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Norsampsones A–D, Four New Decarbonyl Polycyclic Polyprenylated Acylphloroglucinols from *Hypericum sampsonii*

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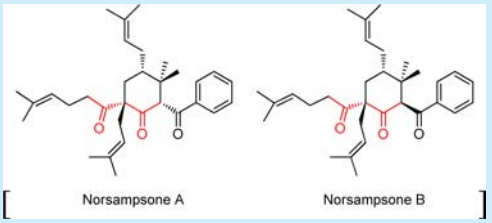
Supporting Information

ABSTRACT: Norsampsones A–D (**1**–**4**), four new decarbonyl polycyclic polyprenylated acylphloroglucinols, together with a new biogenetically related compound hypersampsone M (**5**), were isolated from the aerial parts of *Hypericum sampsonii*. Norsampsones A–D featured an unprecedented carbon skeleton with the loss of C-2 carbonyl in the phloroglucinol ring. All structures were determined by extensive NMR spectroscopic methods, ECD calculation, and single-crystal X-ray diffraction.



Guttiferae (Clusiaceae) is a large family of plants that includes about 37 genera and 1600 species. Several plants of the Guttiferae family have been widely used as folk medicines due to their broad-spectrum antibacterial and healing properties.[1] A series of polycyclic polyprenylated acylphloroglucinols (PPAPs) have been isolated from the plants of the Clusiaceae family, which possesses various biological activity.[2]

Hypericum sampsonii belongs to the *Hypericum* genus of the Guttiferae family[3] with abundant complex caged PPAPs,[4−12] exhibits anticancer activity, and has been used as a promising anticancer herb in Taiwan.[13] In our efforts for more novel PPAPs, four new decarbonyl PPAPs norsampsones A-D (**1**–**4**), together with hypersampsone M (**5**) (Figure 1), were isolated from the 60% EtOH extract of the aerial parts of *H. sampsonii*.

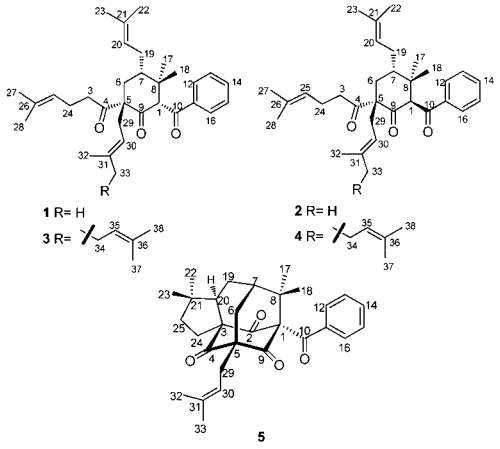


Figure 1. Structure of **1**–**5**.

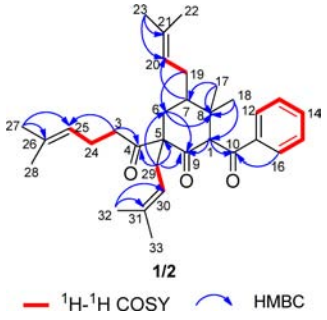


Figure 2. Key ^{1}H–^{1}H COSY and HMBC correlations of **1**–**2**.

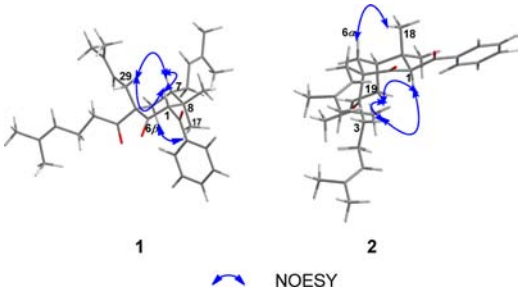


Figure 3. Key NOESY correlations of **1** and **2**.

Norsampsones A–D featured an unprecedented carbon skeleton with the loss of C-2 carbonyl in the phloroglucinol ring. Herein, we describe the structural elucidation, plausible

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biogenetic pathway, and biological evaluation of new compounds.

Norsampsone A (**1**) was obtained as colorless oil, $[[\alpha]_D^{23}$ +23.4 (c = 0.50, $CHCl_3$)]. A molecular formula of $C_{32}H_{44}O_3$ was established from its HR-ESI MS (m/z 477.3369 $[M + H]^+$, calcd 477.3369), indicating 11 degrees of unsaturation. The ^{13}C NMR and DEPT spectra showed 32 carbon signals. Twenty four of them demonstrated the presence of two carbonyls [δ_C 208.6 × 2], one benzoyl group [δ_C 197.4, 139.1, 133.1, 128.8 × 2, 127.9 × 2] and three prenylated groups [(δ_C 27.6, 122.8, 133.6, 18.1, 26.1), (δ_C 23.0, 123.3, 132.7, 17.8, 25.9), (δ_C 32.6, 118.7, 135.4, 18.5, 26.1)], which accounted for 10 degrees of unsaturation. The remaining one degree of unsaturation required a monocyclic structure in **1**. All the features mentioned above indicated a skeleton of PPAPs. The $^1H-^1H$ COSY and HMBC correlations established the planar structure of **1** (Figure 2).

The relative configuration of **1** was determined by NOESY experiment. The NOESY correlations of H-1 (δ_H 4.50)/H-7 (δ_H 1.78), H-1/H-29 (δ_H 2.78) and H-7/H-29 suggested that the cyclohexanone moiety adopted a chair conformation, and all these three protons were located at the axial position on the same orientation. In addition, the NOESY correlation between H-6β (δ_H 1.95) and H_3-17 (δ_H 1.23) indicated that these two protons were also situated at the axial position on the other side (Figure 3). It was further supported by the large coupling constant observed between H-6β and H-7 (12.9 Hz).

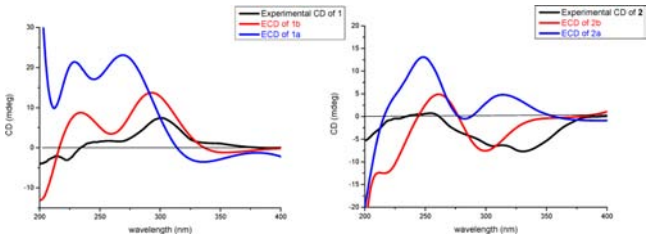

Figure 4. Calculated and experimental ECD spectra of **1** and **2**.

Norsampsone B (**2**), colorless oil, $[[\alpha]_D^{23}$ −28.6 (c = 0.50, $CHCl_3$)] also has a molecular formula of $C_{32}H_{44}O_3$, on the basis of the HR-ESI MS (m/z 477.3366 $[M + H]^+$, calcd 477.3369). Comprehensive analysis of the 1D and 2D NMR spectra data built the gross structure of **2**, with the same planar structure as **1** (Figure 2). The relative configuration of **2** was determined through inspection of the NOESY spectrum. The NOESY correlations of H-1 (δ_H 4.48)/H-3 (δ_H 2.47), H-1/H-19 (δ_H 1.81) and H-3/H-19 demonstrated that these three

Table 1. ^1H (300 MHz) and ^{13}C (75 MHz) NMR Data of 1−4 in $CHCl_3$ (δ in ppm, J in Hz)

	1		2		3		4	
no.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	4.50 (s)	64.7	4.48 (s)	66.9	4.52 (s)	64.6	4.49 (s)	66.5
3	2.47 (m)	40.4	2.47 (m)	39.4	2.48 (m)	40.5	2.47 (m)	39.3
4		208.6		209.9		208.5		210.0
5		66.3		67.4		66.3		67.4
6α	1.81 (m)	34.1	1.85 (m)	32.2	1.81 (m)	33.9	1.86 (m)	32.2
6β	1.95 (dd, 14.4, 12.9)		2.16 (m)		1.96 (m)		2.17 (m)	
7	1.78 (m)	44.8	2.14 (m)	41.3	1.78 (m)	44.9	2.15 (m)	41.6
8		44.0		41.5		44.0		41.6
9		208.6		207.1		208.5		207.0
10		197.4		196.4		197.3		196.1
11		139.1		138.7		139.1		138.6
12,16	7.74 (dd, 7.2, 1.5)	127.9	8.01 (dd, 7.2, 1.5)	128.8	7.75 (br.d, 7.2)	127.9	8.01 (dd, 7.2, 1.5)	128.8
13,15	7.40 (tt, 7.2, 1.5)	128.8	7.43 (tt, 7.2, 1.5)	128.9	7.40 (br t, 7.2)	128.8	7.43 (tt, 7.2, 1.5)	128.9
14	7.51 (tt, 7.2, 1.5)	133.1	7.52 (tt, 7.2, 1.5)	133.3	7.51 (br t, 7.2)	133.2	7.52 (tt, 7.2, 1.5)	133.3
17	1.23 (s)	16.9	1.01 (s)	24.5	1.22 (s)	17.0	1.01 (s)	24.6
18	1.10 (s)	27.4	1.14 (s)	25.9	1.09 (s)	27.4	1.15 (s)	25.9
19	2.28 (m) 1.76 (m)	27.6	2.27 (m) 1.81 (m)	27.6	2.27 (m) 1.75 (m)	27.7	2.27 (m) 1.80 (m)	27.5
20	5.05 (br t, 7.2)	122.8	5.11 (br t, 6.9)	123.4	5.06 (br t, 7.5)	122.8	5.12 (br t, 7.2)	123.4
21		133.6		133.3		133.6		133.4
22	1.59 (s)	18.1	1.60 (s)	18.2	1.60 (s)	18.1	1.58 (s)	17.9
23	1.69 (s)	26.1	1.70 (s)	26.1	1.69 (s)	26.1	1.71 (s)	26.1
24	2.24 (m)	23.0	2.21 (m)	22.9	2.23 (m)	23.0	2.21 (m)	22.9
25	5.04 (br t, 7.2)	123.3	5.01 (tt, 7.2,1.2)	123.0	5.03 (br t, 7.2)	123.3	5.00 (tt, 7.2,1.2)	123.0
26		132.7		132.9		132.7		132.9
27	1.56 (s)	17.8	1.58 (s)	17.8	1.56 (s)	17.9	1.57 (s)	18.2
28	1.62 (s)	25.9	1.63 (s)	25.9	1.62 (s)	25.9	1.62 (s)	25.9
29	2.78 (m)	32.6	2.59 (m) 2.44 (m)	32.3	2.79 (m)	32.6	2.57 (m) 2.46 (m)	32.1
30	4.82 (br t, 6.9)	118.7	4.71 (br t, 6.9)	118.9	4.84 (br t, 6.9)	118.3	4.76 (br t, 6.9)	118.6
31		135.4		135.6		139.2		139.3
32	1.71 (s)	18.5	1.58 (s)	18.3	1.70 (s)	16.8	1.60 (s)	16.6
33	1.63 (s)	26.1	1.48 (s)	25.9	1.90 (m)	40.0	1.81 (m)	40.0
34					1.92 (m)	26.7	1.86 (m)	26.7
35					4.96 (br t, 6.6)	124.0	4.95 (br t, 6.6)	124.3
36						131.8		131.6
37					1.52 (s)	17.8	1.52 (s)	17.8
38					1.62 (s)	25.9	1.62 (s)	25.9

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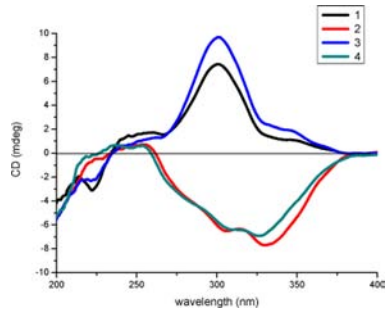


Figure 5. Experimental CD spectra of **1**−**4**.

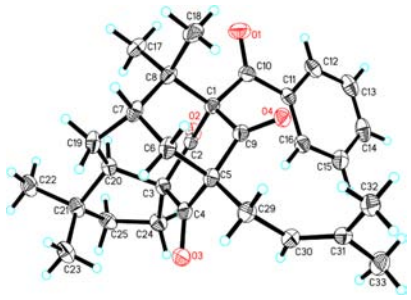


Figure 6. Single-crystal X-ray structure of **5**.

protons were situated at the axial position on one side of a chair conformation of cyclohexanone moiety. Furthermore, H-6α (δ_H 1.85) and H_3-18 (δ_H 1.14) were located at the axial position on the other side due to the obvious NOESY correlation between H-6α and H_3-18 (Figure 3).

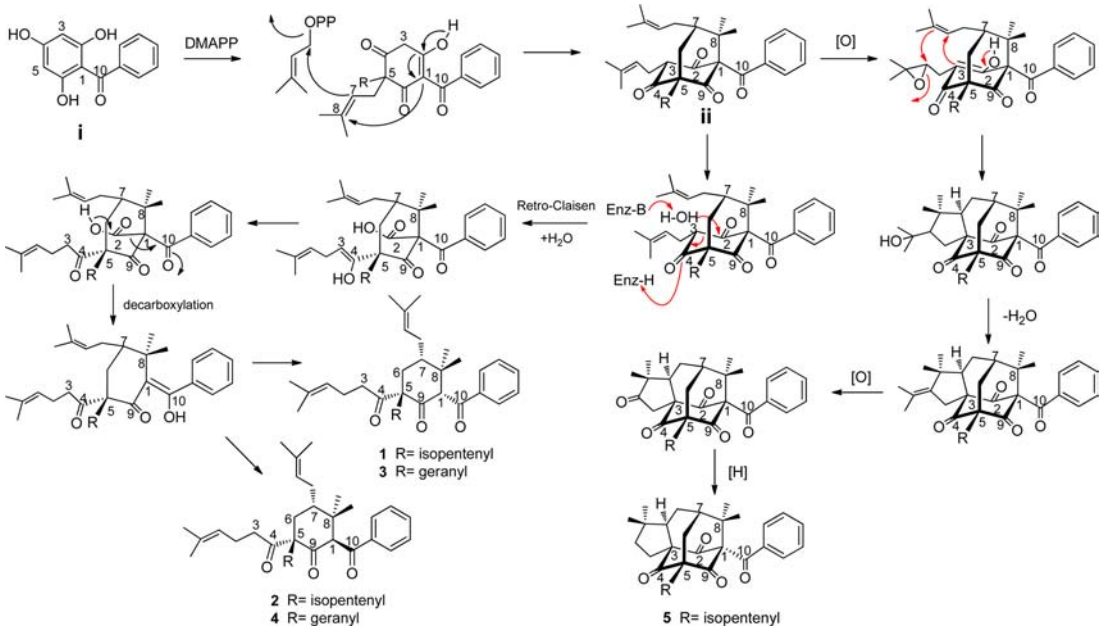
The absolute configurations of **1** and **2** were elucidated by ECD calculations. Two pairs of enantiomers (1*S*,5*R*,7*R*)-**1a**, (1*R*,5*S*,7*S*)-**1b**, (1*R*,5*R*,7*R*)-**2a**, and (1*S*,5*S*,7*S*)-**2b** were calculated for ECD spectra based on the known relative configuration of **1** and **2**. As a result, the overall pattern of calculated ECD spectra of **1b** and **2b** were in good agreement with the experimental data of **1** and **2**, respectively (Figure 4). Thus, the absolute configurations of the chiral carbons were established as 1*R*,5*S*,7*S* in **1** and 1*S*,5*S*,7*S* in **2**.

Norsampsones C (**3**) and D (**4**) were both obtained as colorless oil with a pair of opposite optical rotation [$[\alpha]_D^{23}$ +26.0 (c = 0.50, $CHCl_3$) for **3**, $[\alpha]_D^{23}$ −28.2 (c = 0.50, $CHCl_3$) for **4**]. Their molecular formula were assigned as $C_{37}H_{53}O_3$ by HR-ESI MS (m/z 545.3996 $[M + H]^+$ and 545.3995 $[M + H]^+$, calcd 545.3995) . The 1D NMR data of **3** were identical to those of **1** (Table 1), except for an additional prenylated group in **3**. This additional prenylated group was located at C-33 (δc 40.0), according to the key HMBC correlations of H-33 (δ_H 1.90) to C-34 (δc 26.7) and C-35 (δc 124.0). The relative configuration of **3** was determined by the NOESY correlations, which resulted in the same configuration as that of **1**. Moreover, the CD spectrum of **3** had a high degree of similarity to that of **1** (Figure 5). Thus, the absolute configuration of **3** was also determined to be 1*R*,5*S*,7*S*. Similarly, by comparation of NMR data with those of **2**, the structure of **4** was deduced. In addition, the CD spectrum of **4** was recorded, which was very similar to that of **2** (Figure 5). Therefore, the absolute configuration of **4** was assigned as 1*S*,5*S*,7*S*.

The molecular formula of hypersampsone M (**5**) was determined to be $C_{30}H_{36}O_4$ by its HR-ESI MS (m/z 461.2694 $[M + H]^+$, calcd 461.2692). Extensive analysis of the 1D and 2D NMR spectra (Supporting Information) revealed that **5** was closely related to the PPAPs hypersampsone I,[9] except for the loss of a prenylated group at C-33. Fortunately, an X-ray diffraction experiment with suitable crystals was conducted by Cu Kα radiation with a Flack parameter of 0.1(2) (Figure 6). Thus, the absolute configuration of **5** was established to be 1R,3R,5S,7S,20R, which was consistent with the absolute configurations of compounds **1**−**4** determined by ECD calculations.

Generally, most of the discovered PPAPs isolated from *H. sampsonii* form a unique family of structurally related caged metabolites, which are probably biosynthesized from the biogenetically acceptable 2,4,6-trihydroxybenzophenon (**i**) via a series of C-alkylations with dimethylallyl diphosphate (DMAPP). The intermediate **ii** is the common precursor of these compounds.[7,9] The plausible biosynthetic pathway to **1**−**5** was proposed

Scheme 1. Plausible Biogenetic Pathway for 1−5



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(Scheme 1). Norsampsones A-D (**1**−**4**) could be considered as the PPAPs with the loss of C-2 carbonyl in the phloroglucinol ring. The plausible biogenetic pathway of **1**−**4** was also proposed to be generated from **ii** through the Retro-Claisen[14] and decarboxylation[15] reactions. Hypersampsone M (**5**) was probably biosynthesized from the same precursor **ii** by epoxidation, followed by intramolecular cyclization, oxidation, dehydration, and reduction reactions.[7,9]

Compounds **1**, **3**, **4**, and **5** were investigated for their effects on RXRα transcriptional-inhibitory activities using a reporter gene assay. Besides, their cytotoxicity against Hela cells were also evaluated. As a result, compound **3** (5−20 μM) caused a dose-dependent decrease in the transcriptional activity of RXRα and inhibited cell proliferation in Hela cells at a concentration of 20 μM.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures; physicochemical properties; UV, IR, HR-ESI-MS, and 1D and 2D NMR spectra of compounds **1**−**5**; X-ray data of **5**; ECD calculation method of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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