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Cytotoxic Polyprenylated Benzoylphloroglucinol Derivatives with an Unusual Adamantyl Skeleton from *Hypericum sampsonii* (Guttiferae)

L. H. Hu and K. Y. Sim*

Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 119260

chmsimky@nus.edu.sg

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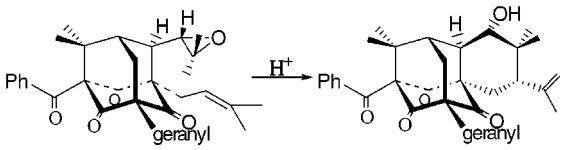
ABSTRACT



sampsonione J (2) **sampsonione I (1)**

The structures of sampsoniones I and J, isolated from the aerial parts of the Chinese medicinal plant *Hypericum sampsonii*, have been elucidated by detailed spectral analysis. They are complex adamantyl derivatives, and sampsonione I is the first polyprenylated benzoylphloroglucinol derivative with the unique caged tetracyclo[7.3.1.1^{3,11}.0^{3,8}]tetradecane-2,12,14-trione skeleton. Cytotoxic sampsonione I has also been obtained by the biomimetic transformation of sampsonione J.

A few structurally complex polyprenylated benzoylphloroglucinol derivatives with the rare tricyclo skeleton have been isolated from Guttiferous plants.[1] Our previous investigations[2] on *Hypericum sampsonii* yielded eight metabolites, sampsoniones A−H, possessing the novel tetracyclo skeleton with a homoadamantyl-like core formed by complex cyclizations of prenyl substituents. Continuing work on this plant has resulted in the isolation of two new natural products, sampsoniones I and J, with an unusual adamantyl caged skeleton.

The dried plant material was extracted with 95% EtOH, and the ethanolic concentrate was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2-soluble portion was separated into nine fractions by silica gel cc eluting with hexane−ethyl acetate (1:0, 20:1, 10:1, 5:1, 2:1, 1:1, 1:2, 1:5, 0:1). The fraction eluted with hexane−ethyl acetate (10:1) was further chromatographed on silica gel, ODS, and PTLC to afford **1** and **2**.

Sampsonione I (**1**) (6.4 mg, 0.00013%, Figure 1) was isolated as an optically active colorless oil, $[\alpha]_D^{31.2}$ +16.88

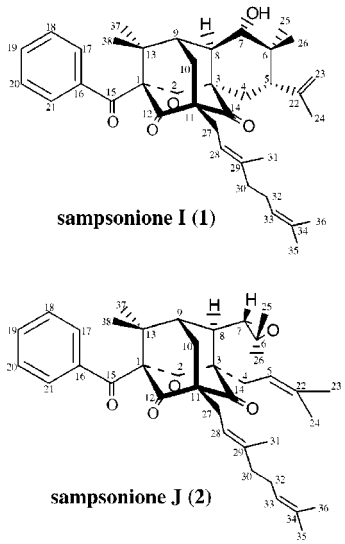


Figure 1. Structures of sampsoniones I and J.

(1) (a) Henry, G. E.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Yang, J. P. *Tetrahedron Lett.* **1995**, *36*, 4575. (b) De Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. *Tetrahedron Lett.* **1996**, *37*, 6427. (c) Henry, G. E.; Jacobs, H.; Carrington, C. M. S.; McLean, S.; Reynolds, W. F. *Tetrahedron Lett.* **1996**, *37*, 8663.

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Table 1. NMR Data for Sampsoniones I (**1**) and J (**2**)

	sampsonione I (**1**)				sampsonione J (**2**)			
no.	$^1H^a$	$^{13}C^b$	DEPT	HMBC[c]	$^1H^a$	$^{13}C^b$	DEPT	HMBC[c]
1		81.8				81.8		
2		200.7				201.0		
3		68.6				70.5		
4	α 2.04 m	25.5	CH_2	2, 3, 5, 6, 14	α 2.51 dd (15.0, 6.7)	26.1	CH_2	2
	β 1.90 dd (14.5, 3.7)			3, 5, 6, 8, 14	*β* 2.42 dd (15.3, 7.0)			2, 3, 14
5	*β* 2.32 dd (13.3, 3.7)	47.0	CH	4, 22, 23, 24, 25	5.05 m	118.0	CH	4
6		39.7				61.0		
7	*β* 3.31 d (11.1)	75.7	CH	8, 25, 26	2.62 d (8.8)	60.5	CH	3, 8
8	α 2.81 brd (11.0)	51.4	CH	2, 3, 7, 9, 10, 14	α 2.69 ddd (8.8, 2.8, 2.5)	50.7	CH	6, 7, 10, 14
9	2.12 m	41.9	CH	1, 3, 8, 11	1.90 dd (8.8, 2.8)	44.3	CH	1, 3, 11
10	2.53 m (2 H)	37.2	CH_2	8, 9, 11, 12, 13, 14	2.59 m	40.2	CH_2	12, 14
11		68.6				68.9		
12		201.3				201.9		
13		56.2				55.4		
14		203.3				202.8		
15		192.9				192.7		
16		134.9				134.6		
17	7.14 d (7.7)	128.7	CH	15, 19, 21	7.16 d (7.9)	129.0	CH	15, 19, 21
18	7.26 t (7.8)	127.9	CH	16, 20	7.26 t (8.3)	127.8	CH	16, 20
19	7.39 t (7.3)	132.3	CH	17, 21	7.41 t (7.6)	132.3	CH	17, 21
20	7.26 t (7.8)	127.9	CH	16, 18	7.26 t (8.3)	127.8	CH	16, 18
21	7.14 d (7.7)	128.7	CH	15, 17, 19	7.16 d (7.9)	129.0	CH	15, 17, 19
22		144.7				134.8		
23	α 4.98 brs	114.5	CH_2	5, 22, 24	1.66 s	25.6	CH_3	5, 22, 24
	β 4.79 brs			5, 22, 24				
24	1.81 s	23.7	CH_3	5, 22, 23	1.67 s	18.0	CH_3	5, 22, 23
25	0.86 s	13.8	CH_3	5, 6, 7, 26	1.25 s	19.4	CH_3	6, 7, 26
26	1.00 s	26.1	CH_3	5, 6, 7,25	1.35 s	24.2	CH_3	6, 7, 25
27	2.53 m	27.5	CH_2	10, 11, 12, 14, 28, 29	2.58 d (7.0)	27.4	CH_2	10, 11, 12, 14, 28, 29
28	5.23 t (7.0)	118.1	CH	27, 30, 31	5.22 t (7.0)	118.0	CH	27, 30, 31
29		138.9				138.9		
30	2.03 m	39.9	CH_2	28, 29, 32	2.01 m	39.9	CH_2	28, 29, 31, 32
31	1.66 s	16.3	CH_3	28, 29, 30	1.66 s	16.3	CH_3	28, 29, 30
32	2.05 m	26.7	CH_2	30, 33, 34	2.04 m	26.6	CH_2	29, 30, 33
33	5.07 t (6.8)	124.0	CH	35, 35	5.05 m	124.0	CH	32
34		131.4				131.4		
35	1.66 s	25.6	CH_3	33, 34, 36	1.66 s	25.9	CH_3	33, 34, 36
36	1.58 s	17.6	CH_3	33, 34, 35	1.58 s	17.6	CH_3	33, 34, 35
37	1.49 s	23.0	CH_3	1, 9, 13, 38	1.43 s	22.5	CH_3	1, 9, 13, 38
38	1.49 s	23.7	CH_3	1, 9, 13, 37	1.49 s	23.3	CH_3	1, 9, 13, 37

[a] Recorded in $CDCl_3$ at 500 MHz. [b] Recorded in $CDCl_3$ at 125 MHz. [c] Carbons that correlate with the proton resonance.

(*c* 0.128, $CHCl_3$), with the following spectral characteristics: IR (film) ν_{max} 3482 (OH), 1750, 1709 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 304 (3.13), 280 (3.52), 246 (4.08), 214 (4.08) nm; ^1H and ^{13}C NMR, Table 1.

The molecular formula was established by HREIMS $[M]^+$ 584.34820, calcd for $C_{38}H_{48}O_5$, 584.35016. The ^1H and ^{13}C NMR spectra indicated that it was a polyprenylated benzophenone derivative closely related to sampsoniones A−H. On the basis of 1- and 2-D NMR spectral data, readily identifiable pendant residues on the main skeleton were (a) a benzoyl group on C_1, (b) a geranyl side chain on C_{11}, (c) the *gem*-dimethyl group (C_{37} and C_{38}) correlated by HMBC to each other and to C_{13}, (d) the *gem*-dimethyl group (C_{25} and C_{26}) correlated by HMBC to each other and to C_6, and (e) the 2-propenyl group on C_5.

The structure of the tetracyclic core of the molecule was determined by tracing the connectivities shown in the HMBC spectra. Starting with the *gem*-dimethyl at C_{13}, cross-peaks were observed between protons of both methyl groups and (a) the quaternary carbon signal at δ 81.8 ppm (C_1) which, from its deshielded position, had to be flanked by three carbonyl groups (shown as C_2, C_{12}, and C_{15}) and (b) the methine carbon at δ 41.9 ppm (C_9). Moreover, the C_9 methine proton at δ 2.12 ppm was correlated with the quaternary carbon signals at δ 81.8 (C_1), 68.6 (C_3), and 68.6 ppm (C_{11}) and the methine carbon signal at δ 51.4 ppm (C_8). The C_{10}

(2) (a) Hu, L. H.; Sim, K. Y. *Tetrahedron Lett.* **1998**, *39*, 7999. (b) Hu, L. H.; Sim, K. Y. *Tetrahedron Lett.* **1999**, *40*, 759.

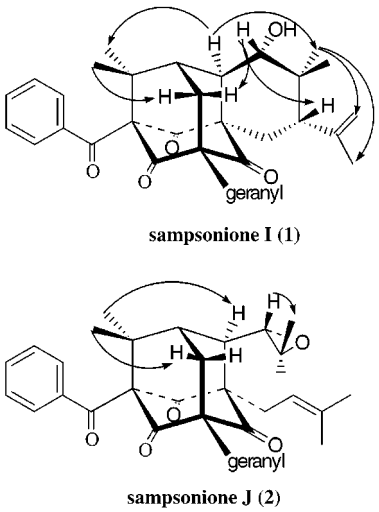

Figure 2. Selected NOESY cross-peaks of I and J.

methylene protons at δ 2.53 ppm were correlated with the quaternary carbon signals at δ 68.6 (C_{11}), 201.3 (C_{12}), 56.2 (C_{13}), and 203.3 ppm (C_{14}) and the methine carbon signals at δ 51.4 (C_8) and 41.9 ppm (C_9). Therefore, the carbons 1, 2, 3, 8, 9, 10, 11, 12, 13, and 14 formed a tricyclic adamantyl fragment.

The fourth six-membered ring of the tetracyclic core was established from the cross-peaks between (i) one of the C_4 methylene protons at δ 2.04 ppm and the quaternary carbon signals at δ 200.7 (C_2), 68.6 (C_3), 39.7 (C_6), and 203.3 ppm (C_{14}) and the methine carbon signal at δ 47.0 ppm (C_5); (ii) the other C_4 methylene proton at δ 1.90 ppm and the quaternary carbon signals at δ 68.6 (C_3), 39.7 (C_6), and 203.3 ppm (C_{14}) and the methine carbon signals at δ 47.0 (C_5) and 51.4 ppm (C_8); (iii) the C_7 methine proton at δ 3.31 ppm and the methine carbon signal at δ 51.4 ppm (C_8) and the C_{25}, C_{26} methyls at δ 13.8, 26.1 ppm.

The $^1H-^1H$ COSY spectrum, which showed correlations between H-10 (δ 2.53 ppm) and H-9 (δ 2.12 ppm), H-9 and H-8 (δ 2.81 ppm), and H-8 and H-7 (δ 3.31 ppm), indicated that the four protonated carbons in the core of sampsonione I are contiguous.

Molecular models disclosed that, by its formation, the tetracyclic system itself sets up the relative configurations at the chiral centers C_1, C_3, C_9, and C_{11} of the rigid adamantyl core and the fourth six-membered ring adopting the chair conformation. The relative stereochemistry of the remaining chiral carbons at C_5, C_7, and C_8 was deduced from 2-D NOESY (Figure 2) by cross-peaks between (i) the C_8 methine proton at δ 2.81 ppm and the C_{25}, C_{37} methyls (δ 0.86 and 1.49 ppm); (ii) the C_{10} methylene protons at δ 2.53 ppm and the C_{38} methyl (δ 1.49 ppm), as well as the C_7 methine proton (δ 3.31 ppm); and (iii) the C_7 methine proton at 3.31 ppm and the C_5 methine proton (δ 2.32 ppm) which also established the C_5, C_7 protons in the β configuration and C_8 proton in the α configuration. Further support of the diaxial orientation of H-7 and H-8 comes from the large coupling ($J_{H-7,H-8} = 11.0$ Hz). Hence, these spectral data corroborated the structure **1** for sampsonione I.

Sampsonione J (**2**) (58.4 mg, 0.00117%) was isolated as a colorless oil, $[\alpha]_D^{31.2}$ +1.48 (*c* 0.18, $CHCl_3$), with the following spectral characteristics: IR (film) ν_{max} 1734, 1704 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 286 (3.03), 274 (3.05), 244 (3.06), 214 (2.92) nm; ^1H and ^{13}C NMR, Table 1.

HREIMS indicated a molecular formula of $C_{38}H_{48}O_5$ (*m*/*z* 584.34931), an isomer of sampsonione I (**1**). Extensive analyses of 1- and 2-D NMR spectra of **2** indicated that it is similar to plukenetione A, obtained from *Clusia plukenetii*.[1c] They differ only in the side chains. Sampsonione J has a 1,2-epoxy-3-methylpropyl group at C_8 and a geranyl group at C_{11}, while plukenetione A has a 2-methylpropenyl group at C_8 and a 3-methyl-2-butenyl at C_{11}.

The chiral centers at C_1, C_3, C_9, and C_{11} were determined by its adamantyl backbone. The relative stereochemistry of the remaining chiral carbons at C_7 and C_8 was established

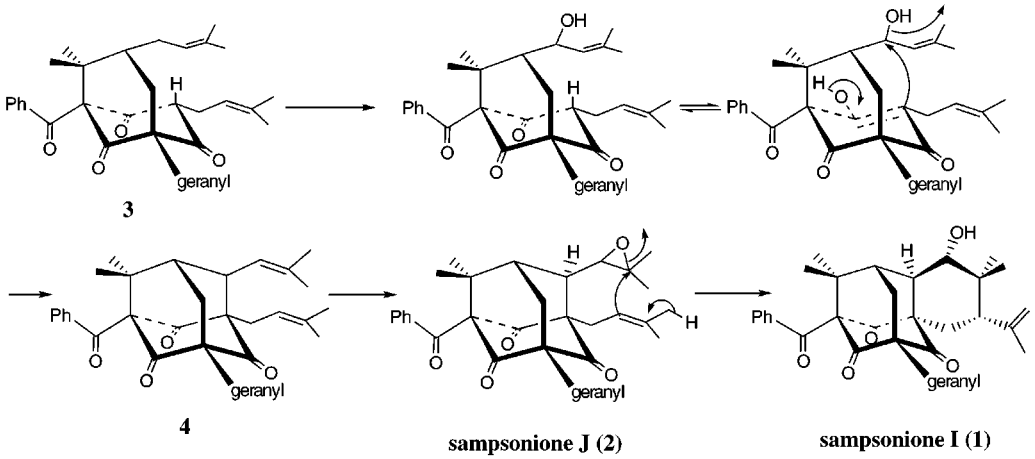

Figure 3. Possible biosynthesis pathway of sampsoniones J and I.

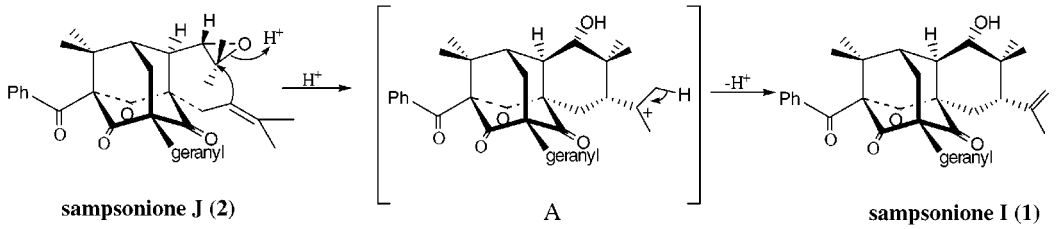

Figure 4. Biomimetic transformation of sampsonione J into sampsonione I.

by a 2-D NOESY spectrum (Figure 2). A cross-peak between H-7 (δ 2.62 ppm) and C_{25} methyl (δ 1.25 ppm) indicated they are of cis configuration. The stereochemistry at C_8 was determined by (i) the w-coupling of H-8 to H-10 and (ii) a NOE interaction of H-8 with the C_{37} methyl protons.

Sampsonione I (**1**) is the first polyprenylated benzoylphloroglucinol derivative possessing a novel rigid caged tetracyclo-[7.3.1.$1^{3,11}$.$0^{3,8}$]tetradecane-2,12,14-trione skeleton. It is presumably biosynthesized from the biogenetically acceptable intermediate **3**, which also leads to sampsoniones A−H.[2] Allylic hydroxylation and intramolecular cyclization of **3** give the adamantyl backbone intermediate **4**, which subsequently epoxidizes to form sampsonione J (**2**). **2** undergoes further intramolecular cyclization to yield sampsonione I (**1**) (Figure 3).

Some support for the above biosynthetic proposal was provided by an acid-catalyzed intramolecular cyclization of sampsonione J (**2**) in an aprotic solvent. Treatment of **2** with *p*-toluenesulfonic acid in toluene at room temperature afforded a product in 90% yield which was identical to sampsonione I (**1**) in its ^{1}H and ^{13}C NMR spectra and optical rotation. This formation of sampsonione I (**1**) probably involves the initial intramolecular cyclization of **2** to give the intermediate cation A followed by the loss of a proton from C_{23} (Figure 4).

Sampsoniones I and J have been tested for their cytotoxicity on P388 cell line, where sampsonione I was found to be active with ED_{50} of 6.9 μg/mL while sampsonione J showed no significant activity (ED_{50} >30 μg/mL).

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