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The Constituents of *Schizandra chinensis* Baill. X.[1] The Structures of γ-Schizandrin and Four New Lignans, (−)-Gomisins L_1 and L_2, (±)-Gomisin M_1 and (+)-Gomisin M_2

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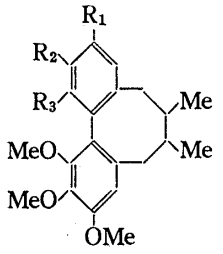
Four new dibenzocyclooctadiene lignans, named (−)-gomisins L_1 (**6**) and L_2 (**7**), (±)-gomisin M_1 (**8**) and (+)-gomisin M_2 (**9**), were isolated from the fruits of *Schizandra chinensis* Baill. (Schizandraceae). Their absolute structures were elucidated by means of chemical and spectral studies.

The stereostructure of γ-schizandrin (**1**, *dl*-form), the plane structure of which had already been suggested by Kochetkov *et al.*[2] and Liu *et al.*,[3] was also elucidated on the basis of chemical and spectral studies.

Keywords——*Schizandra chinensis* Baill.; Schizandraceae; dibenzocyclooctadiene; lignan; (−)-gomisin L_1; (−)-gomisin L_2; (±)-gomisin M_1; (+)-gomisin M_2; γ-schizandrin; ^{13}C-NMR

In 1964, Kochetkov *et al.* isolated an optically inactive dibenzocyclooctadiene lignan, named γ-schizandrin, from the seed oil of *Schizandra chinensis* Baill. (Schizandraceae), and assigned the structure as **1'** (Chart 1). They also reported the isolation of an optically active lignan, pseudo-γ-schizandrin, which possesses the same plane structure as γ-schizandrin.[2] After that, γ-schizandrin (wuweizisu B) was also isolated by Chen *et al.* from the same source,[4] and its plane structure was revised to **1''**, by Liu *et al.*[3] on the basis of intramolecular nuclear Overhauser effects in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum.



1': R_1=OMe, R_2+R_3=OCH_2O
1'': R_1+R_2=OCH_2O, R_3=OMe

Chart 1

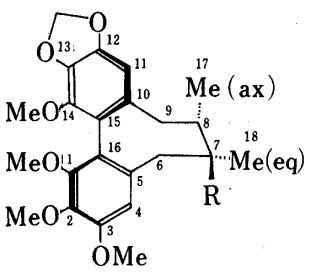
During the course of studies on the constituents of the fruits of this plant, we isolated gomisin N, which possesses the same functional group as γ-schizandrin and elucidated its absolute structure as **2** on the basis of chemical and spectral studies.[5,6] This paper deals with the isolation and stereostructure of γ-schizandrin as well as structure elucidations of four new phenolic dibenzocyclooctadiene lignans, named (−)-gomisins L_1 (**6**) and L_2 (**7**), (±)-gomisin M_1 (**8**) and (+)-gomisin M_2 (**9**) (Chart 2).

γ-Schizandrin (**1**) was obtained as colorless prisms (from MeOH), $C_{23}H_{28}O_6$, mp 126.5—128°C, $[\alpha]_D^{24}$ 0°, ultraviolet (UV) spectrum, λ_{max}^{EtOH} nm (log ε): 220 (4.67), 253 (sh 4.10) and 279 (sh 3.60) (ref. 2, mp 93—95°C, ref. 3, mp 116—118°C, $[\alpha]_D$ 0°). The ^{1}H-NMR spectrum of **1** (Table I) closely resembles that of **2** and shows the presence of two secondary methyls, two benzylic methylenes, a methylenedioxyl moiety and four methoxyls. The carbon (^{13}C)-NMR spectrum (Table II) also shows that **1** has the same skeleton and the same functional groups as **2**: an axial methyl (δ 12.4), an equatorial methyl (δ 21.9), two methines (δ 33.9 and 40.8), two benzylic methylenes (δ 35.5 and 38.9), a methylenedioxyl moiety (δ 100.7) and four aromatic methoxyls (δ 55.9, 59.6, 60.5 and 60.9).

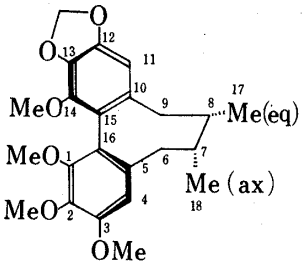
On the basis of the above physical constants and spectral data, **1** was considered to be γ-schizandrin.[2,4] The stereostructure of **1** was elucidated by ^{13}C-NMR spectral analysis[7]

and chemical studies as described below. In the ^{13}C-NMR spectrum of **1**, the appearance of a methoxyl signal at δ 55.9 and three methoxyl signals at δ 59.6, 60.5 and 60.9 indicates that a methoxyl (δ 55.9) is located adjacent (C-3 or C-12) to the aromatic proton and the other ones are located at C-1, C-14 and C-2 or C-13, and consequently a methylenedioxyl moiety is present at the C-(12, 13) or C-(2, 3) position. Although the chemical shifts of the carbons of **1** resemble those of **2**, the protonated aromatic carbons (C-4 and C-11) are quite different. The signal at δ 107.5 (d) can be assigned to the protonated aromatic carbon adjacent to the methoxyl, which is the equatorial methyl side, and that at δ 105.9 (d) can be assigned to the carbon adjacent to the methylenedioxyl moiety, which is the axial methyl side (see ref. 7).

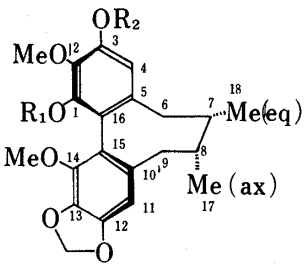
On the basis of the above spectral analysis, the stereostructure of γ-schizandrin was suggested to be **1** (all of the carbon shifts are reasonably assigned as shown in Table II). Next, the structure of **1** was confirmed by chemical correlation with gomisin A (**3**).[8] Treatment



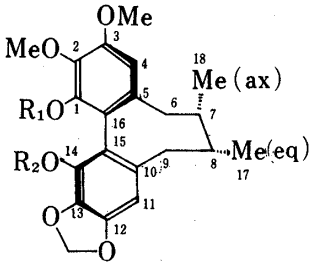
1: R=H(*dl*-form)
3: R=OH
5: R=H



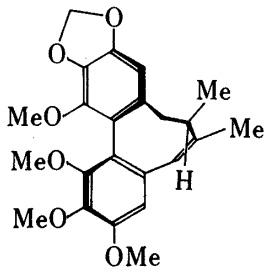
2



6 : R_1=H, R_2=Me
6a: R_1=R_2=Me
6b: R_1=Ac, R_2=Me
7 : R_1=Me, R_2=H
7a: R_1=Me, R_2=-CO-C$_6$H$_4$-Br



8 : R_1=H, R_2=Me (*dl*-form)
8a: R_1=R_2=Me (*dl*-form)
8b: R_1=Ac, R_2=Me (*dl*-form)
9 : R_1=Me, R_2=H
9a: R_1=R_2=Me
9b: R_1=Me, R_2=Ac



4

ax=axial
eq=equatorial
6a is an antipode of **5**.
9a is an antipode of **2**.
1 is a racemate of **5** (or **6a**)
8a is a racemate of **2** (or **9a**)

Chart 2

Table I. ^{1}H-NMR Spectral Data for **1** (**5** and **6a**), **2** (**8a** and **9a**), **6**, **7**, **8** and **9** (δ in $CDCl_3$, 60 MHz)

Compd.	4-H, s 11-H, s	OCH_2O s	OCH_3 s	OH[a] s	6-H (2H, m)	9-H (2H, m)	7-H, 8-H (2H, m)	7-CH_3 (d, J=Hz)	8-CH_3 (d, J=Hz)
1, 5, 6a	6.56 6.49	5.93	3.55, 3.83 3.90(×2)	—	2.10 (center)	2.55 (center)	1.85	0.97 (6.5)	0.73 (6.5)
2, 8a, 9a	6.56 6.49	5.93	3.55, 3.83 3.90(×2)	—	2.55 (center)	2.10 (center)	1.85	0.73 (6.5)	0.97 (6.5)
6	6.37 6.50	5.95	3.87 3.90(×2)	5.70	2.10 (center)	2.50 (center)	1.80	0.95 (6.5)	0.73 (6.5)
7	6.63 6.50	5.95	3.52, 3.78 3.95	5.78	2.10 (center)	2.52 (center)	1.78	0.97 (6.5)	0.73 (6.5)
8	6.34 6.47	5.89	3.83, 3.85 3.88	5.70	2.50 (center)	2.10 (center)	1.80	0.73 (6.5)	0.95 (6.5)
9	6.66 6.45	6.00 (q, J=1.5)	3.57 3.93(×2)	5.35	2.55 (center)	2.10 (center)	1.83	0.78 (7)	0.98 (6.5)

a) Hydroxyl signals were confirmed on addition of D_2O.
b) d=doublet, m=multiplet, q=quartet, s=singlet.

TABLE II. ^{13}C-NMR Spectral Data for **1**, **2**, **5**, **6**, **7**, **8**, **9**, **6a**, **6b**, **7a**, **8a**, **8b**, **9a** and **9b** (δ in $CDCl_3$, ^{13}C: 20 MHz at 25°C)

Carbon	Compound (configuration of biphenyl)									
	1 (*dl*), **5** (*R*), **6a** (*S*)	**6** (*S*)	**6b** (*S*)	**7** (*S*)	**7a**[a] (*S*)	**2** (*S*), **8a** (*dl*), **9a** (*R*)	**8** (*dl*)	**8b** (*dl*)	**9** (*R*)	**9b** (*R*)
1	151.5	146.8	139.5[b]	150.4	151.8	151.7	147.0	142.5	150.4	151.4
2	139.8	133.3	139.1[b]	137.5	142.4	140.2[b]	133.7	139.4	140.4	139.9
3	152.9	151.7	152.8	148.8	143.6	151.6	150.5	151.4	152.1	151.9
4	107.5	103.9	110.1	110.4	117.7	110.7	107.3	113.1	112.4	111.0
5	139.4	133.9	139.5	140.3	139.9	134.1	134.5	134.2	135.6	135.1
6	35.5	35.4	35.4	35.1	34.9	39.2	39.3	39.2	39.0	38.8
7	40.8	40.8	40.7	40.9	40.9	33.6	33.6	33.6	33.3	33.4
8	33.9	33.9	33.7	33.9	33.6	40.8	40.8	40.6	40.7	40.7
9	38.9	39.0	38.5	39.0	38.8	35.6	35.7	35.4	35.6	35.4
10	132.5	133.1	133.9	132.7	132.5	137.8	138.4	139.0	137.8	137.7
11	105.9	106.4	106.2	106.1	106.1	103.0	103.5	103.2	102.1	106.4
12	147.7	147.8	147.9	140.7	148.0	148.7	148.9	148.9	148.5	148.6
13	134.9	135.0	134.4	135.1	135.0	134.6	134.7	134.0	133.3	137.2
14	141.3	141.2	141.0	141.3	141.1	141.1[b]	141.1	140.9	136.9	131.2
15	122.3[b]	121.4	120.9	121.5[b]	121.9	121.4	120.3	123.3	121.6	121.8[b]
16	122.5[b]	115.8	123.9	122.5[b]	128.2	123.4	116.8	119.8	118.6	122.7[b]
17	12.4	12.3	12.3	12.4	12.3	21.5	21.5	21.3	21.5	21.6
18	21.9	21.9	21.9	21.8	21.9	12.9	13.0	12.3	12.8	12.7
OCH_3 C-1, 14	60.5, 59.6	—, 59.7	—, 59.6	60.1, 59.6	60.4, 59.6	60.5, 59.6	—, 59.7	—, 59.6	61.3[b], —	60.6, —
OCH_3 C-2, 13	60.9, —	61.0, —	60.8, —	61.0, —	60.9, —	61.0, —	61.0—	60.8, —	61.4[b], —	61.0, —
OCH_3 C-3, 12	55.9, —	55.7, —	56.0, —	—, —	—, —	55.9, —	55.7, —	56.0, —	56.4, —	55.9
OCH_2O	100.7	100.8	100.8	100.8	100.9	100.7	100.8	100.8	101.3	101.8
$CO-CH_3$	—	—	168.6, 20.5	—	—	—	—	168.6, 20.5	—	167.6.20.4

a) Other signals: 164.1(s), 132.0(d), 131.7(d), 128.5(s) (–CO–C_6H_4Br).
b) Assignments within any column may be reversed.

of **3** with $POCl_3$ in anhydrous pyridine at 100°C for 1 h[7] gave dehydrated gomisin A (**4**), $C_{23}H_{26}O_6$, colorless needles, mp 149—151°C, $[\alpha]_D^{23}$ −11.1°, which shows the presence of a $-CH(CH_3)-C(CH_3)=CH-$ system [δ in $CDCl_3$: 1.07 (3H, d, J=6.5 Hz), 1.65 (3H, br, s), 2.72 (1H, m), 6.22 (1H, br s)] in the ^{1}H-NMR spectrum and the absence of the hydroxyl group in the infrared (IR) spectrum. Catalytic hydrogenation of **4** (PtO_2 in MeOH) gave two compounds, which were separated by preparative high performance liquid chromatography (prep. HPLC) to give compound **5** [(+)-γ-schizandrin], $C_{23}H_{28}O_6$, colorless prisms, mp 110—111°C, $[\alpha]_D^{23}$ +78.6°, as a major product.[9] Except for the $[\alpha]_D$ value, **5** was fully consistent with **1** by comparisons of the IR, ^{1}H- and ^{13}C-NMR spectra and retention time (t_R) on HPLC. The structure of γ-schizandrin was thus elucidated as **1** (*dl*-form of **5**).

(−)-Gomisins L_1 (**6**) and L_2 (**7**), and (±)-gomisin M_1 (**8**) were isolated from fractions 5 and (+)-gomisin M_2 (**9**) was isolated from fraction 6 of the first silica gel column chromatography of the petroleum ether extract of the plant[8] as described in Experimental.

These compounds (**6**—**9**) possess the same molecular formula, $C_{22}H_{26}O_6$, and show a hydroxyl band in the IR spectra. The ^{1}H- and ^{13}C-NMR spectra indicate that these compounds (**6**—**9**) are dibenzocyclooctadiene lignans, possessing a methylenedioxyl moiety, a phenolic hydroxyl (^{1}H-NMR: δ 5.35—5.78, D_2O-exchangeable) and three methoxyls on aromatic rings.[10]

Compound **6** was obtained as colorless prisms, mp 194—196°C, $[\alpha]_D^{24}$ −53.5°, and afforded a monomethyl ether (**6a**), $C_{23}H_{28}O_6$, mp 114—115.5°C, $[\alpha]_D^{24}$ −73.8° on methylation with $(CH_3)_2SO_4$ and K_2CO_3 in acetone, and a monoacetate (**6b**), $C_{24}H_{28}O_7$, mp 110—111°C, $[\alpha]_D^{24}$ −18.2° on acetylation with Ac_2O in pyridine.

Compound **7** was purified as the *p*-bromobenzoate (**7a**) and was obtained as an amorphous powder, $[\alpha]_D^{24}$ −98.1°, on hydrolysis of **7a**. On methylation [$(CH_3)_2SO_4$ and K_2CO_3 in acetone], **7** gave a monomethyl ether, $C_{23}H_{28}O_6$, mp 114—115.5°C, $[\alpha]_D^{23}$ −81.4°, which was identified as **6a** (mixed mp, IR, ^{13}C-NMR and $[\alpha]_D$). Circular dichroism (CD) spectra of **6** and **7a** show that **6** and **7** possess an *S*-biphenyl configuration.[8,11] On the other hand, **6a** gave the same IR, ^{1}H- and ^{13}C-NMR spectra as **5**, but the $[\alpha]_D$ value was opposite to that of **5**. These findings indicate that **6a** [(−)-γ-schizandrin] is the antipode of **5**. The detailed structures of **6** and **7** were elucidated by ^{13}C-NMR spectral analysis. In the spectrum of **6**, an upfield methoxyl (δ 55.7) and two downfield methoxyls (δ 59.7 and 61.0) are observed, showing that a methoxyl is located at C-3 (adjacent to the aromatic proton) and a hydroxyl must be at C-1, C-2 or C-14.

On comparison of the chemical shifts of protonated aromatic carbons in **6** and **6b** with those of **6a**, the signals (δ 106.4 in **6**, and δ 106.2 in **6b**) that appeared at the same region as C-11 of **6a** (δ 105.9) are assignable to C-11, and the other ones (δ 103.9 in **6** and δ 110.1 in **6b**) are assignable to C-4 (the latter show an upfield shift of 3.6 ppm in **6** and a downfield shift of 2.6 ppm in **6b**) (C-4 of **6a**: δ 107.5). These findings indicate that the hydroxyl in **6** is located at C-1 (*para*-position relative to the aromatic proton $C_{(4)}$–H). The C-1, C-2 and C-16 signals also show reasonable upfield shifts [in **6**: $\Delta\delta$, C-1, −4.7 ppm; C-2, −6.5 ppm and C-16, −6.5 ppm; in **6b**: $\Delta\delta$, C-1, −12.0 (or −12.4) ppm], compared with **6a**.[7] The structure of (−)-gomisin L_1 was thus elucidated as **6**.

In the ^{13}C-NMR spectrum of **7**, three downfield methoxyl signals were observed at δ 59.6, 60.1 and 61.0, but no upfield methoxyl signal at around δ 56.0 was observed. These findings suggest that the hydroxyl in **7** is located at C-3. On comparison of the protonated aromatic carbons of **7** and **7a** with those of **6a** (methyl ether of **7**), the C-11 signals of **7** and **7a** (each δ 106.1) are observed at almost the same region as that of **6a** (δ 105.9), but the C-4 signals of **7** (δ 110.4) and **7a** (δ 117.7) show downfield shifts of 2.9 ppm and 10.2 ppm, respectively (C-4 of **6a**: δ 107.5). All of the above results indicate that the hydroxyl in **7** is located at C-3. The structure of (−)-gomisin L_2 was thus elucidated as **7**.

(±)-Gomisin M_1 (**8**) was purified as the acetate (**8b**) and obtained as colorless needles, mp 116—119°C, $[\alpha]_D^{23}$ 0°, on hydrolysis of **8b**. The CD spectrum of **8** shows no absorption between 200 and 400 nm, indicating that **8** is a racemic compound. The monomethyl ether

(**8a**) [$(CH_3)_2SO_4$ and K_2CO_3 in acetone], colorless prisms, $C_{23}H_{28}O_6$, mp 121—122°C, $[\alpha]_D^{23}$ 0°, gave the same IR (in $CHCl_3$), ^{1}H- and ^{13}C-NMR spectra as **2**.

(+)-Gomisin M_2 (**9**) was obtained as colorless prisms, mp 159—160°C, $[\alpha]_D^{24}$ +54.2°, and gave a monomethyl ether (**9a**) [$(CH_3)_2SO_4$ and K_2CO_3 in acetone], $C_{23}H_{28}O_6$, mp 101—102.5°C, $[\alpha]_D^{24}$ +91.0° and a monoacetate (**9b**) (Ac_2O in pyridine), $C_{24}H_{28}O_7$, mp 121—123°C, $[\alpha]_D^{24}$ +58.2°. Compound **9a** gave the same IR (in $CHCl_3$), ^{1}H- and ^{13}C-NMR spectra as **2**, but the $[\alpha]_D$ value is opposite to that of **2** [mp 105—107°C, $[\alpha]_D^{23}$ −84.7°], indicating that **9a** is an antipode of **2**.[5-7] The CD spectrum of **9** (in MeOH, at 23°C, $[\theta]_{279}$ +11000, $[\theta]_{249}$ +87000, $[\theta]_{232}$ 0, $[\theta]_{217}$ −80000) also shows that **9** possesses an *R*-biphenyl configuration.

The positions of the hydroxyl in **8** and **9** were also elucidated by ^{13}C-NMR spectral analysis (**8** and **9** show the upfield aromatic methoxyl signals at δ 55.7 and 56.4, respectively, indicating the presence of a methoxyl at C-3).

In the spectra of **8** and **8b**, the signals (δ 103.5 in **8** and δ 103.2 in **8b**) that appeared at the same region as C-11 of **8a** (δ 103.0) are assignable to C-11 and the other ones are assignable to C-4 (the latter show an upfield shift of 3.4 ppm in **8** and a downfield shift of 2.4 ppm in **8b**, compared with the C-4 signal of **8a** at δ 110.7). These findings indicate that the hydroxyl in **8** is located at C-1. The absolute structure of (±)-gomisin M_1 was thus elucidated as **8** (*dl*-form). The assignments of the carbon signals of **8** and **8b**, listed in Table II, are consistent with the structure **8**.

In order to define the position of the hydroxyl in **9**, the ^{13}C-NMR spectrum of **9b** was compared with that of **9a**. Namely, in the spectrum of **9b**, the protonated aromatic carbon signal at δ 111.0, which appears at the same region as C-4 of **9a** (δ 110.7), can be assigned to C-4 and that at δ 106.4 can be assigned to C-11; the latter shows a downfield shift of 3.4 ppm, compared with the signal of **9a** (δ 103.0). These findings suggest the presence of a hydroxyl at C-14 (*para*-position relative to the C-11 proton) in **9**. In fact, C-14 and C-13 of **9b** are reasonably assigned as shown in Table II, and show an upfield shift ($\Delta\delta$ −10.1 ppm) and a downfield shift ($\Delta\delta$+2.6 ppm), respectively, compared with the signals of **9a**, while other signals appear at the same regions as those of **9a**. On the basis of the above observations, as well as the carbon assignments of the spectrum of **9**, the position of a hydroxyl in **9** is proved to be at C-14. The absolute structure of (+)-gomisin M_2 was thus elucidated as **9**.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus (a hot-stage type) and are uncorrected. The UV spectra were recorded with a Hitachi 624 digital spectrophotometer and the IR spectra with a Hitachi EPI-G2 machine. The ^{1}H-NMR spectra were recorded with a Varian T-60 spectrometer and the ^{13}C-NMR spectra were recorded with a Varian FT-80 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a Hitachi RMU-7L double focusing mass spectrometer. The specific rotations were measured with a JASCO DIP-SL polarimeter and the CD spectra with a JASCO J-20 unit. Preparative layer chromatography (PLC) was carried out on plates (20×20 cm, 0.75 mm thick) coated with Kieselgel PF_{254} (Merck). For silica gel column chromatography, Kieselgel 60 (Merck) was used. Preparative HPLC was carried out on a JASCO Trirotar chromatograph with a UVIDEC-100-II detector.

Isolation of Compounds——In the previous paper,[8] it was reported that the petroleum ether and the methanolic extracts of the fruits of *Schizandra chinensis* Baill. (4.671 kg) afforded twelve fractions (fr. 1—12) on silica gel column chromatography, developing with hexane, acetone–benzene and acetone solvent systems.

Isolation of **1**: Crystallization of fr. 5 (64.89 g) from a mixture of ether and hexane gave a mixture of **1** and **2** (7.72 g), which was recrystallized from MeOH to give **1** (551 mg, yield 0.012%). The presence of **1** and **2** in a ratio of 4: 11 in the mother liquor of the recrystallization of **1** was demonstrated by HPLC. Conditions: column, μ-Bondapak C_{18} (Waters Associates, 4 mm i.d.×30 cm); mobile phase, CH_3CN–MeOH–H_2O (1: 1: 1); flow rate, 1 ml/min; temp., room temperature; detection, UV 254 nm; t_R(min), **1**: 23.3; **2**: 24.8.

Isolation of **6** and **8**: The mother liquor of the first crystallization of fr. 5 was concentrated to give a residue (57.07 g), which was subjected to silica gel column chromatography (SiO_2 500 g, 7×38 cm) to give nine fractions (fr. 5-a—5-i) (Table III). Fr. 5-g (5.21 g) was rechromatographed on silica gel (120 g), with an acetone–hexane solvent system. The fractions eluted with 8% acetone–hexane were combined and

Table III. Silica Gel Column Chromatography of Fr. 5

Fr. No.	Solvent	Volume (l)	Residue (g)
5-a	Hexane–EtOAc (96: 4)	0.3	0.38
5-b	Hexane–EtOAc (94: 6)	1.8	0.40
5-c	Hexane–EtOAc (92: 8)	1.6	2.79
5-d	Hexane–EtOAc (90: 10)	4.2	15.63
5-e	Hexane–EtOAc (88: 12)	2.3	11.59
5-f	Hexane–EtOAc (85: 15)	0.7	3.27
5-g	Hexane–EtOAc (80: 20)	1.8	5.21
5-h	Hexane–EtOAc (75: 25)	0.7	1.60
5-i	Hexane–EtOAc (70: 30)	0.5	1.72
	Hexane–EtOAc (50: 50)	0.8	
	EtOAc	0.5	

concentrated to give a residue (1.51 g). Repeated PLC [i) hexane–EtOAc (4: 1), *Rf* 0.24; ii) hexane–acetone (7: 3), *Rf* 0.43] of this residue gave a mixture (573 mg) of **6** and **8**. Repeated crystallization of this mixture from ether–hexane gave pure **6** (112 mg, yield 0.0024%). The first mother liquor of recrystallization of the mixture of **6** and **8** was concentrated. The residue (98 mg) was acetylated with Ac_2O (0.3 ml) in dry pyridine (0.6 ml) and purified by PLC [hexane–acetone (4: 1)] to give **8b** (from ether–hexane) (78 mg) as colorless prisms, mp 137—139°C, $[\alpha]_D^{24}$ 0° (c=2.76, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1752 (C=O), 1605, 1570 (aromatic). ^{13}C-NMR spectral data are given in Table II. *Anal.* Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.47; H, 6.77.

Compound **8b** (66 mg) was dissolved in 3% ethanolic potassium hydroxide (2 ml) and the reaction mixture was kept at 65°C for 2 h, then diluted with H_2O (10 ml) and extracted with ether (15 ml×3). The ethereal extract was washed with H_2O, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by PLC [hexane–ether (1: 1)] to give **8** (53 mg, 0.0012%).

Isolation of **7**: Fr. 5-e (11.59 g) was rechromatographed on silica gel (260 g), with an acetone–hexane solvent system. The fractions eluted with 8% acetone–hexane were combined and concentrated to give a residue (3.51 g). Repeated PLC [i) hexane–acetone (7: 3), *Rf* 0.46; ii) benzene–EtOH (19: 1), *Rf* 0.76] of the residue gave crude **7** (848 mg), which was treated with *p*-bromobenzoyl chloride (848 mg) in dry pyridine (5 ml). The resulting *p*-bromobenzoate was purified by PLC [hexane–acetone (3: 1)] to give **7a** (115 mg) as colorless needles (from CH_2Cl_2–MeOH), mp 182—186°C, $[\alpha]_D^{23}$ −53.8° (c=2.23, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1738 (C=O), 1611, 1582 (aromatic). MS *m/z* (%): 570 (42), 568 [$C_{29}H_{29}BrO_7$ (M^+), 41], 183 (100). CD (c= 0.0189, MeOH) $[\theta]^{23}$ (nm): +24500 (218), 0 (224), −25000 (231), −17000 (239), −61000 (254). ^1H-NMR (δ in $CDCl_3$): 0.73 [3H, d, J=7 Hz, $C_{(18)}$–H], 0.95 [3H, d, J=7 Hz, $C_{(17)}$–H], 1.85 [2H, m, $C_{(7)}$–H and $C_{(8)}$–H], 2.10 (center) [2H, m, $C_{(9)}$–H], 2.53 (center) [2H, m, $C_{(6)}$–H], 3.55, 3.82, 3.84 (each 3H, s, 3×OCH_3), 5.95 (2H, s, $-OCH_2O-$), 6.48 [1H, s, $C_{(4)}$–H], 6.82 [1H, s, $C_{(11)}$–H], 7.65 (2H, d, J=9 Hz), 8.10 (2H, d, J=9 Hz) ($-C_6H_4Br$). A solution of **7a** (78 mg) in 3% ethanolic potassium hydroxide (2 ml) was kept at 60°C for 2 h. The reaction mixture was diluted with ether–CH_2Cl_2 (1: 1) (40 ml), washed with H_2O, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by PLC [hexane–acetone (7: 3), *Rf* 0.46] to give **7** (48 mg, 0.001%).

Isolation of **9**: Fr. 6 (10.97 g)[8] was chromatographed on silica gel (240 g), developing with an EtOAc–hexane solvent system. The fractions eluted with 25% EtOAc–hexane were combined and concentrated to give a residue (1104 mg), which was rechromatographed on silica gel (30 g) with a benzene–ether solvent system. The fractions eluted with 2% benzene–ether were combined and concentrated to give a residue (385 mg). Repeated PLC [i) hexane–acetone (7: 3), *Rf* 0.62; ii) benzene–ether (2: 1), *Rf* 0.57] of this residue gave **9** (34 mg, yield 0.0007%).

γ-Schizandrin (1)——Compound **1** was obtained as colorless prisms (from MeOH), mp 126.5—128°C, $[\alpha]_D^{24}$ 0° (c=1.62, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 220 (4.67), 253 (sh 4.10), 279 (sh 3.60). IR ν_{max}^{KBr} cm^{-1}: 1612, 1592 (aromatic). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.90; H, 7.27.

(−)-Gomisin L_1 (6)——Compound **6** was obtained as colorless prisms (from ether–hexane), mp 194—196°C, $[\alpha]_D^{24}$ −53.5° (c=1.70, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 222 (4.59), 252 (sh 4.00), 282—288 (3.44). CD (c=0.0209, MeOH) $[\theta]^{23}$ (nm): −17000 (228), −16000 (230), −96000 (252), −1400 (287), −3700 (298). IR ν_{max}^{KBr} cm^{-1}: 3405 (OH), 1600, 1571 (aromatic). *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.13; H, 6.94.

(−)-Gomisin L_2 (7)——Compound **7** was obtained as a white amorphous powder, $[\alpha]_D^{24}$ −98.1° (c=0.52, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 218 (4.58), 253 (sh 3.97), 280 (3.50). IR ν_{max}^{KBr} cm^{-1}: 3425 (OH), 1611, 1582 (aromatic). MS *m/z* (%): 386 (M^+, 100), 300 (4.2), 219 (5.2). High resolution MS Calcd for $C_{22}H_{26}O_6$ (M^+): 386.1729. Found: 386.1740.

(±)-Gomisin M_1 (8)——Compound **8** was obtained as colorless needles (from ether–hexane), mp 116—119°C, $[\alpha]_D^{23}$ 0° (c=0.530, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 222 (4.65), 252 (sh 4.05), 290 (3.61). CD (c=0.0211, MeOH) $[\theta]^{23}$ (nm): 0 (200—400). IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 1603, 1579 (aromatic). *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.56; H, 6.94.

(+)-Gomisin M_2 (9)——Compound **9** was obtained as colorless prisms (from ether–hexane), mp 159—160°C, $[\alpha]_D^{24}$ +54.2° (c=2.25, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 218 (4.64), 253 (sh 4.04), 279 (sh 3.36). CD (c=0.0237, MeOH) $[\theta]^{23}$ (nm): −80000 (217), 0 (232), +87000 (249), +11000 (sh 279). IR ν_{max}^{KBr} cm^{-1}: 3325 (OH), 1629, 1592, 1575 (aromatic). *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.53; H, 6.94.

Dehydration of Gomisin A (3)——A solution of **3** (1050 mg) and phosphorus oxychloride (2 ml) in anhydrous pyridine (10 ml) was heated at 100°C for 1 h. After cooling, the reaction mixture was diluted with ether (80 ml) and poured into ice-water. The ethereal solution was washed with H_2O, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by PLC [hexane–EtOAc (4: 1)] to give **4** as colorless prisms (from ether–hexane) (540 mg, yield 54%), mp 149—151°C, $[\alpha]_D^{23}$ −11.1° (c=2.07, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1611, 1589, 1579 (aromatic). ^{1}H-NMR (δ in $CDCl_3$): 1.07 (3H, d, J=6.5 Hz, CH_3–CH), 1.65 (3H, br s, CH_3–C=CH), 2.72 (1H, m, –CH), 2.92 (center) (2H, m, $ArCH_2$–), 3.53, 3.70, 3.80, 3.83 (each 3H, s, 4×OCH_3), 5.85 (2H, s, $-OCH_2O-$), 6.22 (1H, br s, H–C=C–), 6.33, 6.40 (each 1H, s, 2×arom. -H). *Anal.* Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.19; H, 6.67.

Catalytic Hydrogenation of 4 with H_2——Compound **4** (431 mg) in MeOH (6 ml) was shaken with H_2 in the presence of PtO_2 (120 mg) as a catalyst at 23°C for 6 h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by PLC [benzene–ether (5: 1)] and prep. HPLC to give **5** (189 mg) and a minor product (78 mg). Preparative HPLC conditions: column, semi prep. μ-Bondapak C_{18} (Waters Associates, 8 mm i.d.×30 cm); mobile phase, CH_3CN–MeOH–H_2O (10: 10: 12); flow rate, 3 ml/min; temp., room temperature; detection, UV 290 nm; t_R of **5**: 17.0 min; t_R of minor product: 14.2 min.

Compound **5**: colorless prisms (from MeOH), mp 110—111°C, $[\alpha]_D^{23}$ +78.6° (c=1.92, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1612, 1592 (aromatic). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1595, 1580 (aromatic). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.09; H, 7.18. The ^{1}H-NMR, ^{13}C-NMR and IR (in $CHCl_3$) spectra are the same as those of **1**.

Methylation of 6——$(CH_3)_2SO_4$ (0.2 ml) and K_2CO_3 (200 mg) were added to a solution of **6** (25 mg) in dry acetone (3 ml). The reaction mixture was stirred at 45°C for 3 h, then diluted with H_2O (20 ml) and extracted with ether (15 ml×3). The combined ethereal extract was washed with H_2O, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by PLC [hexane–acetone (4: 1)] to give a monomethyl ether (**6a**, 20 mg) as colorless prisms (from ether–hexane), mp 114—115.5°C, $[\alpha]_D^{24}$ −73.8° (c=0.610, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1615, 1593, 1576 (aromatic). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.15; H, 7.10. The ^{1}H-NMR, ^{13}C-NMR and IR (in $CHCl_3$) spectra are the same as those of **5**, while $[\alpha]_D$ is opposite to that of **5**.

Acetylation of 6——A solution of **6** (33 mg) in a mixture of pyridine (0.6 ml) and Ac_2O (0.3 ml) was allowed to stand at room temperature overnight, then diluted with H_2O (15 ml) and extracted with ether (15 ml×3). The combined ethereal extract was washed with 1 N HCl, 5% $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC [hexane–acetone (4: 1)] to give a monoacetate (**6b**, 33 mg) as colorless needles (from ether–hexane), mp 110—111°C, $[\alpha]_D^{24}$ −18.2° (c=1.10, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1751 (C=O), 1603, 1589 (aromatic). *Anal.* Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.34; H, 6.80.

Methylation of 7——$(CH_3)_2SO_4$ (0.3 ml) and K_2CO_3 (100 mg) were added to a solution of **7** (34 mg) in dry acetone (4 ml). The reaction mixture was treated as described for the methylation of **6** to give a monomethyl ether (33 mg) as colorless needles, mp 114—115.5°C, $[\alpha]_D^{23}$ −81.4° (c=0.970, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1615, 1593, 1576 (aromatic). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.18; H, 7.07. This compound was identified as **6a** by direct comparison with an authentic sample (IR, ^{13}C-NMR, $[\alpha]_D$ and mixed mp).

Methylation of 9——$(CH_3)_2SO_4$ (0.2 ml) and K_2CO_3 (200 mg) were added to a solution of **9** (25 mg) in dry acetone (2 ml). The reaction mixture was stirred at 50°C for 3 h, and treated as described for the methylation of **6** to give a monomethyl ether (**9a**, 20 mg) as colorless prisms (from ether–hexane), mp 101—102.5°C, $[\alpha]_D^{24}$ +91.0° (c=1.01, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1614, 1592, 1570 (aromatic). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.66; H, 7.09. The ^{1}H-NMR, ^{13}C-NMR and IR (in $CHCl_3$) spectra are the same as those of gomisin N (**2**), while $[\alpha]_D$ is opposite to that of **2**.

Acetylation of 9——A solution of **9** (47 mg) in a mixture of pyridine (0.5 ml) and Ac_2O (0.25 ml) was allowed to stand at room temperature overnight, then diluted with H_2O (20 ml) and extracted with ether (15 ml×3). The combined ethereal extract was washed with 1 N HCl, 5% $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC [benzene–ether (4: 1)] to give a monoacetate (**9b**, 48 mg) as colorless prisms (from ether–hexane), mp 121—123°C, $[\alpha]_D^{24}$ +58.2° (c=1.58, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1780 (C=O), 1628, 1615, 1593, 1570 (aromatic). ^{1}H-NMR (δ in $CDCl_3$): 0.72 [3H, d, J=7 Hz, CH_3–$C_{(7)}$H], 0.97 [3H, d, J=7 Hz, CH_3–$C_{(8)}$H], 1.87 (2H, m, 2×–CH), 1.97 (3H, s, $COOCH_3$), 2.12 (center)

[2H, m, $C_{(9)}$–H], 2.52 (center) [2H, m, $C_{(6)}$–H], 3.53 (3H, s), 3.88 (6H, s) ($3\times OCH_3$), 5.97 (1H, d, $J=1$ Hz), 6.02 (1H, d, $J=1$ Hz) (OCH_2O), 6.55 [1H, s, $C_{(11)}$–H], 6.67 [1H, s, $C_{(4)}$–H]. *Anal.* Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.44; H, 6.67.

Methylation of 8——$(CH_3)_2SO_4$ (0.2 ml) and K_2CO_3 (200 mg) were added to a solution of **8** (28 mg) in dry acetone (2 ml). The reaction mixture was stirred at 45°C for 3 h, and treated as described for the methylation of **6** to give a monomethyl ether (**8a**, 24 mg) as colorless prisms, mp 121—122°C, $[\alpha]_D^{23}$ 0° ($c=1.02$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1610, 1596, 1571 (aromatic). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1614, 1592 (aromatic). *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.88; H, 7.10. The ^{1}H-NMR, ^{13}C-NMR and IR (in $CHCl_3$) spectra are the same as those for **2**.

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References and Notes

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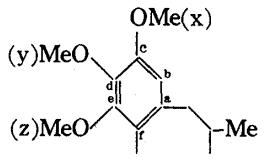
6) A comparison of the physical data, as well as spectral analysis, suggests that gomisin N (**2**) (mp 105—107°C, $[\alpha]_D^{23}$ −84.7°) might be pseudo-γ-schizandrin (mp 93—95°C, $[\alpha]_D^{20}$ −87°).
7) *a*) Y. Ikeya, H. Taguchi, H. Sasaki, K. Nakajima, and I. Yosioka, *Chem. Pharm. Bull.*, **28**, 2414 (1980); *b*) Y. Ikeya, H. Taguchi, and I. Yosioka, *ibid.*, **28**, 2422 (1980); *c*) In the above two of our articles, we studied the ^{13}C-NMR spectral analysis of dibenzocyclooctadiene lignans and made four predictions for the protonated aromatic carbons of lignans possessing the partial structure [A] and the twist boat chair conformation of the cyclooctadiene ring. i) When the methyl group is in axial orientation, the protonated aromatic carbon (C-b) appears at δ 110.6 ± 0.3 (in $CDCl_3$, at 25°C), and when the methyl group is in equatorial orientation, it appears at δ 107.3 ± 0.3. ii) The replacement of OMe(x) by a hydroxyl group or acetoxyl group produces a downfield shift of *ca.* 3 ppm or *ca.* 10 ppm, respectively, for C-b. iii) The replacement of OMe(z) by a hydroxyl group or acetoxyl group produces an upfield shift of *ca.* 3 ppm or a downfield shift of *ca.* 2.5 ppm for C-b. iv) The replacement of OMe(x and y) by the methylenedioxyl moiety produces an upfield shift of *ca.* 4 ppm for C-b.



[A]

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9) Detailed examinations of the minor product have not been carried out; it may be the 7-epimer of **5**, formed by addition of H_2 from the α-side of **4**.
10) The ^{1}H-NMR spectra of **6** and **8** show no upfield methoxyl signal at around δ 3.55, indicating the lack of a methoxyl at the C-1 position.
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