Biogenetic-Type Synthesis of (+)-Cymbodiacetal, a Constituent of *Cymbopogon martinii*†

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A biogenetic-type synthesis of (+)-cymbodiacetal (**1**), a novel bismonoterpenoid dihemiacetal, is described.

Cymbodiacetal (**1**) was isolated from the essential oil of the aerial parts of flowering *Cymbopogon martinii* (Graminaceae).[1] The structure of **1** was established by spectroscopic methods (MS, IR, ^{1}H and ^{13}C NMR) and further confirmed by X-ray diffraction studies of its 1:1 solvate with $CDCl_3$, which also established its absolute stereochemistry. The stereochemistry at C-2 and C-7 of **1** was shown to be the same as that in *R*-(+)-limonene (**2**), the other component isolated from the essential oil.[1]

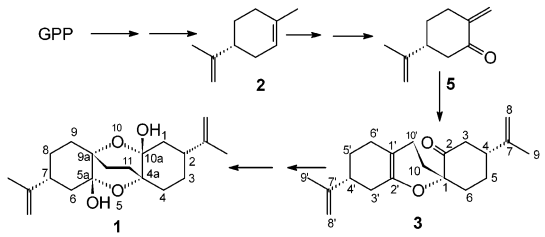
The biogenesis of **1** involving the key intermediate **3** (Scheme 1) looked more attractive than the earlier proposal[1] especially in view of the fact that a large number of natural dimers, including **3**, have been reported to be formed by heteroatom Diels−Alder self-dimerization.[2−11] We have now achieved biogenetic-type synthesis of (+)-cymbodiacetal (**1**) starting with (+)-limonene oxide (**4**) via the key intermediate **3**. This is the first report of the synthesis of **1**.[1]

Our synthetic strategy was based on the assumption that the dimer **3** should be accessible through simple Diels−Alder dimerization of the conjugated enone **5**, which, in turn, can be obtained from epoxide **4** (Scheme 2). The dimer **3** could then be transformed into monoepoxide **6** on treatment with 1 equiv of moist peroxy acid. The free acid formed in the reaction could open the epoxide **6** in the desired manner by the participation of ether and carbonyl oxygens followed by attack of water to give **1** (Scheme 2).

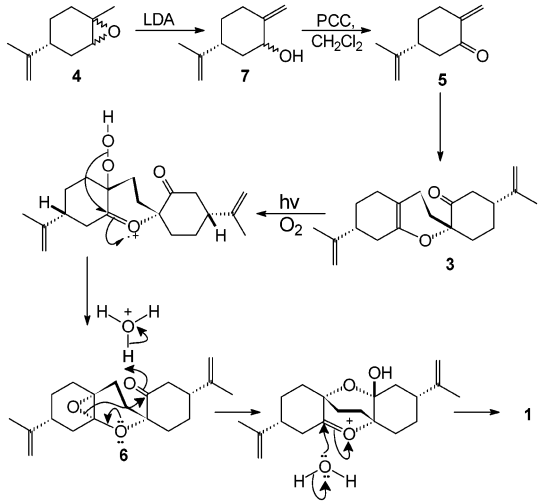
Reaction of (+)-limonene oxide (**4**) with lithium diisopropylamide (LDA)[12] followed by oxidation of the resultant allylic alcohols (exocarveols **7**) with pyridiniumchlorochromate (PCC)[13] gave the expected enone **5** in 68% yield. In view of the unstable nature of **5**,[12] no other physical data except GC/MS were recorded for further characterization.

α-Alkylidenecyclanones are reported to undergo regioselective heteroatom Diels−Alder dimerization on standing at room temperature[3,6] to give spirochroman derivatives.[11] Therefore, the enone **5** was kept in a stoppered flask at room temperature. A week later, GC showed the appearance of a peak (≈10%) at retention time t_R = 66.5 min and considerable reduction in the peak size of **5** at t_R = 29.9 min, which disappeared almost completely at the end of 10 days. Careful column chromatographic separation over silica gel using 5% diethyl ether in hexane gave fractions rich in dimer **3** (77%), as indicated by GC. Further purification by HPLC using 5% diethyl ether in hexane as the mobile phase gave **3** of 97% purity, and it was used immediately for the acquisition of its ^{1}H, ^{13}C, and other 3D NMR data. The ^{1}H chemical shift values agree closely with the previously reported[10] values for **3**, and the structure is further supported by the ^{13}C assignments being reported here. The latter were derived from the ^{13}C DEPT and ^{1}H−^{13}C COSY data. The GC/MS of **3** showed prominent peaks at *m/z* 300 (M^+, 55), 150 (23), and 107 (100). The genesis of the major fragment ions in the mass spectrum of **3** is shown in Scheme 3.

Scheme 1. Possible Biogenetic Pathway for Cymbodiacetal (**1**)



Scheme 2. Synthetic Route to Cymbodiacetal (**1**)



The transformation of **3** into (+)-cymbodiacetal (**1**) took place in an unusually simple and unexpected manner, supporting the proposed biogenetic pathway (Scheme 1). Interesting observations were made while handling **3**. It was difficult to obtain **3** in pure form, and the GC/MS of 97% pure **3** showed an additional peak at *m/z* 316. A reasonable explanation for these observations could be a slow transformation of **3** into **6** by air oxidation.[14,15] Therefore, the flask containing **3** was exposed to diffused daylight expecting to obtain the desired epoxy intermediate **6** without using peroxy acid. Most likely **6** was formed but

† Dedicated to the late Professor Albert T. Bottini, Department of Chemistry, University of California, Davis, CA 95616.

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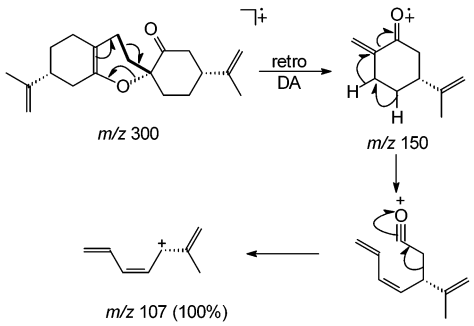
Scheme 3. Mass Spectral Fragmentation of Dimer **3**



could not be characterized because silica gel chromatography of the contents of the flask led directly to the isolation of crystalline cymbodiacetal (**1**), identified by the correspondence of its mp, optical rotation, and other spectral data (IR, ^{1}H and ^{13}C) with those reported for **1** isolated from *C. martinii*.[1]

Experimental Section

General Experimental Procedures. Chemical shifts are expressed in parts per million (δ) relative to TMS as the internal standard. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on Varian Gemini 300 and Bruker WT 300 FT-NMR spectrometers. IR spectra were recorded on a Shimadzu 8101A FT-IR spectrophotometer. Gas chromatographic analyses were performed on a Varian 3700 GC with a 30 m × 0.25 mm HP-5 capillary column. An identical column was used for the GC/MS system, which consisted of an Agilent 6865 GC interfaced with a 5973 Network Mass Selective Detector, with the mass spectrometer operating at 70 eV. High-performance liquid chromatography was carried out using a Waters 3000 HPLC system with a 25 cm × 1.0 cm semipreparative 10 μm silica gel column under isochratic conditions. Column chromatography utilized 60−120 mesh silica gel (Acme Synthetic Chemicals). TLC was performed with silica gel impregnated with 13% calcium sulfate (Merck India).

(5*R*)-2-Methylene-5-(1-methylethenyl)-1-cyclohexanol (7). A solution of *n*-butyllithium in hexane (0.12 mol, 85.5 mL, 1.4 M) was added to 11.1 g (0.11 mol) of diisopropylamine in anhydrous diethyl ether (300 mL) at 0 °C under a N_2 atmosphere, and the solution was stirred. *R*-(+)-Limonene oxide (**4**) [15.2 g, 0.10 mol, purchased from Aldrich Chem. Co. (Aldrich 21832-4) as a mixture of *cis* and *trans* isomers] in anhydrous diethyl ether (60 mL) was added dropwise over a period of 30 min. The resulting reaction mixture was allowed to warm to room temperature and then stirred for another 12 h. The reaction mixture was cooled in an ice-bath, and water (300 mL) was added. The ether phase was separated and washed successively with 100 mL of 2 N HCl, water, saturated aqueous $NaHCO_3$, and saturated NaCl. The aqueous phase and each washing was extracted two times each with 50 mL portions of diethyl ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, and distilled under reduced pressure through a short distillation head to yield **7**[12] (81%). GC analysis of **7** indicated it to be a mixture of two diastereomers with t_R = 27.95 and 30.1 min in the ratio of 1:1.82, respectively. This mixture was used for the next reaction without further purification. IR (film) ν_{max} 3370 (OH), 2930, 2850, 1640 (C=C), 1430, 890 cm^{-1}.

(5*R*)-2-Methylene-5-(1-methylethenyl)-1-cyclohexanone (5). A solution of the diastereomeric mixture of **7** (3.0 g, 20 mmol) in CH_2Cl_2 (40 mL) was added to a suspension of PCC (3.0 g) in CH_2Cl_2 (75 mL) and stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether (110 mL), stirred for 1 min, and allowed to stand overnight. The liquid phase was decanted from the residue (tarry mass), successively extracted with 7% NaOH (3 × 65 mL), 10% HCl (3 × 10 mL), saturated $NaHCO_3$ (2 × 50 mL), and saturated NaCl (50 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a viscous oil (2.38 g, 80.4%). TLC of this oil (hexane/diethyl ether, 9:1) showed a single spot under UV. However, GC showed a major peak (67.6%) at t_R = 29.9 min in addition to some minor peaks. It was purified by column chromatography over silica gel (hexane/diethyl ether, 9:1) to give **5**[12] (2.013 g, 68%) as a colorless oil: *m*/*z* (rel intensity) 150 (M^+, 15), 135 (30), 122 (36), 107 (60), 91 (48), 79 (100), 67 (92), 53 (32), 41 (15).

Dimerization of Enone 5 to 3. The enone **5** was kept in a loosely stoppered flask for a period of one week. GC showed a peak (≈10%) at t_R = 66.5 min (**3**) and a decrease in size of the peak at t_R = 29.9 min, corresponding to **5**. At the end of 10 days, the peak at t_R = 29.9 min almost completely disappeared, while the size of the peak at t_R = 66.5 min increased correspondingly. TLC (hexane/diethyl ether, 19:1) showed a faint spot different from and just above that of **5**. Column chromatography over silica gel (hexane/diethyl ether, 19:1) gave fractions rich in peak at t_R = 66.5 min (GC), which were combined. GC/MS of the major peak (77% intensity) showed *m*/*z* (rel intensity) 300 (M^+, 55), 151 (23), 135 (28), 107 (100), 95 (50), 79 (47), 67 (32), 55 (36), 41 (30), indicating it to be the dimer **3**,[10] molecular formula $C_{20}H_{28}O_2$. Further purification of a small sample (<50 mg) by preparative HPLC (hexane/diethyl ether, 95:5) gave 97.4% pure (GC) **3** (11 mg). The purified sample did not solidify. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (6H, s, 2CH_3), 1.4−2.3 (16Hs, m, 7CH_2 and 2C*H*), 2.8 (2H, t, J = 12.1, 11.6 Hz, −CH_2−CO), 4.58 (2H, s, −C=CH_2), 4.72 (2H, s, −C=CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3 (CH_3, C-9 or C-9′), 20.8 (CH_3, C-9 or C-9′), 22.6 (CH_2, C-10), 25.4 (CH_2, C-6′), 27.3 (CH_2, C-10′), 27.7 (CH_2, C-5), 28.5 (CH_2, C-5′), 33.0 (CH_2, C-6), 38.9 (CH_2, C-3′), 41.7 (CH, C-4′), 43.4 (CH_2, C-3), 48.5 (CH, C-4), 79.3 (C, C-1), 105.5 (C, C-1′), 108.7 (CH_2, C-8 or C-8′), 109.9 (CH_2, C-8 or C-8′), 143.8 (C, C-2′), 147.4 (C, C-7 or C-7′), 149.2 (C, C-7 or C-7′), 212.4 (C, C-2); GC/MS of the minor (10% peak showed *m*/*z* (rel intensity) 316 (M^+, 43), 163 (26), 149 (58), 135 (72), 120 (100), 107 (86), 95 (48), 79 (57), 67 (40), 55 (53), 41 (38), indicating it to be the epoxide **6**, molecular formula $C_{20}H_{28}O_3$.

Cymbodiacetal (1). The remaining portion of impure **3** (1.0 g) on chromatography over silica gel in diffused daylight (hexane/diethyl ether, 4:1) gave colorless needles (0.288 g), mp 213 °C [lit.[1] mp 206−7 °C]; $[\alpha]^{25}_D$ +24.2° (*c* 3.0, $CHCl_3$) [lit.[1] $[\alpha]^{25}_D$ +26° ± 5° (*c* 0.12, $CHCl_3$)]; IR (KBr) ν_{max} 3379 (OH), 2941, 1649, 1450, 1180, 1128, 1080, 1006, 891 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68 (3H, s, CH_3), 1.49−1.92 (6H, m, C_8, C_9, C_{11}−Hs), 2.09 (2H, m, C_1−Hs), 4.66 (2H, s, =CH_2); ^{13}C NMR (CD_3OD, 75 MHz) δ 21.1 (CH_3), 27.3 (CH_2, C-1 or C-3), 27.5 (CH_2, C-1 or C-3), 34.1 (CH_2, C-11), 41.9 (CH or CH_2, C-2 or C-4), 42.4 (CH or CH_2, C-2 or C-4), 72.8 (C, C-4a), 98.9 (C, C-10a), 109.1 (CH_2, =*C*H_2), 150.7 (C, −*C*=CH_2).

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