SYNTHESIS AND REACTIONS OF UNSATURATED
14-MEMBERED LACTONES

by

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Date ___02-10-91___

ABSTRACT

Via a lactonization of the open chain hydroxy acid, the 14-membered unsaturated lactones **14** and **15** were synthesised. Treatment of these two lactones with borane dimethylsulphide, disiamyl borane and 9BBN led to formationof hydroxy lactones **30, 31, 32** and **33**. The structures of **31** and **32** were determined by comparison with known compounds whereas structures **30** and **33** were deduced by considering the transition structures of the hydroboration reaction. Although both the regio and the stereoselectivity of the reactions were poor the π-face selectivity was high. Product distributions were estimated by the conformational control induced by the ring, using Houk's parameters for the hydroboration transition structures, in an MM2 force field, to calculate their relative strain energies.
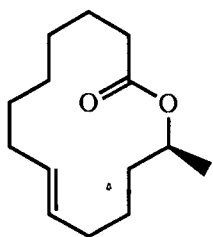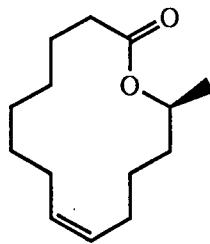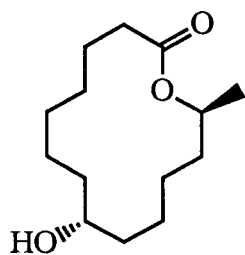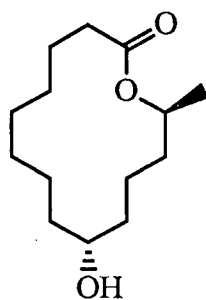
14   **15**

30   **31**   **32**   **33**

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LIST OF ABBREVIATIONS

Ac	acetyl
9BBN	9-borabicyclo[3.3.1]nonane
calcd	calculated
CD	circular dichroism
d	doublet
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulphoxide
Et	ethyl
eV	electron volts
FT	fourier transform
GC	gas chromatography
IR	infrared
J	coupling constant
LAH	lithium aluminium hydride
LRMS	low resolution mass spectroscopy
M	molar
m	multiplet
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MM	molecular mechanics
Ms	mesyl
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
PPL	porcine pancreatic lipase
qn	quintet

Ra-Ni	Raney nickel
s	singlet
Sia_2BH	disiamylborane
t	triplet
TBDMS	*tert*-butyldimethylsilyl
tert	tertiary
THF	tetrahydrofuran
TMS	trimethylsilyl

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To my parents

CHAPTER I

Introduction

The chemistry of macrocyclic compounds began in 1926 with the isolation and structural elucidation of the musk components, civetone **1** and muscone **2**, by Ruzicka.[1] This discovery revealed the inadequacies of the Baeyer strain theory[2] which had predicted that large ring compounds would be too unstable to exist, due to overextension of internal bond angles. Perhaps more important were the ensuing efforts to discover synthetic routes to these, and related compounds. A challenge which, with the further isolation of naturally occuring macrocyclic compounds, continues to attract the attention of chemists today.
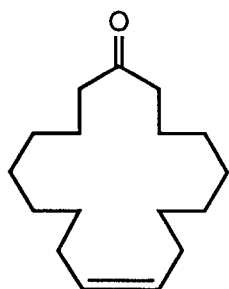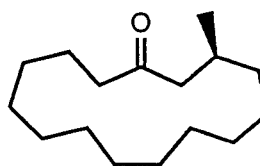
1   **2**

1.1   THE CONFORMATION OF MANY-MEMBERED RINGS.

Ruzicka's work on macrocyclic compounds embodied two specific aims, those being the synthesis of the highly prized musk-like perfumes and the study of the physical and chemical properties of large ring compounds.

Using the acyloin condensation[3] as a basis, Ruzicka et al.[4] and Prelog[5] synthesized and investigated the properties of medium and large ring hydrocarbons, alcohols and ketones. Surprisingly they found that the physical and chemical properties of these macrocyclic compounds had an unexpected dependence on ring size.

In 1961 Duntiz and co-workers' demonstration,[6] by X-ray diffraction, of a unique conformation (Figure 1) of the ten-membered ring skeleton in several cyclodecane derivatives led to an understanding of the conformational effects controlling these phenomena. From his observations Dunitz concluded that this conformation must correspond to a potential energy minimum for this ring skeleton.
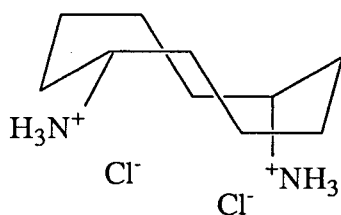
Figure 1. The formation of *cis*-1,6-diaminocyclodecane dihydrochloride.[6]

Two years later Dale[7] pointed out that the aforementioned solid state conformations closely resembled the diamond lattice - a network of ideal carbon-carbon bond lengths and bond angles. It follows that any conformation which can be superimposed on the diamond lattice must possess a minimum in angular and torsional strain. By using molecular models Dale was able to predict low energy conformations for all even membered cycloalkanes

from C_6 to C_{16} (Figure 2).[7] Subsequent theoretical calculations and X-ray crystallography have shown these predictions to be very accurate.[8]

$(CH_2)_6$ $(CH_2)_8$ $(CH_2)_{10}$

$(CH_2)_{12}$ $(CH_2)_{14}$

$(CH_2)_{16}$
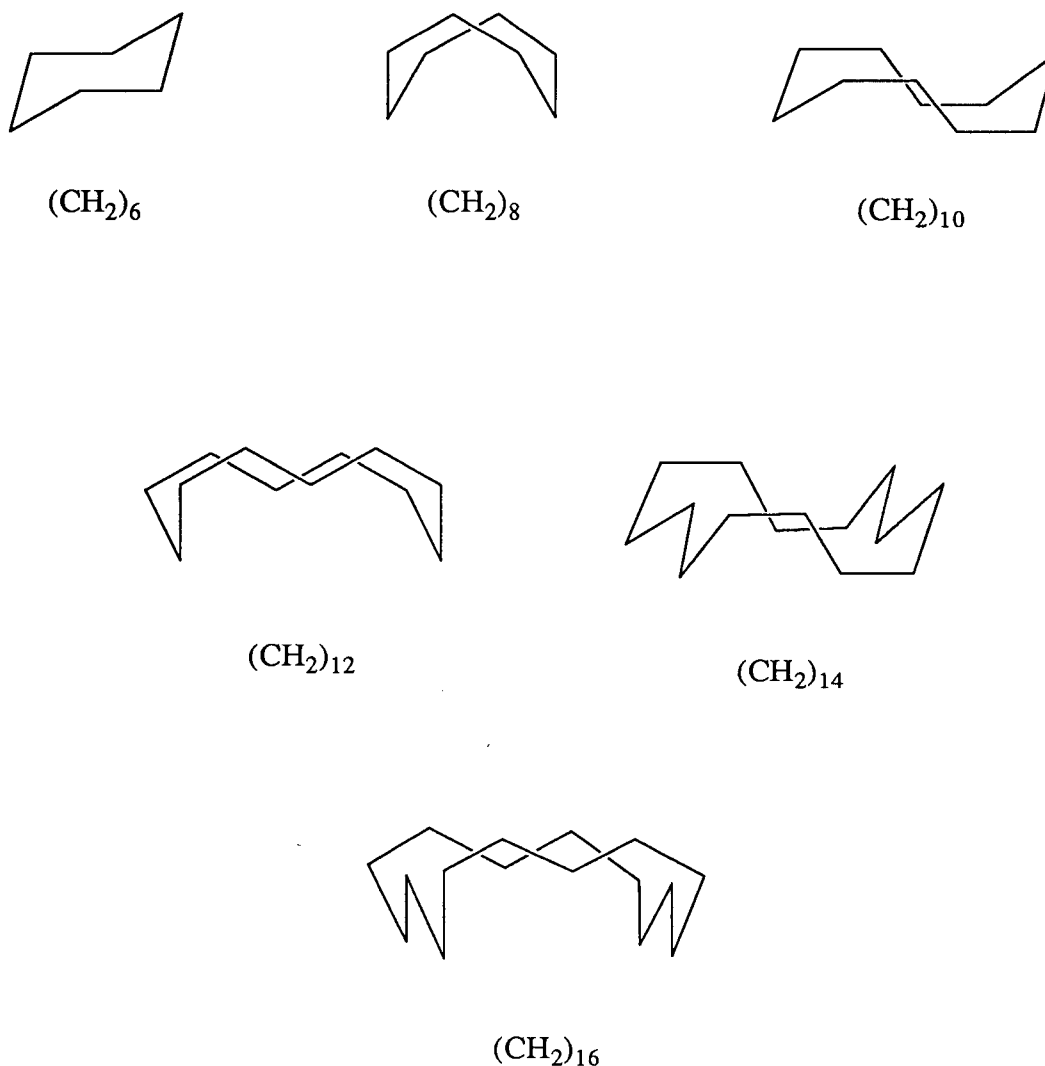
Figure 2. Low energy conformations of even membered cycloalkanes C_6 to C_{16}.[7]

A typical feature of these macrocyclic conformations is that each contains four "corners." Dale realised that these corner positions are unique in that they can always carry two substituents without causing severe transannular interactions (Figure 3) and he defined

a corner atom as having two adjoining gauche dihedral angles of the same sign flanked on either side by an anti dihedral angle.[8]

number of
internal
hydrogen
interactions

−◯ : 1

−⊘ : 2

−● : 3
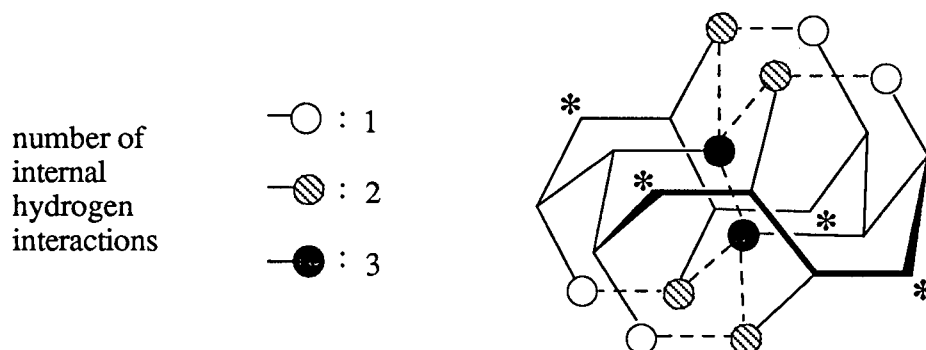
Figure 3. Corner positions (shown with an asterisk) in the strain free conformation of cyclotetradecane.

From this definition of corner atoms Dale also devised a system of nomenclature for macrocyclic compounds.[9] Using a shorthand notation the ring is represented as a series of numbers in brackets (Figure 4), each number indicating the bonds between each corner atom. The ring is named such that the smallest number is listed first within the brackets.
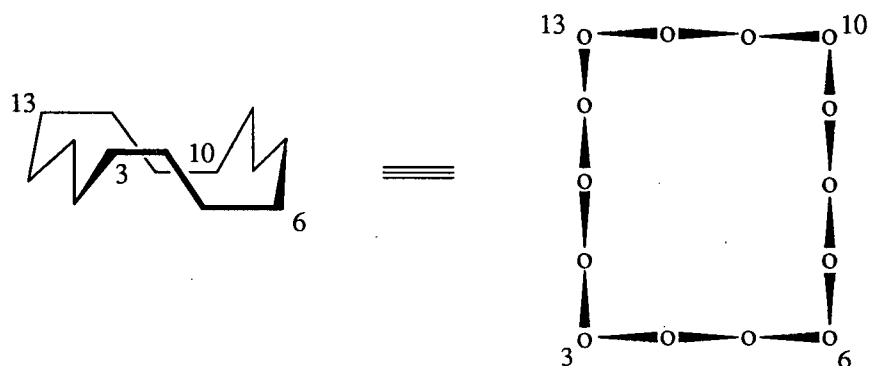
Figure 4. [3434] conformation of cyclotetradecane.[9]

Dale's initial work on conformational analysis was carried out on a semi-quantitative scale using modified Dreiding models.[9] However, with the use of molecular mechanics calculations, demonstrated by Anet and Cheng[10a] to be applicable to large rings, Dale discovered two other low energy conformations of cyclotetradecane that were non-superimposable on the diamond lattice.[10b] These were designated the [3344] and [3335] conformations (Figure 5) and were calculated to have strain energies of 1.1 kcal/mol and 2.4 kcal/mol respectively, relative to the [3434] conformation.
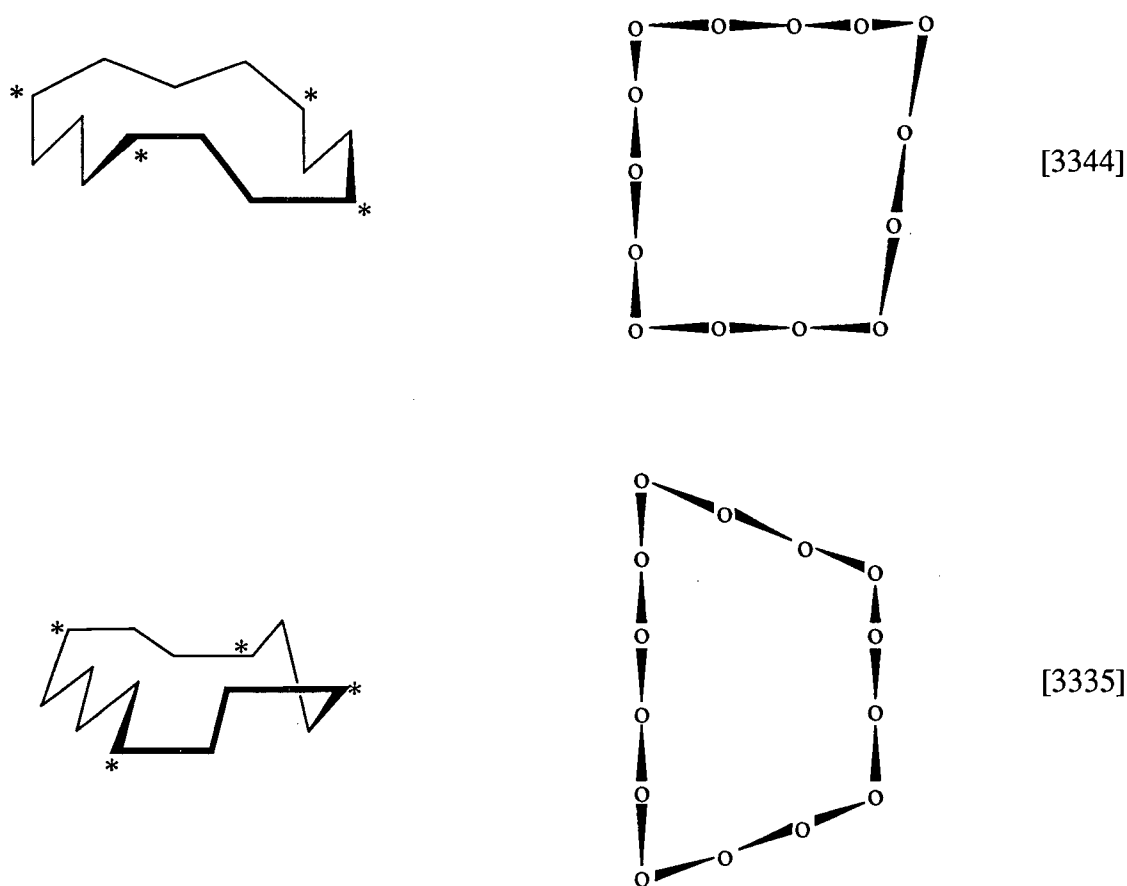
[3344]

[3335]

Figure 5. The [3344] and [3335] conformations of cyclotetradecane (* = corner position).[10b]

1.2 THE CONFORMATION OF UNSATURATED MACROCYCLES.

The introduction of a double bond into a cycloalkane makes strain-free conformations based on the diamond lattice impossible for any ring size and it has been shown that nearly all known cycloalkenes are liquids, reflecting their conformational flexibility.[7] Although there is a lack of molecular mechanics data on cycloalkenes, a good indication of the relative strain in a cycloalkene compared to the corresponding cycloalkane, and also the relative stabilities of cis and trans isomers, is gained from their heats of hydrogenation.[11] The evidence tends to suggest that the trans-olefin is more strained than its cis-isomer in the medium ring systems but, as ring size increases to twelve and further, the relative stabilities are reversed. These enthalpy differences are in good agreement with values obtained by equilibration of medium size cycloalkenes.[12]

1.3 MACROLIDES

The chemistry of large ring compounds experienced another leap forward in 1950 when Brockmann et al. isolated the first macrolide antibiotic, pikromycin (3), from an Actinomyces culture.[13] Soon afterward Streptomyces organisms yielded several other antibiotics which appeared to be chemically and anti-microbially related to pikromycin. The family of macrolides has expanded to more than one hundred physiologically active metabolites of which approximately half are subgrouped as polyoxo-macrolides.
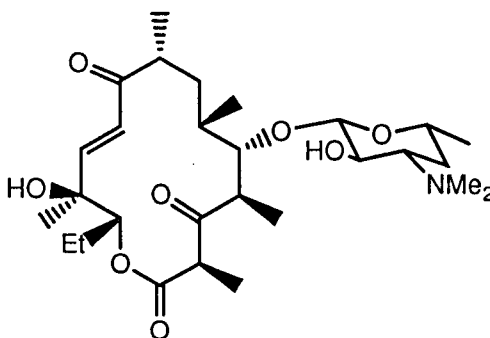
3

The polyoxo-macrolides are characterized structurally by a 12, 14 or 16 membered lactone ring with one or more deoxy-sugars attached and up to 12 asymmetric centres incorporated into the aglycone.

The complexity of conformational possibilities for these macrolides has aroused a great deal of interest. In 1965 Celmer[14] proposed a model for a preferred conformer of erythronolide B (Figure 6) based on the [3434] conformation of cyclotetradecane.[9]
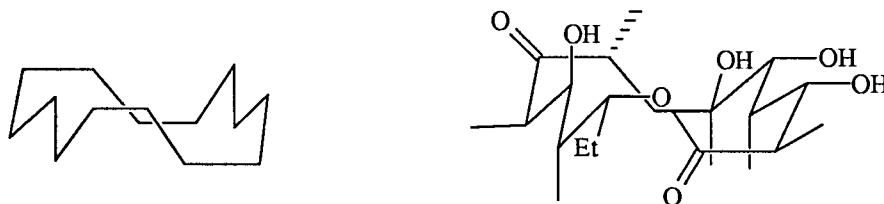
Figure 6. Celmer model for erythronolide B.[14]

Although the ^{1}H NMR data was in reasonable agreement with this model, earlier X-ray analysis[15a] and CD studies[15b] were in conflict. A later model (Figure 7) proposed by Perun,[15b] appeared to accommodate quite well with the ^{1}H NMR data as well as eliminating, at the same time, the unfavourable 1,3 interaction between the C_4 and C_6 methyl groups.
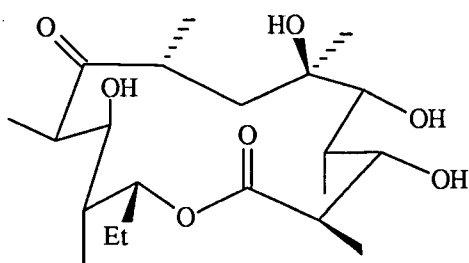
Figure 7. Perun model for erythronolide B.[15b]

Further work in this field has been carried out by Ogura et al.[16] leading to new diamond-lattice conformations of kromycin and oleandomycin (Figure 8).
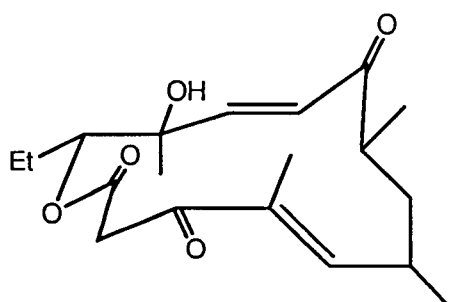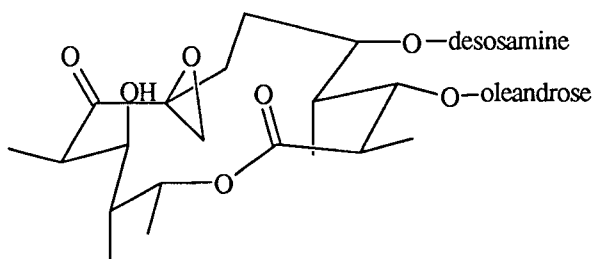
kromycin   oleandomycin

Figure 8. Ogura models for kromycin and oleandomycin.[16]

1.4 SYNTHESIS OF MACROCYCLIC LACTONES

Although many methods exist for the synthesis of macrolides[17] by far the most general and commonly used method is lactonization of a long chain hydroxy acid. For this reason it will be the only example discussed.

The macrolactonization process depends upon carboxyl and/or hydroxyl activation techniques to overcome unfavourable entropic factors and competing polymerisation processes. The Corey-Nicolau method[18] employs 2-pyridylthiol and relies upon a double activation sequence (Scheme 1) to form the lactone.
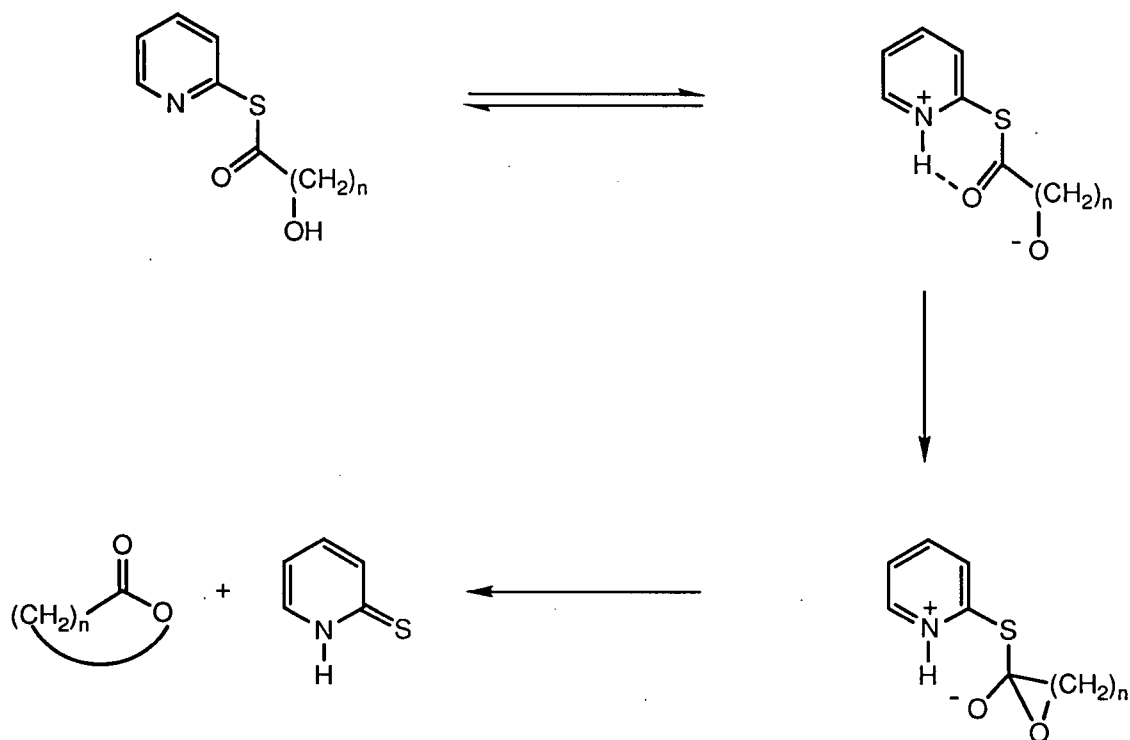
Scheme 1. Corey-Nicolau double activation sequence to form macrolides.[18]

A modification of Corey's procedure was developed by Dietsche and Schmidt[19] using 1-phenyl-2-tetrazoline-5-thione and *tert*-butyl isocyanide as the activating agents (Scheme 2).
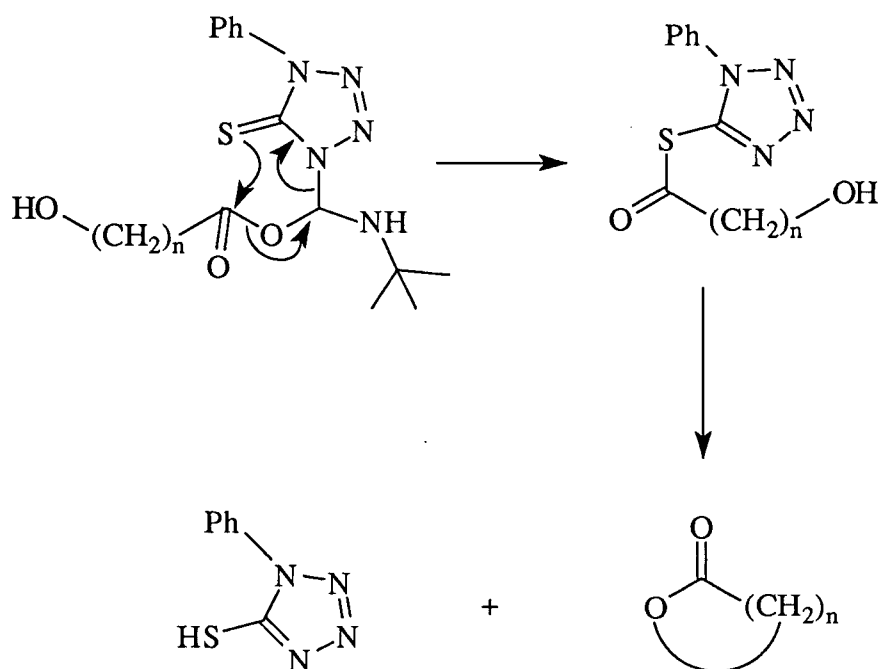
Scheme 2. Dietsche-Schmidt modification of Corey-Nicolau macrolactonization.[19]

A more traditional approach was advanced by Yamaguchi et al.[20] who used trichlorobenzoyl chloride to activate the carboxylic functionality as its mixed anhydride (Scheme 3).
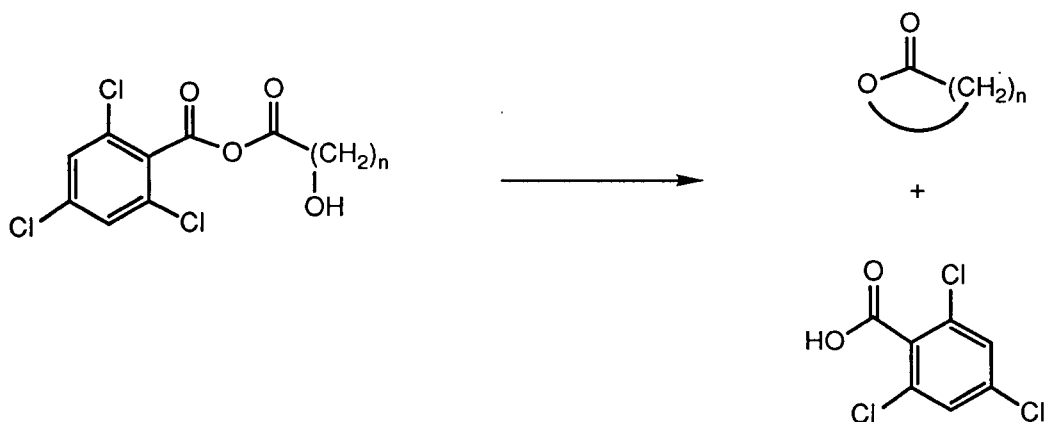
Scheme 3. Yamaguchi method for macrolactonization.[20]

Other notable examples of the double activation method include Mukaiyama's use of N-methyl-2-chloropyridinium iodide[21a] and Masamune's thiolate ester-Hg(II) mediated lactonization,[21b] as well as enzyme catalysed lactonization.[21c] It should be emphasized, however, that the latter technique has enjoyed limited success and tends to be substrate specific.

1.5 CONFORMATIONALLY CONTROLLED REACTIONS IN MACROLIDE SYNTHESIS.

In 1983 Still and Novack[22] elegantly displayed the power of macrocyclic stereocontrol with the synthesis (Scheme 4) of 3-deoxyrosaranolide (4).

First the 16-membered ring of the target structure was prepared by a Horner-Emmons cyclization to give the keto macrolide 5 which was kinetically deprotonated at C_8 and methylated with better than 95% stereoselectivity to give, after deprotection, 6. Introduction of the C_6 side chain was achieved by alkylation of the kinetically generated enolate to give 7 with better than 95% regioselectivity and 85% stereoselectivity. The methyl-bearing chiral centre at C_4 was then controlled by hydroxymethylation of the lithium enolate followed by elimination to the methylene ketone. Conjugate addition of thiophenol and desulphurisation with Raney nickel gave 8 with better than 95% stereoselectivity. Ester hydrolysis and sodium borohydride reduction of the derived mixed anhydride then gave the desired C_5 alcohol 9 with 83% stereoselectivity. Finally oxidation at C_9, epoxidation and selective oxidation of the primary hydroxyl group gave 3-deoxyrosaranolide(4) with better than 93% stereoselectivity.
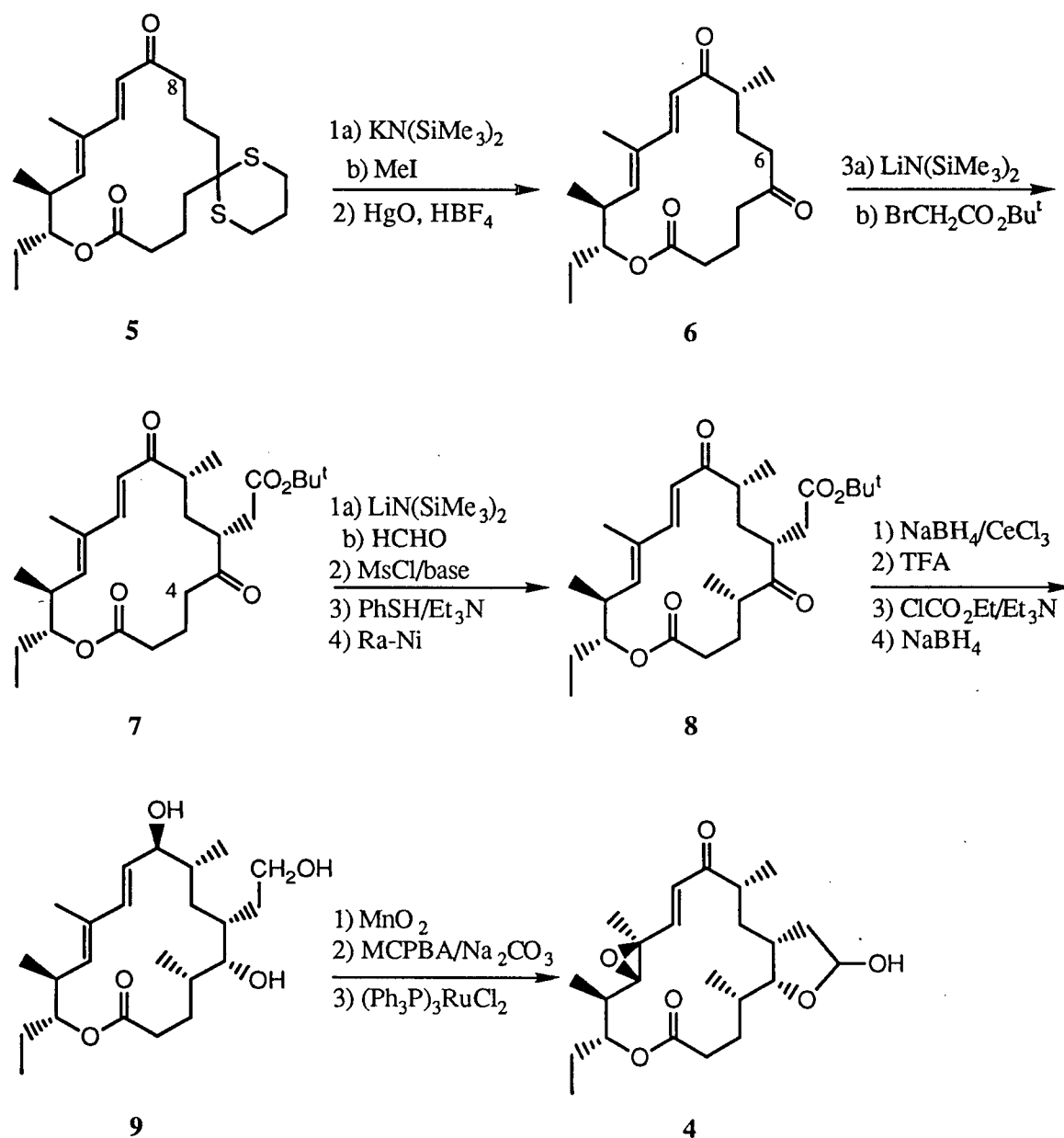
Scheme 4. Synthesis of 3-deoxyrosaranolide (**4**) using macrocyclic stereocontrol.[22]

A more recent report by Paterson and Rawson[23] describes the synthesis of (+)-9(S)-dihydroerythronolide (**10**) based on a combination of acyclic and macrocyclic stereocontrol. Scheme 5 outlines how four of the ten stereocentres were generated using the conformational bias of the ring.
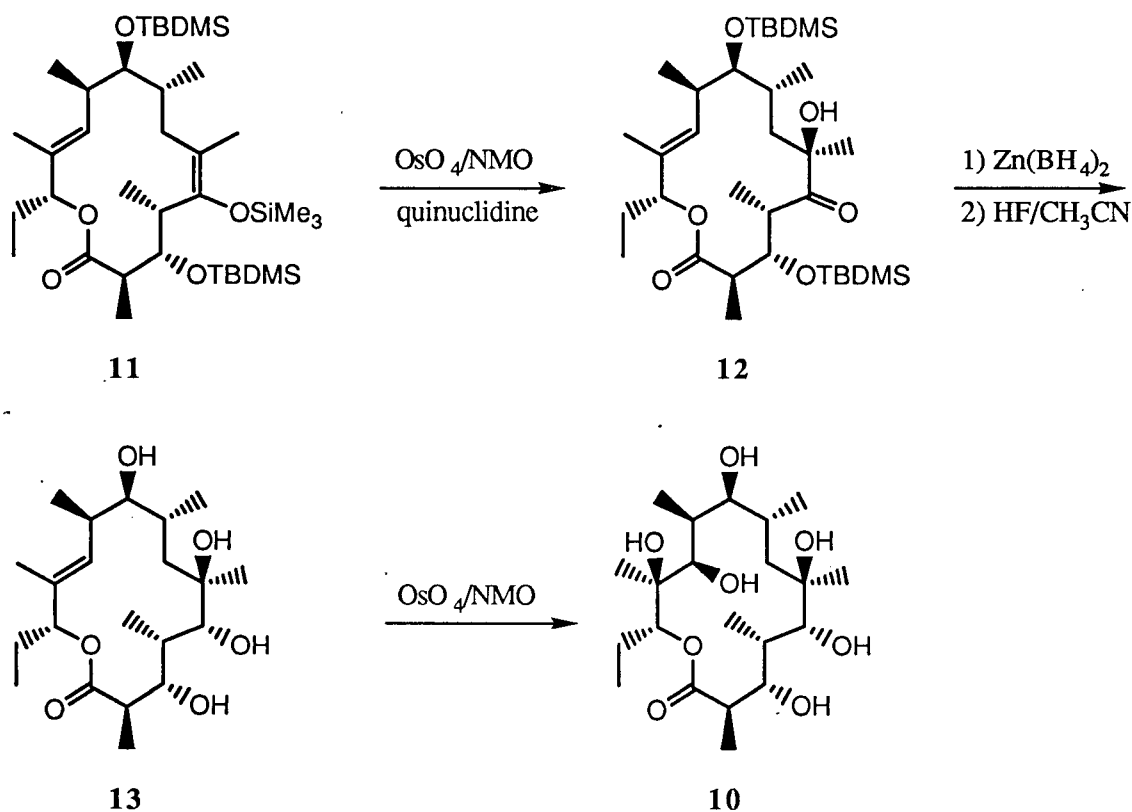
Scheme 5. Conformationally controlled reactions in the synthesis of dihydroerythronolide (**10**).[23]

Osmylation of the intermediate **11** proceeded with essentially 100% π-faced selectivity to give the hydroxy ketone **12**. Subsequent reduction of the carbonyl gave, after deprotection, **13** again as a single product. A second osmylation, although low yielding, proceeded with high selectivity to give **10** thereby completing the synthesis.

Vedejs et al.[24] have also reported the use of macrocyclic control in the epoxidation and osmylation of medium and large ring cycloalkenes. The local ring segment containing the alkene tends to adopt only certain conformations which control the stereochemical outcome of the reaction. Further restrictions in conformational possibilities arise for molecules having an allylic alkyl substituent, the alkyl group occupying a pseudoequatorial position if possible. Attack of the reagent then occurs from the least hindered face (Scheme 6).
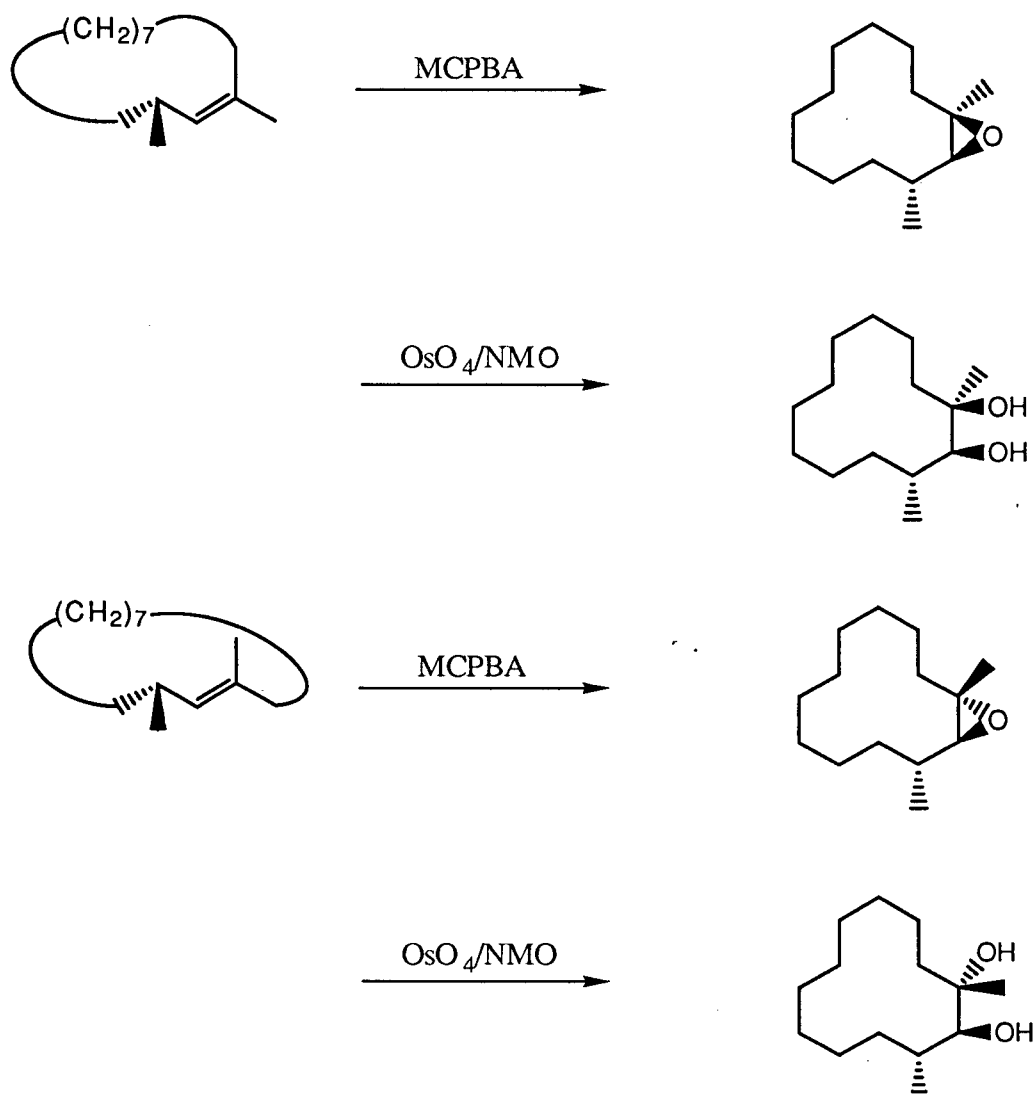
Scheme 6. Local conformer effects in reactions of cycloalkenes.[24]

This procedure has been used by Vedejs and co-workers in the stereocontrolled synthesis of an erythronolide fragment, the key step being the osmylation of a 9-membered ring alkene to give a single diol.[25]

As demonstrated from these examples, the use of macrocyclic stereocontrol is a viable approach to the synthesis of macrolides. However, only sparse attempts have been made to analyse the factors controlling the conformational preferences in reactions of large rings, hence our interest in this field.

CHAPTER II

Results and Discussion

2.1 SYNTHESIS OF *(E)*- AND *(Z)*-13-TETRADEC-8-ENOLIDE

We chose to study an unsaturated macrocyclic lactone in which the double bond was remote from the lactone functional group to determine if reactions of the alkene could be controlled by the conformation of the ring.

The retrosynthetic analysis of the unsaturated lactone **15** for this study is shown in Scheme 7. Since a large quantity of each lactone was required, commercially available and inexpensive starting materials were chosen.

Dale's work on the conformational analysis of cycloalkenes[7,11] implied that lactone **14** would be thermodynamically more stable than **15**. Accordingly, isomerisation of the cis-double bond in **15** should lead to **14** thus necessitating only one synthesis for both lactones. Previous results obtained in our laboratory, as well as a wealth of literature,[18-21] indicated lactonization of the corresponding seco-acid **16** to be the method of choice for cyclisation. A second disconnection at the double bond leads to the protected hydroxy aldehyde **17** and the phosphonium salt **18**, the precursors of which are ethyl 5-oxohexanoate (**19**) and 8-bromooctanoic acid (**20**) respectively.
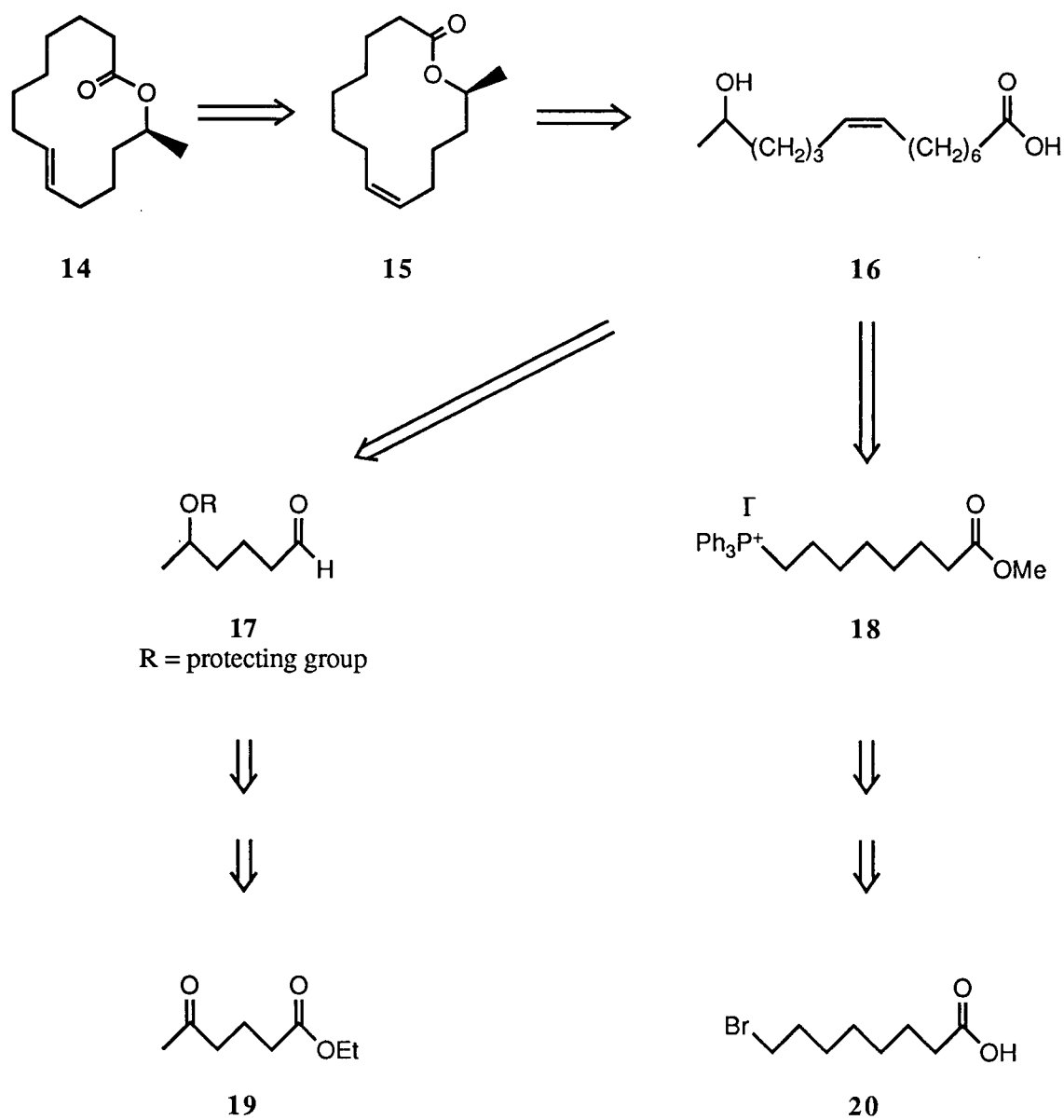
Scheme 7. Retrosynthetic analysis of macrolide **15**.

2.1.1 Synthesis of 5-(*tert*-butyldimethylsiloxy)hexanal (17)

The synthesis of **17** is outlined in Scheme 8. Ethyl 5-oxohexanoate (**19**) was reduced using lithium aluminium hydride to give the diol **21** which was then selectively acylated under enzyme catalysed conditions[26] to give the primary acetate **22**. Protection of the secondary hydroxyl function in **22** as its TBDMS ether gave **23** which in turn was deacylated to give the mono-protected diol **24**. Finally, Swern oxidation[27] of **24** gave the target molecule **17** in 58% overall yield from **19**.
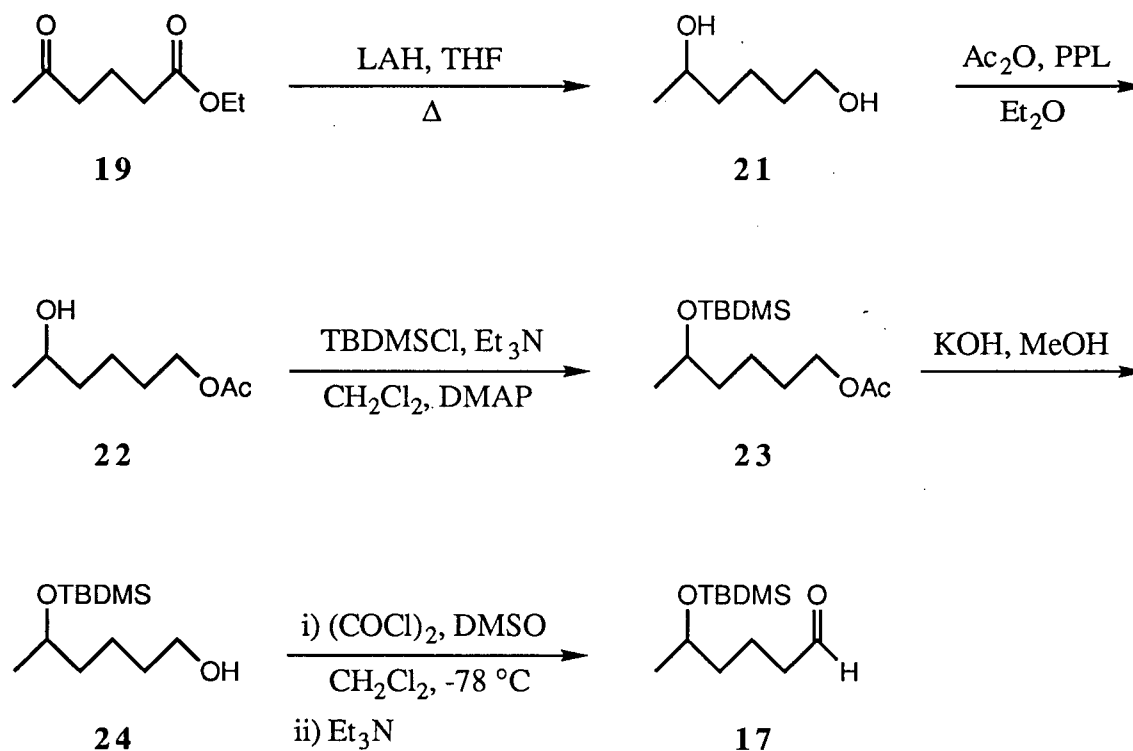
Scheme 8. Synthesis of aldehyde **17**.

2.1.2 Synthesis of 7-carbomethoxyheptyltriphenylphosphonium iodide (18)

The synthesis of **18**, as shown in Scheme 9, is relatively straightforward. Acid catalysed esterification of 8-bromooctanoic acid (**20**) gave bromo ester **25** which was then converted to iodo ester **26** via a Finkelstein reaction.[28] Treatment of **26** with triphenylphosphine and a stoichiometric amount of Hunig's base in refluxing acetonitrile proceeded smoothly to give **18**, which was used immediately in the next step without further purification.
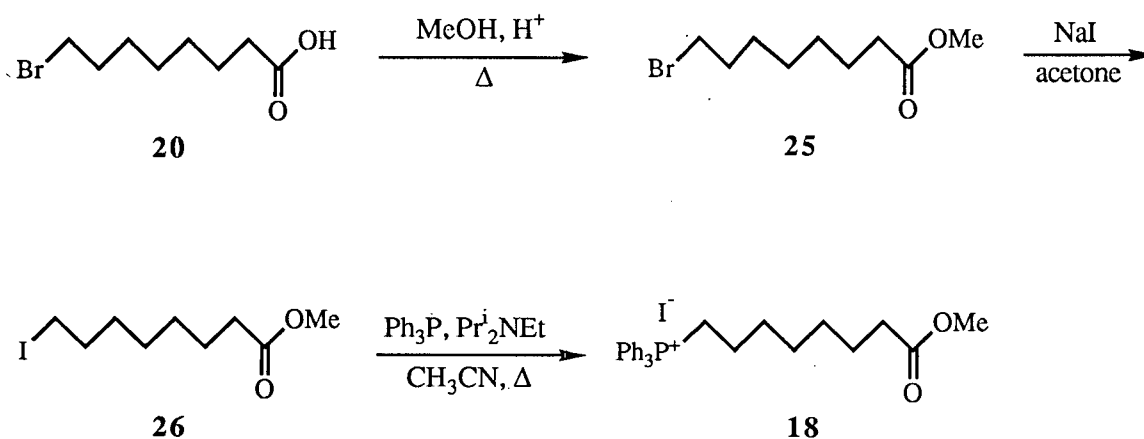
Scheme 9. Synthesis of phosphonium salt **18**.

2.1.3   Preparation of macrolides 14 and 15

The coupling of fragments **17** and **18** was based on the Wittig olefination.[29] High

selectivity for (Z) or (E) alkenes is available, depending on the particular circumstances,

such as type of ylid, carbonyl compound, or reaction conditions.[30] However, generation

of the ylid of **18** with sodium bis(trimethylsilyl)amide and subsequent reaction with **17** at

low temperature gave the unsaturated protected hydroxy ester **27** in a disappointing

cis:trans ratio of 2.5:1. Nevertheless we were not too discouraged since both geometrical

isomers of the unsaturated lactone, **14** and **15**, were desired and we therefore decided to

proceed with the synthesis and carry out separation of the geometric isomers at the lactone

stage. Hence desilylation of **27** gave hydroxy ester **28** which was hydrolysed to the

hydroxy acid **29**. Cyclisation of **29** was achieved using the Dietsche-Schmidt double-

activation method to give lactones **14** and **15** in a ratio of 1:1.25. Separation of the two

lactones was carried out by flash chromatography[31] using silver nitrate impregnated silica

gel[32] thus completing the synthesis (Scheme 10).
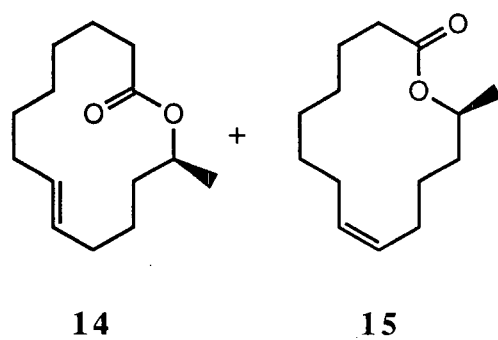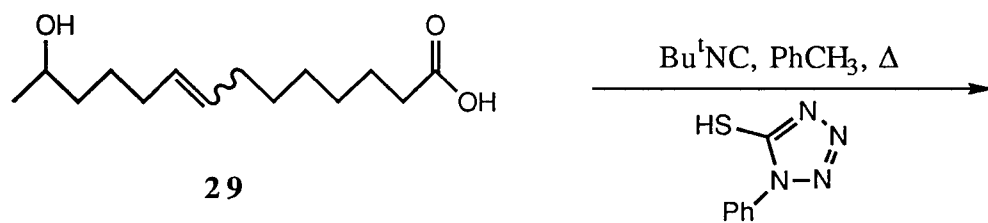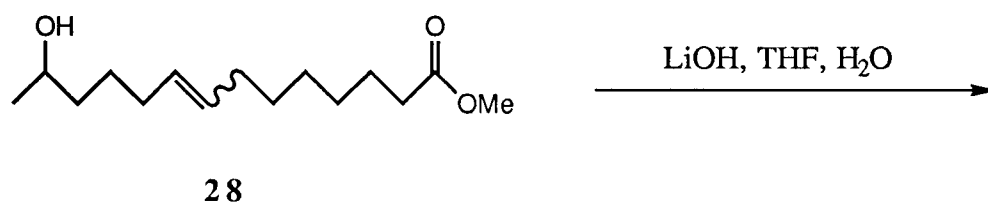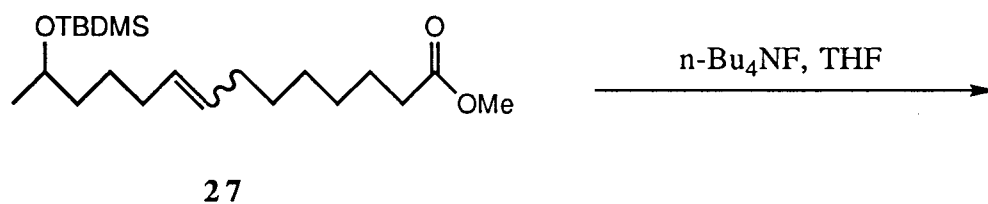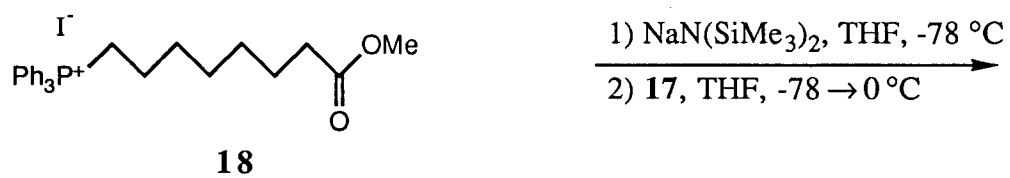
Scheme 10. Synthesis of macrolides **14** and **15**.

2.2 THE CONFORMATIONAL ANALYSIS OF 14-MEMBERED LACTONES

2.2.1 The conformational analysis of cyclotetradecane

Dale's work on conformational analysis revealed that the [3434], [3344] and [3335] were the three lowest energy conformations for cyclotetradecane.[10b] However Saunders,[33] using a ring-building computer program, has reported an additional twelve diamond lattice conformations that are theoretically possible. At this stage the conformational analysis of 14-membered rings appeared overwhelming. Fortunately calculations in our laboratory[40] showed the majority of these conformations to have significantly higher strain energies than the lowest energy [3434] conformation making many of them irrelevant to the conformational analysis of substituted derivatives (Figure 9).

[3434]	[3344]	[3335]	Conf. D	Conf. C
0.0	1.1	2.3	3.0	5.0

Conf. E	Conf. F	Conf. G	Conf. H	Conf. I
6.8	7.1	7.5	7.6	7.7

Conf. J	Conf. B	Conf. K	Conf. L	Conf. M
7.9	8.5	11.0	11.1	12.0
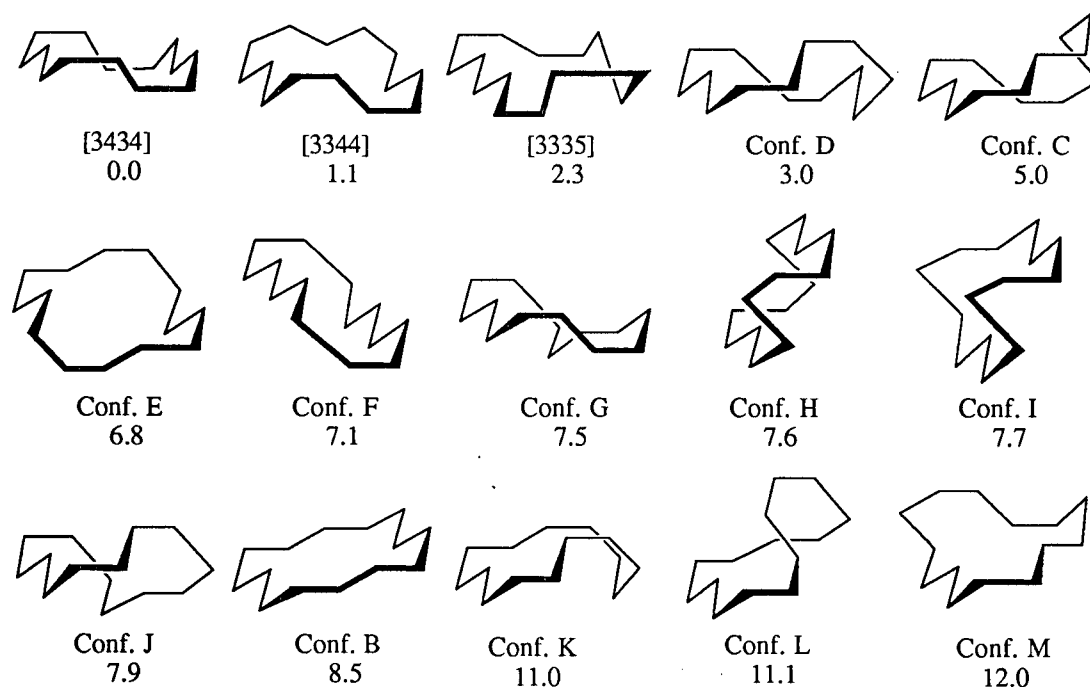
Figure 9. Conformations and relative strain energies in kcal/mol for cyclotetradecane.

2.2.2 Polar maps

The concept of polar maps was introduced by Ogura[34] to simplify the identification and comparison of the many conformations possible for large rings. Polar maps are circular graphs that plot the magnitude and sign of the internal dihedral angles versus the bond number (Figure 10). Since the dihedral angles are unique for the three dimensional structure of a molecule, each conformation will give a distinctive pattern in a polar map.
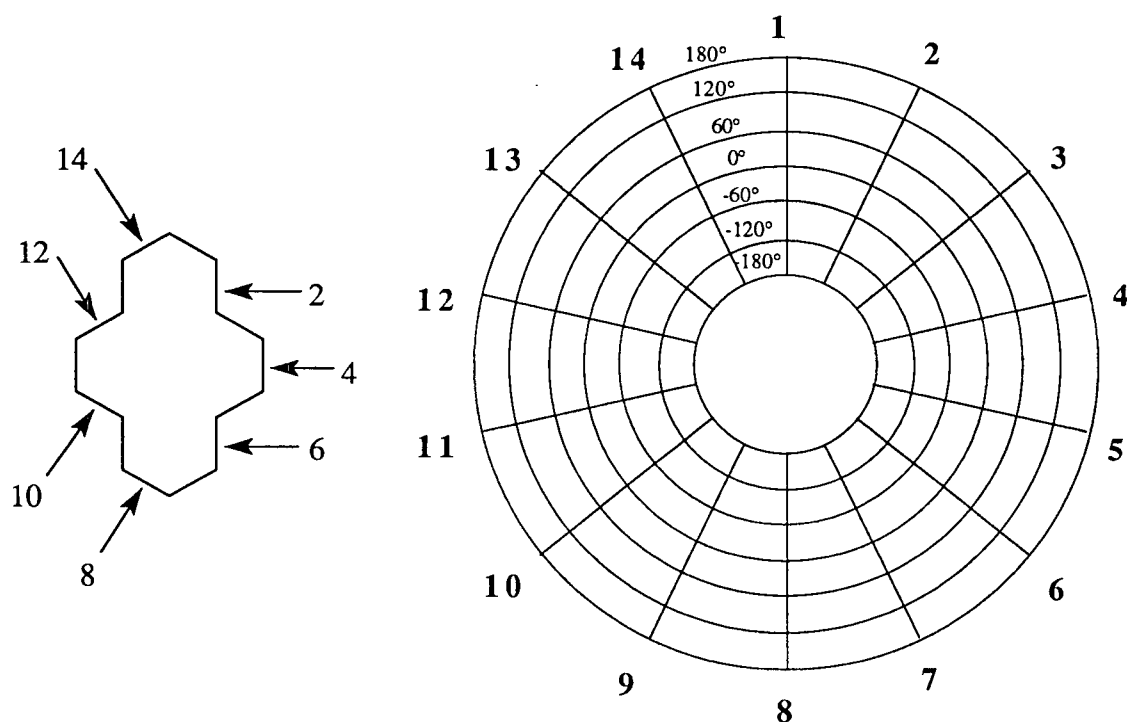
Figure 10. The polar map convention.

Ambiguity arises in determining the sign of a dihedral angle as it approaches 180°. To overcome this difficulty it was proposed that only the endocyclic anti dihedral angle be considered for the generation of polar maps (Figure 11).[35]
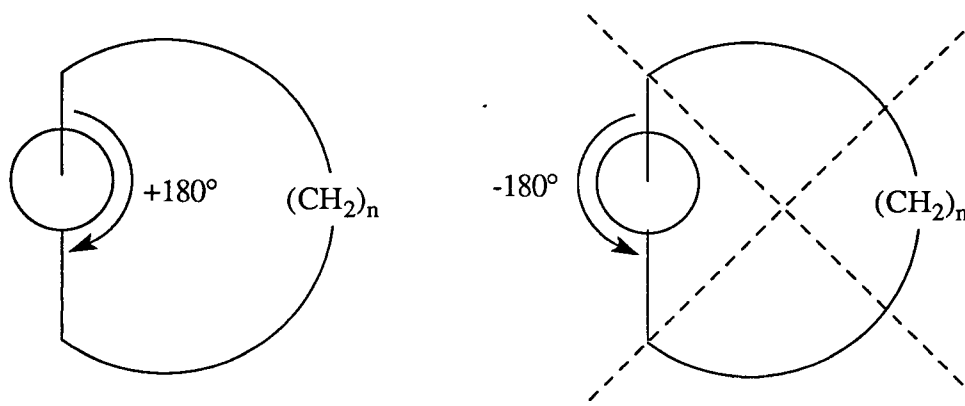
Figure 11. Rule for determining the sign of the anti dihedral angle.

Complications arose when applying this rule since MM2 calculations or X-ray crystallographic data reported angles that are less than or equal to 180° whether formed inside or outside the ring. A simple solution to this problem is to reverse the sign of the angle obtained from the X-ray/MM2 data and plot this value instead. Thus an exocyclic dihedral angle of -175° becomes, for convenience, +175° when in fact it should be +185°. Although this convention introduces a slight error it allows for the quick and reproducible generation of polar maps.
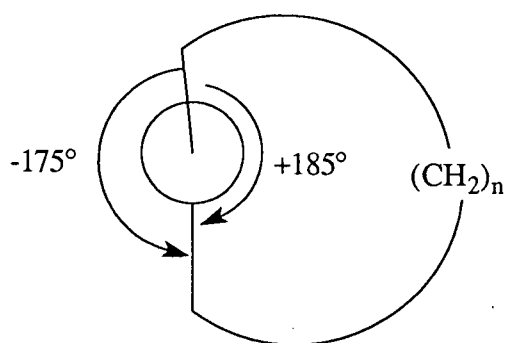
The polar maps for the three lowest energy conformations of cyclotetradecane are shown in Figure 12.

[3434]　　　　　　[3344]　　　　　　[3335]
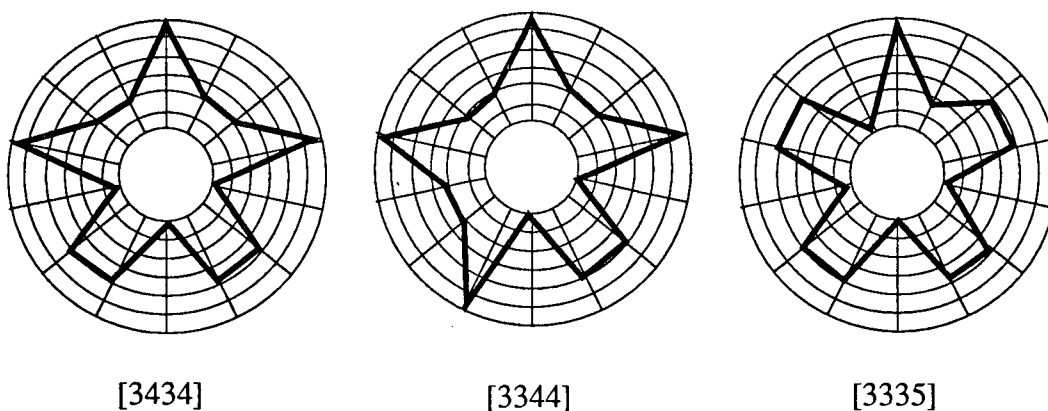
Figure 12. Polar maps for the three lowest energy conformations of cyclotetradecane.

2.2.3 The lactone linkage

The introduction of an ester linkage into a ring system would be expected to have a greater effect on its conformation than just the sum of a carbonyl and an ether group. The s-trans geometry of esters (Figure 13) is more stable than the s-cis form[36] and since a 14-membered ring is large enough to accomodate an s-trans lactone, any conformation containing an s-cis lactone can be eliminated from our consideration of conformational analysis.

s-trans　　　　　　　s-cis
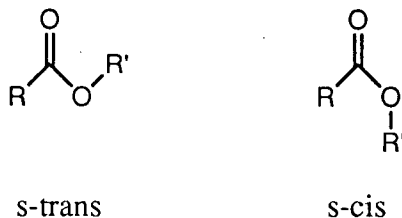
Figure 13. The two possible conformations of esters.

Furthermore, studies carried out on the conformational preferences of esters of secondary alcohols revealed that the C-O-C-H dihedral angle was invariably in the range of 0-60° (Figure 14).[37] Application of this trend to lactones of secondary alcohols can be used to simplify our analysis.
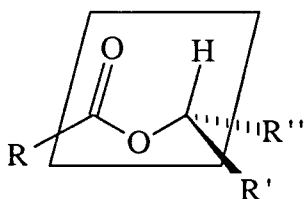
Figure 14. The C-O-C-H dihedral angle of secondary esters.
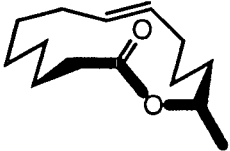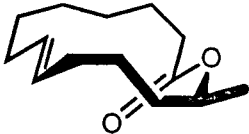
2.3 LOW ENERGY CONFORMATIONS OF MACROLIDES 14 AND 15

In order to simplify the conformational analysis of large ring lactones the following restrictions can be applied.

1. Substituents should occupy the exterior positions of a macrolide.

2. Geminally substituted atoms must occupy a corner position.

3. The lactone linkage must have the s-trans geometry.

4. The C-O-C-H dihedral angle must be in the range of 0-60°.

With this in mind we subjected our macrolides to a detailed conformational analysis using MM2 calculations.[38] As expected the introduction of an endocyclic double-bond makes the adoption of a strain free conformation impossible,[7] therefore increasing the conformational mobility of macrolides **14** and **15**.

Table I. The three lowest energy conformations of **14**.

Low energy conformations		Strain energy[a]	Conformation
14a		0.00 kcal/mol	[3344]
14b		0.06 kcal/mol	[3344]
14c		0.17 kcal/mol	[3344]

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

The three lowest energy conformations for macrolide **14** are shown in Table I. The conformational analysis of **14** proved to be quite complex, with over thirty conformations being within 2 kcal/mol of the global minimum.

The three lowest energy conformations turned out to have the [3344] geometry. All three conformations also had the same local conformation around the olefinic double bond, as can be seen from their polar maps (Figure 15).

14

14a   14b   14c
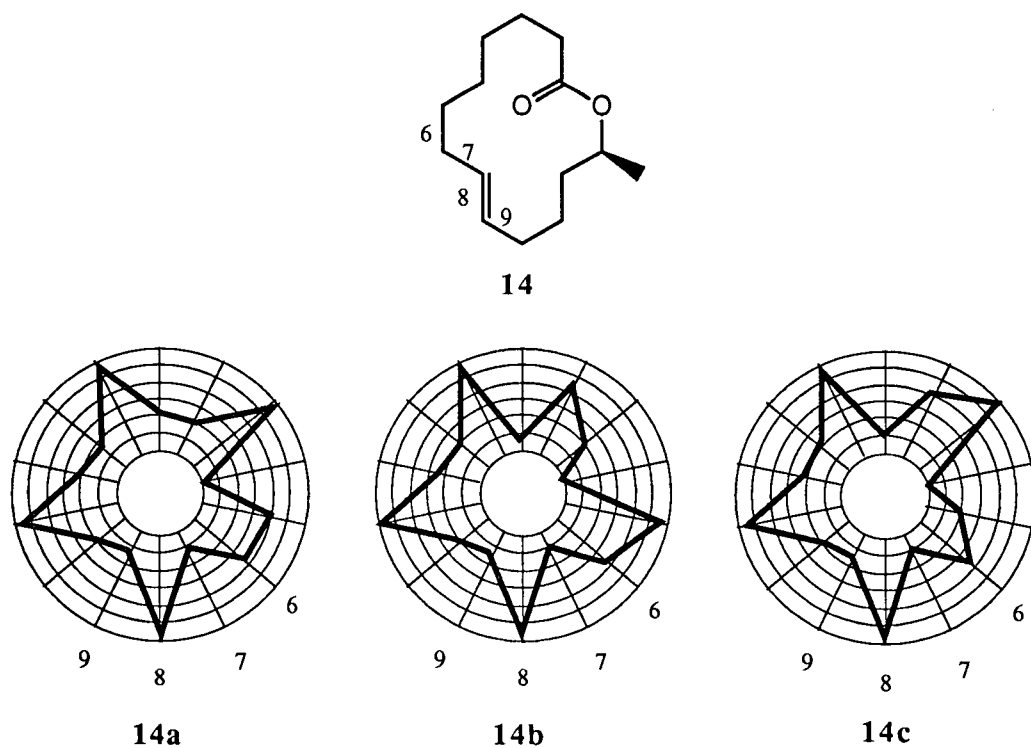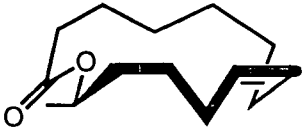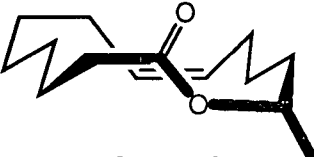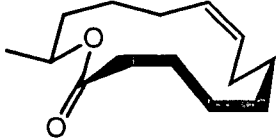
Figure 15. Polar maps of the three lowest energy conformations of **14**.

As with **14** the conformational analysis of macrolide **15** proved complex with twenty-six conformations within 2 kcal/mol of the global minimum. As shown in Table II the lowest energy conformation is again a [3344] conformation followed by a [3434] and [3344] respectively.

Table II. The three lowest energy conformations of **15**.

Low energy conformations	Strain energy[a]	Conformation
15a	0.00 kcal/mol	[3344]
15b	0.06 kcal/mol	[3434]
15c	0.17 kcal/mol	[3344]

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

The polar maps for the three conformations are shown in Figure 16. Again, the local conformation around the olefinic double bond remains constant.

15

15a **15b** **15c**
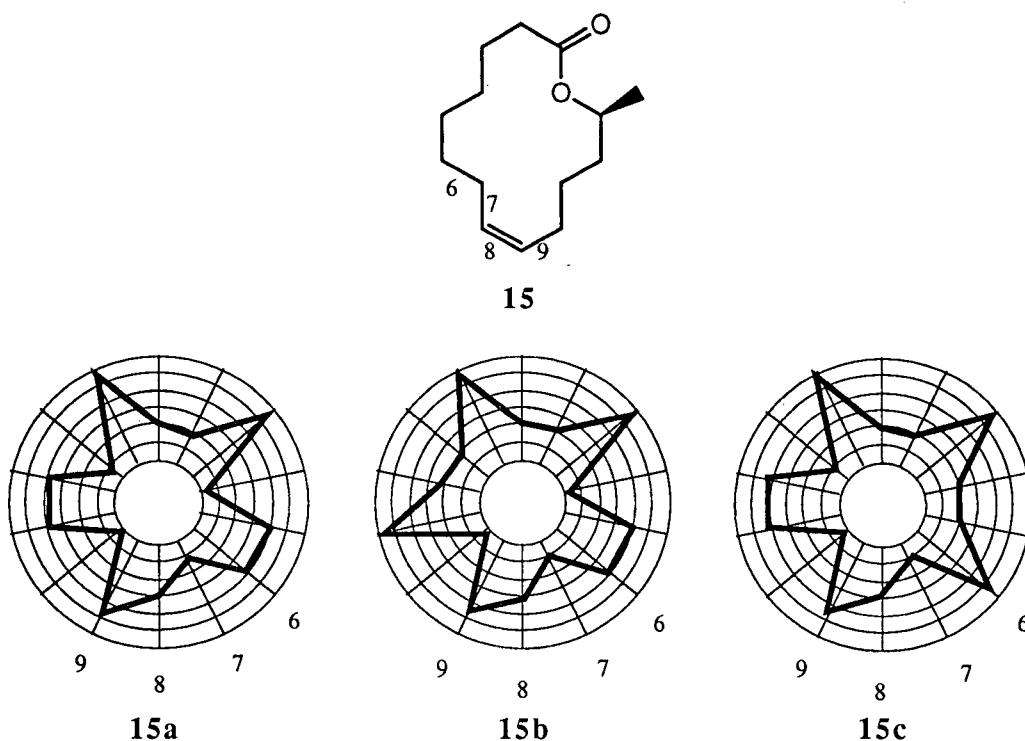
Figure 16. Polar maps of the three lowest energy conformations of **15**.

2.4 HYDROBORATION OF 14 AND 15

With the possibility of four isomeric hydroxy lactones being formed in the hydroboration of **14** or **15** our initial aim was to isolate and characterise each of the isomers for future reference. We therefore hydroborated a mixture of **14** and **15** with borane dimethylsulphide complex to give, after work-up, a mixture of hydroxy lactones **30, 31, 32** and **33** (Scheme 11).
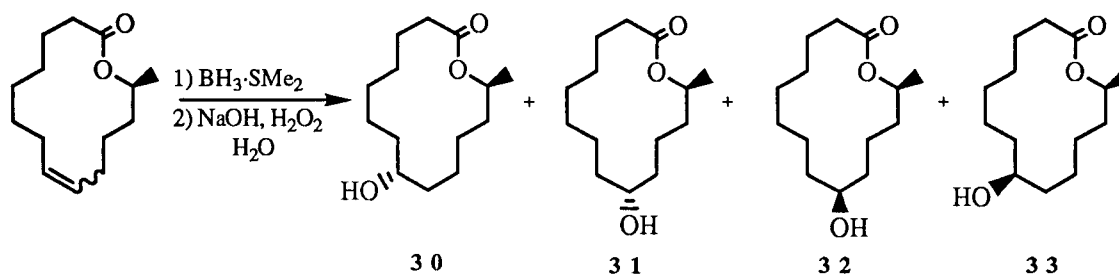
Scheme 11. Hydroboration of **14** and **15**.

Separation of the hydroxy lactones (Scheme 12) was achieved by initially forming their respective silyl ethers **34, 35, 36** and **37** which were then separated, by radial chromatography, into two fractions containing **34** and **35**, and **36** and **37** respectively. Desilylation of **34** and **35** followed by separation, again by radial chromatography, gave hydroxy lactones **30** and **31**, the latter being identified by comparison of its NMR spectrum with an original sample previously made in our laboratory.[40a] Unfortunately desilylation of **36** and **37** yielded an inseparable mixture of hydroxy lactones **32** and **33**. We were however able to confirm the structure of **32** again by comparison of its NMR spectrum with that of a previously synthesized sample.[40a]
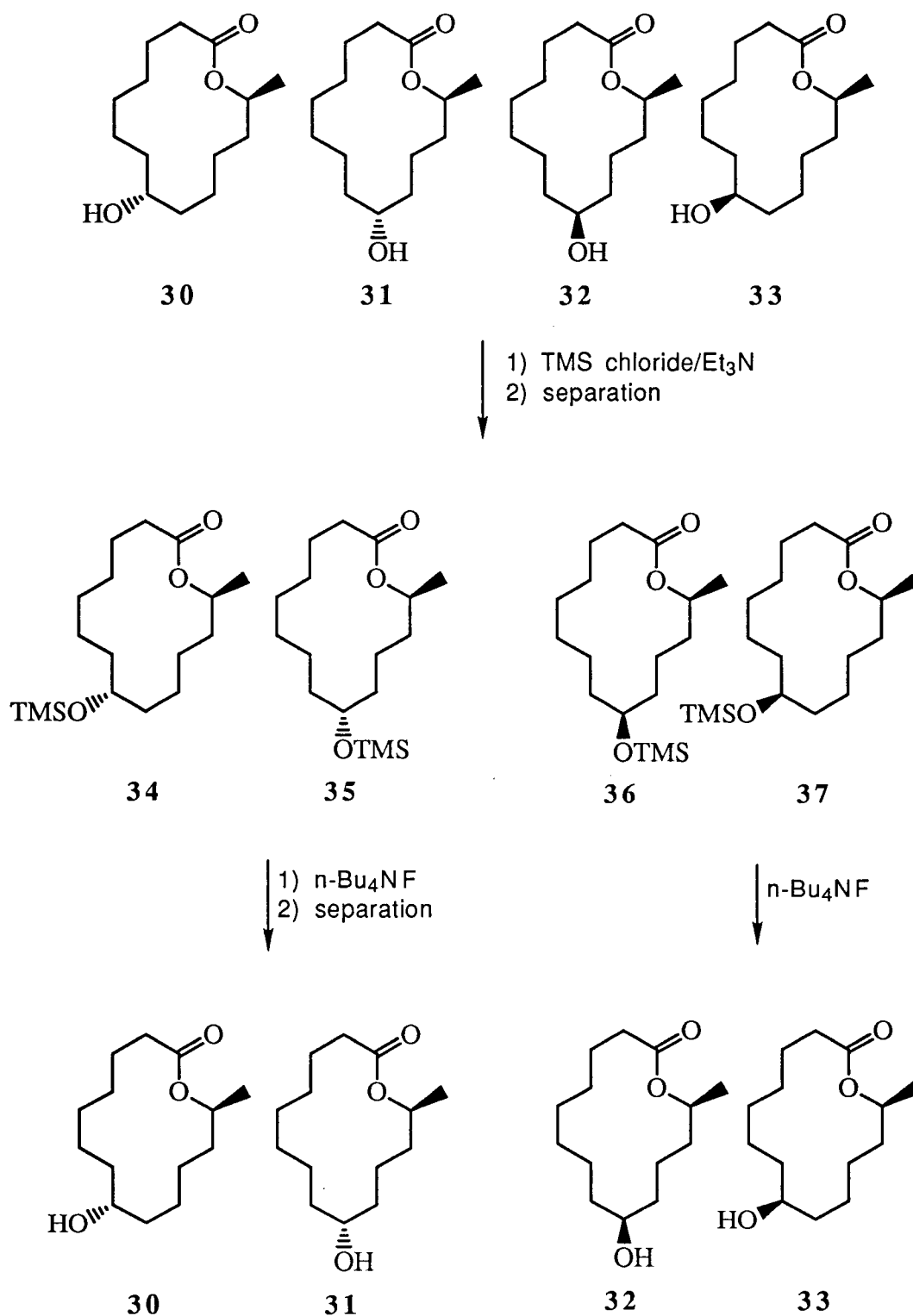
Scheme 12. Separation of hydroxy lactones **30**, **31**, **32** and **33**.

2.4.1 Hydroboration of 14

Previous literature results indicated that the hydroboration of alkenes with diborane proceeded with low regio and stereoselectivity. Hydroboration of **14** using borane dimethylsulphide gave, from GC analysis of their respective TMS ethers, a 44:26:18:12 mixture of four isomeric hydroxy lactones **30, 31, 32** and **33**. We therefore turned our attention to bulkier hydroborating agents in the hope of gaining increased selectivity. Unfortunately hydroboration of **14** with 9BBN, perhaps because of the elevated reaction temperature required, gave a slightly decreased 43:24:26:7 mixture of the four isomeric hydroxy lactones **30, 31, 32** and **33**. However, when **14** was treated with disiamylborane the reaction proceeded with 100% regioselectivity to give two diastereomeric hydroxy lactones **30** and **33** in a ratio of 9:1. The results for the various hydroborations performed on **14** are summarised in Table III.

Table III. Hydroboration of *(E)*-13-tetradec-8-enolide (**14**) with various hydroborating agents.

Hydroborating agents	Temperature	Selectivity				Yield %
		30	**31**	**32**	**33**	
BH$_3$·SMe$_2$	-78 °C	44	26	18	12	96
9BBN	25 °C	43	24	26	7	93
Sia$_2$BH	25 °C	90			10	96
Predicted Selectivity (MM2)		37	59	4		

2.4.2 Hydroboration of 15

Hydroborations of **15** were carried out with the same reagents as for **14**. Again the reaction of borane dimethylsulphide with **15** proceeded with low selectivity to give four isomeric hydroxy lactones **30, 31, 32** and **33** in a ratio of 45:28:19:8. The use of the bulkier hydroborating agents resulted in an increase in selectivity although the outcome in both cases was still disappointing. Reaction of **15** with 9BBN gave four isomeric hydroxy lactones **30, 31, 32** and **33** in a ratio of 51:36:6:7, whereas with disiamylborane three hydroxy lactones **30, 31** and **33** were produced in a ratio of 53:37:10. The results for the reactions of **15** are summarised in Table IV.

Table IV. Hydroboration of *(Z)*-13-tetradec-8-enolide (**15**) with various hydroborating agents.

Hydroborating agents	Temperature	Selectivity				Yield %
		30	**31**	**32**	**33**	
$BH_3 \cdot SMe_2$	-78 °C	45	28	19	8	96
9BBN	25 °C	51	36	6	7	93
Sia_2BH	25 °C	53	37		10	96
Predicted Selectivity (MM2)		50	40	2	8	

We were now faced with the problem of assigning the relative stereochemistry of the products in the hydroboration of **14** and **15**. As was previously mentioned, two hydroxy lactones **31** and **32** were identified by comparison with their original NMR spectra,[40a] however there still remained the identification of lactones **30** and **33**.

Still and Galynker[42] have shown that reagents attack the π-system of a macrolide almost exclusively from the periphary of the ring. Using this model as a basis we suggest that peripheral attack of a hydroborating agent on the C$_8$ carbon of macrolide **15** (Figure 17) would lead to the hydroxy lactone with the *8R*, 13S** stereochemistry. Thus the major product in the hydroborations was assigned the *8R*, 13S** stereochemistry **30**, and **33** the *8S*, 13S**.
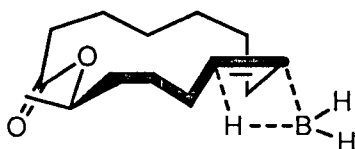
Figure 17. Peripheral attack of diborane on the C$_8$ carbon of **15**.

2.4.3   Molecular modelling of hydroboration transition states

From ab initio calculations based on the transition state of the gas phase reaction between borane and ethylene, Houk and co-workers[41] have recently developed a method wherein MM2 calculations can be performed on the transition structures of the reaction between hydroborating agents and alkenes.

Following this methodology we were able to perform MM2 calculations on the transition structures of the reaction between diborane and macrolides **14** or **15** (Figure 18). To accomplish this it was necessary to input a set of parameters that defined atom types and bond orders in the transition structure. The product ratio could then be determined from a Boltzmann distribution using the relative strain energies of the individual transition structures.
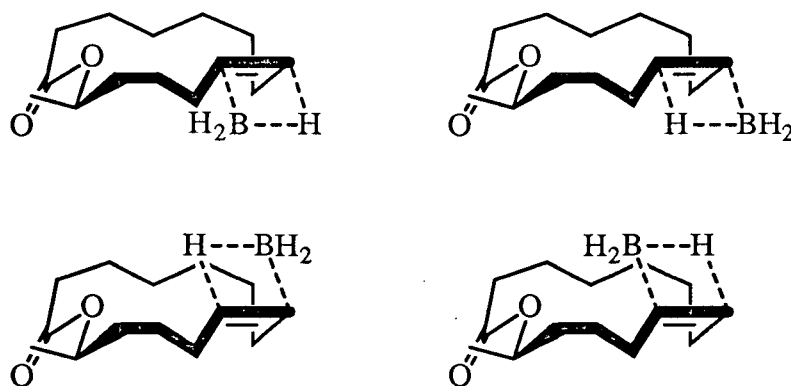
Figure 18. Transition structures in the hydroboration of **15**.

2.5   CONCLUSION

In the conformational analysis of unsaturated 14-membered lactones we have found their behaviour to be very complex with the macrocyclic ring exhibiting a high degree of flexibility.

We performed a number of hydroborations on the unsaturated lactones **14** and **15** to investigate the conformational control induced by the ring. Although the results of the hydroborations were disappointing we were able to show that the reactions proceeded with high π-face selectivity. Thus new applications of conformationally controlled reactions in unsaturated macrolides could be found in asymmetric osmylations and epoxidations.

CHAPTER III

Experimental

3.1 GENERAL

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

Anhydrous reagents and solvents were prepared according to literature procedure.[39]

Preparative flash chromatography[31] was performed using silica gel 60, 230-400 mesh. supplied by E. Merck Co.

Infrared spectra were recorded on a BOMEM FT-IR Michaelson-100 connected to an IBM compatible computer. IR spectra were recorded either neat or in a chloroform solution using NaCl cells of 0.2 mm thickness. Proton nuclear magnetic resonance spectra were recorded in deuterochloroform solution on a Bruker WH-400 (400 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) on the δ scale versus tetramethylsilane (δ 0) as internal standard. Signal multiplicities, coupling constants and integration ratios are given in parentheses.

Low resolution mass spectra were recorded on either a Kratos-AEI model 50 or MS9 spectrometer. Only peaks with greater than 20% relative intensity or those which were analytically useful are reported. High resolution mass spectra were recorded on a Kratos AEI model MS 50 spectrometer. An ionization potential of 70 eV was used in all measurements.

3.2   SYNTHESIS AND REACTIONS OF 13-TETRADEC-8-ENOLIDES

1,5-Hexanediol   (21)

OH

[structure of 1,5-hexanediol]
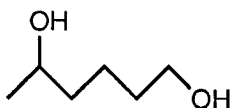
A solution of ethyl 4-acetylbutyrate (15.0 g, 0.095 mol) in THF (100 mL) was added to a stirred suspension of lithium aluminium hydride (10.0 g, 0.245 mol) in THF (150 mL) at 0 °C. The mixture was allowed to warm to room temperature and then heated at reflux for 24 h. The mixture was cooled to 0 °C and a saturated solution of sodium sulphate was added. The resulting slurry was filtered and the filtrate washed with ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic extracts were dried (MgSO$_4$) and the solvent was removed under reduced pressure. Flash chromatography of the crude product using methylene chloride-methanol (12:1) as eluant yielded **21** as a colourless oil (11.1 g, 99%).

IR (neat, cm^{-1}): 3700-3100, 2940, 2855, 1458, 1374, 1071, 940, 845

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.82 (m, J= 6 Hz, 1H), 3.67 (t, J= 6 Hz, 2H), 1.56-1.66 (m, 4H), 1.39-1.56 (m, 4H), 1.21 (d, J= 6 Hz, 3H)

LRMS (m/z): 118 (M$^+$, 0.6), 75 (27), 56 (91), 55 (22), 45 (100), 43 (40), 41 (54)

1-Acetoxy-5-hexanol (22)

A solution of 1,5-hexandiol **(21)** (11.0 g, 0.093 mol) and acetic anhydride (13.1 mL, 0.14 mol) in diethyl ether (70 mL) was added to a suspension of PPL in Et$_2$O (70 mL) and the mixture stirred for 30 h. The lipase was removed by filtration, washed with Et$_2$O and the combined organic solutions washed with 1 M HCl, saturated NaHCO$_3$ and water. The aqueous layers were extracted with Et$_2$O and the combined organic extracts dried (MgSO$_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (3:2) as eluant yielded **22** as a colourless liquid (11.2 g, 75%).

IR (neat, cm^{-1}): 3600-3250, 2945, 2850, 1730, 1376, 1250, 1071, 845

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 4.09 (t, J=6 Hz, 2H), 3.83 (m, J=6 Hz, 1H), 2.06 (s, 3H), 1.71-1.61 (m, 2H), 1.53-1.35 (m,5H), 1.21 (d, J=6 Hz,3H)

LRMS (m/z) from CI: 178 (M$^+$+18, 53)

LRMS (m/z) from EI: 101 (25), 85 (36), 67 (22), 61 (63), 57 (24), 58 (23), 45 (68), 43 (100), 41 (43)

Exact Mass calculated for C$_8$H$_{16}$O$_2$: 160.1099; found: 160.1090

1-Acetoxy-5-(*tert*-butyldimethylsiloxy)hexane (23)

$$\text{OTBDMS}$$

(structure: TBDMS-protected chain with OAc terminus)
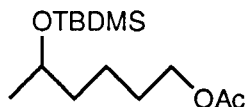
1-Acetoxy-5-hexanol (11.1 g, 0.069 mol) in methylene chloride (100 mL) was added to a solution of TBDMS chloride (15.7 g, 0.104 mol) in methylene chloride (200 mL). Triethylamine (19.3 mL, 0.139 mol) and a catalytic amount of DMAP were added and the mixture heated at reflux for 48 h. The reaction mixture was cooled to room temperature and quenched with 1 M HCl. The organic layer was separated, washed with saturated $NaHCO_3$, water and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (20:1) as eluant gave **23** as a colourless liquid (19.0 g, 100%).
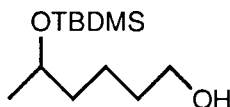
IR (neat, cm^{-1}): 2944, 2856, 1743, 1476, 1370, 1244, 1136, 1055, 835, 775

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 4.06 (t, J=8 Hz, 2H), 3.78 (m, 1H), 2.05 (s, 3H), 1.67-1.55 (m, 2H), 1.23-1.52 (m, 4H), 1.12 (d, J=8 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H)

LRMS (m/z) from CI: 292 (M^++ 18, 7)

LRMS (m/z) from EI: 217 (M^+-57, 9), 117 (100), 83 (56), 75 (35), 73 (21), 55 (37)

Exact Mass calculated for $C_{14}H_{30}O_3Si$: 273.1886; found: 273.1886

5-(*tert*-Butyldimethylsiloxy)-1-hexanol (24)

$$OTBDMS$$

TBDMS ether **23** (7.5 g, 0.027 mol) was added to a solution of KOH (9.1 g, 0.163 mol) in methanol (60 mL) and the resulting solution was stirred for 24 h. The methanol was removed under reduced pressure and the residue dissolved in Et_2O. The organic layer was washed with water, saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (8:1) as eluant yielded **24** as a colourless liquid (5.59 g, 88%).

IR (neat, cm^{-1}): 3600-3150, 2941, 2859, 1466, 1371, 1253, 1138, 1104, 1056, 1006, 834, 775

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.80 (m, 1H), 3.66 (t, J=8 Hz, 2H), 1.57 (m, 2H), 1.50-1.34 (m, 5H), 1.13 (d, J=8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H)

LRMS (m/z): 175 (M$^+$-57, 9), 159 (26), 119 (87), 93 (25), 83 (92), 75 (100), 73 (72), 55 (87)

Exact Mass calculated for $C_{12}H_{27}O_2Si$: 231.1781; found: 231.1780

5-(*tert*-Butyldimethylsiloxy)hexanal   (17)

OTBDMS   H

To a solution of oxalyl chloride (2.5 mL, 0.026 mol) in methylene chloride (50 mL) at -78 °C was added a solution of DMSO (3.8 mL, 0.052 mol) in methylene chloride (10 mL). The mixture was stirred for 15 min. and then a solution of alcohol **24** (5.5 g, 0.024 mol) in methylene chloride (10 mL) was added to the reaction mixture. Stirring was continued for another 15 min., triethylamine (16.5 mL, 0.118 mol) added and the mixture allowed to warm to room temperature. The reaction mixture was poured into water, extracted with methylene chloride and the combined organic layers dried (MgSO$_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (20:1) as eluant yielded **17** as a colourless liquid (4.86 g, 89%).

IR (neat, cm^{-1}): 2917, 2715, 1731, 1465, 1373, 1251, 1138, 1053, 834

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 9.76 (t, J=2 Hz, 1H), 3.81 (m, J=4 Hz, 1H), 2.43 (dt, J=2, 4 Hz, 2H), 1.76-1.60 (m, 2H), 1.40-1.33 (m, 2H), 1.14 (d, J=4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H)

LRMS: 230 (M$^+$, 1), 171 (29), 143 (47), 115 (38), 99 (100), 97 (25), 83 (27), 81 (43), 75 (44), 69 (25), 55 (26)

Exact Mass calculated for C$_{12}$H$_{25}$O$_2$Si: 229.1624; found: 229.1624

Methyl 8-bromooctanoate (25)

8-Bromooctanoic acid (7.0 g, 0.031 mol) was added to a catalytic amount of sulphuric acid in methanol (150 mL) and the mixture heated at reflux for 24 h. The solution was cooled to room temperature, poured into ice-cold water, extracted with methylene chloride and the combined organic layers dried (MgSO₄). Evaporation of the solvent and flash chromatography using hexanes-ethyl acetate (10:1) as eluant yielded **25** as a colourless liquid (6.98 g, 94%).

IR (neat, cm^{-1}): 2928, 2875, 1738, 1442, 1213

^{1}H NMR (CDCl₃, 400 MHz) δ: 3.66 (s, 3H), 3.40 (t, J=6 Hz, 2H), 2.31 (t, J=6 Hz, 2H), 1.86 (qi, J=6 Hz, 2H), 1.63 (m, 2H), 1.44 (m, 2H), 1.34 (m, 6H)

LRMS (m/z): 238 (^{81}Br, M$^+$, 0.2), 236 (^{79}Br, M+, 0.2), 157 (33), 125 (46), 97 (32), 87 (83), 75 (24.3), 74 (100), 69 (21), 59 (42), 55 (86), 43 (45)

Exact Mass calculated for C₁₉H₁₇^{81}BrO₂: 236.0391; found: 236.0383

$\qquad\qquad\qquad\quad$ C₁₉H₁₇^{79}BrO₂: 236.0411; found: 236.0415

Methyl 8-iodooctanoate (26)

Bromo ester **25** (6.9 g, 0.029 mol) was added to a solution of sodium iodide (43.6 g, 0.29 mol) in acetone (200 mL) and the mixture stirred for 24 h. The solvent was then removed under reduced pressure and the residue dissolved in Et_2O. The organic phase was washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (25:1) as eluant yielded **26** as a colourless liquid (8.15 g, 99%).

IR (neat, cm^{-1}): 3458, 2918, 1736, 1443, 1232, 1012, 866, 724

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.66 (s, 3H), 3.2 (t, J=8 Hz, 2H), 2.32 (t, J=8 Hz, 2H), 1.82 (qn, J=8 Hz, 2H), 1.63 (m, 2H), 1.47-1.30 (m, 8H)

LRMS (m/z): 284 (M$^+$, 0.1), 157 (69), 125 (81), 97 (79), 83 (84), 74 (64), 69 (29), 59 (52), 55 (100), 43 (28), 41 (37)

Exact Mass calculated for C$_9$H$_{17}$IO$_2$: 284.0273; found: 284.0272

Methyl 13-(*tert*-butyldimethylsiloxy)tetradec-8-enoate (27)

OTBDMS

O

OMe

Iodide **26** (6.17 g, 0.022 mol) was added to a solution of triphenyl phosphine (6.84 g, 0.026 mol) and diisopropylethylamine (3.8 mL, 0.022 mol) in acetonitrile (70 mL) and the mixture heated under reflux for 48 h.

The solution was cooled, the solvent removed under reduced pressure and the crude phosphonium salt dried under high vacuum for 12 h.

To a solution of the crude phosphonium salt **18** in THF (250 mL), cooled to -78 °C, was added a solution of sodium bis(trimethylsilyl)amide (3.96 g, 0.021 mol) in THF (50 mL). Stirring was continued for 30 min. and aldehyde **17** (4.50 g, 0.02 mol) in THF (25 mL) was added. The mixture was stirred for 1 h., allowed to warm to room temperature and filtered through celite. Evaporation of the solvent and column chromatography using petroleum ether-ethyl acetate (50:1) as eluant yielded **27** (4.1 g, 57%) as a colourless oil.

IR (neat, cm^{-1}): 2935, 2851, 1740, 1451, 1369, 1251, 834, 774

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.34 (m, 2H), 3.77 (m, 1H), 3.66 (s, 3H), 2.30 (t, J=8 Hz, 2H), 2.02 (m, 4H), 1.61 (br. m, 4H), 1.51-1.24 (m, 12H), 1.12 (d, J=6 Hz, 3 Hz), 0.90 (s, 9H), 0.06 (s, 6H)

LRMS (m/z): 370 (M$^+$, 0.2), 313 (35), 281 (52), 262 (82), 183 (61), 159 (20), 109 (25), 108 (45), 107 (45), 95 (41), 81 (48), 75 (100), 73 (58), 69 (20), 67 (34), 55 (33)

4 5

Methyl 13-hydroxytetradec-8-enoate (28)
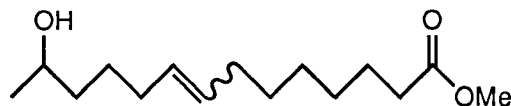
A 1 M solution of tetrabutylammonium fluoride in THF (21.6 mL, 0.022 mol) was added to the *tert*-butyldimethylsilyl ether **27** (4.00 g, 0.011 mol). The resulting solution was stirred for 48 h. and then the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with water and dried (MgSO$_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (6:1) as eluant yielded **28** as a colourless liquid (1.98 g, 72%).

IR (neat, cm^{-1}): 3610-3160, 2931, 2857, 1734, 1449, 1372, 1225, 1046

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.37 (m, 2H), 3.80 (m, 1H), 3.68 (s, 3H), 2.30 (t, J=8 Hz, 2H), 2.04 (m, 4H), 1.70-1.24 (m, 13H), 1.20 (d, J=6 Hz, 2H)

LRMS (m/z): 256 (M$^+$, 2.1), 164 (75), 142 (45), 136 (22), 135 (26), 123 (20), 122 (43), 121 (25), 112 (21), 110 (20), 109 (35), 108 (25), 107 (24), 98 (55), 97 (34), 96 (46), 95 (60), 94 (31), 93 (23), 87 (25), 84 (23), 83 (32), 82 (57), 81 (100), 80 (28), 79 (32), 74 (25)

Exact Mass calculated for C$_{15}$H$_{28}$O$_3$: 256.2038; found: 256.2038

13-Hydroxytetradec-8-enoic acid (29)

A solution of hydroxy ester **28** (1.95 g, 7.62 mmol) in THF (100 mL) was added to a solution of lithium hydroxide (0.62 g, 38.6 mmol) in water (50 mL) and the resulting mixture was stirred for 6 h. The solution was neutralised with 1 M HCl, extracted with Et$_2$O and the combined organic extracts dried (MgSO$_4$). Evaporation of the solvent and flash chromatography using petroleum ether-ethyl acetate (3:2) as eluant yielded **29** as a colourless oil (1.46 g, 80%).

IR (neat, cm^{-1}): 3580-3530, 2929, 2857, 1712, 1459, 1408, 1374, 1252, 1126, 1081, 938

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.36 (m, 2H), 3.83 (m, 1H), 2.35 (t, J=8 Hz, 2H), 2.06 (m, 4H), 1.65 (m, 2H), 1.58-1.36 (m, 11H), 1.20 (d, J=6 Hz, 3H)

LRMS (m/z): 242 (M$^+$, 0.4), 182 (35), 149 (22), 126 (25), 122 (50), 112 (20), 109 (28), 98 (46), 96 (33), 95 (56), 83 (21), 82 (58), 81 (89), 80 (21), 79 (22), 71 (49), 69 (35), 68 (100)

Exact Mass calculated for C$_{14}$H$_{26}$O$_3$: 224.1882; found: 224.1884

(E/Z)-13-Tetradec-8-enolide (14,15)
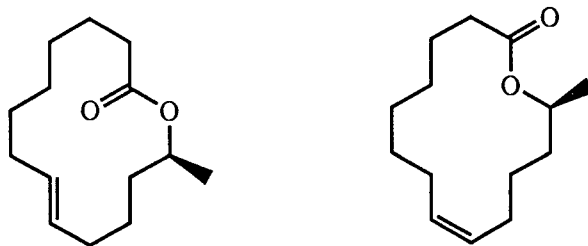
1-Phenyl-1 H-tetrazole-5-thiol (1.24 g, 6.94 mmol) in toluene (50 mL) was added to *tert*-butylisocyanide (0.8 mL, 6.94 mmol)·and the resulting mixture stirred until homogeneous. Hydroxy acid **29** (1.40 g, 5.78 mmol) was then added, the solution was diluted with toluene (1.0 L) and the mixture heated under reflux for 24 h. Removal of the solvent and flash chromatography using petroleum ether-ethyl acetate (25:1) as eluant yielded a 1:1.25 mixture of **14** and **15** as a yellow oil (901 mg, 70%).

Separation of **14** and **15** was achieved by flash chromatography using silver nitrate impregnated silica gel, and petroleum ether-diethyl ether (25:1) as eluant to give **14** (402 mg) as a colourless oil and **15** (491 mg) as a pale yellow oil.

Data for **14**

IR (neat, cm^{-1}): 2927, 2855, 1730, 1447, 1368, 1273, 1211, 1178, 1142, 1101, 1017, 970, 868, 732

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.46 (dt, J=16, 8 Hz, 1H), 5.30 (dt, J=16, 8 Hz, 1H), 5.06 (m, 1H), 2.28 (m, 2H), 2.15-1.98 (m, 4H), 1.90-1.72 (m, 4H), 1.64-1.18 (m, 8H), 1.20 (d, J=8 Hz, 3H)

LRMS (m/z): 224 (M$^+$, 29), 182 (72), 164 (22), 122 (50), 109 (30), 108 (21), 96 (41), 95 (59), 94 (23), 93 (20), 82 (71), 81 (88), 80 (23), 79 (29), 69 (24), 68 (100)

Exact Mass calculated for C$_{14}$H$_{24}$O$_2$: 224.1777; found: 224.1775

Data for **15**

IR (neat, cm^{-1}): 3426, 2931, 2858, 1729, 1453, 1368, 1251, 1132, 1081, 1040, 994, 882, 714

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.45 (dt, J=11, 8 Hz, 1H), 5.25 (dt, J=11, 8 Hz, 1H), 4.94 (m, 1H), 2.28 (m, 4H), 1.87 (m, 2H), 1.80-1.16 (m, 11H), 1.25 (d, J=6 Hz, 3H)

LRMS (m/z): 224 (M$^+$, 15), 182 (48), 164 (21), 122 (52), 109 (28), 96 (38), 95 (62), 94 (24), 93 (24), 82 (61), 81 (92), 80 (26), 79 (37), 69 (26), 68 (100)

Exact Mass calculated for C$_{14}$H$_{24}$O$_2$: 224.1777; found: 224.1774

(8R, 13S*)*-8-Hydroxy-13-tetradecanolide (30)
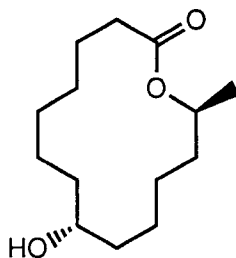
(a) **Hydroboration of (E/Z)-13-Tetradec-8-enolide (14,15) with borane-dimethylsulphide**

Borane-dimethylsulphide (70 μL, 0.74 mmol) was added to a 1:1 mixture of **14** and **15** (150 mg, 0.67 mmol) in THF (15 mL) and the resulting solution stirred for 4 h. The solution was then cooled to 0 °C and 3 M NaOH (600 μL, 1.8 mmol) and 30% H_2O_2 (1.2 mL) were added sequentially. Stirring was continued for a further 30 min. then the mixture was diluted with water, extracted with methylene chloride and the combined organic layers dried ($MgSO_4$). Evaporation of the solvent and purification by chromatotron using chloroform-methanol (99:1) as eluant yielded a mixture of **30, 31, 32** and **33** (130 mg, 80%) as a colourless oil.

The mixture of hydroxy lactones (130 mg, 0.54 mmol) was dissolved in THF (10 mL) and TMS chloride (169 μL, 1.1 mmol) and triethylamine (186 μL, 1.1 mmol) were added. The resulting solution was stirred for 24 h., diluted with diethyl ether, washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent and purification by chromatotron using petroleum ether-ethyl acetate (99:1) as eluant to give a mixture of **36** and **37** (54 mg) and **34** and **35** (98 mg), in a total yield of 90%.

A 1 M solution of tetrabutylammonium fluoride (340 μL, 0.34 mmol) in THF was added to a solution of **36** and **37** (54 mg, 0.17 mmol) in THF (5 mL) and the resulting mixture stirred for 2 h. The mixture was diluted with water, extracted with ether and the combined organic layers dried (MgSO$_4$). Evaporation of the solvent and purification by chromatotron using chloroform-methanol (99:1) as eluant yielded hydroxy lactones **32** and **33** (37 mg, 90%).

Desilylation of **34** and **35** (98 mg, 0.31 mmol) followed the same procedure as above using tetrabutylammonium fluoride (620 μL, 0.62 mmol) to give hydroxy lactones **30** (40 mg) and **31** (28 mg) as colourless oils (90%).

Data for **30**

IR (neat, cm^{-1}): 3620-3120, 2936, 2859, 1719, 1452, 1371, 1243, 1141, 755

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.00 (m, 1H), 3.73 (m, 1H), 2.44 (m, 1H), 2.25 (m, 1H), 1.80-1.16 (m, 19H), 1.21 (d, J=8 Hz, 3H)

LRMS (m/z) from CI: 258 (M$^+$+18, 3)

LRMS (m/z) from EI: 224 (M$^+$-18, 2), 141 (88), 113 (39), 95 (100), 69 (41), 68 (26), 67 (22)

Exact Mass calculated for C$_{14}$H$_{26}$O$_3$: 242.1882; found: 242.1874

Data for **31**

    IR (neat, cm^{-1}): 3600-3175, 2934, 2863, 1719, 1453, 1371, 1250, 1122, 934, 755

    ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 4.98 (m, 1H), 3.84 (m, 1H), 2.40 (m, 1H), 2.27 (m, 1H), 1.72-1.20 (m, 19H), 1.23 (d, J=8 Hz, 3H)

    LRMS (m/z): 224 (M$^+$+18, 13), 173 (25), 156 (25), 156 (25), 155 (91), 115 (58), 109 (56), 100 (25), 99 (100), 98 (52), 97 (30), 96 (20), 95 (36), 34 (29), 83 (50), 82 (43), 81 (80), 73 (44)

Data for **32** and **33**

    IR (neat, cm^{-1}): 3600-3115, 2933, 2862, 1720, 1453, 1371, 1251, 1112, 755

    ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 5.03 (m, 1H), 4.95 (m, 1H), 3.78 (m, 2 × 1H), 2.43 (m, 2 × 1H), 2.30 (m, 2 × 1H), 1.74-1.20 (m, 2 × 19H), 1.23 (d, J=8 Hz, 2 × 3H)

    LRMS (m/z): 242 (M$^+$, 0.2), 224 (6), 155 (87), 141 (58), 115 (24), 113 (32), 109 (31), 99 (100), 98 (26), 95 (67), 83 (25), 82 (24), 81 (69), 73 (26)

b) Hydroboration of *8E*-tetradecen-13-olide (14) with borane-dimethylsulphide

Borane-dimethylsulphide (22 μL, 0.22 mmol) was added to a solution of lactone **14** (25 mg, 0.11 mmol) in THF (3 mL) at -78 °C and the resulting mixture stirred for 24 h. Standard work-up and purification, as outlined in method (a), yielded hydroxy lactones **30, 31, 32** and **33** (26 mg, 96%) in a ratio of 44:26:18:12 (GC analysis of TMS ethers) as a colourless oil.

(c) Hydroboration of *8E*-tetradecen-13-olide (14) with 9BBN

A solution of 9BBN (54 mg, 0.22 mmol) in THF (1 mL) was added to a solution of lactone **14** (25 mg, 0.11 mmol) in THF (2 mL) and the resulting solution stirred for 10 h. Standard work-up and purification yielded hydroxy lactones **30, 31, 32** and **33** (25 mg, 93%) in a ratio of 43:24:26:7 (GC analysis of TMS ethers) as a colourless oil.

(d) Hydroboration of *8E*-tetradecen-13-olide (14) with disiamylborane

A 0.5 M solution of disiamylborane in THF (1.8 mL, 0.40 mmol) was added to lactone **14** (40 mg, 0.18 mmol) in THF (4 mL) and the resulting solution stirred for 30 h. Standard work-up and purification yielded hydroxy lactones **30** and **33** (42 mg, 96%) in a ratio of 89:11 (GC analysis of TMS ethers) as a colourless oil.

(e) Hydroboration of *8Z*-tetradecen-13-olide (15) with borane-dimethylsulphide

Borane-dimethylsulphide (22 μL, 0.22 mmol) was added to a solution of lactone **15** (25 mg, 0.11 mmol) in THF (3 mL) at -78 °C and the resulting mixture stirred for 24 h. Standard work-up and purification yielded hydroxy lactones **30, 31, 32** and **33** (27 mg, 100%) in a ratio of 45:28:19:8 (GC analysis of TMS ethers) as a colourless oil.

(f) Hydroboration of _8Z_-tetradecen-13-olide (15) with 9BBN

A solution of 9BBN (54 mg, 0.22 mmol) in THF (1 mL) was added to a solution of lactone **15** (25 mg, 0.11 mmol) in THF (2 mL) and the resulting mixture stirred for 10 h. Standard work-up and purification yielded hydroxy lactones **30, 31, 32** and **33** (25 mg, 93%) in a ratio of 51:7:6:36 (GC analysis of TMS ethers) as a colourless oil.

(g) Hydroboration of _8Z_-tetradecen-13-olide (15) with disiamylborane

A 0.5 M solution of disiamylborane in THF (1.5 mL, 0.34 mmol) was added to lactone **15** (30 mg, 0.14 mmol) in THF (4 mL) and the resulting mixture stirred for 18 h. Standard work-up and purification yielded hydroxy lactones **30, 31** and **33** (30 mg, 93%) in a ratio of 53:37:10 (GC analysis of TMS ethers) as a colourless oil.

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SPECTRAL APPENDIX

21

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22

OTBDMS

OAc

23

OTBDMS

24

OTBDMS H

17

25

26

OTBDMS
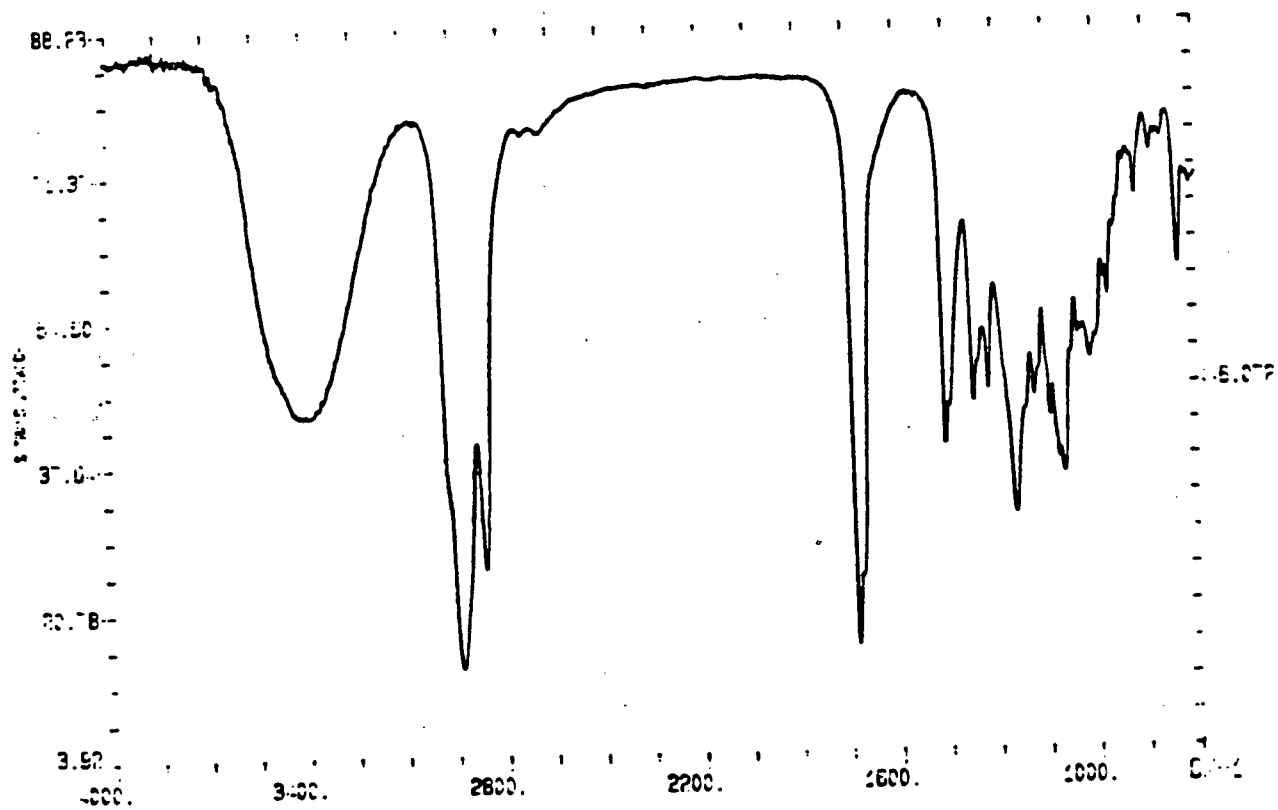
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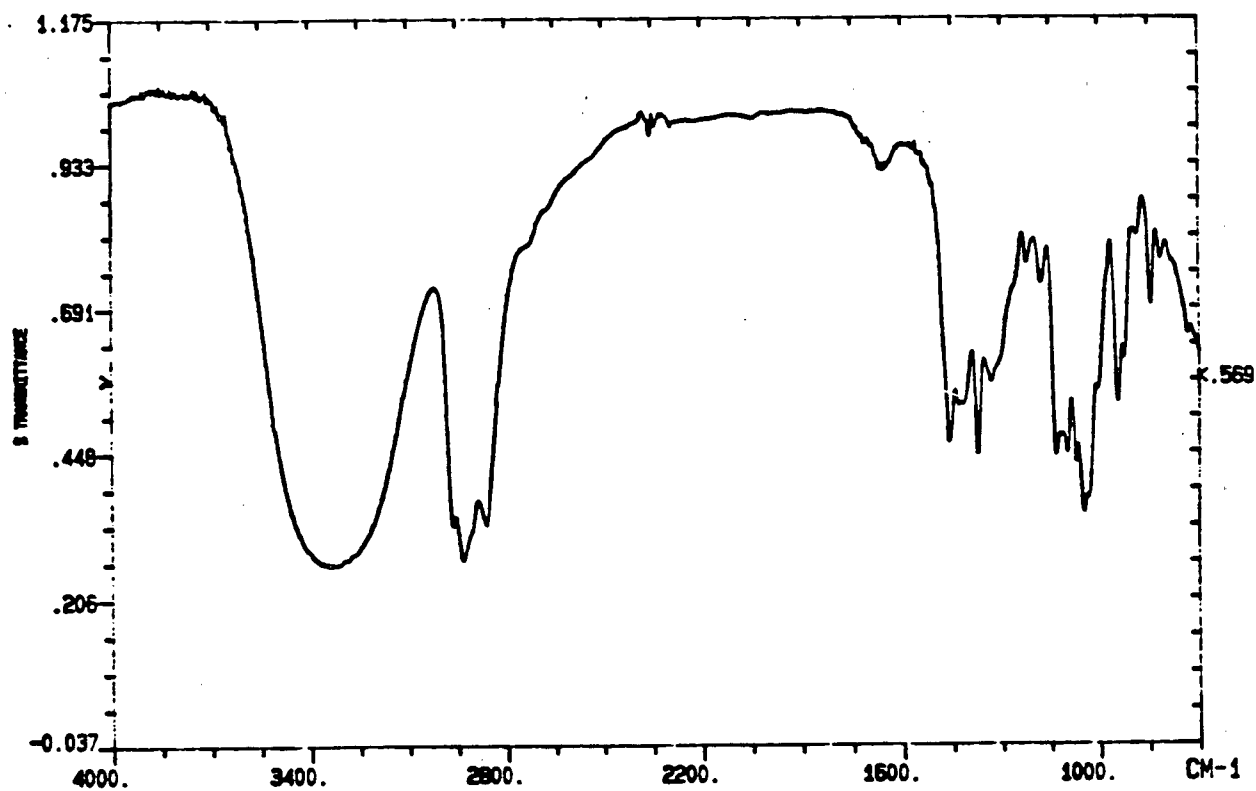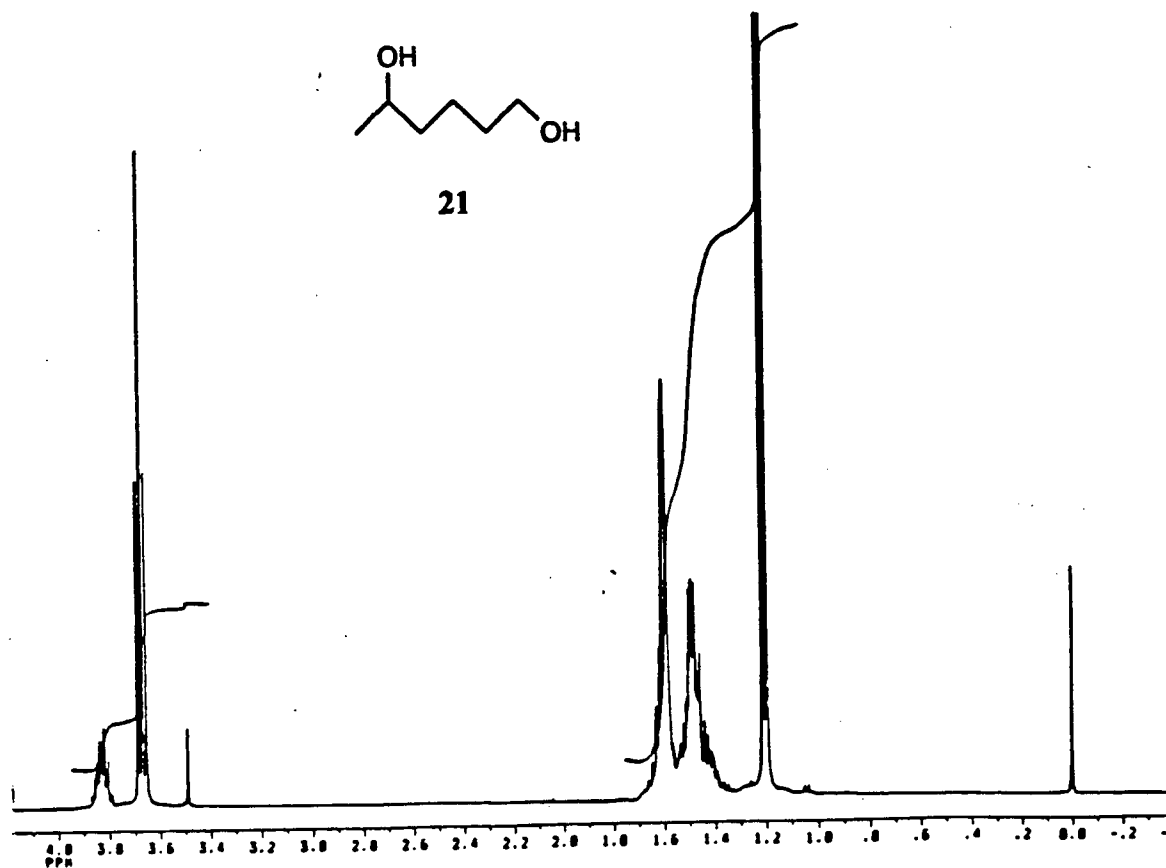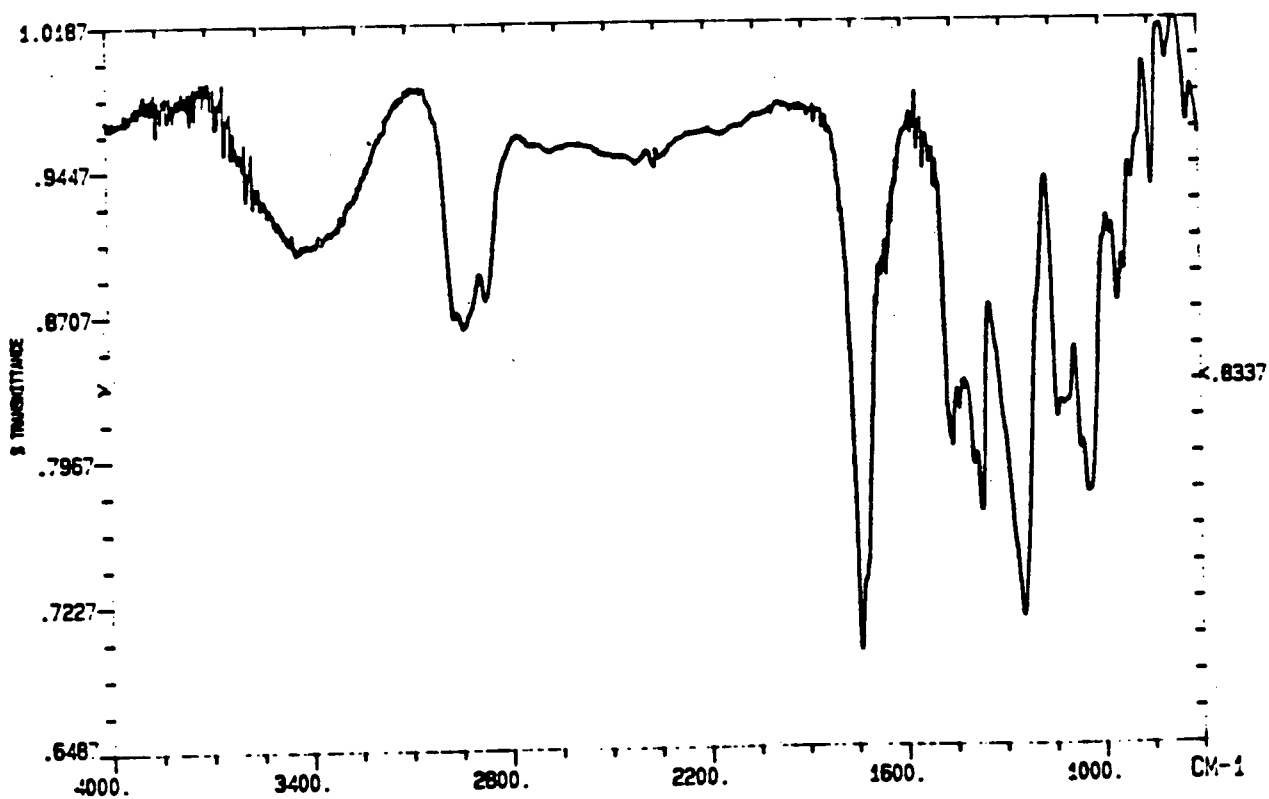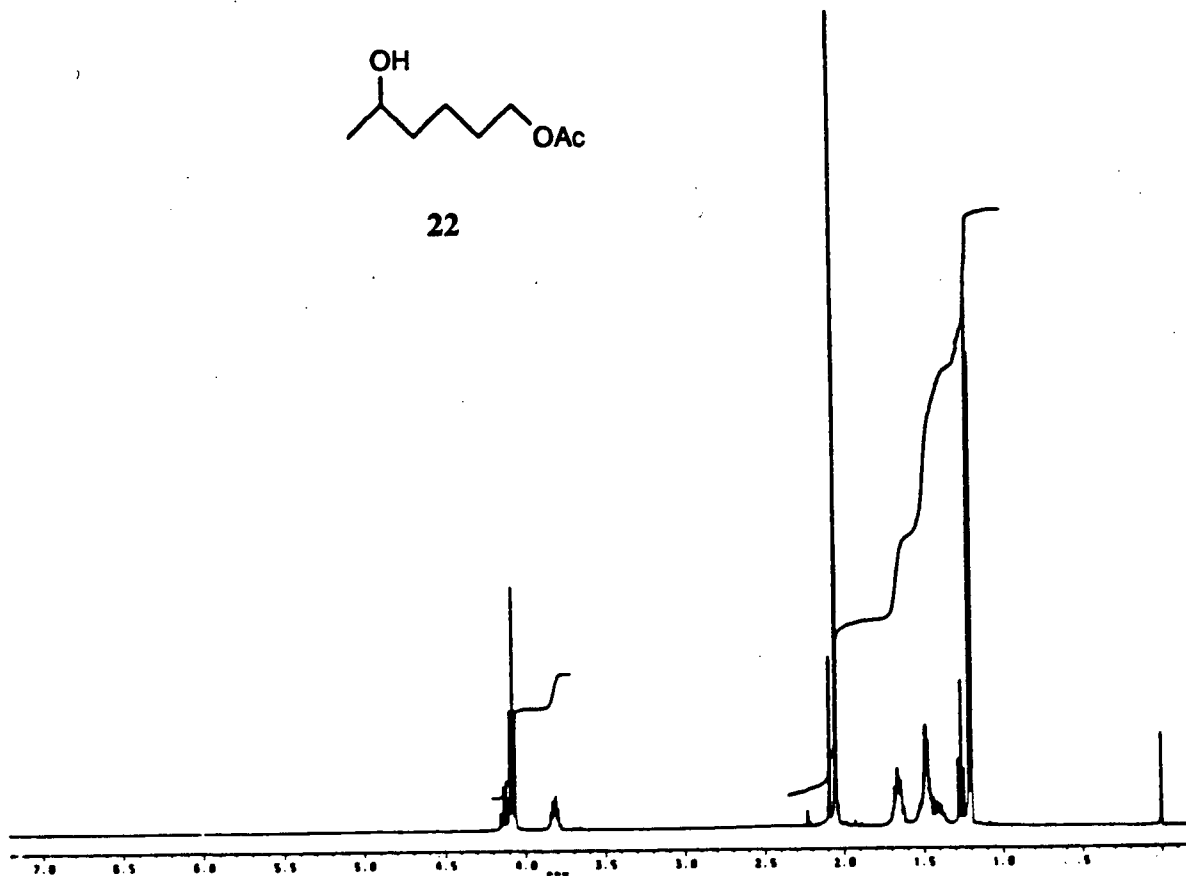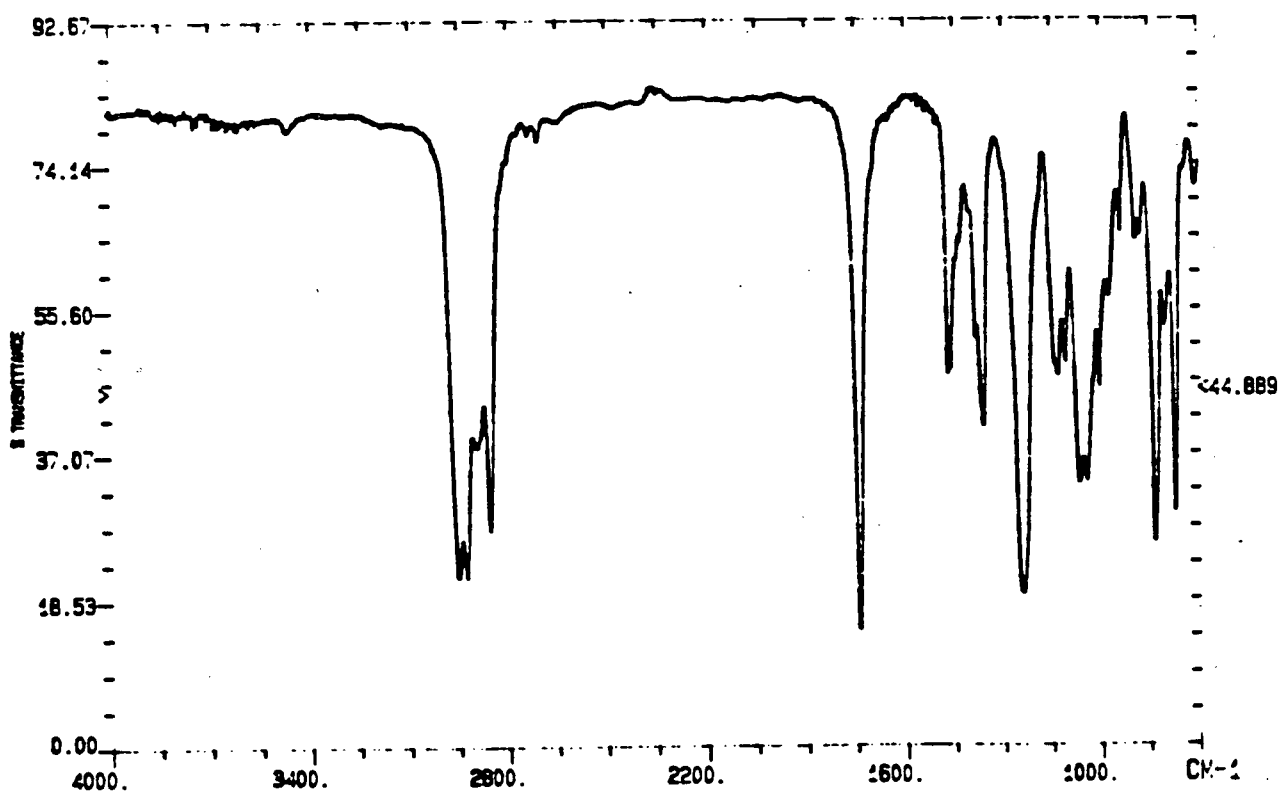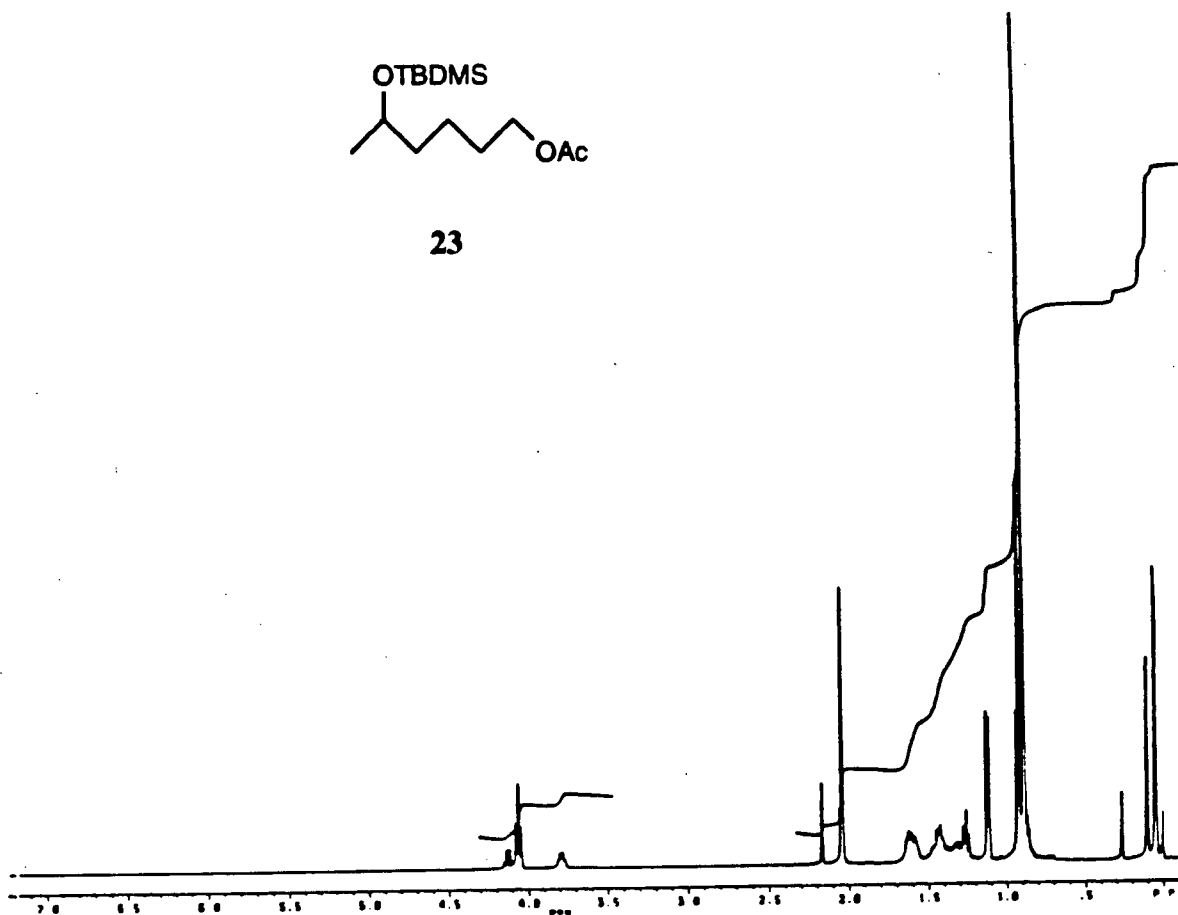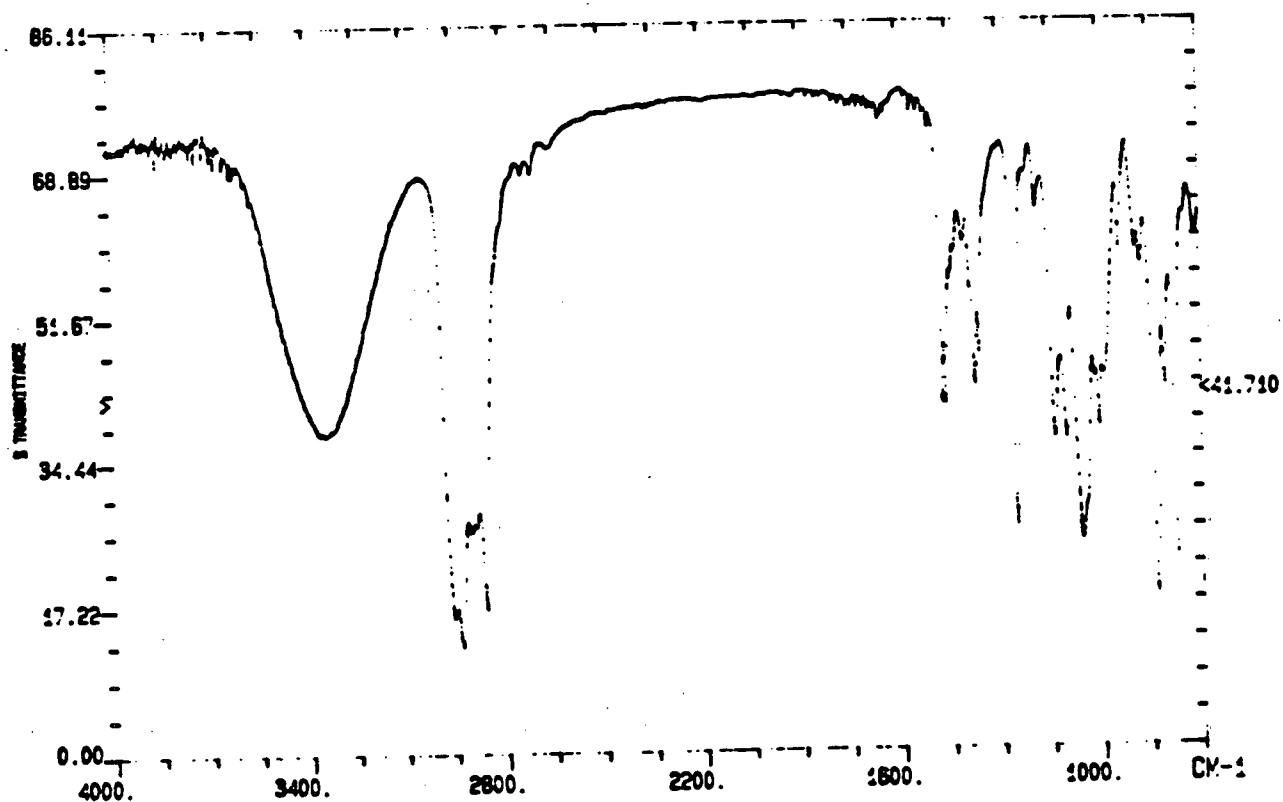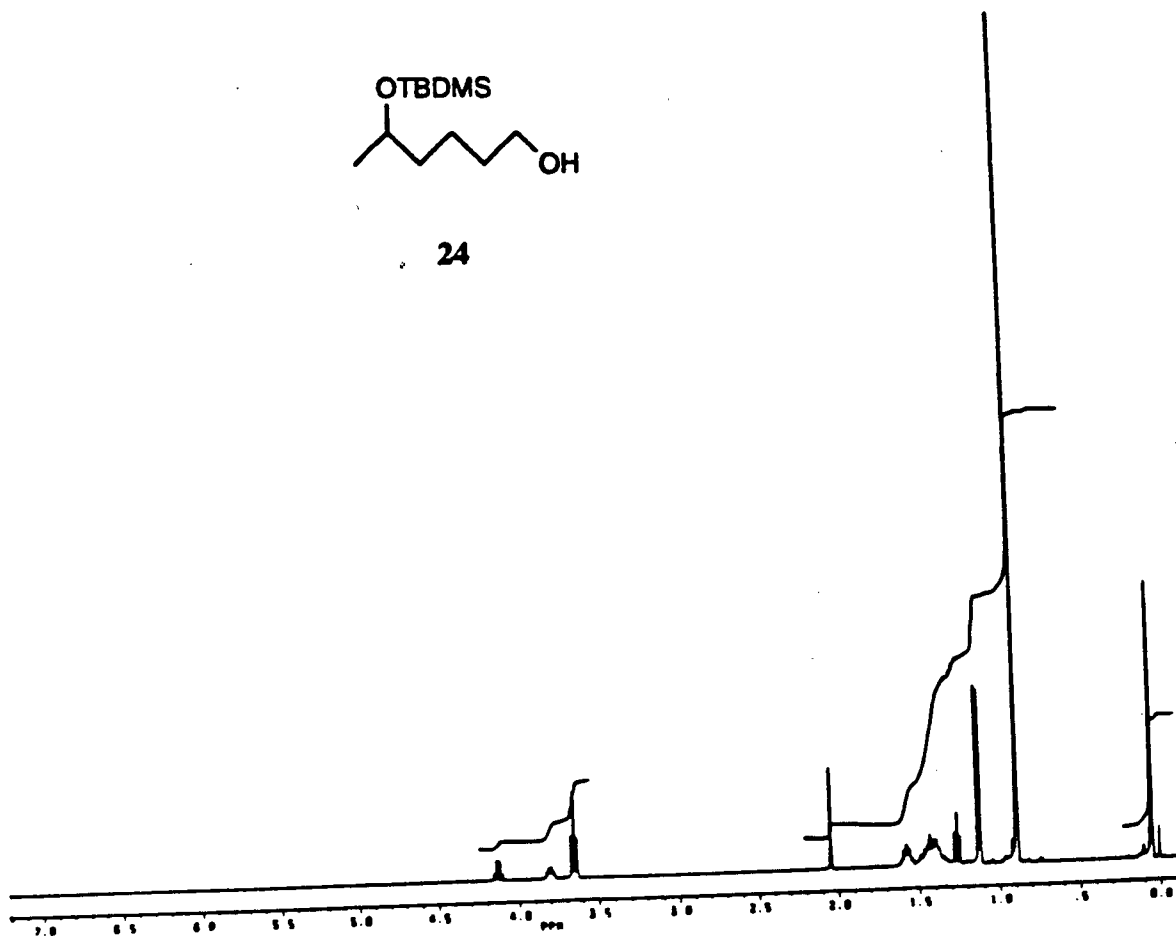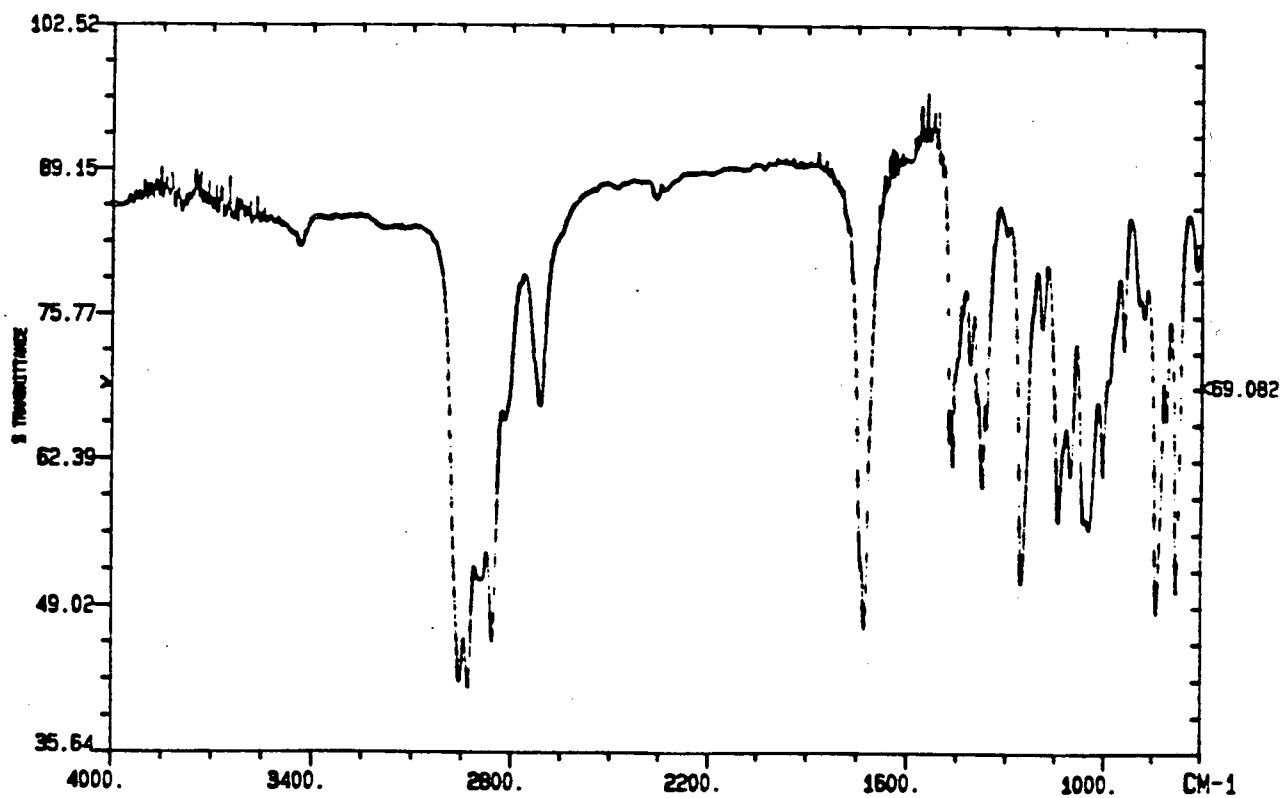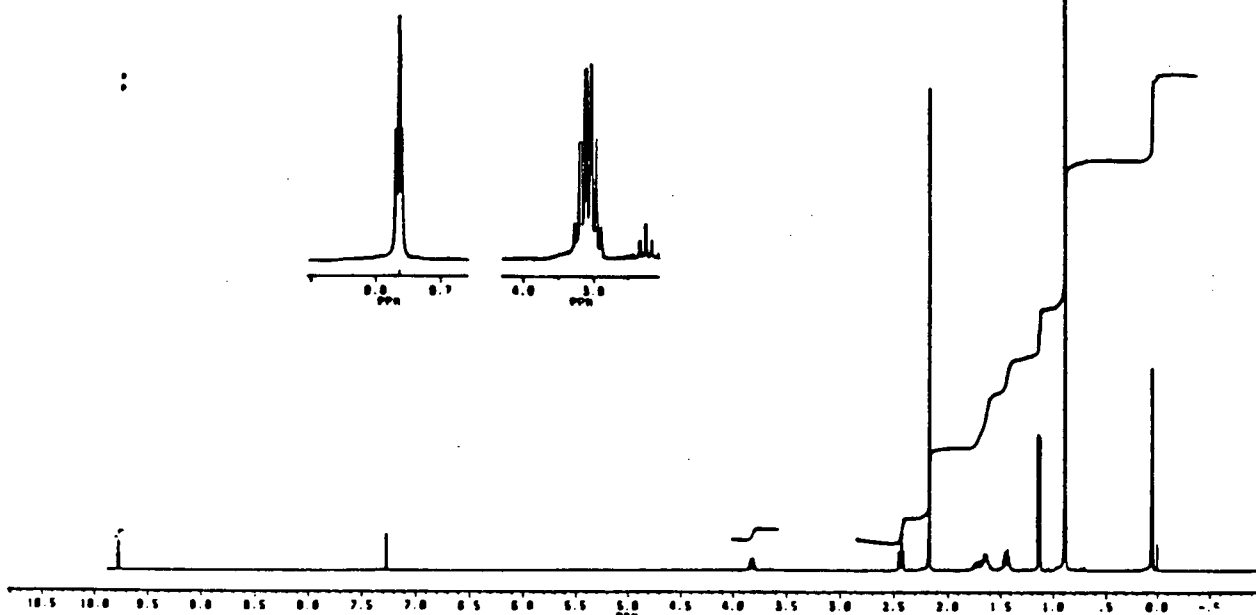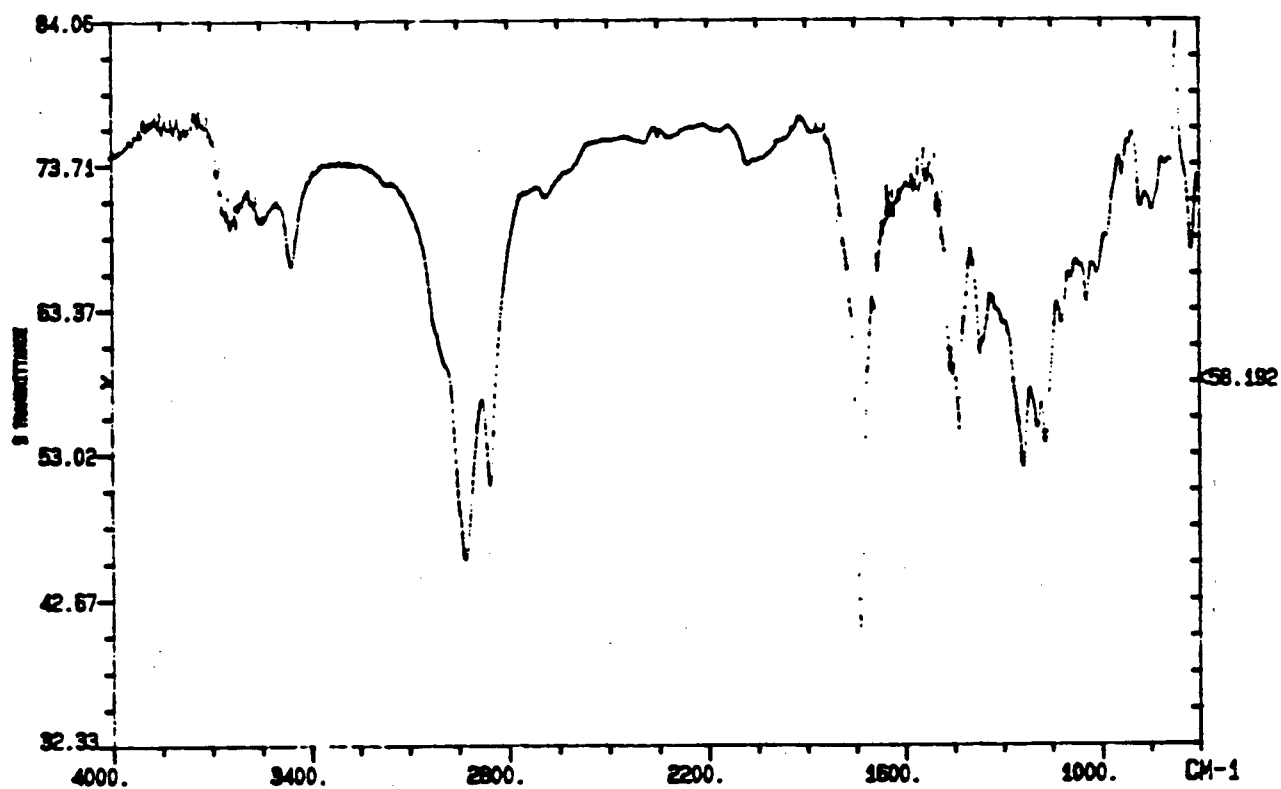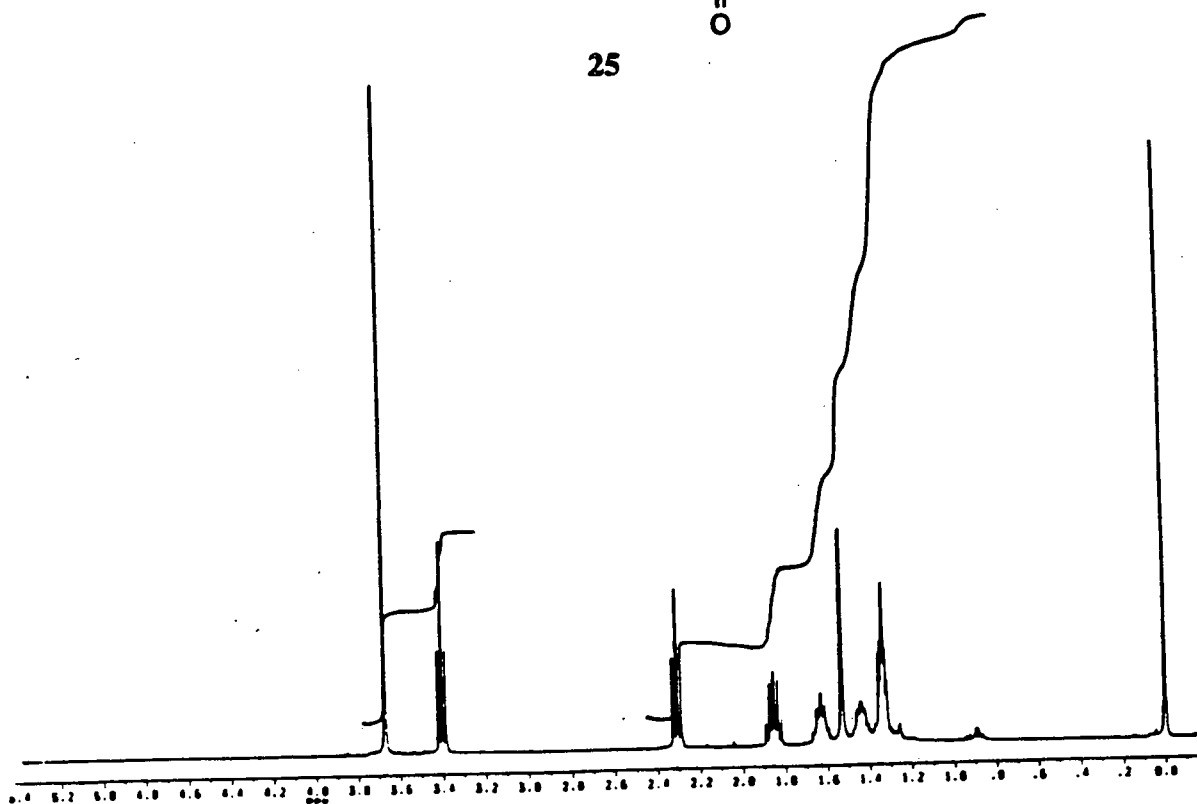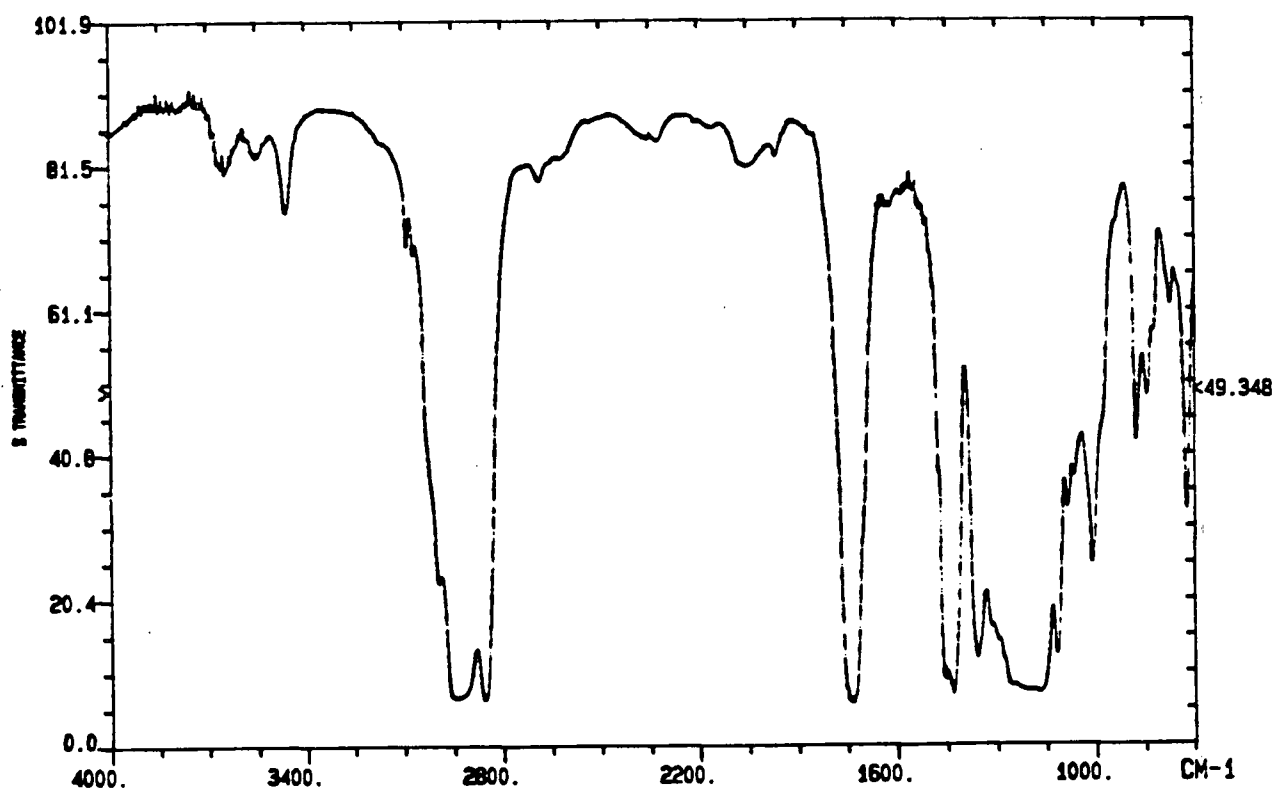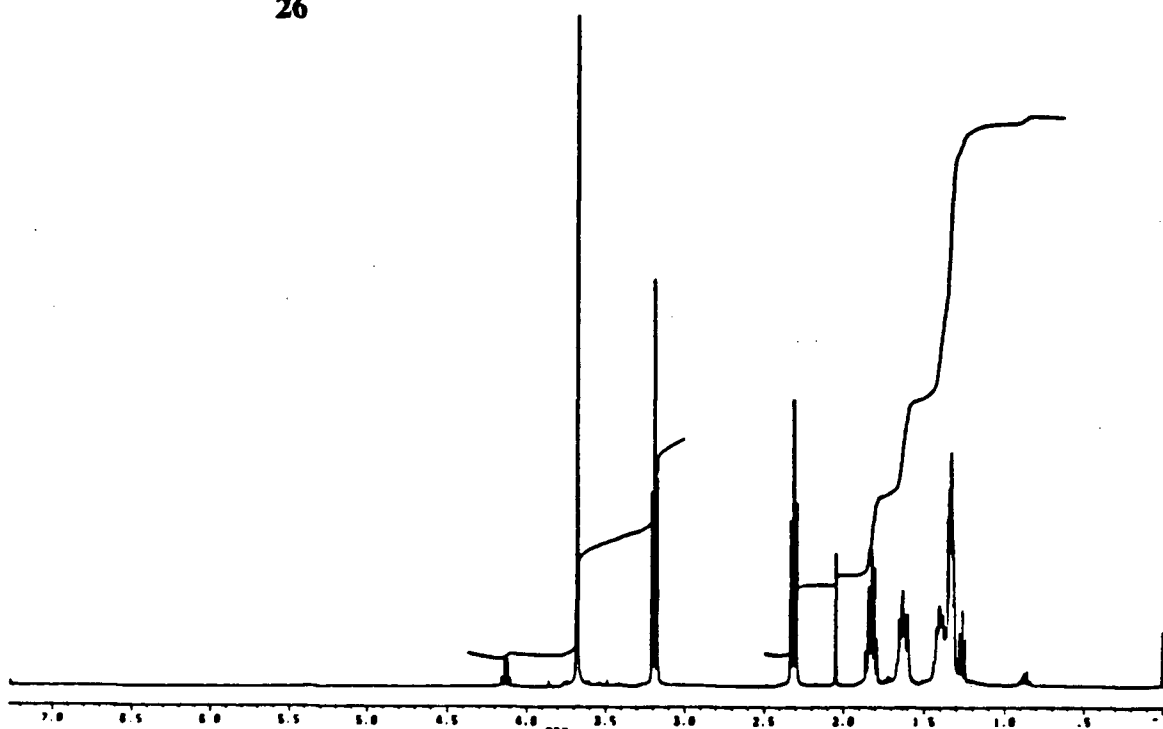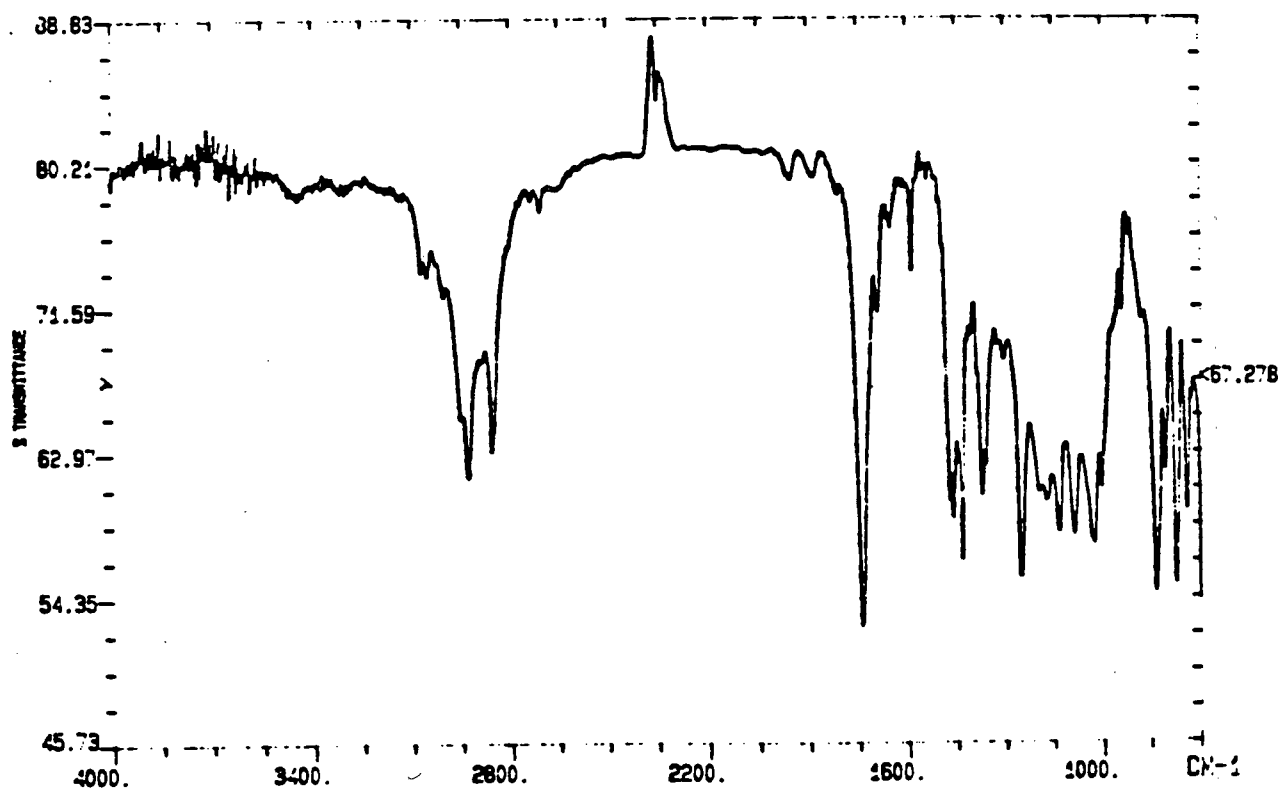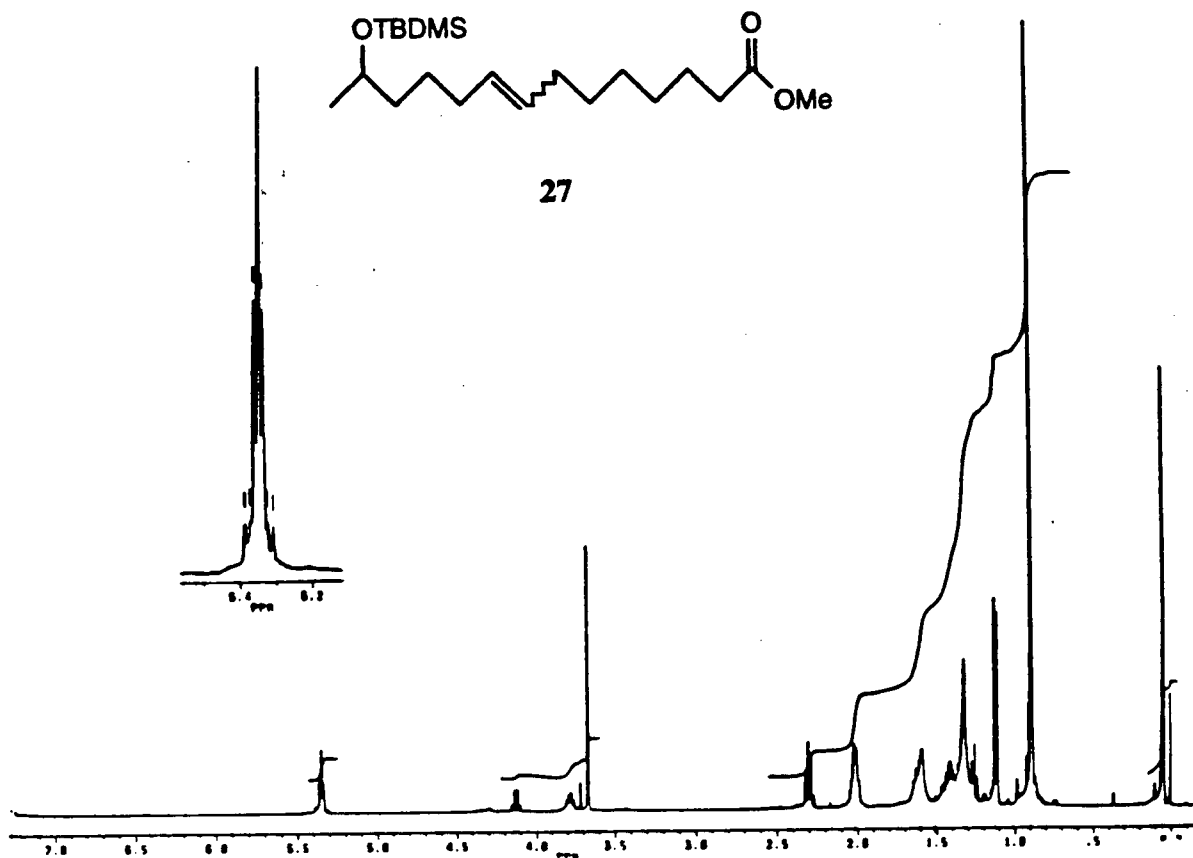
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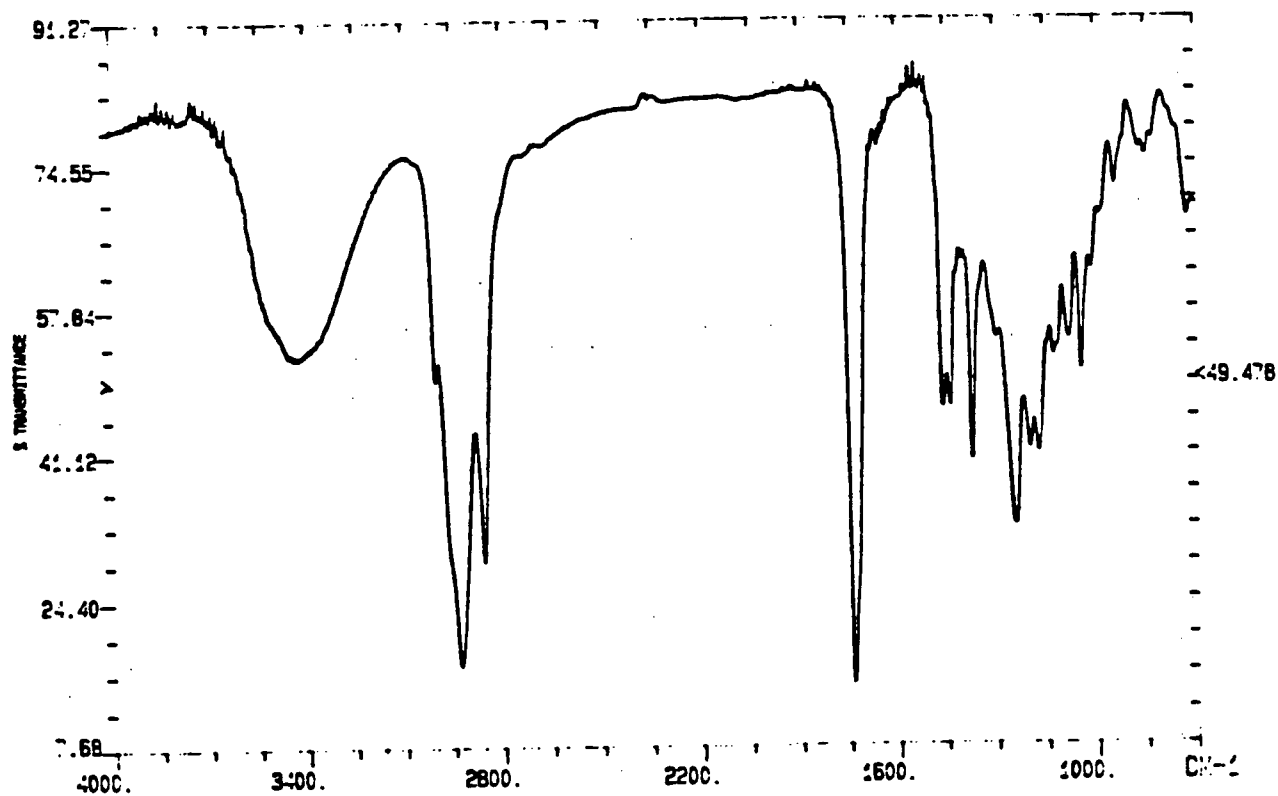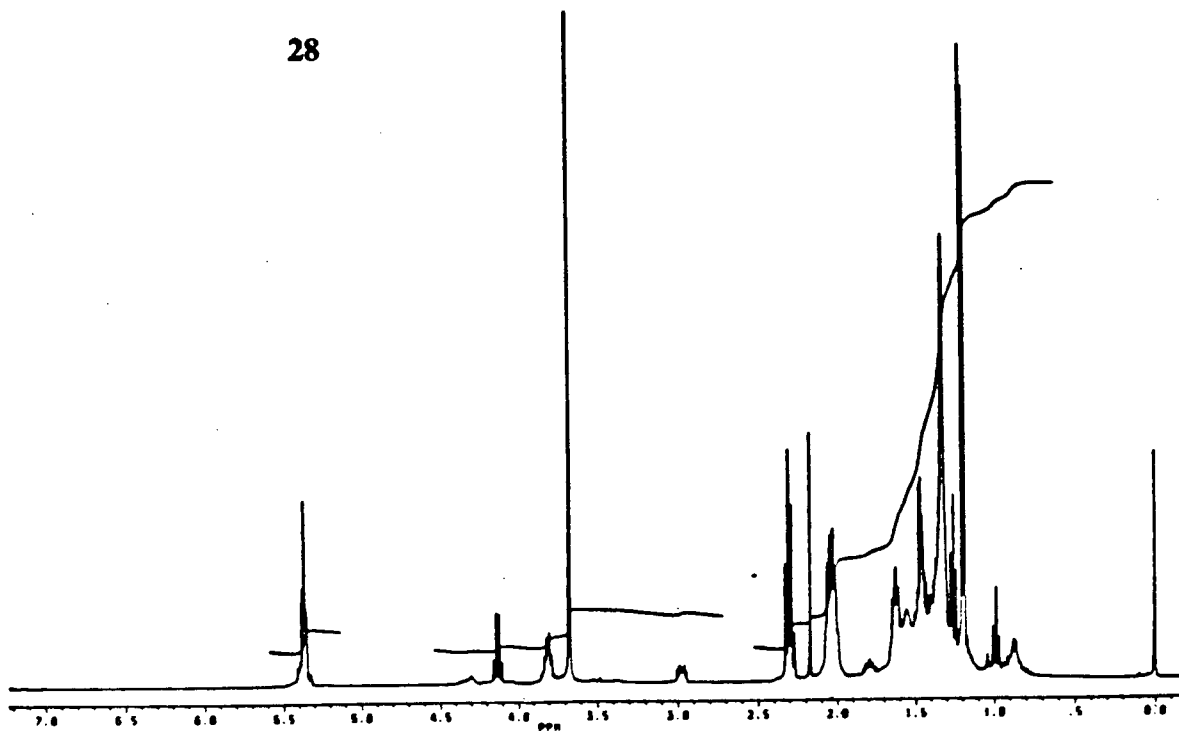
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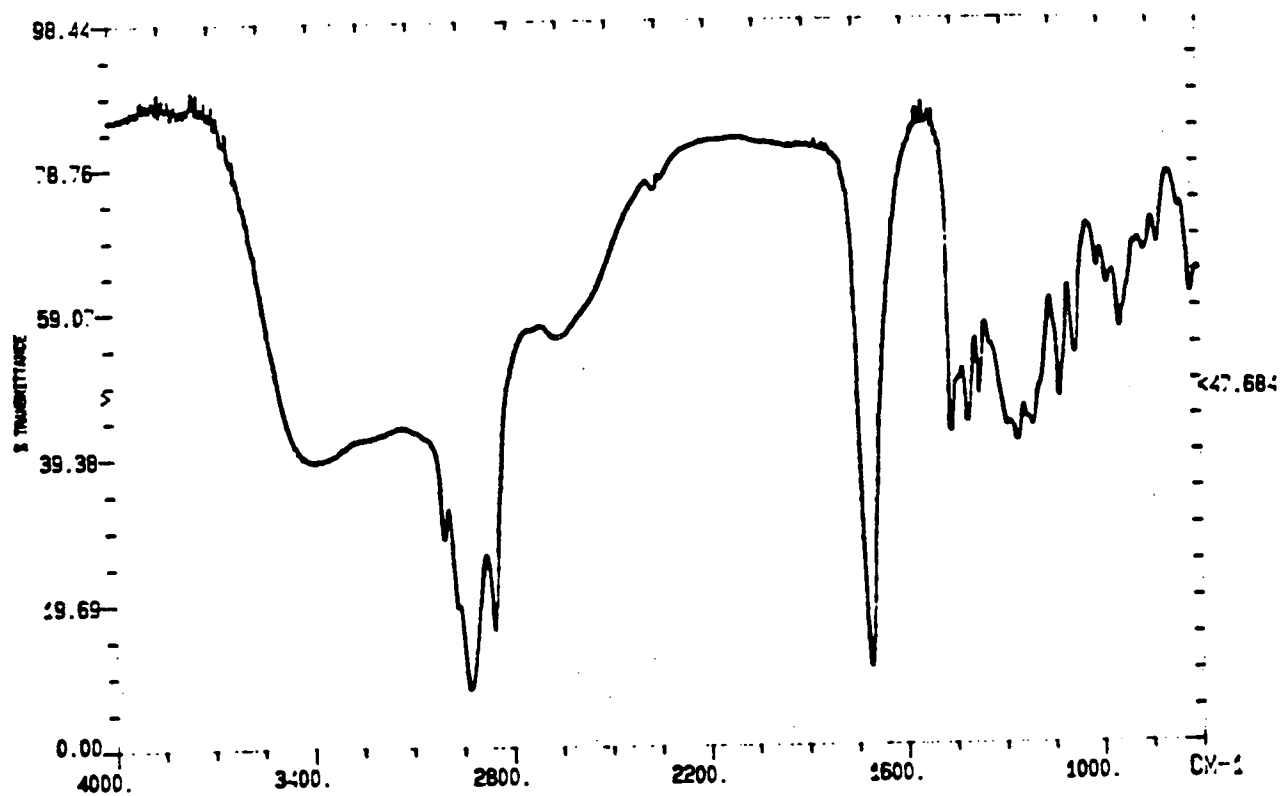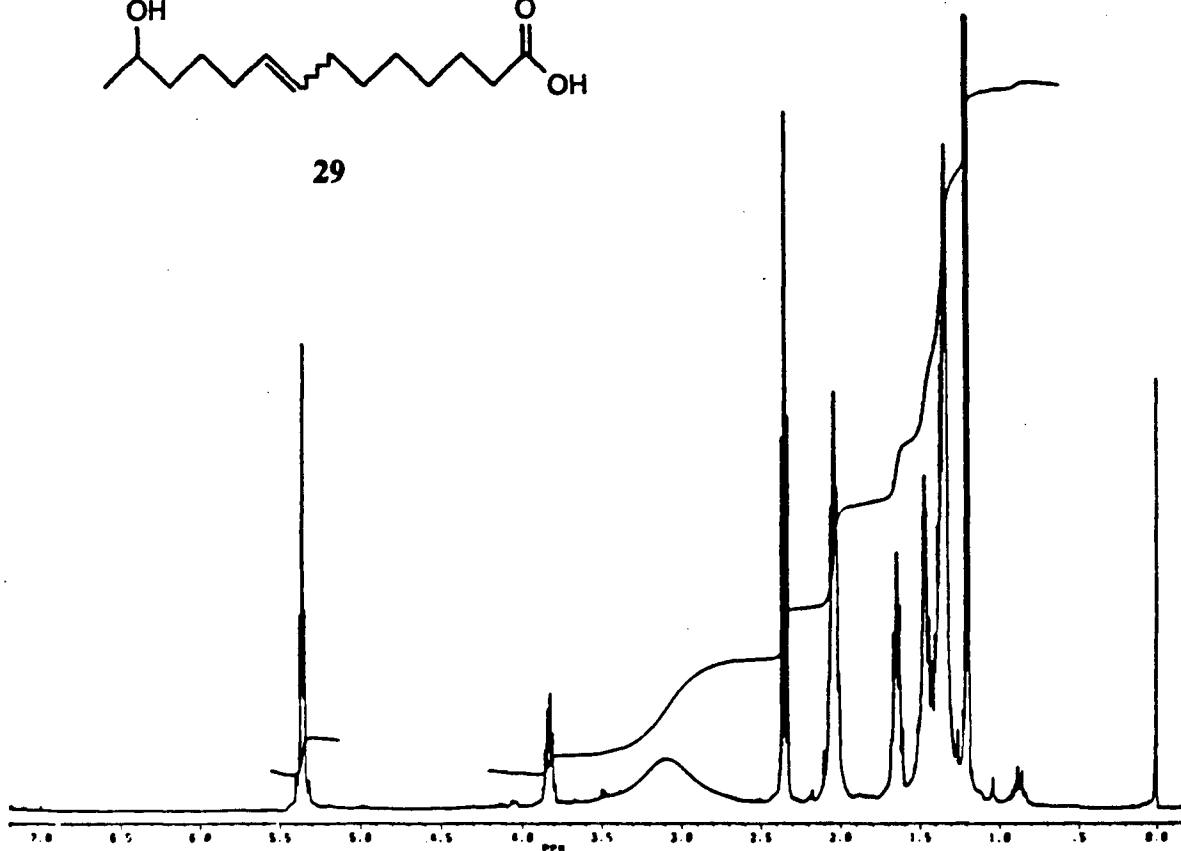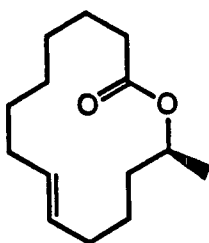
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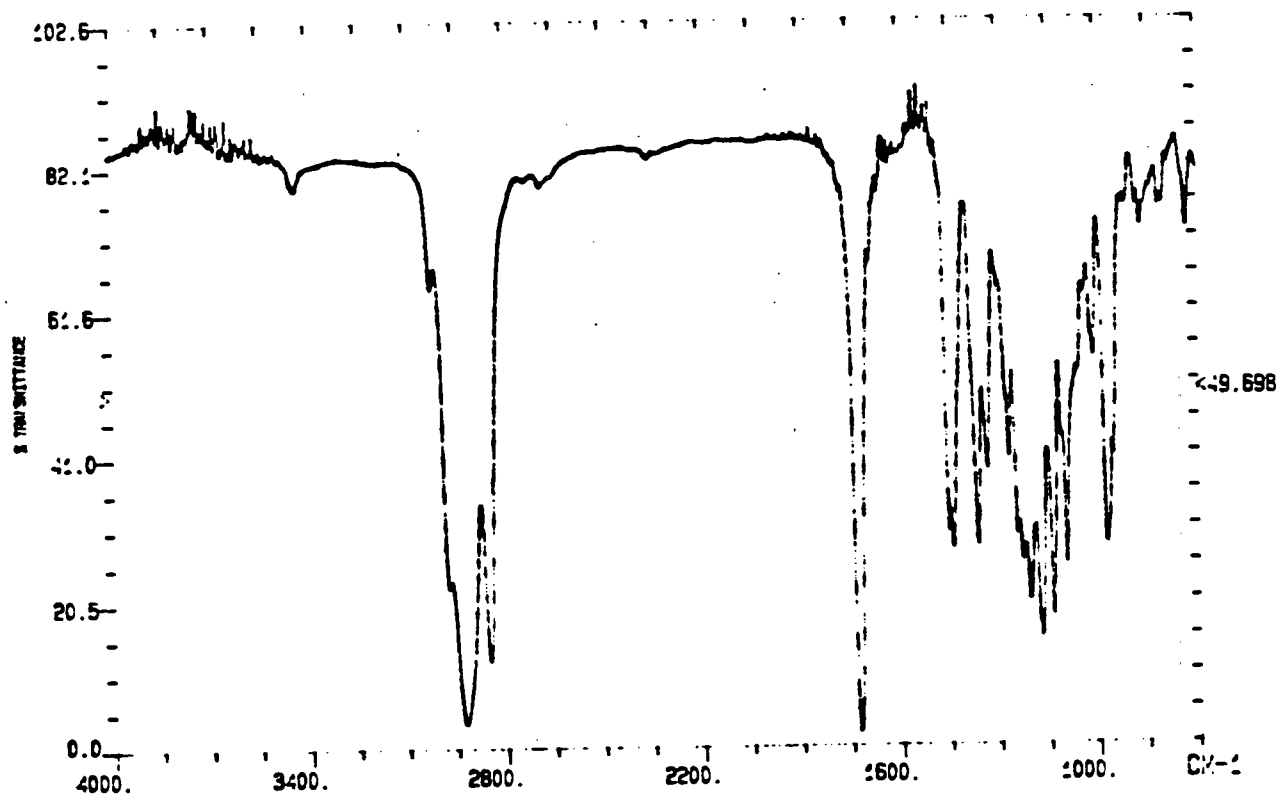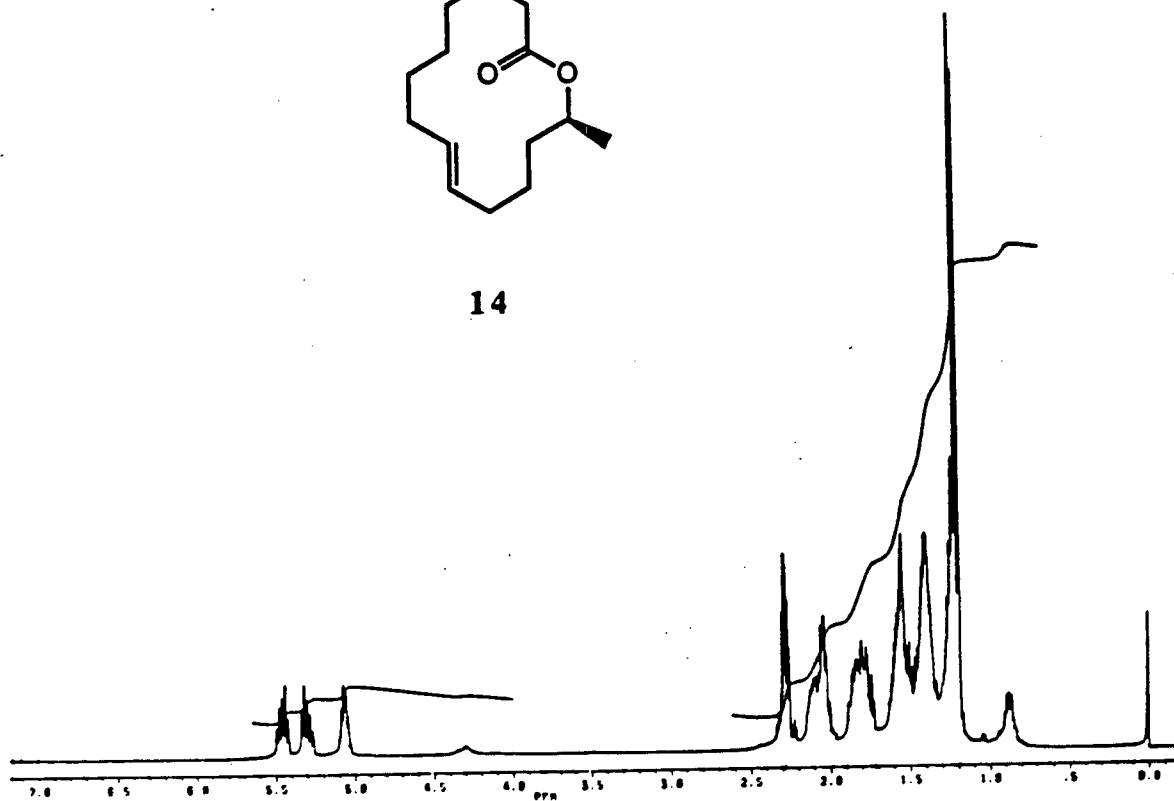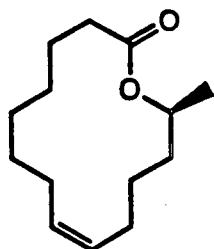
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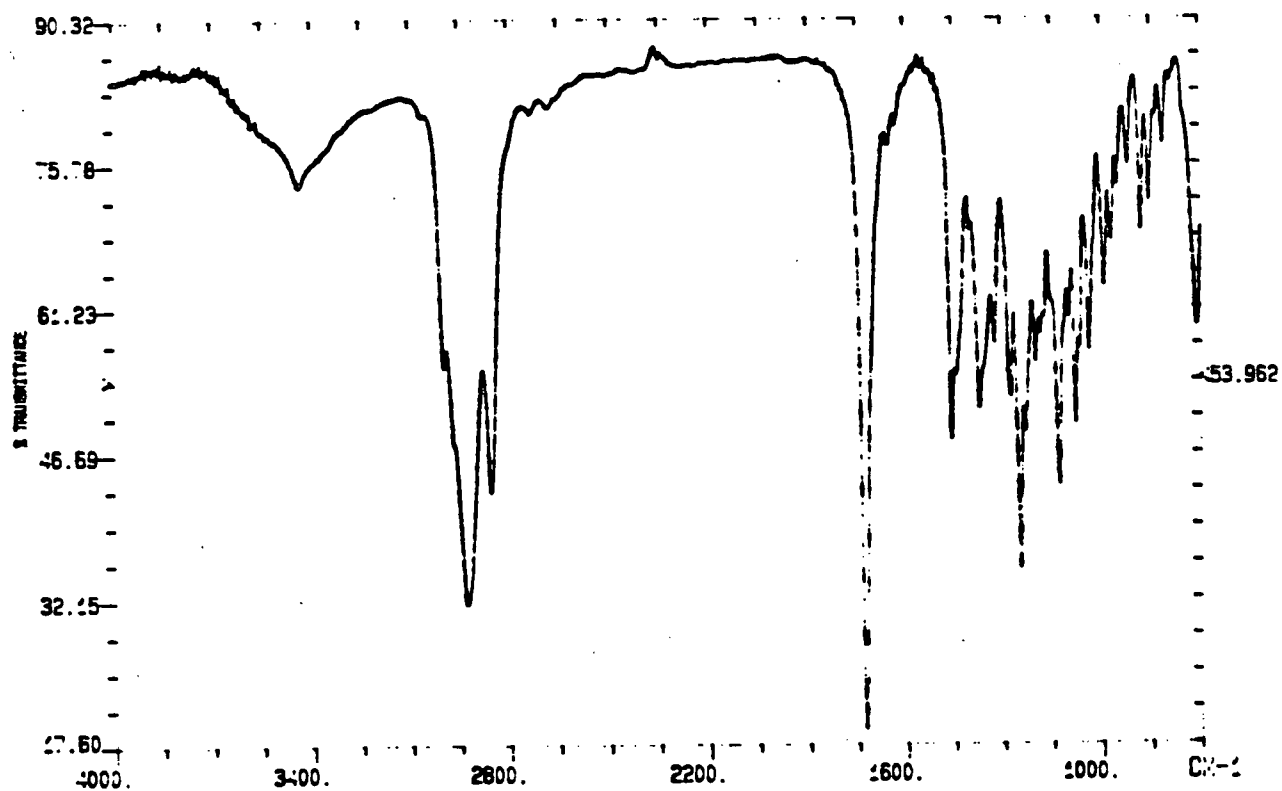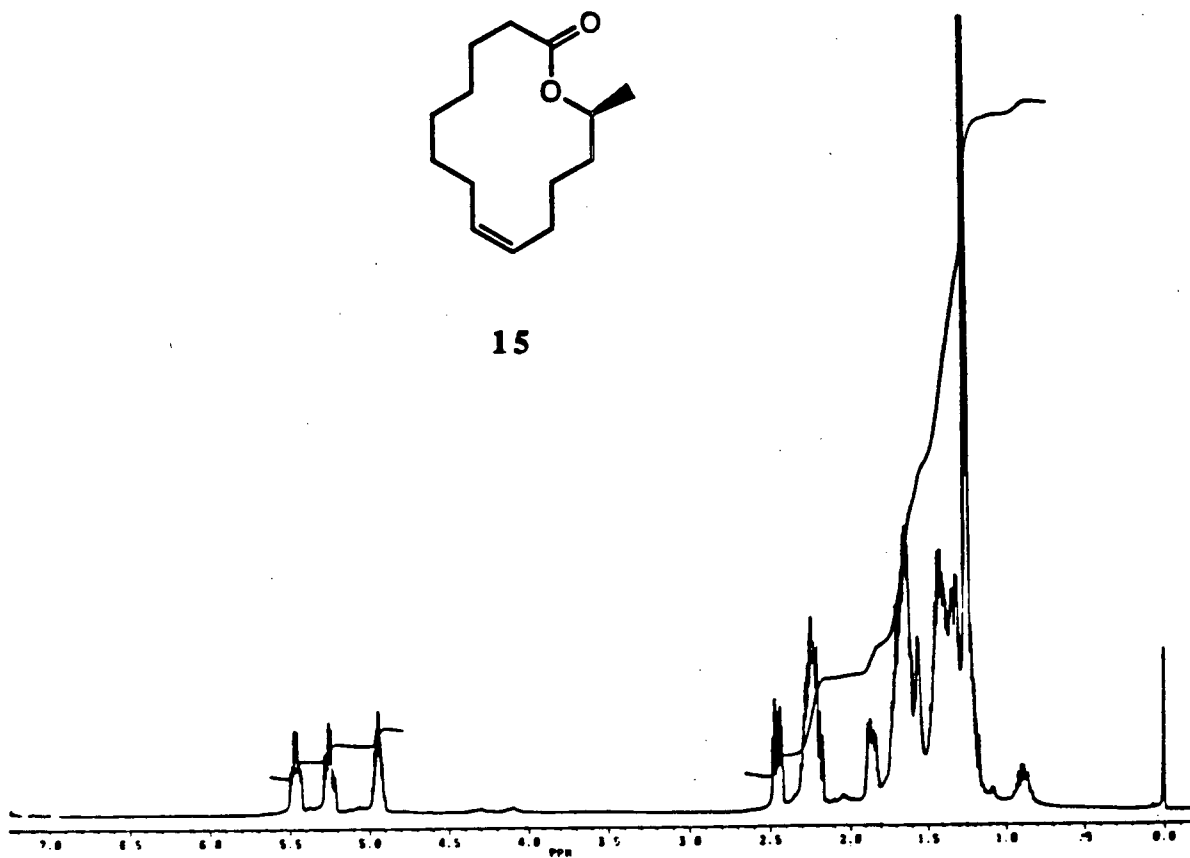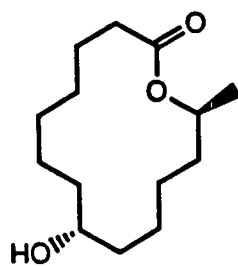
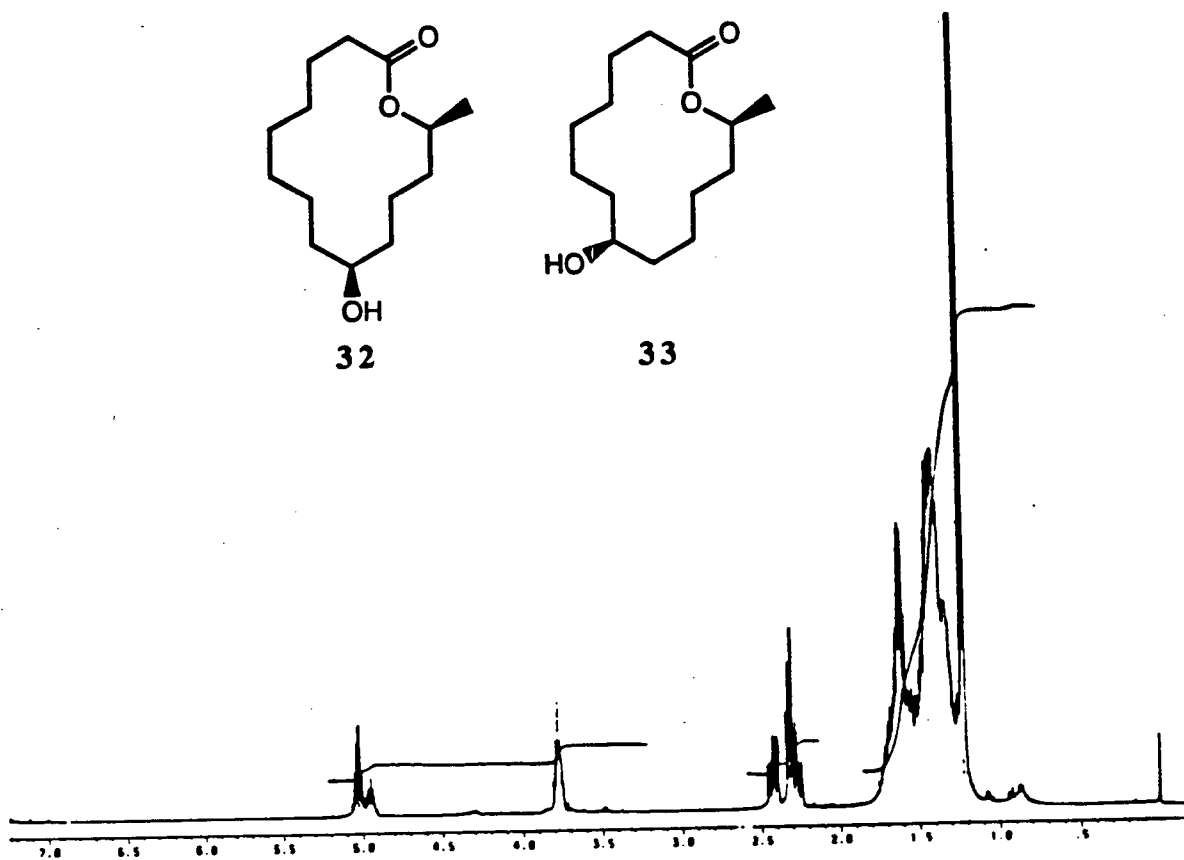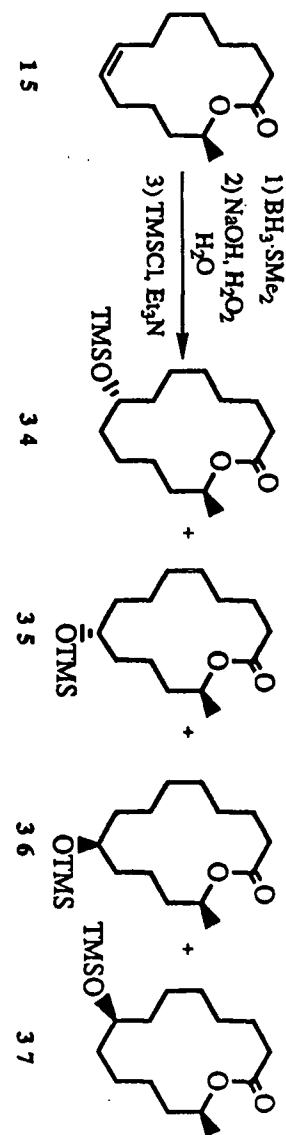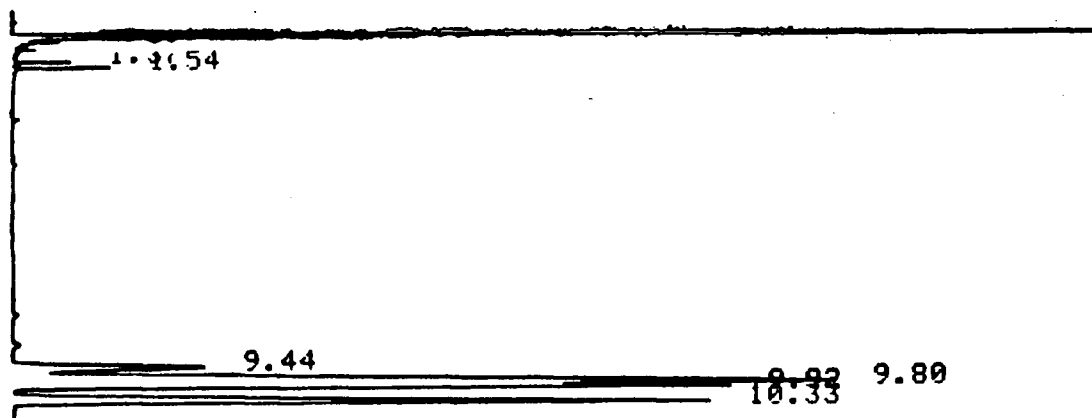**30**
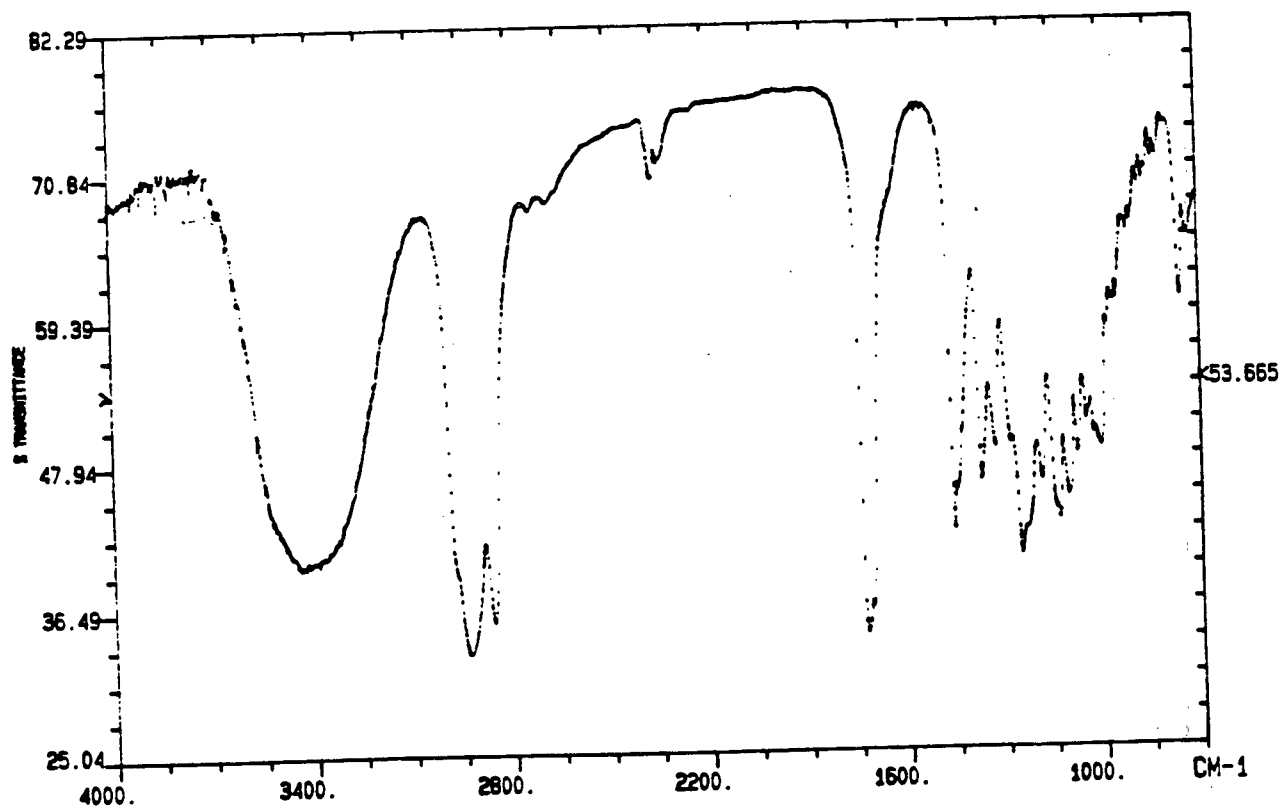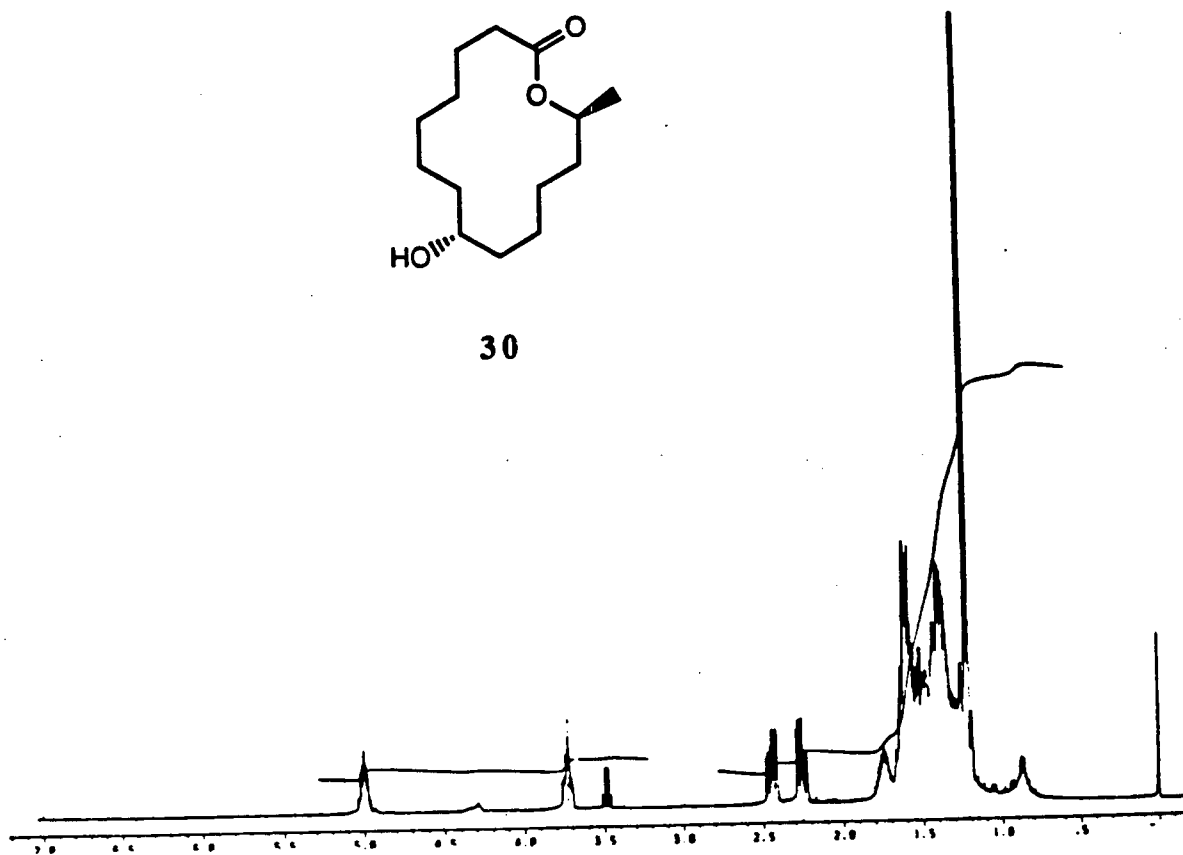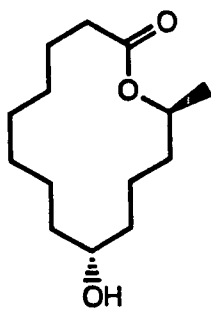
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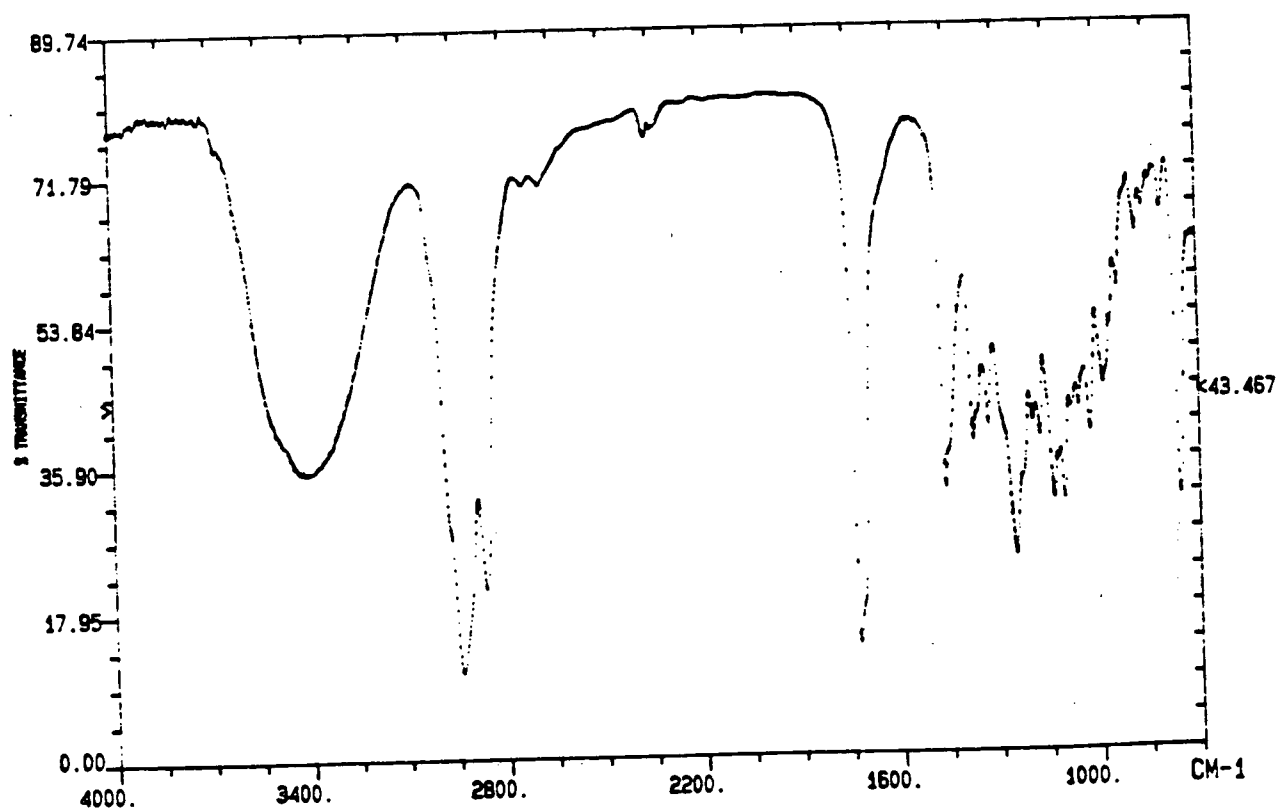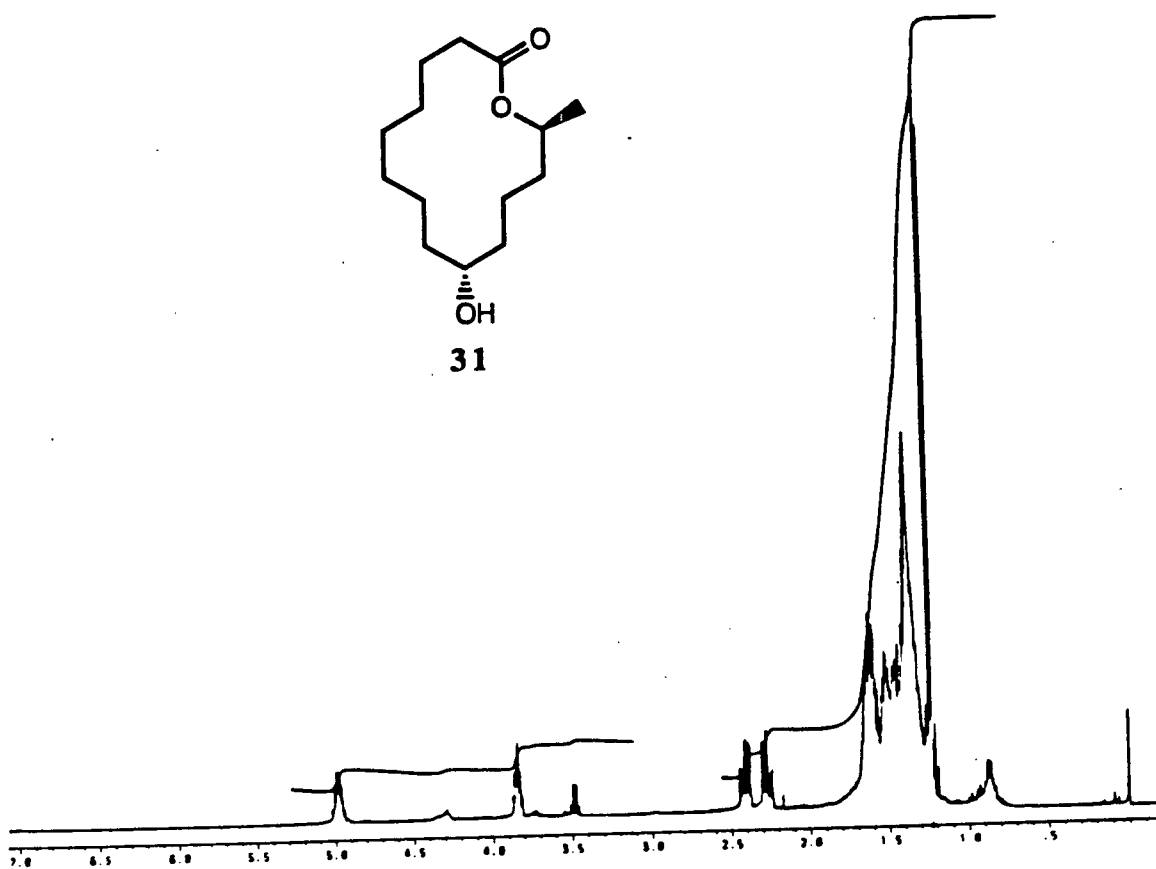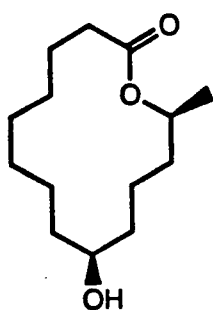
32
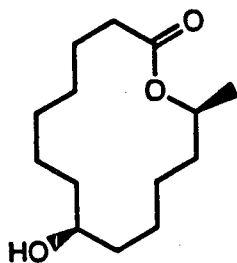
33

Representative GC spectrum for analysis of product distribution in hydroboration reactions.

[hp] 5880A   MANUAL INJECTION @ 21:49   JAN 17, 1991

AREA %

RT	AREA	TYPE	AREA %
1.37	5.68	BB	0.284
1.54	11.24	BB	0.561
9.44	168.53	BV	8.411
9.80	883.23	VV	44.077
9.92	385.83	VP	19.255
10.33	549.32	PB	27.414

TOTAL AREA = 2003.84
MULTIPLIER = 1