Water-Soluble Constituents of Fennel. IV.[1] Menthane-Type Monoterpenoids and Their Glycosides

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Two free forms and five glycosyl forms of menthane-type monoterpenoids were isolated from the water-soluble portion of the methanolic extract of fennel. From the spectral evidences, these were characterized as *cis-p*-menthane-1,7,8-triol, *trans-p*-menthane-1,7,8-triol, *cis-p*-menthane-1,7,8-triol 8-*O*-β-D-glucopyranoside, *trans-p*-menthane-1,7,8-triol 8-*O*-β-D-glucopyranoside, *trans-p*-menthane-7,8-diol 7-*O*-β-D-glucopyranoside, *trans-p*-menthane-7,8-diol 8-*O*-β-D-glucopyranoside and (4*R*)-*p*-menth-1-ene-7,8-diol 8-*O*-β-D-glucopyranoside.

Key words fennel; *Foeniculum vulgare* fruit; Umbelliferae; hydroxy-*p*-menthane; *p*-menthane-type glycoside

In previous papers, we reported the isolation and characterization of fenchane-type monoterpenoid glycosides[1] and 1,8-cineole type monoterpenoid glycosides[2] from the herbal medicine, fennel. In this paper, we describe the isolation and structure elucidation of seven menthane-type monoterpenoids (two of them were in the free form and five of them were glycosides).

The methanolic extract of commercial fennel [prepared from the fruit of *Foeniculum vulgare* MILLER (Umbelliferae)] was suspended in water and successively extracted with ether and ethyl acetate. The aqueous layer obtained was evaporated, and the residue was chromatographed on Amberlite XAD-II to give water and methanol fractions. The methanol fraction was subjected to a combination of Sephadex LH-20, silica gel and Lobar RP-8 column chromatography and HPLC to give mixtures[3] of triols (**1** and **2**) and glycosides (**3** and **4**, and **5**, **6** and **7**). These mixtures were separated into separate components using reversed-phase columns after acetylation.

Triol **1** ($C_{10}H_{20}O_3$, mp 137—139 °C, $[\alpha]_D^{22}$ ±0°) showed $[M+Na]^+$, $[M+H]^+$, $[M-H_2O+H]^+$, $[M-2H_2O+H]^+$ and $[M-3H_2O+H]^+$ ion peaks at *m/z* 211, 189, 171, 153 and 135 in the positive FAB-MS. The ^1H-, ^{13}C- and ^{13}C–^1H correlation spectroscopy (COSY) NMR spectral data (Tables 1 and 2) for **1** revealed the presence of one pair of *tert*-methyls, two pairs of methylenes (each pair has the same δ value in ^1H- and ^{13}C-NMR), one hydroxymethyl and one methine, and two oxygenated quaternary carbons. So, **1** was suggested to be a *p*-menthane-type monoterpenoid triol which has planar symmetry. The planar structure was obtained by analysis of its heteronuclear multiple-bond correlation (HMBC) spectral data which showed a correlation from the *tert*-methyl protons to the C-4 and C-8 carbons, the hydroxymethyl protons to the C-1 and C-2(6) carbons, and the methine proton to the C-2(6) carbons. So, the position of the hydroxyl group was concluded to be C-1, C-7 and C-8. The stereochemistry of **1** was found to be the 7–8 *cis* form from the observed cross peaks between H_2-7 and H-2(6)α, H_2-7 and H-3(5)α, H-4β and H-2(6)β in its nuclear Overhauser enhancement and exchange spectroscopy (NOESY) spectrum (Fig. 1). From these results, **1** was concluded to be *cis-p*-menthane-1,7,8-triol.

Triol **2** ($C_{10}H_{20}O_3$, mp 107—109 °C, $[\alpha]_D^{22}$ ±0°) showed a similar fragmentation pattern to that of **1** in the positive FAB-MS. Comparison of its ^1H- and ^{13}C-NMR data (Tables 1 and 2) with those of **1** suggested that **2** has the same planar structure as **1**, and the stereochemistry of **2** was considered to be the 7–8 *trans* form from the downfield chemical shift of its H-3(5)α protons [**1**: δ 1.47; **2**: δ 2.04] due to the influence of an *axial*-hydroxyl group. This was also supported by the observed cross peaks in its NOESY spectrum described in Fig. 1. From these results, **2** was concluded to be *trans-p*-menthane-1,7,8-triol. **1** and **2** were synthesized from δ-terpineol and the reported ^{13}C-NMR data were identical with our data.[4] *p*-Menthane-1,7,8-triol has been reported as a constituent of the roots of *Cynanchum hancockianum*, but the stereochemistry was not determined.[5]

Glycoside **3** ($C_{16}H_{30}O_8$, an amorphous powder, $[\alpha]_D^{22}$ −12.8°) showed $[M+K]^+$, $[M+Na]^+$, $[M+H]^+$, $[M-H_2O+H]^+$, $[M-2H_2O+H]^+$ and $[M-C_6H_{12}O_6+H]^+$ ion peaks at *m/z* 389, 373, 351, 333, 315 and 171 in the positive FAB-MS. Acid hydrolysis of **3** gave D-glucose as a sugar component. The ^1H-, ^{13}C- and ^{13}C–^1H COSY NMR spectral data (Tables 1 and 2) for **3** revealed the presence of one β-glucopyranosyl, two *tert*-methyls, four methylenes, one hydroxymethyl and one methine group, and two oxygenated quaternary carbons. Comparison of its ^1H- and ^{13}C-NMR data with those of **1** and **2** indicated that **3** was the β-glucopyranoside of **1**. Analysis of the HMBC spectral data, gave a planar structure for **3**, and the location of the glucosyl unit was confirmed to be C-8 by the cross peak between the glucosyl H-1 and C-8. So, **3** was concluded to be *cis-p*-menthane-1,7,8-triol 8-*O*-β-D-glucopyranoside.

Glycoside **4** ($C_{16}H_{30}O_8$, an amorphous powder, $[\alpha]_D^{22}$ −10.0°) showed the same ion peaks as **3** in the positive FAB-MS. By comparison of ^1H- and ^{13}C-NMR data (Tables 1 and 2) with those of **2** and **3**, **4** was confirmed to be the β-glucopyranoside of **2**. The location of the glucosyl unit was suggested to be C-8 from the similarity in its ^{13}C signal chemical shifts of C-4, C-8, C-9, C-10 and glucosyl C-1 to that of **3**. So, **4** was concluded to be *trans-p*-menthane-1,7,8-triol 8-*O*-β-D-glucopyranoside.

Glycoside **5** ($C_{16}H_{30}O_7$, an amorphous powder, $[\alpha]_D^{22}$ −23.1°) showed $[M+Na]^+$, $[M-H_2O+H]^+$ and $[M-C_6H_{12}O_6+H]^+$ ion peaks at *m/z* 357, 317 and 155 in the positive FAB-MS, and D-glucose was produced by acid hydrolysis. The ^1H-, ^{13}C- and ^{13}C–^1H COSY NMR spectral data (Tables 1 and 2) for **5** revealed the presence of one β-glucopyra-

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nosyl, two *tert*-methyls, one hydroxymethyl, four methylenes and two methines, and one oxygenated quaternary carbon. By comparison of its ^{1}H- and ^{13}C-NMR data with those of **1** and **2**, and by an HMBC experiment, **5** was suggested to be the β-glucopyranoside of *p*-menthane-7,8-diol. The location of the glucosyl unit was confirmed to be C-7 by the cross peak between the glucosyl H-1 and C-7. The similarity in its ^{13}C signal chemical shifts of C-4, C-8, C-9 and C-10 to that of **1** and **2**, also supported this structure. As the cross peaks described in Fig. 1 were observed in the NOESY spectrum of **5**, the aglycone of **5** was shown to be the *trans* form. From these facts, **5** was concluded to be *trans-p*-menthane-7,8-diol 7-*O*-β-D-glucopyranoside.

Glycoside **6** ($C_{16}H_{30}O_7$, an amorphous powder, $[\alpha]_D^{22}$ $-15.3°$) showed $[M+H]^+$, $[M-H_2O+H]^+$, and $[M-C_6H_{12}O_6+H]^+$ ion peaks at *m/z* 335, 317 and 155 in the positive FAB-MS. Comparison of ^{1}H- and ^{13}C-NMR data (Tables 1 and 2) with those of **3**, **4** and **5**, indicated that **6** was a β-glucopyranoside having the same aglycone as **5**. The location of the glucosyl group of **6** was suggested to be C-8 from comparison of the ^{13}C signal chemical shifts of its C-4, C-8, C-9, C-10 and glucosyl C-1 with that of **3** and **4**. As the cross peaks described in Fig. 1 were observed in the NOESY spectrum, the aglycone of **5** should be in the *trans* form. From

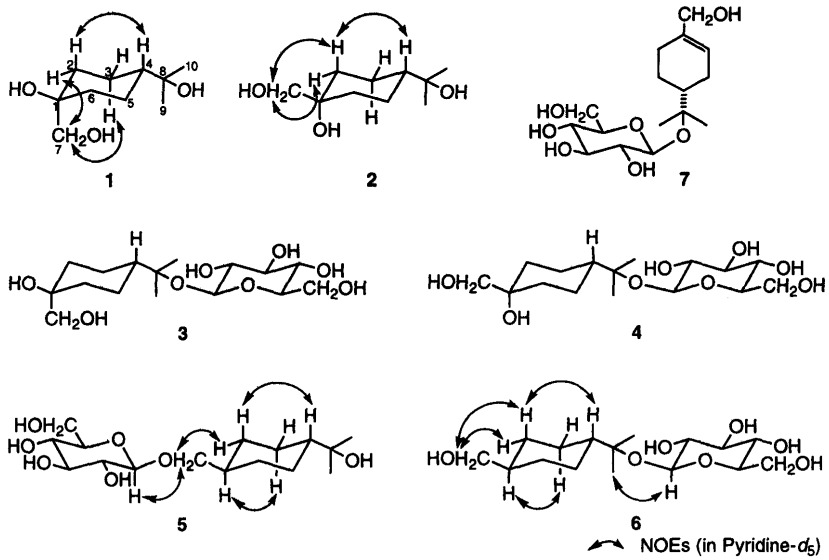

Fig. 1. Structures of **1**—**7** and NOE Interactions Observed in the NOESY Spectra of **1**, **2**, **5** and **6**

Table 1. ^{1}H-NMR Chemical Shifts of **1**—**7** (in Pyridine-d_5, 500 MHz)

	1	2	3	4
H-2,6α	2.39 ddd (3.5, 3.5, 13.5)	2.14 ddd (3.0, 3.0, 13.0)	2.31 br d (13.5)	1.94 ddd (3.5, 3.5, 13.0)
β	1.78 ddd (3.5, 13.5, 13.5)	1.71 ddd (3.0, 13.0, 13.0)	1.73 ddd (3.5, 13.5, 13.5)	1.67 ddd (3.5, 13.0, 13.0)
H-3,5α	1.47 dddd (3.5, 12.0, 13.5, 13.5)	2.04 m	1.33 br ddd (3.5, 13.5, 13.5)	2.08 m
β	2.04 br dd (3.5, 13.5)	2.04 m	2.02 br dd (3.5, 13.5)	2.08 m
			2.05 br dd (3.5, 13.5)	
H-4β	1.62 dddd (3.5, 3.5, 12.0, 12.0)	1.61 dddd (3.0, 3.0, 13.0,13.0)	1.71 m	1.73 dddd (3.5, 3.5, 13.0, 13.0)
H_2-7	4.04 br s	3.84 br s	3.98 br s	3.81 br s
H_3-9,10	1.33 s	1.40 s	1.36 s	1.43 s
			1.38 s	1.46 s
Glc-1			5.03 d (7.5)	5.08 d (8.0)

	5	6		7
H-1α	1.67 m	1.63 m	H-2	5.90 br d (3.0)
H-2,6α	1.99 dddd (3.0, 3.0, 3.0, 13.0)	2.05 br d (13.0)	H_2-3	2.23 m
β	1.00 dddd (3.0, 3.0, 13.0, 13.0)	1.09 br dd (13.0, 13.0)	H-4β	1.88 dddd (2.0, 2.0, 13.0, 13.0)
H-3,5α	1.14 dddd (3.0, 13.0, 13.0, 13.0)	1.15 br ddd (13.0, 13.0, 13.0)	H_2-5	1.32 br ddd (5.0, 13.0, 13.0)
β	2.03 dddd (3.0, 3.0, 3.0, 13.0)	2.11 br d (13.0)		2.27 br d (13.0)
		2.16 br d (13.0)	H_2-6	1.95 br dd (13.0, 13.0)
H-4β	1.41 dddd (3.0, 3.0, 13.0, 13.0)	1.61 m		2.31 ddd (2.0, 5.0, 13.0)
H_2-7	3.50 dd (6.5, 9.5)	3.68 d (6.0)	H_2-7	4.26 d (8.5)
	3.94 dd (6.5, 9.5)			4.28 d (8.5)
H_3-9,10	1.29 s	1.36 s	H_3-9,10	1.37 s
		1.38 s		1.39 s
Glc-1	4.85 d (7.5)	5.03 d (8.0)	Glc-1	5.03 d (8.0)

δ in ppm from TMS [coupling constants (J) in Hz are given in parentheses].

Table 2. ^{13}C-NMR Chemical Shifts of **1**—**7** (in Pyridine-d_5, 125 MHz)

	1	2	3	4	5	6	7
C-1	72.09	72.42	72.02	72.35	38.67	41.52	139.26
C-2	36.35	34.94	36.18	34.87	30.48[c]	30.42	121.33
C-3	25.20	23.10	24.93[a]	22.93[a]	27.28	27.38[a]	27.14[d]
C-4	49.55	50.19	48.15	48.56	49.81	48.58	44.59
C-5	25.20	23.10	24.85[a]	22.81[a]	27.28	27.26[a]	23.96
C-6	36.35	34.94	36.18	34.87	30.43[c]	30.42	27.12[d]
C-7	66.31	71.10	66.23	71.13	75.54	68.05	66.55
C-8	71.24	71.62	79.30	79.82	71.34	79.53	79.30
C-9	27.80	27.78	24.59[b]	24.63[b]	27.54[b]	24.47[b]	24.34[b]
C-10	27.80	27.78	23.96[b]	24.12[b]	27.49[b]	23.85[b]	23.71[b]
Glc-1			98.63	98.70	104.90	98.56	98.63
Glc-2			75.40	75.48	75.25	75.37	75.43
Glc-3			78.88	78.94	78.54	78.83	78.96
Glc-4			71.87	71.96	71.68	71.85	71.94
Glc-5			78.04	78.07	78.46	77.95	78.15
Glc-6			63.01	63.08	62.79	62.97	63.05

δ in ppm from TMS. *a*—*d*) Assignments may be interchanged in each column.

these results, **6** was concluded to be *trans-p*-menthane-7,8-diol 8-*O*-β-D-glucopyranoside.

Glycoside **7** ($C_{16}H_{28}O_7$, an amorphous powder, $[\alpha]_D^{22}$ +7.5°) showed $[M+K]^+$, $[M+Na]^+$, $[M+H]^+$, $[M-H_2O+H]^+$ and $[M-C_6H_{12}O_6+H]^+$ ion peaks at *m/z* 371, 355, 333, 315 and 153 in the positive FAB-MS. The ^{1}H-, ^{13}C- and ^{13}C–^{1}H COSY NMR spectral data (Tables 1 and 2) for **7** revealed the presence of one β-glucopyranosyl, one tri-substituted double bond, two *tert*-methyls, three methylenes, one hydroxymethyl and one methine, and one oxygenated quaternary carbon. From analysis of the HMBC spectral data which showed the correlation from the two *tert*-methyl protons to the C-4 and C-8 carbons, one hydroxymethyl protons to the C-1, C-2 and C-6 carbons, one methine proton to the C-2 and C-6 carbons, and the glucosyl H-1 to the C-8 carbon, the aglycone of **7** and the location of the glucosyl unit were confirmed to be *p*-menth-1-ene-7,8-diol and C-8, respectively. Since the glucose was considered to be the same D-form as the other glucosides, the aglycone of **7** was suggested to be the (+)-form from its $[M]_D$ value (+25°), which was plus when calculated using the value for methyl β-D-glucopyranoside (−62°; **7**−methyl β-D-glucopyranoside=+87°).[6] As the 4*R* form of *p*-menth-1-ene-7,8-diol was reported to have a positive optical rotation,[7] the aglycone of this glucoside should be the 4*R* form.[8] From these facts, **7** was concluded to be (4*R*)-*p*-menth-1-ene-7,8-diol 8-*O*-β-D-glucopyranoside.

Glycosides **3** to **7** are new compounds occurring as natural products.

Experimental

The instruments used and the experimental conditions for obtaining spectral data and for chromatography were the same as in the preceding paper.[9]

Extraction and Isolation of Menthane-Type Monoterpenoids and Their Glycosides Commercial fennel (purchased from Kinokuniya Chinese Medicine Pharmacy, Ltd., lot. No. A0CJ0D28J; 2.0 kg) was extracted with methanol at room temperature. The methanol extract (329.4 g) was partitioned between ether–water and then ethyl acetate–water, the aqueous fraction obtained was subjected to Amberlite XAD-II (H_2O→MeOH) chromatography. The methanol eluate (29.5 g) was chromatographed over Sephadex LH-20 (MeOH) to give seven fractions (frs. A—G). Fraction C (16.9 g) was chromatographed over silica gel [$CHCl_3$–MeOH–H_2O (4 : 1 : 0.1)→MeOH] to give fifteen fractions (frs. C_1–C_{15}). Fraction C_5 (1.7 g) was passed through a Lobar RP-8 column [CH_3CN–H_2O (3 : 17)] to give twelve fractions (frs. $C_{5\text{-}1}$—$C_{5\text{-}12}$). Fraction $C_{5\text{-}4}$ was acetylated with Ac_2O and pyridine at room temperature and the product was subjected to HPLC [octadecyl silica (ODS), MeOH–H_2O (2 : 3)] to give two fractions and each fraction was deacetylated by heating on a water bath with 5% NH_4OH–MeOH for 2 h to give **1** (6 mg) and **2** (3 mg). Fraction C_6 (1.9 g) was passed through a Lobar RP-8 column [CH_3CN–H_2O (3 : 17)] to give thirteen fractions (frs. $C_{6\text{-}1}$—$C_{6\text{-}13}$). Fraction $C_{6\text{-}8}$ was acetylated and the product was subjected to HPLC [ODS, MeOH–H_2O (3 : 2)] to give five fractions (frs. $C_{6\text{-}8\text{-}1}$—$C_{6\text{-}8\text{-}5}$). Fraction $C_{6\text{-}8\text{-}1}$ and fr. $C_{6\text{-}8\text{-}4}$ were deacetylated by heating on a water bath with 5% NH_4OH–MeOH for 2 h to give **5** (18 mg) and **7** (4 mg) in pure form, respectively. Fraction $C_{6\text{-}8\text{-}5}$ was deacetylated by heating on a water bath with 15% NH_4OH–MeOH for 4 h to give **6** (16 mg). Fraction C_{10} (0.4 g) was passed through a Lobar RP-8 column [MeOH–H_2O (1 : 4)] to give seven fractions (frs. $C_{10\text{-}1}$—$C_{10\text{-}7}$). Fraction $C_{10\text{-}4}$ was acetylated and the acetylated fraction was separated into two components by silica gel column chromatography [hexane–EtOAc (1 : 1)]. Then, each fraction was deacetylated by heating on a water bath with 5% NH_4OH–MeOH for 2 h to give **3** (9 mg) and **4** (5 mg) in pure form.

***cis-p*-Menthane-1,7,8-triol (1)** Colorless needles (MeOH), mp 137—139 °C, $[\alpha]_D^{22}$ ±0° (*c*=0.4, MeOH). Positive FAB-MS *m/z*: 377 $[2M+H]^+$, 211 $[M+Na]^+$, 189.1469 $[M+H]^+$ (Calcd for $C_{10}H_{21}O_3$: 189.1491), 171 $[M-H_2O+H]^+$, 153 $[M-2H_2O+H]^+$ (base), 135 $[M-3H_2O+H]^+$.

***trans-p*-Menthane-1,7,8-triol (2)** Colorless needles (MeOH), mp 107—109 °C, $[\alpha]_D^{22}$ ±0° (*c*=0.2, MeOH). Positive FAB-MS *m/z*: 377 $[2M+H]^+$, 211 $[M+Na]^+$, 189.1481 $[M+H]^+$ (Calcd for $C_{10}H_{21}O_3$: 189.1491), 171 $[M-H_2O+H]^+$, 153 $[M-2H_2O+H]^+$ (base), 135 $[M-3H_2O+H]^+$.

***cis-p*-Menthane-1,7,8-triol 8-*O*-β-D-Glucopyranoside (3)** An amorphous powder, $[\alpha]_D^{22}$ −12.8° (*c*=0.4, MeOH). Positive FAB-MS *m/z*: 443 $[M+H+glycerol]^+$, 389 $[M+K]^+$, 373 $[M+Na]^+$ (base), 351.2032 $[M+H]^+$ (Calcd for $C_{16}H_{31}O_8$: 351.2019), 333 $[M-H_2O+H]^+$, 315 $[M-2H_2O+H]^+$, 171 $[M-C_6H_{12}O_6+H]^+$.

***trans-p*-Menthane-1,7,8-triol 8-*O*-β-D-Glucopyranoside (4)** An amorphous powder, $[\alpha]_D^{22}$ −10.0° (*c*=0.2, MeOH). Positive FAB-MS *m/z*: 701 $[2M+H]^+$, 443 $[M+H+glycerol]^+$, 389 $[M+K]^+$, 373 $[M+Na]^+$ (base), 351.2023 $[M+H]^+$ (Calcd for $C_{16}H_{31}O_8$: 351.2019), 171 $[M-C_6H_{12}O_6+H]^+$.

***trans-p*-Menthane-7,8-diol 7-*O*-β-D-Glucopyranoside (5)** An amorphous powder, $[\alpha]_D^{22}$ −23.1° (*c*=0.8, MeOH). Positive FAB-MS *m/z*: 357.1888 $[M+Na]^+$ (base, Calcd for $C_{16}H_{30}O_7Na$: 357.1889), 317 $[M-H_2O+H]^+$, 155 $[M-C_6H_{12}O_6+H]^+$.

***trans-p*-Menthane-7,8-diol 8-*O*-β-D-Glucopyranoside (6)** An amorphous powder, $[\alpha]_D^{22}$ −15.3° (*c*=0.6, MeOH). Positive FAB-MS *m/z*: 427 $[M+H+glycerol]^+$, 335.2075 $[M+H]^+$ (Calcd for $C_{16}H_{31}O_7$: 335.2070), 317 $[M-H_2O+H]^+$, 155 $[M-C_6H_{12}O_6+H]^+$ (base).

(4*R*)-*p*-Menth-1-ene-7,8-diol 8-*O*-β-D-Glucopyranoside (7) An amorphous powder, $[\alpha]_D^{22}$ +7.5° (*c*=0.2, MeOH). Positive FAB-MS *m/z*: 425 $[M+H+glycerol]^+$, 371 $[M+K]^+$, 355 $[M+Na]^+$, 333.1931 $[M+H]^+$ (base, Calcd for $C_{16}H_{29}O_7$: 333.1913), 315 $[M-H_2O+H]^+$, 153 $[M-C_6H_{12}O_6+H]^+$.

Acid Hydrolysis of 3 and 5 Glycosides **3** (4 mg) and **5** (8 mg) were dissolved in aq. 2 N H_2SO_4 and heated on a water bath for 3 h. The hydrolysate

was neutralized with $NaHCO_3$, the salt filtered off, and the filtrate passed through Sephadex LH-20 (MeOH). The sugar fraction was subjected to HPLC [column; carbohydrate analysis (Waters: size, 3.9×300 mm), detector; JASCO RI-930 detector and JASCO OR-990 chiral detector, solv., CH_3CN–H_2O (17 : 3), 2 ml/min, t_R 4.53 min (same location as that of D-glucose)] to show the presence of D-glucose.

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