The 2-Hydroxycitronellols, Convenient Chirons for Natural Products Synthesis

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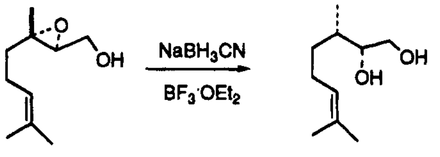
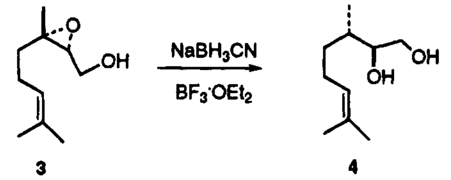
We have found that reduction[2–4] of the Sharpless-derived[5] epoxide **1** of geraniol proceeds to give the 3-alkyl 1,2-diol **2** with both relative and absolute stereocontrol. The epoxide **3** derived from nerol is reduced to **4**. The 2-hydroxycitronellols[6] **2** and **4** made available by this approach should be generally useful chirons[7] for natural product synthesis.



1 **2**

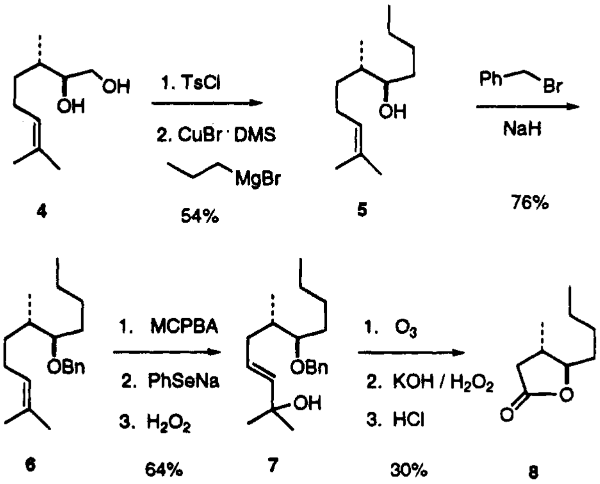


3 **4**

Several reagent combinations have been developed for the reduction of epoxides at the more substituted end.[2–4] Of these, we have found the easiest and cleanest to be NaBH$_3$CN/BF$_3$·OEt$_2$.[4] With this reagent, **1** was smoothly reduced to **2**, as a single diastereomer (^{13}C, ^{1}H NMR, TLC). The stereochemical fidelity of the reduction was demonstrated by conversion of epoxide **3**, derived from nerol, to alcohol **4**. Alcohol **2** and alcohol **4**, though identical by TLC, were clearly diastereomers (^{1}H, ^{13}C NMR).

The absolute configuration of these diols is established by the initial Sharpless epoxidation. We assigned the relative configuration of **4** by conversion (Scheme 1) to quercus lactone (**8**), both diastereomers of which are known.[8]

Scheme 1



Three-carbon homologation of **4** (Scheme 1) was effected by monotosylation, followed by Cu-mediated coupling with excess *n*-propylmagnesium chloride. This reaction may well be proceeding *via* an oxirane intermediate.

Initial attempts to convert **5** to quercus lactone (**8**) were plagued by the volatility of the intermediates. We therefore prepared benzyl ether **6**. Epoxidation followed by selenide addition and oxidation[9] then set the stage for oxidative cleavage of the alkene, with concomitant oxidation[10] of the benzyl ether to the benzoate. Saponification of the benzoate followed by acidification then provided the lactone **8** as a fragrant oil. The observed chemical shift of the lactone methine at 4.01 δ confirmed[8c] that the epoxide reduction had indeed proceeded with inversion of absolute configuration, not a foregone conclusion under the acidic conditions employed.

The 2-hydroxycitronellols, now readily available from geraniol and nerol, should be convenient chirons[7] for natural product synthesis.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-250 or WM-250 spectrometer as solutions in CDCl$_3$. ^{13}C Multiplicities were determined with the aid of a JVERT sequence, separating methylene and quaternary carbons = up (u), from methyl and methine carbons = down (d). The infrared (IR) spectra were determined as neat oils. Mass spectra (MS) were obtained by FTMS at an ionizing potential of 15 eV. Substances for which C,H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Optical rotations were measured on a Rudolph Autopol III polarimeter as solutions in absolute ethanol except as noted. Samples for determination of optical rotation and C,H analyses were purified by column chromatography, followed by bulb-bulb distillation. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF and developed in the solvent indicated. Column chromatography was per-

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[1] Undergraduate research participant.

[2] (a) For the initial report of epoxide reduction with NaBH$_3$CN/BF$_3$·OEt$_2$, see Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. J. Org. Chem. **1981**, *46*, 5214. For reports of Lewis acid-promoted hydride reduction of epoxy alcohols, see (b) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (c) Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857. (d) Wakamatsu, T.; Nakamura, H.; Nishikimi, Y.; Yoshida, K.; Noda, T.; Taniguchi, M.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 4343. (e) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569. (f) Wood, H. B., Jr.; Ganem, B. *Tetrahedron Lett.* **1993**, *34*, 1403.

[3] Several other procedures have been reported to give selective reduction of an epoxide at the more substituted end: (a) Ph$_3$B/KH: Yoon, N. M.; Kim, K. E. *J. Org. Chem.* **1987**, *52*, 5564. (b) LiBH$_4$/BH$_3$: Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1968**, *90*, 2686. (c) LiBH$_4$/Ti(OR)$_4$: Dai, L.-x.; Zhang, Y.-z.; Guo, G.-z. *Tetrahedron Lett.* **1986**, *27*, 4343. (f) NiCRA: Fort, Y.; Vanderesse, R.; Caubere, P. *Tetrahedron Lett.* **1985**, *27*, 3111. (d) Zn/TMSCl: Vankor, Y. D.; Arya, P. S.; Rao, C.T. *Syn. Comm.* **1983**, *13*, 869.

[4] For a reduction of an epoxy alcohol involving hydride migration, see Jung, M.E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208.

[5] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R.M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

[6] For the preparation of 2-hydroxycitronellal as a mixture of diastereomers, see Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206.

[7] Hanessian, S. *Total Synthesis of Natural Products, the "Chiron" Approach*; Pergamon Press: New York, 1983.

[8] For leading references to the isolation and synthesis of quercus lactone, see (a) Sharma, G. V. M.; Vepachedu, S. R.; Chandrasekhar, S. *Synth. Commun.* **1990**, *20*, 3403. (b) Suzuki, Y.; Mori, W.; Ishizone, H.; Naito, K.; Honda, T. *Tetrahedron Lett.* **1992**, *33*, 4931. (c) Günther, C.; Mosandl, A. *Liebigs Ann. Chem.* **1986**, 2112.

[9] Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

[10] For leading references to the oxidative cleavage of benzyl ethers, see Schuda, P. F.; Chichowicz, M. B.; Hermann, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829.

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formed on TLC-mesh silica gel, as described elsewhere.[11] Solvent mixtures are volume/volume mixtures. THF and ether were distilled from sodium/benzophenone under N_2 and used immediately. CH_2Cl_2 was distilled from CaH_2 under N_2 immediately before use. Anhydrous Na_2SO_4 was used as the drying agent unless otherwise specified, and all reactions were carried out in flame-dried glassware under a positive pressure of N_2 unless indicated otherwise.

(2*S*,3*R*)-3,7-Dimethyloct-6-ene-1,2-diol (2). Sodium cyanoborohydride (9.53 g, 151.7 mmol) was added in one portion at room temperature to the epoxide **1** (10.33 g, 60.8 mmol), from Sharpless asymmetric epoxidation[5] of geraniol (10.0 g, 64.9 mmol), in 200 mL of THF containing a little bromcresol green. $BF_3{\cdot}Et_2O$ was added dropwise until the indicator turned yellow. Further additions were made when the indicator turned to green. After all of the acid had been added (total ≈15 mL; the indicator now stayed yellow), the reaction was stirred until complete by TLC (3−4 h). Aqueous hydrochloric acid (15 mL of 6 M) was added, and the mixture was stirred for 20 min. The solution was filtered, and the filtrate was neutralized with 10% aqueous NaOH and then extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated, and filtered through a pad of silica gel with ethyl acetate/CH_2Cl_2 to give 8.01 g (46.5 mmol, 77% from epoxide **1**, 72% overall yield from geraniol) of the diol as a colorless oil: ^{1}H NMR δ 0.95 (d, J = 6.8 Hz, 3H), 1.1−1.8 (m, 5H), 1.60 (s, 3H), 1.68 (s, 3H), 3.35−3.80 (m, 5H), 5.09 (bt, 1H); ^{13}C NMR δ 131.6, 124.3, 75.7, 65.1, 35.4, 33.1, 25.6, 25.5, 17.6, 14.4; IR (cm^{-1}) 3360 (broad), 2966, 2924, 2727, 1447, 1377, 1229, 1068; MS (*m/z*) 172 (34), 141 (52), 123 (95), 121 (31), 101 (100); $[\alpha]_D$ = 6.6° (c = 0.22, EtOH).

(2*R*,3*R*)-3,7-Dimethyl-2,3-epoxy-6-octen-1-ol (3). Epoxidation was performed using the catalytic Sharpless procedure.[5b] Thus at −10 °C, 1.26 mL (1.50 g) of D-(−)-diethyl tartrate, 1.5 mL of $Ti[OCH(CH_3)_2]_4$, and 27 mL of *tert*-butyl hydroperoxide (3.7 M solution in CH_2Cl_2) were added sequentially to 150 mL of CH_2Cl_2 over 2.0 g of powdered, oven-dried 4-Å molecular sieves. The mixture was stirred for 10 min at −10 °C and then cooled to −20 °C. A volume of 5.9 mL of nerol (16 g, 102 mmol) was then added dropwise over 20 min. The reaction was stirred at −20 °C for 3 h and then warmed to 0 °C. A volume of 50 mL of water was added. After 10 min, 15 mL of 30% NaOH in saturated brine was also added. After 15 min, the layers were separated. The aqueous layer was extracted twice with 50 mL of CH_2Cl_2. The combined organic extract was dried over $MgSO_4$ and filtered through a pad of Celite. The solution was concentrated *in vacuo*, and then the residue was distilled bulb-to-bulb ($bp_{0.5}$ = 100 °C (bath)) to give 16.0 g (92% yield) of **2** as a colorless oil: TLC R_f = 0.43 (40% EtOAc/petroleum ether); ^{1}H NMR δ 1.34 (s, 3 H), 1.40−1.58 (m, 2 H), 1.61 (s, 3 H), 1.68 (s, 3H), 2.0−2.25 (m, 3H), 2.43 (bs, 1H), 2.97 (m, 1H), 3.65 (m, 1H), 3.79 (m, 1H), 5.09 (m, 1H); ^{13}C NMR δ u: 24.1, 33.1, 61.2, 61.5, 132.4; d: 17.5, 22.1, 25.6, 64.3, 123.2; IR (cm^{-1}) 3423, 2973, 2924, 2860, 2727, 1666, 1452, 1380, 1065, 1034, 866; MS (*m/z*, %) 170.130, 110 (44), 109 (100), 95 (32), 82 (45), 67 (48), 61 (19).

(5*R*,6*S*)-6,10-Dimethyl-9-undecen-5-ol (5). Sodium cyanoborohydride (11.8 g, 188 mmol) was added in one portion to bulb-to-bulb distilled epoxide from the Sharpless reaction (16.0 g, 92 mmol) in 300 mL of THF at rt. Boron trifluoride etherate (11.5 mL) in 5 mL of THF was slowly added dropwise. After all of the acid had been added, the reaction was stirred until complete by TLC (8−12 h). A volume of 50 mL of petroleum ether and 100 mL of 5% aqueous NaOH were added. The layers were separated, and the aqueous layer was extracted once with petroleum ether and then twice with diethyl ether. The organic extract was dried (Na_2SO_4), concentrated by rotary evaporation under reduced pressure, and used without further purification for the next reaction. (Previous runs of this reaction in which the product was purified gave a chemical yield of 67%. No appreciable amount of the 1,3 diol was produced). An analytical sample of **4** (silica gel chromatography, followed by bulb-to-bulb distillation) gave the following data: colorless oil ($bp_{1.0}$ = 130 °C); ^{1}H NMR δ 0.86 (d, J = 7.0 Hz, 3H), 1.05 −1.19 (m, 1H), 1.44−1.55 (m, 1H), 1.56 (s, 3H), 1.64 (s, 3H), 1.79−2.16 (m, 3H), 3.03 (bs, 2H), 3.45 (m, 2H), 3.63 (m, 1H), 5.06 (dt, J = 1.3,7.0 Hz, 1H); ^{13}C NMR δ d: 15.1, 17.6, 25.6, 35.7, 76.2, 124.4; u: 25.3, 32.4, 64.5, 131.5; IR (cm^{-1}) 3079, 2966, 2924, 2877, 2858, 1641, 1452, 1329, 1271, 1240, 1141, 1057, 1029, 986, 964, 911, 884, 830, 741; MS (FTMS 15 eV, *m/z*, %) 172.148 (7), 141.130 (52), 123.118 (35), 88.052 (42), 82.077 (100), 67.054 (35); $[\alpha]_D$ = −4.36°.

The above diol, 180 mL of CH_2Cl_2, 0.7 g of benzyltriethylammonium chloride, and 110 mL of 50% aqueous NaOH were combined in a 500-mL flask and stirred mechanically (not under N_2). After 15 min, the mixture was chilled in an ice−water bath, and then *p*-toluenesulfonyl chloride (15 g, 79 mmol) was added slowly in small portions. The reaction was *vigorously* stirred and allowed to come to rt over 2 h. Water (250 mL) was added, the layers were separated, and the organic phase was washed three times with distilled water. The organic phase was dried (Na_2SO_4) then concentrated *in vacuo* (heating bath at rt) to one-quarter of the original volume. A volume of 50 mL of THF was added, and evaporation to one-quarter of the volume was repeated. The residue was dissolved in 25 mL of THF and used without further purification.

The Grignard reagent was prepared from 2.43 g of Mg turnings and 9.4 mL of 1-bromopropane (100 mmol) in 100 mL of dry THF. The resulting cloudy grey solution was cooled to −30 °C, and then 2 g of freshly prepared CuBr·DMS (10 mol %) was added. The THF solution of crude epoxide from the previous reaction was added dropwise. After addition was complete, the reaction was allowed to warm to 0 °C. After 3 h, 40 mL of saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted three times with ether. The combined organic phases were filtered through Celite (to remove a fine, black precipitate), dried (Na_2SO_4), and chromatographed to give 6.82 g (34 mmol, 33% from nerol) of **5** as a colorless oil: TLC R_f = 0.39 (10% EtOAc/petroleum ether); ^{1}H NMR δ 0.92 (m, 6H), 1.14 (m, 1H), 1.25−1.58 (m, 9H), 1.61 (s, 3H), 1.69 (s, 3H), 1.82−2.22 (m, 2H), 3.44 (m, 1H), 5.10 (m, 1H); ^{13}C NMR δ u: 22.8, 25.7, 28.4, 32.0, 33.0, 131.5; d: 14.1, 15.2, 17.7, 25.6, 38.4, 76.0, 124.8; IR (cm^{-1}) 3370, 2962, 2928, 2862, 2729, 1456, 1378, 1322, 1267, 1208, 1151, 1115, 1088; MS (FTMS 15 eV, *m/z*, %) 198.198 (20), 127.111 (33), 114.104 (45), 82.077 (100); $[\alpha]_D$ = + 4.7°. Anal. Calcd for $C_{13}H_{26}O$: C, 78.7; H, 13.2. Found: C, 78.7; H, 13.1.

(5*R*,6*S*)-5-(Benzyloxy)-6,10-dimethyl-9-undecene (6). In a flame-dried flask, 3 g (60 mmol of NaH) of 60% NaH in mineral oil was washed twice with petroleum ether, and then 15 mL of dry THF was added. The alcohol from the previous reaction was added slowly. After foaming and bubbling died down, the reaction was stirred for 1 h at rt. A volume of 6 mL (50 mmol) of benzyl bromide was added, and the reaction was stirred at rt for 10 h and then heated to reflux for 90 min. After cooling the reaction mixture to rt, distilled water was added very slowly to decompose any remaining NaH. The mixture was neutralized with 1 N aqueous HCl, the layers were separated, and the aqueous layer was extracted three times with ether. The combined organic phase was washed with saturated aqueous sodium bicarbonate and then with saturated brine. The organic extract was then dried (Na_2SO_4), concentrated *in vacuo*, and chromatographed to give the benzyl ether 6 (7.44 g, 76 % yield) as a colorless oil: TLC R_f = 0.76 (10% EtOAc/petroleum ether); ^{1}H NMR δ 0.85−0.92 (m, 6H), 1.12−1.55 (m, 9H), 1.60 (s, 3H), 1.70 (s, 3H), 1.76−2.15 (m, 3H), 3.25 (m, 1H), 4.01 (AB quartet, 2H), 5.10 (m, 1H), 7.23−7.40 (m, 5H); ^{13}C NMR (δ) u: 22.9, 25.7, 25.9, 28.2, 29.3, 33.0, 71.3, 1331.3, 139.3; d: 14.1, 14.5, 17.6, 25.7, 34.6, 83.1, 124.8, 127.3, 127.7, 128.2; IR (cm^{-1}) 3089, 3065, 3030, 2959, 2931, 2873, 2859, 2730, 1496, 1454, 1377, 1306, 1206, 1093, 1069, 1029; MS (*m/z*, %) 288.2479 (31), 204 (46), 182 (20), 177 (22), 141 (42), 109 (19), 82 (100); $[\alpha]_D$ = +12.2°.

(6*S*,7*R*)-7-(Benzyloxy)-2,6-dimethyl-3-undecen-2-ol (7). An amount of 7.0 g of benzyl ether **6** (24 mmol) was dissolved in 72 mL of dry CH_2Cl_2 at 0 °C. An amount of 12 g of 50% 3-chloroperbenzoic acid (38 mmol, 1.6 equiv) was added with stirring, and the cooling bath was removed. After 20 min at rt, the reaction mixture was diluted with ether and 60 mL of 10% aqueous NaOH. Distilled water was added until all precipitate dissolved, and solution was mostly clear. The layers were separated, and the aqueous layer was extracted once with 1:1 ether:petroleum ether. The combined organic phases was washed twice with saturated aqueous $NaHCO_3$, and then twice with saturated brine. The clear organic solution was concen-

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[11] Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

trated by rotary evaporation under reduced pressure, diluted with ethanol, concentrated again, and used directly for the next reaction.

Diphenyl diselenide (5.5 g, 24 mmol) was suspended in 8 mL of ethanol, and then 1.8 g (48 mmol) of $NaBH_4$ was added in portions with stirring. After the bubbling had subsided, the mixture was stirred for an additional 30 min, and then the epoxide from the previous reaction was added. After 12 h, the reaction mixture was maintained at reflux for 2.5 h and then was cooled to 0 °C.

The mixture was diluted with 50 mL of THF, and 24 mL of 30% aqueous H_2O_2 was added. Cooling was maintained until the solid which formed upon addition of the hydrogen peroxide had completely dissolved. After 1 h, 50 mL of saturated aqueous sodium bicarbonate was added. The layers were separated, and the light red aqueous layer was extracted twice with ether. The combined organic phase was washed sequentially with saturated aqueous sodium bicarbonate, distilled water, and saturated brine. After drying (Na_2SO_4), the solution was concentrated and chromatographed to give **7** (4.69 g, 64% yield for the three steps) as a light golden oil: TLC $R_f = 0.45$ (20% EtOAc/petroleum ether); ^1H NMR δ 0.80−1.10 (m, 7H), 1.32 (s, 6H); 1.3−1.6 (m, 7H), 1.88 (m, 1H), 2.18 (m, 1H), 3.23 (m, 1H), 4.53 (bs, 2H), 5.60 (m, 2H), 7.22−7.45)m, 5H); ^{13}C δ u: 22.6, 27.6, 29.3, 35.6, 70.5, 71.3, 139.1; d: 14.0, 14.7, 29.8, 35.4, 82.3, 125.6, 127.3, 127.7, 128.2, 139.3; IR (cm^{-1}) 3380, 3090, 3066, 3031, 2961, 2933, 2873, 2862, 1497, 1454, 1377, 1361, 1330, 1305, 1236, 1206, 1148, 1095, 1069, 1028; MS (*m/z*, %) 287.2280 (100; $M^+ - OH$), 230 (13), 179 (12). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 78.5; H, 10.4.

(3*S*,4*R*)-3-Methyl-4-octanolide (8). Alcohol **7** (1.5 g, 5 mmol) was dissolved in 80 mL of CH_2Cl_2 in an ozonolysis flask. A minimum amount of Sudan III dye was added (just enough for a noticeable red color). Ozone (1.5% ozone in O_2) was bubbled through at −78 °C until the red color of Sudan III faded. The mixture was then allowed to warm to 0 °C. Ozonolysis was continued for another 45 min. After purging excess ozone with N_2, 2 mL of 30% aqueous H_2O_2 was added, followed by 30 mL of 30% aqueous KOH. N_2 was bubbled through the solution until the volume was reduced to approximately 40 mL. After stirring for 12 h, the mixture was acidified with 6 M aqueous HCl and extracted with ether. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed to give **8** (0.226 g, 30% yield) as a fragrant oil: TLC $R_f = 0.42$ (20% EtOAc/petroleum ether); ^1H NMR δ 0.92 (t, $J = 7.0$ Hz, 3H), 1.13 (d, $J = 5.9$ Hz, 3H), 1.26−1.77 (m, 7H), 2.09−2.30 (m, 2H), 2.58−2.67 (m, 1H), 4.01 (m, 1H); ^{13}C NMR δ u: 22.4, 27.8, 33.6, 37.1, 176.6; d: 13.8, 17.4, 36.0, 87.4; IR (cm^{-1}) 2960, 2935, 2874, 1780, 1454, 1432, 1383, 1362, 1303, 1319; MS (*m/z*, %) 156.1105 (1.3), 138 (5), 128 (7), 114 (6), 99 (100); $[\alpha]_D = +45.7°$ (in MeOH).

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