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The Constituents of *Schizonepeta tenuifolia* Briq. I. Structures of Two New Monoterpene Glucosides, Schizonepetosides A and B

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Two new glucosides, named schizonepetosides A (**1**) and B (**2**), were isolated from the spikes of *Schizonepeta tenuifolia* (Labiatae). The structure of **1** was elucidated as (1*S*, 4*R*, 8*E*)-9-O-β-D-glucopyranosyl-*p*-menth-8(9)-en-3-one on the basis of chemical and spectral studies.

Compound **2** was identified as a glucoside possessing a dioxane ring formed by the double linkage between glucose and the aglycone, (1*S*, 4*R*, 8*R*)-8,9-dihydroxy-*p*-menth-3-one, by X-ray crystallographic analysis.

Keywords——*Schizonepeta tenuifolia*; Labiatae; monoterpene glucosides; schizonepetoside A; enol glucoside; (1*S*, 4*R*, 8*E*)-9-O-β-D-glucopyranosyl-*p*-menth-8(9)-en-3-one; schizonepetoside B; X-ray analysis; ^{13}C-NMR

The spikes of *Schizonepeta tenuifolia* Briq. (syn., *Nepeta japonica* Maxim.) (Labiatae) are used as an antifebrile, an analgesic, an anti-inflammatory, and a hemostatic under the name of "Jingzie" in China (Japanese name, "Keigai 荊芥").[1]

The essential oil of this plant was examined in detail by Fujita *et al.*, who reported the presence of (+)-menthone and (−)-pulegone as main components.[2] Very recently, Yamahara *et al.* studied the biological activity of the essential oil and reported that (+)-menthone showed an analgesic activity and (−)-pulegone showed an anti-inflammatory activity in mice.[3] However, the water-soluble constituents of this plant have not been investigated. Now, we wish to report the isolation and the structure elucidation of two new monoterpene glucosides, named schizonepetosides A (**1**)[4] and B (**2**).

These two compounds possess the menthone skeleton as the aglycone; **1** is a rare aldehyde enol glucoside and **2** is a glucoside possessing a dioxane ring formed by the double linkage between glucose and the aglycone.

The dried and pulverized spikes of the plant were extracted with ether and then methanol. The methanolic extract was dissolved in water, and extracted with chloroform and butanol. The butanolic extract was successively subjected to polyamide, charcoal, and silica gel column chromatographies to give the crude **1** and pure **2** as colorless plates (yield, 0.004%).

Compound **1** was further purified by preparative high performance liquid chromatography (prep. HPLC) and pure **1** was obtained as a very hygroscopic white amorphous solid (yield, 0.04%), $[\alpha]_D \simeq 0°$ (in MeOH), which afforded a crystalline tetraacetate (**1a**), $C_{24}H_{34}O_{11}$, mp 132—133°, $[\alpha]_D$ −15.4° (in $CHCl_3$) on acetylation with acetic anhydride and pyridine.

The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** (in C_5D_5N) shows a secondary methyl signal at δ 0.87 (3H, d, J=5 Hz) and a vinyl methyl signal at δ 1.83 (3H, br s). A broad singlet (1H) at δ 6.53 is attributable to an olefinic proton coupled with the methyl (δ 1.83) and a doublet at δ 5.07 (1H, J=7 Hz) is suggested to be an anomeric proton signal of the sugar moiety. In the carbon (^{13}C)-NMR spectrum (in C_5D_5N), **1** exhibits sixteen signals (Table I). Among them, six signals between δ 62.4 and 104.7 can be assigned to the carbons of the β-D-glucopyranosyl moiety by comparison with the carbon shifts of methyl β-D-glucopyranoside[5] and the other ten signals are ascribed to the carbons of the aglycone moiety. The signal at δ 209.7 (s) is identified as that of a ketone carbon and those at δ 113.6 (s) and

141.9 (d) are assigned to tri-substituted olefinic carbons. The signal at δ 141.9, which absorbs at considerably lower field, suggests the presence of a vinyl ether system (-Ċ=CH-O-) in **1**. Further, since the ^{13}C chemical shifts of the aglycone moiety, except for the vinyl ether carbons, resemble those of (−)-menthone reported by Bohlmann *et al.*,[6] **1** is inferred to be the glucoside of a menthone derivative having a vinyl ether side chain.

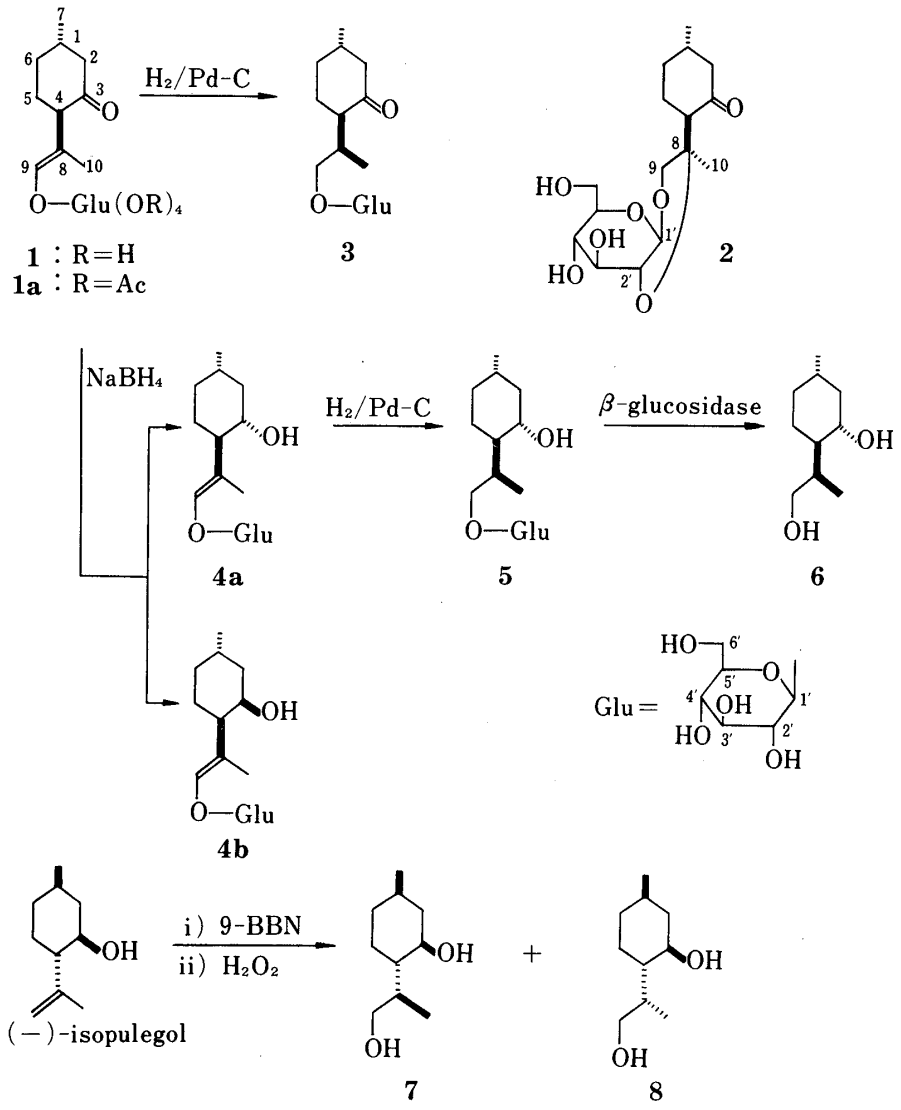

Chart 1

Catalytic hydrogenation of **1** with palladized charcoal (Pd-C) in methanol gave a dihydro derivative (**3**) as a major product.[7] The ^1H-NMR spectrum of **3** (in C_5D_5N) does not show the vinyl methyl signal (δ 1.83) observed in that of **1**, but shows a doublet methyl at δ 0.90 (J=7 Hz). The ^{13}C-NMR spectrum (in C_5D_5N) of **3** lacks the olefinic carbon signals observed in **1** (δ 113.6 and 141.9), but it shows two signals at δ 31.6 (d) and 72.9 (t), which are ascribed to a methine carbon and an oxymethylene carbon, respectively. These observations indicate the presence of a side chain such as $CH_3\dot{C}$=CH-O- in **1**.

On enzymatic hydrolysis with β-glucosidase, **1** furnished glucose, but no aglycone was obtained owing to its instability. Thus, the following chemical modification of **1** was carried out in order to obtain a stable aglycone (Chart 1). Namely, **1** was reduced with $NaBH_4$ to give two alcoholic derivatives, **4a** and **4b** in a ratio of 3: 1. In the ^{13}C-NMR spectra of **4a** and **4b**, C-1 and C-5 (the γ-position relative to OH) in **4b** appear at higher field (*ca.* 6 ppm) than

Table I. ^{13}C Chemical Shifts (δ ppm from TMS in C_5D_5N, 20 MHz)[a]

	1	2	3	4a	4b	5	6	7	8	(−)-Menthone[b]
C-1	35.0	35.1	35.0	31.9	26.2	31.9[c]	31.6	31.5	31.6	35.5
C-2	50.5	51.4	50.5	44.9	43.2	46.0	45.1	44.5	45.0	50.9
C-3	209.7	210.4	211.2	70.0	68.6	70.3	71.6	69.9	71.5	211.5
C-4	54.1	48.3	49.8	50.4	46.6	45.3	45.5	48.6	45.5	55.9
C-5	31.3	25.5	26.6	30.5	24.6	24.0	25.2	29.6	25.2	28.0
C-6	33.9	33.6	33.7	34.8	35.6	34.8	34.4	34.7	34.4	34.0
C-7	22.3	22.2	22.3	22.5	22.7	22.5	22.2	22.1	22.2	22.3
C-8	113.6	73.5	31.6	116.3	118.1	32.0[c]	35.5	38.6	35.5	26.0
C-9	141.9	73.3	72.9	141.3	140.9	74.5	66.5	66.8	66.4	18.7
C-10	12.1	19.3	13.2	10.0	13.4	11.6	12.5	12.1	12.5	21.2
Sugar moiety							Me-glu[d]			
C-1′	104.7	100.3	104.9	104.5	104.7	105.2	105.5			
C-2′	74.7	80.5	75.0	74.9	74.9	75.2	74.9			
C-3′	78.8	74.1	78.3	78.8	78.8	78.5	78.3			
C-4′	71.2	71.8	71.5	71.3	71.3	71.8	71.6			
C-5′	78.2	75.2	78.2	78.4	78.4	78.4	78.3			
C-6′	62.4	62.4	62.7	62.4	62.4	62.9	62.7			

a) Spectra were recorded at 25° in 5 mm spinning tubes as 0.1—0.5 M solutions. Compounds **6**, **7** and **8** were measured in $CDCl_3$. FT-NMR conditions: spectral width, 5 kHz; pulse flipping angle, 30—50°; acquisition time, 1.638 sec; number of data points, 16384.
b) Ref. 6.
c) These assignments may be reversed.
d) Ref. 5. Me-glu=methyl β-D-glucopyranoside.

those of **4a**. This result indicates that **4a** possesses an equatorial hydroxyl and **4b** possesses an axial one (Table I). Catalytic hydrogenation of **4a** with Pd–C in methanol afforded predominantly a dihydro derivative (**5**),[7a] enzymatic hydrolysis of which gave a diol **6** as colorless needles, mp 89—90°, $C_{10}H_{20}O_2$ (M^+, 172), $[\alpha]_D$ +46.6° (in $CHCl_3$). The infrared (IR) spectrum of **6** shows an absorption band at 3240 cm^{-1} (OH) and the ^{13}C-NMR (in $CDCl_3$) spectrum exhibits signals of two carbons bearing a hydroxyl at δ 66.5 (t) and 71.6 (d). On the basis of the above spectral data as well as ^1H-NMR spectral analysis (see "Experimental"), **6** was assumed to be *p*-menthane-3,9-diol. The structure of **6** was confirmed as described below.

Hydroboration of (−)-isopulegol with 9-borabicyclo[3,3,1]nonane (9-BBN),[8a] followed by oxidation with H_2O_2 gave *p*-menthane-3,9-diols **7** [mp 106—107°, $C_{10}H_{20}O_2$ (M^+, 172), $[\alpha]_D$ −15.1° (in $CHCl_3$)] and **8** [mp 89—90°, $C_{10}H_{20}O_2$ (M^+, 172), $[\alpha]_D$ −39.5° (in $CHCl_3$)] (Chart 1), which were identified as (−)-(1*R*, 3*R*, 4*S*, 8*R*)- and (−)-(1*R*, 3*R*, 4*S*, 8*S*)-*p*-menthane-3,9-diol, respectively, by comparison with authentic samples.[8b] Except for the specific rotation, **6** was identical with **8** by comparison of IR, MS, ^1H- and ^{13}C-NMR spectra, indicating that **6** is the antipode of **8**, *i.e.*, (+)-(1*S*, 3*S*, 4*R*, 8*R*)-*p*-menthane-3,9-diol. Thus, the aglycone of **1** was confirmed to have the (1*S*, 4*R*)-9-hydroxy-*p*-menth-8(9)-en-3-one skeleton. Consequently, **1** was identified as (1*S*, 4*R*)-9-O-β-D-glucopyranosyl-*p*-menth-8(9)-en-3-one. The geometry of the $C_{(8)}$–$C_{(9)}$ double bond was assumed to be *E* based on measurement of intramolecular nuclear Overhauser effect (NOE) in **1** (in CD_3OD): irradiation at δ 1.57 (vinyl methyl) produced no increase of the integrated intensity of the vinyl proton signal (δ 6.16).[9] Further, the fact that in the ^{13}C-NMR spectra of **1**, **4a** and **4b**, the vinyl methyl (C-10) appears at considerably higher field (δ 10.0—13.4) supports the *E*-configuration of the $C_{(8)}$–$C_{(9)}$ double bond.

The absolute structure of **1** was thus elucidated as (1*S*, 4*R*, 8*E*)-9-O-β-D-glucopyranosyl-*p*-menth-8(9)-en-3-one.

Compound **2**, $C_{16}H_{26}O_7$, mp 270° (dec.), $[\alpha]_D$ +8.6° (in pyridine), was presumed to be a glucoside like **1** from its behavior on TLC and coloration with the spray reagent. Enzymatic hydrolysis of **2** with β-glucosidase gave no reaction product, but acid hydrolysis with 2 N

TABLE II. Atomic Parameters of **2**

	Atom	x	y	z	β_{11} or B	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
1	C (1)	−4091(3)	2654(9)	2480(6)	29(2)	249(15)	189(7)	6(4)	6(3)	−50(9)
2	C (2)	−3891(3)	4312(9)	3794(6)	42(2)	196(12)	189(8)	23(4)	1(3)	−48(8)
3	C (3)	−3714(2)	3304(8)	5391(5)	31(2)	207(12)	175(7)	13(4)	5(3)	−68(8)
4	C (4)	−2997(2)	1573(7)	5659(5)	30(1)	141(10)	138(5)	−1(3)	14(2)	−54(6)
5	C (5)	−3285(3)	−140(8)	4397(5)	34(2)	184(12)	169(7)	6(4)	9(3)	−54(8)
6	C (6)	−3401(3)	858(9)	2762(5)	38(2)	239(13)	149(6)	13(4)	7(3)	−50(8)
7	C (7)	−4164(3)	3752(12)	929(7)	54(2)	383(23)	209(9)	29(7)	18(4)	5(13)
8	C (8)	−2745(2)	641(7)	7319(5)	28(2)	165(11)	163(6)	−10(3)	22(2)	−47(7)
9	C (9)	−2341(2)	2401(8)	8494(4)	39(2)	214(12)	116(5)	12(4)	20(2)	−40(7)
10	C (10)	−3499(3)	−523(11)	7865(6)	39(2)	338(17)	200(8)	−36(5)	43(3)	−58(10)
11	C (1′)	−885(2)	1425(6)	8383(4)	31(1)	117(9)	81(4)	−4(3)	12(2)	−15(5)
12	C (2′)	−1225(2)	−291(0)	7172(4)	31(1)	105(8)	93(4)	−8(3)	14(2)	−4(5)
13	C (3′)	−549(2)	−2092(5)	7362(4)	33(1)	83(8)	84(4)	2(3)	13(2)	−5(5)
14	C (4′)	340(2)	−1135(6)	7175(4)	29(1)	112(9)	88(4)	7(3)	15(2)	−1(5)
15	C (5′)	623(2)	757(6)	8311(4)	29(1)	115(9)	76(4)	17(3)	8(2)	−2(5)
16	C (6′)	1447(2)	1930(7)	8079(4)	32(1)	168(10)	101(4)	−4(3)	4(2)	−19(6)
17	O (3)	−4143(2)	3869(8)	6376(4)	53(2)	393(16)	213(6)	50(4)	27(3)	−113(9)
18	O (1′)	−1492(1)	3163(5)	8222(3)	30(1)	127(6)	108(3)	4(2)	12(1)	−26(4)
19	O (2′)	−2067(2)	−1043(5)	7380(3)	29(1)	130(7)	141(4)	−11(2)	19(2)	−12(5)
20	O (3′)	−817(2)	−3732(4)	6217(3)	51(1)	87(6)	85(3)	−8(2)	16(2)	−14(4)
21	O (4′)	1059(2)	−2647(6)	7565(4)	36(1)	154(8)	176(5)	24(3)	1(2)	−33(5)
22	O (5′)	−81(1)	2341(4)	8166(3)	29(1)	91(6)	98(3)	−1(2)	10(1)	3(4)
23	O (6′)	1310(2)	3151(5)	6670(3)	50(1)	147(7)	120(4)	−18(3)	36(2)	−20(4)
24	H (C1)	−462(3)	189(11)	256(5)	50(11)					
25	H (C2)	−443(2)	545(9)	366(5)	37(10)					
26	H′(C2)	−333(2)	529(11)	367(5)	45(11)					
27	H (C4)	−228(3)	232(12)	546(5)	51(12)					
28	H (C5)	−286(3)	−141(10)	468(5)	48(12)					
29	H′(C5)	−386(3)	−72(10)	447(5)	40(10)					
30	H (C6)	−354(3)	−41(13)	185(6)	60(13)					
31	H′(C6)	−283(3)	163(12)	234(6)	59(13)					
32	H (C7)	−357(3)	429(12)	80(5)	59(13)					
33	H′(C7)	−461(3)	509(12)	89(6)	65(14)					
34	H″(C7)	−445(2)	259(10)	4(5)	39(10)					
35	H (C9)	−229(2)	194(10)	968(4)	39(10)					
36	H′(C9)	−269(3)	368(12)	829(6)	58(14)					
37	H (C10)	−401(4)	33(13)	793(6)	62(13)					
38	H′(C10)	−371(3)	−171(12)	700(6)	63(13)					
39	H″(C10)	−326(3)	−68(14)	896(6)	67(15)					
40	H (C1′)	−73(3)	64(11)	951(5)	47(11)					
41	H (C2′)	−134(3)	51(10)	616(5)	39(10)					
42	H (C3′)	−33(2)	−296(11)	838(5)	44(11)					
43	H (C4′)	23(3)	−53(11)	601(5)	47(11)					
44	H (C5′)	74(3)	12(12)	964(6)	52(12)					
45	H (C6′)	204(3)	71(12)	825(6)	60(13)					
46	H′(C6′)	170(2)	264(10)	885(5)	36(10)					
47	H (O3′)	−81(3)	−483(13)	668(7)	68(15)					
48	H (O4′)	80(3)	−360(13)	677(5)	64(14)					
49	H (O6′)	120(3)	246(12)	585(5)	50(12)					

The values for C and O atoms are multiplied by 10^4 and those for H atoms by 10^3 for x, y and z and 10 for B.
The temperature factors are of the form:
$T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$ for C and O
and
$T=\exp[-B(\sin\theta/\lambda)^2]$ for H.

H_2SO_4 gave glucose. The IR spectrum (KBr) of **2** shows absorption bands at 3370 (OH) and 1708 (C=O) cm^{-1} and the ^1H-NMR spectrum (in C_5D_5N) exhibits two methyl signals at δ 0.80 (d, $J=6$ Hz, 7-H) and 1.32 (s, 10-H). The ^{13}C-NMR spectrum (in C_5D_5N) of **2** resembles that of **3** except for signals due to the side chain, indicating that **2** possesses a *p*-menthone skeleton. Differences between **2** and **3** are observed in the following points. In **2**, the methine carbon (C-8) observed at δ 31.6 in **3** is absent, but one oxygenated carbon signal is observed at δ 73.5 (s). One methyl carbon (C-10) in **2** is shifted downfield by 6.1 ppm, compared with that (C-10) of **3**. On the other hand, the ^{13}C chemical shifts of the glucose moiety of **2** differ from those of ordinary β-D-glucopyranosides such as **1** and **3**. Namely, the C-2′ signal is deshielded by *ca.* 5 ppm, and C-1′, 3′ and 5′ are shielded by 3—4 ppm in **2**, compared with **1** and **3**.

On the basis of the above chemical and spectral observations, **2** was assumed to be a glucoside with a double linkage between C-1′ and C-2′ of glucose and C-8 and C-9 of the aglycone.

In order to clarify the structure of **2**, a single crystal X-ray analysis was performed. The molecular structure of **2** is shown in Fig. 1 as an ORTEP drawing. The final atomic parameters are listed in Table II. The bond lengths and angles lie in the normal ranges, as listed in Tables III and IV, respectively.

The absolute structure of **2** was shown in Fig. 1 by taking that of the β-D-glucose moiety. The optical rotatory dispersion (ORD) and circular dichroism (CD) spectra showed a negative Cotton effect [ORD: $[\phi]$ $-1200°$ (315 nm, trough), $0°$ (295 nm), $+2000°$ (270 nm, peak); CD: $[\theta]$ -1100 (295 nm) (in MeOH)], which are opposite to those of (−)-menthone,[10] indicating that the absolute configuration in **2** are 1*S*, 4*R* and 8*R*.

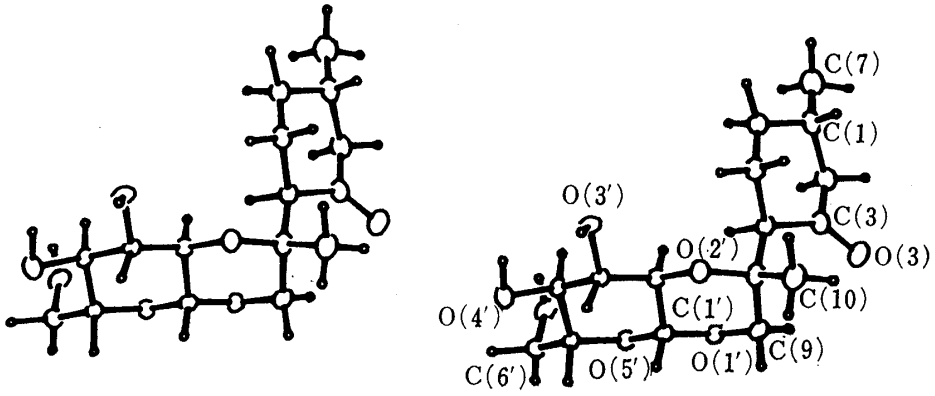

Fig. 1. Perspective View of the Molecule of **2**

TABLE III. Bond Lengths and Their Standard Deviations (Å)

C (1)-C (2)	1.529(7)	C (1′)-C (2′)	1.517(4)
C (1)-C (6)	1.517(7)	C (1′)-O (1′)	1.409(4)
C (1)-C (7)	1.508(8)	C (1′)-O (5′)	1.401(4)
C (2)-C (3)	1.508(7)	C (2′)-C (3′)	1.507(4)
C (3)-C (4)	1.516(6)	C (2′)-O (2′)	1.415(4)
C (3)-O (3)	1.243(6)	C (3′)-C (4′)	1.521(5)
C (4)-C (5)	1.533(6)	C (3′)-O (3′)	1.429(4)
C (4)-C (8)	1.542(6)	C (4′)-C (5′)	1.543(5)
C (5)-C (6)	1.541(7)	C (4′)-O (4′)	1.429(5)
C (8)-C (9)	1.540(6)	C (5′)-C (6′)	1.504(5)
C (8)-C (10)	1.521(7)	C (5′)-O (5′)	1.442(4)
C (8)-O (2′)	1.464(5)	C (6′)-O (6′)	1.430(5)
C (9)-O (1′)	1.447(5)		

Table IV. Bond Angles for Non-hydrogen Atoms and Their Standard Deviations (°)

C (2) - C (1) - C (6)	110.4 (4)	C (2′) - C (1′) - O (1′)	110.2 (3)
C (2) - C (1) - C (7)	110.2 (4)	C (2′) - C (1′) - O (5′)	111.6 (3)
C (6) - C (1) - C (7)	113.3 (4)	O (1′) - C (1′) - O (5′)	104.6 (3)
C (3) - C (2) - C (1)	113.1 (4)	C (3′) - C (2′) - C (1′)	108.5 (2)
C (4) - C (3) - C (2)	114.8 (4)	C (3′) - C (2′) - O (2′)	111.2 (2)
C (4) - C (3) - O (3)	124.1 (4)	C (1′) - C (2′) - O (2′)	109.0 (2)
C (2) - C (3) - O (3)	121.1 (4)	C (4′) - C (3′) - C (2′)	107.7 (3)
C (5) - C (4) - C (3)	106.9 (3)	C (4′) - C (3′) - O (3′)	109.3 (3)
C (5) - C (4) - C (8)	113.7 (3)	C (2′) - C (3′) - O (3′)	111.2 (3)
C (3) - C (4) - C (8)	116.1 (3)	C (5′) - C (4′) - C (3′)	111.2 (3)
C (6) - C (5) - C (4)	110.9 (4)	C (5′) - C (4′) - O (4′)	104.3 (3)
C (1) - C (6) - C (5)	112.7 (4)	C (3′) - C (4′) - O (4′)	112.1 (3)
C (9) - C (8) - C (4)	110.8 (3)	C (6′) - C (5′) - C (4′)	114.1 (3)
C (9) - C (8) - C (10)	110.3 (4)	C (6′) - C (5′) - O (5′)	106.8 (3)
C (9) - C (8) - O (2′)	107.5 (3)	C (4′) - C (5′) - O (5′)	111.0 (3)
C (4) - C (8) - C (10)	115.0 (4)	O (6′) - C (6′) - C (5′)	113.6 (3)
C (4) - C (8) - O (2′)	109.5 (3)	C (8) - O (2′) - C (2′)	114.6 (3)
C (10) - C (8) - O (2′)	103.2 (3)	C (9) - O (1′) - C (1′)	109.1 (3)
O (1′) - C (9) - C (8)	111.5 (3)	C (1′) - O (5′) - C (5′)	111.7 (2)

The possibility that **2** is derived from **1** by addition of the C-2′ hydroxyl to the C-8 position during the extraction procedure can be ruled out, because **2** was not formed from **1** by the same procedures as used in the isolation process.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (a hot stage type) and are uncorrected. The IR spectra were recorded with a Hitachi EPI-G2 unit. The ^{1}H-NMR spectra were taken with Varian T-60 and JEOL-100 (for NOE measurement) spectrometers, and ^{13}C-NMR spectra were taken with a Varian FT-80A spectrometer with tetramethylsilane as an internal standard. The mass spectra were recorded with a Hitachi double focusing mass spectrometer. The specific rotations were measured with a JASCO DIP-SL unit. The ORD and CD spectra were measured with a JASCO J-20 spectrometer. GLC was run on a Hitachi 073 unit with a hydrogen flame ionization detector. Prep. HPLC was performed on a JASCO TRIROTAR apparatus with a refractive index monitor [prep. HPLC conditions: column, μ-Bondapak C_{18} (8 mm i.d. × 30 cm, Waters Assoc.); solvent, CH_3CN–MeOH–H_2O (1 : 1 : 4); flow rate, 3 ml/min]. TLC was carried out on Merck plates precoated with Kieselgel 60 F_{254} and preparative layer chromatography (PLC) was carried out on plates (20 × 20 cm, 0.75 mm thick) coated with Kieselgel PF_{254} (Merck).

Isolation of Schizonepetosides A(1) and B(2)——The dried and pulverized spikes of *Schizonepeta tenuifolia* (2.5 kg) were extracted with ether (25 l × 3) and then with MeOH (25 l × 3) under reflux. The MeOH extracts were concentrated *in vacuo* to give a brown mass (279 g), which was dissolved in H_2O (1.5 l), and the solution was extracted with $CHCl_3$ (700 ml × 3) and BuOH (1 l × 3). The BuOH extract was concentrated *in vacuo* to give a residue (68 g). A portion of the BuOH extract (38 g) was dissolved in H_2O and the solution was filtered. The filtrate was subjected to column chromatography over polyamide (300 g, Wako Pure Chemical Industries Ltd.), developing with H_2O (1 l) and then MeOH. The H_2O eluate was concentrated to afford a brown syrup (17 g), which was rechromatographed on charcoal (50 g), developing with H_2O (400 ml) and then MeOH (2.4 l). The MeOH eluate (4.5 g) was subjected to column chromatography over silica gel (110 g), developing with a $CHCl_3$–MeOH solvent system, to give **2** (50 mg, yield, 0.004%) and the crude fraction of **1** (1.55 g). The latter was purified by silica gel column chromatography (SiO_2, 30 g) using a mixture of AcOEt saturated with H_2O and MeOH, and by prep. HPLC to give **1** (500 mg, yield, 0.04%).

Schizonepetoside A (1)——White hygroscopic amorphous solid, $[\alpha]_D^{24} \simeq 0°$ (c=1.02, MeOH), ^{1}H-NMR (δ in C_5D_5N): 0.87 (3H, d, J=5 Hz, 7-H), 1.83 (3H, br s, 10-H), 5.07 (1H, d, J=7 Hz, 1′-H), 6.53 (1H, br s, 9-H); (δ in CD_3OD): 1.03 (3H, d, J=5 Hz, 7-H), 1.57 (3H, br s, 10-H), 4.46 (1H, d, J=7 Hz, 1′-H), 6.16 (1H, br s, 9-H). ^{13}C-NMR spectral data are given in Table I.

Acetylation of 1 (1a)——A solution of **1** (12 mg) in Ac_2O and pyridine (each 0.5 ml) was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt extract was dried over Na_2SO_4 and concentrated. The residue was purified by PLC (ether) to give a tetraacetate (**1a**) as colorless needles (from ether–pet.ether, 13 mg), mp 132—133°, $[\alpha]_D^{24}$ −15.4° (c=1.16, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1755, 1740 (ester), 1715 (C=O). ^{1}H-NMR (δ in $CDCl_3$): 1.03 (3H, d, J=5 Hz, 7-H), 1.57 (3H, br s, 10-H), 2.03, 2.08 (each 6H, s, 4 × OAc), 3.5—4.0 (1H, m, 5′-H), 4.23 (2H, m, 6′-H), 6.08 (1H, br s, 9-H). *Anal.* Calcd for $C_{24}H_{34}O_{11}$: C, 57.82; H, 6.87. Found: C, 57.90; H, 6.90.

Enzymatic Hydrolysis of 1——β-Glucosidase (Miles Laboratories (PTY) Ltd., 5 mg) was added to a solution of **1** (12 mg) in 0.1 M acetate buffer solution (pH 5, 2 ml). The mixture was allowed to stand overnight at 37° and then extracted with $CHCl_3$. Several spots were detected in the $CHCl_3$ layer on TLC. The aqueous layer was concentrated *in vacuo* and a small portion of the residue was trimethylsilylated by a usual method. The presence of glucose was demonstrated by GLC.

GLC conditions: column, 3% SE-52 on Chromosorb W, 3 mm×2 m; oven temperature, 170°; injection temperature, 220°; carrier gas, N_2; flow, 45 ml/min. t_R (min): 8.9 and 13.6.

Catalytic Hydrogenation of 1, giving 3——A solution of **1** (120 mg) in MeOH (1 ml) was stirred with 10% Pd–C (55 mg) in a hydrogen atmosphere at room temperature for 1.5 hr. The catalyst was removed by filtration, and the reaction mixture was purified by prep.HPLC to give a white amorphous solid (**3**, 37 mg).[7] ^{1}H-NMR (δ in C_5D_5N): 0.83 (3H, d, J=5 Hz, 7-H), 0.90 (3H, d, J=7 Hz, 10-H), 4.77 (1H, d, J=7 Hz, 1′-H). ^{13}C-NMR spectral data are given in Table I.

Acetylation of **3** (42 mg) in the manner described for the acetylation of **1** gave a tetraacetate (37 mg) as colorless needles (from ether–pet.ether), mp 98—100°, $[\alpha]_D^{26} \simeq 0°$ (c=0.47, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1750, 1740 (ester), 1700 (C=O). ^{1}H-NMR (δ in $CDCl_3$): 0.83 (3H, d, J=7 Hz, 10-H), 1.00 (3H, d, J=5 Hz, 7-H), 2.03 (9H, s, 3×OAc), 2.08 (3H, s, OAc). *Anal.* Calcd for $C_{24}H_{36}O_{11}$: C, 57.59; H, 7.25. Found: C, 57.53; H, 7.19.

Reduction of 1 with $NaBH_4$, giving 4a and 4b——$NaBH_4$ (15 mg) was added to a solution of **1** (20 mg) in MeOH (2 ml) and the whole was allowed to stand at room temperature for 2.5 hr. The reaction mixture was passed through an Amberlite IR-120B (H^+) column and evaporated to dryness. The residue was purified by prep.HPLC to give **4a** (12 mg) and **4b** (4 mg). **4a**: White amorphous solid, $[\alpha]_D^{24} \simeq 0°$ (c=1.04, MeOH). ^{1}H-NMR (δ in C_5D_5N): 0.87 (3H, d, J=5 Hz, 7-H), 1.77 (3H, br s, 10-H), 5.06 (1H, d, J=7 Hz, 1′-H), 6.70 (1H, br s, 9-H). **4b**: White amorphous solid. ^{1}H-NMR (δ in C_5D_5N): 0.85 (3H, d, J=6 Hz, 7-H), 1.92 (3H, br s, 10-H), 5.12 (1H, d, J=7 Hz, 1′-H), 6.68 (1H, br s, 9-H). ^{13}C-NMR spectral data of **4a** and **4b** are given in Table I. Acetates of **4a** and **4b** were prepared in the manner described for the acetylation of **1**. Compound **4a** (21 mg) gave a pentaacetate (24 mg) as colorless needles (from EtOH), mp 131—132°, $[\alpha]_D^{25}$ −25.4° (c=0.81, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1745 (ester), 1685 (–C=CHO–). ^{1}H-NMR (δ in $CDCl_3$): 0.90 (3H, d, J=5.5 Hz, 7-H), 1.47 (3H, br s, 10-H), 2.00, 2.02 (each 6H, s, 4×OAc), 2.07 (3H, s, OAc), 6.08 (1H, br s, 9-H). *Anal.* Calcd for $C_{26}H_{38}O_{12}$: C, 57.55; H, 7.06. Found: C, 57.62; H, 7.08. Compound **4b** (16 mg) gave a pentaacetate (18 mg) as colorless needles (from ether–pet.ether), mp 132—134°, $[\alpha]_D^{24}$ −16.9° (c=0.93, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1750, 1725 (ester), 1670 (–C=CHO–). ^{1}H-NMR (δ in $CDCl_3$): 0.88 (3H, d, J=6 Hz, 7-H), 1.57 (3H, br s, 10-H), 2.02, 2.03 (each 6H, s, 4×OAc), 2.08 (3H, s, OAc), 6.05 (1H, br s, 9-H). *Anal.* Calcd for $C_{26}H_{38}O_{12}$: C, 57.55; H, 7.06. Found: C, 57.53; H, 7.11.

Catalytic Hydrogenation of 4a, giving 5——Compound **4a** (60 mg) was hydrogenated with 10% Pd–C (80 mg) in the manner described for the hydrogenation of **1**, and then purified by prep. HPLC to afford **5** (49 mg) as a major product.[7a] Compound **5** was obtained as a white amorphous solid, $[\alpha]_D^{25}$ −2.2° (c=1.53, MeOH). ^{1}H-NMR (δ in C_5D_5N): 0.82 (3H, d, J=6 Hz, 7-H), 0.92 (3H, d, J=7 Hz, 10-H), 4.82 (1H, d, J=7 Hz, 1′-H). Acetylation of **5** (21 mg) in the manner described for the acetylation of **1** gave a pentaacetate (20 mg) as colorless needles (from EtOH), mp 157.5—159°, $[\alpha]_D^{24} \simeq 0°$ (c=0.60, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1750, 1735, 1720 (ester). ^{1}H-NMR (δ in $CDCl_3$): 0.73 (3H, d, J=7 Hz, –CH–C$\underline{H}_3$), 0.88 (3H, d, J=6 Hz, –CH–C$\underline{H}_3$), 2.02, 2.03 (each 6H, s, 4×OAc), 2.07 (3H, s, OAc). *Anal.* Calcd for $C_{26}H_{40}O_{12}$: C, 57.34; H, 7.40. Found: C, 57.34; H, 7.38.

Enzymatic Hydrolysis of 5, giving 6——β-Glucosidase (9 mg) was added to a solution of **5** (19 mg) in H_2O (5 ml). The mixture was allowed to stand at 37° overnight, then extracted with ether and concentrated. The residue was repeatedly recrystallized from cyclohexane to give **6** as colorless needles (9 mg), mp 89—90°, $[\alpha]_D^{28}$ +46.6° (c=0.84, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3240 (OH). ^{1}H-NMR (δ in $CDCl_3$): 0.85 (3H, d, J=7 Hz, –CH–C$\underline{H}_3$), 0.92 (3H, d, J=6 Hz, –CH–C$\underline{H}_3$), 3.05 (2H, br s, 2×OH), 3.40 (1H, m, –C$\underline{H}$–OH), 3.53 (2H, d, J=6.5 Hz, –CHC$\underline{H}_2$–OH). High resolution MS, Calcd for $C_{10}H_{20}O_2$ (M^+): 172.1463. Found: 172.1472. MS m/z (%): 172 (M^+, 2), 154 (7), 139 (7), 124 (18), 112 (22), 95 (24), 81 (50), 71 (41), 55 (43), 41 (33), 28 (100).

Hydroboration of (−)-Isopulegol, giving 7 and 8[8a]——A solution of 9-BBN (460 mg) in dry THF (5 ml) was refluxed in an oil bath. To this reagent, a solution of (−)-isopulegol (Tokyo Kasei Industry Co. Ltd., 240 mg)[11] in dry THF (2 ml) was added and the mixture was stirred under reflux for 1 hr. The mixture was allowed to cool, then EtOH (1.5 ml), 6 N NaOH (0.5 ml), and 30% H_2O_2 (1 ml) were added and the whole was kept at 50° for 1 hr with stirring. The aqueous layer was saturated with K_2CO_3 and the organic layer was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, developing with a hexane–acetone solvent system, to give **7** (132 mg) and **8** (6 mg). **7**: Colorless needles (from cyclohexane), mp 106—107°, $[\alpha]_D^{24}$ −15.1° (c=1.86, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3240 (OH). ^{1}H-NMR (δ in $CDCl_3$): 0.90 (3H, d, J=5.5 Hz, –CH–C$\underline{H}_3$), 0.95 (3H, d, J=7 Hz, –CH–C$\underline{H}_3$), 3.47 (1H, m, –C$\underline{H}$–OH), 3.62 (2H, d-like, –CHC$\underline{H}_2$–OH), 4.33 (2H, br s, 2×OH). MS m/z (%): 172 (M^+, 3), 154 (8), 139 (8), 124 (34), 112 (33), 95 (37), 81 (76), 71 (53), 55 (58), 41 (50), 28 (100). **8**: Colorless needles (from cyclohexane), mp 89—90°, $[\alpha]_D^{25}$ −39.5° (c=0.70, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3240 (OH). ^{1}H-NMR (δ in $CDCl_3$): 0.85 (3H, d, J=7 Hz, –CH–C$\underline{H}_3$), 0.92 (3H, d, J=6 Hz, –CH–C$\underline{H}_3$), 2.63 (2H, br s, 2×OH), 3.4 (1H, m, –C$\underline{H}$–OH), 3.53 (2H, d, J=6.5 Hz, –CHC$\underline{H}_2$–OH). MS m/z (%): 172 (M^+, 3),

154 (10), 139 (10), 124 (23), 112 (26), 95 (27), 81 (71), 71 (52), 55 (52), 41 (48), 28 (100). The IR and ^{1}H-NMR spectra of **7** and **8** were superimposable with those of (−)-(1*R*,3*R*,4*S*,8*R*)- and (−)-(1*R*,3*R*,4*S*,8*S*)-*p*-menthane-3,9-diol, respectively.[8b]

Schizonepetoside B (2)——Colorless plates (from MeOH–H_2O), mp 270° (dec.), $[\alpha]_D^{25}$ +8.6° (c=0.69, pyridine). ORD (c=0.016, MeOH) $[\phi]^{25}$ (nm): 0° (370), −1200° (315) (trough), 0° (295), +2000° (270) (peak). CD (c=0.016, MeOH) $[\theta]^{25}$ (nm): −1100 (295). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1708 (C=O). ^{1}H-NMR (δ in C_5D_5N): 0.80 (3H, d, J=6 Hz, 7-H), 1.32 (3H, s, 10-H). MS m/z (%): 312 (M^+-H_2O, 1), 252 (2), 218 (10), 200 (8), 73 (100). *Anal.* Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.14; H, 7.92.

Acid Hydrolysis of 2——A few mg of **2** was hydrolyzed with 2 N H_2SO_4 (5 ml) on a boiling water bath for 2 hr. After cooling, the reaction mixture was neutralized with $BaCO_3$ and filtered. The filtrate was concentrated *in vacuo* and the residue was trimethylsilylated by a usual method. The presence of glucose was demonstrated by GLC.

X-Ray Analysis of 2——Crystal Data: $C_{16}H_{26}O_7$ (MW 330.38), monoclinic, space group: $P2_1$, a=15.271 (7), b=6.201 (3), c=8.798 (4) Å, β=102.21 (2)°, U=814.3 Å^3, D_{cal}=1.346 g/cm^3, Z=2. Intensity data were collected on a Philips PW 1100 automatic four-circle diffractometer using the θ-2θ scan method with Cu$K\alpha$ radiation monochromated by means of a graphite plate; 1512 independent reflections within 2θ=6° −156° were measured and corrected for the Lorentz and polarization factors. The structure was solved by the direct method using MULTAN[12] and was refined by the block-diagonal least-squares procedure (HBLS).[13] The final R value was 0.047 after several cycles of least-squares calculation assuming anisotropic thermal parameters for the nonhydrogen atoms and isotropic ones for the hydrogen atoms.

Treatment of 1 by the Isolation Procedure to confirm that 2 is not an Artifact——i) A solution of **1** (23 mg) in MeOH (5 ml) was refluxed for 3 hr and concentrated (TLC check).

ii) The residue was dissolved in BuOH (5 ml) and added to H_2O (5 ml). The solution was concentrated *in vacuo* (TLC check).

iii) The residue was subjected to polyamide column (25 mm i.d. × 40 mm) chromatography with H_2O (30 ml) (TLC check).

iv) The H_2O eluate was rechromatographed on a charcoal column (25 mm i.d. × 30 mm) using H_2O (30 ml) and MeOH (50 ml) as eluents.

v) The MeOH eluate (TLC check) was subjected to silica gel column (25 mm i.d. × 40 mm) chromatography with $CHCl_3$–MeOH (3: 1) (TLC check).

In each process, no formation of **2** from **1** was detected.

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