Indonesian Medicinal Plants. I. New Furanoditerpenes from *Arcangelisia flava* MERR. (2). Stereostructure of Furanoditerpenes Determined by Nuclear Magnetic Resonance Analysis

YOSHIYUKI KAWAKAMI,* YASUSHI NAGAI, YUKUO NEZU, TADASHI SATO, TOSHINOBU KUNII, and KENGO KAGEI

Tsukuba Research Laboratories, Eisai Co., Ltd., 1–3, Tokodai 5-chome, Toyosato-machi, Tsukuba-gun, Ibaraki 300–26, Japan

(Received February 4, 1987)

The stereostructures of four furanoditerpenes which were isolated from *Arcangelisia flava* MERR., 6-hydroxyarcangelisin, 2-dehydroarcangelisinol, tinophyllol, and 6-hydroxyfibleucin, were elucidated by a differential nuclear Overhauser effect (NOE) method and two-dimensional nuclear magnetic resonance (2D NMR). The stereostructures of two franooiditerpenes, fibraurin and 6-hydroxyfibraurin, which had not been completely determined, were also elucidated.

**Keywords**——*Arcangelisia flava*; Menispermaceae; furanoditerpene; stereochemistry; NOE difference NMR spectroscopy; two-dimensional NMR

The stem of *Arcangelisia flava* MERR. (Menispermaceae) is an important component of folk medicine in Indonesia (Indonesian name: Jamu). In the previous paper,1) we reported the isolation of four new [6-hydroxyarcangelisin (1), 2-dehydroarcangelisinol (2), tinophyllol (3), and 6-hydroxyfibleucin (4)] and three known furanoditerpenes [fibraurin (5),2) 6-hydroxyfibraurin (6),2) and fibleucin3)] from *A. flava* and the elucidation of their plane structures.

Numerous furanoditerpenes, including fibraurin,2) 6-hydroxyfibraurin,2) fibleucin,3) chasmanthin,4–6) palmarin,5,7,8) columbin,5,7–10) jateorin,5) isojateorin,5,7) and tinophyllon,11,12) have been isolated from Menispermaceae plants. The plane structural relationships of these compounds have been reported.2,5) However, the stereochemical features of fibraurin and its hydrogenated derivative, palmarin, were not established. Hori et al.2) determined the α-epoxide configuration of fibraurin by an optical rotatory dispersion (ORD) technique. On the other hand, Islam et al.13,14) reported that the 2,3-epoxide of palmarin has the β-configuration based on X-ray analysis.

This paper deals with stereostructural studies on six furanoditerpenes, 1, 2, 3, 4, 5, and 6 (Chart 1), by nuclear Overhauser effect (NOE) difference nuclear magnetic resonance (NMR) spectroscopy and two-dimensional NMR (2D NMR) spectroscopy.

**6-Hydroxyarcangelisin (1)**

Detailed 400 MHz 1H-NMR decoupling experiments disclosed that 1 has the same structure of rings A and C as 52): two epoxide protons at δ 3.88 and δ 3.67 were coupled (J = 4.4 Hz) to each other, and the signal at δ 3.88 (H-2) was coupled to a signal at δ 5.00 (H-1) (J = 2.5 Hz). The signal at δ 5.46 (J = 12.1 Hz) due to H-12 was coupled to C11 methylene proton signals at δ 2.31 and δ 1.88, and the coupling constant of H-12 (J = 12.1 Hz) indicated the axial orientation. These 1H-NMR data showed that the furan ring exists in equatorial orientation at C12 as in 5 and 6.2) The 2D NMR spectrum was measured in order to confirm the configuration. Figure 1 shows a spectrum of 1 obtained by 2D correlated spectroscopy (COSY).
A very small coupling constant ($J=0.3$ Hz) due to an almost $90^\circ$ angle was observed between the H-1 and H-10 protons. Also, long-range couplings between 9-CH$_3$ and H-8, 9-CH$_3$ and H-10, and 9-CH$_3$ and H-11 were observed, whereas no long-range coupling was observed for the 5-CH$_3$ protons. These W-configuration couplings between 9-CH$_3$, H-8, H-10, and H-11 indicated that 9-CH$_3$, H-8, H-10 and H-11 were axially oriented. In order to confirm the spatial relationships of other protons in 1, the 2D NOE correlated NMR spectrum (NOESY) was measured (Fig. 2).

No cross-peaks between the 5-CH$_3$ and the 9-CH$_3$ were observed in the NOESY spectrum. This result indicated that 5-CH$_3$ and 9-CH$_3$ were on opposite sides of the plane defined by ring B. Thus, it can be presumed that 5-CH$_3$ and 9-CH$_3$ have $\alpha$-configuration (axial) and $\beta$-configuration (axial), respectively, assuming that the lactone on the ring A
retains β-configuration. Reliable NOE cross-peaks were observed between 5-CH₃ and H-8, 5-CH₃ and H-10, and 5-CH₃ and H-3. Further NOE cross-peaks were observed between 9-CH₃ and H-6, and 9-CH₃ and H-12. These results indicated that the hydroxyl group at C-6 has α-configuration, the furan ring at C-12 has α-configuration, and the 2,3-epoxide has β-configuration. Moreover, cross-peaks were observed between 9-CH₃ and H-8, 9-CH₃ and H-10, and 9-CH₃ and H-11α, reflecting W-configurations of the protons.

Next, we carried out NOE difference spectroscopy experiments. The results are presented in Figs. 3 and 4.

Figure 3 shows an NOE difference spectrum of 1 with irradiation of the 9-CH₃ protons (δ 1.03). Clear NOE enhancements were observed at H-1, H-6, and H-12, but not at H-8, H-10, and H-11α. Thus the cross-peaks on 9-CH₃ between H-1, H-6, and H-12 were real NOE cross-peaks in the NOESY spectrum (Fig. 2). A large NOE (10%) was observed at the H-6 proton when the 9-CH₃ protons (δ 1.03) were irradiated and a 6% NOE was observed at H-8 when the 5-CH₃ protons (δ 1.26) were irradiated. The infrared (IR) spectrum implies the presence of intramolecular hydrogen-bonding between 4-OH and 6-OH (3300 cm⁻¹). Furthermore, the coupling constant between H-6 and H-7 (J = 8.8 Hz), and also that between

Fig. 2. NOESY Spectrum of 1 (in DMSO-d₆)

Fig. 3. NOE Measurement of 1 Irradiated at δ 1.03 (9-CH₃)

Fig. 4. NOE Results for 1

Values are percent increase of signal area.
H-7 and H-8 ($J = 9.9 \text{ Hz}$) indicated a conformational distortion of ring B. On the basis of these results, it seemed reasonable to assume that ring B exists in a twist boat conformation. Ring C exists in a chair conformation based on the large NOE (9%) between 9-CH$_3$ and H-12 and the spin coupling (W-configuration long-range coupling) between 9-CH$_3$ and H-11$\alpha$.

From the above results, the stereostructure of 6-hydroxyarcangelisin is represented by formula 1 (Chart 1).

2-Dehydroarcangelisinol (2)

The $^1$H-NMR spectra of 2 and 1 showed almost identical in chemical shifts and coupling values of the H-6, H-7$\alpha$, H-7$\beta$, H-8, H-11$\alpha$, H-11$\beta$, H-12, and 9-CH$_3$ protons. The only difference was the presence of an olefin group ($\delta$ 6.53, dd, $J = 8.0$, 5.0 Hz, H-2; 6.14, dd, $J = 8.0$, 1.8 Hz, H-3) in the former. From all the above data, it is clear that 2 has the partial structure with the 6$\alpha$-equatorial hydroxyl group and the 12$\alpha$-equatorial furan ring as shown in Chart 1. This conclusion was firmly supported by NOE experiments. Irradiation of the 9-CH$_3$ protons ($\delta$ 1.03) afforded a 10% NOE enhancement of the H-6 signal and a 9% NOE enhancement of the H-12 signal (Fig. 5). Furthermore, irradiation of the 5-CH$_3$ protons ($\delta$ 1.06) caused an NOE enhancement in the H-8 (8%) signal, which is in agreement with all the above conclusions.

The stereostructure of 2-dehydroarcangelisinol (2) is thus as depicted in Chart 1.

Tinophyllol (3)

A large NOE (14%) was observed at the H-2 proton when the 9-CH$_3$ protons ($\delta$ 0.84) were irradiated (Fig. 6). This result indicated that the hydroxyl group at C-2 has the $\alpha$-configuration. The furan ring at C-12 was determined to take the $\beta$-equatorial configuration because an NOE enhancement (17%) was observed at the H-12 proton when the H-8 proton was irradiated, whereas no NOE enhancement was observed between the 9-CH$_3$ and H-12 protons. The substitution pattern of the furan ring was supported by the fact that ring C of tinophyllon$^{11,12}$ retains a boat conformation with the furan ring at C-12 in the $\beta$-equatorial configuration. Furthermore, the coupling constant between H-1 and H-2 ($J = 8.0 \text{ Hz}$) indicated that ring A exists in a diplanar conformation (10$\beta$ sofa form). Finally, the conformation of ring B was determined to be chair because of the NOE between 9-CH$_3$ and H-7$\beta$ and the NOE between H-6$\alpha$ and H-8 (1,3-diaxial interaction).

The stereostructure of tinophyllol (3) was thus determined to be as depicted in Chart 1.

6-Hydroxyfibleucin (4)

A large NOE enhancement (20%) between the 9-CH$_3$ and H-6 protons indicated that the hydroxyl group at C-6 has $\alpha$-configuration and ring B existed in a boat conformation. Also,
the furan ring at C-12 was determined to take \( \alpha \)-configuration because a large NOE (19\%) was observed between the 9-CH\(_3\) and H-12 protons (Fig. 7). The stereostructure of 6-hydroxyfibraurin (4) was determined to be as depicted in Chart 1.

**Fibraurin (5)**

It was reported by Hori et al.\(^2\)) that the 2,3-epoxy group of fibraurin takes the \( \alpha \)-configuration on the basis of ORD experiments. However, Islam et al.\(^1,3,14\)) proposed the \( \beta \)-configuration for a palmarin derivative based on X-ray analysis. The 2,3-epoxy groups of fibraurin and palmarin must have the same configuration. In our experiments (Fig. 8), 14\% NOE was observed at H-3 when the 5-CH\(_3\) protons were irradiated. Thus, it was concluded that the 2,3-epoxy group takes the \( \beta \)-configuration as in the structure of 1, in agreement with the X-ray analysis of palmarin.

Consequently, the stereostructure of fibraurin should be revised at the 2,3-epoxide group as presented in Chart 1.

**6-Hydroxyfibraurin (6)**

The structure of 6-hydroxyfibraurin had been determined by Hori et al.\(^2\)) except for the configuration of the hydroxyl group at C-6. The NOESY experiment showed reliable NOE
cross-peaks between the 9-CH₃ and the H-6 protons (Fig. 9). The configuration of the hydroxyl group at C-6 was thus confirmed to be α-equatorial. Consequently, the stereostructure of 6-hydroxyfibraurin (6) should be revised as in the case of 5 (Chart 1). Further work on the structural elucidation of other new furanoditerpenes from A. flava is in progress, and will be reported elsewhere.

**Experimental**

'H-NMR spectra were obtained in dimethyl sulfoxide-δ₆ at 35 °C on a JEOL GX400 spectrometer operating at 400 MHz. The 2D correlated spectra (COSY) were measured by the use of a 2D correlation sequence with a 90° mixing pulse, and P-type peak selection. Data processing was carried out with the standard JEOL software. An f₂ spectral width of 3333.3 Hz over 1024 data points gave a digital resolution of 6.51 Hz. A total of 512 spectra, each of 6-Hydroxyfibraurin (6)-mp 295-304 °C (dec.), colorless plates from MeOH, +26.3 (pyridine, c = 0.5).

Tinophyllol (3) - mp 229-231 °C (dec.), colorless prisms from MeOH, -19.3 (pyridine, c = 0.5).

2-Dehydroarcangelisolin (2) mp 208-212 °C (dec.), colorless prisms from MeOH, [α]D₂₀ +98.8 (pyridine, c = 0.25).

Analytical data for C₂₀H₂₁O₇: C, 67.3% (found 67.2%); H, 7.0% (found 7.0%); UV max (MeOH) nm: 211, 231. FD-MS (m/z): 370 (M+), IR cm⁻¹: 3330, 1780, 1705, 1602, 1508, 875, 812. **Experimental**

1H-NMR spectra in progress, and will be reported elsewhere.

Further work on the structural elucidation of other new furanoditerpenes from A. flava is in progress, and will be reported elsewhere.
(M'). EI-MS (m/z): 389 (M' + 1). IR νNujol cm⁻¹: 3300, 1782, 1698, 1507, 873, 810. ¹H-NMR (400 MHz, DMSO-d₆) δ: 7.76 (1H, d, J=1.6 Hz, H-16), 7.69 (1H, dd, J=1.8, 1.6 Hz, H-15), 6.86 (1H, d, J=2.8 Hz, H-7), 6.64 (1H, d, J=1.8 Hz, H-14), 6.34 (1H, s, 4-OH), 5.68 (1H, dd, J=12.0, 2.0 Hz, H-12), 5.51 (1H, br s, 6-OH), 5.10 (1H, d, J=2.9 Hz, H-1), 4.33 (1H, d, J=2.8 Hz, H-6), 3.91 (1H, dd, J=4.2, 2.9 Hz, H-2), 3.74 (1H, d, J=4.2 Hz, H-3), 2.29 (1H, dd, J=14.0, 2.0 Hz, H-11β), 2.04 (1H, dd, J=14.0, 12.0 Hz, H-11α), 1.90 (1H, s, H-10), 1.18 (3H, s, 5-CH₃), 1.16 (3H, s, 5-CH₃).

Acknowledgement The authors thank Drs. Y. Miyake and M. Kuwada of Eisai Co., Ltd. for their valuable suggestion and discussion.

References