(A) of the carbonyl products. The pseudo-first-order rate constants (k_{obsd}) were taken from the slopes of plots of ln $[A_\infty - A_t]$ against time. The second-order rate constants (k) were obtained by dividing k_{obsd} by activity of H^+ ($a_{H^+} = 4.39 \times 10^{-4}$ and 3.44×10^{-3} mol/dm^3, respectively, for the low and high HCl solutions) calculated according to Debye-Hückel equation.[19]

Registry No. **1a**, 68375-97-3; **1b**, 110523-60-9; **1c**, 110523-61-0; **1d**, 81194-61-8; **1e**, 110523-62-1; **1f**, 118798-97-3; **2a**, 534-15-6; **2b**, 1125-88-8; **2c**, 4316-35-2; **2d**, 2235-01-0; **2e**, 116143-54-5; **2f**, 118798-98-4.

(19) Debye, P.; Hückel, E. *Phys. Z.* **1923**, *24*, 185.

Synthesis of Oxoisodehydroleucodin: A Novel Guaianolide from *Montanoa imbricata*

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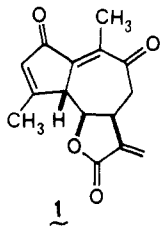
α-Santonin, owing to its well-placed functionality and ready availability, is frequently used as the starting material for the synthesis of terpene natural products.[1] We have previously employed this sesquiterpene[2] for the formal total syntheses of naturally occurring (+)-α- and (+)-β-cyperones,[3a] (-)-frullanolide,[3b] (+)-arbusculin B,[3b] (+)-dihydroestafiatone,[3c] (+)-desacetoxymatricarin,[3c] (-)-estafiatin,[3c] (+)-pachydictyol A,[3d] and (-)-dictyolene.[3d] In this paper we report a short, stereoselective synthesis from α-santonin of oxoisodehydroleucodin (**1**), a highly unsaturated guaianolide isolated from *Montanoa imbricata* by Seaman, Fischer, and Mabry.[4] The synthesis serves to corroborate the structure and relative stereochemistry, which were assigned to the natural product solely on the basis of spectroscopic evidence.



Oxoisodehydroleucodin

1

α-Santonin (**2a**, Scheme I) was converted in 61% yield to its 6-epi isomer (**2b**) through treatment with anhydrous hydrogen chloride in hot dimethylformamide. Photolysis of this material under conditions similar to those described by Barton and co-workers[6] then generated 6-*epi*-isophoto-α-santonic lactone (**3**), which has the guaiane skeleton of **1** (31%). This alcohol on dehydration with thionyl chloride in cold tetrahydrofuran-pyridine afforded regioselectively and in good yield the endocyclic olefin **4**. It is interesting to note that isophoto-α-santonic lactone on similar treatment is converted regioselectively to the corresponding exocyclic olefin.[3d,6]

Kabalka's "alkene walk" procedure,[7] a reduction-olefin transposition method that we had previously shown to be useful for the introduction of a ring-fusion hydrogen on the *more* hindered face of a molecule,[3d] when applied to **4** was once again highly stereoselective and provided the required 5β derivative **5a** in 56% yield. Bromination-dehydrobromination[3b,8] of this cis-fused α-methyl-γ-butyrolactone next efficiently served to produce the desired α-methylene-γ-butyrolactone **5c** to the exclusion of the corresponding endocyclic isomer.

The conversion of triene **5c** to the natural product proved to be surprisingly easy. When stirred overnight at room temperature in dichloromethane in the presence of a large excess of Collins' reagent[9] and 4-Å molecular sieves, triene **5c** cleanly afforded the *double* oxidation product, oxoisodehydroleucodin (52% yield, 68% conversion).[10] The identity of the synthetically and naturally derived substances, which was established through comparison of their spectral data, serves to confirm the structure and relative stereochemistry previously proposed for this novel guaianolide.[4]

The approach illustrated in this paper may be useful for the synthesis of several other, structurally related natural products.[11]

Experimental Section

Solvents were generally distilled prior to use: tetrahydrofuran from lithium aluminum hydride; toluene, dimethylformamide, and hexamethylphosphoric triamide from calcium hydride; and dichloromethane from calcium chloride.

Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70-230 silica gel 60 was employed for column chromatography. A Perkin-Elmer 397 spectrophotometer was used to record IR spectra (as Nujol films). The UV spectra were recorded on a Beckman DB-GT spectrophotometer. A Bruker AM 300 spectrometer was employed for the ^1H and ^{13}C NMR spectra ($CDCl_3$ solutions). Mass spectra were obtained on an AEI MS-30 or VG 30F mass spectrometer (70 eV, direct insert probe) or on a VG Micromass 70 70F instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were obtained with a Büchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS. Santonin was purchased from Sigma.

(3*S*,3a*S*,5a*S*,9b*R*)-3a,5,5a,9b-Tetrahydro-3,5a,9-trimethylnaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione (6-*epi*-α-Santonin, 2b). The procedure described by Piers and Cheng[12]

(1) See: Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1973; Vol. 2. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5.

(2) Previously prepared by total synthesis: Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *Proc. Jpn. Acad.* **1952**, *28*, 425-428; **1953**, *29*, 113-114; **1954**, *30*, 116-118, 119-121; *J. Am. Chem. Soc.* **1956**, *78*, 1422-1426. Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1978**, *43*, 1086-1089. Santonin is available from Aldrich, Sigma, and Fluka.

(3) (a) Greene, A. E.; Muller, J.-C.; Ourisson, G. *Tetrahedron Lett.* **1971**, 4147-4149. (b) Greene, A. E.; Muller, J.-C.; Ourisson, G. *J. Org. Chem.* **1974**, *39*, 186-191. (c) Edgar, M. T.; Greene, A. E.; Crabbé, P. *Ibid.* **1979**, *44*, 159-160. (d) Greene, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 5337-5343.

(4) Seaman, F. C.; Fischer, N. H.; Mabry, T. J. *Phytochemistry* **1986**, *25*, 2663-2664. Neither the absolute configuration nor the optical rotation was reported for oxoisodehydroleucodin. However, sesquiterpene lactones from higher plants invariably belong to the same enantiomeric series,[5] and thus the absolute configuration of the natural product is undoubtedly that of α-santonin-derived **1**. A sample of the natural product (or copies of its spectra) could not be obtained from the authors.

(5) See: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2.

(6) Barton, D. H. R.; Levisalles, J. E. D.; Pinhey, J. T. *J. Chem. Soc.* **1962**, 3472-3482. See also: Barton, D. H. R.; de Mayo, P.; Shafiq, M. *Ibid.* **1957**, 929-935.

(7) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574-575. Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *Ibid.* **1977**, *42*, 512-517.

(8) See also: Marco, J. A.; Carda, M. *Tetrahedron* **1987**, *43*, 2523-2532.

(9) Fullerton, D. S.; Chen, C.-M. *Synth. Commun.* **1976**, *6*, 217-220.

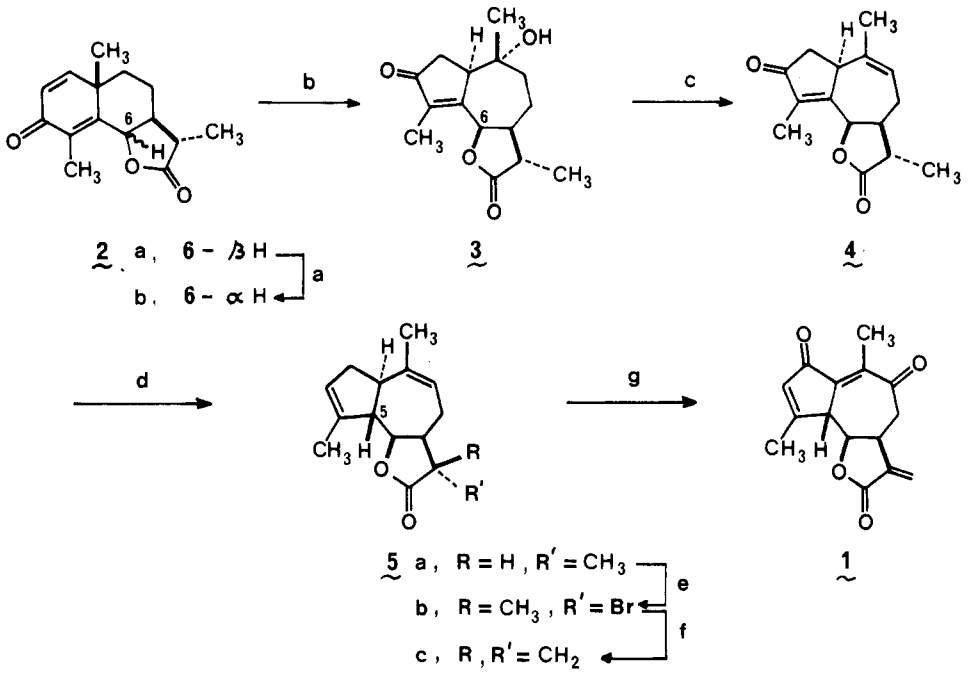
(10) At no time during the conversion of **5c** to **1** could more than a possible trace amount of any monoketone be detected by TLC.

(11) See: Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972; Vol. 2.

(12) Piers, E.; Cheng, K. F. *Can. J. Chem.* **1968**, *46*, 377-383.

0022-3263/89/1954-1468$01.50/0

Scheme I[a]



[a] (a) HCl, DMF, 61%. (b) $h\nu$, CH_3CO_2H, H_2O, 31%. (c) $SOCl_2$, C_5H_5N, THF, 73%. (d) $TsNHNH_2$, C_2H_5OH; catecholborane, $CHCl_3$; CH_3CO_2Na, 56%. (e) LDA, THF; $BrCH_2CH_2Br$, HMPA, 82–89%. (f) DBU, $C_6H_5CH_3$, 66–69%. (g) $CrO_3 \cdot (C_5H_5N)_2$, 4-Å molecular sieves, CH_2Cl_2, 36–52%.

was followed. A solution of 20.0 g (81.3 mmol) of α-santonin (**2a**) in 200 mL of dry dimethylformamide containing 5% anhydrous hydrogen chloride was heated under argon at 100 °C for 1 h (closed system). After being cooled to room temperature, the reaction mixture was diluted with 150 mL of water and then thoroughly extracted with dichloromethane. The combined extracts were washed with 20% aqueous hydrochloric acid, aqueous sodium bicarbonate, and water and then concentrated under reduced pressure (<50 °C). The resulting oil was filtered through 150 g of neutral alumina (activity 1) with toluene, and the product was crystallized from ethyl acetate–hexane (ether wash) to give, in two crops, 12.3 g (61%) of 6-*epi*-α-santonin (**2b**): mp 101–103 °C (ethyl acetate–hexane) (lit.[11] mp 103–104 °C); $[\alpha]^{21}_D$ −302° (*c* 1.0, methanol) [lit.[11] $[\alpha]^{28}_D$ −308° (*c* 0.9, methanol)]; ^{1}H NMR δ 6.53 (AB q, J = 9.8 Hz, $\Delta\nu_{ab}$ = 148 Hz, 2 H), 5.55 (d, J = 5.0 Hz, 1 H), 2.55 (q, J = 7.7 Hz, 1 H), 2.18 (m, 1 H), 2.07 (s, 3 H), 2.00–1.40 (m, 4 H), 1.40 (d, J = 7.7 Hz, 3 H), 1.30 (s, 3 H); IR 1770, 1655, 1625, 1185, 965, 940, 835 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.44; H, 7.33.

(3*S*,3a*S*,6*R*,6a*R*,9b*R*)-3a,5,6,6a,7,9b-Hexahydro-6-hydroxy-3,6,9-trimethylazuleno[4,5-*b*]furan-2,8(3*H*,4*H*)-dione (6-*epi*-Isophoto-α-santonic Lactone, 3). A refluxing solution of 5.50 g (22.4 mmol) of 6-*epi*-α-santonin (**2b**) in 70 mL of glacial acetic acid and 83 mL of water was irradiated under argon with a Hanau TQ 150 high-pressure mercury arc lamp in a quartz immersion well apparatus (no cooling water). After 6.5 h of irradiation, the solvents were removed under reduced pressure (<40 °C) and the resulting oil was purified by dry-column silica gel chromatography with acetone in dichloromethane. Recrystallization of the product from ethyl acetate gave, in two crops, 1.85 g (31%) of 6-*epi*-isophoto-α-santonic lactone (**3**): mp 178–180 °C (ethyl acetate) (lit.[6] mp 180–181 °C); $[\alpha]^{20}_D$ −101° (*c* 0.5, chloroform) [lit.[6] $[\alpha]_D$ −105° (*c* 1.34, chloroform)]; ^{1}H NMR δ 5.53 (d, J = 6.3 Hz, 1 H), 2.92 (m, 1 H), 2.60–2.40 (m, 3 H), 2.21 (quin, J = 6.7 Hz, 1 H), 2.00–1.65 (m, 5 H), 1.84 (m, 3 H), 1.32 (d, J = 7.2 Hz, 3 H), 1.04 (s, 3 H); IR 3450, 1760, 1690, 1630, 1180 cm^{-1}; mass spectrum, m/e 264 (M$^+$).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.15; H, 7.59.

(3*S*,3a*S*,6a*S*,9b*R*)-3a,6a,7,9b-Tetrahydro-3,6,9-trimethylazuleno[4,5-*b*]furan-2,8(3*H*,4*H*)-dione (4). A 3.70-g (14.0 mmol) sample of **3** suspended in 24 mL of tetrahydrofuran at −45 °C was treated rapidly with a solution of 12.0 mL (19.6 g, 165 mmol) of thionyl chloride in 12 mL of pyridine and 12 mL of tetrahydrofuran at −45 °C.[3d] After being stirred at −45 °C for 15 min, the reaction mixture was poured into cold water–ether, and the crude product was isolated with ether in the usual manner. Recrystallization of the product from ether afforded, in two crops, 2.50 g (73%) of olefin **4**: mp 152–154 °C (dichloromethane–cyclohexane); $[\alpha]^{22}_D$ +5° (*c* 0.5, chloroform); ^{1}H NMR δ 5.50 (br t, J = 7.2 Hz, 1 H), 5.33 (d, J = 9.8 Hz, 1 H), 3.33 (br s, 1 H), 2.85 (dd, J = 7.0, 18.5 Hz, 1 H), 2.65–2.80 (m, 1 H), 2.25–2.00 (m, 4 H), 1.81 (m, 3 H), 1.75 (m, 3 H), 1.28 (d, J = 7.0 Hz, 3 H); IR 1775, 1690, 1640, 1165, 1000, 805 cm^{-1}; mass spectrum, m/e 246 (M$^+$).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.06; H, 7.26.

(3*S*,3a*S*,6a*R*,9a*S*,9b*R*)-3a,4,6a,7,9a,9b-Hexahydro-3,6,9-trimethylazuleno[4,5-*b*]furan-2(3*H*)-one (5a). A 1.76-g (7.15 mmol) sample of **4** and 1.76 g (9.45 mmol) of tosylhydrazine in 7.0 mL of absolute ethanol were heated under argon at 80 °C for 2 h, whereupon the solvent was removed under reduced pressure.[3d,7] The resulting material was dissolved in 21 mL of chloroform and treated dropwise at 0 °C under argon with 1.75 mL of catecholborane. After 1 h at 0 °C and 1 h at room temperature, the mixture was treated with 7.0 g (51.4 mmol) of sodium acetate trihydrate and then heated at 65 °C for 1 h. The cooled reaction mixture was filtered with chloroform through a pad of sand, and the filtrate was concentrated under reduced pressure. The crude product was purified by dry-column silica gel chromatography with dichloromethane followed by recrystallization from aqueous methanol to provide 933 mg (56%) of diene **5a**: mp 138–139 °C (methanol–water); $[\alpha]^{20}_D$ −157° (*c* 0.5, chloroform); ^{1}H NMR δ 5.42 (br s, 2 H), 4.47 (dd, J = 5.5, 9.4 Hz, 1 H), 2.83–2.65 (m, 2 H), 2.50–2.35 (m, 2 H), 2.35–2.20 (m, 3 H), 1.98 (dd, J = 8.0, 16.3 Hz, 1 H), 1.83 (m, 3 H), 1.75 (s, 3 H), 1.31 (d, J = 7.3 Hz, 3 H); IR 3035, 1745, 1215, 1000, 960, 805 cm^{-1}; mass spectrum, m/e 232 (M$^+$).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.70.

(3*S*,3a*R*,6a*R*,9a*S*,9b*S*)-3-Bromo-3a,4,6a,7,9a,9b-hexahydro-3,6,9-trimethylazuleno[4,5-*b*]furan-2(3*H*)-one (5b). A solution of 150 mg (0.65 mmol) of **5a** in 5 mL of tetrahydrofuran was added dropwise to a stirred solution at −78 °C under argon of lithium diisopropylamide in tetrahydrofuran (from the addition of 850 μL (1.28 mmol) of 1.5 M *n*-butyllithium in hexane to 200

μL (144 mg, 1.42 mmol) of diisopropylamine in 5 mL of tetrahydrofuran at room temperature). After the addition, the solution was allowed to warm to −50 °C over 1 h, whereupon it was recooled to −78 °C and treated dropwise with a solution of 2.0 mL (4.4 g, 23.2 mmol) of 1,2-dibromoethane in 2.0 mL of hexamethylphosphoric triamide.[3b] The reaction mixture was allowed to warm to −30 °C over 1 h, and was then treated with 1.0 mL of saturated aqueous ammonium chloride solution. The product was isolated with ether in the usual manner and purified by dry-column silica gel chromatography with dichloromethane in pentane to give 12 mg of starting material and 165 mg (82%, 89% based on consumed **5a**) of bromide **5b**: mp 71–75 °C (hexane); $[\alpha]^{22}_D$ −86° (*c* 0.5, chloroform); ^{1}H NMR δ 5.40 (m, 2 H), 4.75 (ddd, *J* = 0.8, 4.8, 10.3 Hz, 1 H), 2.85 (m, 2 H), 2.68 (br q, 9.6 Hz, 1 H), 2.40 (m, 1 H), 2.25–2.00 (m, 3 H), 1.85 (s, 3 H), 1.82 (m, 3 H), 1.71 (d, *J* = 1.4 Hz, 3 H); IR 3050, 3040, 1775, 1195, 950, 880, 810, 800 cm^{-1}; mass spectrum, *m/e* 312, 310 (M^+).

Anal. Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.75; H, 6.13.

(3a*S*,6a*R*,9a*S*,9b*S*)-3a,4,6a,7,9a,9b-Hexahydro-6,9-dimethyl-3-methyleneazuleno[4,5-*b*]furan-2(3*H*)-one (5c). A solution of 354 mg (1.14 mmol) of **5b** and 850 μL (865 mg, 5.68 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 25 mL of toluene was heated at 112 °C (bath) under argon for 1 h.[3b] The crude product was isolated with ether in the usual way and purified by dry-column silica gel chromatography with dichloromethane in pentane to afford 15 mg of starting material and 173 mg (66%, 69% based on consumed **5b**) of triene **5c**: mp 82–84 °C (methanol–water); $[\alpha]^{20}_D$ −210° (*c* 0.5, chloroform); ^{1}H NMR δ 6.19 (d, *J* = 1.6 Hz, 1 H), 5.58 (d, *J* = 1.6 Hz, 1 H), 5.41 (m, 2 H), 4.36 (dd, *J* = 6.2, 10.5 Hz, 1 H), 3.25–3.15 (m, 1 H), 2.97 (br t, 10 Hz, 1 H), 2.70–2.35 (m, 3 H), 2.30–2.15 (m, 1 H), 1.84 (m, 3 H), 1.80 (m, 1 H), 1.71 (m, 3 H); IR 3040, 1750, 1660, 1260, 1145, 995, 960, 810 cm^{-1}; mass spectrum, *m/e* 230 (M^+).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.28; H, 7.93.

(3a*S*,9a*R*,9b*S*)-3a,4,9a,9b-Tetrahydro-6,9-dimethyl-3-methyleneazuleno[4,5-*b*]furan-2,5,7(3*H*)-trione (Oxoisodehydroleucodin, 1). To a rapidly stirred solution of 125 μL (122 mg, 1.55 mmol) of pyridine in 1.5 mL of dichloromethane at 0 °C under argon was added 75 mg (0.75 mmol) of chromium trioxide (dried over phosphorus pentoxide for 12 h under vacuum) and 20 4-Å molecular sieve beads.[9] The burgundy mixture was stirred for 5 min at 0 °C and 30 min at room temperature whereupon a solution of 10.0 mg (0.04 mmol) of **5c** in 1.0 mL of dichloromethane was added. After being stirred for 14 h, the mixture was processed with dichloromethane in the usual manner, and the crude product was purified by dry-column silica gel chromatography with ether in dichloromethane to give 3.2 mg of starting material and 4.0 mg (36%, 52% based on consumed **5c**) of oxoisodehydroleucodin (1):[4] mp 194–195 °C dec (cyclohexane–dichloromethane);[13] $[\alpha]^{20}_D$ −92° (*c* 0.25, methanol); ^{1}H NMR δ 6.41 (d, *J* = 2.0 Hz, 1 H), 6.30 (q, *J* = 1.3 Hz, 1 H), 5.79 (d, *J* = 1.8 Hz, 1 H), 4.41 (dd, *J* = 7.1, 10.4 Hz, 1 H), 3.72 (br d, *J* = 10.4 Hz, 1 H), 3.44–3.34 (m, 1 H), 3.06 (A of AB q, dd, *J* = 13.2, 17.1 Hz, 1 H), 2.76 (B of AB q, dd, *J* = 2.5, 17.1 Hz, 1 H), 2.38–2.35 (m, 6 H); ^{13}C NMR δ 200.09, 195.89, 171.92, 168.42, 141.54, 137.82, 137.01, 135.04, 124.85, 79.78, 50.18, 45.57, 38.50, 19.34, 12.30; IR 3100, 1750, 1685, 1660, 1625, 1600, 1280, 1150, 995, 945, 905 cm^{-1}; UV 267 nm (ε 13 000, methanol); mass spectrum, *m/e* 258 (M^+, 100), 230 (3.1), 212 (34.8), 121 (28), 91 (90.5).

Anal. Calcd for $C_{15}H_{14}O_4$: M_r, 258.0892. Found: M_r (mass spectrum), 258.0951.

Acknowledgment. We thank Professor J. Lhomme and Dr. J.-L. Luche for their interest in this work, C. Gey and S. Lavaitte for their help in recording the high-field NMR spectra, and the CNRS (UA 332) for financial support.

Registry No. 1, 107693-44-7; **2a**, 481-06-1; **2b**, 1618-78-6; **3**, 1618-99-1; **4**, 118172-14-8; **5a**, 118172-15-9; **5b**, 118172-16-0; **5c**, 118332-00-6.

(13) Reported to be an oil.[4]

First Asymmetric Synthesis of Enantiomerically Pure (1*R*,2*S*)-(−)-(1,2-Epoxypropyl)phosphonic Acid (Fosfomycin)

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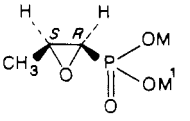
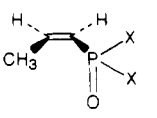
(1*R*,2*S*)-(−)-(1,2-Epoxypropyl)phosphonic acid (**1a**) (fosfomycin) is an antibiotic of unusual structure originally isolated from fermentation broth of *Streptomyces fradiae*.[1] Fosfomycin is present on the pharmaceutical market as the disodium (**1b**),[2] calcium (**1c**),[3] and tris(hydroxymethyl)ammonium (**1d**)[4] salts. Most syntheses of **1a** have





1a: M = M^1 = H
b: M = M^1 = Na
c: M = M^1 = Ca
d: M = H, M^1 = $NH_2[C(CH_2OH)_3]$

2a: X = OH
b: X = Cl

been accomplished by stereospecific cis-epoxidation of (*Z*)-1-propenylphosphonic acid derivatives,[1,5] followed by optical resolution of the racemic epoxide with optically active amines.[1,6,7] Recently, tartaric acid has been shown to be a useful chiral auxiliary for asymmetric functionalization of prochiral olefins such as α,β-unsatured ketones,[8] aldehydes,[9] and enol ethers.[10] We now report the first nonmicrobial[11] asymmetric synthesis of **1a**, based on the use of tartaric acid as a chiral auxiliary in directing an appropriate bifunctionalization of prochiral (*Z*)-1-propenylphosphonic acid (**2a**).

The phosphonic group of **2a** offers the possibility of binding the chiral auxiliary to the (*Z*)-1-propenylphosphonic acid through the formation of its monoesters **5** (Scheme I eq 1). Thus, the reaction of (2*S*,3*S*)-tartaric acid derivatives **3**, such as esters (R = OMe), monoalkyl-

(1) Hendlin, D.; Stapley, E. O. Jackson, M.; Wallick, H.; Miller, A. K.; Wolf, F. J.; Miller, T. W.; Chaiet, L.; Kahan, F. M.; Foltz, E. L.; Woodruff, H. B.; Mata, J. M.; Hernandez, S.; Mochales, S. *Science* **1969**, *166*, 122. Christensen, B. G.; Leanza, J. W.; Beattie, T. R.; Patchett, A. A.; Arison, B. H.; Ormond, R. F.; Kuehl, F. A.; Albers-Shongerg, G.; Jardetzky, O. *Science* **1969**, *166*, 123.

(2) Inouye, S.; Niizato, T.; Komiya, I.; Yuda, Y.; Yamada, Y. *J. Pharm. Dyn.* **1982**, *5*, 941.

(3) *Merck Index*, 10th ed.; Merck & Co. Inc.: Rahway, NJ, 1983; p 607.

(4) *Scrip World Pharm. News* **1986**, *1110*, 23. Chiarino, D.; Della Bella, D.; Ferrari, V. Eur. Pat. App. EP 27597, 1982.

(5) Redmore, D. *Chem Rev.* **1971**, *71*, 326. Smith, D. G.; Smith, D. J. H. *Tetrahedron Lett.* **1973**, 1249. Sobolev, V. G.; Ionin, R. I. *Zh. Obshch. Khim.* **1985**, *55*, 225; *Chem. Abstr.* **1985**, *103*, 22654p.

(6) Glamkowski, E. J.; Gal, G.; Purick, R.; Davidson, A. J.; Sletzinger, M. *J. Org. Chem.* **1970**, *35*, 3510.

(7) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1969**, 4647.

(8) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1985**, 367; *Tetrahedron Lett.* **1985**, 6481; *Bull. Soc. Chem. Jpn* **1986**, *59*, 3559. Fukutani, Y; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, 5911. Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254.

(9) Giordano, C.; Castaldi, G.; Cavicchioli, S.; Minisci, F. It. Pat. Appl. 23216 A85, 1985.

(10) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. It. Pat. Appl. IT 7204A84, 1984; USP 4,697,036 1987; *J. Org. Chem.* **1987**, *52*, 3018 and references cited therein; *J. Org. Chem.* **1987**, *52*, 5642. Castaldi, G.; Cavicchioli, S.; Giordano, C.; Restelli, A. Eur. Pat. Appl. EP 217,375, 1987. Castaldi, G.; Giordano, C. Eur. Pat. Appl. EP 214,426, 1987.

(11) For microbial preparation of **1a**: White, R. F.; Birnbaum, J.; Meyer, R. T.; Broeke, J.; Chemerda, J. M.; Demain, A. L. *Appl. Microbiol.* **1971**, *22*, 55.

0022-3263/89/1954-1470$01.50/0