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The Constituents of *Schizandra chinensis* Baill. IV.[1] The Structures of Two New Lignans, Pre-gomisin and Gomisin J[2]

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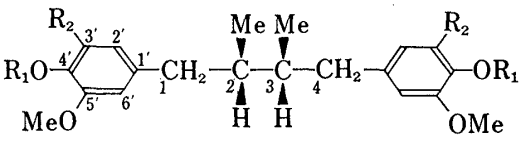
Two new lignans named pre-gomisin (**1**) and gomisin J (**2**) were isolated from the fruits of *Schizandra chinensis* Baill. (Schizandraceae). The structure of the former was elucidated as (2*S*,3*R*)-1,4-bis(3′-hydroxy-4′,5′-dimethoxyphenyl)-2,3-dimethylbutane (**1**) by its preparation from guaiaretic acid. The structure and conformation of the latter were elucidated by chemical and spectral studies.

Keywords——*Schizandra chinensis* Baill.; Schizandraceae; 1,4-bis-phenyl-2,3-dimethylbutane type lignan; pre-gomisin; *meso*-dihydroguaiaretic acid; dibenzocyclooctadiene lignan; gomisin J; NMR; CD

In the previous papers of this series,[4] we have reported a number of dibenzocyclooctadiene lignans isolated from the fruits of *Schizandra chinensis* Baill. (Schizandraceae). This paper deals with two additional new lignans, pre-gomisin (**1**, yield 0.012%) and gomisin J(**2**, 0.023%) isolated from the same source together with a known lignan, *meso*-dihydroguaiaretic acid (**3a**).



1 : R_1=Me, R_2=OH
1a : R_1=Me, R_2=OAc
3a : R_1=H, R_2=H
3b : R_1=Me, R_2=H
3c : R_1=Ac, R_2=H
3d : R_1=H, R_2=NO_2
3e : R_1=Me, R_2=NO_2
3f : R_1=Me, R_2=NH_2

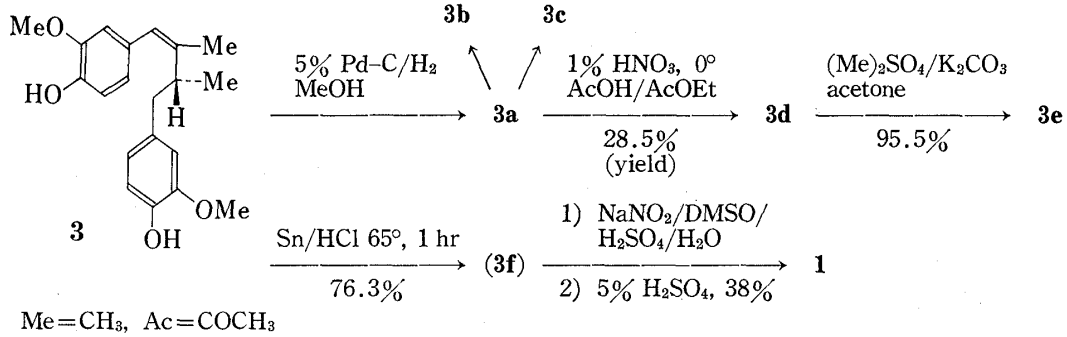


Chart 1

1) Part III: Y. Ikeya, H. Taguchi, I. Yosioka, and H. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **27**, 1576 (1979).
2) Preliminary communication, see: Y. Ikeya, H. Taguchi, and I. Yosioka, *Chem. Pharm. Bull.* (Tokyo), **26**, 682 (1978).
3) Location: *a) Izumi 1421, Komae-shi, Tokyo, 201, Japan*; *b) Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) *a*) Y. Ikeya, H. Taguchi, I. Yosioka, and H. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **27**, 1383 (1979); *b*) Y. Ikeya, H. Taguchi, I. Yosioka, Y. Iitaka, and H. Kobayashi, *ibid.*, **27**, 1395 (1979).

Pre-gomisin (**1**), $C_{22}H_{30}O_6$, mp 130—131.5°, $[\alpha]_D^{25}$ 0° (in $CHCl_3$) was isolated as colorless prisms; it gave a green coloration with ethanolic ferric chloride and a blue color in the Gibbs test. The infrared (IR) spectrum of **1** showed a strong hydroxyl band at 3370 cm^{-1}, and the ultraviolet (UV) spectrum, with absorption maxima at 208 (log ε 4.81), 225 (sh 4.30) and 270 nm (3.15), was very similar to those of *meso*-dihydroguaiaretic acid[5] and *seco*-isolariciresinol,[6] indicating that **1** might be a 1,4-bis-phenyl-dimethylbutane type lignan. The proton nuclear magnetic resonance (PMR) spectrum of **1** (in $CDCl_3$) revealed the presence of two secondary methyls (δ 0.85, J=6 Hz), two benzylic methylenes (δ 1.9—2.87, m), four methoxyls (δ 3.83 and 3.87, each 6H, s), two phenolic hydroxyls (δ 5.87, 2H, br s, D_2O exchangeable) and four aromatic protons (δ 6.28 and 6.43, each 2H, J=2 Hz, *meta*-coupling). On acetylation with acetic anhydride in pyridine, **1** afforded a diacetate (**1a**) as colorless prisms, $C_{26}H_{34}O_8$, mp 124—125°, which showed two equivalent acetyl signals at δ 2.30 in the PMR spectrum (in $CDCl_3$).

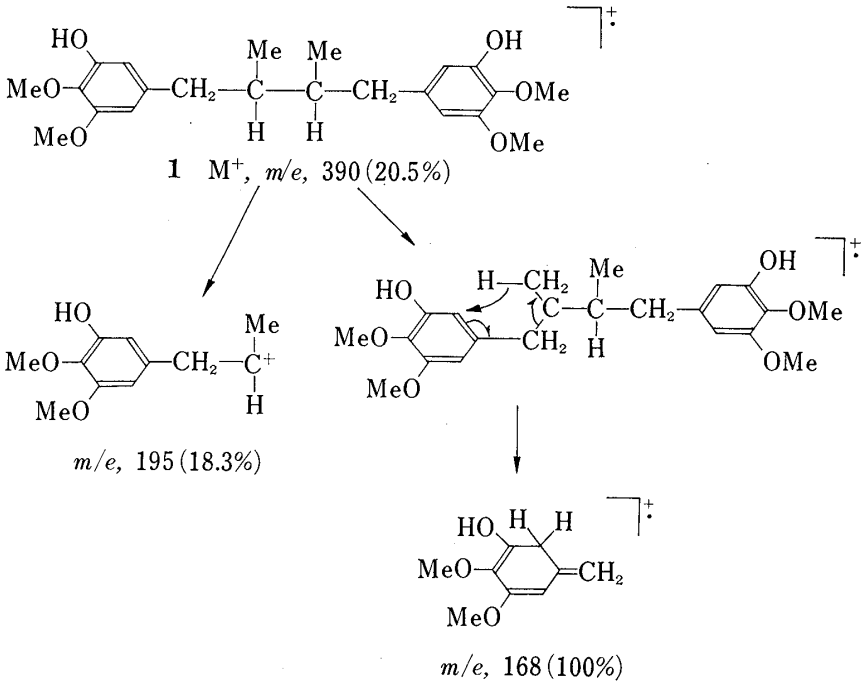


Chart 2. Mass Spectral Fragments of **1**

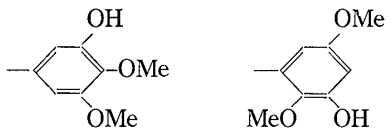


Chart 3

The above results, as well as analysis of the mass spectrum (Chart 2), suggested that **1** is a symmetrical 1,4-bis-phenyl-2,3-dimethylbutane type lignan. In addition, the circular dichroism (CD) spectrum, which showed no absorption between 200—400 nm, suggested that **1** has 2*S* and 3*R* configurations (*meso*-form). On the other hand, the positive Gibbs test of **1** and the appearance of a pair of *meta*-coupled aromatic protons in the PMR spectra of **1** and **1a** suggested the presence of the aromatic ring system [A] or [B] in **1** (Chart 3); ring system [A] seemed more reasonable for **1** on the basis of biogenetic considerations.

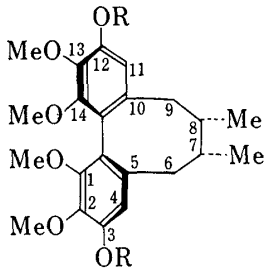
Thus, **1** was prepared from guaiaretic acid (**3**) isolated from the guaiacum resin[5] as shown in Chart 1. Catalytic hydrogenation of **3** gave crude *meso*-dihydroguaiaretic acid (**3a**),[5,7]

5) A.W. Schrecker and J. Hartwell, *J. Am. Chem. Soc.*, **77**, 432 (1955); F.E. King and J.G. Wilson, *J. Chem. Soc.*, **1964**, 4011.
6) L.H. Briggs, R.C. Cambie, and J.L. Hoare, *Tetrahedron*, **7**, 262 (1959).
7) A.W. Schrecker, *J. Am. Chem. Soc.*, **79**, 3823 (1957); C.W. Perry, *C.A.*, **73**, 45118*t* (1970).

which afforded a dimethyl ether (**3b**), $C_{22}H_{30}O_4$, mp 99.5—100.5° (Ref. 5, *meso*-form, mp 101—102°; *dl*(*trans*)-form, mp 70.4—71.8°), $[\alpha]_D^{24}$ 0° (in EtOH) by methylation [$(CH_3)_2SO_4$/K_2CO_3 in acetone] and also afforded a diacetate (**3c**), $C_{24}H_{30}O_6$, mp 115—116.5° (Ref. 5, mp 115°), $[\alpha]_D^{23}$ 0° (in $CHCl_3$) by acetylation (Ac_2O/pyridine), indicating that compound **3a** is *meso*-dihydroguaiaretic acid. On treatment with 15% nitric acid in a mixture of acetic acid and ethyl acetate (6: 1), **3a** afforded a dinitroderivative (**3d**), $C_{20}H_{24}N_2O_8$, mp 173—174.5°, IR (in KBr), 3200 (chelated OH), 1615 (aromatic), 1540, 1325 cm^{-1} (NO_2), which showed four *meta*-coupled aromatic protons in the PMR spectrum (in acetone-d_6, δ 7.05, 7.15, 7.32 and 7.42, each 1H, d, J=2 Hz), indicating that two nitro groups are linked to the positions adjacent to hydroxyls. The IR spectrum also indicated the presence of chelated hydroxyls in **3d**. On methylation with dimethyl sulfate and potassium carbonate, **3d** afforded a dimethyl-dinitro-dihydro derivative (**3e**), $C_{22}H_{28}N_2O_8$, mp 107.5—110°. On reduction with tin and hydrochloric acid in a mixture of chloroform and ethanol, followed by treatment with sodium nitrite and sulfuric acid, **3e** afforded a phenolic compound (**1**), $C_{22}H_{30}O_6$, mp 128.5—130.5°, $[\alpha]_D^{24}$ 0° (in $CHCl_3$) as colorless prisms; it was shown to be identical with natural pre-gomisin by direct comparison (IR, mixed mp and PMR).

Thus, the structure of pre-gomisin was elucidated as (2*S*, 3*R*)-1,4-bis(3′-hydroxy-4′,5′-dimethoxyphenyl)-2,3-dimethylbutane (**1**).

Gomisin J(**2**) was isolated as colorless needles (from ether–*n*-hexane), $C_{22}H_{28}O_6$, mp 149—150°, $[\alpha]_D^{24}$ −43.9° (in $CHCl_3$), giving a green coloration with ferric chloride in a mixture of chloroform and pyridine. The UV spectrum, with absorption maxima at 214 (log ε 4.70), 248 (4.15) and 276 nm (3.53), and the IR spectrum, with the bands at 3545, 3450 (OH), 1610 and 1583 cm^{-1} (aromatic), indicated that **2** is a dibenzocyclooctadiene lignan having a hydroxyl group. The PMR spectrum of **2** showed the presence of two secondary methyls (δ 0.75 and 0.99, each d, J=7 Hz), two benzylic methylenes (δ 2.0—2.7, 4H, m), four methoxyls (δ 3.50 and 3.94, each 6H, s), two hydroxyls (δ 5.91, 2H, br s, D_2O exchangeable) and two aromatic protons (δ 6.63, 2H, s). The appearance of two distinct methyl signals and two distinct methoxyl signals suggested that one methyl (δ 0.75)[8] and two methoxyls (δ 3.50)[9] are shielded by the aromatic rings, and therefore that **2** has a *cis*-dimethyl moiety on the cyclooctadiene ring and two methoxyls at C-1 and C-14 on the aromatic rings.



2 : R=H
2a: R=Me

Chart 4

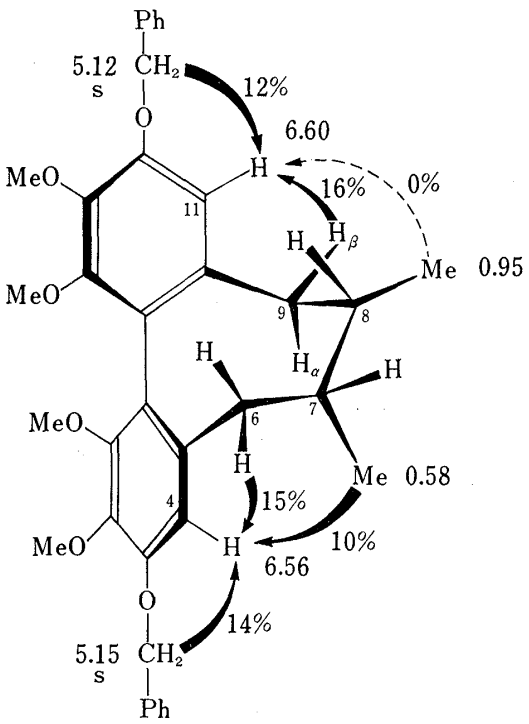


Fig. 1. NOE in **2b** (δ in$CDCl_3$)

8) E. Ghera, Y. Ben-David and D. Becker, *Tetrahedron Lett.*, **1977**, 463.
9) A.F.A. Wallis, *Tetrahedron Lett.*, **1968**, 5287.

On methylation, **2** afforded a dimethyl ether (**2a**) as colorless prisms (from ether–*n*-hexane), $C_{24}H_{32}O_6$, mp 113.5—115°, $[\alpha]_D^{26}$ −65.7° (in $CHCl_3$). The structure of **2a** was confirmed by comparison of the IR and PMR spectra with those of (+)-deoxyschizandrin (mirror image of **2a**),[10] isolated from the same source, and the CD spectrum showed that **2a** has an S-biphenyl configuration.[4a]

The structure of **2**, including the conformation of the cyclooctadiene ring was elucidated by measurements of the intramolecular nuclear Overhauser effects (NOE) in **2** and the dibenzyl ether (**2b**) of **2** (in $CDCl_3$). Irradiation of the methoxyl signals in **2** showed no enhancement of the integrated intensities of the aromatic proton signals, but, as shown in Fig. 1, irradiation of the benzylic methylene signals (δ 5.12 and 5.15) in the case of **2b** did produce enhancement of the integrated intensities of both aromatic proton signals, indicating that two hydroxyls are linked at positions adjacent to the aromatic protons. On the other hand, irradiation of the methylene signal (δ 2.47, $C_{(6)}$–H_2) and the higher field methyl signal (δ 0.58, $C_{(7)}$-methyl) caused 15% and 10% increases in the integrated intensity of the higher field aromatic proton signal, respectively. Irradiation of a methylene proton signal (δ 1.96, d,d, J=13.5/1 Hz, $C_{(9\beta)}$–H) caused a 16% increase in the integrated intensity of the lower field aromatic proton signal (δ 6.60). However, irradiation of the lower field methyl signal produced no enhancement of the signal intensities of the aromatic protons.

On the basis of the above NOE results and the J value between C-9 methylene and C-8 methine protons ($J_{8,9\alpha}$=8 Hz, $\phi_{8,9\alpha} \fallingdotseq 150°$; $J_{8,9\beta}$=1 Hz, $\phi_{8,9\beta} \fallingdotseq 90°$), the conformational structure of the dibenzyl ether of gomisin J was elucidated as **2a**. Consequently, the absolute structure of gomisin J was elucidated as **2** (*vide* CD).

The occurrence of **1**, **2** and **3a** in this plant is interesting, since they have been suggested to be precursors in a possible biogenetic route to the oxygenated dibenzocyclooctadiene lignans such as the gomisin A—D, F, G and H series.[1,4]

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 unit. The PMR spectra were recorded with Varian T-60 and JEOL PS-100 spectrometers. Mass spectra were measured with a Hitachi double-focusing mass spectrometer. The specific rotations were measured with a JASCO DIP-SL machine and the CD spectra with a JASCO J-20. TLC plates were made with Silica gel (Kieselgel GF_{254}, Merck), and Silica gel (Kieselgel 70—325 mesh, Merck) was used for column chromatography.

Isolation of Pre-gomisin and Gomisin J——As we reported in our previous papers,[1,4a] the petroleum ether and methanol extracts obtained from 4.671 kg of the dried fruits of *Schizandra chinensis* were subjected to column chromatography on silica gel using benzene–*n*-hexane and benzene-acetone solvent systems to give twelve fractions (fr. 1—12); frs. 7, 8 and 9 were combined and rechromatographed on silica gel using a benzene-ether solvent system to give nine fractions [fr. (7—9)-a—fr. (7—9)-i]. Fr. (7—9)-d (5.11 g) was rechromatographed on silica gel (120 g, 3×35 cm) using an *n*-hexane–acetone solvent system and the fractions eluted with *n*-hexane–acetone (17: 3) were combined and concentrated to give a residue (1.31 g), which was purified by preparative TLC (PLC) using benzene–EtOH (9: 1). The zone with *Rf* 0.46 was extracted with $CHCl_3$–MeOH (4: 1) and the extract was concentrated to give pre-gomisin (**1**) (540 mg, 0.012%). The fractions eluted with *n*-hexane–acetone (22: 3) were combined and concentrated to give a residue (1.02 g), which was purified by PLC using *n*-hexane–acetone (7: 3). The zone with *Rf* 0.58 was extracted with $CHCl_3$–MeOH (4: 1) and the extract was concentrated to give gomisin J (**2**) (350 mg). Fr. (7—9)-f and -g were combined and rechromatographed on silica gel as described in the previous paper.[1] The fractions eluted with 17% EtOAc–*n*-hexane were concentrated to give a residue, which was purified by PLC using benzene–EtOH (9: 1) to give **2** (724 mg, total yield 1.074 g, 0.023%).

Pre-gomisin (1)——Pure pre-gomisin was obtained as colorless prisms by recrystallization from ether–*n*-hexane, mp 130—131.5°, $[\alpha]_D^{25}$ 0° (c=0.443, $CHCl_3$). $FeCl_3$ in EtOH: green; Gibbs test: blue. UV λ_{max}^{EtOH} nm (log ε): 208 (4.81), 225 (sh 4.30), 270 (3.15). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1608, 1588 (aromatic). CD (c=0.0324,

10) *a*) (±)-Deoxyschizandrin (mp 113.5—115°) has been isolated from another source obtained in a market; *b*) The isolation procedure of natural deoxyschizandrin will be reported in the following paper.

MeOH), $[\theta]^{23}_{200-400}$: 0. PMR (δ in $CDCl_3$): 0.85 (6H, d, J=6 Hz, 2×C<u>H</u>$_3$–CH), 1.77 (2H, m, 2×–CH), 1.90—2.87 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.83 (6H, s, 2×OCH_3), 3.87 (6H, s, 2×OCH_3), 5.87 (2H, s, 2×OH, D_2O exchangeable), 6.28 (2H, d, J=2 Hz, 2×arom.-H), 6.43 (2H, d, J=2 Hz, 2×arom.-H). *Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.96; H, 7.79.

Gomisin J (**2**)——Pure gomisin J was obtained as colorless needles by recrystallization from ether–*n*-hexane, mp 149—150°, $[\alpha]^{24}_D$ −43.9° (c=1.00, $CHCl_3$). UV λ^{EtOH}_{max} nm (log ε): 214 (4.70), 248 (4.15), 276 (3.53). IR ν^{KBr}_{max} cm^{-1}: 3545, 3450 (OH), 1610, 1583 (aromatic). PMR (δ in $CDCl_3$): 0.75 (3H, d, J=7 Hz, C<u>H</u>$_3$–C$_{(7)}$–H), 0.99 (3H, d, J=7 Hz, C<u>H</u>$_3$–C$_{(8)}$–H), 1.5—2.4 (2H, m, 2×–CH), 2.0—2.7 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.50 (6H, s), 3.94 (6H, s) (4×OCH_3), 5.91 (2H, s, 2×OH), 6.63 (2H, s, arom.-H). MS, *m/e* (%): 388 (M^+, 100), 332 (4). *Anal.* Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.71; H, 7.15.

Isolation of *meso*-Dihydroguaiaretic Acid (**3a**) **from the Plant**——Fr. 6 (10.97 g) from the first column chromatography was rechromatographed on silica gel (240 g, 4.5×29 cm) using an EtOAc–*n*-hexane solvent system. The fractions eluted with *n*-hexane–EtOAc (21: 4) were combined and concentrated to give a residue (875 mg), which was purified by PLC using *n*-hexane–EtOAc (3: 2). The zone with *Rf* 0.52 was extracted with $CHCl_3$–MeOH (4: 1) and the extract was concentrated. The residue was purified by PLC using *n*-hexane–acetone (7: 3) to give **3a** as colorless prisms (125 mg, 0.0027%), mp 88—89.5°, $[\alpha]^{25}_D$ 0° (c=1.44, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.92; H, 8.03. PMR (δ in $CDCl_3$): 0.83 (6H, d, J=6 Hz, 2×C<u>H</u>$_3$–CH), 1.67 (2H, m, 2×–CH), 2.07—2.90 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.83 (6H, s, 2×OCH_3), 5.63 (2H, s, 2×OH, D_2O exchangeable), 6.72 (6H, m, 6×arom.-H). This compound (48 mg) was dissolved in a mixture of Ac_2O (0.3 ml) and pyridine (0.6 ml). The reaction mixture was allowed to stand at room temperature overnight, then it was diluted with H_2O, and extracted with ether. The ethereal extract was washed with 5% $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC [ether–*n*-hexane (2: 1)] to give a diacetate (**3c**) as colorless prisms (45 mg), mp 115.5—116.5°, $[\alpha]^{23}_D$ 0° (c=1.55, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.72; H, 7.32. This compound was identified as diacetyl-*meso*-dihydroguaiaretic acid (**3c**) by direct comparison with authentic material (IR and mixed mp).

Acetylation of 1——A solution of **1** (34 mg) in a mixture of pyridine (0.5 ml) and Ac_2O (0.2 ml) was allowed to stand at room temperature overnight, then diluted with H_2O and extracted with ether. The ethereal extract was washed with 5% $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC using benzene–ether (4: 1) to give a diacetate (**1a**) as colorless prisms (from ether–*n*-hexane (32 mg), mp 124—125°, $[\alpha]^{25}_D$ 0° (c=0.648, $CHCl_3$), $FeCl_3$ in EtOH: negative. UV λ^{EtOH}_{max} nm (log ε): 205 (4.79), 223 (sh 4.22), 274 (3.45). IR ν^{KBr}_{max} cm^{-1}: 1758 (C=O), 1603, 1580 (aromatic). PMR (δ in $CDCl_3$): 0.85 (6H, d, J=6 Hz, 2×C<u>H</u>$_3$–CH), 1.70 (2H, m, 2×–CH), 2.30 (6H, s, 2×OAc), 2.08—3.00 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.80 (6H, s, 2×OCH_3), 3.83 (6H, s, 2×OCH_3), 6.47 (2H, d, J=2 Hz, 2×arom.-H), 6.57 (2H, d, J=2 Hz, 2×arom.-H). *Anal.* Calcd. for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.58; H, 7.19.

Isolation of Guaiaretic Acid (**3**) **from Guaiacum Resin**——Guaiacum resin (25 g, Kokusan Chemical Works Ltd., Tokyo) was chromatographed on silica gel using an *n*-hexane–acetone solvent system and the fractions eluted with *n*-hexane–acetone (17: 3) were combined and concentrated to give crude guaiaretic acid (**3**) as colorless needles (from ether–*n*-hexane), mp 95—96°, $[\alpha]^{25}_D$ −81° (c=1.00, $CHCl_3$) (Ref. 5, mp 100—101°, $[\alpha]^{16}_D$ −91°). UV λ^{EtOH}_{max} nm: 206, 260, 287 (sh). IR ν^{KBr}_{max} cm^{-1}: 3400 (OH), 1640 (C=C), 1600 (aromatic).

Catalytic Hydrogenation of 3——A solution of **3** (1.82 g) in MeOH (50 ml) was shaken with H_2 in the presence of 5% Pd-C as a catalyst at room temperature for 45 min, then filtered and concentrated. The residue was recrystallized from MeOH–H_2O to give crude *meso*-dihydroguaiaretic acid (**3a**) as colorless needles (1.65 g), mp 64—66° (Ref. 5, mp 87—88°), $[\alpha]^{21}_D$ 0° (c=1.18, EtOH). UV λ^{EtOH}_{max} nm (log ε): 205 (4.60), 229 (4.09), 282 (3.74) (Ref. 5, λ^{EtOH}_{max}: 229, 281). PMR (δ in CCl_4): 0.80 (6H, d, J=6 Hz, 2×C<u>H</u>$_3$–CH), 1.68 (2H, m, 2×–CH), 2.02—2.83 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.70 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.37 (2H, s, 2×OH, D_2O exchangeable), 6.55 (6H, m, 6×arom.-H).

Methylation of 3a——Compound **3a** (25 mg) was methylated with $(CH_3)_2SO_4$ and K_2CO_3 in dry acetone to give a dimethyl ether (**3b**) as colorless needles (from ether–*n*-hexane) (23 mg), mp 99.5—100.5° (Ref. 5, mp 101—102°, *cf. dl*-dihydroguaiaretic acid dimethyl ether, mp 70.4—71.8°), $[\alpha]^{24}_D$ 0° (c=0.80, EtOH). UV λ^{EtOH}_{max} nm (log ε): 205 (4.80), 229 (4.26), 280 (3.80), 285 (sh 3.72). PMR (δ in CCl_4): 0.82 (6H, d, J=6 Hz, 2×C<u>H</u>$_3$–CH), 1.72 (2H, m, 2×–CH), 2.02—2.83 (4H, m 2×Ar–C<u>H</u>$_2$–), 3.73 (12H, s, 4×OCH_3), 6.38 (6H, m, 6×arom.-H). *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.55; H, 8.38.

Acetylation of 3a——A solution of **3a** (32 mg) in a mixture of Ac_2O (0.2 ml) and pyridine (0.5 ml) was allowed to stand at room temperature overnight, then diluted with H_2O (10 ml) and extracted with ether. The ethereal extract was washed with 5% $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC using ether–*n*-hexane (2: 1) to give a diacetate (**3c**) as colorless prisms (from MeOH) (20 mg), mp 115—116.5° (Ref. 5, mp 115°), $[\alpha]^{23}_D$ 0° (c=0.67, $CHCl_3$). IR ν^{KBr}_{max} cm^{-1}: 1760 (C=O), 1600 (aromatic). PMR (δ in $CDCl_3$): 0.88 (6H, d, J=6.5 Hz, 2×C<u>H</u>$_3$–CH), 1.80 (2H, m, 2×–CH), 2.15—2.97 (4H, m, 2×Ar–C<u>H</u>$_2$–), 2.30 (6H, s, 2×OAc), 3.82 (6H, s, 2×OCH_3), 6.83 (6H, m, 6×arom.-H). *Anal.* Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.76; H, 7.30.

Nitration of 3a——A mixture of conc. HNO_3 (0.5 g) and AcOH (1.5 g) was added dropwise to a solution of **3a** (660 mg) in a mixture of EtOAc (4 ml) and AcOH (24 ml) at 0°. The reaction mixture was stirred for 5 min, diluted with H_2O and extracted with ether. The ethereal extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give a residue (730 mg), which was chromatographed on silica gel using an *n*-hexane–acetone solvent system. The fractions eluted with *n*-hexane–acetone (9:1) gave 1,4-bis(4′-hydroxy-5′-methoxy-3′-nitro-phenyl)-2,3-dimethylbutane (**3d**) as orange prisms (from acetone) (239 mg, 28.5%), mp 173—174.5°, $[\alpha]_D^{23}$ 0° ($c=0.295$, EtOH). UV λ_{max}^{EtOH} nm (log ε): 225 (4.32), 254 (sh 3.87), 296 (3.90). IR ν_{max}^{KBr} cm^{-1}: 3200 (chelated OH), 1615 (aromatic), 1540, 1325 (NO_2). PMR (δ in acetone-d_6): 0.88 (6H, d, $J=7$ Hz, 2×C<u>H</u>$_3$–CH), 1.85 (2H, m, 2×–CH), 2.22—3.00 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.05, 7.15, 7.32, 7.42 (each 1H, d, $J=2$ Hz, 4×arom.-H). *Anal.* Calcd. for $C_{20}H_{24}N_2O_8$: C, 57.12; H, 5.75; N, 6.66. Found: C, 57.30; H, 5.77; N, 6.39.

Methylation of 3d——$(CH_3)_2SO_4$ (2 ml) and K_2CO_3 (6 g) were added to a solution of **3d** (526 mg) in dry acetone (15 ml), and the reaction mixture was stirred at 50° for 1 hr then diluted with H_2O. After the acetone had been removed, the solution was extracted with ether and the ethereal extract was washed with H_2O, dried over Na_2SO_4, and concentrated to give **3e** as yellow prisms (from MeOH) (536 mg, 95.5%), mp 107.5—110°, $[\alpha]_D^{21}$ 0° ($c=1.11$, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 222 (4.43), 265 (3.66), 330 (3.23). IR ν_{max}^{KBr} cm^{-1}: 1610 (aromatic), 1540, 1350 (NO_2). PMR (δ in CCl_4): 0.85 (6H, d, $J=6$ Hz, 2×C<u>H</u>$_3$–CH), 1.75 (2H, m, 2×–CH), 2.05—2.95 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.82 (3H, s, OCH_3), 3.88 (9H, s, 3×OCH_3), 6.73, 6.80, 6.90, 6.97 (each 1H, d, $J=2$ Hz, 4×arom.-H). *Anal.* Calcd. for $C_{22}H_{28}N_2O_8$: C, 58.92; H, 6.29; N, 6.25. Found: C, 58.96; H, 6.27; N, 6.11.

Reduction of 3e followed by Treatment with Sodium Nitrite (Preparation of 1)——Sn powder (896 mg) and conc. HCl (1 ml) were added to a solution of **3e** (224 mg) (0.5 mmol) in a mixture of $CHCl_3$ (4 ml) and EtOH (4 ml). The reaction mixture was kept at 65° for 1 hr, then cooled, made alkaline with 5% NaOH and extracted with ether. The ethereal extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give an amine (**3f**) as a pale yellow oil (148 mg, 76.3%). IR ν_{max}^{KBr} cm^{-1}: 3450, 3350 (NH_2), 1610 (aromatic). PMR (δ in CCl_4): 0.87 (6H, d, $J=6$ Hz, 2×C<u>H</u>$_3$–CH), 1.72 (2H, m, 2×–CH), 2.02—2.92 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.72 (4H, s, 2×NH_2), 3.72 (12H, s, 4×OCH_3), 5.95 (2H, d, $J=2$ Hz), 6.00 (2H, d, $J=2$ Hz) (4×arom.-H).

A solution of $NaNO_2$ (40 mg) in H_2O (0.15 ml) was added to a solution of **3f** (97 mg) in a mixture of dimethylsulfoxide (0.5 ml), H_2O (0.5 ml) and conc. H_2SO_4 (0.17 ml) at 0°, and the reaction mixture was stirred for 5 min, then dropped into boiling 5% H_2SO_4 solution. The solution was boiled for 1 hr, then cooled and extracted with ether. The ethereal extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC using *n*-hexane–acetone (3:2) to give a phenolic compound as colorless prisms (from ether-*n*-hexane) (37 mg, 38%), mp 128.5—130.5°, $[\alpha]_D^{24}$ 0° ($c=1.02$, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.51; H, 7.67. The compound obtained here was identified as **1** by direct comparison with authentic material (IR, mixed mp and PMR).

Methylation of 2——$(CH_3)_2SO_4$ (0.25 ml) and K_2CO_3 (500 mg) were added to a solution of **2** (20 mg) in dry acetone (2.5 ml). The reaction mixture was stirred at 40° for 5 hr, then diluted with H_2O and extracted with ether (15 ml×3). The combined ethereal extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was recrystallized from ether–*n*-hexane to give a dimethyl ether (**2a**) as colorless prisms (15 mg), mp 113.5—115°, $[\alpha]_D^{26}$ −65.7° ($c=1.37$, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 218 (4.66), 248 (4.16), 284 (sh 3.40). IR ν_{max}^{KBr} cm^{-1}: 1591, 1576 (aromatic). CD ($c=0.0077$, MeOH), $[\theta]^{23}$ (nm): +62000 (214), −62000 sh (236), −83000 (248), −9800 sh (278). MS, *m/e* (%): 416 (M^+, 100), 370 (5), 181 (2.4). PMR (δ in $CDCl_3$): 0.73 (3H, d, $J=7$ Hz, C<u>H</u>$_3$–C$_{(7)}$–H), 0.98 (3H, d, $J=7$ Hz, C<u>H</u>$_3$–C$_{(8)}$–H), 1.82 (1H, m, –CH), 1.92 (1H, m, –CH), 2.00—2.67 (4H, m, 2×Ar–C<u>H</u>$_2$–), 3.58 (6H, s, 2×OCH_3), 3.90 (12H, s, 4×OCH_3), 6.55 (2H, s, 2×arom.-H). *Anal.* Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.18; H, 7.72. The IR and PMR spectra of this compound were identical with those of (+)-deoxyschizandrin.

Benzylation of 2——Benzylchloride (150 mg) and K_2CO_3 (500 mg) were added to a solution of **2** (45 mg) in a mixture of dimethylformamide and H_2O (100:1) (3 ml), and the reaction mixture was kept at 100° for 1 hr. After adding H_2O (10 ml), the reaction mixture was extracted with ether (15 ml×3) and the combined extract was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was purified by PLC using *n*-hexane–acetone (7:3) to give the dibenzyl ether (**2b**) as an amorphous powder (53 mg), $[\alpha]_D^{25}$ −51.6° ($c=1.57$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1590, 1575. PMR (δ in $CDCl_3$): 0.58 (3H, d, $J=7$ Hz, C<u>H</u>$_3$–C$_{(7)}$–H), 0.95 (3H, d, $J=7$ Hz, C<u>H</u>$_3$–C$_{(8)}$–H), 1.68 (1H, m, –CH), 1.85 (1H, m, –CH), 1.96 (1H, d,d, $J=$ 13.5/1 Hz, C$_{(9\beta)}$–H), 2.24 (1H, d,d, $J=13.5/8$ Hz, C$_{(9\alpha)}$–H), 2.47 (2H, m, C$_{(6)}$-methylene), 3.60 (6H, s, 2×OCH_3), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.12 (2H, s, C_6H_5–C<u>H</u>$_2$–), 5.15 (2H, s, C_6H_5–C<u>H</u>$_2$–), 6.56 (1H, s, C$_{(4)}$–H), 6.60 (1H, s, C$_{(11)}$–H), 7.37 (10H, m, 2×C_6H_5–). High resolution MS, Calcd. for $C_{36}H_{40}O_6$(M^+): 568.282. Found: 568.285.

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