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Sessilifoliamine A and sessilifoliamide J: new alkaloids from *Stemona sessilifolia*

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ABSTRACT

Two new alkaloids, sessilifoliamine A and sessilifoliamide J, having novel alkaloid skeletons were isolated from the roots of *Stemona sessilifolia* (Miq.) Miq. (Stemonaceae). The structure of sessilifoliamine A was determined by interpretation of its spectroscopic data and that of sessilifoliamide J by X-ray crystallography.

Plants belonging to the genus *Stemona* (family Stemonaceae) are noted for producing a series of alkaloids with unique structures, most of which are characterized by incorporating a pyrrolo[1,2-*a*]azepine core.[1–3] Of the genus *Stemona* plants, *Stemona japonica* (Blume) Miq., *S. tuberosa* Lour., and *S. sessilifolia* (Miq.) Miq. have been used in China and Japan as an insecticide and also as a remedy for cough, and their biological activities are considered to be related to their alkaloid components.[4–6] In our studies on the chemical constituents of *S. sessilifolia*,[7] we isolated two new alkaloids, sessilifoliamine A (**1**) and sessilifoliamide J (**2**), with novel alkaloid skeletons (Fig. 1). The present Letter describes their isolation and structure determination.

From 15 kg of the roots of *Stemona sessilifolia*, 8 kg of a crude MeOH extract was obtained, from which 300 g of a neutral/acidic fraction and 250 g of a basic fraction were prepared.[7] By chromatographic separation, those two fractions gave sessilifoliamine A (**1**, 0.9 mg, 0.000006%) and sessilifoliamide J (**2**, 2.5 mg, 0.000017%), respectively.

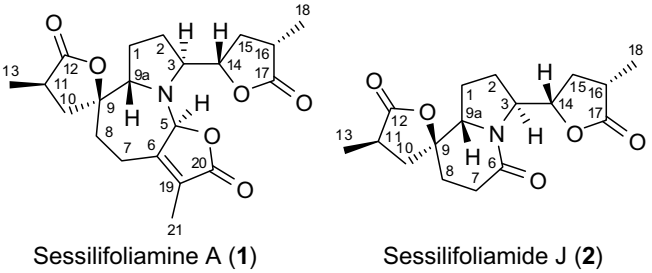

Figure 1. Structures of sessilifoliamine A (**1**) and sessilifoliamide J (**2**).

Sessilifoliamine A (**1**), $[\alpha]_D^{25}$ +145 (*c* 0.05, $CHCl_3$), was obtained as an amorphous solid. Its molecular formula was determined to be $C_{21}H_{27}NO_6$ from the $[M+Na]^+$ peak at *m/z* 412.1709 (calcd for $C_{21}H_{27}NO_6Na$, 412.1736) in the HRESIMS. The UV spectrum (MeOH) showed absorption bands at 206 nm (log ε 4.16) and 278 nm (log ε 2.80), and the IR spectrum indicated the presence of carbonyl groups (1767 and 1749 cm^{-1}). Its ^1H NMR spectrum showed the presence of two secondary methyl groups (δ_H 1.29 and 1.37), one allylic methyl group (δ_H 1.89), and four heteroatom-substituted methine protons (δ_H 3.41, 3.45, 4.94, and 6.23) (Table 1). Its ^{13}C NMR spectrum showed 21 signals caused by three methyls, six methylenes, six methines, and six quaternary carbons, including three carbonyl carbons. Analysis of the ^1H–^1H COSY and HMQC spectra revealed the presence of three molecular fragments: fragment A of an eight-carbon chain (C-9a–C-1–C-2–C-3–C-14–C-15–C-16–C-18) in which C-18 was a secondary methyl and C-3, C-9a, and C-14 were heteroatom-substituted methines, fragment B of a three-carbon chain (C-10–C-11–C-13) in which C-13 was a secondary methyl, and fragment C of a two-carbon chain (C-7–C-8) comprising two methylenes (Fig. 2). As regards the relations between these three carbon-chain fragments, HMBC data revealed the nature of the other skeleton atoms which join these fragments. Correlations from H-1a, H-7a, H-7b, H-8a, H-8b, H-9a, H-10a, H-10b, and H-11 to C-9 (δ_C 87.0) indicated that C-9, an oxygen-bearing quaternary carbon, was connected to fragments A, B, and C at C-9a, C-10, and C-8, respectively.

The strong UV absorption bands mentioned above and HMBC correlations from H-5 and H_3-21 to C-6 (δ_C 158.6), C-19 (δ_C 127.4), and C-20 (δ_C 173.5) suggested that one methine (C-5),

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Table 1
NMR data for sessilifoliamne A (**1**) and sessilifoliamide J (**2**) in $CDCl_3$

Position		Sessilifoliamne A (**1**)			Sessilifoliamide J (**2**)	
		δ_H[a,b]	δ_C[c,d]		δ_H[a,e]	δ_C[c,f]
1	a	2.10 (m)	26.9	a	2.16 (m)	27.3
	b	1.35 (m)		b	1.53 (m)	
2	a	1.79[g]	28.4	a	2.11 (m)	24.3
	b	1.47 (m)		b	1.82 (m)	
3		3.41 (ddd, 11.9, 9.1, 4.3)	67.7		4.60 (td, 7.7, 4.0)	57.7
5		6.23 (d-like, 1.7)	94.4			
6			158.6			168.4
7	a	2.72[g]	21.0	a	2.70 (ddd, 18.3, 6.4, 3.8)	28.7
	b	2.27 (td, 13.5, 2.5)		b	2.40 (ddd, 18.3, 11.0, 6.4)	
8	a	2.01 (ddd, 13.1, 4.9, 2.5)	43.6	a	2.26 (ddd, 13.0, 11.0, 6.4)	33.7
	b	1.80[g]		b	1.92 (ddd, 13.0, 6.4, 3.8)	
9			87.0			81.3
9a		3.45 (t, 8.4)	62.8		3.80 (dd, 10.3, 5.9)	65.4
10	a	2.57 (dd, 14.2, 11.7)	34.5	a	2.45 (dd, 13.6, 10.9)	35.5
	b	1.70 (dd, 14.2, 6.4)		b	1.66[g]	
11		2.78 (m)	35.6		2.77 (m)	35.3
12			179.0			177.7
13		1.37 (d, 7.4, 3H)	19.0		1.34 (d, 7.2, 3H)	16.9
14		4.94 (ddd, 10.5, 9.1, 5.3)	77.5		4.86 (ddd, 10.6, 5.5, 4.0)	78.5
15	a	2.50 (ddd, 12.3, 8.3, 5.3)	35.8	a	2.35 (ddd, 12.8, 8.6, 5.5)	32.4
	b	1.52 (m)		b	1.67[g]	
16		2.70[g]	35.0		2.65 (ddq, 12.2, 8.6, 7.1)	35.5
17			178.9			178.7
18		1.29 (d, 7.0, 3H)	14.8		1.27 (d, 7.1, 3H)	14.9
19			127.4			
20			173.5			
21		1.89 (d, 1.7, 3H)	8.7			

[a] Chemical shifts referenced to residual $CHCl_3$ (7.26 ppm); *J*-values given in Hz in parentheses.
[b] Recorded at 600 MHz.
[c] Chemical shifts referenced to $CDCl_3$ (77.03 ppm).
[d] Recorded at 150 MHz.
[e] Recorded at 500 MHz.
[f] Recorded at 125 MHz.
[g] Multiplicity patterns were unclear due to signal overlapping.

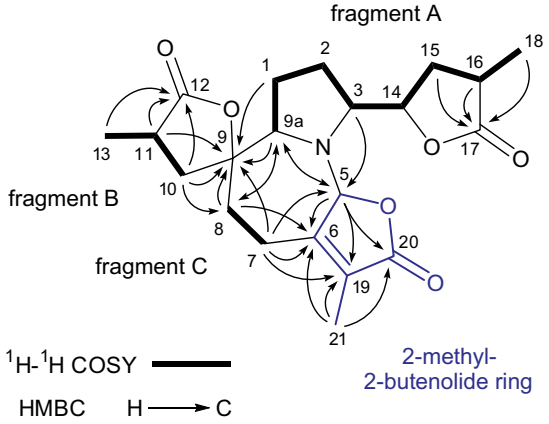

Figure 2. ^{1}H–^{1}H COSY and selected HMBC correlations for sessilifoliamine A (**1**).

two quaternary sp^2 carbons (C-6 and C-19), and a carbonyl carbon (C-20) constructed a 2-methyl-2-butenolide ring. The HMBC correlations from H-7a and H-7b to C-5, C-6, and C-19, and from H-8a and H-8b to C-6 indicated that C-7 of fragment C was connected to C-6, the β-position of the butenolide ring. On the basis of the chemical shift values of the signals of C-3 (δ_C 67.7), C-5 (δ_C 94.4), and C-9a (δ_C 62.8), and of the HMBC correlations from H-3 to C-5, from H-5 to C-9a, and from H-9a to C-5, the nitrogen atom was shown to be connected to fragment A at C-3 and C-9a, and to the butenolide ring at C-5.

The HMBC correlations from H-10a, H-10b, H-11, and H_3-13 to C-12 (δ_C 179.0) and from H-15a, H-16, and H_3-18 to C-17 (δ_C 178.9) placed the two γ-lactones between C-12 and C-9, and between C-17 and C-14. From these observations, alkaloid **1** was concluded to possess the gross structure as shown in Figure 2.

The relative stereochemistry of **1** was established by the NOESY experiments (Fig. 3). The correlations between H-3/H-10a, H-5/H-7b, and H-7b/H-10b indicated that H-3, H-5, and the C-10 methylene group were α-oriented, whereas those between H-2b/H-9a, H-8b/H-9a, and H-8a/H_3-13 indicated that H-9a was β-oriented and that the C-8 methylene group and the C-13 methyl group were in a *cis* relationship. A large *J*-value (9.1 Hz) between H-3 and H-14 and observation of NOE correlations between H-2a/H-15a, H-2b/H-14, and H-3/H-15b indicated that H-3 and H-14 were arranged in an antiperiplanar orientation with the C-2 and C-15 carbons being gauche to each other. The correlation between H-14/H-16 revealed a *cis* relationship between H-14 and H-16.

Thus established stereochemistry of **1** agreed with the results of the molecular modeling studies. In the energetically most stable conformation of **1** found in the Monte Carlo conformational search,[8] the distances between the relevant protons, involved in the above-mentioned diagnostic NOE correlations in **1**, were all less than 2.9 Å, the spacing reasonable for producing NOE cross-peaks (Fig. 3). Accordingly, alkaloid **1** was determined to have the (3*R**, 5*R**, 9*R**, 9a*R**, 11*S**, 14*R**, 16*R**) relative configuration.

Sessilifoliamide J (**2**), $[\alpha]_D^{26}$ −73 (*c* 0.13, $CHCl_3$), was obtained as colorless needles, mp 156–159 °C (H_2O/MeOH). Its molecular formula was determined to be $C_{17}H_{23}NO_5$ from the $[M+H]^+$ peak at *m/z* 322.1666 (calcd for $C_{17}H_{24}NO_5$, 322.1654) in the HRESIMS. Its UV spectrum showed no strong absorption maximum between 200 and 400 nm, and the IR spectrum indicated the presence of γ-lactone (1771 cm^{-1}) and amide (1636 cm^{-1}) carbonyl groups. Its ^{1}H NMR spectrum showed the presence of two secondary

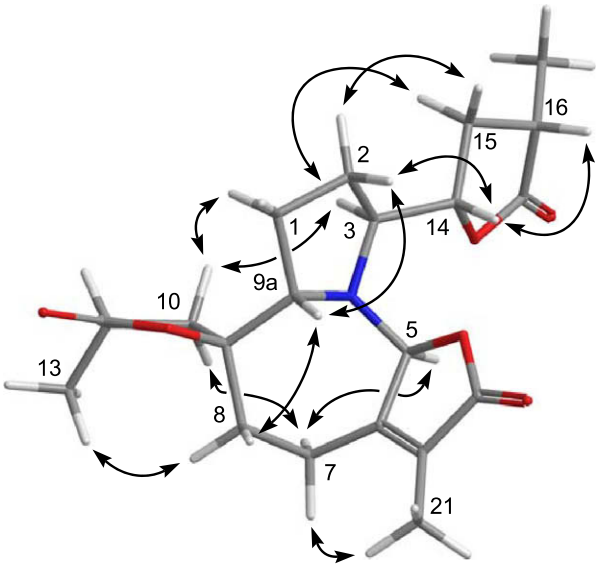

Figure 3. Most stable conformation of **1** found in the Monte Carlo conformational search with the observed key NOE correlations (arrows).

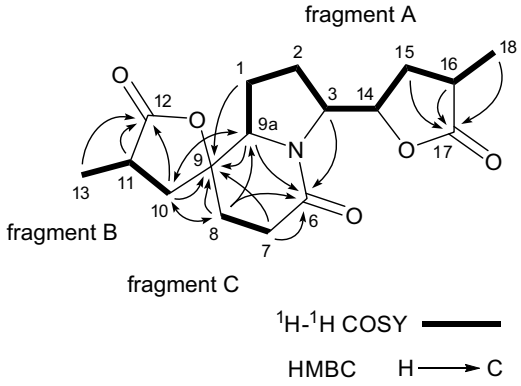

Figure 4. ^{1}H–^{1}H COSY and selected HMBC correlations for sessilifoliamide J (**2**).

methyl groups (δ_H 1.27 and 1.34) and three heteroatom-substituted methine protons (δ_H 3.80, 4.60, and 4.86) (Table 1). Its ^{13}C NMR spectrum showed 17 signals caused by two methyls, six

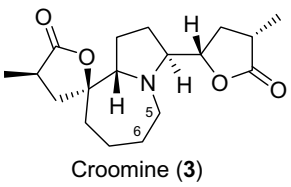

Figure 6. Structure of croomine (**3**) from *Croomia heterosepala*.[10]

methylenes, five methines, and four quaternary carbons, including three carbonyl carbons. Analysis of the ^{1}H–^{1}H COSY and HMQC spectra disclosed the presence of three molecular fragments A, B, and C, which had the same characteristics as those from **1** (Fig. 4). Although the HMBC experiments revealed that **2** possessed generally similar structural features as **1**, the HMBC correlations from H-3 and H-9a to C-6 (δ_C 168.4) indicated that C-3, C-9a, and the C-6 carbonyl carbon were connected to the nitrogen atom, and the HMBC correlations from H-7a, H-7b, H-8a, and H-8b to C-6 indicated that the C-6 carbonyl carbon was connected to fragment C at C-7. From these observations, the gross structure of **2** was determined to be as shown in Figure 4.

The relative stereochemistry of **2** was established by X-ray crystallographic analysis (Fig. 5) to be (3*R**, 9*R**, 9a*R**, 11*S**, 14*R**, 16*R**) as shown in Figure 1.[9]

Sessilifoliamine A (**1**) and sessilifoliamide J (**2**) have novel alkaloid skeletons. These skeletons are related to that of croomine (**3**) (Fig. 6), previously isolated from *Croomia heterosepala* (Baker) Okuyama (Stemonaceae).[10] In **1**, a 2-methyl-2-butenolide segment fuses **3** at its positions 5 and 6, whereas in **2**, the seven-membered azepane ring of **3** is contracted to a six-membered piperidin-2-one ring.

References and notes

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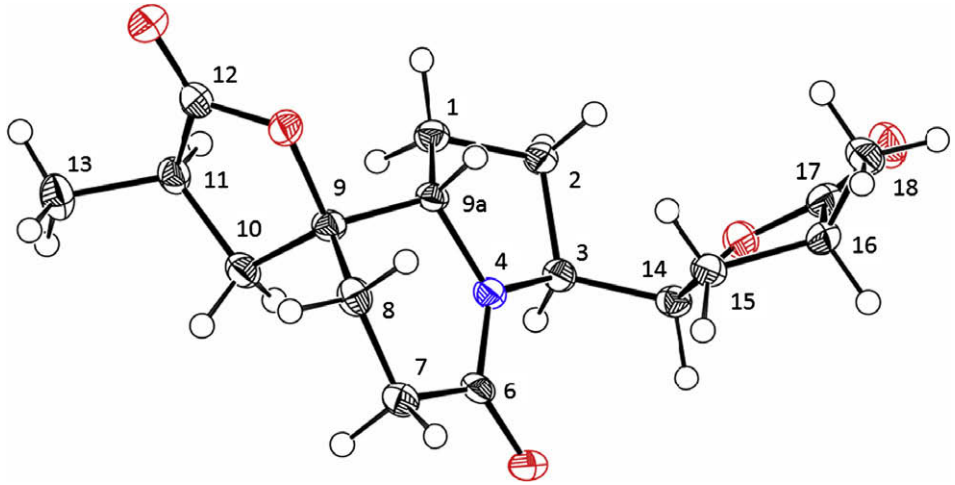

Figure 5. ORTEP representation of sessilifoliamide J (**2**).

7. (a) Hitotsuyanagi, Y.; Hikita, M.; Oda, T.; Kakuta, D.; Fukaya, H.; Takeya, K. *Tetrahedron* **2007**, *63*, 1008–1013; (b) Hitotsuyanagi, Y.; Hikita, M.; Nakada, K.; Fukaya, H.; Takeya, K. *Heterocycles* **2007**, *71*, 2035–2040.
8. A Monte Carlo conformation search was performed using the Macromodel 8.1 implementation of the MMFF force field and using the Maestro 5.1 graphical interface. A total of 20000 search steps were performed.
9. *Crystallography of* **2**: $C_{17}H_{23}NO_5$, $M = 321.36$, $0.67 \times 0.08 \times 0.06$ mm, monoclinic, space group $P2_1$, $a = 9.280(3)$ Å, $b = 5.8995(17)$ Å, $c = 15.080(4)$ Å, $\beta = 98.943(3)^\circ$, $V = 815.5(4)$ Å^3, $Z = 2$, $D_X = 1.309$ Mg m^{-3}, Mo Kα radiation ($\lambda = 0.71073$ Å), $\mu = 0.096$ mm^{-1}, $T = 90$ K, 8793 measured reflections, 3644 independent reflections [$R_{int} = 0.0449$], $R1 = 0.0403$ (3511 reflections with [$I > 2\sigma(I)$]), $wR2 = 0.1123$ (3644 reflections), $S = 1.049$. The structure was solved by direct methods using SHELXS-97,[11] and refined by full-matrix least-squares on F^2 using SHELXL-97.[12] Crystallographic data for compound **2** reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre under the reference number CCDC 700830. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing to data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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