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Sarusubine A, a new dimeric Lythraceae alkaloid from *Lagerstroemia subcostata*

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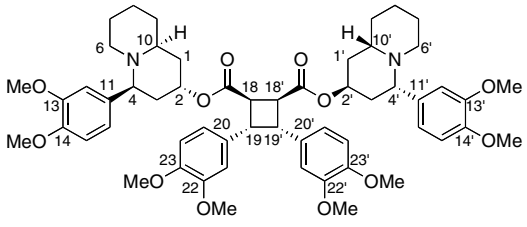
Abstract—A new dimeric Lythraceae alkaloid with a cyclobutane ring, sarusubine A (**1**), has been isolated from the leaves of *Lagerstroemia subcostata*, and the structure and stereochemistry were elucidated by spectroscopic data.

Lythraceae alkaloids are a group of natural products with arylquinolizidine skeleton, which have attracted great interest from biogenetic and synthetic points of view.[1] In our search for structurally unique and biogenetically interesting alkaloids,[2] sarusubine A (**1**),[3] a new dimeric alkaloid with a cyclobutane ring, was isolated from the leaves of *Lagerstroemia subcostata* (Lythraceae). Here we describe the isolation and structure elucidation of **1**.



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The relative stereochemistries for C-2/C-18 and C-2′/C-18′ are not confirmed.

The leaves of *L. subcostata* corrected at Okinawa were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% aqueous tartaric acid. Water-soluble materials, which were adjusted to pH 10 with saturated Na_2CO_3, were extracted with $CHCl_3$, and $CHCl_3$-soluble materials were subjected to a silica gel column chromatography ($CHCl_3$/MeOH and then EtOAc/MeOH) to afford sarusubine A (**1**, 0.0047% yield) as a pale yellow amorphous solid.

Sarusubine A (**1**) {$[\alpha]_D^{23}$ +40.1 (*c* 1.0, MeOH)} showed that the pseudomolecular ion peak at *m*/*z* 963 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{56}H_{70}N_2O_{12}$, was established by HRESIMS [*m*/*z* 963.5012, $(M+H)^+$, Δ +0.5 mmu]. The IR absorption at 1732 cm^{-1} implied the presence of ester carbonyl functionality. ^1H and ^{13}C NMR data of **1** were similar to those of subcosine II,[4,5] except for lack of signals due to a double bond of the latter compound.

The ^{13}C NMR data of **1** revealed carbon signals due to two ester carbonyls, twelve sp^2 quaternary carbons, twelve sp^2 methines, ten sp^3 methines, twelve sp^3 methylenes, and eight methyls. Among them, two methylene carbons [δ_C 53.0 (2C)] and four methine carbons [δ_C 63.8 (2C), 57.2, and 57.1] were ascribed to those bearing a nitrogen atom. The ^{13}C NMR signal pattern as well as the molecular weight indicated that **1** had a dimeric structure of a Lythraceae alkaloid such as subcosine II.

The ^1H–^1H COSY and TOCSY spectra of **1** revealed connectivities of four structural units, **a** (C-1 to C-4, C-6 to C-10, and C-1 to C-10), **b** (C-18 to C-19), **c**

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Table 1. ^{1}H and ^{13}C NMR data of sarusubine A (**1**) in $CDCl_3$

Position	δ_H	δ_C	
1(1′)a	1.80 (2H, m)	37.1 (2C)	t
1(1′)b	1.65 (2H, m)		
2(2′)	5.11 (2H, br s)	69.0 (2C)	d
3(3′)	1.82 (4H, m)	39.6 (2C)	t
4(4′)	3.12 (2H, br d, 10.4)	63.8 (2C)	d
6(6′)	2.65 (4H, br d, 10.6)	53.0 (2C)	t
7(7′)a	1.52 (2H, m)	26.0 (2C)	t
7(7′)b	1.36 (2H, m)		
8(8′)a	1.65 (2H, m)	24.8 (2C)	t
8(8′)b	1.17 (2H, m)		
9(9′)a	1.52 (2H, m)	33.5 (2C)	t
9(9′)b	1.23 (2H, m)		
10(10′)	2.21 (2H, br t, 10.4)	57.2 (2C)	d
11(11′)	—	136.8 (2C)	s
12(12′)	6.67–6.84 (2H, m)	111.9 (2C)	d
13(13′)	—	148.6 (2C)	s
14(14′)	—	147.9 (2C)	s
15(15′)	6.67–6.84 (2H, m)	110.7 (2C)	d
16(16′)	6.67–6.84 (2H, m)	120.0, 119.9	d
17(17′)	—	171.9 (2C)	s
18(18′)	3.85 (2H, br s)	43.8 (2C)	d
19(19′)	4.37 (2H, br s)	45.4 (2C)	d
20(20′)	—	131.4, 131.3	s
21(22′)	6.67–6.84 (2H, m)	111.9, 111.8	d
22(22′)	—	148.6 (2C)	s
23(23′)	6.67–6.84 (2H, m)	147.9 (2C)	s
24(24′)	6.67–6.84 (2H, m)	110.7 (2C)	d
25(25′)	6.67–6.84 (2H, m)	120.0, 119.9	d
OMe	3.65–3.85 (24H, m)	55.8–55.9 (8C)	q

(C-15 to C-16), and **d** (C-24 to C-25) as shown in Figure 1. HMBC correlations from H-4 to C-6 (δ_C 53.0), H-6 to C-10 (δ_C 57.2), and H-10 to C-4 (δ_C 63.8) suggested that C-4, C-6, and C-10 were connected to each other through a nitrogen atom (N-5). The connection of C-2 and C-18 via an ester carbonyl group was implied by HMBC cross-peaks for H-2 and H-19 to C-17 (δ_C 171.9). HMBC correlations observed for H-4 to C-12 (δ_C 111.9) and H-21 to C-19 (δ_C 45.4) indicated that 3,4-dimethoxyphenyl groups were attached to C-4 and C-19.

The fragment ion observed at *m*/*z* 300 in the EIMS spectrum of **1** suggested the presence of 1,2-bis(3,4-dimethoxyphenyl)ethane moiety (C-19 to C-25 and C-19′ to C-25′). Sarusubine A (**1**) was treated with K_2CO_3 in MeOH (Scheme 1) to afford two hydrolysis products **2** and **3**. The molecular formulae of **2** ($C_{17}H_{25}NO_3$) and **3** ($C_{24}H_{28}O_8$) derived from

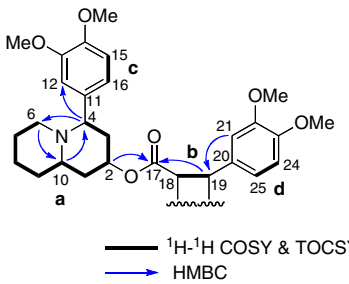
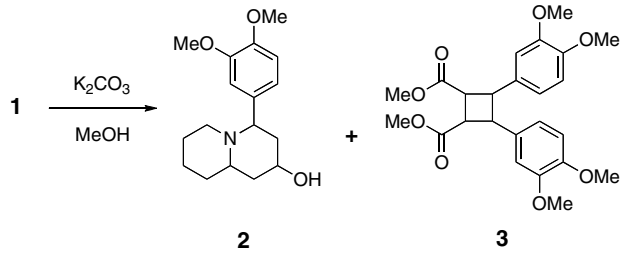


Figure 1. Selected 2D NMR correlations for a half part of sarusubine A (**1**).



Scheme 1. Methanolysis products (**2** and **3**) of sarusubine A (**1**).

HRESIMS [**2**, *m*/*z* 292.19252 $(M+H)^+$, Δ −1.26 mmu] and [**3**, *m*/*z* 467.16628 $(M+Na)^+$, Δ +1.9 mmu] supported the proposed structure (**1**).

The relative stereochemistry of the quinolizidine rings in **1** was deduced from NOESY correlations as shown in Figure 2. An axial orientation of H-4 and chair conformations of the two six-membered rings in the trans quinolizidine ring were derived from NOESY correlations of H-4/H-6b and H-10, H-6b/H-8b and H-10, and H-8b/H-10. The NOESY correlations of H-1b/H-2 and H-2/H-3a indicated an equatorial orientation of H-2.

The relative stereochemistry of the cyclobutane ring in **1** was elucidated as follows. Since ^{1}H and ^{13}C NMR data suggested a symmetrical nature of **1**, four possible stereostructures (**A**–**D**) were considered for the cyclobutane ring in **1** (Fig. 3). Possibilities of **C** and **D** were eliminated from the NOESY correlation observed between H-18 and H-21. For known cyclobutanes, in the case of **A**, protons corresponding to H-18 and 18′, and

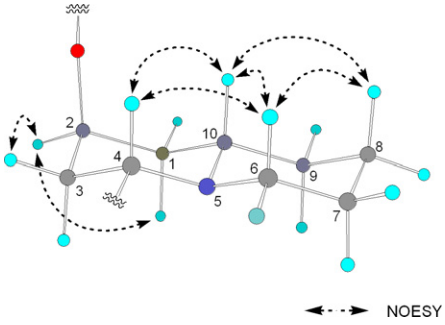


Figure 2. Selected NOESY correlations and relative stereochemistry for quinolizidine ring in sarusubine A (**1**).

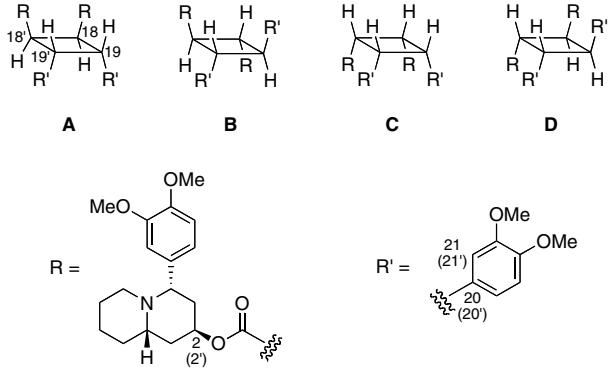


Figure 3. Possible stereostructures (**A**–**D**) for cyclobutane ring in sarusubine A (**1**).

H-19 and H-19′ are observed in δ_H 3.78–3.85 and 4.17–4.34,[6] respectively, while in the case of **B**, those protons are observed in δ_H 3.40–3.50 and 3.60–3.75,[7] respectively. Since H-18 and 18′, and H-19 and 19′ of **1** appeared at δ_H 3.85 and 4.37, respectively, relative stereochemistry of the cyclobutane ring in **1** was assigned as stereostructure **A**.

Since sarusubine A (**1**) is optically active[3] and not a *meso* compound, the absolute stereochemistries of two quinolizidine rings in **1** could be the same. Thus, the structure of sarusubine A was elucidated to be **1**.

Sarusubine A (**1**) is the first dimeric alkaloid with a cyclobutane ring among a number of Lythraceae alkaloids reported so far. Sarusubine A (**1**) showed weak antimicrobial activity against *Cryptococcus neoformans* and *Trichophyton mentagrophytes* (both MIC, 33.3 μg/ml).

Acknowledgements

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3. *Sarusubine A* (**1**): pale yellow amorphous solid; $[\alpha]_D^{23}$ +40.1 (*c* 1.0, MeOH); UV (MeOH) λ_{max} 280 (ε 10,100) and 229 (27,880) nm; IR (neat) ν_{max} 1732 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; ESIMS *m*/*z* 963 $(M+H)^+$; HRESIMS *m*/*z* 963.5012 $(M+H)^+$, Δ +0.5 mmu.
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