Notes

Nonenzymatic Asymmetric Synthesis of (*R*)-(−)- and (*S*)-(+)-Mevalolactone in High Enantiomeric Purity

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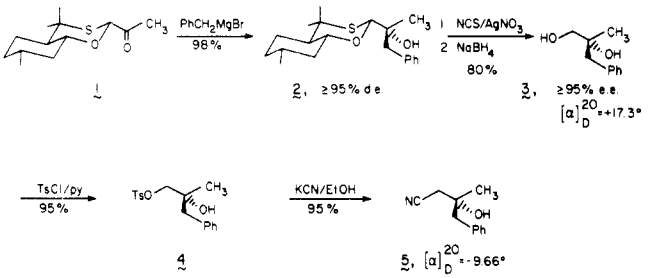
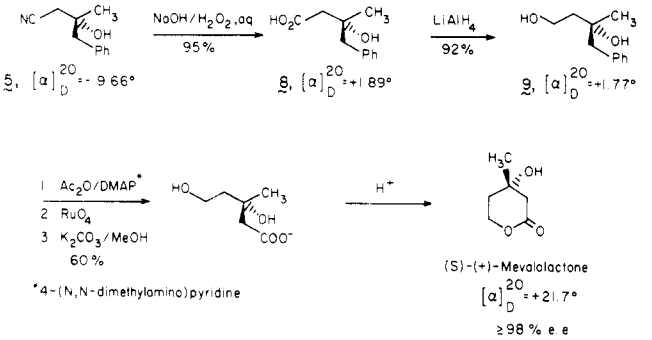
Mevalolactone, the biosynthetic percursor of most terpenoids and steroids, was discovered, had its structure elucidated, and was synthesized and resolved by Folkers and co-workers.[1] Eberle and Arigoni[2] showed that the naturally occurring (−) isomer has the *R* configuration by correlation of the (+) enantiomer with (−)-quinic acid. Cornforth et al.[3] synthesized both enantiomers in essentially 100% enantiomeric excess (ee) from (+)- and (−)-linalool. Since then several enzymatic syntheses starting from achiral precursors have been published.[4-7] Chemical transformation of (*S*)-glutamic acid yields mevalolactone in essentially 100% ee[8] but two nonenzymatic asymmetric syntheses from achiral starting materials[9,10] produced material in only 17 and 58% ee, respectively.[18] One of us, in a preliminary publication,[11] has disclosed the synthesis of (*R*)-(−)-mevalolactone in high enantiomeric purity, but attempts to improve the yield in this preparation foundered because the last step (hydroboration–oxidation of a vinyl to a β-hydroxyethyl compound) could not be made to proceed cleanly.[12]

We have now developed an asymmetric synthesis of both (*R*)-(−)- and (*S*)-(+)-mevalolactone in over 98% ee through the common intermediate (*R*)-(−)-3-hydroxy-3-methyl-4-phenylbutanonitrile (**5**, Scheme I). This compound is available in three steps from the previously synthesized[11,13] (2*R*,4a*S*,7*R*,8a*R*)-2-acetyl-4,4,7-trimethyl-4a,5,6,7,8,8a-hexahydrobenzoxathiane (**1**).[14] The intermediate is converted into (*S*)-(+)-mevalolactone in three steps as shown in Scheme II (overall yield from 1 38%) or in three steps into (*R*)-(−)-mevalolactone as shown in Scheme III (overall yield 41%). The enantiomeric purity of each isomer was estimated to be in excess of 98% using the chiral shift reagent method described by Wilson et al.[15] with controls to check its sensitivity.

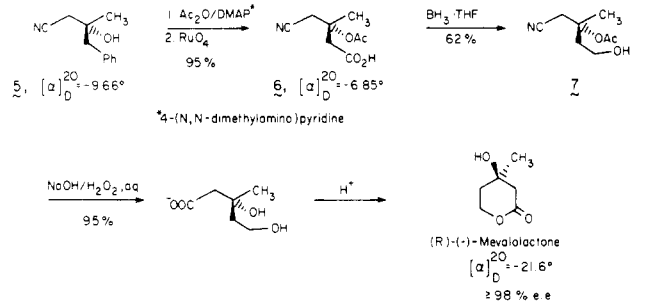
Scheme I



Scheme II



Scheme III



Experimental Section

Proton and carbon-13 NMR spectra were recorded on a Bruker WM-250 (250 MHz or 62.89 MHz) spectrometer equipped with an Aspect 2000 computer. Chemical shifts are expressed as parts per million dowfield from internal tetramethylsilane (Me_4Si); coupling patterns are designated s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet).

IR spectra were obtained as dilute (1–5%) solutions in 0.5-mm sodium chloride cavity cells, as neat liquid films, or as Nujol muls between sodium chloride plates on a Beckman 4250 spectrometer and were calibrated with the 1601-cm^{-1} band of polystyrene.

(1) Folkers, K.; Shunk, C. H.; Linn, B. O.; Robinson, F. M.; Wittreich, P. E.; Huff, J. W.; Gilfillan, J. L.; Skeggs, H. R. "Discovery and Elucidation of Mevalonic Acid" in Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols; Wolstenholme, G. E. W., O'Connor, M., Eds.; J. S. A. Churchill, Ltd: London, 1959; pp 20–43.
(2) Eberle, M.; Arigoni, D. *Helv. Chim. Acta* **1960**, 43, 1508.
(3) Cornforth, R. H.; Cornforth, J. W.; Popjak, G. *Tetrahedron* **1962**, *18*, 1351.
(4) Huang, F.-C.; Lee, L. F. H.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J.; Caspi, E.; Eck, C. R. *J. Am. Chem. Soc.* **1975**, *97*, 4144.
(5) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556.
(6) Ohta, H.; Tetsukawa, H.; Noto, N. *J. Org. Chem.* **1982**, *47*, 2400.
(7) Francis, C. J.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 579.
(8) Takano, S.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 82.
(9) Abushanab, E.; Reed, D.; Suzuki, F.; Sih, C. J. *Tetrahedron Lett.* **1978**, 3415.
(10) Kawakami, Y.; Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1984**, 779.
(11) Eliel, E. L.; Soai, K. *Tetrahedron Lett.* **1981**, *22*, 2859.
(12) T. Kogure, unpublished observations.
(13) Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333.
(14) The synthesis of the precursor (4a*S*,7*R*,8a*R*)-4,4,7-trimethyl-4a,5,6,7,8,8a-hexahydro-1,3-oxathiane has been accepted for checking in *Organic Synthesis*. Directions may be obtained from E.L.E. upon request.
(15) Wilson, W. K.; Scallen, T. J.; Morrow, C. J. *J. Lipid Res.* **1982**, *23*, 645.

0022-3263/85/1950-3402$01.50/0

Intensities are reported as a (strong), m (medium), w (weak), and b (broad).

Optical rotations were measured on a Perkin-Elmer 141 polarimeter equipped with sodium and mercury light sources by using a 1-dm thermostated cell; reported temperatures are uncorrected.

Melting points were observed on an Electrothermal melting point apparatus and are uncorrected.

Acyloxathiane 1. To the optically pure parent oxathiane[14] (1 g, 5 mmol) in absolute THF (10 mL) at −78 °C under N_2 was added, dropwise, 1.6 M *n*-BuLi (3.25 mL, 5.2 mmol) in hexane. After being stirred for 3 min, the solution was allowed to warm to 0 °C and was immediately recooled to −78 °C. Acetaldehyde (440 mg, 10 mmol) in THF (5 mL) was then added dropwise over 1 h. After being stirred at −78 °C 2 h longer, the solution was allowed to stand overnight at −25 °C. Water (1 mL) and saturated NH_4Cl (1 mL) were then added, the layers separated, and the organic layers dried ($MgSO_4$) and concentrated to give a clear oil (1.21 g, 100% crude). Next, to a cold (−78 °C) solution of dry Me_2SO (450 mg, 5.75 mmol) in dry CH_2Cl_2 (5 mL) under N_2 was added, dropwise, TFAA (1.20 g, 5.70 mmol) in dry CH_2Cl_2 (7 mL), and the resulting solution stirred for 0.5 h. The carbinol obtained above was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise to the oxidant solution, the reaction was allowed to stir for 2 h, triethylamine (1.21 g, 12 mmol) added, and the solution was allowed to warm to 0 °C. It was then poured into 5% aqueous HCl (50 mL) and shaken thoroughly; the organic layer was washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), concentrated and flash chromatographed (8% EtOAc/hexane) to give a clear oil (970 mg, 80%) which crystallized on standing. Recrystallization from EtOH/pentane provided an analytical sample: mp 45.0–45.5 °C; $[\alpha]^{25}_D$ +91.7° (*c* 3.05, 95% EtOH); ^1H NMR ($CDCl_3$) δ 5.44 (s, 1 H), 3.42 (m, 1 H), 2.28 (s, CH_3), and others; ^{13}C NMR ($CDCl_3$) δ 203.4, 82.8, 76.9, 50.4, 43.9, 41.6, 34.7, 31.4, 29.4, 25.6, 24.3, 22.5, 22.1; IR (CH_2Cl_2) cm^{-1} 2920, 2860, 1735, 1354, 1146, 1090, 1070, 1015. Anal. Calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15; S, 13.23. Found: C, 64.60; H, 9.34; S, 13.20.

Carbinol 2. To magnesium turnings (100 mg, 4 mmol) in absolute ether (2 mL) at 0 °C under N_2 was added, dropwise, benzyl bromide (340 mg, 2 mmol) in ether (3 mL). This mixture was sonicated for 0.5 h and then added via a double-ended needle to a cold (−78 °C) solution of acyloxathiane **1** (100 mg, 0.4 mmol) in absolute THF (10 mL) under N_2. The resulting solution was stirred overnight and allowed to warm to room temperature at which time H_2O (5 mL) and saturated NH_4Cl (5 mL) were added, and the mixture was stirred until two clear layers formed. The organic layer was washed with brine (15 mL), the combined aqueous layers were extracted with ether (20 mL), and the combined organic solution was dried ($MgSO_4$) and concentrated, giving **2** as an oil, 130 mg (97%). Distillation (Kugelrohr, bp ca. 200 °C/0.1 mm) provided an analytical sample: ^1H NMR ($CDCl_3$) δ 7.23 (m, 5 H), 4.61 (s, 1 H), 3.28 (dt, *J* = 4, 11 Hz, 1 H), 2.90 (d, *J* = 13 Hz, 1 H), 2.81 (d, *J* = 13 Hz, 1 H), 2.66 (s, 1 H), 1.29 (s, CH_3), 1.26 (s, CH_3), 1.23 (s, CH_3), 0.91 (d, *J* = 6 Hz, 3H), and others; ^{13}C NMR ($CDCl_3$) δ 136.9, 130.6, 127.6, 126.2, 83.9, 77.3, 74.1, 50.8, 44.3, 43.0, 41.6, 34.6, 31.3, 29.7, 24.2, 23.5, 22.6, 22.0. No signals due to the diastereomer[22] were observed. Anal. Calcd for $C_{20}H_{30}O_2S$: C, 71.81; H, 9.04. Found: C, 71.63; H, 9.09.

(*R*)-(+)-2-Methyl-3-phenyl-1,2-propanediol (3). Carbinol **2** (830 mg, 2.5 mmol) in CH_3CN (6 mL) and ether (3 mL) was added to 80% CH_3CN/H_2O (30 mL) which contained $AgNO_3$ (850 mg, 5.0 mmol) and *N*-chlorosuccinimide (670 mg, 5.0 mmol). A grey-white precipitate (AgCl) formed immediately and the mixture was stirred for 5 min and quenched by addition of Na_2SO_3, Na_2CO_3, and NaCl (3 mL each, all saturated solutions) at ca. 2-min intervals. The material was then filtered, the filter cake was washed with CH_3CN (20 mL), the combined solutions were placed in a flash, and $NaBH_4$ (500 mg, 13 mmol) was added slowly with vigorous foaming and black precipitate (Ag) formation. The mixture was stirred for 1 h and acetone (5 mL) was added. The material was then filtered through Celite, ether (10 mL) was added, the layers were separated, and the organic solutions were dried ($MgSO_4$), concentrated, and flash chromatographed (50% EtOAc/hexane) to give, in order of elution, the sultine and diol **3** (325 mg, 80%). The diol **3** crystallized upon standing and recrystallization from 10% ether/pentane provided an analytical sample: mp 66.5–67.5 °C; $[\alpha]^{20}_D$ +17.3° (*c* 1.121, 95% EtOH); ^1H NMR ($CDCl_3$) δ 7.23 (m, 5 H), 3.44 (d, *J* = 11 Hz, 1 H), 3.39 (d, *J* = 11 Hz, 1 H), 2.78 (s, 3 H), 1.10 (s, CH_3). A chiral shift experiment[16] ($Eu(hfc)_3$) with the optically active diol **3** (before recrystallization) and with the racemic diol **3** (prepared by condensation of $C_6H_5CH_2MgBr$ with acetol) as a control did not show the minor enantiomer, suggesting ≳95% ee. ^{13}C NMR ($CDCl_3$) δ 137.1, 130.4, 128.2, 126.5, 73.1, 69.1, 44.7, 23.4. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.96; H, 8.62.

(*R*)-(−)-3-Hydroxy-3-methyl-4-phenylbutanonitrile (5). TsCl (900 mg, 4.7 mmol) in pyridine (3 mL) was added to the recrystallized optically active diol **3** (630 mg, 3.8 mmol) in pyridine (2 mL) at 0 °C under N_2. This solution was stirred for 0.5 h and then placed in a refrigerator overnight. Next the solution was poured into ice water (20 mL), the water was extracted with ether (4 × 15 mL), and the combined ether layers were washed with 4 N HCl (2 × 20 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (40% EtOAc/hexanes) to give 1.12 g (95%) of tosylate **4** and 20 mg of recovered diol **3**. The tosylate **4** was dissolved in 60% $EtOH/H_2O$ (10 mL) at 0 °C, KCN (1.14 g, 17 mmol) was added and the solution was allowed to warm to room temperature. After being stirred for 10 h, the solution was concentrated, brine was added (10 mL), the liquid was extracted with $CHCl_3$ (5 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give 586 mg (92% from the diol **3**) of the hydroxy nitrile **5** which crystallized on standing. Recrystallization from 10% ether/pentane provided an analytical sample: mp 101.5–103.0 °C; $[\alpha]^{20}_D$ −9.69° (*c* 1.481, 95% EtOH). [The corresponding racemic nitrile (prepared by condensation of the lithium salt of acetonitrile with phenylacetone) had mp 77.8–78.5 °C after three recrystallizations and is very probably a conglomerate.[17]]; ^1H NMR ($CDCl_3$) δ 7.23 (m, 5 H), 2.90 (d, *J* = 11 Hz, 1 H), 2.87 (d, *J* = 11 Hz, 1 H), 2.46 (d, *J* = 15 Hz, 1 H), 2.44 (d, *J* = 15 Hz, 1 H), 1.37 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.0, 130.5, 128.7, 127.3, 117.9, 71.9, 47.5, 30.7, 27.0; IR (Nujol) cm^{-1} 3500–3300 (s), 2900 (m), 2250 (m), 1600 (m). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.37; H, 7.44.

(*S*)-(−)-3-Acetoxy-4-cyano-3-methylbutanoic Acid (6). Hydroxy nitrile **5** (230 mg, 1.3 mmol) was added to Ac_2O (10 mL) containing 4-(dimethylamino)pyridine (DMAP, 50 mg, 30 mol %), the resulting solution was heated to 95 °C, and the reaction was followed by TLC (30% EtOAc/hexanes). After 6.5 h the reaction was complete (two spots on TLC, R_f 0.7 product, R_f 0.1 DMAP) so the solution was cooled to 0 °C, poured into ice water (20 mL), stirred for 1 h, and extracted with CH_2Cl_2 (5 × 25 mL). The combined extracts were washed with saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated, eventually at 50 °C/0.1 mm to give 280 mg (99%) of the acetylated hydroxy nitrile. This oil was dissolved in a mixture of CH_3CN (5 mL), CCl_4 (5 mL), and H_2O (12 mL), and $NaIO_4$ (5.6 g, 26 mmol) and $RuCl_3$ (50 mg, 15 mol %) were added sequentially. The mixture was heated at 70 °C for 14 h, cooled, and filtered through Celite, the filter pad was washed with CH_2Cl_2 (10 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic solutions were then dried ($MgSO_4$), concentrated, diluted with ether (which precipitates dissolved Ru complexes), filtered through silica, and concentrated to give 250 mg (95%) of the acid **6** as a strong smelling yellow oil: $[\alpha]^{20}_D$ −6.85° (*c* 4.461, 95% EtOH); ^1H ($CDCl_3$) δ 9.25 (s, 1 H), 3.27 (d, *J* = 15

(16) Sullivan, G. R. *Top. Stereochem.* **1978**, *10*, 287.

(17) Jacques, J.; Collet, A.; Wilen, S. H. "Enantiomers, Racemates and Resoltuions", Wiley: 1981, Chapter 2.2; Wilen, S. H., personal communication.

(18) After this paper was submitted, we learned of the asymmetric synthesis of (*R*)-(−)-mevalolactone, 81.8–85% e.e. by Mori and Okada,[19] in 38.7% overall yield from (*E*)-4-chloro-3-methyl-2-buten-1-ol and of the synthesis of both (*R*)-(−)- and (*S*)-(+)-mevalolactone (88–89% e.e.) by Bonadies et al.[20] in 28.7% yield from 3-methyl-2-pentenolactone. In both syntheses the asymmetric epoxidation procedure of Katsuki and Sharpless[21] was employed.

(19) Mori, K.; Okada, K. *Tetrahedron* **1985**, *41*, 557.

(20) Bonadies, F.; Rossi, B.; Bonini, C. *Tetrahedron Lett.* **1984**, *25*, 5431.

(21) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(22) This diastereomer has been prepared in connection with another problem [Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.*, in press] and shows substantial differences in the C-13 and proton spectra.

Hz, 1 H), 3.13 (d, J = 15 Hz, 1 H), 3.08 (m, 2 H), 2.09 (s, CH_3), 1.72 (s, CH_3); IR (neat) cm^{-1} 3600–2800 (mb), 2950 (s), 2250 (m), 1740 (s), 1400 (m), 1260 (s), 1100–1000 (s).

(*R*)-(−)-Mevalolactone. A solution of BH_3·THF (1.2 mL, 1 M) was added to the acid **6** (225 mg, 1.2 mmol) dissolved in THF (12 mL) under N_2 at −50 °C. The solution was allowed to warm to room temperature and stirred for 20 h. Next H_2O (5 mL) and K_2CO_3 were added, the mixture stirred for a few minutes, the layers were separated, and the aqueous layer was extracted with ether (5 × 10 mL). The combined extracts were then washed with saturated NH_4Cl (20 mL), dried ($MgSO_4$), and concentrated to give 210 mg of a mixture of the desired **7** (63% by ^1H NMR) and other compounds. [The optically active material was carried on to mevalolactone without purification at this stage; however, racemic **7**, prepared from racemic **5**, was purified (flash chromatography 50% EtOAc/hexanes) to allow estimation of the yield in the optically active compound by ^1H NMR analysis of the mixture obtained. Purified racemic **7**: ^1H NMR ($CDCl_3$) δ 4.29 (t, J = 6 Hz, 2 H), 2.62 (s, 3 H), 2.09 (s, CH_3), 2.00 (dt, J = 4 Hz, 7 Hz, 2 H), 1.42 (s, CH_3); IR (neat) cm^{-1} 3500 (s), 2950 (m), 2250 (m), 1740 (s), 1400 (m), 1250 (s).] The impure optically active **7** (ca. 0.75 mmol) was hydrolized with a mixture of 3 N NaOH (5 mL) and 30% H_2O_2 (1.7 mL) by heating at 70 °C for 6 h. The solution was then cooled to 0 °C, acidified to pH 3 with 6 N HCl, let stir 0.5 h, and continously extracted with $CHCl_3$ for 16 h. The $CHCl_3$ extract was dried ($MgSO_4$), concentrated, and flash chromatographed (100% EtOAc) to give 90 mg (58% from acid **7**) of pure (*R*)-(−)-mevalolactone: $[\alpha]^{20}_D$ −21.6° (*c* 1.565, 95% EtOH) [lit. $[\alpha]^{20}_D$ −23.0° (*c* 6, EtOH)[3]]. The ^1H NMR of this compound was identical with that of a sample of racemate purchased from the US Biological Corporation. A chiral shift experiment following the method of Wilson, Scallen, and Morrow[15] revealed no *S* isomer in the material. Addition of 7% of the racemate and integration of the upfield wing of the AB pattern from the CH_2 α to the carbonyl following Lorentzian to Gaussian line-shape transformation indicated ≥98% ee.

(*R*)-(+)-3-Hydroxy-3-methyl-4-phenylbutanoic Acid (8). A mixture of 3 N NaOH (12 mL) and 30% H_2O_2 (4.5 mL) was added to hydroxy nitrile **5** (330 mg, 1.9 mmol), and the mixture was heated at 65 °C for 1 h and then at 100 °C for 1 h and allowed to cool to room temperature over 1 h. Next the solution was cooled to 0 °C, 6 N HCl was added until the material was acidic, the resulting aqueous suspension was extracted with ether (4 × 20 mL), and the ether was dried ($MgSO_4$) and concentrated to give 350 mg (95%) of **8**, a strong smelling oil, pure by TLC: $[\alpha]^{20}_D$ +1.89° (*c* 1.214, 95; EtOH); ^1H NMR ($CDCl_3$) δ 7.80 (s, 2 H), 7.23 (m, 5 H), 2.88 (s, 2 H), 2.56 (d, J = 15 Hz, 1 H), 2.48 (d, J = 15 Hz), 1.28 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.0, 136.6, 130.5, 128.2, 126.7, 71.7, 47.9, 44.2, 26.8; IR (neat) cm^{-1} 3600–2900 (sb), 1710 (s), 1600 (w).

(*R*)-(+)-3-Methyl-4-phenyl-1,3-butanediol (9). Acid **8** (150 mg, 0.78 mmol) was dissolved in absolute THF (10 mL) under N_2, $LiAlH_4$ (ca. 200 mg) was added via a powder addition tube, and the mixture refluxed for 2.5 h. The material was then cooled to 0 °C and quenched with saturated NH_4Cl, the salts were dissolved with concentrated HCl, the layers were separated, and the aqueous layer was extracted with ether (4 × 20 mL). The combined organic solution was washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (50% EtOAc/hexanes) to give 118 mg (92%) of **9**, a clear oil; $[\alpha]^{20}_D$ +1.77° (*c* 1.811, 95% EtOH); ^1H NMR ($CDCl_3$) (as the bis-trifluoroacetate) δ 7.26 (m, 5 H), 4.48 (t, J = 6 Hz, 2 H), 3.28 (d, J = 14 Hz, 1 H), 3.16 (d, J = 14 Hz, 1 H), 2.42 (m, 1 H), 2.27 (m, 1 H), 1.58 (s, CH_3).

(*S*)-(+)-Mevalolactone. The diacetate of diol **9** (360 mg, 1.4 mmol) was formed in the same fashion as the acetate derivative of **6** and was dissolved in a mixture of CH_3CN (6 mL), CCl_4 (6 mL), and H_2O (15 mL) and then $NaIO_4$ (5.7 g, 27 mmol) and $RuCl_3$ (50 mg, 15 mol %) were added sequentially to this mixture. The material was stirred at 70 °C for 14 h, cooled to room temperature, and worked up as before to give 317 mg of crude material (95% pure by ^1H NMR). [Racemic material was purified at this stage: ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 4.18 (m, 2 H), 3.06 (d, J = 15 Hz, 1 H), 2.94 (d, J = 15 Hz, 1 H), 2.37 (m, 1 H), 2.16 (m, 1 H), 2.04 (s, CH_3), 2.01 (s, CH_3), 1.58 (s, CH_3).] The crude diacetate of mevalonic acid (ca. 1.3 mmol) obtained above was dissolved in 90% MeOH (20 mL), K_2CO_3 (1 g, 7 mmol) was added, and the mixture was stirred overnight at 70 °C. Next the MeOH was removed, H_2O (10 mL) was added, and the solution was cooled to 0 °C, acidified to pH 3 with 6 N HCl, and continuously extracted with $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$), concentrated, and flash chromatographed (100% EtOAc) to give 105 mg (60% from diol **9**) of pure (*S*)-(+)-mevalolactone: $[\alpha]^{26}_D$ +21.7° (*c* 0.751, 95% EtoH) [lit. $[\alpha]^{20}_D$ +22.8° (*c* 10, EtOH)[3]]; ^1H NMR identical with racemate. A chiral shift experiment (vide supra) indicated ≥98% ee.

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Registry No. **1**, 79563-75-0; **1** (carbinol), 79563-69-2; **2**, 96948-91-3; **3**, 96948-92-4; (±)-**3**, 96998-28-6; **3** (aldehyde), 96949-05-2; **4**, 96948-93-5; **5**, 96948-94-6; (±)-**5**, 96998-29-7; **5** (acetate), 96948-95-7; (±)-**5** (acetate), 96998-30-0; **6**, 96948-96-8; (±)-**6**, 96998-31-1; **7**, 96948-97-9; (±)-**7**, 96998-32-2; **8**, 96948-98-0; (±)-**8**, 96998-33-3; **9**, 96948-99-1; (±)-**9**, 96998-34-4; **9** (bis-trifluoroacetate), 96949-00-7; **9** (diacetate), 96949-01-8; (±)-**9** (diacetate), 96998-35-5; $HOCH_2COCH_3$, 116-09-6; $LiCH_2CN$, 55440-71-6; $PhCH_2COCH_3$, 103-79-7; (*S*)-mevalonic acid diacetate, 96949-02-9; (±)-mevalonic acid diacetate, 96998-36-6; sodium (*R*)-mevalonate, 96949-03-0; potassium (*S*)-mevalonate, 96949-04-1; (*R*)-(−)-mevalolactone, 19115-49-2; (*S*)-(+)-mevalolactone, 19022-60-7; (4a*S*,7*R*,8a*R*)-4,4,7-trimethyl-4a,5,6,7,8,8a-hexahydro-1,3-benzoxathiane, 79618-03-4.

Synthesis of Natural (−)-Combretastatin[1]

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In 1982 we reported the isolation and crystal structure determination of (−)-combretastatin (**1**).[1b] Isolation of this substance from the South African tree *Combretum caffrum* (Eckl. Zeyh.) Kuntze was based upon its activity in reversing the differentiation of AC glioma cells into astrocytes; this represented the first isolation of a natural product guided by bioassay using the U.S. National Cancer Institute's (NCI) astrocyte reversal system (9ASK).[2] Subsequently, combretastatin was found to inhibit growth (in vitro) of the NCI P388 lymphocytic leukemia, cause a significant rise in the mitotic index of L1210 cells (evidence for an effective antimitotic agent), inhibit tubulin polymerization, stimulate tubulin-dependent GTP hydrolysis, and competitively inhibit the binding of colchicine (**2**) to tubulin.[3] The obvious need to obtain larger quantities of combretastatin for evaluation against key NCI in vivo antineoplastic systems led us to devise a convenient synthesis[4] of this interesting isovanillin derivative.

One of the most attractive synthetic routes to combretastatin involves coupling 3,4,5-trimethoxybenzaldehyde with a suitably substituted benzylic bromide using a

(1) (a) Contribution 113 in the series "Antineoplastic Agents". Part 112 refer to Pettit, G. R.; Cragg, G. M.; Suffness, M. I. *J. Org. Chem.*, in press. (b) Pettit, G. R.; Cragg, G. M.; Herald, D. L.; Schmidt, J. M.; Lohavanijaya, P. *Can. J. Chem.* **1982**, *60*, 1374–1376.

(2) (a) Baden, D. G.; Mende, T. J.; Lichter, W.; Wellham, L. *Toxicon* **1981**, *19*, 455. (b) Igarashi, K.; Ikeyama, S.; Takeuchi, M.; Sugino, Y. *Cell Struct. Funct.* **1978**, *3*, 103.

(3) Hamel, E.; Lin, C. M. *Biochem. Pharmacol.* **1983**, *32*, 3864–3867.

(4) During the course of this investigation an eight-step synthesis (13% overall yield) was reported: Annapurna, G. S.; Deshpande, V. H. *Synth. Commun.* **1983**, *13*, 1075. We thank Dr. Deshpande for thoughtfully informing us of his interesting synthesis prior to publication.

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