Geranyl Bearing Polyisoprenylated Benzoylphloroglucinol Derivatives from *Hypericum sampsonii*

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Two new geranyl bearing polyisoprenylated benzoylphloroglucinol derivatives, hypersampsone G (**1**) and hypersampsone H (**2**) were isolated from the fruit of *Hypericum sampsonii*. Their structures were determined on the basis of spectroscopic data and the structure of **1** was confirmed by X-ray crystallographic analysis. Antitumor activities on A549 human cancer cells of the two compounds were tested.

Hypericum sampsonii (Hyperiaceae) is a Chinese herbal medicine used in the treatment of numerous disorders such as backache, burn, diarrhoea, snakebite, and swelling.[1] This plant has been found to have metabolites such as polyisoprenylated benzoylphloroglucinol derivatives,[2,3] xanthones, and other phenolic principles.[4] In our further search for biologically active compounds we have isolated two new polyisoprenylated benzoylphloroglucinol derivatives, named hypersampsone G (**1**) and hypersampsone H (**2**), from the petroleum ether extract for fruits of *H. sampsonii*. Their structures were determined on the basis of spectroscopic data. The structure of compound **1** was confirmed by X-ray crystallographic analysis. In the cytotoxicity assay hypersampsone H (**2**) exhibited marginal inhibitory activity.

The powdered fruit of *Hypericum sampsonii* (8 kg) were extracted with 95% EtOH. These extracts (1168 g) were re-extracted successively with petroleum ether (bp 60–90 °C), $CHCl_3$, and H_2O. The petroleum ether-soluble fraction (730.1 g) was separated on silica gel and purified by RP-18 column with acetonitrile: H_2O (95:5) to yield **1** (92 mg) and **2** (28 mg).

Hypersampsone G (**1**) was obtained as colorless prism-like crystals, mp 141–142 °C, $[\alpha]_D^{22}$ +10.25° (*c* 0.401, $CHCl_3$). Its molecular formula was assigned as $C_{38}H_{50}O_4$ on the basis of HRESIMS *m*/*z*: 593.3602 $[M + Na]^+$ (calcd for $C_{38}H_{50}O_4Na$, 593.3607). Carbonyl group bands were present at absorptions of 2968, 1735, 1683, 1447, 1392, 1371 cm^{-1} in the IR spectrum of **1**. The ^{13}C NMR spectrum showed 38 carbon signals comprising a monosubstituted benzene ring (δ 135.1 s, 127.9 d × 2, 129.1 d × 2), 131.9 (d, C-19), four carbonyl groups (δ 205.3 s, 205.2 s, 206.1 s, 193.0 s), nine methyls, six methylenes, six methines, and seven quaternary carbons. These spectral features together with the biogenesis of metabolites from *H. sampsonii*[2,3] suggested that compound **1** possessed a skeleton of polyisoprenylated benzoylated phloroglucinol derivate. The structure of **1** had a high degree of similarity to that of hypersampsone D, a metabolite from the same plant.[3] Analysis of ROESY spectral data (Figure 1) revealed the structures of **1** differed from that of hypersampsone D at C-5 and C-7, in which H-5 and H-7 formed cis configuration in **1** (Figure 1), instead of the trans configuration observed in hypersampsone D. Compound **1** was

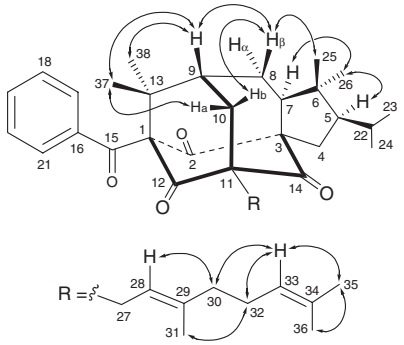

Figure 1. The structure and key ROESY correlation of **1**.

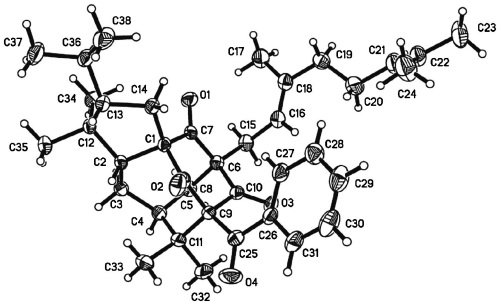

Figure 2. ORTEP for X-ray crystallography of **1**.

therefore elucidated its relative configuration as shown in Figure 1, and was given the trivial name hypersampsone G.

Hypersampsone G (**1**) was finally isolated via multiple column chromatographic procedures then successfully crystallized as prisms. This structure was confirmed by X-ray crystallographic analysis (Figure 2). Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 656286 (deposit@ccdc.cam.ac.uk).

Hypersampsone H (**2**) was obtained as a colorless oil, $[\alpha]_D^{22}$ +44.37° (*c* 0.222, $CHCl_3$). The same molecular formula, $C_{38}H_{50}O_4$, to that of compound **1** was assigned on the basis of HRESIMS *m*/*z*: 571.3789 $[M + H]^+$ (calcd for $C_{38}H_{50}O_4H$, 571.3787). Carbonyl group bands were present at absorptions of 3063, 2975, 2923, 2855, 1721, 1652, 1615, 1447, 1386 cm^{-1} in the IR spectrum of **2**. Furthermore **2** exhibited similar ^1H NMR spectral features to those of **1**, with a benzoyl group, triplet vinyl proton signals, together with several singlet methyl group signals, suggesting that compound **2** was also a polyisoprenylated benzoylated phloroglucinol derivative. By comparison of their ^{13}C NMR spectral data, two of three oxygen-bearing carbon signals at δ 205.3 in **1** were upfield in **2** and were found to

Table 1. NMR spectral data for hypersampsone H (**2**)

C/H	$^{1}H^{a}/\delta$	$^{13}C^{b}/\delta$	HMBC (H → C)
1		71.1 (s)[d]	
2		167.7 (s)	
4		80.3 (s)	
5α	1.55 m	31.2 (t)	C-4, 6, 21, 22
5β	1.36 m		C-4, 6, 21, 22
6	2.36 m	16.3 (t)	C-2, 4, 5, 7, 8
7		113.6 (s)	
8		195.0 (s)	
9		63.8 (s)	
10a	2.06 d (14.1)[c]	40.7 (t)	C-8, 9, 11, 12, 33
10b	2.18 m	—	C-8, 9, 11, 33
11	1.43 m	48.7 (d)	C-9, 10, 33, 36, 38
12		49.0 (s)	
13		208.5 (s)	
14		194.0 (s)	
15		137.1 (s)	
16	7.55 d (8.2)	128.3 (d)	C-14, 18, 20
17	7.23 t (7.8)	127.7 (d)	C-15, 19
18	7.39 t (7.4)	132.0 (d)	C-16, 20
19	7.23 t (7.8)	127.7 (d)	C-15, 17
20	7.55 d (8.2)	128.3 (d)	C-14, 16, 18
21	1.24 s	27.5 (t)	C-4, 5, 22
22	0.55 s	25.2 (t)	C-4, 5, 21
23a	2.52 dd (6.7, 14.1)	30.0 (t)	C-8, 9, 10, 24, 25
23b	2.60 dd (6.7, 14.1)		C-9, 10, 24, 25
24	5.11 t (7.8)	119.4 (d)	C-23, 26, 27
25		138.1 (s)	
26	1.95 m	40.0 (t)	C-24, 25, 27, 28, 31
27	1.70 s	16.6 (q)	C-24, 25, 26, 28
28	2.01 m	26.9 (t)	C-26, 27, 29, 30
29	5.07 t (7.0)	124.3 (d)	C-28, 31, 32
30		131.2 (s)	
31	1.63 s	25.7 (q)	C-26, 29, 30, 32
32	1.57 s	17.7 (q)	C-29, 30, 31
33a	2.24 m	29.6 (t)	C-34
33b	1.95 m		C-10, 34, 35
34	4.85 t (7.1)	124.9 (d)	C-33, 36, 37
35		132.7 (s)	
36	1.66 s	25.8 (q)	C-11, 34, 35, 37
37	1.53 s	17.9 (q)	C-34, 35, 36
38	1.39 s	27.2 (q)	C-1, 11, 12, 39
39	1.47 s	23.3 (q)	C-1, 11, 12, 38

Spectra recorded at [a]400 and [b]100 MHz in $CDCl_3$ at 25 °C, respectively. [c]J values (in Hz) in parentheses. [d]Multiplicity deduced by DEPT and indicated by usual symbols.

be at 167.7 (C-2), an oxygen-bearing α,β-unsaturated olefinic quaternary carbon and at 195.0 (C-8), an conjugated carbonyl carbon in **2**, respectively. The carbon signal at 80.3 (C-4) and fourteen unsaturated degrees, along with the HMBC correlations between CH_3-21 and C-4/C-5, especially between H-6 and C-2, C-4, C-5, C-7, C-8 suggested the presence of an oxygen-bearing six-membered ring in **2**. Careful examination of the HMBC and ROESY spectral data (Table 1 and Figure 3) indicated that compound **2** possessed a similar structure to hypersampsone F, a polyisoprenylated benzoylated derivative ($C_{38}H_{48}O_4$) isolated from the same species.[3] However, in **2** C-5 and C-6 existed as

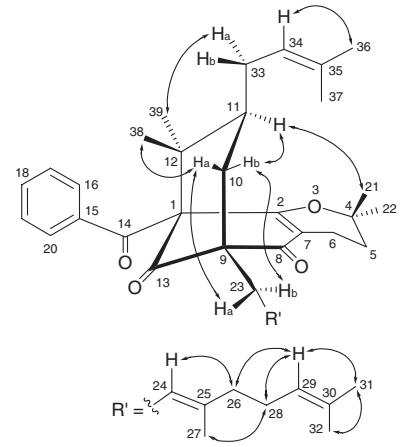

Figure 3. The structure and key ROESY correlation of **2**.

two methylenes,[5] instead of double bond carbons in hypersampsone F. Further differences existed in the type of alkyl side chains present. Unlike hypersampsone F, in which an isoprenyl group is connected to C-39, compound **2** bears a geranyl moiety at C-9. The correlations of H-10a/CH_3-38, H-10b/H-11, H-10b/H-23b, and H-11/CH_3-21 in the ROESY supported this relative stereochemical structure. Therefore **2** was elucidated and given the trivial name as hypersampsone H.

Compounds **1** and **2** were tested for cytotoxicity against human lung adenocarcinoma A549 cells, using the MTT method[6] with etoposide as a positive control. In the bioassay hypersampsone H (**2**) exhibited marginal inhibitory activity with an IC_{50} of 120 μM, while etoposide showed an IC_{50} of 7.3 μM.

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