Characterization of 13-Hydroxyneocembrene from Soft Corals[1)]

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Synopsis. The isolation and structural elucidation of 13-hydroxyneocembrene from soft corals were carried out.

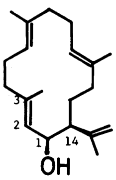
In the previous paper, some of us (Hiroshima group) have reported the characterization of a hydroxyneocembrene (**1**), named mayol, from a soft coral, *Sinularia mayi*.[2)] The structural elucidation of **1** was based on the spectral coincidence with the authentic *dl-cis*-1-hydroxyneocembrene synthesized by Tohoku group.[3)] The absolute configuration of the natural mayol, $[\alpha]_D$ +138.5° ($CHCl_3$) however, has remained unsolved because of limited amounts of the material.

In order to determine the absolute configuration, optical resolution of the synthetic *dl*-compound was performed by converting to *l*-camphanates followed by separation with high pressure liquid chromatography-(HPLC). Subsequent chemical transformation of the resultant enantiomers having $[\alpha]_D$ +156° and −156°, respectively, led to the conclusion that mayol has 1*S*,14*R* absolute stereochemistry although the value of optical rotation of the mayol is somewhat less than that of the resolved compound.[4)] For the sake of clarification of the difference of the specific rotation, the natural mayol was converted into the corresponding *l*-camphanate and subjected to HPLC analysis. It was soon made clear that the natural specimen was contaminated with minute amounts of an isomeric hydroxyneocembrene (**2**). It was found later that mayol and the isomeric hydroxyneocembrene could be separated by the repeated column chromatographies of the crude extracts. This paper concerns with the characterization of the isomeric compound.

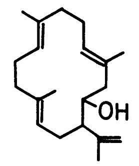
The isomeric compound (**2**) has a molecular formula of $C_{20}H_{32}O$ (M^+ 288.2428, Calcd. *MW*=288.2451) having $[\alpha]_D$ −30.3° (*c* 0.93, $CHCl_3$). The gross structure was deduced from ^1H- and ^{13}C-NMR spectra, which were indicative of the existence of three CH=CMe- and an isopropenyl groups in addition to a secondary hydroxyl group. Oxidation of **2** with Collins' reagent afforded the corresponding ketone (**3**) having the carbonyl absorption at 1705 cm^{-1} in the IR spectrum, exhibiting that the carbonyl moiety is *not* conjugated with the double bond. This deduction was supported by the observation of only end absorption in its UV spectrum. Wolff-Kishner reduction of **3** gave a hydrocarbon, the mass fragmentation of which was completely identical with the authentic *dl*-neocembrene (**4**).[5)]

The evidence described so far demonstrates the isomeric alcohol (**2**) is 13-hydroxyneocembrene. Recently Faulkner and his co-worker reported the isolation of 2,3-epoxy derivative (**5**) of 13-hydroxyneocembrene from a marine organism.[6)]

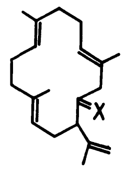
Determination of the relative stereochemistry of the 13-hydroxyneocembrene (**2**) by the synthetic study will be the future subject. It should be noticed that the naturally occurring mayol is not enantiomerically mixed with the corresponding antipode as suspected previously.[4)]



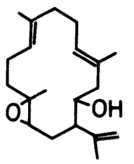
1



2



3 X = O
4 X = H_2



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Experimental

Measurements. NMR spectra were recorded with Varian EM-390 (90 MHz) and Varian XL-200 (200 MHz) spectrometers. Mass spectra were determined with a JEOL DX-300 spectrometer.

Isolation of Mayol (1) and 13-Hydroxyneocembrene (2). Crude MeOH extracts (30 g) from *Lobophytum denticulatum* Tixie-Durivault collected at coral reef of Miyako of Okinawa was eluted through a SiO_2 column with hexane–EtOAc (10:1) and the resultant fractions containing hydroxyneocembrenes (**1** and **2**) were developed on preparative TLC of 10% $AgNO_3$–SiO_2 with the same solvents. Repetition of TLC gave mayol (**1**) (37 mg) and the isomeric alcohol (**2**) (16 mg), respectively. **2** has the following physical data. IR(neat) 3400, 3070, 1660, 1640, 1050, and 890 cm^{-1}; ^1H-NMR ($CDCl_3$) δ= 1.54 (3H, t, 1.1 Hz), 1.58 (3H, s), 1.64 (3H, d, 0.9 Hz), 1.79 (3H, q, 0.7 Hz), 3.88 (1H, bt, 6 Hz), 4.83 (1H, bs), 4.92 (1H, bs), and 4.7—5.2 (3H, m); ^{13}C-NMR ($CDCl_3$) δ=14.9 (q), 15.3 (q), 16.7 (q), 22.8 (q), 24.2 (t), 24.8 (t), 24.9 (t), 38.7 (t), 39.9 (t), 43.9 (t), 49.9 (d), 71.6 (d), 111.6 (t), 125.4 (d), 125.9 (d), 127.2 (d), 131.1 (s), 132.9 (s), 134.0 (s), and 147.6 (s).

Purification of 13-Hydroxyneocembrene (2) by the Formation of l-*Camphanate.* To a solution of *l*-camphanyl chloride (22 mg) in pyridine (0.6 ml) was added a benzene solution (1 ml) of 13 mg of the crude mayol with $[\alpha]_D$ +138.5° (a mixture of mayol (**1**) and 13-hydroxyneocembrene (**2**)) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and then at rt for an additional 1 h. The mixture was diluted with ether (20 ml) and sequentially washed with dil $CuSO_4$ and brine, and then dried over Na_2SO_4 and filtered. The filtrate was evaporated *in vacuo* to give a viscous oil. Repeated HPLC (Lichrosorb SI 100) of the oil with hexane-ether (20:1) provided *l*-camphanates of mayol (9 mg) and of 13-hyroxyneocembrene (5 mg).

l-Camphanate of **2** $[\alpha]_D$ −33.8° (*c* 0.83, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ= 0.95 (3H, s), 1.05 (3H, s), 1.10 (3H, s), 1.49 (3H, s), 1.56 (3H, s), 1.64 (3H, s), 1.74 (3H, s), 4.73 (1H, s), 4.85 (1H, m), and 4.8—6.0 (4H, m). The *l*-camphanate of **2** (4 mg) was dissolved in 2M KOH-MeOH (2 ml (1 M=1 mol dm^{-3})). The solution was stirred at rt for 17 h, poured into water, and extracted with ether. The combined organic layers were sequentially washed with 1M HCl, sat $NaHCO_3$, and brine, dried over Na_2SO_4, and then filtered. The filtrate was evaporated *in vacuo* to afford a crude product. The crude product was passed through a SiO_2 column eluted with hexane–EtOAc (10:1) to give pure 13-hydroxyneocembrene (1.8 mg).

Oxidation of 13-Hydroxyneocembrene (2). To a stirred solution of Collins' reagent (11 mg, 0.04 mmol) in CH_2Cl_2 (1 ml) was added a solution of the alcohol (**2**) (1.2 mg, 0.004 mmol) in CH_2Cl_2 (0.1 ml) at room temperature. The resultant mixture was stirred for 5 min and then diluted with EtOAc (3 ml). The EtOAc layer was passed through a short SiO_2 column and the solvent was evaporated to give a light brown oil. Filtration through a SiO_2 column with hexane–EtOAc (30:1) afforded a colorless oil (**3**)(0.6 mg). The ketone (**3**) has the following physical data. M^+ 286; $[\alpha]_D$ +482.4° (*c* 0.09, $CHCl_3$); IR(CCl_4) 3010, 1705, 1645, and 905 cm^{-1}, ^1H-NMR ($CDCl_3$) δ=1.57 (6H, s), 1.66 (3H, s), 1.69 (3H, s), 2.63 (1H, ddd, 11.0, 11.0, 7.0 Hz), 2.71 (1H, bd, 13 Hz), 3.23 (1H, d, 13 Hz), 3.30 (1H, bd, 11 Hz), 4.86 (2H, bs), and 4.8—5.2 (3H, m).

Wolff-Kishner Reduction of the Ketone (3). The ketone (**3**) (0.6 mg) was dissolved into a mixture of 80% hydrazine hydrate (18 μl), NaOH (18 mg) and diethylene glycol (0.3 ml) and gradually heated to 190 °C and kept for 3 h at 190 °C. After cooling, the reaction mixture was diluted with ether, washed successively with 0.5 M HCl, sat. $NaHCO_3$ and then brine and dried over Na_2SO_4. The ether solution was evaporated and the residue was passed through a SiO_2 column with hexane to afford a hydrocarbon (**4**)) (*dl*-neocembrene) (0.1 mg). M^+ 272 (30%) and *m/z* at 121 (62), 107 (66), 93 (92), 81 (80), 68 (100), and 67 (58). The fragmentation pattern was identical with that of *dl*-neocembrene (**4**).

References

1) This constitutes part 43 of the series of "Cyclization of Polyenes" of Tohoku group.

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