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Brazilide A, a novel lactone with an unprecedented skeleton from *Caesalpinia sappan*

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Abstract—A novel lactone, brazilide A **1** has been isolated from an oriental crude drug, the heartwood of *Caesalpinia sappan*, and its structure was established by spectroscopic analyses and X-ray crystallography.

Sappan Lignum, the dried heartwood of *Caesalpinia sappan* L., is used in traditional Chinese medicine as an emmenagogue, hemostatic and antiinflammatory agent, as well as for the treatment of contusion and thrombosis. Brazilin **2** (see Fig. 1), one of the main homoisoflavonoid components, has interesting immunomodulating activities and protective effects on liver injury.[1,2] During the course of our investigations, a novel lactone was isolated from Sappan Lignum, designated as brazilide A **1** (see Fig. 1). The structure is the first representative of a new type of skeleton derived from brazilin **2**, which undergoes various oxidation reactions on the catecholic moiety of ring B.[3] There is a possibility that brazilin A might not be a natural product and was formed by autooxidation during the separation process. We now report the isolation of compound **1** and the structural elucidation of the unprecedented skeleton.

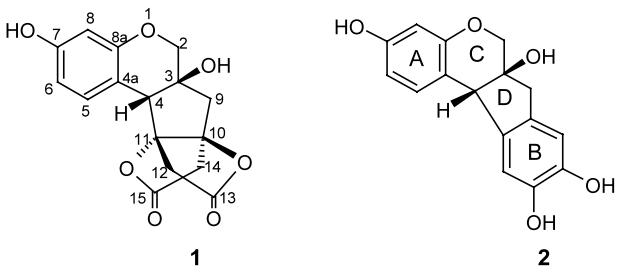

Figure 1. Structure and relative configuration of **1** and **2**.

The ethyl acetate soluble materials from the ethanol extract of Sappan Lignum were subjected to repeated column chromatography over silica gel to furnish brazilide A **1** (0.006% yield), colorless crystals from acetone (mp 251–252°C), $[\alpha]_D^{20}$ +3.3 (*c* 3.00, acetone). The M^+ at *m/z* 318.0744 in the HREIMS is in agreement with the molecular formula $C_{16}H_{14}O_7$ (calcd *m/z* 318.0735) requiring ten degrees of unsaturation. This indicates a highly oxygenated molecule. The absorption bands in the UV spectrum were observed at 225, 279 and 284 nm (log ε 3.84, 3.38, and 3.35, respectively), consistent with a chromene chromophore. The presence of two hydroxyl absorption bands (3435, 3342 cm^{-1}), two γ-lactone carbonyls (1755.3, 1754.9 cm^{-1}) and an aromatic ring (1624, 1502 cm^{-1}) were inferred from its IR spectrum.

The ^{13}C NMR spectrum (Table 1) gave a total of 16 separated carbon resonances and the DEPT spectrum suggested the presence of four methylenes, four methines, and eight quaternary carbons including two lactone carbonyls. Four oxygenated carbon signals were located at 69.6 (C-2), 78.3 (C-3), 94.8 (C-10) and 96.6 (C-11) ppm, three of which were quaternary carbons. The fourth was a hydroxyl methylene carbon, which was supported by the presence of a pair of proton signals at 3.80 (H-2β) and 3.90 (H-2α) ppm. A comparison of the ^1H and ^{13}C NMR data with those reported in the literature[4] for brazilin, indicated that brazilide A **1** contains the same three-ring subunit (rings A, D and C, from O-1 to C-11) as brazilin. The construction of the entire molecule from linking of the fragments so far revealed, is based on the HMBC data (Table 1). The key observations from the HMBC spectrum which disclosed the presence of two five-membered lactone rings,

Keywords: natural product; brazilide A; *Caesalpinia sappan*; X-ray crystal structure.

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Table 1. ^{1}H and ^{13}C NMR data of brazilide A **1**

Position	δ_C	δ_H (mult, J in Hz)	HMBC	NOESY
2	69.6	α 3.90, d, 10.9	C-3, C-4, C-9, C-8a	H-9α
		β 3.80, d, 10.9	C-3, C-4, C-9, C-8a	H-4
3	78.3			
4	54.0	3.66	C-2, C-3, C-4a, C-5, C-8a	H-2β, H-5, H-12β
4a	109.2		C-9, C-10, C-11, C-12	
5	134.5	7.11, dd, 0.7, 8.6	C-4, C-7, C-8a	H-4, H-6
6	110.1	6.47, dd, 2.5, 8.6	C-4a, C-7	H-5
7	158.5			
8	103.9	6.31, d, 2.5	C-4a, C-6, C-7, C-8a	
8a	155.7			
9	45.7	α 2.60, d, 15.6	C-2, C-3, C-4, C-10, C-11, C-14	H-2α, H-14α
		β 2.42, d, 15.7	C-2, C-3, C-4, C-10, C-11, C-14	
10	94.8			
11	96.6			
12	44.3	β 3.55, d, 18.8	C-4, C-10, C-11, C-13	H-4
		α 3.24, d, 18.7	C-4, C-10, C-11, C-13	
13	174.3			
14	42.9	α 3.00, d, 19.2	C-9, C-10, C-11, C-15	H-9α
		β 2.62, d, 19.2	C-9, C-10, C-11, C-15	
15	173.9			

All spectra were recorded in acetone-d_6 (^{1}H, 400 MHz; ^{13}C, 100 MHz).

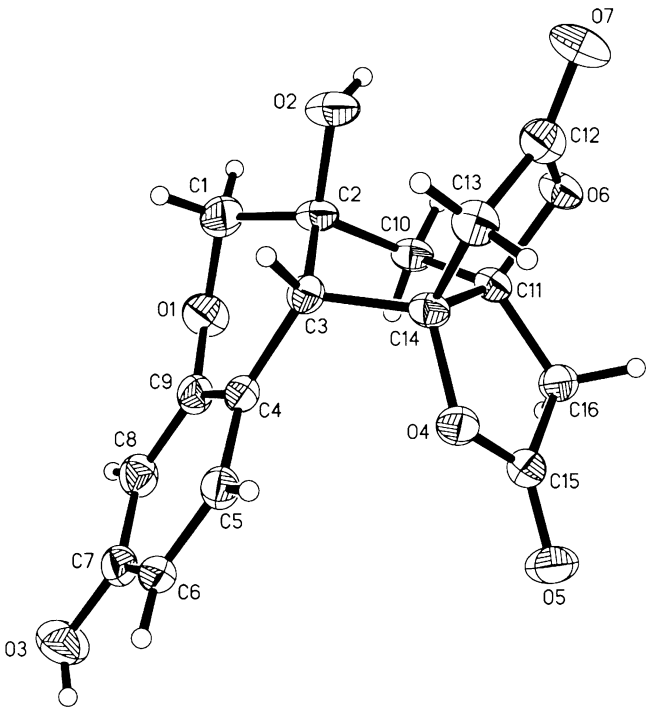

Figure 2. X-Ray structure of brazilide A **1**.

were the correlations from H-12 (a pair of protons due to an isolated methylene with a large geminal coupling) to C-4, C-10, C-11 and C-13, and H-14 (a pair of protons due to another isolated methylene) to C-9, C-10, C-11 and C-15, respectively. This data indicated that the two γ-lactone groups are fused, sharing the same downfield oxygen-bearing quaternary carbons (C-10 and C-11). Consequently, the unique structure of brazilide A was established as **1**. The relative stereochemistry of **1** was disclosed by NOESY spectroscopy (Table 1), i.e. NOEs were observed between H-2β and H-4, H-2α and H-9α, between H-4 and H-12β, and between H-9α and H-14α.

Finally, the structure of **1** was confirmed by X-ray structure analysis. The crystals of **1** were grown in an acetone–petroleum ether solution as colorless prisms. A view of the solid-state conformation is provided in Fig. 2 and this result is in agreement with the above conclusions based on the physicochemical evidence.[5]

Compound **1** has a novel carbon skeleton, which is thought to be derived from autooxidation of the homoisoflavonoid precursor, brazilin **2**. To our knowledge, the fused bis-lactone ring system found in **1** has not been previously described from nature. An investigation on the biosynthesis as well as the biological activity of **1** is currently under way.

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5. Crystal data for **1** were acquired with a Rigaku AFC7R diffractometer, Mo Kα radiation ($\lambda = 0.71073$ Å), graphite monochromator, $C_{16}H_{14}O_7$ (318.27), monoclinic, space group $P2_1$, cell dimensions $a = 9.2517(12)$, $b = 7.6301(9)$, $c = 9.6762(12)$ Å, $V = 667.88(14)$ Å^3, $D_{calcd} = 1.583$ Mg/m^3, $Z = 2$, $F(000) = 332$, $\mu = 0.126$ mm^{-1}. The data were collected at a temperature of 20±2°C using the ϕ–ω scan technique in the range = 2.15–28.28° ($-10 \leq h \leq 12$, $-8 \leq k \leq 10$, $-12 \leq l \leq 12$). A total of 4099 reflections were collected, 2576 were unique ($R_{int} = 0.0278$). The intensities of three representation reflections were measured after every 264 reflections. The structure was solved by direct methods with the program SHELXS-97 (Sheldrick, 1990) and refined by full-matrix least-squares on F^2. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. Atomic coordinates, bond lengths, angles and thermal parameters will be deposited at the Cambridge Crystallographic Data Centre (CCDC).