AN ABSTRACT OF THE THESIS OF

Palaykotai Rajagopalan Raghavan for the degree of Doctor of Philosophy in Chemistry presented on July 18, 1978

Title: APPROACHES TO THE SYNTHESIS OF METHYMYCIN

Abstract approved: Redacted for Privacy

Dr. James D. White

Several approaches to the synthesis of methymycin were investigated. Segment A (39), containing functionality corresponding to C-9, 10, and 11 of methynolide was made in six steps from propionaldehyde in an overall yield of 37%. Oxidation of 34 with silver nitrate gave 35 which, upon hydroxylation with hydrogen peroxide, gave the erythro isomer of dihydroxy acid 36. This acid was resolved with brucine and its absolute configuration determined by Horeau's method. The (+) acid was found to have R,R configuration. This substance was converted to its acetonide (+)-37, which was reduced with lithium aluminium hydride to give (+)-38. Oxidation of (+)-38 with Collins' reagent gave (+)-39.

An approach to the B segment (31), corresponding to C_1-C_8 of methymycin, from dicyclopentadiene was investigated. Dicyclopentadiene, on reaction with selenium dioxide followed by oxidation by Jones' reagent, gave 53. Treatment of 53 with methyl magnesium iodide in the presence of cu-

prous chloride gave 54. The latter was converted to ketal 55, which was subjected to Lemieux-von Rudloff oxidation to give diacid 56. This diacid was converted to its diester 57 which, on reduction with lithium aluminium hydride, gave diol 58. Efforts to reduce the two primary alcohol functions to methyl groups were unsuccessful. The ketal 55 was converted to the dialdehyde 63 with sodium metaperiodate and osmium tetroxide. However, attempted tosylhydrazone formation led to complex mixtures.

An alternative approach via cycloaddition of 2,4-dibromo-3-pentanone (64) to furan, using zinc-copper couple, gave a mixture of adducts 65, 66 and 67 in a 8:1:1 ratio. Efforts at reducing the ketone in these cycloadducts to a methylene group led to recovery of starting material. The mixture of cycloadducts was reduced with sodium borohydride to yield alcohols 76 and 77 in a 2:1 ratio. On treatment of this mixture with methanesulfonyl chloride only the exo mesylate 78 was formed. Attempts to displace this mesylate with various reducing agents were unsuccessful. Hydroboration of 65, followed by oxidation, led to diketone 82. However efforts directed towards a Baeyer-Villiger oxidation of this substance led to decomposition.

A cycloaddition approach to methynolide, using 2-furfuryl benzyl ether (84), was also investigated. The reaction of 64 with 84 in the presence of zinc-copper couple gave 85, reduction of which with sodium borohydride led to

alcohol 86. Epoxidation of 86 with m-chloroperbenzoic acid gave alcohols 87 and 88 in a 85:15 ratio. The major isomer was converted to its mesylate 89, but attempts to displace the mesylate reductively were unsuccessful. Alcohol 86 was converted to its mesylate 97 which, on reaction with m-chloroperbenzoic acid, gave epoxide 98. Reduction of 98 with lithium aluminium hydride afforded a mixture of olefinic alcohols assigned as 99 which, upon hydroboration, gave 100. Attempts at oxidizing alcohols 99 and 100 were unsuccessful. Also, an attempt to transform the alcohol 86 to bromohydrin 106 led instead to the bridged bromoethers 109 and 110 in a 1:1 ratio. Treatment of the mixture of 109 and 110 with lithium dimethylcuprate regenerated 86.

Cycloaddition of 64 with 3-methylfuran was briefly investigated and was found to yield 112. Hydroboration of 112, followed by oxidation with sodium dichromate, gave diketone 116 which, on treatment with sodium methoxide, gave the epimeric diketone 117. An attempted Baeyer-Villiger oxidation of 117 with trifluoroperacetic acid was unsuccessful.

Approaches to the Synthesis of Methymycin

by

Palaykotai Rajagopalan Raghavan

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Professor of Chemistry
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Dean of Graduate School

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Typed by Frau U. Binder for Palaykotai Rajagopalan Raghavan

To

Rama, Malakondiah and Om. Dhingra

and

to my 3M company

Martin, Marguerite and Mark

without whom this might not have been possible

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The author wishes to thank Dr. J.D. White for suggestion of the problem and for his guidance, patience, and understanding during my tenure at Oregon State University. Thanks are also due to a gracious lady Mrs. Susan Randall for NMR spectra and to Dr. Wielesek of University of Oregon for the high resolution mass spectra.

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APPROACHES TO THE SYNTHESIS OF METHYMYCIN

CHAPTER I

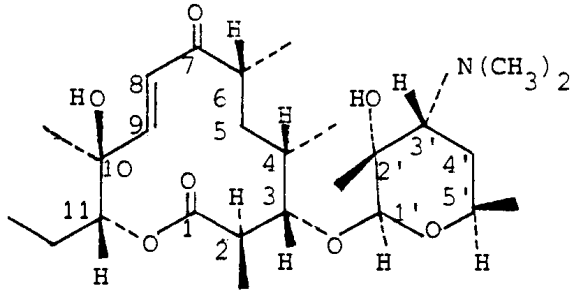
INTRODUCTION

The macrolides are one of the most diverse group of natural products.[1a-d] The number and variety of these substances have grown enormously over the last decade, due primarily to advances in isolation and structural elucidation techniques.

A macrolide is defined as a molecule containing a medium or, more usually, a large lactone ring as its central feature, hypothetically (and perhaps biogenetically) derived from the corresponding hydroxy acid by internal esterification. The macrolides are common metabolites of Streptomyces and are extensively used in medicine as antibiotics.[2] The macrocyclic lactone of these antibiotics is usually fourteen- or sixteen-membered, and possesses a number of substituents placed on the ring, including one to three glycoside units.

Methymycin (1) is the only macrolide whose ring is twelve-membered. Examples of fourteen-membered ring macrolides are erythromycins A (2) and B (3)[3] and oleandomycin (4).[4] The sixteen-membered ring macrolides include leucomycin A_3 (5)[5] and carbomycin A (6) [also known as magnamycin A].[6] In addition, a group of polyene antibiotics, exempli-

fied by amphotericin B (7),[7] a thirty-eight-membered macro-



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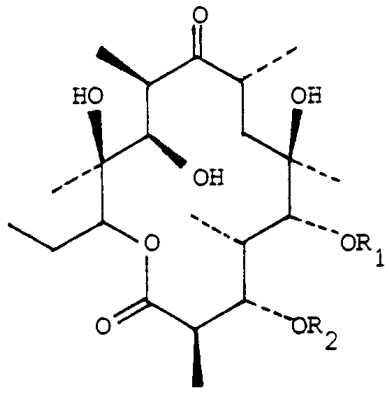
lide and chainin (8),[8] containing a twenty-eight-membered ring, occur in certain Streptomyces and Chainia species and show strong antifungal activity.

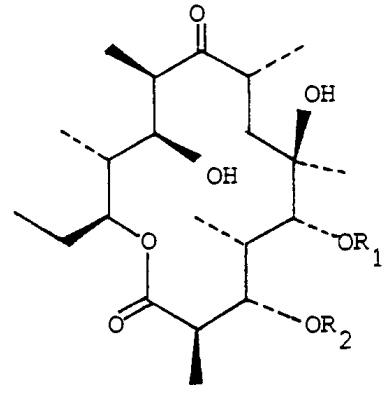
Biosynthetic studies[9] have established that the macrolide antibiotics are derived from simple metabolites, principally acetate and propionate precursors. The insertion of propionate chains is characteristic of all macrolide antibiotics. In polyene antibiotics, the ratio of acetate units to propionate units tends to be much larger than in the twelve-, fourteen- or sixteen-membered macrolides.

Methymycin (1) was first isolated from Streptomyces venezuelae.[10,11] It is a wide-spectrum antibiotic and is active against various bacteria in vitro.[12] These include Salmonella typhosa, Aerobacter aerogens, Shigella dysentriae, Streptococus facealis, and Myobacterium tuberculosis BCG. Biogenetically, methymycin is derived from one acetate and five propionyl units, as seen in 9. The chemi-



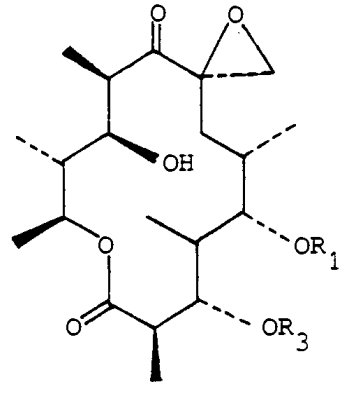
ERYTHROMYCIN A

2



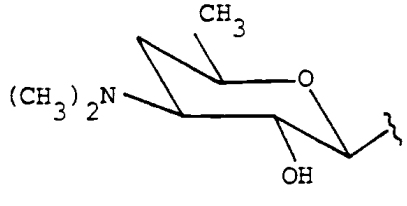
ERYTHROMYCIN B

3

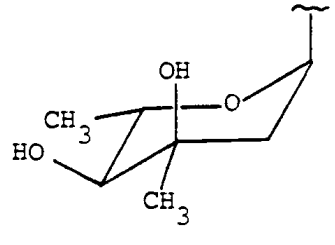


OLEANDOMYCIN

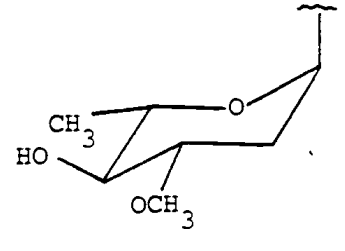
4



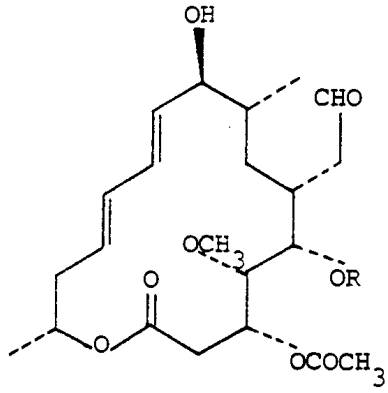
R_1 = DESOSAMINE



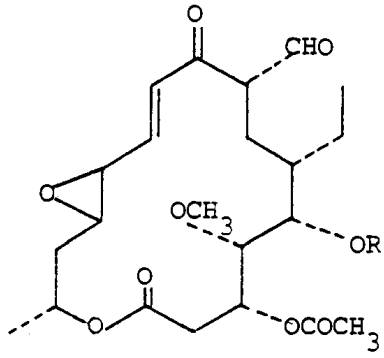
R_2 = L-CLADINOSE



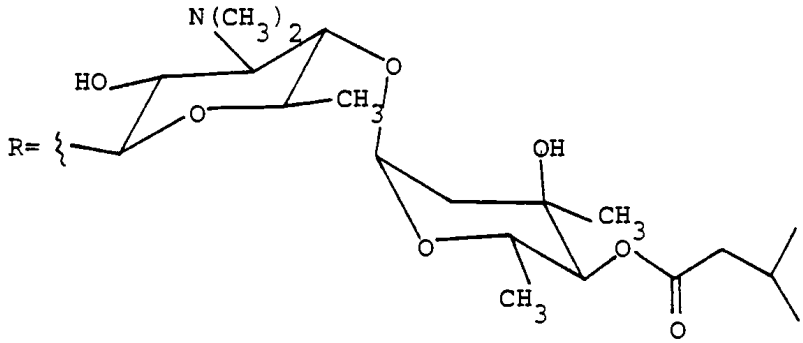
R_3 = L-OLEANDROSE

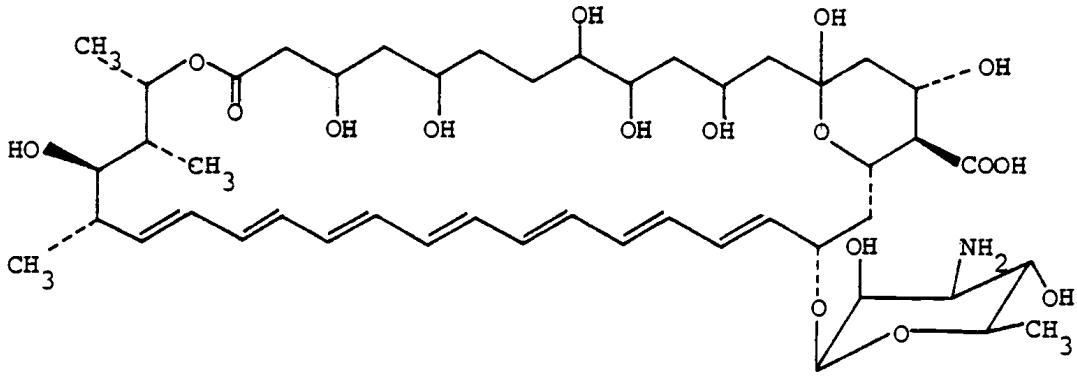


LEUCOMYCIN A_3 (5)

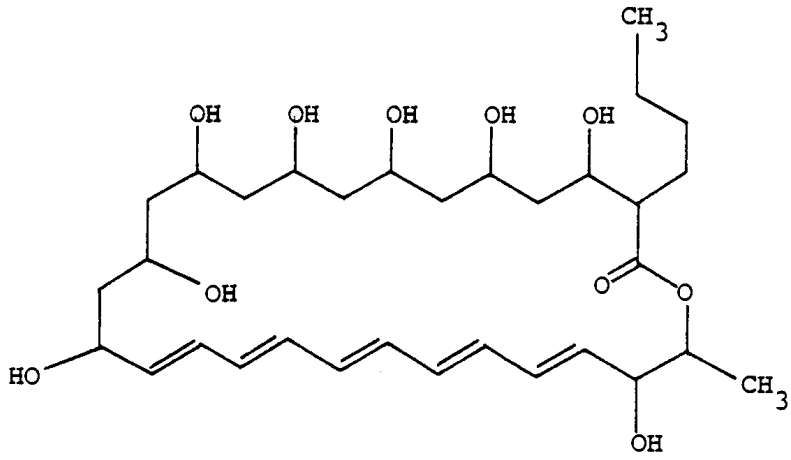


CARBOMYCIN A(6)

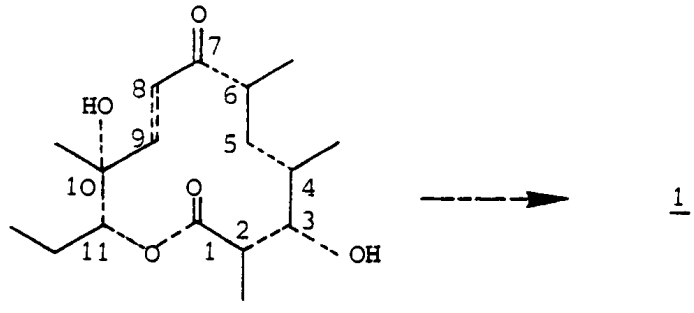




AMPHOTERICIN B(7)



CHAININ(8)



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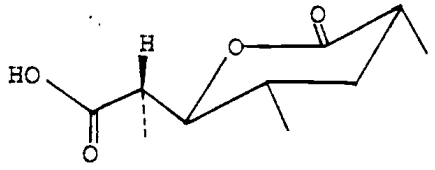
cal synthesis of methymycin is of particular interest, since this metabolite is the simplest of the natural macrolides and its synthesis would lay the foundation for the construction of the more complex macrolides.

The absolute configuration of methymycin was assigned as 2R, 3S, 4S, 6R, 10S, 11R, 1'S, 2'R, 3'S, 4'R by Celmer.[14] This assignment has been confirmed by Djerassi,[15] Prelog,[16] and Rickards[17] on the basis of degradative studies. Methymycin, on treatment with dilute acid, gives the Prelog-Djerassi lactone 10, in which three methyl groups retain the stereochemical relationship present in methymycin. The lactone 10 was a key intermediate in the first



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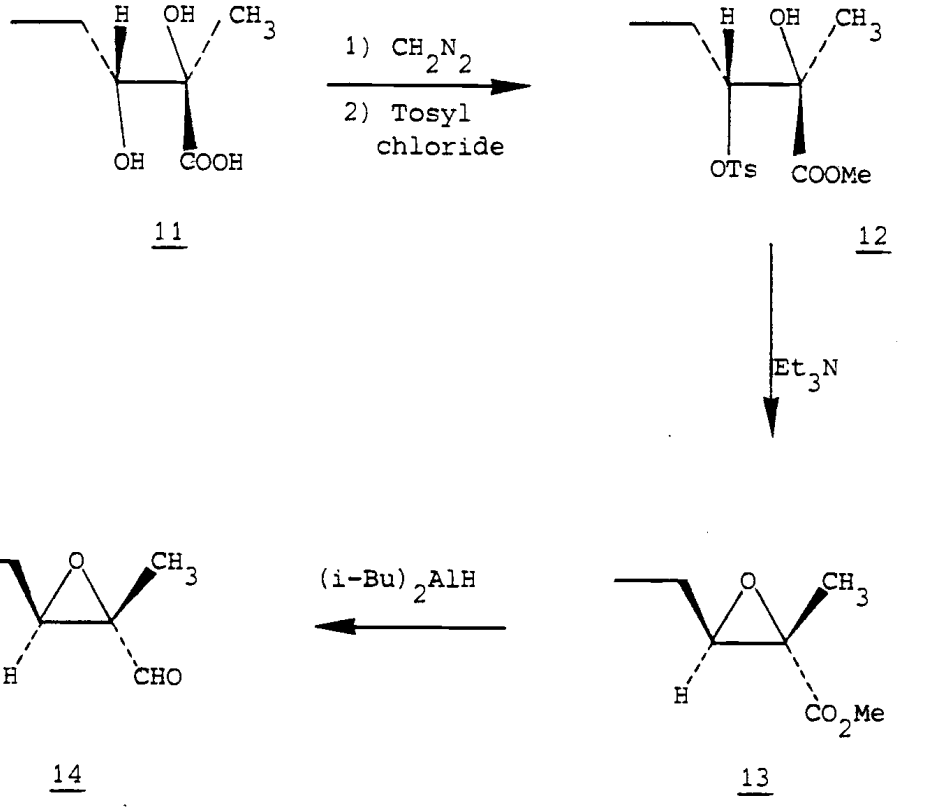
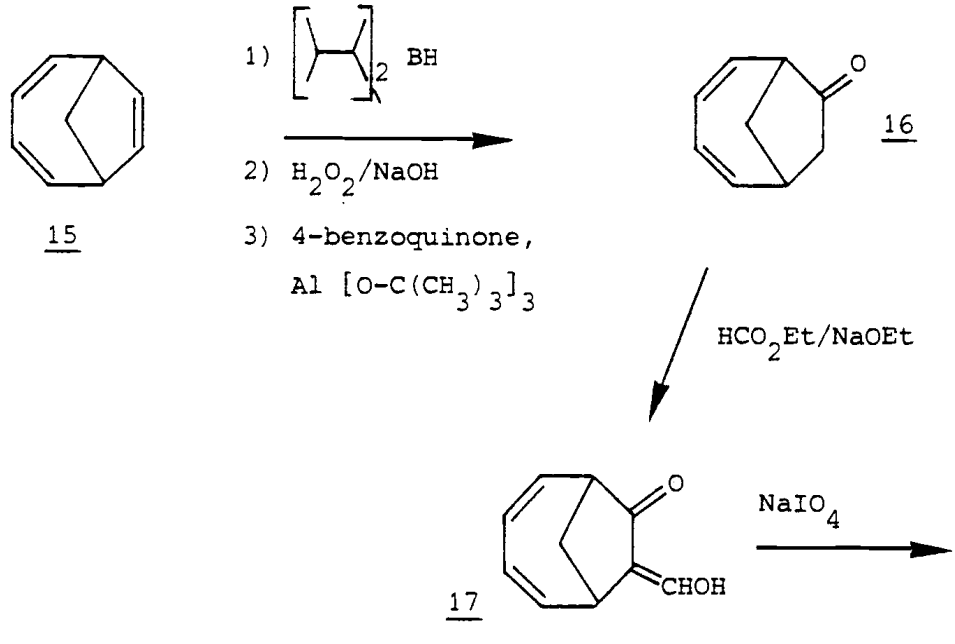
total synthesis of methymycin, reported in 1975 by Masamune.[18] Masamune's strategy involved the synthesis of segment A (C-9 through C-11), as shown in Scheme 1, and a second segment B (C-1 through C-8) as shown in Scheme 2, with a subsequent condensation between the two segments leading to methymycin 1. An important step in this synthesis was the introduction of a methyl group (required at C-2 of 1) by a trans opening of the epoxide 19 with lithium dimethylcuprate. The epoxide 19 was made in a stereospe-

Scheme 1

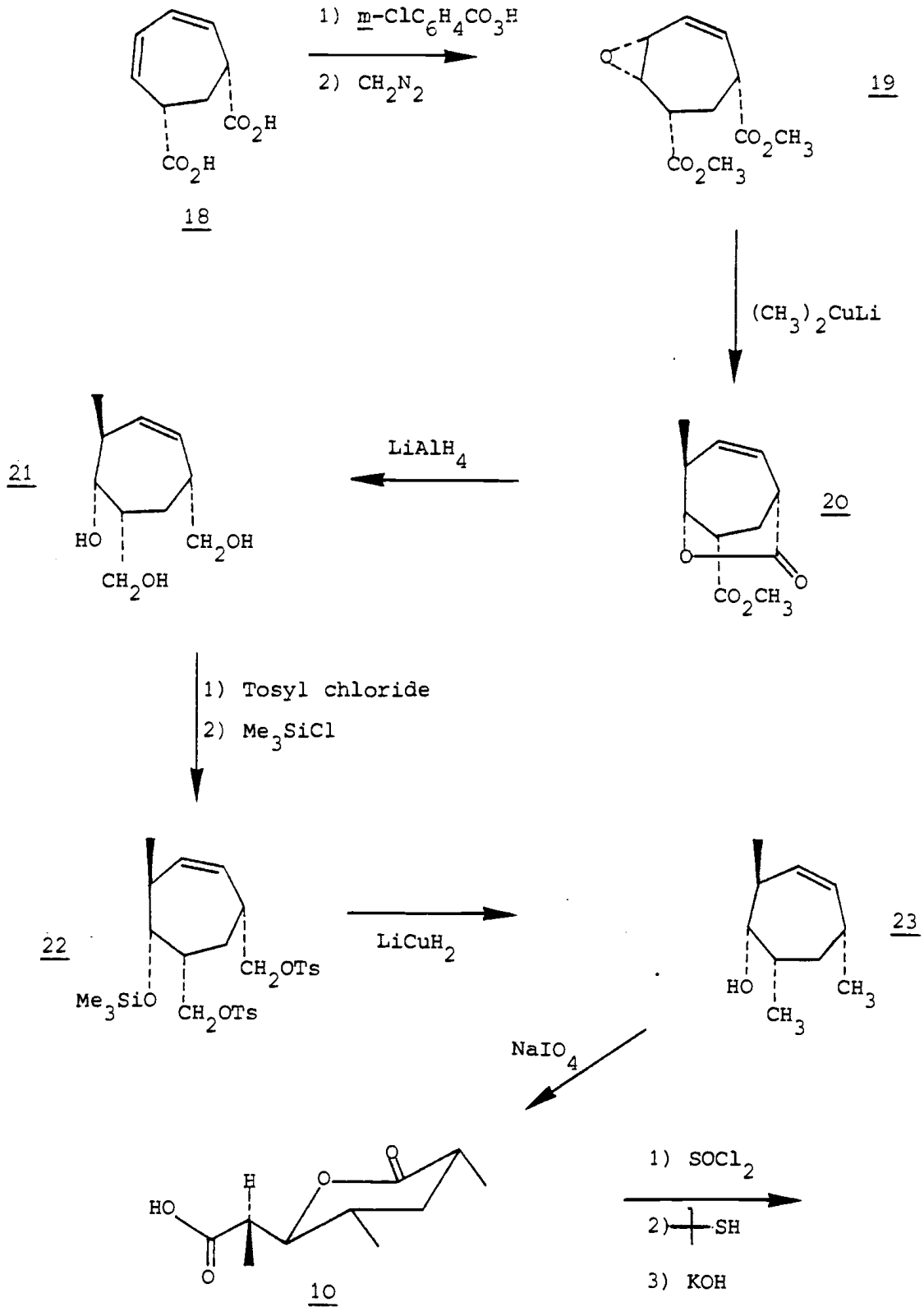


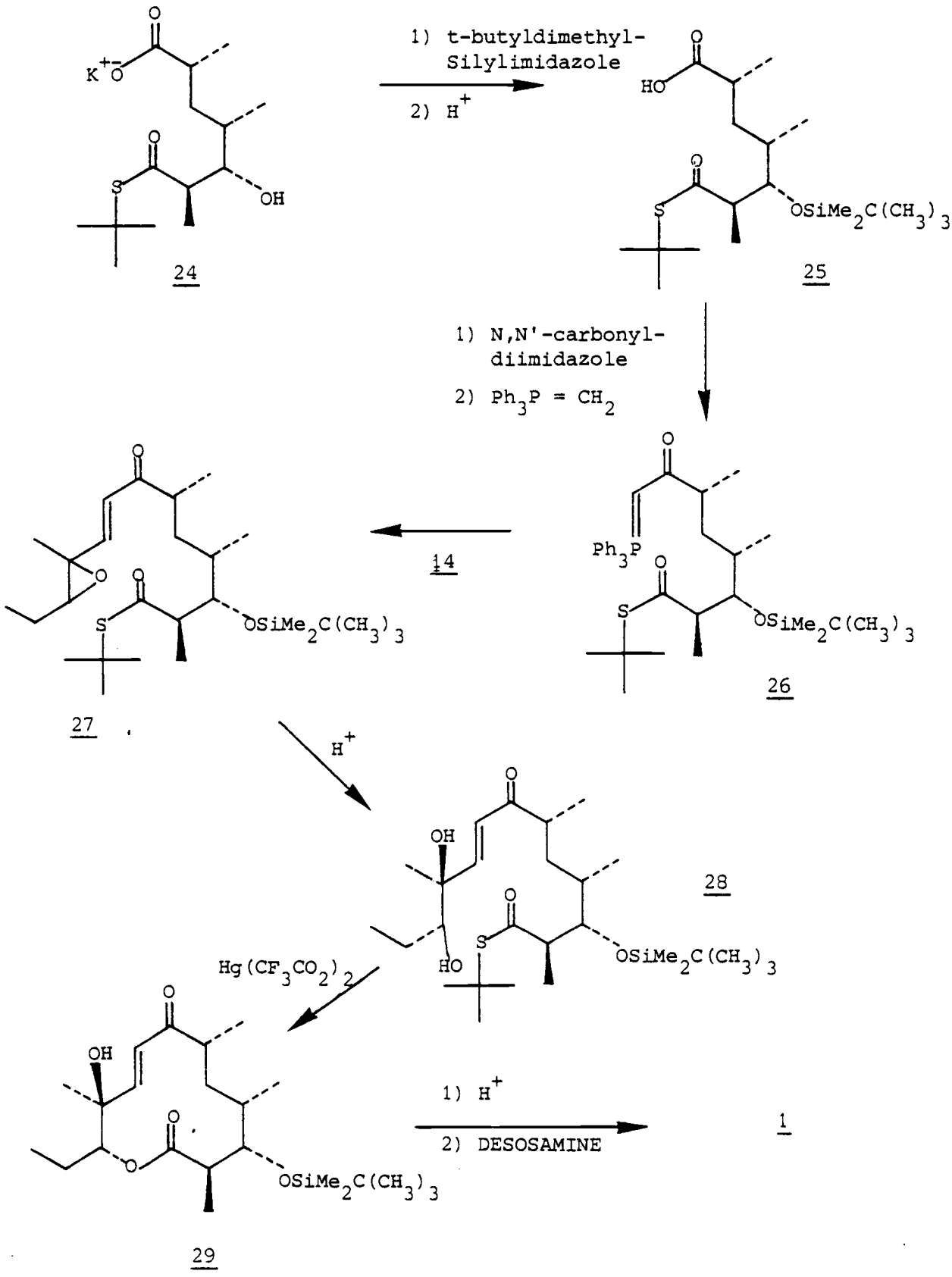
11 12 13 14

Scheme II



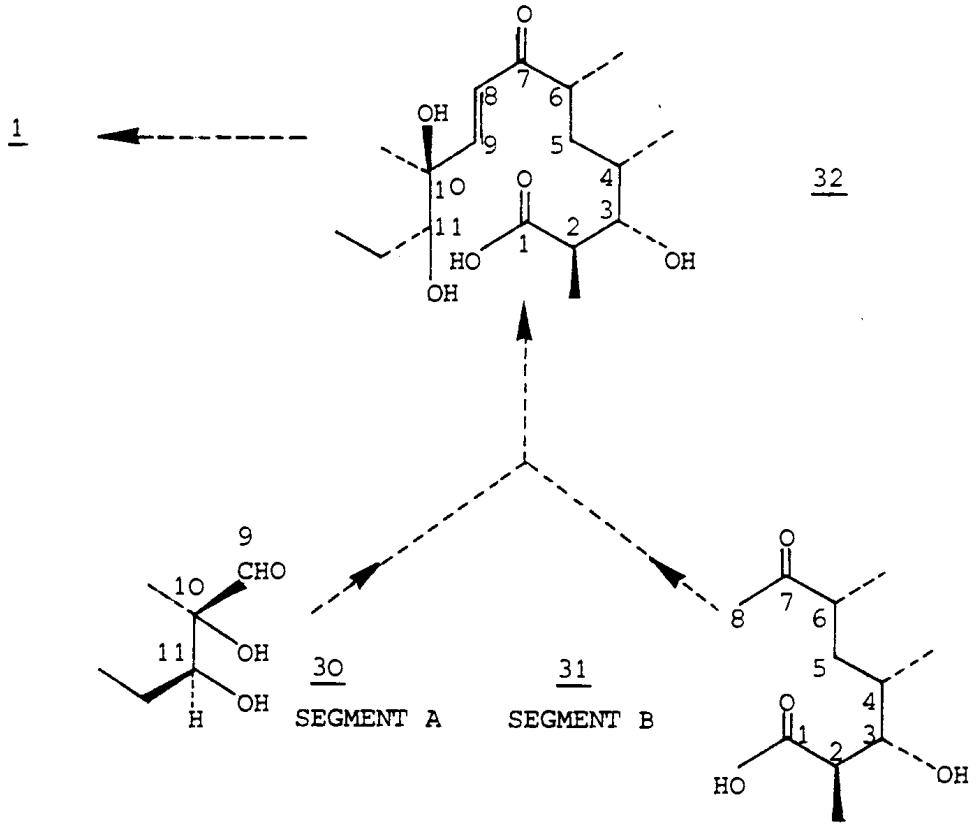
15 16 17


1) m-ClC6H4CO3H
2) CH2N2
18
19
(CH3)2CuLi
20
LiAlH4
21
1) Tosyl chloride
2) Me3SiCl
22
LiCuH2
23
NaIO4
10
1) SOCl2
2) SH
3) KOH


1) t-butyldimethyl-
Silylimidazole
2) H+
1) N,N'-carbonyl-
diimidazole
2) Ph3P = CH2
14
H+
Hg(CF3CO2)2
1) H+
2) DESOSAMINE
OSiMe2C(CH3)3
24
25
26
27
28
29
1

cific manner from 18, using the carboxyl groups to direct epoxidation. The trans 8,9-double bond was introduced by a Wittig condensation between 26 and 14. Finally the ring closure of 28 to 29 was effected using mercuric trifluoroacetate.

Our approach to methymycin is planned around synthesis of segments A (30, C-9 through C-11) and B (31, C-1 through C-8). Condensation of these two fragments by means of an aldol reaction should lead to the hydroxy acid 32, with a trans double bond at the 8,9-position. Ring closure of the hydroxy acid 32 could be effected by use of triphenylphosphine



and 2,2'-dipyridyl disulphide, reagents developed by Corey and Nicolaou for macrolide synthesis,[19] or by diethyl azodicarboxylate, developed by Mitsunobu[20] and used successfully in a total synthesis of (±) vermiculine.[21]

The planned synthesis of segment B would ideally involve an intermediate which could be then converted to the Prelog-Djerassi lactone 10, since this would provide confirmation of stereochemistry in the sequence. An important consideration in the synthesis of the segment B is placement of the methyl groups at C-4 and C-6 in the correct orientation during the sequence of reactions leading to 31. It was decided to introduce these methyl substituents at an early stage in the construction of the B component and then assemble other functionality on this framework. This approach seemed advantageous, since stereoselective generation of methyl groups with a 1,3 relationship is difficult. The synthesis of segment A (30) and several approaches to segment B (31) are described in chapters that follow.

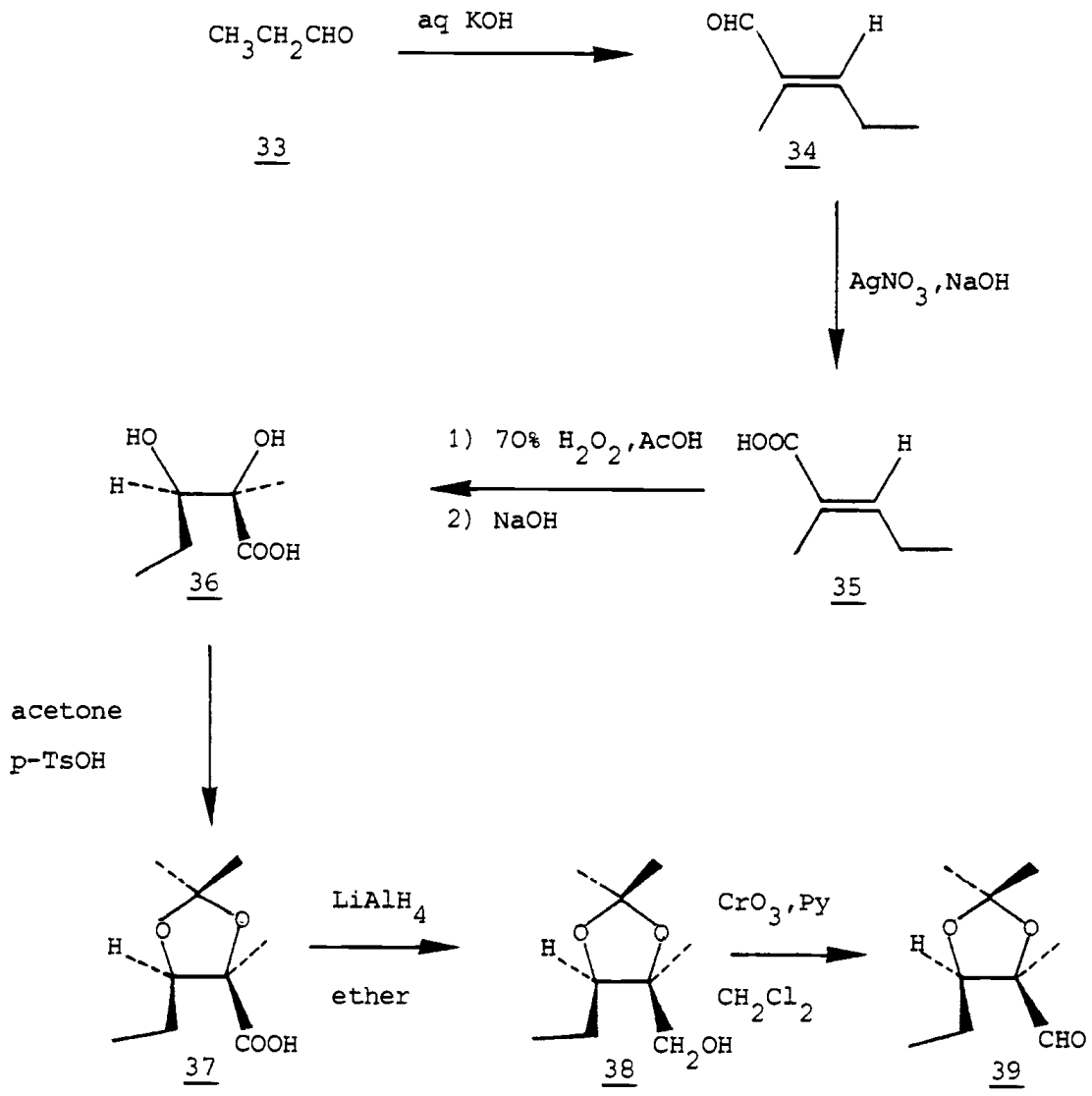
CHAPTER II

SYNTHESIS OF (+)2R,3R,2-METHYL-2,3-ISOPROPYLIDENEDIOXY-PENTANAL (39)

The synthesis of segment A (30) required for methymycin possesses an erythro relationship between the centers which correspond to C-10 and C-11 of the macrolide. The starting material for preparation of this segment was the erythro acid 36, which could be readily made from 2-methylpentenoic acid (35) by an overall trans hydroxylation.[22] The reaction sequence leading to 39 is summarized in Scheme III.

The aldehyde 34 was obtained in 50% yield from the condensation[23] of propionaldehyde with aqueous potassium hydroxide, and was oxidized to the corresponding acid 35 with silver nitrate and aqueous sodium hydroxide. Treatment of acid 35 with 70% hydrogen peroxide in acetic acid at 50°C for 6 hours, followed by base hydrolysis, led to the erythro acid 36 in 50% yield. This acid, on treatment with acetone in the presence of p-toluenesulphonic acid, gave acetonide 37 in quantitative yield. Reduction of 37 with lithium aluminium hydride in refluxing ether produced alcohol 38 in 90% yield, which was converted to the aldehyde 39 upon treatment with Collins' reagent. The overall yield of 39 from 35 was 37%.

Scheme III

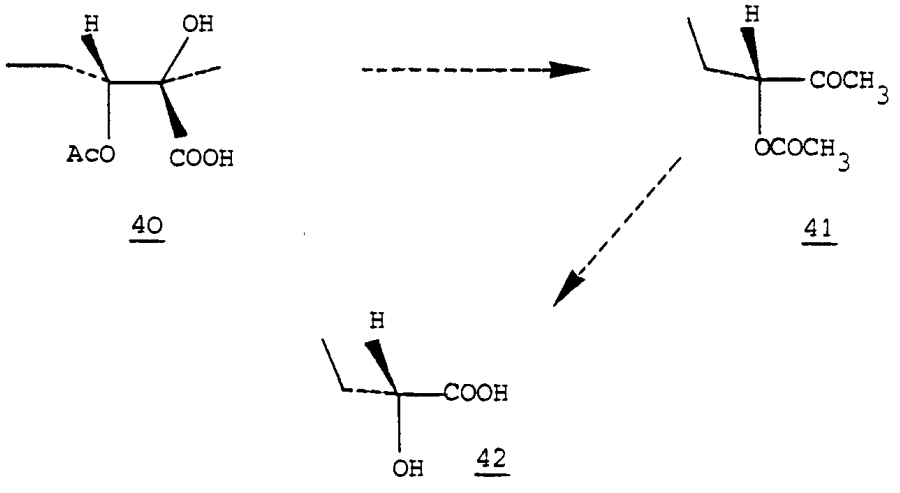


In a converging synthesis it is desirable to have at least one of the segments in optically active form. Condensation would lead to diastereomers which could be separated and the diastereomer with the correct absolute stereochemistry carried to completion.

The plan for total synthesis of methymycin required optically active aldehyde 39 with R configuration at both

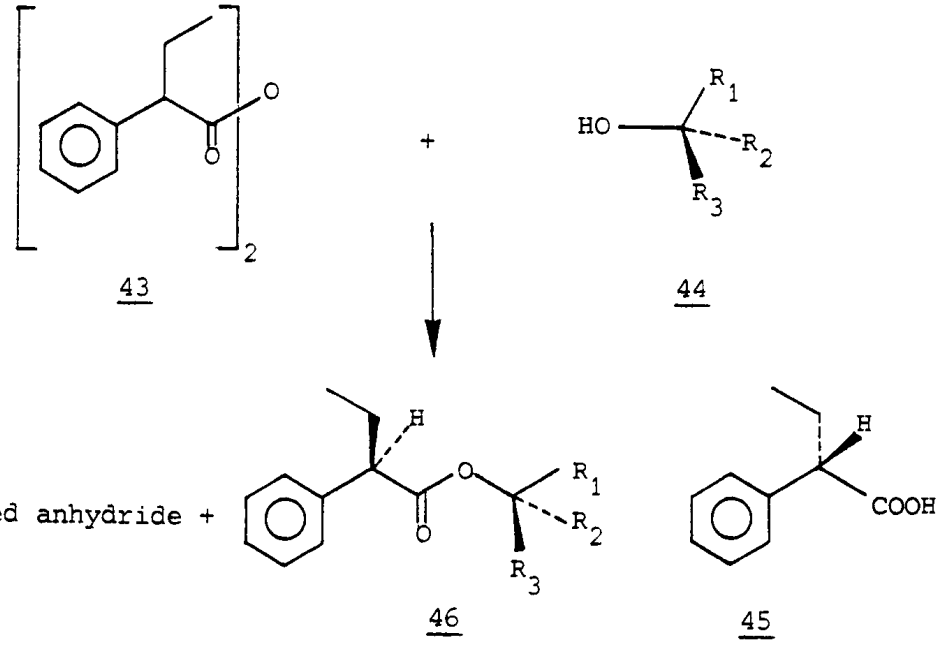
chiral centers. This absolute configuration corresponds to the chiralty of C-10 and C-11 in methymycin. The resolution of acid 36 was achieved readily by treatment with brucine. A single crystallization of the crude solid from acetone gave a pure salt with a rotation of +41.6°. Acidification of this material, followed by continuous extraction with ether, furnished (-) 36, $[\alpha]_D^{25}$-13.6°. Acidification of the mother liquor and continuous extraction with ether gave (+) 36 with $[\alpha]_D^{25}$+13.5°.

An attempt was made to establish the absolute configuration of (-) 36 by converting it into α-hydroxybutric acid (42), whose absolute configuration is known.[24] The (-) acid 36 was converted into acetate 40, $[\alpha]_D^{25}$-31.6°, by treatment with acetic anhydride and pyridine. However, treatment of



40 with sodium metaperiodate or lead tetraacetate led to only minor amounts of a product with negligible rotation.

For secondary alcohols, an alternative to the determination of absolute configuration by chemical correlation is the indirect method of Horeau.[25] In this method, a kinetic resolution using racemic 2-phenylbutyric anhydride 43 leads to selective acylation of the chiral alcohol 44 and hence an enantiomeric excess of 2-phenylbutyric acid (45). An empirical rule, devised and verified by Horeau, states that secondary alcohols having R configuration react preferentially with racemic 2-phenylbutyryl derivative, to produce an enantiomeric excess of S-2-phenylbutyric acid (45), having a positive sign of rotation. The scheme, as represented by Horeau, is shown below, with the group R_1, R_2, and R_3 arranged in order of increasing bulkiness. The rotation of recovered 2-phenylbutyric acid (45) is measured and, if positive, the enantiomer of alcohol with which the

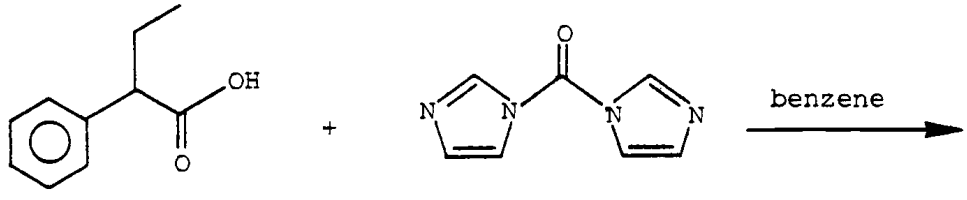


acid has reacted is presumed to have R configuration. Simi-

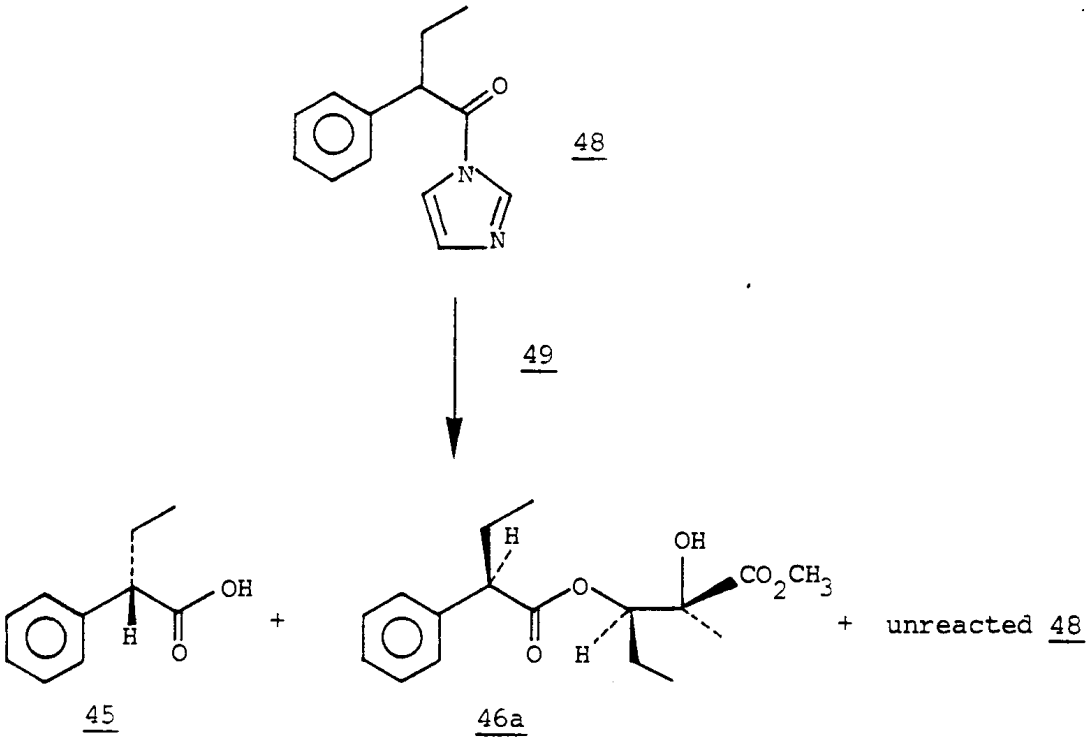
larly an enantiomeric excess of levo 2-phenylbutyric acid (45), implies an alcohol of S configuration.

The basis for the application of Horeau's rule lies in the kinetic preference for formation of one of the two diastereomeric esters 46. In general, the R enantiomer of 2-phenylbutyric acid (45) reacts more rapidly with the alcohol possessing the configuration 44, the rate difference being largest when the difference in size of the substituent is greatest (i.e., $R_3 >> R_1$). This enantiomer of 44 is most commonly of R configuration.

One of the drawbacks in using 2-phenylbutyric anhydride (43) as the acylating agent is that the optical yield of the resulting 2-phenylbutyric acid is small. Brockman and Risch[26] have modified Horeau's procedure by replacing anhydride 43 by 1-(2-phenylbutyroyl)imidazole (48), which is easily accessible from 2-phenylbutyric acid (45) and N,N'-carbonyldiimidazole (47). This procedure, which gives consistently higher optical yields than that of Horeau, was used for determination of absolute configuration of the methyl esters 49 and 49a as shown below.



45 47



The methyl ester 49 and its enantiomer 49a were made from the respective enantiomers of acid 36 by treatment with diazomethane. The enantiomeric methyl esters were then reacted separately with 48 in benzene at room temperature for twenty hours, and the rotation of the recovered 2-phenylbutyric acid was measured. The results are summarized in Table 1. Application of Horeau's rule establishes unambiguously that the (+) ester 49 has R,R configuration and the (-) ester 49a S,S configuration.

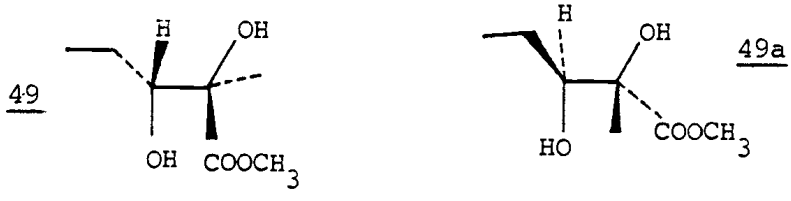


TABLE I

Rotation and Configuration of Esters 49 and 49a

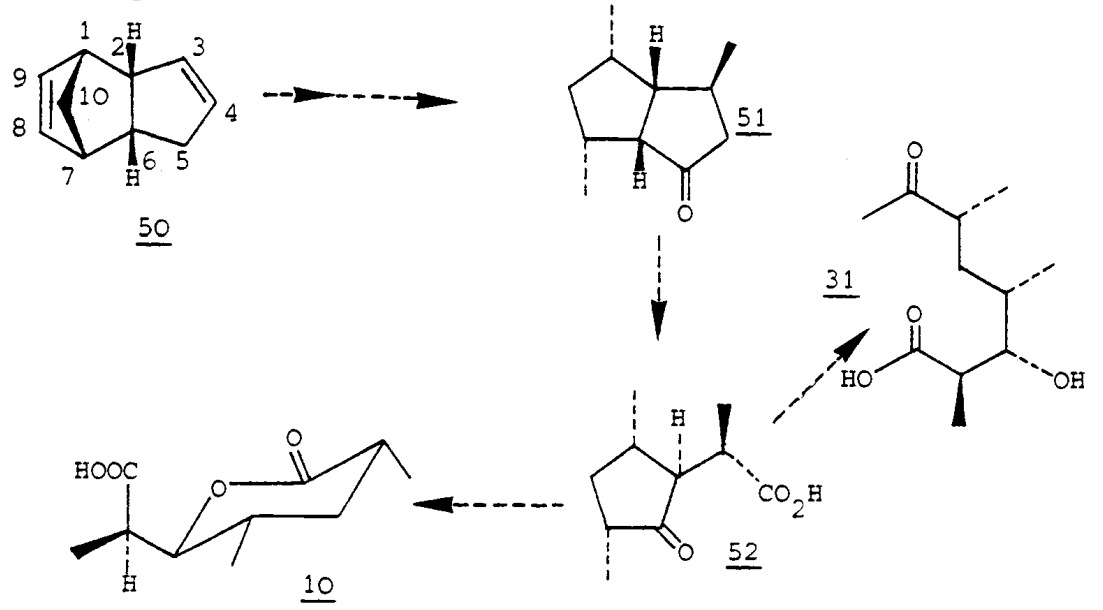
Compound	Rotation $[\alpha]_D^{25}$	Rotation of recovered 2-phenyl-butyric acid (45) $[\alpha]_D^{25}$	Configuration of Ester
(+)methyl ester 49	$+25.8^{\circ}$	$+0.56^{\circ}$	2R, 3R
(-)methyl ester 49a	-25.6°	-0.48°	2S, 3S

The (+) acid 36 was converted to the aldehyde 39 by the sequence of reactions shown in Scheme III to give 39, $[\alpha]_D^{25}+51.6^{\circ}$. This substance, corresponding to segment A, has both chiral centers with R configuration, and thus possesses the correct chirality for C-10 and C-11 of methymycin. A similar conclusion was reached by Masamune,[18] in the course of his synthesis of methymycin.

CHAPTER III

AN APPROACH TO SEGMENT B FROM DICYCLOPENTADIENE

The C_1-C_8 segment 31 of methymycin could, in principle, be derived from the bicyclic ketone 51 via keto acid 52. The cyclopentanone 52 would be a particularly versatile intermediate since it could be converted into the Prelog-Djerassi lactone 10 by a Baeyer-Villiger oxidation, or transformed into 31 and subsequently condensed with 30 to yield 32.

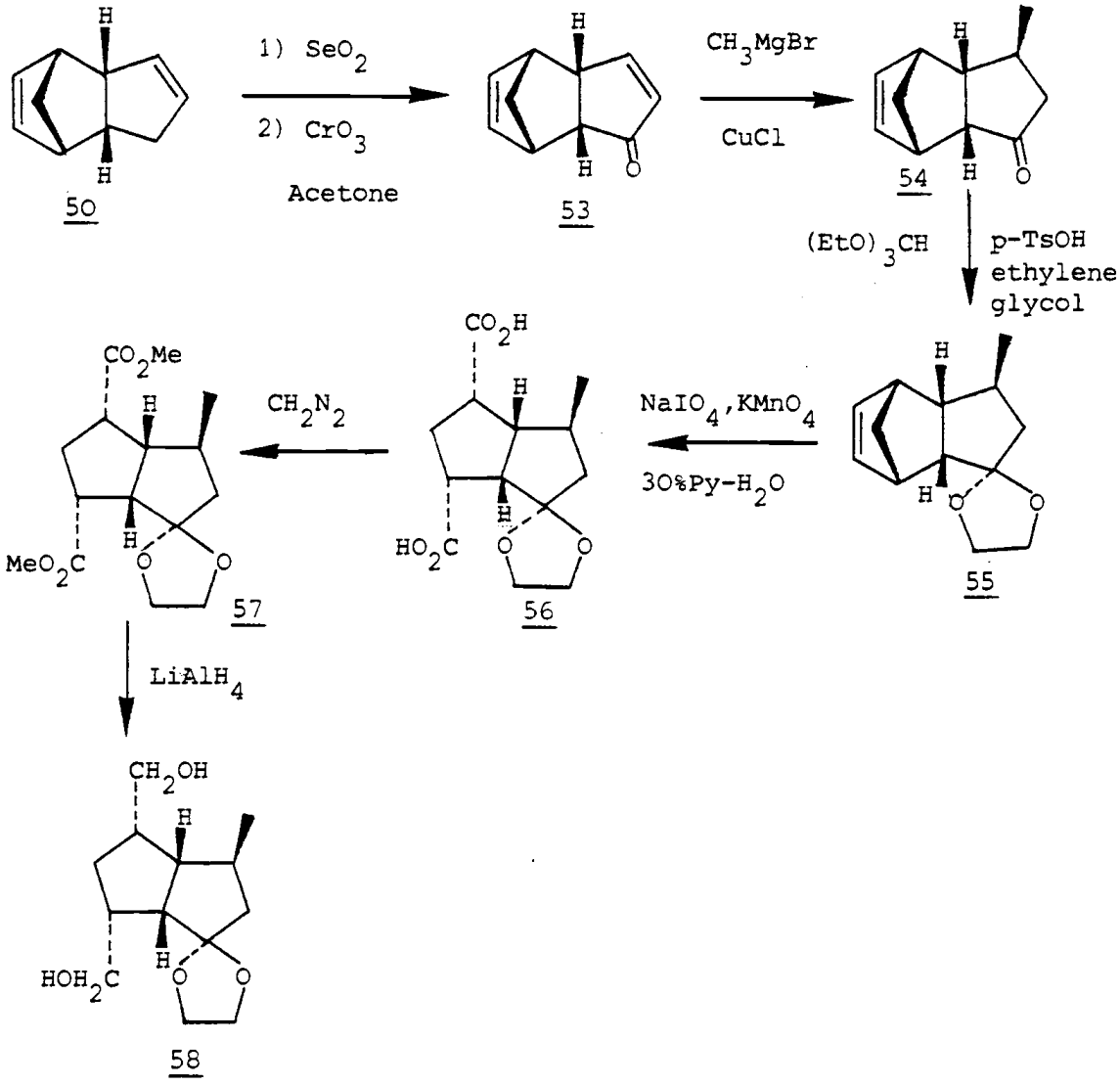


Dicyclopentadiene 50 appeared to be an ideal starting material for the preparation of 51; it has the cis ring fusion that is needed in 51 and is also readily available at low cost. If the C-5 position could be oxygenated, this would facilitate introduction of a methyl group at C-3, with the correct (exo) configuration by means of a 1,4-conjugate addition. The cis methyl groups at C-4 and C-6 of 10

could be generated by oxidative cleavage of the 8,9 double bond of 50, followed by reduction of the corresponding dialdehyde. Thus, all four of the asymmetric centers present in 51, and hence in 10, could be controlled.

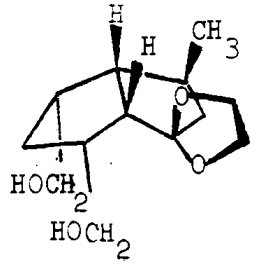
An approach towards the synthesis of 51 is recorded in Scheme IV. Dicyclopentadiene 50, upon treatment with selenium dioxide in dioxane at 65°C followed by oxidation of the

Scheme IV



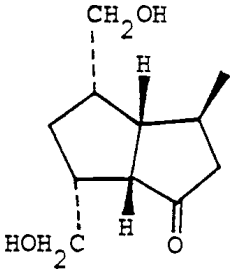
crude product with chromium trioxide in acetone, gave 53 in 50% yield.[27] A Grignard reaction of 53 with an ether solution of methyl magnesium iodide in the presence of a catalytic ammount of cuprous chloride gave 54 in 81% yield.[28] The keto group of 54 was protected as its ethylene ketal by treatment with triethyl orthoformate, ethylene glycol and p-toluenesulphonic acid at room temperature overnight. This ketal was subjected to Lemieux-Rudloff oxidation[29] with potassium permanganate and sodium metaperiodate in 30% pyridine-water to give the dicarboxylic acid 56 in quantitative yield. The acid 56 was converted to its diester 57 (80% yield) by treatment with diazomethane, and this, without purification, was reduced with lithium aluminium hydride in ether at $0^{\circ}C$ to give the diol 58 cleanly.

For the preparation of 62 it now remained only to reduce the two primary alcohol functions to methyl groups. Attempted formation of the bismesylate of 58 led to decomposition, but the unstable bistosylate of 58 could be generated *in situ*. All efforts at reduction of this substance led to complex mixtures. The reason for the instability of



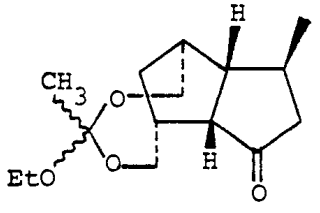
59

the bismesylate and bistosylate of 58 is clear from the conformation 59 shown above. The two primary alcohols lie on the endo side of the bicyclo[3.3.0]octane framework where the endo oxygen of the ketal provides further steric congestion.



60

In order to alleviate the steric compression in 58, the ketal was hydrolyzed to ketone 60 with silica gel in wet benzene. However, attempted preparation of the bistosylate of 60 was unsuccessful. On treatment of 60 with ethyl acetate and magnesium sulfate, the stable ortho ester 61



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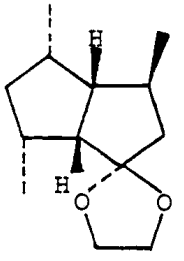

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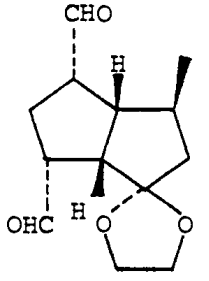


63

was obtained in 80% yield. This selective protection of the hydroxyl groups of 60 would permit further synthetic elaboration based upon reactions at the cyclopentanone ring, but this strategy was not pursued further.

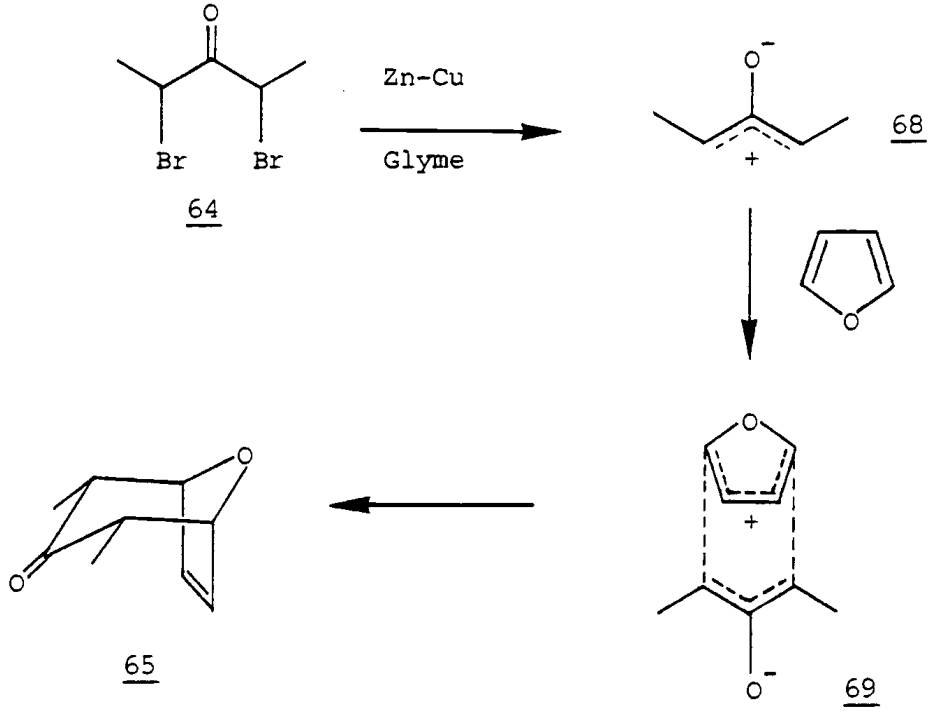
Having failed to reduce 58 to 62, an alternative approach via the dialdehyde 63 was investigated. The latter was obtained in 70% yield upon reaction of 55 with sodium metaperiodate and a catalytic amount of osmium tetroxide. However, efforts at forming a bistosylhydrazone of 63 in the hope of accomplishing reduction with sodium cyanoborohydride[30] led to complex mixtures.

These difficulties, associated with reduction of the carboxyl groups of 56 to the methyl substituents required at C-4 and C-6 of 31, clearly originate in the endo configuration of the cyclopentadiene dimer, which places the two carboxyl functions of 56 on the same side of a cyclopentane ring as the second fused cyclopentane. Since there seemed to be no obvious solution to this dilemma other than a major revision of the scheme requiring substantial perturbation of stereochemistry, this approach was abandoned.

CHAPTER IV

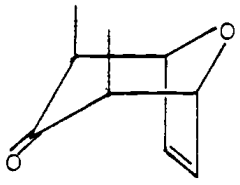
AN APPROACH TO SEGMENT B VIA CYCLOADDITION OF 2,4-DIBROMO-3-PENTANONE TO FURANS

Since, in the previous approach, all efforts at reducing the diol 58 to 62 had failed, it was decided to adopt a strategy in which the two methyl groups would be introduced directly. Hoffmann[31] reported in 1972 that furan reacts with 2,4-dibromo-3-pentanone[32] 64 in the presence of zinc-copper couple[33] to yield adducts 65, 66, 67, in a 8:1:1 ratio. Noyori[34] obtained similar results using diiron nonacarbonyl in place of the metal couple. The reaction is believed to involve an oxyallylic cation 68 as an intermediate, which gives the major product (e.g., 65) through a "boat" or "endo" transition state 69.



64 68 65 69

Stereoisomers 66 and 67 are believed to arise from oxalylic cations 70 and 71, respectively.



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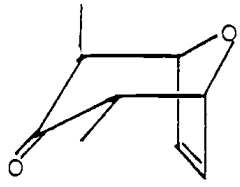

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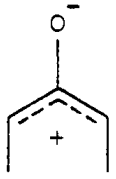

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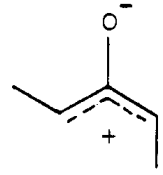

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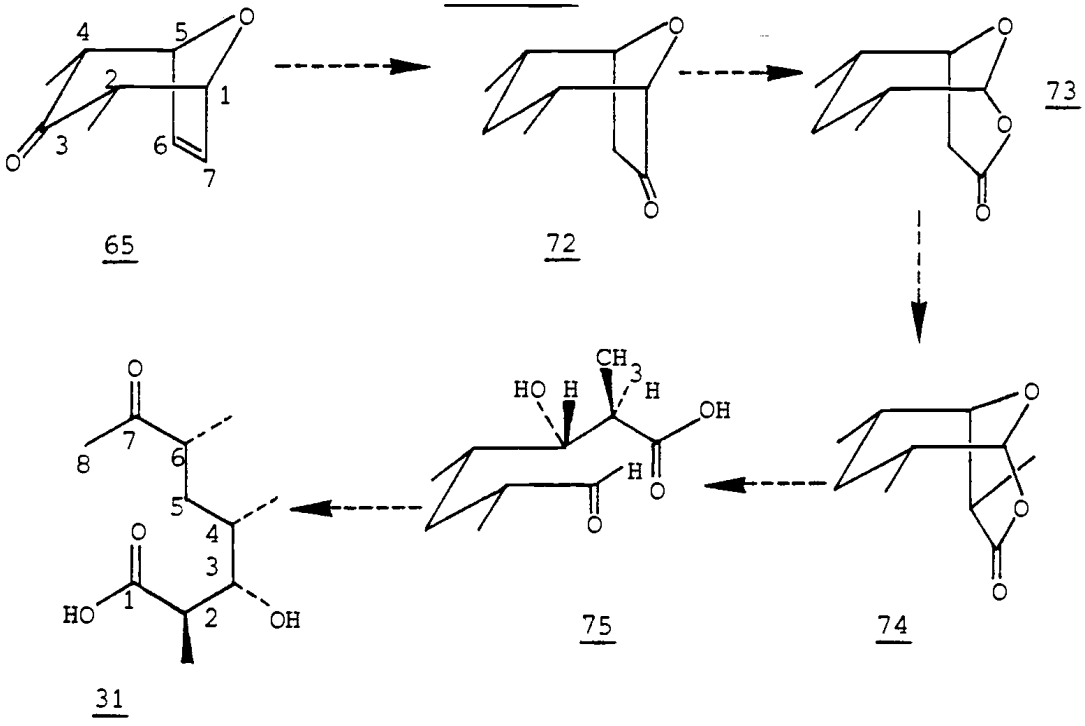
The strategy behind using 65 as a starting material for the synthesis of C_1-C_8 segment 31 is shown in Scheme V, and depends critically on the selective manipulation of

Scheme V



functional groups while leaving the configuration of the two methyl groups intact. Thus, after reduction of the keto group at C-3, the C-6,7 double bond could be oxidized to introduce a keto group at C-7. A Baeyer-Villiger reaction of 72 should preferentially lead to 73. A methyl group could be introduced at C-6 of 73 by alkylation from the exo side to form 74, which could be hydrolyzed to 75.

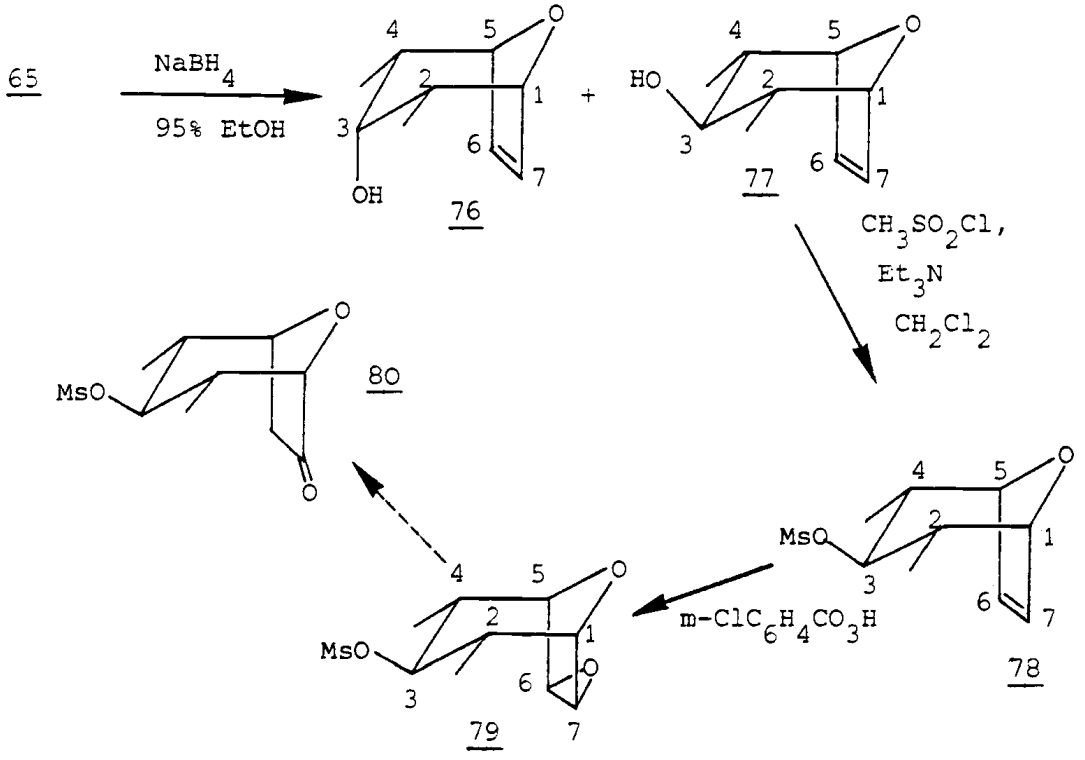
1. Furan

The reaction of 2,4-dibromo-3-pentanone 64 with furan was carried out by a modification of the method of Hoffmann,[31] and the mixture of 65, 66, and 67 was carried forward without separation of isomers. The equatorial methyl groups of 65 appear as a doublet at 0.98 ppm, whereas the axial methyl groups of 66 and 67 appear downfield due to the interaction between the π system of the carbonyl group[31] and the methyl protons. Further, the bridgehead hydrogens at C-1 and C-5 of 65 appear at δ 4.72 and are coupled (5 Hz) to the axial hydrogens at C-2 and C-4.

Efforts were now directed towards reduction of the keto group at C-3 in the mixture of 65 and its minor isomers 66 and 67. Attempted formation of a thioketal and hydrazone,[35] as well as Clemmensen reduction,[36] all failed, and the unreacted cycloadducts were recovered quantitatively. The failure of the ketone to react indicates that it

is hindered and, consequently, an indirect approach shown below was adopted in which the ketone was first reduced to an alcohol (Scheme VI).

Scheme VI

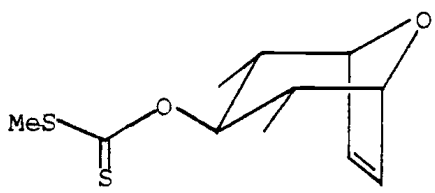


Reduction of 65 with sodium borohydride led to a mixture of alcohols 76 and 77 in a ratio of 2:1, The NMR spectrum (see Table 2) shows the C_3 proton of 76 as a triplet at δ 3.72 with a coupling constant of 4 Hz, whereas in 77, this proton appears as a triplet at δ 2.88 with a coupling constant of 9 Hz, indicating that it is axial.[37] The alcohol 76 was obtained exclusively on reduction of 65 with diisobutyl aluminium hydride.

On treatment of the mixture of 76 and 77 with methanesulfonyl chloride in triethylamine only the exo-mesylate 78 was formed. The C_3-H appeared as a tripet at δ 4.2 with a

coupling constant of 9 Hz (see Table 2), indicative of a diaxial coupling. Efforts to prepare the endo-mesylate of 76 were unsuccessful. The failure to obtain the endo-mesylate is probably due to interference by the π system of the C_6-C_7 double bond. Attempts to reductively cleave the mesylate in 78 with lithium aluminium hydride or with lithium triethylborohydride[38] led to complex mixtures. In the hope of introducing the keto group required at C-7, the mesylate 78 was epoxidized with m-chloroperbenzoic acid in methylene chloride to give 79 in 70% yield. However, efforts at rearranging the epoxide 79 to ketone 80 with lithium bromide[39] and boron trifluoride etherate[40] were unsuccessful. Attempts at displacing the mesylate in this system were also unrewarded. The mesylate group in both 78 and 79 is exo and trans elimination is not possible. Similarly, displacement of the mesylate by attack from the endo side is sufficiently hindered that alternative pathways intervene.

Barton[41] has reported that secondary alcohols can be deoxygenated by forming the xanthate with sodium hydride, carbon disulphide and methyl iodide and then reducing the



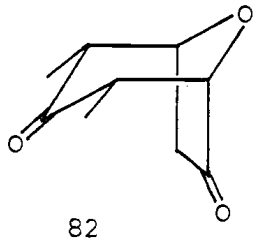
81

TABLE 2

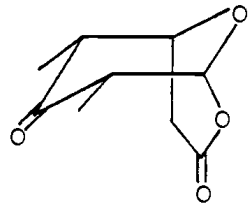
NMR Data for Cycloadducts and Derivatives from addition of 2,4-Dibromo-3-pentanone to Furan

Compound	Chemical shift (δ), Splitting pattern and Coupling constant (J).		
	C_1-H, C_5-H	C_3-H	C_6-H, C_7-H
65	4.72 d 5Hz	-	6.38
76	4.52 d 4Hz	3.72 d 4Hz	6.54 s
77	4.56 d 4Hz	2.88 t 9Hz	6.28 s
78	4.64 d 4Hz	4.20 t 9Hz	6.3 s
79	4.24 d 4Hz	4.5 t 9Hz	3.6 s
81	4.5 d 4Hz	4.58 t 9Hz	6.42 s

resulting xanthate with tri-n-butyltin hydride.[42] When the mixture of alcohols 76 and 77 was treated under these conditions, only the exo-xanthate 81 was formed, and efforts at reducing this xanthate failed, presumably for the same reason that displacement of the exo mesylate was unsuccessful. Having been unable to introduce a keto function at C-7 by indirect methods, the ketone 65 was treated directly with diborane and then oxidized with sodium dichromate and sulphuric acid by the procedure of Brown.[43] The diketone 82 was obtained in 50% yield. This, at first, seemed to be an



82



83

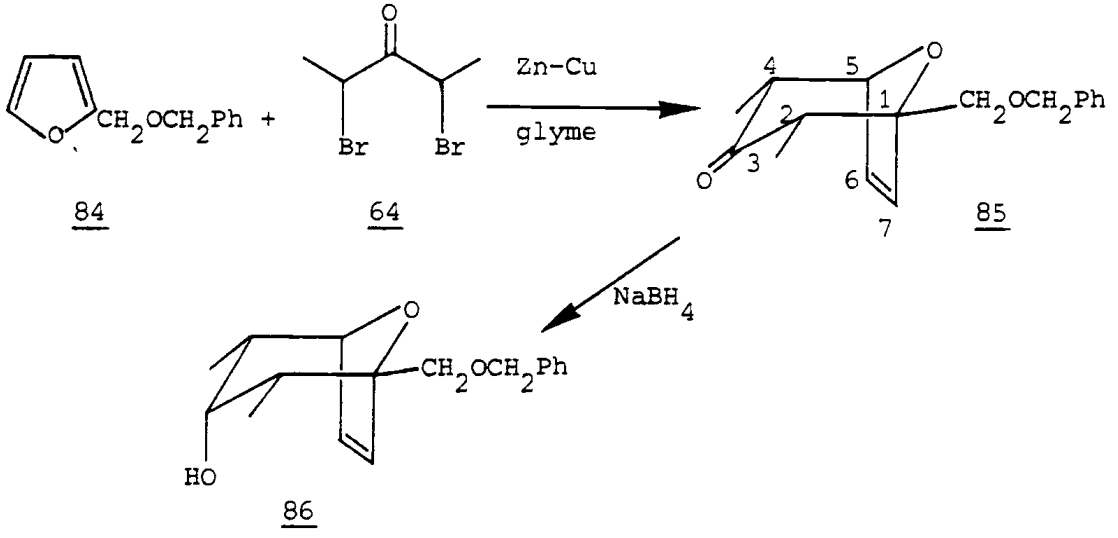
ideal intermediate for the conversion to lactone 83. Selectivity in the Baeyer-Villiger oxidation of 83 could be expected as there is more strain present in the five-membered ketone and hence this should react faster.[44] However, all efforts at reacting 82 with trifluoroperacetic acid, or with m-chloroperbenzoic acid under normal as well as the forcing conditions of Kishi[45] led to decomposition.

These difficulties, in conjunction with the failure to obtain stable endo substituents at C-3 of the oxabicyclooctane system, prompted abandonment of this route. Attention was then turned to a modification of the cycloaddition

approach using 2-furfuryl benzyl ether 84.

2. Furfuryl Benzyl Ether 84

The bicyclic ether 85 offers an advantage over the simpler adducts 65, prepared from furan, in that it includes from the outset the carbon (C-8), which provides the connection of this moiety with segment A. There remains the task of incorporating the C-2 methyl group of methynolide which must be introduced at C-6 of 85 from the exo direction. Finally, functional group manipulation, including removal of the C-3 ketone and an oxidative cleavage of the C-1,7 bond must be performed to transform 85 into a useful precursor for segment B. The chemistry described in this section emanated from 85, and was pursued with the intention of realizing its conversion to a precursor (e.g., 31), suitable for coupling with the previously prepared aldehyde 39.



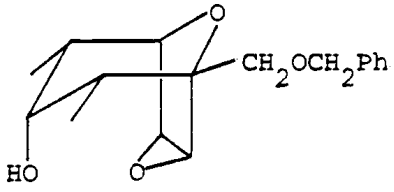
84 64 85 86

Reaction of a three-fold excess of 2-furfuryl benzyl ether 84 with 2,4-dibromo-3-pentanone in the presence of zinc-copper couple gave 85 in 65% yield. The methyl groups appear as doublets at 0.92 and 0.94 ppm in the NMR spectrum of this compound, indicating that they are equatorial. These values correspond with those reported by Hoffmann for 65. The axial methyl substituents would, in this system, appear at δ 1.3 and in this case, no isomeric adduct was detectable. As in the case of 65 efforts at reduction of C-3 in 85 by formation of a thioketal[46] (with reduction by Raney nickel intended) or by the Wolf-Kishner[47] method failed. Consequently, the 3-keto group was reduced to the endo alcohol 86 with sodium borohydride in benzene methanol 1:1, for the purpose of a subsequent dehydration, followed by hydrogenation. Treatment of 86 with m-chloroperbenzoic acid in methylene chloride gave a mixture of products 87 and 88 in a 85:15 ratio, which was separated by chromatography on silica gel. Neither product exhibited proton signals in the nmr spectrum expected for an epoxide (δ 3.0-3.5), but instead showed signals between δ 4.0-4.5, typical of secondary alcohols and ethers. The major isomer was converted to the mesylate 89 with methanesulfonyl chloride in pyridine, but the mesylate function was unreactive toward dimethyl sulphoxide,[48] hexamethylphosphoramide in collidine,[49] lithium aluminium hydride in ether, and sodium iodide-zinc in hexamethyl-

phosphoramide.[50]

Furthermore although 87 could be converted to a mixture of secondary chlorides 90 and 91 with thionyl chloride and pyridine in benzene, attempts to remove the halogen in this substance with tri-n-butyltin hydride or with butyl lithium gave no reaction.

These data are clearly inconsistent with formulations 92 and 93 as products of epoxidation of 86. On the other hand, the tricyclic ether 87 accounts well for the observa-



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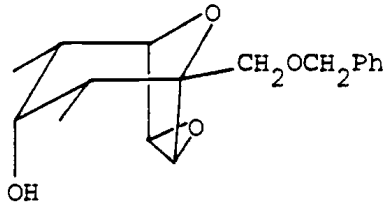
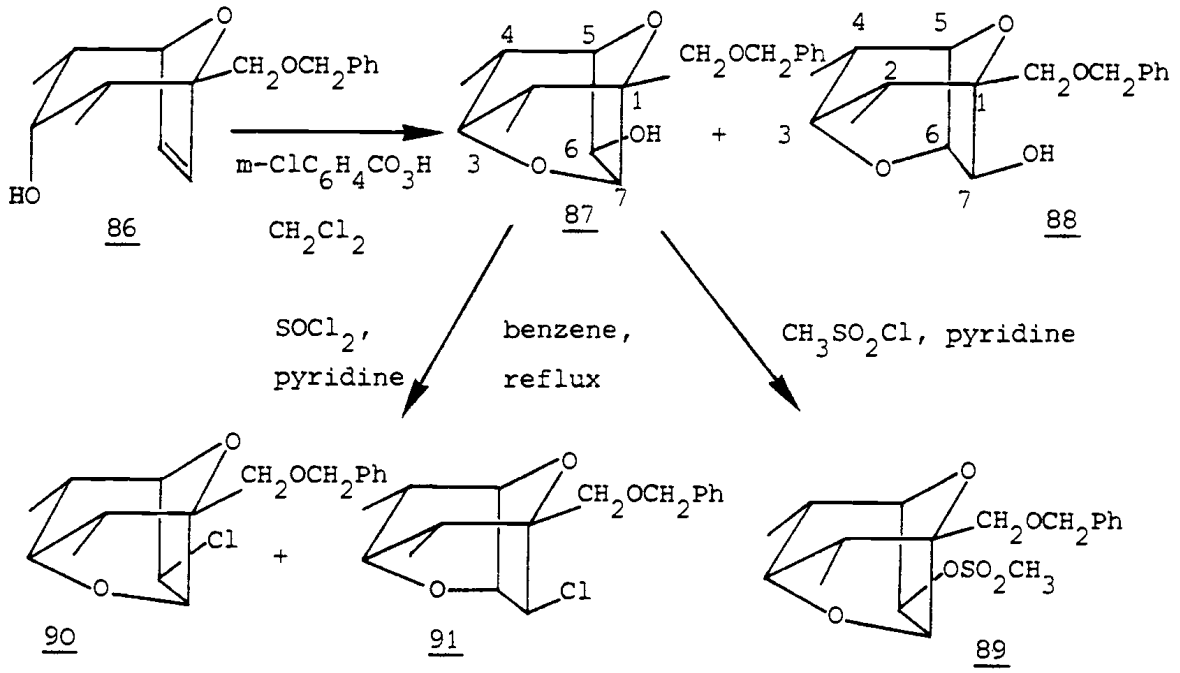


93

tion that the derived mesylate 89 and chlorides 90 and 91 are unreactive towards reagents which promote elimination, and is also in good agreement with nmr chemical shifts (see Table 3). Elimination of mesylate from 89 is prohibited by the fact that it would generate a highly strained, bridgehead double bond in this tricyclic system, while displacement from the hindered, endo side of this system is seriously obstructed. Structure 87 is assigned to the major product of epoxidation of 86, on the grounds that the C-5 proton in this isomer, appears as a sharp singlet at δ 4.5. A Dreiding model of 87 shows that the dihedral angle bet-

ween this proton and the endo C_6-H is close to 90° and hence no coupling would be expected. Negligible coupling between the bridgehead and axial C-4 protons is expected and observed for the same reason. In the minor isomer 88, the C-5 proton appears as a broadened singlet at δ 4.36, indicating that it is weakly coupled to the C-6 hydrogen. This requires that the proton at C-6 be in the exo configuration (dihedral angle < 90°), and therefore suggests that the ether bridge is connected to this center.



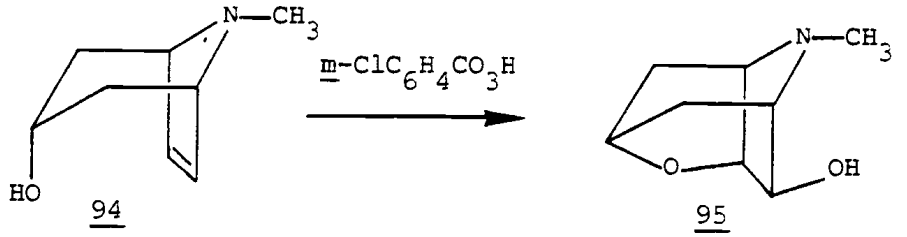
The formation of tricyclic ethers 87 and 88 is evidently the result of attack by peracid on 86 from the exo side of the double bond followed by an internally assisted opening of the epoxide by the endo, C-3 hydroxyl group. A

TABLE 3

NMR Data for Peracid Oxidation Products and their Mesylates derived from 86

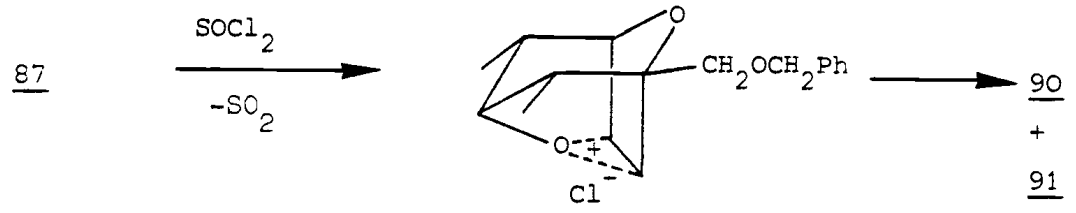
Compound	Chemical shifts (δ), Splitting pattern, and Coupling constant (J)				
	C_3-H	C_2-H, C_4-H	C_5-H	C_6-H	C_7-H
87	3.74 s	2.3 q 6Hz 2.02 q 6Hz	4.5 s	4.12 s	4.5 s
88	3.68 s	2.28 q 6Hz 2.04 q 6Hz	4.36 b s	4.16 s	4.12 s
89	3.8 b s	2.32 q 6Hz 2.18 q 6Hz	4.74 b s	5.00 s	4.56 s
98	4.98 t 3 Hz	2.48 m	4.1 d 5 Hz	3.68 d 2Hz	3.74 d 2Hz

close analogy to this process is found in the chemistry of the tropane alkaloids, where 94, on epoxidation with m-chloroperbenzoic acid, gave 95 as the exclusive product.[51]



94 95

The chloride 90 and 91 result from 87 presumably by participation of the oxygen at C-3. The resulting oxonium ion intermediate[52] 96 is attacked by chloride ion at C-6 or

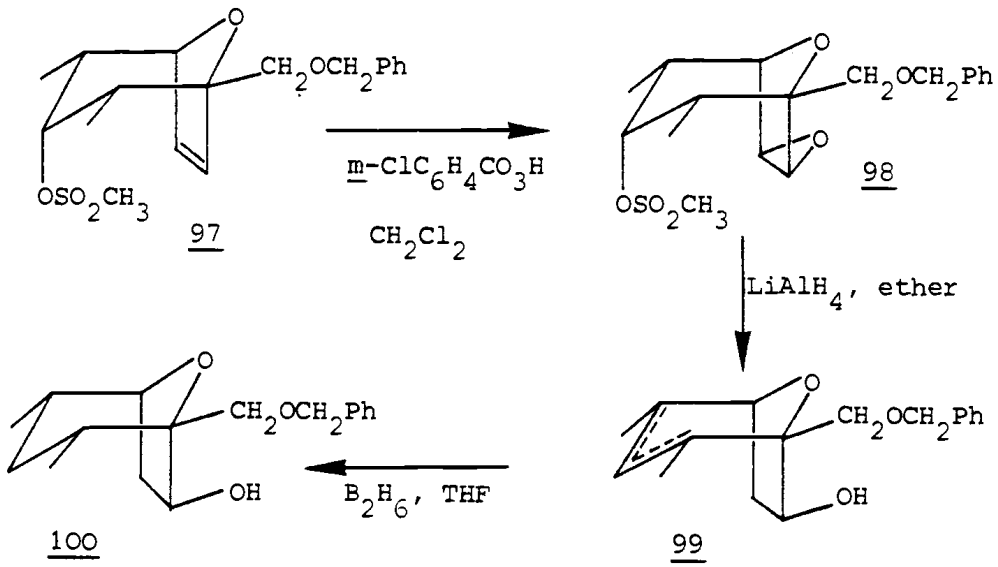


96

C-7 to give the products observed. As judged from the signals in the nmr spectrum, due to the phenyl residues in this mixture, the two chlorides are produced from 87 in a 1:1 ratio.

To overcome the problem of the participation by the hydroxy group in epoxidation of 86, the alcohol was converted to its mesylate 97 with methanesulfonyl chloride. Epoxidation of 97 with m-chloroperbenzoic acid gave 98, the

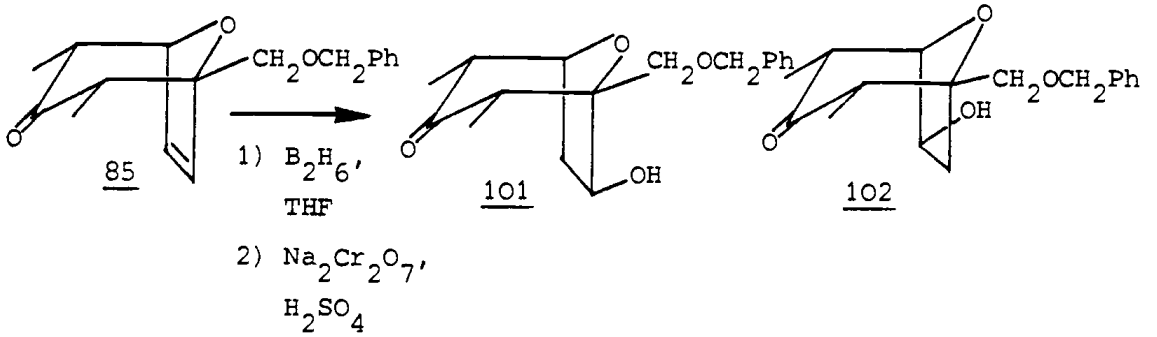
nmr spectrum of which is fully consistent with the structure assigned (see Table 3). The epoxide hydrogens at C-6 and C-7 now appear as doublets with a coupling constant of 2 Hz, at δ 3.68 and 3.74 respectively. The mesylate in this derivative, being endo, should be readily displaced or eliminated, and in fact, treatment of 98 with lithium aluminium hydride in ether gave in 70% yield a mixture of olefins with a parent peak in the mass spectrum at 274. The nmr spectrum of this mixture showed a multiplet at δ 5.06 and a three-proton signal at δ 1.74, corresponding to an olefinic hydrogen and methyl group attached to a double bond. The location of the alcohol group is difficult to assign based on data available. One would expect attack by hydride at C-6 rather than C-7 based on steric considerations and



hence the product is tentatively formulated as 99.

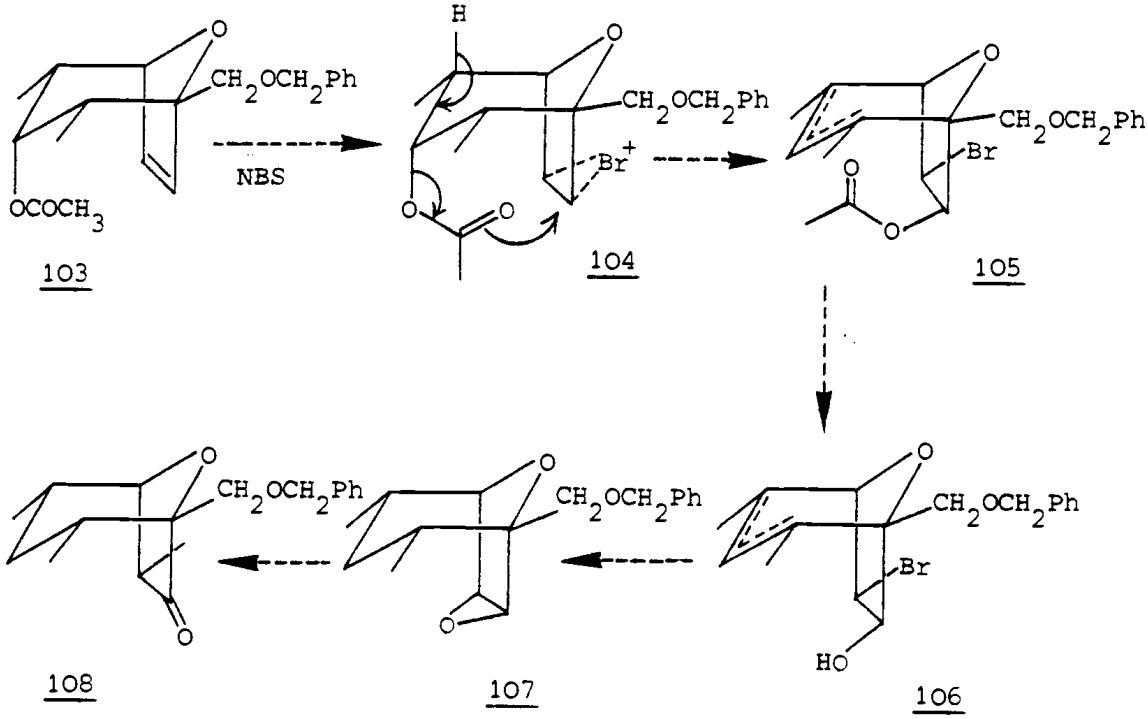
Attempted oxidation of the hydroxyl function in 99 with various oxidizing agents led to recovery of starting material. Hoping that saturation of the double bond would provide a suitable substrate, 99 was treated with diborane in tetrahydrofuran to give 100 in 55% yield. However, efforts at oxidation of 100 also failed. Wiberg[53] has shown that in the oxidation of cyclohexanols with chromic acid, the rate determining step is the abstraction of α-hydrogen from the intermediate chromate ester. In case of 99 and 100, the hydrogen at C-7 is endo and sterically hindered, so that its removal could conceivably be inhibited.

An attempt to directly introduce a keto group at C-7 by hydroboration and oxidation of 85 led to a mixture of keto alcohols 101, 102 in a 1:1 ratio. The C_5-H in 102 appears as a doublet of δ 4.48, and as a multiplet at δ 4.68 in 101, and assignment of the two structures is made primarily on this basis. Thus oxidation of borane derived from 85 is subject to the same constraints as oxidation



of 99.

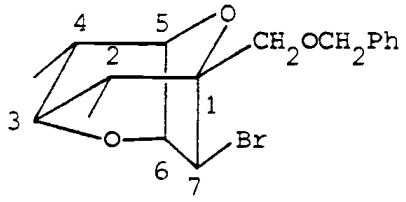
Since it proved impossible to oxidize the exo alcohol of 99 and 100, the isomeric 7-hydroxy versions of these systems were sought, since these would appear to be more readily oxidized to the ketone. In this scheme, an endo acetate 103 was to participate in bromination of the C-6,7 double bond and a trans diaxial elimination[54] would yield the bromo acetate 105. Elimination of the derived bromohy-



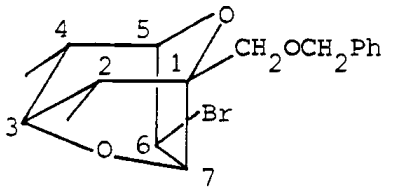
drin 106 would then afford endo epoxide 107 which hopefully could be transformed into 108.

In practice, the reaction of acetate 103 with N-bromosuccinimide in dimethyl sulfoxide containing water led to a 1:1 mixture of the tricyclic, bromo compounds 109 and 110.

The mass spectrum of this mixture showed a parent peak at



109

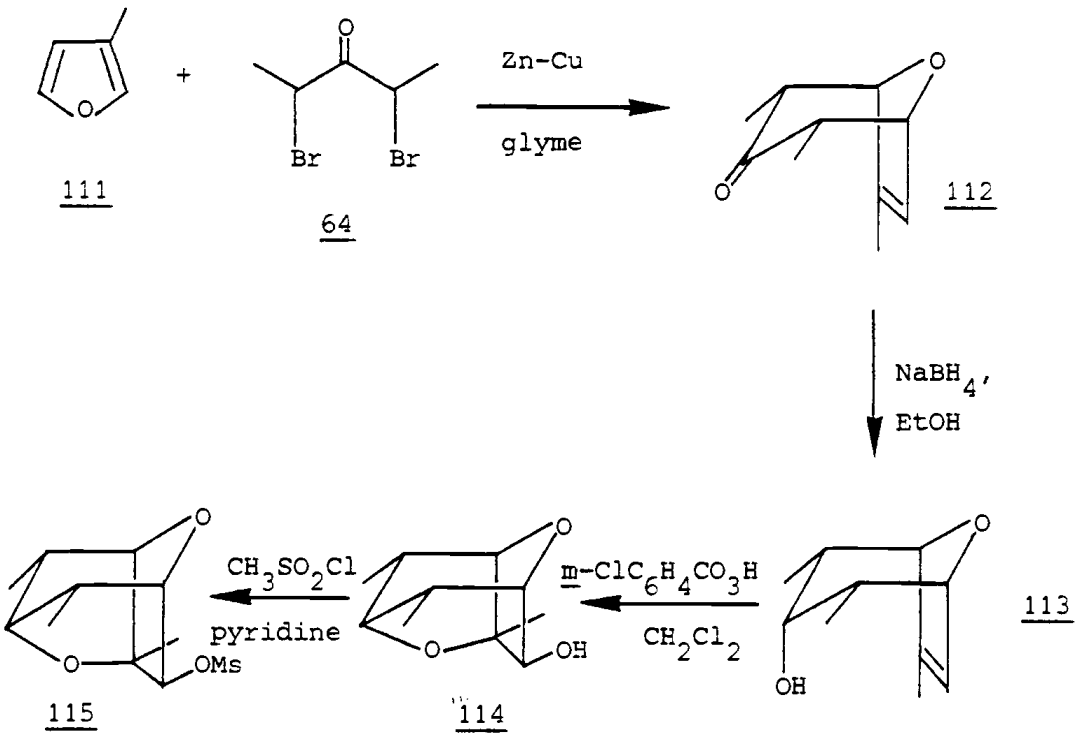


110

352 (M^+), and the nmr spectrum showed a broad singlet at δ 3.62 corresponding to the C_3-H hydrogen in 109 and 110. The formation of these two compounds suggested that hydrolysis of the acetate precedes bromination, and, on reaction of alcohol 86 under the same conditions, the products 109 and 110 were isolated in a ratio of 1:1. The reaction of 109 and 110 with lithium dimethyl cuprate gave 86 in quantitative yield, indicating that reductive elimination of the bromo ether with this reagent is preferred over replacement of the bromo substituent by a methyl group.

3. 3-Methylfuran

Failure to devise a means for introducing the C-6 methyl substituent (required for the C-2 methyl group of methynolide) into any of the bicyclic derivatives obtained thus far, suggested that this substituent should be incorporated at the outset. Attention was therefore directed to the cycloaddition of 2,4-dibromo-3-pentanone with 3-methyl-



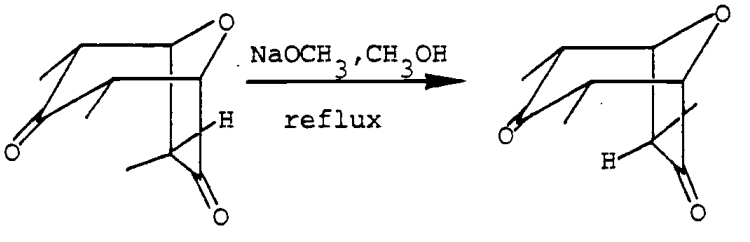
111 64 112 113 114 115

furan[55] (111), which would correctly place the three methyl groups at C-2, C-4 and C-6 as shown above.

The cycloaddition of 3-methylfuran with 2,4-dibromo-3-pentanone proceeded smoothly to give 112 in 65% yield and reduction of this ketone with sodium borohydride afforded endo alcohol 113 in 85% yield. In contrast to 86, attempts to form mesylate of 113 gave back starting material. The failure to form a mesylate is due probably to steric hindrance of the methyl group at C-6 in 113, and also interference by the π system of the trisubstituted double bond. As was observed in the epoxidation of 86, treatment of 113 with m-chloroperbenzoic acid gave the tricyclic ether 114. The structure 114 was confirmed by conversion to its mesy-

late 115, which as in the case of 89, was resistant towards reduction and elimination. The C-7 proton appears in this compound as a singlet at δ 5.00.

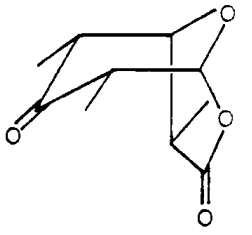
Hydroboration of 112, followed by oxidation with sodium dichromate and sulphuric acid, led to a diketone 116, in which the endo configuration of the C-6 methyl group resulted from addition of borane to the exo side of the double bond in 112. In the nmr spectrum of 116 the C-6 methyl appears as a doublet at δ 1.06 with a coupling constant of 6 Hz. Upon reflux with sodium methoxide in methanol, 116 was converted to the exo isomer 117 in 61% yield. The C-6 methyl in this isomer now appears at δ 1.30. The introduction of a keto group at C-7, together with a methyl group of correct stereochemistry at C-6, into the bicyclic precursor of segment B required for methynolide seemed promising since it should, in principle, be possible to treat the two ketones independently. Numerous attempts at Baeyer-Villiger reaction of 117, in the hope of producing



116 117

a δ-lactone 118 led in all cases to recovery of starting material. For reasons not entirely clear, both the carbonyl

groups of 117 are exceptionally resistant to peracid oxidation. With the fading prospect of effecting an oxidative



118

cleavage of the C-1,7 bond in this bicyclic system, this approach to segment B of methymycin was abandoned.

IV. CONCLUSION

Of the two segments 30 and 31 required for the synthesis of methymycin 1, 30 has been prepared in optically active form with the correct absolute stereochemistry. The approaches to 31 have shown that it is possible to reduce the C-3 ketone in 8-oxabicyclo[3.2.1]octane adducts to a methylene group, as in 100. It is also possible to introduce the three methyl substituents at C-2, C-4 and C-6 of methymycin with the correct relative stereochemistry, as in 117. The work carried out so far has resulted in an improved understanding of the chemistry of the 8-oxabicyclo(3,2,1)octane system which, it is hoped, will lay the foundation for a synthesis that can ultimately be extended to methymycin.

EXPERIMENTAL

General

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137 or 727B infrared spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates Model EM-360A or HA-100 spectrometer, with tetramethylsilane as internal standard. Mass spectra and exact mass determinations were measured using a CEC-103B spectrometer at an ionizing potential of 70 ev by Dr. Wielesek at the Department of Chemistry, University of Oregon, Eugene, Oregon. The abbreviations, s, d, t, q, m refer to singlet, doublet, triplet, quartet, multiplet, respectively. Dry tetrahydrofuran (THF) was obtained under nitrogen by distillation over lithium aluminium hydride. Hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO) were dried by distillation from calcium hydride at reduced pressure. Other solvents were purified using standard procedures.

E-2-Methyl-2-pentenal (34)

To 100 ml of propionaldehyde was added 25 ml of 10%

aqueous potassium hydroxide at 0°C with stirring. After 10 minutes, the solution was neutralized with 10% sulphuric acid and the mixture was steam-distilled. The distillate was extracted with ether, and the ether layer was dried over $MgSO_4$ and distilled. The fraction boiling at 130-131°C (lit[23] bp 131-132°C) was collected to give 35 g (50%) of 34: ir (film) 2685, 1695, 1605 cm^{-1}; nmr ($CDCl_3$) δ 9.48 (s, 1H), 6.5 (m, 1H), 2.4 (m, 2H), 1.76 (s, 3H) and 1.12 (t, 3H, J = 8Hz).

E-2-Methyl-2-pentenoic Acid (35)

To a solution of 34 (9.0 g, 0.09 mol) in 150 ml of water was added silver nitrate (51.0 g, 0.33 mol) in 100 ml of water and the mixture was heated to 40°C. To this was added sodium hydroxide (19.0 g, 0.48 mol) in 180 ml of water over a 3 hour period and the mixture was allowed to stand overnight. The solution was acidified to pH 1 and extracted with ether. The ethereal layer was extracted with 10% aqueous sodium hydroxide and the aqueous layer was then acidified to pH 1 and extracted with ether. The ether layer was dried over $MgSO_4$ and solvent was removed *in vacuo*. Distillation of the residue gave 9.0 g (85%) of 35: bp 112-114°C/15 mm (lit[22] bp 111-114°C/15 mm); ir (film) 3600-2500, 1690 cm^{-1}; nmr (d_6-acetone) δ 10.00 (s, 1H, exchanged with D_2O), 6.7 (m, 1H), 2.2 (m, 2H), 1.8 (s,

3H) and 1.00 (t, 3H, J = 8Hz).

erythro-2,3-Dihydroxy-2-methylvaleric Acid (36)

To a solution of 35 (8.1 g, 80 mmol) was added 40 ml of glacial acetic acid, 5 drops of concentrated sulphuric acid, and 7 ml of 70% hydrogen peroxide. The mixture was heated at 50°C for 6 hours. The excess hydrogen peroxide was reduced by a stream of sulphur dioxide and the acetic acid was removed in vacuo. The residue was heated with a solution of 10 g of sodium hydroxide in 50 ml of water. The alkine mixture was extracted with ether and the aqueous layer was then acidified with 10% hydrochloric acid and subjected to continuous extraction with ether for 8 hours. The ether extract was dried over $MgSO_4$ and solvent was removed in vacuo. The residue crystallized from ethyl acetate to yield 4.3 g (50%) of 36: mp 151-152°C; (lit[22] mp 152-153°C).

(+)-erythro-2-Methyl-2,3-isopropylidenedioxypentanoic Acid (37)

To a solution of (+)-36 (275 mg, 2.0 mmol in 75 ml of benzene and 25 ml of acetone was added 10 mg of p-toluene-sulphonic acid and the mixture was refluxed for 8 hours.

The benzene layer was washed with water and dried over $MgSO_4$. Benzene was removed *in vacuo* to yield 310 mg (100%) of 37: $(\alpha)_D^{25}+17^o$ (acetone); ir (film) 3600-2400, 1710, 1420, 850 cm^{-1}; nmr (d_6-acetone) δ 7.8 (broad, 1H exchanged with D_2O), 3.7 (d of d, 1H, J = 3,6Hz), 1.6-1.4 (m, 2H), 1.5 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 0.9 (t, 3H, J = 8Hz).

(+)-erythro-2-Methyl-2,3-isopropylidenedioxypentanol (38)

To a solution of (+)-37 (275 mg, 1.5 mmol) in 25 ml of ether was added lithium aluminium hydride (50 mg, 1.5 mmol) at 0^oC, and the mixture was refluxed for 6 hours. The excess hydride was destroyed by addition of ethyl acetate at 0^oC and the mixture was extracted with ether. The solution was dried over $MgSO_4$. Evaporation of solvent *in vacuo* furnished 240 mg (90%) of 38 as a light yellow liquid: $(\alpha)_D^{25}+36^o$ ($CHCl_3$); ir (film) 3600-3400, 2950, 1420, 1380, 1100 cm^{-1}; nmr ($CDCl_3$) δ 3.72 (t, 1H, J = 6Hz), 3.48 (AB q, 2H, J = 10Hz), 2.2 (m, 1H, exchanged with D_2O), 1.32 (s, 3H), 1.28 (s, 3H), 1.6-1.3 (m, 2H), 1.2 (s, 3H), 1.00 (t, 3H, J = 8Hz); mass spectrum m/e 159.101 (M^+-15), calcd for $C_8H_{15}O_3$ 159.102.

(+)-erythro-2-Methyl-2,3-isopropylidenedioxypentanal (39)

Anhydrous chromium trioxide (1.6 g, 16 mmol) was added to a stirred mixture of pyridine (2.5 g, 30 mmol) and 10 ml of methylene chloride. After 15 minutes, a solution of (+)-38 (170 mg, 1 mmol) in 10 ml of methylene chloride was added and the mixture was stirred at room temperature for 15 minutes. The liquid was decanted and the residual solids extracted with ether. The combined organic phase was washed with 4% sodium hydroxide solution, saturated sodium bicarbonate solution, and finally water. The organic layer was dried over $MgSO_4$. Evaporation of solvent in vacuo furnished 130 mg' (75%) of 39: $(\alpha)_D^{25}$+51.0°($CHCl_3$); ir (film) 2700, 1725, 1350, 815 cm^{-1}; nmr ($CDCl_3$) δ 9.65 (s, 1H), 3.82 (t, 1H, J = 6Hz), 1.8-1.6 (m, 2H), 1.56 (s, 3H), 1.46 (s, 3H), 1.46 (s, 3H), 1.3 (s, 3H), 1.02 (t, 3H, J = 8Hz); mass spectrum m/e 157.088 (M^+-15), calcd for $C_8H_{13}O_3$ 157.086.

(-)-erythro-3-Acetoxy-2-hydroxy-2-methylvaleric Acid (40)

To (+)-36 (275 mg, 2 mmol) was added 5 ml of pyridine and 5 ml of acetic anhydride and the mixture was allowed to stand overnight at room temperature. The solution was extracted with ether, and the ether layer was washed with dilute hydrochloric acid and water. Evaporation of solvent in vacuo gave 350 mg (95%) of 40: $(\alpha)_D^{25}$-31.6° ($CHCl_3$); ir

(film) 3600-2400, 1740, 1700, 1240 cm^{-1}; nmr ($CDCl_3$) δ 8.00 (2H, exchanged with D_2O), 5.3 (m, 1H), 2.12 (s, 3H), 2.1 (m, 2H), 1.56 (s, 3H), 1.00 (t, 3H, J = 8Hz); mass spectrum m/e 145.088 (M^+-45), calcd for $C_7H_{13}O_3$ 145.086.

Methyl (-)-erythro-2,3-Dihydroxy-2-methylvalerate (49)

To (-)-36 (275 mg, 2.0 mmol in 10 ml of tetrahydrofuran was added an etheral solution of diazomethane until a persistent yellow color was observed. The solvent was removed *in vacuo* to give 330 mg (98%) of 49a as a syrup: $(\alpha)_D^{25}$-25.6° ($CHCl_3$), (lit[22] $(\alpha)_D^{25}$-26.8°); ir (film) 3600-3300, 1745 cm^{-1}.

Resolution of erythro-2,3-Dihydroxy-2-methylvaleric Acid (36)

To 3.2 g of brucine tetrahydrate in 25 ml of 95% ethanol was added 36 (1.0 g, 6.7 mmol) and the mixture was stirred at room temperature for 0.5 hour. The solvent was removed *in vacuo* and the residual solid was crystallized twice from acetone to give 1.8 g of a salt with mp 166-168°C, $(\alpha)_D^{25}$+41.6° (water). This material was treated with 10% hydrochloric acid and continuously extracted with ether for 8 hours. The ether extract was dried over $MgSO_4$. Evaporation of solvent *in vacuo* and crystallization of the

solid from ethyl acetate gave 400 mg (80% based on racemate) of (-)-36: mp 151-152°C, $(\alpha)_D^{25}$-13.6° (water), (lit[22] $(\alpha)_D^{25}$-13.8° (water)). Acidification and extraction of the mother liquor from this resolution gave 380 mg (75%) of (+)-36: mp 151-152°C; $(\alpha)_D^{25}$+13.5° (water).

Determination of the Absolute Configuration of (+)- and (-)-erythro-2,3-Dihydroxy-2-methylvaleric Acids (36)

(±)-2-Phenylbutyric acid 45 (328 mg, 2.0 mmol) was added to a suspension of 1,1-carbonyldiimidazole (47, 324 mg, 2.0 mmol) in 5 ml of anhydrous benzene until the evolution of carbon dioxide ceased. To this was added (-)-49 (163 g, 1.0 mmol), $(\alpha)_D^{25}$-25.6° ($CHCl_3$), in 5 ml of benzene and the mixture was allowed to stand at room temperature for 22 hours. The mixture was shaken with 20 ml of 10% sodium hydroxide, and the aqueous layer was acidified with 10% hydrochloric acid and extracted with benzene. The benzene extract was washed with water and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 150 mg of 45 which had $(\alpha)_D^{25}$-0.46° (benzene). The (+)-ester 49 by a similar procedure, gave 45 which had $(\alpha)_D^{25}$+0.54° (benzene).

endo-Tricyclo(5.2.1.$O^{2,6}$)deca-3,8-dien-5-one (53)

Freshly distilled dicyclopentadiene 50 (90 g, 0.7 mol) was dissolved in a mixture of 250 ml of dioxane and 50 ml of water. Selenium dioxide (33 g, 0.3 mol) was added and the mixture was refluxed for 3 hours. The resulting dark brown mixture was filtered from selenium, poured into 300 ml of water, and extracted with 500 ml of ether in three portions. The organic solutions were combined, washed with water, and dried over $MgSO_4$. Removal of solvent *in vacuo* gave a dark red oil weighing 70 g. This was dissolved in 300 ml of acetone, and 200 ml of Jones' reagent was added at 0°C over a period of 1 hour. The acetone was removed *in vacuo* and the residue was washed with water and extracted into ether. The ether layer was dried over $MgSO_4$. Evaporation of the solvent *in vacuo*, followed by distillation, gave 45 g (50%) of 53: bp 79°C/2 mm (lit[27] bp 81°C/2 mm). The distillate crystallized on standing overnight to give 66 as pale yellow crystals: mp 58-59°C (lit[26] mp 58-59°C); ir (Nujol) 1700, 1340, 840, 780 cm^{-1}; nmr ($CDCl_3$) δ 7.28 (d of d, 1H, J = 2,6Hz), 5.92 (m, 2H) 5.76 (d of d, 1H, J = 3,6Hz), 3.36 (m, 1H), 3.2 (m, 1H), 2.94 (m, 1H), 2.68 (t, 1H, J = 6Hz), 1.76 (m, 1H), 1.58 (m, 1H).

endo-5-Methyltricyclo(5.2.1.$O^{2,6}$)dec-8-en-3-one (54)

To a suspension of 2.5 g (0.1 g atom) of magnesium in 30 ml of anhydrous ether was added under nitrogen a solution of methyl iodide (14 g, 0.1 mol) in 30 ml of anhydrous ether over a period of 1 hour until most of the magnesium had dissolved. The mixture was cooled to -10°C and 100 mg of cuprous chloride was added. The mixture was stirred at -10°C for 10 minutes. A solution of 53 (14.0 g, 0.1 mol) in 50 ml of ether was added over a period of 30 minutes and the solution was allowed to rise to room temperature. The reaction mixture was poured into ice and extracted with ether. The extract was washed with dilute hydrocholoric acid and sodium bicarbonate solution. The ether layer was dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by distillation, gave 12.2 g (80%) of 54: bp 80°C/3 mm (lit[28] bp 81°C/4 mm); ir (film) 1735, 760 cm^{-1}.

endo-3,3-Ethylenedioxy-5-methyltricyclo(5.2.1.$O^{2,6}$)dec-8-ene (55)

Ketone 54 (6.0 g, 30 mmol) was stirred with excess ethylene glycol (10 ml), 100 mg of p-toluenesulphonic acid and trimethyl orthoformate (3 g, 30 mmol) at room temperature overnight. The solution was washed with water and sat-

urated sodium bicarbonate, and the organic layer was dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 7.7 g (98%) of 55: ir (film) 1320, 1100, 740 cm^{-1}; nmr ($CDCl_3$) δ 6.1 (d of d, 1H, J = 2,8Hz), 3.8 (broad, 4H), 2.8 (broad, 2H), 2.62 (t, 1H, J = 4Hz), 2.3 (m, 1H), 2.1-1.5 (m, 3H), 1.36 (broad, 1H), 1.28 (broad, 1H), 0.98 (d, 3H, J = 6Hz); mass spectrum, m/e 206 (M^+).

cis,anti,cis,syn-8,8-Ethylenedioxy-6-methylbicyclo-(3.3.0)octan-2,4-dicarboxylic Acid (56)

To 1 g of potassium carbonate in 10 ml of water was added 40 ml of 30% pyridine in water and 100 ml of 2% potassium permanganate. The mixture was stirred at room temperature for 5 minutes and then sodium metaperiodate (3 g, 15 mmol) was added, followed by 55 (1.3 g, 6.5 mmol) in 10 ml of dioxane. The mixture was stirred at room temperature for 3 hours, then cooled to 0°C and solid sodium bisulphite added to decolorize the solution. The mixture was acidified to pH 4 with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 1.8 g of a solid, which was recrystallized from acetone to give 1.5 g (98%) of 56 as light yellow crystals: mp 157-158°C; ir (Nujol) 3600-2500, 1690, 1260, 1180 cm^{-1}; nmr (DMSO-d_6)

δ 3.62 (broad, 4H), 2.92 (t, 1H, J = 7Hz), 2.5-2.1 (m, 5H), 1.7 (m, 3H), 1.3-1.1 (m, 2H), 0.86 (d, 3H, J = 6Hz); mass spectrum m/e 270.108 (M^+), calcd for $C_{13}H_{18}O_6$ 270.110.

Dimethyl cis,anti,cis,syn-8,8-Ethylenedioxy-6-methylbicyclo(3.3.0)octan-2,4-dicarboxylate (57)

To a solution of 56 (800 mg, 3 mmol) in 10 ml of tetrahydrofuran was added freshly prepared diazomethane in ether until a permanent yellow color remained. The solvent was removed in vacuo to give 850 mg (95%) of 57 as a light yellow liquid: ir (film) 2950, 1740, 1480, 1180, 700 cm^{-1}.

cis,anti,cis,syn-8,8-Ethylenedioxy-2,4-dihydroxymethyl-6-methylbicyclo(3.3.0)octane (58)

To a solution of 57 (850 mg, 2.8 mmol) in 25 ml of anhydrous ether was added lithium aluminium hydride (1.35 mg, 4.0 mmol) at 0°C and the mixture was allowed to stir at that temperature for 3 hours. The excess hydride was carefully destroyed with ethyl acetate, and the mixture was washed with water and dried ($MgSO_4$). Evaporation of the ether gave 590 mg (80%) of 58 as colorless needles: mp 121-122°C; ir (Nujol) 3400-3200, 1080, 1020, 980 cm^{-1}; nmr ($CDCl_3$) δ 4.0-3.6 (m, 4H), 2.96 (t, 1H, J = 7Hz), 2.26 (m,

3H), 2.0-1.5 (m, 4H), 1.25 (m, 2H), 1.08 (d, 3H, J = 6Hz); mass spectrum m/e 242.142 (M^+), calcd for $C_{13}H_{22}O_4$ 242.152.

cis,anti,cis,syn-8,8-Ethylenedioxy-6-methylbicyclo-(3.3.0)octan-2,4-dicarboxaldehyde (63)

To a solution of 55 (1.8 g, 9.0 mmol) in 25 ml of dioxane and 25 ml of water was added 27 ml of a 1% aqueous osmium tetroxide solution. Sodium metaperiodate (7.0 g, 25 mmol) was added in portions over 30 minutes and the mixture was stirred for 4 hours. The mixture was extracted with ether, washed with water, and dried over $MgSO_4$. Evaporation of solvent in vacuo, followed by column chromatography on 30 g of silica gel (Activity II), with 1% methanol in chloroform as eluent, gave 1.35 g (70%) of 63 as a light yellow liquid: ir (film) 2725, 1720, 1120, 860 cm^{-1}; nmr ($CDCl_3$) δ 10.5 (s, 1H), 10.4 (s, 1H), 3.9 (broad, 4H), 3.48 (t, 1H, J = 8Hz), 2.8-2.5 (m, 3H), 2.32 (d, 1H, J = 12Hz), 2.2-1.8 (m, 3H), 1.4 (d, 1H, J = 12Hz), 1.02 (d, 3H, J = 6Hz); mass spectrum m/e 238.119 (M^+), calcd for $C_{13}H_{18}O_4$ 238.114.

cis,anti,cis,syn-6,8-Dihydroxymethyl-4-methyl-bicyclo(3.3.0)octan-2-one (60)

A solution of 59 (500 mg, 2.1 mmol) in 20 ml of benzene was refluxed with 2 g of silica gel (Activity II) and 2 ml of Water for 3 hours. The mixture was filtered and the filtrate was washed with water and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 320 mg (80%) of 60: ir (film) 3600-3400, 2950, 1745, 760 cm^{-1}; nmr ($CDCl_3$) δ 3.76 (m, 4H), 2.98 (t, 1H, J = 7Hz), 2.7 (m, 2H), 2.3-1.9 (m, 4H), 1.62 (d, 1H, J = 10Hz), 1.26 (m, 1H), 1.02 (d, 3H, J = 6Hz); mass spectrum m/e 198 (M^+).

endo-5-Ethoxy-5,12-dimethyl-4,6-dioxatricyclo-(9.3.$1^{2,8}O^{1,9}$)tridecan-10-one (61)

To 60 (200 mg, 1.0 mmol) in 10 ml of ethyl acetate was added 100 mg of $MgSO_4$ and the mixture was stirred at room temperature overnight. The mixture was then filtered. Evaporation of solvent *in vacuo* gave 220 mg (80%) of 61. A clean sample of 61 was obtained by preparative t.l.c., using 5% ethyl acetate in chloroform as eluent: ir (film) 1740, 1460, 1360, 1240, 1000 cm^{-1}; nmr ($CDCl_3$) δ 4.2-3.5 (m, 6H), 3.00 (t, 1H, J = 7Hz), 2.68 (m, 1H), 2.4-2.1 (m, 4H), 2.06 (s, 3H), 2.0-1.8 (m, 2H), 1.48 (t, 1H, J = 10Hz),

1.22 (t, 3H, J = 6Hz), 1.00 (d, 3H, J = 6Hz); mass spectrum m/e 268.169 (M^+), calcd for $C_{15}H_{24}O_4$ 268.167.

cis,endo-2,4-Dimethyl-8-oxabicyclo(3.2.1)oct-6-en-3-one (65)

To furan (20 ml) and 5.0 g of zinc-copper couple in 15 ml of glyme was added 2,4-dibromo-3-pentanone (5.0 g, 20 mmol) in 10 ml of glyme at 0°C under nitrogen over a period of 15 minutes. The mixture was allowed to rise to room temperature, when an exothermic reaction took place. After one hour the reaction mixture was poured into ether and washed with sodium bicarbonate. The ether layer was dried over $MgSO_4$ and the solvent evaporated in vacuo to give 4.0 g of crude 65. This was purified by column chromatography on silica gel (Activity II). Elution with chloroform gave 2.4 g (80%) of adducts 65, 66, and 67 in a ratio 8:1:1 respectively: ir (film) 2950, 1720 cm^{-1}; nmr ($CDCl_3$) of 65 δ 6.38 (s, 2H), 4.72 (d, 2H, J = 5Hz), 2.84 (d of q, 2H, J = 5 and 6Hz), 0.98 (doublet, 6H, J = 6Hz).

cis,endo-2,4-Dimethyl-8-oxabicyclo(3.2.1)oct-6-en-3-ol (76)

To 65 (150 mg, 1.0 mmol) in 10 ml of dry tetrahydro-

furan, cooled to 0.°C under nitrogen, was added diisobutylaluminium hydride solution (2 ml, 2 mmol). The mixture was allowed to stir at 0°C for a half hour and at room temperature for one hour, and then poured into ice and extracted with ether. The ether extract was washed with dilute hydrochloric acid and dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by column chromatography on silica gel (Activity II) and elution with 10% ether in chloroform gave 120 mg (80%) of 76: ir (film) 3500-3300 (broad), 1520, 1060, 760 cm^{-1}; nmr ($CDCl_3$) δ 6.54 (s, 2H), 4.52 (d, 2H, J = 4Hz), 3.72 (t, 1H, J = 4Hz), 3.7 (m, 1H, exchanged with D_2O), 2.3 (m, 2H), 1.00 (d, 6H, J = 6Hz); mass spectrum m/e 154.099 (M^+), calcd for $C_9H_{14}O_2$ 154.099.

Reduction of 65 with Sodium Borohydride

To 65 (1.0 g, 6.5 mmol) in 25 ml of ethanol was added sodium borohydride (68 mg, 2.0 mmol). The mixture was stirred at room temperature overnight and extracted into ether. The extract was washed with 1% hydrochloric acid and the ether layer was dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 1.0 g of a mixture of 76 and 77 in a 2:1 ratio respectively.

trans,trans-2,4-Dimethyl-3-methanesulfonyloxy-8-oxabicyclo(3.2.1)oct-6-ene (78)

To a mixture of 76 and 77 (250 mg, 1.6 mmol) in 15 ml of methylene chloride was added 0.5 ml of triethylamine and 0.5 ml of methanesulfonyl chloride at 0°C. The mixture was stirred at that temperature for a half hour and extracted with ether. The extract was washed with 1% hydrochloric acid, saturated sodium bicarbonate, and water. After drying the ether layer, solvent was removed in vacuo and the residue was chromatographed on silica gel (Activity II). Elution with chloroform gave 90 mg (30%) of 78: ir (film) 2950, 2900, 1420, 1170, 1040 cm^{-1}; nmr ($CDCl_3$) δ 6.3 (s, 2H), 4.64 (d, 2H, J = 4Hz), 4.2 (t, 1H, J = 9Hz), 3.08 (s, 3H), 2.1 (m, 2H), 1.02 (d, 6H, J = 6Hz); mass spectrum m/e 232.077 (M^+), calcd for $C_{10}H_{16}O_4S$ 232.077.

trans,trans,trans-2,4-Dimethyl-6,7-epoxy-3-methanesulfonyloxy-8-oxabicyclo(3.2.1)octane (79)

To 78 (80 mg, 0.3 mmol) in 10 ml of methylene chloride was added 100 mg of m-chloroperbenzoic acid and the mixture was allowed to stir at room temperature for 12 hours. The precipitated m-chlorobenzoic acid was filtered and the filtrate was extracted with ether. The extract was washed with

saturated sodium bicarbonate and dried over $MgSO_4$. Evaporation of solvent *in vacuo* and crystallization of the residue from ehter gave 40 mg (70%) of 79: mp 128-129°C; ir (Nujol) 2920, 1320, 1170, 1040, 930 cm^{-1}; nmr ($CDCl_3$) δ 4.5 (t, 1H, J = 9Hz), 4.24 (d, 2H, J = 4Hz), 3.6 (s, 2H), 3.06 (s, 3H), 2.14 (m, 2H), 1.12 (6H, J = 7Hz); mass spectrum m/e 248 (M^+).

trans,trans-2,4-Dimethyl-3,5-methyldithiocarbonato-8-oxabicyclo(3.2.1)oct-6-ene (81)

To sodium hydride (500 mg, 6.0 mmol) in 5 ml of tetrahydrofuran was added a mixture of 76 and 77 (300 mg, 2.0 mmol) in 5 ml of tetrahydrofuran. The mixture was stirred at room temperature until the evolution of hydrogen ceased. Carbon disulphide (10 ml) was added and the mixture was refluxed for 15 minutes. Methyl iodide (1 ml) was then added and the mixture was refluxed for a further 15 minutes. Acetic acid was added and the mixture was extracted with ether. The extract was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* followed by column chromatography of the residue on Florisil (eluting with chloroform), gave 110 mg (30%) of 80 as a light yellow oil: nmr ($CDCl_3$) δ 6.42 (s, 2H), 4.58 (t, 1H, J = 9Hz), 4.5 (d, 2H, J = 4Hz), 2.52 (s,

3H), 2.5-2.2 (m, 2H), 0.82 (6H, J = 6Hz); mass spectrum m/e 244 (M^+).

cis-2,4-Dimethyl-8-oxabicyclo(3.2.1)octa-3,7-dione (82)

To 65 (160 mg, 1.1 mmol) in 5 ml of tetrahydrofuran was added diborane (2 ml, 2 mmol) solution in tetrahydrofuran at 0°C under nitrogen. The mixture was stirred at room temperature for one hour. Water was added to destroy the residual hydride and a solution of sodium dichromate (1.9 g) in conc sulphuric acid (1 ml) and 5 ml of water was added. The solution was refluxed until two layer separated, and was extracted with ether. The extract was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of solvent followed by preparative thin layer chromatography on silica gel, using chloroform as solvent, yielded 80 mg (53%) of 82: ir (film) 2920, 1750, 1710, 1170 cm^{-1}; nmr ($CDCl_3$) δ 4.86 (d of d, 1H, J = 1,5Hz), 4.22 (d of d, 1H, J = 2,5Hz), 2.9 (m, 1H), 2.5-2.3 (m, 2H), 1.06 (d, 3H, J = 7Hz), 1.00 (d, 3H, J = 7Hz); mass spectrum m/e 168.078 (M^+), calcd for $C_9H_{12}O_3$ 168.079.

Furfuryl Benzyl Ether (84)

Furfuryl alcohol (22.0 g, 0.25 mmol) was dissolved in 60 ml of dry glyme and added at 0°C to a stirred suspension

(12.0 g, 0.5 mmol) of sodium hydride (50% suspension in mineral oil) in 40 ml of glyme. Stirring was continued until the evolution of hydrogen ceased. After 30 minutes, benzyl bromide (40.0 g, 0.25 mmol) in 25 ml of glyme was added and the reaction mixture was stirred overnight. The mixture was cooled at 0°C and water was carefully added. The mixture was extracted with ether and the extract was washed with water and dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by distillation of the residue, gave 38.0 g (96%) of **84**: bp 80°/0.1 mm: ir (film) 2950, 1520, 1460, 1360, 1140, 1080, 740 cm^{-1}; nmr ($CDCl_3$) δ 7.39 (s, 6H), 6.32 (m, 1H), 6.30 (m, 1H), 4.52 (s, 1H), 4.46 (s, 1H).

cis-1-Benzyloxymethyl-2,4-dimethyl-8-oxabicyclo(3.2.1)oct-6-en-3-one (85)

To a solution of **84** (15.0 g, 90 mmol) in 25 ml of glyme was added zinc-copper couple (5 g). The mixture was cooled to 0°C and 2,4-dibromo-3-pentanone (5.0 g, 20 mmol) was added under nitrogen over a period of 10 minutes. The mixture was allowed to warm to room temperature and, after 3 hours, was extracted with ether. The extract was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by di-

stillation to remove excess 84, left 3.3 g of a residue. Column chromatography of this material on silica gel (Activity II) and elution with chloroform gave 2.2 g (62%) of 85: ir (film) 3000, 2940, 2900, 1710, 1090 cm^{-1}; nmr ($CDCl_3$) δ 7.34 (s, 5H), 6.32 (q, 1H, J = 6Hz), 6.06 (d, 1H, J = 6Hz), 4.9 (q, 1H, J = 5,2Hz), 4.64 (d, 2H, J = 12Hz), 3.7 (d of d, 2H, J = 10Hz), 2.96 (q, 1H, J = 7Hz), 2.76 (d of q, 1H, J = 5,7Hz), 0.94 (d, 3H, J = 7Hz), 0.92 (d, 3H, J = 7Hz); mass spectrum m/e 272.140 (M^+), calcd for $C_{17}H_{20}O_3$ 272.141.

cis,cis-1-Benzyloxymethyl-2,4-dimethyl-8-oxabicyclo-(3.2.1)oct-6-en-3-ol (86)

To a solution of 85 (2.2 g, 8.0 mmol) in 30 ml of benzene and 30 ml of methanol was added sodium borohydride (450 mg, 13.0 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was acidified with 1% hydrochloric acid and extracted with ether. The extract was dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 2.1 g (93%) of 86: ir (film) 3600-3400, 2950, 1490, 1190 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H), 6.49 (q, 1H, J = 2,6Hz), 6.2 (d, 1H, J = 6Hz), 4.62 (d, 2H, J = 12Hz), 4.6 (m, 1H), 3.6 (d, 2H, J = 10Hz), 3.68 (m, 1H), 1.7 (m, 1H, exchanged with D_2O), 0.98 (d, 3H, J = 8Hz) and 0.92 (d, 3H, J = 7Hz).

Epoxidation of (86)

To 86 (2.0 g, 7.0 mmol) in 15 ml of methylene chloride was added m-chloroperbenzoic acid (25.0 g, 12 mmol) and the mixture was stirred at room temperature for 12 hours. The mixture was extracted with ether and the extract was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of solvent *in vacuo* and column chromatography of the residue on silica gel (Activity II) gave after elution with benzene-ether (7:3), 1,1 g (55%) of 87: ir (film), 3600-3400, 2950, 1490, 1360, 1195, 980, 880 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H), 4.60 and 4.50 (AB q, 2H, J = 12Hz), 4.50 (s, 2H), 4.12 (broad, 1H), 3.74 (s, 3H), 2.7 (broad, 1H, exchanged with D_2O), 2.30 (q, 1H, J = 6Hz), 2.02 (q, 1H, J = 6Hz), 0.95 (d, 3H, J = 7Hz), 0.82 (d, 3H, J = 7Hz); mass spectrum m/e 290.152 (M^+), calcd for $C_{17}H_{22}O_4$ 290.152. Further elution gave 210 mg (15%) of 88: ir (film) 3600-3400, 2950, 1490, 1370, 1180, 980 cm^{-1}; nmr ($CDCl_3$) δ 7.34 (s, 5H), 4.64 (s, 2H), 4.36 (broad, 1H), 4.16 (s, 1H), 4.12 (s, 1H), 3.84 and 3.68 (AB q, 2H, J = 10Hz), 3.68 (s, 1H), 3.00 (m, 1H, exchanged with D_2O), 2.28 (q, 1H, J = 6Hz), 2.04 (q, 1H, J = 6Hz), 1.00 (d, 3H, J = 7Hz), 0.86 (d, 3H, J = 6Hz); mass spectrum m/e 290.152 (M^+), calcd for $C_{17}H_{22}O_4$ 290.152.

cis,trans-1-Benzyloxymethyl-2,4-dimethyl-6-methanesulfonyloxy-8,9-dioxatricyclo-(3.2.1.$1^{3,7}$)nonane (89)

To a solution of 87 (1.0 g, 3.0 mmol) in pyridine (2 ml) cooled to 0°C was added methanesulfonyl chloride (2 ml) and the mixture was left at room temperature overnight. The solution was extracted into ether, an the extract was washed with 7% hydrochloric acid and saturated sodium bicarbonate and dried over $MgSO_4$. Evaporation of solvent in vacuo gave 1.2 g (95%) of 89: ir (film) 2950, 1490, 1140, 1070, 860, 785 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H), 5.00 (s, 1H), 4.74 (broad, 1H), 4.56 (s, 1H), 4.66 and 4.46 (AB q, 2H, J = 12Hz), 3.8 (broad, 1H), 3.74 and 3.60 (AB q, 2H, J = 10Hz), 2.98 (s, 3H), 2.32 (q, 1H, J = 6Hz), 2.18 (q, 1H, J = 6Hz), 1.06 (d, 3H, J = 6Hz), 0.86 (d, 3H, J = 6Hz); mass spectrum m/e 368.130 (M^+), calcd for $C_{18}H_{24}O_6S$ 368.129.

Reaction of (87) with thionyl chloride

To 87 (160 mg, 0.60 mmol) was added pyridine (2 ml) and thionyl chloride (1 ml) and the mixture was refluxed in 15 ml of benzene for 3 hours. The excess thionyl chloride was removed in vacuo and the mixture was diluted

with ether. The ether extract was washed with 7% hydrochloric acid and saturated sodium bicarbonate, and dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by column chromatography of the residue on silica gel and elution with chloroform, gave 100 mg (67%) of a mixture of 90 and 91: ir (film) 2950, 1500, 1450, 1375, 1200, 1100, 740 and 680 cm^{-1}; nmr ($CDCl_3$) δ 7.33 (two s, 5H), 4.7-4.1 (m, 5H), 3.8 (s, 2H), 370 (s, 1H), 2.3 (m, 2H), 1.00 (m, 6H); mass spectrum m/e (308.118) (M^+), calcd for $C_{17}H_{21}ClO_3$ 308 118.

cis,cis-1-Benzyloxymethyl-3-methanesulfonyloxy-2,4-dimethyl-8-oxabicyclo(3.2.1)oct-6-ene (97)

To 86 (2.1 g, 8.0 mmol) was added 5 ml of pyridine and 5 ml of methanesulfonyl chloride at $0^{\circ}C$. The mixture was left overnight at room temperature and then taken up into ether. The ethereal solution was washed with 7% hydrochloric acid and saturated sodium bicarbonate solution, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo*, followed by column chromatography on silica gel (Activity II) and elution with chloroform, gave 2.2 g (75%) of 97: ir (film) 3010, 2950, 1190, 1110 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H) 6.34 (q, 1H, J = 2,6Hz), 6.03 (d, 1H, J = 6Hz), 5.02 (t, 1H, J = 5Hz), 4.70 and 4.54 (AB q, 2H, J = 12Hz), 4.56

(m, 1H), 3.72 and 3.5 (AB q, 2H, J = 10Hz), 2.94 (s, 3H), 2.50 (m, 2H), 1.00 (d, 3H, J = 7Hz), and 0.92 (d, 3H, J = 7Hz).

cis,cis,trans-1-Benzyloxymethyl-6,7-epoxy-3-methanesulfonyloxy-2,4-dimethyl-8-oxabicyclo(3.2.1)octane (98)

To a solution of 97 (1.1 g, 3.0 mmol) in 15 ml of methylene chloride was added m-chloroperbenzoic acid (500 mg, 3.0 mmol) and the mixture was stirred at room temperature for 12 hours. The reaction mixture was taken up into ether, and the ether extract was washed with saturated sodium bicarbonate solution, and dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by column chromatography of the residue on silica gel (Activity II) and elution with benzene-ether (8:2) gave 800 mg (75%) of 98: ir (film) 2940, 1490, 1340, 1160, 1090, 875 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H), 4.98 (t, 1H, J = 3Hz), 4.68 and 4.58 (AB q, 2H, J = 12Hz), 4.1 (d, 1H, J = 5Hz), 3.74 (d, 1H, J = 2Hz), 3.68 (d, J = 2Hz), 3.72 (2d, 1H each, J = 10Hz), 3.06 (s, 3H), 2.48 (m, 2H), 1.02 (d, 6H, J = 7Hz); mass spectrum m/e 368.130 (M^+), calcd for $C_{18}H_{24}O_6S$ 368.129.

Reduction of 98 with Lithium Aluminium Hydride

To 98 (700 mg, 2.0 mmol) in 25 ml of anhydrous ether

was added lithium aluminium hydride (34 mg, 1.0 mmol) and the mixture was refluxed for 3 hours. The excess hydride was destroyed by addition of ethyl acetate and the organic material was extracted with ether. The ether extract was washed with sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of solvent in vacuo gave 400 mg of crude alcohol which was purified by column chromatography on silica gel. Elution with chloroform containing 2% methanol gave 320 mg (70%) of 99: ir (film) 3600-3400, 2975, 1460, 1080, 980, 700 cm^{-1}; nmr ($CDCl_3$) δ 7.4 (s, 5H), 4.68 (s, 2H), 4.3 (d of d, 1H, J = 4,4Hz), 4.2 (broad, 1H), 3.86 (m, 3H), 2.3 (m, 2H), 2.00 (m, 1H, exchanged with D_2O), 1.7 (t, 3H, J = 2Hz), 0.82 (d, 3H, J = 7Hz); mass spectrum m/e 274.156 (M^+), calcd for $C_{17}H_{22}O_3$ 274.157.

cis,trans-1-Benzyloxymethyl-7-hydroxy-2,4-dimethyl-8-oxabicyclo(3.2.1)octane (100)

To 99 (200 mg, 0.70 mmol) in 15 ml of dry tetrahydrofuran was added diborane solution (1 ml, 1 mmol) at 0°C and the mixture was stirred under nitrogen for 2 hours. Water was added to destroy excess hydride and the mixture was stirred with 2 ml of propionic acid for 10 minutes. The solution was extracted with ether, and the extract was washed with saturated sodium bicarbonate and dried over

$MgSO_4$. Evaporation of solvent *in vacuo*, followed by chromatography on silica gel and elution with chloroform containing 2% methanol gave 100 mg (50%) of *100*: ir (film) 3500-3400, 2900, 1480, 1100, 880, 800 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H), 4.64 and 4.54 (AB q, 2H, J = 12Hz), 4.2 (m, 1H, exchanged with D_2O), 4.1 (d of d, 1H, J = 3,6Hz), 3.74 and 3.52 (AB q, 2H, J = 10Hz), 3.56 (d, 1H, J = 3Hz), 2.2 (m, 3H), 1.7 (d of d, 1H, J = 2,3Hz), 1.3-1.1 (m, 2H), 0.96 (d, 3H, J = 6Hz), 0.84 (d, 3H, J = 6Hz); mass spectrum *m/e* 185 (M^+-91).

cis,trans-1-Benzyloxymethyl-7-hydroxy-2,4-dimethyl-8-oxabicyclo(3.2.1)octan-3-one (*101*) and *cis,trans*-1-Benzyloxymethyl-6-hydroxy-2,4-dimethyl-8-oxabicyclo-(3.2.1)octan-3-one (*102*)

To *85* (150 mg, 0.60 mmol) in tetrahydrofuran (10 ml) at 0°C was added a solution of diborane in tetrahydrofuran (3 ml, 3.0 mmol). The mixture was allowed to warm to room temperature over a period of 1 hour. Water was added to destroy excess hydride and a solution of sodium dichromate (1 gm) in water (5 ml) and concentrated sulphuric acid (1 ml) was added. The mixture was heated at reflux for 1 hour and extracted with ether. The extract was washed with saturated sodium bicarbonate and water, and dried over

$MgSO_4$. Evaporation of solvent *in vacuo* gave 90 mg of a mixture of 105 and 106, which was subjected to preparative t.l.c. on silica gel using benzene-ethyl acetate (1:1) as solvent, to give 30 mg of 101: ir (film) 3600-3400, 1710, 1480, 1070, 730 cm^{-1}; nmr ($CDCl_3$) δ 7.34 (s, 5H), 4.76 and 4.6 (AB q, 2H, J = 12Hz), 4.68(m, 1H), 4.1 (d of d, 1H, J = 3,6Hz), 3.8 (s, 2H), 2.86 (m, 2H), 2.56 (m, 1H exchanged with D_2O), 2.1 (d of d, 1H, J = 2,6Hz), 1.9 (d of d, 1H, J = 2.6Hz), 1.02 (d, 3H, J = 7Hz), 0.92 (d, 3H, J = 7Hz); mass spectrum m/e 290.151 (M^+), calcd for $C_{17}H_{22}O_4$ 290.152. Further elution gave 26 mg of 102: ir (film) 3600-3400, 2950, 1610, 1480, 1070, 730 cm^{-1}; nmr ($CDCl_3$) δ 7.34 (s, 5H), 4.76 and 4.54 (AB q, 2H, J = 12Hz), 4.48 (d, 1H, J = 6Hz), 4.12 (d of d, 1H, J = 2,6Hz), 3.6 (s, 2H), 2.84 (m, 2H), 2.6 (m, 1H, exchanged with D_2O), 2.08 (d, 1H, J = 6Hz), 1.4 (d of d, 1H, J = 3,6 Hz), 1.06 (d, 3H, J = 7Hz), 0.92 (d, 3H, J = 7Hz); mass spectrum m/e 290.151 (M^+), calcd for $C_{17}H_{22}O_4$ 290.152.

cis,cis-3-Acetoxy-1-benzyloxymethyl-2,4-dimethyl-8-oxabicyclo(3.2.1)oct-6-ene (103)

To 86 mg, 1 mmol) was added acetic anhydride (5 ml) and pyridine (5 ml) and the mixture was allowed to stand at room temperature for 12 hours. The reaction mixture was taken up into ether, and the ether extract was washed with

dilute hydrochloric acid and saturated sodium bicarbonate and dried over $MgSO_4$. Evaporation of solvent *in vacuo*, followed by column chromatography on silica gel using chloroform as eluent, gave 305 mg (95%) of 103 as a pale yellow liquid: ir (film) 2950, 2925, 2875, 1735, 1480, 1240, 1070 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (s, 5H), 6.4 (d of d, 1H, J = 2,6Hz), 6.02 (d, 1H, J = 6Hz), 5.12 (t, 1H, J = 5Hz), 4.7 and 4.52 (AB q, 2H, J = 12Hz), 4.60 (d, 1H, J = 4Hz), 3.7 and 3.52 (AB q, 2H, J = 10Hz), 2.38 (m, 2H), 2.00 (s, 3H), 0.80 (overlapping d, 6H, J = 7Hz).

Bromination of 103 with N-Bromosuccinimide

To a solution of 103 (100 mg, 0.3 mmol) in dimethyl sulphoxide (10 ml) and water 1 ml) was added (100 mg, 0.45 mmol) of N-bromosuccinimide and the mixture was allowed to stir at room temperature overnight. The mixture was extracted with ether and the extract was washed with water and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 70 mg of crude product, which was recrystallized from ethyl acetate to furnish 60 mg (50%) of 109 and 110 as colorless crystals: mp 42-46°C; ir (Nujol) 3125, 2975, 2875, 1500, 1450, 1380, 900 cm^{-1}; nmr ($CDCl_3$) δ 7.3 (s, 5H), 4.8-4.2 (m, 5H), 3.8 (m, 2H), 3.62 (s, 1H), 2.32 (m, 2H), 1.00 (d, 3H, J = 7Hz), 0.82 (d, 3H, J = 7Hz); mass

spectrum m/e 352.066 (M^+), calcd for $C_{17}H_{21}BrO_3$ 352.067.

cis-2,4,6-Trimethyl-8-oxabicyclo(3.2.1)oct-6-en-3-one (112)

To a solution of 3-methylfuran (2.4 g, 20 mmol) in 10 ml of glyme was added zinc-copper couple (5 g) and the mixture was cooled to 0°C. 2,4-Dibromo-3-pentanone (2.0 g, 8.0 mmol) in glyme (10 ml) was added over a period of 10 minutes under argon and the mixture was allowed to warm to room temperature. After 1 hour the reaction mixture was extraced with ether and the extract was washed with saturated sodium bicarbonate and dried over $MgSO_4$. Evaporation of solvent in vacuo, followed by column chromatography on silica gel (Activity II) and elution with chloroform, gave 900 mg (65%) of 112: ir (film) 2975, 2950, 2875, 1710, 1640, 1440, 1380, 1000, 920 cm^{-1}; nmr ($CDCl_3$) δ 5.92 (d of d, 1H, J = 1,4Hz), 4.74 (d of d, 1H, J = 1,4Hz), 4.62 (d, 1H, J = 4Hz), 2.86 (m, 2H), 1.88 (d, 3H, J = 1Hz), 1.06 (d, 3H, J = 7Hz), 0.96 (d, 3H, J = 7Hz); mass spectrum m/e 166 (M^+).

cis,cis-2,4,6-Trimethyl-8-oxabicyclo(3.2.1)oct-6-en-3-ol (113)

To a solution of 112 (620 mg, 3.7 mmol) in 10 ml of 95% ethanol was added sodium borohydride (70 mg, 2.0 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was extracted with ether, and the extract was washed with 1% hydrochloric acid and dried over $MgSO_4$. Evaporation of solvent in vacuo gave 480 mg (80%) of 113: ir (film) 3500-3300, 2975, 1320, 975, 920 cm^{-1}; nmr ($CDCl_3$) δ 6.00 (q, 1H, J = 4,1.5Hz), 4.42 (m, 1H), 4.20 (m, 1H), 4.20 (m, 1H exchanged with D_2O), 4.20 (d, 1H, J = 3Hz), 3.74 (m, 1H), 2.2 (m, 2H), 1.98 (d, 3H, J = 1.5Hz), 1.06 (d, 3H, J = 7Hz), 0.95 (d, 3H, J = 6Hz).

cis,trans-2,4,6-Trimethyl-8,9-dioxatricyclo-(3.2.1.$1^{3,6}$)nonan-7-ol (114)

To a solution of 112 (160 mg, 0.8 mmol) in 10 ml of methylene chloride was added m-chloroperbenzoic acid (280 mg, 1.6 mmol) and the mixture was stirred at room temperature overnight. The mixture was taken up into ether, and the ethereal solution was washed with saturated sodium bicarbonate and dried over $MgSO_4$. Evaporation of solvent in vacuo gave 150 mg of crude product, which was purified by

column chromatography on silica gel. Elution with chloroform containing 10% ether gave 120 mg (75%) of 114: ir (film) 3500-3300, 2975, 1440, 1170, 1080, 900 cm^{-1}; nmr ($CDCl_3$) δ 4.02 (s, 1H), 2.98 (s, 1H), 3.9 (broad, 1H), 3.76 (s, 1H), 2.5 (m, 1H, exchanged with D_2O), 2.28 (q, 1H, J = 7Hz), 2.04 (q, 1H, J = 7Hz), 1.52 (s, 3H), 0.98 (overlapping d, 6H, J = 7Hz).

cis,trans-2,4,6-Trimethyl-7-methanesulfonyloxy-8,9-dioxatricyclo(3.2.1.$1^{3,6}$)nonane (115)

To a solution of 114 (300 mg, 1.7 mmol) in 3 ml of pyridine at 0°C was added 3 ml of methanesulfonyl chloride and the mixture was allowed to stand overnight. The mixture was diluted with ether, and the ethereal solution was washed with hydrochloric acid and saturated sodium bicarbonate solution, and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 250 mg (75%) of 115: ir (film) 2850, 1460, 1340, 1180, 950 and 820 cm^{-1}; nmr ($CDCl_3$) δ 4.96 (s, 1H), 4.3 (d, 1H, J = 3Hz), 4.00 (d, 1H, J = 2Hz), 3.84 (broad, 1H), 3.08 (s, 3H), 2.32 (q, 1H, J = 7Hz), 2.10 (q, 1H, J = 7Hz), 1.54 (s, 3H), 1.08 (d, 3H, J = 7Hz), 0.96 (d, 3H, J = 7Hz); mass spectrum m/e 262 (M^+).

cis,cis-2,4,6-Trimethyl-8-oxabicyclo(3.2.1)octan-3,7-dione (116)

To a solution of 112 (170 mg, 1.0 mmol) in 5 ml of tetrahydrofuran was added diborane solution (3 ml, 3 mmol) in tetrahydrofuran under argon. The mixture was stirred at room temperature for 30 minutes and water was then added to destroy excess hydride. To this mixture was added a solution of sodium dichromate (1 g) in water (5 ml) and concentrated sulphuric acid (1 ml), and the mixture was refluxed for 1 hour. The solution was extracted with ether, and the extract was washed with saturated sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of the solvent *in vacuo*, followed by chromatography on silica gel (Activity II) and elution with chloroform containing 1% methanol gave 100 mg (55%) of 116: ir (film) 2975, 2875, 1750, 1710, 1450, 1380, 930 cm^{-1}; nmr ($CDCl_3$) δ 4.84 (d of d, 1H, J = 4,4Hz), 4.36 (d of d, 1H, J = 2,6Hz), 2.86 (m, 3H), 1.04 (d, 3H, J = 6Hz), and 1.00 (overlapping d, 6H, J = 6Hz); mass spectrum m/e 182 (M^+).

cis,trans-2,4,6-Trimethyl-8-oxabicyclo(3.2.1)octan-3,7-dione (117)

To a solution of 116 (180 mg, 1.0 mmol) in 10 ml of dry methanol was added sodium methoxide (54 mg, 1.0 mmol)

and the mixture was refluxed for 3 hours under an atmosphere of nitrogen. The mixture was poured into water and extracted with ether. The etheral extract was dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave 160 mg of crude product, which was purified by column chromatography on silica gel (Activity II). Elution with chloroform containing 2% methanol gave 120 mg (61%) of 117: ir (film) 2950, 2900, 1755, 1440, 1380, 940, 730 cm^{-1}; nmr ($CDCl_3$) δ 4.40 (d, 1H, J = 5Hz), 4.24 (d of d, 1H, J = 1,3Hz), 2.92 (m, 2H), 2.16 (m, 1H), 1.30 (d, 3H, J = 7Hz), 1.02 (overlapping d, 6H, J = 7Hz); mass spectrum m/e 182.093 (M^+), calcd for $C_{10}H_{14}O_3$ 182.094.

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