SYNTHONS FOR THE CONSTRUCTION OF ERYTHROMYCIN

by

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SCOPE AND CONTENTS:

A unique approach to the synthesis of Erythromycins, involving the stereoselective synthesis of acyclic precursors, was studied. The simple materials; 3-pentanone, ethyl formate, and propionic anhydride were assembled to give the allylic ester 51. Subsequent stereoselective enolate formation of the propionate unit followed by a stereospecific Claisen rearrangement gave erythro-γ,δ-heptenoic acid 46. Stereoselective epoxidation of the γ,δ-heptenoic acid followed by lactonization gave the γ-lactone system 49. This γ-lactone contains the correct array of functional groups and stereochemistry of the C_9-C_{13} fragment of Erythronolide A, the aglycone of Erythromycin A and C.

The above starting materials; 3-pentanone, ethyl formate, and propionic anhydride together with propylene oxide were also assembled to give the allylic ester 55, which contains all of the carbon atoms and correct stereochemistry of the C_1-C_8 fragment of Erythronolide A (and B). The Claisen rearrangement of this ester is expected to give the carbon framework of the C_1-C_8 fragment. An important step in the synthesis of ester 55 was the mercuric assisted solvolysis of the α-methylthiohydrazone 61, which proceeded in a stereoselective manner. The reduction of enone 57, contrary to expectations, proceeded in a non-stereoselective manner.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Professor R. A. Bell, for his continuous encouragement, friendship, and guidance during the course of this work. Helpful discussions with Drs. B. E. McCarry, J. M. Rosenfeld, D. B. McLean, J. Warkentin, R. F. Childs, and N. H. Werstiuk are gratefully acknowledged.

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CHAPTER 1

INTRODUCTION

1.1 Synthesis of Natural Products

As in any field of intellectual endeavor, synthetic organic chemistry has its outstanding achievements. The total synthesis of naturally occuring compounds has been the domain where significant milestones have been reached. The larger and more complex materials not only possess complicated carbon skeletons and arrays of functional groups, but also complex stereochemistry as an important added feature. The Erythromycin macrolide antibiotics are a typical example of such natural compounds. Their synthetic conquest was once remarked by R.B. Woodward as "being quite hopeless because of the propensity of functional groups and its plethora of asymmetric centers".[1]

Although in the last two decades expertise in organic synthesis attained a high level of sophistication, as is evident from the synthesis of steroids, terpenes, alkaloids, penicillins, cephalosporins, and tetracyclins, the reported syntheses of macrolides have been few and very recent. A need to develop methodology for the generation of the complex macrolide antibiotics has stimulated research in this relatively unexplored area of organic chemistry. This thesis presents an approach to the synthesis of intermediates for the construction of the 14-membered lactone ring present in the antibiotic Erythromycin.

Erythromycin belongs to a class of natural product compounds

known as the macrolides, which are molecules containing a large membered lactone ring in their structure. The macrolide antibiotics, numbering in the hundreds, are of immense pharmacological importance. Their structures feature a macrocyclic lactone, usually a 12- to 16-membered ring, with numerous substituents placed on the periphery of the ring. Frequently, one to three carbohydrate units are attached to the main ring and their presence appears necessary for the antibiotic to be fully active. Below, a number of macrolides, representing a wide range of structural type, are illustrated. Inspection of the macrolide structures shows the problems associated with the synthesis of such complex molecules: the presence of so many substituent groups and the large number of asymmetric centers.

1.2 Structure of Macrolides

The vast number of lactonic natural products commonly referred to as macrolides, are characterized into subgroups. The "polyoxo" macrolide subgroup includes at least fifty antibiotics. Methymycin, 1, is the only member containing a 12-membered lactone ring. Typical 14-membered "polyoxo" macrolides include Erythromycin A, 2, and Pikromycin, 3, the isolation of which by Brockmann and Henkel in 1950 began the chemistry of macrolide antibiotics. Carbomycin A (Magnamycin), 4, and Tylosin, 5, are representative of 16-membered macrolides.

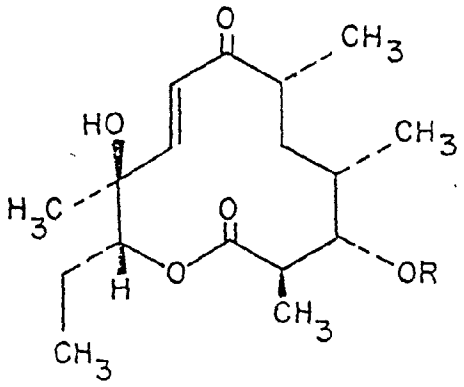
The polyene macrolide antibiotics are a group of compounds which are characterized by antifungal activity. These substances, some of which are under clinical use, are also characterized by large rings and distinct hydrophilic (polyhydroxy) and hydrophobic (polyene) regions in the molecule. Amphotericin B, 6, a 38-membered ring macrolide, is an example of a polyene macrolide.

Ionophoric macrolides, exemplified by nonactin, 7, contain two or more lactone groups in a very large ring system. An antibiotic of this group has a hydrophilic "hole" capable of binding an alkali metal cation and thus of transporting ions in biological systems.

A number of alkaloids contain macrocyclic lactones in their structures and are therefore considered as macrolides. Carpaine, Clivorine, and Vertaline are examples of alkaloid macrolides. Macrocyclic lactams such as the important Ansa macrolides, Rifamycins, and Maytansenoids are also rather loosely included into the macrolide field. These antibiotics

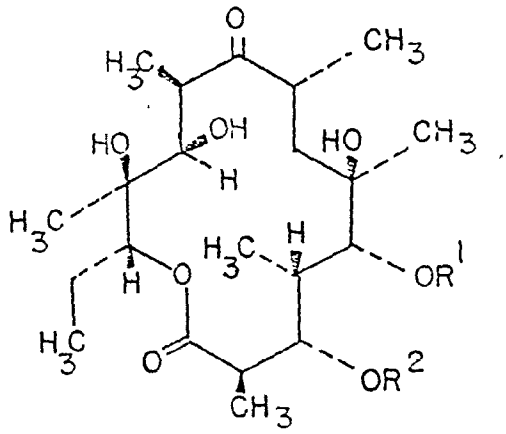
are noted for their broad spectra of antibacterial activity and are also promising as potential antitumor agents. Rifamycin B, 8, and Maytansine, 9, are representative of this subgroup.

Other macrolides include Vermiculine, and the related Pyrenophorin, Brefeldin A, as well as some members of the Cytochalasan family.[2,3] The overall variety and complexity of structure inherent in the macrolides present the chemist with a formidable challenge for their total synthesis.



METHYMYCIN 1

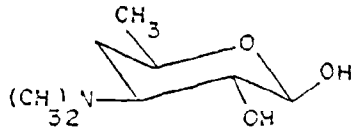
R = Desosaminyl



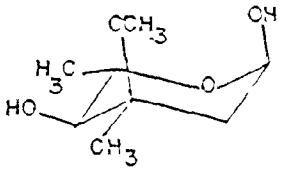
ERYTHROMYCIN A 2

R_1 = Desosaminyl

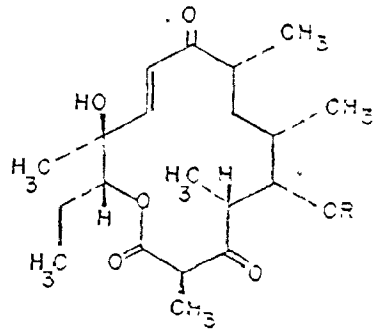
R_2 = Cladinosyl



D-DESOSAMINE

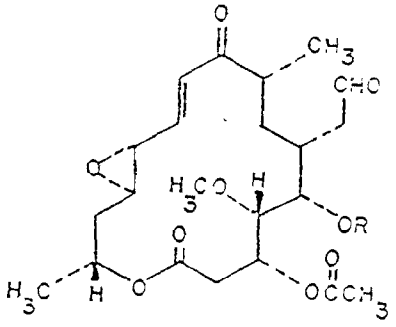


L-CLADINOSE



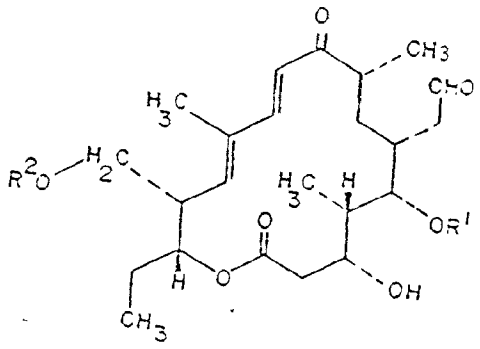
PIKROMYCIN 3

R = Desosaminyl



CARBOMYCIN A 4

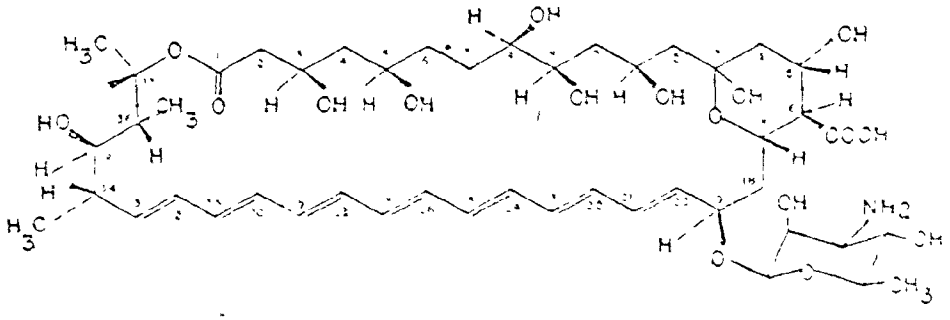
R = (isovaleryl)-mycarosyl-mycaminosyl



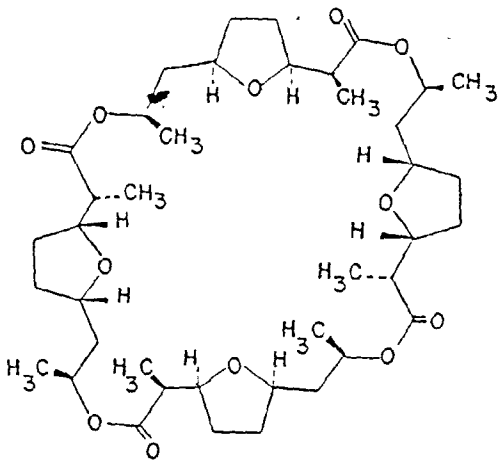
TYLOSIN 5

R_1 = Mycarosyl-mycaminosyl

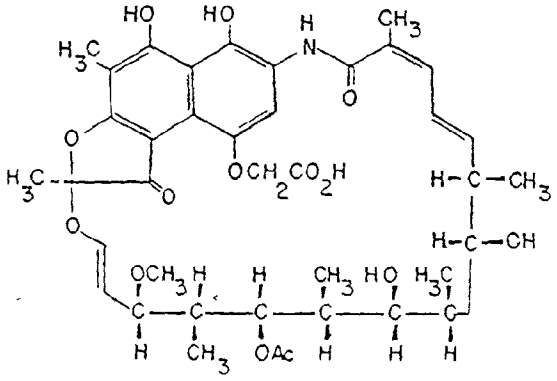
R_2 = Mycinosyl



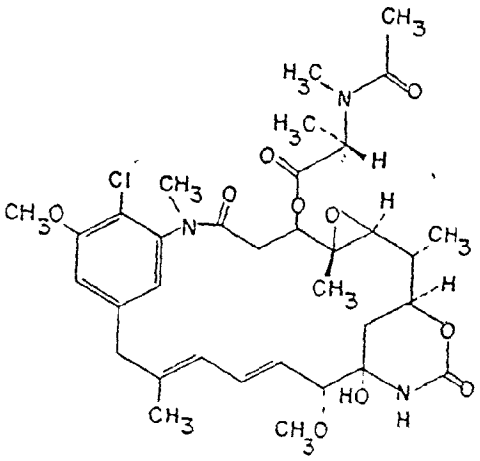
AMPHOTERICIN B 6



Nonactin 7



Rifamycin B 8

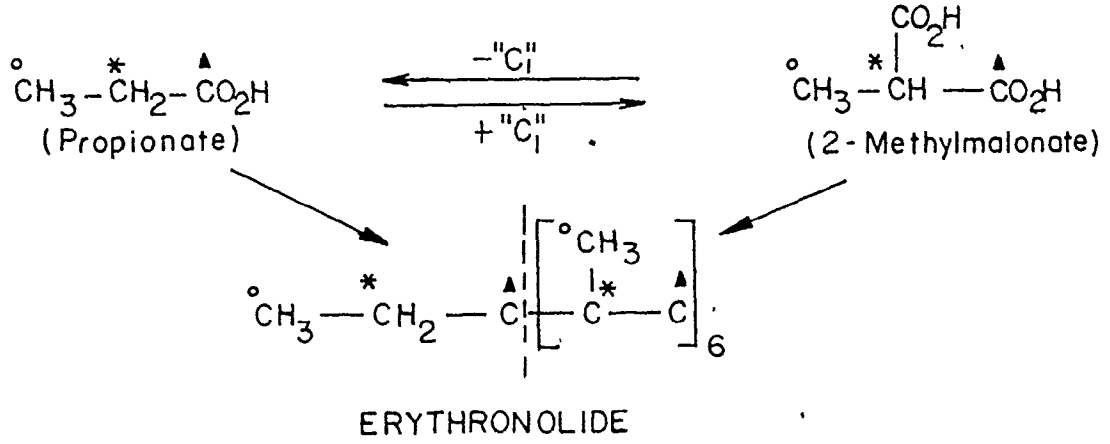


Maytansine 9

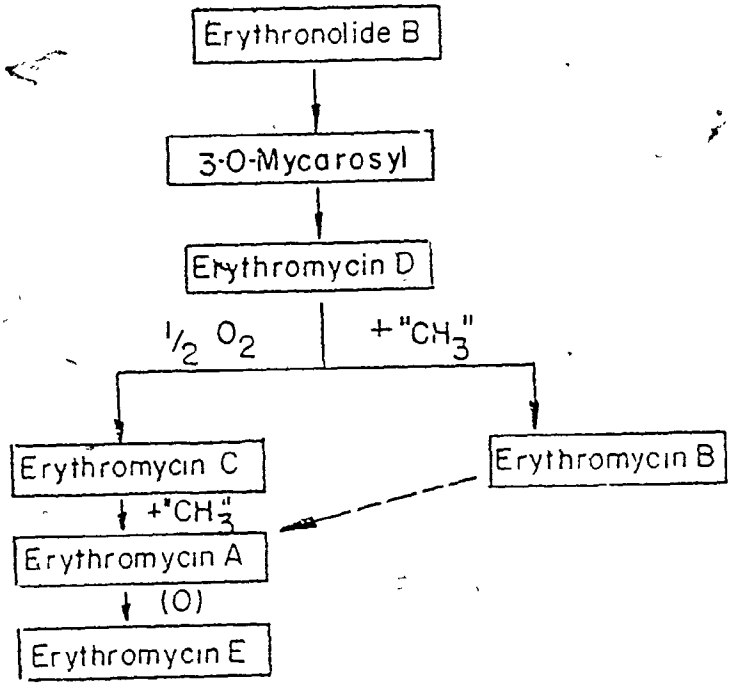
1.3 Pharmacology and Biochemical Interrelationship of Erythromycin

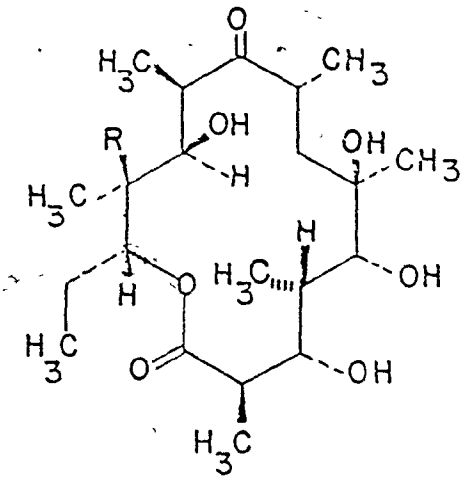
The Erythromycin family of antibiotics has been widely and effectively used as drugs over the past decades and is currently one of the most important classes of antibiotics in medicine. They are broad-spectrum antibiotics, interfering selectively with protein synthesis by binding to a highly specific "site" on the 50S ribosomal subunit. The Erythromycins are particularly used in treating respiratory, skin, and soft tissue infections. Erythromycin has the same general spectrum of activity as benzyl penicillin and can be used as an alternative in patients who are hypersensitive to penicillin. Commercially, they are prepared by fermentation of the fungus Streptomyces Erythreus.

The biosynthesis of "polyoxo" macrolides ~~involves~~ simple metabolic intermediates, in much the same way as saturated long chain fatty acids are synthesized. Recent evidence[2] indicates that the various Erythromycins are produced in nature from the precursor Erythronolide B (the aglycone of Erythromycin B) by a sequence involving glycosidation at the C-3 and C-5 hydroxyls. The aglycone arises from one propionate and six 2-methyl-malonate units as shown below.



Erythronolide B is transformed by a hydroxylase system into a 3-O-Mycarosyl derivative which accepts activated D-Desosamine yielding the first biologically active bis-glycoside, Erythromycin D. This intermediate can be either hydroxylated to yield Erythromycin C or receive a methyl group from S-adenosyl-L-methionine to give Erythromycin B. Erythromycin A may originate from the C form by the latter process or under some conditions from Erythromycin B. Oxidative degradation of Erythromycin A occurs, yielding the E form with an ortho ester linkage between oxidized L-Cladinose and C-3 of the ring.[2]

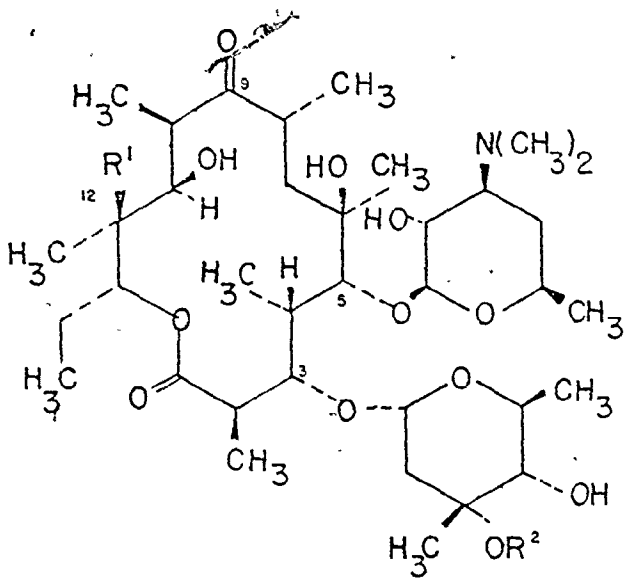




Erythronolide

R=H (B), 10

R=OH (A), 11

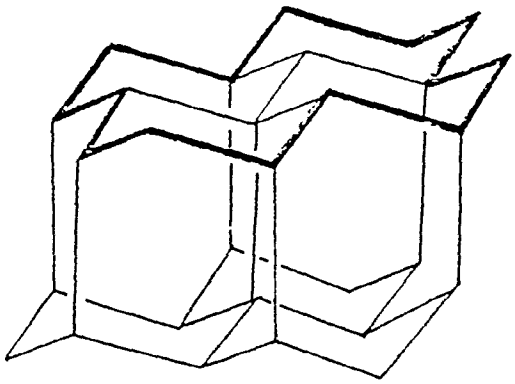


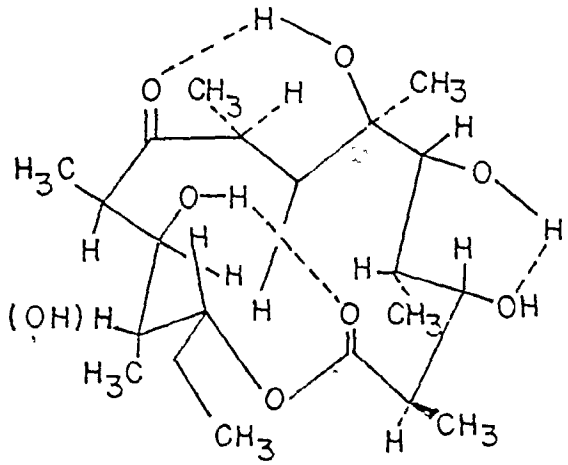
Erythromycin	R^1	R^2
A	OH	CH_3
B	H	CH_3
C	OH	H
D	H	H

1.4 Stereochemistry and Conformation of Erythronolides

The stereochemistry of the "polyoxo" macrolides is correlated in terms of Celmer's stereochemical model. 12-Membered Methymycin and the 14-membered macrolides, all follow the pattern of the model.

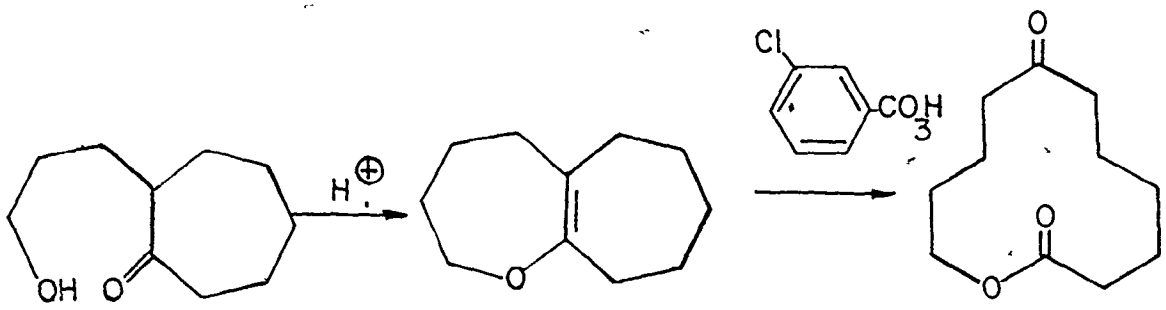
The conformational model for the Erythronolide ring, the nucleus of Erythromycin, proposed by Perun[4] is a "diamond lattice" type in which the ring atoms occupy cyclohexane chair-like positions with a slight dislocation to incorporate the lactone and keto groups. Erythronolides A and B do not undergo facile ring inversion or pseudorotation, suggesting the presence of single stable conformations. Important features of the proposed conformation, as shown below, include the syn-periplanar relationship between the C_3- and C_5-OH groups, the axial orientation of the C_{11}-OH group, and the proximity of the C_6-OH group to the ketone. Further, all the O-containing substituents (OH and sugar) are located on one side of the aglycone and all alkyl groups on the other side.





1.5 Synthesis of Macrolides

The large membered lactone rings of the macrolides have been chemically synthesised by two main methods: 1) cyclization of open, long chain precursors or 2) by cleavage of the internal bonds in preformed polycyclic systems. The latter concept has been applied with some success. For example, Borowitz et al.[3] have developed a method which involves oxidative cleavage of a vinyl ether, creating ketone and lactone functional groups simultaneously as shown in figure 1.



12 13 14

Figure 1

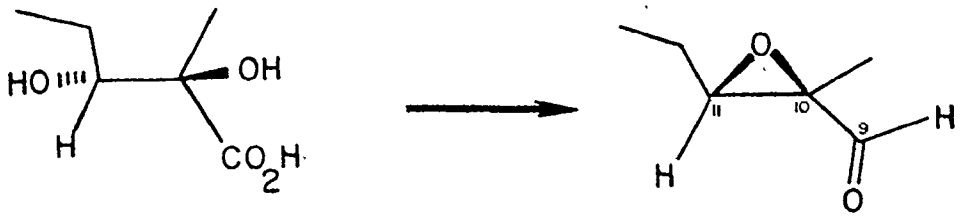
The approach using the cyclization of long chain precursors is perhaps a more general one. The ring closure though, is disfavoured entropically and polymerization because of intermolecular rather than intramolecular reaction is often a serious problem. Despite these problems, recent interest in the chemistry of macrolides has resulted in the development of several new synthetic methods for macrolide formation (vide infra). Several reviews have appeared on this topic.[2,3,5]

Efforts directed toward the total synthesis of macrolides began

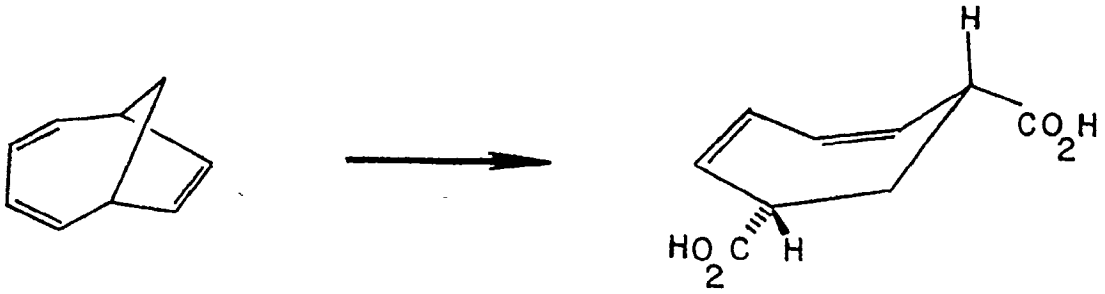
in the late 1960s and intensified in the late 1970s. Syntheses of Nonactin, Pyrenophorin, Vermiculine, Methymycin, Brefeldin A and other macrolides have already been reported.[2,3] During this study, the synthesis of Erythronolide A and B by Corey and his associates,[6] and the assembly of the carbon skeleton of Erythronolide A by Hanessian[7] were also reported. Maytansine has been synthesised by several groups.[8]

The problems associated with macrolide synthesis are the construction of a large-sized lactone, the stereochemical control of numerous chiral centers, the preservation of the various functionalities present in the molecule, and the attachment of a sugar or sugars to the aglycone. All of these obstacles have been overcome by Masamune et al[2,3] in the total synthesis of Methymycin. The scheme used (see figures 2 and 3) involved the condensation of the optically pure C_9-C_{11} segment, 16, and a racemic C_1-C_7 segment, 21, in a Wittig reaction followed by elaboration of the product to the dihydroxy t-butylthioester 23. This ester was cyclized, employing mercuric trifluoroacetate to induce lactonization, to Methylnolide 24. Finally the synthesis was completed by attachment of the sugar Desosamine to the C_3-hydroxyl group of 24.

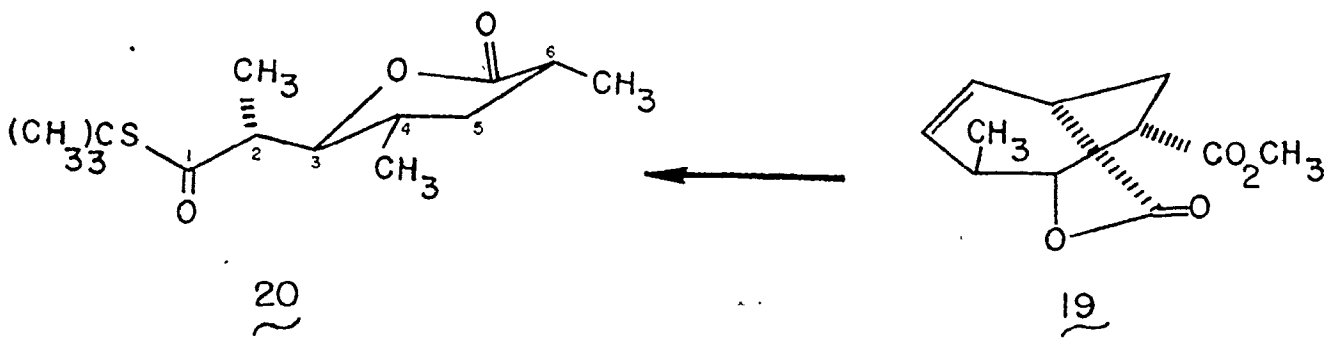
The aldehyde 16 (C_9-C_{11} fragment) was obtained from (±)-2(R),3(R)-2,3-dihydroxy-2-methylvaleric acid. The construction of the C_1-C_7 fragment used bicyclo[4.2.1]nona-2,4,7-triene 17 as starting material. Through several selective manipulations the thioester 20 was obtained and upon potassium hydroxide treatment afforded a hydroxycarboxylate, which was then transformed into a Wittig reagent 21. Condensation with 16 gave 22 which was converted on mild acid treatment into the Methylnolide seco-acid derivative 23. Lactonization and glycosylation completed the synthesis



15 16

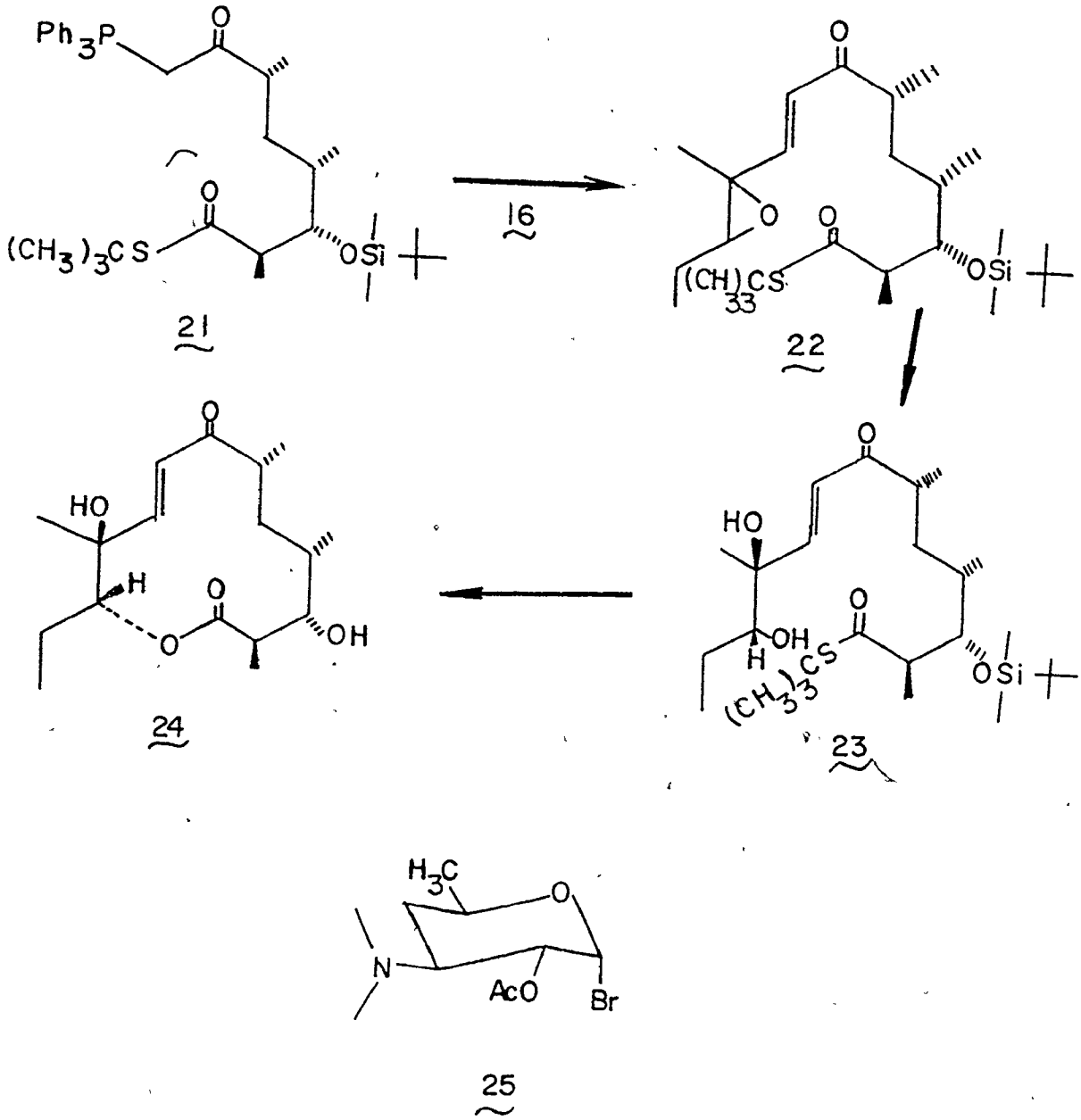


17 18



20 19

Figure 2



21 22 23 24

25

Figure 3

of Methymycin.

The approach taken by Corey[6] in the synthesis of Erythronolides A and B was very similar to Masamune's. With respect to stereochemical control, Corey also used cyclic intermediates to establish the stereo-relationships required for the C_1-C_9 synthon (or the C_1-C_7 synthon in Methymycin). The Corey synthesis involved the condensation of the common fragment 38 with fragments 32 or 29 to yield Erythronolide A or B respectively. Coupling of fragments was accomplished via a Grignard reaction, joining C-9 and C-10, and then lactonization using the double activation method.[2,3] The pathways to these synthons is shown in figures 4 to 6.

Fragment 29 (figure 4) was assembled in ten steps. (±)-trans-2,3-epoxybutyric acid, 26, available by oxidation of trans-crotyl alcohol was resolved and converted through known chemical processes into 27, 28, and finally into a single isomeric iodo-olefin 29.

Synthon 32, (figure 5) was obtained by the initial reaction of 1-lithio-1-propyne and 2-pentanone yielding the corresponding heptynol which on dehydration gave 30. Subsequent reactions yielded 31, which was resolved and transformed into 32.

The synthesis of synthon 38, outlined in figure 6, involved thirteen steps and started with dienone 33, itself available from 2,4,6-trimethyl-phenol and allyl bromide. The bromo-lactonization steps yielding 34 and 35 proceeded stereospecifically and the reductions at C* proceeded with high stereoselectivities. The alkylation of lactone 36 was also stereo-selective. Fortunately, the unwanted isomer could also be epimerized to the desired epimer 37. Coupling of the two fragments was accomplished by

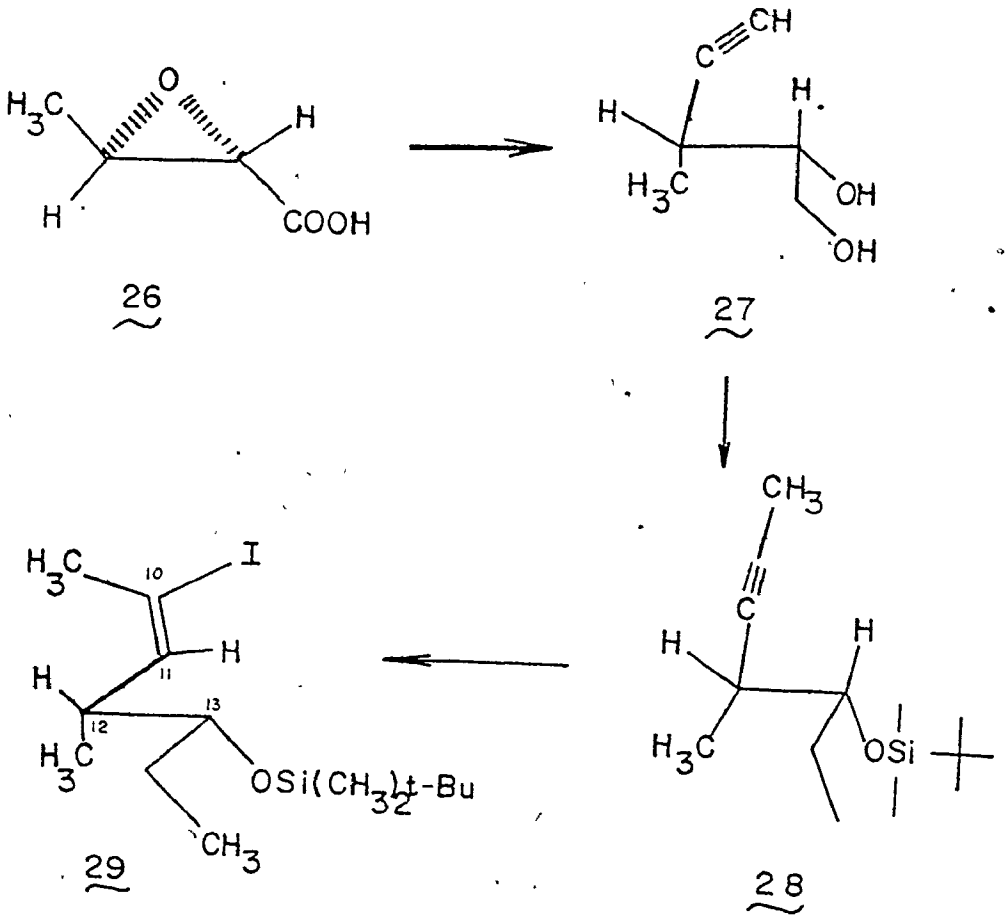


Figure 4

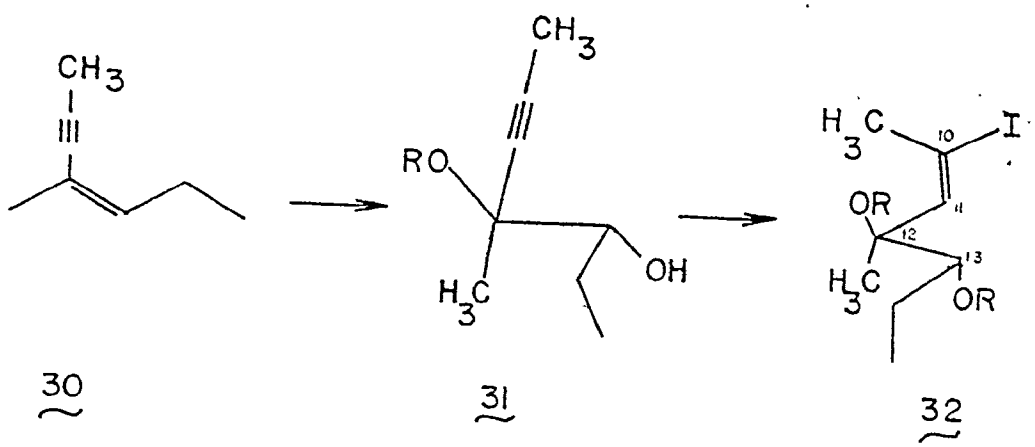


Figure 5

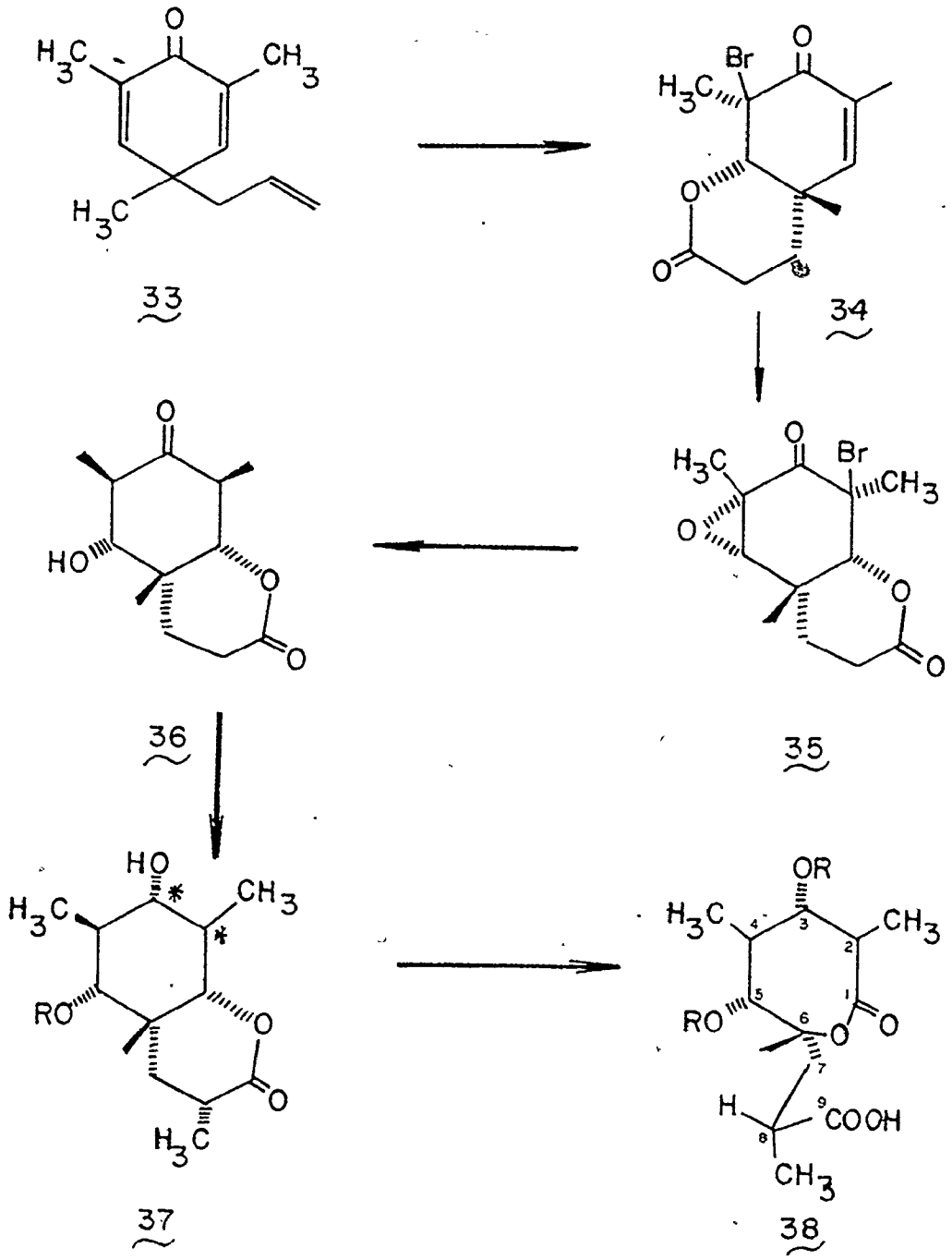


Figure 6

the reaction of the vinyl magnesium reagent of 29 or 32 with the 2-pyridine-thiol ester of 38. Cyclization to the 14-membered lactone was effected in 35-50% yields via a thio ester with a mercaptoimidazole.

Viewing "polyoxo" macrolides as large cyclic sugars is an alternative approach and Hanessian[7] has constructed the carbon chiral framework of Erythronolide A, based on a synthetic strategy that started with D-Glucose (figure 7). Introduction of appropriate functional groups in the precursor 39 gave intermediates 41 and 43 through a sequence of some twenty steps. In a Wittig reaction, similarly performed by Masamune, synthons 42 and 43 were coupled to yield a α,β-unsaturated carbonyl system. Sequential addition of lithium dimethylcuprate and methyllithium gave 44.

The general synthetic approach to macrolides taken by Masamune, Corey, and Hanessian, depends on the tactic of synthesizing fragments and generating the macrocyclic unit by lactonization. Differences arise in the way the fragments are assembled and how the stereochemical problems are handled. Whereas Hanessian utilized carbohydrate chiral precursors, Masamune and Corey made use of cyclic structures as the classical way of handling stereochemical problems. In the present approach to the synthesis of Erythronolides, the study explores the unique use of stereoselective reactions on simple non-cyclic aliphatic molecules.

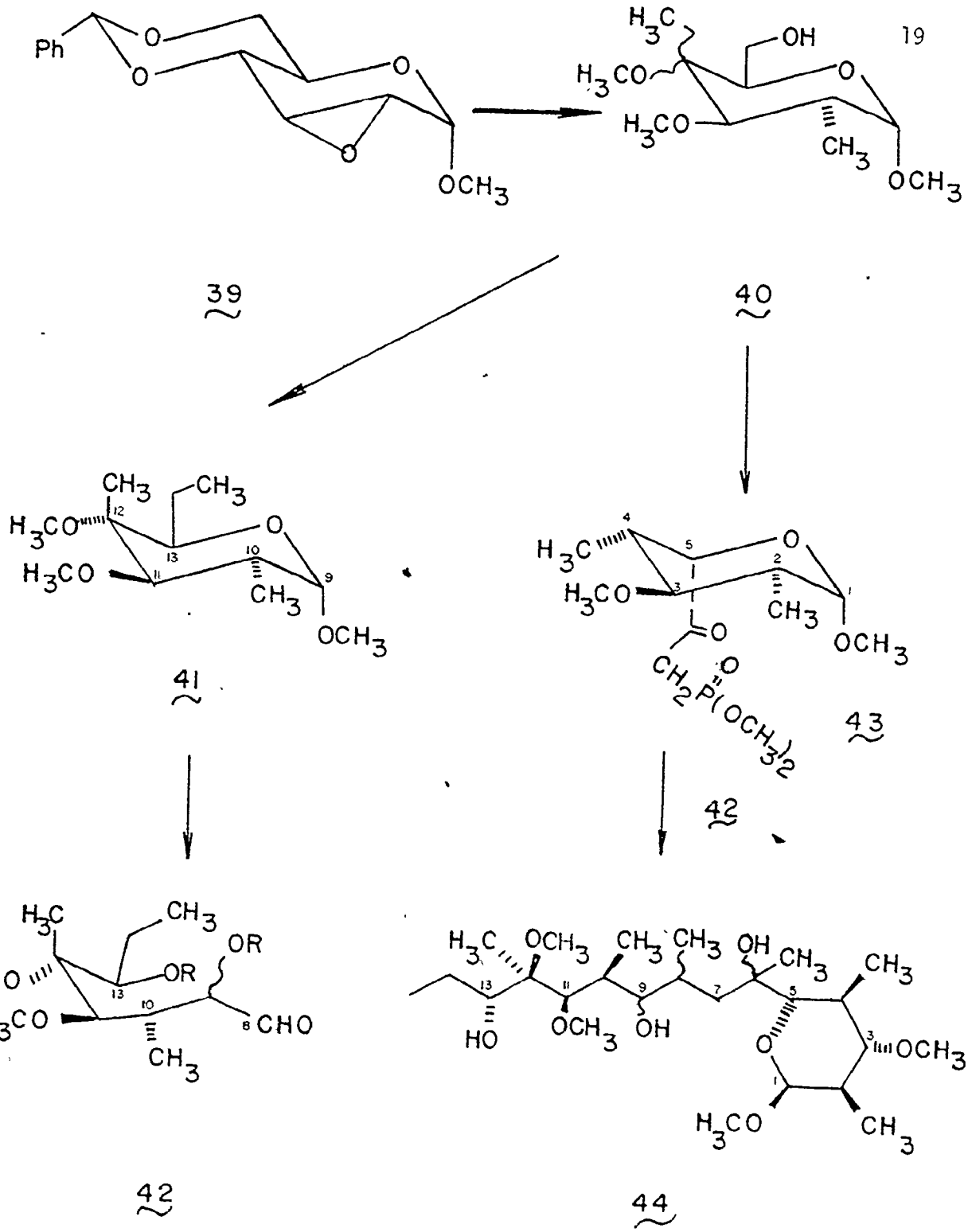

Ph
OCH3
H3C
OH
H3CO
H3CO
CH3
OCH3
39
40
CH3
CH3
H3CO
H3CO
OCH3
41
H3C
CH3
H3CO
OR
OR
H3CO
CHO
CH3
42
H3C
OCH3
CH3
CH3
OH
CH3
CH3
HO
OCH3
OH
OCH3
H3CO
CH3
CH2P(OCH3)2
43
42
44

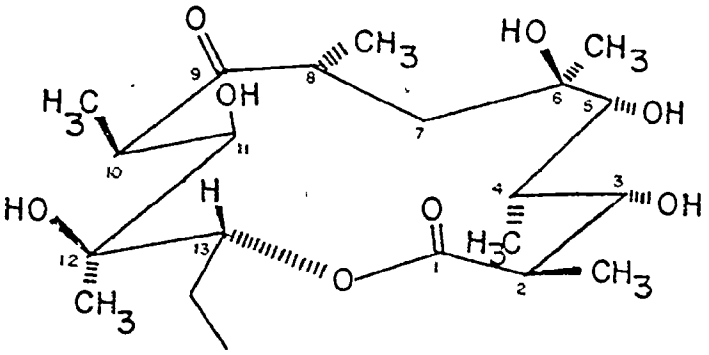
Figure 7

CHAPTER 2

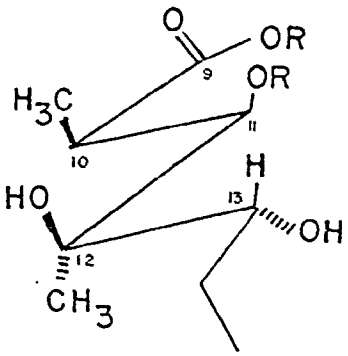
SYNTHETIC PLAN

The synthetic design towards Erythronolide A is a convergent one which requires the construction of two intermediates, 45, and 47, as outlined in figure 3. The scheme contains the following features: Firstly, known methodology may be used to couple the two fragments since appropriate functionalities exist at the termini of both. Carbon-carbon bond formation between C-8 and C-9 can be envisaged to involve known polar processes. For example, final formation of the ring by the alkylation of sulfur stabilized anions has been accomplished.[9] Alternatively, the closure of the lactone ring by bond formation between the C_{13}-hydroxyl and the C_1-carboxyl is also known.[2,3,5] Secondly, the hidden symmetry in Erythronolide A (and B) is incorporated into the synthesis. In the two fragments, C_2-C_3 and C_{10}-C_{11} have identical relative stereochemistries, and the C_1-C_8 synthon, 45, is a 3-carbon homologue of the precursor, 46, of the C_9-C_{13} synthon, 47. Thirdly, use is made of Erythronolide chemistry at C-8 and C-4 to provide the required stereochemistry at these centers. Carbon-8 for instance is easily epimerized to the natural configuration.[10]

The objective then is to synthesize first the C_9-C_{13} synthon and then apply the same methodology to the synthesis of the C_1-C_8 synthon. In this manner, simplicity to the overall synthetic endeavor is introduced.



II



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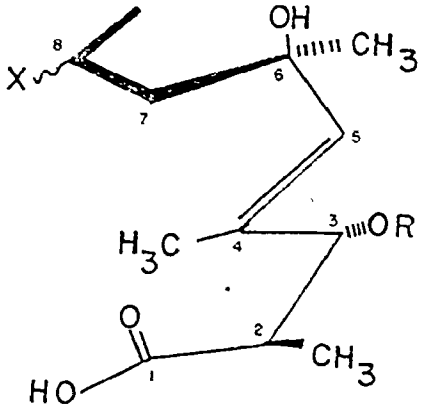

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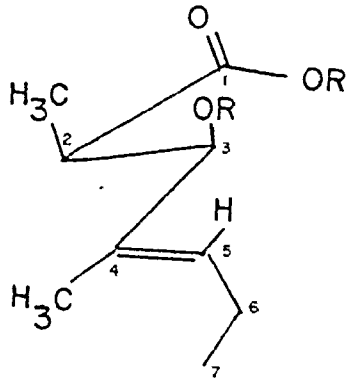


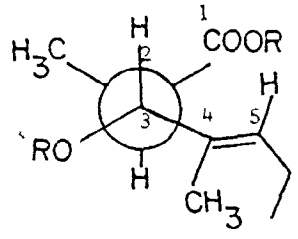
46

Figure 8

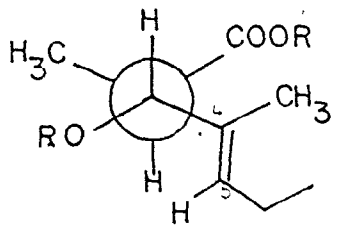
C_9-C_{13} Synthon

The stereoselective route to the intermediate corresponding to C-9 to C-13 of Erythronolide A is illustrated in figure 9. Simple, readily available starting materials supply all of the carbon atoms. A propionic acid unit would become C-9 and C-10, ethyl formate C-11, and 3-pentanone C-12 and C-13.

The principal reactions of stereochemical importance include the conversion of the siloxy-derivative of 51 to 46 via the Claisen rearrangement and the epoxidation of the latter γ,δ-heptenoic acid. The lactone system, 49, the immediate precursor of synthon 47 would be used to determine the selectivity of the Claisen rearrangement and especially of the epoxidation process. The relatively rigid lactone system will undoubtedly aid in stereochemical assignments. The stereoselectivity of the epoxidation should depend on the prefered conformation(s) of the flexible acyclic γ,δ-heptenoic acid. From steric considerations (considering the interactions of C_5-H versus C_4-CH_3 with C_2-H) it is anticipated that conformation 46A will be the most populated, leading to hinderance of the re,re face of the olefin and subsequently preponderance of epoxide 48b. Regardless of the direction of epoxidation, the correct



46A



46B

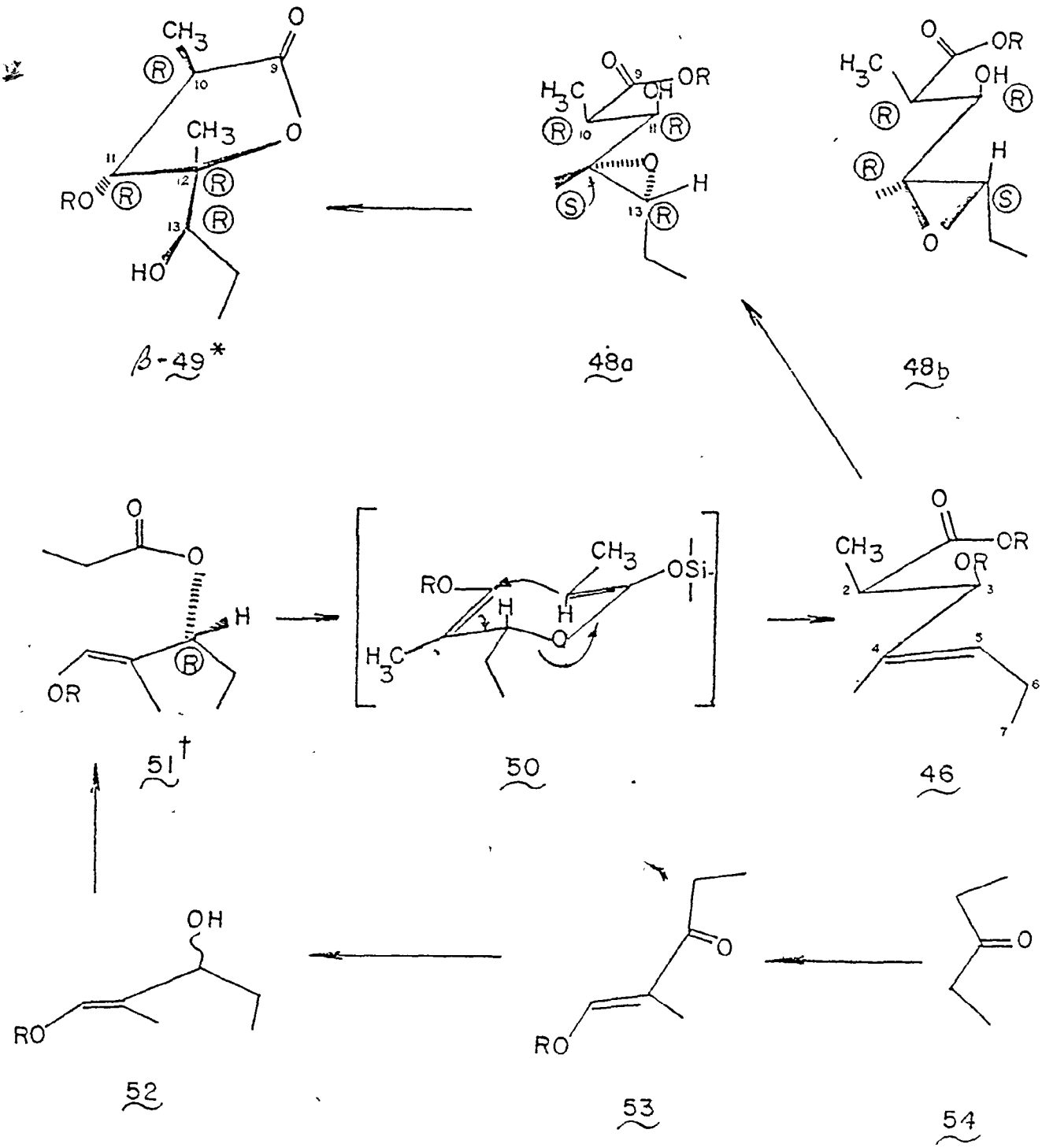


Figure 9

* - Erythronolide numbering used for convenience

† - Compounds prepared in this work were racemates, but for clarity only one enantiomer is depicted in formulas

stereochemistry of the C_9-C_{13} synthon would be obtained by either intramolecular epoxide ring opening by the carboxyl group or intermolecular epoxide ring opening by hydroxide ion. It might be noted that intermediate 46 also allows accessibility to the closely related Erythronolide B skeleton which differs in having no hydroxyl group at C-12.

The stereochemistry for the Claisen rearrangement of allylic esters to γ,δ-unsaturated carboxylic acids via ketene silyl acetals has been explored by Ireland.[11] The relative stereochemistry at C-2 and C-3 of 46 (C-10 and C-11 Erythronolide numbering) originates from the geometry of the enol ether and the stereoselectivity of enolate formation. In the appropriate solvent system, the desired erythro isomer, 46, would predominate over the threo isomer in a 4:1 ratio. This novel way of obtaining the aldol system of Erythronolides also proceeds with intramolecular transfer of asymmetry because of the [3,3] sigmatropic process.[12,13] The synthesis of the optically active heptenoic acid 46 of 2(R),3(R) absolute stereochemistry and (E)-geometry about the 4,5-carbon-carbon double bond would require the (R)-allylic ester 51.

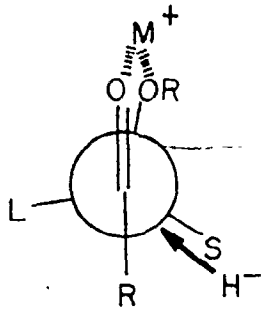
The ester 51, containing all of the carbon atoms of the C_9-C_{13} synthon, would be obtained by acylation of the allylic alcohol 52 with a propionyl unit. Formation of the alcohol 52 was expected to be difficult because of the potential for the enone 53 to reduce in either a 1,2- or a 1,4-manner. The methodology for formation of enone 53 with (E)-geometry exists.[14] Reaction of 3-pentanone 54, with a base and ethyl formate would give a metal enolate, O-alkylation of which would give 53.

C_1-C_8 Synthon

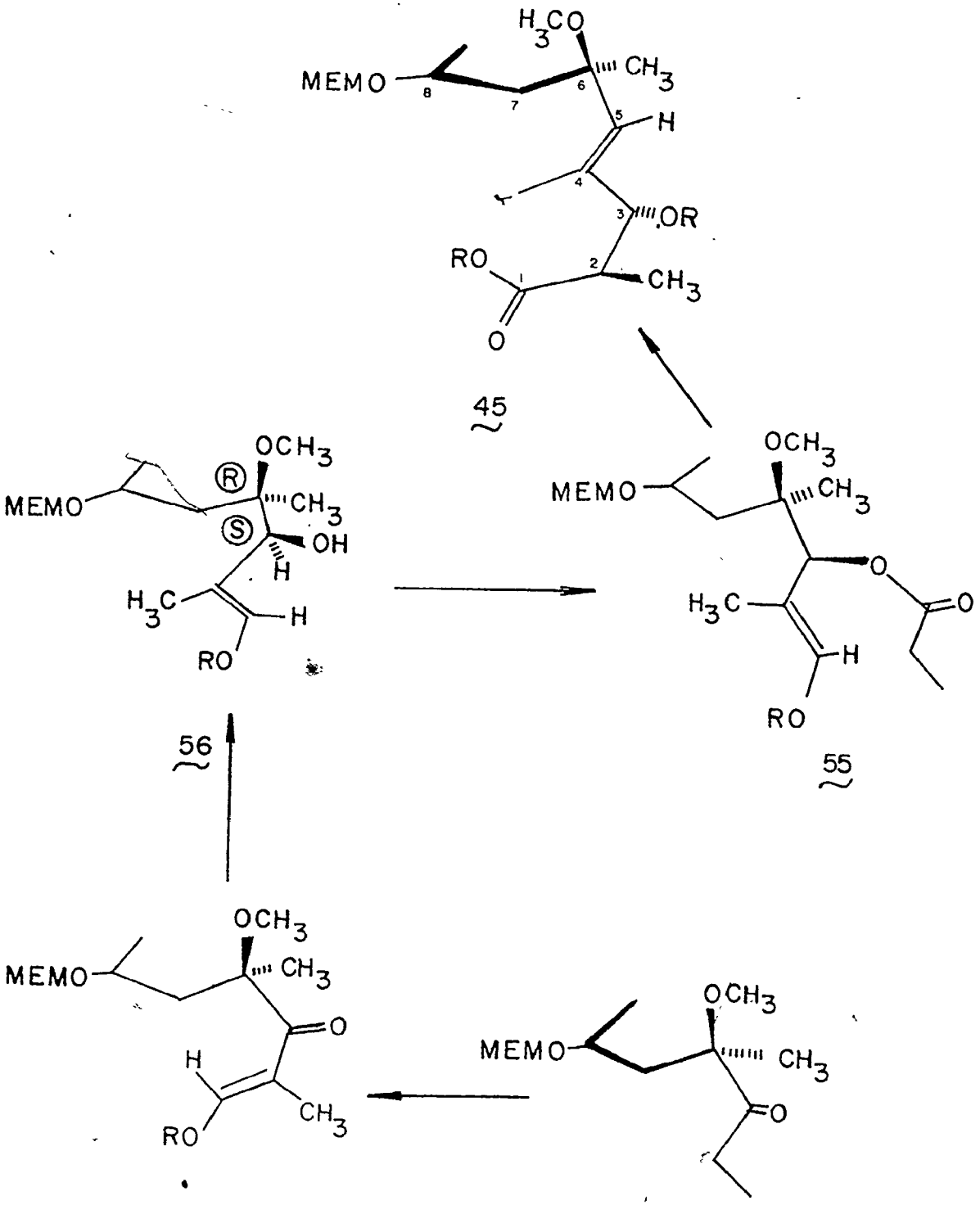
The similarity of the two required synthons allows use of like methodology in the formation of the C_1-C_8 synthon. As indicated in figure 10, the developed methodology would only be applicable after the 3-carbon fragment had been incorporated, with the appropriate stereochemistry, on ketone 58.

The Claisen rearrangement of 55 via the ketene silyl acetal analogue of 50 should give 45, with relative stereochemistry as shown. The ester 55, would be formed from the allylic alcohol 56, itself available from reduction of 57. The enone 57 would arise from 58 again by the use of a base and ethyl formate, followed by O-alkylation of the resulting enolate with an appropriate alkylating agent.

The above route does not involve any new general methodology. However, the enone 57 is structurally different from enone 53. Reduction of 57 would be critical because stereoselection promoted by the vicinal asymmetric center is desired. α-Alkoxyketones coordinate the cationic part of the reducing reagent giving a "cyclic" conformation as shown below.[15] Nucleophilic addition of the hydride occurs from the least



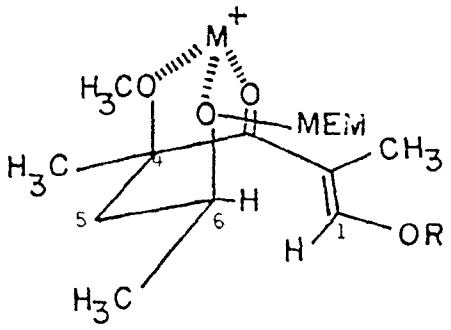
Cyclic model



MEM = $-CH_2OCH_2CH_2OCH_3$

Figure 10

encumbered side. The distal C_6-OMEM ($-CH_2OCH_2CH_2OCH_3$) group is expected to coordinate to the metal cation as shown in the stereostructure 59, and this is expected to block the si face of the carbonyl group. Precedence for similar behaviour is found in the work of Meyers.[16] Attack on the re face of the carbonyl would lead to the desired relative stereochemistry at this center.



59

The synthetic plan adopted to prepare the intermediate ketone 58 is outlined in figure 11. Analogous to the C_9-C_{13} synthon, 3-pentanone (in the form of its N,N-dimethylhydrazone), furnishes carbons 4,5, and 6 of the C_1-C_8 synthon of Erythronolide A (and B). Ethyl formate would supply C-3 and a propionic acid unit C-1 and C-2. The C_7-C_8 segment would be derived from propylene oxide.

α-Functionalization of 3-pentanone would be accomplished by reaction of dimethydisulfide with the anion of 64, giving the methylthio-dimethylhydrazone 63. Introduction of this functionality and subsequent modifications has previously been reported by Corey.[17] Alkylation of the lithio derivative of 63 with propylene oxide has not been reported previously. However, this simple three carbon homologation, besides

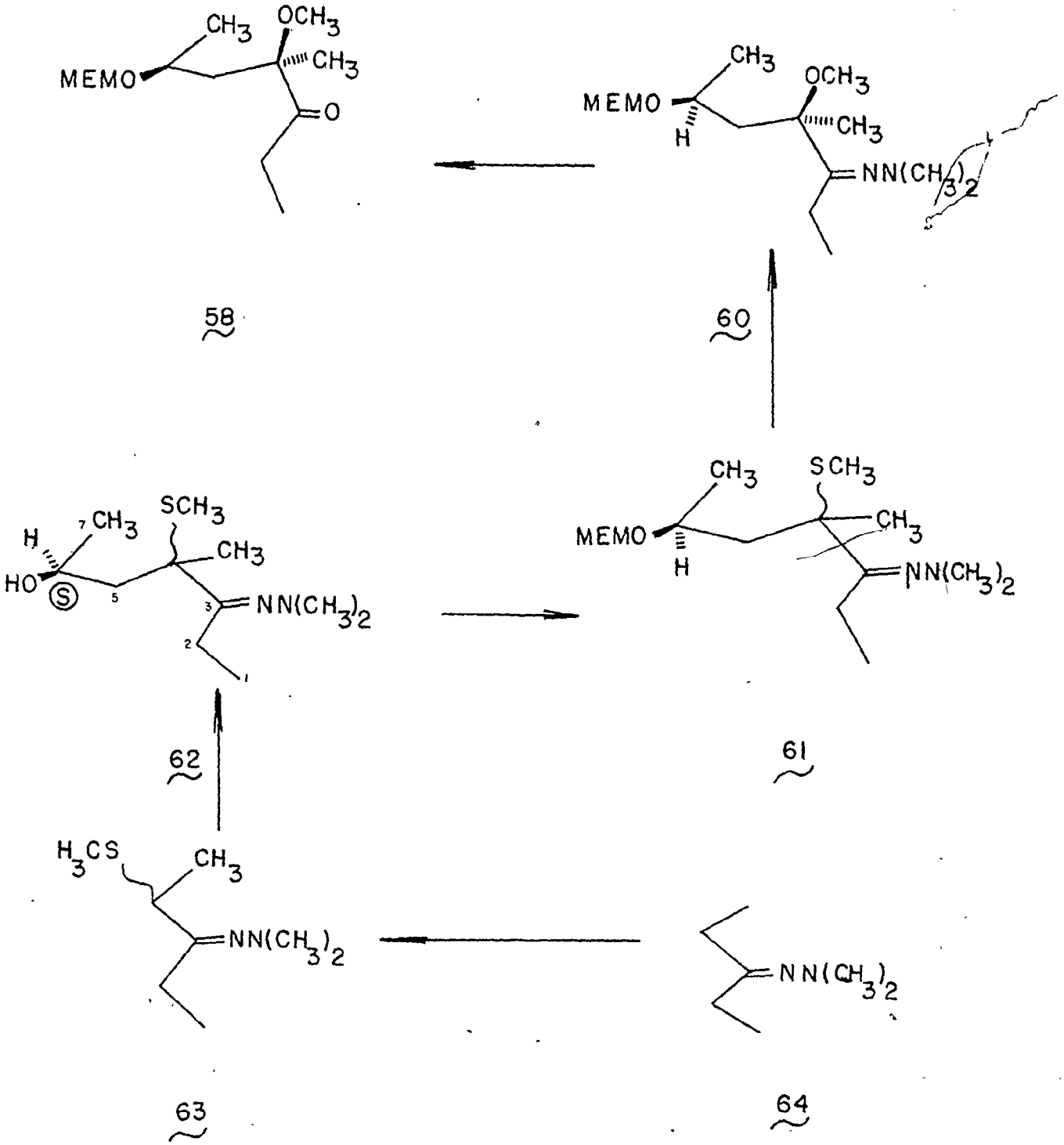
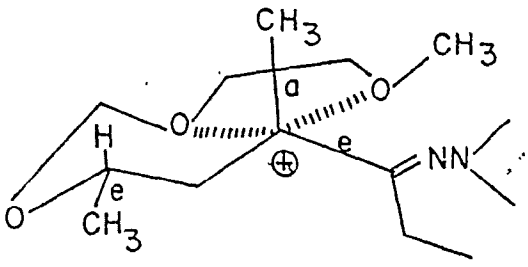


Figure II

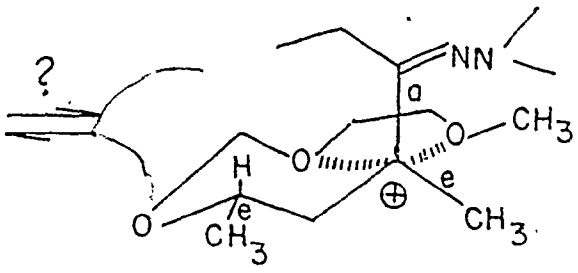
providing C-7 and C-8 of Erythronolides, would also introduce the required functionality at C-8 for the coupling of the synthons in this work.

Although the stereochemistry at C-6 of 62 is not important (the easily epimerized C-8 center of Erythronolides), optical activity may be introduced in the synthon by using the appropriate optically active propylene oxide and subsequently perform stereospecific or stereoselective manipulations directed by this center. The synthetic route is however applied to racemic alcohol at C-6 of 62, although for clarity the (S)-absolute stereochemistry is shown.

The solvolysis of 61, the MEM protected intermediate of 62, catalyzed by mercuric salts would give racemic 60 unless some stereoselective process would operate. A reason for the choice of the MEM protecting group is to stabilize the developing cation at the methylthio ether center, and subsequently direct the approach of the incoming solvent molecule. Indeed, of the two possible intermediates, 65 and 66, it is expected that the former will be relatively stable because of the presence of a smaller axial group ($-CH_3$ versus $-\overset{NN(CH_3)_2}{\overset{\|}{C}}CH_2CH_3$). Assuming that



65



66

these intermediates equilibrate and neighbouring group participation by the MEM protecting group prevails, then the stereoselective hydrolysis should yield the required 4(R),6(S)-hydrazone 60. As indicated above, the back side approach of a nucleophile is hindered by the MEM group.

In summary, the synthetic plan towards Erythromycin involves the use of simple molecules in the construction of complex acyclic intermediates, and uses the conformational preferences of these intermediates to carry out stereoselective reactions.

CHAPTER 3

RESULTS AND DISCUSSION; C_9-C_{13} SYNTHON

3.1 Synthesis of Lactone 49

The proposed synthesis of the lactone 49, which contains the C_9-C_{13} carbon fragment of Erythronolide A, was outlined in figure 9. Diethyl ketone provided five carbon atoms of this lactone through a sequence of reactions begun by the introduction of a hydroxymethylene unit. The sodium enolate of diethyl ketone, formed with sodium hydride in benzene containing a catalytic amount of ethanol, was acylated with ethyl formate giving the 1,3-dicarbonyl enolate salt 67 (figure 12).

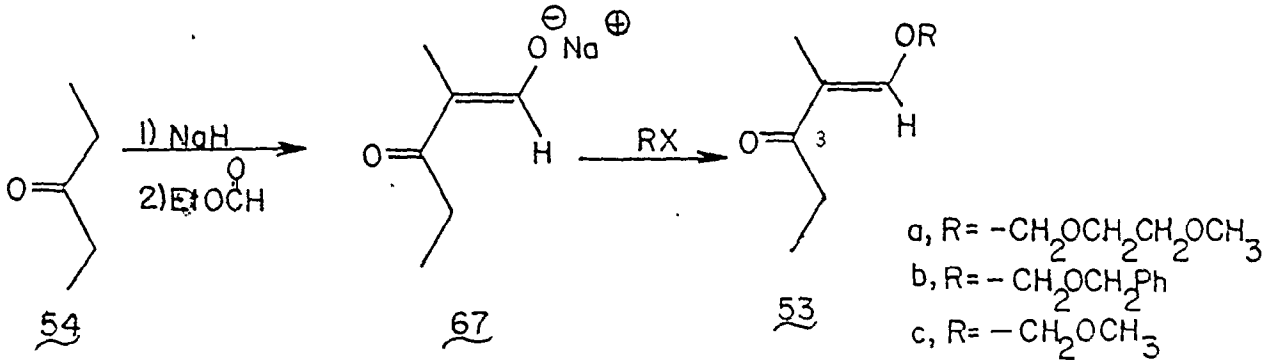


Figure 12

The dried salt was then alkylated in the polar solvent mixture hexamethylphosphoric triamide (HMPA)-benzene (6:4) to encourage maximum O-alkylation and the vinylogous ester, 53, was obtained, when purified, in yields averaging 70%. Examination of the ^1H NMR spectra of the products showed no materials resulting from C-alkylation or O-alkylation at C-3, as was expected from the choice of solvent, cation, and alkylating

agents[18] (vide infra).

Taguchi[14] had previously prepared the vinylogous ester 53c and assigned the (E) configuration about the double bond. Nuclear Overhauser Effect.(NOE) experiments gave no NOE between the C_2-methyl group and the C_1-vinylic proton, indicating that these protons were greater than 3.5 A° apart and consistent with an (E) configuration.[19] The (E)-geometry arose from the E,E (or E,Z) conformation of the sodium salt 67, which in HMPA was overwhelmingly populated (see figure 13). The high degree of dissociation of the sodium enolate in HMPA allowed the free anion to adopt the E,E or "W" shape in which the dipole-dipole interaction was minimized.[20,21] The polar solvent HMPA also had the ability to enhance nucleophilic reactivity and to promote O-alkylation.[21]

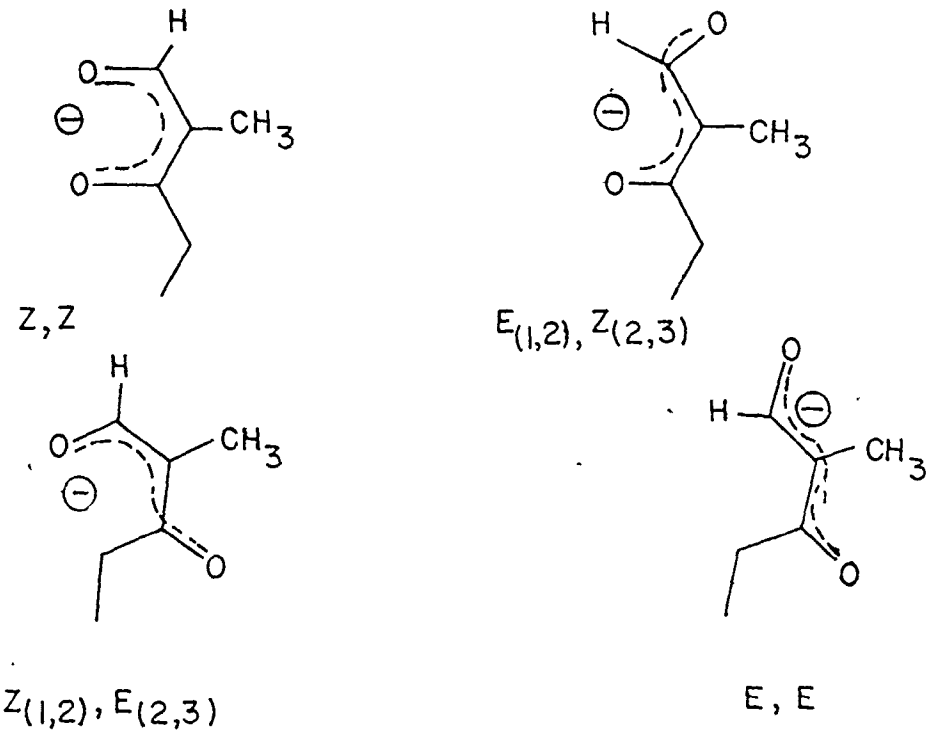
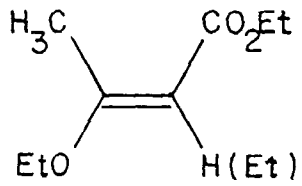
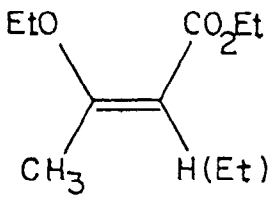


Figure 13

Rhoads[21] has reported similar observations. The (E)-enol ethers 68 were the only isomers obtained in HMPA and the ratio of the rates of carbon to oxygen alkylation (K_c/K_o) was 0.13.



(E)−68



(Z)−68

Since the Erythromycins (and the intermediates used to construct them) are sensitive to both acidic and basic conditions,[22] the protective group introduced at this stage must be able to be removed chemoselectively at a later time, with the preservation of other functionalities. Further, the alkylating agent used to introduce the protective group should promote the O-alkylation of enolate 67. Such a restriction narrowed the spectrum of available alkylating agents to chloromethyl-β-methoethoxy ether (MEM chloride) and chloromethylbenzyloxy ether. Removal of the MEM group had been accomplished under the influence of a mild Lewis acid,[23] whereas the benzyloxy group had been removed reductively with sodium or by catalytic hydrogenation.[24] However at the stage of the heptenoic acid 46, the MEM protective group could not be removed cleanly under the reported conditions using zinc bromide.[23] Subsequently, the benzyloxy protective group was introduced and used successfully in the synthesis. This latter group also introduced a chromophore in the molecule, which facilitated the monitoring of chromatographic separations.

The next sequence of steps involved the selective reduction of

the carbonyl group of 53 to give a racemic mixture of allylic alcohols 52, and the transformation of the alcohols to their propionates. The reduction was accomplished selectively in a 1,2-manner in greater than 95% yield with sodium borohydride. Employing a procedure developed by Taguchi, [14] (propionic anhydride in pyridine-triethylamine) the pleasantly smelling propionates 51 were obtained in greater than 95% yield. Triethylamine was essential to maintain a slightly basic medium throughout the reaction. Neither the alcohols or propionates could be purified by the usual techniques because of their exceeding sensitivity to traces of acid. Storage of these molecules was only possible in pyridine, otherwise decomposition (in benzene at -20°C) to 2-methyl-2-pentenal, 69, resulted. The rearrangement of 51 and 52 to the aldehyde 69 presumably proceeded by a mechanism involving the hemiacetal[25] 70 (see figure 14).

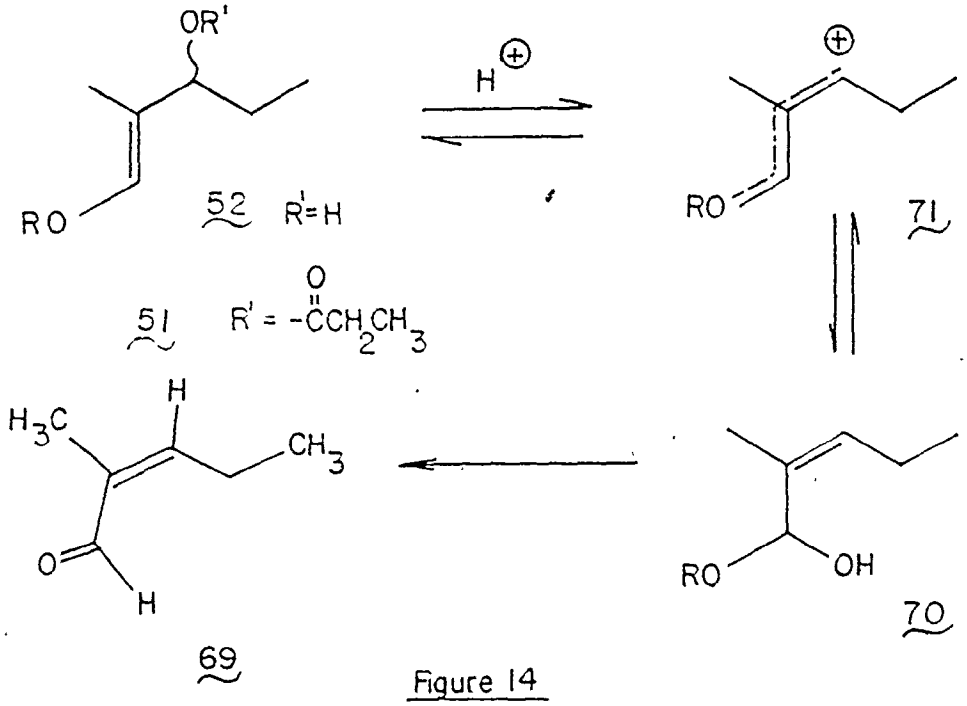
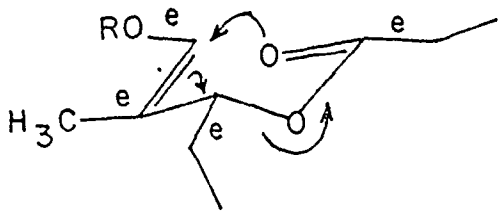


Figure 14

The assignment of the (Z) configuration to aldehyde 69 was based on the allylic coupling constant of the vinylic proton[26] (triplet of quartets at δ 6.40 ^{3}J=7.0Hz, ^{4}J=1.5Hz) and Buchi's[27] assignment of the (E) configuration to the isomer of 69 (triplet of quartets at δ 6.43 ^{3}J=7.0Hz, ^{4}J=0.5Hz). The (Z)-geometry appeared to arise from the prefered conformation of intermediate 71, which was predicted from Dreiding molecular models to be that shown in figure 14. The rearrangement of 51 to (Z)-69 could have involved an acyl Claisen rearrangement. However, the favoured chair transition state C predicts the formation of (E)-69.



C

The Claisen rearrangement of the allylic ester 51 provided a novel way to aldol-type products such as the β-alkoxycarboxylic acid 46. This approach to stereoselective aldols was coincidental and resulted from the initial plan of using the Claisen rearrangement as a technique for creating two new centers of asymmetry in high diastereomeric purity. Recently, a flurry of activity on stereoselective aldol condensations has resulted in other efficient methods.[28]

The crude ester, 51, was converted to its enolate with lithium isopropylcyclohexylamide in 23% HMPA-tetrahydrofuran (THF) and the anion

was trapped with chlorotrimethylsilane giving the siloxy derivative 50. On warming to 50°C, the Claisen rearrangement took place. The carboxylic acid product, isolated via base extraction, was obtained in exceptional purity in yields ranging from 30 to 40%. In an attempt to improve the yields of the rearrangement, a procedure introduced by Ireland[29] was also followed. Acylation of the alkoxide of 52 with propionyl chloride and rearrangement, without isolation of the intermediate unstable ester, gave on one occasion a 60% yield of heptenoic acid (THF as the solvent). However, in general, the yields of the Claisen rearrangement varied erratically. In some cases no product was obtained. Recently, Arnold[30] reported similar behaviour for the Claisen rearrangement of allylic esters via the above ketene-acetal route. By the addition of nitrobenzene prior to the rearrangement, Arnold claimed yields of 70 to 75%. It was assumed that the transition state for the rearrangement was more polar than the former ester, and the addition of nitrobenzene facilitated the process. However, the rearrangements in 23% HMPA-THF proceeded generally in lower yields than those in THF alone, even after careful drying of the hygroscopic HMPA solvent.[31] No experiments were attempted using nitrobenzene.

The Claisen rearrangement, referred to in the Woodward-Hofmann nomenclature as a [3,3]-sigmatropic shift,[32] is known to be highly stereoselective.[12,13] Functionality is introduced in a stereo- and regiospecific manner and the geometry about the newly-formed carbon-carbon double bond is fixed in the process.[12] The rearrangement proceeds through a chair-like transition state ($\Delta\Delta G^{\ddagger}$=2.5-3.0 Kcals) rather than through a boat-like transition state, and a negative entropy ($\Delta S^{\ddagger}$=-10 to

-15 eu) reflects the high degree of order in the transition state.[13] The stereochemical outcome of the reaction product can be predicted by constructing the chair-like transition state which minimizes 1,3-diaxial interactions.[12,13] Thus the rearrangement of the silyl derivative of ester 50 would be expected to occur via the thermodynamically more stable chair conformation shown in figure 15.

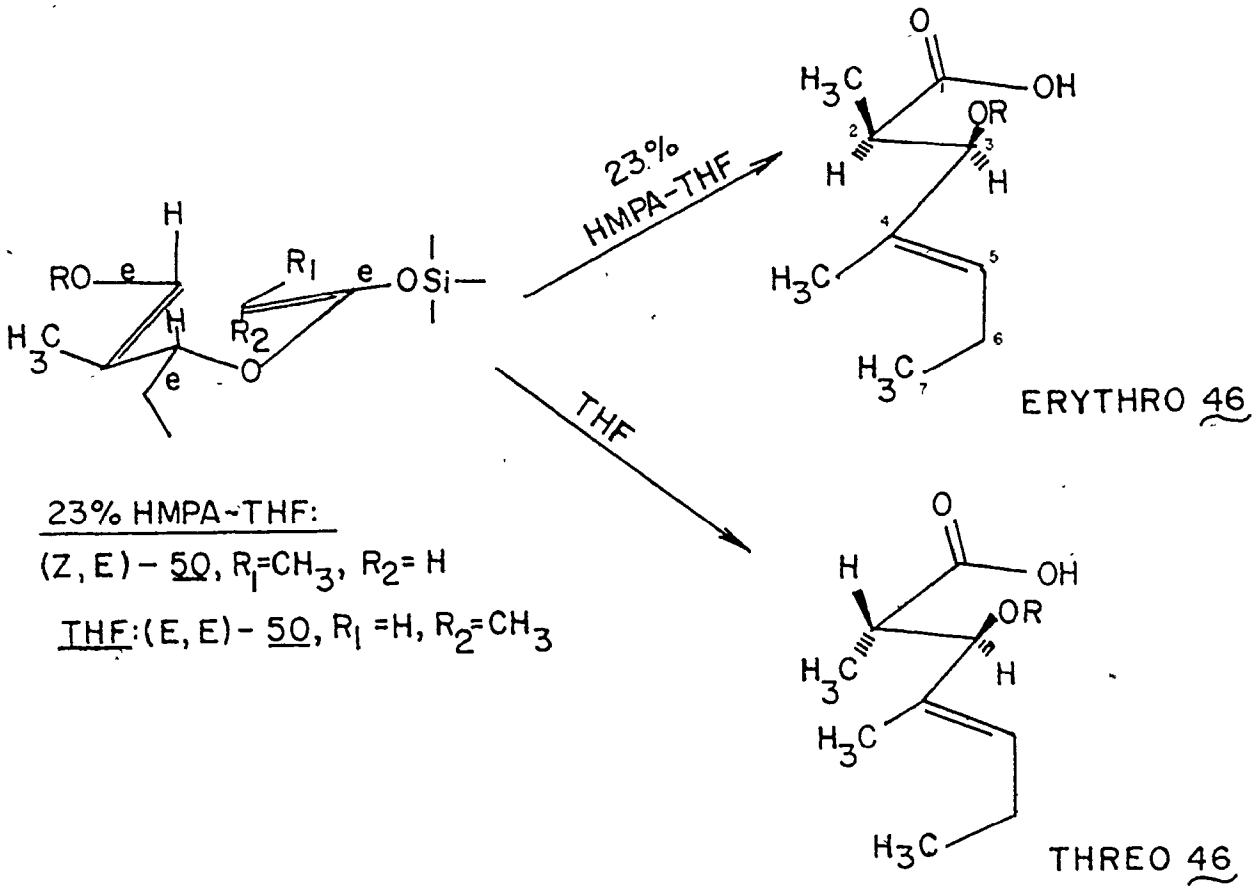


Figure 15

The double bond in the rearrangement product was expected to display a greater than 95% selectivity for the (E) isomer.[13] In the isolated olefin, the allylic coupling constant of the vinylic proton[26]

(triplet of quartets at δ 5.46 ^{3}J=6.9Hz, ^{4}J=0.5Hz) indicated an (E)-olefin. Furthermore, no NOE was observed between the C_4-methyl and the C_5-vinylic proton, which was consistent with an (E)-olefin.

Another consequence of the chair-like transition state was that the stereochemistry about the newly-formed carbon-carbon σ bond could be predicted from the geometries of the double bonds in the starting 1,5-diene system. In the appropriate solvent system, enolization of the allylic ester resulted in selective formation of one of the two isomeric enolates.[11] For example, enolization in THF gave, after quenching with chlorotrimethylsilane, the ketene silyl acetal (E,E)-50 derived from a (Z)-enolate anion. When the solvent was 23% HMPA-THF, the major product was the isomeric acetal (Z,E)-50 (figure 15). Subsequent rearrangement of these intermediates yielded the diastereomeric products; erythro*-46 and threo-46. Assuming the intermediacy of the chair-like transition state, the solvent effect observed in the enolization of ester 51 was reflected in the ratio of erythro/threo 46 (obtained from ^{13}C NMR) shown in table 1.

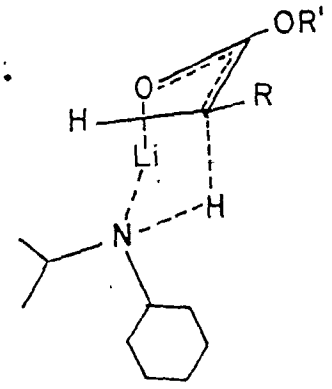
Table 1. Solvent Effect on the Enolization of Ester 51

Solvent	Erythro:Threo 46 (Z,E):(E,E)
23% HMPA:THF	77:23
THF	11:89

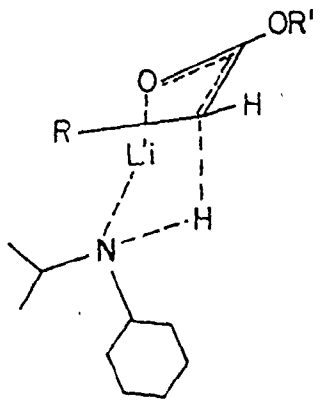
*The prefixes erythro and threo are used in the following sense: When the backbone of 46 is written in an extended (zig-zag) manner, if the α-alkyl substituent and the β-hydroxy substituent both extend toward the viewer, then this is the erythro isomer. The alternative arrangement represents the threo isomer.

Although, only the erythro isomer was to be applied to the construction of the C_9-C_{13} synthon, the threo diastereomer was also made for the purpose of structure determination and its comparative conformational behaviour.

The course of the enolization as a function of solvent employed appeared to be a general case for lithium amide deprotonations of esters, ketones, aldehydes, oxazolines, hydrazones, and thioamides.[33] A rationalization for this dramatic solvent effect has been suggested by Ireland[11] and involved the steric requirements for enolization. When the solvent is the less coordinating THF, the interaction of the carbonyl oxygen with the lithium cation is important and the carbonyl oxygen becomes effectively bulkier than OR'. Because of the steric interaction of these groups with the alkyl substituent R, the enolization proceeds through transition state D, leading to a (Z)-enolate. The presence of HMPA results in a greater degree of solvation of the lithium cation. This weakens the lithium-carbonyl oxygen interaction, favouring transition state E, in which R becomes eclipsed with the now sterically smaller carbonyl oxygen. This explanation, based on the steric bulk of an -OLi group versus an $-O^-$ group and their interaction with the R substituent

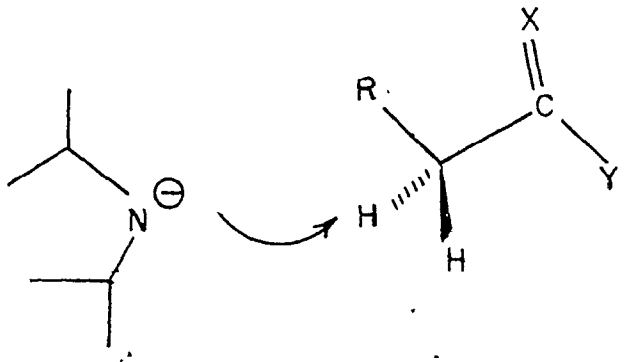


D



E

on the α-carbon, is however, not general for deprotonations in HMPA. Enders, Newcomb, and Bergbreiter[33] have suggested an alternative explanation; in HMPA, an "open" transition state, F, is envisioned. The predominant formation of a (E)-enolate is accounted for by the well known preference for eclipsed conformations of substituted carbonyl compounds.



F

Although the observed stereoselectivities have been thought to arise by a kinetically controlled process, recently, Rathke[34] reported evidence that predominant (Z) stereoselectivity is a consequence of thermodynamic control. In the deprotonations of 3-pentanone, where kinetic control was ensured, (E) stereoselectivity was observed in the presence or absence of HMPA. Addition of a slight excess of 3-pentanone or benzophenone caused a rapid isomerization of enolates with the (Z) isomer predominating. It appears that HMPA promotes the isomerization which for ketones may proceed through a reversible aldol condensation.[34]

As a consequence of the concerted nature and high stereospecifity of the Claisen rearrangement, it is possible to transfer chirality from C-5 of 51 (and 52) to C-3 and C-2 of 46 (see figure 15). The optically

active ester 51, after formation of the E enolate, would give the erythro acid 46, with the 2(R),3(R) configuration and the (E)-geometry about the 4,5-double bond. However, in the present work, both (R) and (S) allylic alcohols 52 (and esters 51) were used.

Since the enolization of the allylic propionates was not stereospecific, then each diastereomeric carboxylic acid contained approximately 10-20% of the other diastereomer. An attempt was made to separate these acids and their methyl esters by chromatographic techniques (thin layer chromatography (tlc) with silica gel, and a reverse phase column). Unfortunately, these materials decomposed under the conditions employed. Undoubtedly, the aldol system underwent elimination and/or retro-aldol reactions. Thus, the 8:2 diastereomeric mixture of erythro acids was subsequently epoxidized. The epoxidation of erythro-heptenoic acid 46 was accomplished with m-chloroperbenzoic acid in methylene chloride at 0°C yielding a 7:3 ratio of epoxides 48 (a+b) (see figure 16). The assignment of the epoxides could not be made because of their similar physical and spectroscopic properties. They were thus converted to the respective lactones 49 (α+β), whose assignments could be made unambiguously.

The selectivity of the epoxidation was not dramatically affected by lowering the temperature. This was expected because a 7:3 ratio of epoxides at 0°C reflects a selectivity for the diastereomeric faces of the olefin of only 460 calories per mole. The rates of epoxidation, k_1 and k_2, are comparable. At -100°C, the ratio (from $\Delta G = RT \ln K$) would be $K \cong 3.8$ or a 79:21 ratio of epoxides. However, the rate of epoxidation made it impracticable to carry out epoxidations below 0°C. While 90 to

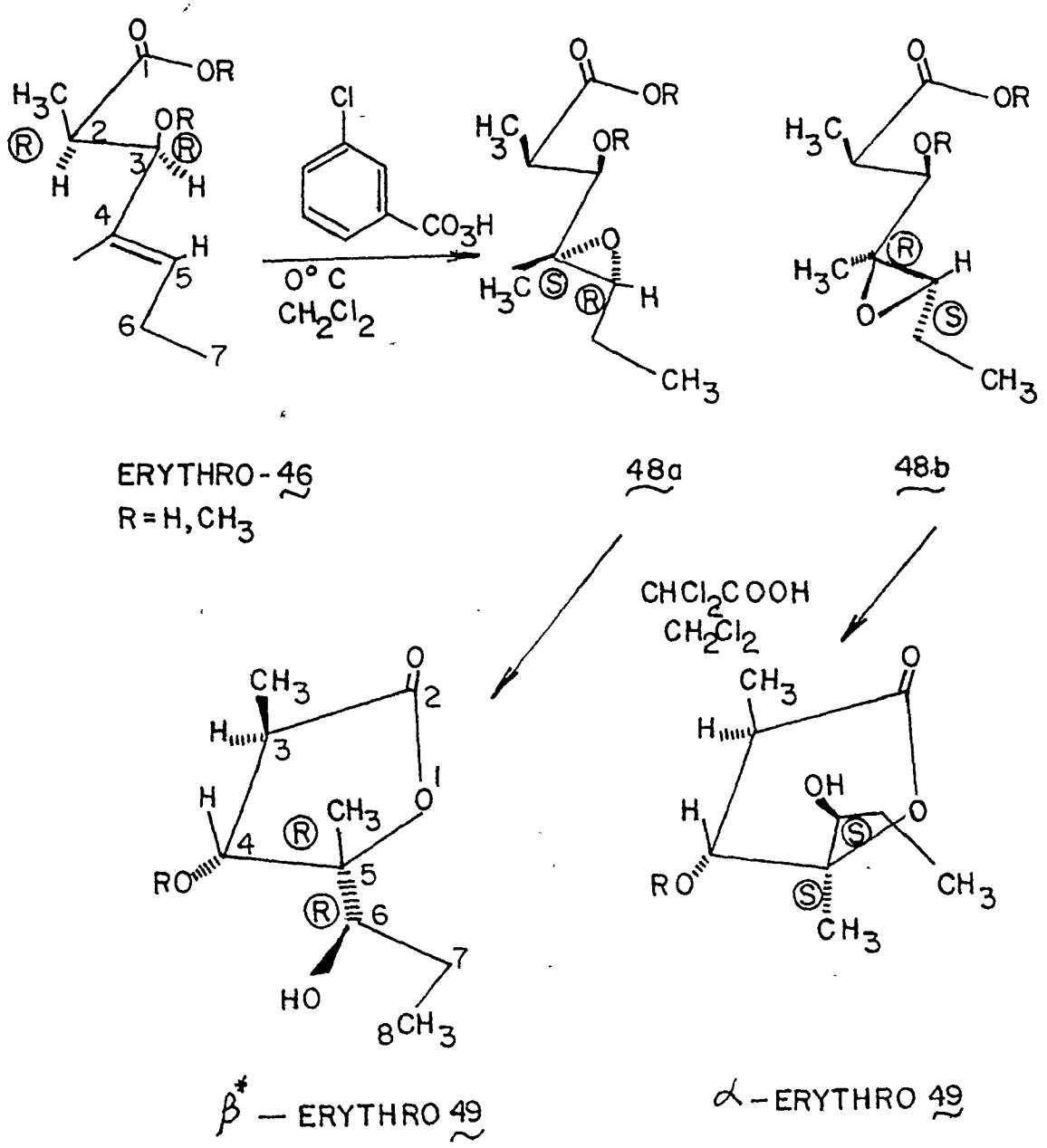


Figure 16

* The β-assignment pertains to that lactone with C_5-CH_3 drawn "up" as shown.

95% of the olefin was converted in 24 hours at room temperature, at -20°C, only 50% of the olefin was converted in three weeks with decomposition of the peracid also taking place. The selectivity of epoxidation was not affected by the concentration of the reactants; 0.06M and 0.014M solutions of the olefin gave similar ratios of epoxides. The yields of the epoxidation were between 70 and 80%.

The epoxides resulting from the erythro-heptenoic acid 46 were easily converted to the corresponding γ-lactones. Epoxidations with three equivalents of peracid led to varying amounts of lactone formation. In chloroform or methylene chloride, use of dichloroacetic acid effectively promoted epoxide ring opening with immediate γ-lactone formation. The ratios of the two lactones produced were consistently identical to those of the epoxides indicating a stereospecific back side, acid catalyzed ring opening by the carboxyl group. The carboxylic ester epoxides were also converted into γ-lactones, although the lactonization required 5 to 10 minutes (one mole of water in the medium was required to generate the lactone and methanol). Because of the greater stability of γ- over δ-lactones,[35] only the former were obtained (IR: 1780 and 3490 cm^{-1}). The corresponding carbonyl stretch for δ-lactones is 1735 cm^{-1}.

The epoxidation of the threo isomer also gave 7:3 ratios of epoxides for the acid and methyl ester. These epoxides were lactonized relatively slowly and the resulting γ-lactones were very sensitive to the acidic medium. Prolonged periods of time (eg. one hour) in this medium led to the decomposition of these lactones to a multitude of unidentifiable products. The expected erythro-lactones resulting from epimerization, relieving the 1,2-cis interactions of C_3-CH_3 and C_4-OR groups, was not

observed under these conditions. Butenolide formation resulting from elimination of the β-alkoxy function was likely because of the mentioned ring strain and the availability of trans-antiperiplanar disposition of atoms required for an E_2-elimination. However, IR and NMR spectroscopies failed to show evidence for this product.

In summary, the synthetic conquest of the C_9-C_{13} fragment of Erythronolide A has been reached with the synthesis of the erythro β-lactone system 49. This lactone was obtained in good yield by the stereoselective epoxidation (followed by lactonization) of the important intermediate, erythro γ,δ-heptenoic acid 46. The latter compound, an aldol system, was obtained in a novel way via stereoselective propionate-enolate formation of the allylic ester 51 followed by stereospecific Claisen rearrangement. Before the accomplishments in preparing the C_1-C_8 fragment are discussed (chapter 4), the following two sections (sections 3.2 and 3.3) provide evidence for the assignment of structure 49 and a rationale for the stereoselective epoxidation of the erythro γ,δ-heptenoic acid 46.

3.2 Structure Proof of Lactones 49 .

(A) Erythro Lactones

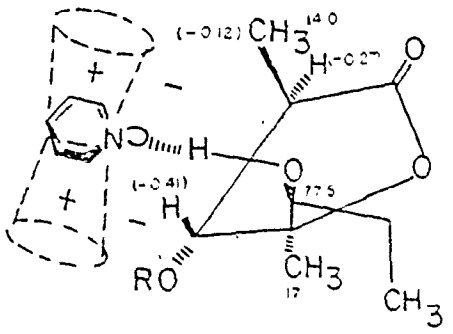
The structural assignment of α- and β-lactones 49 was important because it led to the assignment of the epoxides 48 (a+b) and acids 46. The assignment of the α- and β-lactones in both the erythro and threo series was based on the chromatographic behaviour of the lactones, their spectroscopic properties (carbon-13 NMR and solvent shifts in the proton NMR), and their chemical behaviour (acetonide formation).

In the separation of the erythro-lactone mixture by column chromatography (SiO_2/chloroform), the major isomer was the least retained on the column. Hydroxyl groups normally interact strongly with SiO_2 adsorbents unless they are very hindered or internally hydrogen bonded. Examination of the topology of the two possible lactones 49α, 49β showed that the β-isomer could readily form an intramolecular H-bond between the C_6-OH and the C_4-O atom, whereas the α-isomer could only form an intramolecular H-bond with great difficulty. Dreiding models indicated that steric accessibility to the hydroxyl function was about the same in the two isomers. The C_4-H vicinal coupling constant (d, $^3J_{2,3}(\alpha)$=8.1Hz, $^3J_{2,3}(\beta)$=8.4Hz), which was a monitor of the average conformation of the five-membered ring, indicated an envelope rather than a half-chair conformation for both lactones. The chromatographic evidence was thus consistent with the major isomer possessing the β-structure.

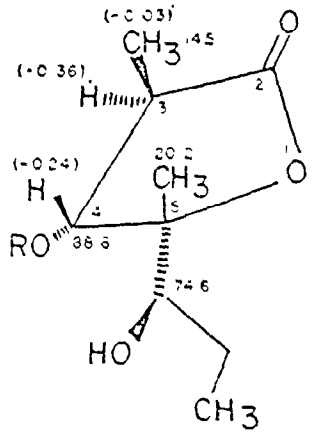
The carbon-13 NMR spectra of the lactones was also very useful in their structural assignment. The relevant ^{13}C-resonances of these molecules are summarised below. In the major lactone, the C_5-CH_3

resonance was at 20.2 ppm and C-6 was at 74.6 ppm. The minor lactone had these resonances at 17.1 and 77.5 ppm respectively. Hence, the minor isomer showed the C_5-CH_3 resonance upfield by ~3 ppm, while the major isomer showed the C-6 resonance also upfield by ~3 ppm relative to the major and minor isomers respectively. This relationship was a consequence of the γ-effect experienced by cis-substituents in five-membered rings.[36] The shielding of the C_5-CH_3 substituent occurred in the α-isomer where it was cis to the C_4-OR group. The shielding of C-6 occurred in the β-isomer, where it was cis to the C_4-OR group. Thus, the ^{13}C signals were consistent with the β-stereochemical assignment to the major lactone.

Further evidence for the assignments came from pyridine-induced solvent shifts in the proton NMR spectra of these isomers. The observed Δ values ($\Delta=\delta_{CDCl_3}-\delta_{C_5D_5N}$), reported below, were useful in establishing the stereochemical nature of the protons situated in the vicinity of the hydroxyl group. The general trend found in saturated cyclic systems, is that protons occupying positions close to a hydroxyl function are deshielded.[37] The deshielding of C_4-H, C_3-H, and C_3-CH_3 groups was of



α -ERYTHRO 49*



β -ERYTHRO 49

* The ^{13}C shifts of carbons are given in small case numbers close to the appropriate carbon atom, and ^1H shifts are given in brackets.

particular interest. While the C_4-proton was deshielded by 0.24 ppm in the major isomer, in the minor isomer it was deshielded by 0.41 ppm. This trend indicated, as expected, a cis-relationship of C_4-H and C_6-OH groups in the minor (α)-isomer.

The C_3-proton and C_3-methyl deshieldings were also consistent with the above assignments as well as the assignments of the erythro and threo heptenoic acids 46. A possible interaction between pyridine and the hydroxyl group involved hydrogen-bonding as shown above for the α-isomer (adopted from Wenkert[37]).

Finally, a chemical distinction was made between the two isomers by taking advantage of the cis and trans relationship of the C_4-O atom and the C_6-OH group. The R protecting group ($PhCH_2OCH_2$-) was removed from the lactone system by hydrogenolysis in methanol over Pd/C to give isomeric diols (see figure 17). The diols, 72, obtained in greater than 90% yield were soluble in water, and surprisingly, the major isomer was the least soluble. This property was probably related to the behaviour of lactones 49 on the SiO_2 adsorbent. The mixture of lactone diols was left for three days at room temperature in methylene chloride with 0.1 equivalent of pyridinium p-toluenesulfonate (PPTS)[38] and 2.0 equivalents of 2,2-dimethoxypropane. Purification of the acetonide(s) was straighforward; the unreacted diol(s) and p-toluenesulfonic acid were separated by washing the organic phase (methylene chloride) with water. The aqueous extraction contained only minor diol (and p-toluenesulfonic acid), whereas the organic residue was pure major acetonide 73, the ^{13}C NMR spectrum of which is shown in figure 21.

The difference in reactivity between the α- and δ-diols, to the

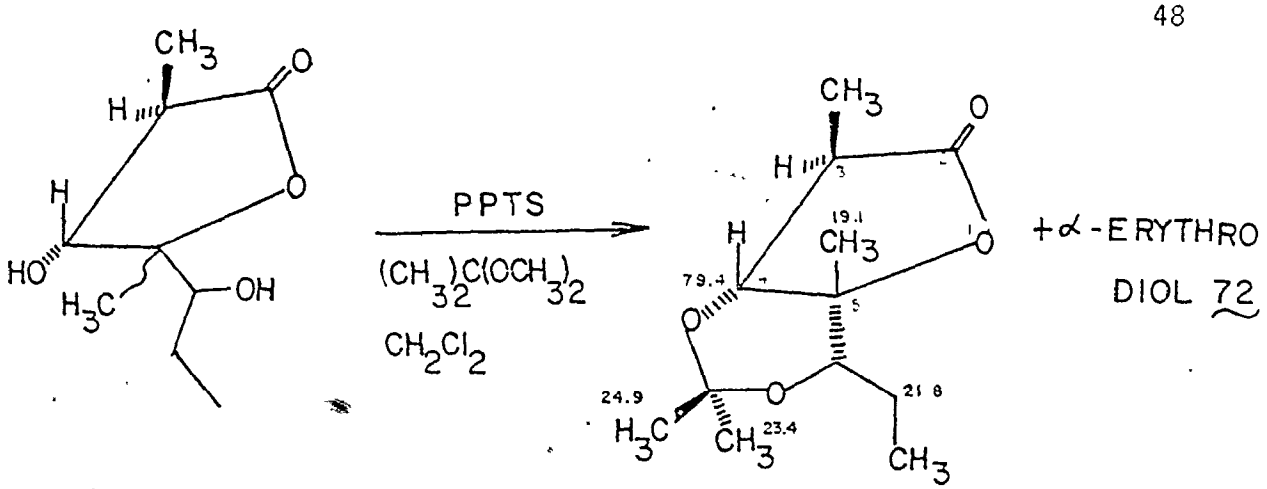
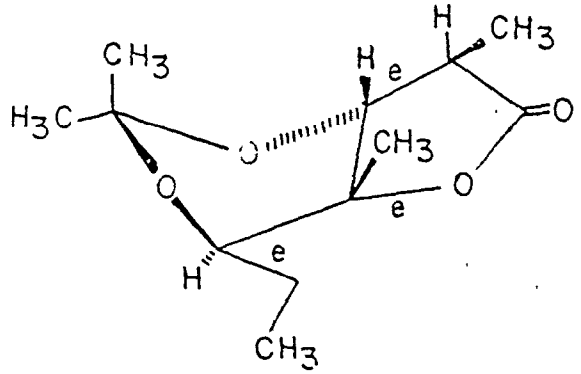


Figure 17

extent that one diol formed an acetonide and the other did not, was rationalized by the inspection of Dreiding models. Formation of the α-acetonide would lead to a strained bicyclic system. In contrast, formation of the β-acetonide 73, led to a flexible, non-strained system. The chair-conformation of the dioxan ring was destabilised relative to the twist-boat because of the number of substituents on the ring and the twist-boat conformation, shown in the stereostructure below, is probably the preferred conformation. This stereostructure imposes little or no stress on the lactone system.



β— ERYTHRO-ACETONIDE 73

The vicinal coupling constant between C_4-H and C_3-H of 1.2Hz indicated a half-chair conformation of the lactone ring. The ^{13}C NMR spectrum of 73 showed the acetonide methyls to be diastereotopic. The C-4 resonance at 79.4 ppm was shielded by 8.5 ppm relative to the resonance in lactone 49 at 88.8 ppm. This was a consequence of a new γ-effect together with a new conformation of the lactone ring. Another new γ-shift resulted from the constrained ethyl group. The $-\underline{C}H_2CH_3$ resonance at 21.8 ppm was shielded by 2.3 ppm relative to that of lactone 49. This γ-shift involved C_5-CH_3, itself upfield by 1.4 ppm to 19.1 ppm, and C_4-H.

In summary, the chromatographic behaviour, the ^{13}C and ^{1}H NMR data, and the chemical behaviour of the lactones 49α and 49β were all consistent with the major isomer in the erythro series being assigned the β-structure 49.

(B) Threo Lactones

Similar assignments in the threo series could not be made unambigously. Impurities and the magnitude of the γ-effects observed, allowed only tentative assignments to be made from the carbon-13 data. However, the chromatographic behaviour of threo lactones 49 and the solubility properties of threo diols, 72, were opposite to those found in the erythro series. The acetonide of the minor diol was also formed readily, indicating that the minor isomer had the β-configuration about C-5.

The minor isomer was the least retained on SiO_2 column chromatography. The C_4-H vicinal coupling constant (d, $^3J_{2,3}$(major)=7.2Hz, $^3J_{2,3}$(minor)=5.7Hz) indicated a slight conformational difference[39] between the two isomers. A cis-interaction of the relatively large $HC(OH)CH_2CH_3$ group with C_3-CH_3 and C_4-OR groups could account for this conformational change which also occurred in the minor lactone diol 72 (d, $^3J_{2,3}$(major)= 7.5Hz, $^3J_{2,3}$(minor)=5.1Hz). The dihedral angle between C_3- and C_4-protons changes from about 0° in the envelope, to about 20° in the half-chair form.

Hydrogenolysis of threo lactones 49 gave threo diols 72 in fair yield. These diols were also obtained by sodium reduction in liquid ammonia and tert-butanol of the threo γ,δ-heptenoic acid 46, followed by epoxidation and lactonization. The diols were also soluble in water, although it was the minor diol which was the least soluble. Under identical conditions with those employed in the erythro series, acetonide formation occurred, this time, with the minor diol. The organic residue contained

only one acetonide, together with unidentifiable impurities as was evident from the proton NMR spectra. Although the pyridinium p-toluenesulfonate catalyst was a weaker acid than acetic acid,[38] the sensitivity of the threo lactone system to acids, as observed before, was extremely high. The proton NMR was consistent with acetonide formation. The C_4-H and C_6-H protons resonated at 3.96 ppm (d, $^3J_{4,3}$=6.0Hz) and at 3.50 ppm (d of d, $^3J_{6,7A}$=4.0Hz, $^3J_{6,7B}$=8.2Hz) respectively. These resonances were upfield by 0.3 and 0.37 ppm relative to the corresponding diol at 4.25 and 3.87 ppm. This pattern was also observed for the erythro acetonide.

The above observations were consistent with the minor isomer possessing the β-stereochemistry. The presence of impurities, though, made assignments of carbon resonances difficult for the minor isomer. For example, the assignment of C_5-CH_3 and C-6 carbon resonances of lactone 49 were only tentative. Hence, the pattern of γ-shifts experienced by these carbons could not be used unequivocally in the structure assignment. However, the purification of diols 72, using their water-soluble properties, provided assignments of their ^{13}C spectra. The C_5-CH_3 and C-6 resonances, shown in the experimental, exhibited the expected γ-shifts; 0.9 and 1.5 ppm respectively, and were again consistent with the minor isomer possessing the β-structure.

The magnitude of the latter shifts was surprising since distinctive upfield shifts of 3-5 ppm are generally recognized in gauche or eclipsed interactions, relative to the behaviour found for anti arrangements.[40,41] Recently though, in dioxane and related systems, Eliel[42] has observed γ-shifts in the opposite direction. It is possible that in the minor β-

isomer 72 such effects may be operating.

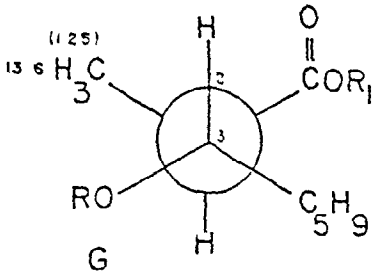
Upfield shifts of ~5 ppm were also observed for the C_3-CH_3 resonances in the threo lactones 49 (10.0 and 9.0 ppm) relative to the resonances for the erythro isomer (14.5 and 14.0 ppm). The shifts were a consequence of the cis γ-OR substituent at C-4 in the threo series, and hence consistent with the assignments of the γ,δ-heptenoic acid 46. Similar resonances have been reported for the santonin,[43] and pilocarpine[44] γ-lactone systems.

3.3 Stereochemistry of the Epoxidation of γ,δ-heptenoic acid 46

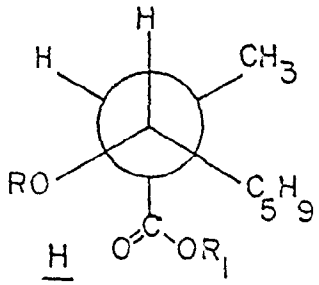
Spectroscopic and chemical evidence as discussed in section 3.2, indicated that erythro 48a and threo 48b were the predominant epoxides from the epoxidation of erythro and threo γ,δ-heptenoic acis, respectively. The rationale[45] for these results required first an understanding of the prefered conformation(s) of the heptenoic acids.

Conformers G and J, were the most populated as indicated by the vicinal coupling constants, $^{3}J_{2,3}$ of 8.7 and 10.5Hz respectively. Coupling constants of 10-13Hz are indicative of predominantly trans hydrogens, whereas values of 1-3Hz are indicative of gauche hydrogens. Intermediate values, usually indicate weighted means of these conformations.[46] Preference for conformers with trans vicinal hydrogens of tetrasubstituted

ERYTHRO



G



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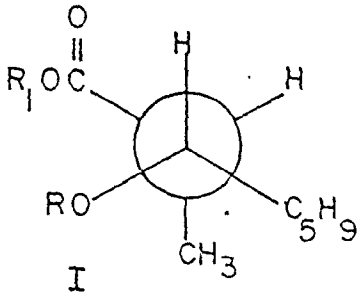
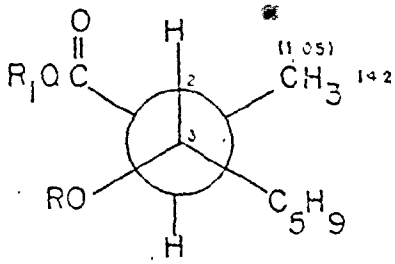


I

THREO



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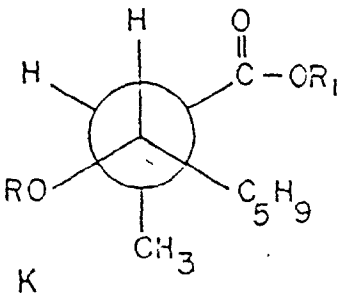

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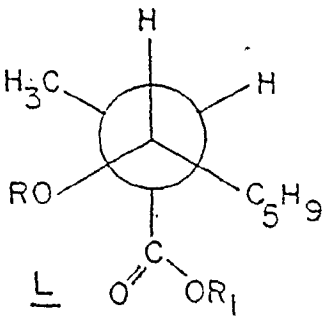


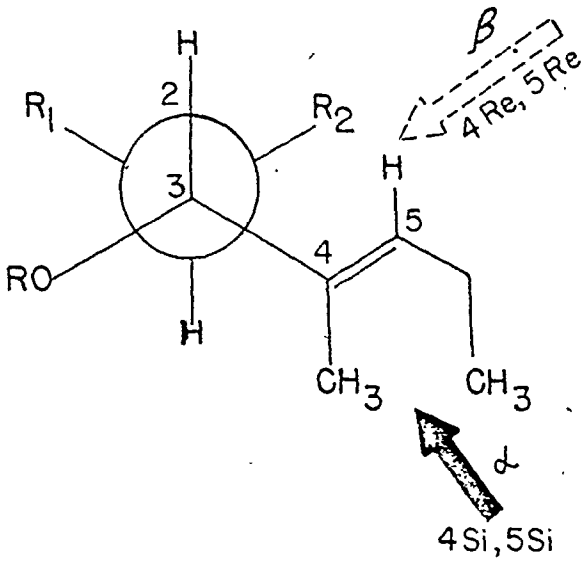
L

R_1=H, CH_3

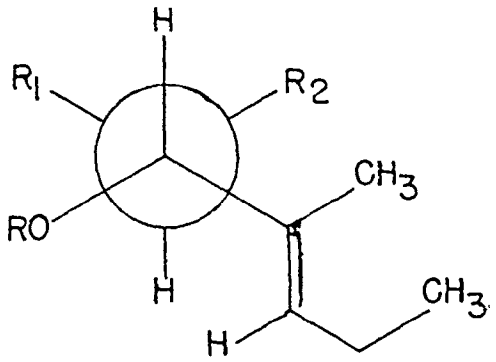
ethanes has been observed by Kingsbury.[47] Conformers G and J were most stable because they had one $CH_3\cdots OR$ or one $COOR\cdots OR$ and one $H\cdots OR$ interaction compared to $CH_3\cdots OR$ or $COOR\cdots OR$ and $COOR\cdots C_5H_9$ or $CH_3\cdots C_5H_9$ interactions in conformers H, I, K, and L. However, changes in bond angles and elongation of bonds are known to give rise to anomalous behaviour.[41,47]

A low temperature NMR study (37 to -100°C) of the erythro and threo acids and their methyl esters showed no change in the coupling constants of the threo isomers with temperature, but the coupling constants of the erythro acid and methyl ester increased by 0.7 and 1.1Hz respectively. These results, within the limits of the NMR experiments, indicated that at ambient temperature, conformer G of the erythro isomer was the dominant but not the only conformer present, while conformer J of the threo isomer was the only conformer present.

The two likely orientations of the carbon-carbon double bond about C_3-C_4, 46A and 46B, were distinguished by NOE experiments. Table 2 shows the distances between nuclei (of 46A and 46B) and the calculated[19] and observed NOEs. Conformation 46A was substantially populated as indicated by a 11.5% NOE between C_3-H and C_5-H, and a 4.2% NOE between $-COOCH_3$ and C_5-H. Since no NOE was observed between C_3-H and C_4-CH_3, then conformation 46B was not significantly populated. Dreiding models indicated that the steric interaction between C_2-H and C_4-CH_3 was of less importance than that involving C_5-H. The coplanar orientation of C_3- and C_5-hydrogen atoms also appears to be a favoured situation. In the synthesis of fumagillin, Corey[48] observed the same orientation for the vinylic and allylic hydrogens of a trisubstituted olefin system.



46A



46B

ERYTHRO:
$R_1 = CH_3$, $R_2 = COOR$
THREO:
$R_1 = COOR$, $R_2 = CH_3$

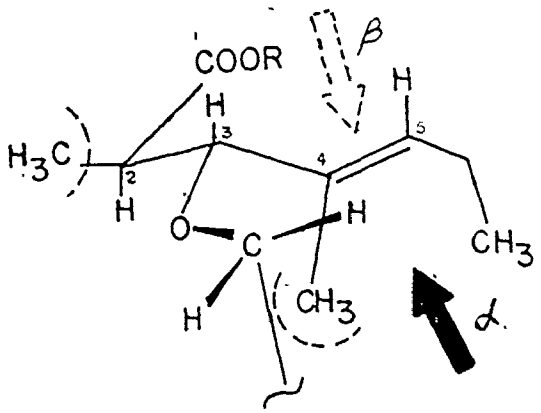
Table 2. Predicted and Experimental NOEs for Compound 46

			Distances and Predicted Values				Experimental
			Conformer 46A		Conformer 46B		NOE%
	Irradiate	Observe	A°	NOE%	A°	NOE%	
	C_5-H	C_3-H	2.3	40	3.7	0	17.8 ± 0.14
Threo Acid	C_4-CH_3	C_2-H	3.1	12	3.7	0	7.62 ± 0.65
	C_4-CH_3	C_3-H	3.7	0	3.0	12	0
	C_4-CH_3	C_5-H	3.7	0	3.7	0	0
Erythro Acid	C_5-H	C_3-H	2.7	20	3.3	7	11.50 ± 0.09
Erythro Methyl Ester	C_5-H	C_3-H	2.7	20	3.3	7	8.84 ± 0.22
	-OCH_3	C_5-H	3.1	12	3.7	0	4.24 ± 0.17

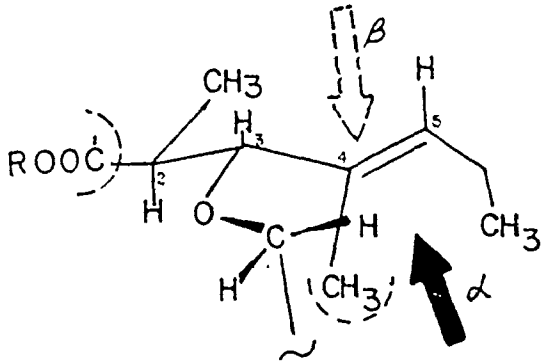
The epoxidation reaction, initiated by an electrophilic peracid,[45] proceeds by the peracid usually attacking the less hindered side of the olefin to produce the less hindered epoxide as the major product.[18] Hence,

in the present case, α-epoxides were expected as the major product because the olefinic face leading to β-epoxides, the 4re,5re face, was inaccessible to the peracid due to interference from R_2 (CH_3 or COOR) (see above structures). Although the experimental results for the threo isomer 46 (7:3 48b:48a) were indeed consistent with the above expectation, those for the erythro isomer 46 (7:3 48a:48b) were not. A proposal which explained the behaviour of these two isomers, involved the differences in the screening of the olefin by the R-protecting group, the C_7-CH_3, and the COOR groups.

A stereostructure of the preferred conformations of the erythro and threo isomers about the C_2-C_3, C_4-C_5, and methylenedioxy bonds is shown below. The rotational restriction imposed on the methylenedioxy unit by the C_4-CH_3 and COOR or C_2-CH_3 groups is indicated. The methylenedioxy protons were non-equivalent (diastereotopic) and formed an AB quartet at δ 4.45, 4.70 J=12.0Hz, because their inherent magnetic non-equivalence (due to the asymmetric centre at C-3) was enhanced by restricted rotation about the O_3, CH_2 bond. When R was the benzyloxy protecting group, the benzyl protons formed an AB quartet as well (in C_6D_6).



ERYTHRO 46A



THREO 46A

Assuming that these conformations predominated during epoxidation, the screening effect of $-OCH_2O-$ would be comparable to that of the C_2-CH_3 and COOR groups. Since the size of a methyl group is larger than that of a carboxyl group, steric interactions with $-OCH_2O-$ and the C_2-CH_3 group in erythro 46A, ought to be larger than the interaction between $-OCH_2O-$ and the COOR group in threo 46A. This could have resulted in a net screening of the 4si,5si face of the olefin, leading to preponderance of erythro epoxide 48a. The opposite would be true for the threo 46A conformation. Here, C_2-CH_3 would screen the 4re,5re (β) face to a greater extent, relative to the carboxyl in the erythro conformation. Less stringent interactions between COOR and $-OCH_2O-$ would at the same time alleviate the steric constraints of the 4si,5si (α) face, and hence result in preponderance of threo epoxide 48b. Such steric constraints of the olefinic bond were undoubtedly, responsible for the relative slow rate of epoxidation.

In addition, for the erythro olefin, the presence of other conformations, as indicated by the variable $^3J_{2,3}$ coupling constant (see page 53), such as conformation I could have been responsible for the predominance of epoxide 48a. For example, this conformer I would have the C_2-H on the 4re,5re face of the olefin. Replacement of hydrogen for the carboxyl group would greatly increase the accessibility of the β-face to the peracid attack.

The involvement of the carboxyl group in directing the stereochemistry of the epoxidation of erythro 46A was also considered. This topic has received much recent attention. For example, Cerefice[49] has claimed that an allylic carboxylic acid is an effective cis-directing

group. In analogy to the well known cis-directive effect of allylic alcohols,[50] Cerefice has hypothesized that hydrogen bonding between the peracid and the carboxyl group stabilizes the transition state leading to cis-epoxidations when the carboxylate is pseudoequatorial. According to Cerefice,[49] the relative order of effectiveness for allylic substituents is OH >> CO_2H > CO_2R >> O_2CR. However, Thomas[51] has repudiated this interpretation and attributed the results to steric or conformational effects. Hence, any suggestion that the carboxyl group played a role in the epoxidation stereochemistry of erythro 46A, is obviously dangerous at this point.

Both the erythro acids 46 and their methyl esters gave the same ratios of epoxides, and a solvent study (see table 3) showed the absence of polar interactions between the carboxyl group and the peracid in the transition state. Paryzek[52] has demonstrated the involvement of an allylic carbonyl group by performing epoxidations in benzene and acetonitrile. In acetonitrile, the stereochemistry was reversed. The same experiments carried out on the erythro acid and ester showed the ratio of epoxides decreasing to 6:4 in acetonitrile:methylene chloride (2:1). This change was likely due to a decrease in the effective steric bulk of the peracid in the transition state.[18]

Table 3. Solvent Effect on the Epoxidation of Erythro 46

Solvent (dry)	% Average of major erythro 48a
Pentane	64
Benzene	69
CH_3CN:CH_2Cl_2 (2:1)	59
CH_3CN	64

Since the hydroxyl group assists the epoxidations of allylic alcohols,[50] and the R-protecting group was thought to screen the α-olefinic face, this group ($PhCH_2OCH_2$-) was removed. This was accomplished for the threo isomer in 96% yield with sodium in liquid ammonia and tert-butanol as the proton source, rather than ethanol as reported.[24] Hydrolysis of this acetal with tosic acid in methanol at 70°C was less satisfactory, as anticipated. The methyl ester of 74 (see figure 18) was formed, as expected, but some epimerization as well as elimination and lactone formation occurred.

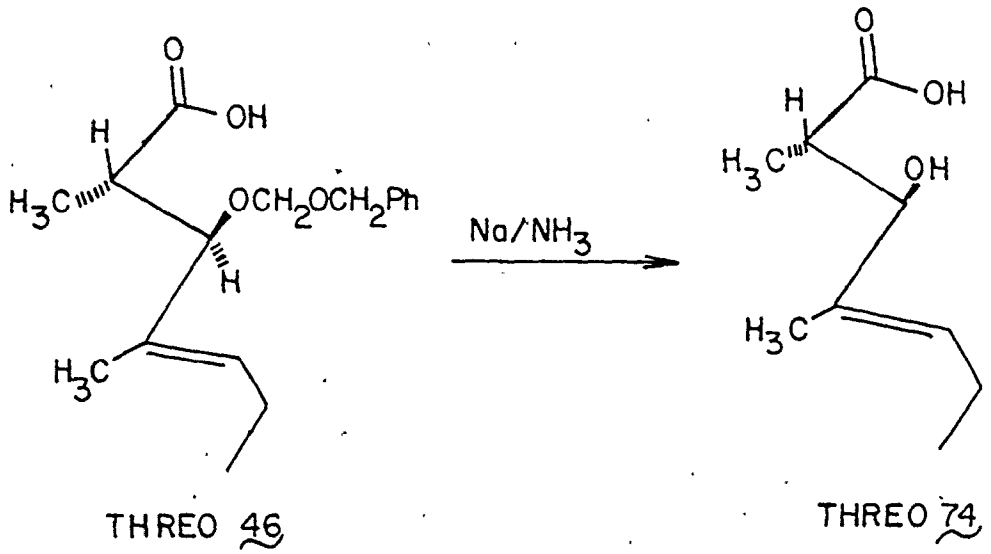
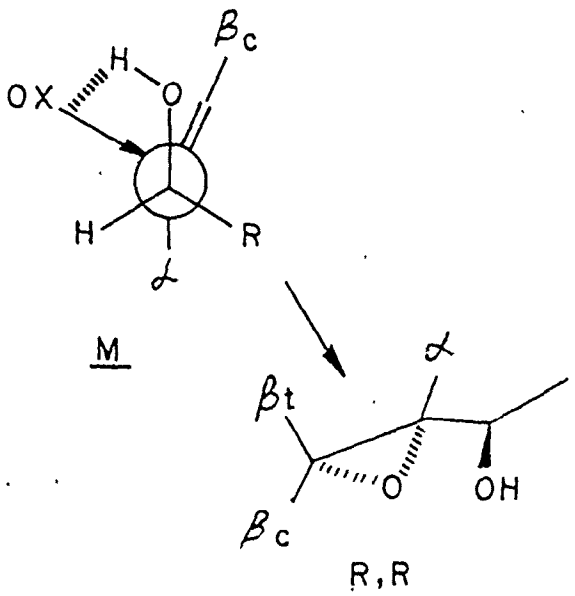


Figure 18

In comparison to the allylic acetal 46, the rate of epoxidation of allylic alcohol 74 was much faster. Thus at -20°C, 74 was completely epoxidized in less than three days. Although the directive effect of the hydroxyl group was envisoned to enhance the rate of epoxidation, it did not affect significantly the stereoselectivity of the epoxidation. A ratio of 8:2 epoxides 75b:75a (compare with 7:3 in 49) was obtained

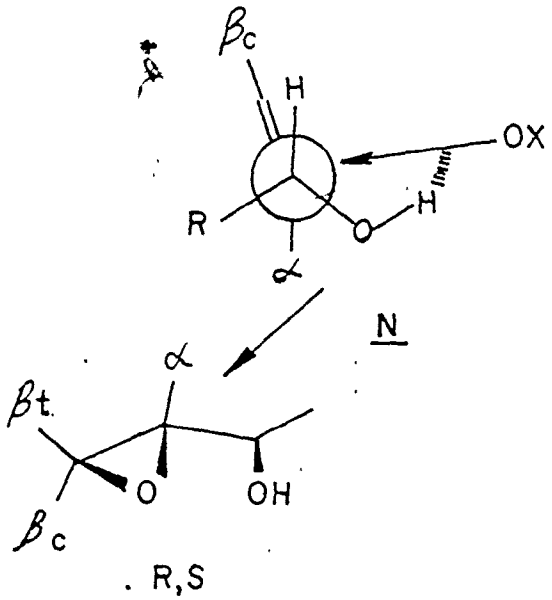
as determined by conversion of the epoxides to the γ-lactone diols 72 (IR: 1755, 3430 cm^{-1}). The vicinal coupling constant of 74, $^3J_{2,3}$=9.0Hz, also indicated a conformation about C_2-C_3 with trans vicinal hydrogens as in conformation J page 53.

The stereochemistry of the reaction of acyclic allylic alcohols has been studied by Pierre[53] using p-nitroperoxybenzoic acid, and by Sharpless[54] using peracids and the more selective transition metal catalyzed t-butylhydroperoxide systems. In a number of instances, very high 1,2-asymmetric induction was obtained. Unfortunately, olefins with a substitution pattern as that of 74; α-CH_3 and trans β-CH_2CH_3 to the hydroxyl function, have given poor selectivities. For example, Pierre[53b] obtained a 45:55 ratio of cis:trans (R,R:S,S) epoxides from the epoxidation of 3-methyl-3-pentene-2-ol. Possibly, the epoxidation of 74 also occurred in conformation M (i.e. threo 46B) which is favoured in these epoxidations when there is a α-substituent.[15] In this conformation, the peracid attack would be on the accessible 4re,5re face of the olefin. This discouraging experience terminated further epoxidations with the threo (or erythro) allylic alcohols 74.



M

R,R



N

R,S

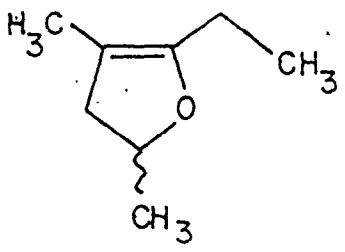
CHAPTER 4

RESULTS AND DISCUSSION; C_1-C_8 SYNTHON

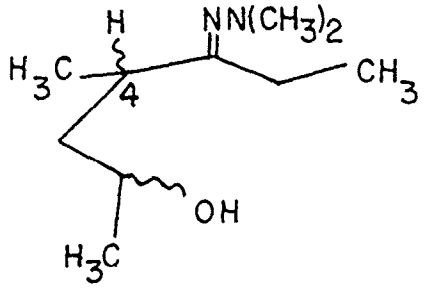
4.1 Synthesis of the C_1-C_8 Synthon

The synthesis of this carbon fragment was outlined in figures 10 and 11 (see pp 62a,b). The introduction of the propyl and formyl carbon units into the synthon and subsequent functional group manipulations, demonstrated the problems in preparing polyfunctional acyclic compounds and the lack of general purification techniques of very labile compounds.

The propyl unit, derived from propylene oxide, was initially introduced by the alkylation of the potassium enolate of 3-pentanone. Dehydration of the resulting γ-hydroxyketone gave 76 which upon peracid oxidation in wet methylene chloride gave a keto-diol. However, further manipulations on this latter intermediate were unsuccessful. Also unsuccessful, was a scheme utilizing intermediate 77, available via the alkylation of the lithio derivative of hydrazone 64 (obtained from 3-pentanone and N,N-dimethylhydrazine[55] in 90% yield), because of the failure to oxidize C-4 at a later stage. The scheme illustrated in figures



76



77

10 and 11 was finally adopted. Hydrazone 64 was metallated with diisopropylamide (LDA) in THF and then alkylated with dimethyldisulfide[17] to yield the methylthioether 63 in quantitative yield. Similar metallation of 63 and propylene oxide alkylation yielded 62 in ~70% yield as a mixture (1:1) of the two possible diastereomers. This simple alkylation proceeded well only after the technique of the slow addition of epoxide to an excess of the metallated hydrazone was used. The hydrazone anion is relatively stable and its reactivity is comparable to that of the alkoxide generated by opening of the epoxide ring. Purification of 62 and subsequent intermediates was only possible on a reverse-phase (RP-8) column, the mobile phase consisting of water-acetonitrile with a disodium hydrogen phosphate buffer of pH ~7.2. Protection of the alcohol group at C-6 of 62 involved generating the alkoxide with potassium hydride and alkylating with MEM-chloride, yielding the hydrazone 61 in about 90% yield. Use of sodium hydride or diisopropylethylamine as for the conditions reported by Corey[23] gave less satisfactory results.

Solvolysis of hydrazones 61 in methanol in the presence of mercuric chloride resulted in the exchange of the thiomethyl for the methoxy group. A 7:3 ratio of diastereomeric α-methoxyhydrazones 60 was obtained in yields higher than 90%. This ratio was more accurately measured (^{1}H NMR spectroscopy) when the hydrazone group was removed in the next step (vide infra).

In a phosphate-buffered system, the crude α-methoxyhydrazone, 60, was then converted by cupric chloride assisted hydrolysis into the ketoglycol 58. The purification and separation of diastereomers 58 was accomplished on neutral alumina as well as on a reverse-phase adsorbent.

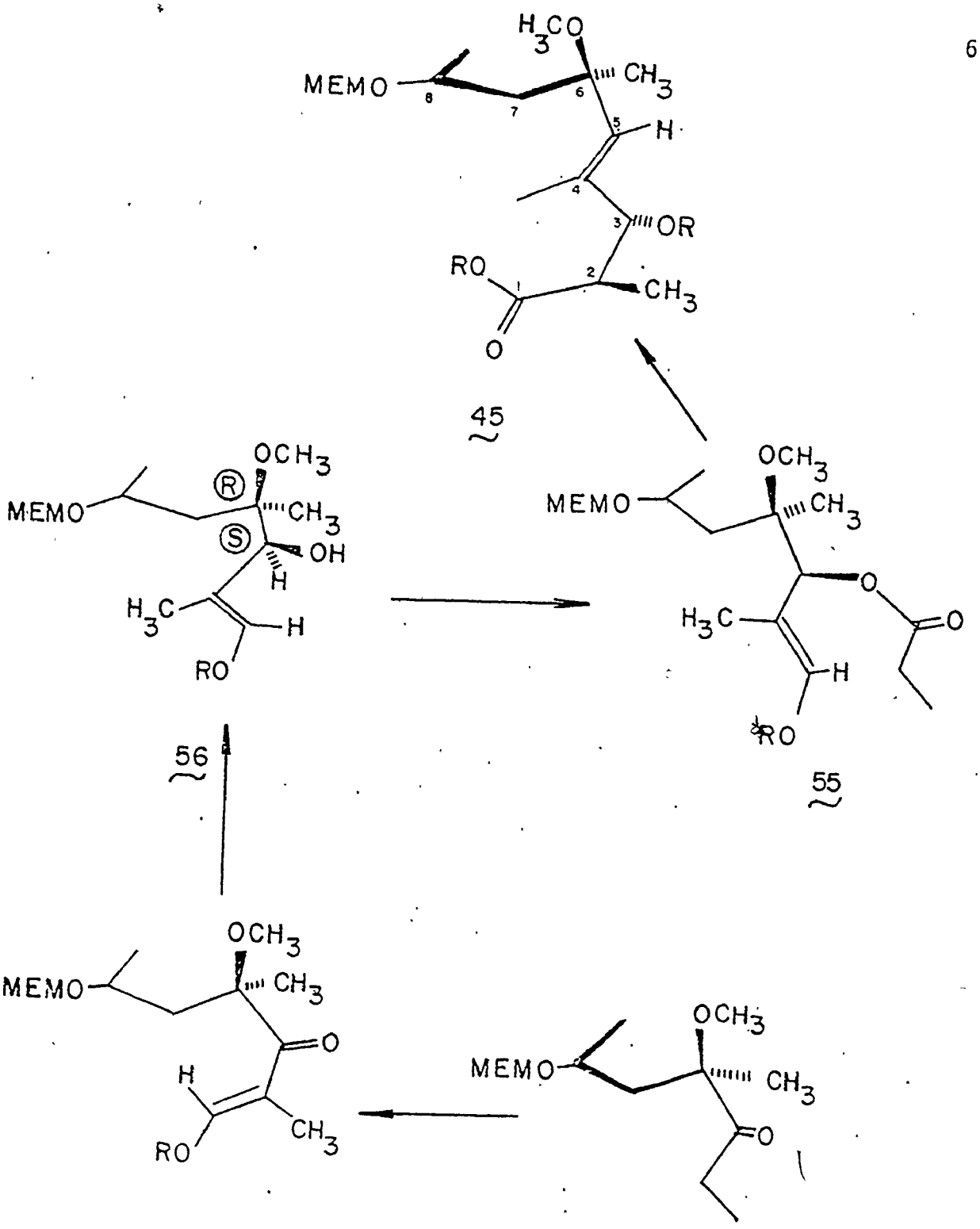

H3CO
MEMO
CH3
H
OR
RO
CH3
O
45
OCH3
MEMO
CH3
OH
H
H3C
H
RO
56
OCH3
MEMO
CH3
O
H3C
H
RO
55
OCH3
MEMO
CH3
O
H
CH3
RO
57
OCH3
MEMO
CH3
O
58
MEM = -CH2OCH2CH2OCH3

Figure 10

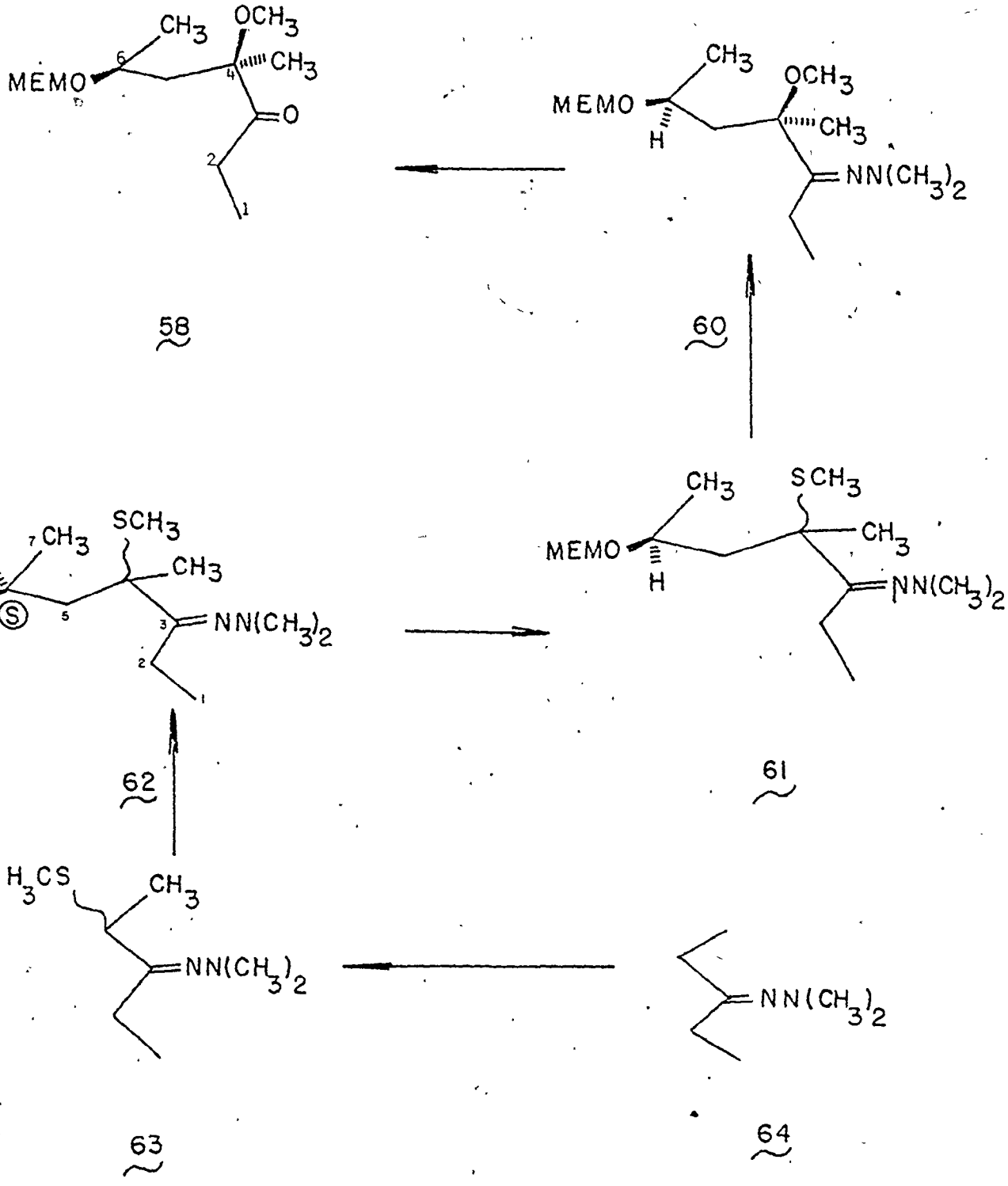
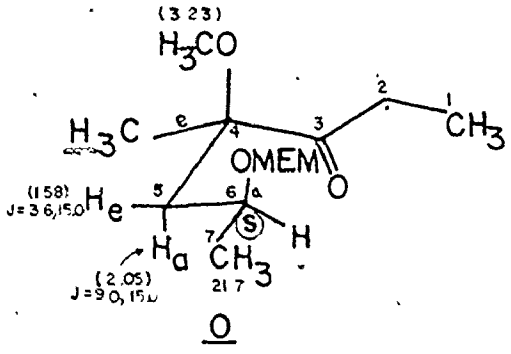

CH3
OCH3
MEMO
6
4
CH3
O
2
1
58
CH3
OCH3
MEMO
H
CH3
NN(CH3)2
60
CH3
SCH3
MEMO
H
CH3
NN(CH3)2
61
H
7CH3
SCH3
HO
S
5
CH3
3
NN(CH3)2
2
1
62
H3CS
CH3
NN(CH3)2
63
NN(CH3)2
64

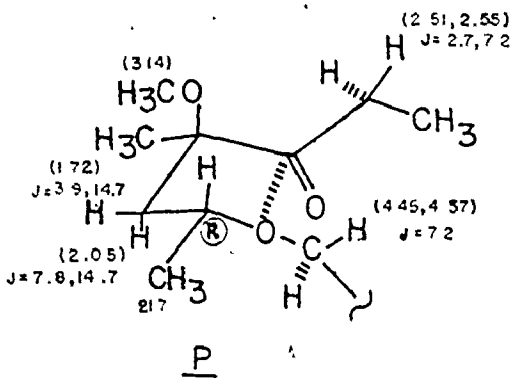
Figure II

However, large separations in alumina led to the total destruction of the ketones. Presumably, the γ-OMEM (i.e. γ-OR) group was more labile to acid than normal because of neighbouring group participation by the carbonyl (or hydrazone) function. The yield of 58 for the RP-8 separation, solvolysis, and hydrolysis steps was about 60% from 61.

The surprising separation of the keto diastereomers 58 allowed tentative assignments of these compounds. The major isomer was the least retained on RP-8 and the most retained on alumina and this isomer was assigned the 4(R),6(S)-configuration. The rationale for this assignment was based on the unique ^{1}H NMR spectra of the 58 diastereomers (see figures 23 and 24, pp 104-5). The carbon atoms from C_4- to C_6 of the two diastereomers appeared to occupy half-chair conformations O and P. These prefered conformations were based on the coupling constants observed in the ^{1}H NMR spectra of the diastereomers for the nonequivalent methylene protons at C-5 together with the identical carbon resonances of C-7 in the ^{13}C NMR spectra of both isomers. In conformation O (assigned the major isomer), C_4-CH_3 and C_6-CH_3 occupied equatorial (or pseudo-equatorial) positions in



O



P

an extended zig-zag form. The oxy groups at C-4 and C-6 consequently occupied axial (or pseudoaxial) positions.

A high degree of preference for conformations O and P also accounted for the anisotropic effects experienced by the C_5-methylene protons ($\Delta\delta$=0.47 ppm for O and 0.33 ppm for P). In the major isomer, the $-CH_2-$ of the $-CH_2CH_3$ group was a simple quartet (δ 2.55 ppm, J=7.2Hz) and the $-OCH_2O-$ group was a sharp singlet (δ 4.63 ppm), indicating no conformational restrictions for these two groups. In contrast, the minor isomer showed the $-CH_2-$ of the $-CH_2CH_3$ group as a doublet of quartets (δ 2.51 and 2.55 ppm, J=2.7 and 7.2Hz), and the $-OCH_2O-$ group formed an AB quartet (δ 4.45 and 4.57 ppm, J=7.2Hz), indicating hindered rotation about the C_2,C_3 and O_6,CH_2 bonds. Such restricted rotation of <u>both</u> $-CH_2-$ groups pertained only to conformation P, where a O$\cdots$C=O interaction would yield a relatively rigid system with the $-OCH_2O-$ methylene group proximal to the $-CH_2CH_3$ group. This interaction, which has also been observed in a bicyclic system,[56] accounted for the chromatographic behaviour of the two diastereomers because it would have decreased the carbonyl dipole as well as increased the steric congestion about the carbonyl of the 4(S), 6(S)- diastereomer as shown in conformation P. The 4(R),6(S)-diastereomer was then the more polar and hence eluted <u>first</u> from an RP-8 adsorbent and <u>last</u> from an alumina column.

The carbonyl stretching absorption in the infrared also suggested that conformation P of the minor diastereomer <u>58</u> was populated. Whereas, the major isomer showed $\nu_{max}^{C=O}$ at 1720 cm^{-1}, the minor isomer showed $\nu_{max}^{C=O}$ at 1715 cm^{-1} ($\Delta\nu$=5 cm^{-1}). In analogy to the known increase in wave number (~20 cm^{-1}) in eclipsed conformations of α-halo carbonyls,[57] the 5 cm^{-1}

difference observed suggested that the major isomer adopted more conformations where the C_4-OCH_3 and C=O groups were eclipsed than the minor diastereomer 58. This was consistent with the ^1H NMR data which suggested a free rotating $-\overset{O}{\overset{\|}{C}}CH_2CH_3$ side chain in the major isomer.

The major ketone 58 was then acylated with ethyl formate by using 2.1 equivalents of potassium hydride in THF. Use of sodium hydride and benzene, the conditions used in the preparation of enone 53, led to polymeric products presumably arising from aldol condensations. Although ketone 58 is a bulky carbonyl and hence normally not prone to aldol condensation, the γ-OMEM group may have affected the reactivity of the enolate. Sodium hydride forms enolates relatively slowly in a heterogeneous reaction mixture with the result that appreciable concentrations of both the free ketone and its enolate anion are present at some point.[18] The extremely reactive potassium hydride base in THF resulted in quantitative metallation of ketone 58.[58] Acylation, followed by O-alkylation with chloromethyl benzyl ether in THF:HMPA (4:6) gave enone 57 in ~70% yield.

A lithium cation reducing agent in an aprotic medium was expected to reduce enone 57 stereoselectively via the "cyclic" conformation[15,59] shown in page 27. Use of lithium tri-sec-butylboron hydride (L-selectride) in THF,[60,61] however, reduced 57 in a 1,4-manner yielding the isopropyl ketone 79. Apparently, the carbonyl group was hindered by the C_4-OCH_3 and $-CH_3$ groups and the bulky hydride could not approach it. Ketone 79 presumably arose from the intermediate 78, formed by addition of the hydride to C-1, which then eliminated to a relatively reactive enone (see figure 19). Further reduction in a 1,4-manner gave 79. Ketone 79 had a

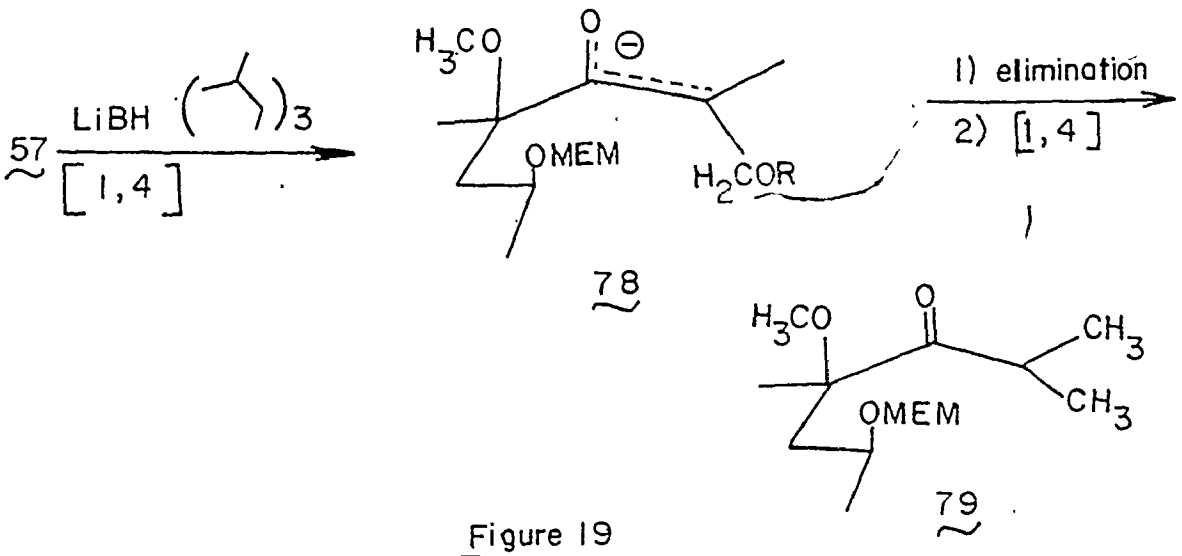
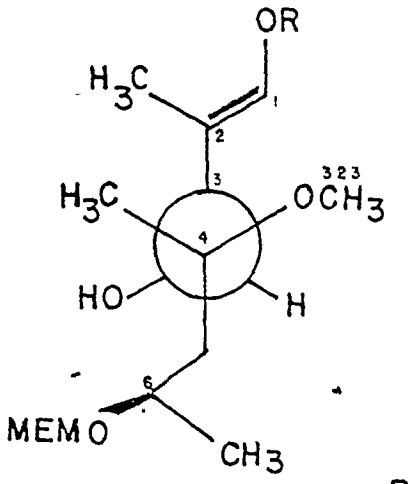
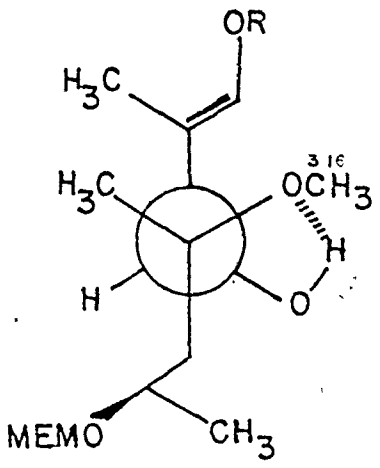


Figure 19

carbonyl stretching frequency of 1715 cm^{-1} and the isopropyl methyls were diastereotopic, each showing a doublet of 6.8Hz at δ 1.01 and 1.07 ppm. Spin-decoupling experiments confirmed the proposed structure.

Reduction of enone 57 with sodium or lithium borohydride in diglyme proceeded in a 1,2-manner in high yields but unfortunately in a non-selective manner. The diastereomeric allylic alcohols 56, obtained in a 1:1 ratio, were separated by chromatography using RP-8. In an attempt to assign the structure of these alcohols, pyridine-induced solvent shifts[37] were performed, but no definite pattern was obtained. A study involving the shift reagent $Eu(fod)_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium) was then carried out and the results are summarized in figure 20. The magnitude of the proton shifts of the more polar alcohol (first eluted from RP-8) were greater, especially for C_4-CH_3 and C_4-OCH_3, indicating a greater contact (large association equilibrium constant, K)[62] between the hydroxyl function and the europium ion. This was consistent with the chromatographic behaviour. Differential interactions of the hydroxyl group with the mobile phase resulted in the separation of the allylic alcohols. The population of

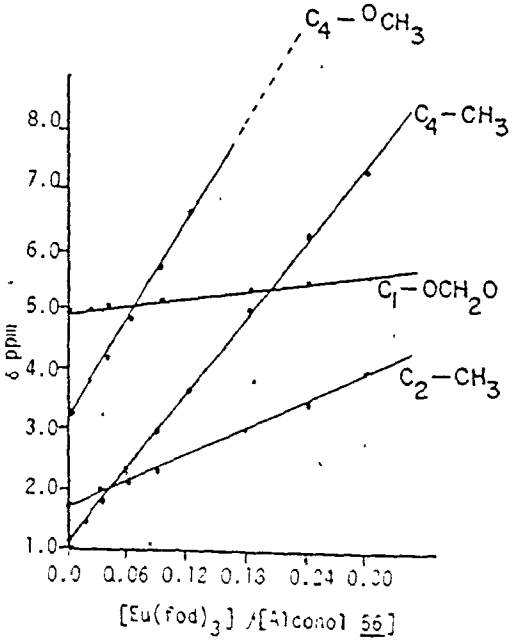




R=$-CH_2OCH_2Ph$

3(S),4(R),6(S)— 56 (Q)

3(R),4(R),6(S)— 56(R)



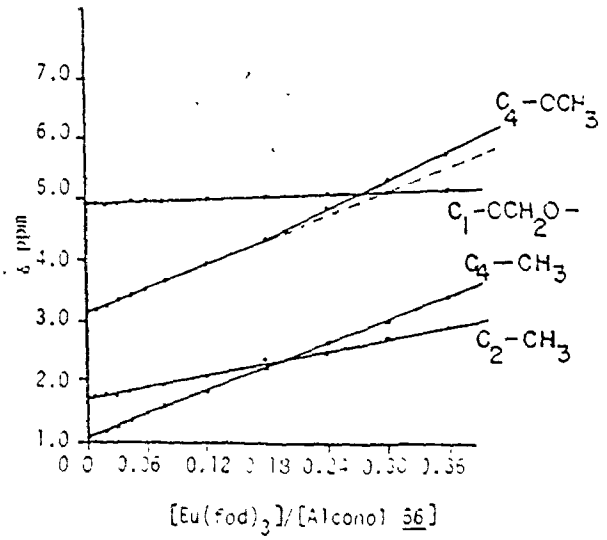


Figure 20

conformers 56Q and 56R would account for these observations. In the latter, intramolecular hydrogen bonding would make the hydroxyl group unavailable for interactions with the mobile polar phase or the europium ion. It must be stressed though, that assignments are tentative. The

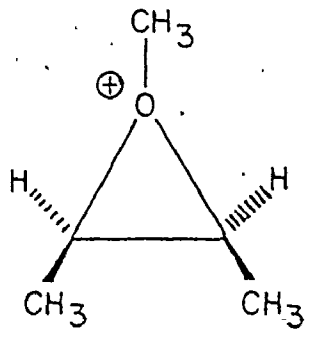
80 MHz proton NMR (in C_6D_6) and the ^{13}C NMR spectra of the more polar alcohol, assigned the 3(S),4(R),6(S)-diastereomer, are shown in figures 28 and 29. Assignment of the carbon resonances is shown on page 113. While the ^{13}C NMR spectra of the two diastereomeric alcohols are different (eg. C_4-CH_3, C-1, C_2-CH_3, and C-3), there was no basis for structure assignment.

An impure sample of the ester 55 was prepared in small quantities by acylating the more polar alcohol with propionic anhydride in pyridine and triethylamine.[14] The reaction required about six days for completion. The proton NMR of the product, 55, indicated the expected deshielding of the C_3-allylic proton to 5.22 ppm (from 3.98 ppm in 56) and the appearance of a quartet at 2.35 ppm from the propionyl unit. The triplet of the $\underline{CH_3}CH_2COO$- was buried in the alkyl envelope. Unfortunately, a large enough sample of this ester was not available for the Claisen rearrangement at the time of writing.

In summary, the synthetic conquest of the C_1-C_8 fragment of Erythronolide A (and B) has almost been reached with the synthesis of the allylic ester 55. The Claisen rearrangement of the silyl ketene derivative of this ester, yielding the framework (correct array of carbon atoms) of the C_1-C_8 fragment, remains to be performed. The important steps in the synthesis of 55; the mercuric assisted solvolysis of the α-methylthiohydrazone 61, and the reduction of enone 57, proceeded with limited stereochemical success. The following two sections (sections 4.2(A) and 4.2(B)) provide rationale for the stereochemical results.

4.2(A) Stereoselectivity in the Formation of Ketone 58

The stereoselectivity observed in the methanolic solvolysis of the methylthiohydrazone 61 was a consequence of neighbouring group participation by the γ-OMEM substituent. However, the 70:30 ratio of hydrazone-glycols 60 obtained at 0°C was close to a 75:25 ratio, suggesting that the solvolysis proceeded with retention of configuration in one diastereomeric methylthiohydrazone, 61, and with racemization in the other. The intermediate acyl cation equivalent, if indeed a full cation developed, did not equilibrate between the expected intermediates 65 and 66 (below). Precedence for this argument was found in the work of Weinstein and Henderson.[63] The reactions of threo- and erythro-2-bromo-3-methoxybutane with silver acetate in acetic acid gave 3-methoxy-2-butyl acetate with retention of configuration in both cases. This indicated that configurational retention resulted from the bridged- ions 80 and 81. Hence, equilibration to avoid the cis-methyl interaction in 80 (analogous to the $-CH_3$ versus $-\overset{\overset{NN(CH_3)_2}{|}}{\underset{|}{C}}CH_2CH_3$ axial interaction in 65 and 66) was not observed.



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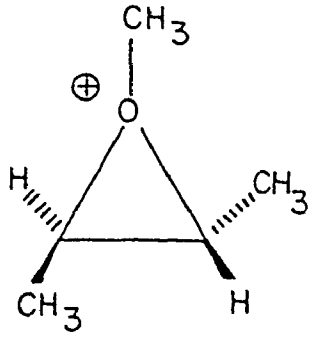
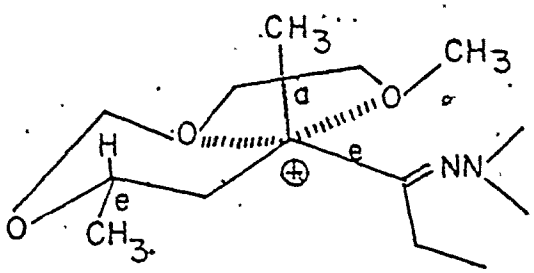
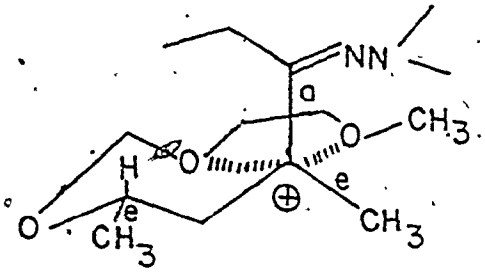


81

The rationale for the 7:3 observed selectivity assumed that stabilization of the incipient cation by the γ-OMEM substituent was not possible in the 4(S),6(S)-methylthiohydrazone 61, because it would result in the six-membered cyclic intermediate 66 with the bulky $-\overset{NN(CH_3)_2}{\overset{|}{\overset{\|}{C}}}CH_2CH_3$ group axial. Instead, the solvolysis of this diastereomer proceeded with racemization of the C-4 center. In contrast, the solvolysis of the 4(R),6(S) diastereomer proceeded with anchimeric assistance, possibly via intermediate 65 with the C_4-CH_3 group axial. The solvent molecule then approached the cationic center from the same side of the departing thiomercurial complex, giving the desired 4(R),6(S)-keto glycol 60 after hydrolysis of the hydrazone function.

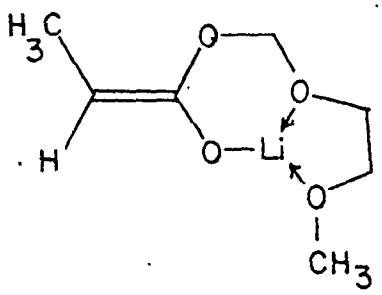


65



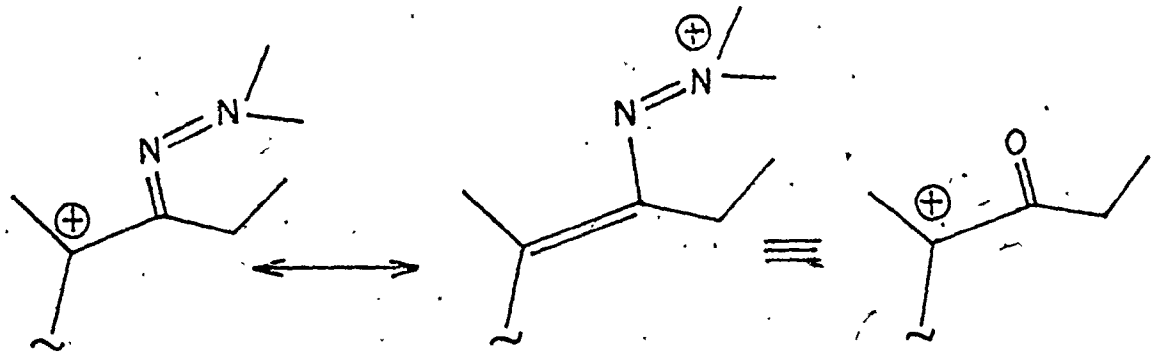
66

Similar behaviour of the MEM protecting group was hypothesized by Meyers[16] in the internal chelation of enolate 82. The oxygens of the ester alkyl group appeared to chelate the lithium of the enolate ion. Further, the bidentate coordination of the MEM group to Lewis acids may



82

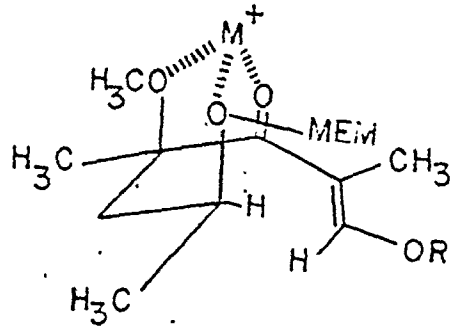
be responsible for the facile cleavage of MEM acetals.[22] Although the dimethylhydrazone function was expected to stabilize the positive charge on the α-carbon, S, geometry prevented the γ-oxygen from stabilizing the positive charge at nitrogen. Hence, the selectivity of the solvolysis likely originated from an intermediate similar to that depicted in 65.



S S

4.2 (B) Lack of Stereoselectivity in the Formation of Alcohol 56

The unfortunate lack of selectivity in the reduction of enone 57, giving a 1:1 ratio of alcohols 56, indicated that the reduction did not proceed through the proposed stereostructure 59. In this conformation, the C_6-OMEM group was expected to chelate the lithium or sodium cations (leading to a 6-membered ring) and screen the si side of the π-bond. The reduction stereochemistry may have not involved the five-membered "cyclic" model[15] either (chelation of α-alkoxy and carbonyl groups; see page 25).

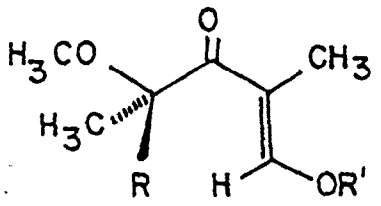


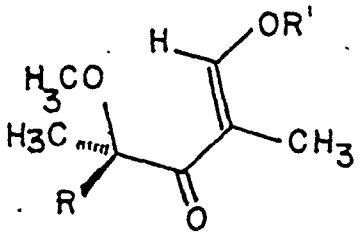
59

The "cyclic" model was probably not applicable as the favoured conformation of the molecule at the transition state of the reduction. Recently, Glass[64] reported highly stereoselective reductions of α-alkoxy-β-keto esters in 2-propanol, which were claimed to proceed via a five-membered ring chelated sodium ion (i.e. the "cyclic" model). Glass also found that the sodium ion was not required for reduction, even though it played an important role in controlling the stereochemistry. Hence, it

is conceivable that the reduction of 57 occurred with the exclusion of the metal ions. In this regard, the use of lithium aluminum hydrides would be desirable. However, these hydrides reduce enones in a 1,4-manner.[65] The hindered carbonyl of 57, as was evident in the L-selectride reduction which also proceeded in a 1,4-manner, may only be reduced with lithium or sodium borohydride. Reduction with other metal cations, eg. magnesium or zinc (borohydride), were not performed.

The reduction of carbonyl groups is also known to proceed via a transition state which follows the "dipolar" model.[15,64] Whichever model(s) was used in examining the reduction of enone 57, was infered from the preferred conformation of the enone unit; conformation 57T (geometry of the "cyclic" model with eclipsed (or gauche) C=O and $-OCH_3$ groups), or alternatively, conformation 57U (geometry of the "dipolar" model).





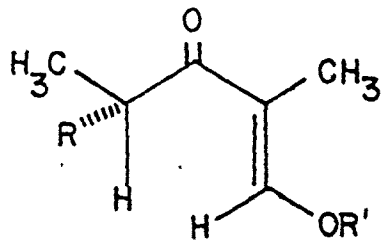
R= $-CH_2CH(OMEM)CH_3$

δ_{C_1-H} = 8.43 ppm

57T 57U

Enone 57 (existing in the s-trans form[66]) appeared to adopt conformation U as indicated by the carbonyl stretching frequency. Whereas the ν_{max} of 57 was at 1627 cm^{-1}, that of enone 53 was at 1647 cm^{-1}. The analogue[67] of 57 (H replacing $-OCH_3$) also showed ν_{max} at 1645 cm^{-1}, and

the C_4-siloxy derivative[67] of 53 showed ν_{max} at 1640 cm^{-1}; all at higher frequencies relative to enone 57 by 15-20 cm^{-1}. In the latter molecules, the prefered conformation was likely V. Interpretation of the infrared results by considering steric hinderance or non-planarity of the enone unit of 57, predicted that the C=O stretching absorption would be at higher rather than lower frequency.[68] Furthermore, the C_1-H chemical shift at δ 8.43 ppm (compared with δ 8.03 ppm for the siloxy-derivative[67] of 53) would not be consistent with enone non-planarity. Hence, the 20 cm^{-1} difference may have been due to the anti-periplanar disposition of carbonyl and C_4-OCH_3 groups.[57,68] Conformation U was also consistent with the proposed conformational behaviour of the (minor)- 4(R),6(R)-ketone 58 on chromatographic adsorbents (see page 63). Although the infrared spectra were useful for rough correlations of the above enones and ketones 58, the interpretation of the infrared phenomena of the α-halocarbonyl analogues is still open to some question.[68,69]



R = H, 53 $\delta_{C_1\text{-}H}$ = 8.03 ppm
= —OSi(CH3)3
= —CH2CH(OMEM)CH3

V

Reduction of 57 in conformation U, and hence the "dipolar" model, would not allow any selectivity in the delivery of the hydride because

the substituents at C-4 ($-CH_3$ and $-CH_2R$) are of comparable size. In analogy to the Grignard additions performed by Cornforth[67] on α-halocarbonyls, the polarization of the carbonyl group would be easier when the dipoles (of C=O and $-OCH_3$) were antiparallel, as in conformation U. In this conformation the reduction process would be enhanced.

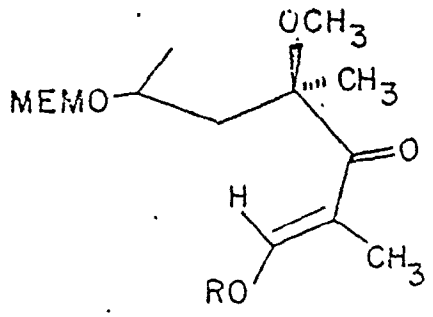
In summary, the reduction of enone 57 may have proceeded via the "dipolar" model, in which case, the potential for a stereoselective reduction was minimal.

CHAPTER 5

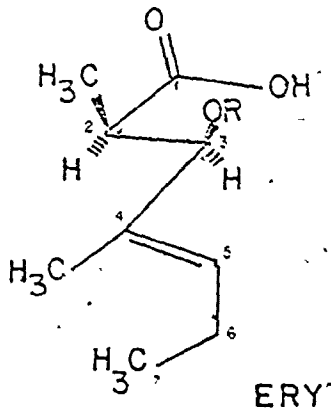
CONCLUSIONS AND POTENTIAL SYNTHETIC SCOPE

Earlier (chapter 1), a comment was made that the overall complexity of Erythromycins presented the chemist with a formidable challenge for their total synthesis. This indeed was realized with the synthetic approach presented in this thesis, which mimicked nature in involving the assembly of simple molecules. Although the carbon atoms of the C_9-C_{13} and C_1-C_8 fragments of Erythronolide A were assembled successfully, the stereochemistry in the reduction of enone 57 was completely non-stereoselective. However, much has been gained in exploring stereoselective reactions on non-cyclic compounds, and the encountered stereochemical problems may have workable solutions (vide infra).

The β-lactone 49, also considered as a C_9-C_{13} synthon since it contained the correct array of functional groups and stereochemistry, was obtained from the stereoselective epoxidation (followed by lactonization) of heptenoic acid 46. The stereochemical behaviour of erythro and



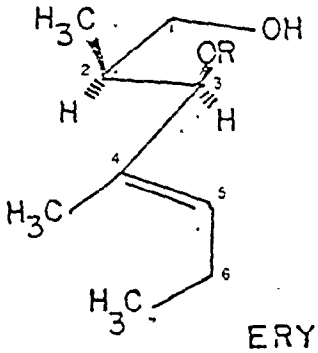
57



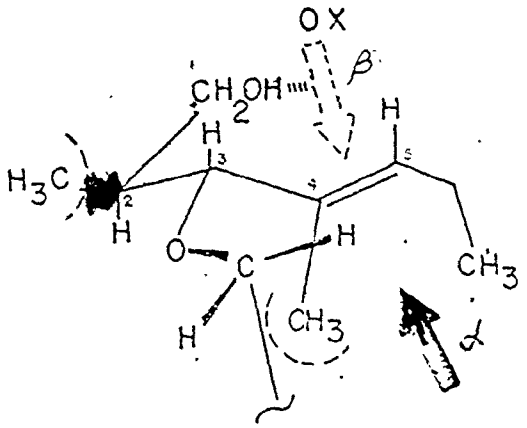
ERYTHRO 46

threo diastereomers, 46, to m-chloroperbenzoic acid was not the same; erythro-46 gave mainly the erythro-β -lactone 49, whereas threo-46 gave mainly the threo-α-isomer. A proposal which accounted for these observations was discussed. The greatest problem in the synthesis of the carboxylic acid 46 was the consistent poor yields in the Claisen rearrangement. A solution to this problem may require the use of a selective base (eg. lithium hexamethyldisilazide) for the enolization step, and/or the use of alternative solvents.[30]

Improvement in the epoxidation stereochemistry may require, first, the reduction of erythro-46 or its methyl ester with lithium aluminum hydride to the alkenol 76. The epoxidation of this bishomoallylic alcohol may be accompained with the cis-directing effect of the hydroxyl function via either hydrogen-bonding[50] to a peracid, or by the intermediacy of an oxygen-vanadium hydroperoxide system[54] (Sharpless procedure). In either case, oxidative addition would be on the 4re,5re (β)-face of the olefin, yielding stereospecifically epoxide 48a. Kishi[70] has recently explored the epoxidation of bishomoallylic alcohols and reported stereospecific epoxidation via the Sharpless procedure (7:1 to >20:1 ratios of diastereomeric epoxides were obtained).

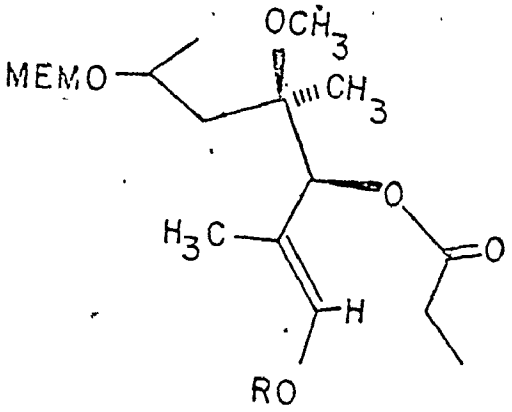


ERYTHRO 76

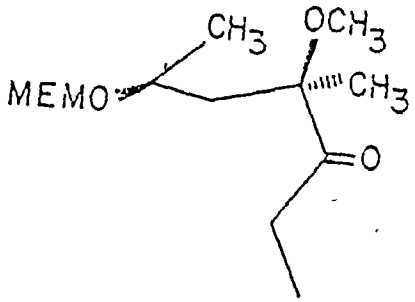


ERYTHRO 76A

The assembly of the carbon atoms for the C_1-C_8 synthon culminated with ester 55. The Claisen rearrangement of the silyl ketene acetal derivative of 55, giving the C_1-C_8 synthon, was not performed because of insufficient material at the time of writing. Ester 55 was obtained by propionic anhydride acylation of alcohol 56 via the Taguchi[14] procedure. The latter intermediate was obtained by 1,2-reduction of enone 57, itself available from ketone 58. These two steps required extensive experimentation to overcome the problems of 1,4-reduction of the enone unit and the aldol condensation of the enolate of 58.

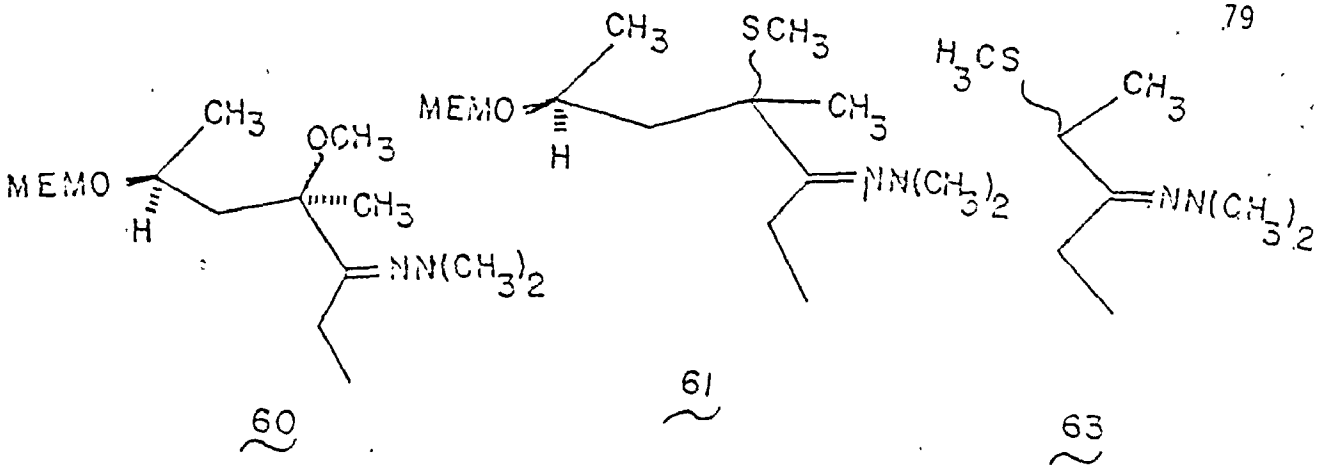


55



58

Ketone 58 was obtained by the hydrolysis of hydrazone 60. This step proved to be time consuming because, ironically, of the number of methods available for the hydrolysis of hydrazones.[55,71] These were not as satisfactory as that using cupric chloride. The mercuric chloride solvolysis of 61 in methanol gave the hydrazone 60 without any complications. Introduction of the MEM protecting group required the development of a procedure using potassium hydride to generate the alkoxide of 62. Optimal conditions for the alkylation of the anion of 63, generating 62,



60 61 63

will require a machine driven syringe to add the propylene oxide.

The purification of the above labile intermediates was a formidable task. This was facilitated somewhat late in the second part of this work with the use of a semi-preparitive, Lobar, reverse-phase (RP-8) chromatographic column.

The solvolysis of 61 proceeded with the predicted stereochemistry. The ratio of isomers obtained though, may not be improved because of the nature of this stereoselective process; only the solvolysis of the 4(R), 6(S)-diastereomer appeared to have involved the MEM protecting group. Changes in the solvent composition (eg. 1% methanol in acetonitrile or tetrahydrofuran) led to elimination processes and hence olefin formation.

The reduction of enone 57 did not proceed in a stereoselective manner. A solution to this problem may require a different approach altogether. For example, replacement of the C_4-OCH_3 group by a C_4-aromatic group would probably effect the desired 1,2-asymmetric induction. A C_4-OCH_2Ph side chain, for instance, could interact with the π-electrons of most of the enone unit, and hence block one face of the carbonyl group. This idea was explored with great success by Corey[60] in a Prostaglandin synthesis. Incorporation of the benzyl group in the molecule would be accomplished by performing the mercuric solvolysis of 61 in benzyl alcohol.

CHAPTER 6

EXPERIMENTAL SECTION

6.1 General Introduction

Infrared spectra were obtained on a Perkin-Elmer infrared spectrophotometer using neat liquids. Proton magnetic resonance (PMR) spectra were recorded on Varian Associates T-60, HA-100, and EM-390 spectrometers as well as on a Brucker WP 80 NMR (fourier transform) spectrometer in deuteriochloroform solutions (exceptions are noted) using tetramethylsilane (and chloroform) as internal stardard. The abbreviations s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, and m=multiplet are used in the recording of the spectra. The nuclear Overhauser effect (NOE) experiments were performed by Dr. D.Hughes, and repeated by the author. Low and high resolution mass spectra were recorded on a C.E.C. 21-110 mass spectrometer by Mr. F.A.Ramelan. The abbreviations s=strong, m=medium, and w=weak are used in the recording of the spectra and refer to the relative intensity of signals. Natural abundance carbon-13 magnetic resonances were recorded on a Brucker WP 80 NMR spectrometer (at 20.115 MHz) in deuteriobenzene solutions (exceptions are noted). Wherever appropriate, starred resonances (^{13}C and ^{1}H) refer to the major isomer in a diastereomeric mixture.

Wherever drying of solvents was required, procedures reported in the literature were used. Hence, tetrahydrofuran, benzene, pyridine, triethylamine, diisopropylamine, and cyclohexylisopropyl amine were dried

with calcium hydride.[72] Methylene chloride, chloroform, and acetonitrile were dried with phosphorous pentoxide.[31] Hexamethylphosphoramide was dried with calcium hydride or phosphorous pentoxide.[31] Ethyl formate was purified by shaking with anhydrous potassium carbonate and then distilling from phosphorous pentoxide.[73] Propylene oxide was distilled from calcium hydride before use. Propionic anhydride and 3-pentanone were fractionally distilled before use. Diglyme was "dried" from calcium hydride, but this dessicant alone did not give a super-dry solvent (i.e. less than 2 ppm of water). The use of lithium aluminum hydride is apparently required after distilling from calcium hydride.[74]

The lithium borohydride reagent was prepared by reaction of sodium borohydride with dry (150°C, 12 hours under high vacuum) lithium chloride (metathesis) in isopropyl amine[75] in 94% yield. A 0.01 M lithium borohydride solution was then made in diglyme.

Wherever diazomethane was required, the procedure of de Boer and Backer,[73] which employed "Diazald" (N-methyl-N-nitroso-p-toluenesulfonamide) was used.

Wherever n-butyllithium was required, it was first standardized using the procedure of Kofron,[76] which employed diphenylacetic acid in tetrahydrofuran. The procedure of Watson and Eastham[77] was also used frequently. This involved adding a 1.0 M sec-butanol solution in xylene to a n-butyllithium solution in xylene containing 1,10-phenanthroline as indicator.

The general procedure for the formation of diisopropylamide and cyclohexylisopropylamide solutions, involved adding dropwise at 0°C with stiring under an inert atmosphere, 1.0 equivalent of a 1.6 M n-butyl-

lithium solution in hexane to 1.1 equivalents of an approximately 0.5 M solution of the required amine in dry tetrahydrofuran. After 10 minutes at 0°C, the generated amide was then used.

m-Chloroperbenzoic acid was purified by the procedure of Schwartz.[78] The peracid was dissolved in methylene chloride and washed three times with an aqueous phosphate buffer (pH 7.5) which removed the m-chlorobenzoic acid contaminant. Drying of the organic layer with anhydrous magnesium sulfate and concentrating in vacuo gave pure m-chloroperbenzoic acid.

Whenever a reverse-phase chromatographic column was used, the mobile phase consisted of water (pH 7.2 phosphate buffer) - acetonitrile mixtures. After the desired fractions were collected, the procedure employed in the isolation of components involved first the removal of most of the acetonitrile with a rotary evaporator. The resulting mixture was then extracted three times with methylene chloride and the combined organic fractions were washed once with a 5% sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated in a rotary evaporator.

6.2 Synthesis of the C_9-C_{13} Synthon

Synthesis of Enone 53[14]

In dry conditions and an inert atmosphere of argon, 13.39 g (0.3 mole) of a 50% dispersion of sodium hydride in oil were washed twice with 10 ml portions of dry pentane, with stiring. Then, 60 ml of dry benzene were added and at 10°C, a mixture containing 24.2 ml (0.25 mole) of 3-pentanone, 38.4 ml (0.445 mole) of ethyl formate, and a catalytic amount, 0.1 ml, of ethanol were added dropwise to the vigorously stirred suspension of sodium hydride in benzene. After an induction period of about 10 minutes, a green-yellow precipitate formed. The mixture was allowed to stand overnight, after which the solvent was removed under pressure in dry conditions, leaving a viscous residue. The viscous enolate was then dissolved in 60 ml of benzene and 80 ml of dry hexamethylphosphoramide, heating to 60°C being required to dissolve the salt. After cooling to 10°C, 47.1 ml (0.369 mole) of chlorometnyl-benzyl ether were added dropwise. After standing for 24 hours at 10°C, the resulting greyish solution was quenched with 400 ml of a 8% sodium bicarbonate solution. The organic residue was then extracted with 4x150 ml of a benzene-ether (1:1) solution. The collected fractions were washed once with 150 ml of a 8% bicarbonate solution, followed by 100 ml of brine, and dried over anhydrous sodium sulfate. Evaporating the solvent with a rotary evaporator, concentrated a yellowish oil. The Enone 53 was then obtained by fractional distillation at 141°C/0.9 mm Hg, as a

faint yellow oil; 43.87 g (75% yield). PMR: δ 1.05 (t, 3H, J=7.0Hz, C_5-H), 1.80 (broad s, 3H, C_2-CH_3), 2.52 (q, 2H, J=7.0Hz, C_4-H), 4.70 (s, 2H, $PhCH_2O$-), 5.17 (s, 2H, -OCH_2O-), 7.33 (s, 5H, Ph), 7.60 ppm (broad s, 1H, C_1-H); ir 1658 cm^{-1} (C=O and C=C); mass spectrum m/e 234 (9) (M^+), 235 (M^{+1}). The methoxyethyl acetal (MEM) derivative was similarly prepared; chloromethyl-β-methoxyethoxy ether (MEM-Cl) being used instead of chloromethyl benzyl ether.

Synthesis of Alcohol 52[14]

At 0°C, 10.56 g (0.279 mole) 20 hydride equivalents) of sodium borohydride were added in small portions to a vigorously stirred solution of 13.06 g (0.0558 mole) of Enone 53 in 300 ml of annydrous methanol. After standing at 0°C for 3 hours, the excess hydride was quenched with 200 ml of 10% sodium bicarbonate, which also resulted in the hydrolysis of borate esters of Alcohol 52. To dissolve the sodium borate salts, 150 ml of water were added. After the effervescence subsided (1 hour), most of the methanol was evaporated with a rotary evaporator. Alcohol 52 was then extracted from the aqueous medium with 5x100 ml portions of a benzene-ethyl acetate (8:2) solution. The combined organic fractions were washed once with 100 ml of water and 100 ml of brine, and then dried over anhydrous sodium sulfate. Concentration in a rotary evaporator gave 12.1 g (92% yield) of a ^1H NMR pure faint yellow oil. PMR: δ 0.90 (t, 3H, J=7.0Hz, C_5-H), 1.70 (broad s, 3H, C_2-CH_3), 1.7 (q, 2H, J=7.0Hz, C_4-H), 2.30 (broad s, 1H, OH), 3.90 (t, 3H, J=7.0Hz, C_3-H), 4.65 (s, 2H, $PhCH_2O$-), 4.95 (s, 2H, -OCH_2O-), 6.35 (broad s, 1H, C_1-H), 7.40 ppm (s, 5H, Ph); ir 3425 (OH), 1680 cm^{-1} (C=C); mass spectrum m/e 218 (M -18

(H_2O)). The methoxyethyl acetal (MEM) derivative was similarly prepared and obtained in greater than 90% yield as well.

Synthesis of Ester 51[14] (A)

In dry conditions and under an inert atmosphere of argon, 12.1 g (0.0513 mole) of Alcohol 52 were diluted in 120 ml of dry pyridine. Then, 21 ml (0.154 mole) of dry triethylamine were added dropwise followed by lowering the temperature to 0°C, and adding dropwise 45.8 ml (0.359 mole) of propionic anhydride (freshly distilled). The reaction mixture was then allowed to stand at room temperature for 2 days, after which it was added dropwise to a two phase system consisting of 300 ml of methylene chloride, 200 ml of a 10% sodium carbonate solution, and 150 ml of a 8% sodium hydroxide solution with vigorous stiring. One hour after the addition, the organic layer was separated and the aqueous phase was extracted once with 50 ml of methylene chloride. The combined organic fractions were then washed thrice with 100 ml of a 5% sodium bicarbonate solution, 100 ml of brine, and dried over anhydrous sodium sulfate. Concentration in a rotary evaporator gave 14.9 g (quantitative yield) of a dark-yellow, pleasantly smelling oil. This oil, contaminated with polymeric residue, was pure Ester 51 by ^1H NMR. PMR: δ 0.77 (t, 3H, J=7.0Hz, C_5-H), 1.08 (t, 3H, J=7.0Hz, $\underline{CH_3}CH_2COO$-), 1.55 (q, 2H, J=7.0Hz, C_4-H), 1.60 (broad s, 3H, C_2-CH_3), 2.25 (q, 2H, J=7.0Hz, $CH_3\underline{CH_2}$-COO-), 4.60 (s, 2H, $PhCH_2O$-), 4.90 (s, 2H, -OCH_2O-), 5.100(t, 1H, J=7.0Hz, C_3-H), 6.40 (broad s, 1H, C_1-H), 7.33 ppm (s, 5H, Ph); ir 1735 cm^{-1} (C=O), mass spectrum m/e 292 (M^+ calcd. for $C_{17}H_{24}O_4$: 292.16745, found 292.17170). The methoxyethyl acetal (MEM) derivative was similarly

similarly prepared and also obtained in quantitative yields.

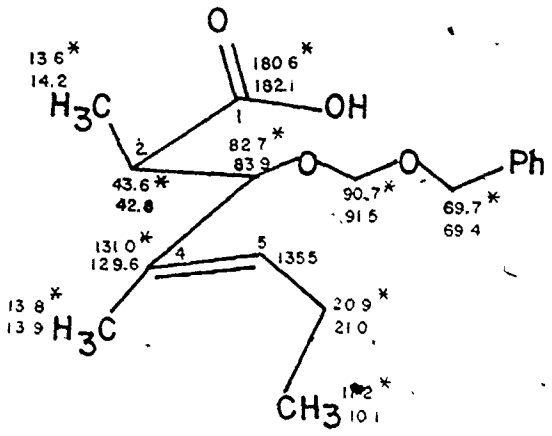
Synthesis of Ester 51 (8)

The in situ preparation of Ester 51 prior to the Claisen rearrengement, involved firstly, cooling to -78°C a 0.4 M tetrahydrofuran solution of the Alcohol 52. Subsequent dropwise addition of one equivalent of a 1.6 M n-butyl lithium hexane solution, generated the corresponding alkoxide in about fifteen minutes. One equivalent of propionyl chloride was then added dropwise and after one hour, the mixture was allowed to reach room temperature over one hour. The resulting mixture was then transfered by syringe to be used in the Claisen rearrangement.

Synthesis of erythro-γ,δ-Heptenoic acid 46

In dry conditions and an inert atmosphere of argon at -78°C, the Ester 51, 2.42 g (8.26 mmole) in 2 ml of tetrahydrofuran was added dropwise with stiring to a solution of 1.4 ml (7.5 mmole) of lithium N-isopropylcyclohexylamide in 10 ml of tetrahydrofuran and 2.7 ml of hexamethylphosphoramide (23%). After standing for 30 minutes, 1.1 ml (9.1 mmole) of a 90% chlorotrimethylsilane were added on one portion. The mixture was then allowed to reach ambient temperatures in one hour and then warmed further to 50°C for three hours. Cooling the reaction vessel to 20°C, the reaction mixture was quenched with 25 ml of a 5% sodium hydroxide solution, followed by the addition of 25 ml of a 0.2 M sodium bicarbonate solution. The basic aqueous mixture was then extracted three times with 25 ml portions of methylene chloride, and then acidified

to pH ~3.0 with 20% hydrochloric acid in a two phase system containing 100 ml of methylene chloride. Separation of the organic phase, followed by 2x 50 ml extractions with methylene chloride of the aqueous phase, the combined organic extractions were washed 3x20 ml of water, followed by 20 ml of brine and dried with anhydrous sodium sulfate. Concentration in a rotary evaporator yielded fairly pure erythro-Heptenoic acid 46 in varying yields (30-40%). The threo isomer was similarly prepared, but hexamethylphosphoramide was excluded. PMR of erythro isomer: δ 0.92 (t, 3H, J=7.5Hz, C_7-H), 1.25 (d, 3H, J=7.2Hz, C_2-CH_3), 1.5 (s, 3H, C_4-CH_3), 2.00 (p, 2H, J=6.75Hz, C_6-H), 2.60 (d of q, 1H, C_2-H), 4.20 (d, 1H, J=8.7Hz, C_3-H), 4.45, 4.76 (AB quartet, 2H, J=12.0Hz, -OCH_2O-), 4.66 (s, 2H, -OCH_2Ph), 5.46 (broad t, 1H, J=6.9Hz, C_5-H), 7.32 (s, 5H, Ph), 10.00 ppm (broad s, 1H, COOH); ir 3700-2400 (broad, COOH), 1745 cm^{-1} (C=O); mass spectrum m/e 292 (M^+ calcd. for $C_{17}H_{24}O_4$: 292.16745, found 292.16770). PMR of threo isomer: δ 0.95 (t, 3H, J=7.5Hz, C_7-H), 1.05 (d, 3H, J=7.5Hz, C_2-CH_3), 1.55 (s, 3H, C_4-CH_3), 2.10 (p, 2H, J=6.75Hz, C_6-H), 2.70 (d of q, 1H, C_2-H, 4.22 (d, 1H, J=10.5Hz, C_3-H), 4.40, 4.65 (AB quartet, 2H, J=12.0Hz, -OCH_2O-), 4.66 ppm (s, 2H, -OCH_2Ph), 5.53 (broad t, 1H, J=6.9Hz, C_5-H), 7.32 (s, 5H, Ph), 10.00 ppm (broad s, 1H, COOH). The natural abundance ^{13}C NMR spectrum of erythro-Heptenoic acid 46 is summarized in the following structure (the non-starred resonances refer to the threo isomer). The methoxyethyl acetal (MEM) derivative (of threo isomer) was similarly prepared.



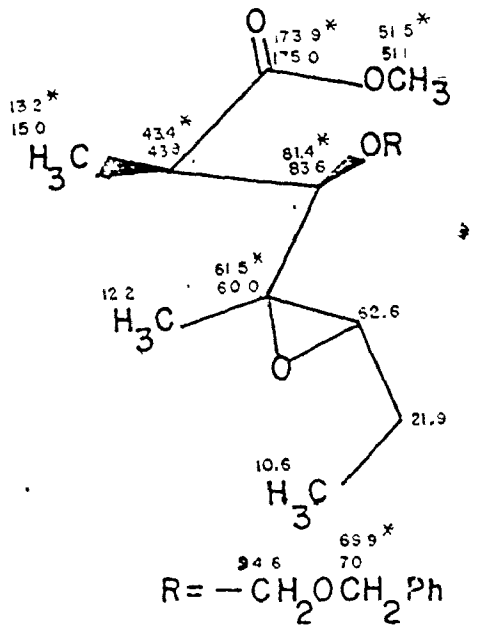
Synthesis of the Methyl Esters of Acids 46

The methyl esters were prepared from the corresponding carboxylic acids by the dropwise addition of a diazomethane solution of diethyl ether to the carboxylic acid solution of diethyl ether; ir 1745 cm^{-1} (C=O); mass spectrum m/e 306.

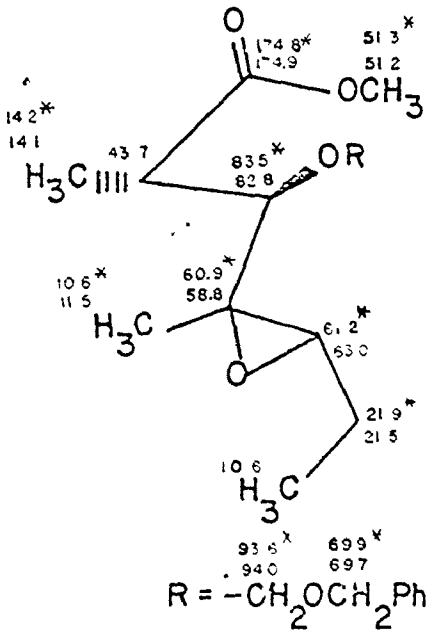
Typical Epoxidation of Acids 46 and their Methyl Esters

The alkene 46, 50 mg, was allowed to stand with 1.1 equivalent of m-chloroperbenzoic acid at the desired temperature for the required period of time in 4 ml of the desired solvent. E.g. in methylene chloride at 0°C, the epoxidation required about one week for completion. The mixture was then diluted with 25 ml of methylene chloride and washed with 2x5 ml of a saturated sodium sulfite solution, which was basic enough to remove most of the m-chlorobenzoic acid, but not the epoxy

acids, 48. Further washing with 10 ml of water, brine, and drying of the organic phase with anhydrous sodium sulfate, gave after evaporation of the solvent with a rotary evaporator, diastereomeric epoxides 48(a+b) in about 75% yields. PMR of erythro Methyl Ester: δ 1.02 (t, 3H, J= 7.5Hz, C_7-H), 1.20 (d, 3H, J=7.5Hz, C_2-CH_3), 1.27*, 1.24 (s, 3H, C_4-CH_3), 1.48 (m, 2H, C_6-H), 2.77 (p, 1H, J=6.75Hz, C_2-H), 2.87 (t, 1H, J=6.3Hz, C_5-H), 3.60*, 3.70 (d, 1H, J=6.0Hz, C_3-H), 3.63 (s, 3H, -OCH_3), 4.50-4.80 (AB quartets, 4H, -OCH_2O-, -OCH_2Ph), 7.32 ppm (s, 5H, Ph); ir 1740 cm^{-1} (C=O); mass spectrum m/e 322 (M^+ calcd. for $C_{18}H_{26}O_5$: 322.17801, found 322.17829). The natural abundance ^{13}C NMR spectra of isomeric Epoxides 48(a+b) are summarized in the following structures.



ERYTHRO 48 (a+b)

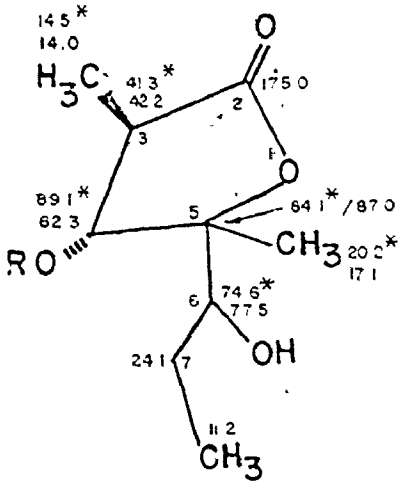


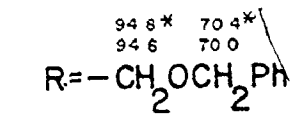
THREO 48 (a+b)

Synthesis of Lactones 49

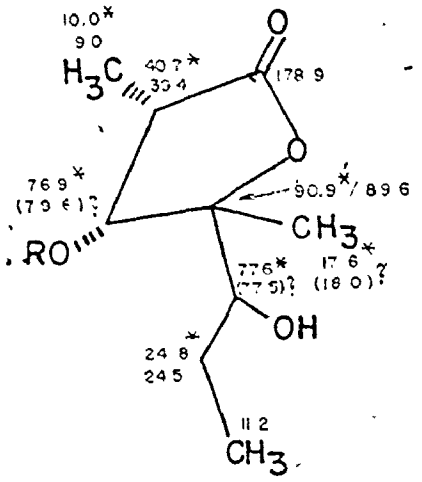
The Epoxides 48 (a+b) were generally converted to the corresponding

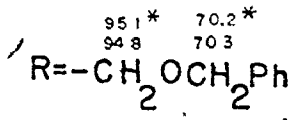
lactones with dichloroacetic acid in methylene choride or chloroform at room temperature for the required period of time. Thus, two to three drops of dichloroacetic acid were added to a one ml chloroform solution containing 50 mg of Epoxides 48. The mixture was then diluted with 20 ml of petroleum ether and the organic phase was washed twice with 5 ml of a 5% sodium carbonate solution, and once with 10 ml of water, brine, and finally dried over anhydrous sodium sulfate. Concentration in a rotary evaporator gave (α+β) Lactones 49 in nearly quantitative yields. The (α+β) lactone mixture was then separated by column chromatography (SiO_2/chloroform). PMR of erythro (α+β)-Lactones 49: δ 1.03 (t, 3H, J=6.75Hz, C_8-H), 1.35 (d, 3H, J=7.5Hz, C_3-CH_3), 1.40, 1.30 (s, 3H, C_5-CH_3), 1.60 (ABX system, 2H, C_7-H), 2.85 (p, 1H, C_3-H), 3.77*, 3.55 (ABX system, 1H, J=3.0,9.75Hz for both α and β isomers, C_6-H), 3.97*, 4.18 (d, 1H, J=8.4Hz,* J=8.1Hz, C_4-H), 4.67 (s, 2H, -OCH_2Ph), 4.85*, 4.83(s, 2H, -OCH_2O-), 7.32 ppm (s, 5H, Ph); ir 3490 (OH), 1780 cm^{-1} (C=O); mass spectrum m/e 308 (high resolution mass spectrum could not be obtained). PMR of threo (α+β)-Lactones 49: δ 1.00 (t, 3H, J=6.75Hz, C_8-H), 1.35 (d, 3H, J=7.5Hz, C_3-CH_3), 1.32,* 1.28 (s, 3H, C_5-CH_3), 1.50 (ABX system, 2H, C_7-H), 2.90 (p, 1H, C_3-H), 3.45*, 3.87 (ABX system, 1H, J=2.25, 9.75 for both α and β isomers, C_6-H), 4.50,* 4.05 (d, 1H, J=7.2Hz*, J=5.7Hz, C_4-H), 4.65,* 4.68 (s, 2H, -OCH_2Ph), 4.76,* 4.57, 4.67 (s,* AB quartet, J=12.0Hz, -OCH_2O-), 7.32 ppm (s, 5H, Ph). The natural abundance ^{13}C NMR spectra of the erythro and threo α and β Lactones 49 are summarized in the following structures.





ERYTHRO 49 ($\alpha+\beta$)



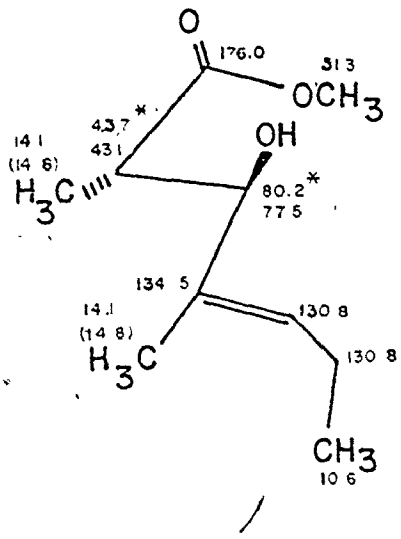


THREO 49 ($\alpha+\beta$)

Synthesis of threo-Heptenoic acid 74

The threo-Heptenoic acid mixture (threo:erythro 46, 88:12), 100 mg (0.34 mmole) was dissolved in 20 ml of ammonia and 4 ml of tert-butanol. With stiring, 45 mg (2.04 mmole) of sodium were then added sequentially. Each addition being made after the initial blue coloration of the solution disappeared. After the complete addition of sodium, 106 mg (2.04 mmole) of ammonium chloride were added in one portion, and the ammonia was allowed to evaporate. The resulting residue was dissolved in 25 ml of ethyl acetate, and this solution was then washed twice with 6 ml of a pH 3.0 sodium dihydrogen phosphate buffer, once with 8 ml of brine, dried over anhydrous sodium sulfate. Concentration in a rotary evaporator yielded a residue which , when purified in a short column (SiO_2/ 5% isopropanol-benzene) or by evaporative distillation (55-65°C 0.5 mm Hg) gave 56 mg (96% yield) of Acid 74. PMR: δ 0.95 (t, 3H, J=7.0Hz, C_7-H), 1.03 (d, 3H, J=7.5Hz, C_2-CH_3), 1.60 (s, 3H, C_4-CH_3), 2.05 (p, 2H, J=7.0Hz, C_6-H), 2.68 (p, 1H, C_2-H), 4.13 (d, 1H, J=9.0Hz, C_3-H), 5.45 (

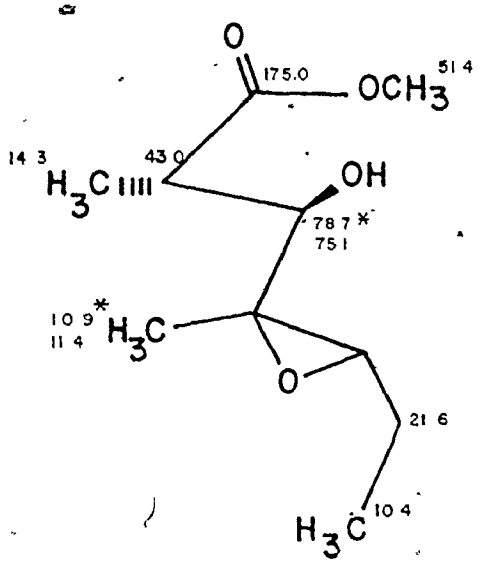
broad t, 1H, J=7.0Hz, C_5-H); ir. 3700-2400 (OH, COOH), 1717 cm^{-1} (broad, C=O, C=C); mass spectrum m/e 172. The threo Methyl Ester of 74 was then made in the usual way by using diazomethane. This ester was also obtained by performing the (Birch) reduction on the Methyl Ester of 46. The natural abundance ^{13}C NMR spectrum of threo Methyl Ester 74 is summarized in the following structure (non-starred resonances pertain to the erythro isomer).



Epoxidation of 74 and its Methyl Ester

The epoxidation of Heptenoic acid 74 followed the general procedure. In this case, the corresponding lactones, 72, were obtained instead of the intermediate Epoxides 75. Epoxidation of the Methyl Ester of 74 also resulted in some lactone formation. Hence, 55 mg (0.32 mmole) of Acid 74 in 6 ml of dry methylene chloride reacted with 72 mg (0.416 mmole) of m-chloroperbenzoic acid at -20 C for 3 days, yielding a 8:2 ratio of Lactone diols 72. Because the epoxides and lactones were soluble in water, the work-up procedure involved passing the reaction

product through a short column (SiO_2/benzene). In this manner, in the conversion of the Methyl Ester of 74, 45 mg (75% yield) of the Epoxy Methyl Ester of 75 was obtained. Its spectral data are shown below. PMR: δ 1.0 - 1.1 (6H, C_7-H and C_2-CH_3), 1.17 (s, 3H, C_4-CH_3), 1.55 (m, 2H, C_6-H), 2.70 (p, 1H, C_2-H), 3.32 (d, 1H, J=8.5Hz, C_3-H), 2.9 (broad s, 1H, OH), 3.65 (s, 3H, -OCH_3). The natural abundance ^{13}C NMR spectra of threo 75(a+b) are summarized in the following structure.

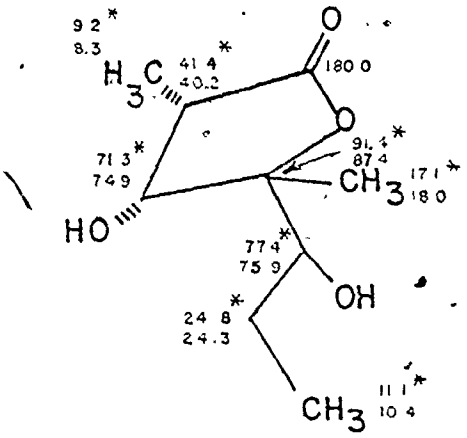


THREO 75 (a+b)

Synthesis of Lactone Diols 72

The Lactone Diols (α+β) 72, were prepared by the epoxidation-lactonization of threo-Heptenoic Acid 74, as mentioned above, and by the catalytic hydrogenolysis of threo-Lactone 49. Hence, 50 mg (0.16 mmole) of 49 in 15 ml of anhydrous methanol containing 20 mg of 5% Pd/C, were subjected to a 40 psi pressure of hydrogen gas for one hour at room temperature. After filtering off palladium-carbon residue, washing the

residue with 15 ml each of anhydrous methanol and methylene chloride, the filtrate was concentrated in a rotary evaporator. The yellow oily residue was then dissolved in 10 ml of chloroform and the lactone diols were extracted with 3x10 ml of water. The aqueous extractions were washed once with 5 ml of chloroform, and concentrated to give 27 mg (98% yield) of a light colored oil, consisting of a 8:2 ratio of Lactone Diols 72. PMR: δ 1.00 (t, 3H, J=7.0Hz, C_8-H), 1.1-1.4 (8H, C_7-H), C_3-CH_3, and C_5-CH_3), 3.05 (p, 1H, C_3-H), 3.55 (ABX system of major diol, J=3.0, ~~9.8Hz,~~ C_6-H), 3.9 (broad m, OH and C_6-H ABX system of minor diol, J=4.5, 8.6Hz), 4.25,* 4.45 (d, 1H, J=7.5Hz*, J=5.5Hz, C_4-H); ir 3430 (OH), 1755 cm^{-1} (C=O); mass spectrum m/e 188 (M^+ calcd. for $C_9H_{16}O_4$: 188.10485, found 188.10903). The natural abundance ^{13}C NMR spectra of threo (α+β)-Lactones 72 are summarized in the following structure.

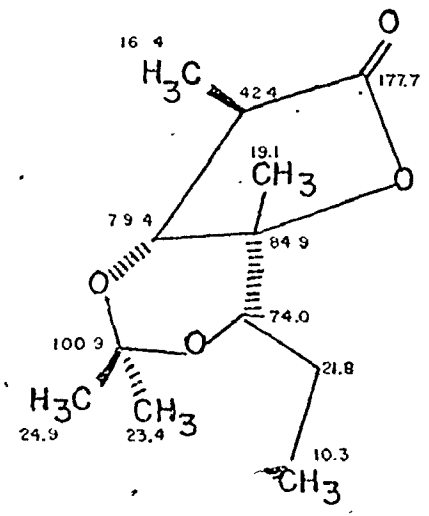


Synthesis of Acetonide 73

A solution of the Lactone Diols 72, 25 mg (0.133 mmole) in 5 ml of dry methylene chloride, containing 30 mg (0.27 mmole) of 2,2-dimethoxypropane and 4 mg (0.0143 mmole) of pyridinium p-toluene-sulfonate, was allowed to stand at room temperature for three days. The solution was then diluted with 25 ml of petroleum ether and washed with 5 ml each of a 5% sodium bicarbonate solution, water, and brine. After evaporation of the solvent under vacuum, 26 mg (~90% yield) of Acetonide 73 was obtained as a single compound. PMR: δ 0.98 (t, 3H, J=7.5Hz, C_8-H), 1.1-2.0 (14H, C_3-CH_3, C_5-CH_3, C_7-H, and $C(CH_3)_2$), 2.68 (p, 1H, J=7.5Hz, C_3-H), 3.56 (ABX system, 1H, J=4.2, 9.0Hz, C_6-H), 3.78 (d, 1H, J=1.2Hz, C_4-H); ir 1785 cm^{-1} (C=O); mass spectrum m/e $228_{(w)}$, $213_{(m)}$(M^+-15 calcd. for $C_{11}H_{17}O_4$: 213.11267, found 213.11152), $170_{(s)}$(M^+-58). threo-Acetonide 73 had the following PMR spectrum: δ 1.00 (t, 3H, J=7.5Hz, C_8-H), 1.2-1.8 (14H, C_3-CH_3, C_5-CH_3, C_7-H, and $C(CH_3)_2$), 2.85 (p, 1H, J=6.9 Hz, C_3-H), 3.50 (ABX system, 1H, J=4.0, 8.2Hz, C_6-H), 3.96 ppm (d, 1H, J=6.0Hz, C_4-H). The natural abundance ^{13}C NMR spectrum of erythro-Acetonide (from major Lactone Diol 72) is shown in figure 18.

Isolation of Aldehyde 69

The isolation of the rearranged product of Alcohol 52 and Ester 51 was performed by distillation. The Aldehyde 69 was obtained at 110°C/760 mm Hg as a light yellow oil. At this temperature, significant decomposition of 69 took place. PMR: δ 1.13 (t, 3H, J=7.5Hz, C_5-H), 1.77 (s, 3H, C_2-CH_3), 2.40 (p, 2H, J=7.5Hz, C_4-H), 6.53 (t of q, 1H, $^3J_{3,4}$=7.0Hz, $^4J_{3,2}$=1.5Hz, C_3-H), 9.50 ppm (s, 1H, C_1-H); ir 1690, 1640 cm^{-1}.



1. 177.7 ppm
2. 100.9
3. 84.9
4. 79.4
5. 74.0
6. 42.4
7. 30.1 (imp.)
8. 24.9
9. 23.4
10. 21.8
11. 19.1
12. 16.4
13. 10.3

ERYTHRO-β-ACETONIDE 73

IR: 1785 cm^{-1}

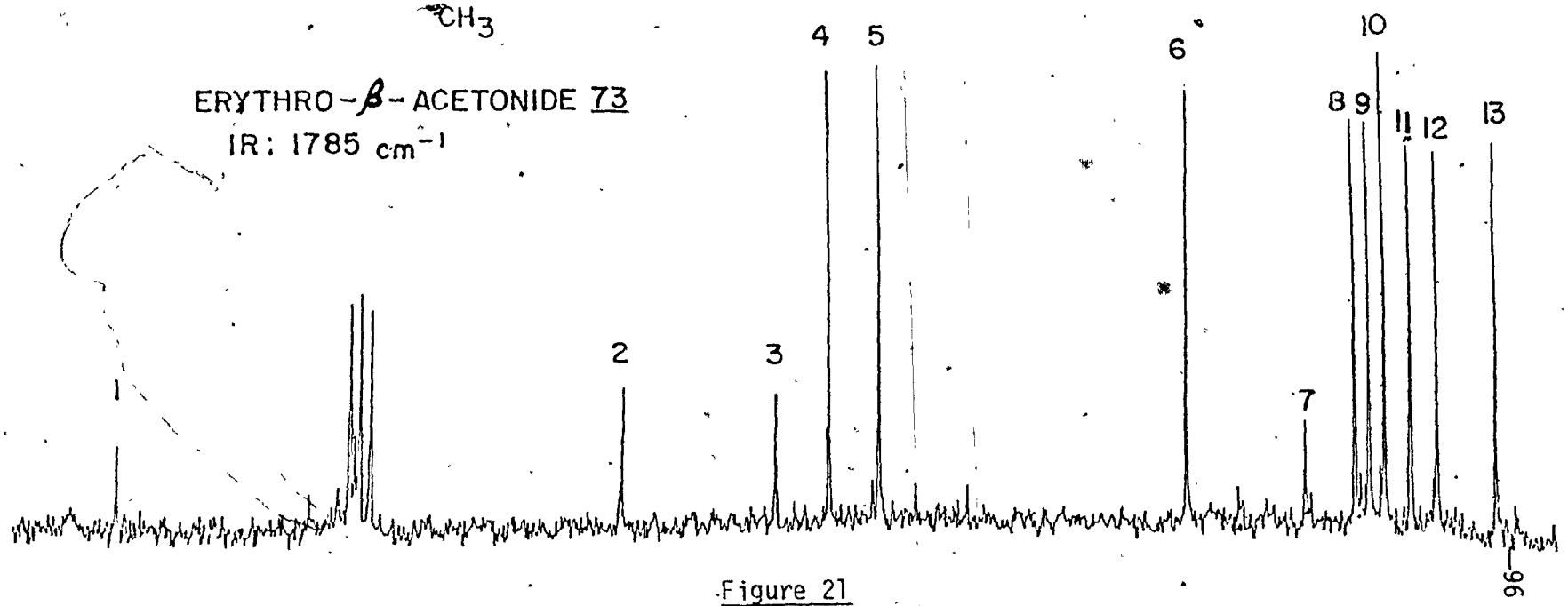


Figure 21

6.3 Synthesis Towards the C_1-C_8 Synthon

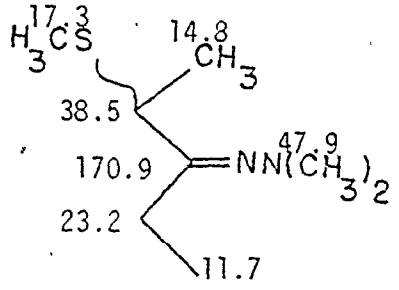
Synthesis of Hydrazone 64

The synthesis of the N,N-dimethylhydrazone of 3-pentanone involved simply heating to 70°C for 8 hours, a mixture containing 15 ml (0.142 mole) of 3-pentanone and 12 ml (0.156 mole) of N,N-dimethylhydrazine. Cooling the mixture to ambient temperature, two layers separated. Separation of the aqueous layer (from the condensation reaction) was followed by drying of the organic layer with anhydrous magnesium sulfate. Filtration followed by fractional distillation, gave a fraction at 133°C/760 mm Hg, consisting of 16.3 g (90% yield) of a colorless oil, whose ^{1}H NMR was consistent with that reported in the literature.[79] PMR: δ 1.07 (t, 6H, J=7.5Hz, C_1-H), 2.22 (q, 2H, J=7.5Hz, C_2-H), 2.41 (s, 6H, $-NN(CH_3)_2$), 2.43 ppm (q, 2H, J=7.5Hz, C_2-H).

Synthesis of α-Methylthiohydrazone 63

Hydrazone 64 was metallated by adding dropwise 3.57 g (27.86 mmole) of this hydrazone in 5 ml of dry tetrahydrofuran to a lithium diisopropylamide (30.65 mmole) solution in 20 ml of dry tetrahydrofuran at 0°C, with stirring under an argon atmosphere. The reaction mixture was left standing overnight at 0°C, after which it was cooled to -78°C and then alkylated by the dropwise addition of 2.8 ml (30.65 mmole) of methyl disulfide. Formation of a white precipitate occurred, and after an hour, the mixture was allowed to warm-up to room temperature over one

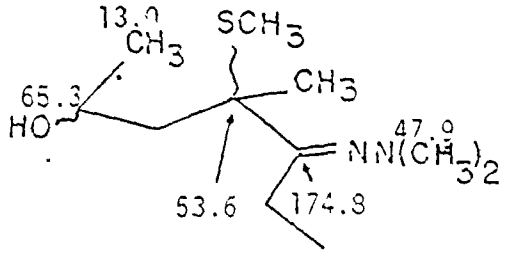
hour. The reaction mixture was then diluted with 100 ml of hexanes and washed twice with 25 ml of a 5% potassium hydroxide solution, and once with 25 ml of water, brine, and finally dried over anhydrous magnesium sulfate. Concentration in a rotary evaporator (water bath at 20°C) gave 4.84 g (quantitative yields) of pure (^{1}H NMR) 63 (stench). Purification by fractional distillation gave 63 at 76°C/10 mm Hg. The Z-isomer formed initially presumably due to chelation of nitrogen of the dimethylamino group with the lithium atom in the metallated intermediate, isomerized upon standing (and distillation) to the more stable E-isomer. PMR (Z-isomer): δ 1.07 (t, 3H, J=7.5Hz, C_5-H), 1.25 (d, 3H, J=7.2Hz, C_1-H), 1.95 (s, 3H, $-SCH_3$), 2.05-2.5 (8H, C_4-H, $-N(CH_3)_2$), 4.70 ppm (q, 1H, J=7.2Hz, C_2-H); ir $1615_{(m)}$ cm^{-1} (C=N). The natural abundance ^{13}C NMR spectrum of the α-methylthiohydrazone 63 is summarized in the following structure.



Synthesis of Hydrazone 62

In dry conditions and an inert atmosphere of argon, the Hydrazone 63 was metallated by the slow, dropwise, addition of 0.776 g (4.58 mmole)

of 63 in 1 ml of dry tetrahydrofuran to a lithium diisopropylamide (5.04 mmole) solution in 10 ml of tetrahydrofuran with stirring at 0°C. After 3 hours at this temperature the mixture turned dull-yellow, and 0.4 ml (5.5 mmole) of dry propylene oxide were added dropwise, over 5 minutes. The mixture was left standing at 0°C for 3 days, after which it was quenched with 30 ml of a saturated sodium bicarbonate solution. Extraction with 4x20 ml of methylene chloride, drying of the combined extracts with anhydrous magnesium sulfate, and concentration in a rotary evaporator gave an oil. This oil consisted (^{1}H NMR) of ~10-15% starting material (Hydrazone 63), Hydrazone 62, and other products, apparently polymeric due to the intensity of peaks at δ 3.5-4.0 ppm. Hydrazone 62 was purified by evaporative distillation at 63-65°C/ 0.05 mm Hg, or better by a chromatographic column (reverse-phase (RP-8)/7:3 water (pH 7.2 phosphate buffer): acetonitrile). After purification, ~0.6 g (~70% yield considering unreacted Thiohydrazone 63) of 62 were obtained as a faint yellow oil (stench). ^{1}H NMR revealed that this product existed in a ~7:3 ratio with its mixed hemi-ketal form. PMR: δ 1.10 (t, 3H, J=7.0Hz, C_1-H), 1.17 (d, 3H, J=6.0Hz, C_7-H), 1.20 (s, 3H, C_4-CH_3), 1.85-1.95 (two singlets, 3H, -SCH_3), 1.80-2.2 (m, 2H, C_5-H), 2.40 (s, 6H, -$N(CH_3)_2$), 2.30-2.80 (m, 2H, C_2-H), 3.7-4.3 (m, 1H, C_6-H), 5.03 ppm (broad s, 1H, -OH); ir 3400 (OH), $1612_{(m)}$ cm^{-1} (C=N); mass spectrum m/e $215_{(w)}$(M^{+1}-18 (H_2O)), $173_{(m)}$(M^+-59 ($CH_3CH(OH)CH_2$-)). The natural abundance ^{13}C NMR spectrum of 62 (hydrazone form) is summarized in the following structure.

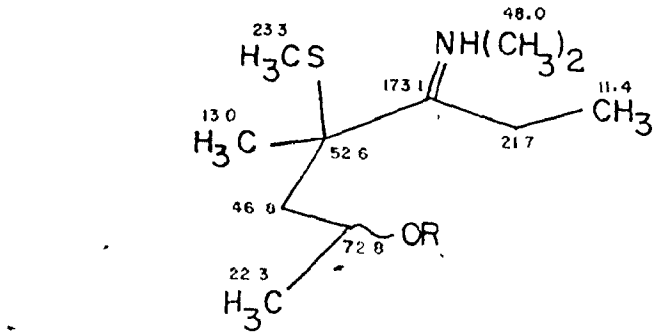


δ(C-2, C_4-CH_3, -SCH_3, C-5) 21.7, 21.7, 24.2, 25.3 ppm

Synthesis of Hydrazone 61

Under an inert atmosphere of argon, 1.19 g (9.48 mmole) of a a 32% potassium hydride suspension in oil were washed twice with 10 ml of dry pentane. Then, 20 ml of dry tetrahydrofuran were added and the reaction mixture cooled to 0°C. Hydrazone 62, 2g (8.62 mmole) in 5 ml of dry tetrahydrofuran was then added dropwise, and after 30 minutes, 1.0 ml (9.48 mmole) of chloromethyl-β-methoxyethoxy ether (MEM-Cl) were added dropwise. The reaction mixture was then left for 48 hours at 0°C, after which it was added dropwise to a two phase medium consisting of 50 ml of a 2% sodium hydroxide solution and 150 ml of methylene chloride. The aqueous layer was removed, and the organic layer was then washed with 20 ml each of a 2% sodium hydroxide solution, water, and brine. Drying over anhydrous magnesium sulfate and concentration in a rotary evaporator gave 2.8 g of Hydrazone 61 contaminated (^{1}H NMR) with polymeric material from MEM-Cl. Purification with a chromatographic column (reverse-phase (RP-8)/4:6 water (pH 7.2 phosphate buffer):acetonitrile) gave 2.5 g (~90% yield) of 61, still containing a small amount of impurity that resulted from MEM-Cl. PMR: δ 1.05-1.30 (d superimposed on a t, 6H, C_1-H, C_7-H), 1.47 (s, 3H, C_4-CH_3), 1.60-2.20 (m, 2H, C_5-H), 1.82 (s, 3H, -SCH_3), 2.20-2.60 (m, 2H, C_2-H), 1.39 (s, 6H, -$N(CH_3)_2$), 3,37 (s, 3H, -OCH_3), 3.40-4.0 (5H, -OCH_2CH_2O-, C_6-H), 4.72 ppm (s, 2H, -OCH_2O-); ir $1615_{(m)}$ cm^{-1} (C=N); mass spectrum m/e $315_{(w)}$(M^+-15 (CH_3)), $273_{(s)}$(M^+-47 (SCH_3)). The natural abundance ^{13}C NMR spectrum of 61 is illustrated in figure 22.

Synthesis of Hydrazone 60



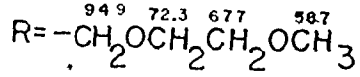
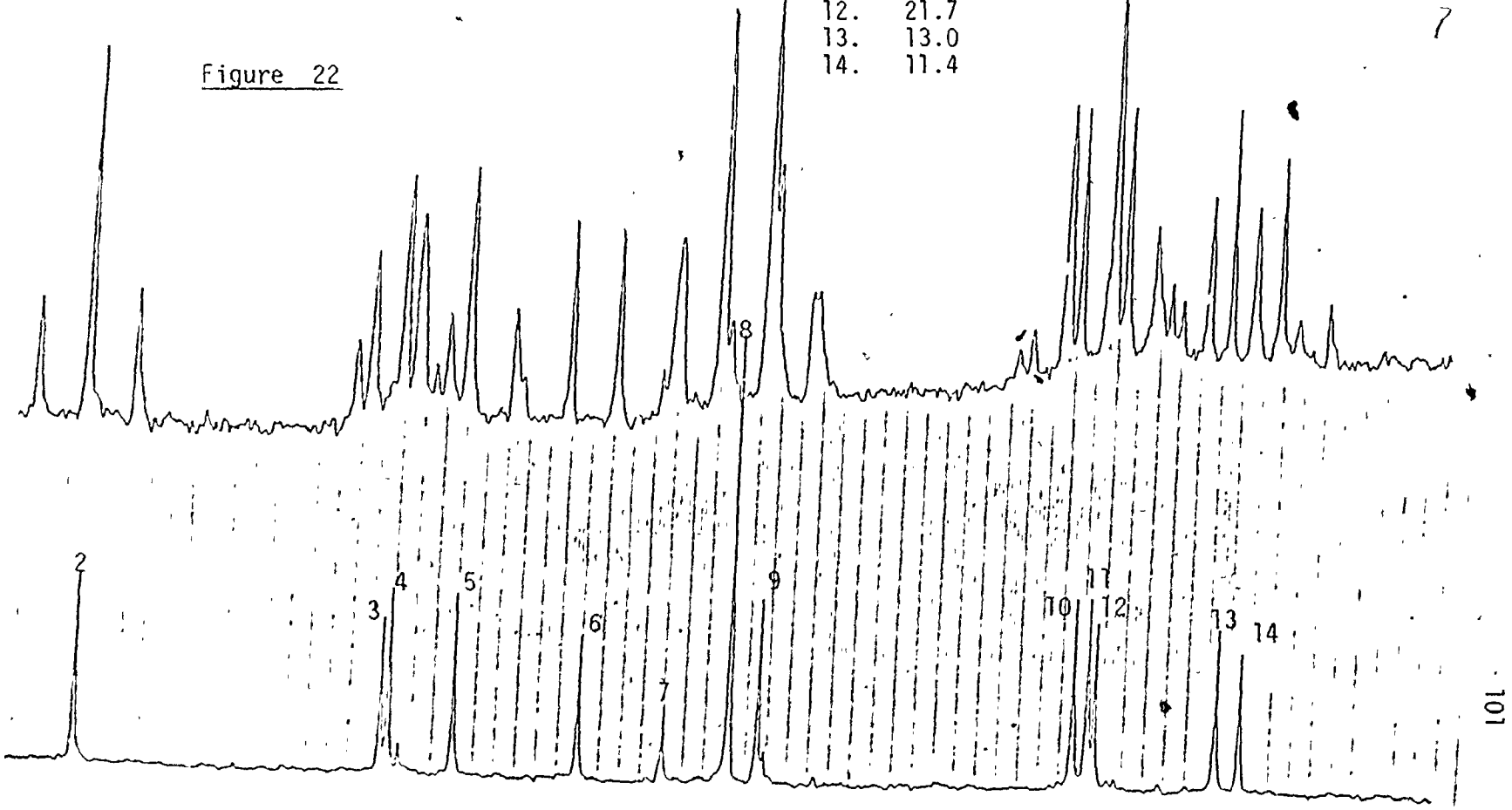


Figure 22

1.	173.1	ppm
2.	94.9	
3.	72.8	
4.	72.3	
5.	67.7	
6.	58.7	
7.	52.6	
8.	48.0	
9.	46.8	
10.	23.3	
11.	22.3	
12.	21.7	
13.	13.0	
14.	11.4	



To 2.1 g (6.56 mmole) of Hydrazone 61 diluted in 60 ml of anhydrous methanol at 0°C, was added portionwise 1.78 g (6.56 mmole) of mercuric chloride with vigorous stiring. After one hour, 120 ml of a 5% sodium carbonate solution were added, and the fine suspension of mercuric salts was filtered. The filtrate was then extracted thrice with 60 ml of methylene chloride, and the combined fractions were dried with anhydrous magnesium sulfate. Concentration in a rotary evaporator gave 1.8 g (~90% yield) of Hydrazone 60. ^{1}H NMR showed total conversion of the sulfide to the methoxy-derivative 60. PMR: δ 1.15 (broad t, 3H, J=7.2Hz, C_1-H), 1.23 (d, 3H, J=6.4Hz, C_6-H), 1.37 (s, 3H, C_4-CH_3), 1.7-2.2 (m, 2H, C_5-H), 2.3-2.6 (m, 2H, C_2-H), 2.42 (s, 6H, -$N(CH_3)_2$), 3.11 (s, 3H, C_4-OCH_3), 3.40 (s, 3H, -OCH_3), 3.5-4.0 (m, 5H, -OCH_2CH_2O-, C_6-H), 4.73 ppm (s, 2H, -OCH_2O-).

Synthesis of Ketone 58

To 1.74 g (5.72 mmole) of crude Hydrazone 60 diluted in 75 ml of tetrahydrofuran and 40 ml of a 0.05 N disodium hydrogenphosphate solution, were added portionwise, with vigorous stiring at 0°C, 0.975 g (5.72 mmole) of dihydrated cupric chloride. The reaction medium immediately turned yellow-green after the cupric chloride addition, and was then left for 48 hours at 10°C. Then, 150 ml of a 5% sodium carbonate solution were added and the greenish suspension was removed by suction filtration. The filtrate was then extracted once with 100 ml and thrice with 40 ml of methylene chloride. The combined organic extractions were washed once with 25 ml of a 5% sodium carbonate solution, 25 ml of brine, and dried over anhydrous magnesium sulfate. Concentration

in a rotary evaporator gave 1.3 g (~86% yield) of a yellow oil. ^{1}H NMR showed a ~7:3 ratio of diastereomers. Purification and separation of the diastereomeric ketones 58 was accomplished with a chromatographic column (reverse-phase (RP-8)/8:2 water (pH 7.2 phosphate buffer):acetonitrile). The major ketone was eluted first. PMR is shown in figure 23 (major isomer) and 24 (minor isomer); ir ν_{major} 1720 cm^{-1}, ν_{minor} 1715 cm^{-1} (C=O); mass spectrum m/e $205_{(m)}$ (M^+-57 ($-\overset{O}{\overset{\|}{C}}CH_2CH_3$, cleavage of C_3,C_4 bond), $187_{(m)}$, $157_{(s)}$ (M^+-105 (OMEM)). The natural abundance ^{13}C NMR spectra of Ketones 58 are illustrated in figures 25 (major isomer) and 26 (minor isomer).

Synthesis of Enone 57

In a dry reaction vessel and under an argon atmosphere, 0.17 g (1.36 mmole of a 32% potassium hydride suspension in oil were washed twice with 5 ml of dry pentane. The reaction vessel was cooled to 0°C, and 10 ml of dry tetrahydrofuran were added. Then, 0.17g (0.65 mmole) of the major Ketone 58 and 0.5 ml (6.5 mmole) of pure ethyl formate in 2 ml of dry tetrahydrofuran were added dropwise over 10 minutes. Some bubbling was evident immediately after the addition of 58. The reaction vessel was then allowed to warm-up to room temperature overnight when a yellowish residue formed. The residue was then taken to dryness by vacuum provided by a water-aspirator, ensuring dry conditions (i.e. cold trap of liquid nitrogen prevented moisture from entering the reaction vessel). The oily residue (enolate salt and potassium ethoxide) was then dissolved in 4 ml of dry tetrahydrofuran and 6 ml of dry hexamethylphosphoramide. Cooling to 0°C, 0.17 ml (1.36 mmole) of chloro-

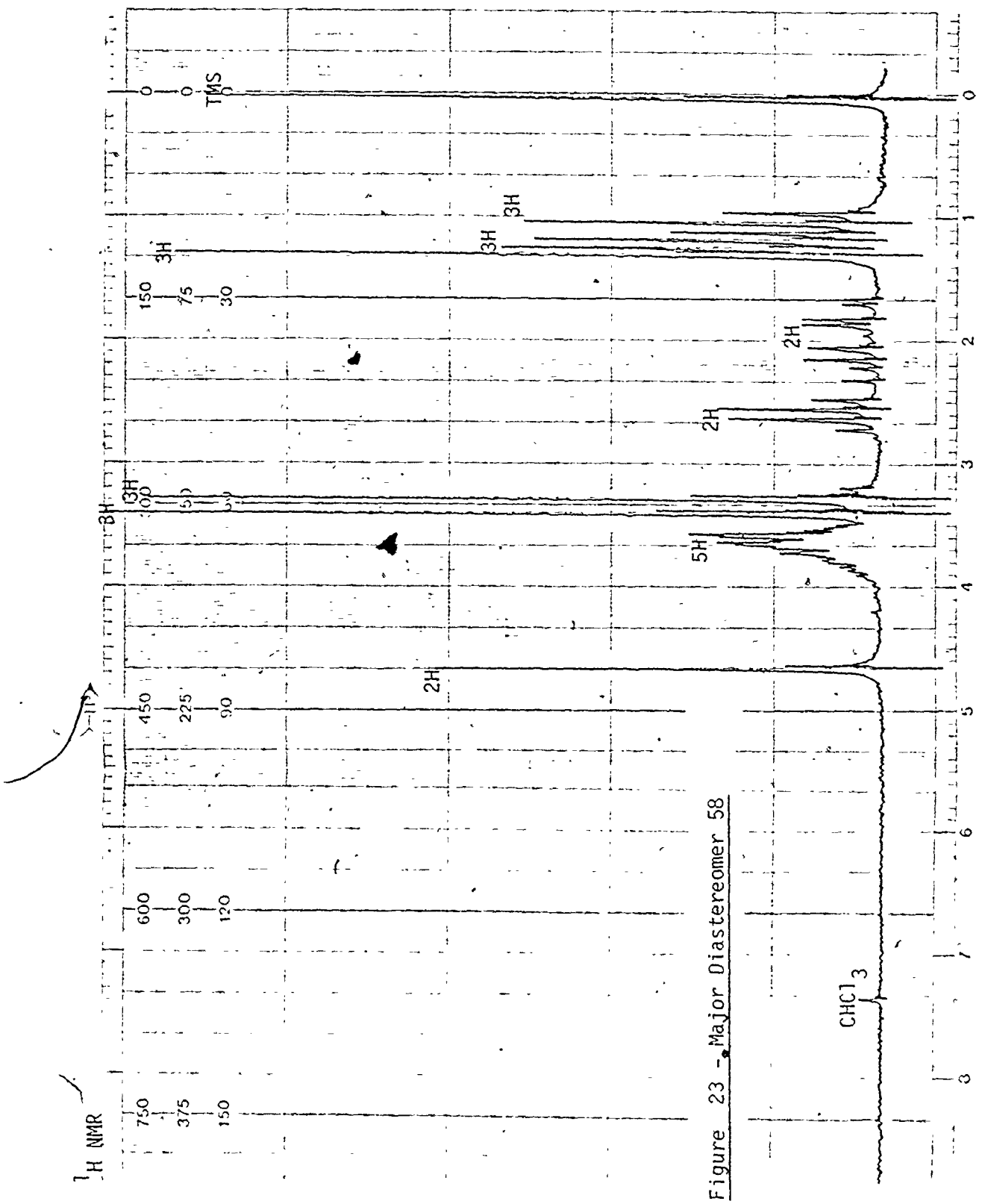


Figure 23 - Major Diastereomer 58

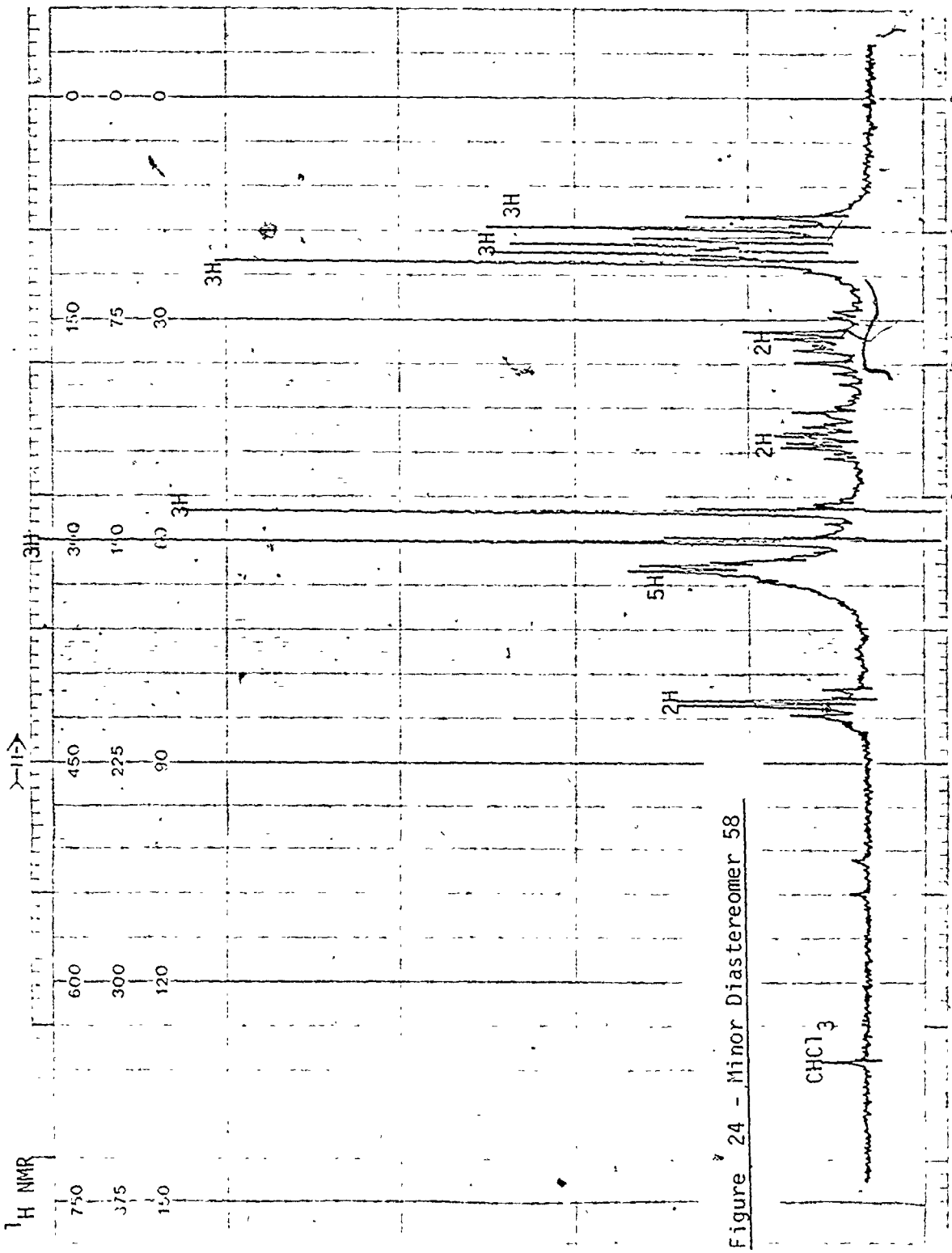


Figure 24 - Minor Diastereomer 58

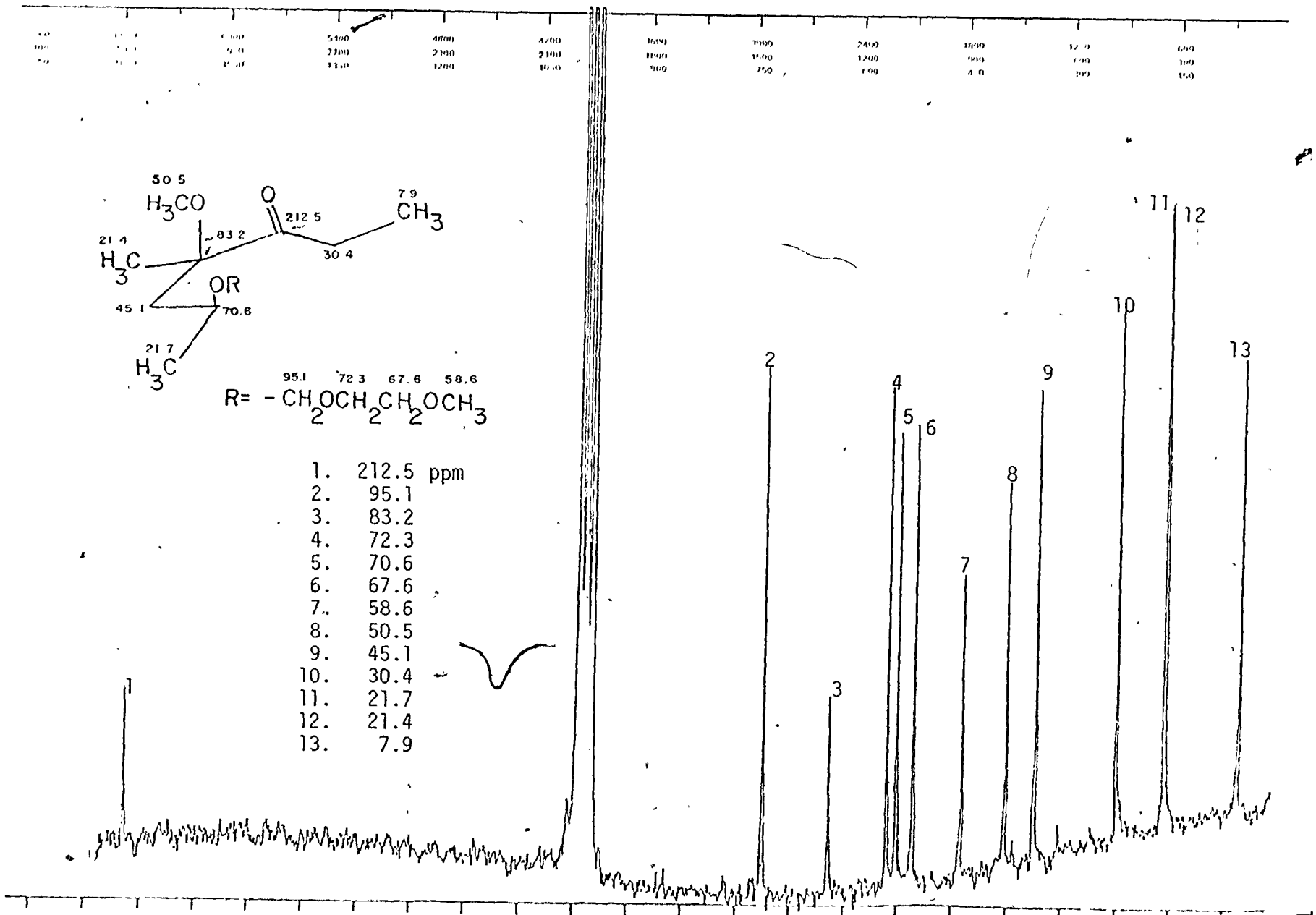

50.5
H_3CO
O
212.5
79
CH_3
83.2
21.4
H_3C
30.4
OR
45.1
70.6
21.7
H_3C
95.1 72.3 67.6 58.6
R= $-CH_2OCH_2CH_2OCH_3$
1. 212.5 ppm
2. 95.1
3. 83.2
4. 72.3
5. 70.6
6. 67.6
7. 58.6
8. 50.5
9. 45.1
10. 30.4
11. 21.7
12. 21.4
13. 7.9
1
2
3
4
5
6
7
8
9
10
11
12
13

Figure 25

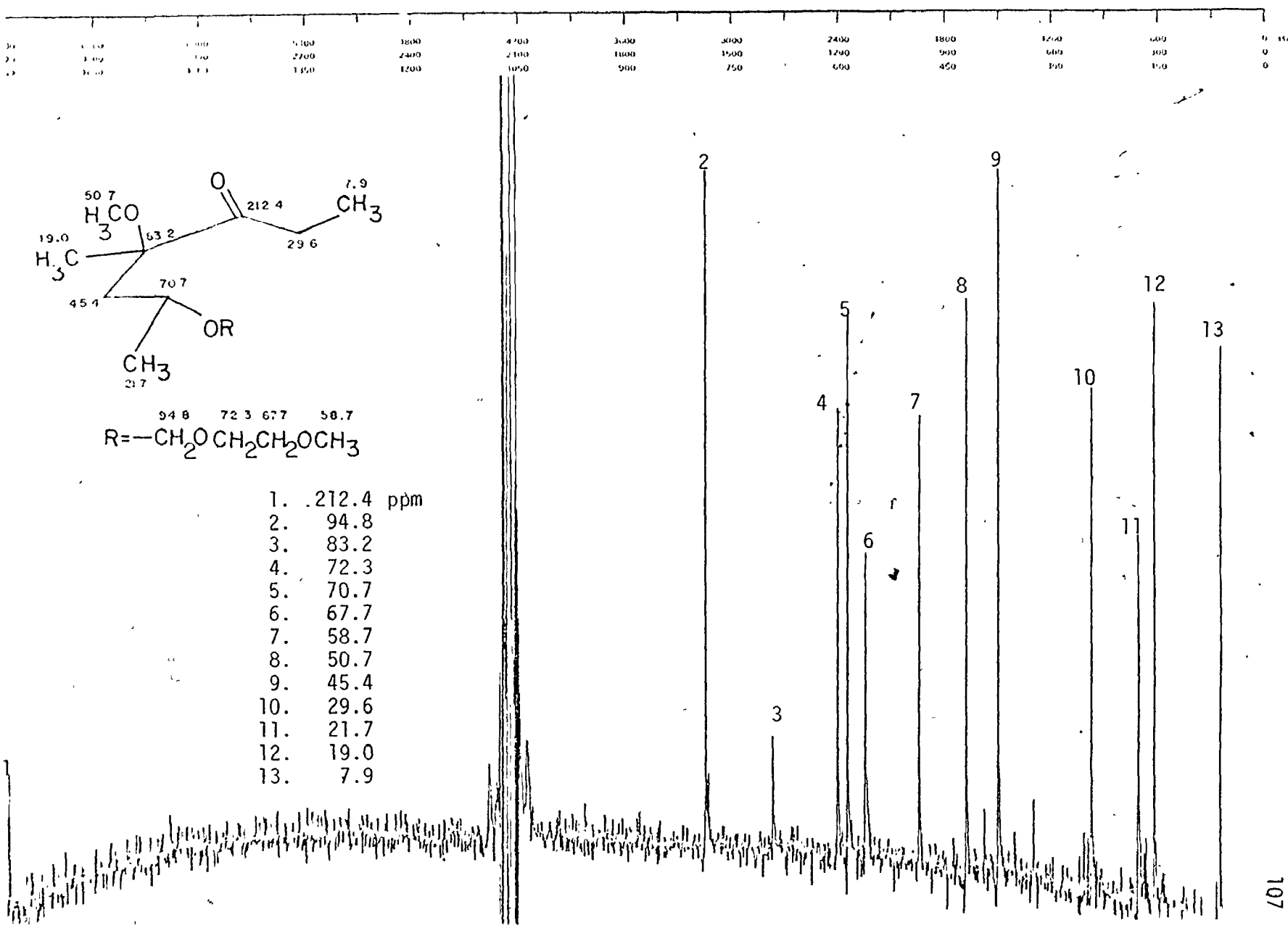

50.7
H3CO
212.4
7.9
CH3
19.0
H3C
83.2
29.6
70.7
45.4
OR
CH3
21.7
94.8 72.3 67.7 58.7
R=—CH2OCH2CH2OCH3
1. 212.4 ppm
2. 94.8
3. 83.2
4. 72.3
5. 70.7
6. 67.7
7. 58.7
8. 50.7
9. 45.4
10. 29.6
11. 21.7
12. 19.0
13. 7.9

Figure 26

methyl benzyl ether were then added dropwise, and the reaction mixture was left for 6 hours after which the O-alkylation was complete. The mixture was then quenched with 50 ml of a 2% sodium hydroxide solution, and 100 ml of petroleum ether were then added. The resulting mixture was transfered to a separatory funnel, and the aqueous layer discarded. The organic layer was washed twice with 20 ml of a 2% sodium hydroxide solution (removing completely the hexamethylphosphoramide solvent), and dried over anhydrous magnesium sulfate. Concentration in a rotary evaporator and then a high vacuum pump gave 230 mg of a yellow oil consisting (^{1}H NMR) of impure Enone 57 and approximately 60% of starting material, 58. Hence, the acylation required ~2-3 days for completion. Purification with a chromatographic column (reverse-phase (RP-8)/ 1:1 water (pH 7.2 phosphate buffer):acetonitrile) gave starting material and slightly impure Enone 57. A 110 mg (~41% yield; the estimated yield of pure Enone 57 with total conversion of Ketone 58 is ~70-75% after chromatography) of Enone 57 was obtained. PMR: δ 1.13 (d, 3H, J=6.0Hz, C_7-H), 1.37 (s, 3H, C_4-CH_3), 1.77 (broad s, 3H, C_2-CH_3), 1.57-2.43 (ABX system, 2H, C_5-H), 3.13 (s, 3H, C_4-OCH_3), 3.35 (s, 3H, -OCH_3), 3.43-4.0 (m, 5H, -OCH_2O-, C_6-H), 4.63 (s, 2H, -OCH_2Ph), 4.67 (s, 2H, C_6-OCH_2O-), 5.10 (s, 2H, C_1-OCH_2O-), 7.32 (s, 5H, Ph), 8.43 ppm (broad s, 1H, C_1-H); ir 1627 cm^{-1} (C=O and C=C); mass spectrum m/e $305_{(w)}$(M^+-105 (OMEM)), $275_{(w)}$(M^+_{305}-30 (CH_2O)), $205_{(m)}$(M^+-205 (cleavage of C_3,C_4 bond)), $175_{(m)}$(M^+_{205}-30 (CH_2O)). The natural abundance ^{13}C NMR spectrum of Enone 57 is illustrated in figure 27.

Synthesis of Alcohol 56

1. 201.8 ppm
2. 158.4
3. 137.6
4. 116.6
5. 95.7
6. 94.6
7. 85.6
8. 72.3
9. 70.6
10. 70.4
11. 67.3
12. 58.7
13. 51.3
14. 47.3
15. 22.4
16. 9.7

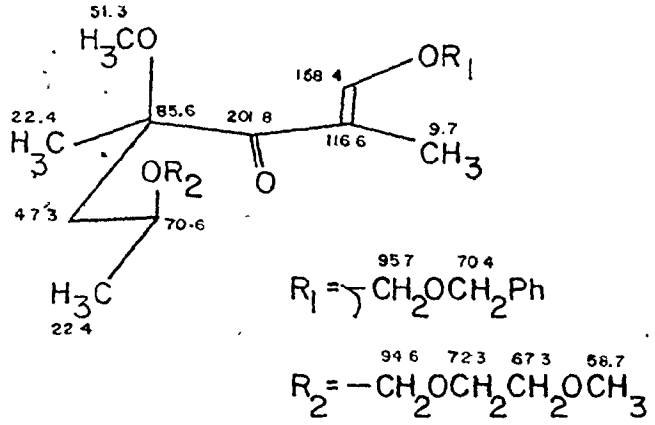
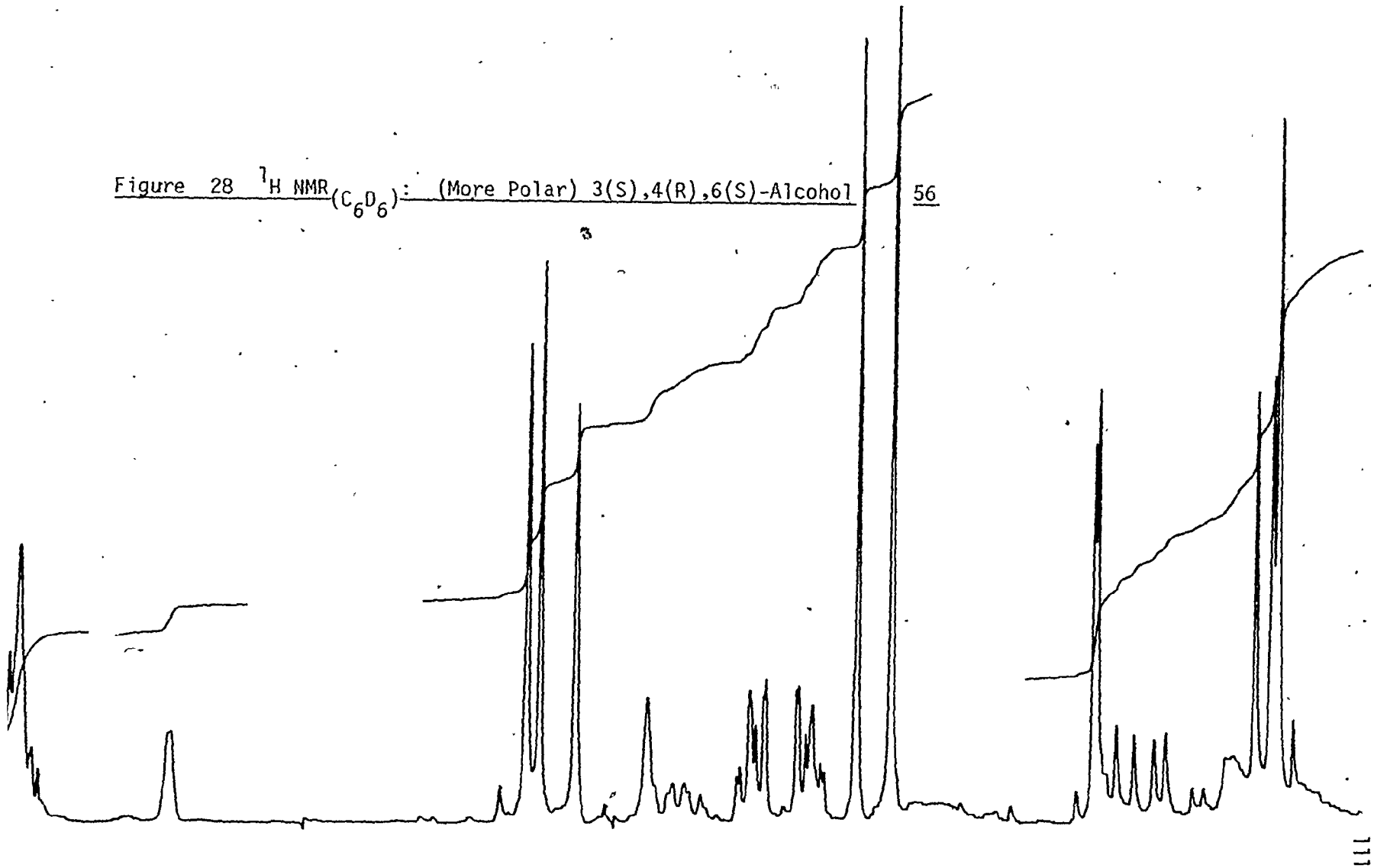


Figure 27

At 0°C and under an inert atmosphere of argon, 24 mg (0.63 mmole) of sodium borohydride were added in one portion to a stiring solution of 26 mg (0.063 mmole) of Enone 57 in 5 ml of fairly dry diglyme.[73] The reaction mixture was then allowed to reach room temperature and left standing for 24 hours. The mixture was then quenched with 20 ml of a saturated sodium carbonate solution. After the effervescence subsided (1 hour), the mixture was extracted with 5x10 ml of methylene chloride. The combined organic fractions were washed once with 10 ml of a 5% sodium bicarbonate solution, dried over anhydrous magnesium sulfate and concentrated in a rotary evaporator. The diglyme solvent was removed using a high vacuum pump, leaving a light-colored oil, the ^{1}H NMR of which showed a ~1:1 ratio of diastereomeric Alcohols 56 (monitoring of C_4-OCH_3 reasonances). Purification with a chromatographic column (reverse-phase (RP-8)/1:1 water (pH 7.2 phosphate buffer):acetonitrile) resulted in separation of the two alcohols yielding 9 mg of each diastereomeric Alcohol 56 (~70% yield of pure isolated alcohols, with an estimated 20-25% loss in the chromatographic column). Use of lithium borohydride in diglyme also resulted in similar yields and a ~1:1 ratio of Alcohols 56. PMR (C_6D_6) of the more polar Alcohol 56, eluted first from the RP-8 column, is illustrated in figure 28. PMR ($CDCl_3$) of the more polar alcohol was: δ 1.10 (s, 3H, C_4-CH_3), 1.21 (d, 3H, J=6.1Hz, C_7-H), 1.4-2.2 (6H, OH, C_5-H, C_2-CH_3), 3.23 (s, 3H, C_4-OCH_3), 3.37 (s, 3H, -OCH_3), 3.61 (m, 4H, -OCH_2CH_2O-), 3.97 (2H, C_3-H, C_6-H), 4.63 (s, 2H, -OCH_2Ph), 4.74 (broad s, 2H, C_6-OCH_2O-), 4.94 (s, 2H, C_1-OCH_2O-), 6.33 (broad s, 1H, C_1-H), 7.30 ppm (s, 5H, Ph). PMR ($CDCl_3$) of the less polar alcohol was: δ 1.09 (s, 3H, C_4-CH_3), 1.22 (d, 3H, J=6.1Hz,

Figure 28 ^{1}H NMR(C_6D_6): (More Polar) 3(S),4(R),6(S)-Alcohol 56



C_7-H), 1.4-2.2 (6H, C_2-CH_3, C_5-H, OH), 3.16 (s, 3H, C_4-OCH_3), 3.37 (s, 3H, -OCH_3), 3.63 (m, 4H, -OCH_2CH_2O-), 3.99 (2H, C_3-H, C_6-H), 4.63 (s, 2H, -OCH_2Ph), 4.78 (broad s, 2H, C_6-OCH_2O-), 4.94 (s, 2H, C_1-OCH_2O-), 6.35 (broad s, 1H, C_1-H), 7.33 ppm (s, 5H, Ph); ir (of both diastereomers) 3480 (OH), 1678 cm^{-1} (C=C); mass spectrum m/e $207_{(m)}$(M^+-205 (C_4-C_6 fragment from C_3,C_4 bond cleavage)), $177_{(s)}$, $129_{(s)}$. The natural abundance ^{13}C NMR spectrum of the more polar Alcohol 56 is illustrated in figure 29. Resonances in brackets pertain to the less polar alcohol.

Synthesis of Ester 55

In dry conditions and an inert atmosphere of argon, ~10 mg (0.024 mmole) of the more polar Alcohol 56 were diluted in 5 ml of dry pyridine and 1.0 ml of triethylamine. The reaction mixture was cooled to 0°C, and 0.3 ml (0.24 mmole) of freshly distilled propionic anhydride were added. The mixture was then left for 3 days at room temperature, after which it was added dropwise to a two phase system consisting of 20 ml of methylene chloride and 20 ml of a 8% sodium hydroxide solution. One hour after, the organic layer was separated and washed repeatedly (three times) with 10 ml of a saturated sodium carbonate solution. Drying the organic layer with anhydrous magnesium sulfate and concentration in vacuo (water aspirator followed by high vacuum) gave ~10 mg of a yellow oil. ^1H NMR showed Ester 55 and about 30% of starting Alcohol 56. Purification was not attempted because Ester 51 decomposed under the conditions of the reverse-phase chromatographic column. PMR: δ 1.0-1.5 (alkyl envelope), 1.5-2.2 (C_5-H, C_2-CH_3), 2.35 (q, -CH_2COO-), 3.25 (s, C_4-OCH_3), 3.38 (s, -OCH_3), 3.37-4.0 (m, -OCH_2CH_2O-, C_6-H), 4.61

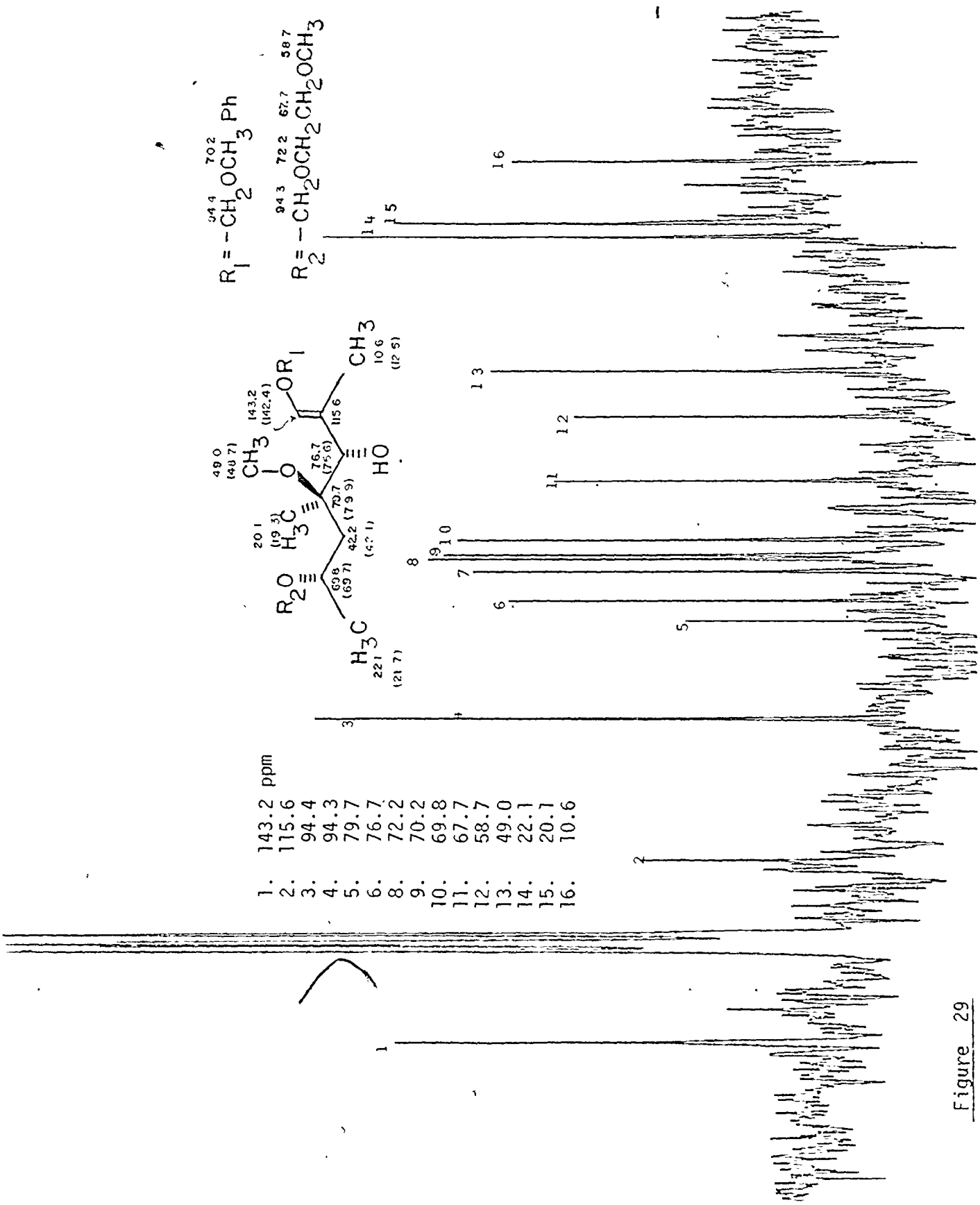

R1 = -CH2OCH3 Ph
R2 = -CH2OCH2CH2OCH3
1. 143.2 ppm
2. 115.6
3. 94.4
4. 94.3
5. 79.7
6. 76.7
8. 72.2
9. 70.2
10. 69.8
11. 67.7
12. 58.7
13. 49.0
14. 22.1
15. 20.1
16. 10.6

Figure 29

(s, $-OCH_2Ph$), 4.75 (s, C_6OCH_2O), 4.94 (s, C_1-OCH_2O-), 5.22 (s, C_3-H), 6.37 (s, C_1-H), 7.32 ppm (s,PPh); ir 1735 (C=O), 1677 cm^{-1} (C=C); mass spectrum m/e $403_{(w)}$(M^+-55 ($-\overset{O}{\overset{\|}{C}}CH_2CH_3$)), $291_{(w)}$ and $177_{(w)}$(possibly fragments from C_2,C_3 bond cleavage), $206_{(m)}$, $127_{(m)}$.

Reduction of Ketone 58 with L-selectride

In 4 ml of dry tetrahydrofuran, 20 mg (0.049 mmole) of Enone 57 were cooled to -78°C under an argon atmosphere. With stiring, 0.5 ml (0.49 mmole) of a 1.0 M L-selectride (lithium tri-sec-butylboron hydride) in tetrahydrofuran were then added dropwise. The reaction required 20 hours for completion, after which it was quenched with 10 ml of a saturated sodium bicarbonate solution at 0°C. Then, 30 ml of petroleum ether were added and the resulting mixture was transfered to a separatory funnel and the aqueous layer discarded. The organic layer was then washed twice with 10 ml of a 5% sodium bicarbonate solution, dried over anhydrous magnesium sulfate and concentrated in a rotary evaporator, followed by a high vacuum pump, yielding a light-colored oil. Purification with a chromatographic column (reverse-phase (RP-8)/ 1:1 water (pH7.2 phosphate buffer):acetonitrile) gave ~10 mg (74% yield) of Ketone 79 having the following spectral properties. PMR: δ 1.01 (d, 3H, J=6.84Hz, $C_{1A}-H$), 1.07 (d, 3H, J=6.84Hz, $C_{1B}-H$), 1.24 (d, 3H, J=7.3Hz, C_6-H), 1.29 (s, 3H, C_4-CH_3), 1.70 and 2.05 (ABX system, 2H, J_{AX}=3.9 and J_{Bx}=9.1Hz, J_{AB}=14.8Hz, C_5-H), 3.27 (s, 3H, C_4-OCH_3), 3.38 (s, 3H, $-OCH_3$), 3.73 (m, 5H, $-OCH_2CH_2O-$, C_6-H), 4.66 ppm (s, 2H, $-OCH_2O-$); ir 1715 cm^{-1} (C=O); mass spectrum m/e $205_{(m)}$(M^+-71 ($-\overset{O}{\overset{\|}{C}}CH(CH_3)_2$, cleavage of C_3,C_4 bond), $171_{(s)}$(M^+-105, (OMEM)).

Europium-(fod)$_3$ NMR study

A 0.0925 M solution of Eu(fod)$_3$ (tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium)) was prepared in deuteriochloroform. Then small additions (totalling 50 to 60 µl) of this solution were made to a 0.034 M solution of each Alcohol 56 in deuteriochloroform (i.e. 7 mg of Alcohol 56 in 0.5 ml of deuteriochloroform). The spectra were recorded after each addition and the shifts for all protons were recorded. Some of these were illustrated in figure 20 (i.e. C_4-CH_3 and C_4-OCH_3 as well as C_1-OCH_2O- and C_2-CH_3, included for comparison).

(7) REFERENCES

1. S.Rakhit, Chemistry in Canada, 8 (1977).
2. S.Masamune, G.S.Bates, and J.W.Corcoran, Angew. Chem. Int. Ed. Engl., 16, 585 (1977).
3. K.C.Nicolaou, Tetrahedron, 33,683 (1977).
4. R.S.Egan, T.J.Perun, J.R.Martin, and L.A.Mitscher, Tetrahedron, 29, 2525 (1973).
5. T.G.Back, Tetrahedron, 33, 3041 (1977).
6. E.J.Corey, E.J.Trybulski, L.S.Melvin, Jr., K.C.Nicolaou, J.A. Secrist, R.Lett, P.W.Sheldrake, J.R.Falck, D.J.Brunelle, M.F. Haslanger, S.Kim, and S.Yoo, J. Am. Chem. Soc., 100,4618(1978). (b) E.J.Corey, S.Kim, S.Yoo, K.C.Nicolaou, L.S.Melvin,Jr., D.L. Brunelle, J.R.Falck, E.J.Trybulski, R.Lett, and P.W.Sheldrake, ibid., 100, 4620 (1978). (c) E.J.Corey, P.B.Hopkins, S.Kim, S.Yoo, K.P. Nambiar, and J.R.Falk, ibid., 101, 7131 (1979).
7. S.Hanessian and G.Rancourt, Can. J. Chem., 55, 1111 (1977). (b) S. Hanessian, G.Rancourt, and Y.Guindon, ibid., 56, 1843 (1978). S. Hanessian, Acc. Chem. Res., 12, 159 (1979).
8. P.T.Ho, Can. J. Chem., 58, 858, 861 (1980).
9. T.Takahashi, K.Kasuga, and J.Tsuji, Tetra. Lett., 4917 (1978).
10. P.Kurath, P.H.Jones, L.S.Egan, and T.J.Perun, Experienta, 27, 362 (1971).
11. R.E.Ireland, R.H.Mueller, and A.K.Willard, J. Org. Chem., 98, 2868 (1976).

12. F.E.Ziegler, Acc. Chem. Res., 10, 227 (1977).

13. G.B.Bennett, Synthesis, 589 (1977).

14. V.YTaguchi Thesis, McMaster University, Hamilton, Ontario, Canada.

15. P.A.Bartlett, Tetrahedron, 3 (1980).

16. A.I.Meyers and P.J.Reider, J. Am. Chem. Soc., 101, 2501 (1979).

17. E.J.Corey and S.Knapp, Tetra. Lett., 4687 (1976).

18. H.O.House "Modern Synthetic Reactions", Benjamin (1972).

19. R.A.Bell and J.K.Saunders "Topics in Stereochemistry", vol. 7, John Wiley (1973).

20. L.M.Jackmann and B.C.Lange, Tetrahedron, 33, 2737 (1977).

21. S.J.Rhoads and R.W.Holder, Tetrahedron, 25, 5443 (1969).

22. R.S.Egan, J.Tadanier, J.R.Martin, A.W.Goldstein, R.S.Stanaszek, E.Hirner, and F.Fischer, J. Org. Chem., 39, 2495 (1974).

23. E.J.Corey, J.L.Gras, and P.Ulrich, Tetra. Lett., 809 (1976).

24. G.Stork and M.Isobe, J. Am. Chem. Soc., 97, 4745 (1975).

25. M.Stiles and A.Lonroy, J. Org. Chem., 32, 1095 (1967).

26. Jackman and Sternhell "NMR Spectroscopy in Org. Chem.", vol. 5, Pergamon (1969).

27. G.Buchi and J.C.Vederas, J. Am. Chem. Soc., 94, 9128 (1972).

28. M.CPirrung and C.H.Heathcock, J. Org. Chem., 45, 1727 (1980).

29. R.E.Ireland and C.S.Wilcox, Tetra. Lett., 33, 2839 (1977).

30. R.T.Arnold and S.T.Kulenovic, J. Org. Chem., 45, 891 (1980).

31. D.R.Burfield and R.H.Smithers, J. Org. Chem., 43, 3966 (1978).

32. C.H.Depuy and O.L.Chapman, "Molecular Reactions and Photochemistry", Prentice-Hall (1972).

33. K.G.Davenport, H.Eichenauer, D.Enders, M.Newcomb, and D.E.

Bergbreiter, J. Am. Chem. Soc., 101, 5654 (1979).

34. Z.A.Fataftah, I.E.Kopka, and M.W.Rathke, J. Am. Chem. Soc., 102, 3959 (1980).

35. H.K.Hall, Jr., M.K.Brandt, and R.M.Meson, J. Am. Chem. Soc., 80, 6420 (1958).

36. F.W.Wehrli and T. Wirthlin "Interpretation of Carbon-13 NMR Spectra", Heyden, (1976).

37. P.A.Demarco, E.Farkas, D.Doddrel, B.L.Mylari, and E.Wenkert, J. Am. Chem. Soc., 90, 5480 (1968).

38. M.Miyaskita, A.Yoshikoshi, and P.A.Grieco, J. Org. Chem., 42, 3772 (1977).

39. C.Gallina, M.Paci, and P.Viglino, Org. Mag. Res., 4, 31 (1972).

40. W.A.Ayer and J.B.Stothers, Org. Mag. Res., 11, 73 (1978).

41. J.B.Stothers "Carbon-13 NMR Spectroscopy", Academ c Press (1972).

42. E.L.Eliel, W.F.Bailey, L.D.Kopp, R.L.Willer, D.M.Grant, R.Bertrand, and D.W.Cochran, J. Am. Chem. Soc., 97, 322 (1975).

43. P.S.Pregosin, E.W.Randall, and T.B.H.McMurry, J. Chem. Soc., Perkin 1, 299 (1972).

44. L.F.Johnson and W.C.Jaukowski, "Carbon-13 NMR Spectra", John Wiley, (1972).

45. V.G.Dryuk, Tetrahedron, 32, 2855 (1976).

46. C.A.Kingsbury and C.Wang, J. Org. Chem., 40, 3811 (1975).

47. C.A.Kingsbury and D.Thoennes, Tetra. Lett., 3037 (1976), R.O.Day, V.O.Day, and C.A.Kingsbury, Tetra. Lett., 3041 (1976).

48. E.J.Corey and B.B.Snider, J. Am. Chem. Soc., 94, 2549 (1972).

49. S.A.Cerefice and E.K.Fields, J. Org. Chem., 41, 355 (1972).

50. G.Berti "Topics in Stereochemistry", vol. 7, p. 93 (1973).

51. T.Mah, H.M.Sirat, and E.J.Thomas, J. Chem. Soc., Perkin1, 2255 (1979).

52. Z.Paryzek, J. Chem. Soc., Perkin 1, 329 (1978).

53. (a) J.L.Pierre, P.Chautemps, and P.Arnaud, Bull. Soc. Chim. Fr., 1317 (1969), (b) P.Chautemps and J.L.Pierre, Tetrahedron, 32, 549 (1976).

54. A.D.Chong and K.B.Sharpless, J. Org. Chem., 42, 1587 (1977) and references therein.

55. D.Enders and H.Eichenauer, Ang. Chem. Int. Ed. Engl., 15, 549 (1976).

56. A.Brown, R.Glen, P.M.Rust, J.M.Rust, and R.F.Newton, J. Chem. Soc., Chem. Comm., 24, 1178 (1979).

57. J.R.Dyer "Applications of Absorption Spectroscopy of Organic Compounds", Prentice - Hall, p. 41 (1965).

58. C.A.Brown, J. Org. Chem., 39, 3913 (1974).

59. H.Handel and J.L.Pierre, Tetrahedron, 31, 997 (1975).

60. E.J.Corey, K.B.Becker, and R.K.Varma, J. Am. Chem. Soc., 94, 8616 (1972).

61. S.Krishnamnrthy, Aldrichimica Acta, 7, 55 (1974).

62. J.K.M.Sanders and D.H.Williams, Nature, 240, 385 (1972).

63. S.Weinstein and R.B.Henderson, J. Am. Chem. Soc., 65, 2196 (1943), A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill (1962).

64. R.S.Glass, D.R.Deardorff, and K.Henegar, Tetra. Lett., 2467 (1980).

65. C.F.Lane, Aldrichimica Acta, 2, 31 (1976).

66. K.Noack and R.N.Jones, Can. J. Chem., 39, 2225 (1961).

67. R.A.Bell private communication

68. R.T.Conley "Infrared Spectroscopy" Allyn and Bacon, Inc., p. 138-142 (1966).

69. J.W.Cornforth, (Mrs.) R.H.Cornforth, and K.K.Mathew, J. Chem. Soc., 112 (1959).

70. T.Fukuyama, B.Vranesic, D.P.Negri, and Y.Kishi, Tetra. Lett., 31, 2741 (1978).

71. E.J.Corey and D.Enders, Tetra. Lett., 3 (1976).

72. D.R.Burfield, K.H.Lee, and R.H.Smithers, J. Org. Chem., 42, 3060 (1977)

73. L.F.Fieser and M.Fieser, "Reagents for Organic Synthesis" John-Wiley, vol. 1 (1967).

74. H.C.Brown, E.J.Mead, and B.C.S.Rao, J. Am. Chem. Soc., 77, 6209 (1955).

75. H.I.Schlessinger, H.C.Brown, and E.K.Hyde, J. Am. Chem. Soc., 75, 209 (1953).

76. W.G.Kofron and L.M.Baclawski, J. Org. Chem., 41, 1879 (1976).

77. S.Watson and J.F.Eastham, J. Organometal Chem., 9, 165 (1967).

78. N.N.Schwarts and J.H.Blumbergs, J. Org. Chem., 29, 1976 (1964).

79. G.J.Karabatsos and R.A.Taller, Tetrahedron, 3923 (1968).