A Synthesis of 6-Myoporol

Tse-Lok Ho* and Rong-Jie Chein

Department of Applied Chemistry, National Chiao Tung University, Hsinchu Taiwan, Republic of China

Received October 28, 1996[⊗]

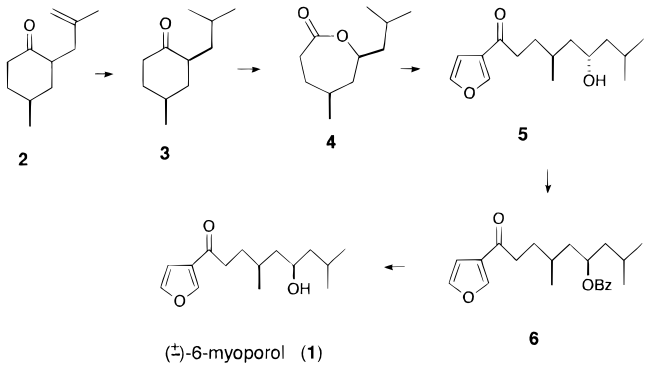
An approach to (±)-6-myoporol (**1**) featured stereocontrol by equilibration of 2,6-disubstituted cyclohexanones to mainly the *cis* isomer. The synthesis was completed by reaction of a lactone intermediate with 3-lithiofuran, Mitsunobu reaction, and hydrolysis.

6-Myoporol (**1**) is a stress metabolite of the furanoterpenoid type, isolated from slices of the root of sweet potato (*Ipomoea batatas*) that had been treated with 0.1% mercuric chloride or with spores of *Ceratocystis fimbriata*.[1] The relative stereochemistry of 6-myoporol was established through a highly diastereoselective hydroboration[2] of (*E*)-2,6-dimethyl-1,4-heptadiene to afford a diol intermediate in which the secondary methyl substituent and the hydroxyl group are *syn*-related. After a rapid hydroboration of the terminal double bond, the second step became intramolecular, which followed a steric course as determined by conformational factors. Later, the absolute configuration of the natural (−)-6-myoporol as *(4S,6R)*-1-(3-furanyl)-6-hydroxy-4,8-dimethyl-1-nonanone was determined by another synthesis[3] featuring elaboration of *(R)*-2,6-dimethyl-1-hepten-4-ol by means of Lewis-acid-induced cleavage of a chiral 4,6-dimethyl-1,3-dioxane with methallyltrimethylsilane as a nucleophile and subsequent disengagement of the γ-hydroxyalkyl unit inherited from the C_2-symmetric diol. Hydroboration of the trifluoroacetate led to a 3:1 diastereomeric mixture, which could be separated into the components by HPLC. The major product was identified as the dextrorotatory form of the nine-carbon diol obtained from the previous synthesis.

Our synthetic approach to racemic 6-myoporol was based on the conformational behavior of 2,4-disubstituted cyclohexanones. Following the same stereochemical relationship of the corresponding cyclohexanes the *cis* isomers are expected to be more stable because both substituents are equatorial. Accordingly, we started our work by alkylation of the pyrrolidino enamine of 4-methylcyclohexanone with methallyl chloride to afford **2**. The ratio of the *cis* and *trans* isomers was estimated by NMR to be 40:60, axial alkylation being favored. The same ratio was retained after hydrogenation. However, when the product was subjected to equilibration with 10% NaOH in hot MeOH, **3** was obtained in a *cis*−*trans* ratio of 84:16 according to ^{1}H-NMR data. As we feared the separated isomers would undergo isomerization again, the mixture was directly used in the subsequent Baeyer−Villger oxidation. With *m*-chloroperbenzoic acid in refluxing $CHCl_3$, the *cis*-lactone (**4**) was obtained in 73% yield. Based on the original content the actual yield from the *cis*-ketone was actually close to 87%. The *trans*-lactone was not isolated. (See Scheme 1.)

Reaction of the lactone (**4**) with 3-lithiofuran at −100 °C furnished *epi*-6-myoporol (**5**), which was separated from the very small amount of impurities.

Scheme 1. Synthesis of Racemic 6-Myoporol (**1**)



The configuration of the carbinolic center of the major product required inversion to complete the synthesis. Thus, a Mitsunobu reaction[4] with benzoic acid as the nucleophile, was performed. The product was *dl*-6-myoporol benzoate (**6**), which was promptly saponified with lithium hydroxide in MeOH. *dl*-6-Myoporol (**1**) was obtained, showing spectral data consistent with those reported.[2]

Experimental Section

General Experimental Procedures. IR spectra of liquid samples were sandwiched between NaCl plates and taken from a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian UNITY-300 instrument at 300 and 75 MHz, respectively; chemical shifts are reported in parts per million downfield from TMS. The EIMS were obtained from a TRIO-2000 mass spectrometer operating at 70 eV ionization voltage, and HRMS were measured on a JEOL JMX-HX 110 mass spectrometer. Melting points were uncorrected. Merck Kieselgel 60 of 70−230 mesh was used for column chromatography. During workup of reactions, solutions were dried over anhydrous Na_2SO_4 and evaporatred *in vacuo* using a Büchi rotary evaporator.

4-Methyl-2-(2-methyl-2-propenyl)cyclohexanone (2). A solution of 4-methylcyclohexanone (1.12 g, 10 mmol), pyrrolidine (0.78 g, 11 mmol), and a trace of *p*-toluenesulfonic acid in benzene (20 mL) was refluxed under a Dean-Stark trap for 8 h. After evaporation of solvent, the residual enamine was redissolved in dioxane (5 mL) and treated with 3-chloro-2-methylpropene (0.91 g) in dioxane (5 mL). The mixture was again refluxed for 6 h to complete the allylation, then hydrolyzed by the addition of 50% HOAc (10 mL) by continuing heating at reflux for 4 h. Dioxane was removed *in vacuo*, and the remaining mixture was taken up in Et_2O and washed with H_2O and aqueous $NaHCO_3$.

* To whom correspondence should be addressed. FAX: 866-35-723764.

⊗ Abstract published in *Advance ACS Abstracts,* May 1, 1997.

S0163-3864(96)00704-5 CCC: $14.00

The dried organic solution was evaporated to give a slightly yellow oil (1.36 g, 82% yield): IR (neat) ν 1712, 1650 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 0.96, 1.03 (total 3H, two d, J = 6.6 Hz), 1.62 (3H, br s), 1.8−2.6 (10H, m), 4.64 (1H, d, J = 12.3 Hz), 4.74 (1H, br s); $M^{+\bullet}$ calcd for $C_{11}H_{18}O$ 166.1358, found 166.1353.

4-Methyl-2-(2-methylpropyl)cyclohexanone (3). 4-Methyl-2-(2-methyl-2-propenyl)cyclohexanone (1.0 g, 6 mmol) was dissolved in MeOH (10 mL), added to a flask containing 10% Pd−C (50 mg) and a stir bar, deaerated by evacuation, and placed under hydrogen. After 5 h the catalyst was filtered, and the solution was evaporated. The residue was redissolved in MeOH (20 mL), to which 10% aqueous NaOH (200 mg) was introduced, and the mixture was refluxed for 18 h. On cooling to room temperature, the base was neutralized with 10% HCl, and MeOH was removed *in vacuo*. The residue was distributed between H_2O and CH_2Cl_2, and the organic layer was separated, dried, and evaporated. Chromatography gave **3** as an oil (0.98 g, 98% yield): IR (neat) ν 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 10.2 Hz), 0.84 (3H, d, J = 10.2 Hz), 0.96 (3H, d, J = 6.6 Hz), 1.2−1.4 (1H, m), 1.4−1.7 (3H, m), 1.8−2.1 (3H, m), 2.2−2.5 (3H, m); $M^{+\bullet}$ calcd for $C_{11}H_{20}O$ 168.1515, found 168.1507.

***cis*-4,8-Dimethyl-6-nonanolide (4).** A mixture of ketone **3** (1.0 g, 6 mmol), *m*-chloroperbenzoic acid (1.86 g, 10.8 mmol) in $CHCl_3$ (4 mL) was refluxed for 40 h. The cooled reaction mixture was filtered, filtrate evaoprated, the residue dissolved in Et_2O, washed with aqueous K_2CO_3 and brine, and dried. Concentration of the solution and chromatography of the resulting residue over a silica gel column furnished the oily lactone **4** (0.8 g, 73%): IR (neat) ν 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), 0.94 (2.52H, d, J = 6.6 Hz), 1.02 (0.48H, d, J = 7.5 Hz), 1.1−1.4 (4H, m), 1.6−2.0 (6H, m), 2.61 (2H, m), 4.29 (0.84H, m), 4.43 (0.16H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.50, 21.40, 21.99, 22.95, 30.12, 32.56, 33.58, 42.35, 44.16, 75.77, 173.67; $M^{+\bullet}$ calcd for $C_{11}H_{20}O_2$ 184.1464, found 184.1462.

(±)-*epi*-6-Myoporol (5). A solution of 3-lithiofuran formed by treatment of 3-bromofuran (600 mg, 4 mmol) in THF (8 mL) with *n*-butyllithium (2.5 M in hexanes, 1.4 mL) was stirred at −100 °C for 0.5 h; the temperature was raised to −78 °C for 1 h and recooled to −100 °C. The lactone (**4**) was added via syringe, and the reaction was allowed to proceed for 1 h at the same temperature, then quenched with saturated NH_4Cl solution. Ether extraction workup followed by column chromatography (eluent, 1:4 EtOAc−hexane) afforded (±)-*epi*-6-myoporol (**5**) (449.5 mg, 65.5%): mp 59−61 °C IR ν 3407, 1681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88−1.0 (9H, m), 1.15−1.3 (2H, m), 1.3−1.5 (3H, m), 1.6−1.8 (4H, m), 2.74 (2H, t, J = 7 Hz), 3.77 (1H, m), 6.74 (1H, d, J = 2.1 Hz), 7.41 (1H, d, J = 2.1 Hz), 8.00 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.16, 22.04, 23.21, 24.40, 28.98, 31.86, 37.92, 44.92, 47.51, 67.29, 108.46, 127.46, 143.98, 147.04, 195.52; $M^{+\bullet}$ calcd for $C_{15}H_{24}O_3$ 252.1726, found 252.1727.

(±)-6-Myoporol Benzoate (6). To a cold (−13 °C), magnetically stirred mixture of *epi*-6-myoporol (30 mg), triphenylphosphine (170 mg), and benzoic acid (60 mg) in THF (1 mL) under a nitrogen atmosphere was slowly added a solution of diethyl azodicarboxylate (128 mg) in THF (1 mL) via a syringe. After 1 h the reaction was allowed to warm to room temperature and stand for 1 day. The solvent was evaporated, and the residue was chromatographed (eluent, 1:9 EtOAc−hexane) to give (±)-6-myoporol benzoate (36.6 mg, 86%): IR (neat) ν 1714, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (6H, d, J = 4.5 Hz), 0.95 (3H, d, J = 5.7 Hz), 1.2−2.0 (8H, m), 2.68 (2H, t, J = 7.5 Hz), 5.30 (1H, m), 6.70 (1H, s), 7.40 (3H, t, J = 7.5 Hz), 7.49 (2H, t, J = 7.5 Hz), 7.99 (1H, s), 8.00 (1H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.89, 22.14, 23.24, 24.64, 29.42, 31.20, 38.19, 42.18, 43.73, 71.73, 108.58, 128.25, 129.48, 130.64, 132.68, 144.01, 147.10, 166.19, 195.12; $M^{+\bullet}$ calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1968.

(±)-6-Myoporol (1). A mixture of **6** (97 mg) and lithium hydroxide (31.5 mg) in MeOH (4 mL containing 0.5 mL of H_2O) was refluxed for 18 h. After removal of solvent the product was dissolved in Et_2O, which was washed with $NaHCO_3$ solution and H_2O, dried over anhydrous $NaSO_4$, and evaporated. Chromatography (eluent, 1:4 EtOAc−hexane) furnished **1** (51 mg, 75%): IR (neat) ν 3440, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86−0.92 (9H, m), 1.19 (2H, m), 1.37 (4H, m), 1.65 (1H, m), 1.80 (1H, m), 1.88 (1H, m), 2.75 (2H, t, J = 7.5 Hz), 3.81 (1H, m), 6.72 (1H, d, J = 2.1 Hz), 7.39 (1H, d, J = 2.1 Hz), 8.01 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.35, 22.04, 23.50, 24.50, 28.98, 29.80, 37.75, 45.41, 46.99, 67.06, 108.58, 127.63, 144.04, 147.01, 195.41; $M^{+\bullet}$ calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1707.

Acknowledgment. We thank the Science Research Council, Republic of China, for financial support.

References and Notes

(1) Burka, L. T.; Iles, J. *Phytochemistry* **1979**, *18*, 873−874.
(2) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385−7387.
(3) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951−3954.
(4) Mitsunobu, O. *Synthesis* **1981**, 1−28.

NP960704F