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Revised structure of tetrapetalone A and its absolute stereochemistry

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Abstract—The chemical structure of tetrapetalone A (**1**), a novel lipoxygenase inhibitor from *Streptomyces* sp., was revised by using the ^{1}H–^{15}N HMBC technique. Furthermore, the absolute stereochemistry of all the asymmetric carbons in **1** was determined based on the detailed NOE data of **1** and its derivative.

We have studied lipoxygenase inhibitors from soil *Streptomyces* sp. strains, and identified a strain, *Streptomyces* sp. USF-4727, that indicated lipoxygenase inhibitory activity. Tetrapetalone A (**1**),[1] $C_{26}H_{33}NO_7$, was isolated as a lipoxygenase inhibitor from a culture broth of that strain. The chemical structure of **1** was elucidated by using HRFAB MS, ^{1}H, ^{13}C NMR, DEPT, ^{1}H–^{1}H COSY, HMQC, ^{1}H–^{13}C HMBC and 2D-INADEQUATE spectra, and was reported as structure **I**[2] (Fig. 2). However, the measurement of the ^{1}H–^{15}N HMBC spectrum[3,4] gave us a revised planar structure of **1** which comprised a new tetracyclic skeleton and a β-D-rhodinosyl moiety (structure **II**, Fig. 2).

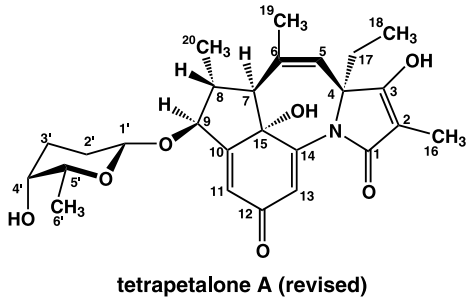

Figure 1. Revised structure of tetrapetalone A (**1**).

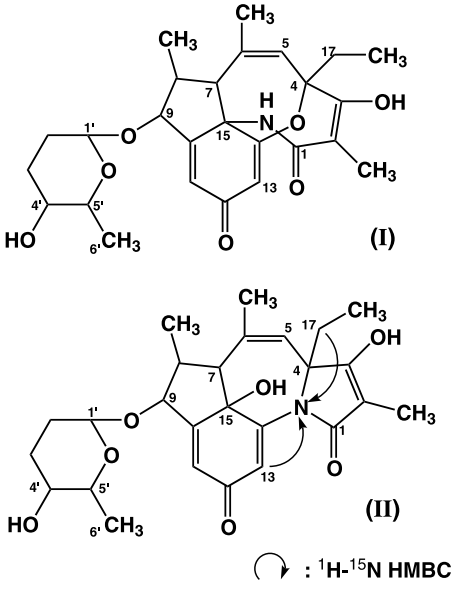

Figure 2. Two proposed structures of tetrapetalone A (**1**).

Keywords: tetrapetalone A; *Streptomyces*; lipoxygenase inhibitor.
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In this paper, we report a revised planar structure of tetrapetalone A (**1**), and also describe the determination of the complete absolute stereochemistry of **1**.

We had estimated a chemical structure (structure **I**, Fig. 2) for **1** in our previous report.[2] For the sake of confirmation of a position and a type of the nitrogen atom, we measured a long-range correlation between a nitrogen atom and a proton using the ^{1}H–^{15}N HMBC technique.[3,4] The ^{1}H–^{15}N HMBC spectrum in CD_3OD showed the presence of an amide nitrogen due to its chemical shift (δ_N: 123.0), and indicated long-range couplings of this nitrogen atom with 13-H and 17-H, respectively. This result, however, was not consistent with structure **I**.

Therefore, we proposed a new structure (structure **II**) for **1**. This proposed structure (**II**) was similar to structure **I** except for the assignment of a nitrogen and an oxygen atom. Formerly, we estimated structure **I** for **1** depending on the existence of an amide proton (δ_H: 6.3 in DMSO-d_6) in the ^{1}H NMR spectrum. Accordingly, this proton was due to the hydroxy proton at C-15, not to an amide proton. The correlation from this hydroxy proton to C-7 and C-15, respectively, in the ^{1}H–^{13}C HMBC spectrum was consistent with structure **II**. The chemical shift of ^{13}C NMR of C-4 (δ_C 69.3), C-14 (δ_C 156.1), C-15 (δ_C 73.9) together with 13-H at 6.75 ppm and all the spectroscopic data[1] of **1** also supported this structure. Therefore, we revised the planar structure of **1** to be structure **II**.

On the stereochemistry of the trideoxyhexose moiety in **1**, we have already assigned this moiety to β-D-rhodinose by the NOESY spectrum and the modified Mosher's method applied to 3-*O*-methyl ether of **1**.[2] Meanwhile, the stereochemistry of the tetracyclic skeleton was reinvestigated by the coupling constant in the ^{1}H NMR spectrum and NOE correlations using a derivative of **1**.

Tetrapetalone A-Me_2 (**2**),[5] obtained by the reaction of **1** with CH_3I/Ag_2O, was used for the investigation of the relative stereochemistry of the tetracyclic skeleton. The structure of **2** was confirmed by 1D, 2D NMR data to have two additional methyl groups, 15-*O*-CH_3 and 2-CH_3, compared with **1** (Fig. 3). Cross peaks were observed at 7-H/9-H and 7-H/17-H in the NOESY spectrum, suggesting that 7-H, 9-H and an ethyl group at C-4 were *syn* configuration. In addition, the strong NOE correlation from the olefinic methyl proton (19-H) to 8-H and the very weak correlation from 19-H to 20-H indicated the relationship of 7-H, 8-H and 9-H to be *anti*/*anti* stereochemistry (Fig. 3). Cross-peaks at 7-H/20-H and 9-H/20-H in the NOESY spectrum also supported this relationship. Furthermore, we observed a cross peak between the methoxy methyl proton at C-15 and 9-H in the NOESY spectrum of **2**, indicating the 1, 3-*syn* stereochemistry of 9-H and 15-OH in **1**.

Two large vicinal coupling constants were observed at 7-H/8-H (10.0 Hz) and 8-H/9-H (10.0 Hz) in the ^{1}H NMR spectrum of **1**. These large values were understood to be generated by the dihedral angle of nearly 180°, respectively (Fig. 3). These dihedral angles were also supported by the MM2 computation for **1** (Fig. 4). Therefore, this newly proposed stereochemistry for this skeleton is consistent with all the NMR data used for the estimation of stereochemistry in our previous investigation.[2]

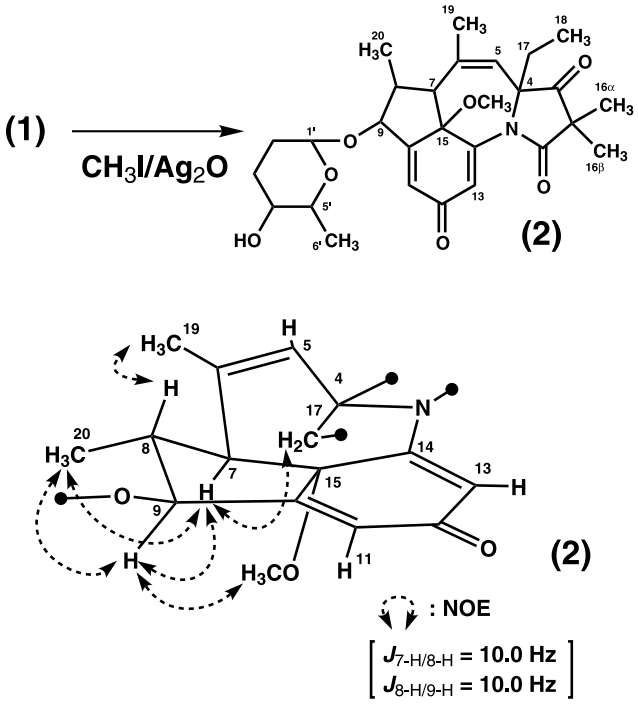

Figure 3. Stereochemistry of tetrapetalone A-Me_2 (**2**).

The absolute stereochemistry of C-9 had been determined by modified Mosher's method to be 9*S* configuration, described in our previous paper.[2] By connecting this absolute stereochemistry with the relative stereochemistry, we could determine the absolute stereochemistry of the tetracyclic skeleton. Because the stereochemistry of **1** was considered to be preserved even after derivation into **2**, we could estimate the absolute stereochemistry of **1** as shown in Figure 1.

In this study, we were able to revise the planar structure of tetrapetalone A (**1**) by using the ^{1}H–^{15}N HMBC technique. This technique is a powerful tool for the structure elucidation of a compound including a nitro-

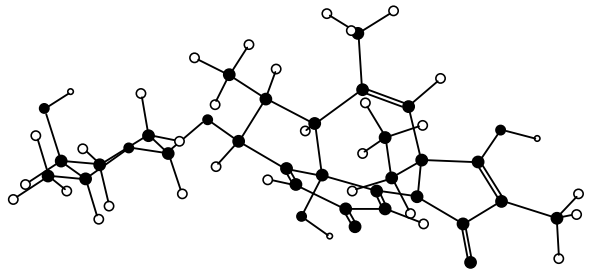

Figure 4. MM2 energy minimized model of tetrapetalone A (**1**) by Chem3D.

gen atom and neighboring quaternary carbon atoms such as **1**. It should be noted that this revised structure of **1** had a characteristic tetracyclic skeleton containing a nitrogen atom and a β-D-rhodinosyl moiety, and this was the first report of a compound with such a skeleton. Furthermore, we estimated the stereochemistry of C-4 and C-15 in addition to the six asymmetric carbons discussed in our previous paper,[2] and we also could revise the stereochemistry of C-8. Therefore, we were able to reveal all the absolute stereochemistry of **1** in addition to its planar structure.

References

1. *Tetrapetalone A (**1**)*: pale yellow amorphous powder, melting point: 190°C. HRFAB MS $[M+H]^+$, m/z 472.2354 (472.2335 calcd for $C_{26}H_{34}NO_7$). UV–vis λ_{max} (MeOH): 240 nm (ε 13,800), 385 nm (ε 10,200); IR ν_{max} (KBr) cm^{-1}: 3400, 1670, 1380, 1300, 1250, 1170, 1060, 1020. ^1H NMR (CD_3OD, 400 MHz) δ_H: 0.70 (3H, t, $J=7.6$ Hz, 18-H), 1.25 (3H, d, $J=6.4$ Hz, 6′-H), 1.35 (3H, d, $J=6.4$ Hz, 20-H), 1.70 (3H, s, 16-H), 1.75 and 1.87 (each 1H, m, 2′-H), 1.78 and 1.95 (each 1H, m, 3′-H), 1.80 (3H, s, 19-H), 1.85 and 3.14 (each 1H, m, 17-H), ca. 2.0 (1H, m, 8-H), ca. 3.3 (7-H, overlapped with solvent peak, δ_H: 3.15 (DMSO-d_6), 1H, br. d, $J=10.0$ Hz), 3.47 (1H, br. s, 4′-H), 3.65 (1H, q, $J=6.4$ Hz, 5′-H), 4.60 (1H, dd, $J=9.2$ and 2.0 Hz, 1′-H), 4.82 (1H, dd, $J=10.0$ and 2.0 Hz, 9-H), 5.72 (1H, br. s, 5-H), 5.95 (1H, t, $J=2.0$ Hz, 11-H), 6.75 (1H, d, $J=2.0$ Hz, 13-H), ^{13}C NMR (CD_3OD, 100 MHz) δ_C: 5.6 (q, C-16), 7.3 (q, C-18), 17.5 (q, C-6′), 20.2 (q, C-20), 22.1 (q, C-19), 24.8 (t, C-17), 26.7 (t, C-2′), 30.9 (t, C-3′), 41.8 (d, C-8), 56.0 (d, C-7), 67.2 (d, C-4′), 69.3 (s, C-4), 73.9 (s, C-15), 75.4 (d, C-5′), 82.8 (d, C-9), 103.0 (s, C-2), 103.3 (d, C-1′), 114.9 (d, C-13), 116.3 (d, C-11), 125.6 (d, C-5), 141.2 (s, C-6), 156.1 (s, C-14), 167.2 (s, C-10), 176.0 (s, C-3), 177.6 (s, C-1), 189.6 (s, C-12).
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3. Martin, G. E.; Hadden, C. E. *J. Nat. Prod.* **2000**, *63*, 543–585.
4. Koshino, H.; Kono, Y.; Yoneyama, K.; Uzawa, J. *Heterocycles* **2000**, *52*, 811–817.
5. *Tetrapetalone A-Me$_2$ (**2**)*: colorless amorphous powder, melting point: 92–95°C. HRFAB MS $[M+H]^+$, m/z 500.2664 (500.2648 calcd for $C_{28}H_{38}NO_7$). UV–vis λ_{max} (MeOH): 214 nm (ε 7,800), 246 nm (ε 7,000), 328 nm (ε 4,500); IR ν_{max} (KBr) cm^{-1}: 3420, 1720, 1650, 1640, 1060. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 0.85 (3H, t, $J=7.2$ Hz, 18-H), 1.27 (3H, d, $J=6.0$ Hz, 6′-H), 1.29 (3H, s, 16β-H)†, 1.34 (3H, d, $J=6.0$ Hz, 20-H), 1.42 (3H, s, 16α-H)†, ca. 1.6 and ca. 1.8 (each 1H, m, 2′-H), ca. 1.7 and ca. 2.1 (each 1H, m, 3′-H), 1.79 (3H, s, 19-H), ca. 1.9 and 2.97 (each 1H, m, 17-H), ca. 2.1 (1H, m, 8-H), 3.12 (1H, br. d, $J=7.6$ Hz, 7-H), 3.18 (3H, s, 15-OCH_3), 3.52 (1H, br. s, 4′-H), 3.63 (1H, q, $J=6.0$ Hz, 5′-H), 4.52 (1H, dd, $J=7.2$ and 3.6 Hz, 1′-H), 4.55 (1H, dd, $J=9.6$ and 1.6 Hz, 9-H), 5.59 (1H, br. s, 5-H), 6.26 (1H, t, $J=1.6$ Hz, 11-H), 6.69 (1H, d, $J=1.6$ Hz, 13-H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 8.5 (q, C-18), 17.1 (q, C-6′), 19.7 (q, C-20), 21.5 (q, C-19), 22.1 (q, C-16β), 23.2 (q, C-16α), 25.4 (t, C-2′), 27.1 (t, C-17), 29.7 (t, C-3′), 40.4 (d, C-8), 46.5 (s, C-2), 51.0 (q, 15-OCH_3), 54.7 (d, C-7), 66.5 (d, C-4′), 72.1 (s, C-4), 74.2 (d, C-5′), 79.5 (s, C-15), 81.8 (d, C-9), 102.1 (d, C-1′), 120.3 (d, C-11), 122.2 (d, C-5), 124.2 (d, C-13), 140.9 (s, C-6), 147.7 (s, C-14), 160.9 (s, C-10), 177.3 (s, C-1), 186.3 (s, C-12), 212.0 (s, C-3).

† The assignment was made by NOE correlations; 16α-H/17-H, 18-H and 16β-H/5-H.