was subjected to HPLC (95:5 dichloromethane–methanol) to afford 0.069 g (89%) of a hygroscopic tan foam, which was dissolved in H_2O–THF and lyophilized to provide material for analysis: IR (film) 2120 cm^{-1} (N_3); ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 and 1.56 (2 s, $C(CH_3)_2$, 6), 2.11 (m, 2 $H_{5'}$, 2), 2.95 (q, 2 $H_{7'}$, 2), 3.20 (t, 2 $H_{8'}$, 2), 3.77 (m, $H_{6'}$, 1), 4.28 (m, $H_{4'}$, 1), 4.86 (m, $H_{3'}$, 1), 5.00 (s, CH_2Ph, 2), 5.40 (m, $H_{2'}$, 1), 5.52 (s, NH_2, 2), 5.94 (br s, $H_{1'}$, 1), 7.22 (s, Ph, 5), 7.77 and 8.22 (2 s, H_2 and H_8, 2); FDMS (Me_2SO), *m/e* 524 [$(M + 1)^+$], 523 [M^+], 481 [$(M - N_3)^+$]. Anal. Calcd for $C_{24}H_{29}N_9O_5 \cdot 1.6H_2O$: C, 52.19; H, 5.88; N, 22.82. Found: C, 52.27; H, 5.70; N, 22.51.

9-[Benzyl 9-(benzyloxycarbonyl)-6-[(benzyloxycarbonyl)amino]-5,6,7,8,9-pentadeoxy-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-decafuranosyluronate]adenine (11e). A solution of 0.6 mL (0.068 g, 0.237 mmol) of dibenzyl malonate and 2 mL of DMF was treated at room temperature with 0.01 g (0.237 mmol) of sodium hydride 60% oil dispersion. After the evolution of hydrogen ceased, a solution of 0.038 g (0.067 mmol) of **11c**, formed as described in the synthesis of **11d**, in 2 mL of DMF was added, and the mixture was heated at 80 °C for 3 h. After the solvent was removed at reduced pressure, the residue was dissolved in dichloromethane and washed with water. The organic extract was dried over magnesium sulfate and concentrated at reduced pressure. The residue was subjected to thick-layer chromatography (95:5 dichloromethane–methanol) to afford 0.011 g (22%) of a tan foam: ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 and 1.59 (2 s, $C(CH_3)_2$, 6), 2.00 (m, 2 $H_{5'}$, 2 $H_{7'}$, 2 $H_{8'}$, 6), 3.47 (t, $H_{9'}$, 1), 3.51 (m, $H_{6'}$, 1), 4.29 (m, $H_{4'}$, 1), 5.04 (m, $H_{3'}$, 1), 5.11 (s, CH_2Ph, 4), 5.47 (m, $H_{2'}$, 1), 5.75 (br s, NH_2, 2), 6.01 (br s, $H_{1'}$, 1), 7.28 (m, Ph and H_2 or H_8, 16), 8.33 (s, H_2 or H_8, 1); FDMS (Me_2SO), *m/e* 788 [$(M + Na)^+$], 765 [$(M + 1)^+$], 764 [M^+].

Registry No. **1**, 58944-73-3; **2a**, 38049-07-9; **2b**, 85680-98-4; **2c**, 85680-99-5; **3a**, 85681-00-1; **4**, 43077-06-1; **5a**, 85681-01-2; **6**, 85681-02-3; **7**, 34932-07-5; **8**, 85681-03-4; **9a**, 85681-04-5; **9b**, 85681-05-6; (*R*)-**10a**, 85681-07-8; (*S*)-**10a**, 85681-10-3; (*R*)-**10b**, 85681-06-7; (*S*)-**10b**, 85701-31-1; (*R*)-**10c**, 85681-08-9; (*S*)-**10c**, 85681-09-0; (*R*)-**10d**, 85681-11-4; (*S*)-**10d**, 85681-12-5; β-D-*allo*-**11a**, 85681-13-6; α-L-*talo*-**11a**, 85681-14-7; β-D-*allo*-**11b**, 85681-15-8; α-L-*talo*-**11b**, 85701-32-2; β-D-*allo*-**11c**, 85681-18-1; α-L-*talo*-**11c**, 85681-19-2; β-D-*allo*-**11d**, 85681-16-9; α-L-*talo*-**11d**, 85681-17-0; β-D-*allo*-**11e**, 85681-20-5; α-L-*talo*-**11e**, 85701-33-3; *a*, 85681-21-6; ethyl 2-(ethoxycarbonyl)-5,5-(ethylenedioxy)pentanoate, 23985-06-0; (2-oxotetrahydro-3-furanyl)triphenylphosphonium bromide, 28228-78-6; dibenzyl malonate, 15014-25-2.

Total Synthesis of β-Santalol

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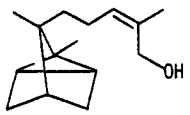
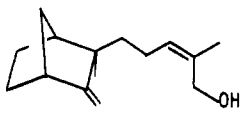
A synthesis of β-santalol (**2**) is described by using camphenesultone (**4**) as the starting material. Alkylation of the sultone **4** with the tetrahydropyranyl ether of 2-bromoethanol (**11**) followed by reaction with phenyllithium and desulfurization with sodium amalgam produced the monoprotected diol **16**. The intermediate **1** was converted to bicycloekasantalal which has been previously transformed into β-santalol (**2**).

There has been considerable interest in recent years in developing syntheses of α-santalol (**1**)[1] and β-santalol (**2**),[2] the main constituents of East Indian sandalwood oil,[3] which are highly prized for their fragrance.



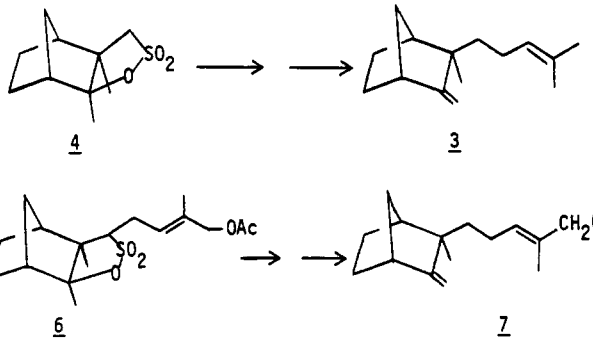
1



2

Work on the construction of β-santalol (**2**) in our laboratory started years ago and resulted in a successful total synthesis of β-santalene (**3**),[4] one of the minor sesquiterpene components of sandalwood oil, on using camphenesultone (**4**) as starting material.

While the alkylation of sultone **4** with *trans*-1-acetoxy-4-bromo-2-methyl-2-butene (**5**)[5] proved successful, attempts to convert the resulting acetate **6** to *trans*-β-santalol (**7**) were disappointing, especially with regard to the very low yields obtained in the desulfurization of **6** on using aluminum hydride–lithium aluminum hydride.[4,6]



4 **3** **6** **7**

We have now turned to a stepwise construction of the allylic alcohol side chain and report a route to bicycloekasantalal (**8**) which has been previously transformed into β-santalol (**2**) with high stereoselectivity.[2b]

In this work, camphenesultone (**4**) was prepared from *d*-10-camphorsulfonic acid (**9**), in 54% overall yield, by reduction with sodium borohydride and conversion to sultone **10** with *p*-toluensulfonyl chloride in pyridine followed by pyrolysis at 126 °C[7] (Scheme I).

(1) (a) Lewis, R. G.; Gustafson, D. H.; Erman, W. F. *Tetrahedron Lett.* **1967**, *401*. (b) Colonge, J.; Descotes, G.; Bahurel, Y.; Menet, A. *Bull. Soc. Chim. Fr.* **1966**, 374. (c) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226. Kamat, S. Y.; Chakravarti, K. K.; Bhattacharyya, S. C. *Tetrahedron* **1967**, *23*, 4487. (e) Julia, M.; Ward, P. *Bull. Soc. Chim. Fr.* **1973**, 3065. (f) Corey, E. J; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314.

(2) (a) Kretschmar, H. C.; Erman, W. F. *Tetrahedron Lett.* **1970**, 41. (b) Christenson, P. A.; Willis, B. J. *J. Org. Chem.* **1979**, *44*, 2012. (c) Sato, K.; Miyamoto, O.; Inove, S.; Honda, K. *Chem. Lett.* **1981**, 1183.

(3) (a) Ruzicka, L.; Thomann, G. *Helv. Chim. Acta* **1935**, *18*, 355. (b) Guenther, E. "The Essential Oils"; D. Van Nostrand: New York, 1952; Vol. V, 173–187.

(4) Wolinsky, J.; Marhenke, R. L.; Lau, R. *Synth. Commun.* **1972**, *2* 165.

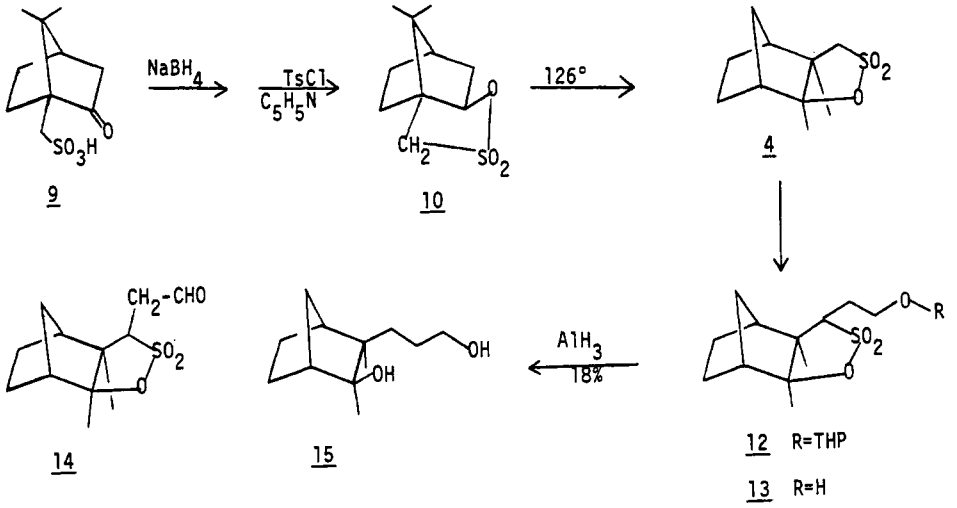
(5) Lau, R. Ph.D. Thesis, Purdue University, 1972.

(6) Smith, M. B.; Wolinsky, J. *J. Org. Chem.* **1981**, *46*, 101.

(7) (a) Wolinsky, J.; Dimmel, D. R.; Gibson, T. W. *J. Org. Chem.* **1967**, *32*, 2087. (b) Dimmel, D. R.; Fu, W. Y. *Ibid.* **1973**, *38*, 3778, 3782.

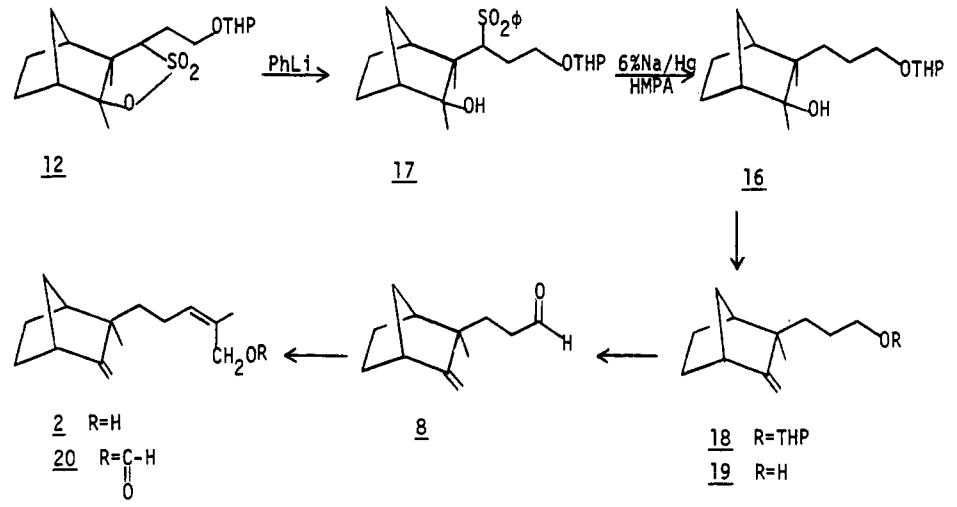
0022-3263/83/1948-1988$01.50/0

Scheme I



9 10 4 14 15 12 R=THP 13 R=H

Scheme II



12 17 16 2 R=H 20 R=C-H (O) 8 18 R=THP 19 R=H

Sultone **4** was alkylated[6,8] with the tetrahydropyranyl ether of 2-bromoethanol (**11**). Attempts to oxidize the alcohol **13**, generated by hydrolysis of **12**, by using Collin's reagent,[9] buffered pyridinium chlorochromate,[10] or the Kornblum[11] procedure failed to produce any noticeable amount of desired aldehyde **14**.[12]

Having failed to oxidize alcohol **13**, attention was directed to its desulfurization to diol **15**. Unfortunately only very small amounts of the desired diol **15** were obtained by exposing the alcohol **13** to excess AlH_3–$LiAlH_4$ complex.

We finally turned to an alternate desulfurization procedure. The THP sultone **12** was treated with an excess of phenyllithium to yield sulfone **17** (Scheme II), which was subsequently desulfurized with 6% sodium amalgam in hexamethylphosphoramide[1e] to give the protected diol **16** in approximately 49% yield from **12**.

Dehydration of **16** with thionyl chloride and pyridine at 0 °C[13] gave the unsaturated pyranyl ether **18**. Hydrolysis of **18**[14] followed by oxidation of the resulting alcohol **19** with Collin's reagent afforded aldehyde **8** in an overall yield of approximately 60% from **16**.

Aldehyde **8** has been converted to β-santalol (**2**) by Kretschmar[2a] and by Willis.[2b] In the Willis approach, a modified Wittig reaction[1d] not only afforded a good yield of the desired allylic alcohol but did so in a stereoselective fashion. In our hands treatment of **8** with ethylidenetriphenylphosphorane followed by addition of 1 equiv of *n*-butyllithium at −78 °C and formaldehyde at 0 °C produced a small amount of **2** (16%) and another compound which by spectral analysis was found to be the formate of β-santalol **20**. Simple treatment of formate **20** with methanol and a few drops of triethylamine converted **20** efficiently to **2**, thereby increasing the overall yield of β-santalol (**2**) from 16% to 51%.

In summary, we have described a reasonably short (seven step) route to β-santalol (**2**) from camphenesultone (**4**).

Experimental Section

All melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Associates A-60 spectrometer or on a Perkin-Elmer Model R-32 spectrometer at 90 MHz. Infrared spectra were obtained with a Perkin-Elmer Infracord Model 137-B.

(8) (a) Durst, T.; du Manior, J. *Can. J. Chem.* **1969**, *47*, 1230. (b) Durst, T. *Tetrahedron Lett.* **1971**, 4171.
(9) Ratcliffe, R.; Rodehorts, R. *J. Org. Chem.* **1970**, *35*, 4000.
(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(11) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.
(12) What appears to be an α,β-unsaturated aldehyde is formed in low yield presumably by a base catalyzed elimination of SO_2 from **14**.
(13) Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.* **1955**, *77*, 1028.
(14) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Chem. Soc.* **1969**, *91*, 4318.

Mass spectra were provided by the Purdue University Mass Spectral Service. Microanalyses were performed by Dr. C. S. Yeh and associates.

Preparation of (±)-Camphenesultone (4). A solution of 46.0 g (0.198 mmol) of *d*-10-camphorsulfonic acid (**9**) in 100 mL of water was cautiously added, with stirring, to 1-L breaker containing 14.0 g (0.37 mol) of solid sodium borohydride. The water was removed by rotary evaporation and the salts dried for 4 h at 110 °C. The dried salts were placed in the thimble of a Soxhlet extractor and extracted for 8 h with refluxing absolute ethanol. The ethanol was removed, and the crude solid was dried for 2 h at 110 °C. The crude solid was dissolved in 80 mL of pyridine, 45 g (0.236 mol) of freshly crystallized *p*-toluenesulfonyl chloride was added, and the mixture was stirred at room temperature for 5 h. The solution was then poured into a slurry of 10 g of ice and 10 mL of water. Water (200 mL) was added, and the mixture was stored at −26 °C. Filtration gave 23.0 g (54%) of 10-isobornyl sultone **10**, mp 114–116 °C.

A suspension of 23.0 g (0.106 mol) of **10** in 500 mL of *n*-octane was refluxed for 18.5 h. The hot yellow solution was decanted and cooled to give a yellow solid. Filtration gave 16 g (64%) of **4**: mp 133–135 °C; NMR ($CDCl_3$) 1.28 (s, 3, CH_3), 1.31 (s, 3, CH_3), 1.50 (br s, 6, CH_2), 2.1 and 2.39 (2 br s, 2, CH), 3.14 ppm (s, 2, CH_2-SO_2).

Tetrahydropyranyl Ether of 2-Bromoethanol (11). A mixture of 11.960 g (0.096 mol) of 2-bromoethanol, 12.071 g (0.144 mol) of dihydropyran, and 1.092 g (0.006 mol) of *p*-toluenesulfonic acid in 120 mL of ether was stirred for 24 h at room temperature. The mixture was washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$), and the ether was removed. Distillation afforded 16 g (80%) of **11**: bp 75 °C (1 mm) [lit.[15] bp 94 °C (14 mm)]; IR (neat) 1124 cm^{-1} (COC); NMR ($CDCl_3$) 1.6 (m, 6, CH_2), 3.35–4.1 (m, 6, CH_2), 4.6 ppm (br s, 1, CH).

Alkylation of Camphenesultone (4) with Bromo Ether 11. To a solution of 0.408 g (1.888 mmol) of freshly sublimed camphenesultone (**4**) in 38 mL of THF was slowly added 1.3 mL (2.067 mmol) of 1.59 M *n*-butyllithium at −78 °C and under argon. The solution was stirred for 10 min and treated with 0.395 g (1.888 mmol) of bromo ether **11** (neat). The solution was stirred at −78 °C for 3 h, and after being warmed to room temperature, it was stirred for an additional 12 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether. The ether extract was washed with water and dried ($MgSO_4$), and the ether was removed to give 0.719 g of crude sultone **12**. Flash chromatography[16] (silica gel, 40% ethyl acetate/hexane) afforded 0.451 g (70% yield) of **12**: IR (neat) 1342 and 1176 cm^{-1} (SO_2); NMR ($CDCl_3$) 1.05 (s, 3, CH_3), 1.45 (br s, 3, CH_3), 2.31 (br, s 1, CH), 3.1–4 (m, 5 H), 4.6 ppm (br s, 1, CH-SO_2); mass spectrum, *m/e* (relative intensity) 345 (1), 262 (4), 261 (36), 179 (4), 163 (0.4), 161 (0.6), 135 (0.4), 123 (0.5), 101 (0.3), 86 (5), 85 (100), 67 (0.5). Anal. Calcd for $C_{17}H_{28}O_5S$: C, 59.28; H, 8.19; S, 9.31. Found: C, 59.18; H, 8.09; S, 9.58.

Reaction of Sultone 12 with Phenyllithium. A solution of 0.119 g (0.347 mmol) of **12** in 1 mL of ether was slowly added to 0.5 mL of 1.6 M phenyllithium in 1 mL of ether. The mixture was stirred at room temperature, under argon, for 6 h. The reaction mixture was poured into a saturated solution of NH_4Cl, and the mixture was extracted with ether. The ether extract was dried ($MgSO_4$), and the ether was removed to give 0.118 g of crude sulfone **17**. Flash chromatography (silica gel, 30% ethyl acetate/pentane) afforded 0.083 g (60% yield) of sulfone **17**: mp 70–75 °C; IR (melt) 3448 (OH), 1299 and 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) 1.28 (s, 3, CH_3), 1.45 (s, 3, CH_3), 4.32 (s, 1, CHO_2), 7.55 and 7.9 ppm (m, 5, C_6H_5); mass spectrum, *m/e* (relative intensity) 405 (1), 321 (7), 197 (11), 179 (9), 178 (4), 161 (6), 137 (4), 135 (8), 125 (5), 109 (6), 105 (4), 95 (7), 93 (8), 85 (100), 77 (13), 67 (24). Anal. Calcd for $C_{23}H_{34}O_5S$: C, 65.37; H, 8.11; S, 7.59. Found: C, 65.16; H, 8.26; S, 7.50.

Desulfurization of Sulfone 17. A solution of 50.7 mg (0.120 mmol) of sulfone **17** in 0.3 mL of absolute ethanol was added at 0 °C to a rapidly stirred mixture of 1.1 mL of hexamethylphosphoramide (HMPA), 0.420 g of 6% Na/Hg, and 0.18 mL of ethanol under argon. After being stirred 40 min at 0 °C, the solution was added rapidly to water and extracted with ether. The ether extract was dried ($MgSO_4$), and the ether was removed to give 36.1 mg of crude THP alcohol **16**. Flash chromatography (silica gel, 30% ethyl acetate/pentane) afforded 27.7 mg (82% yield) of alcohol **16**: IR (neat) 3460 cm^{-1} (OH); NMR ($CDCl_3$) 0.85 (s, 3, CH_3), 1.15 (s, 3, CH_3), 3.2–4.05 (m, 4 H) and 4.55 ppm (br m, 1, CHO_2); mass spectrum, *m/e* (relative intensity) 199 (6), 181 (5), 163 (8), 137 (8), 130 (10), 121 (3), 109 (9), 97 (3), 95 (6), 93 (5), 86 (5), 85 (100), 81 (7), 71 (6), 67 (14).

Dehydration of Alcohol 16. To a stirred solution of 0.102 g (0.361 mmol) of alcohol **16** in 0.2 mL pyridine at 0 °C was slowly added 0.03 mL of thionyl chloride. The mixture was stirred for 5 h at 0 °C under argon. The reaction mixture was poured into ice-cold saturated $NaHCO_3$ solution and extracted with methylene chloride. The methylene chloride extract was dried ($MgSO_4$), and the solvent was removed to give 96.6 mg of crude **18**. Flash chromatography (silica gel, 30% ethyl acetate/pentane) afforded 74.9 mg (79% yield) of alkene **18**: IR (neat) 1639 (C=C), 885 cm^{-1} (=CH_2); NMR ($CDCl_3$) 1.02 (s, 3, CH_3), 2.15 (br s, 1, CH), 3.2–4.05 (m, 4, CH_2O), 4.49 and 4.75 (2 s, 2, C=CH_2), 4.6 ppm (br m, 1, CHO_2); mass spectrum, *m/e* (relative intensity) 264 (9), 247 (1), 218 (0.5), 182 (5), 181 (52), 179 (1), 165 (0.5), 163 (2), 161 (0.5), 112 (0.6), 86 (3), 85 (100). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.17; H, 10.91.

3-(2-*endo*-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-propan-1-ol (19). A solution of 0.370 g (1.402 mmol) of alkene **18** in 5 mL of a 2.8 mM solution of *p*-toluenesulfonic acid in methanol was stirred at 0 °C under argon for 1 h and at room temperature for 2 h. $NaHCO_3$ (1 g) was added to the reaction mixture, and the majority of the methanol was removed by rotary evaporation. The residue was taken up in ether, and the ether was washed with water. The ether was dried ($MgSO_4$) and removed to give 0.266 g of crude alcohol **19**. Flash chromatography (silica gel, 30% ethyl acetate/pentane) afforded 0.213 g (84% yield) of alcohol **19**: IR (neat) 3333 cm^{-1} (OH), 1664 (C=C), 877 cm^{-1} (=CH_2); NMR ($CDCl_3$) 1.02 (s, 3, CH_3), 2.05 and 2.65 (2 br s, 2, CH), 2.59 (t, 2, J = 7 Hz, CH_2O), 4.45 and 4.72 ppm (2 s, 2, C=CH_2); mass spectrum, *m/e* (relative intensity) 180 (0.2), 149 (0.8), 147 (0.9), 137 (0.6), 133 (0.9), 124 (4), 123 (67), 122 (22), 121 (64), 112 (3), 105 (9), 95 (15), 94 (53), 93 (100), 91 (41). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.96; H, 11.16.

3-(2-*endo*-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-propanal (8). To a solution of 0.710 g (7.103 mmol) of chromium trioxide, 1.1 mL of pyridine, and 1.8 mL of methylene chloride (which had been previously stirred for 15 min) was added in one portion a solution of 0.213 g (1.184 mmol) of **19** in a small amount of methylene chloride. The mixture was stirred under argon for 15 min at room temperature. The yellow solution was decanted from the black residue which was washed with ether. The combined organic solutions were passed through a short plug of Florisil, washed with 5% NaOH solution and saturated NaCl solution, and dried ($MgSO_4$), and the solvents were removed to give 0.0175 g (83% yield) of aldehyde **8**: IR (neat) 2740 (O=CH), 1730 (C=O), 1667 (C=C), 887 cm^{-1} (=CH_2); NMR ($CDCl_3$) 1.02 (s, 3, CH_3), 2.0 and 2.65 (br s, 2, CH), 4.5 and 4.8 (2 s, 2, C=CH_2), 9.75 ppm (t, 1, J = 2 Hz, CHO).

Preparation of β-Santalol (2). To a stirred suspension of 0.332 g (0.894 mmol) of ethyltriphenylphosphonium bromide in 7.3 mL of THF at 0 °C and under argon was added 0.81 mL of 1.1 M *n*-butyllithium in hexane. After the mixture showed a negative Gilman test, the solution (deep orange) was cooled to −76 °C, and a solution of 0.159 g (0.894 mmol) of aldehyde **8** in 1 mL of THF was added dropwise. After the mixture was stirred 15 min at −78 °C, 0.81 mL of 1.1 M *n*-butyllithium was added, and the deep burgandy solution was allowed to warm to 0 °C in 3 h. To this solution was added 0.165 g (5.521 mmol) of dry paraformaldehyde in one portion and the reaction mixture was allowed to stir for 20 h at room temperature. The mixture was poured into saturated NH_4Cl solution and extracted with methylene chloride. The methylene chloride extract was dried ($MgSO_4$), and the solvent was removed by rotary evaporation to give 0.435 g of crude **2**. Flash chromatography (silica gel, CH_2Cl_2) afforded 97.4 mg (43% yield of formate **20**: IR (neat) 1730 (C=O), 1664 (C=C), 1156 (CO), 876 cm^{-1} (=CH_2); NMR ($CDCl_3$) 1.05 (s, 3, CH_3), 2.65 (br s, 1, CH), 4.45 and 4.74 (2 s, 2, C=CH_2), 4.7 (s, 2, CH_2O), 5.42 (br t, 1, CH=C), and 8.12 ppm (s, 1, OC(O)H).

(15) Parham, W. E.; Anderson, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 4187.
(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Later fractions gave 30.6 mg (16% yield) of β-santalol (2): IR (neat) 3333 (OH), 1664 (C=C), 877 cm^{-1} (=CH_2); NMR ($CDCl_3$) 1.05 (s, 3, CH_3), 1.78 (br s, 3, CH_3), 2.65 (br s, 1, CH), 4.12 (s, 2, CH_2O), 4.45 and 4.73 (2 s, 2, C=CH_2), 5.29 ppm (br t, 1, CH=C).

A mixture of 97.4 mg of **20**, 1 drop of triethylamine, and 10 mL of methanol was stirred at room temperature for 12 h. The solvents were removed by rotary evaporation, and the residue was placed on a vacuum pump at 0.1 mm for 3 h. This produced 85.8 mg of crude **2** (~80% purity by NMR).

Registry No. (±)-**2**, 27542-07-0; (±)-**4**, 85648-03-9; *d*-**9**, 3144-16-9; **10**, 41348-33-8; **11**, 17739-45-6; **12**, 85612-75-5; **13**, 85612-76-6; (±)-**15**, 85612-77-7; (±)-**16**, 85612-78-8; **17**, 85612-79-9; 2-bromoethanol, 540-51-2; dihydropyran, 110-87-2.

Reductive Transformation and Cyclopropanation of Mevinolin (6α-Methylcompactin). Generation of Chirality in the 1,4-Hydrostannation of a Cyclic Diene

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Conversion of mevinolin by direct reductive procedures as well as by indirect chemical transformations has permitted the preparation of the various di- and tetrahydro derivatives. Cyclopropanation of mevinolin and its derivatives has furnished mono- and dicyclopropanated analogues. These compounds are themselves bioactive to a varying degree as hypocholesterolemic agents.[2b]

Mevinolin or 6α-methylcompactin (1) isolated from *Aspergillus terreus*, is a potent HMG-CoA reductase inhibitor and as such is an effective hypocholesterolemic agent.[1,2a] Conversion of this substance by direct reductive procedures, as well as by indirect chemical transformations, has permitted preparation of the various di- and tetrahydro derivatives, themselves bioactive to a comparable degree with the parent compound.[2b]

Hydrogenation of mevinolin (1) in toluene solution by employing Wilkinson's catalyst produced a 9:1 mixture of 3,4-dihydro (2) and 3,5-dihydro (3) derivatives, respectively[3] (Scheme I), readily separable as their *tert*-butyldimethylsilyl ethers by HPLC. Hydrogenation of 1 in ethanol over palladium on calcium carbonate, on the other hand, proceeded in the opposite sense to a predominant extent to yield the 3,5-dihydro derivative **3** together with varying amounts of the 3,4-dihydro isomer. Depending on the catalyst, nearly exclusive formation of **3** is achievable by this technique. Finally, hydrogenation of 1 with platinum oxide in ethyl acetate yielded the tetrahydro derivative as a mixture (1:3) of *cis*- and *trans*-decalin isomers **4** and **5**, respectively. This mixture in the form of its *tert*-butyldimethylsilyl ethers could be separated by TLC or HPLC on silica gel to give the individual isomers in pure form.

An alternative reductive procedure which converts 1, in effect, exclusively to the 3,5-dihydro derivative **3** consists of the treatment of *tert*-butyldimethylsilyl)mevinolin **1b** with triethylsilane in methylene chloride[4] followed by protolysis with trifluoroacetic acid. This isomer, namely, **3a**, is important in the synthesis of the 4a,5-dihydro isomer vide infra.

The most elusive isomer to prepare synthetically is the 4a,5-dihydro system which also occurs as a congener together with mevinolin from the fermentation process.[5] Several routes to this dihydro compound via chemical sequences have been effected successfully; however, these approaches have all given, for the most part, the *cis*-octalin rather than the natural *trans*-octalin.

Three routes to 4a,5-dihydromevinolin were realized, and only one provided the natural trans isomer in ca. 10% yield. Thus, treatment of the *tert*-butyldimethylsilyl derivative of mevinolin (**1b**) with 1 equiv of osmium tetraoxide in pyridine yielded, on reductive workup, the 3α,4α-diol **6** (65% conversion yield) together with tetrol **7** (Scheme II). Assignment of the α-cis orientation of the hydroxyl functions is based on steric approach considerations, the α side of the molecule at the pertinent site appearing to be the more accessible. In addition, hydrogenation of both **6** and its corresponding acetonide derivative **6a** proceeded in the same directional sense. This was ascertained by the conversion of both series via the corresponding thionocarbonate derivative **9**, followed by pyrolysis at 110 °C in triethyl phosphite **6** and subsequent desilylation to give a 9:1 mixture of the cis vs. trans dihydro isomers **10a** and **11a**, respectively. The fact that the diol and its acetonide both hydrogenated in the same directional sense would appear to disallow any special orientation preference in the diol above and beyond a steric one. Significant, moreover, is the fact that hydrogenation of **6** in cyclohexane led virtually exclusively to **10**. Hydrogenation in nonpolar solvents is presumed to favor maximally the course of hydrogenation from the same side as the hydroxyl functions, a consequence completely contradicted in the present instance. It has further been observed that

(1) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirschfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, (7), 3957.

(2) (a) Endo, A. *J. Antibiot.* **1979**, *32*, 852; **1980**, *33*, 334. (b) The results of biological studies on these and related systems will be published elsewhere.

(3) Numberical designations are those employed in ref 1 for the naphthanoid system.

(4) Jogdao, P. S.; Bhide, G. V. *Steroids* **1980**, *35* (2), 133.

(5) Compare: Albers-Schonberg, G.; Joshua, H.; Lopez, M. B.; Hensens, O.D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Patchett, A. A. *J. Antibiot.* **1981**, *34*, 507.

(6) Prinzbach, H.; Babsch, H. *Angew. Chem., Intl. Ed. Engl.* **1975**, *14*, 753.

0022-3263/83/1948-1991$01.50/0