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Synthesis and Structure of the Diterpenoid Peucelinendiol

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The synthesis of peucelinendiol has been carried out starting from geraniol, and using as a key intermediates the anion of phenylthiogeraniol and (−)-geraniol epoxide obtained by the Sharpless procedure. Its structure was stablished as (6*S*,7*R*)-7-hydroxymethyl-2,6,10,14-tetramethylpentadeca-2,9,13-trien-6-ol. Isopeucelinendiol, epipeucelinendiol, and epiisopeucelinendiol were also synthesized.

Some years ago we isolated from *Magydaris panacifolia* (Umbelliferae) a new diterpenoid named magydardiendiol,[1] for which the irregular isoprenoid structure **1** was recently proposed.[2] The structure of this diol seems to be the result of a head to head coupling of two monoterpene units, i.e. two geranyl units linked through C_1-C_2' and C_3-C_4'.

Although the head to head coupling is normal in the biogenesis of triterpenoids and carotenoids, it is quite unusual in the case of lower terpenoids. We have only found two more diterpenoids with a head to head skeleton, namely digeranyl[3] and peucelinendiol **2**.[4] Moreover the C_1-C_2' union between isoprenoid chains, quite uncommon, is also present for instance in lavandulol and in tetraterpenes like that one isolated from *Elodea canadensis*.[5]

We were interested in peucelinendiol, because it could be a biogenetic precursor of **1**, and the fact that neither the absolute nor the relative stereochemistry for **2** were given, encouraged us to accomplish the total asymmetric synthesis of peucelinendiol.

Peucelinendiol can be envisaged as the product from the attack of anion **A** on the epoxide **B**, both materials easily available from geraniol. The synthesis of each one of the two possible diastereomers for **2** can be done if the suitable cis or trans epoxide **B** is used as starting material.

The nucleophile **A** can be prepared as a magnesium derivative, a cuprate or a sulfur-stabilized anion. However the high nucleophilicity of stabilized sulfur anions allows to carry out the displacement reactions under very mild conditions and formation of secondary by-products (rearrangement, allylic attack, halohydrine formation···) is minimized. Also good yields are reported in the reaction of allylic sulfur-stabilized anions and epoxides.[6,7] We chose the geranyl phenyl sulfide **4**, as a synthetic equivalent of carbanion **A**.

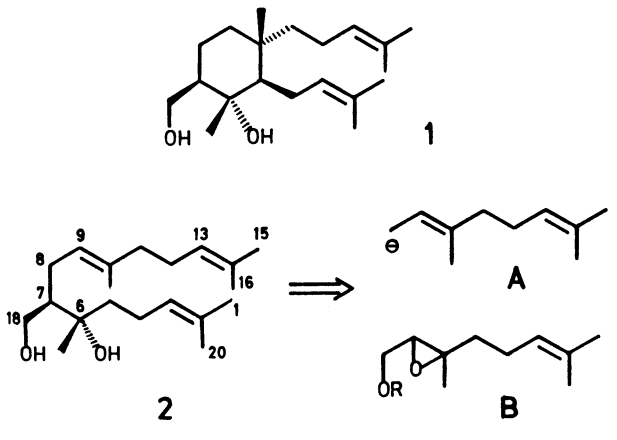

Chart 1.

Treatment of geraniol with 2,4-dinitro-1-fluorobenzene[8] yielded the aromatic ether **3**, which on reaction with potassium benzenethiolate gave the expected allylic sulfide **4** whose physical properties are in good agreement with those reported.[6]

It is known that the hydroxyl group in allylic alcohols can induce the selective epoxidation of the β,γ-double bond in the presence of other olefins. Furthermore, it is possible the asymmetric epoxidation of allylic alcohols with *t*-butyl hydroperoxide, (+)-diethyl tartrate and titanium(IV) isopropoxide.[9] We used this method to prepare the epoxidic substrate **B**. In our hands, the asymmetric epoxidation of geraniol proceeded smoothly to yield the optically active geranyl epoxide **5** in 80% e.e.

The free hydroxyl group of **5** is not compatible with the strong basic conditions needed to the coupling with the anion **A**, so that protection either with butyl vinyl ether, or with methyl isopropenyl ether was used, to give the respective acetal derivatives **6** or **7** in high yield.

Metallation of the allylic sulfide **4** (BuLi, DABCO/THF −25 °C), followed by addition of the protected alcohol epoxide **6** gave in a fast and clean reaction, after deprotection, a single mixture of the phenylthio isomers **8**.

Desulfuration of this material was accomplished either with Raney Ni, or with $Li/NH_3/Et_2NH$. In both cases mixtures of constitutional isomers **2** and **9** were obtained. Although the ratio **2**/**9** was higher when the desulfurization was carried out with $Li/NH_3/Et_2NH$, the product distribution was difficult to control. Chromatography on SiO_2 allowed us to separate both compounds. The physical constants of the diol with the three trisubstituted double bonds were in good agreement with the previously reported for peucelinendiol, and also the optical activity ($[\alpha]_D$+4.4°) was the expected for an 80% e.e. (reported $[\alpha]_D$+5.4°).[4]

According to the stereochemistry of the reactions

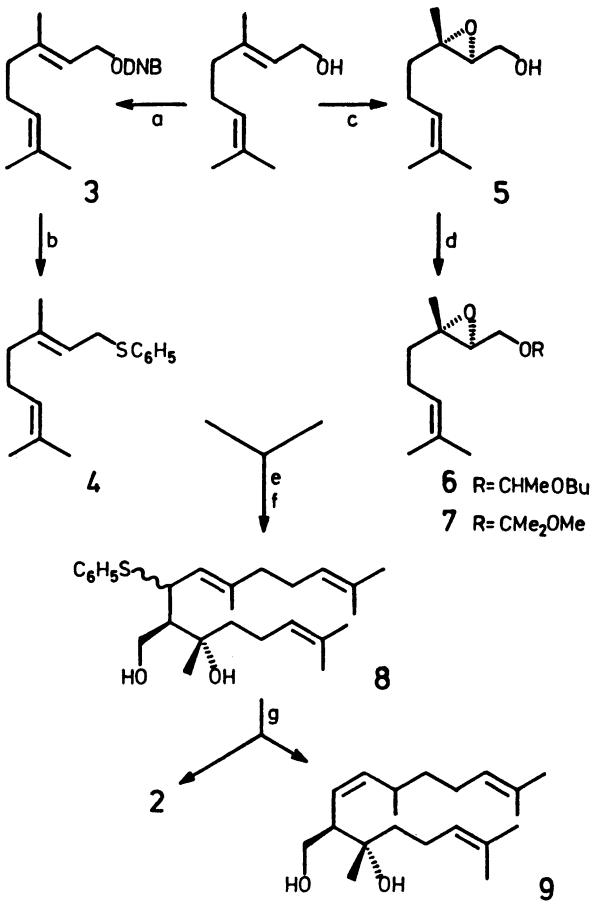

Chart 2.

a) 2,4-DNFB/NEt_3, b) C_6H_5SH, K/EtOH, c) $Ti(OPr)_4$, (+)-DET, THBP/CH_2Cl_2 −20°C, d) BuO-CH=CH_2 or MeOCMe=CH_2/TsOH, e) BuLi, DABCO/THF −25°C, f) HCl 0.5 M, g) Li, NH_3/Et_2NH.

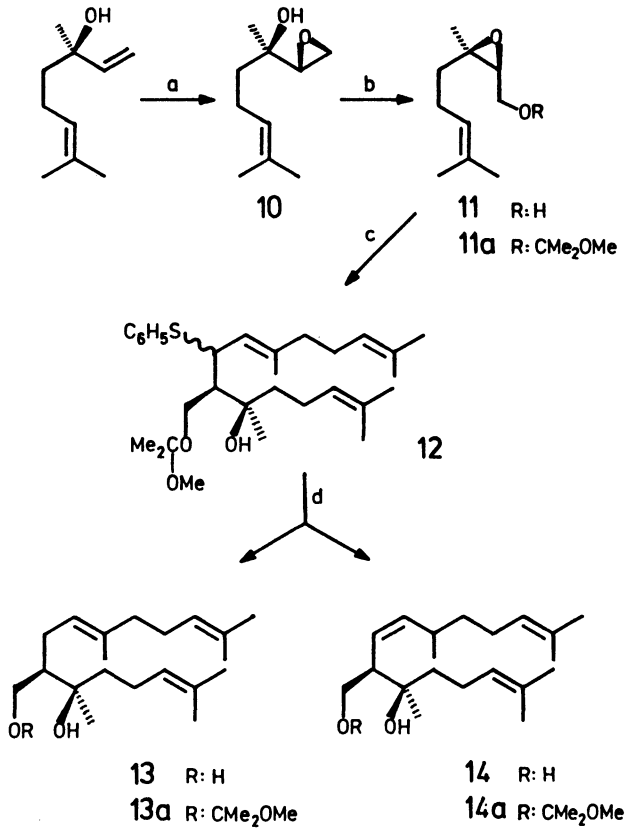

Chart 3.

a) *t*-BuOOH, $VO(acac)_2/C_6H_6$, b) KOH/H_2O, c) MeOCMe=CH_2/C_6H_6 (TsOH); BuLi, DABCO/THF −25°C; **4**, d) Li, NH_3/Et_2NH.

described, we consequently propose for compound **2** the absolute configuration 6*S*, 7*R*.

However to rule out definitively the alternative stereochemistry, we repeated the reaction with the isomeric epoxide **11**. The synthesis of this compound was accomplished starting from (−)-linalool, using *t*-butyl hydroperoxide and $VO(acac)_2$, to get the epoxidation product **10**. This material rearranged cleanly into the trisubstituted epoxide **11** when handled with aqueous KOH.[10] Protection of the hydroxyl group with methyl isopropenyl ether (**11a**), and reaction with the foregoing anion **4**, produced the expected epimeric mixture **12** which upon hydrolysis and desulfurization with $Li/NH_3/Et_2NH$ led to epipeucelinendiol **13** ($[\alpha]_D$−7.5°) and its isomer with the disubstituted double bond **14**.

Comparison of the ^{13}C NMR spectra, specially the signals at 5-C (39.8 vs. 41.6), 7-C (49.6 vs. 47.7), 11-C (38.3 vs. 39.9), and 19-C (26.4 vs. 23.4) of epipeucelinendiol and the already described peucelinendiol, led no doubt about their different structures. As a conclusion we propose the structure **2** for natural peucelinendiol.

Experimental

Optical rotations were measured on a polarimeter Perkin-Elmer 241. IR spectra were recorded on a Beckman Acculab II. NMR were recorded on a Bruker WP 200 SY (200 MHz ^1H, 50.3 MHz ^{13}C).

Protection of Geranyl Epoxide. The alcohol **5** (2.6 g), prepared as described in Ref. 9, was dissolved in ether (30 ml) and reacted with methyl isopropenyl ether or with butyl vinyl ether (5 ml) and a trace of TsOH. After 30 minutes at room temperature, ether and aqueous Na_2CO_3 (4%) were added, the organic layer was dried and the solvent removed in vacuo to yield a crude material (3.2 g) which was used without further purification.

8-Phenylthiopeucelinendiol (8). The sulfide **4** (1.5 g), prepared as described in Ref. 6 in THF (60 ml) and DABCO (750 mg) was cooled down to −20 °C. An excess of BuLi (5 ml, 1.6 M in hexane; 1 M=1 mol dm^{-3}) was then added. The reaction mixture turns then into orange. After 5 minutes, the epoxide **6** (or **7**) was slowly dropped, and the mixture was allowed to warm up to room temperature. Work up, hydrolysis (0.5 M HCl) and chromatography on SiO_2 (60 g, hexane/ether, 6:3) rendered 2.05 g (80%) of a 1:1 mixture of the epimeric hydroxy sulfides **8**. ^1H NMR ($CDCl_3$) δ=7.30 (10H, m), 5.25 (6H, m), 4.10 (6H, m), 1.62 (6H, s), 1.60 (6H, s), 1.56 (6H, s), 1.52 (6H, s), 1.34 (3H, s), 0.95 (3H, s).

Peucelinendiol (2) and Isopeucelinendiol (9). Desulfurization of the foregoing mixture was carried out as follows: over the stirred sulfide mixture (380 mg) in diethylamine (3 ml), was condensed NH_3 (30 ml). Li (100 mg) was added in small pieces and the blue solution was kept at reflux temperature for 30 minutes. MeOH was then dropped in until the blue color vanished and NH_3 was allowed to evaporate. Work up with ether and aqueous HCl (0.5 M) yielded a mixture (280 mg) of two compounds which could be separated on a SiO_2 column (60 g, hexane/ether, 7 : 3) affording 175 mg of peucelinendiol **2** ($[\alpha]_D$ +4.4° *c* 3, $CHCl_3$) and isopeucelinendiol **9** (60 mg), which showed the following physical data: $[\alpha]_D$ −11.0° (*c* 3.3, $CHCl_3$). IR (film) 3400, 2950, 1450, 1380, 1200, 1040, 990 cm^{-1}. ^1H NMR ($CDCl_3$) δ=5.37 (1H, dd *J*=15 and 7 Hz, 9-H), 5.07 (1H, dd, *J*=15 and 9 Hz, 8-H), 5.03 (2H, m, 3-H, 13-H), 3.78 (1H, dd, *J*=9 and 8 Hz, 18-H_A), 3.55 (1H, dd, *J*=9 and 6 Hz, 18-H_B), 2.35 (1H, m, 7-H), 1.60 (6H, s, 1-CH_3, 15-CH_3), 1.54 (3H, s, 16-CH_3), 1.50 (3H, s, 20-CH_3), 1.10 (3H, s, 19-CH_3), 0.89 (3H, d, *J*=7 Hz, 17-CH_3). ^{13}C NMR ($CDCl_3$) δ=140.9 (d, 8-C), 131.7 (s, 2-C), 131.2 (s, 14-C), 125.4 (d, 9-C), 124.6 (d, 3-C), 124.5 (d, 13-C), 75.4 (s, 6-C), 64.2 (t, 18-C), 52.8 (d, 7-C), 4.16 (t, 5-C), 37.1 (t, 11-C), 36.6 (d, 10-C), 25.8 (t, 12-C), 25.6 (q, 1-C, 15-C), 23.5 (q, 19-C), 21.7 (t, 4-C), 20.6 (q, 17-C), 17.6 (q, 16-C, 20-C).

8-(Phenylthio)epipeucelinendiol (12). The alcohol **11** (710 mg) prepared according to Ref. 10, in ether (5 ml) was protected by reacting it with 2 ml of 2-methoxy propene and a trace of pyridinium tosylate during 10 minutes. Work up with aqueous Na_2CO_3 (4%) and ether produced 750 mg of the epoxy acetal **11a** which was used without purification in the next reaction. The sulfide **4** (500 mg) and DABCO (200 mg) in THF (20 ml) at −20 °C were treated with BuLi in hexane (2 ml, 1.6 M). After 5 minutes the epoxy acetal **11a** (400 mg) in THF (10 ml) was added and the reaction was allowed to warm up to room temperature. Usual work up followed by chromatography on SiO_2 (50 g, hexane/ether, 95 : 5) afforded 650 mg of an epimeric sulfide mixture **12** which was further reacted by dissolving it in 6 ml of diethylamine and 50 ml of refluxing NH_3. Li (200 mg) was then added with strong stirring and the reaction mixture was allowed to stand for 30 minutes more. After this time MeOH was added until the blue color disappeared. Evaporation of the NH_3 and usual work up with aqueous HCl (0.5 M) and ether produced a mixture (420 mg) which could be resolved on a SiO_2 column (80 g, hexane/ether, 9 : 1) to yield epipeucelinendiol acetal **13a** (85 mg) and epiisopeucelinendiol acetal **14a** (210 mg).

Epipeucelinendiol Acetal 13a. Oily, $[\alpha]_D$ −11.0° (*c* 0.9, $CHCl_3$). IR (firm) 3400, 2950, 1460, 1380, 1220, 1090, 1050 cm^{-1}. ^1H NMR ($CDCl_3$) δ=5.10 (3H, m, 3-H, 9-H, 13-H), 3.55 (2H, m, 18-H), 3.16 (3H, s, OCH_3), 1.64 (6H, s, 1-CH_3, 15-CH_3), 1.57 (9H, s, 15-CH_3, 17-CH_3, 20-CH_3), 1.30 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.20 (3H, s, 19-CH_3). ^{13}C NMR ($CDCl_3$) δ=136.1 (s, 10-C), 131.3 (s, 2-C), 131.2 (s, 14-C), 124.9 (d, 3-C), 124.2 (d, 13-C), 123.5 (d, 9-C), 100.3 (s, O-C-O), 74.8 (s, 6-C), 61.1 (t, 18-C), 48.8 (q, OCH_3), 47.9 (d, 7-C), 39.8 (t, 5-C), 38.6 (t, 11-C), 26.7 (t, 8-C), 25.9 (q, 19-CH_3), 25.5 (q, 1-CH_3, 15-CH_3), 25.5 (t, 12-C), 24.3 (q, 2CH_3), 22.4 (t, 4-C), 17.5 (q, 16-CH_3, 20-CH_3), 16.2 (q, 17-CH_3).

Epipeucelinendiol (13). The acetal **13a** (110 mg) was hydrolyzed in MeOH (8 ml) with aqueous HCl (1 ml, 0.5 M) for ten minutes. Work up with aqueous Na_2CO_3 (4%), yielded 81 mg of the compound **13**. Colorless oil. $[\alpha]_D$ −7.5° (*c* 0.8, $CHCl_3$). IR (film) 3400, 2950, 1450, 1380, 1150, 1050, cm^{-1}. ^1H NMR ($CDCl_3$) δ=5.05 (3H, m, 3-H, 9-H, 13-H), 3.75 (2H, m, 18-H), 1.65 (6H, s, 1-CH_3, 15-CH_3), 1.58 (9H, s, 16-CH_3, 17-CH_3, 20-CH_3), 1.26 (3H, 19-CH_3). ^{13}C NMR ($CDCl_3$) δ=136.5 (s, 10-C), 131.8 (s, 2-C), 131.6 (s, 14-C), 124.5 (d, 13-C), 124.3 (d, 3-C), 123.3 (d, 9-C), 76.2 (s, 6-C), 63.1 (t, 18-C), 49.6 (d, 7-C), 39.8 (t, 5-C), 38.3 (t, 11-C), 26.7 (t, 8-C), 26.4 (q, 19-C), 25.6 (q, 1-C, 15-C), 25.3 (t, 12-C), 22.4 (t, 4-C), 17.6 (q, 16-C, 20-C), 16.1 (q, 17-C).

Epiisopeucelinendiol Acetal (14a). Oily, IR (film) 3400, 2950, 1450, 1380, 1200, 1090, 980 cm^{-1}. ^1H NMR ($CDCl_3$) δ=5.05 (2H, m, 3-H, 13-H), 3.55 (2H, m, 18-H), 3.16 (3H, s, OCH_3), 1.63 (6H, s, 1-CH_3, 15-CH_3), 1.57 (3H, s, 16-CH_3), 1.54 (3H, s, 20-CH_3), 1.30 (6H, s, 2 CH_3), 1.14 (3H, d, *J*=7 Hz, 17-CH_3). ^{13}C NMR ($CDCl_3$) δ=140.0 (d, 8-C), 131.1 (s, 2-C), 131.0 (s, 14-C), 126.4 (d, 9-C), 100.3 (s, O-C-O), 74.0 (s, 6-C), 63.0 (t, 18-C), 52.1 (q, OCH_3), 48.7 (d, 7-C), 38.8 (t, 5-C), 37.2 (t, 11-C), 36.7 (d, 10-C), 25.9 (t, 12-C), 25.6 (q, 19-C), 25.5 (q, 1-C, 15-C), 24.3 (q, 2 CH_3), 22.1 (t, 4-C), 20.7 (q, 17-C), 17.6 (q, 16-C, 20-C).

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