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A phloroglucinol derivative with a new carbon skeleton from *Hypericum perforatum* (Guttiferae)

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Abstract—Examination of the aerial parts of a Chinese herbal medicine yielded a novel metabolite, perforatumone **1**, which is characterized by its unique carbon skeleton. Its structure was determined by detailed spectroscopic analysis.
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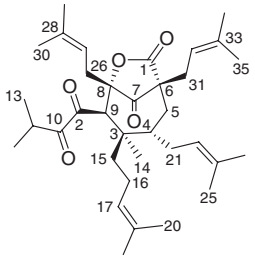
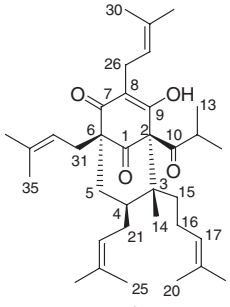
Hypericum perforatum provides an interesting array of polyprenylated phloroglucinol derivatives.[1] Their antidepressant activity has sparked great interest in the chemistry and biochemistry of the constituents of this species.[2–4] In this study, perforatumone **1** was isolated together with other known compounds[5] including hyperforin **2**.



1



2

Perforatumone **1** was obtained as a colorless oil, $[\alpha]_D^{29}$ +153 (*c* 2.9, acetone), from the hexane soluble part (330 g) of *H. perforatum* (aerial parts, collected from Shanxi province of PR China). The molecular formula of $C_{35}H_{52}O_5$ (EIMS, *m/z* 552.3830, $[M]^+$), the IR absorptions of the carbonyl groups (1814, 1760, 1736, and 1707 cm^{-1}) and the NMR data of **1** (Table 1) indicated that the structure was different from the known compounds hyperforin **2** and its derivatives, previously isolated from this species.[6] However, **1** exhibited prominent NMR signals showing the presence of four isoprenyl groups, for example, four olefinic protons at δ_H 4.72 (t, $J = 7.0$ Hz), δ_H 4.91 (t, $J = 6.6$ Hz), δ_H 4.95 (t, $J = 7.1$ Hz), and δ_H 5.00 (dd, $J = 7.0$, 1.2 Hz) as well as four pairs of olefinic carbons between δ_C 113.5 and 138.8 (Table 1) and thus showed some similarities to hyperforin. The methyl groups at δ_H 1.06 (d, $J = 6.7$ Hz) and δ_H 1.03 (d, $J = 6.7$ Hz) and the methine proton at δ_H 2.61 (septet, $J = 6.7$ Hz) suggested the presence of an isopropyl ketone unit as is consistently found in hyperforin and its derivatives.

Two substructures in perforatumone **1** (Fig. 1) were deduced using a combination of homo- and heteronuclear 2D NMR techniques. The presence of a lactone carbonyl carbon (δ_C 171.8, C-1) and the HMBC connectivities between the methylene proton at δ_H 2.57 (H-26a) and carbons at δ_C 95.4 (C-8), 113.5 (C-27), and 206.2 (C-7), and between the methylene proton at δ_H 2.11 (H-31a) and the carbons at δ_C 206.2 (C-7), 56.7 (C-6), and 171.8 (C-1) led to the identification of substructure **A**. Substructure **B** was also assigned by interpretation of the HMBC spectra. The important correlations were those (a) between Me-14 at δ_H 1.08 and the carbons at δ_C 40.0 (C-4), 62.6 (C-9), 48.3 (C-3), and 38.6 (C-15); (b) between the methine singlet at δ_H 4.47 (H-9) and the ketone carbonyl groups at δ_C 206.2 (C-10) and 196.9 (C-2), and the quaternary carbon at δ_C 48.3 (C-3); (c) between the methyl group at δ_H 1.03 (H-12) and the methine carbon at δ_C 42.4 (C-11), the carbonyl

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Table 1. NMR data of perforalactone **1**

	^{1}H NMR	^{13}C NMR	HMBC
1	—	171.8	
2	—	196.9	
3	—	48.3	
4	1.56, m[a]	40.0	
5	1.56, m[a]	36.5	C-3, C-4, C-6, C-7
6	—	56.7	
7	—	206.2	
8	—	95.4	
9	4.47, s	62.6	C-2, C-3, C-4, C-8, C10, C-14
10	—	206.2	
11	2.61, septet, J = 6.7 Hz	42.4	C-12, C-13
12	1.06, d, J = 6.7 Hz	18.9	C-10, C-11, C-13
13	1.03, d, J = 6.7 Hz	18.8	C-10, C-11, C-12
14	1.08, s	17.8	C-3, C-4, C-9, C-15
15	1.30, ddd, J = 16.0, 12.4, 4.2 Hz 1.47, ddd, J = 16.0, 12.4, 5.4 Hz	38.6	C-3, C-4, C-9
16	1.87, m[a] 1.95, m[a]	21.6	C-17, C-18
17	5.00, br dd, J = 7.0, 3.0 Hz	122.5	C-19, C-20
18	—	132.4	
19	1.67, br s	25.7	C-17, C-18, C-20
20	1.63, br s	18.0	C-17, C-18, C-19
21	a. 1.75, d, J = 6.6 Hz b. 2.00, d, J = 6.6 Hz	28.8	C-5, C-22, C-23
22	4.91, br t, J = 6.6 Hz	122.8	C-24, C-25
23	—	134.8	
24	1.75, br s	25.9	C-22, C-23, C-25
25	1.59, br s	18.0	C-22, C-23, C-24
26	a. 2.57, dd, J = 7.1, 17.3 Hz b. 2.86, dd, J = 7.1, 17.3 Hz	29.7	C-7, C-8, C-9, C-27, C-28
27	4.95, br t, J = 7.1 Hz	113.5	C-29, C-30
28	—	138.8	
29	1.65, br s	25.7	C-27, C-28, C-30
30	1.65, br s	18.2	C-27, C-28, C-29
31	a. 2.11, dd, J = 7.0, 15.0 Hz b. 2.51, dd, J = 7.0, 15.0 Hz	27.5	C-6, C-7, C-32, C-33
32	4.72, br t, J = 7.0 Hz	117.5	C-34, C-35
33	—	136.3	
34	1.68, br s	25.8	C-32, C-33, C-35
35	1.61, br s	18.0	C-32, C-33, C-34

Recorded in $CDCl_3$ at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR).
[a] Approximate position of unresolved signal.

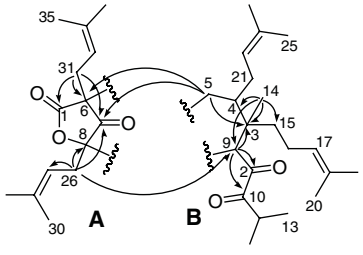

Figure 1. Substructures of perforatumone **1** and selected HMBC correlations.

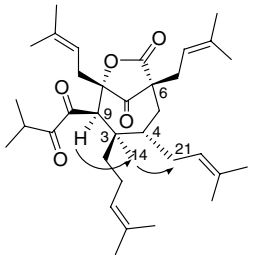

Figure 2. Selected ROESY correlations of perforatumone **1**.

group at δ_C 206.2 (C-10) and the methyl group at δ_C 18.8 (C-13); and (d) between the methylene protons at δ_H 1.56 (H-5) and the quaternary carbon at δ_C 48.3 (C-3). Substructures **A** and **B** were linked by correlations between H-5 and C-6 and C-7. Correlations from H-26 to C-8 and C-9 established that the final bond was therefore between C-8 and C-9.

The relative stereochemistry of **1** was determined using a ROESY experiment (Fig. 2). The key ROESY correlations were between H-9 and the H-14 methyl and H-21a, which indicated that C-14 and C-21 were on the same side of the seven-membered ring. In the ROESY spectrum, a correlation between H-9 and H-26 was observed. Because models showed that the conformation of **1** was flexible, the presence of a correlation between

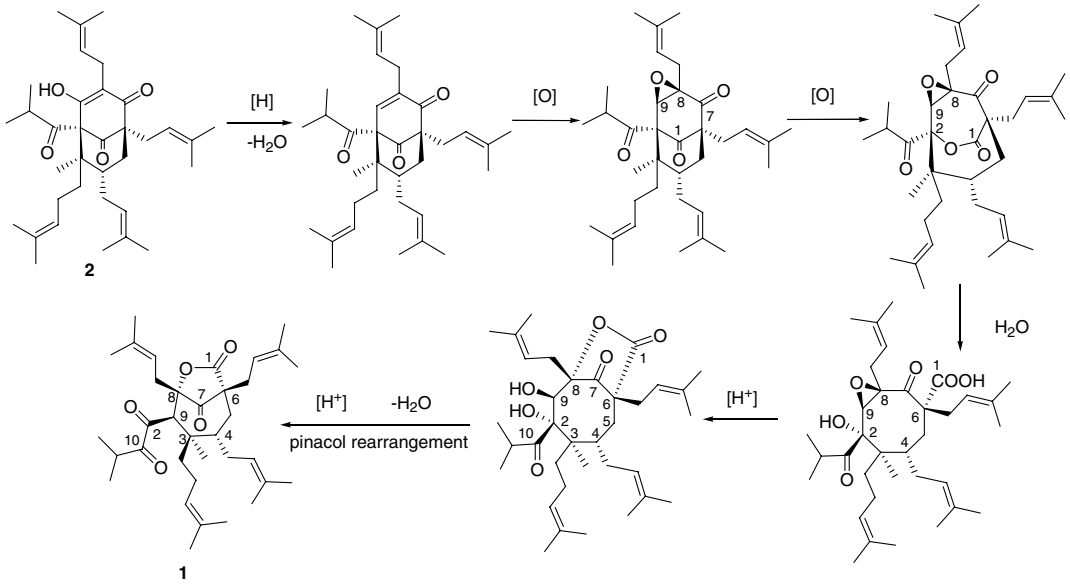

Figure 3. Postulated biosynthetic pathway for perforatumone **1**.

H-9 and H-26 was not sufficient to determine the stereochemistry of C-6 and C-8. However, based on the mechanism of formation of **1** as shown in Figure 3, stereochemistry at C-3, C-4, and C-6 would remain unchanged. Stereochemical constraints require the lactone ring to be fused to the seven-membered ring in a *cis* fashion. The stereochemistry of **1** is therefore as shown in Figure 2.

It is reasonable to assume that **1** is derived from hyperforin **2**, which has known absolute stereochemistry. A plausible biosynthetic route involving a Baeyer–Villiger ring cleavage and a final pinacol rearrangement is given in Figure 3. The absolute configuration of **1** has not been determined but is assumed to be the same as for **2**.

References and notes

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5. Compounds isolated: perforatumone (30 mg, 0.0006%), hyperforin (45 mg, 0.0009%), furohyperforin (50 mg, 0.001%), and 8-hydroxyhyperforin 8,1-hemiacetal (50 mg, 0.001%).
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