AN ABSTRACT OF THE THESIS OF

Jeffrey R. Engebrecht for the degree of Master of Science in Chemistry presented on April 3, 1985.

Title: Chiral Synthesis of Alcohols via Asymmetric Epoxidation

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Dr. James D. White

Enantioselective epoxidation of crotyl alcohol, followed by a cuprate mediated methylation, gave a 1:1 mixture of (2S)-3-methyl-1,2-butanediol and (2R,3S)-2-methyl-1,3-butanediol. The latter was separated as its 2,4,6-trimethylbenzenesulfonate derivative and converted via the iodide to the corresponding phosphonium salt. The separated butanediol derivatives were independently transformed to (S)-3-methyl-2-butanol, thereby proving configuration and establishing optical purity.

The primary trityl ether of the chiral butane-1,3-diol was converted to (2S,3R)-2-methyl-3-tert-butyldimethylsilyloxybutanal. The reaction of this aldehyde with methylmagnesium bromide and with methyllithium gave, after removal of the silyl group, meso and (2S,4S)-3-methyl-2,4-pentanediols. A study of this reaction at various temperatures led to the conclusion that stereoselectivity can

be predicted by the Cram model when methyllithium is the reactant but not when the Grignard reagent is employed. In the latter case, a coordination model in which magnesium complexes in bidentate fashion to the carbonyl and β-oxygen atoms successfully predicts the stereochemical outcome.

Chiral Synthesis of Alcohols via Asymmetric Epoxidation

by

Jeffrey Ronald Engebrecht

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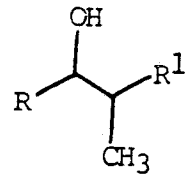
Chiral Synthesis of Alcohols via Asymmetric Epoxidation

I. INTRODUCTION

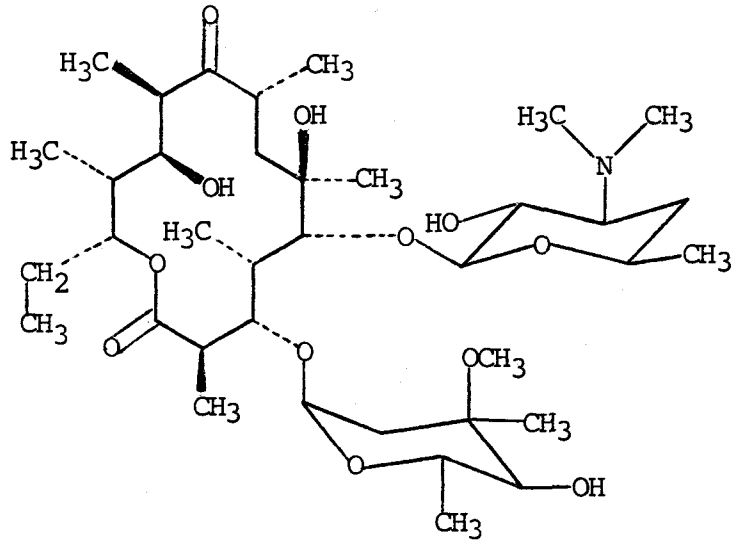
A subunit which frequently occurs in the structure of natural products of the polyketide family consists of vicinal hydroxyl and methyl substituents on a linear carbon backbone. This chiral segment, represented as A, appears as a repeating unit in macrolide antibiotics, such as erythromycin A (1) and rifamycin S (2), and in sections of complex ionophores such as monensin acid (3).[1]



A

Pseudomonic acids A (4),[2] B (5),[3] and C (6)[4] are metabolites of Pseudomonas fluorescens, each of which contains the residue A in one of the side chains appended to the tetrahydropyran nucleus. An interest in devising pathways for the total synthesis of this family of antibiotics and for elaborating A into more highly functionalized assemblies prompted us to investigate methods for the stereoselective construction of this unit in optically active form.

The pseudomonic acids possess a broad spectrum of antibacterial activity and show excellent potential for development as chemotherapeutic agents.[5] Pseudomonic acid A (4) is



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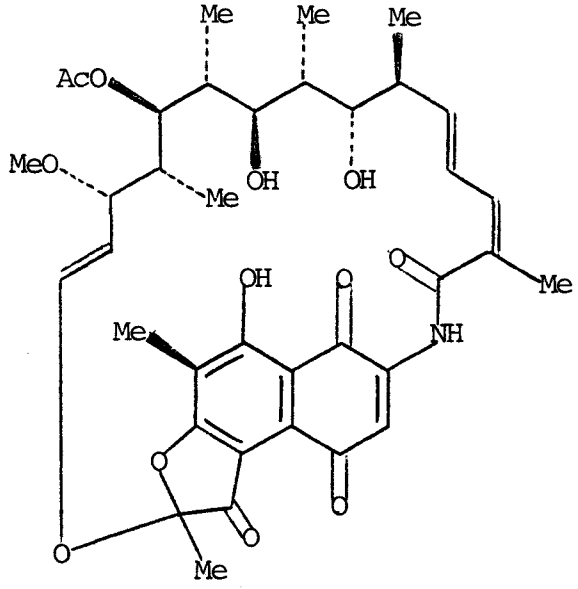

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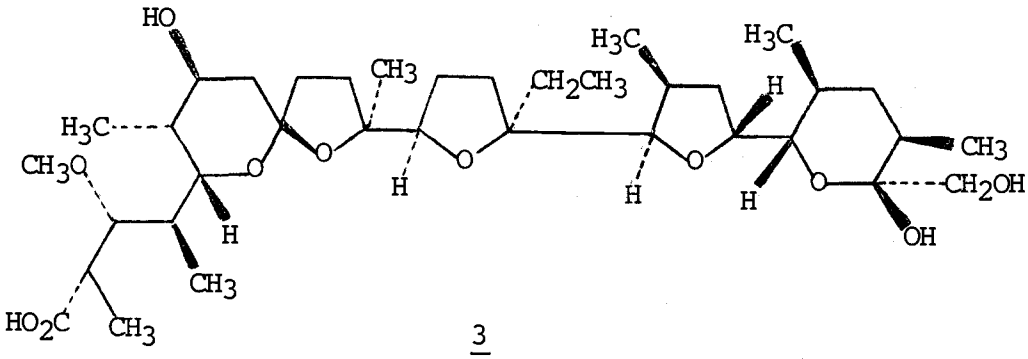

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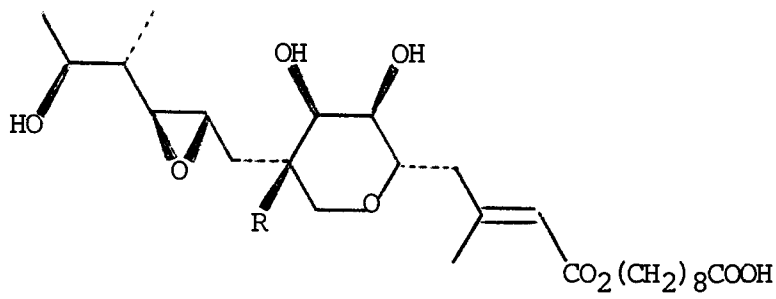
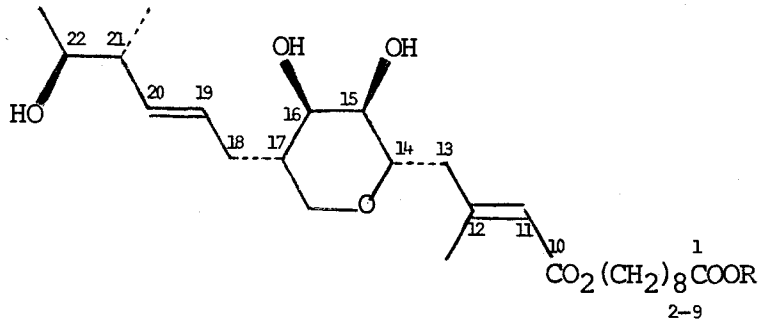


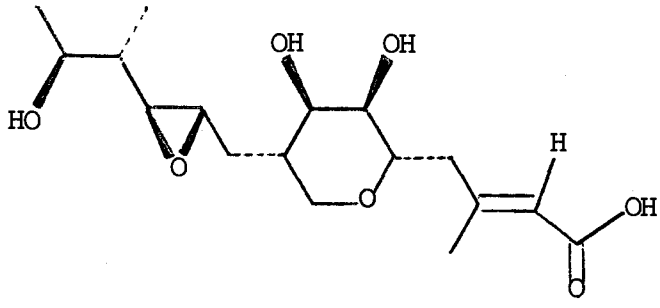
4, R = H

5, R = OH


22
21
OH
OH
HO
20
19
16
15
18
17
14
13
O
12
11
10
1
$CO_2(CH_2)_8$
2–9
COOR

6, R = H

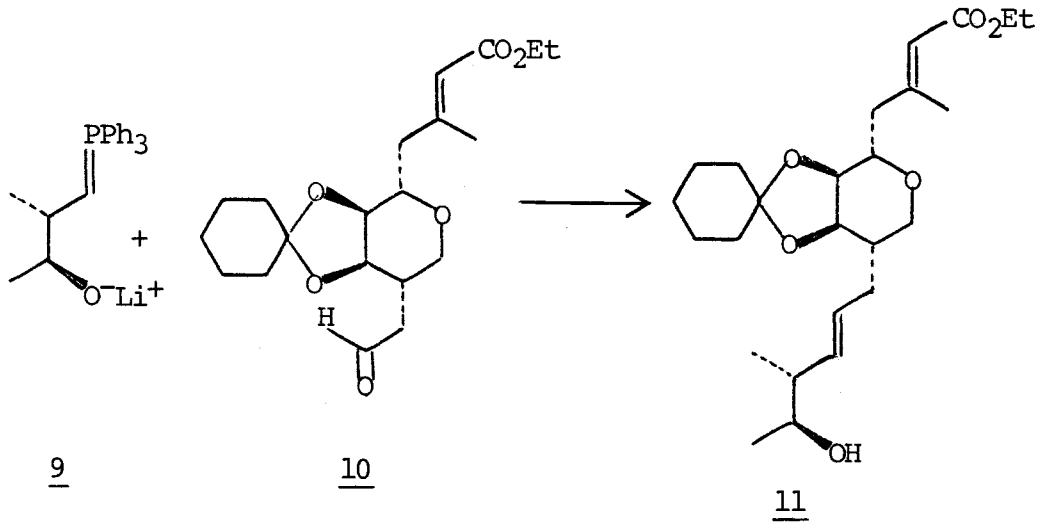
7, R = CH_3


OH
OH
HO
H
O
O
OH
O

8

extensively bound to human serum (>95%), while the methyl ester 7 is bound to a lesser extent (30%).[6] Pseudomonic acids A and B are unstable outside the pH range of 4-9, apparently reflecting reactivity at the epoxide center in these structures, since pseudomonic acid C is appreciably more stable.[7] Monic acid (8), a degradation product of 4, is without biological activity.[6]

Pseudomonic acid A (4) was first synthesized by Kozikowski et al,[8] who employed the racemic phosphorane 9 in a Wittig reaction with aldehyde 10 to assemble the functionalized hexyl side chain (Scheme 1). This led to a mixture of diastereomeric products 11, which included 15% of the cis olefin.

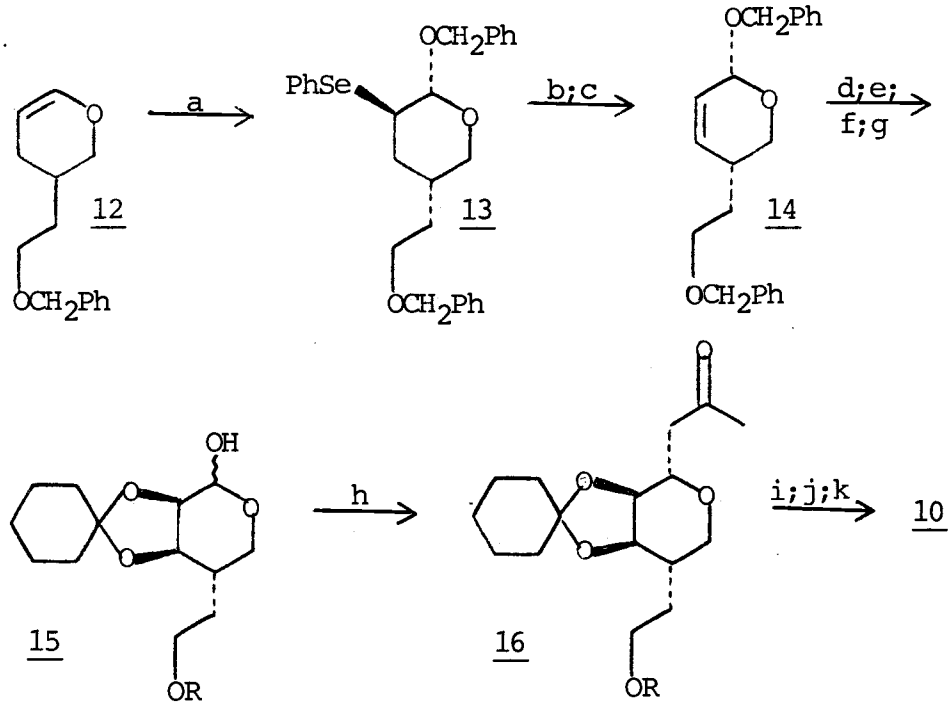


9 10 11

Scheme 1

Aldehyde 10 was derived from an oxyselenation and two Wittig reactions. The oxyselenation converted dihydropyran 12 to cis-2-benzyloxy-5,6-dihydro-2H-pyran 14 via the selenide 13 (Scheme 2).

The first Wittig was done on the silyl-protected hemiacetal 15 to yield 16 as the major isomer (2.5:1). Aldehyde 10 was then obtained by treating 16 first with the anion of ethyl diethyl phosphonoacetate to give the α,β-unsaturated ester (4:1, E:Z), followed by desilylation and oxidation of the primary hydroxyl group.



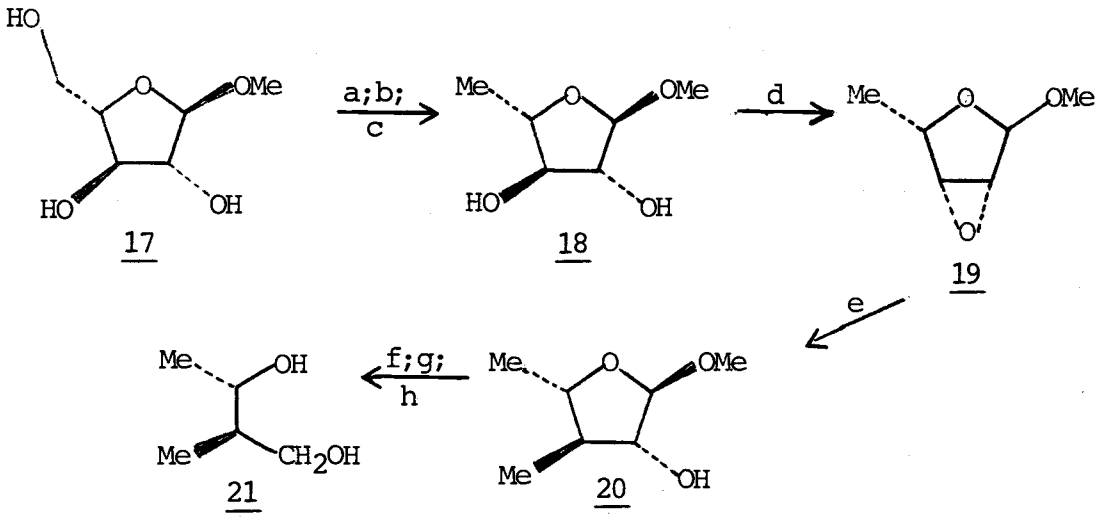
(R=Si(Ph)$_2$t-Bu)

Reagents: a) PhSeCl, Et_3N, $PhCH_2OH$; b) $NaIO_4$, $NaHCO_3$; c) CCl_4, Δ, $CaCO_3$; d) OsO_4; e) Cyclohexanone, H^+; f) 10% Pd/C; H_2; g) ClSi(Ph)$_2$t-Bu/imidazole; h) $CH_3COCHPPh_3$, CH_3CN; i) $(EtO)_2POCH_2CO_2Et$, base; j) $Bu_4N^+F^-$; k) PCC

Scheme 2

Recently, Fleet has published a more highly stereoselective route to the pseudomonic acids which incorporates 9 in optically active form.[9] Fleet's chiral synthesis of 9 (Scheme 3) starts with L-arabinose. The primary alcohol of the kinetic glycoside of L-arabinose 17 was selectively protected as the trimsylate, which was quantitatively converted to the iodide. Subsequent hydrogenolysis (Pd/C) gave methyl 5-deoxy-α-L-arabinofuranoside 18. Reaction of the trans diol 18 with triphenylphosphine and diethyl azodicarboxylate gave epoxide 19 stereospecifically.

The epoxide ring of 19 was opened regiospecifically with the dimethylcyanodilithiocopper species ($Me_2Cu(CN)Li_2$) to the

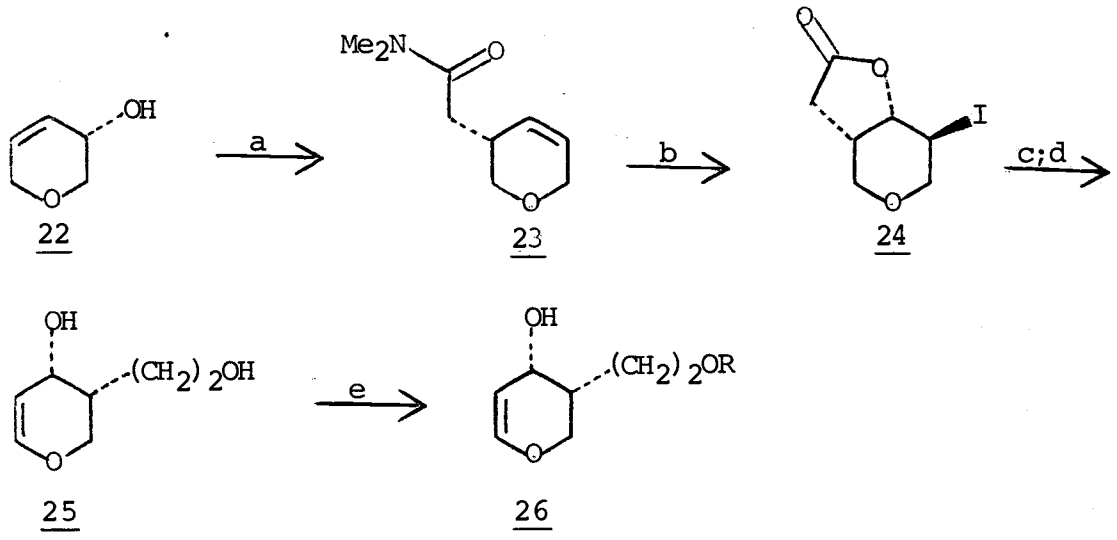


Reagents: a) Trimsylchloride/pyridine; b) NaI; c) Pd/C, H_2, Et_3N, CH_3OH; d) Ph_3P, $EtO_2CN{=}NCO_2Et$; e) $Me_2Cu(CN)Li_2$; f) H_3O^+, g) $NaIO_4$; h) $NaBH_4$

Scheme 3

alcohol 20. Hydrolysis of 20 to the lactol, followed by oxidative cleavage with sodium periodate and reduction of the resulting aldehyde with sodium borohydride, gave diol 21, whose conversion to 9 has been carried out previously.[8]

The reaction of allylic alcohol 22 (which is derived from D-arabinose in two steps) with N,N-dimethylacetamide dimethyl acetal in refluxing xylene gave the Claisen rearrangement product 23 (Scheme 4). Treatment of 23 with iodine in aqueous tetrahydrofuran gave iodolactone 24. Elimination of HI with base and subsequent reduction of the lactone with sodium borohydride gave diol 25, in which the primary hydroxyl group was selectively protected as the tert-butyldiphenylsilyl ether 26.

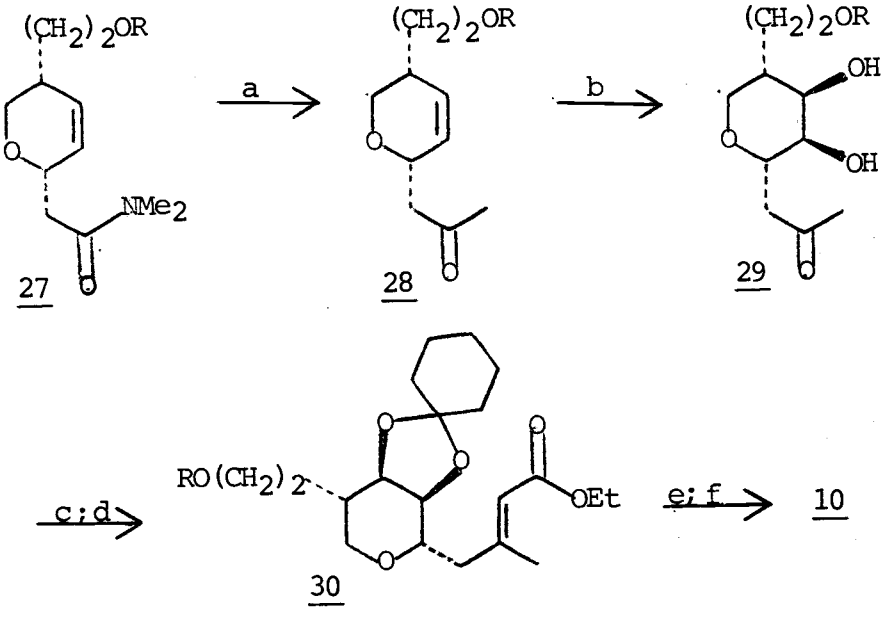


(R=Si(Ph)$_2$t-Bu)

Reagents: a) MeC(OMe)$_2$NMe$_2$; b) I_2, THF/H_2O; c) DBU; d) $NaBH_4$; e) $Ph_2Si(t\text{-}Bu)Cl$/imidazole

Scheme 4

The second carbon chain was next introduced by a second Claisen amide-acetal rearrangement to form the tertiary amide 27 from 26. Treatment of 27 with a small excess of methyllithium led to the methyl ketone 28 (Scheme 5), which was selectively hydroxylated from the least hindered side by osmium tetroxide/N-methylmorpholine-N-oxide to give diol 29. This chiral diol, protected as the cyclohexylidene derivative, was then subjected to a Wadsworth-Emmons olefination with the sodium salt of triethyl phosphonoacetate to give 30 (~4:1 E:Z olefin). The silyl protecting group was removed from 30



(R=Si(Ph)$_2$t-Bu)

Reagents: a) MeLi; b) OsO_4, N-methylmorpholine-N-oxide; c) Cyclohexanone, pTSA; d) NaH, $(EtO)_2POCH_2CO_2Et$; e) Bu_4NF; f) PCC

Scheme 5

with tetrabutyl ammonium fluoride and the resulting alcohol was oxidized with pyridinium chlorochromate to the aldehyde 10.

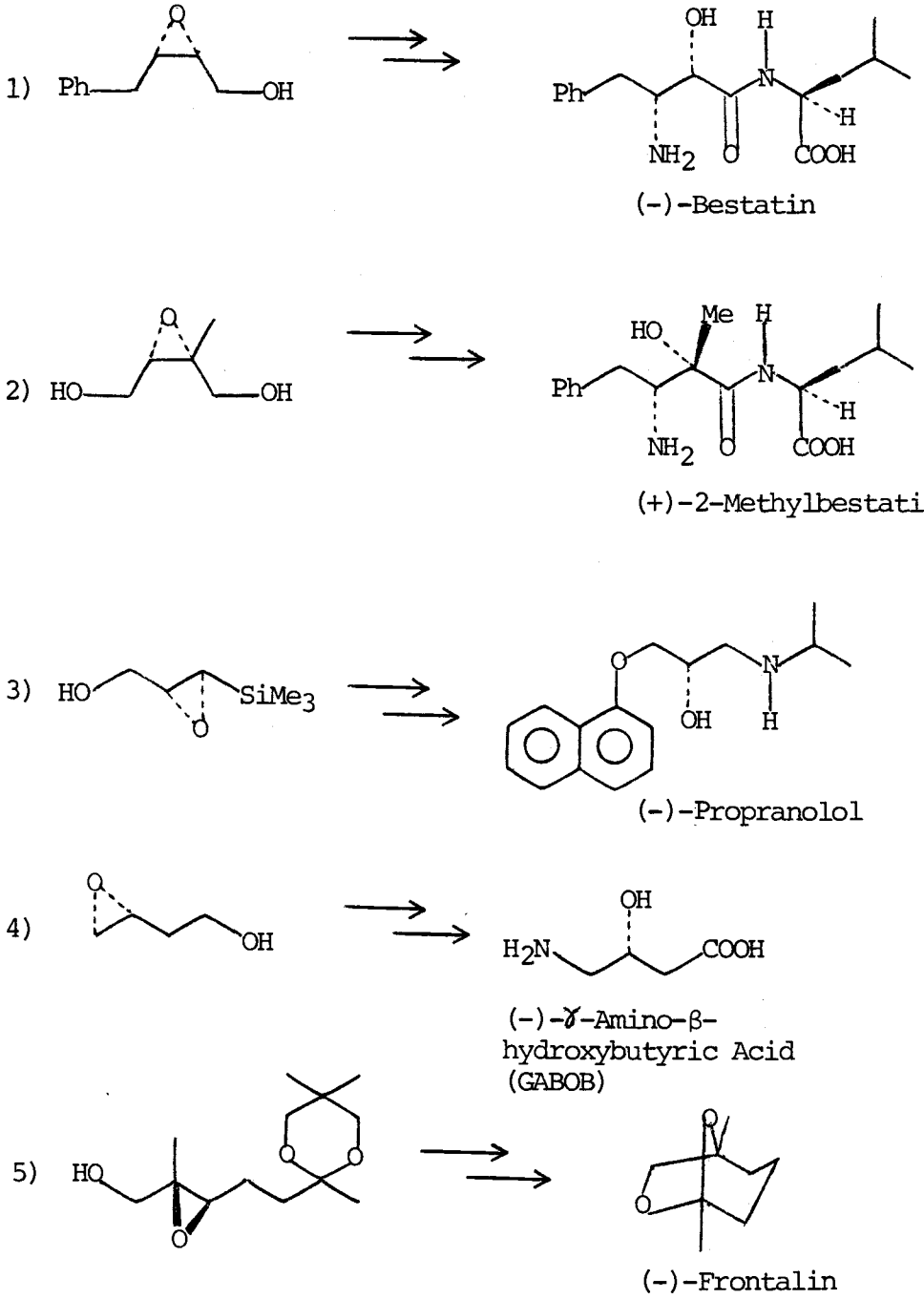
Several other approaches to the pseudomonic acids have been described, including formal total syntheses of 4 by Snider[10] and Raphael.[11] Of these, only the synthesis of Fleet addresses the issue of absolute configuration at C21 and C22. Since our strategy for the synthesis of pseudomonic acids also hinges upon the convergence of the chiral segment 9 with a chiral aldehyde, it became of primary importance to have 9 available in the correct absolute configuration (21S, 22S) by a reasonably direct route.

The tartrate-mediated, enantioselective epoxidation of allylic alcohols developed by Sharpless provides a predictable and efficient means for introducing absolute stereochemistry at oxygen-bearing carbons.[12] In fact, Sharpless has extended this methodology by demonstrating that reduction and alkylation of chiral, epoxy alcohols can lead to the asymmetric synthesis of many natural products and their derivatives. These presently include (-)-bestatin, (+)-2-methylbestatin, (-)-propranolol, (-)-γ-amino-β-hydroxybutyric acid, and both (-) and (+)-frontalin[13] (see Figure I).

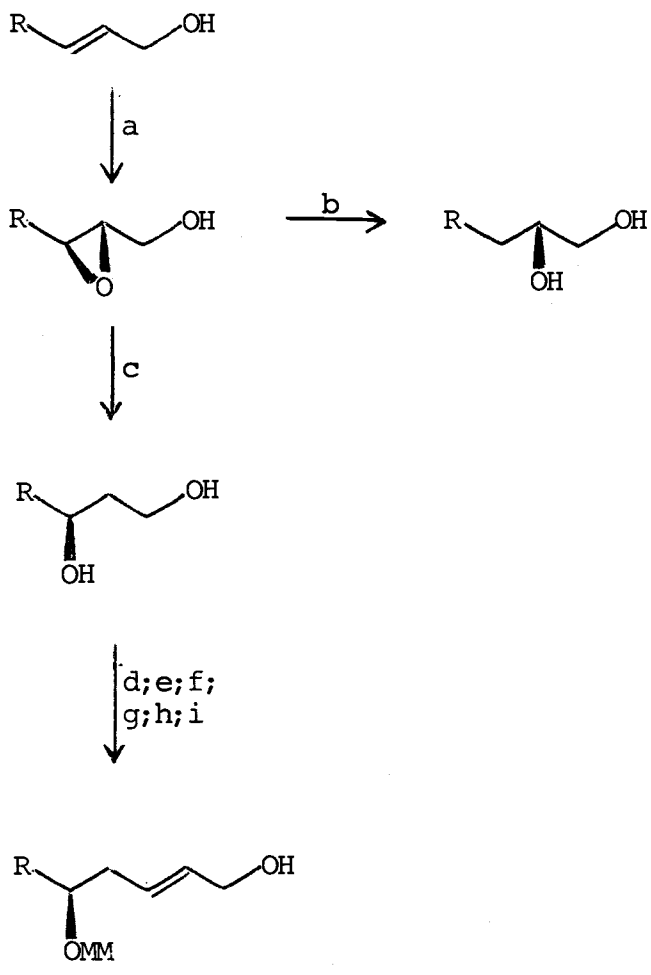
Kishi has also shown that the Sharpless enantioselective epoxidation can be used for the regio- and stereospecific synthesis of 1,3-polyhydroxylated chains often found in

Figure I

Stereo and regioselective openings of chiral 2,3-epoxy alcohols



polyether antibiotics, ansamycin antibiotics and carbohydrates.[14] Employing the Sharpless asymmetric epoxidation of allylic alcohols, followed by regioselective reductive

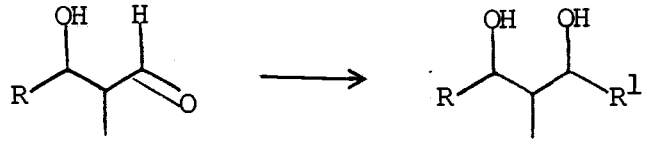


Reagents: a) t-BuOOH, (-)-Diethyl tartrate, $(i\text{-PrO})_4Ti$; b) DIBAL; c) Red-Al; d) $t\text{-Bu(Ph)}_2SiCl$; e) $MeOCH_2Br$; f) $(n\text{-Bu})_4NF$; g) DMSO, $(COCl)_2$, Et_3N; h) $(i\text{-PrO})_2POCH_2CO_2Et$; i) DIBAL

Scheme 6

ring opening of the resulting epoxide with a hydride reagent, Kishi has been able to synthesize 1,2 or 1,3-diols in high yield (Scheme 6).

Although a specific goal of this research was the synthesis of 9, with the absolute configuration shown, the broader aim of generating constructs for systems containing the unit A was also pursued. In particular, we were interested in the homologation of this segment, via the aldehyde B, to a system C which would contain a third chiral center. Since diastereoselection in this process is clearly important, an investigation of the alkylation of B was carried out in order to ascertain whether Cram's Rule was operative here.

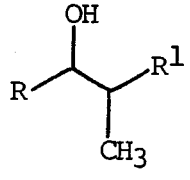


B C

In the following section are described the results of studies which began from (2S,3S)-epoxybutanol and which led to several potentially useful chiral alcohols with high optical purity.

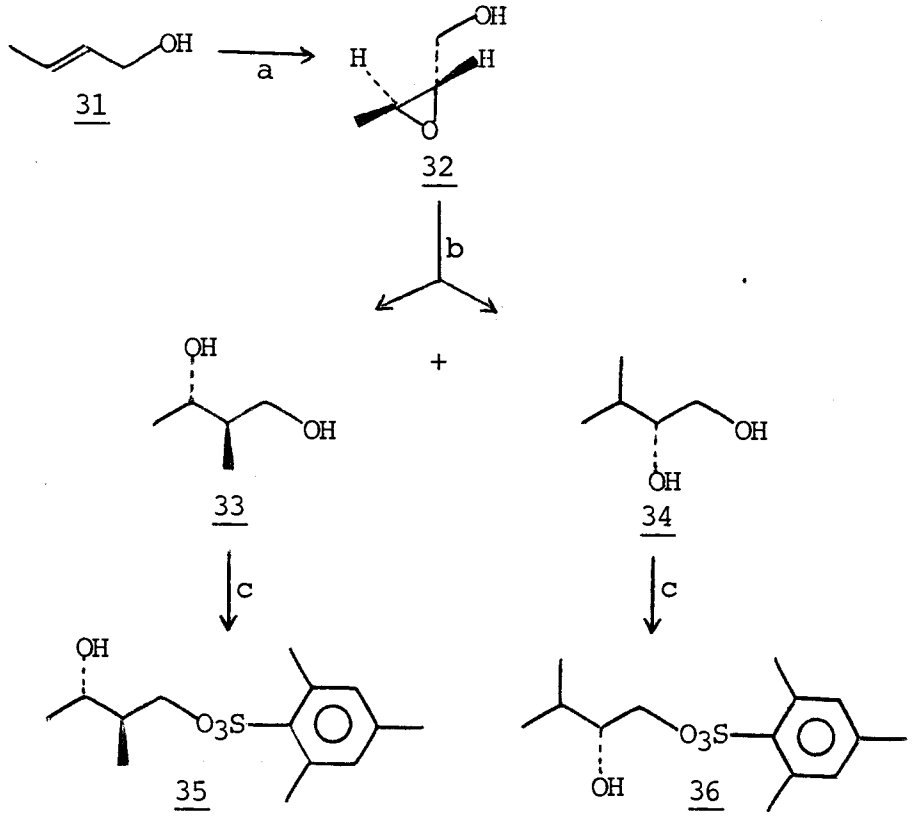
II. CHIRAL SUBUNITS FOR PSEUDOMONIC ACIDS AND RELATED SYSTEMS

In planning a synthesis of the chiral subunit A, we sought a strategy which would incorporate a high level of asymmetric induction at an early stage of the sequence and which could produce either enantiomer of this structure. The enantioselective epoxidation of allylic alcohols developed by Sharpless provides an ideal means for introducing asymmetry in an absolute sense at an oxygen-bearing carbon. Specifically, crotyl alcohol (31) has been shown to react with t-butyl hydroperoxide in the presence of titanium tetraisopropoxide and an optically active tartrate ester to give an epoxide of high optical purity.[12] Since a principal goal of this study was the synthesis of the C(17) side-chain of pseudomonic acid C, a unit which embodies a secondary alcohol of S configuration and a vicinal methyl substituent of R configuration, an epoxy alcohol of S,S stereochemistry was required. Subsequent introduction of the methyl substituent by nucleophilic attack at the epoxide would be accompanied by inversion, yielding a unit with the desired absolute configuration.



A

Epoxidation of 31 in the presence of (+)-diisopropyl-L-tartrate gave (2S,3S)-epoxybutanol (32), with high optical purity, in 58% yield. This epoxide was thermally unstable and underwent decomposition upon distillation. Hence, in order to realize an acceptable yield, flash chromatography was employed to provide bulk material. Characterization was performed on a sample obtained by gas phase chromatography.

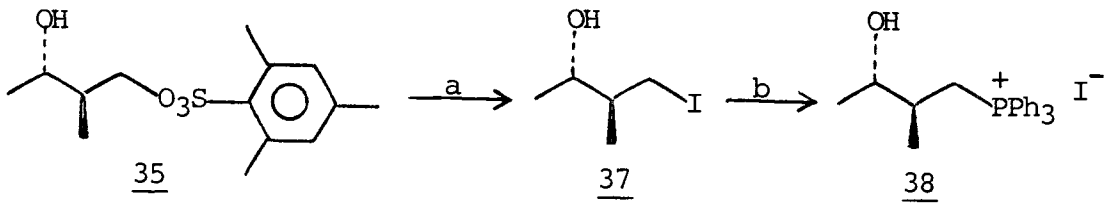


Reagents: a) (+)-Diisopropyl L-tartrate, t-BuOOH, $(i\text{-PrO})_4Ti$; b) $Me_2(CN)CuLi_2$; c) trimsyl chloride/pyridine

Although the unsymmetrically substituted epoxide 32 possesses substituents which differ little in steric size, it was hoped that the hydroxyl moiety would serve to direct the attack of a nucleophilic methyl group at the proximal (C-2) site. On the basis of a report by Lipshutz,[15] which claimed improved yields in epoxide opening with higher order cyanocuprate reagents, 32 was treated with lithio cyanomethylcuprate in tetrahydrofuran. A 1:1 mixture of two diols, subsequently shown to be (2R,3S)-2-methylbutan-1,3-diol (33) and (2R)-3-methylbutan-1,2-diol (34) were obtained in a combined yield of 92%. Unfortunately, these diols proved to be chromatographically indistinguishable, and a derivative was therefore sought which would permit their separation.

It was reasoned that selective derivatization of the primary alcohol function of 33 and 34 should provide an effective means for their separation since, in addition to reducing the polar properties of these compounds, this would leave the secondary hydroxyl in a different environment in each case. Furthermore, a derivative of 33 was envisioned which would transform the primary hydroxyl into a leaving group, thus affording a means for its displacement as, for example, by iodide ion. As seen on the following page, this conversion was employed in the construction of a Wittig reagent from 33.

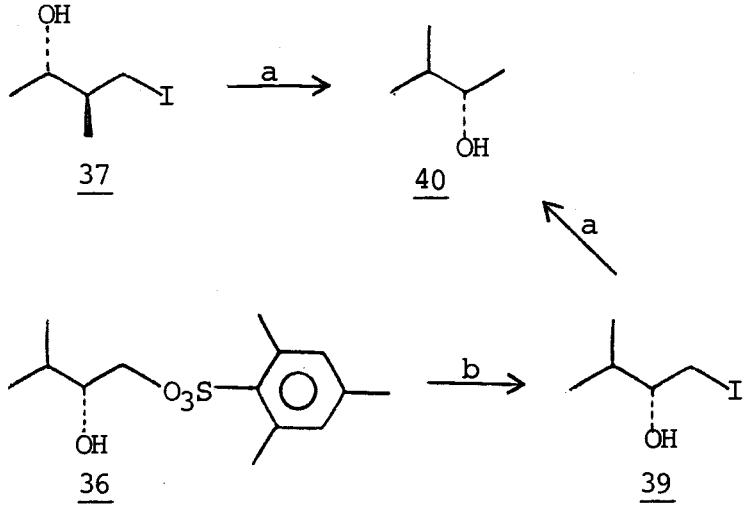
Kozikowski, in his synthesis of pseudomonic acid C,[8] showed that 33 reacted with 3,4,5-trimethylphenylsulfonyl ("trimsyl") chloride with high selectivity for the primary alcohol. It was hoped that 34 would exhibit similar selectivity and, in fact, when the mixture of 33 and 34 was treated with trimsyl chloride, two monosulfonate esters 35 and 36, were produced in excellent yield. As expected, these derivatives were easily separated by column chromatography. The sulfonate ester 35, upon exposure to sodium iodide in hot acetone, underwent displacement to give the unstable iodide 37. Significant loss of material was sustained when attempts were made to purify this iodide, and so it was treated promptly with triphenylphosphine in acetonitrile. The resulting phosphonium iodide 38, obtained in 95% yield from 35, was a nicely crystalline substance which was readily characterized. The overall yield of this chiral substance was therefore 18% from crotyl alcohol. This phosphonium salt, possessing 2S, 3S configuration, now awaits an appropriate aldehyde for coupling via the Schlosser modification of the Wittig reaction[16] to generate the trans olefinic linkage of the pseudomonic acid C side chain.



35 37 38

Reagents: a) NaI; b) PPh_3

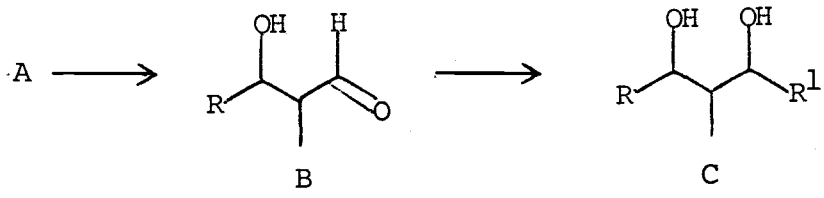
Although the configurations of 33 and 34 could be assumed with reasonable confidence based upon the chemical transformations leading to these diols, it seemed prudent to compare these compounds with a standard in order to determine their optical purity. The most direct method involved reduction to (S)-3-methyl-2-butanol (40), the optical rotation of which has been measured.[17] Accordingly, 37 was reacted with sodium borohydride in dimethyl sulfoxide. Measurement of the rotation of the resulting S alcohol 40 indicated a 95% enantiomeric excess. In a parallel sequence, the trimsylate 36 was converted to 39 with sodium iodide in hot acetone, and the latter was reduced under



Reagents: a) $NaBH_4$/DMSO; b) NaI

the same conditions as were used for 37. As expected, this also furnished the S enantiomer of 3-methyl-2-butanol. This convergence not only verifies the configurations of 33 and 34 but also demonstrates that, despite negligible regioselectivity in the opening of the epoxide 32 with cuprate, crotyl alcohol can afford efficient access to the chiral alcohol 40.

Elaboration of A to a homologous unit C would substantially enlarge the scope of this approach to chiral alcohols, since the 2-methyl-1,3-diol substructure of C is a common component of macrolides and other polyketide-derived natural substances. An important consequence of the extrapolation from A to B is the incorporation of a third chiral center,



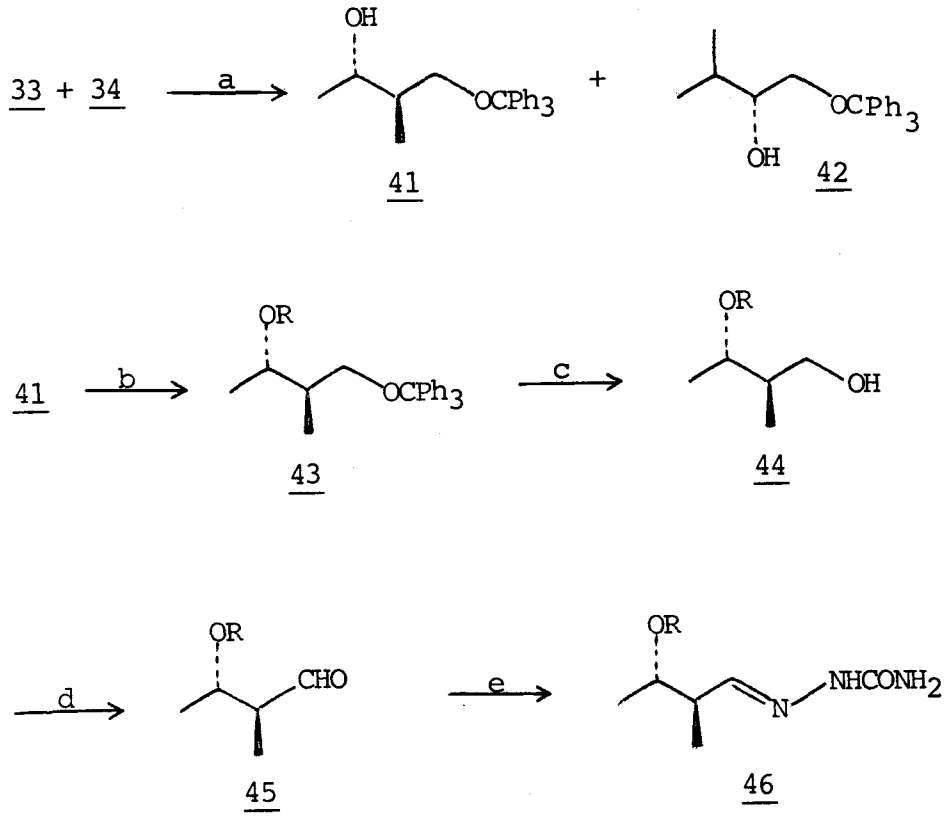
and the configurational relationship of this carbon to pre-existing chirality in A is clearly a primary concern here. It was decided to investigate a route to C, where R represents methyl substituents, in order to determine whether satisfactory stereoselectivity could be induced in the genesis of this third chiral center. Specifically, the question to be answered was

whether Cram selectivity[18] would prevail in the formation of a secondary alcohol unit in C from an aldehyde precursor such as B.

(2R,3S)-2-Methylbutan-1,3-diol (33) was selected as the precursor to C. However, in order to separate this compound from its isomer 34, a derivative which would provide protection of the secondary alcohol was required. Since there are no known methods to selectively block a secondary hydroxyl function in the presence of a primary alcohol, it became necessary to first mask the more exposed primary hydroxyl group. Triphenylmethyl (trityl) ethers are well known to exhibit the type of selectivity required in this case[19] and, hence, the mixture of 33 and 34 was treated with trityl chloride in pyridine. The primary ethers 41 and 42 were produced in virtually quantitative yield and, as in the case of the trimsylates 35 and 36, they were easily separated by column chromatography.

For masking the secondary alcohol of 41, a protecting group was required that would survive a variety of subsequent reactions, including the removal of a trityl ether and oxidation of the primary alcohol to an aldehyde. A silyl ether appeared ideal for this purpose and 41 was therefore treated with t-butyldimethylsilyl chloride in the presence of imidazole to furnish the differentially protected diether 43 in 88% yield. The trityl blocking

group was then removed with hydrogen over a 10% palladium-on-carbon catalyst. This hydrogenolysis proved to be a relatively slow process, requiring 32 psig hydrogen for 12 hours for complete reaction, but afforded the primary alcohol 44 in 90% yield after chromatographic purification.



(R = $SiMe_2tBu$)

Reagents: a) Ph_3CCl; b) t-$BuMe_2SiCl$; c) 10% Pd/C, H_2; d) CrO_3/pyridine; e) $H_2NNHCONH_2 \cdot HCl$

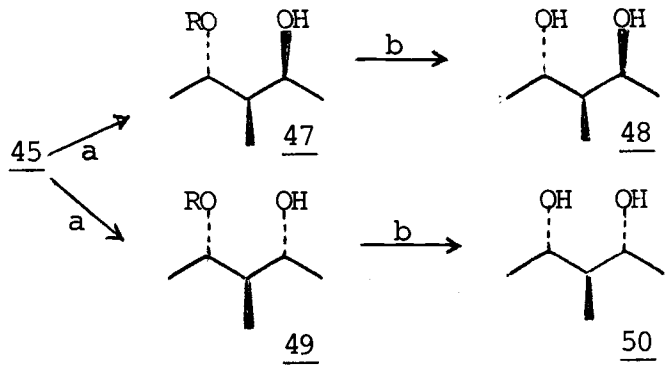
In selecting a method for the oxidation of 44 to the aldehyde 45, it was recognized that elimination of this

β-siloxy carbonyl system or epimerization at the α carbon could pose a threat to the structural and stereochemical integrity of the product. It was found, after considerable experimentation, that oxidation of 44 with Collins' reagent,[20] prepared from scrupulously dried chromium trioxide and pyridine (two equivalents), afforded the most reliable means for effecting this conversion. Even so, the isolation of pure 45 proved difficult, and this was further complicated by loss of material due to its high volatility. It was, nevertheless, possible to prepare a crystalline derivative of 45 in the form of its semicarbazone 46, and the latter was fully characterized.

With the aldehyde 45 in hand, attention was next turned to its reaction with methylmagnesium bromide and with methyllithium. Since the major focus of this study was the stereochemical outcome of the reaction, it was crucial to have a ready means of distinguishing the "syn" and "anti" products. Methylation of 45 was chosen so that the symmetry of the product could be used for this purpose. Thus, the conversion of 45 to the "syn" alcohol 47 would result in a product which, after removal of the silyl protecting group, was a chiral (S,S)-1,3-diol 48, whereas the "anti" product 49, after deprotection, would afford an achiral (meso) diol 50.

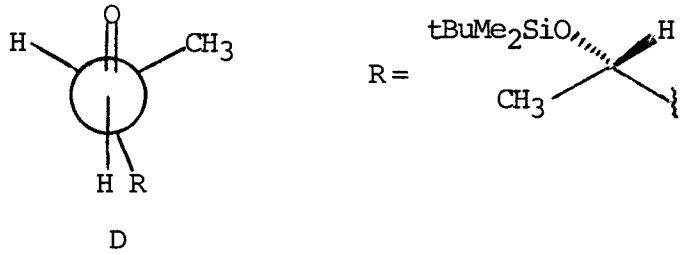
At first glance, the substantially different steric dimensions of the three substituents attached to the α carbon

atom of aldehyde 45 presage a high degree of diastereoselectivity in its reactions at the carbonyl group. In fact, a straightforward application of the Cram model for this process clearly predicts a preferred conformation D and, hence, preference for the S alcohol 47 over 49 from a Grignard reaction with 45.[18]



(R = $tBuMe_2Si$)

Reagents: a) MeLi; b) Bu_4NF



D

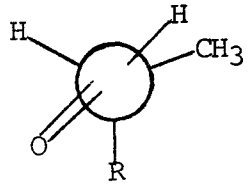
In Table I the ratio 47:49 is given for the Grignard reaction of 45 with methylmagnesium bromide at several

Table I. Ratio of Stereoisomeric Products from (2S,3S)-Methyl-t-butyldimethylsilyloxybutanal and Methylmagnesium Bromide or Methyllithium.

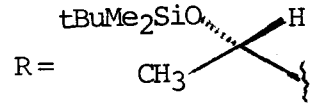
Alkylating Agent	Temp. °C	Ratio 47:49	%Overall Yield from 45
CH_3MgBr	25	1.5:1	56%
CH_3MgBr	0	1.3:1	81%
CH_3MgBr	-20	1:1.4	67%
CH_3MgBr	-78	1:1.5	85%
MeLi	0	1:1	66%
MeLi	-78	2:1	73%

reaction temperatures. For comparison, this ratio is also given for the reaction of 45 with methyllithium. Several observations and some tentative conclusions can be drawn from the results in this Table.

First, diastereoselection is lower than might be expected on the basis of a simple Cram model for both the Grignard reagent and the alkyl lithium species. Typical Cram selectivities are in the range of 4-6:1 for the reaction of aldehydes such as 45[21]. The rather low stereoselection could be due to the presence of conformer E in



E

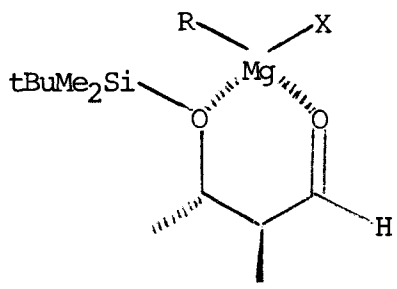


significant proportion, which would favor attack at the carbonyl group from a direction which would produce R alcohol 49. Although the t-butyldimethylsilyl ether is intrinsically a bulky group (and would, therefore, steer an incoming nucleophile away from the proximal face of the carbonyl group), the relatively long silicon-oxygen bond may render conformations D and E comparable in energy.

Further studies with a different blocking group would verify or refute this speculation.

Second, although diastereoselection is low, there is a clear trend in the Grignard reaction of 45 with changing temperature. This trend indicates a reversal of the isomer ratio as the reaction temperature is increased. Most significant, however, is the observation that the anti-Cram product 49 is favored at lower temperature. This finding is contrary to expectations based upon a reaction pathway through an equilibrating conformer population, in which D represents the conformational energy minimum of the system. Consequently, a refinement of the simple model presented above must be considered.

It is well known that α-hydroxy and α-alkoxy carbonyl compounds undergo chelation with certain metal cations, and that this can reverse the stereoselection predicted by Cram's Rule for nucleophilic attack at the carbonyl group.[18] If such a chelation effect were obtained in the reaction of 45 with a Grignard reagent, the major conformer would be F. Assuming that the α methyl substituent in F exercises the



F

larger steric influence on the direction of the incoming nucleophile, attack at the aldehyde carbonyl group should occur predominantly from the rear face. This leads to the anti-Cram product 49. It seems reasonable that, as the temperature of the Grignard reaction is raised, the chelated conformer gives way to other conformers resulting from C-C bond rotation and, hence, to an increase in the population of D. This would account for the trend towards Cram stereochemistry as the temperature is increased from -78°C to 25°C.

The lithium ion, which is not as effective as magnesium in coordinating to oxygen in a bidentate fashion, would not be expected to stabilize a chelated conformer analogous to F. At low temperature, therefore, the predominant stereoisomer formed in the reaction of 45 with methyllithium is the expected Cram product 47, reflecting the stability of conformer D. That the degree of stabilization is small relative to other conformers is reflected in the fact that, at room temperature, no stereoselectivity is observed with methyllithium.

In summary, this research has demonstrated that methodology based upon enantioselective epoxidation and alkylation can lead to a chiral system, embracing two accurately defined asymmetric centers. The utility of this approach is illustrated by the asymmetric synthesis of a side-chain component

of the antibiotic pseudomonic acid C. Extension of this strategem to a homologous unit containing a third chiral center, while lacking precise stereocontrol, may nevertheless offer a useful entry to more complex chiral segments found in natural products.

III. EXPERIMENTAL

Melting points were obtained on a Buchi melting-point apparatus and are uncorrected. Infrared spectra (IR) were obtained with a Perkin-Elmer 727B infrared spectrometer. Nuclear magnetic resonance spectra (NMR) were obtained with either a Varian EM-360A or FT-80A instrument for proton spectra, and are reported in δ units with tetramethylsilane (TMS) as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, p=pentuplet, h=hextuplet, m=multiplet, bs=broad singlet, etc., are used throughout. Carbon NMR spectra were obtained on a FT-80A spectrometer. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. Vapor-phase chromatography (VPC) was done on a Varian Aerograph model 2700, equipped with a differential thermal conductivity detector. Helium was used as the carrier gas, and separations were effected with the following columns: (A) 6 ft x 1/4", 7.5% TCEP on 80-100 mesh Chromosorb W; (B) 5 ft x 1/4", 1.5% OV-101 on 100-120 mesh Chromosorb G. Columns were made of coiled aluminum tubing. Elemental analyses were performed by MicAnal, Tucson, Arizona. Column chromatography was performed using neutral silica gel, 230-400 mesh ASTM. Analytical thin-layer chromatography (TLC) plates were obtained from

Analtech. Optical rotations were measured with a Perkin-Elmer Model 243 polarimeter. Dry tetrahydrofuran (THF) and ethyl ether were obtained by distillation over sodium and benzophenone. Dry dichloromethane was obtained by distillation from calcium hydride. Residual solvent was removed under vacuum, usually at less than 2 Torr. All glassware was dried in an oven at 150°C.

(2S,3S)-2,3-Epoxybutanol (32)

A 500 mL oven-dried flask equipped with a magnetic stir-bar and rubber septum was flushed with dry nitrogen and charged with 200 mL of dry dichloromethane. To the stirred, cooled solvent (-23°C) was added, via syringe, 5.94 mL (5.68 g, 20 mmol) of titanium tetraisopropoxide, followed by 4.20 mL (4.68 g, 20 mmol) of (+)-diisopropyl L-tartrate. The mixture was stirred for five minutes, and then 1.7 mL (1.44 g, 20 mmol) of crotyl alcohol and a solution of anhydrous tert-butylhydroperoxide (ca. 11 mL, 3.67 M, ca. 40 mmol) in dichloromethane were added. The resulting mixture was kept at -20°C for 20 hours. To this cold mixture was added an equal amount of ether (ca. 200 mL) with stirring until a homogeneous solution was obtained, and then a saturated solution of sodium sulfate (6 mL) was added with vigorous stirring. The resulting slurry was filtered through a Celite pad and freed of solvent under reduced pressure. The residual oil was chromatographed on a column of silica gel, using an 8:2 ethyl ether-petroleum ether

(35-60°C) mixture as an eluent, to yield 1.01 g (57.6%) of 32. A sample for characterization was obtained by preparative VPC, column A, at 110°C: IR (neat) 3450, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, d, J=5 Hz), 2.4 (1H, bs), 2.95 (2H, m), 3.75 (2H, dd, J=12, 3 Hz); ^{13}C NMR ($CDCl_3$) 17.18, 52.04, 59.58, 61.71; $[\alpha]_D^{20}$ -50.0° (c 0.52, benzene) [lit. $[\alpha]_D^{20}$ -49° (c 5, benzene)][22]; MS m/e (rel. int.) 60 (8.3, M^+-CO), 45 (72), 43 (100), 31 (43).

(2R,3S)-2-Methyl-1,3-butanediol (33) and (2S)-3-Methyl-1,2-butanediol (34)

Copper cyanide (3.58 g, 40 mmol) was placed in a three-necked 200 mL round-bottom flask equipped with a magnetic stir-bar. The copper salt was azeotropically dried with two 15 mL portions of toluene under a continuous stream of nitrogen. Dry tetrahydrofuran (40 mL) was added to the slurry which was cooled to -78°C with a Dry Ice/acetone bath. Methyllithium (51.7 mL, 80 mmol, 1.55 M in ether) was added dropwise and produced a pale green solution which was warmed to -20°C (carbon tetrachloride/Dry Ice). A solution of (2S,3S)-2,3-epoxybutanol (32, 0.88 g, 10 mmol) in tetrahydrofuran (4 mL) was cooled to 0°C and added dropwise by syringe. Additional tetrahydrofuran (2 mL) was used to ensure complete epoxide addition and the mixture was allowed to stir at -20°C for two hours. The reaction was then quenched with 50 mL of a 9:1 saturated aqueous ammonium

chloride:ammonium hydroxide mixture and left to stir for thirty minutes at room temperature. Saturated sodium chloride solution (25 mL) was added, the mixture was separated, and the aqueous layer was extracted three times (100 mL portions) with ether. The organic layers were combined and dried over anhydrous potassium carbonate. The solvent was removed *in vacuo* to yield 0.955 g (91.8%) of an approximately 1:1 mixture of *33* and *34* as an oil. These diols proved inseparable by column chromatography and were converted, as later described, to their triphenylmethyl ethers. These were separated chromatographically, and the protecting groups removed to yield pure *33* and *34*.

33 : IR (neat) 3400, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, d, J=8 Hz), 1.23 (3H, d, J=6 Hz), 1.65 (1H, m), 2.55 (1H, bs), 2.95 (1H, bs), 3.70 (3H, m); ^{13}C NMR ($CDCl_3$) 13.64, 22.00, 41.79, 68.09, 73.67; MS *m/e* (rel. int.) 86 (4.1, $M^+ - H_2O$), 71 (17.0), 58 (20.9), 45 (70.6), 43 (100); $[\alpha]_D^{20}$ +3.47° (*c* 1.7, EtOH).

34 : IR (neat) 3420, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, d, J=4 Hz), 0.98 (3H, d, J=4 Hz), 1.65 (1H, m), 2.80 (2H, bs), 3.50 (3H, m); ^{13}C NMR ($CDCl_3$) 18.22, 18.73, 30.94, 64.93, 77.30; MS *m/e* (rel. int.) 105 (59.3, M+1), 87 (88.2), 73 (92.8), 43 (91.3); $[\alpha]_D^{20}$ -6.37° (*c* 1.46, cyclohexane) (lit. $[\alpha]_D^{20}$ -6.32° (*c* 2.0, cyclohexane)).[23]

(2S,3R)-3-Methyl-4-(2,4,6-trimethylbenzenesulfonyloxy)-butan-2-ol (35)[8] and (3R)-2-Methyl-4-(2,4,6-trimethylbenzenesulfonyloxy)butan-3-ol (36)

A freshly distilled mixture of 33 and 34 (0.608 g, 5.8 mmol) was dissolved in 30 mL of pyridine and cooled to -20°C in a Dry Ice/carbon tetrachloride bath. A solution of mesitylenesulfonyl chloride (1.54 g, 6.96 mmol, 1.2 equivalents) in ca. 10 mL of pyridine was cooled to -20°C before addition to the solution of 33 and 34. The mixture was kept in a freezer (-20°C) for 3 days. The pyridine was removed in vacuo and the residue was extracted into ether. The ethereal extract was concentrated in vacuo to an oil, which was purified by column chromatography. Elution with 4:1 petroleum ether (35-60°)/ethyl ether gave 0.596 g (94.6%) of 35 and 0.799 g (47.9%) of 36 as oils.

35 : IR (neat) 3500, 3030, 1350, 1170, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, d, J=6 Hz), 1.15 (3H, d, J=7 Hz), 1.80 (1H, m), 2.27 (3H, s), 2.6 (6H, s), 3.65 (1H, bs), 3.95 (3H, m) 6.92 (2H, s); ^{13}C NMR ($CDCl_3$) 13.38, 20.46, 20.85, 21.04, 22.60, 40.44, 68.55, 71.59, 131.77, 139.89, 143.29; MS m/e (rel. int.) 286 (42.8, M^+), 200 (100), 91 (55), 45 (90.5); $[\alpha]_D^{20}$ +10.73° (c, 1.24, EtOH).

36 : IR (neat) 3600, 3010, 1345, 1165, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, d, J=8 Hz), 0.91 (3H, d, J=8 Hz), 1.68 (1H, m), 2.28 (3H, s), 2.62 (6H, s), 3.55 (1H, bs), 3.95 (3H, m), 6.92 (2H, s); ^{13}C NMR ($CDCl_3$) 17.54, 18.61, 21.05,

22.54, 30.61, 71.67, 74.24, 131.75, 139.89, 143.30; MS m/e (rel. int.) 286 (18.4, M^+), 184 (76.0), 120 (79.7), 119 (100.0), 91 (48.8), 43 (56.9); $[\alpha]_D^{20}$ -2.63° (c 1.18, EtOH).

(2S,3S)-1-Iodo-2-methyl-3-butanol (37)

A stirred solution of 35 (290 mg, 1.07 mmol) and sodium iodide (1.5 g, 10 mol equivalents) in reagent grade acetone (20 mL) was refluxed for seven hours. The solvent was removed under reduced pressure to give a red-orange solid. The solid was triturated with ether and the ether was removed in vacuo to yield crude 37 as a red oil, which was used without purification.

(2S)-1-Iodo-3-methyl-2-butanol (39)

A stirred solution of 36 (290 mg, 1.07 mmol) and sodium iodide (1.5 g, 10 mol equivalents) in reagent grade acetone (20 mL) was refluxed for seven hours. The solvent was removed under reduced pressure to give a red-orange solid. The solid was triturated with ether and was removed by filtration through a Celite pad to yield a yellow solution. The ether was removed in vacuo to give 39 as a red oil which was used without purification.

(2S,3S)-3-Hydroxy-2-methylphenylphosphonium Iodide (38)

Crude 37 was dissolved in 35 mL of acetonitrile. To this stirred solution was added 4.2 g (16 mmol, 5 equivalents)

of triphenylphosphine and the mixture was refluxed for 36 hours. Most of the solvent (25 mL) was removed by distillation, leaving a small amount of a colorless precipitate. The mixture was diluted with ether (40 mL) and stirred for five minutes. The solvent was decanted from the solid, and the same operation of washing and decantation with ether was repeated twice to yield 1.40 g (95% based on 35) of 38 as a colorless solid: mp (dec) 190-192°C. A sample was recrystallized from methanol: mp (dec) 252-254°C; IR (KBr) 3400, 1100, 745 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.68 (3H, d, J=7 Hz), 1.11 (3H, d, J=5 Hz), 2.0 (1H, bs), 3.6 (4H, m), 7.25 (15H, m); ^{13}C NMR (CD_3OD) 17.41, 20.46, 26.34, 37.28, 72.44, 120.77, 131.48, 134.98, 136.16; MS m/e (rel. int.) 348 (0.4, M^+-HI), 271 (100.00), 262 (72.7), 201 (70.0), 183 (72.3), 77 (36.7); $[\alpha]_D^{20}$ -2.06° (c 1.26, CH_3CN). Anal. calcd. for $C_{23}H_{26}$ OPI : C, 58.00%, H, 5.46%. Found: C, 58.05%; H, 5.26%.

(2R,3S)-2-Methyl-1-triphenylmethoxy-3-butanol (41) and (2S)-3-Methyl-1-triphenylmethoxy-2-butanol (42)

A freshly distilled mixture of 33 and 34 (310 mg, 2.98 mmol) was dissolved in 10 mL of dry dichloromethane and triphenylmethyl chloride (1.25 g, 4.47 mmol, 1.5 equivalents) and 4-dimethylaminopyridine (0.545 g, 4.47 mmol) were added. The mixture was stirred at reflux for 48 hours and the solvent was removed in vacuo to yield a light orange, gummy

solid. This solid was stirred with ether (two 50 mL portions) and filtered over a Celite bed to remove a colorless precipitate. The filtrate was concentrated *in vacuo* to yield a light orange, sticky oil. This was chromatographed on a silica column and eluted with 4:1 hexane-ethyl acetate to yield 0.487 g (47%) of **41** as a clear, viscous oil: IR (neat) 3500, 3020, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, d, J=7 Hz), 1.08 (3H, d, J=5 Hz), 1.24 (1H, s), 1.75 (1H, m), 3.15 (2H, m), 3.61 (1H, m), 7.25 (15H, m); ^{13}C NMR ($CDCl_3$) 13.25, 20.20, 40.79, 68.09, 71.95, 86.90, 127.17, 127.96, 128.76, 143.98; MS *m/e* (rel. int.) 346 (4.8, M^+), 259 (23.7), 243 (100.00), 183 (25.1), 165 (35.7); $[\alpha]_D^{20}$ -24.9° (*c* 1.68, $CHCl_3$).

Further elution of the column gave 0.538 g (52%) of **42** as a clear, viscous oil: IR (neat) 3520, 3010, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.74 (3H, d, J=7 Hz), 0.85 (3H, d, J=7 Hz), 1.23 (1H, bs), 1.63 (1H, m), 2.23 (1H, d, J=3 Hz), 3.1 (2H, m), 3.35 (1H, m), 7.25 (15H, m); ^{13}C NMR 17.83, 18.60, 30.87, 65.99, 75.71, 86.78, 127.00, 127.75, 128.66, 143.96; MS *m/e* (rel. int.) 346 (4.1, M^+), 243 (100), 183 (24.9), 165 (32.4), 105 (26.2); $[\alpha]_D^{20}$ -10.2° (*c* 1.53, $CHCl_3$).

(2R,3S)-2-Methyl-1-triphenylmethoxy-3-tert-butyldimethylsilyloxybutane (**43**)

To a stirred solution of **41** (330 mg, 1 mmol) in dry dimethylformamide (20 mL) were added tert-butyldimethylsilyl chloride (2 mmol, 30 mg) and imidazole (2 mmol, 1.38 mg),

and the mixture was stirred at room temperature for 12 hours. Evaporation under reduced pressure gave a clear oil which was extracted with two 25 mL portions of ethyl ether. The ethereal layers were combined and evaporated to give a clear oil. This was chromatographed on a silica gel column, using 4:1 ether-petroleum ether (35-60°) as eluent, to yield 0.404 g (88%) of 43: IR (neat) 3010, 1600 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.08 (6H, d, J=5 Hz), 0.93 (9H, s), 0.94 (3H, d, J=3Hz), 1.07 (3H, d, J=6 Hz), 2.03 (1H, m), 3.07 (2H, m), 3.88 (1H, m), 7.40 (15H, m); ^{13}C NMR ($CDCl_3$) 0.0, 12.58, 17.95, 19.56, 25.80, 41.43, 66.05, 69.82, 86.40, 126.72, 127.57, 128.78, 144.55; MS m/e (rel. int.) 244 (39.3) 243 (100), 165 (32.4); $[\alpha]_D^{20}$ +6.1° (c 1.21, $CHCl_3$).

(2R,3S)-2-Methyl-3-tert-butyldimethylsilyloxybutanol (44)

A mixture of 43 (175 mg, 0.38 mmol) and 10% palladium-on-carbon (50 mg) in 4.0 mL of 100% ethanol was placed in a Parr hydrogenator and pressurized to 32 psig with hydrogen. This mixture was shaken for 12 hours. After removal from the apparatus, the mixture was filtered through a Celite pad. The filtrate was evaporated under reduced pressure to yield crude material which was purified by silica column chromatography. Elution with 3:1 petroleum ether (35-60°)-ethyl ether gave 0.0745 g (90%) of 44 as a clear oil: IR (neat) 3440, 1020, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.085 (6H, s),

0.90 (9H, s), 0.96 (3H, d, J=8 Hz), 1.18 (3H, d, J=7 Hz), 1.51 (1H, m), 2.76 (1H, t, J=7 Hz), 3.10 (3H, m); ^{13}C NMR ($CDCl_3$) 0.00, 14.45, 18.01, 22.03, 25.88, 42.10, 65.88, 73.71; MS m/e (rel. int.) 161 (29.5), 115 (6.2), 103 (4.0), 75 (100), 43 (47.9); $[\alpha]_D^{20}$ +16.23° (c 1.14, $CHCl_3$).

(2S,3R)-2-Methyl-3-tert-butyldimethylsilyloxybutanal (45)

To a vigorously stirred solution of 44 (60 mg, 0.275 mmol) in 4 mL of dry dichloromethane was added a solution of Collins' reagent in dichloromethane in 1 mL increments until reaction was complete, as indicated by TLC (Collins' reagent was prepared as follows: 360 mg of chromium trioxide was placed in a dry flask, and 0.29 mL of dry pyridine and 8 mL of dry dichloromethane were added). The entire reaction mixture was placed on a flash silica chromatographic column and eluted with 4:1 ether-petroleum ether (35-60°) to yield 45. Due to its volatility, 45 was characterized as its semicarbazone 46, which was prepared by the addition of semicarbazide hydrochloride (18.9 mg, 0.17 mmol) and sodium acetate (28.3 mg) to a solution of 45 (0.17 mmol) in 1 mL of 95% EtOH. The mixture was shaken vigorously then allowed to stand, with occasional shaking, for 10 minutes. The mixture was cooled in ice-water and filtered to yield a colorless solid, which was recrystallized from methanol-water and vacuum dried over P_2O_5 giving 46 : mp 126 - 127.5°C; IR (KBr) 3500, 1690, 1580, 820 cm^{-1}; ^1H NMR (DMSO)

δ 0.03 (6H, s), 0.85 (9H, s), 1.00 (6H, t, J=7 Hz), 1.80 (1H, m), 3.75 (1H, t, J=6 Hz), 6.00 (2H, bs), 7.05 (1H, d, J=7 Hz), 9.73 (1H, s); MS m/e (rel. int.) 229 (19.7), 216 (30.8), 172 (54.0), 159 (51.3), 115 (24.0), 73 (100); $[\alpha]_D^{20}$ +12.6° (c 1.2, EtOH). Anal. calculated for $C_{12}H_{27}N_3O_2Si$: C, 52.75%, H, 9.89%, N, 15.38%. Found: C, 52.42%, H, 9.61%, N, 15.41%.

Reaction of (2S,3R)-2-Methyl-3-tert-butyldimethylsilyloxybutanal (45) with Methyllithium and Methylmagnesium Bromide

A solution of 45 (ca. 0.29 mmol) in petroleum ether was placed in 10 mL of dry ether. At the appropriate reaction temperature (see Table I), the methylmagnesium bromide or methyllithium solution (ca. 9 equivalents) was added dropwise and the mixture was stirred for 30 minutes. After the reaction was complete, as determined by TLC, saturated ammonium chloride (3 mL) and then 1 N hydrochloric acid were added dropwise until the solution became clear. The aqueous layer was separated and extracted three times with 25 mL portions of ether. The organic layers were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to yield a mixture of (2S,3R,4S)-3-methyl-4-tert-butyldimethylsilyloxypentan-2-ol (47) and (2R,3R,4S)-3-methyl-4-tert-butyldimethylsilyloxypentan-2-ol (49), which were separated by silica gel chromatography eluting with 9:1 Hexane:EtOAc.

47 : IR (neat) 3470, 1020, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.09 (6H, s), 0.90 (9H, s), 0.96 (3H, d, J=8 Hz), 1.13 (3H, d, J=6 Hz), 1.25 (3H, d, J=7 Hz), 1.35 (1H, m), 3.50 (1H, bs), 3.92 (1H, dq, J=3 Hz), 4.26 (1H, m); ^{13}C NMR ($CDCl_3$) 11.06, 17.83, 20.44, 21.97, 25.78, 44.18, 66.32, 74.08; MS m/e (rel. int.) 227 (21.4) 175 (27.4) 159 (86.2) 115 (23.4) 75 (100); $[\alpha]_D^{20}$ + 20.76 (c 1.71, EtOH).

49 : IR (neat) 3440, 1045, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.13 (6H, s), 0.80 (3H, d, J=7 Hz), 0.92 (9H, s), 1.18 (6H, m), 1.38 (1H, h, J=7 Hz), 3.33 (1H, bs), 3.46 (1H, d, J=7 Hz), 3.70 (1H, m); ^{13}C NMR ($CDCl_3$) 12.60, 17.94, 20.79, 21.93, 25.84, 26.03, 47.82, 70.64, 73.37; MS m/e (rel. int.) 227 (6.5), 183 (33.0), 175 (19.7) 159 (70.3), 119 (72.2), 75 (100); $[\alpha]_D^{20}$ +9.03° (c 2.89, EtOH).

(2S,4S)-2,4-Dihydroxy-3-methylpentane (48)

To a stirred solution of 47 (38.9 mg, 0.133 mmol) in dry tetrahydrofuran (4 mL) at room temperature was added tetra-n-butylammonium fluoride (0.25 mL, 2 equivalent, 1 M in tetrahydrofuran) dropwise by syringe. After one hour the solvent was removed in vacuo. The residue was placed on a flash silica chromatographic column and eluted with 3:1 ethyl acetate-hexane to yield 15.5 mg (79%) of 48 : ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, d, J=7 Hz), 1.19 (3H, d, J=7 Hz), 1.25 (3H, d, J=7 Hz), 1.58 (1H, dq, J=7 Hz), 2.60 (2H, bs),

3.85 (2H, m); ^{13}C NMR ($CDCl_3$) 12.01, 19.06, 22.03, 44.63, 69.53, 70.89; $[\alpha]_D^{20}$ +12.96° (c 0.98, EtOH).

(2R,3S,4S)-2,4-Dihydroxy-3-methylpentane (50)

To a stirred solution of 49 (31.7 mg, 0.137 mmol) in dry tetrahydrofuran (4 mL) at room temperature was added tetra-n-butylammonium fluoride (0.60 mL, 5 equivalent, 1 M in tetrahydrofuran) dropwise by syringe. After one hour the solvent was removed in vacuo. The residue was placed on a flash silica chromatographic column and eluted with 3:1 ethyl acetate - hexane to yield 7.9 mg (49%) of 50: ^1H NMR ($CDCl_3$) δ 0.79 (3H, d, J=7 Hz) 1.23 (6H, d, J=7 Hz), 1.48 (1H, m), 2.85 (2H, bs) 4.25 (2H, m).

(2S)-3-Methyl-2-butanol (40)

A. From 37

To a stirred solution of crude 37 (ca. 0.56 mmol) in 3 mL of dimethyl sulfoxide was added sodium borohydride (104 mg, 5 equivalents) and the mixture was stirred overnight at room temperature. With vigorous stirring, 3 mL of saturated aqueous sodium chloride solution was slowly added and the mixture was stirred for 30 minutes. This solution was extracted three times with 20 mL portions of ether, the ether layers were combined and dried over anhydrous sodium sulfate, and the solvent was removed by distillation. The residual oil was purified by flash column

chromatography on silica, eluting with 1:1 ether-petroleum ether (35-60°), to give a partially purified product. This was further purified by preparative VPC (column B) at 40°C to yield 16.6 mg (33% from 35) of 40 : IR (neat) 3400, 1040, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.15 (3H, d, J=7 Hz), 1.35 (1H, bs), 1.63 (1H, m), 3.53 (1H, bs); ^{13}C NMR ($CDCl_3$) 17.72, 18.15, 20.07, 35.07, 72.83; MS m/e (rel. int.) 87 (1.2, M^+-1), 55 (15.6), 45 (100), 43 (30.5); $[\alpha]_D^{20}$ + 5.00° (c 1.66, EtOH) (lit.[17] $[\alpha]_D^{20}$ + 5.34° (c 5, EtOH).

B. From 39.

A solution of crude 39 (ca 1.9 mmol) in 3 mL of dimethyl sulfoxide was reduced with sodium borohydride (370 mg. 5 equivalent) as described for 37 above to give 65.2 mg. (39% from 36) of 40 : $[\alpha]_D^{20}$ + 4.79°(c 1.53, EtOH). The spectral properties of this material were identical with those of 40 as prepared in part A.

IV. BIBLIOGRAPHY

1. Kaufman, G.; Cook, F.; Schechter, H.; Bayless, J.; Friedman, L.; J. Am. Chem. Soc., 1967, 89, 5737.

2. Chain, E.B.; Mellows, G.; J. Chem. Soc. Perkin Trans. I, 1977, 294.

3. Chain, E.B.; Mellows, G.; J. Chem. Soc. Perkin Trans. I, 1977, 318.

4. Clayton, J.P.; O'Hanlon, P.J.; Rogers, N.H.; Tetrahedron Lett., 1980, 881.

5. Basker, M.J.; Comber, K.R.; Clayton, J.P.; Hannan, P.C. T.; Mizen, L.W.; Rogers, N.H.; Slocombe, B.; Sutherland, R.; Curr. Chemother. Infect. Dis.; Proc. Int. Congr. Chemother., 11th 1979, I, 471.

6. Clayton, J.P.; Luk, K.; Rogers, N.H.; J. Chem. Soc. Perkin Trans. I, 1979, 308.

7. Clayton, J.P.; Oliver, R.S.; Rogers, N.H.; J. Chem. Soc. Perkin Trans. I, 1979, 838.

8. Kozikowski, A.P.; Schmiesing, R.J.; Sorgi, K.L.; J. Am. Chem. Soc., 1980, 102, 6577.

9. Fleet, G.W.J.; Gough, M.J.; Shing, T.K.M.; Tetrahedron Lett., 1983, 3661.

10. Snider, B.B.; Phillips, G.B.; J. Am. Chem. Soc., 1982, 104, 1113.

11. Jackson, R.F.W.; Raphael, R.A.; Stibbard, J.H.A.; Tidbury, R.C.; J. Chem. Soc. Perkin Trans. I, 1984, 2159.

12. Rossiter, B.E.; Katsuki, T.; Sharpless, K.B.; J. Am. Chem. Soc.; 1981, 103, 464.

13. Sharpless, K.B.; Behrens, C.H.; Tsutomu, K.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodard, S.S.; Pure & Appl. Chem., 1983, 55, No. 4, 589.