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Orthosiphol A, a Highly Oxygenated Diterpene from the Leaves of *Orthosiphon stamineus*

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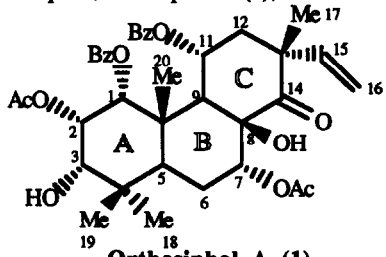
Key Words: orthosiphol A; pimarane diterpene; structure determination; Orthosiphon stamineus

Abstract: *The structure of orthosiphol A (1), a highly oxygenated pimarane diterpene, has been established on the basis of spectroscopic and chemical methods.*

Orthosiphon stamineus Benth is a popular medicinal herb known as *Kumis-kuching* in South-East Asia, and the leaves have been introduced to Europe and Japan as a healthy tea having potent diuretic activity.[1] Although many chemical studies on its constituents have been carried out since 1886, no report of chemotaxonomically typical compound has appeared.[2] Chemotaxonomical interest prompted us to examine the constituents in the leaves. This paper deals with the structure determination of a new highly oxygenated diterpene, orthosiphol A (**1**), isolated from this plant as a diterpene compound for the first time.



Orthosiphol A (1)

Orthosiphol A (**1**),[3] $C_{38}H_{44}O_{11}$, was isolated by repeated silica gel chromatography from the CH_2Cl_2 extract of the leaves of *Orthosiphon stamineus*. The highly oxygenated pimarane structure of **1** was determined based on HH-COSY, CH-COSY and COLOC spectra.[4] The two acetyl and one of two benzoyl groups were found to be attached to C2, C7 and C1, respectively, by COLOC spectrum. The other benzoyl group was determined to be at C11 by the chemical shift of H11 (5.79 ppm). The stereochemistry of the A and B rings was analyzed by NOEs and coupling constants in ^{1}H-NMR of **1** as shown in Fig. 1. A strong NOE was observed between 7-acetyl protons and a vinyl proton (4.81 ppm) at C16, and disclosed α-orientation of the vinyl group and a boat-like conformation of the C ring. The conformation of the C ring impeded the determination of orientation of 11-benzoyl group by the coupling constant ($J_{H9,H11}$=5.5 Hz). It was presumed that one of the reasons of boat conformation for the C ring depended on the 2-alkylketone effect [5] caused by the carbonyl group at 14-position. To remove the effect, **1** was reduced by excess $LiAlH_4$, and subsequently acetylated with Ac_2O in pyridine to give 2, 11-diacetate (**2**) as a sole product. The ^{1}H-NMR of **2** showed a long range coupling between H14 and H12 (J=1 Hz), revealing a chair conformation for the C ring. From the diaxial coupling constant between H9 and H11 (J=10 Hz), the 11-benzoyl group was concluded to be α-oriented. (Fig. 2) The absolute stereochemistry of **1** was determined by exiton chirality method. A positive cotton effect caused by 1 and 11-benzoyl groups in the CD spectrum[3] of **1** revealed C11 has *R* configuration. Thus, the structure of orthosiphol A should be expressed as structure **1**.

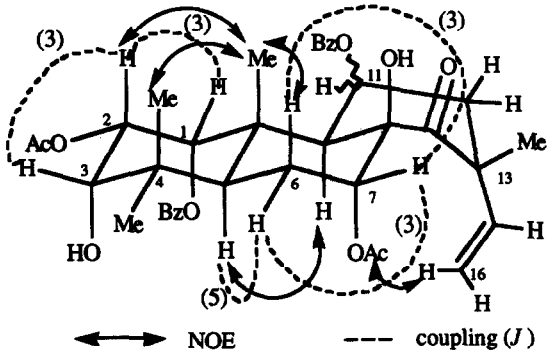


Fig. 1 Selective NOEs and *J* values of 1

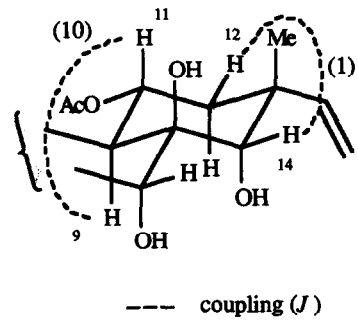


Fig. 2 C ring of 2

Acknowledgement We thank Dr. Takeshi Kitahara (Faculty of Agriculture, The University of Tokyo) for elementary analyses and Dr. Tadao Kondo and Dr. Kumi Yoshida (Chemical Instruments Center, Nagoya University) for CD measurement.

References and Notes

1 Fujimoto, T.; Tsuda, Y. *Yakugaku Zasshi*, **1972**, *92*, 1060; references cited therein.

2 Itallie, V. *Nieuw tijdshrift voor de Pharmacie in Nederland*, **1886**, 232.

3 **1**; colorless plates; mp 210°C; $[\alpha]_D^{26}$ -127° (c 1.0, $CHCl_3$); SIMS m/z 677 $[M+H]^+$; Anal. Found: C, 67.99; H, 6.65, Calcd. for $C_{38}H_{44}O_{11}$: C, 67.44; H, 6.55 %; IR (film) ν max : 3425, 2967, 1723, 1283, 1240, 756, 710 cm^{-1}; UV (MeOH) λmax (ε) : 230 (22000) nm; CD (MeOH) λmax (θ): 234 (+35000) nm; ^{13}C-NMR ($CDCl_3$) δ: 74.2 (C1), 67.7 (C2), 77.4 (C3), 38.3 (C4), 35.5 (C5), 21.4 (C6), 70.6 (C7), 75.8 (C8), 42.1 (C9), 43.7 (C10), 68.6(C11), 39.7 (C12), 47.8 (C13), 208.6 (C14), 142.0 (C15), 113.1 (C16), 26.6 (C17), 22.3 (C18), 28.9 (C19), 16.8 (C20), 20.9 (2-Ac), 170.1 (2-Ac), 21.0 (7-Ac), 168.9 (7-Ac), 164.0 (1-Bz), 166.2 (11-Bz), 132.9 (1- or 11-Bz), 132.2 (1- or 11-Bz), 130.8 (1- or 11-Bz), 130.2 (1- or 11-Bz), 129.7 (1- or 11-Bz), 128.6 (1- or 11-Bz), 128.2 (1- or 11-Bz), 127.8 (1- or 11-Bz); ^{1}H-NMR ($CDCl_3$) δ: 5.30 (1H, brd, *J*=2.7Hz, H1), 5.45 (1H, brt, *J*=3.3Hz, H2), 3.49 (1H, m, H3), 2.45 (1H, dd, *J*=11.0 and 4.9Hz, H5), 1.99-2.12 (2H, m, H6), 5.43 (1H, brt, *J*=3.0Hz, H7), 3.11 (1H, brd, *J*=5.5Hz, H9), 5.79 (1H, m, H11), 1.96 (1H, dd, *J*=16.0 and 1.7Hz, H12), 2.57 (1H, dd, *J*=16.0 and 4.9Hz, H12), 5.66 (1H, dd, *J*=17.7 and 10.4Hz, H15), 4.75 (1H, d, *J*=10.4Hz, H16), 4.81 (1H, d, *J*=17.7Hz, H16), 1.14 (3H, s, H17), 1.04 (3H, s, H18), 1.07 (3H, s, H19), 1.49 (3H, s, H20),1.94 (3H, s, 2-Ac), 2.17 (3H, s, 7-Ac), 7.60 (2H, d, *J*=7.3Hz, 1- or 11-Bz), 7.58 (2H, d, *J*=7.3Hz, 1- or 11-Bz), 7.54 (1H, t, *J*=7.3Hz, 1- or 11-Bz), 7.41 (1H, t, *J*=7.3Hz, 1- or 11-Bz), 7.29 (2H, t, *J*=7.3Hz, 1- or 11-Bz), 7.11 (2H, t, *J*=7.3Hz, 1- or 11-Bz), 2.23 (1H, d, *J*=5.5Hz, 3-OH), 2.80 (1H, brs, 8-OH).

4 COLOC correlations (C/H): C1/H3 and H20, C2/H1, C3/H1, H19 and H18, C4/H5, H19 and H18, C5/H7, H12 and H20, C7/H6, C8/H9, C9/H7, H12 and H20, C10/H1, H5, H6 and H9, C11/H9 and H12, C12/H17, C13/H11, H5, H16 and H17, C14/H12 and H17, C15/H12, H16 and H17, 2-Ac/H2, 7-Ac/H7, 11-Bz/H11.

5 Allinger,N. L.; Blatter, H. M. *J. Am. Chem. Soc.*, **1961**, *83*, 994.

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