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Constituents of *Wikstroemia sikokiana*. II.¹⁾ Absolute Configurations of 1,5-Diphenylpentane-1,3-diols

MASATAKE NIWA,* PEI-FENG JIANG,²⁾ and YOSHIMASA HIRATA

Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468, Japan

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Further examination of the chemical constituents of *Wikstroemia sikokiana* FRANCH. *et* SAV. (Thymelaeaceae) afforded (+)-chamaejasmenin B (C-3/C-3''-biflavanone) and (–)-*erythro*-1,5-diphenylpentane-1,3-diol. The unsettled absolute configuration of the 1,3-diol was established as 1(*S*) and 3(*S*) on the basis of a synthesis using chiral styrene oxide as a starting material.

Keywords—Thymelaeaceae; *Wikstroemia sikokiana*; biflavanone; chamaejasmenin B; 1,5-diphenylpentane-1,3-diol; absolute configuration; (*R*)-styrene oxide; chiral epoxide

Introduction

In the previous paper,¹⁾ we reported two new C-3/C-3''-biflavanones from the roots of *Wikstroemia sikokiana* FRANCH. *et* SAV. (Ganpi in Japanese) (Thymelaeaceae). We further examined the chemical constituents of the same plant and isolated two known compounds: (+)-chamaejasmenin B (**1**), which is a C-3/C-3''-biflavanone,³⁾ and (–)-*erythro*-1,5-diphenylpentane-1,3-diol (**2**).⁴⁾ In order to establish the absolute configuration of the latter compound, a chiral synthesis was carried out. In this paper, we wish to report the isolation of (+)-chamaejasmenin B and (–)-*erythro*-1,5-diphenylpentane-1,3-diol from the above plant and the syntheses of optically active (–)-*erythro*-1,5-diphenylpentane-1,3-diol and its epimer using the commercially available chiral epoxide as a starting material.

Results and Discussion

Isolation and Identification

The benzene-soluble fraction described in the previous paper¹⁾ was separated by a combination of column chromatography and preparative thin layer chromatography (TLC) to give two compounds. One was identified as chamaejasmenin B (**1**), a C-3/C-3''-biflavanone isolated from the root of *Stellera chamaejasme* L. (Thymelaeaceae), by direct comparison of the infrared (IR) and proton nuclear magnetic resonance (¹H-NMR) spectra with those of an authentic sample.³⁾

The IR, ¹H-NMR and ¹³C-NMR spectra of the other compound, mp 91–92 °C, [α]_D –19.2 ° and its diacetate (**4**) suggested that it was *erythro*-1,5-diphenylpentane-1,3-diol (**2**) isolated from the wood of *Flindersia laevicarpa* C. T. WHITE *et* FRANCIS (Rutaceae)⁴⁾ or *threo*-1,5-diphenylpentane-1,3-diol (**3**) isolated from the bark of the same plant.⁵⁾ The stereochemistry between the C-1 and C-3 positions was established by the following experiments. Treatment of the natural diol (**2**) with acetone in the presence of camphorsulfonic acid afforded the corresponding acetonide (**5**). The ¹H-NMR spectrum of **5** showed two methyl protons at δ 1.53 (3H, s) and 1.54 (3H, s) and two methine protons at δ 3.96 (1H, m) and 4.86 (1H, dd, *J* = 11.7, 2.7 Hz). The coupling constant (*J* = 11.7 Hz) indicated that 1-H must be in an axial configuration. In a nuclear Overhauser effect (NOE) experiment on the acetonide (**5**),

irradiation of the methine signal at δ 3.96 (3-H) caused a 9.4% enhancement of the signal at δ 4.86 (1-H). This result suggested the relationship between 1-H and 3-H in **5** to be *syn*. Therefore, the original diol should be *erythro*-1,5-diphenylpentane-1,3-diol (**2**).

Synthesis

In order to establish the absolute configuration of the *erythro*-diol, an asymmetric synthesis of the diol was carried out as follows. Dithiane (**6**),⁶⁾ which was prepared from 3-phenylpropionaldehyde and propane-1,3-dithiol by using chloroform as a solvent and boron trifluoride etherate as a catalyst, was converted into 2-lithiodithiane by adding a 1.1-fold molar excess of *n*-butyllithium to a tetrahydrofuran (THF) solution of **6**, and then the 2-lithiodithiane was reacted with the commercially available chiral epoxide, (*R*)-styrene oxide (**7**), $[\alpha]_D + 32.5$ (7) to afford the adduct (**8**). The presence of a hydroxy group was indicated by the following spectral data; ν 3570 and 3460 cm^{-1} ; δ 5.10 (1H, dt, $J=9$, 4 Hz, changed to a double doublet ($J=9$, 2 Hz) on addition of deuterium oxide). The adduct was subjected to hydrolysis with mercuric chloride and mercuric oxide in aqueous methanol to give a mixture of the dimethylacetal (**9**), mp 66–67 °C, $[\alpha]_D - 8.5$ ° and the ketone (**10**) as an oil, $[\alpha]_D - 28$ ° in 38 and 57% yields, respectively. The ^1H -NMR spectrum of **9** showed two methoxyl groups (δ 3.18 (3H, s) and 3.25 (3H, s). The structure of the ketone (**10**) was supported by the IR and ^1H -NMR data (ν 3450 and 1710 cm^{-1} , δ 5.10 (1H, m, changed to a double doublet ($J=5$, 7 Hz) on addition of deuterium oxide). Next, the ketone (**10**) was reduced with sodium borohydride in THF to afford a mixture of two diols separable by reversed-phase high-performance liquid chromatography (HPLC). One, mp 89.5–91 °C, $[\delta]_D - 23.0$ °, having the larger retention time (t_R) on HPLC, was identical with natural (–)-*erythro*-1,5-diphenyl-

Fig. 1

pentane-1,3-diol (**2**) isolated from *Wikstroemia sikokiana*, by IR, ^1H -NMR, and HPLC comparisons. Consequently, the stereochemistry of **2** should be 1(*S*) and 3(*S*). Finally, the other diol, mp 91–92°C, $[\alpha]_{\text{D}} -23.3^\circ$, having the smaller t_{R} on HPLC should be the *threo*-isomer (**11**). The sign of the optical rotation of the natural *threo*-diol (**3**) ($[\alpha]_{\text{D}} +29.8^\circ$) isolated from the bark of *Flindersia laevis* C. T. WHITE *et* FRANCIS⁵⁾ was opposite to that of the optical rotation of the synthetic diol (**11**) ($[\alpha]_{\text{D}} -23.3^\circ$), whose absolute configuration should be 1(*S*) and 3(*R*). Consequently, the absolute configuration of natural (+)-*threo*-1,5-diphenylpentane-1,3-diol (**3**) is 1(*R*) and 3(*S*).

Experimental

Optical rotations were measured on JASCO DIP-181 and DIP-360 digital polarimeters. Infrared (IR) spectra were taken on a JASCO IR-2 spectrometer. ^1H - and ^{13}C -NMR spectra were taken on JEOL GX-400 and/or FX-100 spectrometers in CDCl_3 unless otherwise stated. Chemical shifts are given in ppm relative to internal tetramethylsilane (TMS). Mass spectra (MS) were obtained on a Hitachi M-80 spectrometer operating at an ionization potential of 70 eV. Column chromatography (CC) and preparative TLC were performed with silica gel. HPLC was carried out with a JASCO TRIOTAR-V (detector: JASCO UVIDEC-100-V, 254 nm).

Isolation—The benzene soluble fraction (7.5 g) reported in the previous paper,¹⁾ was chromatographed (Merck 7734, 200 g) with mixtures of benzene and AcOEt (9:1, 7:3 and 5:5) (each 1000 ml) to afford five fractions (0.67, 1.93, 2.14, 0.53 and 0.28 g). The second fraction (1.93 g) eluted with the first half (500 ml) of benzene–AcOEt (7:3) was subsequently separated by CC (Merck 7734, 60 g, CHCl_3 –AcOEt (9:1)), medium-pressure liquid chromatography (MPLC) (Fuji gel, CQ-3, $\phi 3 \times 23$ cm, CHCl_3 –AcOEt (7:3)) and preparative TLC (Merck 13895, CHCl_3 –AcOEt (1:1)) to afford 1,5-diphenylpentane-1,3-diol (**2**) (100 mg, 0.003%) as colorless needles, mp 91–92°C (hexane–Et₂O). $[\alpha]_{\text{D}} -19.2^\circ$ ($c=0.52$, MeOH). MS m/z : 238 ($\text{M}^+ - \text{H}_2\text{O}$). IR $\nu_{\text{max}}^{\text{KBr}}$: 3310 cm^{-1} . ^1H -NMR δ : 1.6–1.9 (4H, complex), 2.5–2.8 (2H, complex), 3.44 (2H, br s, OH, disappeared on addition of D₂O), 3.90 (1H, complex), 4.89 (1H, dd, $J=10.0$, 2.9 Hz), 7.0–7.4 (10H, complex). ^{13}C -NMR δ : 31.6 (t), 39.5 (t), 45.2 (t), 71.8 (d), 75.1 (d), 125.6 (d $\times$ 2), 125.8 (d), 127.5 (d), 128.4 (d $\times$ 6), 141.9 (s), 144.4 (s). *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2$: C, 79.65; H, 7.87. Found: C, 79.30; H, 7.93. The third fraction (2.14 g) eluted with the latter half (500 ml) of CHCl_3 –AcOEt (7:3) was subsequently separated by CC (Katayama Chemical K230, 60 g, CHCl_3 –AcOEt (7:3)) and preparative TLC (Merck 13895, CHCl_3 –AcOEt (1:1)) to afford chamaejasmenin B (**1**) (51 mg, 0.006%) as an amorphous powder, $[\alpha]_{\text{D}} +143.9^\circ$ ($c=0.57$, MeOH), which was identified by comparison of the IR and ^1H -NMR spectra with those of an authentic sample.³⁾

Acetylation of the Diol (2**)**—A mixture of **2** (5 mg), Ac₂O (0.5 ml) and pyridine (0.5 ml) was left to stand at room temperature overnight. After concentration, the residue was purified by preparative TLC (Merck 5715, CHCl_3) to afford **4** (4 mg) as a colorless oil. High-resolution MS Found m/z : 280.1459 ($\text{M}^+ - \text{CH}_3\text{COOH}$); $\text{C}_{19}\text{H}_{20}\text{O}_2$ requires 280.1461. IR $\nu_{\text{max}}^{\text{film}}$: 1735 cm^{-1} . ^1H -NMR δ : 1.95 (3H, s), 2.01 (3H, s), 4.85 (1H, m), 5.79 (1H, t, $J=7$ Hz), 7.0–7.4 (10H, complex).

Acetalization of the Diol (2**)**—A solution of **2** (13 mg) and camphorsulfonic acid (2 mg) in acetone (3 ml) was left to stand at room temperature overnight. After evaporation of acetone, the residue was separated by preparative TLC (Merck 5715, CHCl_3 –hexane (2:1)) to afford an acetonide (**5**) (6 mg) as a colorless oil. High-resolution MS Found m/z : 281.1555 ($\text{M}^+ - \text{CH}_3$); $\text{C}_{19}\text{H}_{21}\text{O}_2$ requires 271.1541. IR $\nu_{\text{max}}^{\text{film}}$: 1600, 1495 cm^{-1} . ^1H -NMR δ : 1.53 (3H, s), 1.54 (3H, s), 3.96 (1H, m), 4.86 (1H, dd, $J=11.7$, 2.7 Hz), 7.1–7.4 (10H, complex).

Preparation of 2-(2-Phenylethyl)-1,3-dithiane (6**)**—A solution of 3-phenylpropionaldehyde (2.56 g, 18.5 mmol), propane-1,3-dithiol (2.20 g, 20.3 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.0 ml) in CHCl_3 (50 ml) was kept at -10°C for 30 min and then at room temperature for 3 h. The CHCl_3 solution was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by CC (Merck 7734, 190 g, hexane–benzene (2:1)) to afford **6** (4.21 g, 81%). The spectral data were in good agreement with the reported values.⁶⁾

Reaction of (*R*)-Styrene Oxide (7**) with **6****—A solution of **6** (2.028 g, 8.9 mmol) in THF (50 ml) was cooled to -40°C under argon, treated with 15% *n*-butyllithium in hexane (4.2 ml, 9.7 mmol) and kept at -40°C for 30 min and then at -20°C for 30 min. The solution was cooled to -50°C , treated with (*R*)-styrene oxide (**7**) (1.068 g, 8.9 mmol) in THF (10 ml), kept at -50°C for 30 min and at -20°C at 1 h, and diluted with AcOEt (100 ml). The solution was successively washed with aqueous NH_4Cl , water and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residue was separated by CC (Merck 7734, 150 g, CHCl_3) to afford the unreacted dithiane (**6**) (0.610 g, 30.1%) and the adduct (**8**) (1.996 g, 65.0%) as colorless needles, mp 103–104°C from hexane–ether. $[\alpha]_{\text{D}} -31.3^\circ$ ($c=0.54$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$: 3570, 3460 cm^{-1} . ^1H -NMR δ : 3.52 (1H, d, $J=2$ Hz, disappeared on addition of D₂O), 5.10 (1H, dt, $J=9$, 4 Hz, changed to a double doublet ($J=9$, 2 Hz) on addition of D₂O). ^{13}C -NMR δ : 24.9 (t), 26.0 (t), 26.3 (t), 30.7 (t), 41.7 (t), 47.2 (t), 52.2 (s), 71.2 (d), 125.6 (d $\times$ 2), 125.9 (d), 127.4 (d), 128.4 (d $\times$ 6), 141.6 (s), 144.7 (s). *Anal.* Calcd for $\text{C}_{20}\text{H}_{24}\text{OS}_2$: C, 69.72; H, 7.02. Found: C, 69.72; H, 7.14.

Hydrolysis of the Adduct (8)—Mercuric oxide (820 mg, 3.8 mmol) and mercuric chloride (1030 mg, 3.8 mmol) were added to an efficiently stirred solution of **8** (800 mg, 2.3 mmol) in aqueous 90% MeOH at room temperature. The mixture was stirred at the same temperature for 2 h and filtered through Super Cel. The filter cake was washed thoroughly with MeOH and the filtrate was concentrated. The residue was separated by CC (Merck 7734, 50 g, CHCl_3 –AcOEt (15:1)) to afford the dimethylacetal (**9**) (260 mg, 38%) as colorless needles and the ketone (**10**) (330 mg, 57%) as an oil.

The Dimethylacetal (9)—Colorless needles from hexane–ether, mp 66–67 °C. $[\alpha]_D -8.5^\circ$ ($c=1.0$, MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$: 3480 cm^{-1} . $^1\text{H-NMR}$ δ : 3.18 (3H, s), 3.25 (3H, s), 3.95 (1H, d, $J=1$ Hz, disappeared on addition of D_2O), 4.90 (1H, br d, $J=10$ Hz, changed to a sharp double doublet ($J=10$, 3 Hz) on addition of D_2O). *Anal.* Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_3$: C, 75.97; H, 8.05. Found: C, 75.94; H, 8.25.

The Ketone (10)— $[\alpha]_D -28.0^\circ$ ($c=1.0$, MeOH). High-resolution MS Found m/z : 254.1340 (M^+); $\text{C}_{17}\text{H}_{18}\text{O}_2$ requires 254.1306. IR $\nu_{\text{max}}^{\text{film}}$: 3450, 1710 cm^{-1} . $^1\text{H-NMR}$ δ : 3.21 (1H, d, $J=3$ Hz, disappeared on addition of D_2O), 5.10 (1H, m, changed to a double doublet ($J=7$, 5 Hz) on addition of D_2O).

Reduction of the Ketone (10)—**10** (300 mg) in THF (20 ml) was reduced with NaBH_4 (20 mg) at room temperature for 2 h. The mixture was concentrated under reduced pressure, diluted with AcOEt (40 ml) and washed with water and then with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was roughly separated by preparative TLC (Merck 13895, CHCl_3 –AcOEt (10:1)) using the method of repeated developments (3 times) to afford two fractions. Each fraction was further separated by preparative HPLC (Develosil ODS-5, $\phi 10 \times 250$ mm, MeOH– H_2O (75:25)) to afford the diols **11** (61 mg) and **2** (118 mg), as colorless needles, respectively. HPLC analyses of the synthetic diols **2** and **11** were performed under the following conditions: column, Wakogel ODS-5K, $\phi 4.6 \times 250$ mm; solvent, MeOH– H_2O (70:30); flow rate, 0.7 ml/min; chart speed, 10 mm/min.

2: mp 89.5–91 °C from hexane–ether. $[\alpha]_D -23.0^\circ$ ($c=1.0$, MeOH). t_R 12.6 min.

11: mp 91–92 °C from hexane–ether. $[\alpha]_D -23.3^\circ$ ($c=1.0$, MeOH). t_R 12.1 min. MS m/z : 238 ($\text{M}^+ - \text{H}_2\text{O}$). IR $\nu_{\text{max}}^{\text{KBr}}$: 3350 cm^{-1} . $^1\text{H-NMR}$ δ : 1.65–1.95 (4H, complex), 2.56 (1H, complex), 2.70 (1H, complex), 3.13 (1H, br s, disappeared on addition of D_2O), 3.61 (1H, br s, disappeared on addition of D_2O), 3.84 (1H, complex), 4.97 (1H, dd, $J=8.2$, 3.4 Hz), 7.10–7.30 (10H, complex). $^{13}\text{C-NMR}$ δ : 32.0 (t), 39.0 (t), 44.7 (t), 68.6 (d), 71.4 (d), 125.5 (d $\times$ 2), 125.8 (d), 127.2 (d), 128.4 (d $\times$ 6), 141.9 (s), 144.4 (s). *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2$: C, 79.65; H, 7.87. Found: C, 79.50; H, 7.93.

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