6H total), 0.90-0.98 (3s, 9H total), 1.20 (m, 3H), 1.25-2.10 (m, 14H), 2.37 (m, 4H), 4.45-4.65 (4m, 1H total), 4.95-5.13 (2m, 1H total).

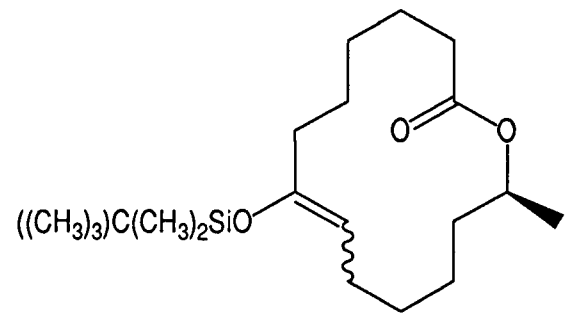
LRMS (m/z) 354 (M^+, 0.3), 297 (46), 205 (22), 199 (28), 163 (28), 145 (30), 75 (100), 73 (67), 41 (21).

HRMS calcd for $C_{20}H_{38}SiO_3$: 354.2590; found: 354.2590.

3.39 7-(*tert*-Butyldimethylsilyloxy)-6-tetradecen-13-olide and 7-(*tert*-butyldimethylsilyloxy)-7-tetradecen-13-olide



87



88

7-Oxo-13-tetradecanolide (54 mg, 0.23 mmol) and triethylamine (78 μL, 0.56 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (130 μL, 0.56 mmol) was added and the reaction mixture was stirred at 0°C for 1 hour, after which time the cooling bath was removed. After an additional hour, the reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The ether phase was washed successively with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried ($MgSO_4$) and filtered. Removal of solvent and column chromatography (19:1 petroleum ether-ethyl acetate as eluant) gave 59 mg (74%) of a 69:6:16:9 mixture (GC) of isomeric enol ethers as a clear oil.

R_t (DB-210, 160 °C, 20 psi) 5.05, 5.45, 5.58, 6.10 min.

IR ($CHCl_3$) 2939, 2858, 1720, 1712, 1670, 1602, 1446, 1360, 1255, 835 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 0.10-0.15 (4s, 6H total), 0.90-0.97 (3s, 9H total), 1.18-2.20 (m, 15H), 2.03 (m, 4H), 2.30 (m, 2H), 4.28-4.70 (4m, 1H total), 4.83-5.05 (2m, 1H total).

LRMS (m/z) 354 (M^+, 0.3), 239 (2), 199 (78), 157 (32), 129 (29), 75 (100), 55 (22), 41 (18).

HRMS calcd for $C_{20}H_{38}SiO_3$: 354.2590; found: 354.2584.

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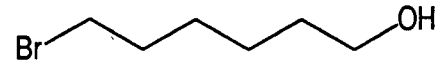
SPECTRAL APPENDIX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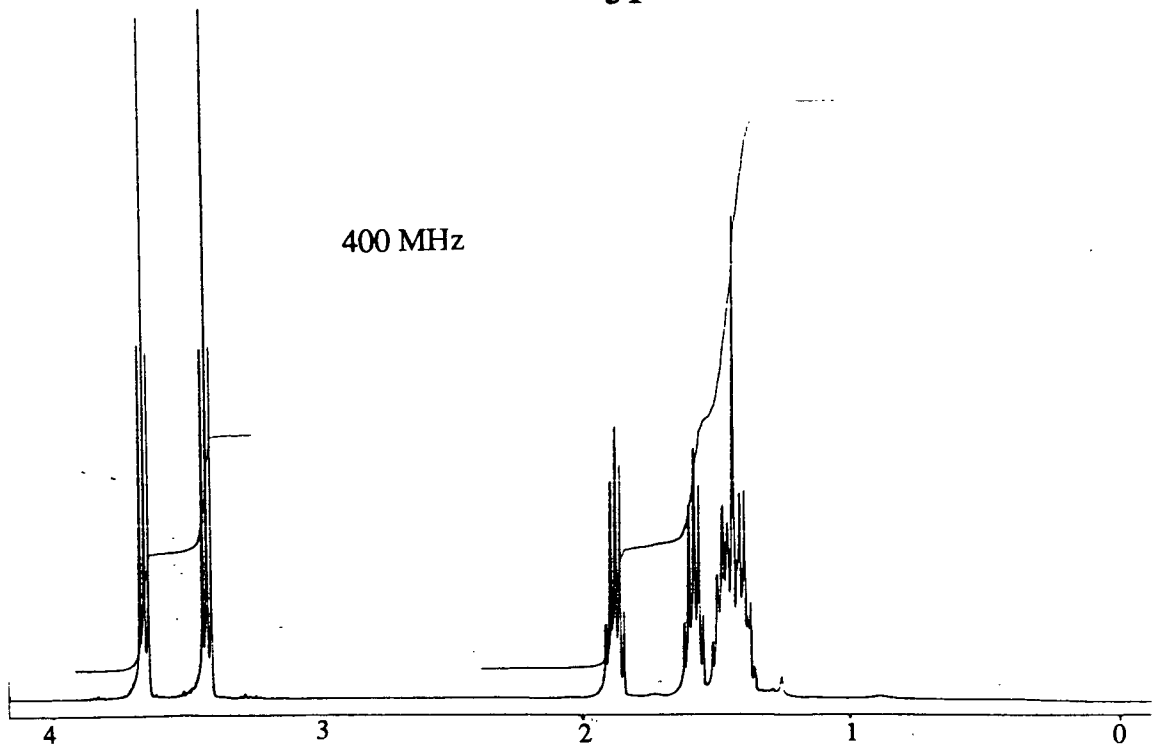
31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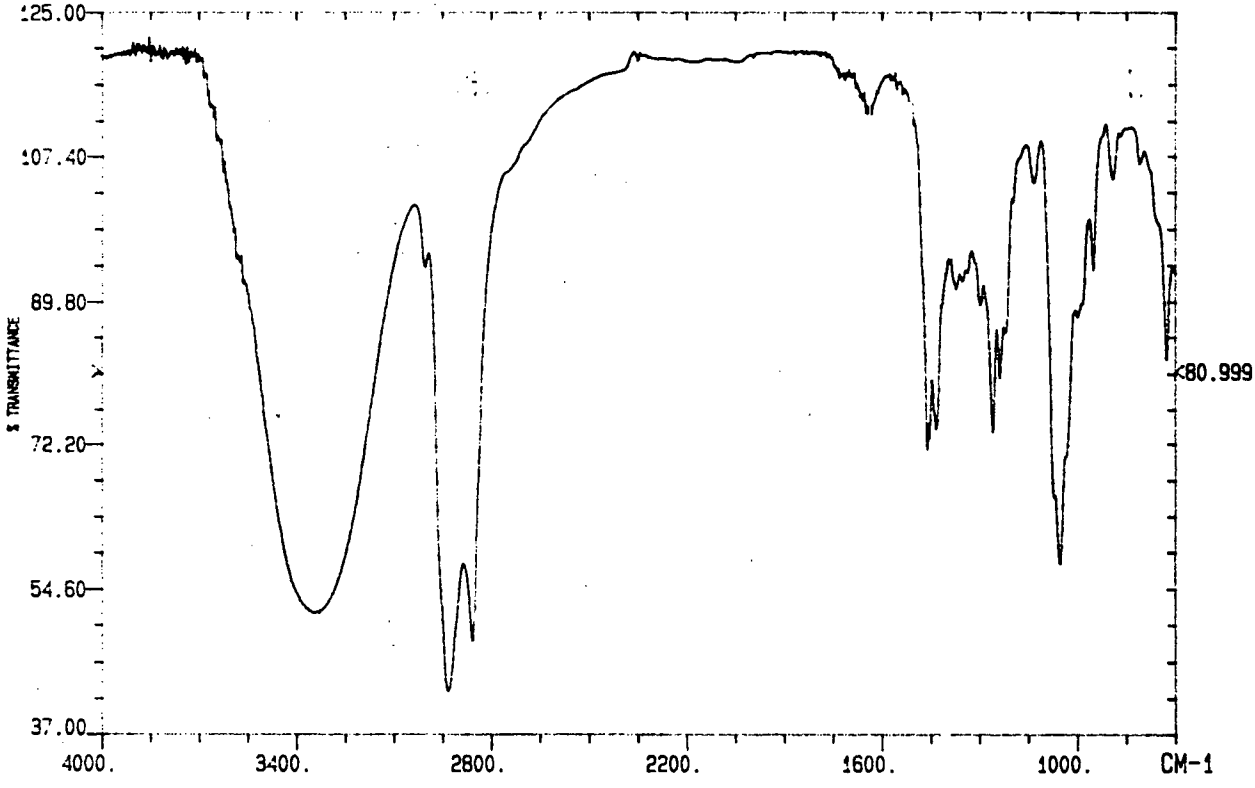
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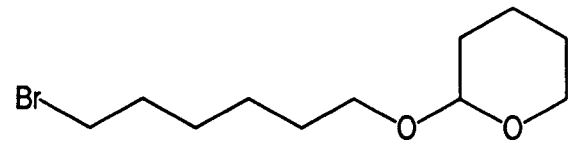
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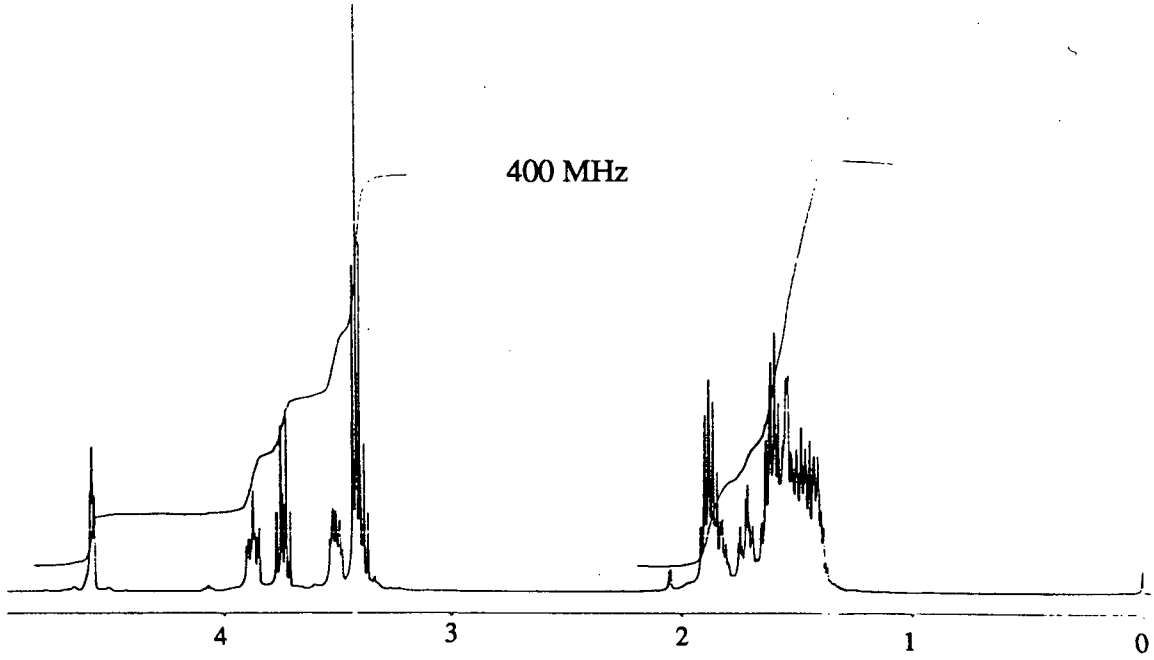
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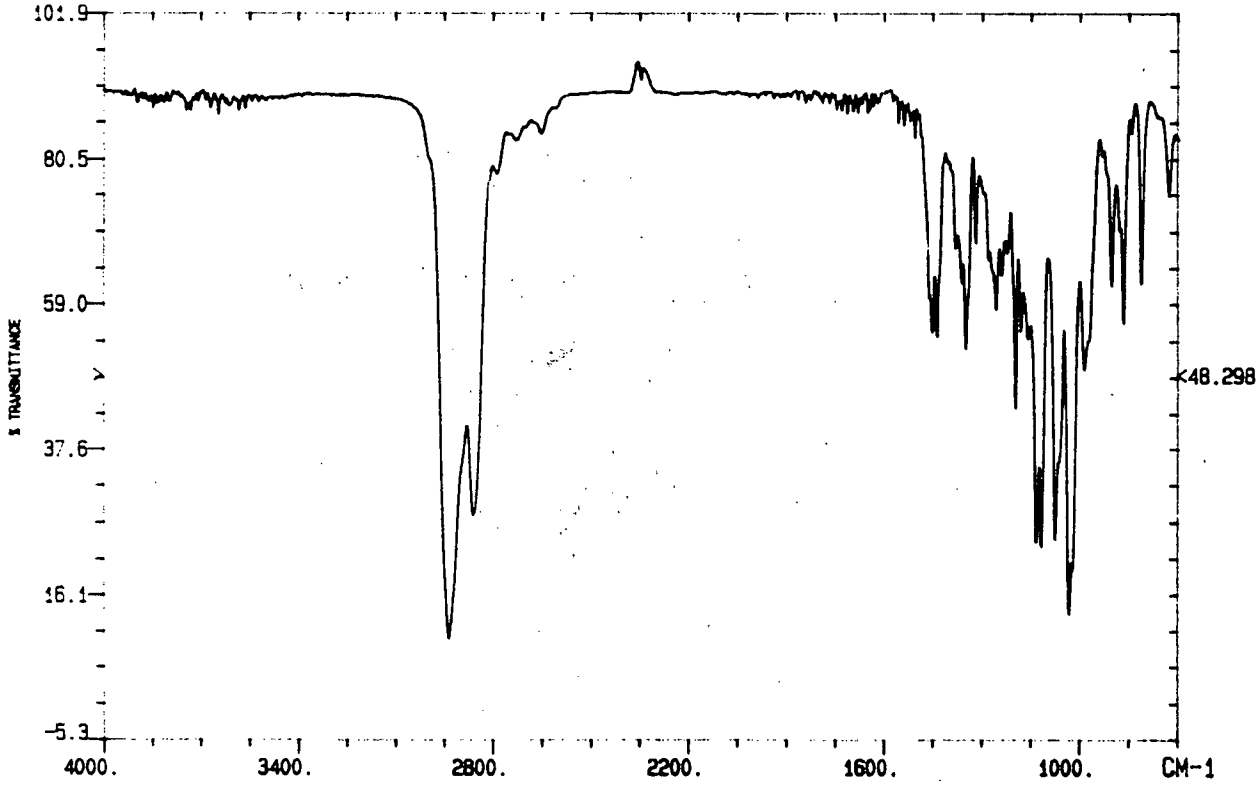
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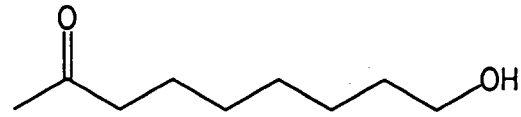
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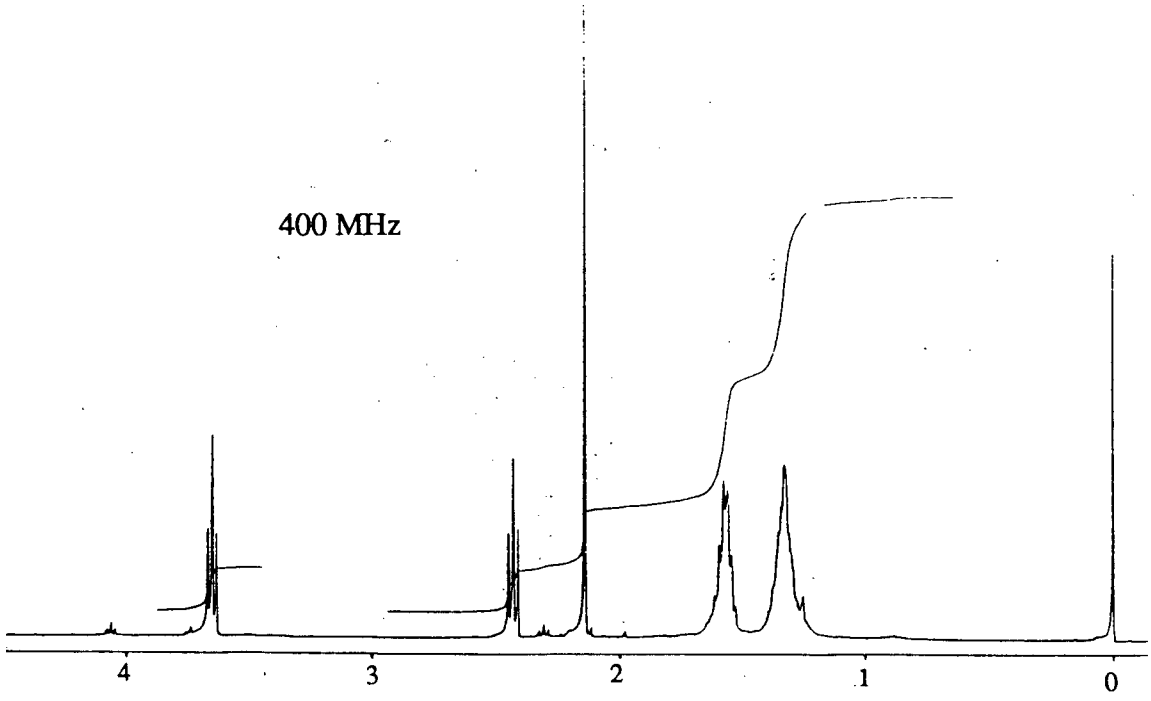
34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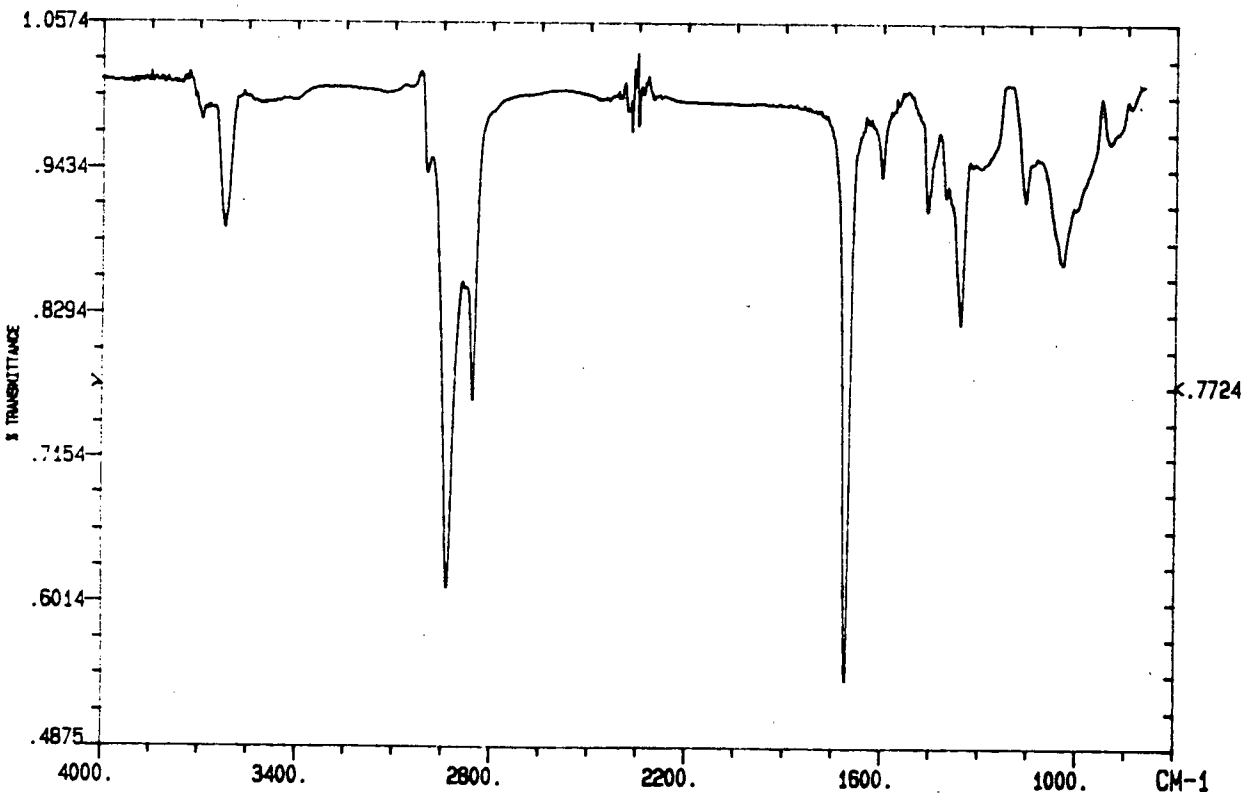
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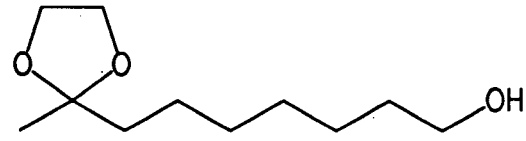
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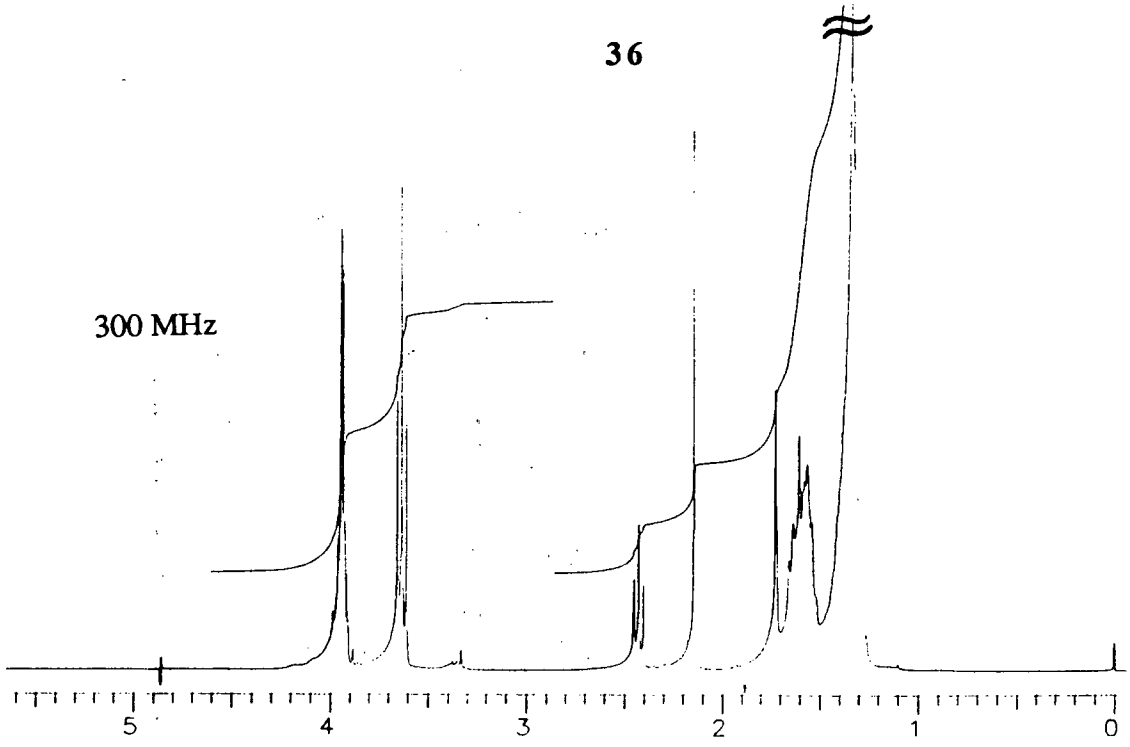
36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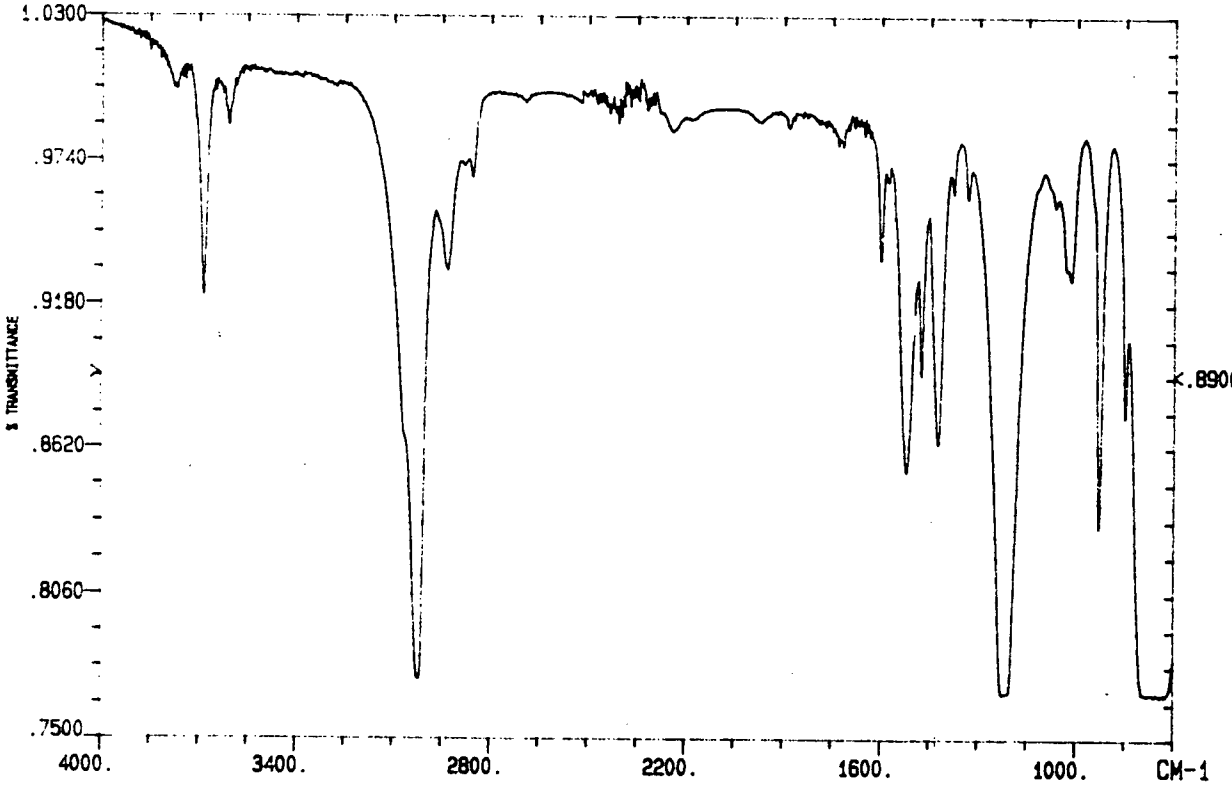
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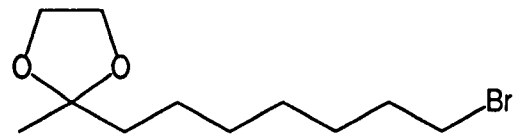
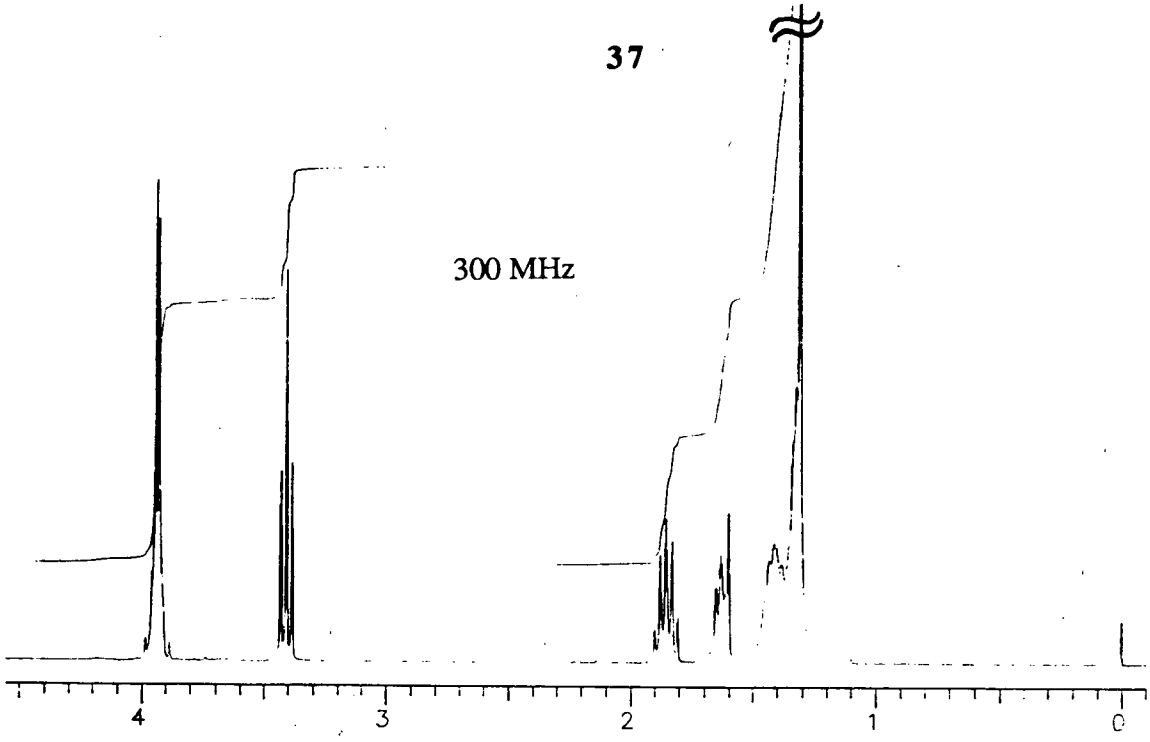
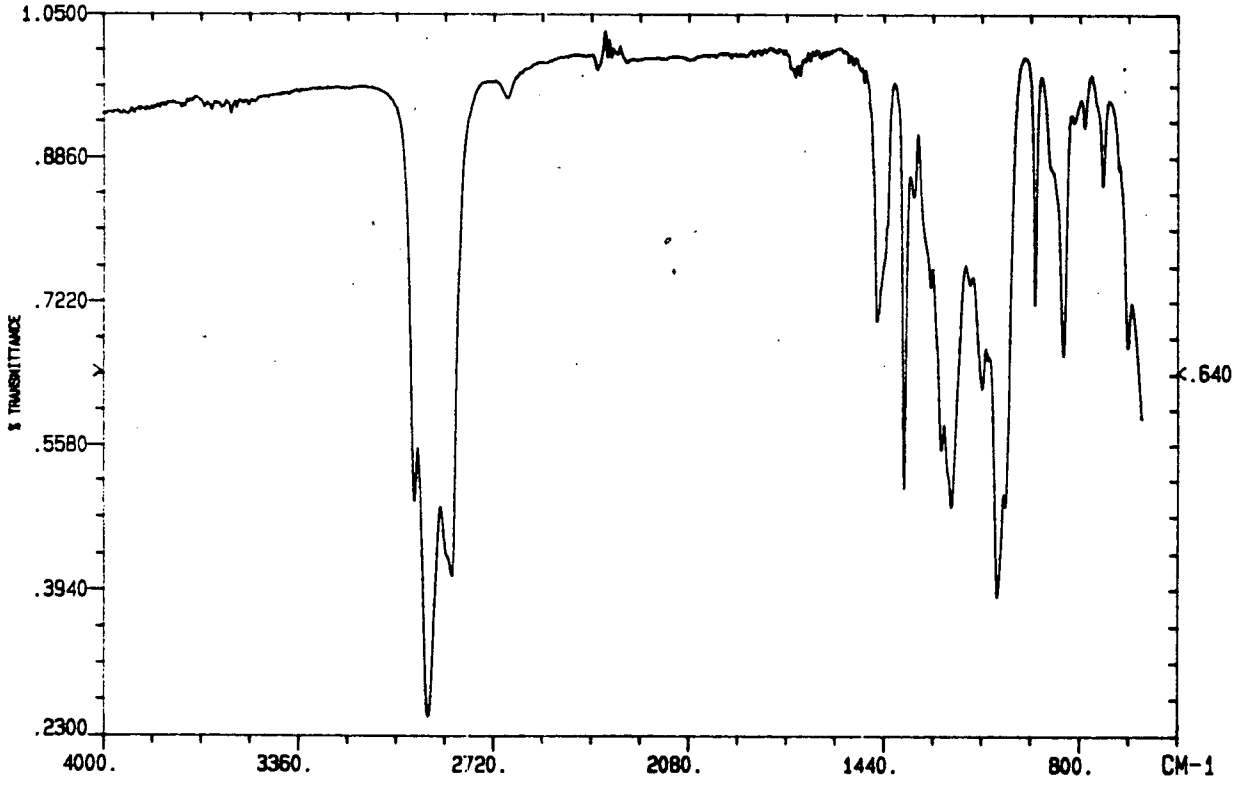
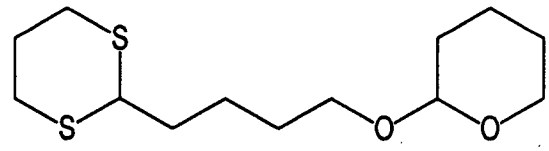

Br

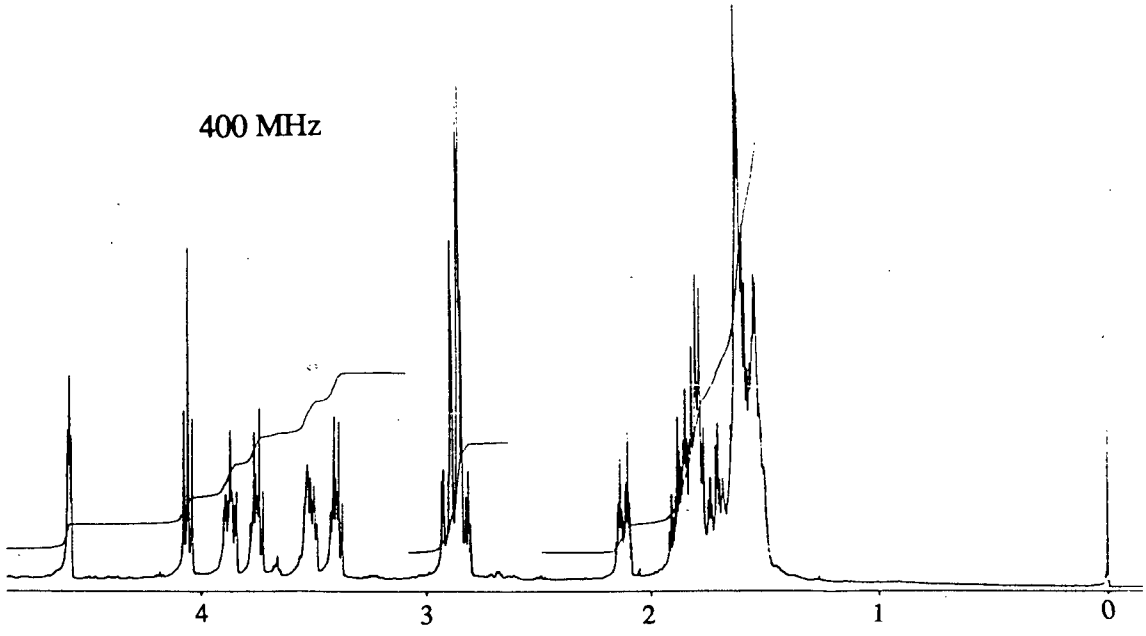
37

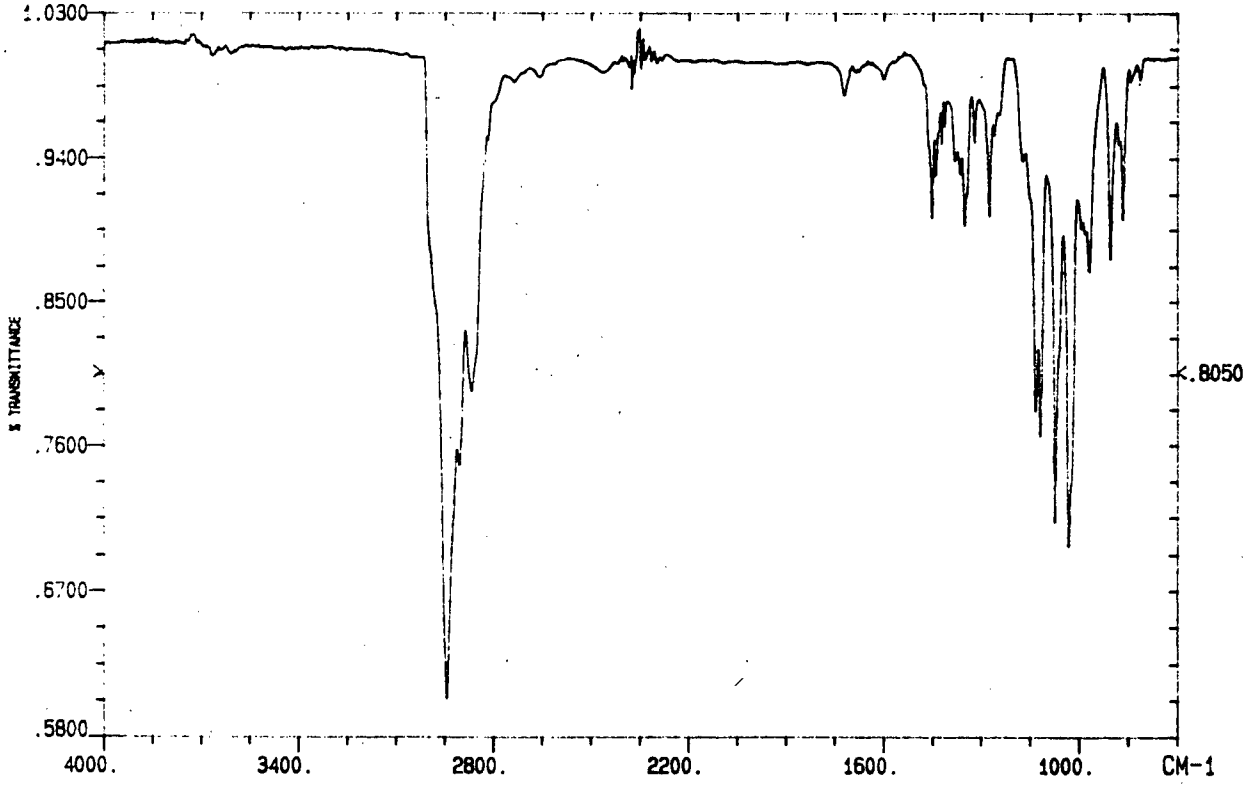

300 MHz
4
3
2
1
0

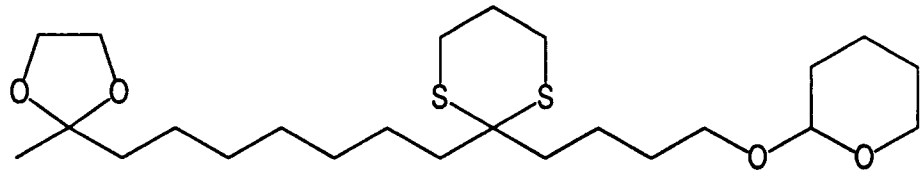

1.0500
.8860
.7220
.5580
.3940
.2300
% TRANSMITTANCE
Y
.640
4000.
3360.
2720.
2080.
1440.
800.
CM-1


S
S
O
O

41

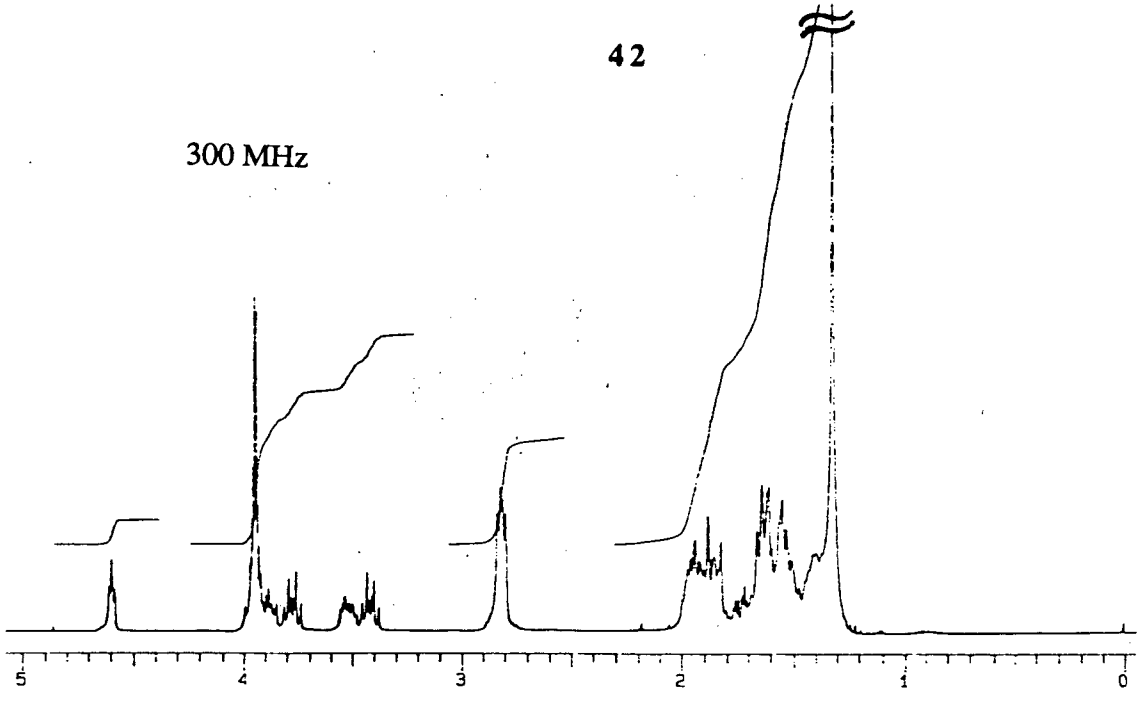

400 MHz
4
3
2
1
0

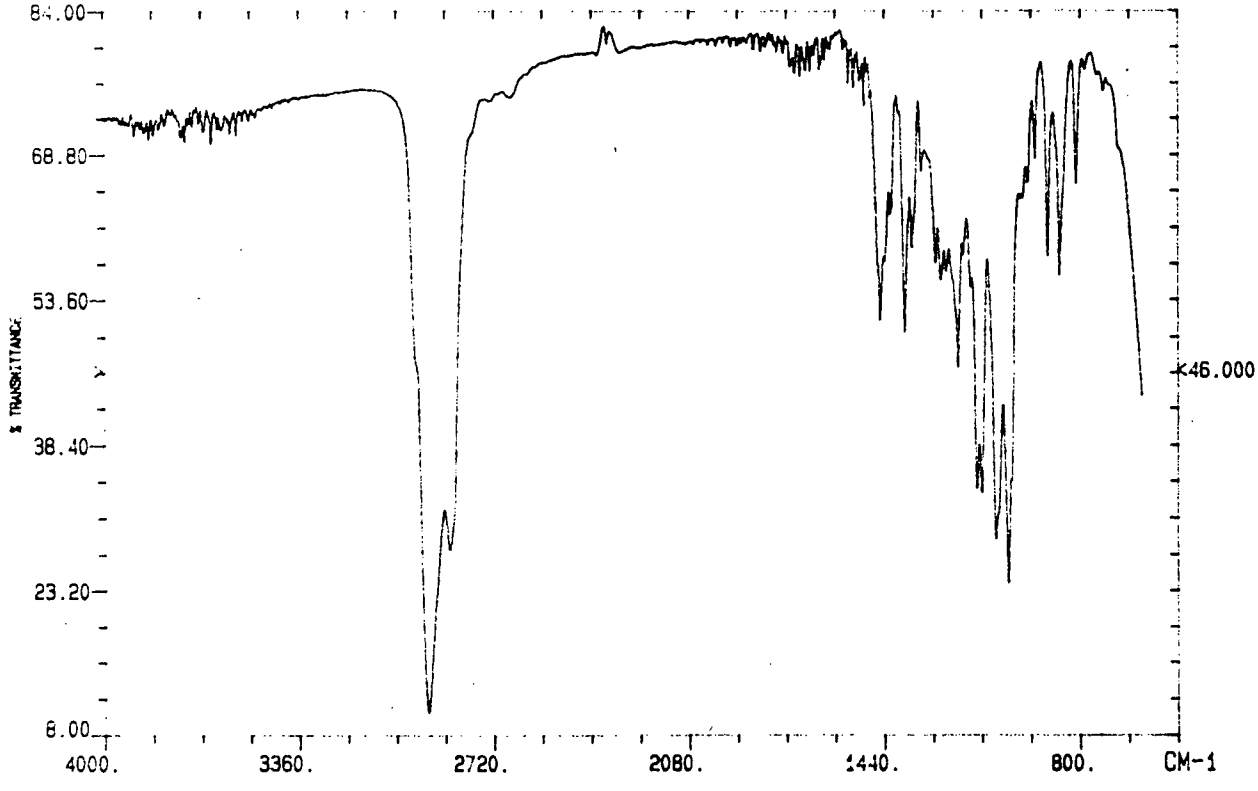

1.0300
.9400
.8500
.7600
.6700
.5800
% TRANSMITTANCE
.8050
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

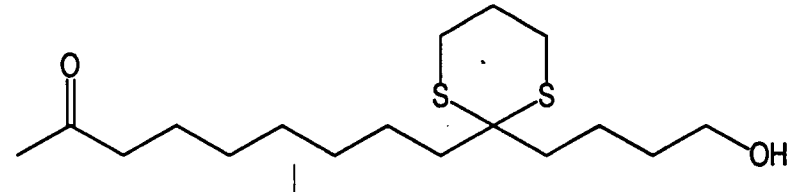


42

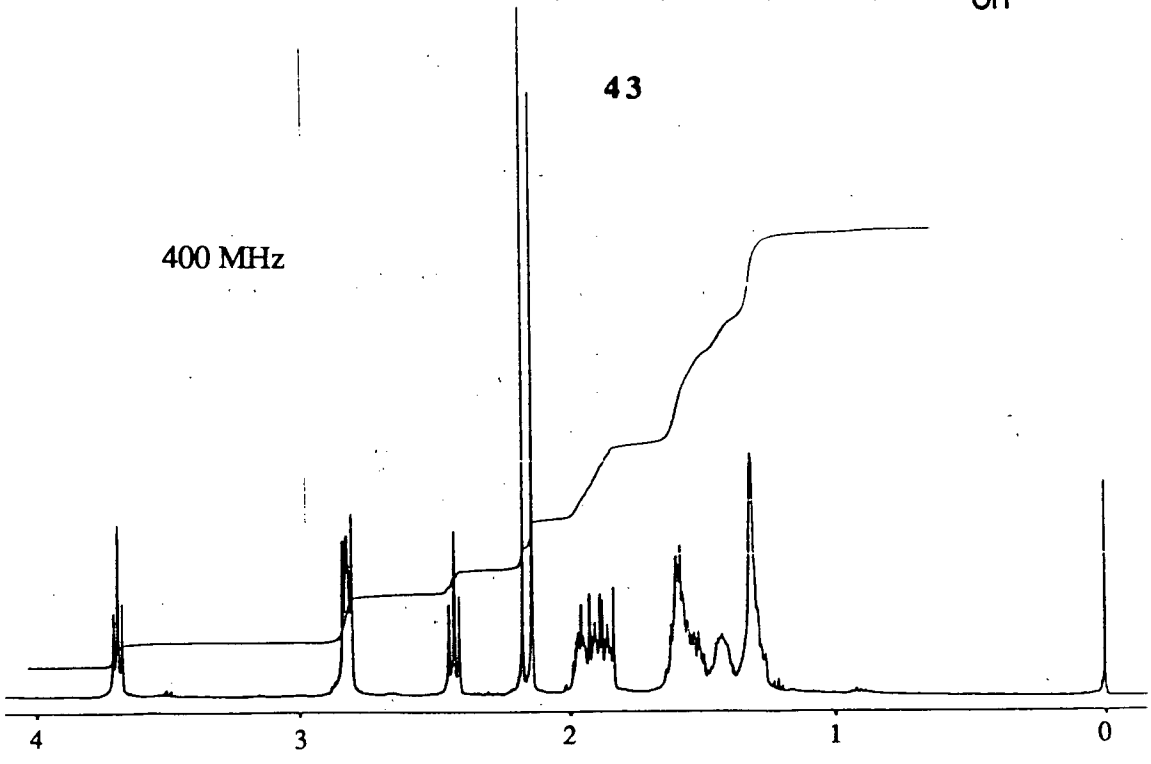
300 MHz

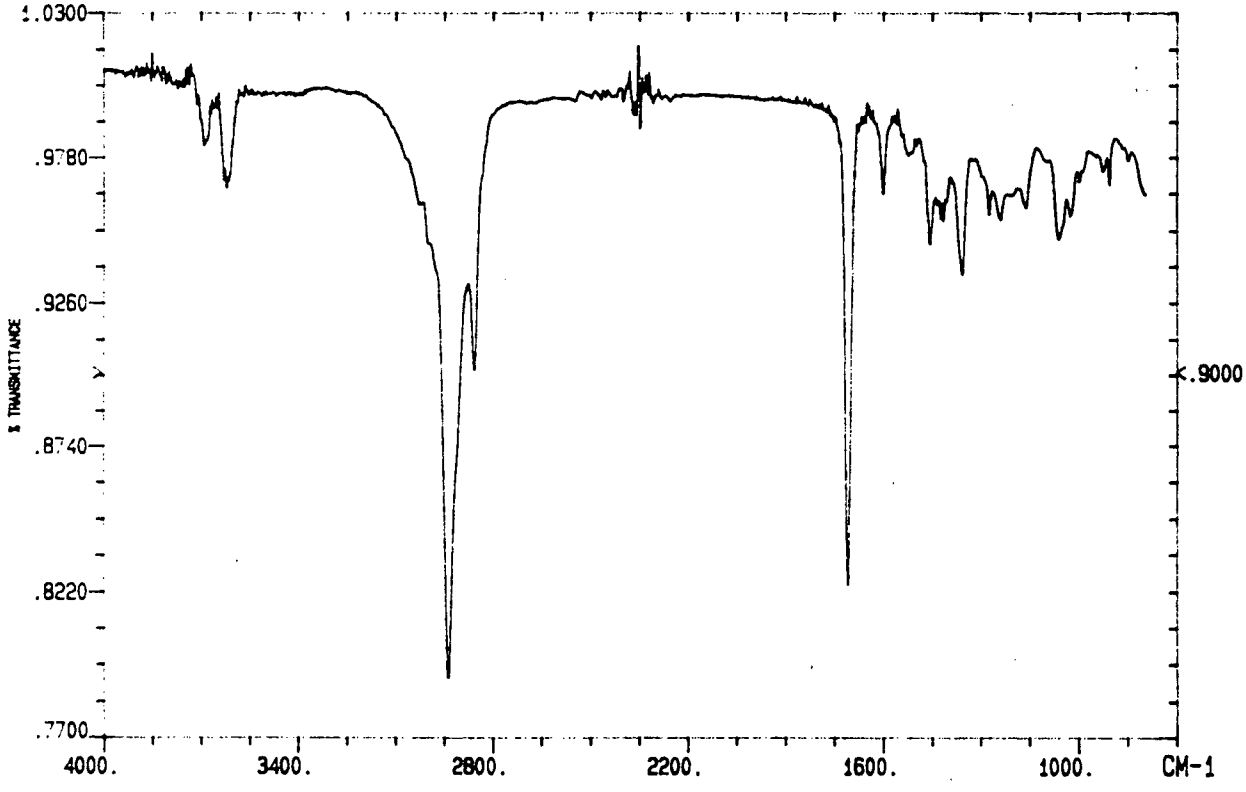

5
4
3
2
1
0

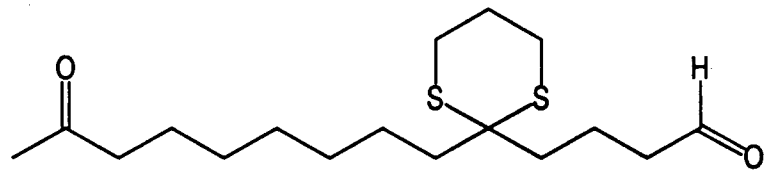

84.00
68.80
53.60
38.40
23.20
8.00
% TRANSMITTANCE
4000.
3360.
2720.
2080.
1440.
800.
CM-1
46.000


O
S
S
OH

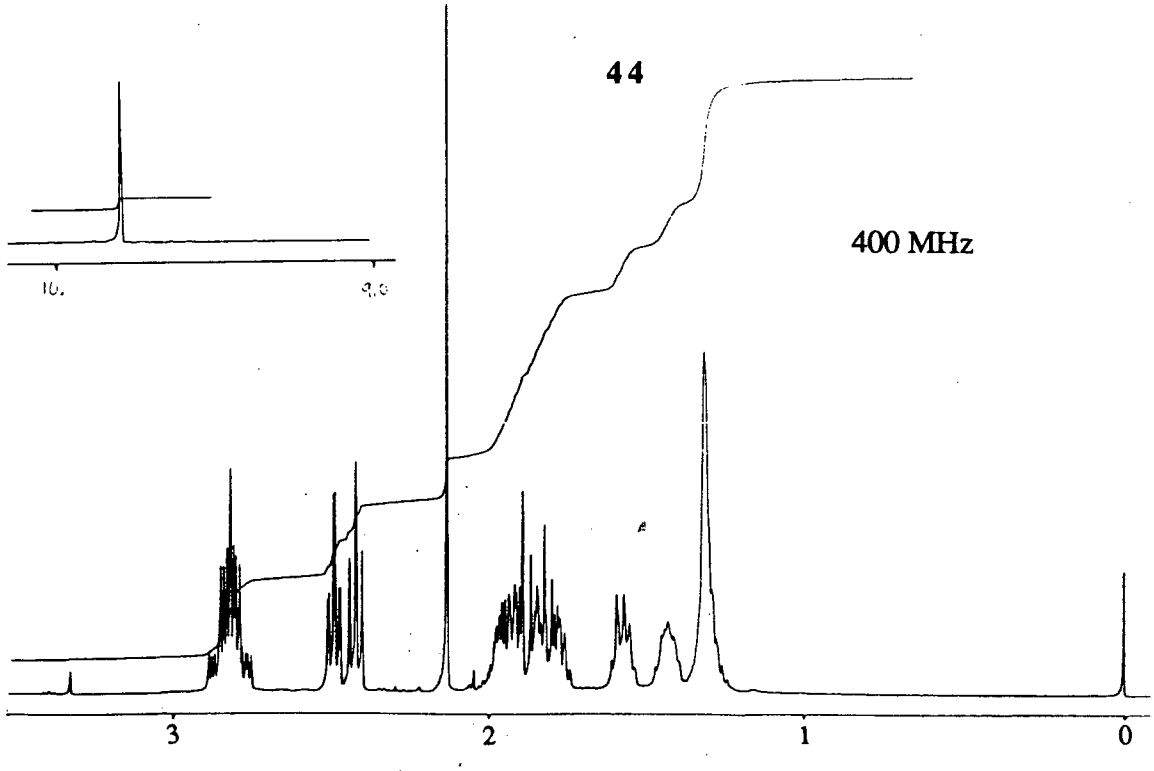
43

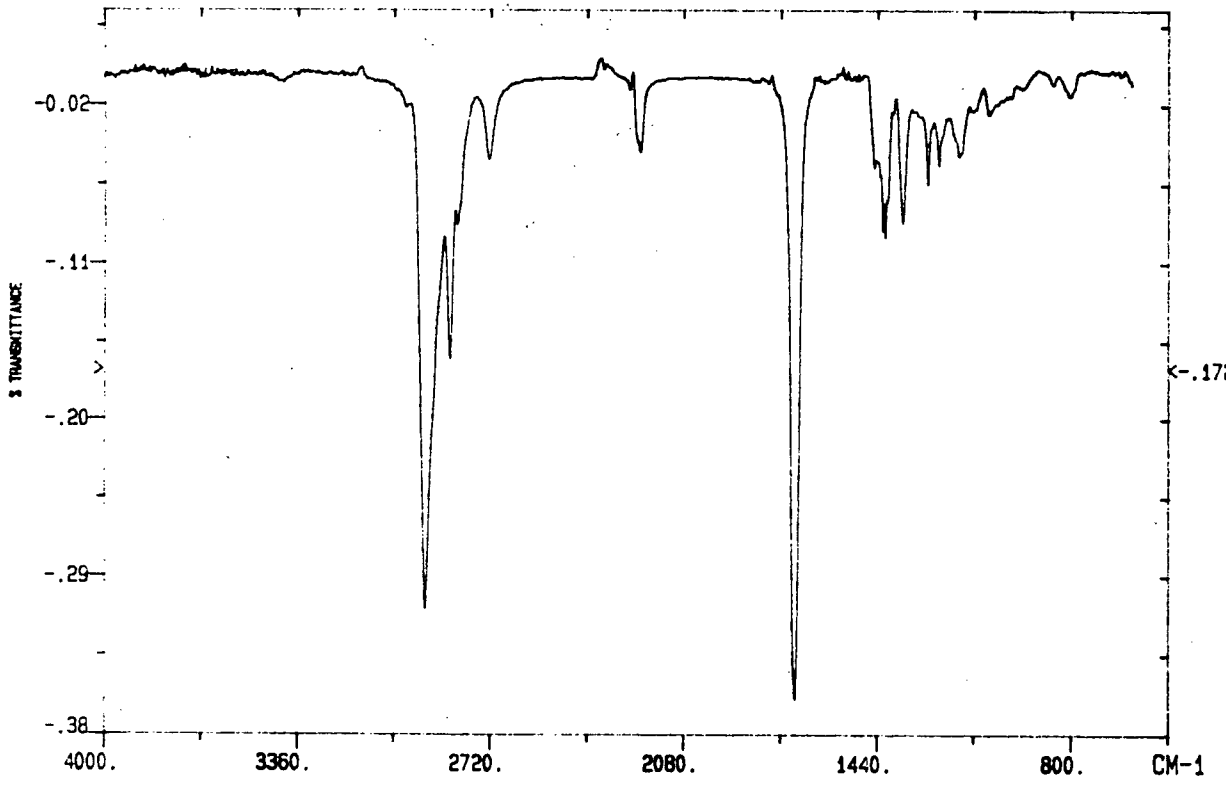

400 MHz
4
3
2
1
0

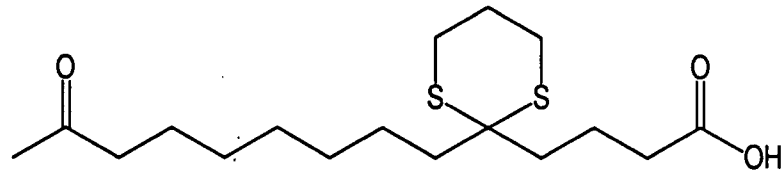

1.0300
.9780
.9260
.8740
.8220
.7700
% TRANSMITTANCE
Y
X
.9000
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


O
S
S
H
O

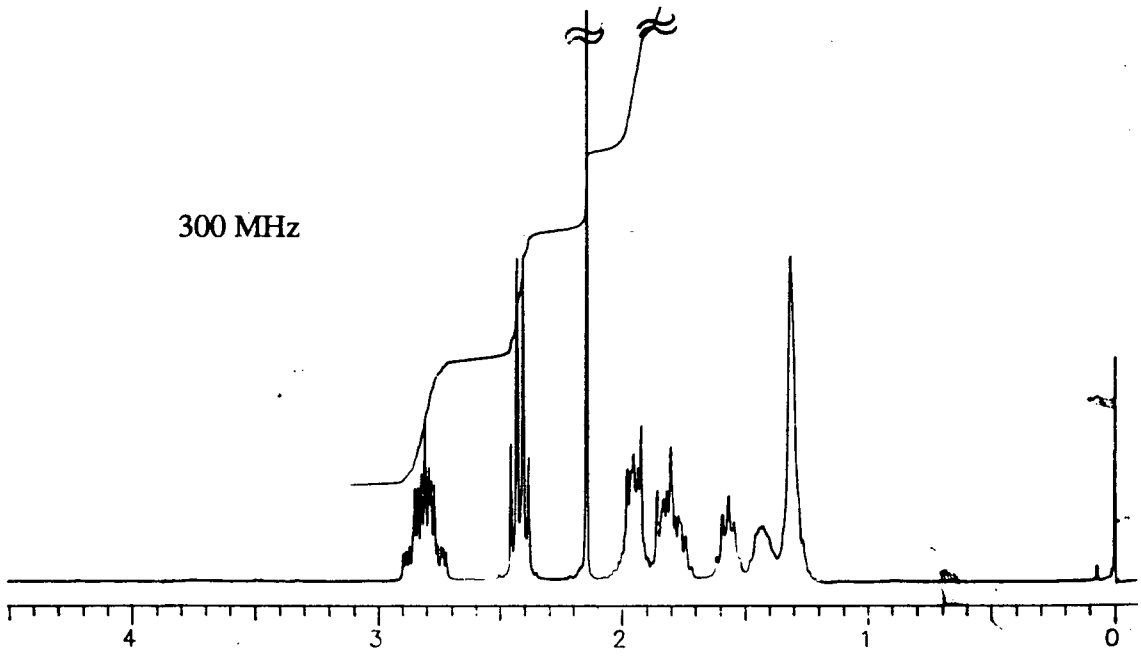
44

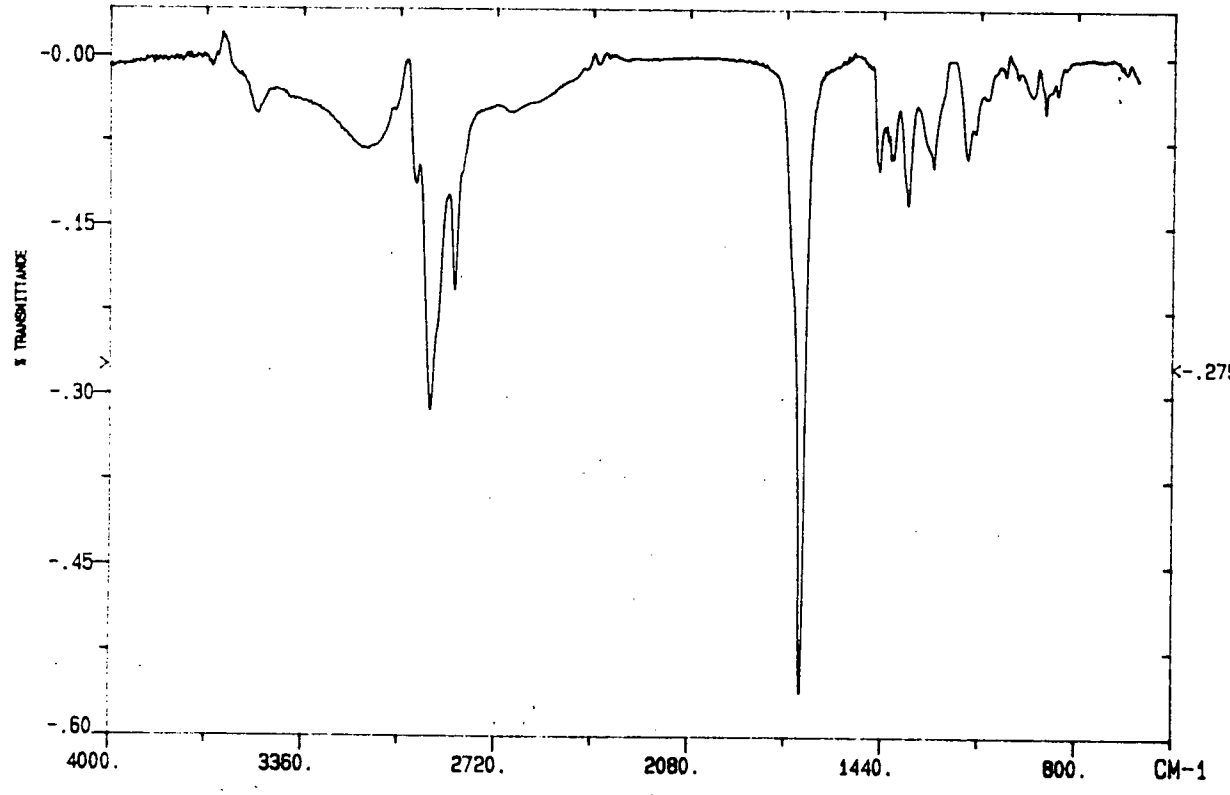

400 MHz
3
2
1
0

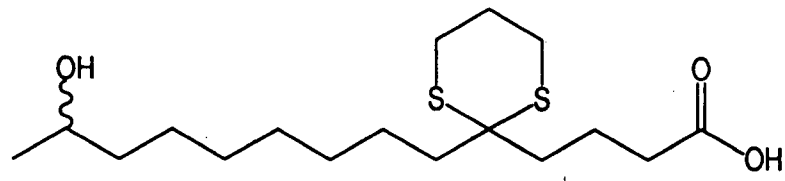

-0.02
-.11
-.20
-.29
-.38
% TRANSMITTANCE
<-.172
4000.
3360.
2720.
2080.
1440.
800.
CM-1


O
S
S
O
OH

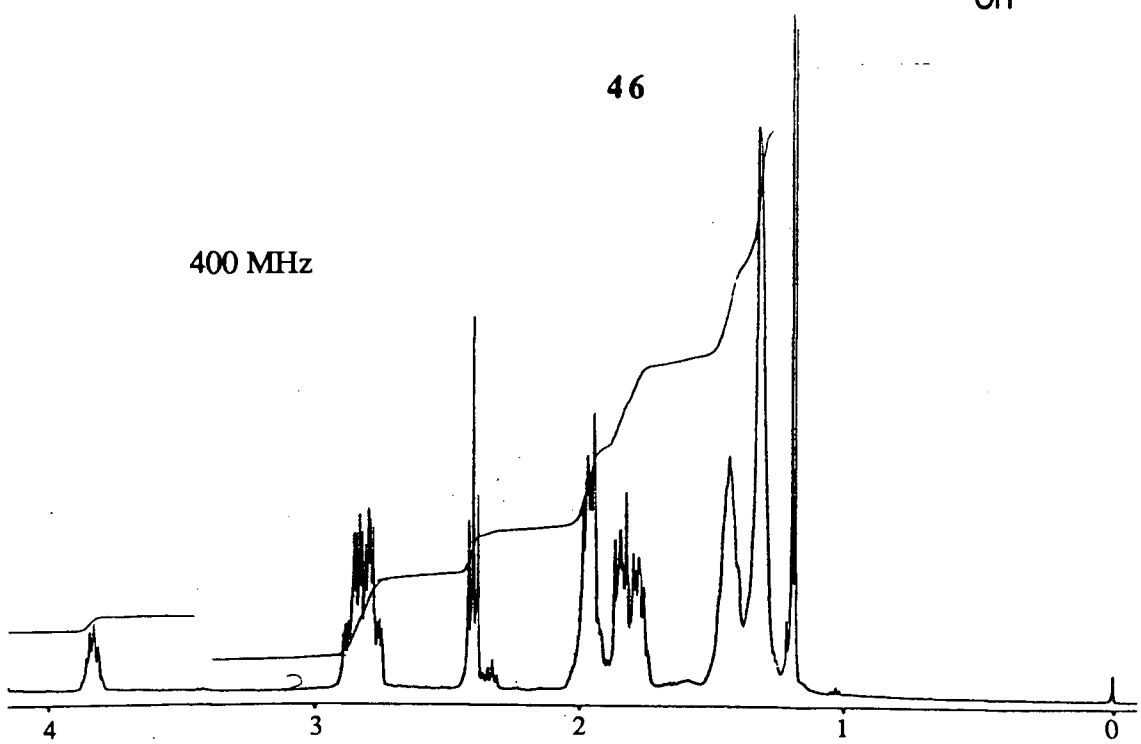
45

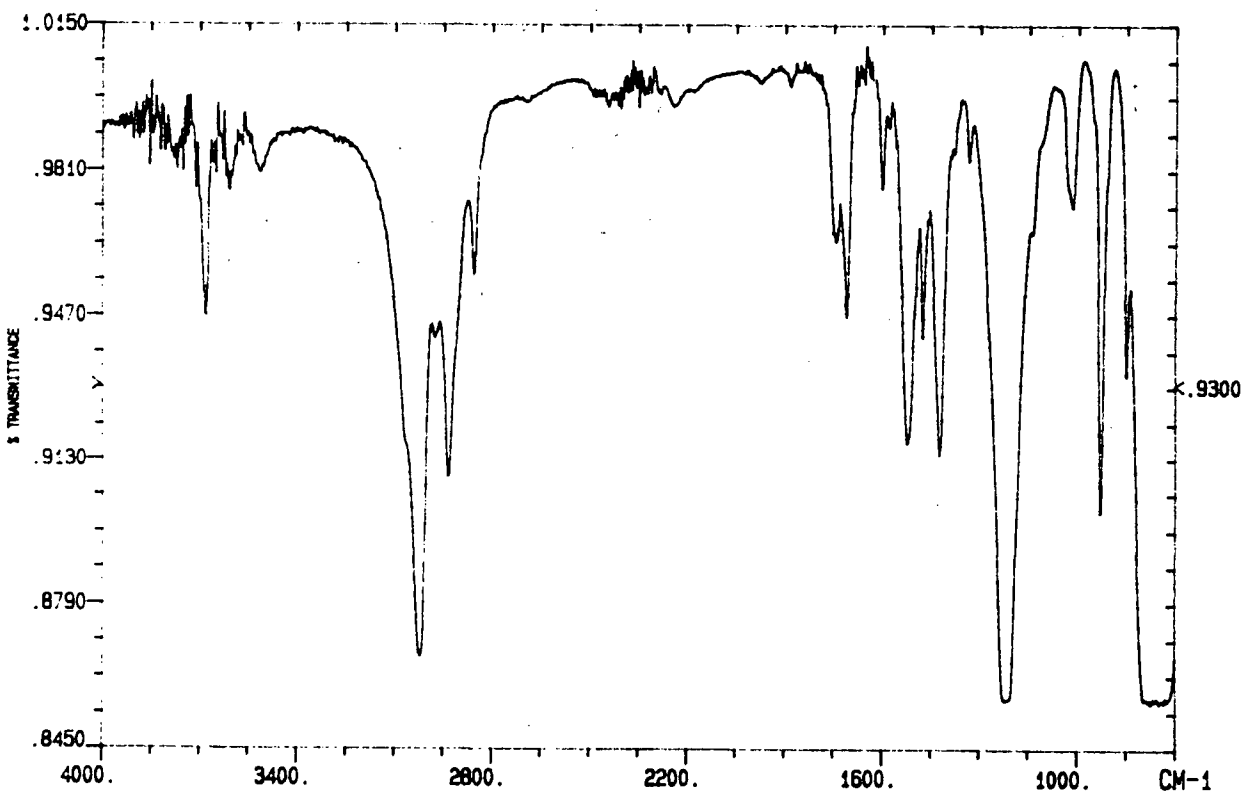

300 MHz
4
3
2
1
0

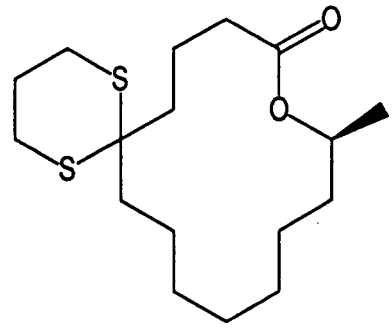

-0.00
-.15
-.30
-.45
-.60
% TRANSMITTANCE
-.275
4000.
3360.
2720.
2080.
1440.
800.
CM-1


OH
S
S
O
OH

46

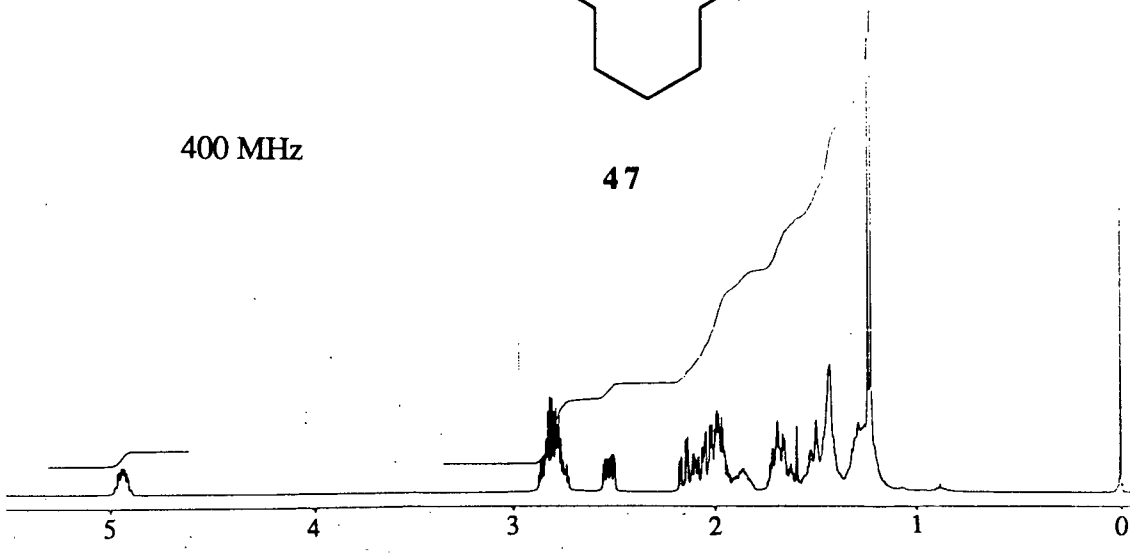

400 MHz
4
3
2
1
0

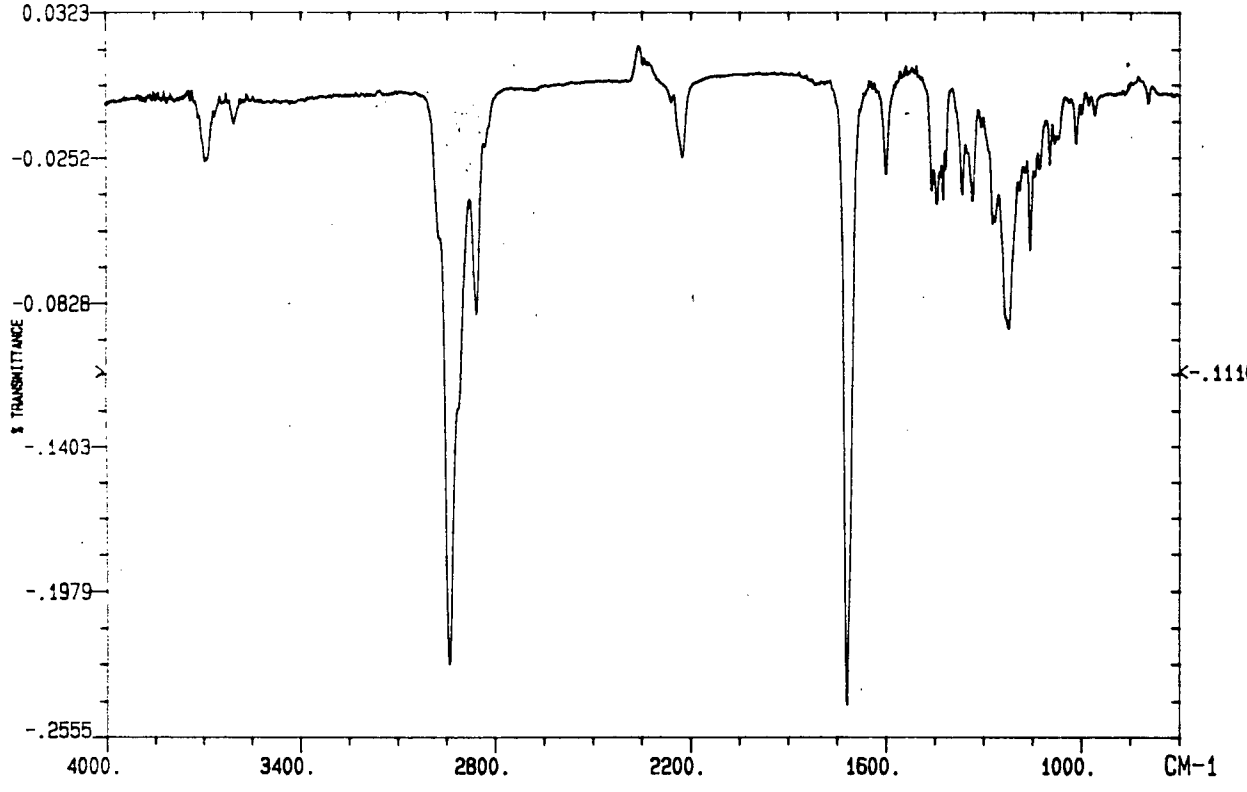

1.0150
.9810
.9470
.9130
.8790
.8450
% TRANSMITTANCE
.9300
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

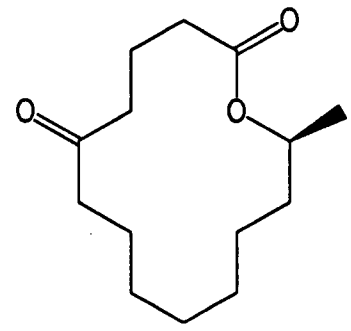

O
S
O
S

400 MHz

47

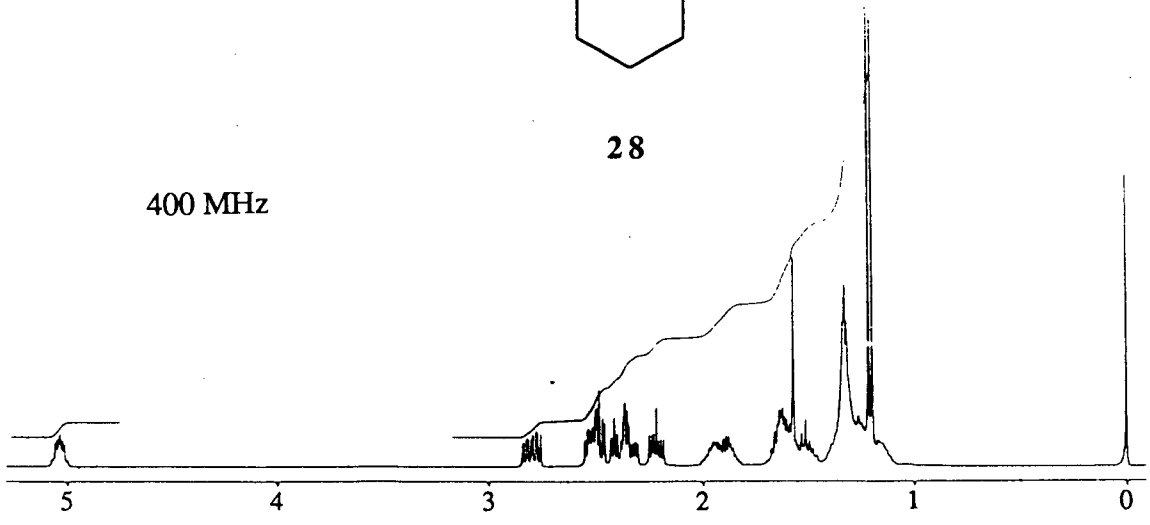

5
4
3
2
1
0

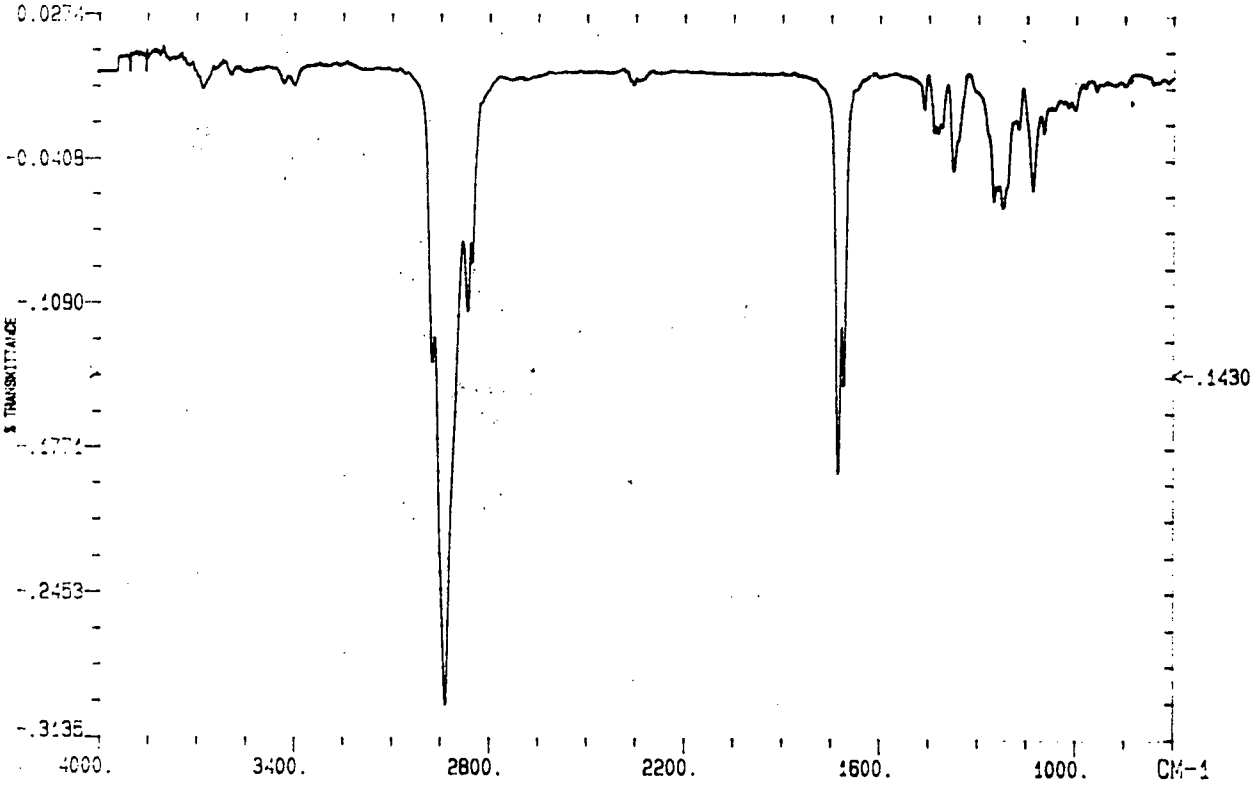

0.0323
-0.0252
-0.0828
-.1403
-.1979
-.2555
% TRANSMITTANCE
Y
-.1116
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

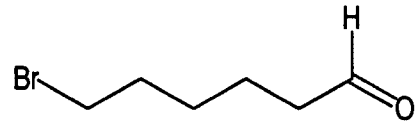


28

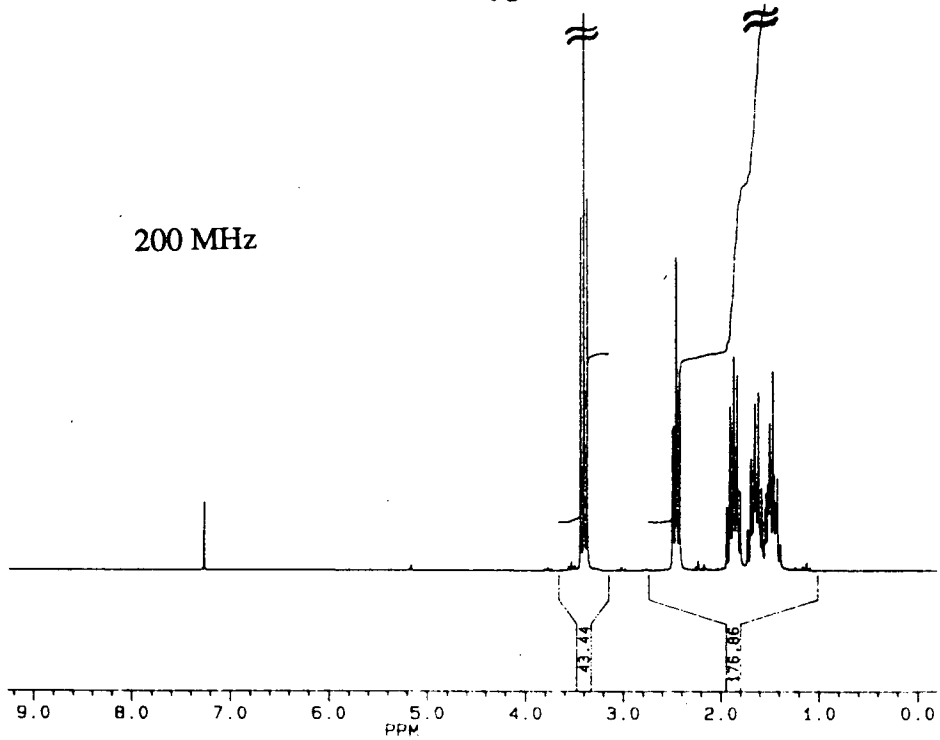
400 MHz

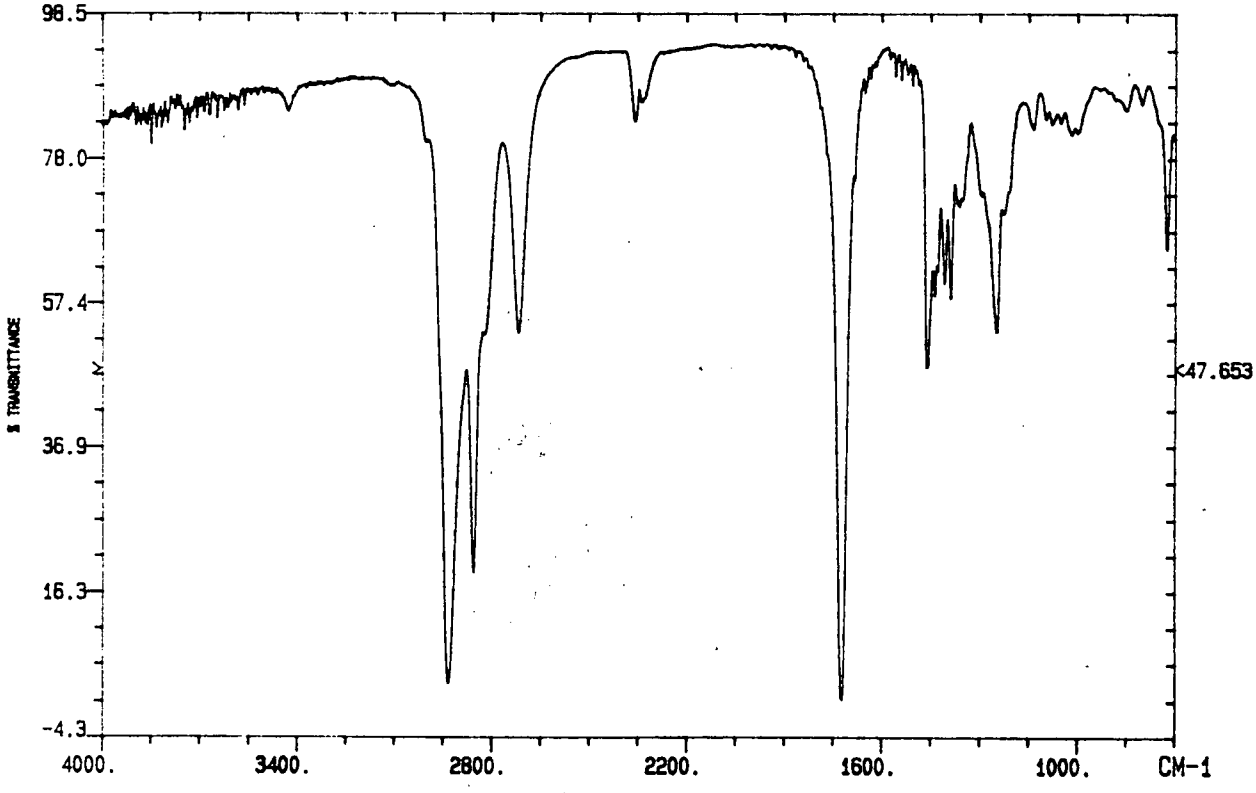

5
4
3
2
1
0

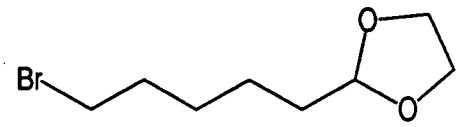

-0.0408
-.1090
-.2453
-.3135
4000.
3400.
2800.
2200.
1600.
1000.
CM-1
<-.1430


H
Br
O

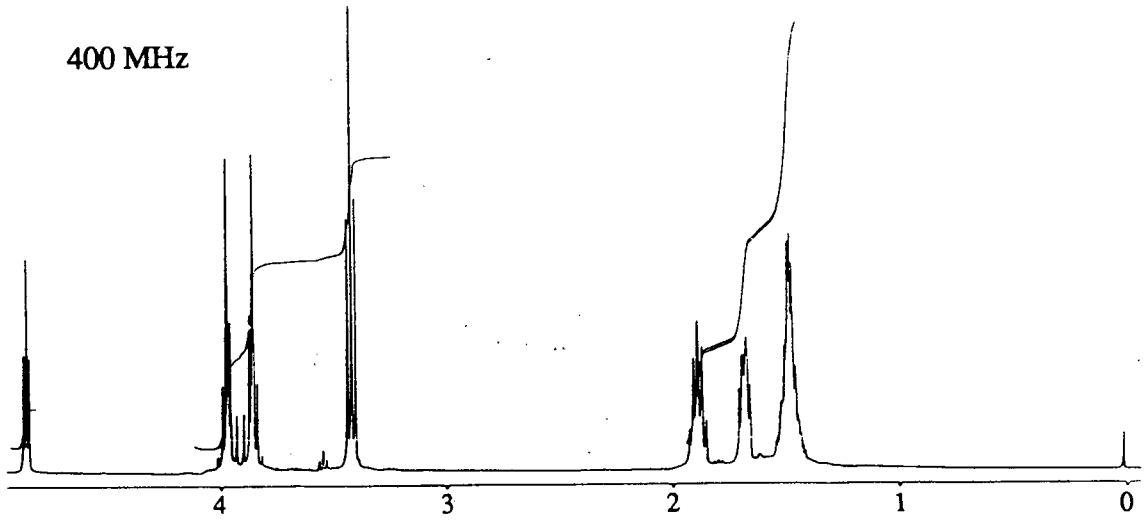
48

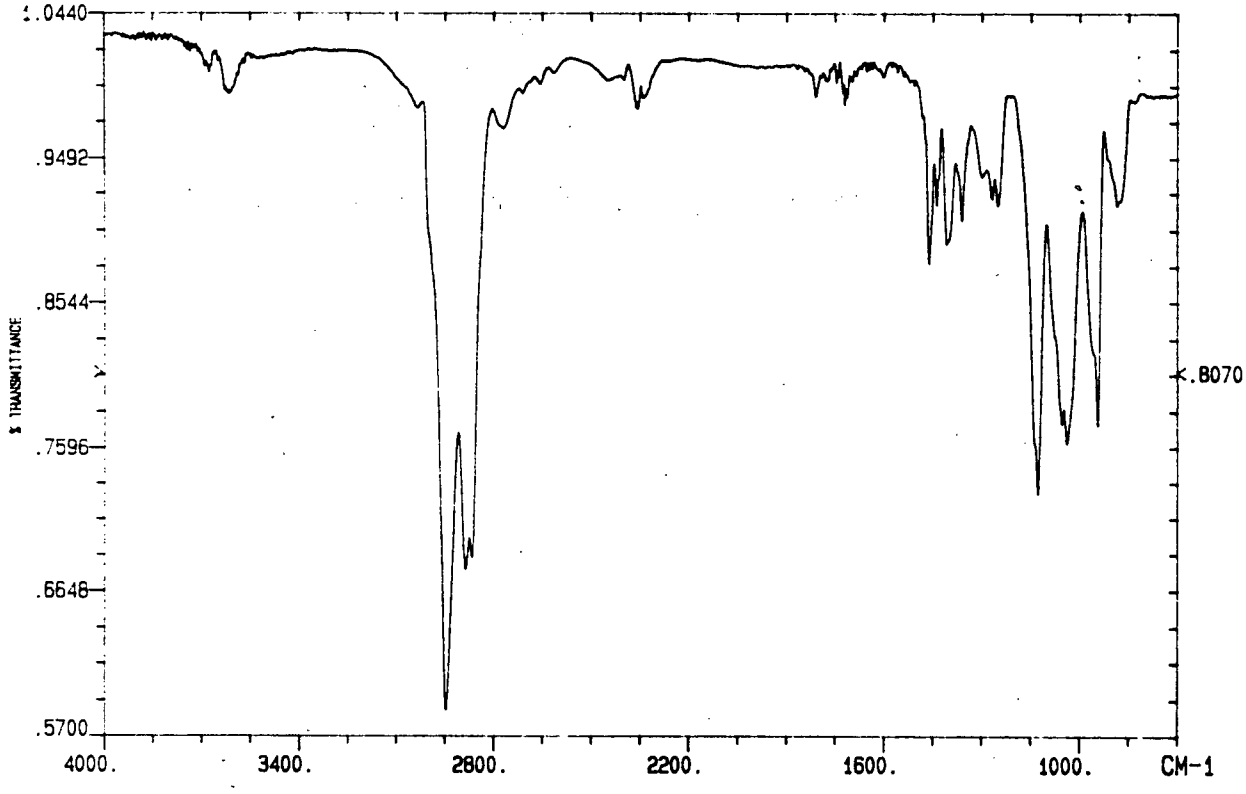

200 MHz
43.44
176.86
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

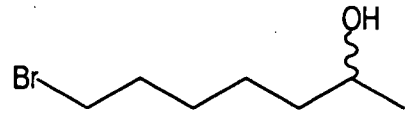

98.5
78.0
57.4
36.9
16.3
-4.3
% TRANSMITTANCE
47.653
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


Br
O
O

51

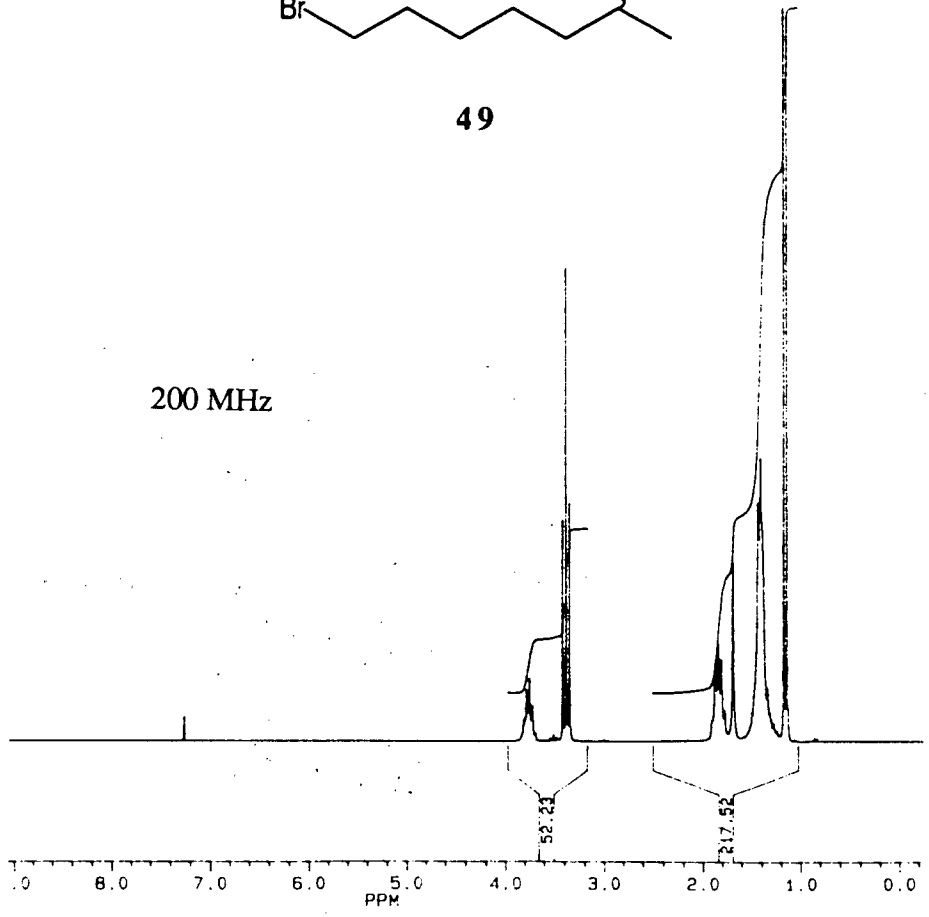

400 MHz
4
3
2
1
0

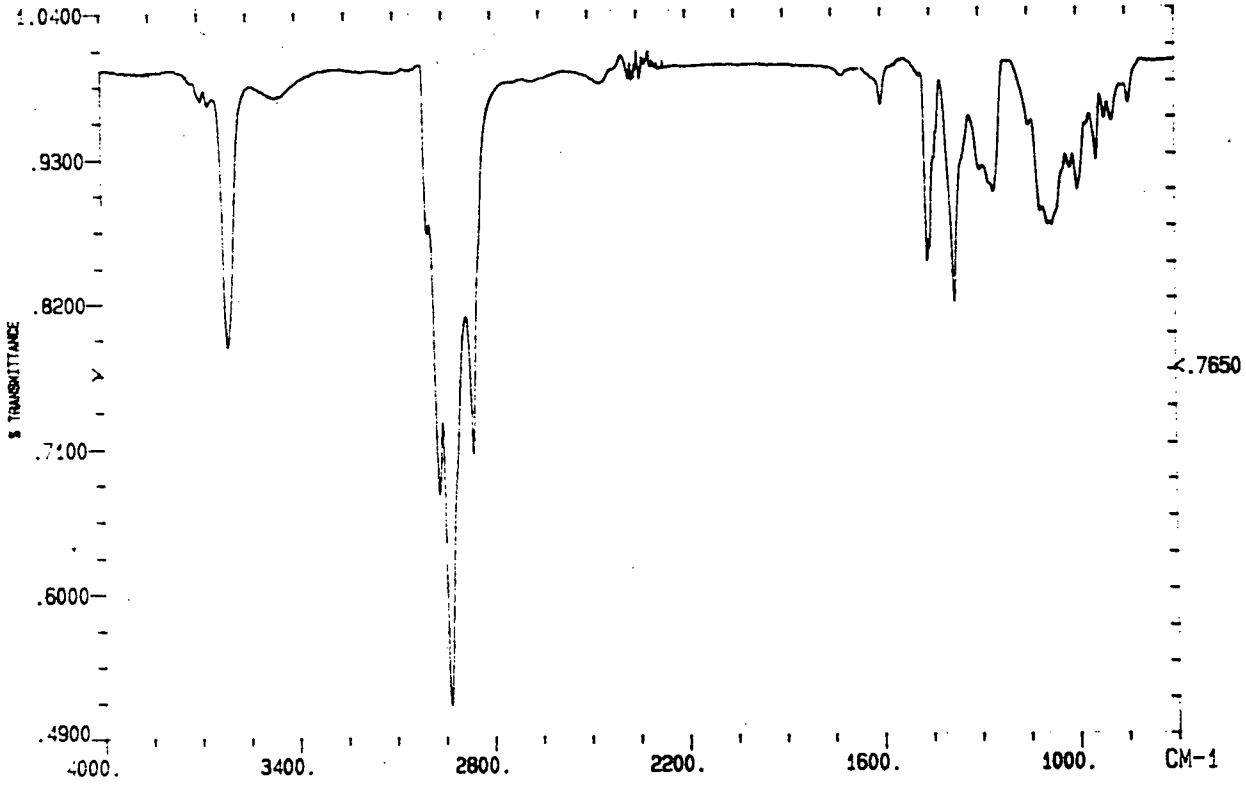

1.0440
.9492
.8544
.7596
.6648
.5700
% TRANSMITTANCE
Y
.8070
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

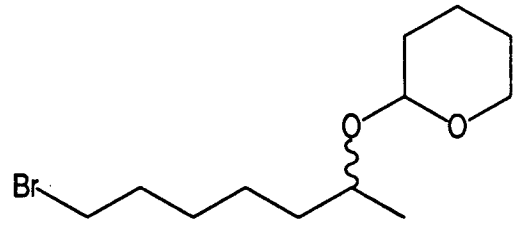

OH
Br

49

200 MHz

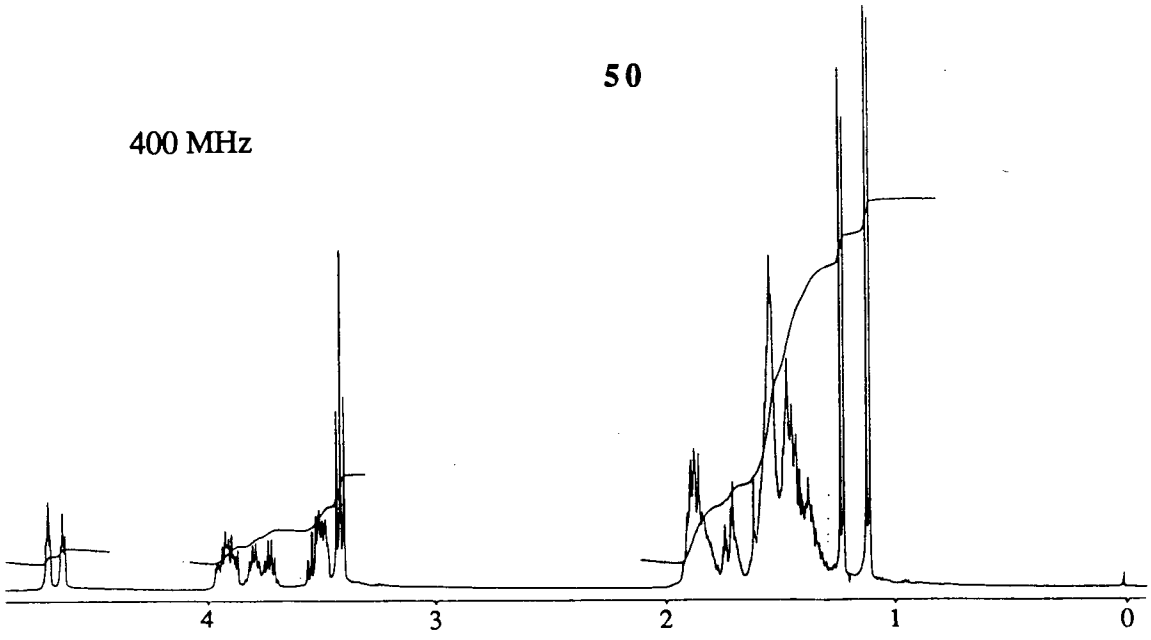

52.33
217.52
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

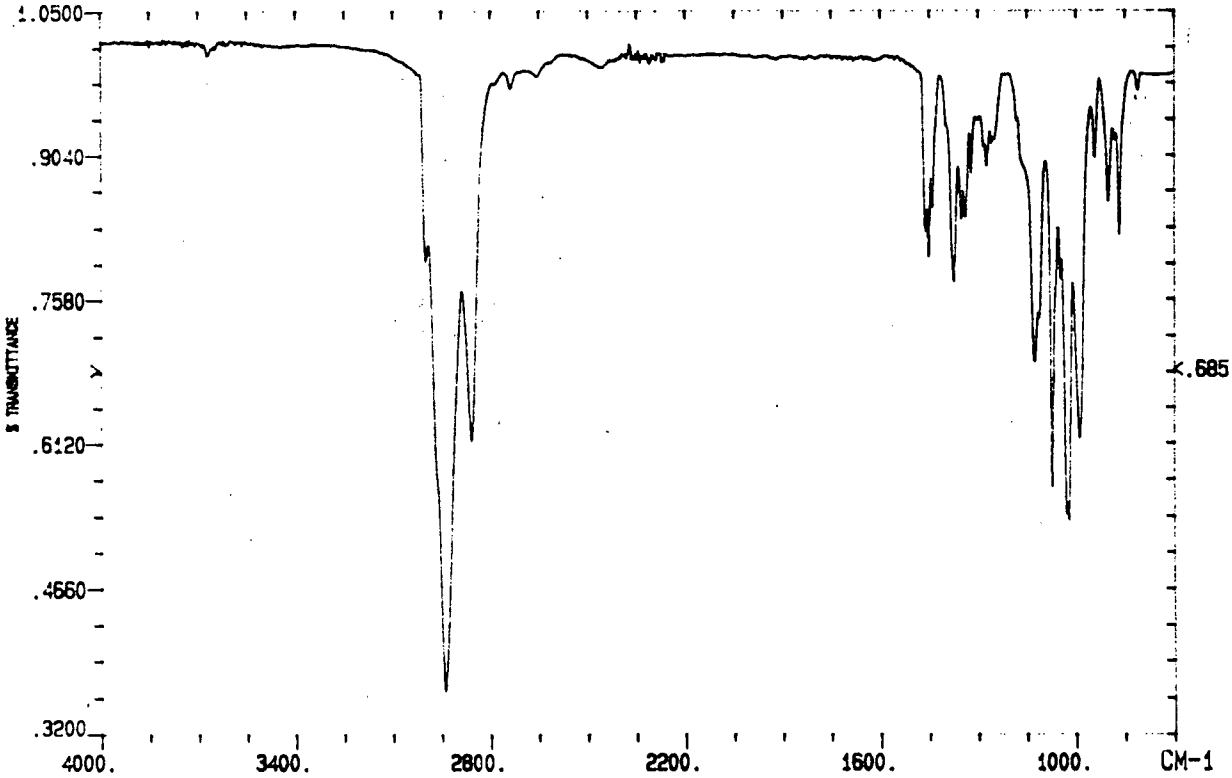

1.0400
.9300
.8200
.7100
.6000
.4900
% TRANSMITTANCE
Y
.7650
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

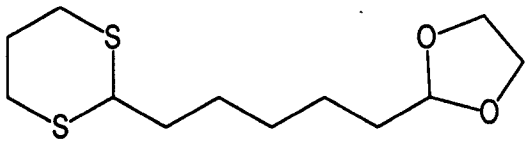

Br
O
O

50

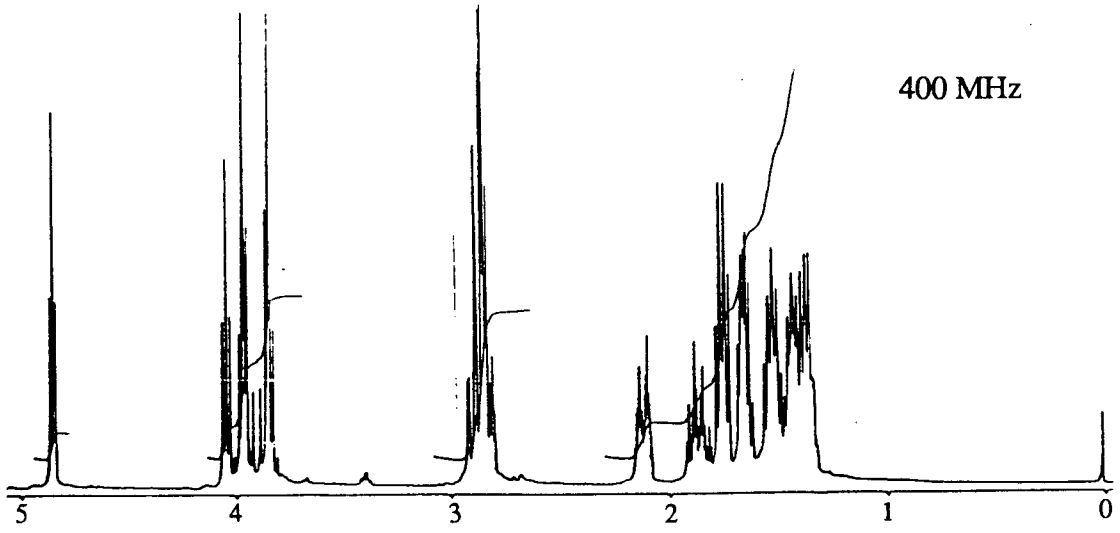
400 MHz

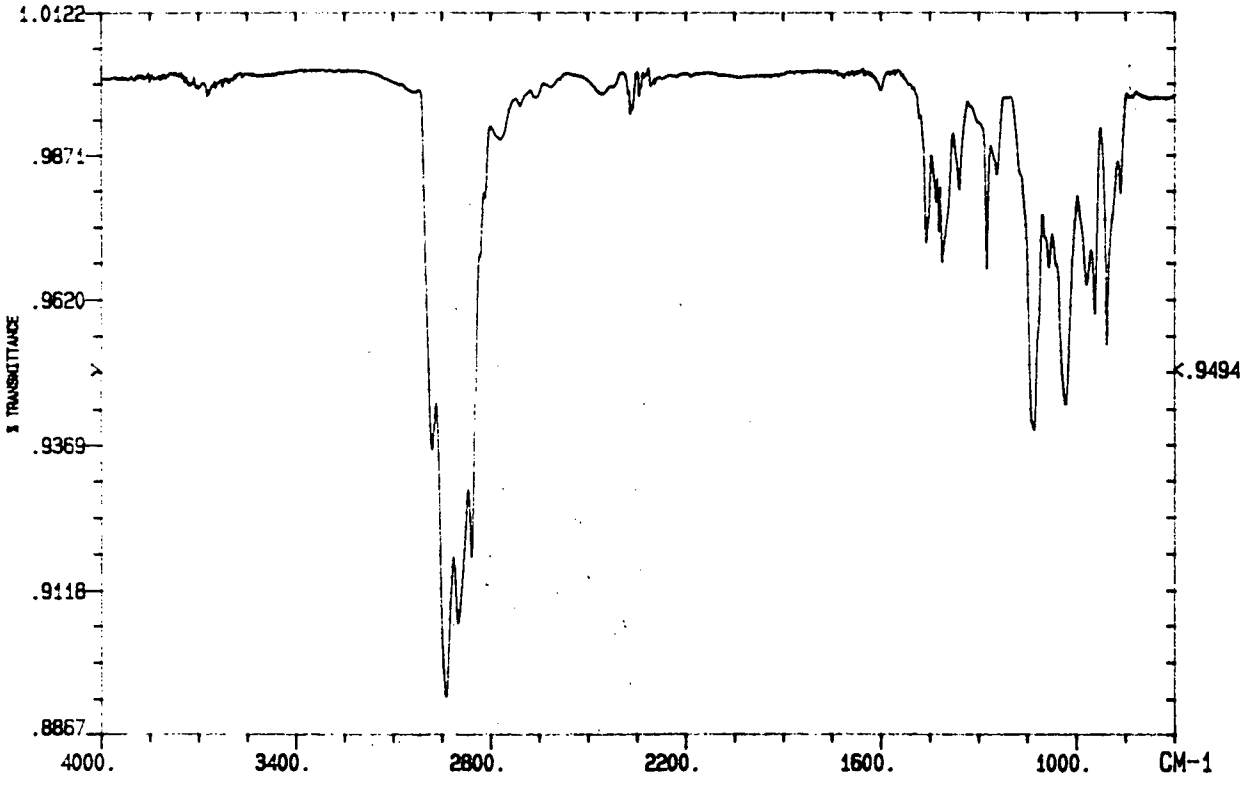

4
3
2
1
0

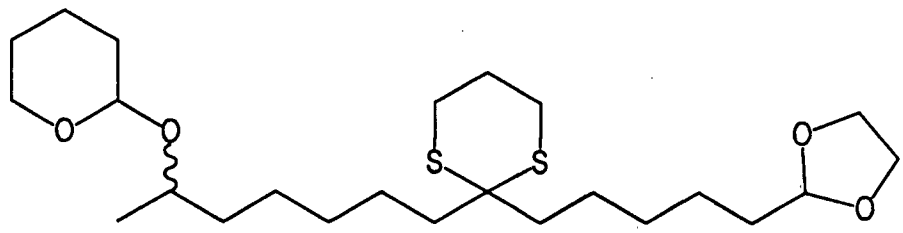

1.0500
.9040
.7580
.6120
.4660
.3200
% TRANSMITTANCE
.685
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


S
S
O
O

53

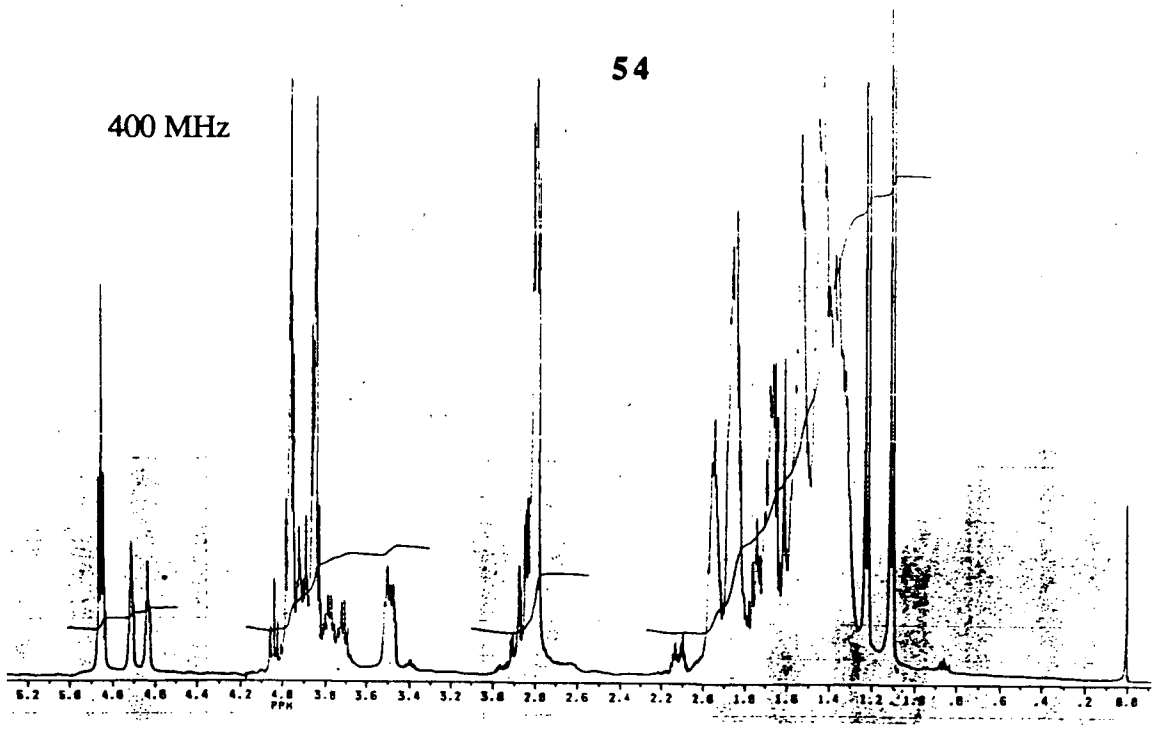

400 MHz
5
4
3
2
1
0

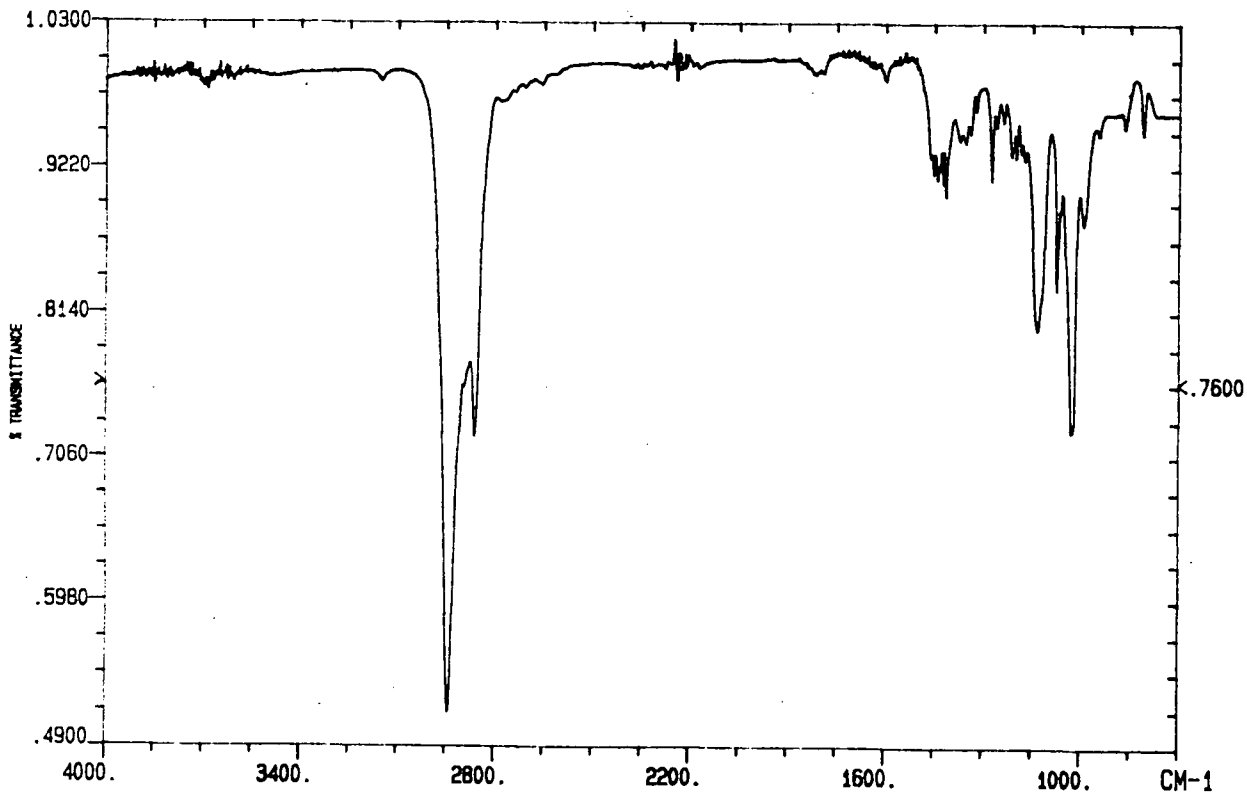

1.0122
.9871
.9620
.9369
.9118
.8867
% TRANSMITTANCE
.9494
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

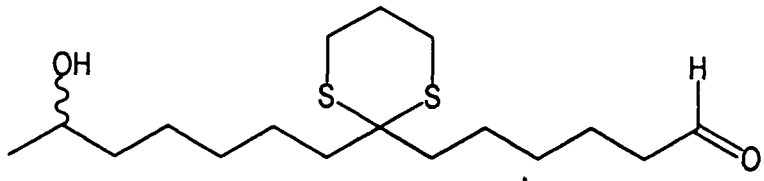


54

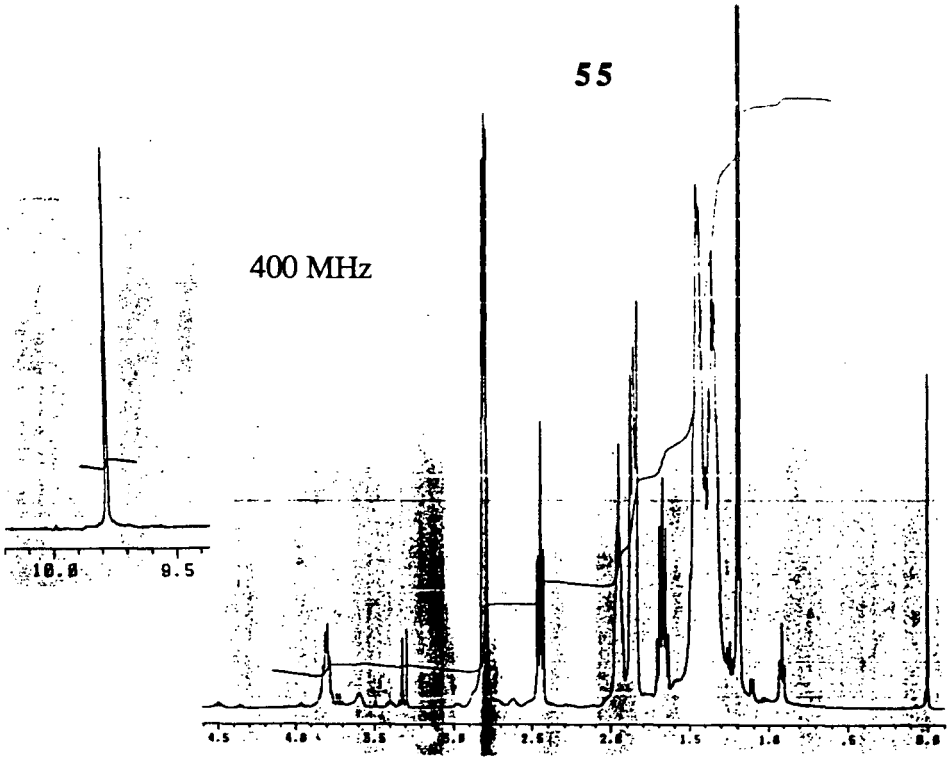
400 MHz

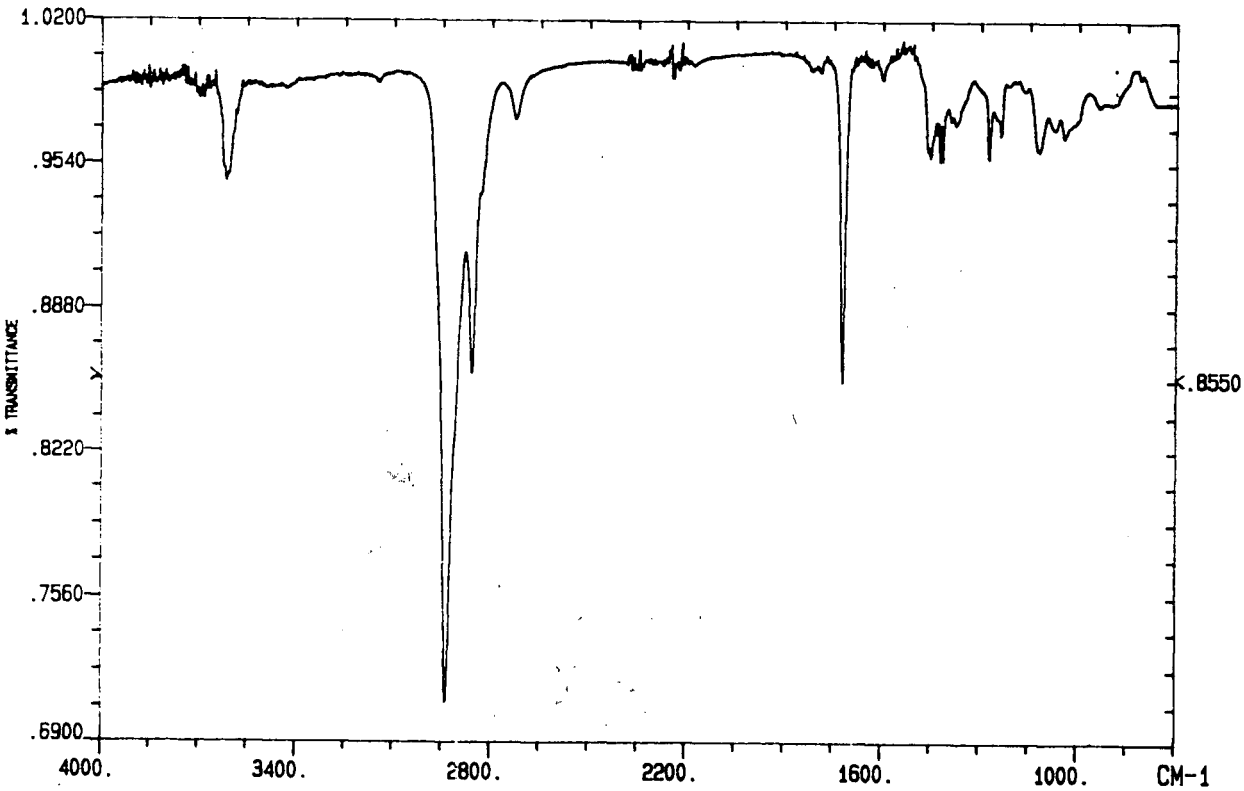


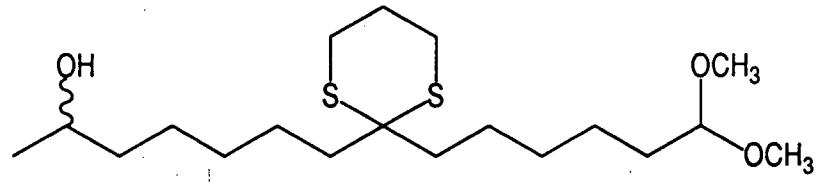

1.0300
.9220
.8140
.7060
.5980
.4900
% TRANSMITTANCE
.7600
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


OH
S
S
H
O

55

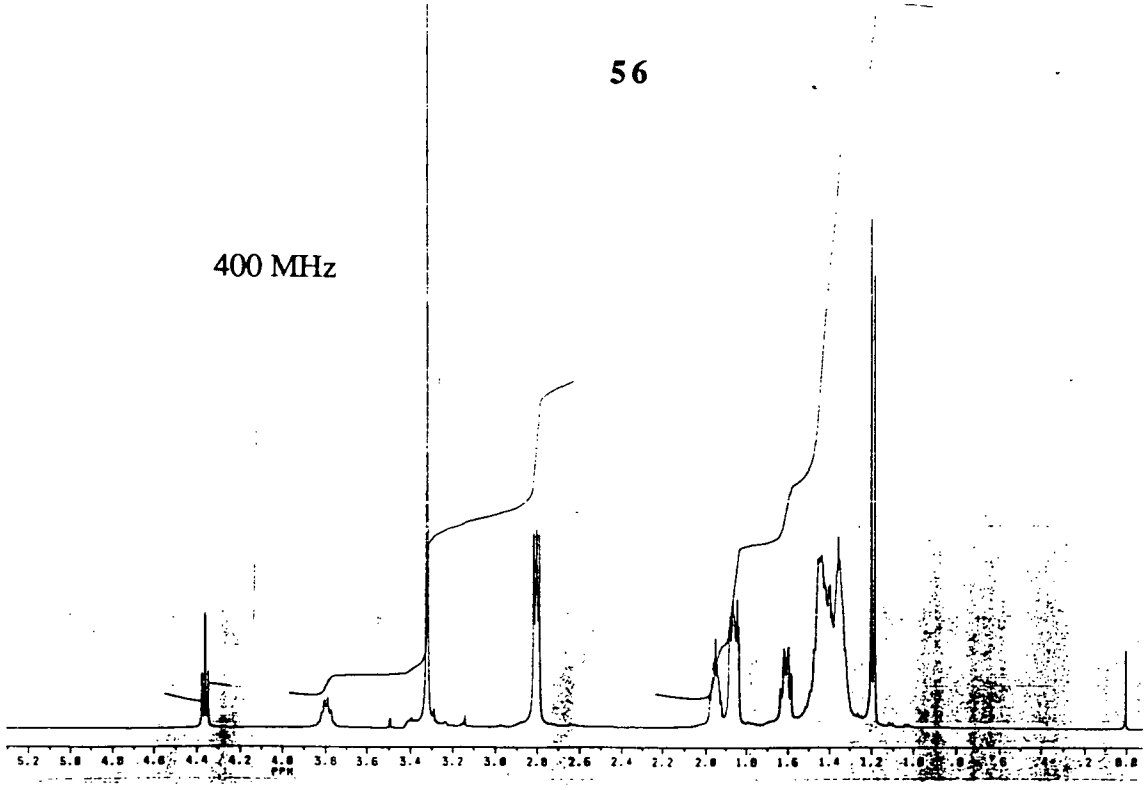

400 MHz
10.0
9.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

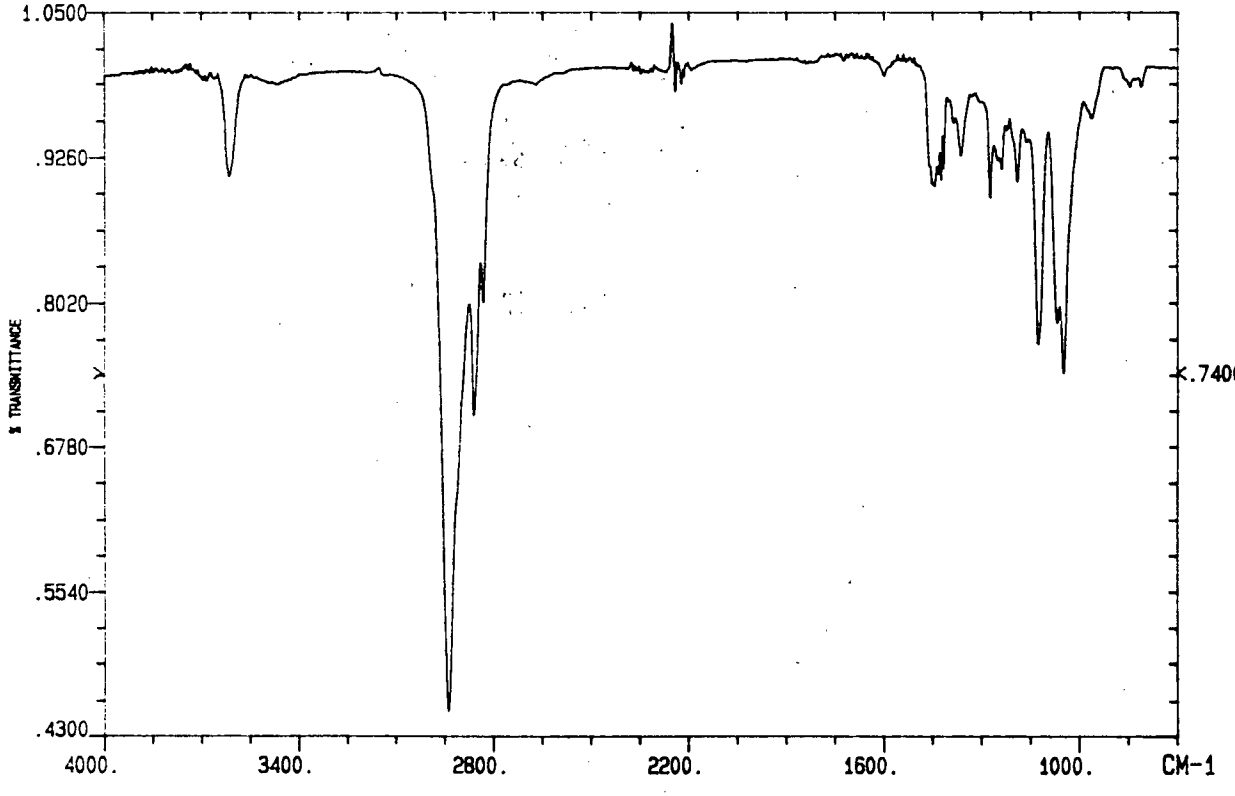

1.0200
.9540
.8880
.8220
.7560
.6900
% TRANSMITTANCE
Y
.8550
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

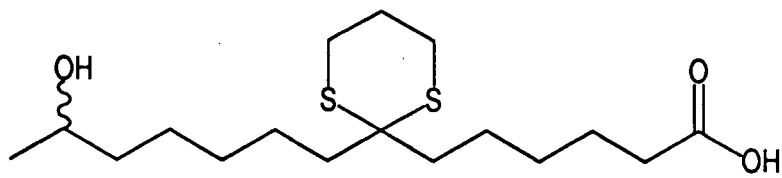

OH
S
S
OCH3
OCH3

56

400 MHz

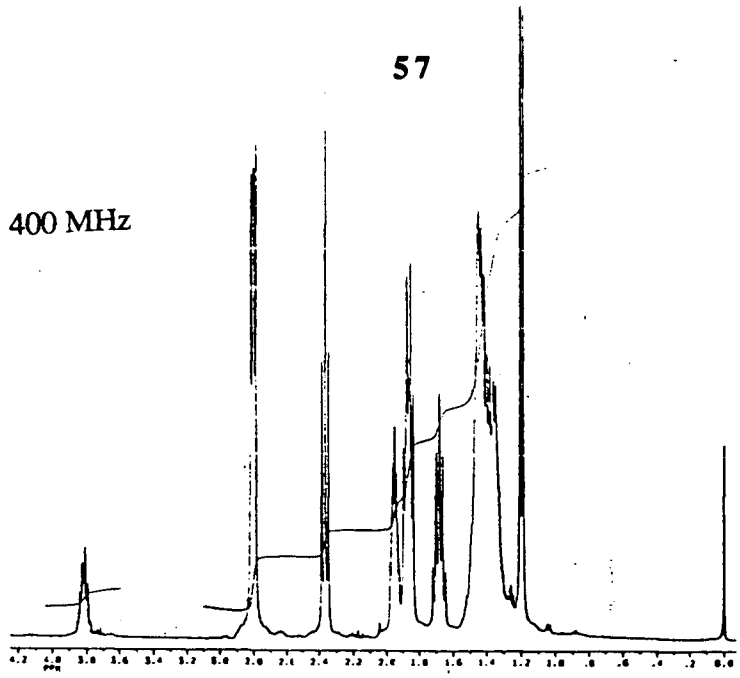


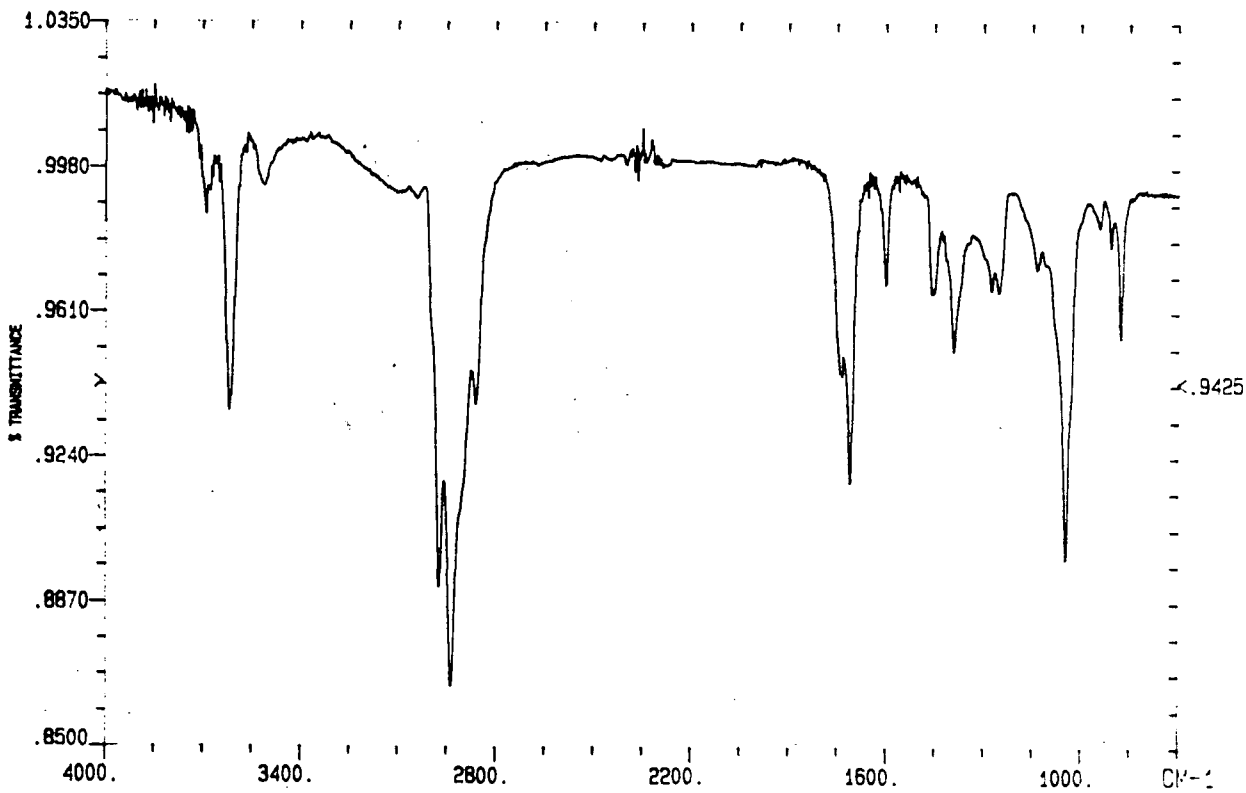

1.0500
.9260
.8020
.6780
.5540
.4300
% TRANSMITTANCE
Y
.7400
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

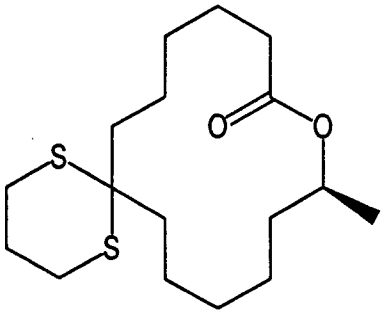

OH
S
S
O
OH

57

400 MHz

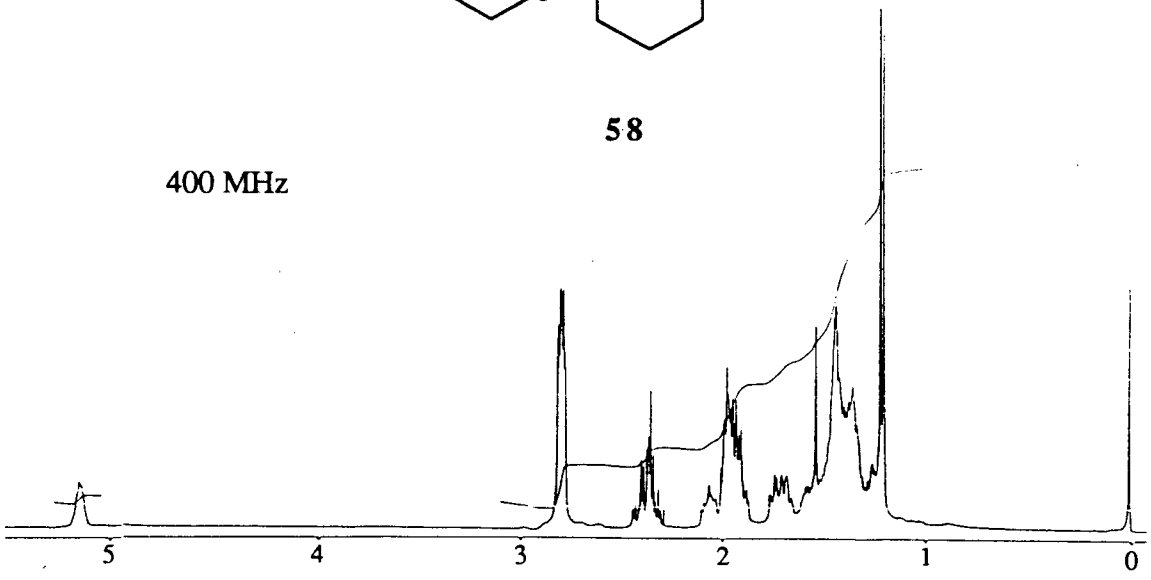


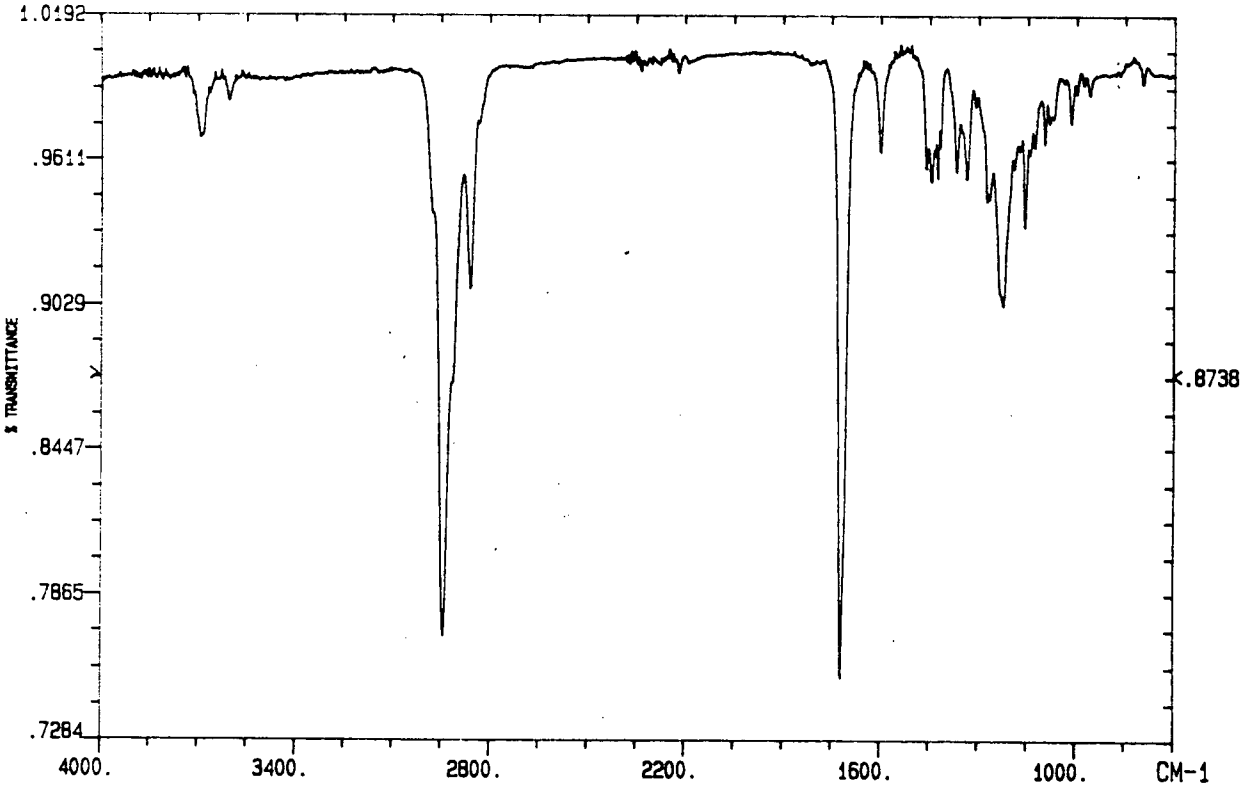

1.0350
.9980
.9610
.9240
.8870
.8500
% TRANSMITTANCE
.9425
4000.
3400.
2800.
2200.
1600.
1000.

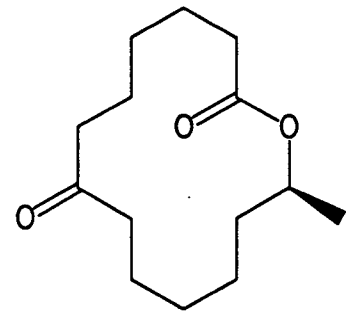

O
O
S
S

58

400 MHz

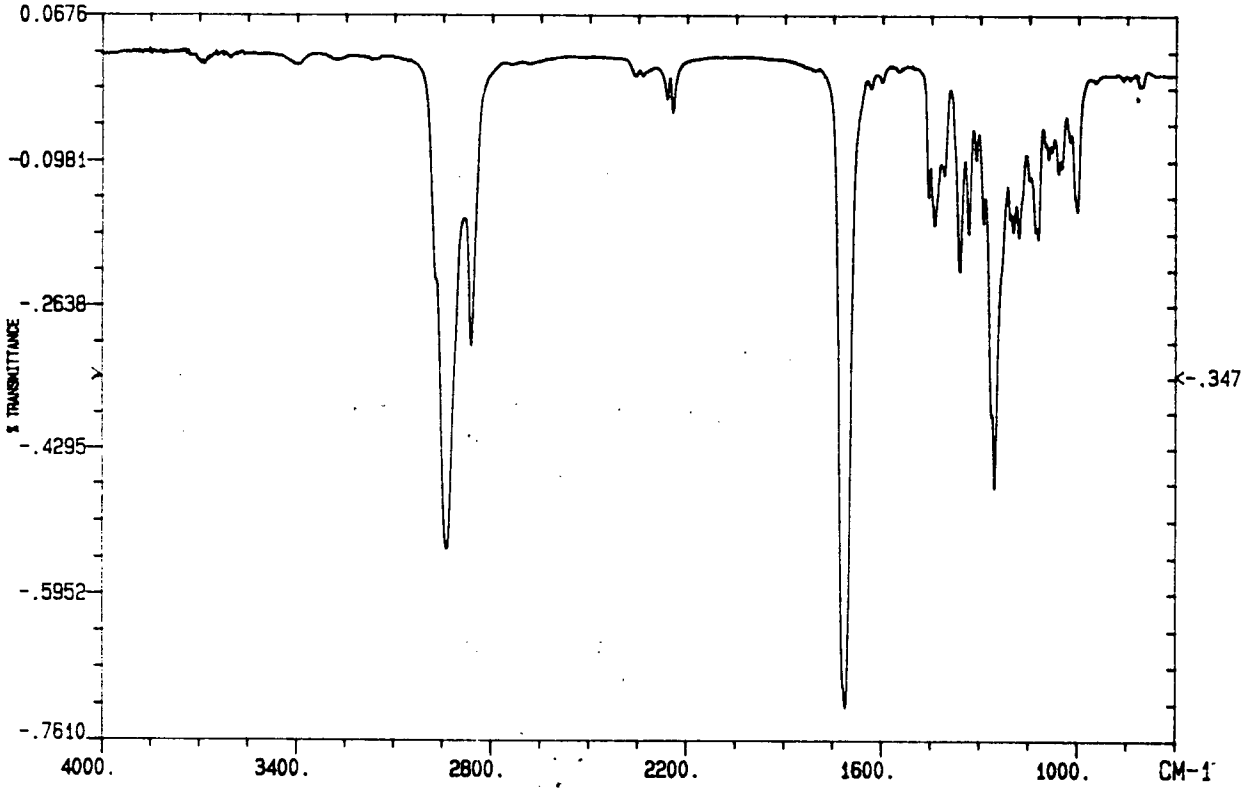

5
4
3
2
1
0

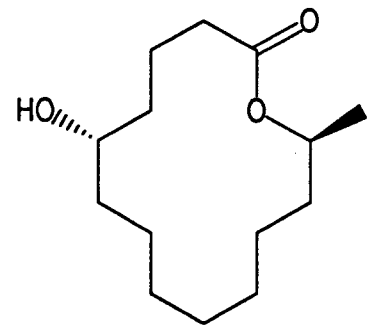

1.0192
.9611
.9029
.8447
.7865
.7284
% TRANSMITTANCE
.8738
4000.
3400.
2800.
2200.
1600.
1000.
CM-1



29

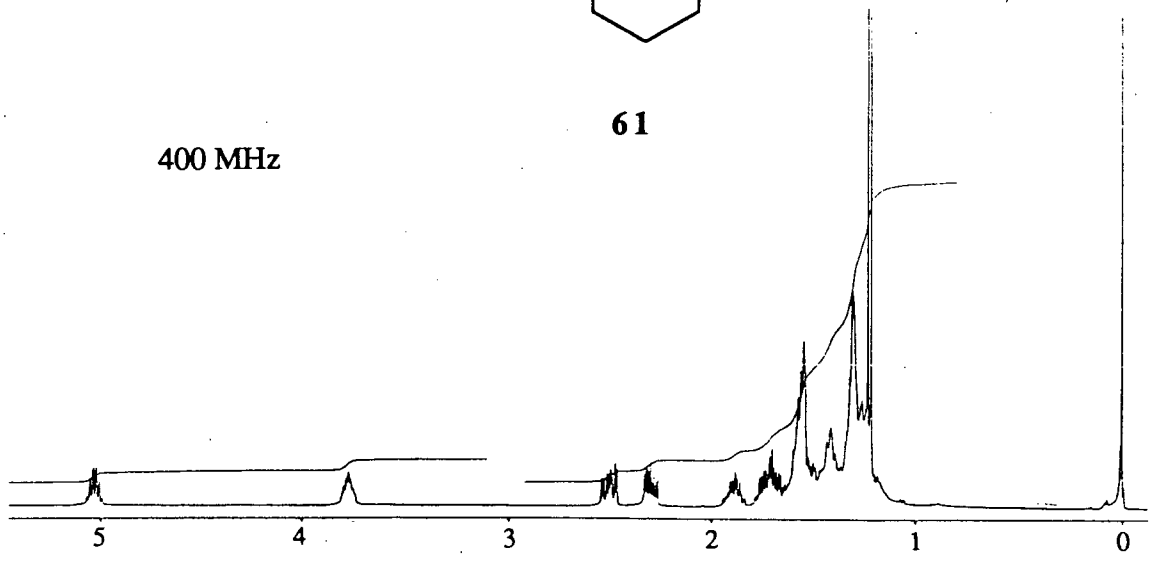
400 MHz

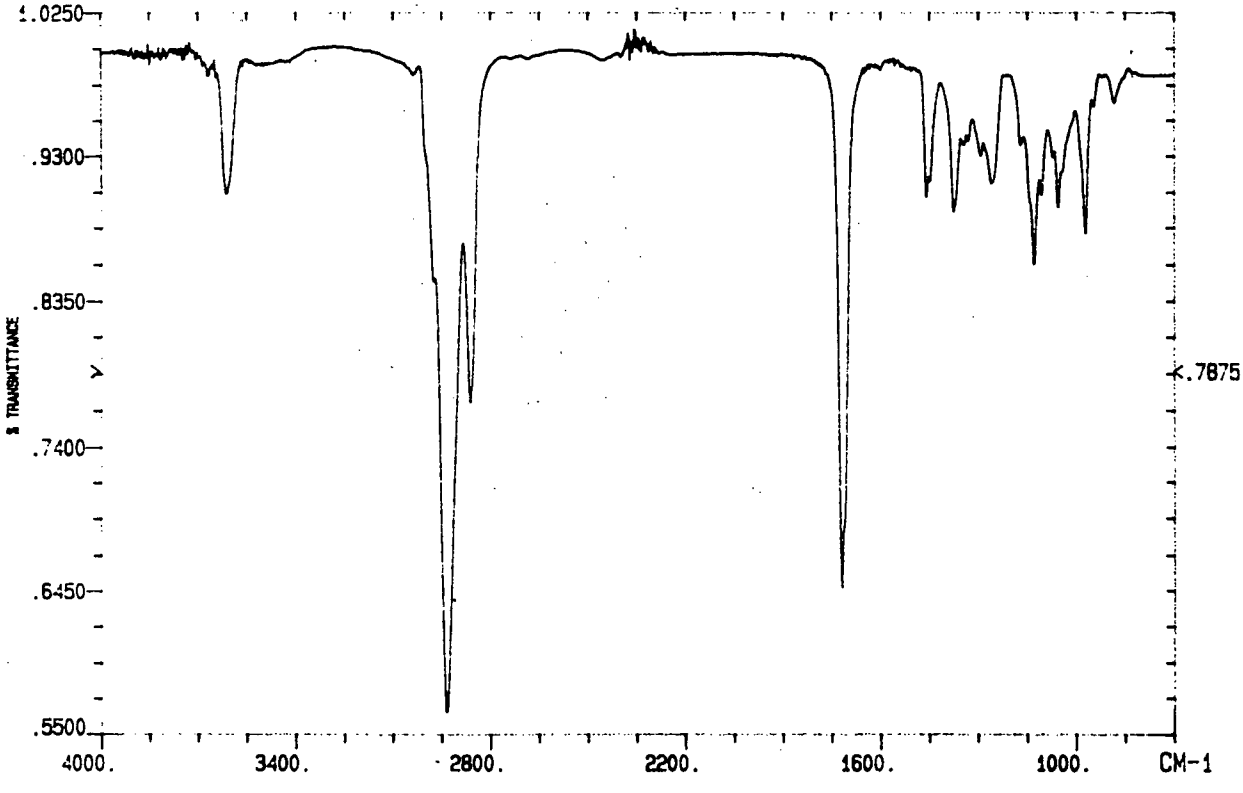

0.0676
-0.0981
-.2638
-.4295
-.5952
-.7610
% TRANSMITTANCE
<-.347
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

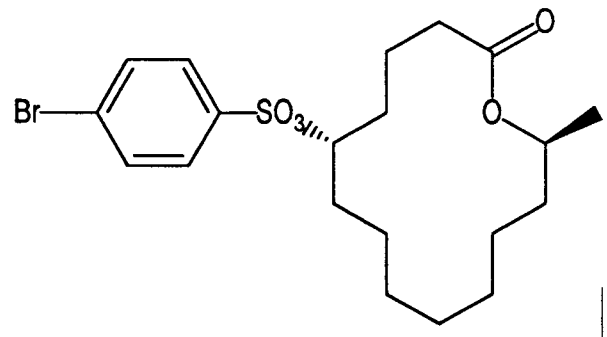

HO
O
O

61

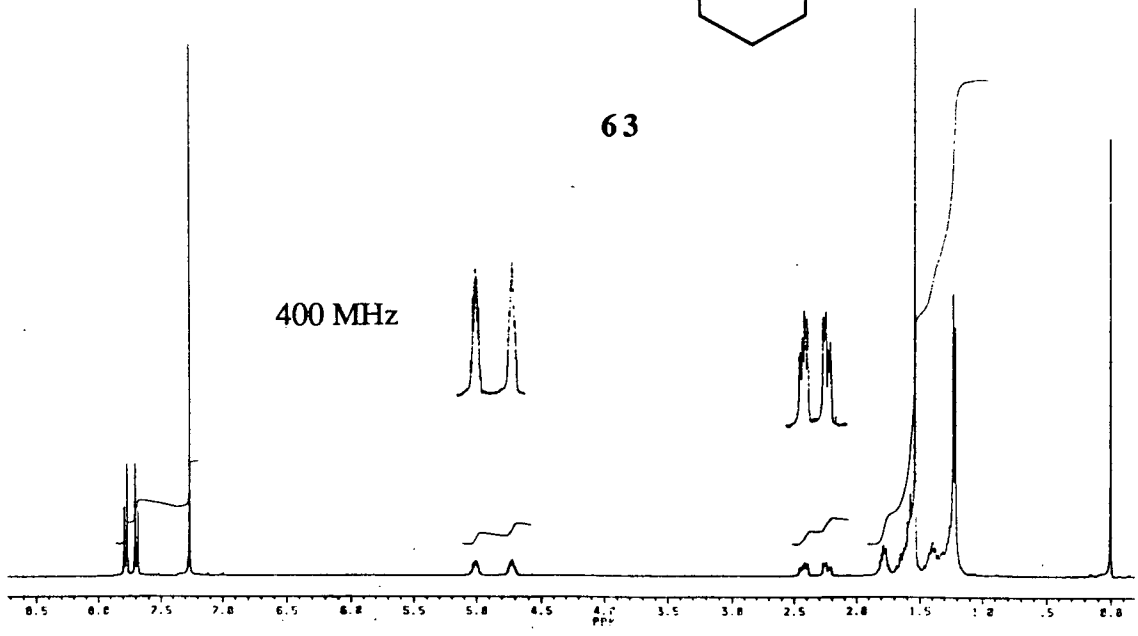
400 MHz

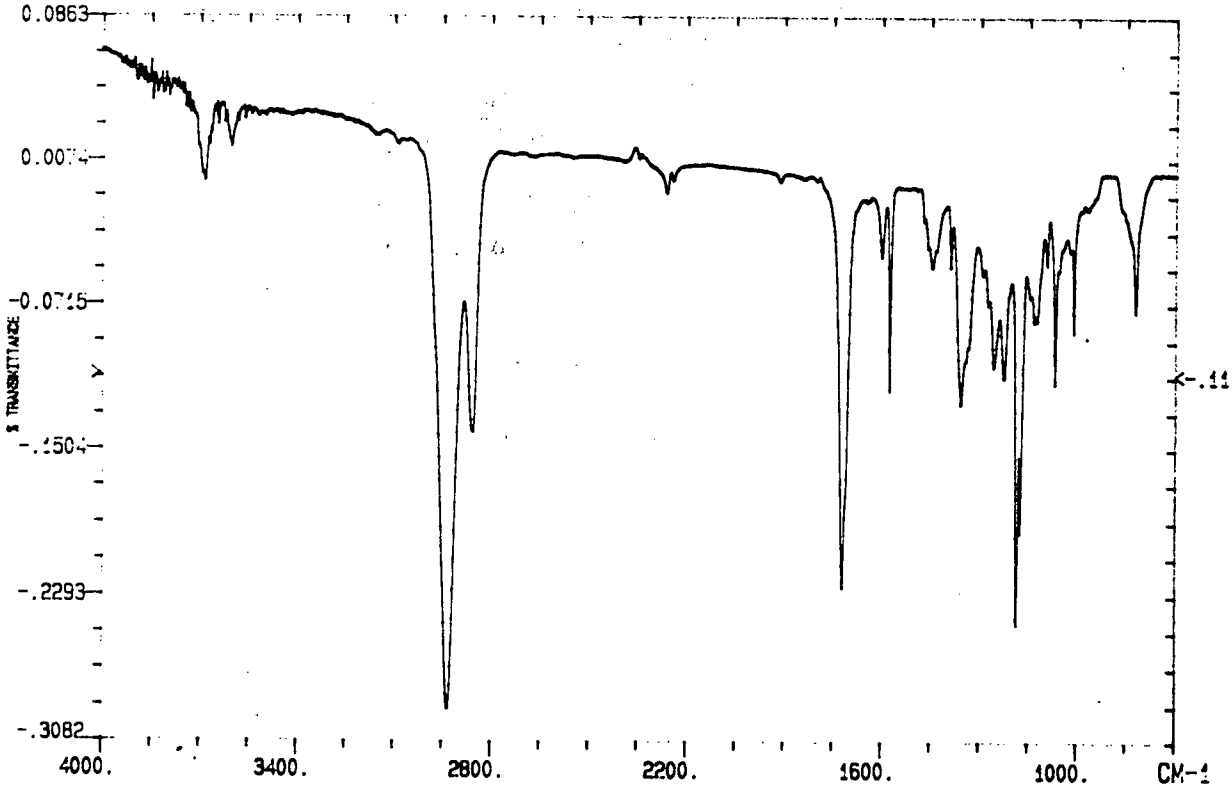

5
4
3
2
1
0

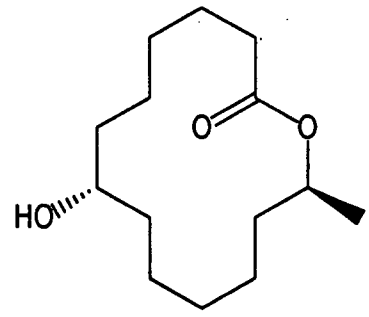

1.0250
.9300
.8350
.7400
.6450
.5500
% TRANSMITTANCE
.7875
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


Br
SO3
O
O

63

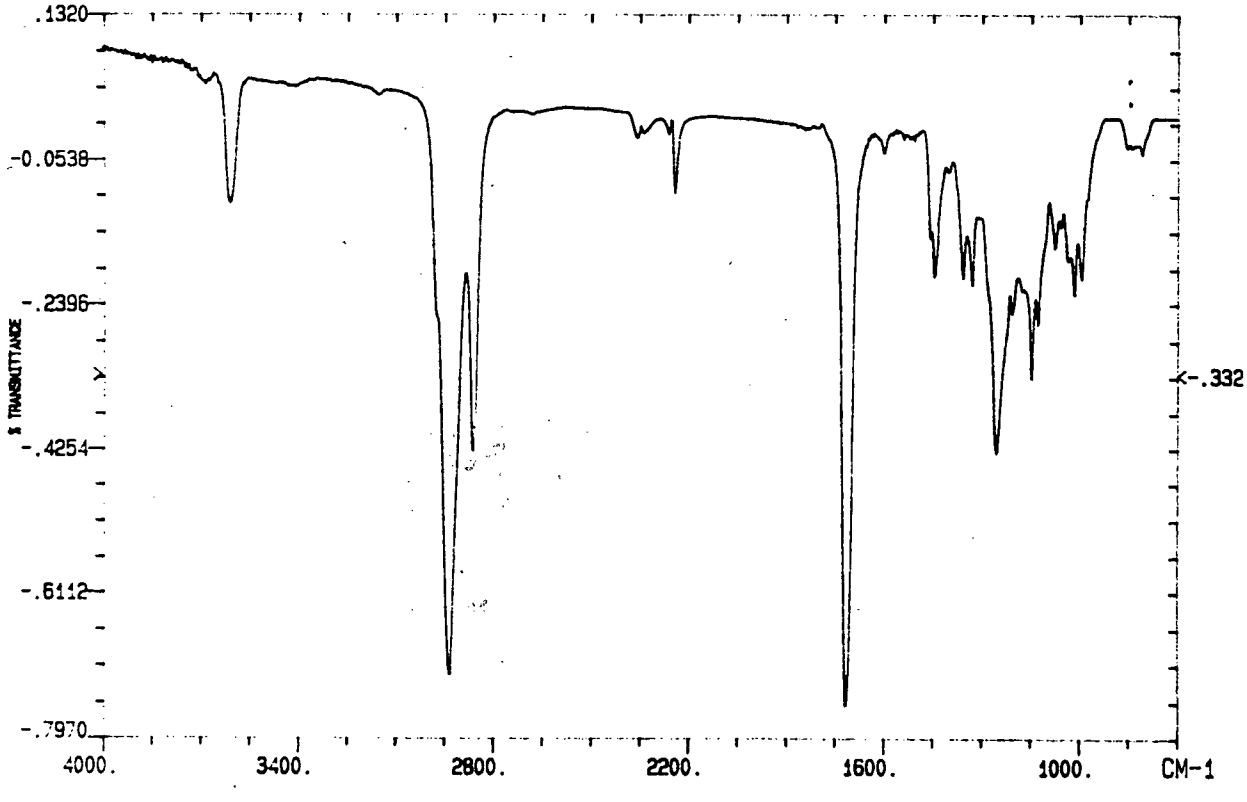

400 MHz

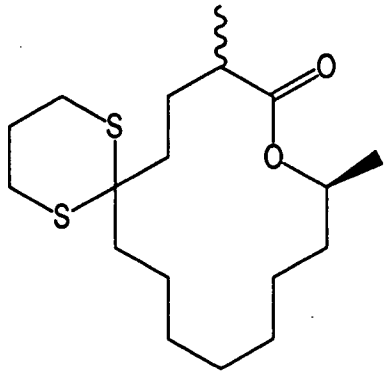

0.0863
0.0074
-0.0715
-.1504
-.2293
-.3082
% TRANSMITTANCE
-.111
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


HO
O
O

67

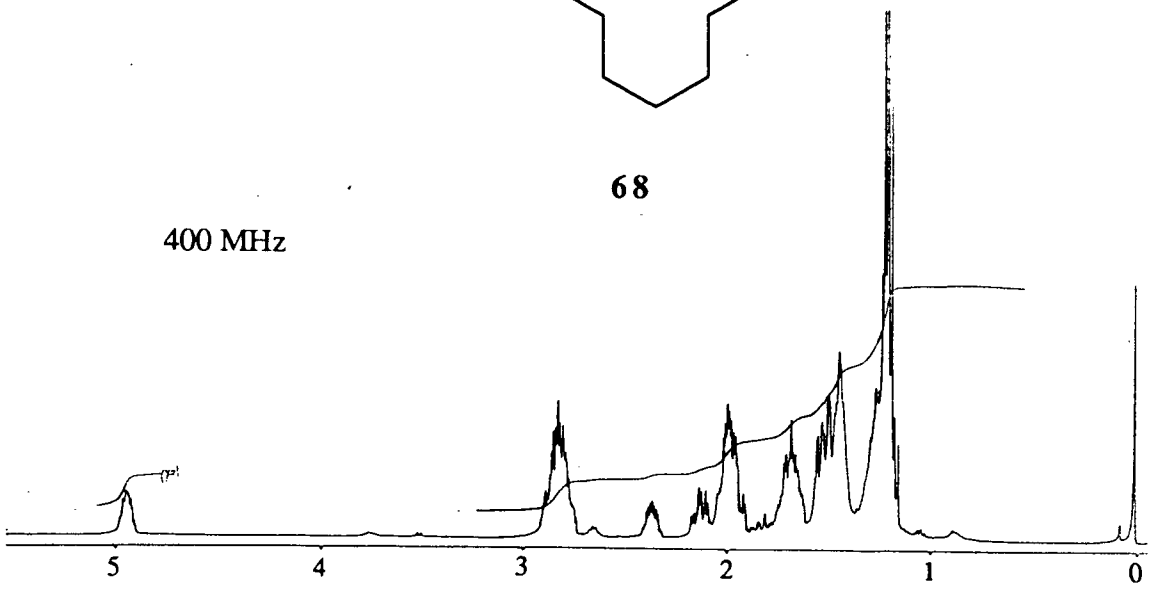
400 MHz

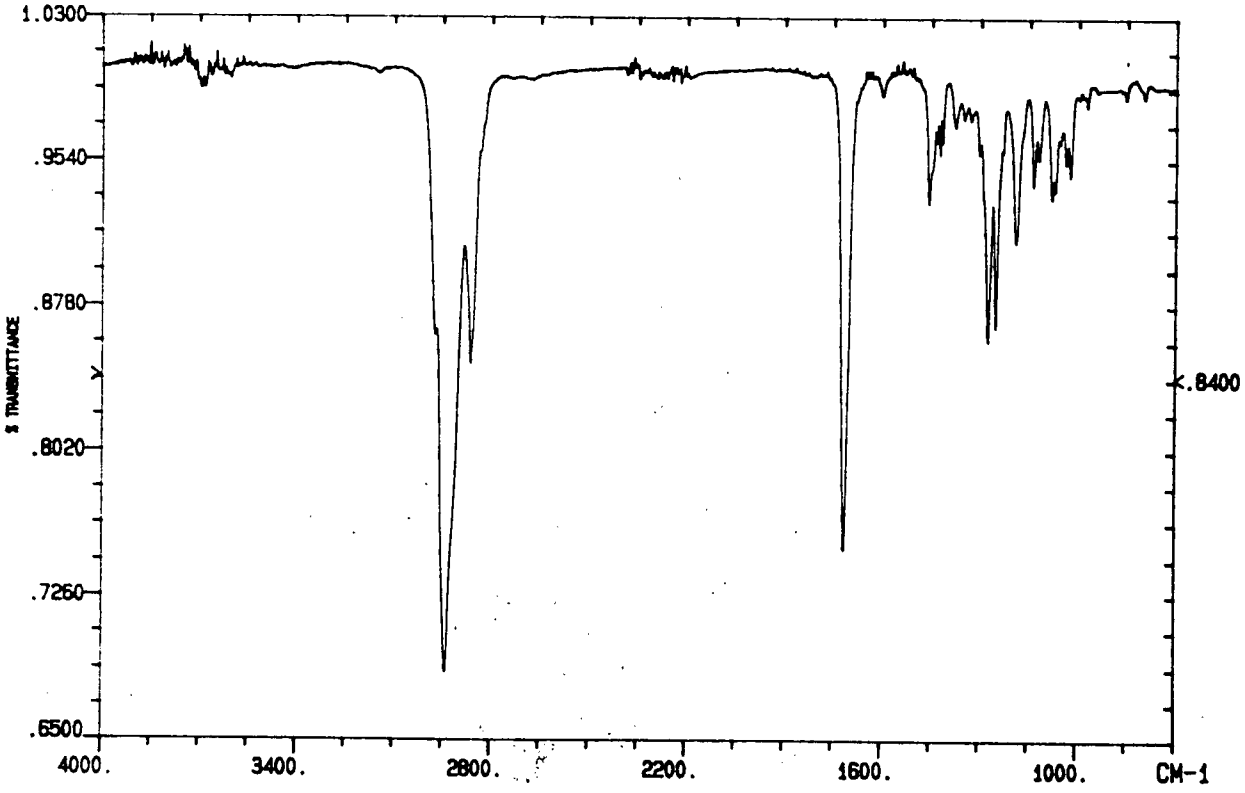

.1320
-0.0538
-.2396
-.4254
-.6112
-.7970
% TRANSMITTANCE
<-.332
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

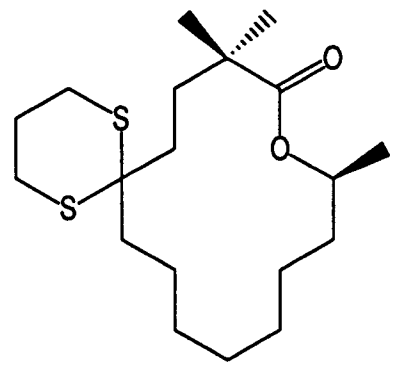

S
S
O
O

68

400 MHz


5
4
3
2
1
0

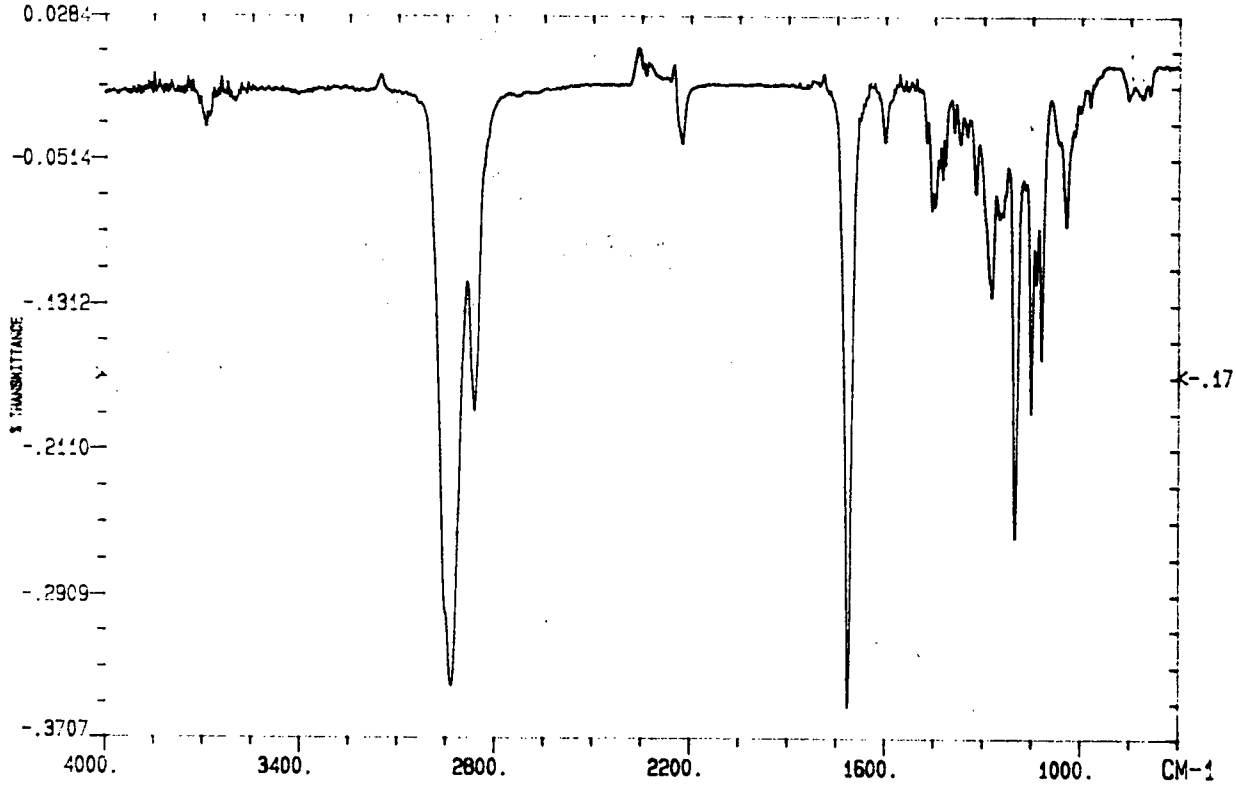

1.0300
.9540
.8780
.8020
.7260
.6500
% TRANSMITTANCE
Y
.8400
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

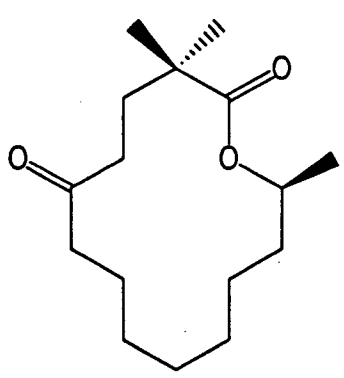

S
S
O
O

74

400 MHz

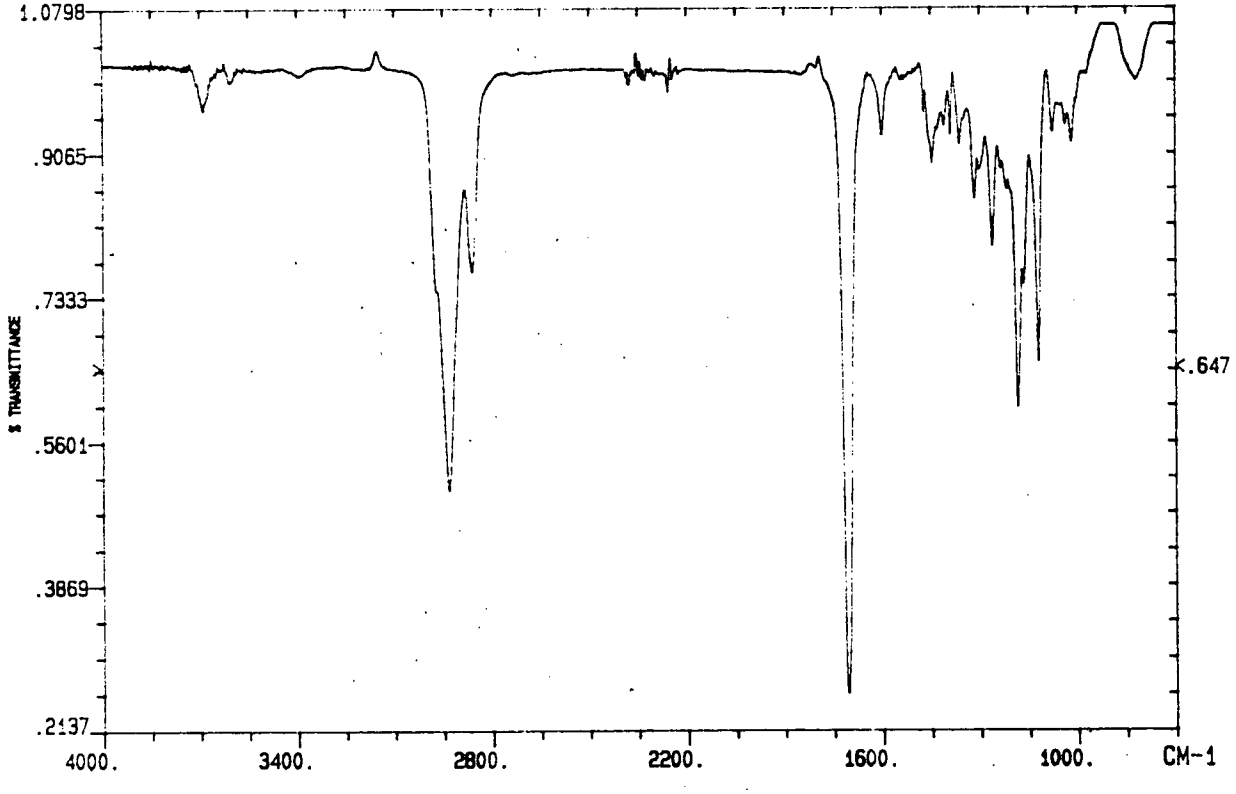
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

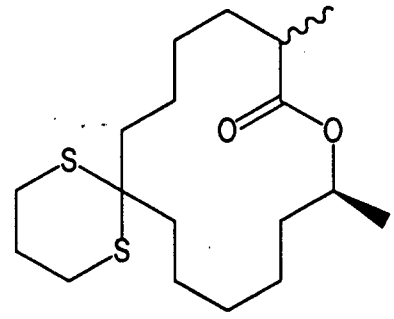

0.0284
-0.0514
-.1312
-.2110
-.2909
-.3707
% TRANSMITTANCE
-.171
4000.
3400.
2800.
2200.
1600.
1000.
CM-1



75

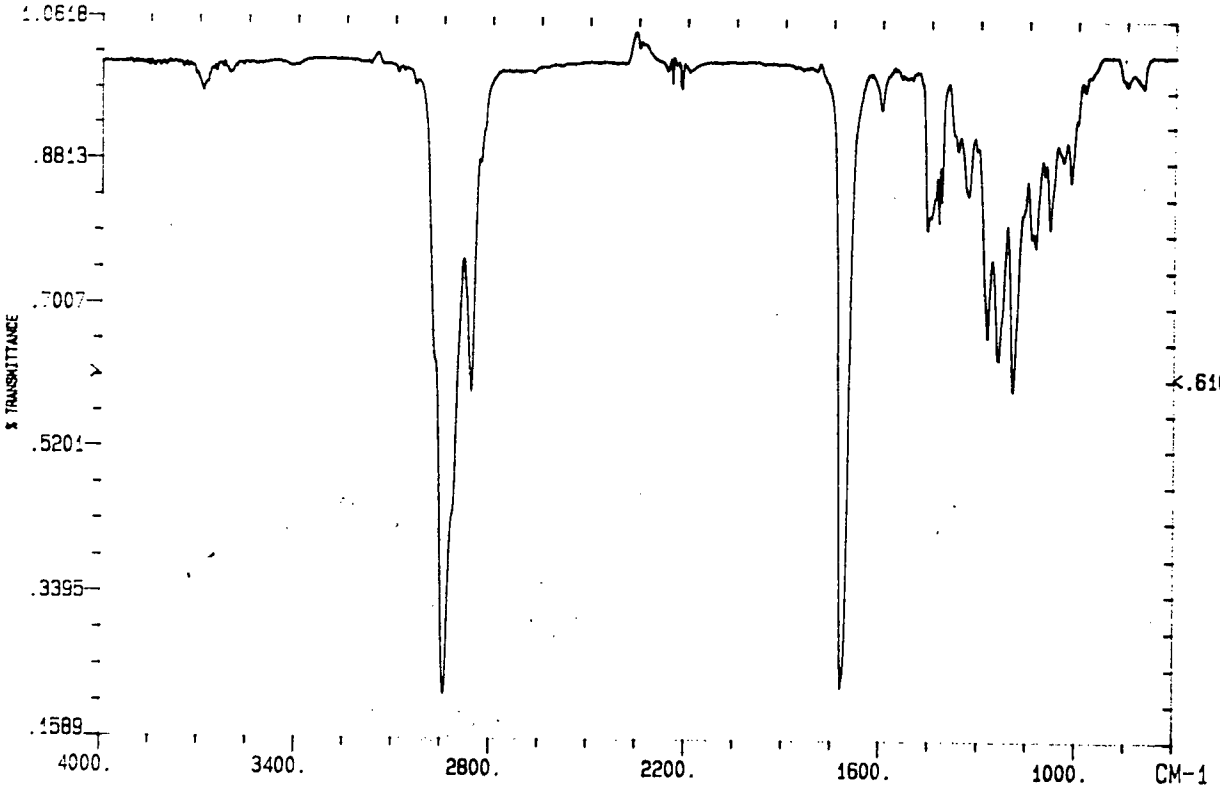
400 MHz

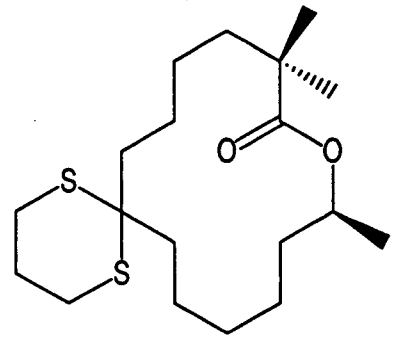

1.0798
.9065
.7333
.5601
.3869
.2137
% TRANSMITTANCE
.647
4000.
3400.
2800.
2200.
1600.
1000.
CM-1


O
O
S
S

77

400 MHz

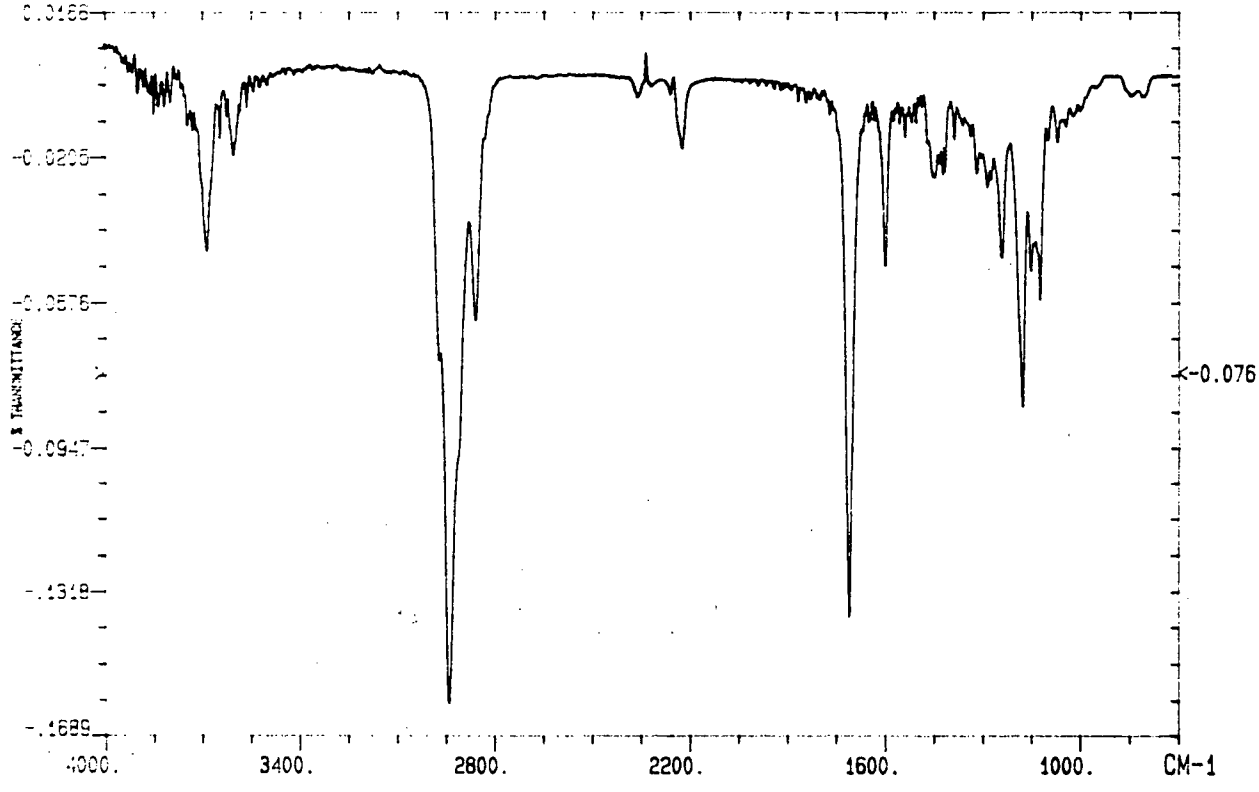

1.0618
.8813
.7007
.5201
.3395
.1589
% TRANSMITTANCE
.610
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

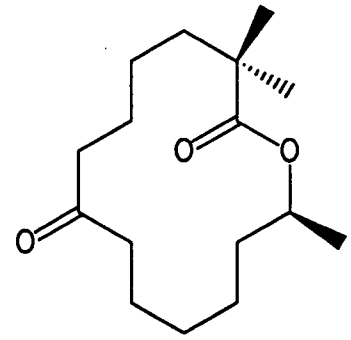

O
O
S
S

79

400 MHz

5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

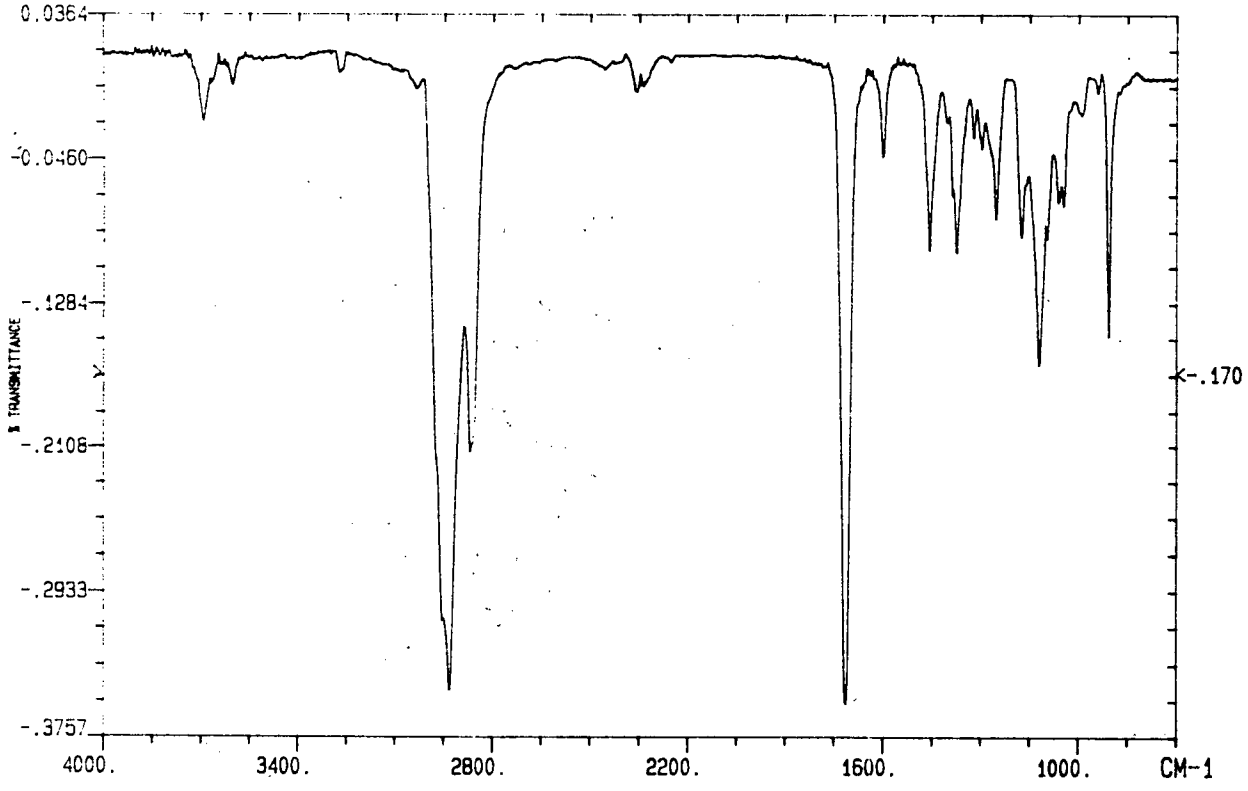

-0.0205
-0.0576
-0.0947
-.1318
-.1689
4000.
3400.
2800.
2200.
1600.
1000.
CM-1
-0.076

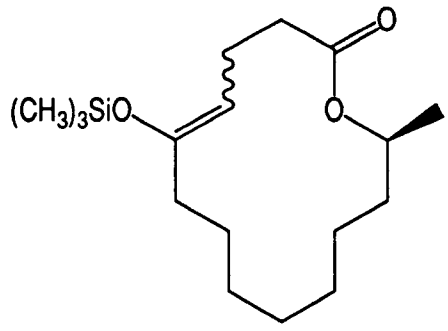


80

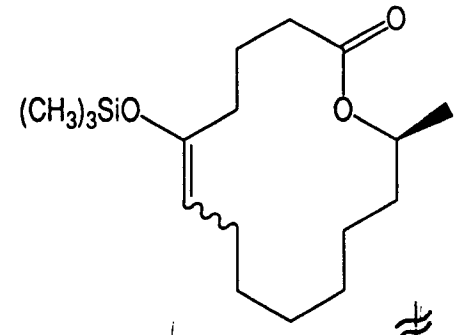
400 MHz

5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

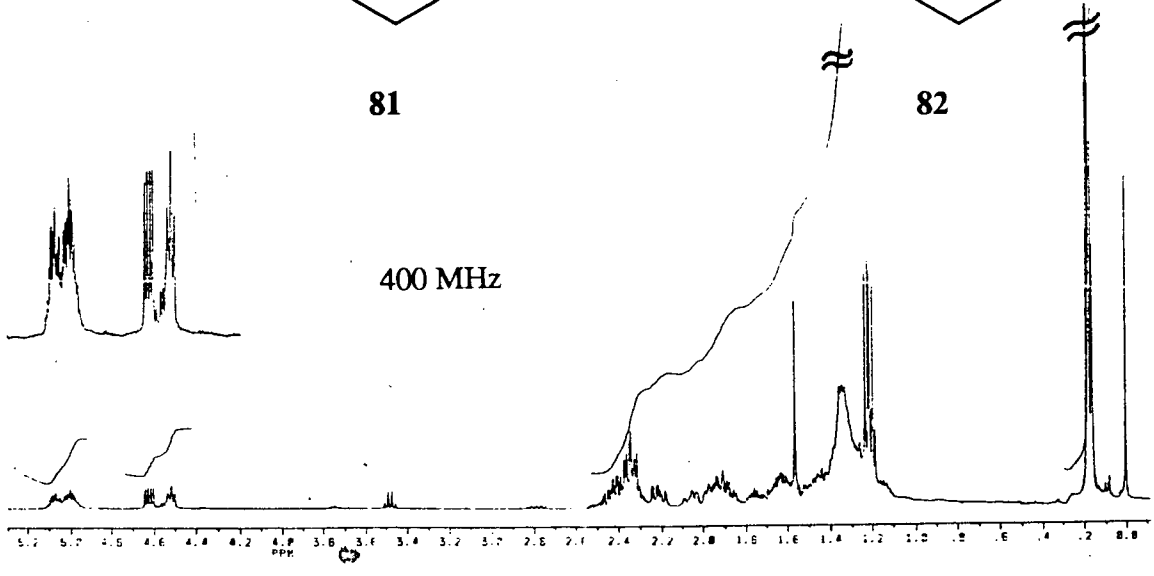

0.0364
-0.0460
-.1284
-.2108
-.2933
-.3757
% TRANSMITTANCE
Y
-.170
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

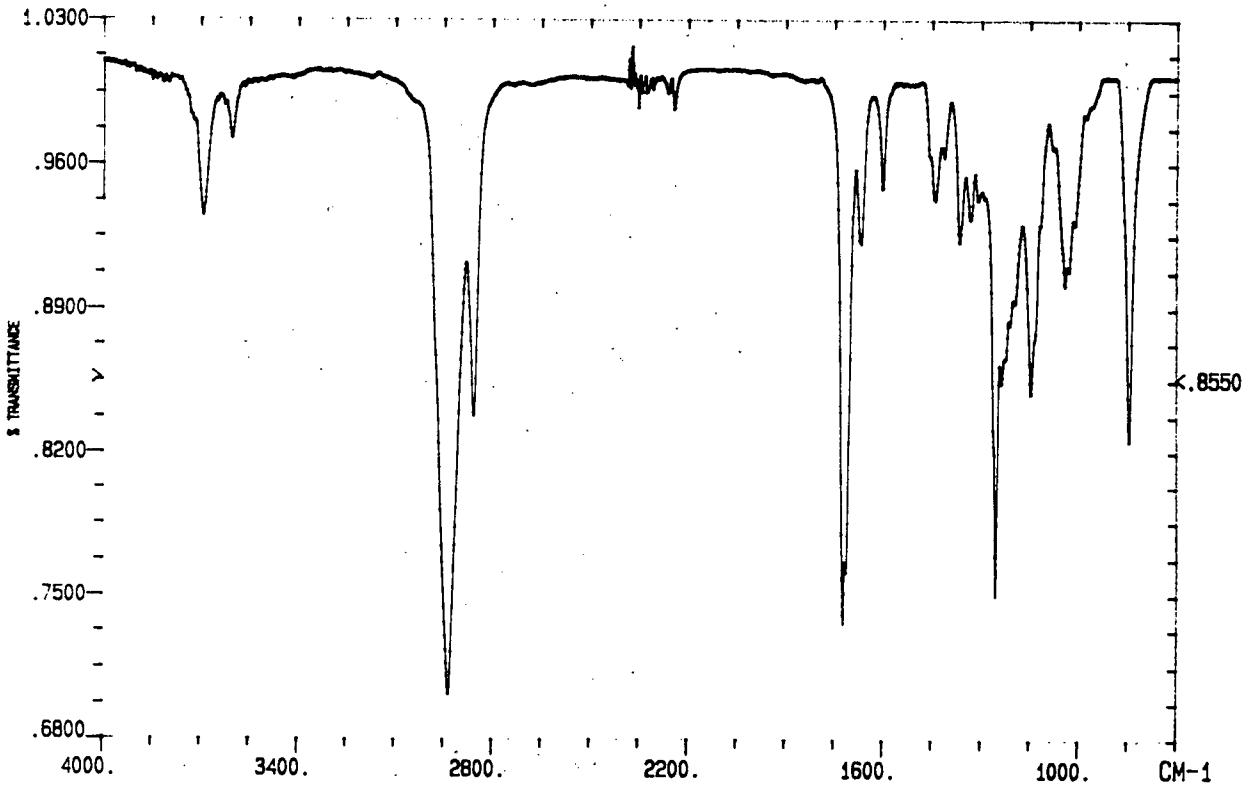

(CH3)3SiO
O
O

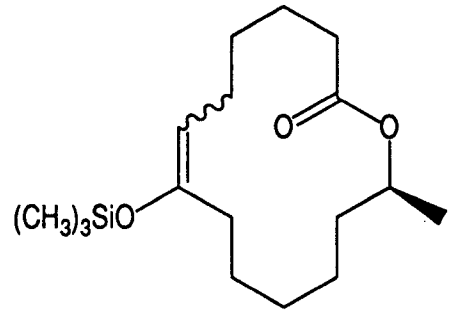
81


(CH3)3SiO
O
O

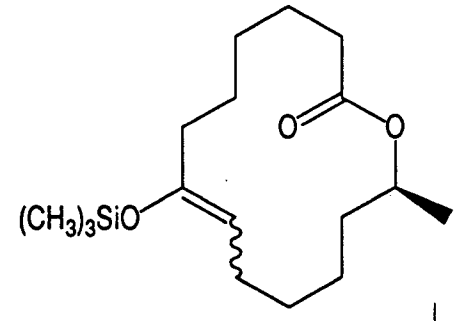
82


400 MHz

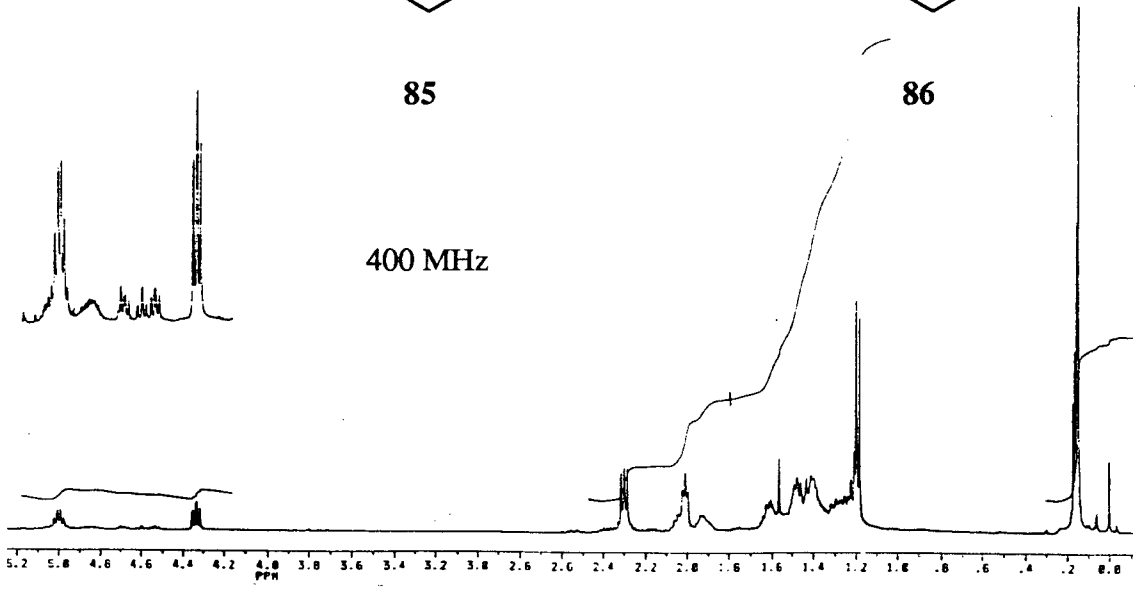

1.0300
.9600
.8900
.8200
.7500
.6800
% TRANSMITTANCE
.8550
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

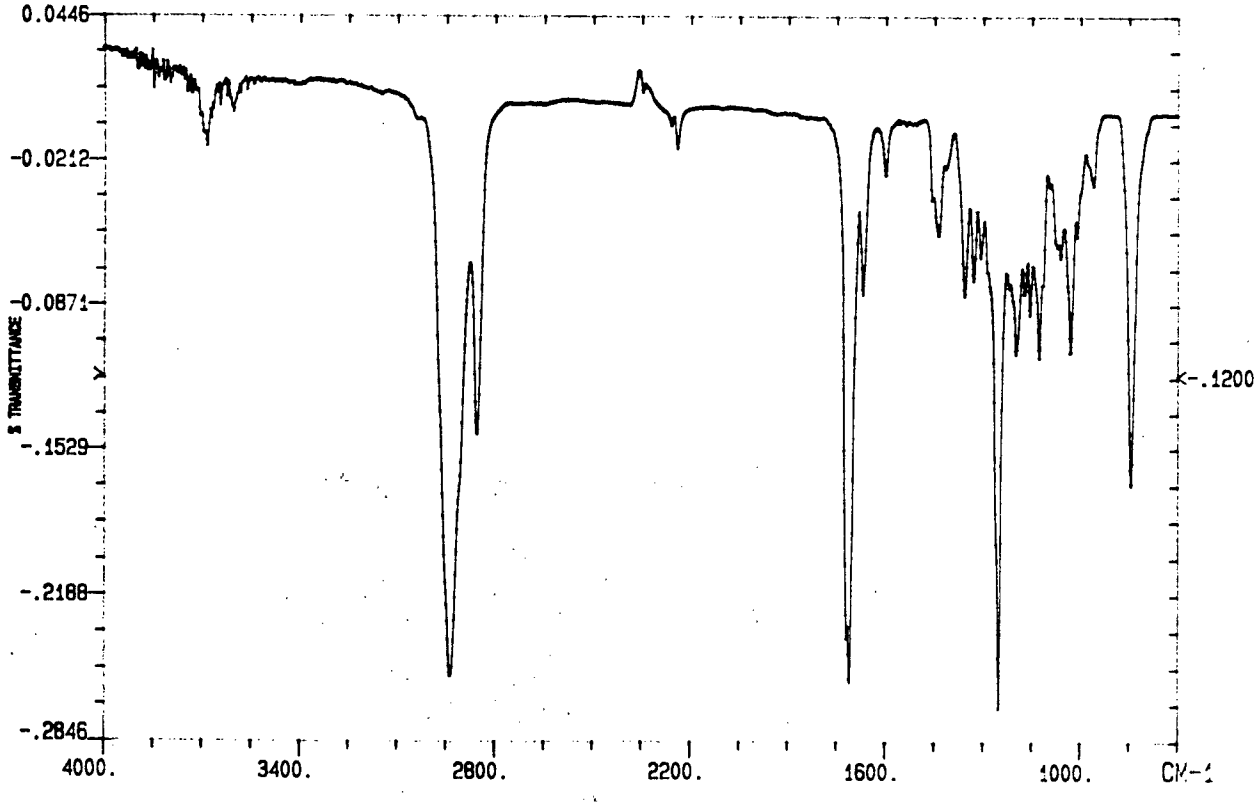

(CH3)3SiO
O
O

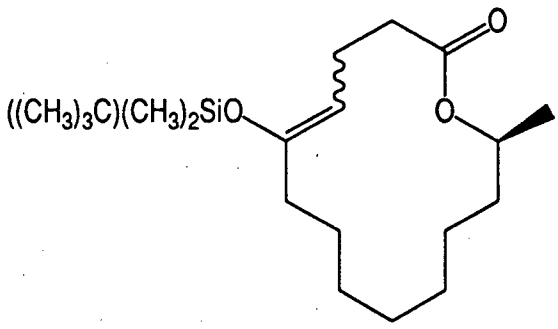
85


(CH3)3SiO
O
O

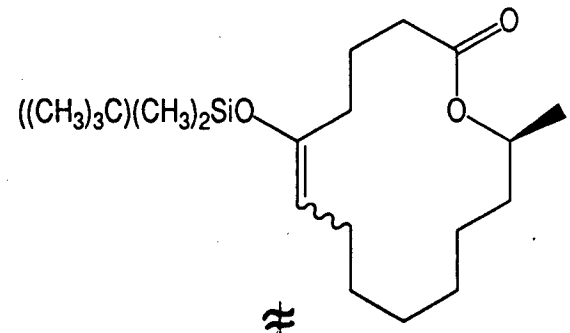
86


400 MHz
PPM

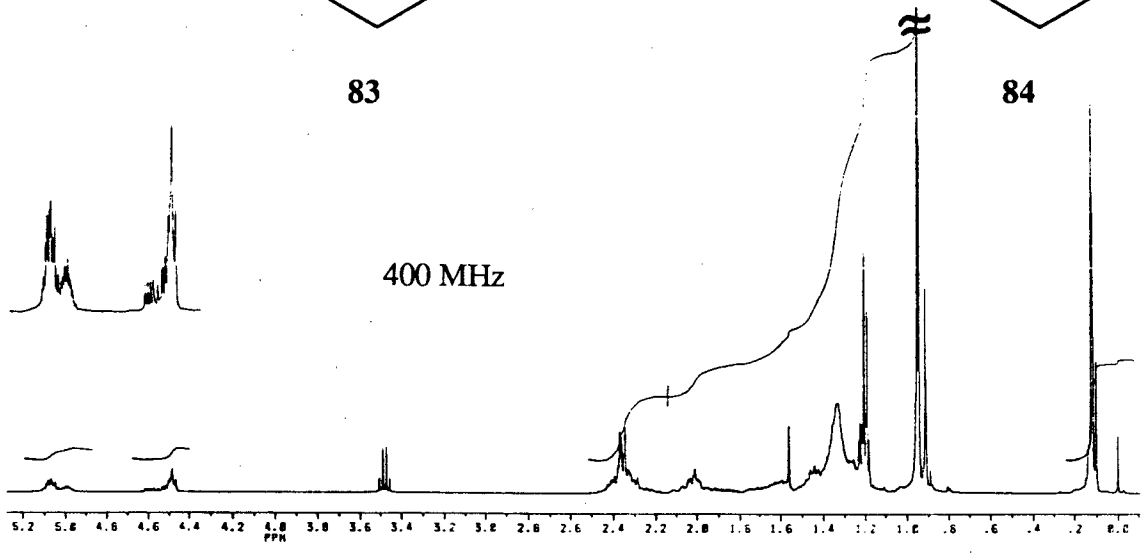

0.0446
-0.0212
-0.0871
-.1529
-.2188
-.2846
% TRANSMITTANCE
-.1200
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

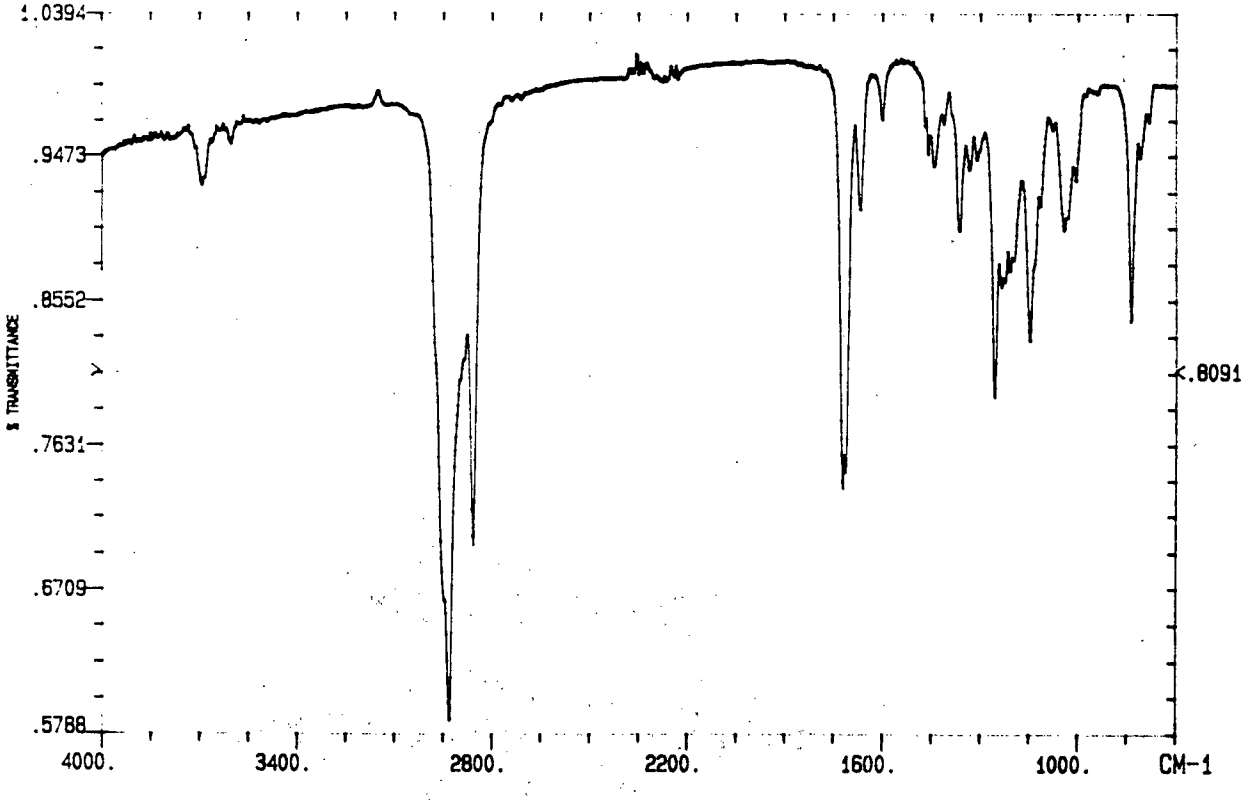

((CH3)3C)(CH3)2SiO
O
O

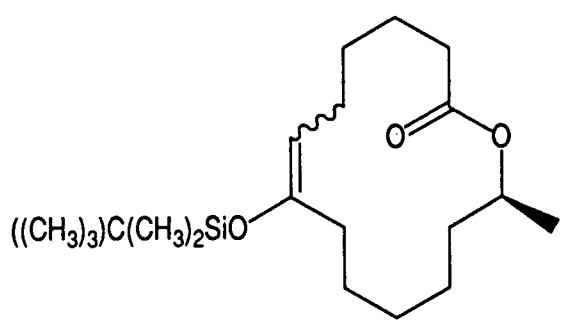
83


((CH3)3C)(CH3)2SiO
O
O

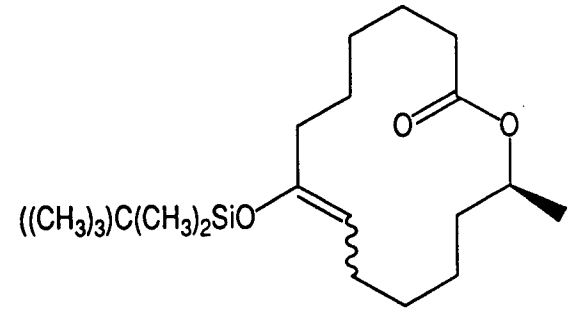
84


400 MHz
PPM

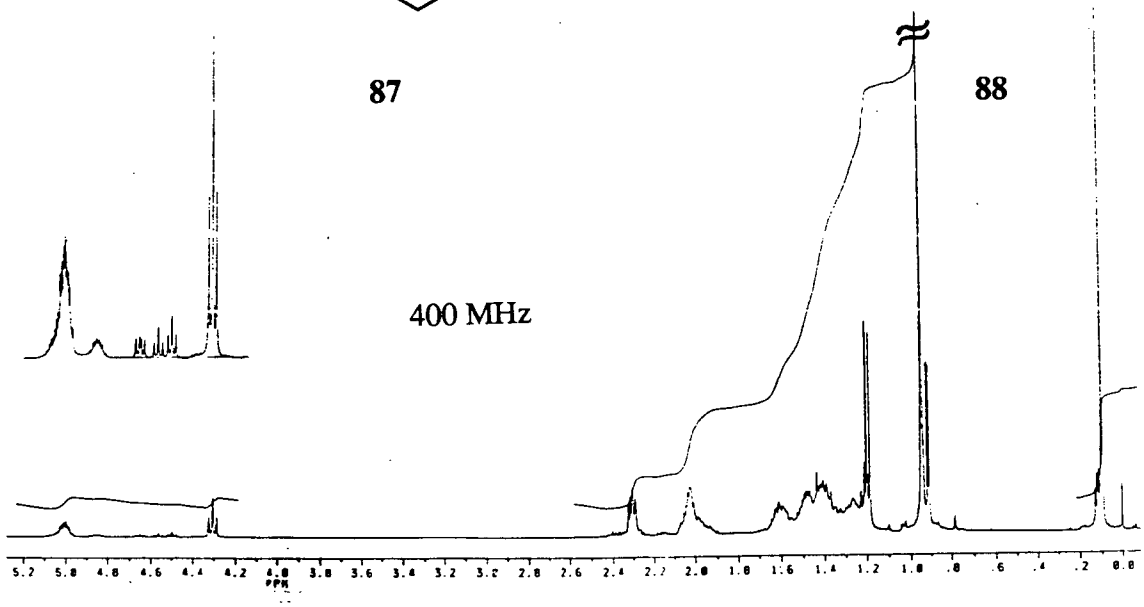

1.0394
.9473
.8552
.7631
.6709
.5788
% TRANSMITTANCE
.8091
4000.
3400.
2800.
2200.
1600.
1000.
CM-1

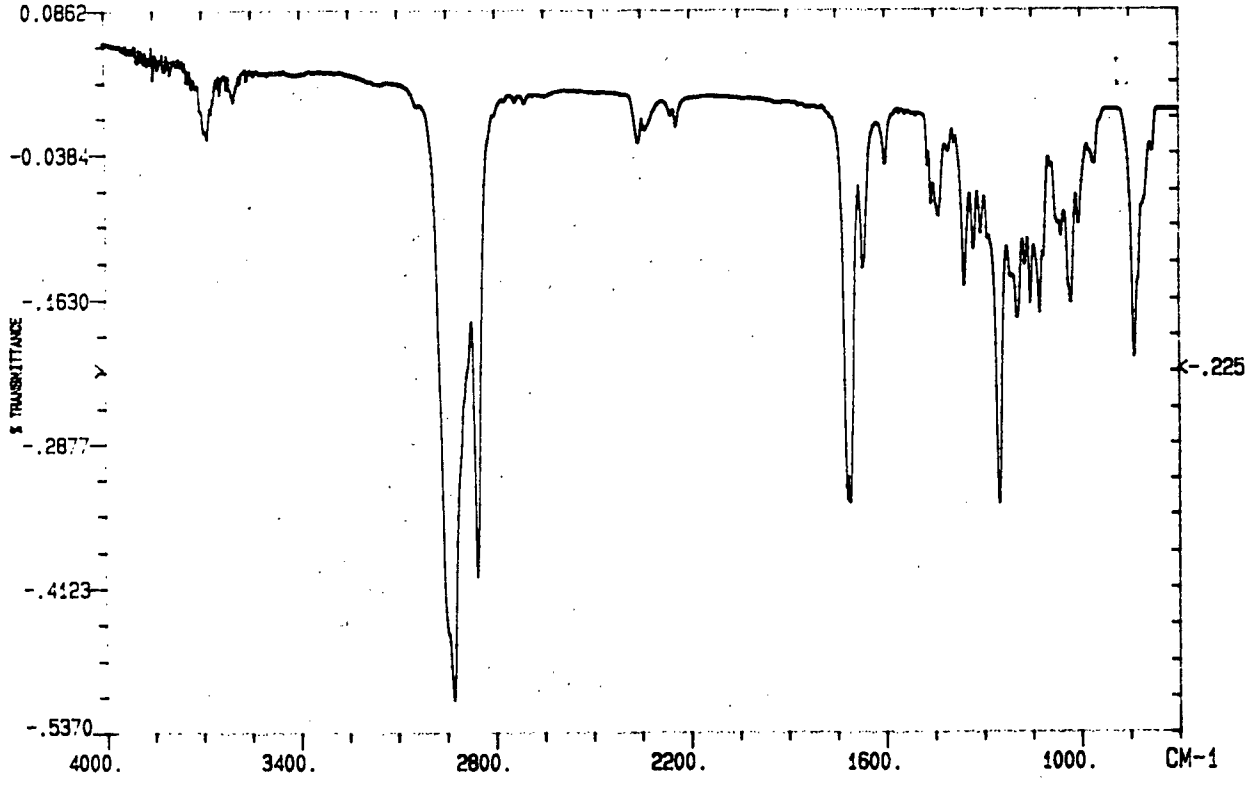

((CH3)3)C(CH3)2SiO
O
O

87


((CH3)3)C(CH3)2SiO
O
O

88


400 MHz
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 .8 .6 .4 .2 0.0
PPM


0.0862
-0.0384
-.1630
-.2877
-.4123
-.5370
% TRANSMITTANCE
-.225
4000.
3400.
2800.
2200.
1600.
1000.
CM-1