Cytotoxic Polyprenylated Xanthones from the Resin of *Garcinia hanburyi*

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Twelve new xanthones (**1**−**12**), a pair of new natural products (**13** and **14**), and 18 known related compounds were isolated from the resin of *Garcinia hanburyi*. The structures of **1**−**14** were elucidated by detailed spectroscopic analyses. A cytotoxic assay of the isolated compounds revealed that, with the exception of **2**, these compounds were active against the HeLa tumor cell line.

Gamboge is the dried resin most often exuded from the stems of *Garcinia hanburyi* Hook. f. (Guttiferae), which is found throughout Thailand, Cambodia, India, and southern China. It is used as a dye or folk medicine for an internal purgative and externally infected wounds.[1] Previous phytochemical analyses of *G. hanburyi* led to the isolation of more than 30 caged polyprenylated xanthones.[2−8] In our continuing search for biologically active and structurally unique compounds from medicinal plants, we have chemically investigated the resin of *G. hanburyi*. Twelve new polyprenylated xanthones (**1**−**12**), a pair of new natural products (**13** and **14**), and 18 known xanthones were isolated from the resin, including the known gambogic acid as a major active constituent.[9−12] Herein, we report the isolation and structural elucidation of compounds **1**−**14**, as well as the assessment of their cytotoxicity against HeLa tumor cells.

Results and Discussion

Compound **1** was obtained as a yellow gum. Its molecular formula was determined to be $C_{37}H_{46}O_7$, established by HRESIMS ($[M + Na]^+$ at *m/z* 625.3138, calcd 625.3141). Its ^1H and ^{13}C NMR spectra, in conjunction with the HSQC spectrum, revealed the presence of eight methyl, six methylene, eight methine, and 15 quaternary carbons. The NMR data of **1** (Tables 1 and 2) did not indicate much similarity to those of the caged pentaprenylxanthonoids such as gambogic acid ($C_{38}H_{44}O_8$), which was previously isolated from *G. hanburyi*.[2] The presence of a ketal carbon (δ_C 107.6) was similar to that of gaudispirolactone, a highly rearranged tetraprenylxanthonoid isolated from the bark of *Garcinia gaudichaudii*.[13] The aforementioned features suggested that **1** was a degraded and rearranged pentaprenylxanthonoid. Interpretation of the $^1H-^1H$ COSY and HMBC spectra afforded two subunits (**a**, **b**) (Figure 1). In the partial structure **a**, the HMBC correlations between a hydrogen-bonded hydroxy proton (δ_H 12.21) and C-1, C-2, and C-9a and between a hydroxy proton (δ_H 6.50) and C-2, C-3, and C-4 indicated the location of the two hydroxy groups at C-1 and C-3. A geranyl and a prenyl group were assigned to C-2 and C-4, respectively, which was confirmed by the HMBC correlations of H-11/C-1, C-2, and C-3 and H-21/C-3, C-4, and C-4a. Thus, the structure of subunit **a** was established, which was identical to the partial structure of gambogenic acid.[3] Partial structure **b** was determined by the $^1H-^1H$ COSY and HMBC data. In the HMBC spectrum, the correlations of H-27/C-26, C-28, and C-29, H-28/C-26 and C-27, and H-31/C-28, C-29, and C-30 suggested the presence of an α,β-unsaturated δ-lactone moiety. The $^1H-^1H$ COSY experiment indicated a contiguous spin system comprising H-8a/H-8/H-7/H-6/H-5. In conjunction with the HMBC correlations of H-5/C-8a and C-10a, it showed the presence of a six-membered ring. In addition, the HMBC correlations of H-5/C-10a, C-26, C-32, C-33, and C-34, H-33/C-32, and H-34/C-32 suggested the presence of a five-membered ring, hence completing the partial structure **b**, which was similar to that of gaudispirolactone.[13] The only difference between these two partial structures was that the α,β-unsaturated γ-lactone moiety in gaudispirolactone was replaced by a *cis*-double bond in **1**. The pentaprenylxanthonoid structure was finally established by combining the two partial structures. The HMBC correlation from H-8 to C-9 permitted the linkage of subunits **a** and **b**. Scheme 1 outlined a postulated biosynthesis pathway of **1**. The relative configuration of **1** was assessed by analyzing the ROESY spectrum and a computer-generated 3D structure, which was obtained by Chem 3D Ultra V 9.0, with MM2 forcefield calculations for energy minimization (Figure 2). Key ROESY correlations were observed between H-8a and H-27, H-33, and between H-5 and H-6a, H-34. Thus, the relative configuration of **1** was elucidated as shown in Figure 2, and the structure was established as gambospiroene.

Compound **2** was isolated as a yellow gum. Its molecular formula, $C_{34}H_{40}O_8$, was established on the basis of HREIMS ($[M]^+$ at *m/z* 576.2708, cald 576.2723), with 15 degrees of unsaturation. The UV absorption bands at λ_{max} 366, 314, 275, and 266 nm were similar to those of moreollic acid (**2a**).[3] The ^1H NMR spectrum of **2** (Table 1) revealed the presence of a hydrogen-bonded hydroxy group [δ_H 11.96 (1H, s, 1-OH)], two prenyl olefinic protons [δ_H 5.02 (1H, t, $J = 7.2$ Hz), δ_H 6.45 (1H, t, $J = 7.2$ Hz)], a *cis*-double bond [δ_H 5.50 (1H, d, $J = 10.0$ Hz), δ_H 6.61(1H, d, $J = 10.0$ Hz)], a methoxy group [δ_H 3.67 (3H, s)], and seven methyl groups [δ_H 1.13, 1.34, 1.39, 1.45, 1.64, 1.75, 1.93 (each 3H, s)]. The aforementioned features suggested that **2** had a caged polyprenylated xanthone moiety without a C_8-C_{8a} double bond.[4] In the ^{13}C NMR spectrum, the upfield shift of C-24 (−3.1 ppm), compared to **2a**, and the HMBC correlations of *O*-methyl protons with C-24 suggested the location of a methoxy group at C-24. Additionally, the ^{13}C NMR data of **2** showed one more CH_2 and one less CH than in **2a**. This, in conjunction with the HMBC correlation of H_2-8/C-26, supported the presence of a methylene at C-8. From the ROESY cross-peak between H-22 (δ_H 6.45) and H-25 (δ_H 1.93), the olefinic bond of this prenyl group had a *Z*-configuration. Therefore, the structure of **2** was established as methyl 8,8a-dihydromorellate.

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Table 1. ^{1}H NMR Data for Compounds **1**−**12**[a]

position	1	2	3	4	5	6	7	8	9	10	11	12
1-OH	12.21 s	11.96 s	12.76 s	13.31 s	12.58 s	12.67 br s	12.69 s	11.87 br s	11.88 br s	12.78 s	12.83 s	12.63 br s
2			6.10 s									
3-OH	6.50 s								6.51 brs			
5	3.25 d (8.8)											
6	a 2.45 m b 2.13 m											
7	5.99 m	2.42 m	3.49 dd (4.4, 6.8)	3.47 dd (4.4, 6.4)				2.66 m	2.67 m	3.50 m	3.50 m	
8	5.56 m	1.71, 2.84 m	7.45 d (7.2)	7.55 d (7.2)	7.56 s	7.61 s	7.63 s	4.80 d (3.6)	4.77 d (4.0)	7.50 d (7.2)	7.49 d (6.8)	7.47 s
8a	3.17[b]	3.22[b]						3.22[b]	3.16[b]			
11	3.30[b]	6.61 d (10)	4.59 d (6.8)	3.18 m	3.42 m	6.56 d (10.4)	6.56 d (10.4)	6.58 d (9.6)	3.20[b]	6.63 d (10)	3.05, 3.22 m	6.64 d (10)
12	5.18 t (7.2)	5.50 d (10)	5.44 dt (1.2, 7.2)	6.34 br s	1.73, 1.78[b]	5.37 d (10.4)	5.40 d (10.4)	5.50 d (9.6)	5.18 t (6.8)	5.32 d (10)	5.15 t (7.2)	5.53 d (10)
14	2.05 m	1.39 s	2.09 m	2.14 m	1.54, 1.90 m	1.56, 1.72 m	1.64, 1.77 m	1.38 s	2.00 m	2.26, 2.48 m	1.92 m	1.44 s
15	2.08 m	1.45 s	2.11 m	1.38, 1.88 m	1.26, 1.38 m	2.00 m	2.07 m	1.44 s	2.04 m	5.63[b]	2.00 m	1.44 s
16	5.04 t (6.8)	3.16, 3.30 m	5.09 dt (1.2, 7.2)	1.62 m	2.12 m	5.03[b]	5.09 t (7.2)	3.15, 3.25 m	5.02 t (7.0)	5.63[b]	5.05 t (6.8)	3.30 m
17		5.02 t (7.2)						4.97 t (6.8)				5.20 m
18	1.66 s		1.68 s	1.43 s	4.20, 4.55 s	1.64 s	1.66 s		1.62 s	1.28 s	1.64 s	
19	1.58 s	1.75 s	1.61 s	1.08 s	1.85 s	1.53 s	1.57 s	1.73 s	1.55 s	1.22 s	1.55 s	1.76 s
20	1.78 s	1.64 s	1.72 s	1.65 s	1.33 s	1.36 s	1.32 s	1.62 s	1.75 s	1.44 s	1.69 s	1.67 s
21	3.20, 3.33 m	3.18, 3.25 m	3.33 m	3.10, 3.30 m	3.11, 3.26 m	3.11, 3.28 m	3.12, 3.30 m	3.20 m	3.26 m	3.26 m	2.93, 3.10 m	2.64 m
22	5.16 t (7.2)	6.45 t (7.2)	5.20 dt (1.2, 7.2)	4.97 m	5.05 t (6.8)	5.00[b]	5.00 t (6.4)	6.58 t (6.8)	5.08 t (6.8)	5.09 t (6.4)	4.55 t (8.8)	4.78 m
24	1.77 s		1.72 s	1.71 s	1.72 s	1.71 s	1.72 s		1.76 s	1.75 s	1.14 s	1.06 s
25	1.69 s	1.93 s	1.66 s	1.60 s	1.64 s	1.61 s	1.62 s	1.93 s	1.70 s	1.65 s	1.23 s	3.66[b]
26		a 1.96 m	2.58 d (7.6)	2.85, 3.00 m	3.00 d (7.6)	3.00 d (7.2)	2.98 m	a 1.90[b]	3.10, 3.30 m	2.92, 3.20 m	2.82, 3.42 m	a 2.37 d (13.2)
		b 1.54 m						b 1.38[b]				b 1.62[b]
27	2.54 dd (2.0, 4.0)	2.58 d (8.4)	4.40 dt (1.2, 7.2)	6.12 t (6.8)	6.04 t (7.2)	6.13 t (7.2)	6.17 t (7.2)	2.43 d (8.4)	6.61 t (6.8)	5.72 t (7.2)	5.67 m	2.58 d (9.6)
28	6.18 m											
29		1.13 s	0.99 s					1.12 s				1.31 s
30		1.34 s	1.37 s	1.71 s	1.72 s	1.73 s	1.74 s	1.33 s	1.89 s	1.69 s	1.72 s	1.70 s
31a	1.70 s		2.34 dd (4.4, 13.2)	2.30 dd (4.8, 13.6)	2.31 d (12.8)	2.31 d (12.8)	2.30 d (12.8)		1.86[b]	2.34 dd (4.8, 13.6)	2.31 dd (4.2, 13.2)	
31b			1.35 dd (9.6, 13.2)	1.37 dd (9.2, 13.2)	1.66[b]	1.66[b]	1.66[b]		1.34[b]	1.38 dd (9.2, 13.6)	1.37 dd (10, 13.2)	
32			2.49 d (9.2)	2.49 d (9.6)	2.60 d (9.2)	2.58 d (9.2)	2.57 d (9.2)		2.39 d (8.0)	2.50 d (10)	2.45 d (9.2)	
33	1.13 s											
34	1.45 s		1.28 s	1.28 s	1.31 s	1.30 s	1.30 s		1.09 s	1.28 s	1.29 s	
35			1.71 s	1.69 s	1.69 s	1.67 s	1.68 s		1.30 s	1.68 s	1.66 s	
7-OCH_3					3.63 s	3.62 s	3.62 s					3.63 s
24-OCH3		3.67 s										

[a] Recorded at 400 MHz in $CDCl_3$. δ_H in ppm, J in Hz. [b] J were omitted, as the signals were overlapped.

Table 2. ^{13}C NMR Data for Compounds **1**−**12**[a]

position	**1**	**2**	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	11	12
1	159.3 (qC)	156.0 (qC)	163.6 (qC)	161.5 (qC)	160.8 (qC)	157.4 (qC)	157.5 (qC)	156.4 (qC)	159.1 (qC)	157.4 (qC)	163.1 (qC)	157.4 (qC)
2	107.3 (qC)	102.3 (qC)	93.5 (CH)	105.3 (qC)	104.2 (qC)	102.7 (qC)	102.9 (qC)	103.0 (qC)	108.0 (qC)	102.0 (qC)	105.1 (qC)	103.1 (qC)
3	163.7 (qC)	160.5 (qC)	165.7 (qC)	162.3 (qC)	164.6 (qC)	161.6 (qC)	161.5 (qC)	161.1 (qC)	163.1 (qC)	161.3 (qC)	167.4 (qC)	161.2 (qC)
4	106.6 (qC)	108.8 (qC)	108.8 (qC)	108.1 (qC)	106.3 (qC)	107.6 (qC)	107.8 (qC)	109.0 (qC)	106.1 (qC)	107.3 (qC)	103.8 (qC)	108.5 (qC)
4a	155.3 (qC)	155.8 (qC)	157.3 (qC)	155.0 (qC)	155.1 (qC)	157.1 (qC)	157.1 (qC)	155.7 (qC)	153.8 (qC)	157.7 (qC)	152.9 (qC)	157.5 (qC)
5	44.3 (CH)	86.5 (qC)	84.7 (qC)	84.0 (qC)	83.8 (qC)	83.4 (qC)	83.3 (qC)	86.5 (qC)	86.3 (qC)	83.7 (qC)	84.1 (qC)	83.8 (qC)
6	21.2 (CH_2)	210.7 (qC)	203.6 (qC)	203.5 (qC)	202.2 (qC)	201.9 (qC)	201.9 (qC)	209.7 (qC)	210.0 (qC)	203.8 (qC)	203.0 (qC)	201.6 (qC)
7	128.4 (CH)	38.6 (CH)	46.9 (CH)	46.7 (CH)	84.6 (qC)	84.7 (qC)	84.7 (qC)	46.6 (CH)	46.3 (CH)	47.1 (CH)	46.8 (CH)	84.9 (qC)
8	121.4 (CH)	21.8 (CH_2)	133.8 (CH)	135.0 (CH)	134.5 (CH)	135.4 (CH)	135.6 (CH)	65.6 (CH)	65.4 (CH)	134.7 (CH)	134.4 (CH)	134.7 (CH)
8a	44.6 (CH)	39.1 (CH)	133.8 (qC)	133.5 (qC)	132.3 (qC)	131.7 (qC)	131.5 (qC)	50.0 (CH)	49.7 (CH)	133.7 (qC)	133.7 (qC)	132.2 (qC)
9	195.5 (qC)	195.6 (qC)	179.6 (qC)	178.9 (qC)	177.8 (qC)	178.1 (qC)	178.2 (qC)	194.1 (qC)	194.0 (qC)	179.0 (qC)	178.1 (qC)	179.6 (qC)
9a	101.3 (qC)	102.8 (qC)	100.7 (qC)	100.2 (qC)	99.6 (qC)	100.4 (qC)	100.6 (qC)	101.8 (qC)	101.8 (qC)	100.5 (qC)	100.7 (qC)	100.8 (qC)
10a	83.7 (qC)	88.7 (qC)	90.3 (qC)	90.4 (qC)	89.1 (qC)	89.6 (qC)	89.7 (qC)	88.3 (qC)	88.2 (qC)	90.6 (qC)	90.0 (qC)	89.2 (qC)
11	21.1 (CH_2)	115.4 (CH)	65.7 (CH_2)	32.8 (CH)	28.8 (CH)	115.7 (CH)	115.8 (CH)	115.3 (CH)	21.0 (CH_2)	116.0 (CH)	21.2 (CH_2)	115.4 (CH)
12	121.4 (CH)	126.2 (CH)	118.6 (CH)	123.4 (CH)	36.4 (CH_2)	124.5 (CH)	124.8 (CH)	126.3 (CH)	121.5 (CH)	123.3 (CH)	121.5 (CH)	126.4 (CH)
13	138.7 (qC)	78.3 (qC)	141.8 (qC)	133.7 (qC)	77.2 (qC)	81.4 (qC)	81.2 (qC)	78.4 (qC)	137.1 (qC)	81.2 (qC)	135.4 (qC)	78.8 (qC)
14	39.7 (CH_2)	28.2 (CH_3)	39.4 (CH_2)	31.1 (CH_2)	39.2 (CH_2)	41.9 (CH_2)	41.6 (CH_2)	28.2 (CH_3)	39.6 (CH_2)	45.0 (CH_2)	39.7 (CH_2)	28.3 (CH_3)
15	26.4 (CH_2)	28.5 (CH_3)	26.2 (CH_2)	24.8 (CH_2)	22.7 (CH_2)	22.7 (CH_2)	22.7 (CH_2)	28.5 (CH_3)	26.3 (CH_2)	121.1 (CH)	26.7 (CH_2)	28.3 (CH_3)
16	123.8 (CH)	21.5 (CH_2)	123.6 (CH)	45.0 (CH)	48.0 (CH)	123.7 (CH)	123.8 (CH)	21.5 (CH_2)	123.9 (CH)	141.4 (CH)	124.2 (CH)	21.6 (CH_2)
17	131.9 (qC)	122.7 (CH)	131.9 (qC)	80.0 (qC)	147.8 (qC)	131.8 (qC)	132.0 (qC)	122.6 (CH)	131.4 (qC)	71.8 (qC)	131.3 (qC)	121.8 (CH)
18	25.7 (CH_3)	131.0 (qC)	25.7 (CH_3)	27.4 (CH_3)	108.6 (CH_2)	25.6 (CH_3)	25.6 (CH_3)	131.0 (qC)	25.5 (CH_3)	30.1 (CH_3)	25.7 (CH_3)	132.0 (qC)
19	17.7 (CH_3)	18.0 (CH_3)	17.7 (CH_3)	19.9 (CH_3)	23.0 (CH_3)	17.6 (CH_3)	17.6 (CH_3)	18.1 (CH_3)	17.5 (CH_3)	29.1 (CH_3)	17.6 (CH_3)	18.2 (CH_3)
20	16.2 (CH_3)	25.6 (CH_3)	16.7 (CH_3)	23.3 (CH_3)	28.4 (CH_3)	27.7 (CH_3)	26.9 (CH_3)	25.6 (CH_3)	16.0 (CH_3)	28.7 (CH_3)	16.1 (CH_3)	25.8 (CH_3)
21	21.8 (CH_2)	28.1 (CH_2)	21.8 (CH_2)	21.8 (CH_2)	21.8 (CH_2)	21.5 (CH_2)	21.6 (CH_2)	27.9 (CH_2)	21.8 (CH_2)	21.7 (CH_2)	26.8 (CH_2)	28.3 (CH_2)
22	121.7 (CH)	137.4 (CH)	122.2 (CH)	122.5 (CH)	122.2 (CH)	122.0 (CH)	122.0 (CH)	139.7 (CH)	121.6 (CH)	122.3 (CH)	91.3 (CH)	118.0 (CH)
23	133.9 (qC)	127.5 (qC)	131.8 (qC)	131.1 (qC)	131.2 (qC)	131.6 (qC)	131.6 (qC)	127.0 (qC)	135.2 (qC)	131.2 (qC)	71.6 (qC)	138.3 (qC)
24	17.9 (CH_3)	168.2 (qC)	18.1 (CH_3)	18.1 (CH_3)	18.1 (CH_3)	18.0 (CH_3)	18.1 (CH_3)	172.9 (qC)	17.8 (CH_3)	18.2 (CH_3)	24.2 (CH_3)	12.6 (CH_3)
25	25.8 (CH_3)	20.7 (CH_3)	25.8 (CH_3)	25.8 (CH_3)	25.8 (CH_3)	25.6 (CH_3)	25.7 (CH_3)	20.5 (CH_3)	25.6 (CH_3)	25.8 (CH_3)	25.8 (CH_3)	68.0 (CH_2)
26	107.6 (qC)	23.5 (CH_2)	28.8 (CH_2)	29.3 (CH_2)	29.1 (CH_2)	29.1 (CH_2)	29.2 (CH_2)	20.2 (CH_2)	27.6 (CH_2)	29.7 (CH_2)	29.6 (CH_2)	30.1 (CH_2)
27	29.6 (CH_2)	44.4 (CH)	117.9 (CH)	137.2 (CH)	137.9 (CH)	138.4 (CH)	137.9 (CH)	42.8 (CH)	140.5 (CH)	136.2 (CH)	137.5 (CH)	49.7 (CH)
28	135.2 (CH)	82.2 (qC)	135.0 (qC)	127.6 (qC)	127.9 (qC)	127.6 (qC)	127.7 (qC)	82.2 (qC)	126.1 (qC)	128.7 (qC)	129.1 (qC)	84.2 (qC)
29	127.6 (qC)	27.3 (CH_3)	16.7 (CH_3)	170.8 (qC)	171.2 (qC)	171.7 (qC)	171.1 (qC)	27.1 (CH_3)	172.6 (qC)	168.8 (qC)	171.8 (qC)	29.0 (CH_3)
30	164.2 (qC)	29.7 (CH_3)	25.5 (CH_3)	20.8 (CH_3)	20.7 (CH_3)	20.7 (CH_3)	20.7 (CH_3)	29.7 (CH_3)	20.4 (CH_3)	20.9 (CH_3)	20.6 (CH_3)	30.2 (CH_3)
31	16.5 (CH_3)		25.5 (CH_2)	25.2 (CH_2)	30.2 (CH_2)	30.2 (CH_2)	30.4 (CH_2)		20.0 (CH_2)	25.3 (CH_2)	25.0 (CH_2)	
32	82.6 (qC)		49.2 (CH)	48.9 (CH)	49.4 (CH)	49.4 (CH)	49.5 (CH)		42.6 (CH)	48.9 (CH)	48.7 (CH)	
33	24.1 (CH_3)		83.2 (qC)	83.8 (qC)	84.3 (qC)	84.2 (qC)	84.2 (qC)		82.0 (qC)	83.8 (qC)	84.0 (qC)	
34	31.6 (CH_3)		29.1 (CH_3)	28.8 (CH_3)	28.8 (CH_3)	28.8 (CH_3)	28.7 (CH_3)		27.0 (CH_3)	29.0 (CH_3)	28.9 (CH_3)	
35			30.1 (CH_3)	29.8 (CH_3)	30.0 (CH_3)	29.9 (CH_3)	30.0 (CH_3)		29.5 (CH_3)	30.0 (CH_3)	30.0 (CH_3)	
7-OCH_3					54.1	54.1	54.1					54.0
24-OCH_3		51.3										

[a] Recorded at 100 MHz in $CDCl_3$.

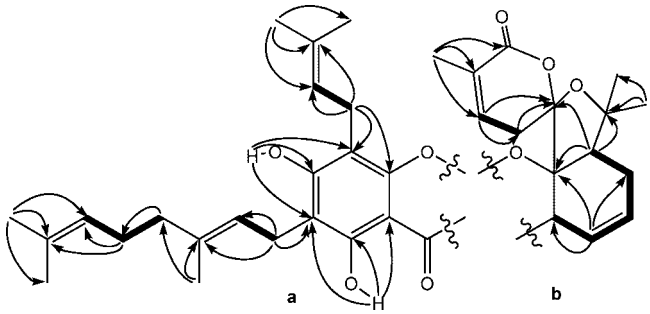


Figure 1. Key COSY (bold lines) and HMBC (H→C) of fragments of **1**.

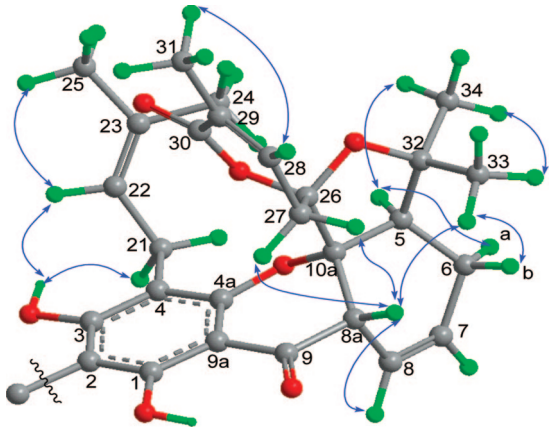


Figure 2. Key ROESY (H↔H) correlations of **1**.

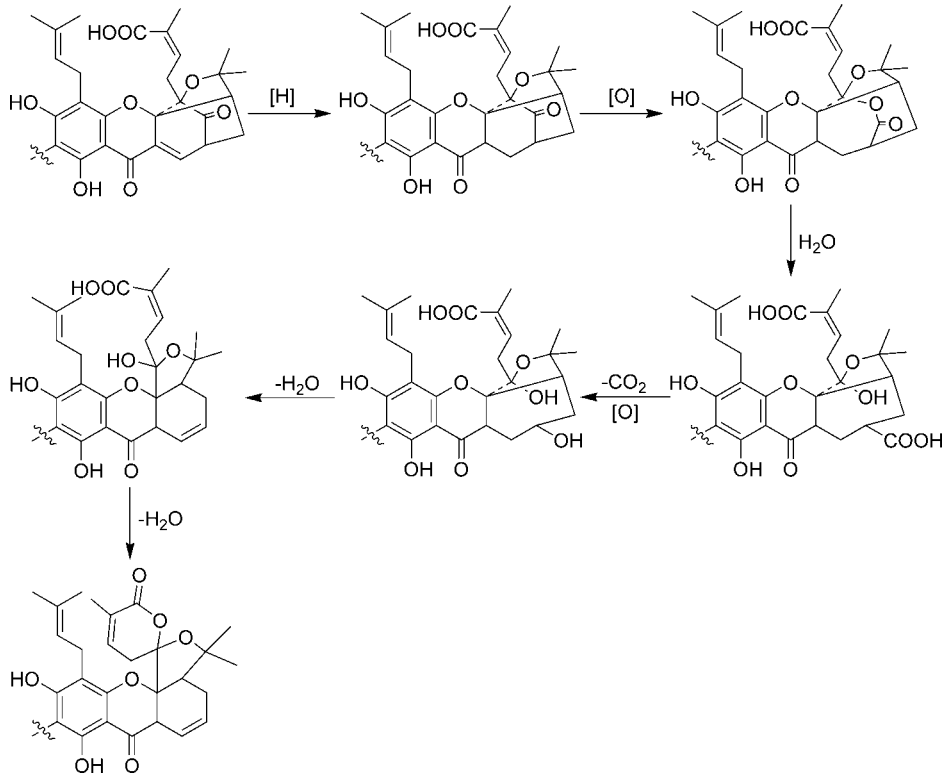
Compound **3** was obtained as a yellow gum. The HREIMS established the molecular formula as $C_{38}H_{48}O_6$ ([M]$^+$ at *m*/*z* 600.3464, calcd 600.3451), possessing 15 degrees of unsaturation. The ^{1}H NMR spectrum of **3** (Table 1) revealed the presence of one hydrogen-bonded hydroxy group [δ_H 12.76 (1H, s, 1-OH)], four prenyl olefinic protons [δ_H 4.40 (1H, dt, J = 1.2, 7.2 Hz), 5.09 (1H, dt, J = 1.2, 7.2 Hz), 5.20 (1H, dt, J = 1.2, 7.2 Hz), 5.44 (1H, dt, J = 1.2, 7.2 Hz)], an olefinic proton [δ_H 7.45 (1H, d, J = 7.2 Hz)], an aromatic proton [δ_H 6.10 (1H, s)], and nine methyl groups [δ_H 0.99, 1.28, 1.37, 1.61, 1.66, 1.68, 1.71, 1.72, 1.72 (each 3H, s)]. Comparison of the NMR data of **3** and forbesione (**3a**) revealed the only difference was that the hydroxy group at C-3 in **3a** was replaced by a 3-*O*-geranyl group in **3**,[14] which could be confirmed by the HMBC correlations of H-11/C-3, C-12, and C-13 and the ROESY correlations of H-2/H-11. Thus, compound **3** was assigned as 3-*O*-geranylforbesione.

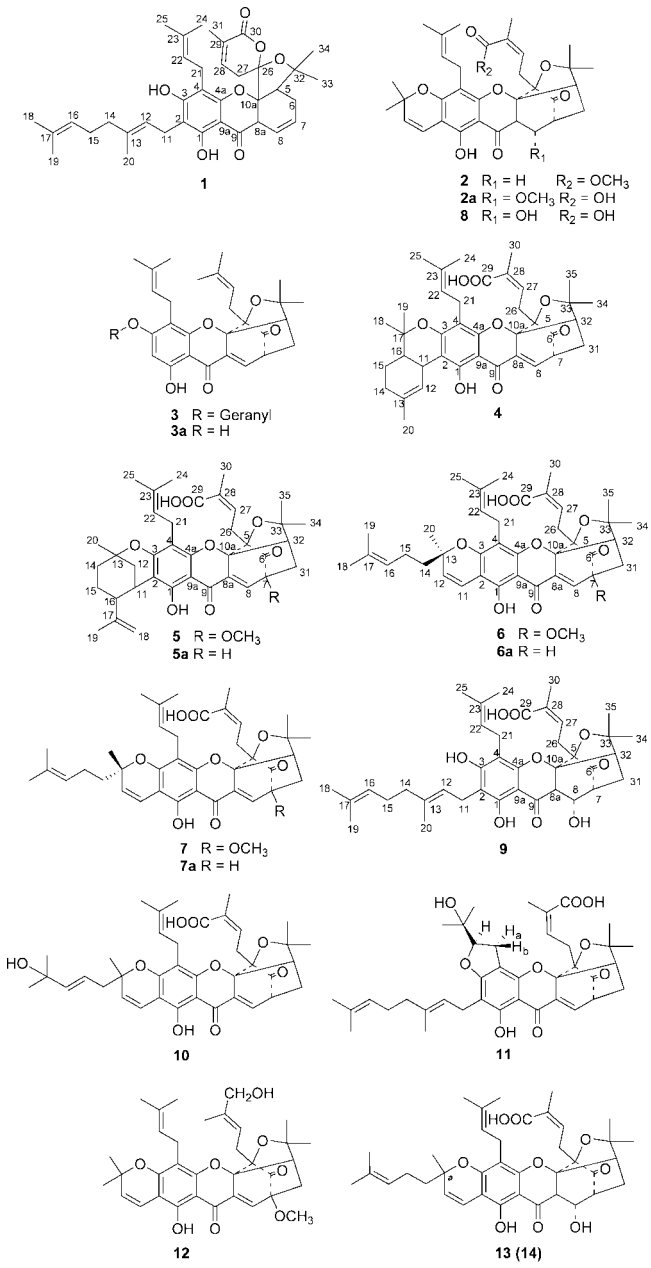
Compound **4** was isolated as a yellow gum. Its molecular formula of $C_{38}H_{44}O_8$ was established from HREIMS ([M]$^+$ at *m*/*z* 628.3082, calcd 628.3036), with 17 degrees of unsaturation. Comparison of its NMR spectra (Tables 1 and 2) with those of morellic acid[15] showed the presence of a 1-methylcyclohexene ring fused with dimethylpyran ring[16] via C-11 (δ_C 32.8) and C-16 (δ_C 45.0) and the absence of the C_{11}/C_{16} double bond in **4**. The HMBC correlations of H-12/C-2, C-11, C-14, C-16, and C-20 and H-15/C-11 and C-16 confirmed the fusion of the two rings. The ROESY correlations of H-11/H-16 suggested the *cis* relative configuration of these two protons. The structure of **4** was thus elucidated as gambogefic acid.

Compound **5** was obtained as yellow needles. The molecular formula was assigned as $C_{39}H_{46}O_9$ by HREIMS ([M]$^+$ at *m*/*z* 658.3147, cald 658.3142), 30 mass units more than that of gambogellic acid (**5a**).[3] The ^{1}H and ^{13}C NMR data (Tables 1 and 2) of **5** were compared to those of **5a**. It was observed that the H-7 signal at δ 3.46 (dd, J = 4.6, 6.9 Hz) of **5a** was replaced by a methoxyl singlet at δ 3.63 in **5**. The attachment of a methoxy group to C-7 was indicated by the HMBC correlations from its protons to C-7. The olefinic proton doublet at δ 7.49 [d, J = 6.9 Hz, (H-8)] was also replaced by a singlet at δ 7.56 since it no longer has a coupling partner on C-7. Thus, the planar structure of **5** was established as 7-methoxygambogellic acid.

Compounds **6** and **7** were isolated as a yellow gum and gave the same molecular formula $C_{39}H_{46}O_9$ by their HREIMS ([M]$^+$ at

Scheme 1. Postulated Biosynthetic Pathway Leading to **1**





[a] The only difference of the two compounds was the configuration at C-13

m/z 658.3133 and 658.3135, cald 658.3142). Both compounds displayed similar NMR features (Tables 1 and 2) and the same fragmentation patterns in the EIMS, suggesting that **6** and **7** were isomers. The UV absorption bands at λ_{max} 365 and 290 nm were similar to those of *R*-gambogic acid (**6a**) and *S*-gambogic acid (**7a**).[17] Spectroscopic analyses revealed that they were 7-methoxylated derivatives of **6a** and **7a**. The HMBC correlations from the methoxy group to C-7 confirmed the assignment. In the previous report, the single crystal of **6a** had been obtained from recrystallization of the pyridine salt of gambogic acid, and its stereochemistry was then determined by X-ray crystallographic analysis.[18] According to the literature, the methoxy group substitution at C-7 only changed the chemical shifts and peak patterns of the neighboring atoms, such as desoxymorellin[19] and 7-methoxydesoxymorellin,[7] forbesione,[14] and gaudichaudione H,[20] as well as gambogellic acid[3] and **5**. Therefore, the configurations at C-13 in **6** and **7** were determined as *R* and *S*, respectively, by comparing the NMR spectroscopic patterns with those of **6a** and **7a**.[17] On the basis of the above data, the structures of **6a** and **7a** were assigned as 7-methoxygambogic acid and 7-methoxyepigambogic acid, respectively.

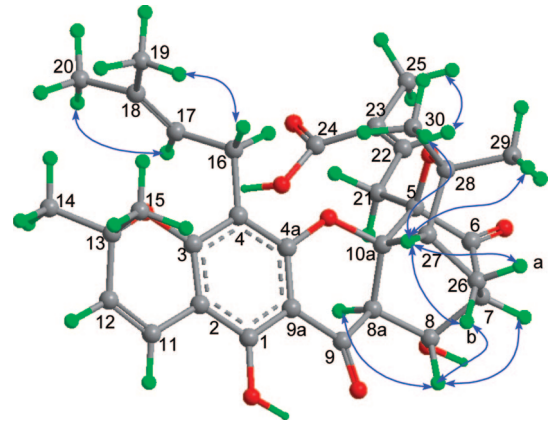


Figure 3. Key ROESY (H↔H) correlations of **8**.

Compound **8** was isolated as a yellow gum. Its molecular formula was established as $C_{33}H_{38}O_9$ on the basis of HREIMS at *m/z* 578.2523 ([M]$^+$, calcd 578.2516), 18 mass units more than that of morellic acid.[15] The UV absorption bands at λ_{max} 364, 316, 276, and 266 nm were similar to those of **2a**.[3] Analysis of the NMR data (Tables 1 and 2) of **8** and **2a** showed that these two compounds are similar except for the presence of a hydroxy group at C-8 in **8** instead of a methoxy group in **2a**.[3] The relative configuration of **8** was assigned the same as that of **2a** by comparing their NMR data and the ROESY correlations of H-8/H-7, H-8/H-8a, and H-8/H-26b (Figure 3). Thus, the structure of **8** was established as 8,8a-dihydro-8-hydroxymorellic acid.

Compound **9**, a yellow gum, was assigned a molecular formula of $C_{38}H_{48}O_9$ from its HREIMS ([M]$^+$ at *m/z* 648.3323, calcd 648.3298), 18 mass units more than that of gambogenic acid.[3] Analysis of its 1D and 2D NMR spectra showed that the only difference between **9** and gambogenic acid was the presence of a hydroxy group at C-8 in **9**. ROESY correlations of H-8/H-7, H-8/H-8a, and H-8/H-31b revealed that **9** has the same relative configuration as that of **2a**. Therefore, the structure of **9** was assigned as 8,8a-dihydro-8-hydroxygambogenic acid.

Compound **10** had a molecular formula of $C_{38}H_{44}O_9$, established by HREIMS ([M]$^+$ at *m/z* 644.2965, calcd 644.2985), 16 mass units more than that of gambogic acid.[17] Detailed analysis of the NMR spectra of **10** and gambogic acid showed the presence of 3-hydroxy-3-methlbut-1-enyl instead of 3-methylbut-2-enyl group substitution at C-14, which was confirmed by the HMBC correlations of H-14/C-15 and C-16, H-16/C-17, H-18/C-16 and C-17, and H-19/C-16 and C-17. The configuration of the C_{15}/C_{16} double bond was not clear owing to the overlapped signals of H-15 and H-16. Consequently, compound **10** was defined as oxygambogic acid.

Compound **11** exhibited a molecular formula of $C_{38}H_{46}O_9$, determined by HREIMS, which was 16 mass units more than that of gambogenic acid, implying one more oxygen atom in **11**. The ^{1}H NMR, ^{13}C NMR, HMBC, and ROESY spectra revealed the presence of one 2-(2-hydroxypropyl)dihydrofuran ring [δ_H 2.93 (dd, J = 7.6, 15.2 Hz, H_b-21), 3.10 (dd, J = 10, 15.2 Hz, H_a-21), 4.55 (t, J = 8.8 Hz, H-22), 1.14 (s, H_3-24), and 1.23 (s, H_3-25)] attached to C-3 and C-4.[21] The HMBC correlations from H-21 to C-3, C-4, C-4a, and C-22 and from H-24, H-25 to C-22 and C-23 supported the structure assignment (Tables 1 and 2). The relative configuration at C-22 was assigned the same as that of cantleyanone B by the ROESY correlations of H-21a/H-22, H-21a/H-30, H-21b/H-24, H-21b/H-25, and H-21b/H-35.[21] Compound **11** was named gambogenific acid.

Compound **12** exhibited a molecular formula of $C_{34}H_{40}O_8$ by HREIMS ([M]$^+$ ion at *m/z* 576.2707, calcd 576.2723), 30 mass units more than that of isomorellinol.[2] Spectroscopic analyses revealed that the only difference between **12** and isomorellinol was

an additional methoxy group located at C-7 in **12**. Therefore, compound **12** was identified as 7-methoxyisomorellinol.

Compounds **13** and **14** gave the same molecular formula, $C_{38}H_{46}O_9$, which was established by their HREIMS, showing 18 mass units more than that of gambogic acid.[17] Both compounds displayed similar NMR spectroscopic features and the same fragmentation patterns in the EIMS, suggesting that **13** and **14** were isomers. The UV absorption bands of **13** and **14** were similar to those of **8.** Spectroscopic analyses revealed that they were 8-hydroxylated derivatives of gambogic acid. Thus, compounds **13** and **14** were established as 8,8a-dihydro-8-hydroxygambogic acid and its isomer, respectively. However, the configuration of C-13 in **13** and **14** has not been identified yet.

The structures of known compounds were identified as desoxymorellin,[19] desoxygambogenin,[3] gambogin and its diastereoisomer,[3] isomorellin,[3] isogambogenin,[3] hanburin,[3] gambogellic acid (**5a**),[3] gambogenic acid,[3] morellic acid,[15] gambogic acid (**6a**),[17] epigambogic acid (**7a**),[17] isogambogic acid,[2] epiisogambogic acid,[2] isomorellinol,[2] gaudichaudic acid,[5] isogambogenic acid,[5] and isomorellic acid,[15] respectively, by comparison of their spectroscopic data with those of related literatures.

All isolated compounds were evaluated for their cytotoxicity against HeLa human cervical carcinoma cells, with adriamycin as the positive control. All but compound **2** displayed potent cytotoxicity. The IC_{50} values of the new compounds (**1**−**14**) and *R*-gambogic acid are given in Table 3.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a Shimadzu UV-2450 spectrometer. IR spectra were recorded on a Perkin-Elmer 577 spectrometer. NMR spectra were measured on a Bruker AM-400 spectrometer for ^{1}H, ^{13}C, HSQC, and HMBC and a Varian Inova-600 spectrometer for COSY and ROESY. The pulse conditions were as follows: for ^{1}H, spectrometer frequency (SF) 400.16 MHz, acquisition time (AQ) 2.048 s, relaxation delay (RD) 1.0 s, spectral width (SW) 8000 Hz, and FT size 32 768 data points; for ^{13}C, SF 100.639 MHz, AQ 0.803 s, RD 1.0 s, SW 20 408.1 Hz, line broadening 2.0 Hz, and FT size 32 768; for HSQC, AQ 0.341 s, RD 1.0 s, SW 6008.6 Hz (^{1}H) and 21 978.0 Hz (^{13}C), number of points (NP) 4096, number of increments (NI) 2 × 200, FT size 2048 × 4096; for HMBC, AQ 0.205 s, RD 1.0 s, SW 5000.0 Hz (^{1}H) and 22 988.5 Hz (^{13}C), NP 2048, NI 300, FT size 2048 × 2048; for COSY, AQ 0.128 s, RD 1.0 s, SW 8000.0 Hz, NP 2048, NI 320, FT size 2048 × 2048; for ROESY, AQ 0.213 s, RD 1.0 s, SW 10 999.6 Hz, NP 2048, NI 2 × 512, mixing time 0.230 s. EIMS (70 eV) were carried out on a Finnigan-MAT 95 mass spectrometer, and ESIMS was carried out on a Finnigan LCQ^{DECA} instrument. Analytical and semipreparative HPLC was performed on an Agilent 1100 with an Agilent DAD spectrophotometer and a SB-C_{18} column (4.6 × 250 mm, 5 μm) or Exlipse XDB-C_{18} column (10 × 250 mm, 5 μm). All solvents used were of analytical grade (Shanghai Chemical Reagents Company, Ltd.). Silica gel (200−300 mesh, Qingdao Haiyang Chemical Co., Ltd.) and Sephadex LH-20 gel (Amersham Biosciences) were also used for column chromatography.

Plant Material. The gamboge resin of *G. hanburyi* was purchased in Shanghai, China, in September 2007. The voucher specimen (SC0091009) was identified by one of the authors (D.-A.G.) and deposited in Shanghai Research Center for TCM Modernization.

Extraction and Isolation. The dried gum resin of *G. hanburyi* (800 g) was powdered and extracted with acetone (3 × 4 L) at room temperature for two days. The acetone extract (550 g) was chromatographed on a silica gel column eluted successively with a petroleum ether/acetone gradient (100:0 to 0:100) to obtain seven fractions. Fraction 2 (5 g) was subjected to a silica gel column eluting with petroleum ether−EtOAc (30:1 to 4:1) to afford six major fractions, F2a−F2f. F2c was then subjected to Sephadex LH-20 (petroleum ether−$CHCl_3$−MeOH, 2:1:1) to afford three major fractions, which were further purified by semipreparative HPLC (ACN−H_2O, 94:6) to afford **1** (5 mg), **2** (3 mg), desoxymorellin (56 mg), desoxygambogenin (200 mg), **3** (7 mg), gambogin (12.4 mg), and its diastereoisomer (11.8 mg). Fraction 3 (2 g) was subjected to column chromatography over

Table 3. Cytotoxicity of Compounds **1**−**14** Against HeLa Cells

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	*R*-gambogic acid
IC_{50} (μM)[a]	8.68 ± 0.18	111 ± 4.58	4.09 ± 0.37	0.56 ± 0.03	0.91 ± 0.02	0.93 ± 0.09	0.85 ± 0.10	1.71 ± 0.14	5.08 ± 0.92	1.91 ± 0.17	1.79 ± 0.14	1.21 ± 0.05	0.64 ± 0.02	0.63 ± 0.02	0.70 ± 0.08

[a] Inhibitory activity was expressed as the mean ± SEM of 50% inhibitory concentration of triplicate determinations and was obtained by interpolation of concentration−inhibiton curves.

Sephadex LH-20 (petroleum ether−$CHCl_3$−MeOH, 2:1:1) and silica gel (petroleum ether−Me_2CO, 20:1) to obtain four major fractions, F3a−F3d. F3b was further purified by semipreparative HPLC (ACN−H_2O, 94:6) to afford isomorellin (40 mg) and isogambogenin (60 mg). F3c was further purified by recrystallization from $CHCl_3$−Me_2CO (5:1) to obtain hanburin (20 mg). Fraction 4 (8 g) was chromatographed on a silica gel column ($CHCl_3$−MeOH, 100:0 to 10:1) to obtain five major fractions, F4a−F4e. F4e was further purified by semipreparative HPLC (MeOH−H_2O−0.08% CF_3COOH, 89:9:2) to afford **4** (5 mg), gambogellic acid (35 mg), **5** (4 mg), **6** (18 mg), and **7** (15 mg). Fraction 5 (380 g) was separated on a silica gel column eluting with $CHCl_3$−Me_2CO (100:0 to 5:1) to afford six major fractions, F5a−F5f. F5e was separated on Sephadex LH-20 (petroleum ether−$CHCl_3$−MeOH, 2:1:1) to obtain five major fractions, which were further purified by semipreparative HPLC (MeOH−H_2O−0.08% CF_3COOH, 95:3:2) to obtain gambogenic acid (30 g), morellic acid (4 g), and gambogic acid epimers (80 g). Gambogic acid epimers (100 mg) were subjected to semipreparative HPLC (MeOH−H_2O−0.08% CF_3COOH, 87:11:2) to afford gambogic acid (40 mg) and epigambogic acid (30 mg). F5f was subjected to column chromatography over silica gel and Sephadex LH-20 (petroleum ether−$CHCl_3$−MeOH, 2:1:1) to obtain five major fractions, which were further purified by semipreparative HPLC (MeOH−H_2O−0.08% CF_3COOH, 90:8:2) to get **8** (30 mg), **9** (250 mg), **13** (250 mg), **14** (230 mg), and isogambogic acid (500 mg). In the same manner, fraction 6 (70 g) was separated on a silica gel column eluting with $CHCl_3$−MeOH (100:0 to 4:1) to afford four major fractions, which were further purified by semipreparative HPLC (MeOH−H_2O−0.08% CF_3COOH, 86:12:2) to obtain **10** (8 mg), **11** (16 mg), **12** (9 mg), isomorellinol (20 mg), epiisogambogic acid (100 mg), gaudichaudic acid (10 mg), isogambogenic acid (300 mg), and isomorellic acid (250 mg).

Gambospiroene (1): yellow gum; $[\alpha]^{20}_D$ +36.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 351 (3.69), 307 (4.27) nm; IR (KBr) ν_{max} 3423, 2966, 2918, 2850, 1730, 1708, 1633, 1616, 1448, 1367, 1174, 1103, 1016, 937 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; positive ESIMS *m/z* 603.2 $[M + H]^+$; HRESIMS *m/z* 625.3138 $[M + Na]^+$ (calcd for $C_{37}H_{46}O_7Na$, 625.3141).

Methyl 8,8a-dihydromorellate (2): yellow gum; $[\alpha]^{20}_D$ −49.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 366 (3.25), 314 (3.82), 302 (3.77), 275 (4.32), 266 (4.29) nm; IR (KBr) ν_{max} 3423, 2964, 2923, 1737, 1628, 1440, 1261, 1097, 1022, 800 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 576 $[M]^+$ (100), 561 (48), 529 (38), 489 (13), 463 (13), 287 (38), 231 (26), 215 (14); HREIMS *m/z* 576.2708 $[M]^+$ (calcd for $C_{34}H_{40}O_8$, 576.2723).

3-*O*-Geranylforbesione (3): yellow gum; $[\alpha]^{20}_D$ −422.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 351 (4.29), 212 (4.74) nm; IR (dry film) ν_{max} 2970, 2925, 1740, 1639, 1593, 1425, 1375, 1307, 1170, 1122 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 600 $[M]^+$ (10), 572 (47), 436 (100), 421 (37), 339 (65), 297 (38), 283 (32), 241 (45), 215 (39), 69 (83); HREIMS *m/z* 600.3464 $[M]^+$ (calcd for $C_{38}H_{48}O_6$, 600.3451).

Gambogefic acid (4): yellow gum; $[\alpha]^{20}_D$ −265.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 361 (4.25), 214 (4.71) nm; IR (KBr) ν_{max} 3430, 2975, 2927, 1739, 1691, 1631, 1587, 1434, 1309, 1130 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 628 $[M]^+$ (12), 600 (12), 473 (18), 431 (7), 355 (8), 297 (8), 69 (100); HREIMS *m/z* 628.3082 $[M]^+$ (calcd for $C_{38}H_{44}O_8$, 628.3036).

7-Methoxygambogellic acid (5): yellow needles (ACN); mp 146−147 °C; $[\alpha]^{20}_D$ −307.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 364 (4.15), 215 (4.45) nm; IR (KBr) ν_{max} 3430, 2929, 1745, 1689, 1637, 1591, 1431, 1379, 1325, 1172, 1118 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 658 $[M]^+$ (4), 630 (100), 585 (15), 504 (53), 503 (49), 447 (17), 421 (15), 353 (20), 277 (19); HREIMS *m/z* 658.3147 $[M]^+$ (calcd for $C_{39}H_{46}O_9$, 658.3142).

7-Methoxygambogic acid (6): yellow gum; $[\alpha]^{20}_D$ −535.0 (*c* 0.085, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 365 (4.41), 290 (4.45) nm; IR (KBr) ν_{max} 3430, 2970, 2923, 1747, 1689, 1639, 1595, 1458, 1436, 1334, 1174, 1135 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 658 $[M]^+$ (8), 630 (100), 575 (17), 547 (48), 529 (12), 503 (25), 421 (14), 355 (16), 277 (31), 215 (24); HREIMS *m/z* 658.3133 $[M]^+$ (calcd for $C_{39}H_{46}O_9$, 658.3142).

7-Methoxyepigambogic acid (7): yellow gum; $[\alpha]^{20}_D$ −576.0 (*c* 0.11, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 365 (4.35), 290 (4.41) nm; IR (KBr) ν_{max} 3430, 2971, 2927, 1747, 1689, 1645, 1595, 1458, 1436, 1334, 1174, 1135 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 658 $[M]^+$ (7), 630 (100), 575 (19), 547 (50), 529 (13), 503 (27), 421 (17), 355 (18), 277 (35), 215 (26); HREIMS *m/z* 658.3135 $[M]^+$ (calcd for $C_{39}H_{46}O_9$, 658.3142).

8,8a-Dihydro-8-hydroxymorellic acid (8): yellow gum; $[\alpha]^{20}_D$ −34.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 364 (3.55), 316 (4.12), 276 (4.61), 266 (4.58) nm; IR (KBr) ν_{max} 3442, 2977, 2927, 1741, 1689, 1645, 1626, 1458, 1380, 1190, 1124 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 578 $[M]^+$ (2), 560 (100), 545 (45), 532 (72), 517 (71), 405 (89), 391 (30), 363 (47), 349 (42), 307 (33), 287 (59), 245 (42), 231 (37), 215 (29); HREIMS *m/z* 578.2523 $[M]^+$ (calcd for $C_{33}H_{38}O_9$, 578.2516).

8,8a-Dihydro-8-hydroxygambogenic acid (9): yellow gum; $[\alpha]^{20}_D$ −67.0 (*c* 0.11, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 351 (3.87), 298 (4.46), 203 (4.90) nm; IR (KBr) ν_{max} 3419, 2972, 2925, 1741, 1689, 1631, 1450, 1375, 1323, 1267, 1155, 1083, 1045 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 630 $[M - H_2O]^+$ (100), 602 (27), 507 (45), 479 (36), 351 (43), 295 (50), 253 (57); HREIMS *m/z* 648.3323 $[M]^+$ (calcd for $C_{38}H_{48}O_9$, 648.3298).

Oxygambogic acid (10): yellow gum; $[\alpha]^{23}_D$ −337.0 (*c* 0.095, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 358 (4.09), 292 (4.17), 204 (4.41) nm; IR (dry film) ν_{max} 3432, 2974, 2927, 1736, 1693, 1633, 1592, 1456, 1437, 1335, 1178, 1140, 1049, 756 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 626 $[M - H_2O]^+$ (3), 545 (100), 517 (8), 499 (9), 271 (8), 245 (12), 215 (26), 189 (12); HREIMS *m/z* 644.2965 $[M]^+$ (calcd for $C_{38}H_{44}O_9$, 644.2985).

Gambogenific acid (11): yellow gum; $[\alpha]^{23}_D$ −402.0 (*c* 0.095, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 358 (4.06), 204 (4.46) nm; IR (dry film) ν_{max} 3458, 2976, 2927, 1737, 1685, 1633, 1593, 1456, 1398, 1338, 1149, 1014, 943, 758 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 646 $[M]^+$ (100), 618 (8), 549 (10), 523 (73), 495 (25), 367 (32), 325 (23), 295 (23), 253 (26), 213 (17); HREIMS *m/z* 646.3138 $[M]^+$ (calcd for $C_{38}H_{46}O_9$, 646.3142).

7-Methoxyisomorellinol (12): yellow gum; $[\alpha]^{23}_D$ −416.0 (*c* 0.090, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 358 (3.94), 288 (4.05), 227 (4.07) nm; IR (dry film) ν_{max} 3475, 2976, 2927, 1745, 1633, 1593, 1437, 1335, 1136, 754 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; EIMS *m/z* 576 $[M]^+$ (8), 548 (100), 517 (16), 479 (20), 435 (34), 379 (17), 287 (24), 263 (24), 245 (23), 231 (18), 215 (14), 135 (15), 69 (42); HREIMS *m/z* 576.2707 $[M]^+$ (calcd for $C_{34}H_{40}O_8$, 576.2723).

8,8a-Dihydro-8-hydroxygambogic acid (13): yellow gum; $[\alpha]^{24}_D$ −77.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 354 (3.59), 315 (4.04), 277 (4.47), 268 (4.42), 204 (4.90) nm; IR (KBr) ν_{max} 3438, 2972, 2926, 1741, 1689, 1628, 1587, 1456, 1375, 1325, 1176, 1045, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 11.86 (1H, s), 6.65 (1H, d, J = 10 Hz), 6.62 (1H, overlapped), 5.45 (1H, d, J = 10 Hz), 5.09 (1H, t, J = 7.2 Hz), 4.98 (1H, t, J = 6.4 Hz), 4.81 (1H, brs), 3.28−3.12 (5H, m), 2.67 (1H, m), 2.44 (1H, d, J = 8.8 Hz), 2.06 (2H, m), 1.94 (3H, s), 1.91 (1H, m), 1.76 (1H, m), 1.72 (3H, s), 1.65 (3H, s), 1.62 (3H, s), 1.59 (1H, m), 1.56 (3H, s), 1.39 (1H, m), 1.36 (3H, s),1.34 (3H, s), 1.12 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.4, 193.7, 172.5, 161.2, 156.2, 155.5, 139.8, 131.6, 130.9, 126.7, 124.8,, 123.5, 122.3, 115.6, 108.5, 102.6, 101.5, 88.1, 86.3, 82.1, 80.8, 65.4, 49.8, 46.4, 42.6, 41.6, 29.5, 27.7, 27.0, 27.0, 25.4, 25.4, 22.6, 21.2, 20.3, 20.0, 17.9, 17.4; EIMS *m/z* 628 $[M - H_2O]^+$ (20), 600 (15), 545 (100), 517 (23), 499 (7), 473 (13), 245 (9), 215 (14), 189 (6); HREIMS *m/z* 646.3130 $[M]^+$ (calcd for $C_{38}H_{46}O_9$, 646.3142).

8,8a-Dihydro-8-hydroxygambogic acid isomer (14): yellow gum; $[\alpha]^{24}_D$ +4.0 (*c* 0.10, $CHCl_3$); UV (CH_3OH) λ_{max} (log ε) 358 (3.53), 316 (3.99), 277 (4.36), 268 (4.31), 204 (4.39) nm; IR (KBr) ν_{max} 3442, 2972, 2927, 1741, 1689, 1628, 1587, 1456, 1375, 1325, 1178, 1045, 754 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ 11.88 (1H, s), 6.65 (1H, d, J = 10 Hz), 6.60 (1H, t, J = 7.2 Hz), 5.43 (1H, d, J = 10 Hz), 5.04 (1H, t, J = 7.2 Hz), 4.97 (1H, t, J = 6.8 Hz), 4.81 (1H, brs), 3.28−3.13 (5H, m), 2.67 (1H, m), 2.45 (1H, d, J = 8.4 Hz), 2.02 (2H, m), 1.94 (3H, s), 1.91 (1H, m), 1.76 (1H, m), 1.72 (3H, s), 1.64 (3H, s), 1.62 (3H, s), 1.59 (1H, m), 1.55 (3H, s), 1.40 (3H, s), 1.38 (1H, m), 1.34 (3H, s), 1.12 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.3, 193.7, 172.3, 161.2, 156.2, 155.5, 139.7, 131.7, 130.9, 126.7, 124.5, 123.4, 122.4, 115.5, 108.4, 102.4, 101.5, 88.1, 86.3, 82.1, 80.9, 65.4, 49.8, 46.4, 42.6, 41.8, 29.5, 27.7, 27.5, 26.9, 25.4, 25.4, 22.5, 21.2, 20.3, 20.0, 17.8, 17.4; EIMS *m/z* 646 $[M]^+$ (2), 628 (16), 600 (15), 545 (100), 517 (24), 499 (8), 473 (12), 245 (12), 215 (21), 189 (10); HREIMS *m/z* 646.3132 $[M]^+$ (calcd for $C_{38}H_{46}O_9$, 646.3142).

Cytotoxicity Assay. Cytotoxicity against HeLa cells was evaluated by using the MTT method according to the protocols described[22] with adriamycin as a positive control ($IC_{50} = 0.41$ μM against HeLa cells).

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Supporting Information Available: 1D and 2D NMR spectra of **1**−**14**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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