in THF (15 mL) and added to a suspension of $LiAlH_4$ (0.1 g, 2.6 mmol) at 0 °C, under argon. After being stirred for 30 min, the reaction mixture was quenched and worked up, as shown before, to give, after chromatographic purification (ether–pentane, 4:1), 0.66 g of **24** (oil, 69% from **23**): ^1H NMR δ 1.47–1.63 (m, 4 H), 2.37–2.55 (m, 2 H), 3.63 (br s, 2 H), 4.40 (s, 2 H), 7.02–7.71 (m, 9 H). Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.10; H, 6.58. Found: C, 67.12; H, 6.53.

1-[5,5-Bis(methoxycarbonyl)-1-pentyl]-2-[(phenylsulfonyl)methyl]benzene (25). The alcohol **24** was converted to the malonate **25** as shown for the preparation of **8c** in 70% yield: mp 109 °C ($CHCl_3$–hexane); ^1H NMR δ 1.27–2.02 (m, 6 H), 2.41 (t, J = 7 Hz, 2 H), 3.34 (t, J = 7 Hz, 1 H), 3.72 (s, 6 H), 4.37 (s, 2 H), 7.02–7.69 (m, 9 H). Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.16; H, 6.22. Found: C, 63.31; H, 6.28.

2,3,3a,4,5,9b-Hexahydro-4-oxo-5-(phenylsulfonyl)benz[*e*]indene (27). Compound **25** (0.33 g, 0.8 mmol) was treated with NBS (as shown for **8c**) to give, after a short chromatographic purification (ether–pentane, 1:1), 0.39 g of bromide **26** (100%), which, without further characterization, was dissolved in a mixture of anhydrous THF (112 mL) and *tert*-BuOH (30 mL). Separately prepared *tert*-BuOK (from 0.2 g of K, 5.1 mmol) in *tert*-BuOH (10 mL) was added dropwise, under argon, to the solutionof **26** during 20 min. After additional stirring during 1 h at room temperature, the mixture was poured into cold aqueous NH_4Cl and brine and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered, evaporated in vacuo, and chromatographed (ether–pentane, 1:4) to give 0.16 g of **27** (62%): mp 129–130 °C; IR (KBr) 1707, 1310, 1150 cm^{-1}; ^1H NMR δ 1.23–2.36 (m, 6 H), 3.57–3.99 (m, 2 H), 4.84 (s, 1 H), 6.80 (d, J = 8 Hz, 1 H), 7.06–7.82 (m, 8 H); MS, m/e (relative intensity) 326 (21) (M^+), 185 (100), (M – SO_2Ph), 184 (22), 167 (41). Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.94; H, 5.52. Found: C, 69.87; H, 5.58.

2,3-Dihydrobenz[*e*]inden-4-ol (28). The compound **27** was reacted with $LiI{\cdot}3H_2O$ in 2,6-lutidine, as shown for **10c** (2 h, 150 °C), to give 86% of **28**: mp 94 °C; ^1H NMR δ 2.18–2.46 (m, 2 H), 2.97–3.36 (m, 4 H), 4.94 (br s, OH), 6.98 (s, 1 H), 7.27–7.74 (m, 4 H); MS, m/e (relative intensity) 184 (100) (M^+), 183 (41), 167 (31). Anal. calcd for $C_{13}H_{12}O$: C, 84.78; H, 6.52. Found: C, 84.91; H, 6.53.

2,3-Dihydrobenz[*e*]indene-4,5-dione (29). Dry oxygen was bubbled into a suspension of CuCl (0.2 g) in dry CH_3CN (2.5 mL), during 30-min at 25 °C. A solution of **28** (50 mg, 0.27 mmol) in CH_3CN (1 mL) was then added to the mixture, which was stirred at 25 °C until TLC showed no more starting material (~30 min). The mixture was then diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered and evaporated in vacuo, and the residue was chromatographed (ether–pentane, 1:4) to give 41 mg of **29** (75%): mp 135–136 °C (from $CHCl_3$–pentane); IR 1657 cm^{-1}; ^1H NMR δ 1.99–2.32 (m, 2 H), 2.72–3.11 (m, 4 H), 7.34–8.11 (m, 4 H); UV (EtOH) λ_{max} 256, 345, 422 nm (log ε 4.27, 3.22, 3.20); MS, m/e (relative intensity) 198 (M^+), 197 (25), 170 (17), 142 (24), 141 (28). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.79; H, 5.05. Found: C, 78.75; H, 5.02.

Acknowledgment. We thank Dr. Felix Frolow for the determination of the X-ray structure and the Israel Academy of Sciences for supporting, in part, this work by a research grant.

Oxidation Reactions of Baccharinoid B5

Bruce B. Jarvis,* S. Nilgün Cömezoğlu, and M. Estela Alvarez

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

Received November 4, 1987

The plant derived macrocyclic trichothecene baccharinoid B5 (1) undergoes oxidative cleavage with Cr(VI) only with difficulty to give a lactone derivative. The presence of a neighboring hydroxy group was shown to impede this reaction. Peracid oxidation of 1 yields two epoxides, one of which readily undergoes acid-catalyzed intramolecular ring-opening to yield a novel tetrahydrofuran derivative.

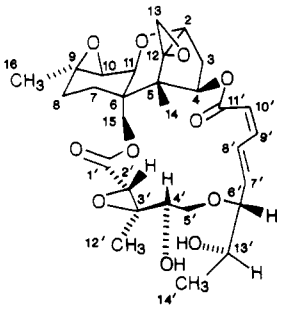
The Brazilian shrub *Baccharis megapotamica* Spreng (Asteraceae) was shown to contain a series of potent in vivo active antileukemic agents known as the baccharinoids.[1] The first member of these sesquiterpene antibiotics reported was baccharinoid B5 (1),[2] but subsequent work has shown that the plant contains over 20 baccharinoids[3–5] whose structures are closely related to roridins, members of the macrocyclic class of trichothecene mycotoxins.[6–8] The principal distinction between the roridins and the baccharinoids is that the latter contain an A-ring oxygen functionality either in the form of an 8β-hydroxy group or, as in 1, a 9β,10β-epoxide group. The presence of this oxygen functionality, especially the 9β,10β-epoxide group, is important for the in vivo antileukemic properties of the baccharinoids.[8] The relatively in vivo inactive roridins have been chemically oxidized to baccharinoid-like derivatives that possess substantial in vivo activity against P388 mouse leukemia.[9,10] Herein, we report some oxidative conversions of baccharinoid B5 (1) in which the macrocyclic ring was the target for synthetic modification.

Results and Discussion

Upon treatment with pyridinium dichromate (PDC), the roridins undergo oxidative cleavage to yield verrucarins

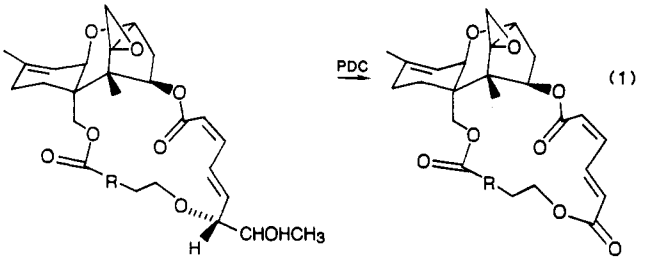
(1) Kupchan, S. M.; Streelman, D. R.; Jarvis, B. B.; Dailey, R. G., Jr.; Sneden, A. T. *J. Org. Chem.* **1977**, *42*, 4221.
(2) Kupchan, S. M.; Jarvis, B. B.; Dailey, R. G., Jr.; Bright, W.; Bryan, R. F.; Shizuri, Y. *J. Am. Chem. Soc.* **1976**, *98*, 7092.
(3) Jarvis, B. B.; Pena, N. B.; Rao, M. M.; Cömezoğlu, S. N.; Cömezoğlu, F. T. In *The Chemistry of Allelopathy*; Thompson, A. C., Ed.; ACS Symposium Series, Washington, D.C., No. 268, 1984; p 149.
(4) Jarvis, B. B.; Cömezoğlu, S. N.; Rao, M. M.; Pena, N. B.; Boettner, F. E.; Tara; Williams, M.; Forsyth, G.; Epling, G. *J. Org. Chem.* **1987**, *52*, 45.
(5) Jarvis, B. B.; Cömezoğlu, S. N.; Ammon, H. L.; Breedlove, C. K.; Bryan, R. F.; Miller, R. W.; Woode, M. K.; Streelman, D. R.; Sneden, A. T.; Dailey, R. G., Jr.; Kupchan, S. M. *J. Nat. Prod.* **1987**, *50*, 815.
(6) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 61.
(7) Jarvis, B. B.; Eppley, R. M.; Mazzola, E. P. In *Trichothecenes-Chemical, Biological, and Toxicological Aspects*; Ueno, Y., Ed.; Halsted-Kodansha Scientific; New York, 1983; p 20.
(8) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *14*, 388.
(9) Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Mazzola, E. P. *J. Med. Chem.* **1980**, *23*, 1054.
(10) Jarvis, B. B.; Midiwo, J. O.; Mazzola, E. P. *J. Med. Chem.* **1984**, *27*, 239.

0022-3263/88/1953-1918$01.50/0 © 1988 American Chemical Society



1

(eq 1).[11] Since 9β,10β-epoxyverrucarins also exhibit



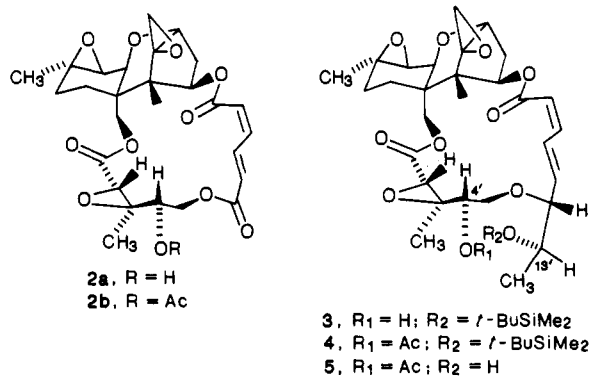
(1)

substantial in vivo anticancer activity,[9,10] conversion of baccharinoid B5 (1) into its corresponding verrucarin was an attractive target for this reaction. However, under conditions where roridins are readily converted to verrucarins (PDC in DMF at 25 °C), baccharinoid B5 (1) was recovered unchanged. When the reaction temperature was increased to 60 °C (DMF solvent) or when dichloroethane at reflux (80 °C) was employed as the solvent, the PDC oxidation led to a complex mixture of products.

Treatment of 1 with tetra-*n*-butylammonium dichromate (TBADC)[12] in DMF at 60 °C or in dichloroethane at 80 °C for 24 h gave the verrucarin derivative **2a** in 35% yield. Although the TBADC oxidation of 1 to **2a** was accompanied by considerably fewer side products, the yield was poor relative to the yields for the PDC oxidation of the roridins.[11] The use of (dimethylamino)pyridinium chlorochromate ($DMAP{\cdot}HCrO_3Cl$)[13] or tetrakis(pyridine)silver dichromate ($Py_4Ag_2Cr_2O_7$)[14] gave trace amounts of **2a** and principally recovered 1.

The low reactivity of 1 toward the chromium reagents was unexpected, since the PDC reaction proceeds smoothly at 25 °C with roridins to give 50–60% yields of verrucarins.[11] The low reactivity of 1 appears to be due to the presence of a hydroxy group at the 4′ position.[15]

The 4′-hydroxy group was masked in order to evaluate its effect on the PDC oxidation. To this end, the 13′-hydroxy group first was selectively silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl)[16] to give **3** and then the 4′-hydroxy group was protected as the acetate (acetic anhydride/triethylamine/DMAP). The 4′-acetyl-13′-silylated B5 **4** was desilylated by exposure to acetic acid–water–tetrahydrofuran (3:1:1)[16] at 80 °C to give 4′-acetyl B5 **5**. The reaction of **5** with PDC, in DMF, at room temperature, gave the acetate **2b** in 65% yield after 18-h reaction time. Compound **2b** was shown to be identical with that of the acetylated TBADC oxidation product of 1. This sequence clearly shows the deleterious effect of 4′-hydroxy group on the reactivity of 1 toward PDC oxidation.

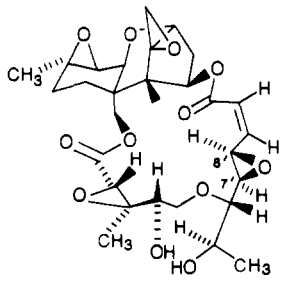


Nonchromium oxidizing agents also were examined for the conversion of 1 to the verrucarin-type compound **2**. Use of dimethyl sulfoxide–trifluoroacetic anhydride (Swern oxidation)[17] or dimethyl sulfoxide–oxalyl chloride (modified Swern oxidation)[18] under the reported conditions led to the recovery of starting material. Use of Dess–Martin periodinane reagent[19] resulted in the formation of a mixture of products, including a low yield of the verrucarin-type compound **2a**. Reaction with ruthenium tetraoxide[20] resulted in the recovery of the starting material. However, roridin A, which lacks the 4′-hydroxy group, also is relatively unreactive under these Swern-type oxidation conditions. Thus treatment of roridin A with dimethyl sulfoxide–trifluoroacetic anhydride gave only 10% conversion to verrucarin A and most of the roridin A was recovered unreacted.

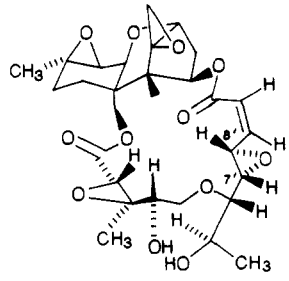
The reaction of 1 with *m*-chloroperoxybenzoic acid (MCPBA) in chloroform at room temperature yielded two epoxides **6a** and **6b** in a 2:1 ratio, after 24-h reaction time. When 3,5-dinitroperoxybenzoic acid was used as the epoxidizing reagent, two products were obtained again in a 2:1 ratio. The minor product has identical properties with the minor epoxide (**6b**) from the MCPBA epoxidation; however, the major product was not a 7′,8′-epoxide derivative of 1. The spectral data suggested that the major product formed with 3,5-dinitroperoxybenzoic acid was a cyclic ether resulting from intramolecular ring-opening of the 7′,8′-epoxide by a hydroxy group. When the 3,5-dinitroperoxybenzoic acid oxidation was repeated in the presence of sodium bicarborate, the two 7′,8′-epoxides **6a** and **6b** were obtained without any formation of the ring-opened compound. Treatment of major 7′,8′-epoxide **6a** with 3,5-dinitroperoxybenzoic acid under the reaction conditions gave the ring-opened product. However, epoxide **6b** is stable under these conditions.

The conformation of the macrolide ring in macrocyclic trichothecenes is considerably more rigid than one would glean from examining ball-and-stick type models of these compounds; space-filling models give a much better appreciation of this point. Furthermore, X-ray diffraction data have been collected for a number of these compounds, including baccharinoids B5 (1),[2] B7,[5] and B2 triacetate,[5] roridins A and isoE,[11] verrucarins A[21] and B,[22] myrotoxins

(11) Jarvis, B. B.; Midiwo, J. O.; Flippen-Anderson, J. L.; Mazzola, E. P. *J. Nat. Prod.* **1982**, *45*, 440.
(12) (a) Cacchi, S.; Latorre, F.; Misiti, D. *Synthesis* **1979**, 356. (b) Santaniello, E.; Ferrabuschi, P. *Synth. Commun.* **1980**, *10*, 75.
(13) Guzice, F. S.; Luzzio, F. A. *J. Org. Chem.* **1982**, *47*, 1789.
(14) Firouzabadi, H.; Serdarian, A.; Gharibi, H. *Synth. Commun.* **1984**, *14*, 89.
(15) Other baccharinoids having a 4′-hydroxy group (B4,[1] B8,[1] and B10[4]) also fail to undergo the oxidative cleavage with PDC.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(18) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(20) Schuda, P. F.; Cichowitz, M. B.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829.



6a

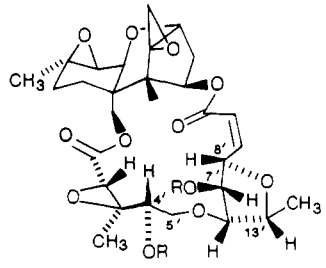


6b

A and C,[23] myrotoxin B hydrate,[24] and myrotoxin C hydrate,[24] and the conformations of the macrolide rings in all these compounds are quite similar. In addition, ^{1}H NMR data for these compounds suggest that the conformations in solution differ little from the conformations in the solid phase. Inspection of the model of 1 reveals that the β-face of 7′,8′ double bond is less hindered than the α-face, and, thus, the major isomer upon epoxidation should be the β-isomer **6a**.

Now the question is which of the hydroxy groups, the one at C4′ or the one at C13′ opens the 7′,8′-epoxide. With some small but perhaps significant twisting of the macrolide chain, the hydroxy group at C4′ could open the epoxide to give a 1,4-dioxane derivative, whereas the hydroxy group at C13′ with little or no distortion of the macrolide chain could open the epoxide at C7′ to give an oxetane or at C8′ to give a tetrahydrofuran. On the basis of stereoelectronic arguements,[25] the 1,4-dioxane would be the expected product unless the macrolide chain lacked the flexibility to orient the hydroxy group at C4′ for ring-opening at C7′.

On the basis of spectra of both the ring-opened product and its diacetate, the product is the tetrahydrofuran **7a**. The most salient feature of the NMR spectra is that upon acetylation of **7a** to give **7b**, neither H8′ nor H13′ change significantly in chemical shift; whereas, both H4′ and H7′ move to higher frequency by ~1 ppm in **7b**. It should be noted that **7a** is the result of a normally unfavorable 5-*Endo-Tet* process[25] and that in similar systems[26] ring-opening occurs 4-*Exo-Tet* to give four-membered ring compounds.



7a, R = H
7b, R = Ac

The conversion of baccharinoid B5 (1) to its verrucarin derivative **2a** results in little change in cytotoxicity, whereas epoxidation of **1** to **6a** and subsequent conversion of epoxide **6a** to tetrahydrofuran **7a** leads to a drop in cytotoxicity of about one order of magnitude in each case. The following are cytotoxicity data (IC_{50}) for compounds **1**, **2a**, **6a**, and **7a** against L1210 cells: **1**, 0.010 μg/mL; **2a**, 0.015 μg/mL; **6a**, 0.22 μg/mL; **7a**, 2.00 μg/mL.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Those compounds isolated as glasses were shown by TLC and ^{1}H NMR to be >90–95% pure. IR spectra were determined in chloroform or dichloromethane on a Perkin-Elmer Model 281 spectrometer. NMR spectra were determined in $CDCl_3$ on an IBM SY-200 MHz spectrometer or a Bruker WP-400 MHz spectrometer with tetramethylsilane as an internal standard; ^{13}C NMR peaks were assigned by using INEPT and by comparison of chemical shift data with those in the literature. Mass spectra were determined on a VG 7070EQ mass spectrometer in the negative-ion mode with ammonia as a reagent gas.

Thin-layer chromatography (TLC) was performed on precoated TLC plates of silica gel 60F-254 (0.2 mm). Visualization was done by viewing the developed plates under short-wavelength UV light and by spraying with vanillin/sulfuric acid. The Model 7942 chromatotron (Harrison Research Laboratories) was used for preparative TLC with the plates, prepared according to instructions in the manual, of 1- or 2-mm thickness, using E. Merck silica gel or alumina on regular glass circular disks.

13′-*tert*-Butyldimethylsilyl Ether of Baccharinoid B5 (1). To a solution of 1 (100 mg, 0.17 mmol) in 0.7 mL of dimethylformamide (DMF) were added imidazole (47.4 mg, 0.70 mmol) and *tert*-butyldimethylsilyl chloride (52.5 mg, 0.35 mmol). The reaction mixture was kept in the refrigerator (~5 °C) overnight. The solution was diluted with 50 mL of water and extracted with ether (3 × 15 mL). The ether extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified on the chromatotron (2-mm silica gel plate; 5% ethyl acetate/hexane as eluent) to give 104.4 mg (80%) of 13′-monosilylated B5 **3** isolated as a glass: IR ($CHCl_3$) 3550, 2940, 1750, 1725, 1175, 1090, 970 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{35}H_{52}O_{11}Si$ *m/e* 676.3279, found 676.3272.

13′-*tert*-Butyldimethylsilyl Ether of 4′-Acetylbaccharinoid B5 (4). A mixture of 13′-monosilylated B5 **3** (70 mg, 0.12 mmol), acetic anhydride (122 mg, 1.2 mmol), triethylamine (TEA) (121 mg, 1.2 mmol), and DMAP (2 crystals) in 4 mL of CH_2Cl_2 was stirred at room temperature for 20 min. Removal of solvent in vacuo was followed by PTLC on the chromatotron (1-mm silica gel plate; 1% MeOH/CH_2Cl_2 as eluent) to give 75.0 mg (86%) of a glass, 4′-acetyl-13′-silylated B5 **4**: IR ($CHCl_3$) 2930, 1740, 1720, 1260, 900 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{37}H_{54}O_{12}Si$ *m/e* 718.3385, found 718.3369.

4′-Acetylbaccharinoid B5 (5). Compound **4** (75.0 mg) was stirred in a solution of acetic acid:water:THF (3:1:1) at 80 °C for 9 h. To the reaction mixture was added 10 mL of heptane and the solution was concentrated in vacuo. Addition of heptane and evaporation was continued until all acid and water were evaporated. The crude product was purified on the chromatotron (1-mm silica gel plate; 1% MeOH/CH_2Cl_2 as eluent) to yield 55.4 mg (88%) of a glass, 4′-acetyl B5 **5**: IR ($CHCl_3$) 3550, 2950, 2880, 1750, 1720, 1170, 970 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{13}H_{40}O_{12}$ *m/e* 604.2520, found 604.2507.

PDC Oxidation of 5: Preparation of 9β,10β-Epoxy-(*R*)-4′-acetoxyverrucarin B (2b). To a solution of 4′-acetyl **5** (10.0 mg, 0.016 mmol) in 0.2 mL of DMF was added pyridinium dichromate (Aldrich) (PDC, 12.0 mg, 0.032 mmol). The reaction mixture was stirred at room temperature for 18 h, another 2 equiv of PDC (12 mg) was added, and the mixture was stirred 8 h and poured into 10 mL of water. Extraction with ether gave 8 mg of crude product which was purified on the chromatotron (1-mm silica gel plate; 0–1% MeOH/CH_2Cl_2 as eluent) to yield 6.3 mg (66%) of a glass **2b**: IR (CH_2Cl_2) 1755, 1725, 1195 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{29}H_{34}O_{12}$ *m/e* 574.2050, found 574.2032; ^{1}H NMR δ 0.82 (3 H, s, 14-H), 1.38 (3 H, s, 12′-H), 1.62 (3 H, s, 16-H), 1.80 (4 H, m, 7- and 8-H), 2.13 (3 H, s, acetate), 2.20 (1 H, m, 3β-H), 2.53 (1 H, dd, J = 8.1 and 15.3 Hz, 3α-H), 2.79 and 3.18 (1 H each, AB, J = 3.9 Hz, 13-H), 3.10 (1 H, d, J = 5.3 Hz, 10-H), 3.52 (1 H, s, 2′-H), 3.57 (1 H, d,

(21) McPhail, A. T.; Sin, G. A. *J. Chem. Soc. C* **1966**, 1394.
(22) Breitenstein, W.; Tamm, C.; Arnold, E. V.; Clardy, J. *Helv. Chim. Acta* **1979**, *62*, 2699.
(23) Jarvis, B. B.; Cömezoğlu, F. T.; Lee, Y.-W.; Flippen-Anderson, J. L.; Gilardi, R. D.; George, C. F. *Bull. Soc. Chim. Belg.* **1986**, *95*, 681.
(24) Jarvis, B. B.; Zeng, M.; Cömezoğlu, F. T.; Flippen-Anderson, J. L., unpublished results.
(25) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; pp 163–177.
(26) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. See also: Masamune, T.; Ono, M.; Sato, S.; Murai, A. *Tetrahedron Lett.* **1978**, 371.

J = 5.3 Hz, 11-H), 3.95 (1 H, d, J = 4.6 Hz, 2-H), 4.17 and 4.54 (1 H each, AB, J = 12.4 Hz, 15-H), 4.24 (1 H, dd, J = 3.8 and 12.0 Hz, 5′B-H), 4.46 (1 H, dd, J = 3.8 and 7.4 Hz, 4′-H), 4.68 (1 H, dd, J = 7.4 and 12.0 Hz), 5.72 (1 H, dd, J = 4.9 and 8.1 Hz, 4-H), 6.07 (1 H, d, J = 15.7 Hz, 7′-H), 6.17 (1 H, d, J = 11.3 Hz, 10′-H), 6.64 (1 H, dd, J = 11.3 and 11.3 Hz, 9′-H), and 7.85 (1 H, dd, J = 11.3 and 15.7, 8′-H).

Oxidation of 1 with Bis(tetrabutylammonium) Dichromate (TBADC): Preparation of 9β,10β-Epoxy-(*R*)-4′-hydroxyverrucarin B (2a). To a solution of 1 (100 mg, 0.17 mmol) in 2 mL of 1,2-dichloroethane was added TBADC (Aldrich) (488 mg, 0.70 mmol), and the solution was stirred at reflux for 12 h, concentrated in vacuo, and filtered through silica gel (10 g) with 3% $MeOH/CH_2Cl_2$. After evaporation of solvent, the crude product was purified on the chromatotron (2-mm silica gel plate; 0–3% $MeOH/CH_2Cl_2$ as eluent) to give crystals of verrucarin-type compound **2a**. Recrystallization from dichloromethane–ether gave 30 mg (32%) of **2a**: mp 214–216 °C: IR (CH_2Cl_2) 1760, 1720, 1195 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{27}H_{32}O_{11}$ m/e 532.1944, found 532.1951; ^1H NMR δ 0.80 (3 H, s, 14-H), 1.38 (3 H, s, 12′-H), 1.60 (3 H, s, 16-H), 1.80 (4 H, m, 7-H, 8-H), 2.19 (1 H, ddd, $J_{2,3\beta} = J_{3\beta,4}$ = 4.8 Hz, J_{gem} = 15.3 Hz, 3β-H), 2.49 (1 H, dd, $J_{3\alpha,4}$ = 8.2 Hz, J_{gem} = 15.3 Hz, 3α-H), 2.78 and 3.19 (1 H each, AB, J = 3.9 Hz, 13-H), 3.11 (1 H, d, J = 5.3 Hz, 10-H), 3.47 (1 H, s, 2′-H), 3.50 (1 H, dd, J = 4.2 and 8.7 Hz, 4′-H), 3.58 (1 H, d, J = 5.3 Hz, 11-H), 3.95 (1 H, d, J = 4.8 Hz, 2-H), 4.13 (1 H, dd, J = 8.7 and 11.9 Hz, 5′B-H), 4.26 and 4.52 (1 H each, AB, J = 12.4 Hz, 15-H), 4.53 (1 H, dd, J = 4.2 and 11.9 Hz, 5′A-H), 5.79 (1 H, dd, J = 4.8 and 8.2 Hz, 4-H), 6.08 (1 H, d, J = 15.8 Hz, 7′-H), 6.16 (1 H, d, J = 11.2 Hz, 10′-H), 6.64 (1 H, dd, J = 11.2 and 11.2 Hz, 9′-H), 7.89 (1 H, dd, J = 11.2 and 15.8 Hz, 8′-H); ^{13}C NMR δ 7.6 (C14), 10.5 (C12′), 17.5 (C7), 22.2 (C16), 26.4 (C8), 34.9 (C3), 43.3 (C6), 47.9 (C13), 49.0 (C5), 57.2 (C2′), 57.7 (C9), 58.1 (C10), 63.7 (C15), 64.3 (C5′), 64.8 (C12 and C3′), 67.5 (C11), 73.8 (C4), 75.6 (C4′), 78.7 (C2), 126.0 (C7′ or C10′), 127.3 (C7′ or C10′), 138.6 (C8′ or C9′), 138.8 (C8′ or C9′), 165.2 (C1′ or C6′ or C11′), 166.3 (C1′ or C6′ or C11′), and 167.0 (C1′ or C6′ or C11′). Acetylation of **2a** (Ac_2O, TEA, DMAP) gave an acetate whose spectral data are identical with that of **2b**.

Oxidation of 1 with 4-(Dimethylamino)pyridinium Chlorochromate. A mixture of 1 (10.0 mg, 0.018 mmol) and 4-(dimethylamino)pyridinium chlorochromate (Aldrich) (23 mg, 0.089 mmol) in 0.3 mL of CH_2Cl_2 was stirred at room temperature for 24 h and diluted with 3 mL of ether, and the mixture was filtered through Celite. After evaporation of solvent, the crude product was separated on the chromatotron (1-mm silica gel plate; 0–4% $MeOH/CH_2Cl_2$ as eluent) to give about 1 mg (~10%) of a compound whose R_f value upon TLC analysis was identical with that of **2a**.

Oxidation of 1 with Tetrakis(pyridine)silver Dichromate. A mixture of 1 (5 mg, 0.009 mmol) and tetrakis(pyridine)silver dichromate[13] (26.1 mg, 0.036 mmol) in 0.5 mL of acetonitrile was stirred at room temperature for 2 days. The reaction mixture was filtered and the solid material was washed with acetonitrile, and the solvent was removed by rotary evaporation. The product was purified by PTLC (two 5 × 10 cm silica gel plates; 2% $MeOH/CH_2Cl_2$ as developing solvent) which afforded about 0.5 mg of a compound whose R_f value upon TLC analysis was identical with that of **2a**, together with 4 mg of starting material.

Epoxidation of 1 with *m*-Chloroperoxybenzoic Acid (MCPBA) To Give 7′,8′-Epoxides of Baccharinoid B5 (6a and 6b). Baccharinoid 1 (80 mg, 0.14 mmol) was dissolved in 2 mL of chloroform and to this solution was added MCPBA (72%, 51 mg, 0.21 mmol). TLC analysis indicated incomplete reaction after 24 h. Another equivalent (24 mg) of MCPBA was added and the reaction was allowed to continue for an additional 24 h. The mixture was diluted with 20 mL of CH_2Cl_2 and washed with 15 mL of saturated sodium bicarbonate solution and then with 10 mL of water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was separated by PTLC on the chromatotron (1-mm silica gel plate; 0.2% $MeOH/CH_2Cl_2$ as eluent) to give two products (both crystallized from dichloromethane–ether–hexane).

Major product, 7′β,8′β-epoxybaccharinoid B5 (**6a**) (42.0 mg, 52%): mp 238–239 °C; IR (CH_2Cl_2) 2940, 1760, 1740, 1190, 970 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{29}H_{38}O_{12}$ m/e 578.2363, found 578.2366; ^1H NMR δ 0.84 (3 H, s, 14-H), 1.28 (3 H, d, J = 6.4 Hz, 14′-H), 1.39 (1 H, s, 12′-H), 1.47 (3 H, s, 16-H), 2.10 (1 H, ddd, $J_{3\beta,4}$ = 3.6 Hz, $J_{2,3\beta}$ = 5.5 Hz, J_{gem} = 15.6 Hz, 3β-H), 2.47 (1 H, dd, $J_{3\alpha,4}$ = 8.0 Hz, J_{gem} = 15.6 Hz, 3α-H), 2.77 and 3.18 (1 H each, AB, J = 3.9 Hz, 13-H), 3.06 (1 H, dd, J = 1.9 and 4.2 Hz, 7′-H), 3.16 (1 H, d, J = 4.8 Hz, 10-H), 3.17 (1 H, m, 6′-H), 3.54 (1 H, br s, 4′-H), 3.60 (1 H, s, 2′-H), 3.78 (1 H, d, J = 4.8 Hz, 11-H), 3.85 (2 H, m, 5′-H), 3.95 (1 H, d, J = 5.0 Hz, 2-H), 4.04 and 4.55 (1 H each, AB, J = 12.5 Hz, 15-H), 4.36 (1 H, dd, J = 1.9 and 8.0 Hz, 8′-H), 5.84 (1 H, dd, J = 8.0 and 11.4 Hz, 9′-H), 6.00 (1 H, dd, J = 3.6 and 8.0 Hz, 4-H), 6.18 (1 H, d, J = 11.4 Hz, 10′-H); ^{13}C NMR δ 6.8 (C14), 12.4 (C12′), 18.7 (C7), 19.0 (C14′), 22.3 (C16), 26.1 (C8), 35.3 (C3), 42.8 (C6), 47.8 (C13), 48.5 (C5), 52.6 (C7′ or C8′), 56.4 (C2′), 57.1 (C9 and C10), 57.9 (C7′ or C8′), 64.0 (C3′ or C12), 64.4 (C15), 64.7 (C3′ or C12), 66.7 (C11), 68.5 (C13′), 71.9 (C5′), 73.7 (C4), 75.6 (C4′), 78.6 (C2), 82.7 (C6′), 125.0 (C10′), 143.5 (C9′), 166.2 (C11′), and 168.1 (C1′). For diacetate of **6a**: mass spectrum (NICI, ammonia reagent gas), calcd for $C_{33}H_{42}O_{14}$ m/e 662.2575, found 662.2559; ^1H NMR δ 0.83 (3 H, s, 14-H), 1.32 (3 H, d, J = 6.5 Hz, 14′-H), 1.38 (3 H, s, 12′-H), 1.59 (3 H, s, 16-H), 2.05 and 2.13 (3 H each, s, acetates), 2.15 (1 H, m, 3β-H), 2.42 (1 H, dd, $J_{3\alpha,4}$ = 8.0 Hz and J_{gem} = 15.3 Hz, 3α-H), 2.78 and 3.18 (1 H each, AB, J = 4.0 Hz, 13-H), 3.07 (1 H, dd, J's = 2.8 Hz, 7′-H), 3.11 (1 H, d, J = 5.3 Hz, 10-H), 3.47 (1 H, s, 2′-H), 3.54 (1 H, dd, J's = 2.8 Hz, 6′-H), 3.61 (1 H, d, J = 5.3, 11-H), 3.77 and 3.89 (2 H, d AB, J = 4.3 and 11.5 Hz, 5′-H), 3.95 (1 H, d, J = 5.0 Hz, 2-H), 4.02 (1 H, dd, J = 2.8 and 8.5 Hz, 8′-H), 4.27 and 4.47 (2 H, AB, J = 12.4 Hz, 15-H), 4.51 (1 H, m, 4′-H), 5.19 (1 H, dq, J = 2.8 and 6.5 Hz, 13′-H), 5.79 (1 H, dd, J = 8.5 and 11.4 Hz, 9′-H), 5.85 (1 H, dd, J = 4.2 and 8.0 Hz, 4-H), and 6.20 (1 H, d, J = 11.4 Hz, 10′-H).

Minor product, 7′α,8′α-epoxybaccharinoid B5 (**6b**) (25.0 mg, 31%): mp 177–178 °C; IR (CH_2Cl_2) 3500, 2940, 1765, 1725, 1090, 970 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{29}H_{38}O_{12}$ m/e 578.2363, found 578.2349; ^1H NMR δ 0.81 (3 H, s, 14-H), 1.30 (3 H, d, J = 6.3 Hz, 14′-H), 1.38 (3 H, s, 12′-H), 1.55 (3 H, s, 16-H), 2.13 (1 H, ddd, $J_{3\beta,4}$ = 4.0 Hz, $J_{2,3\beta}$ = 5.0 Hz, J_{gem} = 15.5 Hz, 3β-H), 2.50 (1 H, dd, $J_{3\alpha,4}$ = 8.2 Hz, J_{gem} = 15.5 Hz, 3α-H), 2.78 and 3.19 (1 H each, AB, J = 4.0 Hz, 13-H), 3.05 (1 H, m, 7′-H), 3.34 (1 H, m, 6′-H), 3.38 (1 H, s, 2′-H), 3.54 (1 H, m, 4′-H), 3.70 (1 H, m, 11-H), 3.72 (1 H, m, 5′-H), 3.89 (1 H, m, 13′-H), 3.95 (1 H, d, J = 5.0 Hz, 2-H), 4.09 and 4.42 (1 H each, AB, J = 12.5 Hz, 15-H), 4.75 (1 H, dd, J = 1.3 and 8.9 Hz, 8′-H), 5.85 (1 H, dd, J = 8.9 and 11.5 Hz, 9′-H), 5.93 (1 H, dd, J = 4.0 and 8.2 Hz, 4-H), 6.11 (1 H, d, J = 11.5 Hz, 10′-H); ^{13}C NMR δ 6.9 (C14), 12.7 (C12′), 18.2 (C14′), 18.3 (C7), 22.2 (C16), 26.1 (C8), 35.3 (C3), 42.6 (C6), 47.7 (C13), 48.5 (C5), 51.4 (C7′ or C8′), 56.0 (C2′), 57.1 (C10), 57.4 (C9), 58.4 (C7′ or C8′), 64.3 (C15), 64.8 (C3′ or C12), 64.9 (C3′ or C12), 67.0 (C11), 68.4 (C13′), 72.3 (C5′), 74.6 (C4), 75.3 (C4′), 78.5 (C2), 82.5 (C6′), 124.1 (C10′), 147.0 (C9′), 166.0 (C11′), and 167.3 (C1′). For diacetate of **6b**: mass spectrum (NICI, ammonia reagent gas), calcd for $C_{33}H_{42}O_{14}$ m/e 662.2575, found 662.2582; ^1H NMR δ 0.79 (3 H, s, 14-H), 1.33 (3 H, d, J = 6.6 Hz, 14′-H), 1.38 (3 H, s, 12′-H), 1.60 (3 H, s, 16-H), 2.08 and 2.14 (3 H each, s, acetates), 2.20 (1 H, m, 3β-H), 2.47 (1 H, dd, $J_{3\alpha,4}$ = 7.8 Hz and J_{gem} = 15.7 Hz, 3α-H), 2.78 and 3.18 (1 H each, AB, J_{AB} = 3.9 Hz, 13-H), 3.05 (1 H, dd, J's = 1.4 Hz, 7′-H), 3.10 (1 H, d, J = 5.3 Hz, 10-H), 3.42 (1 H, s, 2′-H), 3.42 (1 H, m, 4′-H), 3.63 (1 H, m, 6′-H), 3.67 and 3.92 (1 H each, d AB, J's = 4.2 and 10.4 Hz, 5′-H), 3.60 (1 H, d, J = 5.3 Hz, 11-H), 3.95 (1 H, d, J = 4.8 Hz, 2-H), 4.03 and 4.58 (1 H each, AB, J = 12.4 Hz, 15-H), 4.41 (1 H, dd, J = 1.4 and 8.9 Hz, 8′-H), 5.08 (1 H, dq, J = 6.6 Hz, 13′-H), 5.73 (1 H, m, 4-H), 5.77 (1 H, dd, J = 8.9 and 11.5 Hz, 9′-H), and 6.11 (1 H, d, J = 11.5 Hz, 10′-H).

Epoxidation of 1 with 3,5-Dinitroperoxybenzoic Acid. A mixture of 1 (20 mg, 0.36 mmol) and 3,5-dinitroperoxybenzoic acid (Aldrich) (122 mg, 0.53 mmol) in 2 mL of chloroform was allowed to stand at room temperature overnight. The solution was diluted with 20 mL of CH_2Cl_2 and washed with saturated sodium bicarbonate (2 × 20 mL) and then with water (15 mL). After drying (Na_2SO_4) and removal of solvent in vacuo, the crude product was separated by PTLC (2 × 250 μm alumina plates) with 10% 2-propanol/CH_2Cl_2 as developing solvent, to obtain two products which were crystallized from dichloromethane–ether: 7′,8′-epoxy **6b** (40 mg, 20%), identical with that obtained as a

minor product from MCPBA epoxidation of **1**, and compound **7a** (65 mg, 32%): mp 255–257 °C; IR (CH_2Cl_2) 3550, 2940, 1760, 1720, 1180, 1080 cm^{-1}; mass spectrum (NICI, ammonia reagent gas), calcd for $C_{29}H_{38}O_{12}$ *m/e* 578.2363, found 578.2359; ^1H NMR δ 0.76 (3 H, s, 14-H), 1.28 (3 H, d, J = 6.3 Hz, 14′-H), 1.33 (3 H, s, 12′-H), 1.60 (3 H, s, 16-H), 2.19 (1 H, ddd, $J_{3\beta,4}$ = 4.7 Hz, $J_{2,3\beta}$ = 4.8 Hz, J_{gem} = 15.3 Hz, 3β-H), 2.39 (1 H, dd, $J_{3\alpha,4}$ = 8.3 Hz, J_{gem} = 15.3 Hz, 3α-H), 2.73 and 3.13 (1 H each, AB, J = 4.0 Hz, 13-H), 3.07 (1 H, d, J = 5.3 Hz, 10-H), 3.40 (1 H, m, 4′-H), 3.44 (1 H, s, 2′-H), 3.52 (1 H, d, J = 5.3 Hz, 11-H), 3.73 (1 H, dd, $J_{6',7}$ = $J_{6,13'}$ = 4.3 Hz, 6′-H), 3.78 (1 H, m, 7′-H), 3.84 (2 H, m, 5′-H), 3.92 (1 H, d, J = 4.8 Hz, 2-H), 4.30 and 4.42 (1 H each, AB, J = 12.4 Hz, 15-H), 4.39 (1 H, m, 13′-H), 5.46 (1 H, ddd, $J_{8',10'}$ = 1.5 Hz, $J_{8',9'}$ = 7.9 Hz, $J_{7',8'}$ = 8.3 Hz, 8′-H), 5.75 (1 H, dd, J = 8.3 and 4.7 Hz, 4-H), 5.99 (1 H, dd, J = 1.5 and 11.4 Hz, 10′-H), 6.19 (1 H, dd, J = 7.9 and 11.4 Hz, 9′-H); ^{13}C NMR δ 7.5 (C14), 11.5 (C12′), 15.6 (C14′), 17.3 (C7), 22.2 (C16), 26.3 (C8), 34.6 (C3), 43.4 (C6), 47.8 (C13), 49.0 (C5), 52.7 (C2′ or C9), 57.4 (C2′ or C9), 57.7 (C10), 63.6 (C15), 64.8 (C3′), 65.9 (C12), 67.4 (C11), 72.6 (C5′), 74.7 (C13′), 75.2 (C4 or C7′ or C8′), 76.2 (C4 or C7′ or C8′), 76.5 (C4 or C7′ or C8′), 78.2 (C2 or C4′), 78.6 (C2 or C4′), 81.9 (C6′), 121.9 (C10′), 147.5 (C9′), 167.4 (C1′ and C11′). Diacetate **7b**: mass spectrum (NICI, ammonia reagent gas), calcd for $C_{33}H_{42}O_{14}$ *m/e* 662.2575, found 662.2565; ^1H NMR δ 0.78 (3 H, s, 14-H), 1.26 (3 H, d, J = 6.4 Hz, 14′-H), 1.33 (3 H, s, 12′-H), 1.65 (3 H, s, 16-H), 2.17 (1 H, ddd, $J_{3\beta,4}$ = 4.6 Hz, $J_{2,3\beta}$ = 4.7 Hz, J_{gem} = 15.4 Hz, 3β-H), 2.38 (1 H, dd, $J_{3\alpha,4}$ = 8.3 Hz, J_{gem} = 15.4 Hz, 3α-H), 2.73 and 3.15 (1 H each, AB, J = 4.0 Hz, 13-H), 3.07 (1 H, d, J = 5.3 Hz, 10-H), 3.42 (1 H, s, 2′-H), 3.53 (1 H, d, J = 5.3 Hz, 11-H), 3.71 (1 H, dd, J = 5.0 and 10.3 Hz, 5′β-H), 3.90 (2 H, m, 6′-H, 5′α-H), 3.91 (1 H, d, J = 4.7 Hz, 2-H), 4.30 and 4.44 (1 H each, AB, J = 12.3 Hz, 15-H), 4.35 (1 H, dd, J = 7.6 and 5.0 Hz, 4′-H), 4.79 (1 H, dd, J = 3.3 and 9.9 Hz, 7′-H), 5.50 (1 H, dd, J = 8.0 and 9.9 Hz, 8′-H), 5.72 (1 H, dd, J = 4.6 and 8.3 Hz, 4-H), 6.05 (2 H, m, 9′-H and 10′-H).

Acknowledgment. We thank C. D. Pinter of Warner-Lambert Co., Anne Arbor, MI, for the cytotoxicity data and Stephen Missler, USAMRIID, Ft. Detrick, Frederick, MD, for the HRMS data. This work was supported by the National Institutes of Health (Grant No. CA 25967).

1,4- and 1,5-Stereoselection by Sequential Aldol Addition to α,β-Unsaturated Aldehydes Followed by Claisen Rearrangement. Application to Total Synthesis of the Vitamin E Side Chain and the Archaebacterial C_{40} Diol[1]

Clayton H. Heathcock,* Bruce L. Finkelstein, Esa T. Jarvi, Peggy A. Radel, and Cheri R. Hadley

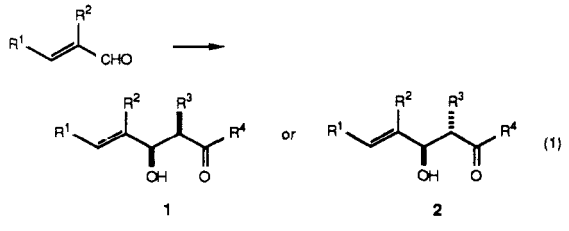
Department of Chemistry, University of California, Berkeley, California 94720

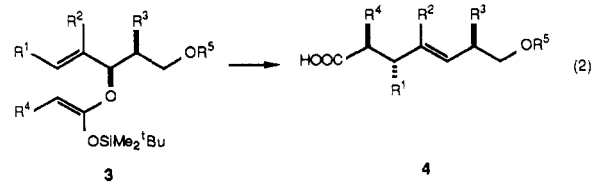
Received October 6, 1987

A synthetic strategy has been developed wherein the high 1,2-stereoselection obtainable from aldol reaction of an α,β-unsaturated aldehyde is parlayed by a subsequent Claisen rearrangement into 1,4- or 1,5-stereoselection. For example, diol monoethers **26** and **31**, obtained in three steps from aldol **11**, are subjected to Claisen rearrangement to obtain amides **40** and **41** or ester **42**. The diastereomeric diol monoethers **29** and **32** are similarly converted into the diastereomeric amides **43** and **44**. The use of this strategy for 1,5-stereoselection is illustrated. Esters **52** and **53** can be converted via the *E* enolates into unsaturated acids **56** and **57**. The same acids are obtainable from the diastereomeric esters **54** and **55**, by conducting the Ireland–Claisen rearrangement with the *Z* enolates. The diastereomeric unsaturated acids **58** and **59** arise via the *Z* enolates of esters **52** and **53** or the *E* enolates of esters **54** and **55**. The 1,4-stereoselection strategy is illustrated with a synthesis of hydrocarbon **45**. This stereorational synthesis establishes the relative stereochemistry of the C_{30} diol from Messel shale kerogen. The 1,5-stereoselection strategy is demonstrated with a synthesis of (±)-**67**, the vitamin E side-chain alcohol. This synthetic protocol is further illustrated with a total synthesis of the archaebacterial C_{40} diol (**69**) and one of its diastereomers (**70**). The latter syntheses provide the final information to fully define the structure of compound **112**, an archaebacterial membrane substance that is a 72-membered ring tetraether with 18 stereocenters.

Introduction

Under certain conditions, the addition of preformed enolates to aldehydes gives α-substituted-β-hydroxy carbonyl compounds with high diastereoselectivity.[2] If an α,β-unsaturated aldehyde is employed as the educt, one may prepare either syn or anti aldols (**1** or **2**, eq 1). Since aldols **1** and **2** are also allylic alcohols, the possibility exists of parlaying the high 1,2 stereoselectivity of the aldol reaction into either 1,4 or 1,5 stereoselectivity by using the Claisen rearrangement. For example, as shown in eq 2,





the *Z* ester enolate **3**, derived from syn aldol **1**, should be transformable into **4**, in which new 1,4 and 1,5 stereorelationships exist. By controlling the relative stereochemistry in the aldol (e.g., **1** or **2**) and the geometry of the enolate double bond,[3] a great deal of synthetic versatility

(1) Part 42 in the series Acyclic Stereoselection. For part 41, see: Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.*, submitted for publication.

(2) (a) Heathcock, C. H. *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. II. (b) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3.

(3) (a) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975. (b) Ireland, R. E.; Willard, A. K. *J. Org. Chem.* **1976**, *41*, 986. (c) Ireland, R. E.; Mueller, R. K.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (d) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, N. R. *Can. J. Chem.* **1979**, *57*, 1743.

0022-3263/88/1953-1922$01.50/0 © 1988 American Chemical Society