Notes

Absolute Configuration of Drim-9(11)-en-8-ol from *Aspergillus oryzae*

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A great deal of effort has been devoted to the study of *Aspergillus oryzae* due to its use in baking and in manufacturing of sake, shoyu, and tamari in Japan. While isolating sporogenic substances from this fungus, K. Wada and co-workers[1] isolated two drim-9(11)-en-8-ols. Structures **1** and **2** were assigned to these compounds on the basis of spectroscopic evidences, and the stereochemistry depicted in **2** was confirmed by a racemic synthesis. The absolute configuration of **1** and **2** was not determined.

We have thus undertaken the synthesis of **1** and **2**, using (5*S*,9*S*,10*S*,13*R*)-8(17),14-labdadien-13-ol (manool, **3**) ($[\alpha]^{25}_D$ +31.9° (*c* 4, $CHCl_3$))[2] as a chiral template.

The key step of the synthesis of **1** and **2** was the photolysis of ketones **8** and **9** in hexane, a Norrish type II cleavage.[3] Ketones **8** and **9** were easily obtained from **3** as delineated in Scheme I. Treatment of **3** with *m*-chloroperbenzoic acid in dichloromethane and 0.5 M $NaHCO_3$, at room temperature, affording 8,17-epoxy-14-labden-13-ols **4** and **5**, which upon reduction with lithium aluminum hydride in THF yielded the diols **6** and **7**.[5] Oxidation of the diols with permanganate yielded ketones **8** and **9**.[6] Chromatographic separation of the photolysis mixture of **8** and **9** yielded **1** and **2** which exhibited mass spectral and NMR data in good agreement with those obtained previously for the natural products. Since the optical rotation showed opposite signs, this led us to the conclusion that the natural products were mirror images of the ones synthesized from manool, thus possessing the absolute configuration depicted in structure **10** and **11**.

Synthesis of the natural enantiomer, (5*R*,8*R*,10*R*)-drim-9(11)-en-8-ol (**10**) was accomplished in three steps beginning with methyl (5*R*,8*R*,9*S*,10*R*)-labd-13-en-8-ol-15-oate (**12**)[7] as outlined in Scheme II. The physical properties of **10** were identical with those of the natural product.

We are now looking for an appropriate chiral template to synthesize **11**.

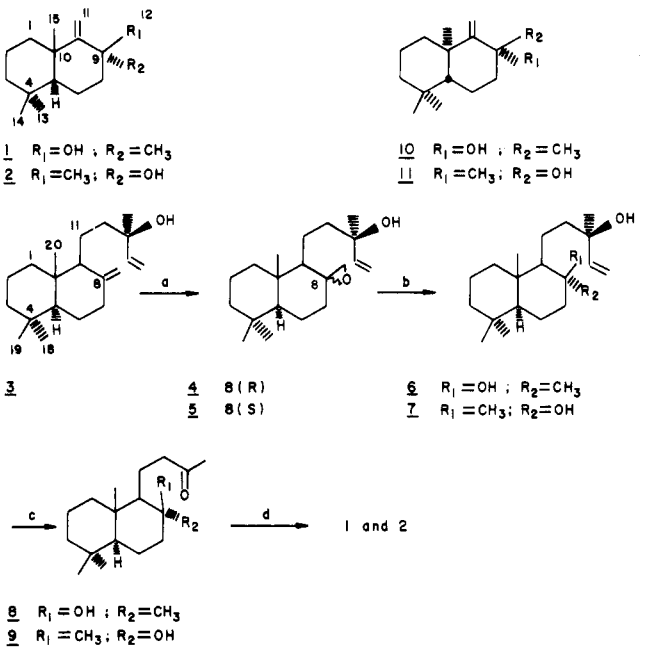
Experimental Section

All melting points were determined on a Reichert hot stage microscope and are uncorrected. Optical rotations were measured in a Carl Zeiss photoelectric polarimeter.

Infrared spectra were run on a Perkin-Elmer 399 B spectrophotometer using thin films or KBr pellets. ^1H NMR spectra were determined on a Varian T-60, Bruker AW 80 or a Varian XL-100 spectrometers. Me_4Si as an internal standard.

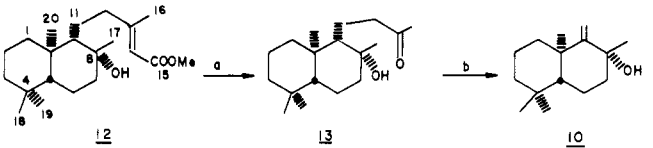
Low-resolution mass spectra were obtained with a Varian MAT 311 A. Merck silica gel GF was utilized for thin-layer plates (TLC), and spots were visualized by spraying.

Scheme I.[a] **Synthesis of (5*S*,8*S*,10*S*)-Drim-9(11)-en-8-ol (1) and Its 8*R* Epimer 2**



[a] (a) MCPBA, CH_2Cl_2, $NaHCO_3$, 4 ' (78% yield); (b) $LiAlH_4$, THF 5 h (75% yield); (**6**/**7** = 1:3); (c) $KMnO_4$, $MgSO_4$, acetone, room temperature; (d) *hν*, hexane, 6 h.

Scheme II.[a] **Synthesis of (5*R*,8*R*,10*R*)-Drim-9(11)-en-8-ol (10)**



[a] (a) $KMnO_4$, $MgSO_4$, acetone, room temperature; (b) *hν*, hexane, 6 h.

Epoxidation of 8(17),14-Labdadien-13-ol 3. Solid *m*-chloroperbenzoic acid (1.60 g, 9.3 mmol) was added to a magnetically stirred mixture of **3** (1.3 g, 4.5 mmol) in dichloromethane (45 mL) and 0.5 M aqueous sodium bicarbonate (13.5 mL). The mixture was stirred at room temperature for 4 h. The reaction was monitored by TLC revealing the total consumption of **3**. The two phases were separated, the organic layer was washed successively with 1 N sodium hydroxide and water, dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed on a silica gel column eluted with diethyl ether/hexane (3:7), yielded a mixture of **4** and **5** (1.10 g, 3.6 mmol 80% yield): IR ν_{max}^{film} (cm^{-1}) 3600–3200 (OH), 3095 (C=C—H), 1645 (C=C), 800 (epoxide); ^1H NMR (60 MHz, $CDCl_3$) δ 0.81, 0.86, 0.87, 0.91, 1.26 (methyl groups) 2.26–2.76 ($C_{17}H$), 5.06 (dd, *J* = 11 and 1.5 Hz, $C_{15}H_c$), 5.23 (dd, *J* = 18 and 1.5 Hz, $C_{15}H_t$), 6.00 (dd, *J* = 18 and 11 Hz, $C_{14}H$).

LAH Reduction of 8,17-Epoxy-14-labden-13-ols 4 and 5. The mixture of **4** and **5** (0.830 g, 2.6 mmol) in dry THF (20 mL) was stirred with excess LAH (1.10 g) at room temperature for 6

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h. Excess LAH was destroyed by addition of wet diethyl ether followed by aqueous HCl (0.5 N). The reaction was extracted with diethyl ether (3 × 70 mL). The organic layer was washed and dried over Na_2SO_4 (anhydrous) and concentrated under reduced pressure. Purification on a short silica gel column yielded a mixture of **6** and **7** (0.64 g, 77% yield). Medium-pressure chromatography using a Lobar column (Merck) eluted with hexane and increasing amounts of diethyl ether of a small sample yielded the two separated diols **6** and **7** in a ratio 1:3. The less polar was **6**: $[\alpha]^{25}_D$ -3.8° (*c* 6, $CHCl_3$) [lit.[5] $[\alpha]^{25}_D$ -5°]; ^1H NMR (80 MHz, $CDCl_3$) δ 0.77 (s, 3 H, $C_{19}H$), 0.84 (s, 3 H, $C_{18}H$), 0.93 (s, 3 H, $C_{20}H$), 1.09 (s, 3 H, $C_{17}H$), 1.32 (s, 3 H, $C_{16}H$), 5.09 (dd, 1 H, J = 11 and 1.5 Hz, $C_{15}H_c$), 5.27 (dd, 1 H, J = 18 and 1.5 Hz, $C_{15}H_t$), 6.02 (dd, 1 H, J = 18 and 11 Hz, $C_{14}H$). The more polar was **7**: $[\alpha]^{25}_D$ +5.0° (*c* 2, $CHCl_3$) [lit.[5] $[\alpha]^{25}_D$ +12°]; ^1H NMR (80 MHz, $CDCl_3$) δ 0.80 (s, 6 H, $C_{19}H$ and $C_{20}H$), 0.86 (s, 3 H, $C_{18}H$), 1.14 (s, 3 H, $C_{17}H$), 1.27 (s, 3 H, $C_{16}H$), 2.64 (br s, 2 H, OH), 5.02 (dd, 1 H, J = 11 and 1.5 Hz, $C_{15}H_c$), 5.23 (dd, 1 H, J = 18 and 1.5 Hz, $C_{15}H_t$), 6.00 (dd, 1 H, J = 18 and 11 Hz, $C_{14}H$).

The reaction was carried on with the remaining mixture.

Oxidation of 14(15)-Labdene-8,13-diols 6 and 7. To a solution of **6** and **7** (0.36 g, 1.2 mmol) in acetone (28 mL) at 20 °C a mixture of $KMnO_4$ (0.62 g) and $MgSO_4$ (0.53 g) was added for 30 min. The reaction was additionally stirred for 30 min. Filtration over a Celite pad and evaporation of the solvent at reduced pressure yielded crude **8** and **9** (0.330 g, 1.2 mmol, 100% yield). Thin-layer chromatography (3:7 diethyl ether/hexane) revealed superimposed spots with R_f 0.3, which would decompose producing a compound with R_f 0.9. Attempts to purify the reaction product by column chromatography would lead to more decomposition product. IR ν_{max}^{film} (cm^{-1}) 3400 (OH), 1720 (C=O); ^1H NMR (60 MHz, CCl_4) δ 0.80, 0.88, 1.08, 1.25, 1.33, 2.05 (methyl groups).

Photolysis of 8 and 9. The ketones **8** and **9** (0.150 g, 0.54 mmol) in petroleum ether (20 mL) under Argon were irradiated in a quartz apparatus with a mercury lamp Phillips HLP 125 W. The temperature was maintained at 0 °C. The reaction was monitored by thin-layer chromatography revealing the formation of three products (R_f 0.6, 0.7 and 0.9; 3:7 diethyl ether/hexane). The solvent was evaporated at reduced pressure and the residue (149 mg) was purified by column chromatography eluted with diethyl ether/hexane (1:99). Compound with R_f 0.9 was the decomposition of the ketones. The second compound (R_f 0.7) was **1** (0.016 g, 13% yield): $[\alpha]^{25}_D$ -9.7° (*c* 0.7, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}) 3400 (OH), 1630 (C=C), 900 (C=CH_2); ^1H NMR (100 MHz, $CDCl_3$) δ 0.87 (s, 3 H, $C_{14}H$), 0.89 (s, 3 H, $C_{13}H$), 1.26 (s, 3 H, $C_{15}H$), 1.38 (s, 3 H, $C_{12}H$), 4.87 (br s, 1 H, $C_{11}H$), 5.04 (br s, 1 H, $C_{11}H$); MS, *m/z* (relative intensity) 222 ($M^{\cdot+}$, 35), 204 (53), 129 (53), 95 (93), 69 (79), 43 (100). The more polar compound (R_f 0.6) **2** was very difficult to purify (0.013 g, 11% yield): $[\alpha]^{25}_D$ +22.5° (*c* 0.6, $CHCl_3$); IR ν_{max}^{film} (cm^{-1}) 3430 (OH), 1630 (C=C), 900 (C=CH_2); ^1H NMR (100 MHz, $CDCl_3$) δ 0.85 (s, 3 H, $C_{14}H$), 0.87 (s, 3 H, $C_{13}H$), 1.09 (s, 3 H, $C_{15}H$), 1.41 (s, 3 H, $C_{12}H$), 4.84 (br s, 1 H, $C_{11}H$), 5.22 (br s, 1 H, $C_{11}H$); MS, *m/z* (relative intensity) 222 ($M^{\cdot+}$, 65).

Oxidation of Methyl (5*R*,8*R*,9*S*,10*R*)-Labd-13-en-8-ol-15-oate (12). A mixture of $KMnO_4$ (0.31 g) and $MgSO_4$ (0.27 g) was added to a solution of **12**[7] (0.20 g, 0.6 mmol) in acetone (14 mL) at 20 °C. After being stirred for 1 h the reaction was filtered over Celite and a decolorizing carbon pad. The solvent was evaporated at reduced pressure, yielding **13** in 50% yield (0.09 g, 0.3 mmol): IR ν_{max}^{film} (cm^{-1}) 3400 (OH), 3010-2940 (C-H), 1710 (C=O); ^1H NMR (60 MHz, CCl_4) δ 0.83 (s, 6 H, $C_{19}H$ and $C_{20}H$), 0.87 (s, 3 H, $C_{18}H$), 1.10 (s, 3 H, $C_{17}H$), 2.05 (s, 3 H, $C_{16}H$).

Photolysis of 13. The ketone **13** (0.024 g, 0.8 mmol) in petroleum ether (20 mL) was submitted to photolysis as described above. Purification of the product on a silica gel column yielded **10** (0.004 g, 0.02 mmol, 21% yield): $[\alpha]^{25}_D$ +9° (*c* 2, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}) 3400 (OH), 1630 (C=C), 900 (C=CH_2); ^1H NMR (100 MHz, $CDCl_3$) δ 0.85 (s, 3 H, $C_{14}H$), 0.87 (s, 3 H, $C_{13}H$), 1.25 (s, 3 H, $C_{15}H$), 1.38 (s, 3 H, $C_{12}H$), 4.82 (br s, 1 H, $C_{11}H$), 5.04 (br s, 1 H, $C_{11}H$). MS, *m/z* (relative intensity) 222 ($M^{\cdot+}$, 35), 204 (53), 185 (53), 95 (100).

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Registry No. **1**, 86546-83-0; **2**, 86546-84-1; **3**, 596-85-0; **4**, 54809-25-5; **5**, 104713-01-1; **6**, 1232-00-4; **7**, 515-03-7; **8**, 104621-31-0; **9**, 16736-51-9; **10**, 104621-32-1; **11**, 104621-33-2; **12**, 13902-85-7; **13**, 104621-34-3.

Superacid-Catalyzed Isomerization of *endo*- to *exo*-Trimethylenenorbornane (Tetrahydrodicyclopentadiene) and to Adamantane[1]

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One of the most significant developments of hydrocarbon chemistry in our time is that of diamondoid cage hydrocarbons, i.e. adamantane and its homologues. Adamantane was first isolated from petroleum by Landa in 1933,[2a] and its structure was confirmed by Prelog's synthesis in 1941.[2b] The single most important discovery that allowed the field to blossom to its present scope and significance was, however, Schleyer's finding of the aluminum trichloride catalyzed isomerization of *endo*-trimethylenenorbornane to adamantane.[3] Schleyer was studying the isomerization of the endo to the exo isomer, when he observed that in the reaction, upon workup, a white crystalline solid also formed that he realized was adamantane. During the facile isomerization of *endo*- to *exo*-trimethylenenorbornane, giving 90% exo isomer, 10% adamantane was obtained in solvent-free $AlCl_3$ sludge system at elevated temperature.[3b,4] Yield of adamantane could not be improved in the same system starting with the exo isomer. Investigations of ways to maximize the yield of adamantane gave a maximum yield of 18.8% using a large excess of $AlBr_3$ with *sec*-butyl bromide as promotor and HBr as cocatalyst.[5] A nearly quantitative yield of the exo isomer was obtained when endo-trimethylenenorbornane was isomerized with $AlCl_3$ in methylcyclohexane solvent. The rearrangement was also brought about with concentrated H_2SO_4. The equilibrium mixture contains 99% exo and 1% endo compound.

Since Schleyer's observation[3b] that concentrated H_2SO_4 readily isomerizes *endo*- to *exo*-trimethylenenorbornane, no systematic report of the use of other strong acid systems in the isomerization appeared. The transformation must involve several energetically unfavorable carbocationic intermediates. A free energy difference of about 3 kcal/mol has to be overcome to reach, after a long reaction at room temperature using H_2SO_4, thermodynamic equilibrium and to obtain 99.6% exo isomer. The amount of acid required is high (more than 1 equiv with respect to hydrocarbon).

Schleyer's discovery of the aluminum halide catalyzed rearrangement of *endo*- and *exo*-trimethylenenorbornane to adamantane prompted extensive further studies.[6,7]

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