APPROACHES TO THE SYNTHESES OF THE ACYLTETRAMIC ACID ANTIBIOTICS STREPTOLYDIGIN, TIRANDAMYCIN A, AND TIRANDAMYCIN B

Thesis by

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To my parents and to Janet

ACKNOWLEDGEMENTS

I am grateful to Professor Robert Ireland for his guidance throughout this work. I wish to thank the members of the Ireland group, both past and present, for advice and encouragement. Special thanks go to Bob Wardle, Mike Varney, and Pat Dussault for always being around, and to Janet for putting up with me.

I also wish to thank Linda Cusimano and Janet Freeman for assistance in the preparation of portions of this manuscript. Finally, financial support for this work, which was provided by the California Institute of Technology and the National Institute of Health, is gratefully acknowledged.

ABSTRACT

An approach to the syntheses of several acyltetramic acid antibiotics is presented. The approach is partially based on a previous synthesis of tirandamycic acid. It involves an ester enolate Claisen rearrangement of an intermediate derived from D-glucose to establish the requisite relative and absolute stereochemical configurations. An application of the Sharpless asymmetric epoxidation reaction is also involved, and is noteworthy due to its success as an intramolecular kinetic resolution of two available allylic alcohols.

A total synthesis of streptolic acid is presented as evidence of the viability of the synthetic scheme employed. A formal synthesis of tirandamycin A is also presented. Furthermore, the sequence employed is shown to provide an excellent approach to tirandamycin B.

A novel de-benzylation is also reported. The reagent lithium di-**tert**-butylbiphenyl is demonstrated to accomplish the deprotection of benzyl ethers rapidly and efficiently.

TABLE OF CONTENTS

Chapter One

INTRODUCTION

1.1. The Acyltetramic Acid Antibiotics

Streptolydigin (**1**) and tirandamycin A (**2**) are members of the small family of acyltetramic acid antibiotics.[1] Other members of the family include tirandamycin B (**3**), Bu2313A (**4**), Bu2313B (**5**), and nocamycin (**6**).[2]

1.2. Isolation and Biological Activity

Streptolydigin was the first of these to be discovered; it was isolated from the culture broth of Streptomyces lydicus in 1956 as a result of standard growth-inhibition screening procedures.[3] It was found to inhibit growth of

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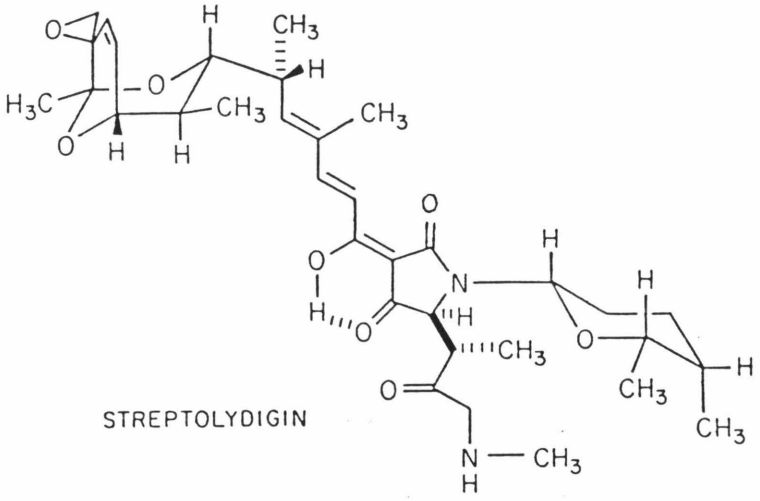
(1) (a) Duchamp, D.J.; Branfman, A.R.; Button, A.C.; Rinehart, K.L., Jr., J. Am. Chem. Soc. **1973**, 95, 4077-4078.
(b) MacKellar, K.L.; Grostic, M.F.; Olson, E.C.; Wnuk, R.J.; Branfman, A.R.; Rinehart, K.L., Jr., Ibid. **1971**, 93, 4943-4945.

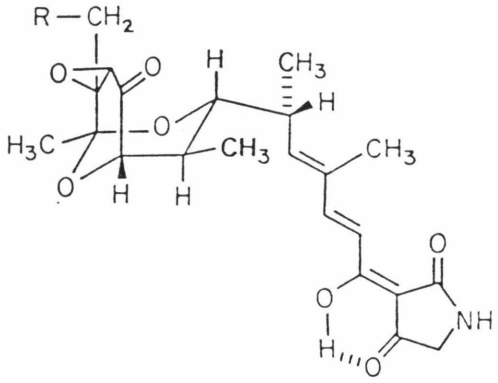
(2) (a) Tirandamycin B: Hagenmaier, H.; Jaschke, K.H.; Santo, L.; Scheer, M.; Zahner, H., Arch. Microbiol. **1976**, 109, 65-71.
(b) Bu2313A and Bu2313B: Tsunakawa, M.; Toda, S.; Okita, T.; Hanada, M.; Nakagawa, S.; Tsukiura, H.; Naito, T.; Kawaguchi, H., J. Antibiot. **1980**, 33, 166-172.
(c) Nocamycin: Horvath, G.; Brazhnikova, M.G.; Konstantinova, N.V.; Tolstykh, I.V.; Potapova, N.P., Ibid. **1979**, 32, 555-558.

(3) (a) DeBoer, C.; Dietz, A.; Silver, W.S.; Savage, G.M., Antibiot. Ann. **1956**, 886-892.
(b) Eble, T.E.; Large, C.M.; DeVries, W.H.; Crum, G.F.; Shell, J.W., Ibid. **1956**, 893-896.



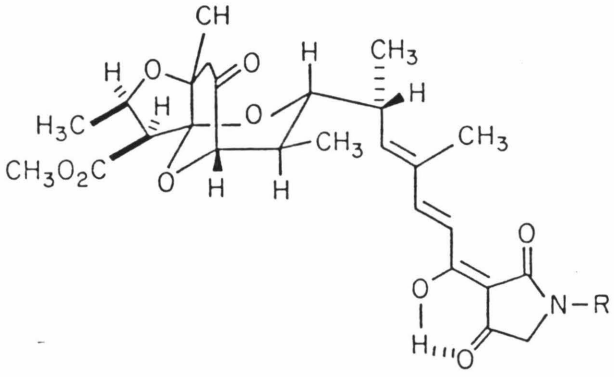
STREPTOLYDIGIN

1



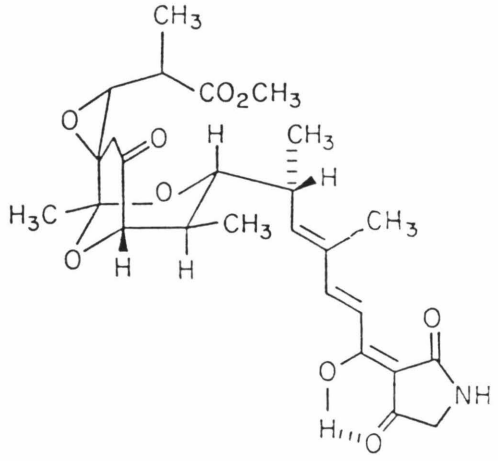
2 TIRANDAMYCIN A: R=H

3 TIRANDAMYCIN B: R=OH



4 Bu2313 A: R=CH_3

5 Bu2313 B: R=H



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gram-positive bacteria **in vitro** and to be effective in treatment of gram-positive bacterial infections in mice. Since it was a potent antibiotic, determination of its mode of activity attracted considerable attention. It was shown to inhibit oxidative phosphorylation in rat liver mitochondria by interfering with electron flow at a point between cytochrome b and cytochrome c reductions.[4] However,

(4) Reusser, F., J. Bacteriol. **1969**, 100, 1335-1341.

its primary mode of antibiotic activity was reported to be inhibition of ribonucleic acid polymerase, which occurred at concentrations ten times lower than those required for interference with oxidative phosphorylation.[5] Thus streptolydigin stopped bacterial RNA synthesis as did the antibiotic rifamycin.[6] More recently, streptolydigin has been shown to inhibit terminal deoxynucleotidyl transferase in leukocytes from a patient with acute lymphoblastic leukemia.[7] Since this enzyme is selectively inhibited (no inhibition of DNA polymerases or of RNA polymerase in these cells was observed) and occurs in anomalously large quantities in leukocytes of certain leukemia victims, where it presumably has some function, streptolydigin has been proposed as a possible leukemia treatment.[7]

1.3. Structure and Stereochemistry

The structure and relative stereochemistry of streptolydigin were reported in 1963 by Rinehart and co-

(5) Siddhikol, C.; Erbstoeszer, J.W.; Weisblum, B., Ibid. **1968**, 99, 151-155.

(6) While both streptolydigin and rifamycin inhibit bacterial RNA polymerase, they do so by different mechanisms. Evidence for this (ref. 5) includes the facts that (a) the inhibitory activity of streptolydigin in cell-free systems is observed almost immediately upon addition while that of rifamycin is delayed, and (b) inhibition by streptolydigin was reversible by removal of the antibiotic, while inhibition by rifamycin was not.

(7) Dicioccio, R.A.; Srivastava, B.I.S., Biochem. Biophys. Res. Commun. **1976**, 72, 1343-1349.

workers.[8] The "top half" was found to be based on a 2,9-dioxabicyclo-[3.3.1]-nonane skeleton and the "bottom half" on a substituted 3-acyltetramic acid nucleus. Determination of the absolute stereochemistry, however, was not accomplished until after the discovery of the closely related antibiotic tirandamycin A in 1970.[9] Tirandamycin A appeared to be very similar to streptolydigin in structure and function.[1b] It possessed both modes of antibiotic activity exhibited by streptolydigin, although significantly higher concentrations were required.[9] Again, **in vitro** inhibition of the growth of gram-positive bacteria was observed; however, **in vivo** activity was not observed for tirandamycin A.[10]

Spectroscopically, the two antibiotics were very similar. The structure reported by Rinehart for tirandamycin A reflected this similarity: both the 3-acyltetramic acid "bottom half" and the 2,9-dioxabicyclo-[3.3.1]-nonane "top half" were present as in streptolydigin.[9] Two years later the absolute stereochemistry of the top half portions of both compounds (tirandamycic acid **7** and streptolic acid **8**) was

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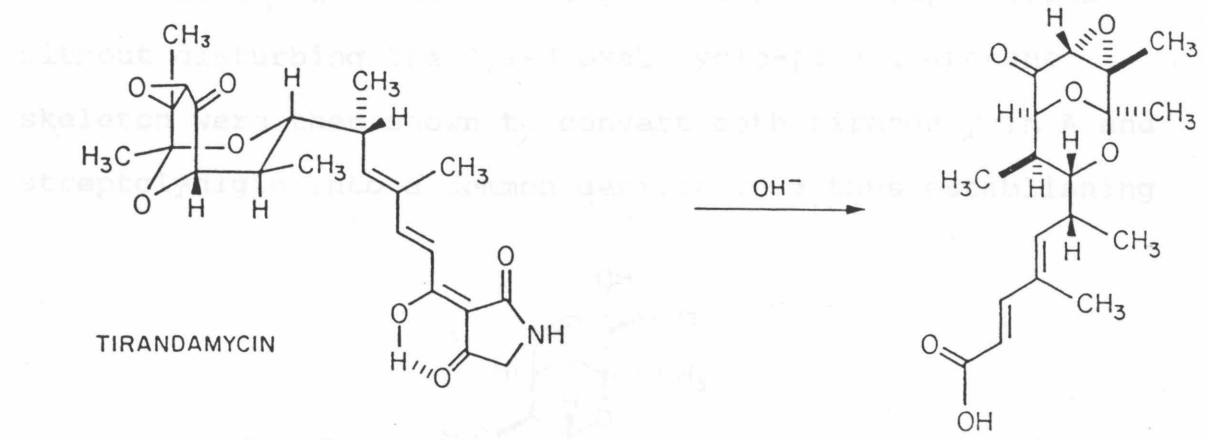
(8) (a) Rinehart, K.L., Jr.; Beck, J.R.; Epstein, W.W.; Spicer, L.D., J. Am. Chem. Soc. **1963**, 85, 4035-4037.
(b) Rinehart, K.L., Jr.; Borders, B.D., Ibid. **1963**, 85, 4037-4038.
(c) Rinehart, K.L., Jr.; Beck, J.R.; Borders, D.B., Ibid. **1963**, 85, 4038-4039.

(9) Meyer, C.E., J. Antibiot. **1971**, 24, 558.

(10) (a) Reusser, F., Infec. Immun. **1970**, 2, 77-81.
(b) Reusser, F., Ibid. **1970**, 2, 82-84.



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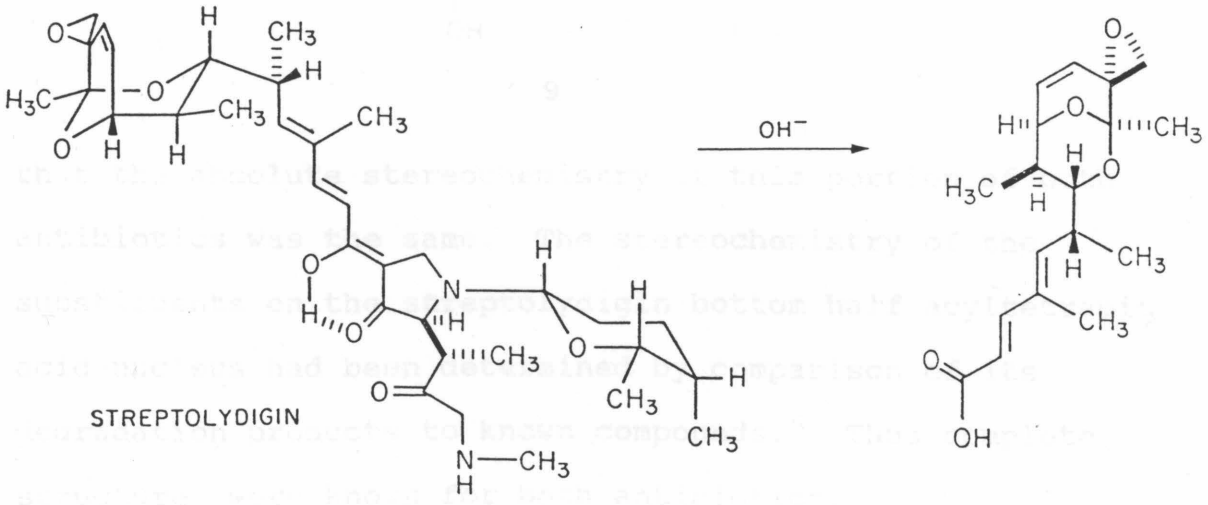

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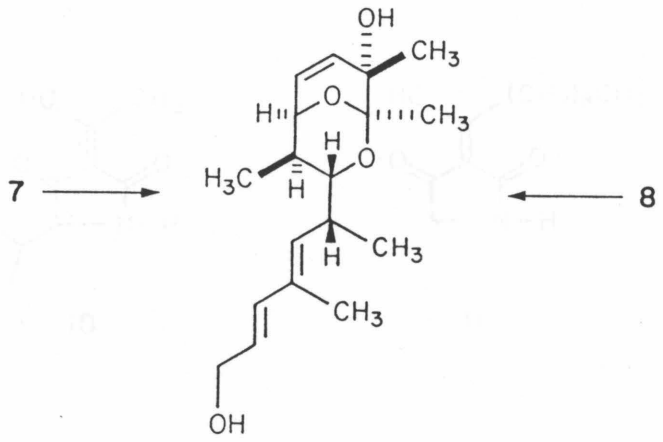
established by transforming tirandamycin A into a p-bromophenacyl ester for which an X-ray crystal structure

determination was made.[11] Simple chemical manipulations without disturbing the 2,9-dioxabicyclo-[3.3.1]-nonane skeleton were then shown to convert both tirandamycin A and streptolydigin into a common derivative **9** thus establishing



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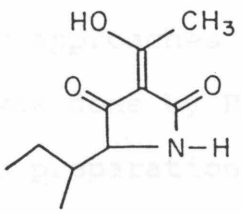
that the absolute stereochemistry of this portion of both antibiotics was the same. The stereochemistry of the substituents on the streptolydigin bottom half acyltetramic acid nucleus had been determined by comparison of its degradation products to known compounds.[8] Thus complete structures were known for both antibiotics.

1.4. Relationship of Structure to Biological Activity

Interestingly, streptolydigin and tirandamycin A differ markedly from simpler acyltetramic acids in specificity and

(11) This work also included analysis of the ^{1}H NMR of the rhodinose appended to the tetramic acid nitrogen in streptolydigin to determine the configuration of the anomeric center. See ref. 1a.

mode of action. For example, tenuazonic acid **10** (a natural product) and various analogues prepared for testing exhibited significant inhibition of tumor growth in human cell systems but little or no antibacterial activity.[12]



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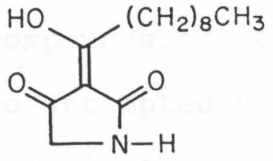

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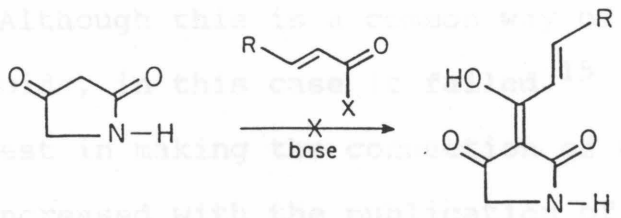
The more lipophilic decanoyl tetramic acid **11** caused reasonable inhibition of the growth of gram-positive bacteria (though not of molds or gram-negative bacteria), and this activity increased when lipophilic character was increased by formation of copper complexes.[13] Thus it appears that the tetramic acid moiety may be responsible for antibiotic activity and that the more lipophilic 2,9-dioxabiclononane top half of the antibiotics may promote transport through membranes and confer specificity. Perhaps more importantly, the antineoplastic activity of tenuazonic

(12) (a) Harris, S.A.; Fisher, L.V.; Folkers, K., J. Med. Chem. **1965**, 8, 478-482.
(b) Gitterman, C.O., Ibid. **1965**, 8, 483-486.
(13) Matsuo, K.; Kitaguchi, I.; Takata, Y.; Tanaka, K., Chem. Pharm. Bull. **1980**, 28, 2494-2502.

acid suggests the possibility of such activity for the more complex compounds if an appropriate "top half" could be designed.

Determination of the structures of the antibiotics, coupled with their potential pharmaceutical values and intriguing structures, predictably precipitated numerous synthetic approaches to these compounds.[14] One of the early studies was done by Rinehart who attempted the semi-synthetic preparation of tirandamycin A starting with tirandamycic acid **7** obtained by degradation of the natural product.[15] Various model systems strongly indicated that the direct acylation of tetramic acid **12** by an acyl halide



12 13

Scheme I

(14) Approaches to synthesis of the top half of tirandamycin A:

(a) DeShong, P.; Ramesh, S.; Perez, J.J., J. Org. Chem. **1983**, 48, 2118-2120.

(b) Ziegler, F.E.; Wester, R.T., Tetrahedron Lett. **1984**, 25, 617-620.

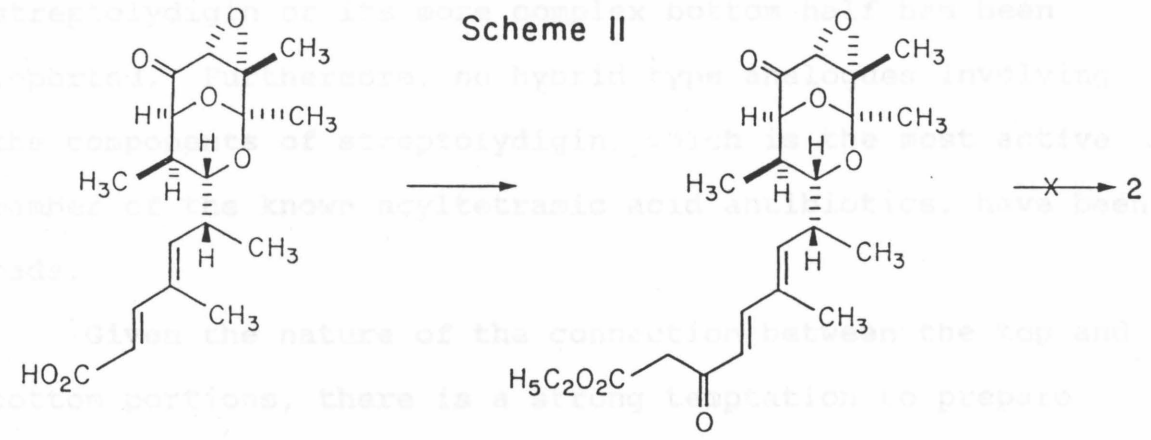
(c) Martin, S.F.; Gluchowski, C.; Campbell, C.L.; Chapman, R.C., J. Org. Chem. **1984**, 49, 2512-2513.

(d) Kelly, T.R.; Chandrakumar, N.S., Tetrahedron Lett. **1985**, 26, 2173-2176.

(15) Lee, V.J.; Branfman, A.R.; Herrin, T.R.; Rinehart, K.L., Jr., J. Am. Chem. Soc. **1978**, 100, 4225-4236.

or activated ester of tirandamycic acid (the obvious and tempting route presented in Scheme I) would not be feasible.[16] These investigators attempted, therefore, to extend tirandamycic acid linearly (Scheme II) in the hope of

Scheme II



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employing a Dieckmann condensation to form the tetramic acid nucleus. Although this is a common way of synthesizing tetramic acids, in this case it failed.[15]

Interest in making the connection of upper and lower portions increased with the publication of an efficient synthesis of optically active tirandamycic acid by Ireland, Ernst, and Wuts.[17] Several approaches to derivatives of the acyltetramic acid bottom portion which could be attached via a Horner-Emmons condensation presented promise for

(16) A few cases of successful applications of the acylation reaction presented in Scheme I are known, most notably the reconstitution of Bu2313A and Bu2313B in 6% and 11% yields, respectively. See Toda, S.; Nakagawa, S.; Naito, T.; Kawaguchi, H., J. Antibiot. **1980**, 33, 173-181. However, it seemed unwise to base an involved synthesis on a reaction that gave such low yields.

(17) Ireland, R.E.; Wuts, P.G.M.; Ernst, B., J. Am. Chem. Soc. **1981**, 103, 3205-3207.

completion of the synthesis of tirandamycin A.[18] This was recently realized but it involved a different bottom half synthesis wherein the acyltetramic acid nitrogen was protected.[19] However, no successful approach to streptolydigin or its more complex bottom half has been reported. Furthermore, no hybrid-type analogues involving the components of streptolydigin, which is the most active member of the known acyltetramic acid antibiotics, have been made.

Given the nature of the connection between the top and bottom portions, there is a strong temptation to prepare hybrid-type analogues by connecting the naturally occurring top portions to various bottom portions. One intriguing question to be addressed by such analogues is that of determining which substituents are essential for activity. Streptolydigin is ten times more effective at inhibition of bacterial growth **in vitro** than tirandamycin A: the difference could be due to the top portion (the vinyl epoxide) or it could be due to either of the two substituents on the acyltetramic acid nucleus. Conceivably all of these differences may be required for the increased

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(18) (a) Boeckman, R.K., Jr.; Thomas, A.J., J. Org. Chem. **1982**, 47, 2823-2824.
(b) DeShong, P.; Lowmaster, N.E.; Barralt, O., Ibid. **1983**, 48, 1149-1150.

(19) (a) Schlessinger, R.H.; Bebernitz, G.R.; Lin, P.; Poss, A.J., J. Am. Chem. Soc. **1985**, 107, 1777-1778.
(b) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J.J., Ibid. **1985**, 107, 5219-5224.

activity. Preparation of the simple hybrid analogues in sufficient quantity for testing could allow this question to be answered. In turn, this could provide insight into design of more effective or more specific antibiotics. An efficient synthesis of the top portion of streptolydigin which allows for the synthesis of top half analogues is essential if this goal is to be realized. A synthetic strategy was developed which should fulfill this requirement and which, furthermore, should allow for divergence late in the synthetic sequence to give the tirandamycin A and B substitution patterns.

Chapter Two

A FIRST APPROACH TO STREPTOLIC ACID

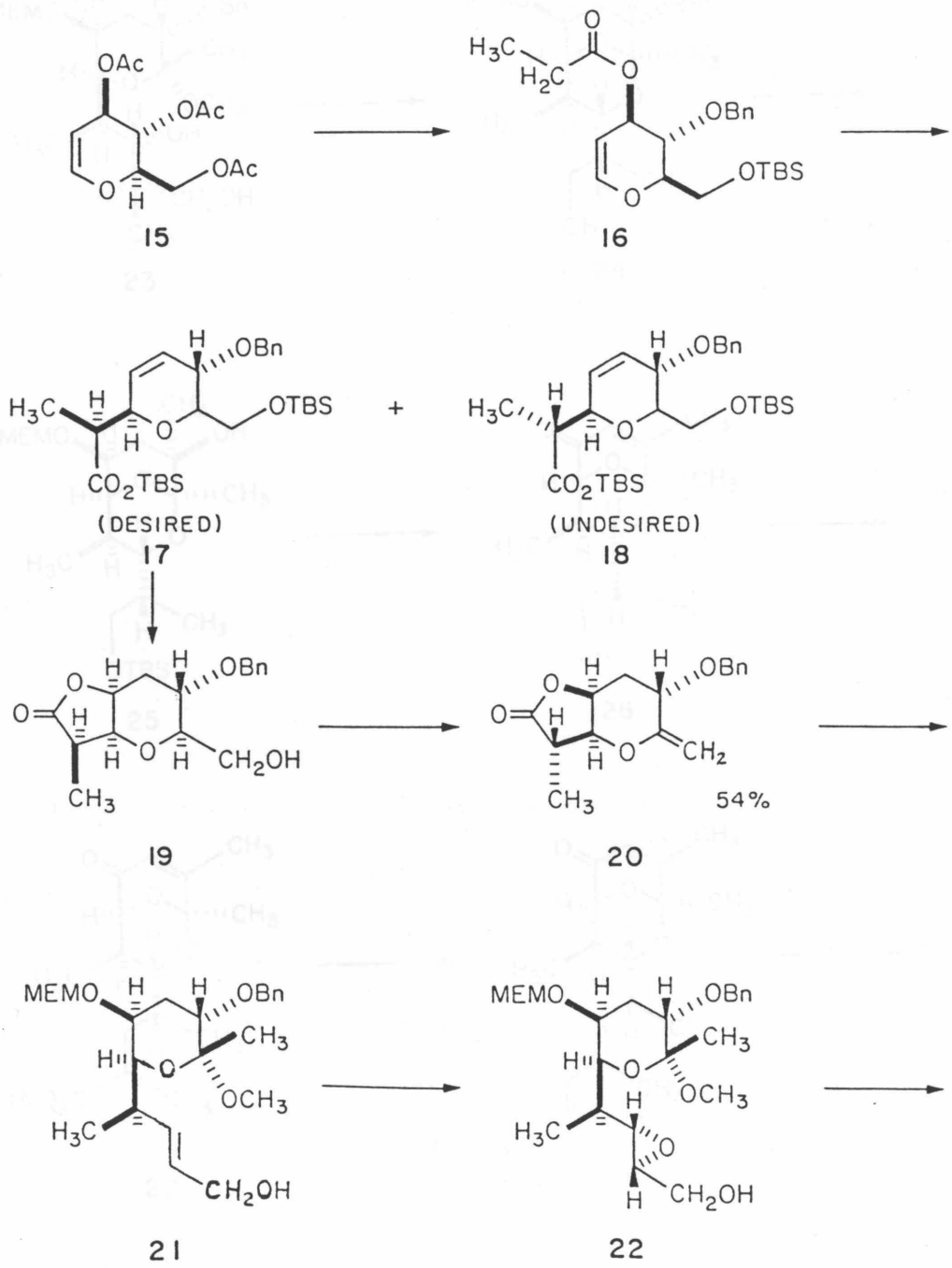
The synthetic approach to streptolydigin which shall be described is based on the Ireland synthesis of tirandamycic acid.[17] As in that synthesis, the relative stereochemistry of the top half is established through an application of the ester enolate Claisen.[20] The absolute stereochemistry is determined by a single asymmetric center of the starting material which, as in the tirandamycic acid synthesis, is derived from D-glucose. Departure from the previous synthesis, however, occurs early in the sequence. This is based partly on a desire to enhance the efficiency of the earlier work and partly on adaptations required to establish a substitution pattern for the synthesis of streptolic acid, **8**, the top half of streptolydigin. It also allows for the somewhat more ambitious goal of maintaining the flexibility to divert material at a relatively late stage in the sequence to the synthetic paths for making other natural products (tirandamycins A and B) or analogues.

2.1. The Ireland Tirandamycic Acid Synthesis

Scheme III outlines the synthesis of tirandamycic

(20) Ireland, R.E.; Mueller, R.H., J. Am. Chem. Soc. **1972**, 94, 5897-5898.

Scheme III


OAc
OAc
OAc
15
H3C
H2C
O
OBn
OTBS
16
H
OBn
H3C
H
O
OTBS
H
CO2TBS
(DESIRED)
17
+
H
OBn
H3C
H
O
OTBS
H
CO2TBS
(UNDESIRED)
18
H
H
OBn
O
O
H
H
O
CH2OH
CH3
19
H
H
OBn
O
O
H
H
O
CH2
CH3
54%
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MEMO
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OBn
CH3
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OCH3
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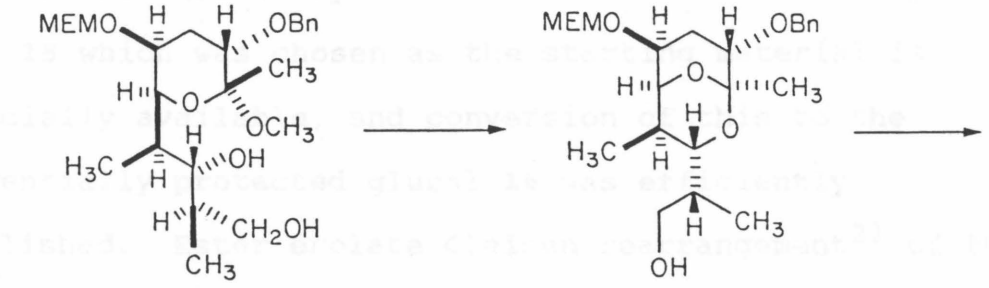

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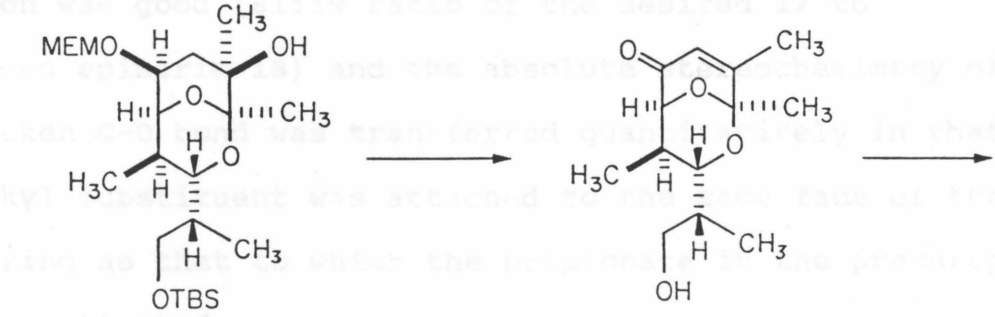

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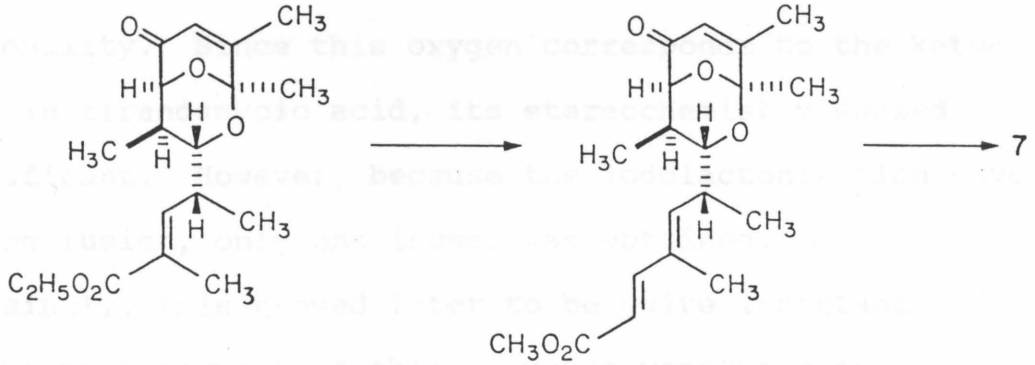

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acid[17] which served as a pattern and in some instances a model for the current synthetic work. The tri-O-acetyl-D-glucal **15** which was chosen as the starting material is commercially available, and conversion of this to the differentially protected glucal **16** was efficiently accomplished. Ester enolate Claisen rearrangement[21] of this propionate ester allowed stereoselective attachment of the -methyl side chain. The diastereoselectivity of the reaction was good (81:19 ratio of the desired **17** to undesired epimeric **18**) and the absolute stereochemistry of the broken C-O bond was transferred quantitatively in that the alkyl substituent was attached to the same face of the pyran ring as that to which the propionate in the precursor had been attached.

An iodolactonization (followed by Bu_3SnH reduction of the iodide) was then used to introduce an oxygen functionality. Since this oxygen corresponds to the keto-oxygen in tirandamycic acid, its stereochemistry seemed insignificant. However, because the iodolactonization gave **cis** ring fusion, only one isomer was obtained. Surprisingly, this proved later to be quite important.

The next segment of this sequence was the most troublesome and least efficient. It involved de-oxygenation of C-6 (using numbering corresponding to that for the parent compound, glucose) by an elimination. This elimination, followed by ketalization, corrected the oxidation states at

C-6 and C-5 to correspond to those required by tirandamycic acid. However, the elimination could only be accomplished in moderate yield (54%) after extensive experimentation.

Once this had been accomplished, the side chain was extended by reducing the lactone to a lactol which was allowed to react with a stabilized Wittig reagent to give an unsaturated ester. This was then protected (as a MEM ether) and reduced to the allylic alcohol **21**. Fortuitously, epoxidation of this compound (MCPBA, dichloromethane, $0^{o}C$) exhibited very high facial selectivity (10:1) to give the desired epoxide **22**. No explanation for this result has been proposed, and the reason for the diastereoselectivity is further obscured by the fact that replacement of the MEM ether by an acetate results in a decrease in stereoselectivity. Thus the MEM ether seems to exert control over the distal olefin epoxidation.

Completion of the synthesis from this point required methyl cuprate opening of the epoxide and an internal ketal exchange to give the 2,9-dioxabicyclononane skeleton (**24**). The benzyl protecting group was removed by hydrogenolysis, and oxidation followed by methyl Grignard addition led to isolation of **25**. Deprotection of the MEM ether allowed oxidation of the secondary hydroxyl and elimination of the tertiary one to give (after desilylation) **26**. The synthesis was then completed by successive Wittig olefinations to establish the conjugated dienoate side chain and a

conformationally controlled epoxidation of the cyclic enone system to give the methyl ester of tirandamycic acid. This was hydrolyzed to the degradation product tirandamycic acid, **7**.

2.2. Refinement of the Tirandamycic Acid Synthesis

C_6-Deoxygenation

The synthesis of streptolic acid, the initial goal of the present work, began with the glucal **16**.[17] However, the troublesome de-oxygenation of C-6 was undertaken immediately, obviating the problems encountered in de-oxygenating <u>after</u> the Claisen rearrangement as had been done for tirandamycic acid. The desired transformation was efficiently accomplished by fluoride deprotection of the silyl ether, followed by tosylation of the revealed primary alcohol. Tosylate **29** was then converted to an iodide, and hydrogen iodide was eliminated by treatment with diazabicycloundecene (DBU) in excellent yield to give the divinyl ether **30**. This compound proved to be surprisingly stable and could be prepared on relatively large scale (50-100 g) and stored for months in the freezer with no decomposition.

2.3. Claisen Rearrangement of the Divinyl Ether

This divinyl ether also proved to be an excellent substrate for the subsequent ester enolate Claisen

rearrangement[21] which, as in the tirandamycic acid synthesis, was used to establish the side chain stereochemistry. The Claisen conditions employed were fairly standard: two equivalents of lithium hexamethyldisilazide (LiHMDS) were used to ensure complete deprotonation. Selection of hexamethyldisilazide as the base promoted preferential formation of the desired **E**-enolate (which corresponds to the **Z**-silyl ketene acetal) as in the tirandamycic acid synthesis. It was observed that the yield of the desired Claisen product could be improved significantly (10-15%) by pre-mixing the base with **tert**-butyldimethylsilyl chloride (TBSCl) and hexamethylphosphoramide (HMPA) before addition of the ester and allowing the reaction to begin warming (i.e., removing the dry ice bath) immediately after addition of the substrate.[22] This prevented formation of any of the elimination product **33** which was generally otherwise observed. It did not noticeably affect the diastereomer ratio, however, the ratio of 84:16 (of inseparable diastereomers) was obtained whether or not HMPA was present during deprotonation of the ester. This ratio was slightly better than that for Claisen rearrangement when accomplished prior to de-oxygenation (the ratio improved from 81:19 to 84:16).[17]

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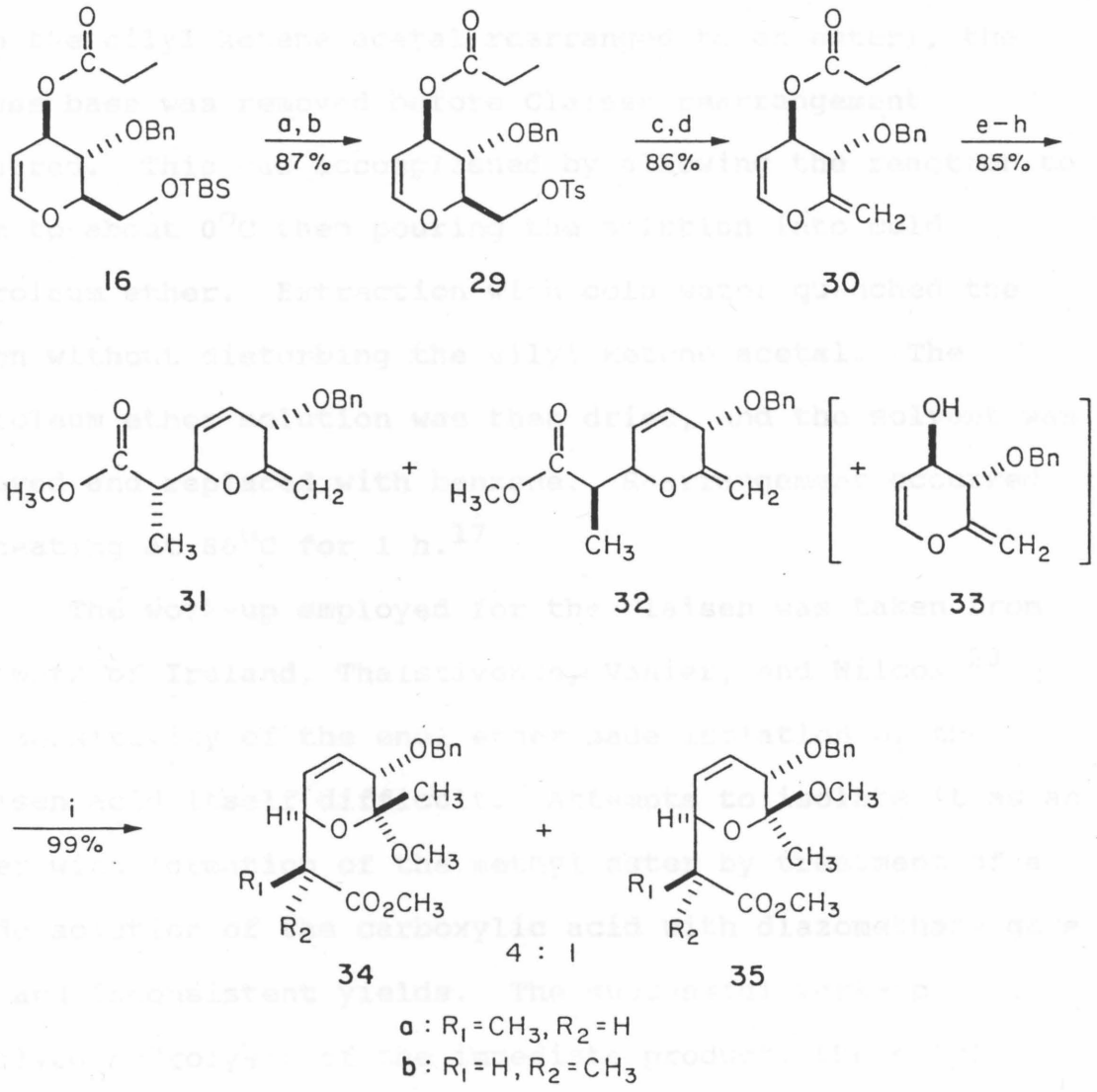
(22) Ireland, R.E.; Norbeck, D.W., J. Am. Chem. Soc. **1985**, 107, 3279-3285.

Scheme IV[a]



[a](a) Bu_4NF, THF. (b) **p**-TsCl, Pyr, CH_2Cl_2. (c) NaI, MEK, reflux. (d) DBU, C_6H_6, reflux. (e) LiHMDS, TBSCl, HMPA, THF, -78°C. (f) C_6H_6, reflux, 1 h. (g) $KF \cdot 2H_2O$, $KHCO_3$, HMPA. (h) CH_3I, HMPA. (i) MeOH, cat. **p**-TsOH.

To avoid epimerization of the α-center and elimination (either of which could occur if the amide base were present when the silyl ketene acetal rearranged to an ester), the excess base was removed before Claisen rearrangement occurred. This was accomplished by allowing the reaction to warm to about 0°C then pouring the solution into cold petroleum ether. Extraction with cold water quenched the anion without disturbing the silyl ketene acetal. The petroleum ether solution was then dried, and the solvent was removed and replaced with benzene. Rearrangement occurred on heating at 80°C for 1 h.[17]

The work-up employed for the Claisen was taken from the work of Ireland, Thaisrivongs, Vanier, and Wilcox.[23] The sensitivity of the enol ether made isolation of the Claisen acid itself difficult. Attempts to isolate it as an ester with formation of the methyl ester by treatment of a crude solution of the carboxylic acid with diazomethane gave low and inconsistent yields. The successful work-up involved hydrolysis of the immediate product, the silyl ester, with $KF \cdot 2H_2O$ and $KHCO_3$ in HMPA, and **in situ** methylation of the potassium carboxylate with methyl iodide.[23] This resulted in yields approaching 90% on moderate scale (up to about 1 g) and 85% for reactions of up to 4 g scale. Attempts to scale up to 8 g and to 12 g gave

(23) Ireland, R.E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C.S., J. Org. Chem. **1980**, 45, 48-61.

lower yields, as C-silylation of the ester enolate became competitive with O-silylation. This was attributed to the fact that cooling of the lithium hexamethyldisilazide solution back to -78°C after addition of the TBSCl/HMPA mixture is less efficient for the larger reactions. Only two to three minutes were allowed to pass before addition of the ester to this mixture to avoid decomposition of the amide base or TBSCl. Therefore, the larger scale reactions probably involve deprotonation and trapping at somewhat higher temperatures. The objective of improving the efficiency of the C_6-deoxygenation of the tirandamycic acid synthesis had thus been accomplished.

Ketalization of the Claisen product (isolated as the methyl ester) was essentially quantitative. Once again the methyl epimers were inseparable, but the two anomers formed, **34** and **35**, were readily separable by flash chromatography. The major and more polar anomer, assumed to be **34** based on a simple conformational analysis, was used for the next reaction to avoid carrying a complex mixture forward. The minor anomer was easily equilibrated so that virtually no material loss occurred. An anomeric ratio of 4.0:1 was measured by capillary gas chromatography as well as by separation of the anomers and comparison of the weights of the two materials obtained. The methyl epimer ratio (84:16) was also determined by capillary gas chromatographic analysis (of the major anomer) and compares very well to

that which is expected from a propionate Claisen[21] and to high field ^{1}H NMR analysis of the major ketal.

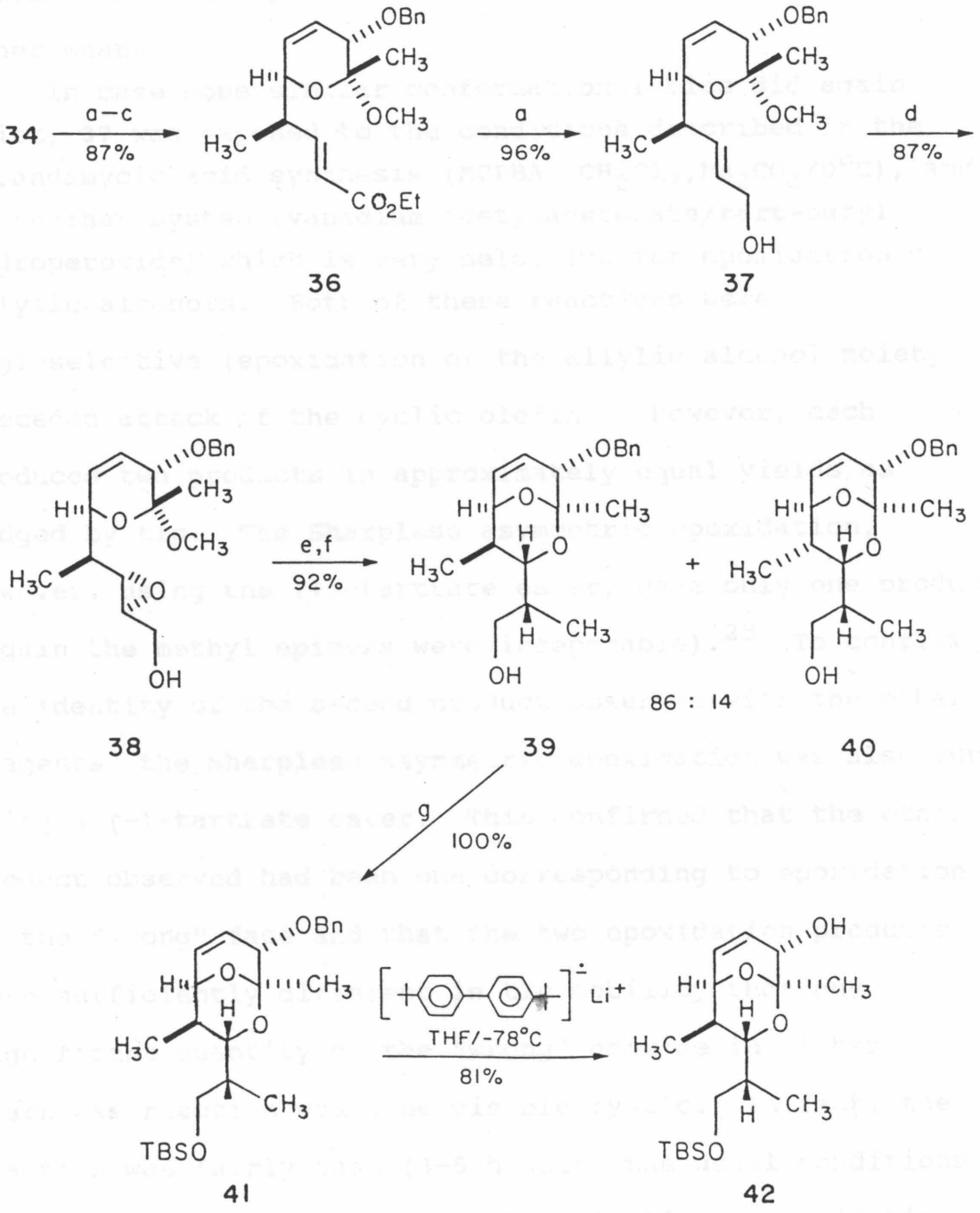
2.4. Development of the Side Chain

Extension of the side chain to provide an allylic alcohol was accomplished by a sequence of standard reactions. The best procedure involved reduction of the ester all the way to the alcohol using di-**iso**-butylaluminum hydride (DIBAL-H) followed by Swern oxidation and **in situ** Wittig olefination.[24] (Although the initial alcohol could be purified by flash chromatography, it was generally used in crude form for the next reaction.) Using this procedure, the overall yield for what is formally three steps was excellent (87%) even on fairly large scale, i.e., up to 20 g. The resultant unsaturated ester was then cleanly reduced with DIBAL-H to the desired allylic alcohol **37**.

In the tirandamycic acid synthesis, the analogous alcohol possessed a MEM ether which apparently controlled epoxidation diastereoselectivity. In the present system this ether has been omitted in order to leave the Claisen-derived olefin intact, since this olefin appears as part of the target molecule. It was deemed preferable to retain the olefin if possible, rather than converting it to the hydroxyl and later regenerating it. Therefore, it was

(24) Ireland, R.E.; Norbeck, D.W., J. Org. Chem. **1985**, 50, 2198-2200.

Scheme V[a]



[a](a) DIBAL-H, ether, -78°C. (b) $(COCl)_2$, DMSO, CH_2Cl_2; Hunig's base. (c) carboethoxymethylidene triphenylphosphorane, CH_2Cl_2. (d) (+)-DIPT, $Ti(OR)_4$, TBHP, CH_2Cl_2, -20°C. (e) Me_2CuLi, ether, -20°C. (f) cat. p-TsOH, $CHCl_3$. (g) TBSCl, DMF, imidazole.

assumed that the epoxidation would have to be controlled by other means.

In case some similar conformational bias did again exist, **37** was exposed to the conditions described in the tirandamycic acid synthesis (MCPBA, CH_2Cl_2,Na_2CO_3/0°C), and to another system (vanadium acetylacetonate/**tert**-butyl hydroperoxide) which is very selective for epoxidation of allylic alcohols. Both of these reactions were regioselective (epoxidation of the allylic alcohol moiety preceded attack of the cyclic olefin). However, each produced two products in approximately equal yields as judged by tlc. The Sharpless asymmetric epoxidation, however, using the (+)-tartrate ester, gave only one product (again the methyl epimers were inseparable).[25] To confirm the identity of the second product observed with the other reagents, the Sharpless asymmetric epoxidation was also run using a (-)-tartrate ester. This confirmed that the other product observed had been one corresponding to epoxidation of the "wrong" face and that the two epoxidation products were sufficiently different in tlc mobility that any significant quantity of the "wrong" epoxide in either Sharpless reaction would be visible by tlc. In fact, the reaction was fairly fast (3-5 h using the usual conditions and concentrations) and extremely selective: epoxidation

(25) (a) Katsuki, T.; Sharpless, K.B., J. Am. Chem. Soc. **1980**, 102, 5974-5976.
(b) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B., Ibid. **1981**, 103, 464-465.

with either tartrate enantiomer gave rise to only one epoxide by tlc.

Methyl cuprate opening of the epoxide **38** to a 1,3-diol was also quite selective, although 6-7 equivalents of the reagent and high concentrations were required for the reaction to go to completion. The highly crystalline product from this reaction could be chromatographed, but it was generally converted directly into the bicyclic compound since chromatography of the crude diol products resulted in virtually no separation. Three products were observed, one of which was by far the major product, but they were not cleanly resolved even by tlc.

2.5. Dioxabicyclononane Formation

Cyclization of the 1,3-diol was precedented in the tirandamycic acid synthesis; the ketal exchange in that case had been accomplished with catalytic **p**-toluenesulfonic acid in chloroform.[17] Thus, the first time the product from methyl cuprate opening of the epoxide was obtained in this work, a crude NMR was recorded in deuteriochloroform solution. A tiny crystal of **p**-toluenesulfonic acid was then added to the NMR sample. The progress of the reaction could readily be followed by tlc, but was especially exciting to observe by ^{1}H NMR: the methyl doublets of starting material and product were easily distinguished and the shift of the methoxy singlet changed significantly as methanol was

liberated. This reaction was generally complete in 15-30 min. depending on the amount of acid catalyst used and was very clean. Two major products were obtained in approximately a 6:1 ratio corresponding to the methyl epimers which had been carried since the Claisen rearrangement and were finally separable at this point. The major product could be obtained as one isomer (judged by 400 MHz ^{1}H NMR) confirming that the methyl epimer had been removed.

While the epimers were separable at this point, for larger scale reactions (over about 1 g) the mixture was generally silylated (TBSCl) and then chromatographed, since separation of the epimers was thereby made slightly easier. Separation at this point also gave the epimeric products in a ratio near the 84:16 Claisen-derived ratio.

2.6. Lithium Di-tert-Butylbiphenyl Debenzylation

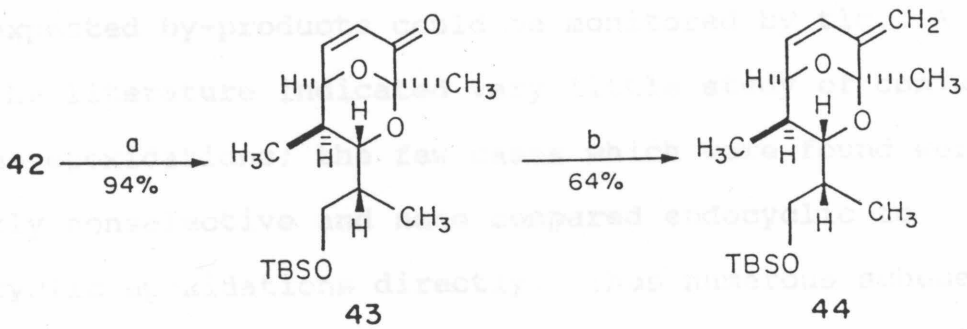
At this stage it seemed advisable to study the chemistry of the top portion of this molecule to determine whether efficient conversion to the requisite vinyl epoxide (see streptolic acid **8**) could be accomplished from the protected allylic alcohol. Therefore, the alcohol had to be deprotected. This opportunity was seized to try a new debenzylation reaction which had been suggested by a member of the Ireland group, Dan Norbeck. The radical anion, lithium di-**tert**-butylbiphenyl, was suggested as an

alternative to lithium/ammonia (Birch conditions) for reductive cleavage of benzyl ethers.[26] This reagent should have a somewhat lower reduction potential than lithium/ammonia and should therefore be more selective. Although the "extra" electron should prefer to occupy the larger -system of the biphenyl, even a small equilibrium concentration of a species with the electron transferred into the benzyl aromatic ring should be sufficient to accomplish debenzylation since the cleavage is irreversible. The experimental observation is that treatment of the benzyl ether in tetrahydrofuran (THF) at -78°C with a solution of lithium di-**tert**-butylbiphenyl (0.17M in THF) results in rapid, convenient, and efficient debenzylation. In this and several other examples (which will be described in due course), this reaction was shown to be a clean and very general way to selectively cleave benzyl ethers. No allyl ether cleavages have been observed even though all of the examples to be cited present opportunities for this side reaction, which is sometimes observed in applications of standard Birch conditions.

This deprotection exposed an allylic alcohol which was oxidized using the Swern oxidation procedure to give an enone. The cage-like structure of this enone virtually guaranteed that any reaction of either the ketone or the

(26) Freeman, P.K.; Hutchison, L.L., J. Org. Chem. **1980**, 45, 1924-1930 and references therein.

adjacent olefin would occur by approach of the attacking reagent from the "exo" or back face (as drawn). This predictable tendency had been observed in the tirandamycic acid synthesis.[16] In essence, it required that the streptolic acid exocyclic epoxide should be created by insertion of the methylenoxy carbon followed by addition of the oxygen in order to establish the correct stereochemistry. Therefore, the enone **43** was treated with the methylene Wittig reagent (methylidene triphenylphosphorane) in an unsuccessful attempt to form the diene **44**. The diene was successfully prepared by treatment of the enone with Tebbe reagent.[27] This gave a 64% yield of the diene which



[a](a) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Hunig's base (94%). (b) Tebbe reagent, THF, -78°C to room temp (64%).

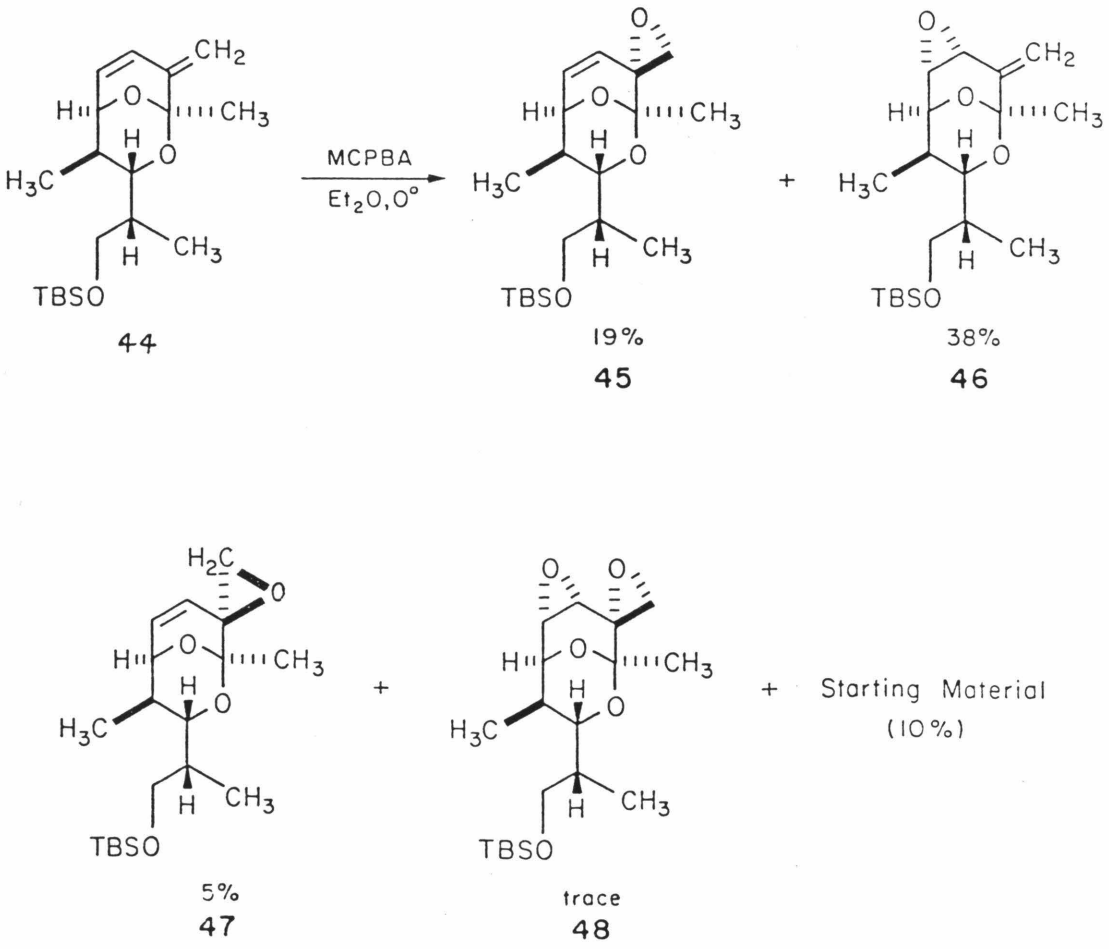
(27) (a) Pine, S.H.; Zahler, R.; Evans, D.A.; Grubbs, R.H., J. Am. Chem. Soc. **1980**, 102, 3270-3272.
(b) Tebbe, F.N.; Parchall, G.W.; Ready, G.S., Ibid. **1978**, 100, 3611-3612.

was sufficient to determine whether an effective epoxidation system or reagent could be found.

2.7. Epoxidation of the Diene

For this path to be viable, some epoxidation system was needed to selectively epoxidize the exocyclic methylene in the presence of the cyclic olefin of the conjugated diene. Treatment of the diene with MCPBA under standard conditions gave a mixture of several products from which the desired product **45** was isolated and identified along with the regioisomeric epoxide **46** and other expected by-products. This allowed other epoxidation systems to be evaluated on small scale since the production of the desired product and of expected by-products could be monitored by tlc. A survey of the literature indicated very little study of conjugated diene epoxidations; the few cases which were found were mostly nonselective and none compared endocyclic to exocyclic epoxidations directly. Thus numerous schemes were examined in search of a promising method. The following

Scheme VI


MCPBA
Et2O, 0°
TBSO
H3C
CH3
CH2
O
H
44
19%
45
38%
46
5%
47
trace
48
+
Starting Material
(10%)

systems were tested:

(1) trimethylsilyl hydroperoxide in THF[28]

(2) benzonitrile and 30% hydrogen peroxide in MeOH[29]

(3) $V(O)acac_2$ and **tert**-butylhydroperoxide[30]

(4) $MoO_5 \cdot 2HMPA$[31]

(5) $Mo(CO)_6$ and **tert**-butylhydroperoxide[30]

(6) MCPBA/CH_2Cl_2, unbuffered

(7) MCPBA/CH_2Cl_2, Na_2CO_3

(8) MCPBA/benzene, $CaHPO_4$

(9) MCPBA/ether, Na_2CO_3

Since the epoxidation products had been identified, each reaction was run on a small scale and monitored by tlc. Of these, the buffered MCPBA epoxidations were the only ones to show any promise, and none of the MCPBA variations changed the product distribution noticeably. In each of the other systems increasingly vigorous conditions were employed until some reaction or decomposition of the diene occurred, and none showed formation of a significant quantity of the desired product. Thus the diene epoxidation produced at best 19% of the desired product. Since this was deemed unacceptable at such a late stage, the synthetic strategy

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(28) Ho, T-L., Syn. Commun. **1979**, 9, 37-39.

(29) (a) Payne, G.B., Tetrahedron **1962**, 18, 763-765.
(b) Ogata, Y.; Sawaki, Y., Ibid. **1964**, 20, 2065-2068.

(30) Gould, R.F., ed., Advances in Chemistry Series Vol. 76: Oxidation of Organic Compounds, American Chemical Society, New York (1978).

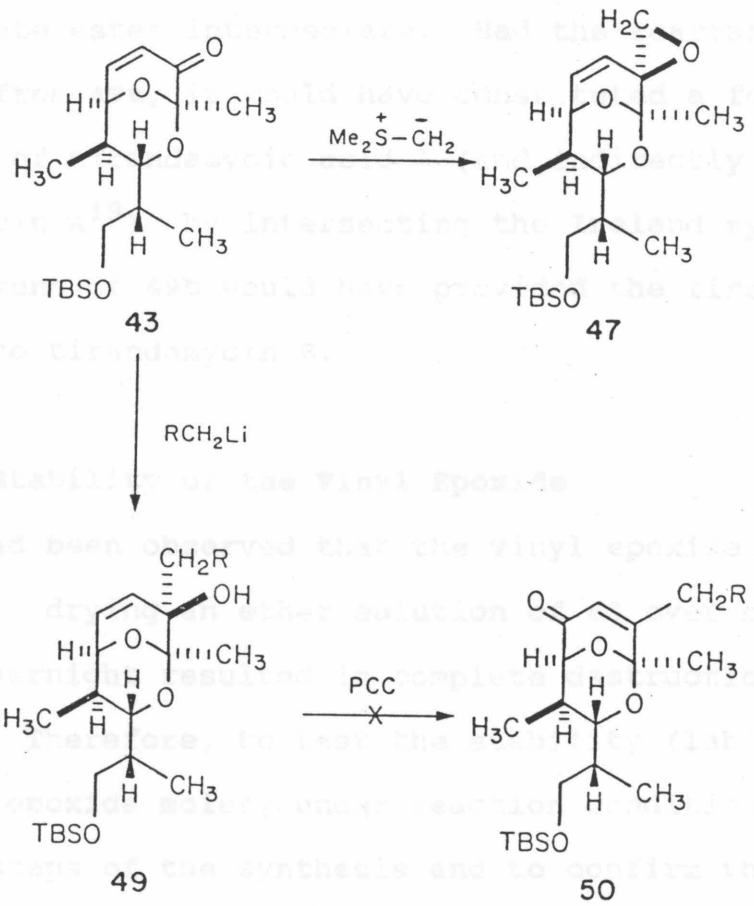
(31) Mimoun, H.; DeRoch, I.S.; Sajus, L., Tetrahedron **1970**, 26, 37-50.

had to be altered. The next approach selected for study involved addition of a functionalized carbon before formation of the bicyclic skeleton in hopes that a method of introducing it with the desired stereochemistry would allow eventual epoxide formation.

2.8. Constraints Introduced by the Dioxabicyclononane Structure

Before studying new potential approaches to streptolic acid several experiments were performed on the bicyclic enone **43**. First, reaction of the enone with the ylide obtained by deprotonation of trimethylsulfonium iodide gave an epoxide which differed from those obtained by diene epoxidation (it had been obtained, in fact, as a minor product) and is presumed to be **47**, resulting from the expected exocyclic attack of the nucleophilic species.[32] This provides an obvious candidate for consideration if synthetic analogues are to be made. Another experiment involved addition of methyllithium to the enone to give tertiary allylic alcohol **49a** quantitatively. This type of system is known to rearrange on treatment with certain chromium oxidants such as pyridinium chlorochromate (PCC) to give an enone with transposition of the oxygen

(32) Corey, E.J.; Chaykovsky, M., J. Am. Chem. Soc. **1965**, 87, 1353-1364.



(Scheme VI).[33] Under various conditions, however, this alcohol failed to rearrange and eventually decomposed as increasingly vigorous conditions were applied. The benzyloxymethyllithium addition product **49b** was also prepared and similarly failed to rearrange. This was attributed to steric congestion of the cage-like structure, which is apparently severe enough to preclude formation of

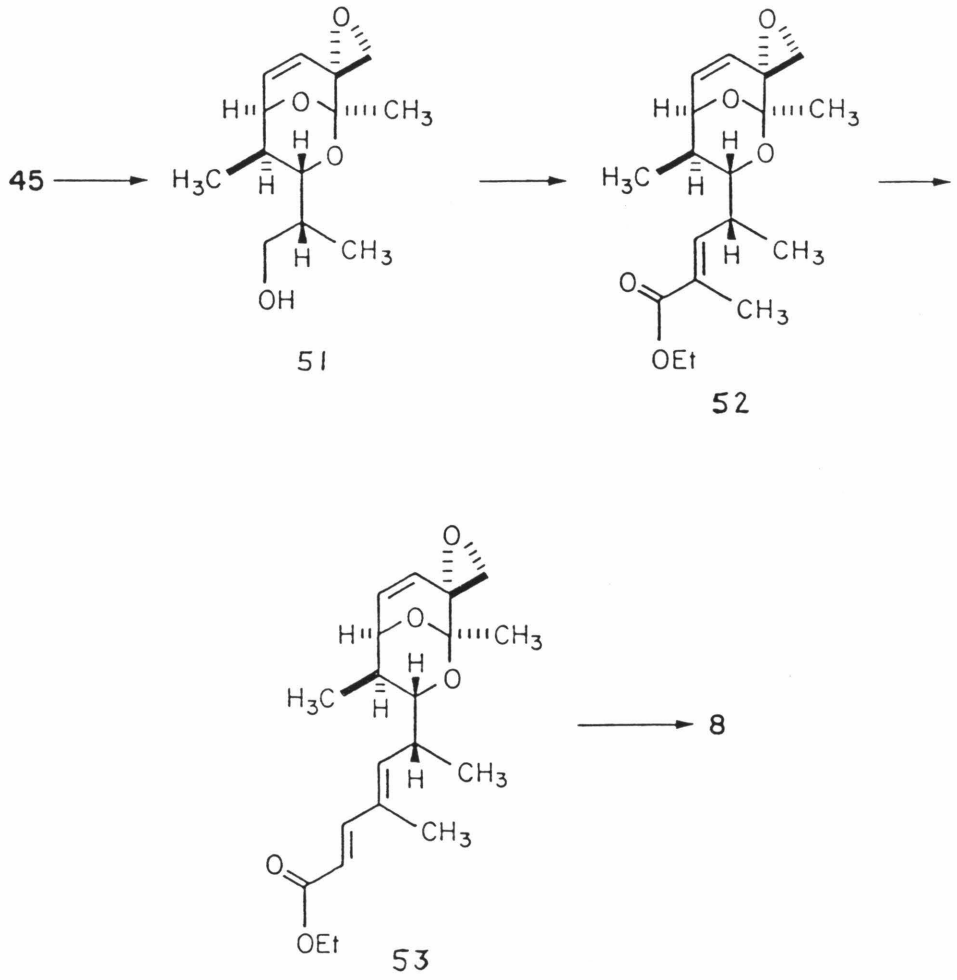
(33) Dauben, W.G.; Michno, D.M., J. Org. Chem. **1977**, 42, 682-685.

the chromate ester intermediate. Had the rearrangement occurred from **49a**, it would have constituted a formal synthesis of tirandamycic acid A (and indirectly of tirandamycin A[19]) by intersecting the Ireland synthesis.[17] Rearrangement of **49b** would have provided the first reported approach to tirandamycin B.

2.9. The Stability of the Vinyl Epoxide

It had been observed that the vinyl epoxide was quite sensitive; drying an ether solution of **45** over magnesium sulfate overnight resulted in complete destruction of the compound. Therefore, to test the stability (lability?) of the vinyl epoxide moiety under reaction conditions needed in the late steps of the synthesis and to confirm the identity of the material believed to be the correct epoxide, the remaining enone was converted to the diene and epoxidized with MCPBA. The material identified as the desired product was then transformed, albeit in low yield, to the ethyl ester of streptolic acid (Scheme VII). Spectral comparison of this material to published data for streptolic acid was quite convincing. (Hydrolysis to the acid itself gave too little pure material for good spectra to be obtained.) Thus the product identification in the epoxidation study was apparently correct. More importantly, if the vinyl epoxide can be introduced at any point beyond the ketal exchange used to form the dioxabicyclononane skeleton, it can be

Scheme VII



successfully carried through desilylation with fluoride anion, DIBAL-H reductions, Swern oxidations, and Wittig olefinations so that the synthesis of streptolic acid can be completed.

Chapter Three

A SECOND APPROACH TO STREPTOLIC ACID

The unsuccessful first approach to streptolic acid indicated that the difficulty in completing a synthesis would be construction of the vinyl epoxide. As an attempt to circumvent the problematic epoxidation, a new approach was conceived. A scheme was designed which would put in the carbon (to eventually become the methylene of that epoxide) before formation of the bicyclic structure. This offered the advantage of establishing the stereochemistry of the troublesome center at a simpler cyclic stage rather than working around the constraints introduced by the 2,9-dioxabicyclononane.

3.1. Addition of Benzyloxymethyllithium to the Enone (55)

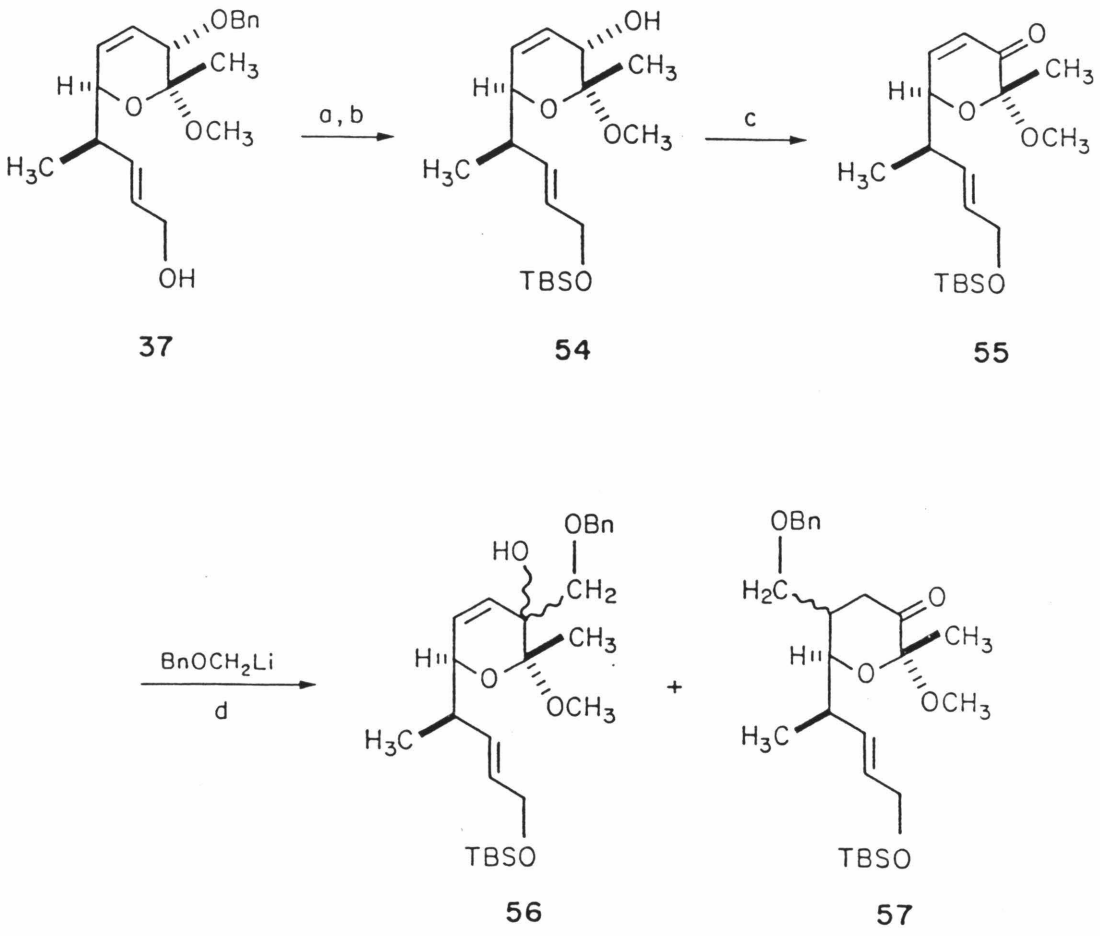
Consideration of the sequence already examined (Chapter 2) suggested that compound **37** was the latest convenient point of departure from known chemistry. This allylic alcohol was therefore protected (TBSCl) and the benzyl ether was cleaved (again using lithium di-**tert**-butylbiphenyl and again with excellent results) to give **54**. This allylic alcohol was oxidized using the Swern procedure (PCC oxidation was not nearly as clean by tlc) to give

enone **55**. It was anticipated that organometallic additions to the carbonyl of this enone would give predominantly axial attack; analysis revealed that the stereochemical relationship this would establish would be that desired for synthesis of the reticent epoxide if the resultant tertiary hydroxyl could eventually be induced to cyclize onto the added carbon, thus becoming the epoxide oxygen. A functionalized carbon nucleophile which would attack the enone selectively at the carbonyl was therefore needed. Benzyloxymethyllithium was selected as the primary candidate for consideration since an alkyllithium reagent should favor 1,2-addition over 1,4-addition.[34] Benzyloxymethyllithium was prepared by Still's procedure, which involves trans-metallation of benzyloxymethyl tri-**n**-butyltin with **n**-butyllithium in THF at -78°C (15 min). Since the reagent is unstable to higher temperatures, the reaction was conducted by adding a THF solution of the enone **55** to the alkyllithium solution maintained at -78°C.

This reaction gave one major product and a very minor by-product. This was reassuring in that the reaction appeared to be very selective: the ratio was better than 10:1 judging by tlc. However, the minor product was isolated and identified as a mixture of the conjugate addition products **57** (probably from attack by the reagent on

(34) Still, W.C., J. Am. Chem. Soc. **1978**, 100, 1481-1486.

Scheme VIII[a]



37 54 55

56 57

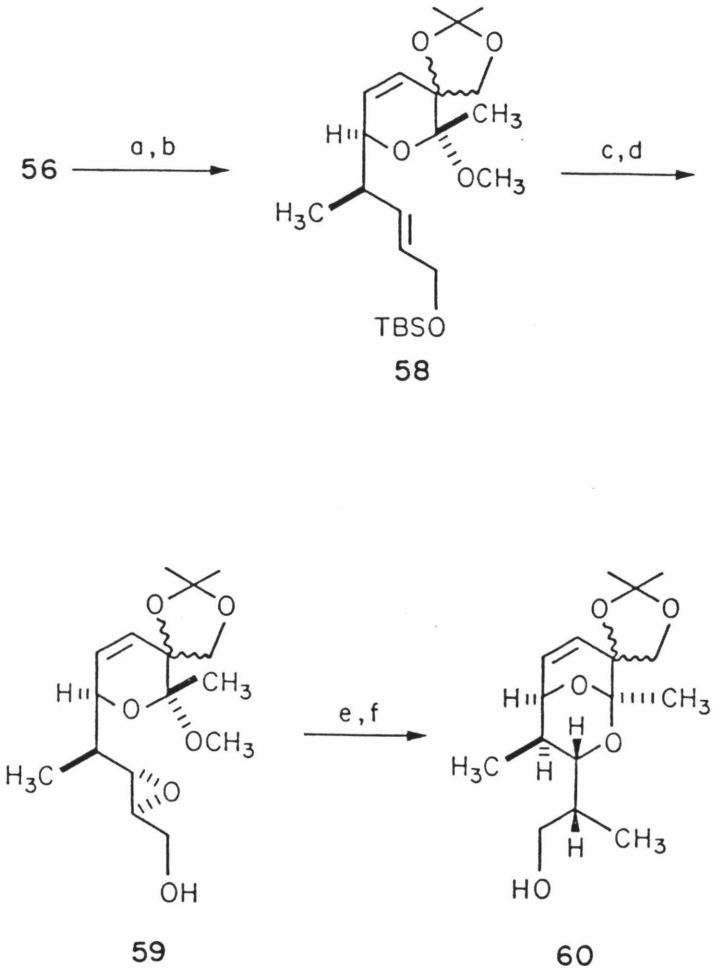
[a](a) TBSCl, imidazole, DMF (97%). (b) Lithium di-**tert**-butylbiphenyl, THF, -78°C (97%). (c) oxalyl chloride, DMSO, CH_2Cl_2, -78°C; Hunig's base (93%). (d) Benzyloxymethyllithium, THF, -78°C.

both faces of the enone at comparable rates, but perhaps because the methyl epimers were distinguishable.) This suggested that the major tlc spot represented both products corresponding to attack at the carbonyl and that they were inseparable by tlc. High field ^{1}H NMR (400 MHz), however, proved that while the major product was still a mixture of methyl epimers (as the starting material had been since the Claisen diastereomers were not separable up to this point) it was <u>not</u> a mixture at the newly formed center. Within the limits of NMR detection (approximately 5%) the alkyllithium reagent had attacked the carbonyl only from one face.

3.2. Proving the Stereochemistry of (56)

This result was surprising. The major 1,2-addition product was expected to be the desired material, but neither isomer had been expected to form to the complete exclusion of its epimer. It remained uncertain, therefore, which stereochemistry had been obtained since this could not be readily established from the spectra of the compound. Thus the product was carried through a series of transformations to give a compound from which the stereochemistry of this center could be unambiguously assigned. The benzyl ether was cleaved (in another application of lithium di-**tert**-butylbiphenyl) and the resultant 1,2-diol was allowed to react with 2-methoxypropene and catalytic anhydrous acid to give a spirocyclic acetonide (**58**). The silyl ether was then

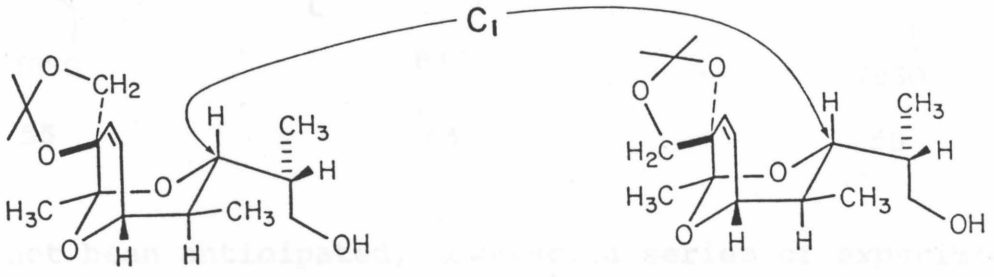
Scheme IX[a]



[a](a) Lithium di-**tert**-butylbiphenyl, THF, -78°C. (b) 2-methoxypropene, cat. **p**-TsOH. (c) $Bu_4NF \cdot 3H_2O$, THF, 0°C. (d) (+)-DIPT, **t**-BuOOH, $Ti(OR)_4$, CH_2Cl_2, -20°C. (e) Me_2CuLi, Et_2O, -20°C. (f) cat. **p**-TsOH, $CHCl_3$.

cleaved and the allylic alcohol side chain was converted, through a sequence analogous to that used previously, to a 2,9-dioxabicyclononane, **60**. This rather rigid cage-like structure was used to determine the stereochemistry of the ambiguous center, since the uncertainty due to the anomeric center had been removed and the diastereomers due to the methyl epimers could be separated.

High field NMR (500 MHz) again confirmed that the product represented complete facial selectivity and not an inseparable mixture at the center in question. Nuclear Overhauser Effect (N.O.E.) experiments were then performed and proved that the product corresponded to **61**.



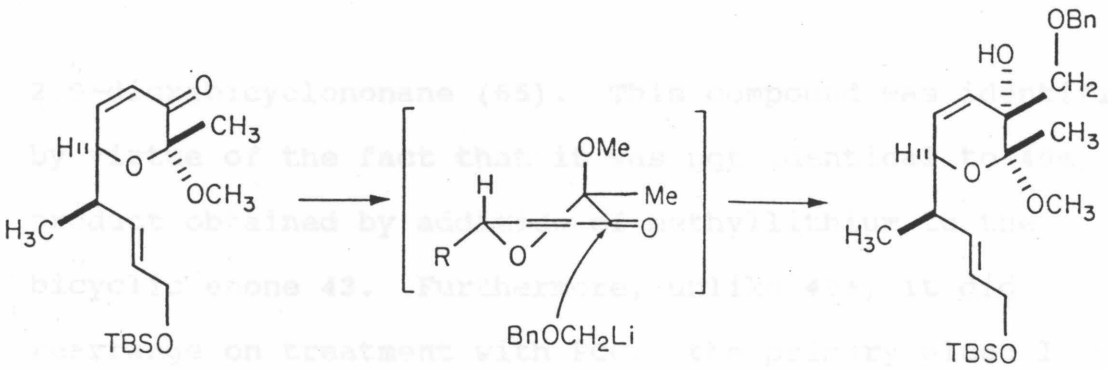
61 62

This interpretation is unambiguous as the methylene of the dioxolane ring (as well as both protons of the olefin), showed an interaction with the C-1 methine proton. Such an interaction would be impossible in **62**. Thus the carbon and oxygen on the chiral center in question are in the same relationship as the corresponding atoms in streptolic acid.

3.3. Probing the Source of the Stereoselectivity of the Benzyloxymethyllithium Addition

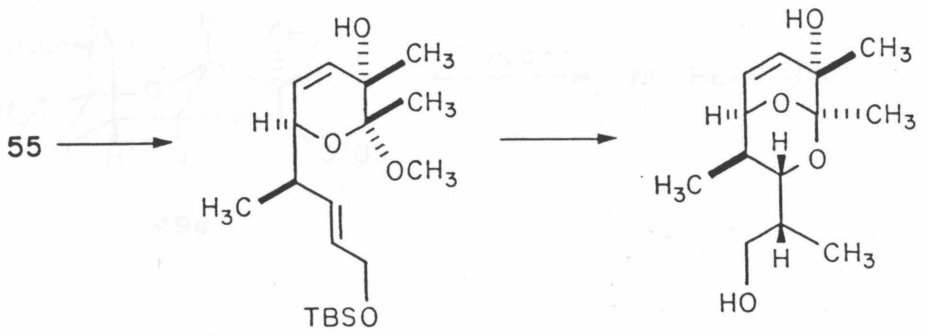
This product stereochemistry indicated that attack occurred exclusively from the "bottom" face (viewed as illustrated in **63**) which corresponds to the anticipated pseudo-axial attack. Since such remarkable selectivity

Scheme X



55 **63** **56**

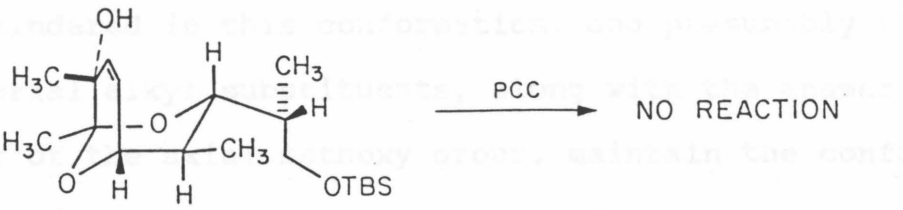
had not been anticipated, however, a series of experiments was performed to probe its source. The instability of the benzyloxymethyllithium species prevented its use under significantly different conditions. Therefore, experiments with methyllithium were used to explore the reaction. Addition of methyllithium under the same conditions (addition of the enone to MeLi in THF at -78°C) gave the corresponding product **64** quantitatively; the stereochemistry again had to be proven by conversion of the product to a



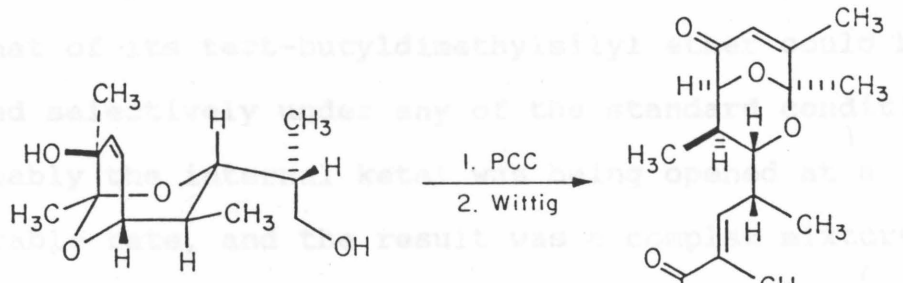
64 65

2,9-dioxabicyclononane (**65**). This compound was identified by virtue of the fact that it was not identical to **49a**, the product obtained by addition of methyllithium to the bicyclic enone **43**. Furthermore, unlike **49a**, it did rearrange on treatment with PCC; the primary alcohol oxidized quickly to the aldehyde, and the tertiary allylic alcohol rearranged on extended exposure to the reagent. Allowing the resultant aldehyde to react with carboethoxyethylidene triphenylphosphorane then gave **66** which constitutes a formal synthesis of tirandamycin A by intersecting Schlessinger's synthesis.[19]

More significant with regard to the stereocontrol observed in additions to the enone is the fact that reaction of the enone with methyllithium at 0°C gave exactly the same result as the reaction at -78°C, i.e., 1,2-addition to one face was observed in very high yield. Reaction with methylmagnesium iodide at either temperature gave the same



49a



65 66

product as well (along with significant quantities of the conjugate addition products.) Also, this same product was obtained whether the enone was added to a solution of methyllithium or the methyllithium was added slowly to a solution of the enone. This precludes a mechanism in which complexation of the methoxy on the top face blocks one side from attack while a second molecule attacks the accessible face. The insensitivity to both temperature and the nature of the organometallic species then strongly suggests that the axial methoxy adjacent to the carbonyl, and perhaps the transannular axial hydrogen, sterically control the reaction by blocking approach to this face. Attack on the other face

is unhindered in this conformation, and presumably the two equatorial alkyl substituents, along with the anomeric effect of the axial methoxy group, maintain the conformation suggested.

Knowing the stereochemistry of the benzyloxymethyllithium addition allowed the new path to be exploited. Unfortunately, neither the acetonide (isopropylidene) of **60** nor that of its **tert**-butyldimethylsilyl ether could be removed selectively under any of the standard conditions.[35] Presumably the internal ketal was being opened at a comparable rate, and the result was a complex mixture. Thus, while this approach seemed to be quite promising, the acetonide prevented completion of the synthesis from this point.

(35) Greene, T.W., Protective Groups in Organic Synthesis, John Wiley and Sons, New York (1981).

Chapter Four

COMPLETION OF THE SYNTHESIS OF STREPTOLIC ACID

A great deal of information had been gleaned at this point from two unsuccessful approaches to streptolic acid. The early stages of the synthesis had been worked out and comprised a considerable improvement on that portion of the tirandamycic acid synthesis.[17] Construction of the vinyl epoxide had been identified as the greatest obstacle in the synthesis, and a reaction for establishing the stereochemistry of this subunit had been found. Also, it had been shown that the vinyl epoxide could be carried through the remaining reactions if it could be formed after construction of the 2,9-dioxabicyclononane skeleton.

To take advantage of this information, a simple adaptation of the approach presented in Chapter 3 was made. Rather than cleaving the benzyl ether of **56** and protecting the diol as an acetonide, the benzyl ether was left intact. The tertiary allylic alcohol, after carefully considering the reactions involved, seemed relatively innocuous and was simply left unprotected.

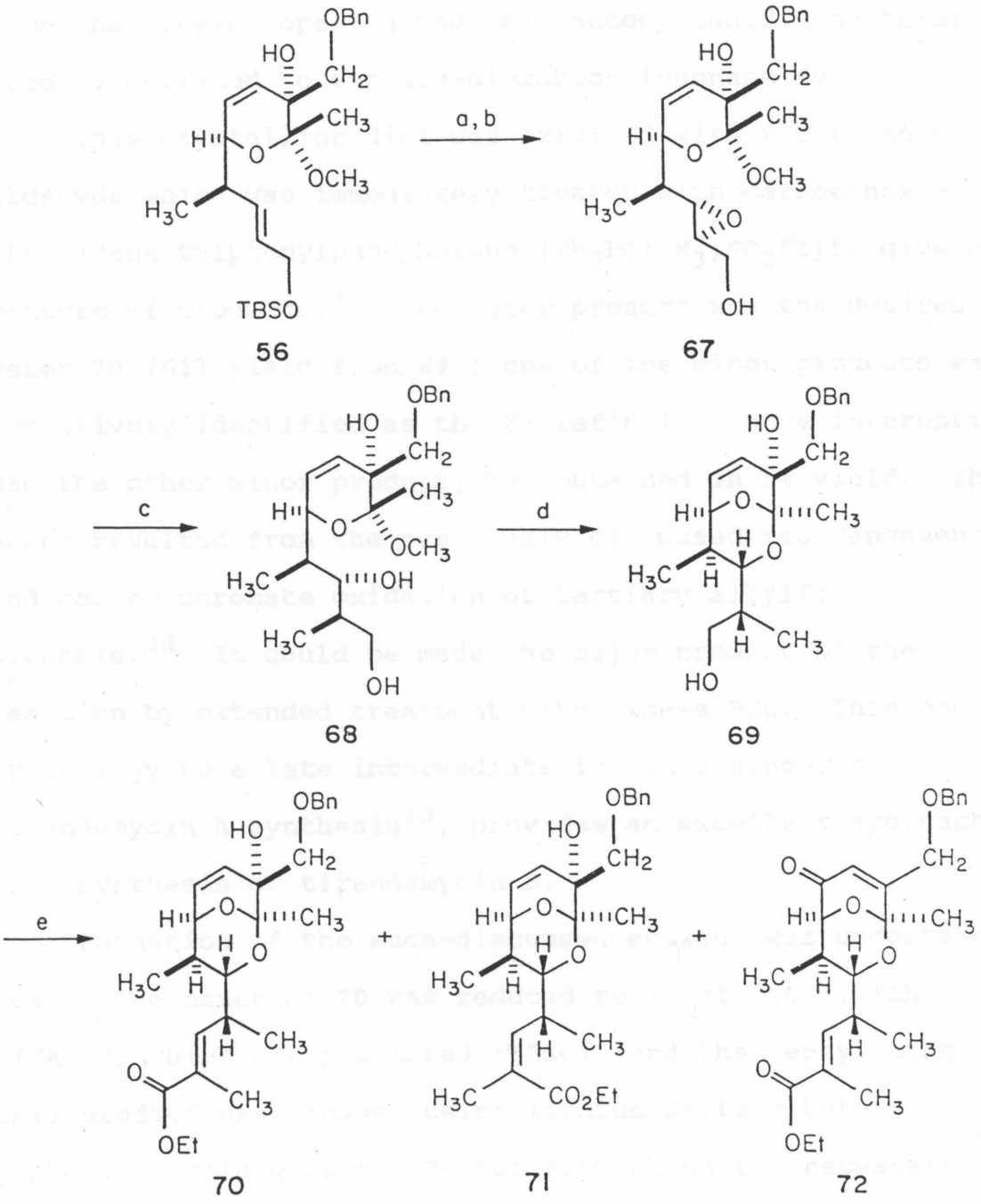
The silyl ether of **56** was cleaved, and the allylic alcohol was epoxidized using the Sharpless asymmetric epoxidation methodology.[25] This reaction proved extremely

selective despite the presence of a second allylic alcohol in the substrate. This was due to the fact that the tertiary hydroxyl was on the wrong face of the ring; the same chirality of the epoxidation complex which induces enantioselectivity in epoxidations of achiral allylic alcohols allows selective epoxidation of one enantiomer of a chiral allylic alcohol. (This 'kinetic resolution' effect has been used to purify one enantiomer of racemic mixtures by selective consumption of the other enantiomer.[36]) In this particular case, the tertiary alcohol cannot assist epoxidation of the cyclic olefin by the epoxidation complex involving the natural (+)-tartrate esters.

The next reaction, opening the epoxide with lithium dimethylcuprate, was the point at which the tertiary hydroxyl interfered. Although the yield and selectivity of the reaction were ultimately both very good, the second free hydroxyl lowered the solubility and reactivity of the starting material. Therefore, a larger excess of the cuprate (10 equivalents), higher reaction temperatures (0°C, then warming to room temperature), and longer reaction times were required. In some instances the reaction could not be driven to completion, and separation of the product from remaining starting material (**67**) and re-submission of this material to the reaction conditions were required. However,

(36) Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B., J. Am. Chem. Soc. **1981**, 103, 6237-6240.

Scheme XI[a]



56 67 68 69 70 71 72

[a](a) Bu_4NF, THF, 0°C (93%). (b) (+)-DIPT, t-BuOOH, $Ti(OR)_4$, CH_2Cl_2, -20°C (90%). (c) Me_2CuLi, Et_2O, 0°C. (d) cat. p-TsOH, $CHCl_3$ (68% **67**. (e) PCC, CH_2Cl_2; $Ph_3PC(CH_3)CO_2Et$, benzene, reflux 12 h (61% of **70**, 5% of **72**).

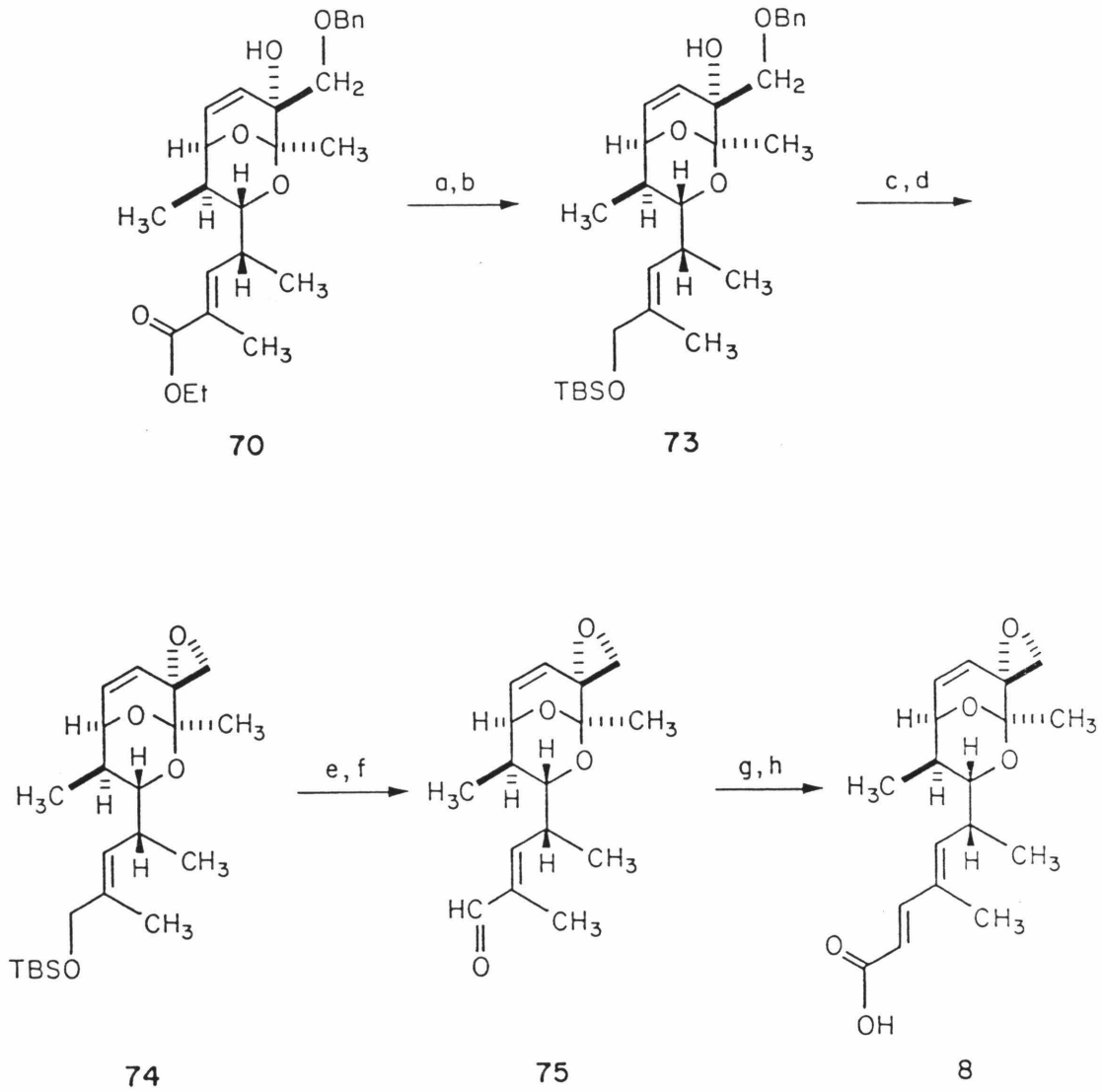
once the epoxide opening had been accomplished, the triol **68** readily cyclized to the 2,9-dioxabicyclononane **69**.

This crystalline diol was oxidized with PCC to an aldehyde which was immediately treated with carboethoxyethylidene triphenylphosphorane ($Ph_3PC(CH_3)CO_2Et$)to give a mixture of products.[17] The major product was the desired ester **70** (61% yield from **69**); one of the minor products was tentatively identified as the **Z**-olefin **71**. More interesting was the other minor product, **72**, obtained in 5% yield. This enone resulted from the previously discussed rearrangement induced by chromate oxidation of tertiary allylic alcohols.[33] It could be made the major product of the reaction by extended treatment with excess PCC. This enone, by analogy to a late intermediate in Schlessinger's tirandamycin A synthesis[19], provides an excellent approach to a synthesis of tirandamycin B.

Formation of the much-discussed epoxide was undertaken next. The ester of **70** was reduced to an alcohol (with DIBAL-H) which was protected (TBSCl) and the benzyl ether of this product was cleaved using lithium di-**tert**-butylbiphenyl. This gave a 1,2-diol from which the necessary epoxide was formed by treatment with sodium hydride and **p**-toluenesulfonyl imidazolide (**p**-TsIm) in THF.[37] Tosylation of the primary alcohol occurred selectively, and

(37) Ireland, R.E.; Courtney, L.; Fitzsimmons, B.J., J. Org. Chem. **1983**, 48, 5186-5198.

Scheme XII[a]



70 73 74 75 8

[a](a) DIBAL-H, Et_2O, -78°C (95%). (b) TBSCl, imidazole, DMF (93%). (c) Lithium di-**tert**-butylbiphenyl, THF, -78°C (94%). (d) p-TsIm, NaH, THF (96%). (e) Bu_4NF, THF, 0°C (97%). (f) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Hunig's base. (g) carboethoxymethylidene triphenylphosphorane, 12 h (74% from alcohol). (h) 10% NaOH, MeOH (100% crude yield).

the tertiary alkoxide displaced the tosylate **in situ** to form the epoxide; the reaction was clean and proceeded in excellent yield. Based on the results reported in Chapter 2, completion of the synthesis of streptolic acid was virtually assured at this point, since the sensitive vinyl epoxide had been shown to survive the reaction condition necessary to transform this molecule into the preliminary target.

The synthesis of streptolic acid from this point (**74**) involved deprotection (Bu_4NF) and Swern oxidation of the alcohol. The resulting aldehyde, **75**, is the compound required for coupling to the bottom half phosphonate reagents reported.[18,19] However, the immediate goal was a synthesis of streptolic acid to prove unambiguously the viability of the top half synthesis. Therefore, the aldehyde was treated with carboethoxymethylidene triphenylphosphorane **in situ** to give the ethyl ester of streptolic acid. Hydrolysis of the ester (10% NaOH in methanol) produced streptolic acid which, by comparison to published physical and spectral data, was identical to that obtained by degradation of the antibiotic streptolydigin.[8]

Chapter Five

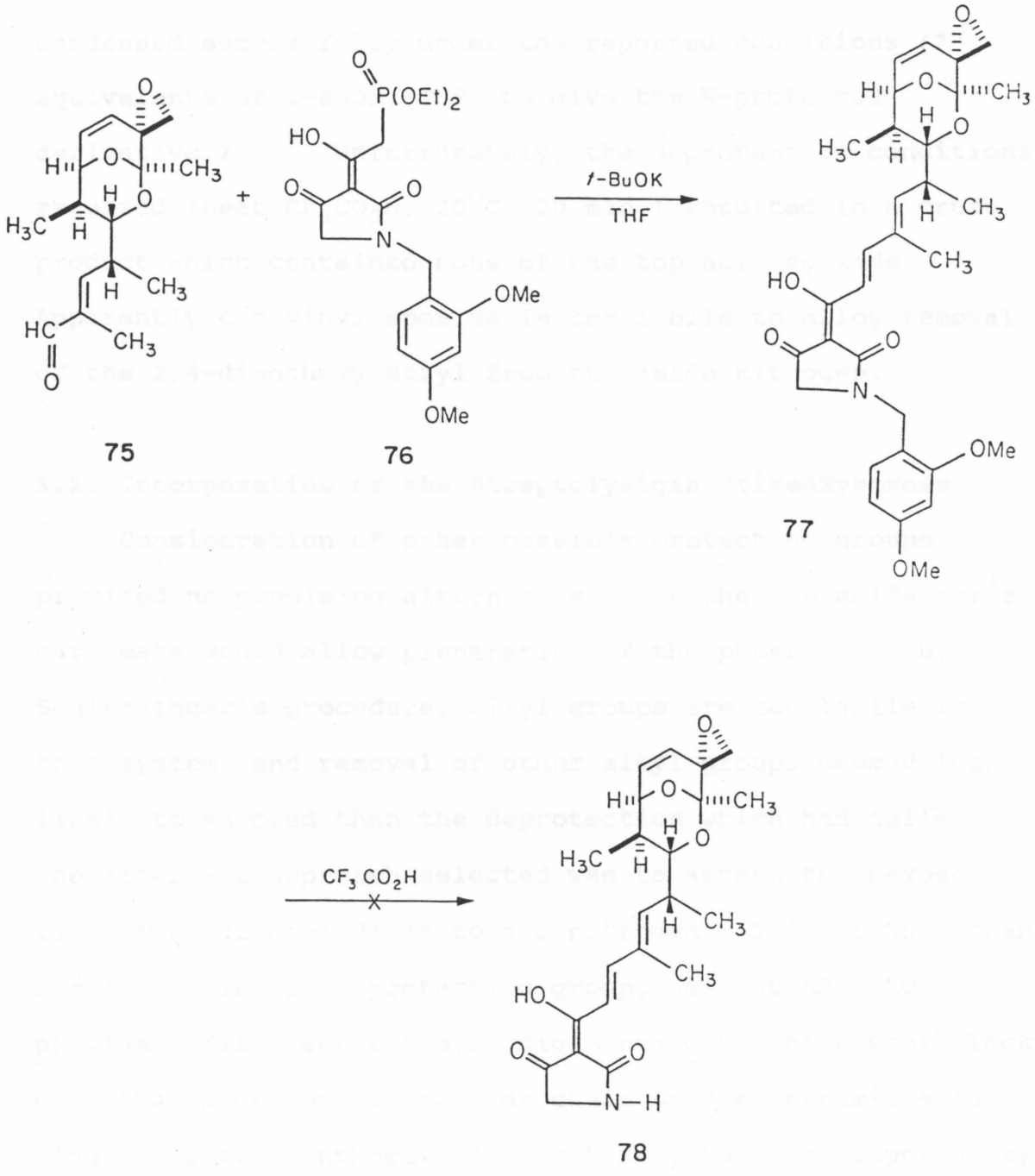
ATTEMPTS TO COMPLETE THE SYNTHESES OF STREPTOLYDIGIN AND ANALOGUES

Completion of the synthesis of streptolic acid confirmed the viability of the synthetic scheme developed for preparation of the top half of the antibiotic streptolydigin. Using this scheme, a relatively large quantity of the top half aldehyde **75** could readily be prepared for connection to acyltetramic acid phosphonates such as that developed by Schlessinger for his synthesis of tirandamycin A.[19] Therefore, work on preparing and connecting such reagents was undertaken in hope of synthesizing analogues of the natural antibiotics and, ultimately, of completing a synthesis of streptolydigin.

5.1. Using Schlessinger's Phosphonate

The first logical approach was to use the reagent and conditions reported by Schlessinger to attach the tirandamycin bottom half, the unsubstituted acyltetramic acid.[19a] Connection of this to the streptolydigin top half would provide the first synthetic analogue of streptolydigin and consequently some insight into the source of the large difference in antibiotic activity between streptolydigin

Scheme XIII



75 76 77 78

and tirandamycin A. Thus the phosphonate **76** was prepared according to the procedure outlined by Schlessinger and condensed successfully under the reported conditions (2 equivalents of t-BuOK, THF) to give the N-protected derivative **77**.[19] Unfortunately, the deprotection conditions required (neat CF_3CO_2H, 20°C, 20 min.) resulted in a crude product which contained none of the top half epoxide. Apparently the vinyl epoxide is too labile to allow removal of the 2,4-dimethoxybenzyl from the amide nitrogen.

5.2. Incorporation of the Streptolydigin Trideoxyhexose

Consideration of other possible protecting groups provided no promising alternatives; neither an amide nor a carbamate would allow preparation of the phosphonate by Schlessinger's procedure, silyl groups are too labile for this system, and removal of other alkyl groups seemed less likely to succeed than the deprotection which had failed. The alternate approach selected was to append the hexose ring from streptolydigin to the nitrogen. This, rather than simply serving as a protecting group, was intended to provide a different streptolydigin analogue which would lack only the amide-containing side chain on the tetramic acid ring. A short synthesis of this hexose had been reported by Kelly.[38] This was expected to provide an easy way to make a

(38) Kelly, T.R.; Kaul, P.N., J. Org. Chem. **1983**, 48, 2775-2777.

protected glycosyl chloride derivative of the hexose subunit. The nitrogen of a protected glycine derivative could then be alkylated with this reactive alkyl halide and the hexose ring would serve as the desired protecting group during the preparation of the corresponding phosphonate.

Difficulties arose almost immediately in the synthetic sequence. Kelly and Kaul reported a 75% yield of the Grignard product **81** and a diastereomeric ratio of about 10:1, with the diastereomers separable by "careful flash chromatography".[38] None of these results could be reproduced. The yield obtained was reproducibly 36-37%, only half of that reported. By tlc, there was only one product (besides the protonated Grignard reagent which could be visualized weakly.) Analysis of this product by ^{1}H NMR indicated that the one tlc spot represented both diastereomers, which were not separable even by tlc.[39] Furthermore, the apparent ratio of diastereomers in this mixture is no better than 2:1. Aqueous acid hydrolysis of this inseparable mixture under the reported conditions gave two products in approximately a 2:1 ratio by tlc confirming that the previous product had been a mixture.

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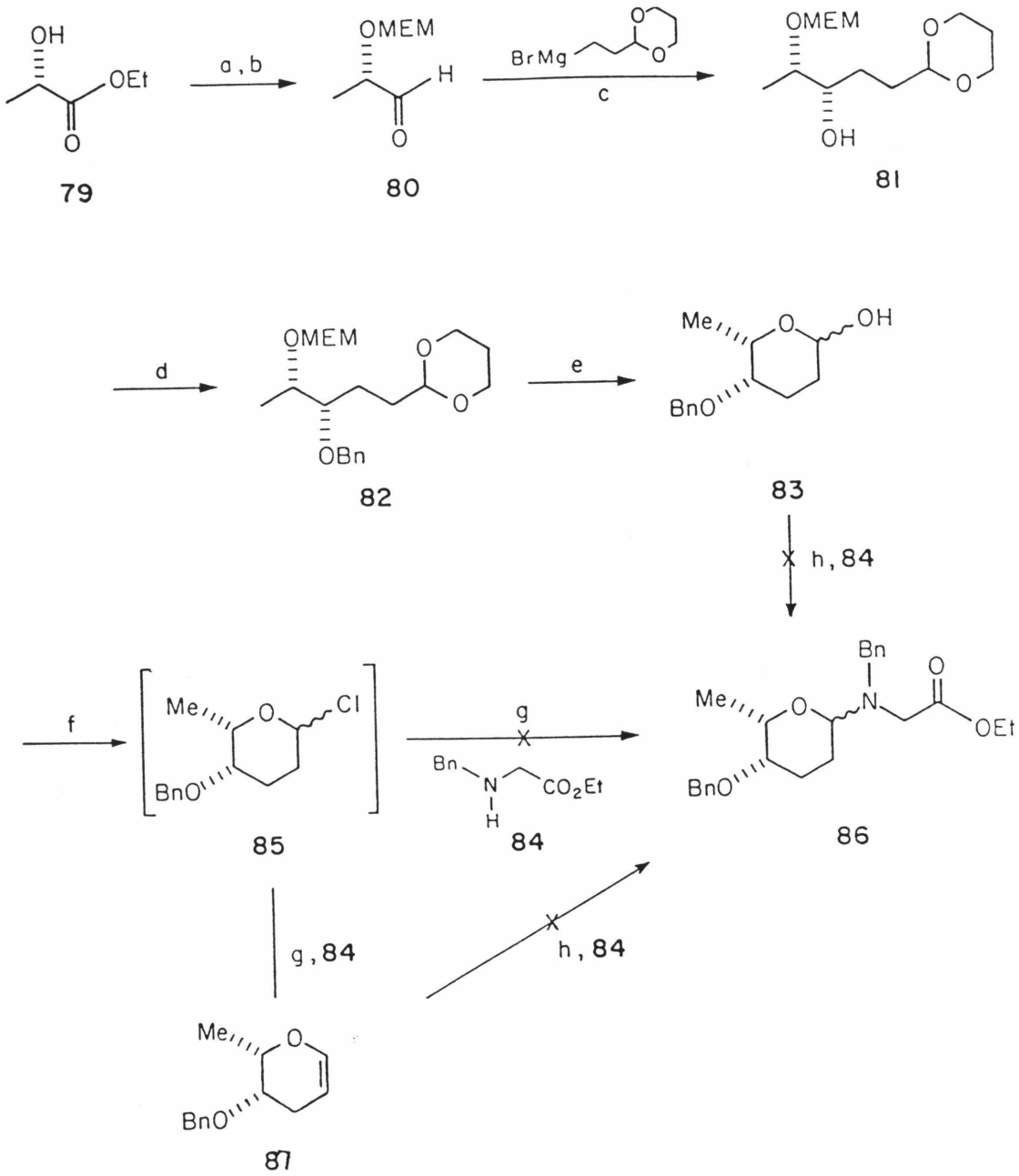
(39) Under the tlc conditions reported (ref. 38), the product had an R_f of about 0.8. Adjusting the solvent polarity to lower the R_f to 0.3-0.4 or changing solvent systems still gave no resolution of the two products by tlc.

Scheme XIV[a]



[a] (a) MEMCl, Hunig's base, CH_2Cl_2. (b) DIBAL-H, CH_2Cl_2, -78°C. (c) THF, -78°C (36%). (d) KH, BnBr, THF (75%). (e) 10% HCl, acetone, reflux, 2 h. (f) CCl_4, TDAP, THF. (g) CH_2Cl_2, 25°C. (h) cat. **p**-TsOH, $CHCl_3$.

For the present application, the hexose was needed in protected form, so the mixture of Grignard products was treated with potassium hydride and benzyl bromide in THF. Again one tlc spot was observed, while the ^{1}H NMR showed what appeared to be two diastereomers. Hydrolysis of this benzylated material gave two products by tlc, although the two compounds were not cleanly separated by chromatography. However, clean samples of each of the two compounds were obtained and were judged to be diastereomers by ^{1}H NMR. That these were not simply separable anomers was confirmed by the fact that aqueous acid did not interconvert them.

Although quite tedious (not nearly as straightforward or efficient as promised by the literature report), this provided the desired hexose along with its diasteromer. Which diastereomer was the correct one was not obvious but it was assumed to be the major one. This was treated with CCl_4 and hexamethylphosphoric triamide (HMPT, also referred to as **tris**-dimethylaminophosphine or TDAP) to form the glycosyl chloride **85**.[23] The chloride was not isolated as it was not stable enough to give a clean tlc; it was treated with N-benzylglycine ethyl ester after a mild work-up. This reaction gave only one new product (by tlc) which proved to be the glycal **87** (based on its characteristic ^{1}H NMR). No product exhibiting the tlc mobility expected for the desired tertiary amine was observed. Subsequent attempts using different solvents and even silver catalysts (silver oxide

and silver carbonate) also resulted in isolation of the glycal.

Two ways of circumventing this problem were tried. First, the hexose **83** was treated with N-benzylglycine ethyl ester and a trace of p-TsOH in $CHCl_3$ over molecular sieves. It was thought that this might give the pyranosyl amine **86** directly. However, it resulted in a complex mixture of products with no single major product by tlc. This was not too surprising since possible side reactions are numerous, and the route was consequently abandoned. Next, several attempts were made to induce the glycal to react with N-benzylglycine ethyl ester under acid catalysis. Since the glycal was obviously formed by elimination of HCl induced by this same amine, and the amine hydrochloride did not add across the glycal in that reaction, it was not surprising that this route also failed.

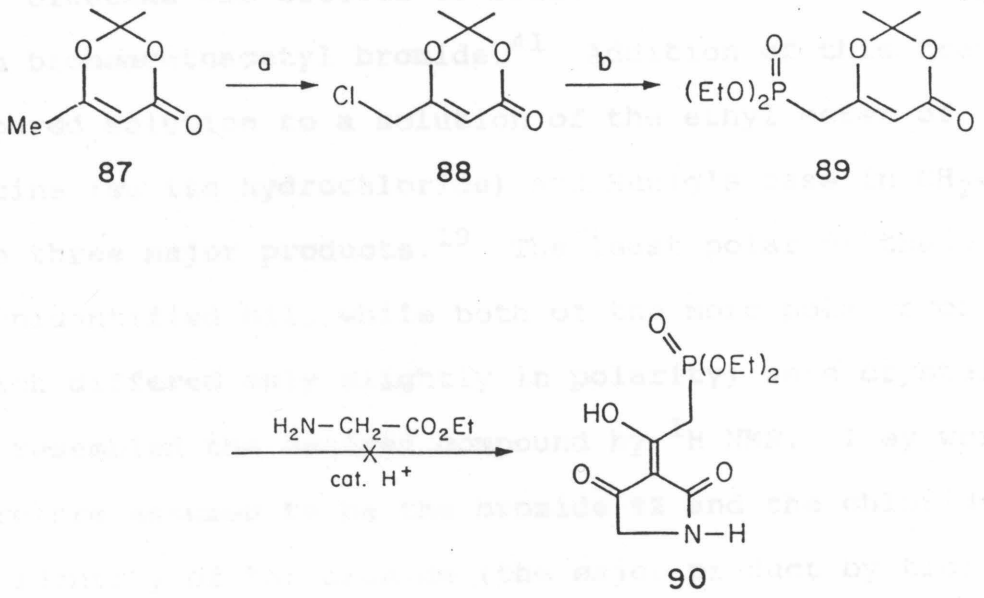
5.3. Using the Boeckman Phosphonate

Lacking any more promising approaches to this tertiary amine, the problem of attaching the simpler bottom half (with the nitrogen unsubstituted) was again addressed. According to Schlessinger, the phosphonate **90**, reported by Boeckman, et al.,[18a] failed to condense with the tirandamycin A top half aldehyde due to the unprotected amide. This could be caused by side reactions involving the top half ketone or the acidity of the protons adjacent to

it. Since these possibilities do not exist with the streptolydigin top half, it was hoped that this phosphonate might be induced to condense with **75**.[40]

Before the report by Schlessinger of the connection of a phosphonate bottom half to the tirandamycin A top half,

Scheme XV[a]



[a](a) LDA, THF, -78°C; 2 equiv. C_2Cl_6. (b) $(EtO)_2P(O)H$, KH, 10% DMF/Et_2O.

(40) The reaction conditions for this Wittig condensation are basic and nucleophilic. While the vinyl epoxide of the top half of streptolydigin is quite susceptible to electrophilic attack as already noted, it is expected to be more stable than the keto-epoxide portion of tirandamycin A under basic and nucleophilic conditions.

the best precedent for this Wittig reaction was the report by Boeckman of a synthesis and some model reactions of the phosphonate **90**.[18a] His synthesis is outlined in Scheme XV. However, numerous attempts to induce the reaction of **89** with the methyl and ethyl esters of glycine under conditions approximating those reported (no experimental detail was given) were all unsuccessful. Therefore, an adaptation of Schlessinger's phosphonate synthesis was tried.[19]

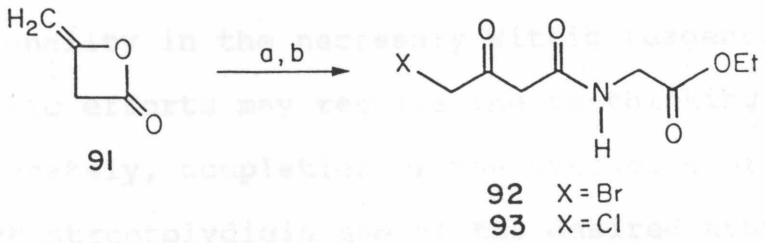
Diketene was allowed to react with bromine in CCl_4 to form bromoacetoacetyl bromide.[41] Addition of this freshly prepared solution to a solution of the ethyl ester of glycine (as its hydrochloride) and Hunig's base in CH_2Cl_2 gave three major products.[19] The least polar of these was an unidentified oil, while both of the more polar products (which differed only slightly in polarity) were crystalline and resembled the desired compound by ^1H NMR. They were therefore assumed to be the bromide **92** and the chloride **93**. The identity of the bromide (the major product by tlc) was confirmed by C, H, and N microanalyses.[42] However, attempts to obtain the desired phosphonate **90** by reaction of either of these compounds with the anion of diethyl phosphite (formed with KH in THF) were unsuccessful.[19] Although in one instance a yield of 2% of the desired product was

(41) Tabei, K.; Kawashima, E.; Kato, T., Chem. Pharm. Bull. **1979**, 27, 1842-1849.

(42) This elemental analysis was performed by L. Henling, Analytical Services, Dept. of Chemistry, California Institute of Technology, Pasadena, CA, 91125.

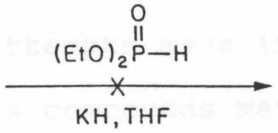
obtained, this result was not reproducible. Reaction of this small quantity of material with the top half aldehyde under Schlessinger's conditions returned the starting aldehyde. However, since the phosphonate could not be recovered and further attempts to prepare it proved futile, this attempt to attach a bottom half to the streptolydigin top half was also finally abandoned.

Scheme XVI[a]



91

92 X = Br
93 X = Cl



90

[a](a) Br_2, CCl_4, -20°C. (b) glycine ethyl ester hydrochloride, Hunig's base, CH_2Cl_2.

Chapter Six
CONCLUSIONS

The preceding work presents a viable and efficient synthesis of streptolic acid. This pathway also offers ready access to the top portions of both tirandamycin A and tirandamycin B as well as synthetic analogues. A formal synthesis of tirandamycin A was also achieved.

Technology for attachment of the bottom halves of these antibiotics is complicated by the high density of functionality in the necessary Wittig reagents, and future synthetic efforts may require the re-thinking of this step. Unfortunately, completion of the synthesis of the natural product streptolydigin and of the desired hybrid-type analogues could not be accomplished using the methods available. The attempts made indicate that a successful synthesis of these compounds may still comprise a major effort despite the availability of the various top halves.

Several examples of cleavages of benzyl ethers using lithium di-**tert**-butylbiphenyl have been presented. These examples all provided excellent yields of very clean products. Since the reagent has been used so successfully with various complex intermediates, it appears to be an excellent reaction for the deprotection of benzyl ethers.

EXPERIMENTAL SECTION

Melting points were measured with a Hoover melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded with a Varian EM 390 spectrometer unless otherwise specified. Data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane as an internal standard (multiplicity, integrated relative intensity, coupling constants). Optical rotations were measured with a Jasco DIP-181 polarimeter in a 1 dm cell of 1 mL capacity; chloroform for these measurements was filtered through activity III alumina immediately prior to use. Infrared (IR) spectra were recorded on a Perkin-Elmer 1310 spectrometer.

Solvents for non-aqueous reactions were distilled immediately before use except for diethyl ether which was at times used directly from freshly-opened cans labeled 'anhydrous ether'. Reactions were run under an atmosphere of argon which had been dried by passage through a drying tower filled with Drierite. Vessels for all non-aqueous reactions were flame dried under vacuum (approximately 0.2mm) then filled with argon via a manifold to avoid exposure to oxygen and moisture. Unless otherwise specified all reagents used were reagent grade chemicals obtained from

standard chemical suppliers and were used without further purification. "Silica" refers to silica gel 60, 70-230 mesh, supplied by E. Merck; "flash silica" refers to silica gel 60, 230-400 mesh, also supplied by E. Merck. Alumina (Woelm) was adjusted to the stated activity as directed. Flash chromatography refers to the procedure developed by Still[43] and adaptations of this procedure. Elemental analyses were performed by Spang Microanalytical Laboratory, Star Route 1, Box 142, Eagle Harbor, MI 49951.

1,5-anhydro-2-deoxy-3-O-propanoyl-4-O-benzyl-6-O-tert-butyldimethylsilyl-D-gluco-hex-1-enitol (16)

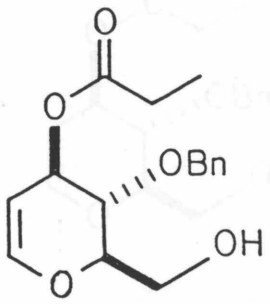
This compound was prepared from tri-O-acetyl-D-glucal (Aldrich) following the procedure of Ireland, Ernst, and Wuts.[17]

1,5-anhydro-2-deoxy-3-O-propanoyl-4-O-benzyl-D-gluco-hex-1-enitol

Silyl ether **16** (692.7 mg, 1.71 mmol), prepared by the procedure of Ireland, et al.,[17] was dissolved in 3.0 mL of THF and cooled to 0° in an ice bath. Tetra-n-butylammonium fluoride trihydrate (642 mg, 2.03 mmol) dissolved in 5.0 mL of THF was added and the mixture was stirred at 0°C for 1 h.

(43) Still, W.C.; Kahn, M.; Mitra, A., J. Org. Chem. **1978**, 43, 2923-2925.

The reaction mixture was then diluted with 100 mL of ether and extracted twice with 25 mL portions of water. The product was purified by flash chromatography (20% ethyl acetate/petroleum ether eluant) providing 490 mg (98% yield) of colorless oil which crystallized slowly (m.p. 43-45°).

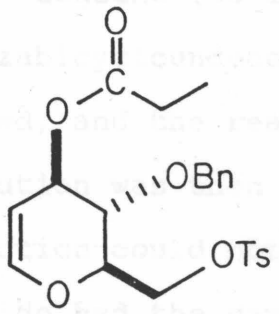


R_f=0.32 (4:1 petroleum ether:ethyl acetate).
IR ($CHCl_3$): 3560, 1715, 1635 cm^{-1}
^1H NMR ($CDCl_3$): 1.10 (t, 3H, J=8 Hz), 2.23 (q, 2H, J=8 Hz), 2.3 (brs, 1H), 3.8 (m, 4H), 4.70 (s, 3H), 5.50 (m, 1H), 5.74 (m, 1H), 6.36 (dd, $J_{1,2}$=6 Hz, $J_{1,3}$=1.5 Hz), 7.32 (s, 5H).
$[\alpha]_D^{23}$=-50.9° (c 1.52, $CHCl_3$).
Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.80; H, 7.00.

1,5-anhydro-2-deoxy-3-O-propanoyl-4-O-benzyl-6-O-(4-methylphenylsulfonyl)-D-gluco-hex-1-enitol (29)

The hydroxymethyldihydropyran (5.44 g, 18.6 mmol) was added to 25 mL of pyridine cooled to 0°C. Crystalline p-toluenesolfonyl chloride (11.0 g, 57.6 mmol) was added, and the suspension was stirred to dissolve it. The reaction was then allowed to warm to ambient temperature and stirred overnight. Judged complete by tlc, the reaction was then poured into 300 mL of dichloromethane and extracted with three 150 mL portions of saturated copper sulfate solution, 150 mL of ammonium chloride, 150 mL of sodium bicarbonate, and 100 mL of brine. The organic layer was then dried over

anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed (15% ethyl acetate/petroleum ether) to provide 7.45 g (90% yield) of the tosylate **29**.



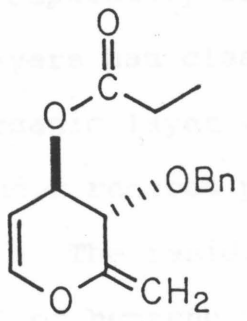
R_f=0.46 (4:1 petroleum ether:ethyl acetate).
IR ($CHCl_3$): 1720, 1638, 1168 cm^{-1}.
^1H NMR ($CDCl_3$): 1.11 (t, 3H, J=8 Hz), 2.25 (q, 2H, J=8 Hz), 2.42 (s, 3H), 3.78 (dd, 1H, $J_{3,4}$=6 Hz, $J_{4,5}$=8 Hz), 4.1 (m, 1H), 4.27 (m, 2H), 4.62 (s, 2H), 4.71 (m, 1H), 5.3 (m, 1H), 6.23 (d, 1H, J=6 Hz), 7.3 (m, 7H), 7.78 (m, 2H).
$[\alpha]_D^{23}$=-9.1° (C 1.20, $CHCl_3$).
Anal. Calcd for $C_{23}H_{26}O_7S$: C, 61.87; H, 5.87. Found: C, 61.79; H, 5.86.

4R-propanoyloxy-5S-benzyloxy-6-methylidenedihydropyran (30)

Freshly prepared tosylate **29** (7.44 g, 16.6 mmol) was dissolved in 35 mL of methyl ethyl ketone and the flask was wrapped with foil to exclude light. Sodium iodide (17.0 g, 113 mmol) was added and the suspension was immersed in a heating oil bath which equilibrated at 80°C. The red suspension was stirred at this temperature for 4 h, allowed to cool to room temperature, and diluted with 400 mL of dichloromethane. Water (100 mL) was added to give two phases with no precipitates. The layers were separated and the organic solution was shaken with 50 mL of sodium sulfite. This reductive process was repeated giving an

almost colorless solution which was washed with brine and dried with $MgSO_4$. The resultant slightly yellow crude iodide (6.07 g, clean by tlc and NMR) was used in the next reaction without further purification.

Benzene (50 mL) was added to the crude iodide. Diazabicycloundecene (DBU: 4.5 mL, 30.1 mmol) was also added, and the reaction flask was wrapped with foil. This solution was then heated in an 84°C oil bath for 4 h. (The reaction could not be monitored by tlc because the starting iodide had the same R_f as the product. Subsequent experiments indicated that the reaction was complete in less than 1 h.) The solvent was then removed under reduced pressure and the residue was flash chromatographed, eluting with 5% ethyl acetate/petroleum ether, to give 3.92 g (86% yield from the tosylate) of the divinyl ether **30**.



R_f=0.26 (10:1 petroleum ether:ethyl ether).
IR ($CHCl_3$): 1715, 1638 cm^{-1}.
^1H NMR ($CDCl_3$): 1.08 (t, 3H, J=8 Hz), 2.21 (q, 2H, J=8 Hz), 3.89 (m, 1H), 4.49 (s, 1H), 4.54 (q, 2H, J=11 Hz), 4.89 (d, 1H, J=1 Hz), 5.0 (m, 2H), 6.45 (d, 1H, J=5 Hz), 7.30 (s, 5H).
$[\alpha]_D^{23}$=-122° (C 4.62, $CHCl_3$).
Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.91; H, 6.59.

Methyl-2S-[1S-3-methylidene-4S-benzyloxy-1,4-dihydropyranyl]-propanoate (31)

Hexamethyldisilazane (3.40 mL, 16.3 mmol) in 30 mL of THF was cooled to -78°C and n-BuLi (5.9 mL of a 2.55 M solution in hexanes, 15.0 mmol) was added dropwise with stirring. After stirring for 10 min. more, tert-butyldimethylsilyl chloride (TBSCl: 2.45 g, 16.2 mmol) dissolved in 10 mL of hexamethylphosphoramide (HMPA) was added and the reaction solution was stirred for 3 min. Divinyl ether **30** (2.05 g, 7.48 mmol) dissolved in 4.0 mL of THF was then added dropwise over 2 min., and after 5 min. more the reaction was allowed to warm slowly. When the reaction was at about 0°C (as judged by the melting of the frost condensed on the flask) the mixture was poured into 300 mL of petroleum ether layered on 200 mL of ice water in a separatory funnel. This mixture was shaken until both layers had cleared, and then it was quickly separated. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure.

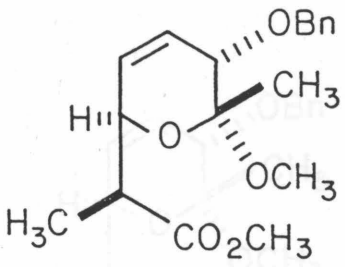
The residue was briefly dried under high vacuum and 20 mL of benzene were added. After refluxing this solution for 1 h to allow the silyl ketene acetal to rearrange, the solvent was again removed and 10 mL of HMPA were added. Potassium fluoride dihydrate (2.2 g, 23 mmol) and potassium bicarbonate (2.2 g, 22 mmol) were added to hydrolyze the

silyl ester resulting from Claisen rearrangement. After 5 min. of stirring this suspension at room temperature, methyl iodide (2.5 mL, 40 mmol) was added and the reaction was stirred overnight at ambient temperature to methylate the potassium carboxylate. The reaction was then diluted with 100 mL of ether and extracted with two 100 mL portions of water, then with 100 mL of brine. The clear solution was dried over $MgSO_4$, the solvent was removed on a rotary evaporator, and the residue was flash chromatographed, eluting with 15% ethyl acetate/peteoleum ether. This provided 1.832 g (85% yield) of the desired enol ether as an inseparable mixture of methyl epimers.

Methyl-2S-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-propanoate (34)

The enol ether products from several Claisen rearrangements were combined to give 9.50 g of crude material which was dissolved in 120 mL of methanol. A few small crystals of anhydrous **p**-toluenesolfonic acid were added and the reaction was stirred overnight at ambient temperature. Ether (500 mL) was then added and the solution was extracted with four 200 mL portions of saturated sodium bicarbonate solution and 50 mL of brine. The yellow organic solution was then dried with $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue resulted in isolation of 3.08 g (29% yield) of **34b**

(inseparable from **35b**), and 7.40 g (70% yield) of the mixed major anomers **34a** and **35a**. This represented Claisens starting with a total of 38.6 mmol, and therefore constituted an 85% yield from the divinyl ether. The minor anomer was readily recycled by treatment with catalytic p-toluene-sulfonic acid in methanol. (It is noteworthy that an anomeric ratio of 4.0:1 was usually observed for this ketalization. This particular reaction provided the anomers in a 2.4:1 ratio which was probably due to stopping the reaction before equilibrium had been established.)

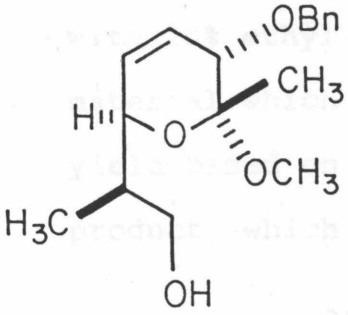


R_f=0.18 (9:1 petroleum ether:ethyl acetate).
IR ($CHCl_3$): 1728 cm^{-1}.
^1H NMR ($CDCl_3$): 1.10 (d, 3H, J=8 Hz), 1.34 (s, 3H), 2.5 (m, 1H), 3.30 (s, 3H), 3.65 (s, 3H), 3.81 (m, 1H), 4.38 (m, 1H), 4.55 (AB, 1H, J=10 Hz), 4.70 (AB, 1H, J=10 Hz), 5.69 (m, 2H), 7.30 (s, 5H).
Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.52; H, 7.59.

2S-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-propan-1-ol

The major anomer from ketalization (**34a** and **35a** mixed: 19.7 g, 61.6 mmol) was dissolved in 400 mL of ether and cooled to -78°C with stirring. A hexane solution of DIBAL-H (160 mL of a 1M solution) was added in 20 mL portions via syringe. After stirring for 1 h in a dry ice bath, the bath

was removed and the reaction was allowed to warm to ambient temperature. Methanol (15 mL) was carefully added resulting in a milky suspension. More ether (300 mL) was added followed by 500 mL of 0.5M aqueous sodium potassium tartrate solution. This biphasic mixture was stirred overnight at room temperature, then separated. The aqueous layer was extracted with 50 mL of ether and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed using a rotary evaporator to give the crude alcohol which was normally used for the next reaction without further purification.

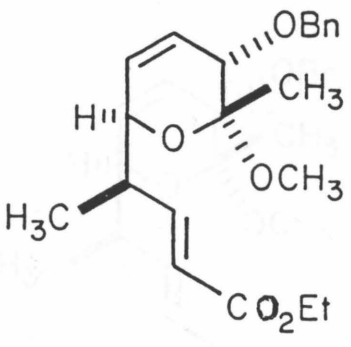


R_f=0.16 (7:3 petroleum ether:ethyl acetate).
IR ($CHCl_3$): 3500 cm^{-1} (br).
^1H NMR ($CDCl_3$): 0.90 (d, 3H, J=8 Hz), 1.48 (s, 3H), 2.1 (brs, 1H), 3.32 (s, 3H), 3.60 (d, 2H, J=5 Hz), 3.87 (m, 1H), 4.22 (m, 1H), 4.57 (AB, 1H, J=12 Hz), 4.73 (AB, 1H, J=12 Hz), 5.74 (m, 2H), 7.35 (s, 5H).
Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.97; H, 8.36.

Ethyl-4R-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-pent-2Z-enoate (36)

Dichloromethane (300 mL) was cooled to -78°C and 7.0 mL of oxalyl chloride (80 mmol) were added with stirring. Dimethyl sulfoxide (DMSO: 7.0 mL, 99 mmol) was then added dropwise over 7 min. After stirring for 20 min., the

alcohol from the preceding experimental dissolved in 20 mL of dichloromethane was added over 5 min. This was stirred for 30 min. giving a milky suspension to which Hunig's base (28 mL, 160 mmol) was added. The dry ice bath was removed and the reaction was allowed to warm slowly. When it had reached approximately 0°C, carboethoxymethylidene triphenylphosphorane (30.3 g, 87 mmol) was added as a crystalline solid. The reaction was stirred overnight at ambient temperature. Work-up of the reaction consisted of dilution with 500 mL of ether and extraction with 200 mL of water then 200 mL of brine. The solvent was removed under reduced pressure and the residue was flash chromatographed (eluting with 20% ethyl acetate/petroleum ether) to give a trace of material which appeared to be the Z-olefin and 19.4 g (87% yield based on the methyl ester **34** and **35**) of the desired product, which was homogeneous by tlc and NMR.



R_f=0.27 (4:1 petroleum ether:ethyl acetate).

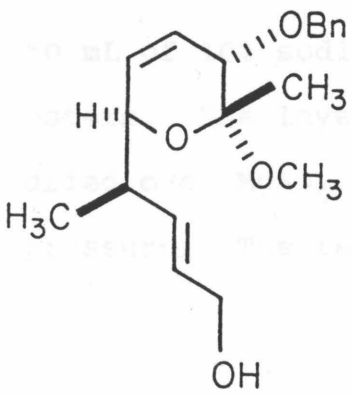
IR ($CHCl_3$): 1700 (br), 1647 cm^{-1}.

^1H NMR ($CDCl_3$): 1.03 (d, 3H, J=7 Hz), 1.17 (t, 3H, J=7 Hz), 1.40 (s, 3H), 2.5 (m, 1H), 3.30 (s, 3H), 3.8 (m, 1H), 3.95 (m, 1H), 4.15 (q, 2H, J=7 Hz), 4.56 (AB, 1H, J=12 Hz), 4.70 (AB, 1H, J=12 Hz), 5.73 (m, 2H), 5.80 (d, 1H, J=16 Hz), 6.96 (dd, 1H, $J_{3,4}$=8 Hz, $J_{2,3}$=16 Hz), 7.35 (s, 5H).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.82; H, 7.74.

4R-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-pent-2Z-en-1-ol (37)

The unsaturated ester (19.4 g, 53.9 mmol) **36** was dissolved in 300 mL of ether and cooled to -78°C. DIBAL-H was added (130 mL of a 1M solution in hexanes, 130 mmol) via syringe in portions and the reaction was stirred for 1 h. It was then allowed to warm to about 0°C and was quenched slowly with methanol. Ether (200 mL) was then added followed by addition of 300 mL of 0.5M sodium potassium tartrate solution. The biphasic mixture was stirred overnight at room temperature and was then separated. The aqueous layer was washed with 50 mL of ether and the combined organic solutions were dried over anhydrous magnesium sulfate. Removal of the solvent and flash chromatography of the residue gave 16.4 g (96% yield) of a colorless, viscous oil.



R_f=0.19 (3:2 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 3590, 3440 (br), 1100 cm^{-1}.

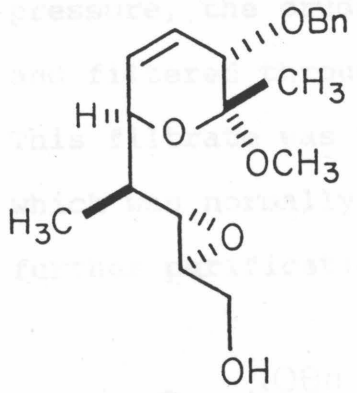
^1H NMR ($CDCl_3$): 1.00 (d, 3H, J=7 Hz), 1.36 (s, 3H), 2.2 (m, 1H), 3.29 (s, 3H), 3.8 (m, 2H), 4.1 (brs, 2H), 4.56 (AB, 1H, J=13 Hz), 4.68 (AB, 1H, J=13 Hz), 5.70 (m, 4H), 7.32 (s, 5H).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.73; H, 8.19.

4R-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-2S,3S-epoxypentan-1-ol (38)

The allylic alcohol (716 mg, 2.25 mmol) was dissolved in 8.0 mL of dichloromethane and was cooled to -40°C with stirring. (+)-Di-**iso**-propyl tartrate (0.90 mL, 4.3 mmol) was added and the solution was stirred for 5 min. Titanium tetra-**iso**-propoxide (0.90 mL, 3.0 mmol) was then added followed after 5 min. by 1.6 mL **tert**-butyl hydroperoxide solution (4.3M solution in dichloroethane, 6.8 mmol). The reaction flask was then sealed and transferred to a freezer maintained at -20°C.[25] After 3 h the reaction was judged complete by tlc, so 1 mL of dimethyl sulfide was added to quench the excess oxidant. The reaction was left in the freezer for 2 h more, then poured into 5 mL of saturated sodium sulfate solution and stirred vigorously for 30 min. It was then filtered through Celite and the Celite and precipitates were washed repeatedly with ether. The organic filtrate was then stirred vigorously with 50 mL of brine and 50 mL of 10% sodium hydroxide to hydrolyze the tartrate esters. The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was flash chromatographed, eluting

with 50% ethyl acetate/petroleum ether to give 649 mg (87% yield) of a colorless and viscous oil.



R_f=0.19 (1:1 ethyl acetate/petroleum ether).

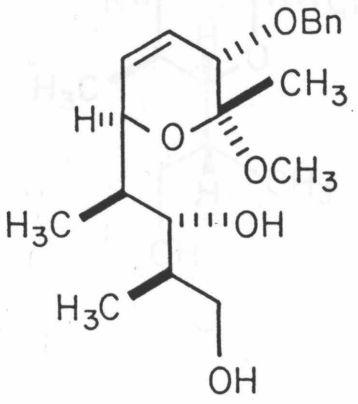
IR ($CHCl_3$) : 3510, 1109, 1060 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.87 (d, 3H, J=7 Hz), 1.39 (s, 3H), 1.60 (br s, 1H), 2.9 (m, 2H), 3.30 (s, 3H), 3.4-3.9 (m, 3H), 4.17 (m, 1H), 4.51 (AB, 1H, J=13 Hz), 4.70 (AB, 1H, J=13 Hz), 5.7 (m, 2H), 7.29 (s, 5H).

4R-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-2R-methylpentan-1,3R-diol

A copper bromide/dimethyl sulfide complex (Aldrich: 16.1 g, 78 mmol) was suspended in 50 mL of ether and cooled to -30°C with stirring. Methyllithium (1.5M in ether) was added until the yellow precipitate which formed had disappeared. This mixture was then stirred for 10 min. and the epoxide **38** (4.0 g, 12 mmol) was added in 15 mL of ether, rinsing in with 5 mL of ether. The yellow suspension was stirred for 1 h at -30°C, 2 h at -20°C, and then 2 h at -15°C, at which time the starting material had been completely consumed (judging by tlc). The suspension was poured into 300 mL of saturated $CuSO_4$ solution, stirred for 3 h, and extracted with three 100 mL portions of ether and two 50 mL portions of dichloromethane. The combined organic

layers were washed with aqueous ammonium chloride and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was dissolved in 25 mL of ether and filtered through Celite to remove suspended solids. This filtrate was then reduced to a very viscous yellow oil which was normally used for the next reaction without further purification.

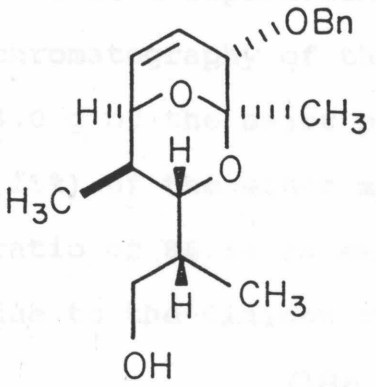


R_f=0.14 (1:1 petroleum ether/ethyl acetate).
^1H NMR ($CDCl_3$) : 0.89 (d, 3H, J=7 Hz), 0.96 (d, 3H, J=6 Hz), 1.40 (s, 3H), 1.7-2.1 (br m, 2H), 3.1 (br m, 2H), 3.36 (s, 3H), 3.3-3.9 (m, 4H), 4.48 (br s, 1H), 4.51 (AB, 1H, J=12 Hz), 4.73 (AB, 1H, J=12 Hz), 5.68 (br q, 2H), 7.30 (s, 5H).

2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4S-benzyloxy-8R-methylnon-5Z-en-1-yl]-propan-1-ol (39)

The crude diol from the above reaction (4.22 g yellow oil, 12 mmol theoretical yield) was dissolved in 25 mL of chloroform and a p-toluenesolfonic acid crystal was added. After 3 h at room temperature the reaction was judged complete by tlc. The solution was then diluted with 100 mL of dichloromethane and washed twice with 50 mL portions of saturated sodium bicarbonate then with 50 mL of brine. After drying ($MgSO_4$) and filtration, the solution was

evaporated to yield 3.94 g of a crystalline material. This bicyclic compound was discernibly a mixture by tlc. The methyl epimers **39** and **40** were separable at this point, but for ease of separation the mixture was carried on to the next reaction without separation. The epimers were slightly better resolved on tlc as the silyl ethers.



R_f=0.15 (4:1 petroleum ether/ethyl acetate.

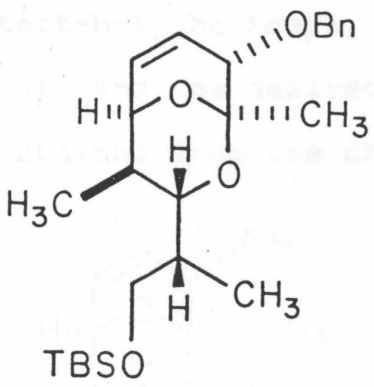
IR ($CHCl_3$) : 3520, 1080 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.70 (d, 3H, J=6 Hz), 1.08 (d, 3H, J=6 Hz), 1.48 (s, 3H), 1.6 (m, 3H), 3.87 (dd, 1H, J_1=3 Hz, J_2=11 Hz), 4.25 (t, 1H, J=4 Hz), 4.58 (s, 2H), 6.1 (m, 2H), 7.27 (s, 5H).

1-tert-butyldimethylsilyloxy-2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4S-benzyloxy-8R-methylnon-5Z-en-1-yl]-propane (41)

The crude crystalline alcohol (theoretical yield 12 mmol) was taken up in 50 mL of dimethylformamide (DMF) and the solution was cooled to 0°C. Imidazole (1.36 g, 20 mmol) was added followed by **tert**-butyldimethylsilyl chloride (TBSCl; 2.33 g, 15 mmol). The reaction was complete in 45 min. at which time it was diluted with 150 mL of ether and washed repeatedly with water then with sodium bicarbonate. The combined aqueous layers were then extracted once with 40

mL of ether. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The resultant oil was chromatographed on 800 g of silica. Gradient elution starting with 3% ether/petroleum ether (4L) and slowly increasing the fraction of ether in the eluant to 4% (4L), then 5% (3L), and finally 6% (3L) provided extensive separation of the methyl epimers. Re-chromatography of the mixed fractions ultimately provided 4.0 g of the major product (77% from the epoxide) and 0.77 g (15%) of the minor methyl epimer. This corresponds to a ratio of 86:14 as expected for the mixture of diastereomers due to the Claisen rearrangement.



R_f=0.49 (9:1 petroleum ether/ethyl acetate).

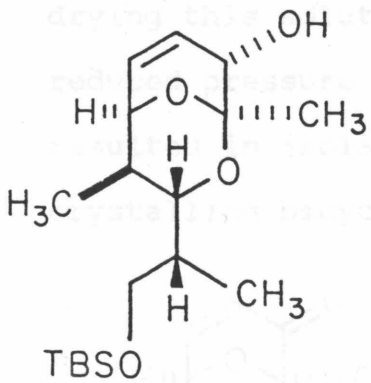
IR ($CHCl_3$) : 2900, 1090, 840 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.06 (s, 6H), 0.69 (d, 3H, J=6 Hz), 0.84 (s, 9H), 0.88 (d, 3H, J=6 Hz), 1.42 (s, 3H), 1.6-2.2 (m, 2H), 3.4 (m, 3H), 3.71 (dd, 1H, J_1=6 Hz, J_2=10 Hz), 4.20 (t, 1H, J=5 Hz), 4.57 (s, 2H), 6.1 (m, 2H), 7.3 (s, 5H).

1-tert-butyldimethylsilyloxy-2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4S-hydroxy-8R-methylnon-5Z-en-1-yl]-propane (42)

Lithium di-tert-butylbiphenyl in THF was prepared as described for **54**.[26] The benzyl ether (3.30 g, 7.62 mmol)

was dissolved in 60 mL of THF and the solution was cooled in a dry ice/acetone bath. The dark green radical anion solution was then added in 2 mL portions until the color persisted in the reaction, and the reaction was stirred for 5 min. more before being quenched with 5 mL of aqueous ammonium chloride. This suspension was stirred while warming to room temperature, then diluted with 500 mL of dichloromethane and extracted with 100 mL of brine. The organic solution was then dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a white solid, mostly di-**tert**-butylbiphenyl. This material was chromatographed with 15% ethyl acetate/petroleum ether; di-**tert**-butylbiphenyl, a small quantity of mixed material (160 mg), and the desired crystalline product (2.11 g, 81%) were obtained from the chromatographic separation.



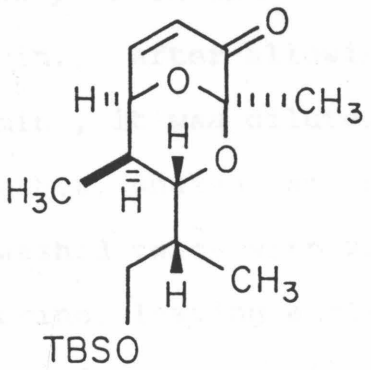
R_f=0.15 (9:1 petroleum ether/ethyl acetate).

IR ($CHCl_3$) : 3540, 1310, 1090, 845 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.08 (s, 6H), 0.72 (d, 3H, J=7 Hz), 0.90 (s, 9H), 1.11 (d, 3H, J=6 Hz), 1.44 (s, 3H), 1.7 (br s, 1H), 2.1-2.6 (m, 2H), 3.6 (m, 3H), 3.88 (dd, 1H, J_1=3 Hz, J_2=11 Hz), 4.24 (t, 1H, J=5 Hz), 6.09 (dq, 2H, J_1=4 Hz, J_2=5 Hz).

1-tert-butyldimethylsilyloxy-2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-8R-methylnon-5Z-en-4-on-1-yl]-propane (43)

A flask containing 0.15 mL of oxalyl chloride (1.72 mmol) in 8.0 mL of dichloromethane was cooled to -78°C with magnetic stirring. Dimethyl sulfoxide (DMSO: 0.18 mL, 2.54 mmol) was added dropwise and the solution was stirred for 20 min. At this time the alcohol **42** (489 mg, 1.43 mmol) was dissolved in 2 mL of dichloromethane and added dropwise to the reaction solution. After 25 min. more, Hunig's base (0.65 mL, 3.6 mmol) was added and the reaction flask was removed from the dry ice/acetone bath. When the solution had reached room temperature it was diluted with 100 mL of dichloromethane and extracted with two 50 mL portions of aqueous ammonium chloride. The yellow oil obtained by drying this solution ($MgSO_4$) and removing the solvent under reduced pressure was flash chromatographed. This process resulted in isolation of 459 mg (94% yield) of the crystalline bicyclic enone.



R_f=0.33 (9:1 petroleum ether/ethyl acetate).

IR ($CHCl_3$) : 1690, 1450, 1090, 830 cm^{-1}.

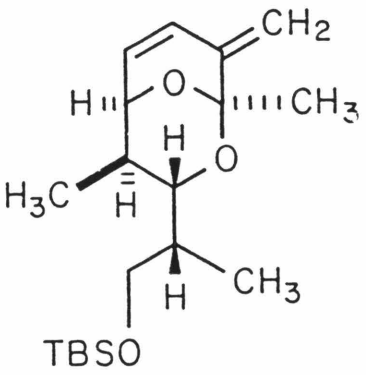
^1H NMR ($CDCl_3$) : 0.06 (s, 6H), 0.81 (d, 3H, J=6 Hz), 0.89 (s, 9H), 0.92 (d, 3H, J=6 Hz), 1.39 (s, 3H), 1.88 (m, 1H), 2.6 (m, 1H), 3.33 (dd, 1H, J_1=4 Hz, J_2=5 Hz), 3.53 (dd, 1H, J_1=2 Hz, J_2=10 Hz), 3.79 (dd, 1H, J_1=7 Hz, J_2=10 Hz), 4.39 (t, 1H, J=5 Hz), 6.28 (d, 1H, J=10 Hz), 7.07 (dd, 1H, J_1=5 Hz, J_2=10 Hz).

1-tert-butyldimethylsilyloxy-2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4-methylen-8R-methylnon-5Z-en-1-yl]-propane (44)

The Tebbe reagent[27] for the folowing transformation was prepared according to a procedure supplied by Steve Buchwald, who also provided advice on experimental details.

Tebbe reagent[27] (410 mg, 1.44 mmol) was cooled to -78°C. THF was added dropwise, and the red solution was given several minutes to cool. Enone **43** (362 mg, 1.06 mmol) was dissolved in 1.5 mL of THF and added dropwise to the reagent solution; the starting material flask and syringe were rinsed with two 1.0 mL portions of THF which were also added dropwise to the reaction. After 5 min. the reaction flask was removed from the dry ice bath and allowed to warm to room temperature. The suspension was then stirred 20 min., quenched with 5 mL of 10% aqueous sodium hydroxide, and diluted with 8 mL of ether to give two distinct phases: a yellow organic suspension and a blue aqueous solution. With stirring, this gradually evolved into a white aqueous suspension and a clear yellow organic layer (over about 30 min.) After allowing this mixture to stir for another 15 min., it was diluted with 20 mL of 10% NaOH and 100 mL of ether, shaken, and separated. The organic layer was then washed twice with 25 mL aliquots of 10% NaOH, then with brine, leaving a clear yellow solution. This was dried over anhydrous magnesium sulfate and the solvent was removed in

vacuo. Flash chromatography of the crude material, eluting with 4% ether/petroleum ether, provided 230 mg (64% yield) of the oily diene **44** which tended to polymerize on standing into an insoluble material.



R_f=0.30 (4% ether/petroleum ether).

IR ($CHCl_3$) : 1583, 1085, 830 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.05 (s, 6H), 0.72 (d, 3H, J=7 Hz), 0.82 (d, 3H, J=6 Hz), 0.89 (s, 9H), 1.52 (s, 3H), 1.9 (m, 1H), 2.3 (m, 1H), 3.4 (m, 2H), 3.78 (dd, 1H, J_1=6 Hz, J_2=10 Hz), 4.25 (t, 1H, J=5 Hz), 4.96 (s, 1H), 5.11 (s, 1H), 5.96 (dd, 1H, J_1=5Hz, J_2=9 Hz), 6.43 (d, 1H, J=9 Hz).

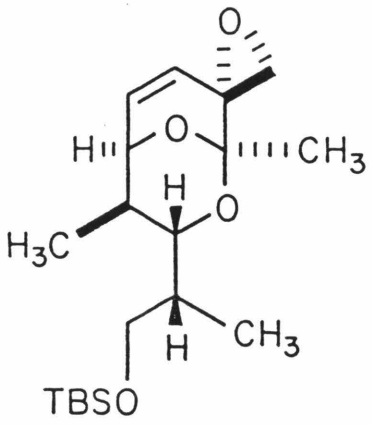
Epoxidation of Diene (44)

The diene (230 mg, 0.678 mmol) was dissolved in 5 mL of dichloromethane and cooled to 0°C, 146 mg sodium carbonate (1.4 mmol) was added, and the suspension was stirred. Crystalline 85% **meta**-chloroperbenzoic acid (164 mg, which is approximately 0.81 mmol assuming 85% by weight) was added and the reaction mixture was stirred for 40 min. at 0°C then for 1 h at ambient temperature. At this time most of the starting material had been consumed by tlc, so the mixture was diluted with 150 mL of ether. The layers were separated and the organic layer was washed with 5% sodium bicarbonate, then with brine. It was then dried over anhydrous sodium

sulfate (as magnesium sulfate had been found to decompose the products of this reaction) and filtered, and the solvent was removed on a rotary evaporatory. Chromatography on 30 g of silica, eluting with 10% ether/petroleum ether, allowed isolation of the following pure materials listed in the order of elution:

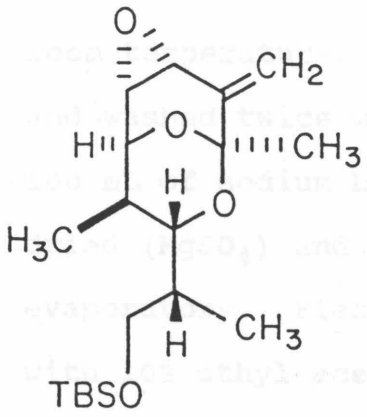
24 mg of recovered starting material	10%
47 mg of desired epoxide **45**	19%
12 mg of diastereomeric epoxide **47**	5%
87 mg of regio-isomer **46**	37%

These materials accounted for 71% of the starting material. A trace of the product corresponding to **bis**-epoxidation of the diene **(48)** was also isolated, and some material was in mixed fractions which were not re-chromatographed.

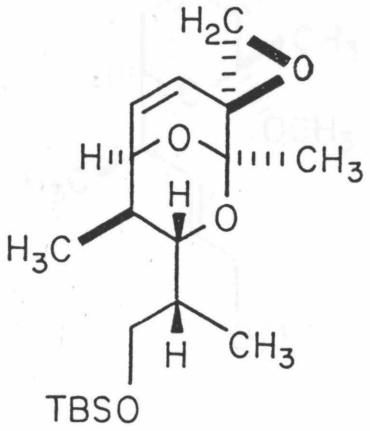


R_f=0.36 (9:1 petroleum ether/ethyl acetate).

^{1}H NMR ($CDCl_3$) : 0.06 (s, 6H), 0.79 (d, 3H, J=6 Hz), 0.92 (s, 9H), 0.97 (d, 3H, J=7 Hz), 1.19 (s, 3H), 1.9 (m, 1H), 2.4 (m, 1H), 2.88 (AB, 1H, J=5 Hz), 2.95 (AB, 1H, J=5 Hz), 3.35 (dd, 1H, J_1=7 Hz, J_2=10 Hz), 3.5-3.8 (m, 2H), 4.33 (t, 1H, J=5 Hz), 5.54 (d, 1H, J=10 Hz), 6.28 (dd, 1H, J_1=5 Hz, J_2=10 Hz).



R_f=0.14 (9:1 petroleum ether/ethyl acetate).
^{1}H NMR ($CDCl_3$) : 0.05 (s, 6H), 0.80 (d, 3H, J=6 Hz), 0.84 (s, 9H), 0.90 (d, 3H, J=6 Hz), 1.40 (s, 3H), 1.9 (m, 1H), 2.4 (m, 1H), 3.2 (m, 2H), 3.6 (m, 3H), 4.05 (t, 1H, J=5 Hz), 5.37 (d, 2H, J=3 Hz).

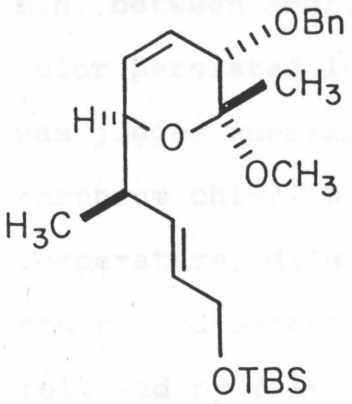


R_f=0.21 (9:1) petroleum ether/ethyl acetate).
^{1}H NMR ($CDCl_3$) : 0.05 (s, 6H), 0.73 (d, 3H, J=6 Hz), 0.87 (s, 9H), 0.98 (d, 3H, J=7 Hz), 1.16 (s, 3H), 2.0 (m, 1H), 2.5 (m, 1H), 2.70 (AB, 1H, J=5 Hz), 3.12 (AB, 1H, J=5 Hz), 3.35 (dd, 1H, J_1=6 Hz, J_2=10 Hz), 3.8 (m, 2H), 4.28 (t, 1H, J=4 Hz), 5.50 (d, 1H, J=9 Hz), 6.18 (dd, 1H, J_1=4 Hz, J_2=9 Hz).

1-tert-butyldimethylsilyloxy-4R-[1S-3R-methoxy-3-methyl-4S-benzyloxy-1,4-dihydropyranyl]-pent-2Z-ene

The allylic alcohol **37** (16.4 g, 51.6 mmol) was dissolved in 50 mL of dichloromethane and 50 mL of dimethylformamide. Imidazole (4.3 g, 63.2 mmol) was added followed by **tert**-butyldimethylsilyl chloride (9.4 g, 62.5 mmol). The reaction was complete by tlc in 30 min. at

room temperature. It was then diluted with 300 mL of ether and washed twice with 100 mL portions of water, then with 100 mL of sodium bicarbonate solution. The solution was dried ($MgSO_4$) and the solvent was removed using a rotary evaporatory. Flash chromatography of the residue, eluting with 10% ethyl acetate/petroleum ether, provided 21.6 g (97% yield) of the silyl ether as a colorless oil.



R_f=0.29 (9:1 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 1060-1100 cm^{-1}.

^1H NMR ($CDCl_3$): 0.08 (s, 6H), 0.88 (s, 9H), 0.98 (d, 2H, J=7 Hz), 1.32 (s, 3H), 2.2 (m, 1H), 3.25 (s, 3H), 3.8 (m, 2H), 4.06 (d, 2H, J=3 Hz), 4.49 (AB, 1H, J=12 Hz), 4.65 (AB, 1H, J=12 Hz), 5.5 (m, 2H), 5.70 (s, 2H), 7.30 (s, 5H).

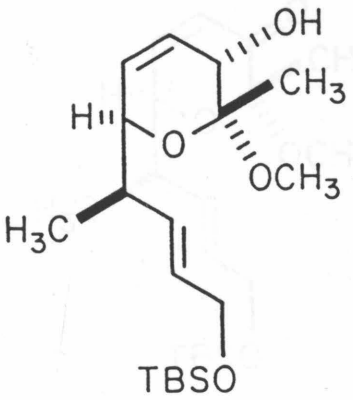
Anal. Calcd for $C_{25}H_{40}O_4Si$: C, 69.40; H, 9.32. Found: 69.45; H, 9.22.

1-tert-butyldimethylsilyloxy-4R-[1S-3R-methoxy-3-methyl-4S-hydroxy-1,4-dihydropyranyl]-pent-2Z-ene (54)

The lithium di-**tert**-butylbiphenyl radical anion reagent solution[26] was prepared as follows: 32 g (0.12 mol) of di-**tert**-butylbiphenyl was dissolved in 700 mL of THF with careful exclusion of oxygen and moisture. Lithium wire (1.0 g, 0.14 mol) in 0.5 cm pieces [which had been washed with petroleum ether to remove oil, immersed in methanol to clean the surface, rinsed in ether, then submerged in anhydrous THF while being mashed with pliers] was added. This mixture was stirred vigorously at room temperature

until the dark green radical anion color developed, at which time the reaction was cooled in an ice bath. Stirring was continued at 0°C for 6 h more before the reagent was used.

The silyl ether substrate (21.40 g, 49.5 mmol) was dissolved in 400 mL of THF and cooled to -78°C in a dry ice/acetone bath with stirring. The dark green reagent solution was added in portions via syringe, allowing 4-5 min. between additions for cooling, until the dark green color persisted in the reaction. At this time the reaction was judged complete by tlc and was quenched with aqueous ammonium chloride. It was allowed to warm to room temperature, diluted with 400 mL of 1:1 ether/petroleum ether, and separated. Drying over magnesium sulfate was followed by filtration and removal of the solvent **in vacuo**. The residue was purified by flash chromatography, eluting with 15% ethyl acetate/petroleum ether. This resulted in recovery of most of the di-**tert**-butylbiphenyl, which could be re-used after a single recrystallization from ethanol, and isolation of 16.4 g (97% yield) of the desired debenzylated material as a colorless oil.



R_f=0.17 (9:1 petroleum ether:ethyl acetate).

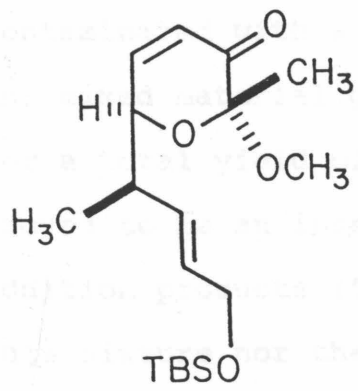
IR ($CHCl_3$): 3540, 1050, 830 cm^{-1}.

^1H NMR ($CDCl_3$): 0.07 (s, 6H), 0.90 (s, 9H), 0.99 (d, 3H, J=7 Hz), 1.40 (s, 3H), 2.2 (m, 2H), 3.27 (s, 3H), 3.7-4.0 (m, 2H), 4.10 (d, 2H, J=4 Hz), 5.6 (m, 5H).

Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.19; H, 9.82.

1-tert-butyldimethylsilyloxy-4R-[1S-3R-methoxy-3-methyldihydropyran-4-on-1-yl]-pent-2E-ene (55)

A 100 mL two-necked flask equipped with a magnetic stirring bar was charged with 60 mL of dichloromethane and cooled in a dry ice/acetone bath. Oxalyl chloride (1.20 mL, 13.7 mmol) was added via syringe followed by dimethyl sulfoxide (1.10 mL, 15.5 mmol), which was added dropwise. After stirring this mixture for 20 min., the alcohol **54** (3.95 g, 11.5), dissolved in 5 mL of dichloromethane, was added and stirring was continued for 30 min. more. Hunig's base (5.0 mL, 28.8 mmol) was added and the reaction mixture was allowed to warm to room temperature. It was then diluted with ether (150 mL) and extracted with water (50 mL) and then with two 50 mL portions of brine. The organic layer was then dried ($MgSO_4$). The solvent was removed using a rotary evaporator and the residue was flash chromatographed. The column was eluted first with 10% ethyl acetate/petroleum ether then with 15% ethyl acetate/petroleum ether to give the enone as a colorless oil (3.65 g, 93% yield).



R_f=0.63 (6:1 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 1680, 1120, 830 cm^{-1}.

^1H NMR ($CDCl_3$): 0.08 (s, 6H), 0.90 (s, 9H), 1.08 (d, 3H, J=7 Hz), 1.43 (s, 3H), 2.5 (m, 1H), 3.30 (s, 3H), 4.2 (m, 3H), 5.6 (m, 2H), 5.96 (dd, 1H, $J_{2',3'}$=3 Hz, $J_{3',4'}$=11 Hz), 6.91 (dd, 1H, $J_{3',4'}$=11 Hz, $J_{2',4'}$=1.5 Hz).

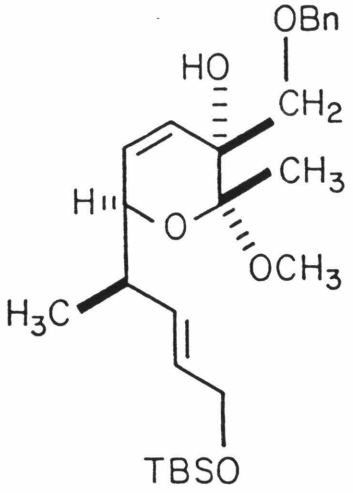
Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.56; H, 9.47.

1-tert-butyldimethylsilyloxy-4R-[1S-3R-methoxy-3-methyl-4R-benzyloxymethyl-4-hydroxy-1,4-dihydropyran-1-yl]-pent-2E-ene (56)

Benzyloxymethyltri-n-bytyltin was prepared by Still's procedure.[34] This material (5.4 g, 13 mmol) was dissolved in 120 mL of THF and the solution cooled to -78°C. n-Butyllithium (5.0 mL of a 2.4M hexane solution, 12 mmol) was then added dropwise giving a pale yellow solution. This was stirred for 15 min.[34]

The enone **55** (3.55 g, 10.4 mmol), dissolved in 15 mL of THF, was added to the above solution over 15 min. After 10 min. more the reaction was complete as judged by tlc. It was then allowed to warm to room temperature, diluted with 200 mL of ether, and extracted twice with 100 mL aliquots of saturated ammonium chloride solution. The clear organic layer was then dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue, eluting with 20% ethyl acetate/petroleum ether, allowed isolation of 4.05 g of pure product and some product contaminated with a slower material. Re-chromatography of the mixed material gave 0.25 g more of the desired material for a total yield of 4.30 g (89%). The slower product proved to be an inseparable mixture of two conjugate addition products (**57** identified by ^1H NMR and IR). Neither this mixture nor the major product (examined by 400 MHz ^1H

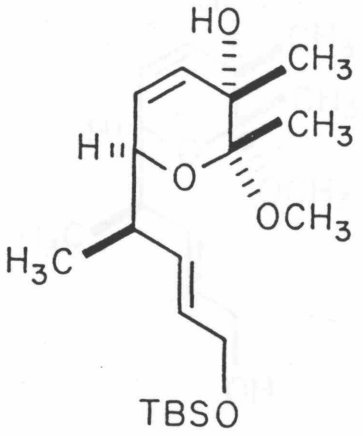
NMR) contained a detectable quantity of the product corresponding to addition of benzyloxymethyllithium to the opposite face of the enone.



R_f=0.32 (6:1 petroleum ether:ethyl acetate).
IR ($CHCl_3$): 3540, 1090, 830 cm^{-1}.
^1H NMR ($CDCl_3$): 0.08 (s, 6H), 0.90 (s, 9H), 0.96 (d, 3H, J=7 Hz), 1.30 (s, 3H), 2.2 (m, 1H), 2.87 (s, 1H), 3.28 (s, 3H), 3.43 (AB, 1H, J=10 Hz), 3.61 (AB, 1H, J=10 Hz), 3.82 (d, 1H, J=5 Hz), 4.08 (d, 2H, J=3 Hz), 4.57 (m, 2H), 5.6 (m, 2H), 5.70 (s, 2H), 7.32 (s, 5H).
Anal. Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found: C, 67.58; H, 9.13.

1-tert-butyldimethylsilyloxy-4R-[1S-3R-methoxy-3-methyl-4S-methyl-4-hydroxy-1,4-dihydropyran-1-yl]-pent-2E-ene (64)

THF (2.5 mL) was cooled to -78°C, and 0.25 mL of a 1M solution of methyllithium (MeLi) in ether were added. The enone **55** (107 mg, 0.31 mmol) dissolved in 2.0 mL of THF was added by syringe. After stirring this solution for 15 min., the starting material had been consumed (judging by tlc.) The reaction was quenched with methanol and diluted with 100 mL of ether. It was then washed with 25 mL of NH_4Cl and 25 mL of water and dried over $MgSO_4$. Flash chromatography, eluting with 10% ethyl acetate/petroleum ether, provided 107 mg (96%) of analytically pure **64**.



R_f=0.50 (15% ethyl acetate/petroleum ether).

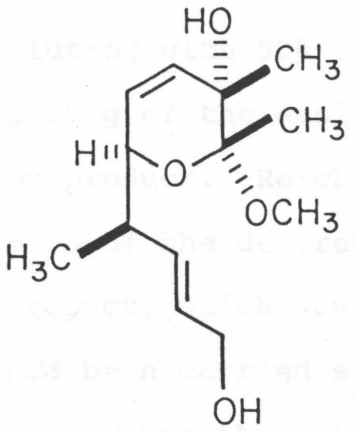
IR ($CHCl_3$) : 3520, 1090, 830 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.08 (s, 6H), 0.88 (s, 9H), 0.99 (d, 3H, J=6 Hz), 1.19 (s, 3H), 1.31 (s, 3H), 2.3 (m, 1H), 2.73 (s, 1H), 3.29 (s, 3H), 3.78 (m, 1H), 4.09 (d, 2H, J=3 Hz), 5.56 (m, 4H).

Anal. Calcd. for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 64.05; H, 10.18.

4R-[1S-3R-methoxy-3-methyl-4S-methyl-4-hydroxy-1,4-dihydropyran-1-yl]-pent-2E-en-1-ol

A sample of **64** (3.465 g, 9.73 mmol) was dissolved in 15 mL of THF, and 12 mL of a 1M solution of Bu_4NF in THF were added. The reaction solution turned orange in 1-2 min., and no starting material could be detected by tlc after 20 min. The reaction was then diluted with 400 mL of ether and extracted with two 100 mL portions of brine. The clear solution thus obtained was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography, eluting with 50% ethyl acetate/petroleum ether, provided 2.320 g (99%) of the deprotected alcohol.



R_f=0.19 (3:2 petroleum ether/ethyl acetate).

IR ($CHCl_3$) : 3519, 3430, 1090 cm^{-1}.

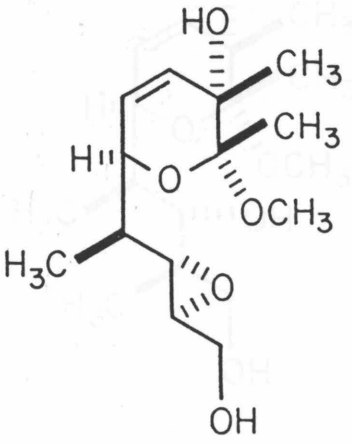
^1H NMR ($CDCl_3$) : 1.02 (d, 3H, J=7 Hz), 1.20 (s, 3H), 1.33 (s, 3H), 2.3 (m, 1H), 2.5 (br s, 1H), 2.9 (br s, 1H), 3.30 (s, 3H), 3.81 (d, 1H, J=5 Hz), 4.06 (m, 2H), 5.56 (m, 4H).

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.24; H, 9.05.

4R-[1S-3R-methoxy-3-methyl-4S-methyl-4-hydroxy-1,4-dihydropyran-1-yl]-2S,3S-epoxypentan-1-ol

The allylic alcohol obtained from the preceding procedure (2.32 g, 9.59 mmol) was dissolved in 80 mL of CH_2Cl_2 and cooled to -40°C. (+)-DIPT (2.8 mL, 13.3 mmol) was added, followed by 3.30 mL $Ti(OR)_4$ (11.1 mmol). This solution was then stirred for 10 min. before 6.0 mL of 4M t-BuOOH in CH_2Cl_2 were added (24 mmol). The solution was then transferred to a -20°C freezer and left there overnight. Dimethyl sulfide (2 mL) was added to consume the excess oxidant and the solution was kept at -20°C for an additional 4 h. It was then stirred vigorously with 3.5 mL of saturated Na_2SO_4 for 1 h and filtered through a pad of Celite. The solvents were removed from the filtrate under reduced pressure and the residue was flash chromatographed,

eluting with 50% ethyl acetate/petroleum ether, to provide 1.65 g of the desired epoxide and some material mixed with a by-product. Re-chromatographing the mixture provided 0.20 g more of the desired product and a pure sample of the by-product, which was identified as the methyl epimer, which had been carried since the Claisen rearrangement. The epimer was thus obtained in 7% yield and the desired epoxide in 75% yield, and a small quantity of the starting material was also recovered.



R_f=0.17 (1:1 petroleum ether/ethyl acetate).

IR ($CHCl_3$) : 3520, 1110, 1076 cm^{-1}.

^1H NMR ($CDCl_3$) : 0.92 (d, 3H, J=7 Hz), 1.25 (s, 3H), 1.38 (s, 3H), 1.9 (br m, 2H), 2.79 (s, 1H), 2.9-3.1 (m, 2H), 3.35 (s, 3H), 3.7 (m, 1H), 4.15 (m, 2H), 5.3-5.7 (m, 2H).

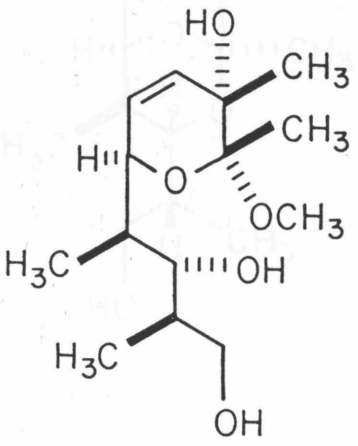
Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.30; H, 8.41.

4R-[1S-3R-methoxy-3-methyl-4S-methyl-4-hydroxy-1,4-dihydropyran-1-yl]-2R-methylpentan-1,3R-diol

Copper bromide-dimethyl sulfide complex (13.5 g, 65.7 mmol) was suspended in 20 mL of ether and cooled to 0°C with stirring. A 1M solution of MeLi in Et_2O was added slowly until the orange precipitate which formed had disappeared.

The epoxide (1.65 g, 6.40 mmol) was dissolved in 10 mL of Et_2O and added slowly to the stirred lithium dimethyl-

cuprate solution. After stirring the yellow-orange suspension for 4 h at 0°C, it was diluted with ether (300 mL) and carefully quenched with aqueous NH_4Cl. The layers were separated. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Drying overnight under vacuum (0.1 mm) gave 1.68 g of an oily crystalline material which was clean by tlc (ethyl acetate).

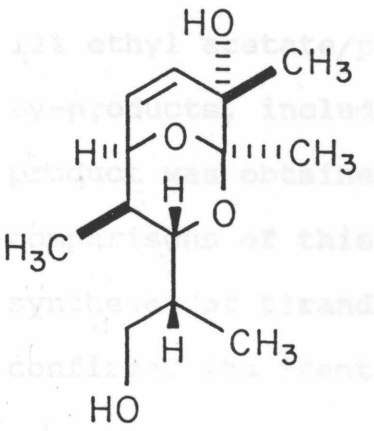


R_f=0.35 (ethyl acetate).
IR ($CHCl_3$) : 3450, 1105, 830 cm^{-1}.
^1H NMR ($CDCl_3$) : 0.86 (d, 3H, J=7 Hz), 0.99 (d, 3H, J=7 Hz), 1.25 (s, 3H), 1.36 (s, 3H), 1.8 (m, 3H), 2.68 (s, 1H), 3.35 (s, 3H), 3.5 (m, 4H), 4.31 (m, 1H), 5.35 (dd, 1H, J_1=1.5 Hz, J_2=10 Hz), 5.64 (dd, 1H, J_1=2 Hz, J_2=10 Hz).
m.p. 115-116°C.
Anal. Calcd. for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 61.10; H, 9.58.

2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4S-methyl-4-hydroxy-8R-methylnon-5Z-en-1-yl]-propan-1-ol (65)

The crude triol from the preceding procedure was dissolved in 70 mL of $CHCl_3$, and a few small crystals of p-TsOH were added. After stirring for 2.5 h, solid anhydrous Na_2CO_3 was added and the suspension was stirred for an additional 2 h. The solids were removed by filtration, and the filtrate was concentrated under reduced pressure. Flash

chromatography, eluting with 40% ethyl acetate/petroleum ether, provided 1.03 g of white crystalline material along with 410 mg of mixed material. Re-chromatography of the mixed material provided an additional 0.23 g of the desired product **65** making the total yield 81% (from the epoxide).



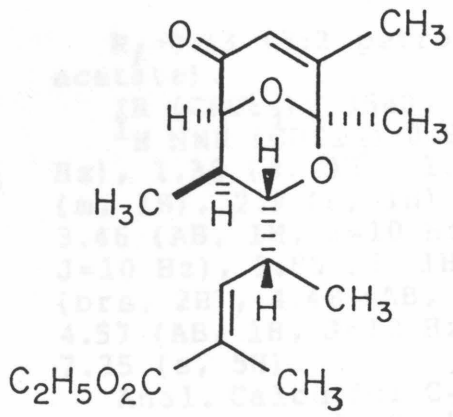
R_f=0.25 (1:1 petroleum ether/ethyl acetate).
IR ($CHCl_3$) : 3520, 1100, 830 cm^{-1}.
^1H NMR ($CDCl_3$) : 0.71 (d, 3H, J=7 Hz), 1.11 (d, 3H, J=8 Hz), 1.20 (s, 3H), 1.41 (s, 3H), 1.8 (m, 1H), 1.95 (s, 2H), 2.2 (m, 1H), 3.5 (m, 2H), 3.89 (dd, 1H, J_1=4 Hz, J_2=11 Hz), 4.2 (m, 1H), 5.82 (dd, 1H, J_1=4 Hz, J_2=10 Hz), 6.02 (d, 1H, J=10 Hz).
m.p. 116-118°C (lit. 124°C)[19].
Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.40; H, 9.22.

Ethyl-4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4-methyl-8R-methylnon-4Z-en-6-on-1-yl]-2-methylpent-2E-enoate (66)

The bicyclic diol **65** (39.8 mg, 0.16 mmol) was dissolved in 1.0 mL CH_2Cl_2. Celite (210 mg) was added followed by PCC (198 mg, 0.92 mmol). The suspension was stirred at 20°C for 4 h, at which time all of the starting material had been consumed (judging by tlc); one major spot which was UV-active was observed at R_f=0.62 (40% ethyl acetate/petroleum ether). The reaction solution was diluted with ether (100 mL) and washed with 20 mL portions of NH_4Cl, $NaHCO_3$,

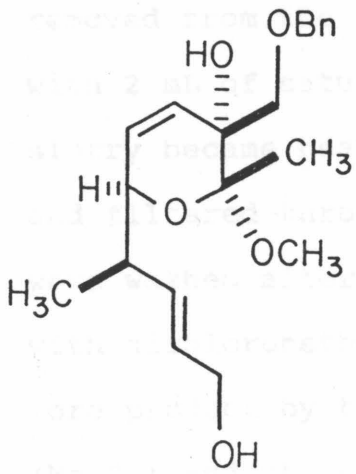
and brine. After drying over $MgSO_4$, the solvent was removed using a rotary evaporator.

Benzene (1,0 mL) was added to this crude material. To this solution, 316 mg (0.87 mmol) of carboethoxyethylidene triphenylphosphorane were added, and the yellow solution was heated at 80°C overnight. The reaction mixture was then poured directly onto a chromatography column and eluted with 12% ethyl acetate/petroleum ether. Along with unidentified by-products, including some unreacted aldehyde, one major product was obtained (20.0 mg, 38% from **65**). Spectral comparisons of this product to the same intermediate in syntheses of tirandamycic acid[17] and tirandamycin A[19] confirmed its identity as the desired compound **66**.



4R-[1S-3R-methoxy-3-methyl-4R-benzyloxymethyl-4-hydroxy-1,4-dihydropyran-1-yl]-pent-2E-en-1-ol

A 4.00 g (8.66 mmol) sample of the silyl ether **56** was dissolved in 10 mL of THF and cooled to 0°. A 1M solution of tetra-n-butylammonium fluoride (Aldrich: 10 mL, 10 mmol) was added slowly and the reaction was stirred for 30 min. It was then allowed to warm to room temperature and stirred for 1 h more, at which time the reaction appeared complete by tlc. The solution was then diluted with 300 mL of ether and extracted twice with 100 mL portions of water, then with 50 mL of brine. The organic solution was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Elution from a flash chromatography column with 60% ethyl acetate/petroleum ether gave the desired primary alcohol (2.79 g) in 93% yield as a viscous oil.

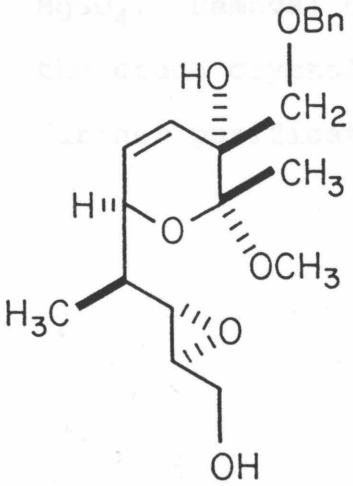


R_f=0.13 (3:2 petroleum ether:ethyl acetate).
IR ($CHCl_3$): 3540, 1100, 1070 cm^{-1}.
^1H NMR ($CDCl_3$) 0.98 (d, 3H, J=7 Hz), 1.32 (s, 3H), 1.5 (brs, 1H), 2.3 (m, 1H), 2.9 (s, 1H), 3.29 (s, 3H), 3.46 (AB, 1H, J=10 Hz), 3.61 (AB, 1H, J=10 Hz), 3.85 (d, 1H, J=5 Hz), 4.03 (brs, 2H), 4.48 (AB, 1H, J=12 Hz), 4.57 (AB, 1H, J=12 Hz), 5.6 (m, 4H), 7.35 (s, 5H).
Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.82; H, 8.17.

4R-[1S-3R-methoxy-3-methyl-4R-benzyloxymethyl-4-hydroxy-1,4-dihydropyran-1-yl]-2S,3S-epoxypentan-1-ol (67)

The allylic alcohol (2.64 g, 7.59 mmol) was dissolved in 30 mL of dichloromethane and the solution was cooled to -40°C. (+)-Diisopropyl tartrate (2.40 mL, 11.4 mmol) was then added via syringe; this was followed by addition of titanium tetraisopropoxide (2.7 mL, 9.1 mmol) with stirring. The solution was stirred for 5 min. more, then 5.7 mL of 4M **tert**-butylhydroperoxide in dichloromethane (23 mmol) was added and the reaction vessel was sealed and transferred to a freezer maintained at -20°C.[25] After 5 h the reaction was judged complete by tlc and the excess oxidant was quenched by addition of 2 mL of dimethyl sulfide to the mixture in the freezer. One hour later the reaction mixture was removed from the freezer and stirred at room temperature with 2 mL of saturated aqueous sodium sulfate until the slurry became nearly solid. It was then diluted with ether and filtered through a Celite pad. The solids and Celite were washed alternately with dichloromethane and ether then with dichloromethane and THF until the washings contained no more product by tlc. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated. Flash chromatography of the crude product, eluting with 60% ethyl acetate/petroleum

ether, allowed isolation of 2.482 g (90% yield) of the epoxy alcohol as a very viscous oil.



R_f=0.35 (2:3 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 3540, 1105, 1062 cm^{-1}.

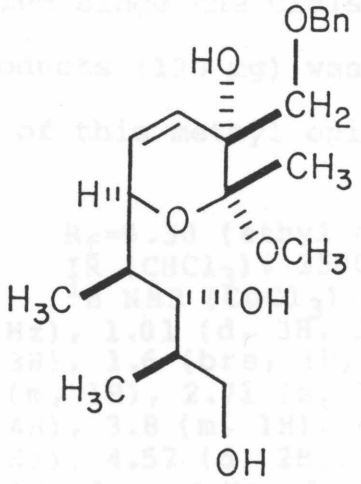
^1H NMR ($CDCl_3$): 0.80 (d, 3H, J=7 Hz), 1.30 (s, 3H), 1.7 (brs, 1H), 2.8-3.1 (m, 3H), 3.30 (s, 3H), 3.5-3.8 (m, 4H), 4.13 (m, 1H), 4.51 (AB, 1H, J=12 Hz), 4.59 (AB, 1H, J=12 Hz), 5.7 (m, 2H), 7.30 (s, 5H).

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.89; H, 7.69.

4R-[1S-3R-methoxy-3-methyl-4R-benzyloxymethyl-4-hydroxy-1,4-dihydropyran-1-yl]-2R-methylpentan-1,3R-diol (68)

Copper bromide-dimethyl sulfide complex (7.53 g, 36.6 mmol) was suspended in 15 mL of ether with stirring and was cooled to 0°C. To this mixture a 1.5M solution of methyllithium in ether was added in portions until the yellow precipitate which formed had almost completely disappeared. After this mixture had stirred for 5 min., 1.31 g (3.60 mmol) of the epoxy alcohol was dissolved in 5 mL of ether and added to the cuprate solution. The yellow suspension was stirred 4 h at 0°C, then quenched carefully with saturated copper sulfate solution (15 mL). This mixture was stirred for 1 h, then diluted with ether

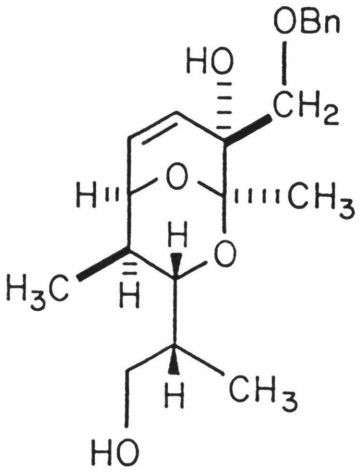
(300 mL) and separated. The ether solution was washed with 100 mL of water, then with 100 mL of brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude crystalline triol **68** which was used without further purification in most cases.



2R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-benzyloxymethyl-4-hydroxy-8R-methylnon-5Z-en-1-yl]-propan-1-ol (69)

The crude triol from the above reaction was dissolved in 50 mL of chloroform and a few crystals of p-toluene-sulfonic acid (approximately 10 mg, anhydrous) were added. The reaction mixture was stirred at ambient temperature, and the reaction appeared complete by tlc after 30 min. Potassium bicarbonate (0.5 g) was then added to quench the acid and the suspension was stirred for 5 min. It was then

filtered through Celite, the solvent was removed on a rotary evaporator, and the crude crystalline material was chromatographed on 125 g of silica, eluting with 40% ethyl acetate/petroleum ether. The major product (851 mg, 68% from the epoxide **67**) was separated from the methyl epimer which had been carried since the Claisen rearrangement. A mixture of minor products (120 mg) was also isolated; it consisted primarily of this methyl epimer.



R_f=0.30 (ethyl ether).
IR ($CHCl_3$): 3500, 1090, 1050 cm^{-1}.
^1H NMR ($CDCl_3$):0.82 (d, 3H, J=7 Hz), 1.01 (d, 3H, J=8 Hz), 1.47 (s, 3H), 1.6 (brs, 1H), 1.7 (m, 1H), 2.3 (m, 1H), 2.71 (s, 1H), 3.3-3.6 (m, 4H), 3.8 (m, 1H), 4.25 (t, 1H, J=4 Hz), 4.57 (d, 2H, J=1.5 Hz), 5.96 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz), 6.21 (d, 1H, J=10 Hz), 7.32 (s, 5H).
m.p. 106-108°C
$[\alpha]_D^{23}$=+104° (c 4.28, $CHCl_3$).
Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.97; H, 8.02.

Ethyl-4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-benzyloxymethyl-4-hydroxy-8R-methylnon-5Z-en-1-yl]-2-methylpent-2E-enoate (70)

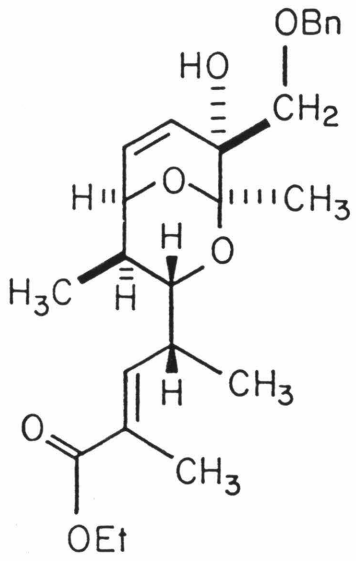
The crystalline bicyclic alcohol (832 mg, 2.39 mmol) was dissolved in 10 mL of dichloromethane; 2.65 g (12.3 mmol) of pyridinium chlorochromate (PCC) was then added with stirring. The reaction mixture turned brown then black and the solids produced interfered with stirring within 5 min. After 45 min. the suspension was poured into 350 mL of ether and the solids were rinsed repeatedly with dichloromethane which was added to the ether solution. This solution was extracted with 50 mL portions of water, saturated sodium bicarbonate (twice), and brine. It was then dried over magnesium sulfate and filtered, and 3.42 g (9.4 mmol) of carboethoxyethylidene triphenylphosphorane was added. The volume of the solution was reduced to about 25 mL on a rotary evaporator, 20 mL of benzene was added, and the volume was again reduced to about 20 mL. More benzene (20 mL) was added and the volume of the solution was reduced to about 15 mL. This solution was then heated in a 75^{o}C oil bath overnight. Most of the solvent was then removed and the crude mixture loaded onto a column of 70 g of silica and eluted with 20% ethyl acetate/petroleum ether. In this manner the following products were obtained:

50 mg of **72** from chromate rearrangement[33] 5%

23 mg of an unidentified product 2%

617 mg of the major product (**70**) 61%

93 mg of (apparently) **Z**-olefin (**71**) 9%



R_f=0.54 (3:2 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 3520, 1695, 1110 cm^{-1}.

^1H NMR ($CDCl_3$): 0.65 (d, 3H, J=7 Hz), 0.93 (d, 3H, J=7 Hz), 1.26 (t, 3H, J=6 Hz), 1.50 (s, 3H), 1.80 (s, 3H), 1.8 (m, 1H), 2.5 (m, 1H), 2.68 (s, 1H), 3.48 (q, 2H, J=10 Hz), 4.2 (m, 3H), 4.57 (AB, 1H, J=9 Hz), 4.65 (AB, 1H, J=9 Hz),5.97 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz), 6.21 (d, 1H, J=10 Hz), 6.87 (brd, 1H, J=10 Hz), 7.35 (s, 5H).

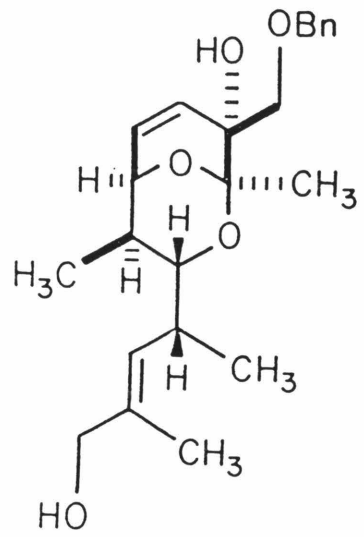
$[\alpha]_D^{22}$=+95.0° (c 2.82, $CHCl_3$).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.68; H, 7.91.

4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-benzyloxymethyl-4-hydroxy-8R-methylnon-5Z-en-1-yl]-2-methylpent-2E-en-1-ol

The ester from the Wittig reaction (538 mg, 1.30 mmol) was dissolved in 10 mL of ether and cooled to -78°C. The solution was stirred while 5.0 mL of 1 M DIBAL-H/hexane were added slowly. After 1 h the reaction was allowed to warm to 0°C and quenched with 1 mL of methanol. It was then stirred with 10 mL of 0.5M sodium potassium tartrate for 3 h at room temperature, separated, dried ($MgSO_4$), and flash chromatographed with 60% ethyl acetate/petroleum ether.

This resulted in isolation of 478 mg of the desired alcohol (95% yield) as a colorless oil.



R_f=0.15 (3:2 petroleum ether: ethyl acetate).

IR ($CHCl_3$): 3520, 1080 cm^{-1}.

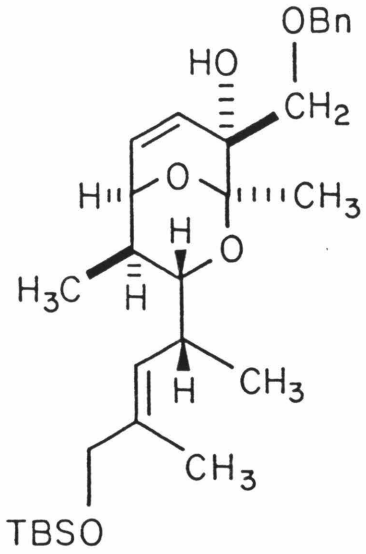
^1H NMR ($CDCl_3$): 0.68 (d, 3H, J=7 Hz), 0.90 (d, 3H, J=7 Hz), 1.45 (s, 3H), 1.64 (s, 3H), 1.8 (m, 1H), 2.5 (m, 2H), 3.4 (m, 2H), 3.46 (q, 2H, J=10 Hz), 3.98 (s, 2H), 4.16 (t, 1H, J=4 Hz), 4.57 (d, 2H, J=2 Hz), 5.53 (brd, 1H, J=10 Hz), 5.93 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz), 6.21 (d, 1H, J=10 Hz), 7.35 (s, 5H).

$[\alpha]_D^{22}$=+92.0° (c 0.65, $CHCl_3$).

Anal. see following compound (silyl ether).

1-tert-butyldimethylsilyloxy-4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-benzyloxymethyl-4-hydroxy-8R-methylnon-5Z-en-1-yl]-2-methylpent-2E-ene (73)

Silylation of the alcohol was accomplished as follows: the alcohol (434 mg, 1.12 mmol) was dissolved in 4.0 mL of DMF. To this, 181 mg of imidazole (2.7 mmol) were added followed by 224 mg of TBSCl (1.49 mmol). The reaction was complete in 30 min. (judged by tlc) and after 30 min. more it was diluted with 120 mL of ether. This solution was washed with three 25 mL portions of water and dried over magnesium sulfate. Flash chromatography of the residue gave 521 mg of clear oil for a 93% yield of the desired product.



R_f=0.76 (3:2 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 3520 (br), 1090, 830 cm^{-1}.

^1H NMR ($CDCl_3$): 0.07 (s, 6H), 0.65 (d, 2H, J=7 Hz), 0.88 (d, 3H, J=7 Hz), 0.93 (s, 9H), 1.44 (s, 3H), 1.55 (s, 3H), 1.8 (m, 1H), 2.5 (m, 1H), 2.60 (s, 1H), 3.38 (d, 1H, J=9 Hz), 3.48 (q, 2H, J=10 Hz), 4.00 (s, 2H), 4.15 (t, 1H, J=4 Hz), 4.58 (d, 2H, J=2 Hz), 5.49 (brd, 1H, J=10 Hz), 5.95 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz), 6.20 (d, 1H, J=10 Hz), 7.35 (s, 5H).

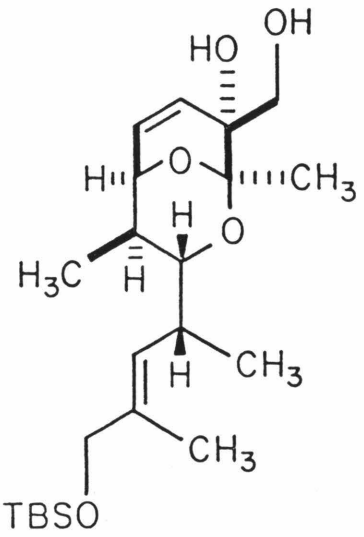
$[\alpha]_D^{22}$=+501° (c 1.03, $CHCl_3$).

Anal. Calcd for $C_{29}H_{46}O_5Si$: C, 69.28; H, 9.22. Found: C, 69.30; H, 9.25.

1-tert-butyldimethylsilyloxy-4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-hydroxymethyl-4-hydroxy-8R-methylnon-5Z-en-1-yl]-2-methylpent-2E-ene

Lithium di-**tert**-butylbiphenyl solution was prepared as usual, starting with 4.2 g of di-**tert**-butylbiphenyl (16 mmol) and 140 mg lithium wire (20 mmol) in 100 mL of THF.[26] The benzyl ether to be deprotected (501 mg, 1.00 mmol) was dissolved in 12 mL of THF and cooled to -78°C. The radical anion solution was then added dropwise until the dark green color persisted in the reaction. An additional 1 mL of the reagent solution was then added and the reaction was stirred one minute more and quenched at -78°C with aqueous ammonium chloride. The suspension was then allowed to warm to room temperature, diluted with ether (100 mL), and extracted with

brine. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (eluting with 35% ethyl acetate/petroleum ether) to yield 386 mg (94%) of the deprotected alcohol as a clear oil.



R_f=0.41 (3:2 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 3530, 3450 (br), 828 cm^{-1}.

^1H NMR ($CDCl_3$): 0.10 (s, 6H), 0.67 (d, 3H, J=7 Hz), 0.91 (s, 9H), 0.96 (d, 3H, J=7 Hz), 1.42 (s, 3H), 1.58 (s, 3H), 2.0 (m, 1H), 2.2 (brs, 1H), 2.4 (m, 1H), 3.5 (m, 3H), 3.99 (s, 2H), 4.13 (t, 1H, J=4 Hz), 5.50 (brd, 1H, J=9 Hz), 5.96 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz), 6.26 (d, 1H, J=10 Hz).

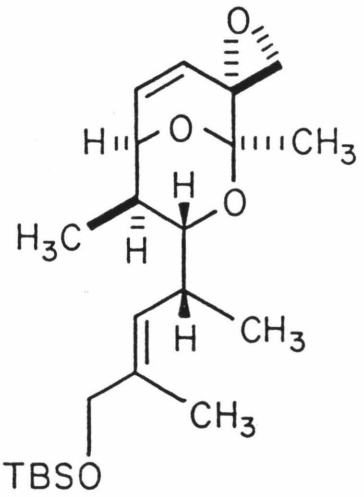
$[\alpha]_D^{22}$=+93.5° (c 0.43, $CHCl_3$).

Anal. Calcd for $C_{22}H_{40}O_5Si$: C, 64.04; H, 9.77. Found: C, 63.91; H, 9.62.

1-tert-butyldimethylsilyloxy-4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-methylenoxy-8R-methylnon-5Z-en-1-yl]-2-methylpent-2E-ene (74)

The diol (298 mg, 0.723 mmol) was dissolved in 15 mL of THF and cooled to 0°C. Sodium hydride (150 mg of a 50% oil dispersion, 3.1 mmol) was added and the mixture was stirred for 10 min. p-Toluenesulfonyl imidazolide (342 mg, 1.54 mmol) was dissolved in 3.0 mL of THF and the solution was

added dropwise to the reaction over 5 min.[37] By tlc, the reaction was not quite complete after 2 h, so it was stirred for 30 min. at room temperature, then carefully quenched with methanol. The mixture was diluted with 250 mL of ether and extracted with 100 mL portions of brine, then water, then brine. Brief drying over $MgSO_4$ was followed by filtration and solvent removal (rotary evaporator). The crude material was flash chromatographed with 9% ethyl acetate/petroleum ether to provide 273 mg (96% yield) of the epoxide which was pure by tlc and NMR.



R_f=0.78 (4:1 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 995, 828 cm^{-1}.

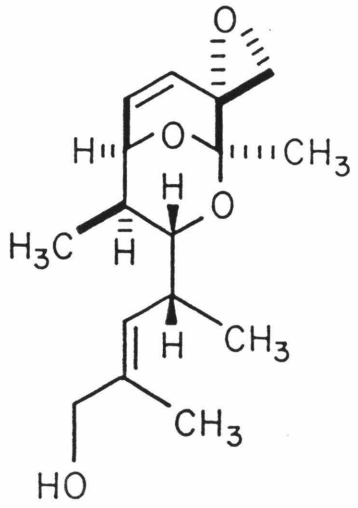
^1H NMR ($CDCl_3$): 0.08 (s, 6H), 0.65 (d, 3H, J=7 Hz), 0.92 (s, 9H), 0.96 (d, 3H, J=7 Hz), 1.19 (s, 3H), 1.60 (s, 3H), 2.0 (m, 1H), 2.5 (m, 1H), 3.53 (dd, 1H, $J_{3,4}$=10 Hz, $J_{3,4'}$=2 Hz), 3.75 (d, 1H, J=5 Hz), 3.92 (d, 1H, J=5 Hz), 4.00 (s, 2H), 4.29 (t, 1H, J=4 Hz), 5.49 (brd, 1H, J=9 Hz), 5.57 (d, 1H, J=10 Hz), 6.30 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz).

$[\alpha]_D^{22}$=+154° (c 0.75, $CHCl_3$).

Anal. see following compound (desilyated).

4R-[1R-2,9-dioxabicyclo-[3.3.1]-3R-methyl-4R-methylenoxy-8R-methylnon-5Z-en-1-yl]-2-methylpent-2E-en-1-ol

The epoxide (91 mg, 0.23 mmol) was dissolved in 2.0 mL of THF and cooled to 0°C. A 1M THF solution of tetra-n-butylammonium fluoride (1 mL) was added and the reaction was stirred for 1 h at which time it was judged complete by tlc. It was diluted with 100 mL of ether and extracted with 25 mL of brine. The organic layer was then dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. Flash chromatography of the residue gave 63 mg (97%) of white crystalline material.



R_f=0.30 (7:3 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 3540, 3460 (br), 992 cm^{-1}.

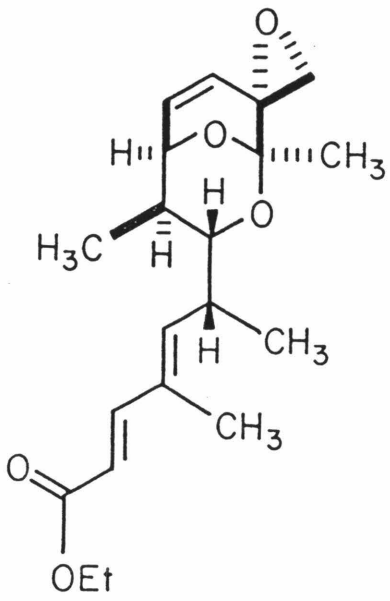
^1H NMR ($CDCl_3$): 0.66 (d, 3H, J=7 Hz), 0.99 (d, 3H, J=7 Hz), 1.21 (s, 3H), 1.68 (s, 3H), 1.7 (brs, 1H), 2.0 (m, 1H), 2.5 (m, 1H), 2.76 (d, 1H, J=5 Hz), 2.97 (d, 1H, J=5 Hz), 3.58 (dd, 1H, $J_{3,4}$=10 Hz, $J_{3,4'}$=2 Hz), 4.01 (s, 2H), 4.32 (t, 1H, J=4 Hz), 5.52 (brd, 1H, J=9 Hz), 5.59 (d, 1H, J=10 Hz), 6.37 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$=10 Hz).

$[\alpha]_D^{23}$=+193° (c 0.859, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.63; H, 8.60.

Streptolic Acid Ethyl Ester

Dichloromethane (2.0 mL) was cooled to -78° and 30 L (0.34 mmol) of oxalyl chloride was added followed by 30 L (0.42 mmol) of DMSO. After stirring for 15 min., the alcohol was added in 1.0 mL of dichloromethane and rinsed in with 1 mL more of dichloromethane. This was stirred for 30 min. and 0.15 mL (0.84 mmol) of Hunig's base was added. It was then allowed to warm to room temperature and 318 mg (0.91 mmol) of carboethoxymethylidene triphenylphosphorane was added. This reaction mixture was stirred overnight at room temperature. It was then diluted with 100 mL of dichloromethane and extracted with brine followed by sodium bicarbonate. The solution was dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. Chromatography on 8 g of silica, eluting with 7% ethyl acetate/petroleum ether gave 49 mg of the ethyl ester (74%).



R_f=0.43 (4:1 petroleum ether:ethyl acetate).

IR ($CHCl_3$): 1690, 1622 cm^{-1}.

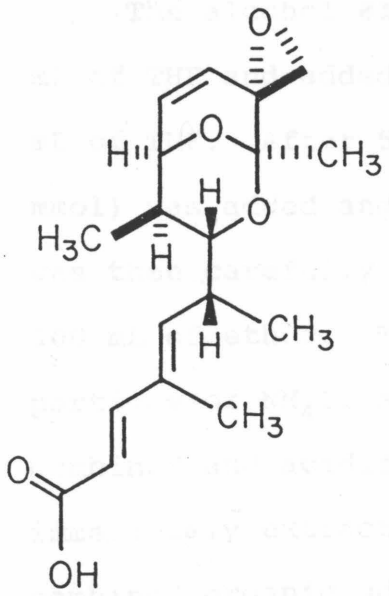
^1H NMR ($CDCl_3$): 0.70 (d, 3H, J=7 Hz), 1.03 (d, 3H, J=7 Hz), 1.23 (s, 3H), 1.31 (t, 3H, J=7 Hz), 1.80 (s, 3H), 1.9 (m, 1H), 2.7 (m, 1H), 2.78 (d, 1H, J=5 Hz), 2.98 (d, 1H, J=5 Hz), 3.62 (dd, 1H, $J_{3,4}$=10 Hz, $J_{3,4'}$=2 Hz), 4.20 (q, 2H, J=7 Hz), 4.33 (t, 1H, J=4 Hz), 5.69 (d, 1H, 10 Hz), 5.88 (d, 1H, J=16 Hz), 6.06 (brd, 1H, J=9 Hz), 6.33 (dd, 1H, $J_{5,6}$=4 Hz, $J_{6,7}$= 10 Hz), 7.34 (d, 1H, J=16 Hz).

$[\alpha]_D^{23}$=+140° (c 0.75, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.87; H, 8.07.

Streptolic Acid (8)

A 19 mg sample of the ester (0.055 mmol) in 5 mL of methanol was treated with 3 mL of 10% aqueous sodium hydroxide. After stirring for 2 h the mixture was diluted with sodium bicarbonate solution, extracted with 15 mL of petroleum ether, acidified to about pH 2 with 10% HCl, and extracted with three 25 mL portions of chloroform. The chloroform solution was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Drying under vacuum resulted in crystallization of the residue (17.6 mg, 100% crude yield). After three recrystallizations (benzene/petroleum ether) the material was identical to streptolic acid (from degradation of streptolydigin) by comparisons of melting point, ^{1}H NMR, IR, and specific rotation.[8]



R_f=0.30 (ethyl acetate).
IR ($CHCl_3$): 3000 (br), 1672, 1617 cm^{-1}.
^{1}H NMR ($CDCl_3$): 0.66 (d, 3H, J=7 Hz), 1.02 (d, 3H, J=7 Hz), 1.20 (s, 3H), 1.79 (s, 3H), 1.8 (m, 1H), 2.7 (m, 1H), 2.76 (d, 1H, J=5 Hz), 2.95 (d, 1H, J=5 Hz), 3.61 (dd, 1H, $J_{3,4}$=10 Hz, $J_{3,4'}$=2 Hz), 4.30 (t, 1H, J=5 Hz), 5.59 (d, 1H, J=10 Hz), 5.78 (d, 1H, J=16 hz), 6.09 (brd, 1H, J=10 Hz), 6.31 (dd, 1H, $J_{5,6}$=5 Hz, $J_{6,7}$=10 Hz), 7.40 (d, 1H, J=16 Hz).
m.p. 168-169°C. (lit. 168-170°C).
$[\alpha]_D^{22}$=+138° (c 0.55, 95% EtOH).
lit. $[\alpha]_D^{25}$=+147 (c 1.21, 95% EtOH).
Anal. Calcd for $C_{18}H_{24}O_5$; C, 67.48; H, 7.55. Found: C, 67.35; H, 7.71.

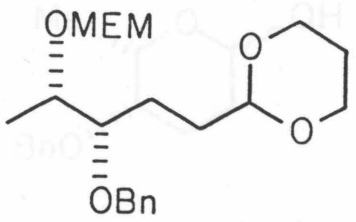
2-[3S-hydroxy-4S-(2-methoxyethoxy)-methoxypentan-1-yl]-1,3-dioxane (81)

Following the procedure of Kelly and Kaul[38], a 5.40 g sample of the distilled aldehyde **80** was dissolved in 150 mL of THF and cooled to -100°C (bath temperature). A solution of the Grignard reagent (from 50 g of alkyl bromide, 0.26 mol, and 7.0 g Mg, 0.29 mol, in 250 mL of THF) was added slowly over 1 h, and the reaction was stirred for an additional hour at -100°C. The work-up described in the literature resulted in isolation of 3.30 g of the desired product (36%). Contrary to the literature report, however, the product was an inseparable mixture of diastereomers.

2-[3S-benzyloxy-4S-(2-methoxyethoxy)-methoxypentan-1-yl]-1,3-dioxane (82)

The alcohol **81** (3.11 g, 11.2 mmol) was dissolved in 40 mL of THF and added carefully to excess KH suspended in 60 mL of THF. After 5 min., benzyl bromide (BnBr: 1.80 mL, 15 mmol) was added and the reaction was stirred overnight. It was then carefully quenched with methanol and poured into 300 mL of ether. This suspension was extracted with 100 mL portions of NH_4Cl and brine. The aqueous layers were combined and acidified with 25 mL of 10% H_2SO_4 and immediately extracted with 200 mL of ether. Drying of the combined organic solutions (Na_2SO_4), followed by flash chromatography (30% ethyl acetate/petroleum ether), provided

3.0 g (75%) of the benzylated material, again as a mixture of diastereomers by 1H NMR.

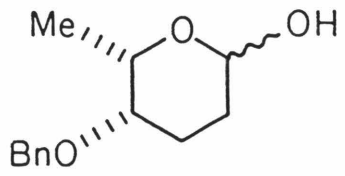


R_f=0.33 (35% ethyl acetate/petroleum ether).
IR ($CHCl_3$) : 1455, 1380, 1144, 1043 cm^{-1}.
^1H NMR ($CDCl_3$) : 1.1 (m, 3H), 1.3-2.2 (m, 6H), 3.36 (s, 3H), 3.4-4.2 (m, 10H), 4.5 (m, 3H), 4.76 (s, 2H), 7.31 (s, 5H).
Anal. Calcd. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.24; H, 8.70.

4-O-benzyl Rhodinose (83)

The benzylated material (2.9 g, 7.9 mmol) was dissolved in 100 mL of acetone. 5% HCl (20 mL) was added, and the solution was heated in a 60°C oil bath for 2.5 h. At this time no starting material could be detected by tlc (4% acetone/chloroform). There were two products, both more polar than the starting material, in approximately equal yields by tlc. The reaction solution was allowed to cool and then was diluted with 600 mL of ether and neutralized with 10% NaOH. The layers were separated and the ether layer was washed with brine and dried over $MgSO_4$. Removal of the solvent left 1.70 g of crude product. By flash chromatography, small pure samples of each compound were

obtained along with 1.35 g (75%) of a mixture of the two. The more polar (lower tlc R_f) compound appeared to be the major product, but the difference was small.



R_f=0.14 (4% acetone/chloroform).
IR ($CHCl_3$) : 3460, 1220, 1137, 1039 cm^{-1}.
^1H NMR ($CDCl_3$) : 1.20 (t, 3H, J=7 Hz), 1.4-2.2 (m, 4H), 3.2 (br s, 1H), 3.3-4.3 (m, 2H), 4.50 (q, 2H, J=11 Hz), 4.6 (m, 1H), 5.25 (br s, 1H), 7.3 (s, 5H).

Attempted Formation of 86

The pyranose **83** (64.1 mg, 0.29 mmol) was dissolved in 1.20 mL of THF and cooled to -78°C. CCl_4 (36 L, 0.36 mmol) was added and then 60 L (0.33 mmol) of TDAP was added. The solution was stirred for 30 min. at -78°C then allowed to warm to 20°C. After stirring for 20 min. more, the reaction was diluted with ether and quickly extracted with 20 mL of water. The ether layer was dried over $MgSO_4$ and filtered.

Addition of the ethyl ester of N-benzylglycine (0.15 mL, 0.79 mmol) and removal of the solvent under reduced pressure gave a mixture of products by tlc. Some of the

pyranose starting material was observed along with the N-benzylglycine ethyl ester, two faint spots which may correspond to the pyranosyl chloride(s), and a significantly less polar product. Chromatography (3% acetone/chloroform) allowed isolation of a pure sample of the least polar product (23 mg) which proved to be the glycal **87** (39%). A mixture of the two products corresponding to the two faint tlc spots indicated that neither of them had incorporated the amine. The recovered pyranose must correspond to hydrolysis of the glycosyl chloride during work-up or in the subsequent reaction (due to incomplete drying of the glycosyl chloride solutiond) since none was detected by tlc in the glycosyl chloride solution before addition of the amine.

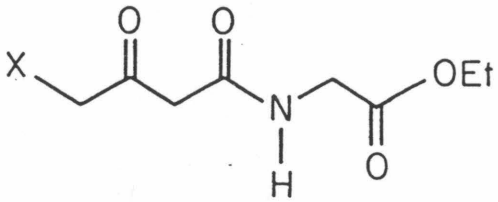
Subsequent attempts to induce the glycosyl chloride to alkylate N-benzylglycine ethyl ester involved using Ag_2O and Ag_2CO_3 in THF and benzene. No new products were observed in these reactions. Treatment of the glycal with excess amine and a catalytic amount of p-TsOH in benzene resulted in no reaction after 4 days at 20°C.

Ethyl-N-(4-bromo-3-oxobutanoyl)-glycinate (92)

Bromine (1.30 mL, 25.4 mmol) was added to a stirred solution of diketene (2.00 mL, 25.4 mmol) in 20 mL of CCl_4 cooled to -30°C. The clear solution was stirred for 10 min. in a 0°C bath.

Glycine ethyl ester hydrochloride (4.7 g, 34 mmol) was suspended in 50 mL of $CHCl_3$ and cooled to -40°C. Hunig's base (6.6 mL, 38 mmol) was added and the mixture was stirred for 20 min. at -40°C, at which time most of the amine hydrochloride had dissolved.

The bromoacetoacetyl bromide solution was added to the gllycine solution using a syringe. Formation of white precipitate was observed. This mixture was allowed to warm to room temperature and stirred for 2 h. It was then diluted with 500 mL of ether and washed with 100 mL portions of 0.2M H_2SO_4 and water. The organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product consisted of 3.5 g of beige crystals; the tlc (Et_2O) of this material showed a minor spot at R_f=0.70 and two major products at R_f=0.21 and R_f=0.18. Flash chromatography (eluting with ether) provided pure samples of each of the slower materials (although most of the material was not separated.) The slower and dominant of these two products was shown to be the expected bromide **92**; spectral comparisons suggested that the other compound was the chloride **93**.



92 X = Br

R_f=0.18 (ether).
IR ($CHCl_3$): 3420, 1745, 1678, 1533, 997 cm^{-1}.
^1H NMR ($CDCl_3$) : 1.26 (t, 3H, J=7 Hz), 3.65 (s, 2H), 4.00 (d, 2H, J=6 Hz), 4.19 (q, 2H, J=7 Hz), 4.30 (s, 2H, 7.2 (m, 1H).
Anal. Calcd. for $C_8H_{12}BrNO_4$: C, 36.11; H, 4.54; N, 5.26. Found: C, 36.34; H, 4.55; N, 5.21.[42]

APPENDIX

3-Acyltetramic Acid Antibiotics.
2. Synthesis of (+)-Streptolic Acid

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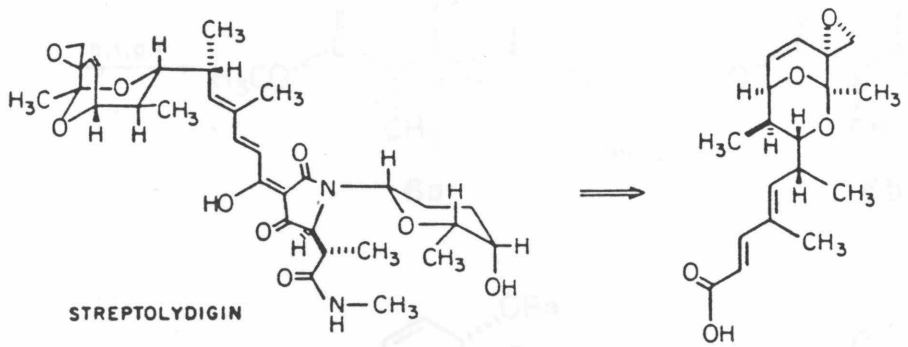
Contribution No.

Abstract: An efficient total synthesis of streptolic acid, a product obtained from cleavage of the antibiotic Streptolydigin, is described. Absolute stereochemistry is controlled through an ester enolate Claisen and an application of the Sharpless asymmetric epoxidation.

Extension of the synthetic strategy developed in these laboratories for construction of the 2,9-dioxabicyclononane skeleton[1] has recently culminated in the synthesis of streptolic acid (2)[2], a degradation product from Streptolydigin the most potent member of the small family of 3-acyltetramic acid antibiotics.[3]

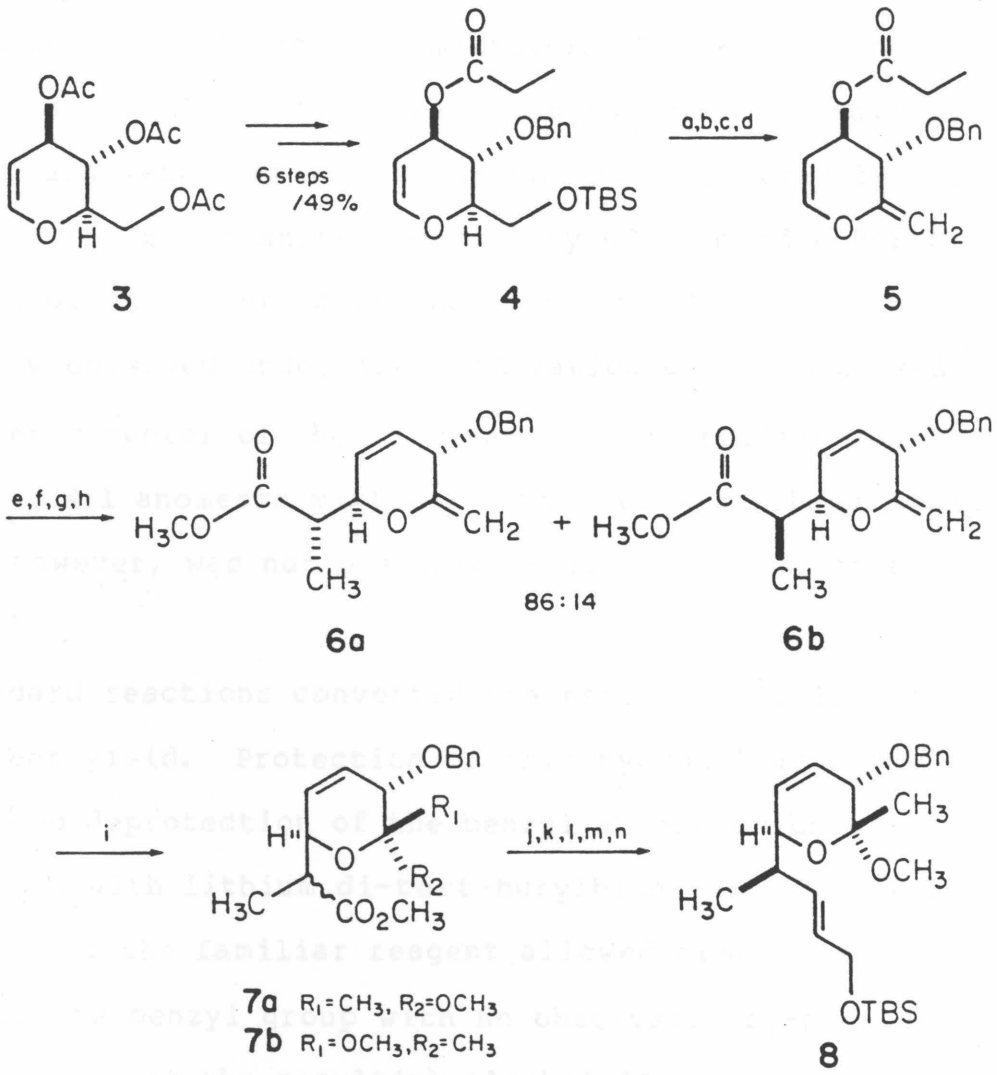


1 2

The current strategy allows divergence from an advanced intermediate, and provides access to the substitution pattern necessary for the synthesis of other members of the family[4] as well as streptolydigin and synthetic analogues.

As in the tirandamycic acid synthesis,[1] development of the bicyclic portion of streptolic acid began with an ester enolate Claisen rearrangement[5] of a glycal derived from D-glucose.

Scheme I Construction of Carbon Framework for Bicyclic Portion[a]

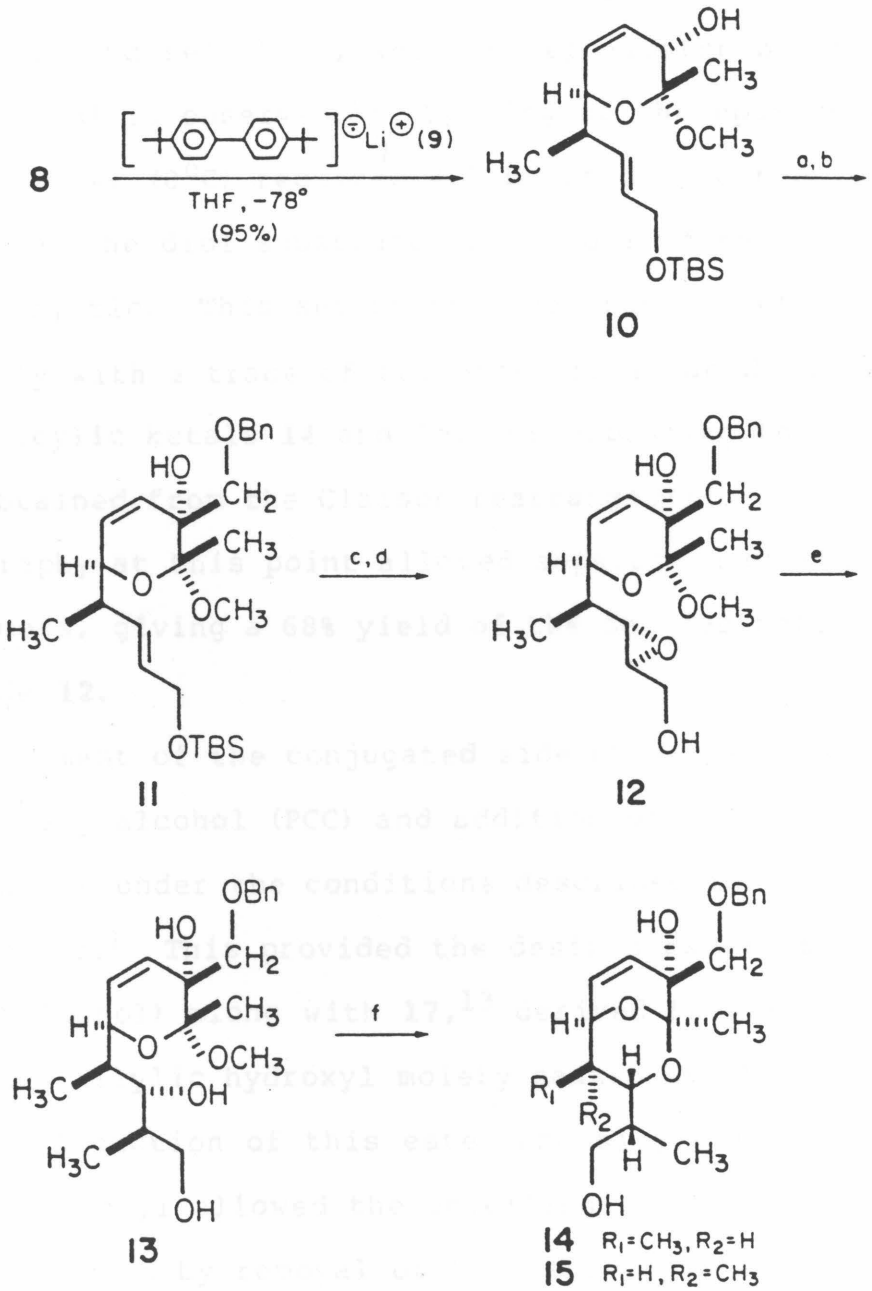


Preparation of the glycal intermediate **4** followed the earlier procedure.[1] To avoid the troublesome elimination sequence required to deoxygenate C_6 of the Claisen product,[1] however, the glycal **4** was transformed into the iodide through the corresponding tosylate and then dehydroiodinated to the surprisingly stable **bis**-enol ether **5**. This proved to be an excellent substrate for the ester enolate Claisen, and the enol ether **6** was thus obtained as a mixture of methyl epimers. The

epimeric ratio was determined after ketalization to the mixed ketals **7a** and **7b** (4:1 anomeric mixture). The anomers proved to be readily separable by flash chromatography, but resolution of the side chain methyl epimmers was not possible even by tlc. Analysis of the major anomer (capillary GC) showed a 86:14 mixture of diastereomers corresponds to the usual geometric selectivity observed under the enolization conditions used.[5] (The anomeric center of the minor anomer was readily equilibrated to the same 4:1 anomeric mixture. Separation of these methyl epimers, however, was not possible until much later in the sequence.)

Standard reactions converted the ester to allylic alcohol **8** in excellent yield. Protection of this hydroxyl as a TBS ether then allowed deprotection of the benzyl ether, which was accomplished with lithium di-**tert**-butylbiphenyl (**9**).[6] This novel application of the familiar reagent allowed almost quantitative removal of the benzyl group with no observable by-products.[7] Swern oxidation of the resulting alcohol **10** gave the enone, which allowed addition of the functionalized carbon required to form the allylic epoxide portion of streptolic acid. The reaction of this enone in THF at -78°C with benzyloxymethyllithium[8] afforded essentially one product, along with traces of a mixture of conjugate addition products. As expected, the major product derived from axial attack of the nucleophile at the carbonyl.[9] Surprisingly, however, none of the product corresponding to equatorial attack was observed.[10] Thus the requisite substituent was efficiently introduced, to give the sensitive allylic epoxide in a protected form.

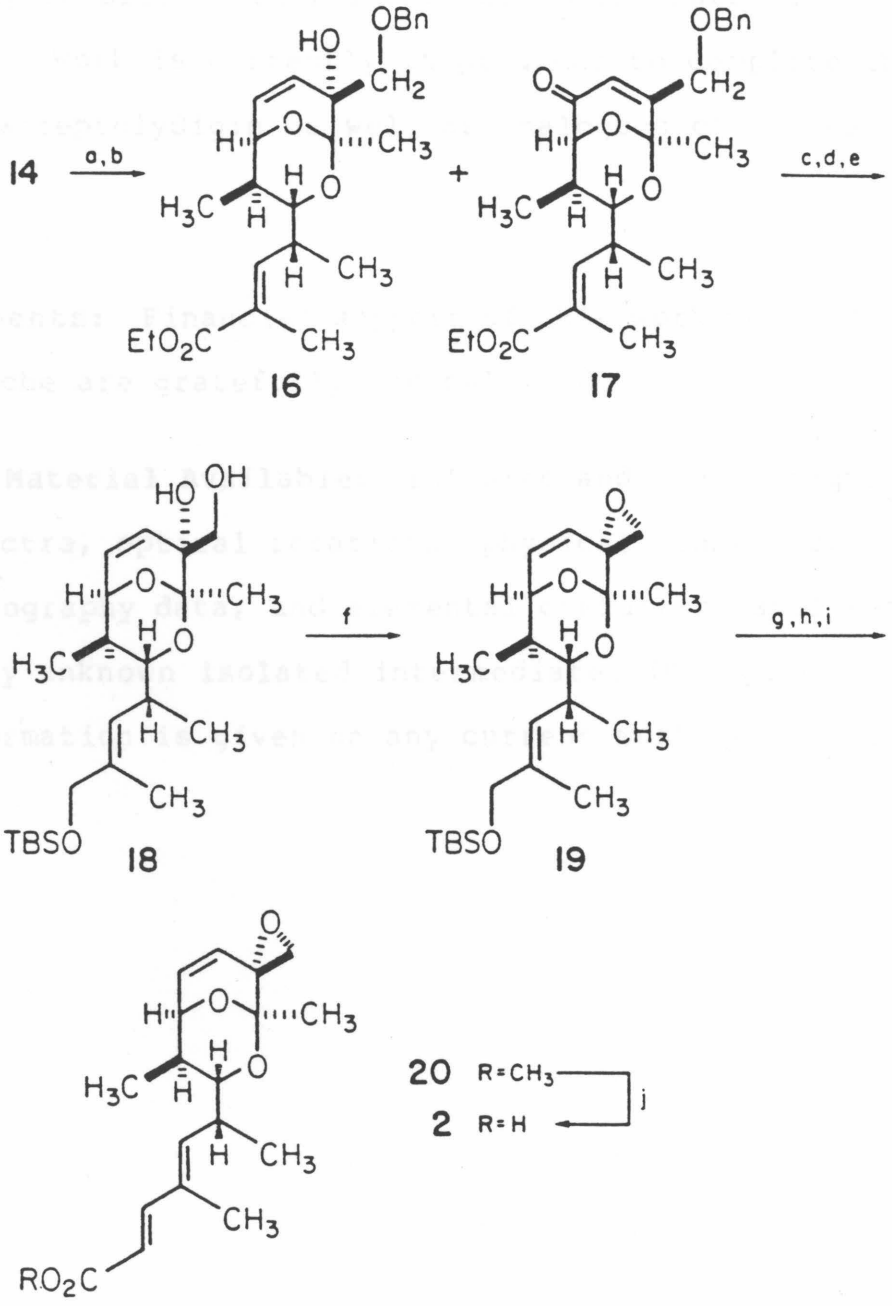
Scheme II Formation of 2,9-Dioxabicyclo [3.3.1]nonane[a]



Cleavage of the silyl ether with fluoride revealed an allylic alcohol for an interesting application of the Sharpless asymmetric epoxidation.[11] As expected, epoxidation of the side chain is fast and selective, while no epoxidaton of the cyclic allylic alcohol is observed.[12] Opening of the epoxide with Me_2CuLi in ether (0°C) required 4-5 hours due to the low solubility of the diol substrate, but provided the triol **13** in good yield by tlc. This set up the cyclization, which occurred very readily with a trace of toluenesulfonic acid in $CHCl_3$, to give the bicylic ketals **14** and **15**, corresponding to the methyl epimers obtained from the Claisen rearrangement. Careful chromatography at this point allowed separation of the diastereomers, giving a 68% yield of the desired material **14** from the epoxide **12**.

Development of the conjugated side chain began with oxidaton of the primary alcohol (PCC) and addition of the stabilized Wittig reagent under the conditions described in the tirandamycic acid synthesis.[1] This provided the desired ester **16** in 61% yield (from the alcohol) along with **17**,[13] derived from rearrangement of the tertiary allylic hydroxyl moiety caused by the chromium reagent.[14] Reduction of this ester and silylation of the resultant hydroxyl allowed the unveiling of the allylic epoxide. This was effected by removal of the benzyl protecting group, again accomplished very efficiently with lithium di-tert-butylbiphenyl (**9**),[7] followed by treatment with tosyl imidazole and sodium hydride in THF (0°C).[15] Deprotection of the silyl ether, Swern oxidation, and addition of the stabilized Wittig then provided the ethyl ester **20** which was hydrolyzed (10%

Scheme III Completion of Streptolic Acid Synthesis[a]



aqueous NaOH in methanol) to streptolic acid (86% yield after chromatography on silica gel), identical to the natural material.[16,17] Work is currently in progress to complete the synthesis of streptolydigin as well as analogues of the natural antibiotics.

Acknowledgements: Financial support of this work by the NIH and Hoffman-La Roche are gratefully acknowledged.

Supplemental Material Available: Infrared and proton magnetic resonance spectra, optical rotations, physical constants, thin layer chromatography data, and elemental combustion analyses of all previously unknown isolated intermediates (8 pages). Ordering information is given on any current mast head page.

Footnotes and References:

1. Ireland, R.E.; Wuts, P.G.M.; Ernst, B., J. Am. Chem. Soc. **1981**, 103, 3205-3207.

2. Rinehart, K.L., Jr.; Beck, J.R.; Epstein, W.W.; Spicer, L.D., ibid. **1963**, 85, 4035-4037.

3. a. DiCioccio, R.A.; Srivastava, B.I.S., Biochem. Biophys. Res. Commun. **1976**, 72, 1343-1349; b. Reusser, F., J. Bacteriol. **1969**, 99, 151-155; c. Reusser, F., ibid. **1969**, 100, 1335-1341.

4. a. Duchamp, D.J.; Branfman, A.R.; Button, A.C.; Rinehart, K.L., Jr., J. Am. Chem. Soc. **1973**, 95, 4077-4078; b. Hagenmaier, H.; Jaschke, K.H.; Santo, L.; Scheer, M.; Zahner, H., Arch. Microbiol. **1976**, 109, 65-70.

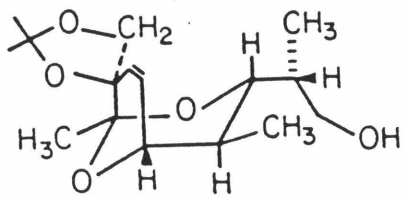
5. Ireland, R.E.; Mueller, R.H.; Willard, A.K., J. Am. Chem. Soc. **1976**, 98, 2868-2877.

6. Freeman, P.K.; Hutchinson, L.L., J. Org. Chem. **1980**, 45, 1924-1930.

7. Several other applications of this reagent for cleavage of benzyl ethers (cf. compound **16** on "conversion to" **18**) suggest that this is an excellent alternative to the Birch conditions generally used when an olefin precludes hydrogenolysis. The reagent (usually 3-5 equivalents) was prepared in THF (0.16 M) at 0°C (see ref. 6) and added *via* syringe in portions to a solution of the substrate in THF (-78°C). Persistence of the dark green color of the radical anion for more than 15 sec. was a reliable indicator of the complete consumption of starting material. Aqueous ammonium chloride quench, standard work-up, and flash chromatography provided easy separation of the product alcohol from the di-tert-butylbiphenyl, which was recovered and re-used after a single recrystallization (95% ethanol).

8. Still, W.C., J. Am. Chem. Soc. **1978**, 100, 1481-1486.

9. The configuration of the product was ascertained by conversion to the rigid tricyclic system **i**



i

through a series of reactions similar to that described for conversion to streptolic acid. Nuclear Overhause Effect experiments confirmed the stereochemistry shown.

10. Subsequent experiments have shown that both methyllithium and methylmagnesium iodide behave similarly: either addition of the enone to methyllithium (THF, -78°C) or of methyllithium to the enone (THF, -78°C) provides exlusively the β-face addition product, and the Grignard reagent (THF, 0° or -78°C) provides the same product plus conjugate addition products. This insensitivity to reaction conditions suggests that addition to the carbonyl is sterically controlled rather than chelation controlled.

11. a. Katsuki, T.; Sharpless, K.B., J. Am. Chem. Soc. **1980**, 102, 5974-5976; b. Rossiter, B.E.; Katsuki, T.; Sharpless, K.B., ibid., **1981**, 103, 464-465.

12. Several factors conspire against epoxidation of the cyclic olefin: (a) it is a Z-olefin which slows epoxidation under these conditions; (b) the allylic hydroxyl is tertiary; and, (c) the tartrate used, (+)-diisopropyl tartrate, would direct epoxidation to occur on the opposite face of the ring from the free hydroxyl.

13. Prolonged exposure to PCC provides **17** as the major product. This provides the top half functionality for a synthesis of tirandamycin B (ref. 4b).

14. Dauben, W.G.; Michno, D.M., J. Org. Chem. **1977**, 42, 682-685.

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16. Spectral data match those published. The synthetic sample exhibited m.p. 168-169° (lit. 168-170°, ref. 2) and $[\alpha]_D^{22}$ +138° (c 0.55, 95% ethanol) (lit. $[\alpha]_D^{26}$ +147° (c 1.22, 95% ethanol). A satisfactory combustion analysis was also obtained.

17. Consistent spectral data (^{1}NMR and IR) and satisfactory combustion analyses were obtained for all new compounds reported.

Scheme I

[a](a) Bu_4NF, THF, 98%. (b) TsCl, pyr, CH_2Cl_2, 89%. (c) NaI, MEK, reflux, 4 h, 87%. (d) DBU, benzene, reflux, 1 h, 99%. (e) $(TMS)_2NLi$, TBSCl, HMPA, THF, -78°C. (f) benzene, reflux, 1 h. (g) $KF{\cdot}2H_2O$, $KHCO_3$, HMPA. (h) CH_3I, HMPA, 85% from 5. (i) MeOH, cat. TsOH, 99%. (j) DIBAL-H, Et_2O, -78°C. (k) $(COCl)_2$, DMSO, Hunig's base, CH_2Cl_2, -78°C. (l) carbethoxymethylidene triphenylphosphorane, CH_2Cl_2, 87% from **7**. (m) DIBAL-H, Et_2O, -78°C. (n) TBSCl, imidazole, DMF.

Scheme II

[a](a) $(COCl)_2$, DMSO, Hunig's base, CH_2Cl_2, -78°C. 93%. (b) $BnOCH_2Li$, THF, -78°C, 89%.[8] (c) Bu_4NF, THF, 93%. (d) (+)-DIPT, $Ti(OiPr)_4$, +-BuOOH, CH_2Cl_2, -20°C, 90%.[11] (e) $(CH_3)_2CuLi$, Et_2O, 0°C. (f) cat. TsOH, $CHCl_3$, 68% yield of **14** from **12**.

Scheme III

[a](a) PCC, CH_2Cl_2. (b) carbethoxyethylidene triphenylphosphorane, benzene, reflux, 12 h, 61% from **14**. (5% yield of **17**). (c) DIBAL-H, Et_2O, -78°C, 95%. (d) TSBCl, imidazole, DMF, 93%. (e) **9**, THF, -78°C, 94%. (f) toluenesulfonyl imidazolide, NaH, THF, 0°C, 96%. (g) Bu_4NF, THF, 97%. (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°. (i) carbethoxymethylidene triphenylphosphorane, CH_2Cl_2, 74% for two steps. (j) MeOH, 10% NaOH; 10% HCl, 100% crude yield.