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Letter

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Hyperuralones A and B, New Acylphloroglucinol Derivatives with Intricately Caged Cores from *Hypericum uralum*

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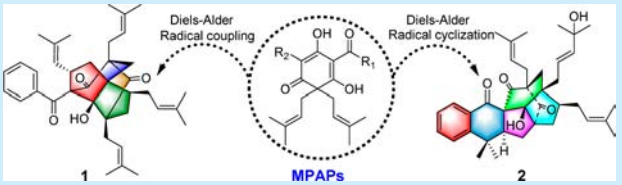
Supporting Information

ABSTRACT: Hyperuralone A (**1**), a polycyclic polyprenylated acylphloroglucinol possessing an unprecedented tetracyclo-[5.3.1.1^{4,9}.0^{4,11}]-dodecane core, was characterized from *Hypericum uralum* together with hyperuralone B (**2**), a congener with another complex caged skeleton. Their structures were determined by extensive spectroscopic analysis and ECD calculations. A plausible biosynthetic pathway of their intriguing architectures via intramolecular Diels−Alder reactions was also proposed. Compound **1** exhibited obviously cytotoxic activities against five human cancer cell lines *in vitro* (IC_{50} 4.6−14.4 μM).



Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a special class of complex natural products that have only been isolated from plants of the family Guttiferae so far.[1] Biogenetically, the acylphloroglucinol cores are presumably derived from a characteristic polyketide-type biosynthesis, and their prenylation is realized through an enzyme-catalyzed addition to afford monocyclic polyprenylated acylphloroglucinols (MPAPs), which may be further cyclized to PPAP-type metabolites with diverse carbon skeletons.[1a,2] The *endo*-bicyclic polyprenylated acylphloroglucinols (*endo*-BPAPs) with a bicyclo[3.3.1]nonane-2,4,9-trione core, as exemplified by hyperforin and garcinol, account for about 2/3 of the reported natural PPAPs, while adamantane-type and *homo*-adamantane PPAPs come second.[1] These kinds of metabolites showed a wide variety of biological activities such as antitumor, antimicrobial, anti-HIV, antioxidant, and antidepressant activities.[1,3,4] In recent years, many novel PPAPs with unique skeletons have been reported, such as garcibracteatone,[5a,b] hypercohin A,[6a] hyphenrone C,[6b] biyouyanagin A,[6c] and ialibinones,[6d] their fascinating chemical structures and intriguing biological activities have attracted increasing attention from phytochemical, organic synthetic, and pharmacological fields.[3]

Hypericum uralum Buch.-Ham. ex D. Don, a perennial shrub mainly distributed in Tibet and northwest of Yunnan, P. R. China, was not phytochemically studied previously.[7] In our systematic study of the PPAPs of *H. uralum*, an unusual PPAP with an unprecedented tetracyclo-[5.3.1.1^{4,9}.0^{4,11}]-dodecane core (hyperuralone A, **1**), was isolated from the aerial parts of this plant (Figure 1), together with hyperuralone B (**2**), the fourth example of the most structurally complex acylphloroglucinols-derived skeleton as exemplified by garcibracteatone.[5b] Biogenetically, it is evident that both hyperuralones A and B could be derived from the same precursor (MPAP) via intramolecular [4 + 2] cycloadditions between geranyl side chains and the acylphloroglucinol core. In this letter, we report their structural elucidation, proposed biosynthetic pathway, and biological evaluation of the new isolates.

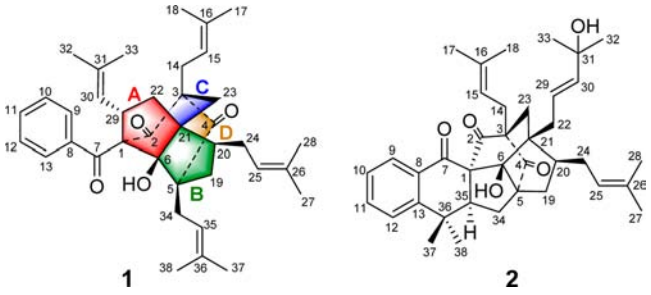


Figure 1. Structures of compounds **1** and **2**.

Hyperuralone A (**1**) was obtained as an optically active colorless oil ($[\alpha]_D^{16}$ + 34.3) and possessed a molecular formula $C_{38}H_{48}O_4$ as established by HR-EI-MS (*m*/*z* 568.3564, M^+) in association with ^1H and ^{13}C NMR data, indicating 15 degrees of unsaturation. The IR spectrum of **1** showed absorption bands due to OH (3440 cm^{-1}), carbonyl groups (1735, 1702, and 1658 cm^{-1}), and aromatic ring (1598 and 1446 cm^{-1}). The ^1H NMR spectrum displayed signals for a monosubstituted benzene ring (δ_H 7.65, 2H, d, *J* = 7.9 Hz; δ_H 7.48, 1H, t, *J* = 7.2 Hz; δ_H 7.35, 2H, dd, *J* = 7.9, 7.2 Hz), four olefinic protons (δ_H 5.44, 1H, t, *J* = 7.2 Hz; δ_H 5.22, 1H, d, *J* = 10.5 Hz; δ_H 5.18, 1H, t, *J* = 7.2 Hz; δ_H 4.99, 1H, t, *J* = 7.2 Hz), and eight methyls (δ_H 1.07−1.76, s) (Table 1).

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Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data of 1 and 2 (δ in ppm, J in Hz)

	1[a]		2[b]	
no.	δ_H	δ_C	δ_H	δ_C
1		76.7		68.3
2		207.1		204.4
3		65.4		62.6
4		211.0		212.9
5		58.4		69.8
6		94.7		92.5
7		205.7		197.5
8		140.9		135.4
9	7.65 (d, 7.9)	130.0	7.63 (d, 7.5)	126.6
10	7.35 (dd, 7.9, 7.2)	128.5	7.38 (t, 7.5)	126.8
11	7.48 (t, 7.2)	132.5	7.59 (t, 7.5)	133.8
12	7.35 (dd, 7.9, 7.2)	128.5	7.43 (d, 7.5)	124.1
13	7.65 (d, 7.9)	130.0		150.5
14	a 2.63 (dd, 7.2, 14.4)	26.4	2.13 (d, 7.2)	25.2
	b 2.23 (m)			
15	5.18 (t, 7.2)	120.1	4.96 (t, 7.1)	119.4
16		135.9		133.2
17	1.76 (s)	26.0	1.57 (s)	25.8
18	1.67 (s)	18.4	1.49 (s)	17.8
19	α 2.31 (dd, 9, 14.4)	48.1	a 1.75 (dd, 11.3,7.9)	32.4
	β 2.24 (m)		b 1.48 (m)	
20	1.71 (m)	46.6	1.81 (m)	55.3
21		60.1		43.8
22	α 1.19 (dd, 11.4, 1.8)	38.7	a 2.94 (dd, 14.5,9.0)	34.0
	β 2.71 (dd, 11.4, 10.8)		b 2.66 (dd, 14.5,4.5)	
23	a 2.20 (br d, 14.4)	42.0	a 1.71, (d, 14.3)	44.6
	b 1.58 (br d, 14.4)		b 1.45 (m)	
24	2.53 (m)	33.7	a 2.37 (m)	32.8
	2.20 (m)		b 2.17, (m)	
25	4.99 (t, 7.2)	125.4	5.01 (t, 6.8)	123.4
26		132.8		131.4
27	1.67 (s)	26.3	1.63 (s)	25.7
28	1.63 (s)	18.2	1.55 (s)	18.1
29	4.02 (ddd, 10.8,10.5,1.8)	52.7	5.52 (m)	121.4
30	5.22 (d, 10.5)	127.0	5.66 (d, 15.4)	142.7
31		135.0		69.2
32	1.07 (s)	17.4	1.14 (s)	30.2
33	1.67 (s)	26.0	1.13 (s)	30.2
34	a 2.47 (dd, 15.0, 8.4)	30.6	α 1.85 (dd, 11.3,7.9)	28.9
	b 2.22 (m)		β 2.08 (dd, 11.3,10.2)	
35	5.44 (t, 7.2)	123.0	2.57 (dd, 10.2, 7.9)	56.1
36		133.5		37.0
37	1.67 (s)	26.1	1.08 (s)	29.4
38	1.63 (s)	18.0	1.24 (s)	27.4

[a]Recorded in CD_3OD. [b]Recorded in DMSO-d_6.

The ^{13}C NMR and DEPT spectra resolved 38 carbon signals (Table 1), and 26 of which could be assigned to a benzoyl, three isoprenyl groups, and an isobutenyl moiety, while 12 other resonances corresponding to seven quaternary carbons (including two ketones and one oxygenated), two methines, and three methylenes were ascribed to the core structure. Analysis of these 12 resonances revealed the characteristic signals of phloroglucinol core including two nonconjugated carbonyls at δ_C 207.1 (C-2) and 211.0 (C-4), one oxygenated quaternary carbon at δ_C 94.7 (C-6), and three quaternary carbons at δ_C 76.7 (C-1), 65.4 (C-3), and 58.4 (C-5). These observations, conjugated with the fact that a number of PPAPs have been isolated from *Hypericum* species,[1] indicated that compound **1** could be ascribed as a PPAP derivative. Moreover, the clear presence of one benzoyl, four double bonds, and another two carbonyls accounted for 11 degrees of unsaturation, thus supporting the identity of **1** as a tetracyclic PPAP-type derivative.

The tetracyclic core structure of **1**, consisting of the 12 carbon signals as mentioned above, was established by comprehensive analysis of 2D NMR spectral data. In the HMBC spectrum, correlations from H-29 (δ_H 4.02) to C-1 (δ_C 76.7), C-21 (δ_C 60.1), and C-22 (δ_C 38.7), from H-30 (δ_H 5.22) to C-1 and C-29 (δ_C 52.7), from H_2-22 (δ_H 2.71 and 1.19) to C-1, C-6 (δ_C 94.7), C-21, C-29, and C-30 (δ_C 127.0), and from H_2-34 (δ_H 2.47 and 2.22) to C-5 (δ_C 58.4), C-6, and C-19 (δ_C 48.1) can all be found (Figure 2). These evidence, conjugated with the ^{1}H−^{1}H COSY

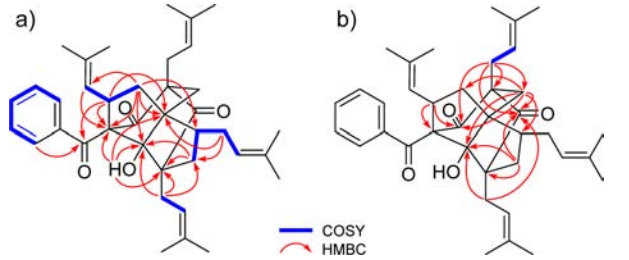

Figure 2. Key HMBC and ^{1}H−^{1}H COSY correlations of **1** (a, correlations of rings A and B; b, correlations of rings C and D).

correlations of H-30/H-29/H_2-22, established the presence of the five-membered ring A (the red ring in Figure 1). In addition, the HMBC correlations from H_2-22 to C-20 (δ_C 46.6), from H_2-19 (δ_H 2.31 and 2.24) to C-5, C-6, C-20, and C-24, and from H_2-24 (δ_H 2.53 and 2.20) to C-20 and C-21, coupling with the spin-coupling system of H_2-19/H-20/H_2-24 observed from the ^{1}H−^{1}H COSY spectrum, defined the five-membered ring B (the green ring in Figure 1).

Apart from the eight carbon signals occupied by rings A and B, only four resonances remained and were assignable to rings C and D. The linkage of C-21/C-23/C-3 unit was supported by HMBC correlations from both H_2-22 and H-20 (δ_H 1.71) to C-23 (δ_C 42.0), from H_2-23 (δ_H 2.20 and 1.58) to C-3 (δ_C 65.4), C-6, C-14 (δ_C 26.4), C-20, C-21, and C-22, and from H_2-14 (δ_H 2.63 and 2.23) to C-3 and C-23. In addition, the HMBC correlations of H-30/C-1, H-29/C-1, and H-29/C-2, conjugated with the obvious HMBC correlations from both H_2-23 and H_2-14 to C-2 and C-3, determined the partial structure of the six-membered ring C (the blue ring in Figure 1). Then, the HMBC correlations of both H_2-19 and H_2-34 with C-4 (δ_C 211.0), C-5, and C-6 and of both H_2-14 and H_2-23 with C-3 and C-4 deduced the linkage of C-3/C-4/C-5 and the formation of the remaining ring D (the brown ring in Figure 1).

Since the complexity and existence of seven quaternary carbons in the tetracyclic core, the NMR spectra in DMSO-d_6 were rerecorded to verify the structure. Most of the 2D NMR spectral signals were identical with those recorded in CD_3OD. Luckily, the intact hydroxyl signal at δ_H 5.15 (OH-6) in the ^{1}H NMR spectrum was observed. Moreover, the HMBC correlations from OH-6 to C-1, C-5, C-6, and C-21 can all be found, which confirmed the core structure furthermore. The locations of side chains of **1** were determined by comprehensive analysis of HSQC and HMBC spectra. Thus, the planar structure of **1** with an unprecedented tetracyclo-[5.3.1.1^{4,9}.0^{4,11}]-dodecane core was defined.

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The relative configuration of **1** was fixed by its rigid skeleton and the NOESY experiment recorded in DMSO-d_6. Obvious NOE correlations of 6-OH/H-29, 6-OH/H-22β, 6-OH/H_2-24, and 6-OH/H_2-34 in the ROESY spectrum showed that they were on the same side with β-orientation (Figure 3). In addition, the

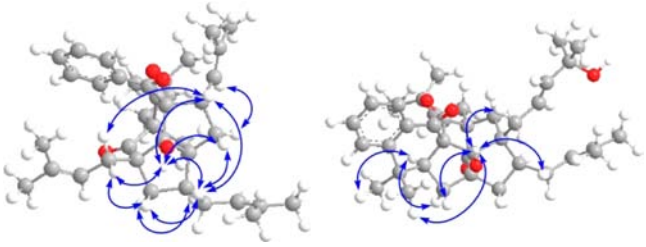

Figure 3. Key ROESY correlations of **1** (left) and **2** (right).

correlations of H-29/H_2-24, H-29/H_2-34, H-22β/H_2-24, H-19β/H_2-24, H-19β/H_2-34, H-22α/H-30, and H-19α/H-20 confirmed the configurations of C-20 and C-29 furthermore.

The molecular formula of hyperuralone B (**2**) was determined to be $C_{38}H_{48}O_5$ on the basis of HR-EI-MS (m/z 584.3510, $[M]^+$), one oxygen atom greater in size than that of **1**. The IR spectrum indicated the presence of hydroxyl group at 3441 cm^{-1}, three ketone functions at 1740, 1710, and 1676 cm^{-1}. The UV absorptions (253 nm) and IR band (763 cm^{-1}) suggested the presence of an *ortho*-disubstituted benzene ring. The ^{13}C and DEPT NMR spectra allowed to number 38 carbons of which eight signals correspond to methyl substituents, six methylenes, ten methines (four aromatic and four olefinic ones), and 14 quaternary carbons (including three keto groups). Careful comparison of the NMR data of **2** with those of garcibracteatone revealed that they were structurally similar except the signal for the methyl at C-21 in garcibracteatone was replaced by a methylene linked with an oxygenated isoprenyl group in **2**.[5] This difference was evidenced by the HMBC correlations from H_2-23 (δ_H 1.71 and 1.45) to C-2 (δ_C 204.4), C-3 (δ_C 62.6), C-4 (δ_C 212.9), C-6 (δ_C 92.5), C-21 (δ_C 43.8), and C-22 (δ_C 34.0) and from H_3-32 (δ_H 1.14) and H_3-33 (δ_H 1.13) to C-30 (δ_C 142.7) and C-31 (δ_C 69.2), coupled with $^1H-^1H$ COSY correlations of H_2-22/H-29/H-30 (Figure 4). The ROESY correlations of 6-OH with H_2-22, H_2-24, H-34β, and H_3-37 and of H-35 with H_3-38 and H-34α suggested that **2** had the same relative configurations as garcibracteatone.

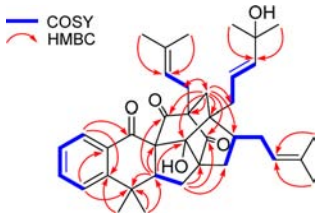

Figure 4. Key HMBC and $^1H-^1H$ COSY correlations of **2**.

The absolute configuration of **1** and **2** was confirmed by comparison of experimental and time-dependent density-functional theory (TDDFT) calculated electronic circular dichroism (ECD) spectra because we failed to obtain any single crystal from X-ray diffraction analysis after trying many methods. ECD calculation using TDDFT, which has demonstrated great success in determining the absolute configurations of chiral molecules,[8] was convenient to be applied. First, conformational analysis was initially carried out using Maestro in Schrödinger 2010 conformational searching, together with the OPLS_2005 molecular mechanics methods. By using the Gaussian09 software package, the selected conformers were included for full geometry optimization at the B3LYP/6-31G** level in the gas phase. Further ECD calculations were performed at the B3LYP-SCRF(PCM)/6-31G**//B3LYP/6-31G** levels in methanol solution, respectively. The calculated weighted ECD spectra of the conformers matched very well with the experimentally observed spectra at the above levels in MeOH (Figure 5). Therefore, the absolute configurations of **1** and **2** were defined to be 1*R*,3*S*,5*R*,7*S*,8*R*,35*R* and 1*S*,3*S*,5*R*,6*S*,20*S*,21*R*,35*S*, respectively.

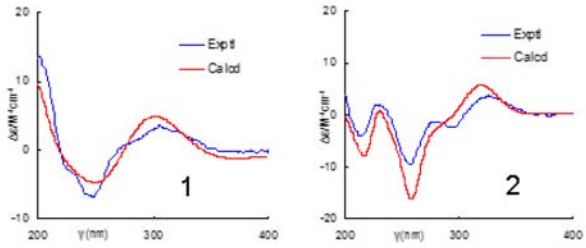

Figure 5. Calculated and experimental ECD spectra of **1** and **2** (red, at the B3LYP-SCRF(PCM)/6-31G**//B3LYP/6-31G** level in MeOH; blue, experimentally observed in MeOH).

Compounds **1** and **2** were tested for their cytotoxic effects against five human cancer cell lines, HL-60, SMMC-7721, A-549, MCF-7, and SW-480 using the MTT method described previously.[9] Compound **1** showed obvious toxicity to the five human cancer cell lines, while compound **2** showed nontoxicity toward these cell lines (Table 2).

Table 2. Cytotoxicity of 1 and 2 (IC_{50}, μM)

	HL-60	SMMC-7721	A-549	MCF-7	SW480
1	7.1	8.1	4.6	14.4	5.6
2	34.8	22.1	>40	>40	10.4
DDP[a]	1.3	13.7	13.4	13.0	12.6

[a]Positive control.

Structurally, compound **1** was elucidated to possess an unprecedented tetracyclo-[5.3.1.$1^{4,9}$.$0^{4,11}$]-dodecane core, while compound **2** was the fourth example of the most structurally complex acylphloroglucinols-derived skeleton as mentioned above. From a biogenetic point of view, both **1** and **2** are presumably derived from the same precursor (**M**), which may be generated through the "mixed" prenylation/polyketide biosynthetic pathway as shown in Scheme 1. An intramolecular Diels–Alder reaction of **M** would form the key intermediate **A**.[5c] Compound **1** was formed via C–C radical coupling to build the tetracyclic ring system, while compound **2** was derived from **A** and underwent radical cyclization (involving carbons C-35 and C-36 on one hand, C-1 and C-13 on the other hand).[5a,b] It is notable that Diels–Alder cycloaddition likely plays an important role in the hypothesized biosynthetic pathway. Recently, sufficient progress has been made for us to ensure the presence of the Diels–Alder reaction in nature.[10] Natural products presumably biosynthesized via a [4 + 2] cycloaddition were frequently encountered, and the Diels–Alder reaction has been postulated as a key step in many biosynthetic conversions.[11] To

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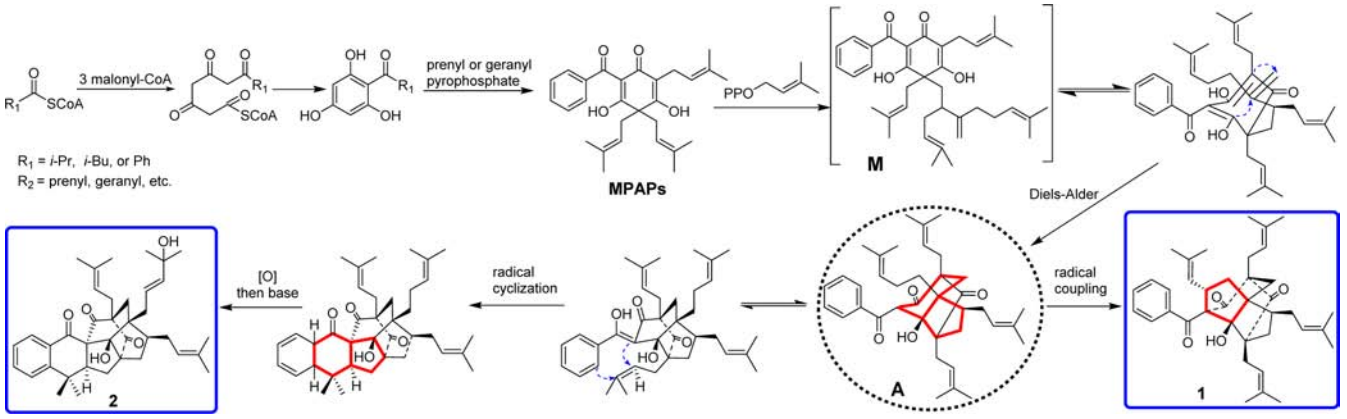
Scheme 1. Plausible Biogenetic Pathway for 1 and 2 (Red, Newly Formed Rings)



date, three natural Diels–Alderases such as solanapyrone synthase, lovastatin nonaketide synthase, and macrophomate synthase have been reported and characterized in the biosynthesis of secondary natural products.[12,13] The rapidly accumulating body of literature in this field suggests that there are enzymes that mediate the Diels–Alder reactions in the biosynthetic pathways of secondary metabolites, and nature is, indeed, able to utilize the Diels–Alder construction to generate a complex array of natural products.[14,15] Then, the existence of abundant double bonds and carbonyl groups in PPAPs may indicate that more acylphloroglucinols derivatives with novel scaffolds can be characterized in the future, especially those from Diels–Alder additions and other cyclizations from PPAPs with known skeletons.

■ ASSOCIATED CONTENT

Supporting Information

Computational details of **1** and **2**, experimental procedures, physical–chemical properties, and MS and NMR spectra for all new compounds. 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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