Studies on the Sesquiterpenoids of Panax ginseng C. A. MEYER. IV

Hisakatsu IWABUCHI, a, b Nobuo KATO, b and Masahiro YOSHIKURA a

San-Ei Chemical Industries, Ltd., a 1-11, Sanwa-cho 1-chome, Toyonaka, Osaka 561, Japan and Institute of Advanced Material Study, Kyushu University. b
Kasugakoen 6-1, Kasuga, Fukuoka 816, Japan. Received August 28, 1989

A tricarbocyclic sesquiterpenoid (1), isolated from the ethereal extract of the rootlets of Panax ginseng C. A. MEYER, showed almost identical nuclear magnetic resonance data to those reported for senecradiosil (2). Detailed spectral analysis of 1 led us to revise the stereochemistry of 2.

Keywords senecradiosil; tricarbocyclic sesquiterpenoid; Panax ginseng; Araliaceae; revised structure; NOE

In our previous papers, we reported the isolation of some sesquiterpenoids from the ethereal extract of the rootlets of Panax ginseng C. A. MEYER. Herein, we wish to describe the structural elucidation of a newly isolated sesquiterpenoid, 1, from the neutral fraction.

Compound 1, [α]D 14.1°, colorless crystals, mp 109—
110 °C, had the molecular formula C15H22O2, confirmed by high-resolution mass spectroscopy (HR-MS). The infrared (IR) spectrum showed hydroxyl absorption (3400—
3600 cm⁻¹). The low-resolution MS of 1 showed the molecular ion peak at m/z 213 and fragment ion peaks at m/z 220 (M⁺–H2O), 202 (M⁺–2H2O), 165 and 123 (base peak). The proton nuclear magnetic resonance (¹H-NMR) spectrum of 1 showed three methyl signals at δ 0.94, 1.00 and 1.19 (each 3H, s), two methine protons at δ 2.48 (1H, m) and 3.33 (1H, br, s), and signals due to the A and B parts of ABX system at δ 1.34 (1H, dd, J = 16.2, 1.6 Hz) and 1.84 (1H, brd, J = 16.2 Hz). The carbon-13 nuclear magnetic resonance (¹³C-NMR) spectrum of 1 showed two signals due to carbon a hydroxyl group (δ 74.1, d, and 72.5, s), six methylene carbon signals (δ 22.0, 27.0, 34.4, 34.7, 36.1 and 38.4), two methine carbon signals (δ 41.6 and 49.0) and two quaternary carbon signals (δ 33.9 and 37.5), but no sp² carbon signals. Therefore, this compound is a saturated tricarbocyclic sesquiterpenoid.

After an intensive survey of reported ¹H- and ¹³C-NMR data, we noticed that the data of 1 closely resembled those of sescrassadiol (2), whose structure was proposed by Bohlmann and Ziesche mainly on the basis of the NMR spectra. Furthermore, the results of a two-dimensional incredible natural abundance double quantum transfer experiment (2D-INADEQUATE) and 2D-NMR (¹H-¹³C and long-range ¹H-¹³C shift correlation spectra (COSY)) of 1 were consistent with the planar structure of 2. Thus, these two compounds, 1 and 2, might be identical. However, since we have isolated a series of compounds related to (−)-β-caryophyllene from Panax ginseng, we considered that the stereochemistry (cis junction of the A/B rings) of 1 should be carefully investigated.

The nuclear Overhauser effect (NOE) correlation spectrum (NOESY) of 4 showed NOE correlations between several protons (2-H and 14-H3, and 5-H and 14-H3), and these were confirmed by the NOE experiments on 4, that is, NOEs were observed between 14-H3 and 2-H (9.8%), and between 14-H3 and 5-H (7.9%). Thus, the cyclobutane ring was condensed in the cis mode.

On the other hand, cross peaks between 2-H and one proton of the methano bridge part (C-12) were observed in the ¹H-¹H COSY spectra of 1 and 3. From the inspection of Dreedin models, these observations are explicable in terms of long-range coupling via W-interaction between the 2- and 12a-H in 1 and 3 rather than 2. To elucidate the relative geometry between 2-H and the methano bridge part (C-12), NOE difference experiments were undertaken using 3b (Fig. 1). Irradiation at the frequency of the 14-H3 signal caused an enhancement of the intensity of the 2-H signal, as well as an ambiguous enhancement of the intensity of the 5-H signal. Next, irradiation of 13-H3 signal caused an enhancement of the intensity of the 6-H signal, whose relative configuration is assigned to be α from the inspection of Dreedin models based on the NOE findings mentioned above in 3 and 4. Furthermore, irradiation of 15-H3 caused an enhancement of the intensity of this 6α-H. These observations indicate that the 13- and 15-methyl groups are spatially close to 6α-H. Other NOE findings are indicated by the double-headed arrows in the structure in Fig. 1. From these results, the relative geometry between 2-H and the methano bridge part was elucidated to be anti. On the other hand, the epimer (5) of 1 was obtained by the lithium aluminium hydride (LAH) reduction of 3, and the secondary hydroxyl group of 1 should be α-oriented, taking the reduction mechanism from 3 to 5 into consideration. This was supported by the observation of long-range coupling between 9β-H and 12β-H in the ¹H-¹H COSY spectrum of 1. Therefore, the stereochemistry of compound 1 should be represented by the formula 1. This is different from the proposed structure 2, and the previous reported structure 2 should be revised.
flow rate, 2.5 ml/min) to give a crystalline substance, which was re-crystallized from hexane–ether mixture to give 1 (138 mg).

**Compound 1** Colorless crystals, mp 109–110 °C. [α]νD20 = −14.1° (c = 0.99, CHCl3). IR (CHCl3): 3400–3600, 2950, 1460, 1375, 1365 cm⁻¹. H-NMR (CDCl3, 200 MHz): δ = 0.94 (3H, s, 13-H), 1.00 (3H, s, 15-H), 1.19 (3H, s, 14-H), 1.34 (1H, dd, J = 16.2, 12-H), 2.48 (1H, m, 2-H), 3.33 (1H, brs, 9-H). 13C-NMR (CDCl3, 50 MHz): δ = 22.0 (t, C-6), 24.4 (C-C-13), 27.0 (t, C-10), 28.7 (q, C-14), 30.0 (q, C-15), 33.9 (s, C-4), 34.4 (t, C-3), 35.7 (t, C-11), 36.1 (t, C-7), 37.5 (s, C-8), 38.4 (t, C-12), 41.6 (d, C-3), 49.0 (d, C-5), 72.5 (s, C-1), 74.1 (d, C-9). MS 205 (2%), MS 204 (1%), 203 (22%), 201 (25%), 199 (13%), 198 (100%), 197 (92), 86 (21), 69 (17), 55 (38), 41 (51). HR-MS m/z: *M* + 1 C18H20O3 (238.193. Found: m/z = 238.194. The 1H- and 13C-NMR, and mass spectra, and [α]νD20 value were in good agreement with those reported for 2.⁶

**Collins Oxidation of 1** A solution of 1 (70 mg) in dry CHCl3 (3 ml) was added to the prepared CrO3/pyridine complex (0.8 g in 3 ml of CHCl3) and stirred at room temperature for 15 min. After usual work-up, the oily substance was subjected to silica-gel chromatography followed by preparative HPLC (solvent, benzene–ether (9:1, v/v)) to give a crystalline substance, which was re-crystallized from hexane–ether mixture to give 3 (39 mg) as colorless crystals, mp 105–106 °C. [α]νD20 = −82.4° (c = 0.61, CHCl3). IR (CHCl3): 3400–3600, 2940, 1705, 1460, 1385 cm⁻¹.

H-NMR (CDCl3, 400 MHz): δ = 0.99 (3H, s, 13-H), 1.09 (3H, s, 15-H), 1.22 (3H, s, 14-H), 1.50 (1H, m, 7a-H), 1.59 (1H, brd, J = 13.8 Hz, 12a-H), 1.74 (1H, m, 6-H), 1.82 (1H, t, J = 11.0 Hz, 3a-H), 2.30 (1H, d, J = 13.8 Hz, 12-H), 2.37 (1H, dt, J = 17.2, 4.4 Hz, 10-H), 2.62 (1H, dd, J = 17.2, 1.0 Hz, 11-H), 5.26 (1H, s, 5-H), 6.2 (1H, d, J = 10.2 Hz, 5a-H). 13C-NMR (CDCl3, 400 MHz): δ = 21.3 (t), 24.3 (q), 25.4 (q), 29.3 (q), 33.0 (t), 33.2 (t), 33.3 (s), 35.1 (t), 36.0 (t), 40.0 (d, J = 24.6, 44.1 (d), 47.1 (d), 71.4 (s). MS m/z (% rel. int.): 236 (M⁺, 2), 218 (17), 178 (6), 163 (22), 144 (42), 129 (31), 123 (100), 105 (26), 96 (37), 79 (26), 69 (28), 55 (55), 41 (84). HR-MS m/z: *M* + 1 C18H18O3 (238.178. Found: m/z = 238.175. The H-NMR spectrum was in good agreement with that reported for 3.⁶

**Wolf-Kishner Reduction of 3** A solution of 3 (30 mg) in triethylene glycol (5 ml) containing KOH (80 mg) and 80% hydrizine hydrate (0.25 ml) was heated at 120 °C for 1.5 h followed by 180 °C for 2 h. The reaction mixture was treated in the usual way to give a residue, which was subjected to preparative HPLC (solvent, benzene–ether (9:1, v/v)). Recrystallization from hexane–ether gave 4 (16.5 mg) as colorless crystals, mp 96–97 °C. [α]νD20 = −10.8° (c = 0.93, CHCl3). IR (KBr): 3300–3600, 2930, 2930, 1460, 1380, 1330, 1100, 1055, 1015 cm⁻¹. H-NMR (CDCl3, 270 MHz): δ = 0.93 (3H, s, 13-H), 0.95 (3H, s, 15-H), 1.18 (3H, s, 14-H), 1.82 (1H, m, 5-H), 2.07 (1H, dt, J = 13.2, 2.2 Hz, 12-H), 2.47 (1H, m, 2-H), 2.59 (3H, s, 10-C), 23.2 (t, C-6), 24.4 (q, C-13), 28.9 (q, C-14), 33.1 (s, C-8), 33.8 (s, C-4), 34.5 (t, C-3), 35.2 (s, C-15), 36.6 (t, C-7), 40.6 (t, C-9), 41.5 (d, C-2), 42.8 (q, C-11), 44.8 (t, C-12), 48.9 (d, C-5), 73.0 (s, C-10). MS m/z (% rel. int.): 222 (M⁺, 2), 207 (1), 204 (4), 166 (11), 149 (25), 120 (100), 95 (29), 55 (36), 41 (52). HR-MS m/z: *M* + 1 C18H18O2 (222.185. Found: m/z = 222.195. MS 203 (2%), MS 202 (1%), MS 201 (100%), MS 199 (95), 198 (25), 197 (92), 196 (21), 195 (17), 194 (9), 193 (7), 192 (5), 191 (4), 190 (3), 189 (1), 188 (1), 187 (1), 186 (1), 185 (1), 184 (1), 183 (1), 182 (1), 181 (1), 180 (1), 179 (1), 178 (1), 177 (1), 176 (1), 175 (1), 174 (1), 173 (1), 172 (1), 171 (1), 170 (1), 169 (1), 168 (1), 167 (1), 166 (1), 165 (1), 164 (1), 163 (1), 162 (1), 161 (1), 160 (1), 159 (1), 158 (1), 157 (1), 156 (1), 155 (1), 154 (1), 153 (1), 152 (1), 151 (1), 150 (1), 149 (1), 148 (1), 147 (1), 146 (1), 145 (1). Acid-Catalyzed Rearrangement of 4 According to the previously outlined procedure,⁴⁴ a 15 mg was treated with concentrated H2SO4 to give a two-component mixture which was subjected to silica-gel chromatography. The fractions eluted with hexane were further subjected to preparative HPLC (solvent, hexane; column temperature, −45 °C) to give pure 6 (5.2 mg) as a colorless oil. [α]νD20 = −30.3° (c = 0.33, CHCl3) lit. [α]νD20 = −27.1° (c = 3.13, CHCl3). IR (CCl3): 3030, 2950, 1460, 1380, 1360 cm⁻¹. H-NMR (CDCl3, 270 MHz): δ = 0.86 (3H, s, 13-H), 0.95 (3H, s, 15-H), 1.05 (3H, s, 14-H), 5.28 (1H, d, J = 5.7 Hz), 5.36 (1H, d, J = 5.7 Hz). MS m/z (% rel. int.): 204 (M⁺), 8, 189 (55), 175 (3), 161 (100), 133 (13), 119 (19), 105 (24), 91 (27), 77 (14), 55 (11), 41 (25). This product was isolated and purified by column chromatography on silica gel using a mixture of hexane–ether (9:1, v/v) to give 7 (7.6 mg) as colorless crystals,
Collins Oxidation of 7 According to the method described above, 7 (5 mg) was oxidized. After usual work-up, the oily substance was subjected to silica-gel chromatography followed by preparative HPLC (solvent, hexane-ether (9 : 1, v/v)) to give pure 8 (4.1 mg) as a colorless oil. [α]D

20 + 19.2° (c=0.68, CHCl3) (lit. [α]D +20.0° (c=2.23, CHCl3)). IR (CHCl3): 3010, 2950, 1725, 1460, 1370 cm⁻¹. 1H-NMR (CDCl3, 270 MHz) δ: 0.89 (3H, s), 0.99 (3H, s), 1.07 (3H, s), 2.13 (1H, d, J=16.1 Hz), 2.28 (1H, d, J=16.1 Hz). MS m/z (% rel. int.): 220 (M⁺, 40), 205 (9), 177 (5), 164 (8), 136 (100), 121 (39), 107 (33), 93 (40), 83 (82), 79 (32), 55 (22), 41 (55). HR-MS m/z: M⁺ Calcd for C11H24O: 220.183. Found: 220.180.

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References and Notes
2) Compound 1 was reported under the name of isocaryolanediol at the 32nd Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Miyazaki, October 1988.
4) In the 1H-NMR spectra of 1 and 3—5, the 5-H signal was observed as a multiplet separated from other signals only in 4. For this reason, 4 was used for the NOE experiments to obtain precise results.
5) Each signal was assigned on the basis of the 1H-1H and 1H-13C COSY spectra and inspection of the Dreiding model of 3.