Biologically Active Arborinane-Type Triterpenoids and Anthraquinones from *Rubia yunnanensis*

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Ⓢ *Supporting Information*

ABSTRACT: Twelve new arborinane-type triterpenoids (**1**−**12**) and four new anthraquinones (**13**−**16**), together with 50 known compounds, were isolated from the roots of *Rubia yunnanensis*. The structures of **1**−**16** were elucidated by spectroscopic data analysis and chemical methods. All compounds were evaluated for their cytotoxic, antibacterial, and antifungal activities. Rubiyunnanol C (**5**) is the first example of an arborinane-type triterpenoid with a double bond at C-8−C-9.
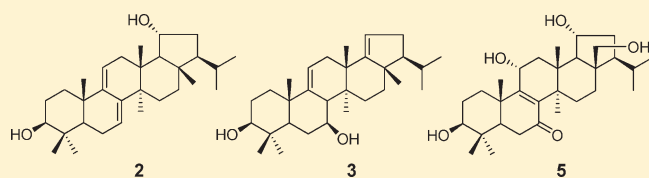
The plant genus *Rubia* belongs to the family Rubiaceae, which consists of about 70 species with commercial, economic, and medicinal importance. Previous phytochemical investigations of *Rubia* species have shown that this genus is a source of cyclic hexapeptides, anthraquinones, and arborinane-type triterpenoids.[1,2] *Rubia yunnanensis* (Franch.) Diels, known as "Xiao-Hong-Shen", is a perennial climbing herb native to mainland China. Its roots have a long history of use in folk medicine to treat cancer, vertigo, insomnia, rheumatism, tuberculosis, menstrual disorders, and contusions[3] and are used as an alternative for *Rubia cordifolia*, a well-known traditional Chinese medicine listed in the Chinese Pharmacopoeia. Previous studies on *R. yunnanensis* also demonstrated the presence of cyclic hexapeptides,[4,5] anthraquinones,[6−8] and arborinane-type triterpenoids.[6,9−13] In a recent study on this species, our group reported a series of bioactive cyclic hexapeptides.[14,15] In the present report, 12 new arborinane-type triterpenoids (**1**−**12**) and four new anthraquinones (**13**−**16**), together with 50 known compounds, were isolated from the roots of the title plant. The 50 known compounds were identified as rubiarbonol K (**17**),[9] rubiarbonol L (**18**),[9] rubiarbonol G (**19**),[10] 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone (**20**),[16] 3-hydroxy-2-hydroxymethyl-9,10-anthraquinone (**21**),[17] 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(6′-*O*-acetyl)-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside (**22**),[16] 2-methoxy-1,4-naphthoquinone (**23**),[18] rubiarbonol A,[19] rubiarbonol F,[19] rubianol-c,[13] rubianol-d,[13] rubiano-e,[13] rubiarbonone A,[10] rubiarbonone B,[11] rubiarbonone C,[11] rubiarbonone E,[6,12] rubianoside I,[13] rubianoside A,[6,9] rubiarboside C,[6,9] rubiarboside G,[12] ursolic acid,[20] 4-epihederagenin,[21] maslinic acid,[22] spathodic acid,[23] lanosta-9(11),24-dien-3-one,[24] parkeol,[25] rubianthraquinone,[6] xanthopurpurin,[26] 1,6-dihydroxy-2-methyl-9,10-anthraquinone,[27] rubiadin,[28] 2-hydroxymethyl-9,10-anthraquinone,[29] 1-hydroxy-2-methyl-9,10-anthraquinone,[16] 2-carbomethoxy-9,10-anthraquinone,[8] 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(6′-*O*-acetyl)-β-D-glucopyranoside,[30] 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside,[16] 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(6′-*O*-acetyl)-β-D-xylopyranosyl-(1→2)-β-D-glucopyranoside,[31] 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(3′-*O*-acetyl)-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside,[32] (2*S*,3*S*,4*R*,9*E*)-1,3,4-trihydroxyl-2-[(2′*R*)-2′-hydroxytetracosanoylamino]-9-octadecene,[33] 5,7,2′-trihydroxy-6-methoxyflavone,[34] (+)-lariciresinol,[35] (+)-isolariciresinol,[35] (−)-secoisolariciresinol,[35] vladinol D,[36] (+)-pinoresinol,[37] 4-hydroxy-3-prenylbenzoic acid,[38] 6-*cis*-docosenamide,[39] 1-*O*-hexadecanolenin, squalene,[40] β-sitosterol, and daucosterol, by comparing their spectroscopic data with those reported in the literature. Furthermore, all isolated compounds were tested for their cytotoxicity against three human cancer cell lines and for antibacterial and antifungal activities. In this paper, the isolation, structure elucidation, and biological evaluation of these compounds are described.
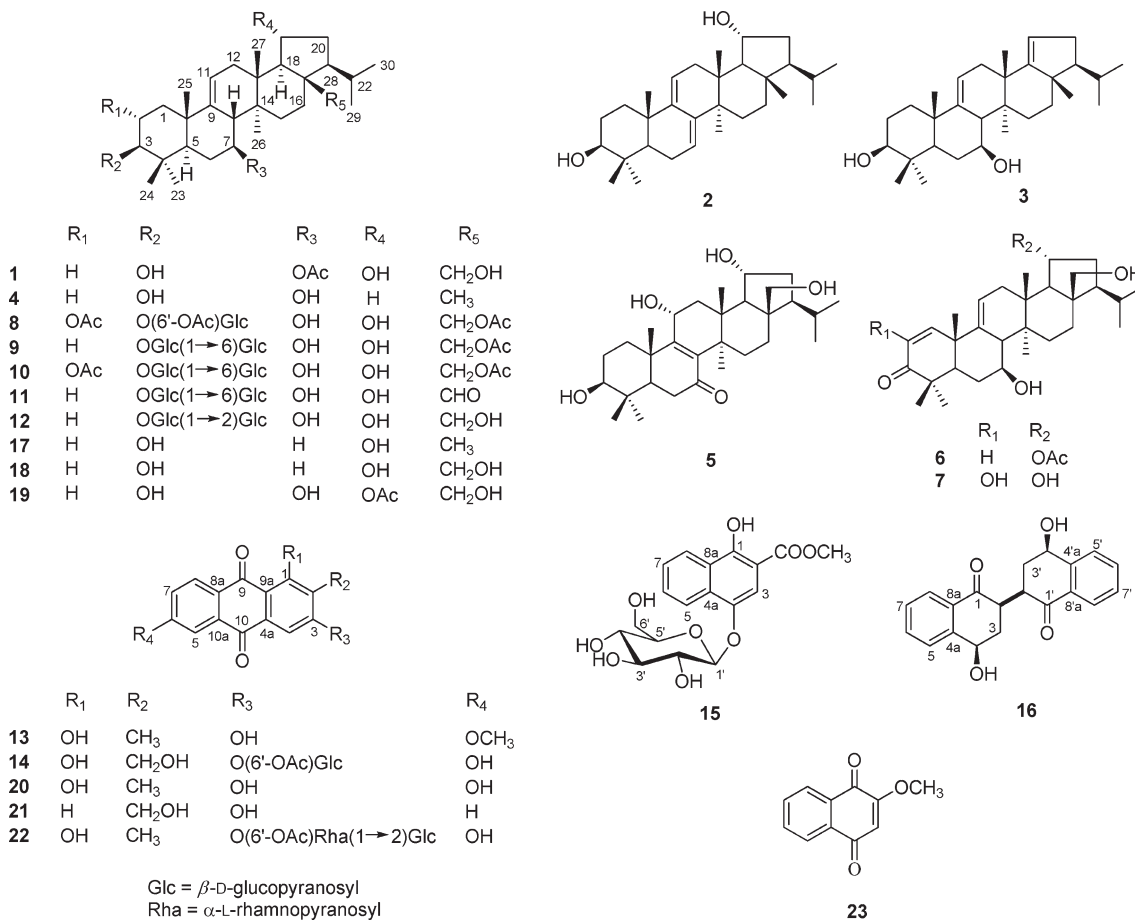
■ RESULTS AND DISCUSSION

Compound **1** was obtained as a white powder with a positive specific rotation ($[\alpha]_D^{23}$ +1.7). Its molecular formula, $C_{32}H_{52}O_5$, was deduced by HRESIMS (m/z 539.3707 [M + Na]$^+$), indicating seven degrees of unsaturation. The IR spectrum showed absorption bands for hydroxy (3423 cm^{-1}), carbonyl (1728 cm^{-1}), and olefinic (1641 cm^{-1}) groups. The ^{1}H NMR spectrum of **1** (Table 1) displayed characteristic resonances for two secondary methyls (δ_H 0.94, 1.08), five tertiary methyls (δ_H 1.05, 1.14, 1.17, 1.20, 1.37), an oxygenated methylene (δ_H 4.08, 4.17), three

Chart 1

Glc = β-D-glucopyranosyl
Rha = α-L-rhamnopyranosyl

oxygenated methines (δ_H 3.45, 5.28, 5.01), and one olefinic proton (δ_H 5.51). The ^{13}C NMR spectrum of **1** (Table 2) exhibited 32 carbons, including a trisubstituted double bond (δ_C 118.7, 146.1) and an *O*-acetyl group (δ_C 170.5, 22.0), together with seven methyls, eight methylenes (one oxygenated), eight methines (three oxygenated), and five quaternary carbons. Comparison of the NMR data of **1** with those of rubiarbonol A[19] revealed that both compounds are based on an arborinane-type triterpenoid skeleton. The only difference found was the presence of an additional acetate group in **1**. The downfield shift of the H-7 proton signal (δ_H 5.28) and HMBC correlations of H-7 with the acetate carbonyl carbon, C-6, C-14, and C-8 enabled the acetate unit to be placed at C-7. The relative configuration of **1** was deduced from the analysis of its ROESY spectrum (Figure 1). The observed NOE correlations of H-3/H-5 and CH$_3$-23, H-5/H-7, H-7/CH$_3$-26, and H-18/H-21 and CH$_3$-26 indicated that H-3, H-5, H-7, H-18, H-21, CH$_3$-23, and CH$_3$-26 are cofacial and assigned as α-oriented. In turn, the cross-peaks of H-8/CH$_3$-25 and CH$_3$-27 and H-19/CH$_3$-27 and H-28 indicated the β-orientation of H-8, H-19, H-28, CH$_3$-25, and CH$_3$-27. From the above evidence, the structure of **1** was established as 7β-acetoxy-3β,19α,28-trihydroxyarbor-9(11)-ene (rubiarbonol A 7-acetate).

Compound **2** gave the molecular formula C$_{30}$H$_{48}$O$_2$, based on HRESIMS (m/z 463.3540 [M + Na]$^+$), requiring seven degrees of unsaturation. The ^{1}H and ^{13}C NMR data of **2** (Tables 1 and 2) were similar to those of rubiarbonol A except for the presence of a

trisubstituted double bond (δ_H/δ_C 5.77/120.0, δ_C 142.4) in the downfield region of **2** and the replacement of a hydroxymethylene group in rubiarbonol A by a tertiary methyl (δ_H/δ_C 0.84/16.0) at C-17. The double bond was placed between C-7 and C-8, as determined by HMBC correlations of H-7 (δ_H 5.77) with C-5, C-6, C-9, and C-14 and of H-11, H-6, and CH$_3$-26 with C-8 (δ_C 142.4). In addition, the observed ^{1}H−^{1}H COSY correlation of H-7 with H-6 and NOE correlations of H-7 with H-15α and H-15β also supported the position of this double bond. The location of the tertiary methyl (CH$_3$-28) at C-17 was confirmed by HMBC correlations of CH$_3$-28 with C-16, C-17, C-21, and C-18. Furthermore, the β-orientation of CH$_3$-28 was deduced from the NOE correlation between CH$_3$-28 and CH$_3$-27 (Figure 2). Accordingly, the structure of **2** (rubiyunnanol A) was established as 3β,19α-dihydroxyarbor-7,9(11)-diene.

Compound **3** exhibited the same molecular formula C$_{30}$H$_{48}$O$_2$ as **2**, as established by HRESIMS at m/z 463.3544 [M + Na]$^+$. Analysis of the ^{1}H and ^{13}C NMR data of **3** (Tables 1 and 2) showed a close structural resemblance to **2**, with the compounds differing in the locations of a trisubstituted double bond (δ_H/δ_C 5.34/119.8, δ_C 159.7) and a hydroxy group. The olefinic proton signal at δ_H 5.34 was assigned to H-19, as deduced by the HMBC correlations of H-19 with C-20, C-13, C-17, and C-21 and ^{1}H−^{1}H COSY correlations of H-19 with H-20α and H-20β. In addition, cross-peaks of CH$_3$-28, CH$_3$-27, H-16, H-19, H-20, and H-12 with the olefinic carbon signal at δ_C 159.7 (C-18) in the HMBC spectrum further supported the

Table 1. ^{1}H NMR Data of Compounds 1−7 in Pyridine-d_5 (δ in ppm, J in Hz)

position	1[b]	2[a]	3[a]	4[a]	5[a]	6[b]	7[a]
1α	1.44, overlap	1.53, m	1.55, m	1.52, overlap	2.54, m	7.26, d (10.5)	6.73, s
1β	1.73, overlap	2.02, m	1.73, overlap	1.79, overlap	2.13, overlap	6.15, d (10.5)	
2	1.92, overlap	1.97, overlap	2.00, overlap	2.00, overlap	1.97, overlap		
3	3.45, dd (10.5, 5.0)	3.50, t (7.6)	3.50, dd (9.6, 5.6)	3.50, dd (9.6, 6.0)	3.47, m		
5	1.10, m	1.30, m	1.11, overlap	1.11, overlap	2.02, m	1.82, overlap	1.85, dd, (12.8, 2.0)
6α	2.31, m	2.23, m	2.26, overlap	2.30, dd (12.0, 2.4)	2.64, overlap	2.24, overlap	2.24, m
6β	1.73, overlap		2.00, overlap	2.00, overlap	2.73, overlap	2.03, overlap	2.03, overlap
7	5.28, m	5.77, brd (3.6)	3.94, m	4.04, m		4.11, m	4.16, m
8	2.63, brd (10.0)		2.40, brd (9.6)	2.41, brd (10.0)		2.55, brd (9.0)	2.66, overlap
11	5.51, brd (5.5)	5.53, brs	5.50, brd (5.6)	5.39, brd (5.6)	4.85, m	5.43, brd (6.0)	5.75, brd (5.6)
12α	2.50, m	2.58, brs	2.26, overlap	1.79, overlap	2.73, overlap	2.24, overlap	2.56, m
12β	2.45, dd (18.0, 5.5)		1.91, overlap	1.52, overlap	3.14, dd (14.0, 9.2)	1.74, overlap	
15α	1.92, overlap	1.45, brd (13.2)	3.07, brd (14.0)	2.78, brd (14.4)	2.90, brd (14.4)	2.64, brd (14.5)	2.69, m
15β	1.58, brd (14.5)	1.78, m	2.00, overlap	1.91, m	2.13, overlap	1.94, dd (14.5, 3.0)	2.03, overlap
16α	1.44, overlap	1.61, brd (12.4)	1.73, overlap	1.52, overlap	1.66, m	1.51, td (13.5, 3.5)	1.56, overlap
16β	1.98, brd (14.0)	1.72, m		1.70, brd (12.8)	1.97, overlap	1.74, overlap	2.03, overlap
18	2.22, d (10.0)	1.97, overlap		1.61, dd (12.4, 7.2)	2.39, d (9.6)	2.36, d (10.0)	2.34, d (10.0)
19	5.01, m	4.46, m	5.34, brs	1.37, overlap	5.08, m	6.05, m	5.19, m
20α	2.11, overlap	1.97, overlap	2.26, overlap	1.19, overlap	2.13, overlap	1.82, overlap	2.16, overlap
20β	2.57, m	2.08, m	1.91, overlap	1.79, overlap	2.64, overlap	2.71, m	2.66, overlap
21	1.51, m	1.38, overlap	1.43, m	0.92, overlap	1.52, m	1.41, m	1.56, overlap
22	2.11, overlap	1.38, overlap	1.64, m	1.37, overlap	2.13, overlap	2.03, overlap	2.16, overlap
23	1.20, s	1.24, s	1.25, s	1.25, s	1.12, s	1.22, s	1.26, s
24	1.05, s	1.16, s	1.11, s	1.11, s	1.10, s	1.03, s	1.08, s
25	1.14, s	1.13, s	1.20, s	1.20, s	1.27, s	1.26, s	1.33, s
26	1.17, s	1.16, s	1.10, s	1.18, s	1.89, s	1.22, s	1.28, s
27	1.37, s	0.97, s	1.17, s	0.92, s	1.38, s	1.35, s	1.45, s
28a	4.17, d (11.5)	0.84, s	1.07, s	0.79, s	4.18, dd (11.2, 2.8)	4.23, d (11.5)	4.22, d (11.6)
28b	4.08, d (11.5)				4.02, brd (11.2)	3.92, d (11.5)	4.09, d (11.6)
29	1.08, d (6.5)	0.91, d (6.0)	0.91, d (6.4)	0.89, d (6.4)	1.04, d (6.4)	0.98, d (6.5)	1.08, overlap
30	0.94, d (6.5)	0.84, overlap	0.88, d (6.4)	0.85, d (6.4)	0.93, d (6.4)	0.89, d (6.5)	0.96, d (6.4)
OAc-7	2.16, s						
OAc-19						2.16, s	

^{a} Recorded at 400 MHz. ^{b} Recorded at 500 MHz.

occurrence of a double bond between C-18 and C-19. Moreover, HMBC correlations of H-7 with C-6, C-8, and C-14 as well as NOE correlations of H-7 with H-5 and CH$_3$-26 demonstrated the hydroxy group to be linked to C-7 and having a β-orientation (Figure 2). Accordingly, the structure of **3** (rubiyunnanol B) was elucidated as 3β,7β-dihydroxyarbor-9(11),18-diene.

Compound **4** was shown to have the molecular formula C$_{30}$H$_{50}$O$_2$, by HRESIMS (m/z 465.3710 [M + Na]$^+$), indicating two mass units more than **3**. Comparison of the ^{1}H and ^{13}C NMR data (Tables 1 and 2) with those of **3** suggested that the only difference was the absence of the trisubstituted double bond between C-18 and C-19 and the appearance of methine (δ_H/δ_C 1.61/52.5) and methylene (δ_H/δ_C 1.37/20.7) substituents in **4**. These changes implied that the additional methine and methylene signals are located at C-18 and C-19, respectively, as confirmed by HMBC correlations of H-18 (δ_H 1.61) with C-17, C-19, C-21, C-27, and C-28, as well as the ^{1}H−^{1}H COSY correlation of H-18 with H-19. Thus, the structure of **4** (19,28-didehydroxyrubiarbonol A) was proposed as 3β,7β-dihydroxyarbor-9(11)-ene.

Compound **5**, a white powder, gave the molecular formula C$_{30}$H$_{48}$O$_5$ from its HRESIMS (m/z 487.3419 [M − H]$^−$),

indicating seven degrees of unsaturation. The IR spectrum showed the absorption bands for hydroxy (3440 cm^{-1}) and conjugated carbonyl (1656, 1651 cm^{-1}) groups, and the UV spectrum displayed an absorption at 251 nm, characteristic of the presence of an α,β-unsaturated carbonyl chromophore in the molecule. The ^{13}C NMR spectroscopic data (Table 2) showed the presence of 30 carbon signals due to one tetrasubstituted double bond (δ_C 141.8, 162.1), one ketone carbon (δ_C 202.1), seven methyls, eight methylenes (one oxygenated), seven methines (three oxygenated), and five quaternary carbons. Comparison of the 1D- and 2D-NMR data of **5** with those of rubiarbonol A suggested that their structures are closely related. The main differences were that a characteristic trisubstituted double bond at C-9−C-11 in conventional arborinane-type triterpenoids was absent in **5**, while a tetrasubstituted double bond, a carbonyl group, and an additional hydroxy group were present. HMBC correlations of H-5, H-6α, and H-6β with the carbonyl carbon indicated that the latter group occurs at C-7. In addition, the position of the additional hydroxy group at C-11 was deduced by correlations of H-11 with H-12α and H-12β in the ^{1}H−^{1}H COSY spectrum combined with HMBC correlations

Table 2. ^{13}C NMR Data of Compounds 1−12 in Pyridine-d_5 (δ in ppm, J in Hz)

position	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]	7[a]	8[a]	9[b]	10[b]	11[a]	12[a]
1	36.9	36.3	36.9	37.1	34.8	155.4	126.0	43.0	36.8	42.9	36.7	36.8
2	28.6	28.8	28.8	28.8	28.6	125.4	145.7	70.2	27.4	70.1	27.4	27.3
3	77.8	78.1	78.0	78.0	77.5	203.8	200.8	88.8	89.1	88.3	89.0	89.0
4	39.6	39.3	39.5	39.5	39.8	44.1	44.2	41.3	39.6	41.3	39.6	39.7
5	48.2	49.5	49.3	49.0	51.6	46.4	46.3	48.4	49.1	48.3	49.2	49.1
6	28.8	23.7	33.9	33.9	39.0	33.1	33.3	33.2	33.6	33.2	33.6	33.6
7	74.6	120.0	73.0	72.2	202.1	70.6	70.6	71.9	72.2	71.9	72.5	72.1
8	45.6	142.4	48.6	49.5	141.8	48.9	49.2	48.9	49.3	48.9	49.6	49.4
9	146.1	146.5	147.3	148.4	162.1	143.4	144.0	146.6	147.5	146.5	147.0	147.6
10	39.5	38.1	39.9	40.0	41.8	42.1	41.3	40.6	39.5	40.6	39.5	39.4
11	118.7	116.5	116.2	116.5	63.1	117.5	118.0	117.5	117.2	117.6	117.0	117.4
12	37.6	38.5	35.1	36.4	46.7	36.4	37.6	37.2	37.3	37.2	35.7	37.7
13	38.2	37.6	39.8	37.6	41.8	38.0	38.4	38.2	38.2	38.2	38.6	38.4
14	40.1	41.3	38.5	39.8	42.4	40.4	40.5	40.1	40.1	40.1	39.5	40.3
15	32.7	29.0	30.9	32.0	29.1	33.1	33.2	32.4	32.4	32.4	32.8	33.1
16	33.4	36.6	37.7	36.8	33.4	33.5	33.3	32.6	32.7	32.6	29.8	33.4
17	48.8	44.4	46.2	42.7	48.9	48.4	49.0	47.3	47.4	47.3	61.1	49.1
18	59.8	59.2	159.7	52.5	60.5	56.3	60.0	59.6	59.7	59.6	61.0	60.1
19	70.6	70.1	119.8	20.7	70.9	74.7	70.7	70.0	70.0	70.0	69.2	70.8
20	43.4	42.1	35.6	28.4	43.8	40.4	43.5	42.7	42.7	42.7	42.1	43.6
21	58.1	57.7	62.8	59.9	57.9	57.5	58.1	57.5	57.5	57.5	55.7	58.1
22	30.8	30.7	29.3	31.1	30.6	30.2	30.8	31.2	31.2	31.1	32.0	30.8
23	28.6	28.9	28.7	28.8	28.1	25.1	25.6	28.3	28.2	28.3	28.2	28.2
24	16.2	16.7	16.5	16.5	16.2	22.0	22.4	18.0	17.0	18.0	17.0	16.8
25	22.0	23.3	21.7	22.1	19.9	22.2	23.7	22.7	22.0	22.7	21.8	22.0
26	17.5	23.8	17.8	16.9	23.6	17.3	17.5	17.3	17.3	17.3	16.6	17.3
27	16.9	17.6	22.5	15.7	20.1	16.3	16.8	16.7	16.7	16.6	16.2	16.8
28	62.6	16.0	19.9	14.2	63.0	63.2	62.9	64.9	65.0	64.9	206.4	63.0
29	23.5	22.2	22.6	22.3	23.3	23.1	23.5	23.0	23.0	23.0	21.8	23.5
30	23.7	23.2	23.1	23.2	23.6	23.3	23.7	23.5	23.6	23.5	23.2	23.7
Glc-												
1′								106.3	107.0	106.2	107.1	105.2
2′								75.7	75.6	75.6	75.6	83.3
3′								78.5	78.6	78.6	78.6	78.4
4′								71.4	71.8	71.5	71.7	71.5
5′								75.1	77.2	77.2	77.2	78.4
6′								65.2	70.4	70.1	70.4	62.7
Glc-												
1″									105.5	105.2	105.5	106.0
2″									75.3	75.3	75.3	77.2
3″									78.5	78.4	78.5	78.2
4″									71.8	71.8	71.8	71.7
5″									78.5	78.4	78.6	78.0
6″									62.8	62.9	62.8	62.8
OAc-2								171.0		171.6		
								21.6		22.3		
OAc-7	170.5											
	22.0											
OAc-19						170.9						
						21.8						
OAc-28								170.8	170.9	170.8		
								21.1	21.2	21.1		
OAc-6′								171.1				
								20.9				

[a] Recorded at 100 MHz. [b] Recorded at 125 MHz.

of H-11 with C-10 and C-13. Furthermore, the tetrasubstituted double bond present between C-8 and C-9 was determined by
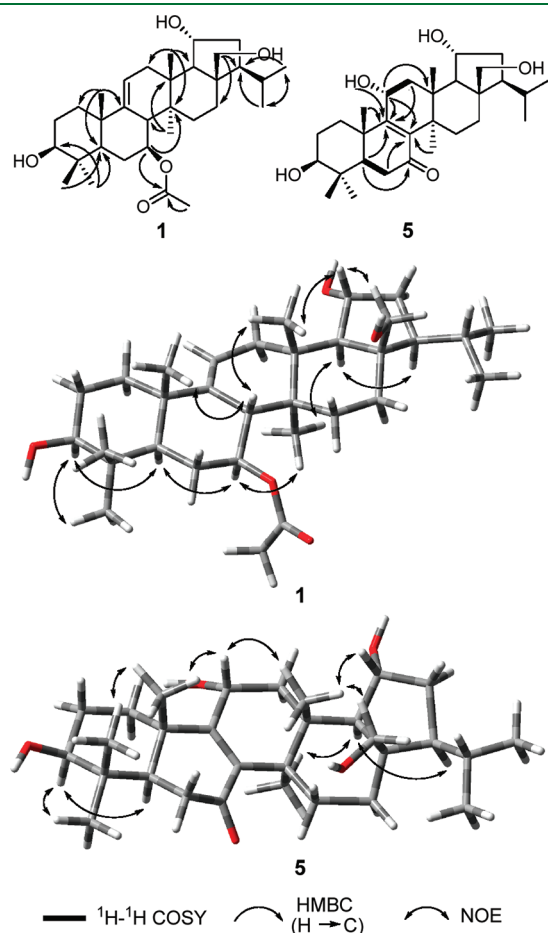
Figure 1. Selected ^{1}H−^{1}H COSY, HMBC, and NOE correlations of **1** and **5**.

HMBC correlations of H-6α, H-11, CH$_3$-26/C-8 and of H-11, OH-11, H-12β, H-5, CH$_3$-25/C-9 and was found to be conjugated with the carbonyl group (Figure 1). Thus, the planar structure of **5** was established.

The relative configurations at C-3, C-5, C-18, C-19, C-21, C-28, CH$_3$-23, CH$_3$-25, CH$_3$-26, and CH$_3$-27 in **5** were established as being the same as those in rubiarbonol A by a ROESY experiment (Figure 1). The α-orientations of H-3, H-5, H-18, H-21, CH$_3$-23, and CH$_3$-26 were established by NOE correlations of H-3/H-5 and CH$_3$-23 and H-18/H-21 and CH$_3$-26, and the β-orientations of H-19, H-28, and CH$_3$-27 were deduced by NOE correlations of CH$_3$-27/H-19 and H-28. Moreover, OH-11 was assigned as α-oriented, as confirmed by NOE correlations of H-11 with CH$_3$-25 and CH$_3$-27. Accordingly, the structure of **5** (rubiyunnanol C) was elucidated as 3β,11α,19α,28-tetrahydroxy-arbor-8-en-7-one. Compound **5** is the first example of an arborinane-type triterpenoid without a double bond at C-9−C-11.

Compound **6** was isolated as white crystals, and its molecular formula C$_{32}$H$_{48}$O$_5$ was established by HRESIMS (m/z 535.3397 [M + Na]$^+$), implying nine degrees of unsaturation. The NMR spectroscopic data of **6** (Tables 1 and 2) were similar to those of rubiarbonone E,[6,12] except for the appearance of an additional acetate group (δ$_H$/δ$_C$ 2.16/21.8, δ$_C$ 170.9) in **6**. The HMBC correlations observed from H-19 (δ$_H$ 6.05) to the acetate carbonyl carbon, C-13, and C-18 indicated that the acetate group is connected to C-19 (Figure 2). Therefore, compound **6** (rubiarbonone E 19-acetate) was established as 19α-acetoxy-7β,28-dihydroxyarbor-1,9(11)-dien-3-one.

Compound **7** gave a molecular formula of C$_{30}$H$_{46}$O$_5$ by HRESIMS at m/z 509.3247 [M + Na]$^+$, 16 mass units higher than that of rubiarbonone E, in accordance with the presence of an additional hydroxy group. Detailed comparison of its ^{1}H and ^{13}C NMR data (Tables 1 and 2) with those of rubiarbonone E strongly supported the similarity in their structures in rings B−E. In ring A, an additional hydroxy group was assigned at C-2, as deduced from HMBC correlations of H-1 (δ$_H$ 6.73) with C-2, C-5, C-9, CH$_3$-25, and the C-3 carbonyl group. Further evidence was obtained from the cross-peaks of H-1 with H-11 and CH$_3$-25
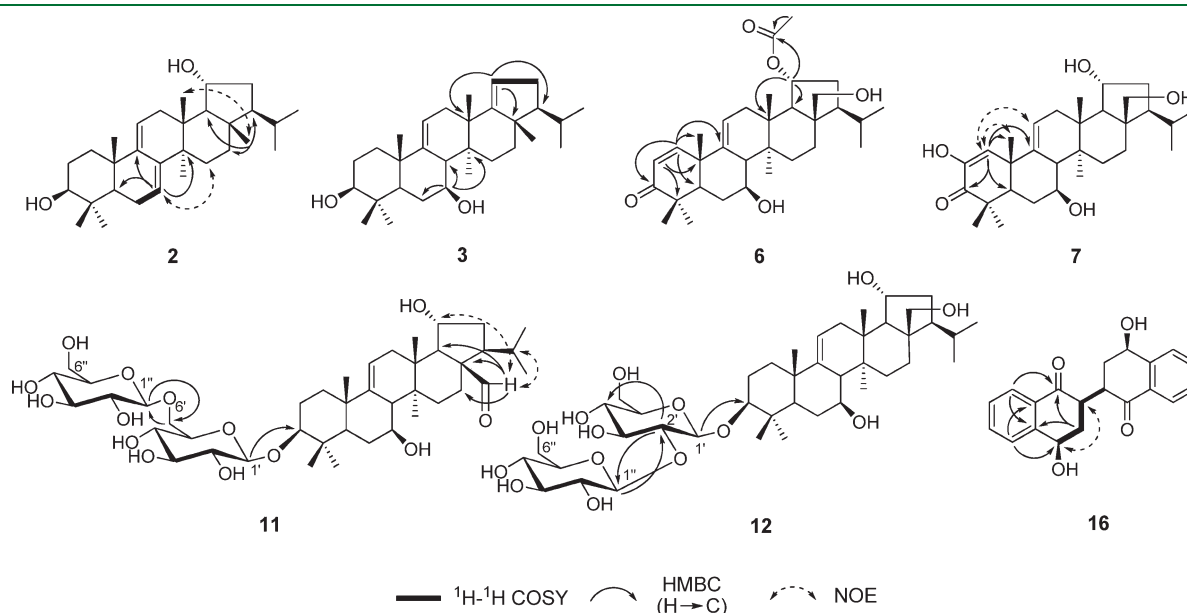
Figure 2. Selected ^{1}H−^{1}H COSY, HMBC, and NOE correlations of **2**, **3**, **6**, **7**, **11**, **12**, and **16**.

Table 3. ^{1}H NMR Data of Compounds 8−12 in Pyridine-d_5 (δ in ppm, J in Hz)

position	8[a]	9[b]	10[b]	11[b]	12[b]
1α	1.65, m	1.52, overlap	1.64, t (12.0)	1.53, m	1.33, m
1β	2.13, overlap	1.73, brd (13.0)	2.05, m	1.73, m	1.58, overlap
2α	5.67, m	2.55, m	5.64, m	2.56, overlap	2.36, overlap
2β		1.98, m		1.97, m	1.89, overlap
3	3.61, d (10.0)	3.37, dd (11.5, 4.0)	3.61, d (10.0)	3.36, dd (11.5, 4.0)	3.31, m
5	1.11, m	0.96, m	1.05, m	0.95, m	0.97, m
6α	2.23, overlap	2.20, overlap	2.19, overlap	2.17, m	2.20, m
6β	1.90, overlap	1.89, overlap	1.87, overlap	1.87, overlap	1.89, overlap
7α	3.99, overlap	3.97, overlap	3.91, overlap	3.95, overlap	3.99, m
8	2.39, overlap	2.36, brd (9.5)	2.36, overlap	2.23, overlap	2.46, overlap
11	5.42, brd (5.6)	5.45, brd (6.0)	5.41, brd (6.0)	5.48, brd (6.0)	5.42, brd (5.0)
12α	2.54, brd (18.0)	2.44, brd (19.0)	2.51, m	2.47, brd (18.5)	2.60, overlap
12β	2.39, overlap	2.29, m	2.36, overlap	2.23, overlap	2.46, overlap
15α	2.80, brd (14.4)	2.78, brd (14.5)	2.76, m	2.90, m	2.80, brd (13.5)
15β	1.90, overlap	1.89, overlap	1.87, overlap	1.87, overlap	2.01, overlap
16α	1.55, overlap	1.52, overlap	1.54, overlap	1.33, overlap	1.58, overlap
16β	1.90, overlap	1.89, overlap	1.87, overlap	2.63, m	2.01, overlap
18	2.31, overlap	2.27, d (9.5)	2.27, d (9.5)	2.56, overlap	2.36, overlap
19	4.69, m	4.64, m	4.66, m	5.02, m	5.10, m
20α	2.13, overlap	2.12, m	2.12, m	2.30, m	2.13, overlap
20β	2.23, overlap	2.20, overlap	2.19, overlap		2.60, overlap
21	1.55, overlap	1.52, overlap	1.54, overlap	1.66, m	1.58, overlap
22	1.55, overlap	1.52, overlap	1.54, overlap	1.33, overlap	2.13, overlap
23	1.38, s	1.28, s	1.34, s	1.27, s	1.31, s
24	1.15, s	1.05, s	1.13, s	1.03, s	1.17, s
25	1.21, s	1.08, s	1.17, s	1.03, s	1.08, s
26	1.29, s	1.24, s	1.23, s	1.24, s	1.33, s
27	1.11, s	1.07, s	1.08, s	0.93, s	1.40, s
28a	4.62, d , (12.0)	4.58, d (12.0)	4.59, d (12.0)	9.98, s	4.17, overlap
28b	4.30, d , (12.0)	4.28, d (12.0)	4.27, overlap		4.10, overlap
29	0.98, d (5.6)	0.96, d (6.0)	0.96, d (6.0)	0.86, d (6.5)	1.08, overlap
30	0.87, d (5.6)	0.85, d (6.0)	0.85, d (6.0)	0.77, d (6.5)	0.95, d (6.5)
Glc-					
1′	4.97, d (8.0)	4.88, overlap	4.93, overlap	4.90, overlap	4.92, d (7.5)
2′	3.99, overlap	3.97, overlap	3.91, overlap	3.95, overlap	4.24, overlap
3′	4.23, m	4.22, overlap	4.17, overlap	4.19, m	4.32, overlap
4′	4.07, overlap	4.12, overlap	4.17, overlap	4.08, overlap	4.17, overlap
5′	4.07, overlap	4.12, overlap	4.08, m	4.14, m	3.94, overlap
6′a	4.92, brd (11.6)	4.88, overlap	4.93, overlap	4.90, overlap	4.51, overlap
6′b	4.86, dd (11.6, 4.4)	4.34, overlap	4.27, overlap	4.34, m	4.42, m
Glc-					
1″		5.13, d (8.0)	5.10, d , (7.5)	5.16, d (8.0)	5.37, d (7.5)
2″		4.06, m	4.02, m	4.08, overlap	4.10, overlap
3″		4.22, overlap	4.22, m	4.26, overlap	3.94, overlap
4″		4.22, overlap	4.17, overlap	4.26, overlap	4.32, overlap
5″		3.97, overlap	3.97, m	3.95, overlap	4.24, overlap
6″a		4.51, brd (12.0)	4.53, brd (12.0)	4.53, dd (12.0, 2.0)	4.51, overlap
6″b		4.34, overlap	4.34, dd (12.0, 5.5)	4.38, m	4.37, dd (12.0, 5.0)
OAc-2	2.31, overlap		2.45, s		
OAc-28	2.07, s	2.06, s	2.05, s		
OAc-6′	2.01, s				

^{a} Recorded at 400 MHz. ^{b} Recorded at 500 MHz.

Table 4. ^{1}H and ^{13}C NMR Data of Compounds 13−16 (δ in ppm, J in Hz)

	13^a		position	14^b		position	15^c		position	16^d	
position	δ_H	δ_C		δ_H	δ_C		δ_H	δ_C		δ_H	δ_C
1		162.3	1		161.8	1		156.7	1, 1'		198.3
2		117.6	2		123.7	2		105.4	2, 2'	3.82, brd (13.2)	47.4
3		162.4	3		161.4	3	7.96, s	108.5	3a, 3'a	2.70, m	37.7
4	7.20, s	107.3	4	7.43, overlap	106.1	4		146.4	3b, 3'b	2.49, m	
4a		131.8	4a		133.9	4a		131.2	4, 4'	5.39, m	68.2
5	7.50, d (2.5)	110.5	5	7.43, overlap	113.1	5	8.66, m	123.1	4a, 4'a		149.5
6		164.0	6		164.8	6	7.56, overlap	129.5	5, 5'	8.19, brd (7.6)	126.9
7	7.39, dd (8.5, 2.5)	120.5	7	7.19, dd (8.4, 2.4)	121.9	7	7.56, overlap	126.8	6, 6'	7.62, brt (7.6)	134.0
8	8.10, d , (8.5)	129.1	8	8.09, d (8.4)	129.9	8	8.57, m	124.1	7, 7'	7.36, brt (7.6)	127.5
8a		126.1	8a		123.7	8a		125.9	8, 8'	8.25, brd (7.6)	127.2
9		185.7	9		186.3	Glc-			8a, 8'a		131.9
9a		108.7	9a		111.3	1'	5.74, d (7.5)	103.7			
10		181.8	10		181.9	2'	4.49, m	75.3			
10a		135.0	10a		135.4	3'	4.41, overlap	78.7			
CH$_3$-2	2.04, s	8.2	Glc-			4'	4.41, overlap	71.4			
OCH$_3$-6	3.93, s	56.1	1'	5.10, d (7.2)	100.6	5'	4.14, m	79.1			
OH-1	13.20, s		2'	3.44, overlap	73.3	6'a	4.59, dd (12.0, 2.0)	62.5			
			3'	3.44, overlap	75.8	6'b	4.41, overlap				
			4'	3.19, m	70.0	COOCH$_3$-2	3.75, s	52.4			
			5'	3.73, m	74.3	OH-1	12.09, s	171.5			
			6'a	4.38, brd (12.0)	63.6						
			6'b	4.05, dd (12.0, 7.8)							
			CH$_2$OH-2	4.63, d (11.4)	51.0						
				4.54, d (11.4)							
			OAc-6'		170.6						
				2.06, s	20.6						
			OH-1	13.39, s							

^{a} ^{1}H at 500 MHz and ^{13}C at 100 MHz in DMSO-d_6. ^{b} ^{1}H at 600 MHz and ^{13}C at 150 MHz in DMSO-d_6. ^{c} ^{1}H at 500 MHz and ^{13}C at 125 MHz in pyridine-d_5. ^{d} ^{1}H at 400 MHz and ^{13}C at 100 MHz in pyridine-d_5.

in the ROESY spectrum (Figure 2). Therefore, the structure of **7** (2-hydroxyrubiarbonone E) was assigned as 2,7β,19α,28-tetrahydroxyarbor-1,9(11)-dien-3-one.

The molecular formula of compound **8** was determined as $C_{42}H_{66}O_{13}$ from the HRESIMS (m/z 777.4425 [M − H]$^-$). Analysis of the ^{1}H and ^{13}C NMR spectroscopic data indicated that **8** is an arborinane-type triterpenoid glycoside with a glucopyranose unit. The NMR data of **8** (Tables 2 and 3) were very similar to those of rubiarboside C,[6] except for signals of a glucopyranosyl unit and an acetate unit. The downfield shift of C-6' (δ_C 65.2) in **8** suggested that the acetate group is attached to the C-6' position of the glucose, which was confirmed by HMBC correlations from H-6' to the acetate carbonyl carbon. The β-anomeric configuration for the glucose was determined from the large $^3J_{H1,H2}$ coupling constant ($J = 8.0$ Hz). Acid hydrolysis of **8** yielded D-glucose, which was determined by GC analysis of its corresponding trimethylsilylated L-cysteine adduct. Therefore, compound **8** was established as 2α,28-diacetoxy-3β,7β,19α-trihydroxyarbor-9(11)-en-3-O-(6'-O-acetyl)-β-D-glucopyranoside (rubianol-e 3-O-(6'-O-acetyl)-β-D-glucopyranoside).

Compound **9** was assigned a molecular formula of $C_{44}H_{72}O_{15}$ from its HRESIMS (m/z 839.4799 [M − H]$^-$). Two anomeric signals (δ_H/δ_C 4.88/107.0, 5.13/105.5) (β form) observed in the ^{1}H and ^{13}C NMR spectra (Tables 3 and 2) and comparison

with analogous data of rubiarboside G[12] suggested that **9** is an arborinane-type triterpenoid diglycoside with two glucopyranosyl units. The addition of an extra acetate functionality in **9** was the only difference determined. The acetate group was located at C-28 by the apparent downfield shift of C-28 (δ_C 65.0) in **9** as well as HMBC correlations of H-28 with the acetate carbonyl carbon, C-16, C-17, C-18, and C-21. Moreover, the H-1'' signal at δ_H 5.13 showed a HMBC correlation with C-6' (δ_C 70.4), in support of a C-1→C-6 linkage of the two glucose moieties. The HMBC correlation between H-1' and C-3 suggested that the sugar unit is attached to C-3. Furthermore, the sugar obtained from acid hydrolysis was identified as D-glucose by GC analysis. Thus, the structure of **9** was established as 28-acetoxy-3β,7β,19α-trihydroxyarbor-9(11)-en-3-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (rubiarboside G 28-acetate).

Compound **10** gave a molecular formula of $C_{46}H_{74}O_{17}$ as established by HRESIMS (m/z 933.4635 [M + Cl]$^-$). The examination of ^{1}H and ^{13}C NMR spectroscopic data (Tables 3 and 2) revealed that **10** is an analogue of **9**, containing an additional acetate group. The acetate group was assigned to C-2 because the methylene signals (δ_H/δ_C 1.98, 2.55/27.4) at C-2 in **9** changed to an oxygenated methine signal (δ_H/δ_C 5.64/70.1) in **10**. This assignment was further confirmed by HMBC correlations of H-2 (δ_H 5.64) with the acetate carbonyl carbon, C-1, and C-3. In

addition, H-2 displayed NOE correlations with CH_3-24 and CH_3-25, indicating the acetate group to be α-oriented. Therefore, compound **10** was characterized as $2\alpha,28$-diacetoxy-$3\beta,7\beta,19\alpha$-trihydroxyarbor-9(11)-en-3-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (2α-acetoxy-28-acetylrubiarboside G).

Compound **11** exhibited a $[M - H]^-$ ion peak at m/z 795.4513 in its HRESIMS, corresponding to the molecular formula $C_{42}H_{68}O_{14}$. Comparison of the NMR spectroscopic data of **11** (Tables 2 and 3) with those of rubiarboside G showed many similarities except that the hydroxymethylene group at C-17 was missing and a formyl group (δ_H/δ_C 9.98/206.4) was present in **11**. This was supported by the significant downfield shift of C-17 (δ_C 61.1), as well as key correlations of the formyl proton (H-28) with C-16, C-17, and C-18 and of H-18, H-21 with the formyl carbonyl carbon (C-28) in the HMBC spectrum. The β-orientation of the formyl group was deduced from NOE correlations of H-28 with H-19 and H-22 (Figure 2). Thus, compound **11** was elucidated as 28β-formyl-$3\beta,7\beta,19\alpha$-trihydroxyarbor-9(11)-en-3-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (rubiarboside G 28-al).

Compound **12** was found to have the same molecular formula, $C_{42}H_{70}O_{14}$, as rubiarboside G, as established by its HRESIMS (m/z 797.4706 $[M - H]^-$). Analysis of the 1D- and 2D-NMR spectroscopic data of **12** (Tables 2 and 3) and comparison with those of rubiarboside G suggested that both compounds possess the same aglycone with two glucopyranosyl units at C-3, differing only in the sequence of the two sugar units. The significant downfield shift of C-2' (δ_C 83.3) and the upfield shift of C-6' (δ_C 62.7) in **12** implied the (1→2) linkage of the two glucose units, as confirmed by the HMBC correlations of H-1'' with C-2' and of H-2' with C-1'' (Figure 2). Moreover, acid hydrolysis of **12** afforded D-glucose by GC analysis. The structure of **12** was therefore established as $3\beta,7\beta,19\alpha,28$-tetrahydroxyarbor-9(11)-en-3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (rubiarbonol A 3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside).

Compound **13** was isolated as yellow needles, and its molecular formula was established as $C_{16}H_{12}O_5$ on the basis of HRESIMS (m/z 307.0578 $[M + Na]^+$), indicating 11 degrees of unsaturation. The IR absorption bands indicated the presence of hydroxy (3409 cm^{-1}), carbonyl (1659 cm^{-1}), and aromatic (1621 and 1593 cm^{-1}) groups. The UV spectrum of **13** exhibited absorptions maxima at 276, 337, and 415 nm, suggesting an anthraquinone as the basic structure. The ^{1}H and ^{13}C NMR spectroscopic data of **13** (Table 4) were closely related to those of 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone,[16] except for the presence of a methoxy group (δ_H/δ_C 3.93/56.1) at the C-6 position in **13**. This deduction was confirmed by the HMBC correlation of the methoxy proton signal (δ_H 3.93) with C-6, as well as NOE correlations of the methoxy proton signal with H-5 and H-7. Therefore, the structure of **13** was elucidated as 1,3-dihydroxy-6-methoxy-2-methyl-9,10-anthraquinone.

Compound **14** was obtained as a pale yellow powder, and its molecular formula was indicated as $C_{23}H_{22}O_{12}$ by HRESIMS (m/z 489.1021 $[M - H]^-$). The ^{1}H and ^{13}C NMR spectra of **14** (Table 4) showed 14 carbon signals of the anthraquinone skeleton, a hydroxymethyl (δ_H/δ_C 4.54, 4.63/51.0), an acetate group, and a β-glucopyranosyl unit. Compound **14** was assigned a similar structure to 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-O-(6'-O-acetyl)-β-glucopyranoside[30] by comparison of their NMR data. The only difference was the replacement of the methyl group at C-2 by the hydroxymethyl group in **14**. This was confirmed by HMBC correlations of CH_2OH-2 with C-2, C-1,

Table 5. IC$_{50}$ Values (μM) of Active Compounds against Three Human Cancer Cell Lines

compound	A549	HeLa	SMMC-7721
2	9.8	NA^a	NA
3	8.2	5.3	NA
6	NA	7.9	NA
9	NA	2.2	NA
19	7.0	2.2	NA
21	NA	3.0	NA
22	NA	4.2	NA
23	NA	NA	4.3
paclitaxel	0.01	0.6	
camptothecin			0.003

^{a} NA: IC$_{50}$ > 10 μM.

Table 6. MIC$_{50}$ Values (μM) of Active Compounds against *Staphylococcus aureus* and *Candida albicans*

compound	S. aureus	C. albicans
19	NA^a	10.8
20	21.5	NA
23	NA	16.0
ampicillin	0.1	
miconazole nitrate		0.9

^{a} NA: MIC$_{50}$ > 25 μM.

and C-3. Acid hydrolysis of **14** gave D-glucose as a sugar residue. Consequently, compound **14** was determined as 1,3,6-trihydroxy-2-hydroxymethyl-9,10-anthraquinone-3-O-(6'-O-acetyl)-β-D-glucopyranoside.

Compound **15** was isolated as a pale yellow powder. Its molecular formula was established as $C_{18}H_{20}O_9$ due to the quasi-molecular ion peak at m/z 379.1030 ($[M - H]^-$) in the HRESIMS, requiring nine degrees of unsaturation. The ^{13}C NMR spectroscopic data of **15** (Table 4) displayed 18 carbon signals corresponding to 10 aromatic carbons, a methyl ester (δ_H/δ_C 3.75/52.4), and signals arising from a β-glucopyranosyl moiety. The above data obtained indicated that **15** is a naphthohydroquinone glycoside derivative like rubinaphthin A,[7] with a methyl ester group. In the HMBC spectrum, the methyl ester proton signal showed correlations with the ester carbonyl carbon (δ_C 171.5) and C-2. Acid hydrolysis of **15** produced D-glucose as determined by GC analysis. Accordingly, the structure of **15** was assigned as 2-carbomethoxy-1,4-naphthohydroquinone-4-O-β-D-glucopyranoside (rubinaphthin A methyl ester).

Compound **16**, a white powder, gave the molecular formula $C_{20}H_{18}O_4$ from the positive-mode HRESIMS (m/z 345.1111 $[M + Na]^+$), indicating 12 degrees of unsaturation. The ^{13}C NMR spectrum (Table 4) displayed 10 carbon signals, including a methylene, six methines (four aromatic and one oxygenated) and three quaternary carbons (one carbonyl and two aromatic). Accordingly, compound **16** was presumed to be a dimer with a symmetrical structure. In the ^{1}H NMR spectrum, four mutually coupled aromatic proton signals resonated at δ_H 8.19 (brd, 7.6), 7.62 (brt, 7.6), 7.36 (brt, 7.6), and 8.25 (brd, 7.6), which suggested that **16** possesses a 1,2-disubstituted benzene ring. The carbonyl signal at δ_C 198.3 (C-1) and the hydroxymethine group at δ_C 68.2 (C-4) were assigned at C-8a and C-4a, respectively,

which were supported by HMBC correlations from H-8 to C-1, C-4a, and C-6 and from H-5 to C-4, C-7, and C-8a. Moreover, the $^1H-^1H$ COSY correlations of H-2/H-3/H-4 and HMBC correlations of H-3/C-4a, C-1, C-2, and C-4 revealed the linkage of C-1/C-2/C-3/C-4. In addition, the connection of the two parts of the dimer was concluded unambiguously to be at C-2/C-2′. In the ROESY spectrum, H-2 showed a correlation with H-4, which indicated that H-2 and H-4 are cofacial and were randomly assigned as α-oriented (Figure 2). Accordingly, the structure of **16** was determined as 4$R'S'$,4′$R'S'$-dihydroxy-2$R'S'$,2′$R'S'$-binaphthalene-1,1′-dione.

Compounds **17** and **18**, named rubiarbonol K and rubiarbonol L, respectively, were initially isolated from *R. yunnanensis* by Zou and co-workers,[9] but their NMR data were not reported. Their ^1H and ^{13}C NMR spectroscopic data were determined (Table S1, Supporting Information).

All compounds isolated were evaluated for their cytotoxicity against three human cancer cell lines, and the active compounds are included in Table 5. Antibacterial activity against *Staphylococcus aureus* and antifungal activity against *Candida albicans* of all compounds were tested using the turbidimetric method[41] with the MIC data shown for the active compounds as shown in Table 6.

■ EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were obtained on an X-4 micromelting point apparatus. Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. IR spectra were obtained by a Tenor 27 spectrophotometer using KBr pellets. 1D and 2D NMR spectra were recorded on Bruker AM-400, DRX-500, or AV-600 spectrometers with TMS as internal standard. Mass spectra were recorded on a VG Autospec-3000 spectrometer or an API QSTAR time-of-flight spectrometer. GC analysis was performed on an Agilent Technologies HP5890 gas chromatograph with a 30QC2/AC-5 quartz capillary column (30 mm × 0.32 mm, 0.25 μm); detection, FID. Analytical or semipreparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Zorbax Eclipse-C$_{18}$ (4.6 mm × 150 mm; 9.4 mm × 250 mm) column. Column chromatography was performed using silica gel (200−300 mesh, Qingdao Yu-Ming-Yuan Chemical Co. Ltd., Qingdao, People's Republic of China), Sephadex LH-20 (Pharmacia Fine Chemical Co., Uppsala, Sweden), and Lichroprep RP-18 gel (40−63 μM, Merck, Darmstadt, Germany). Fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

Plant Material. The roots of *R. yunnanensis* were purchased in September 2007 from the Yunnan Lv-Sheng Pharmaceutical Co. Ltd., Kunming, People's Republic of China. The material was identified by Prof. Su-Gong Wu at Kunming Institute of Botany. A voucher specimen (No. Wu20070905) has been deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried and powdered roots of *R. yunnanensis* (100 kg) were extracted with MeOH (3 × 100 L) under reflux. After removal of the solvent under reduced pressure, the MeOH extract (21 kg) was suspended in H_2O and partitioned successively with EtOAc and *n*-BuOH to give an EtOAc-soluble portion (6.4 kg) and an *n*-BuOH-soluble portion (8 kg). The EtOAc part (6.4 kg) was subjected to silica gel column chromatography eluting with CHCl$_3$−MeOH (1:0, 95:5, 9:1, 8:2, 0:1) to afford a fraction in which cyclopeptides were absent (1.5 kg, CHCl$_3$, Fr.A) and a cyclopeptide-containing fraction (1.2 kg, CHCl$_3$−MeOH, 95:5, 9:1, 8:2, Fr.B).

Fr.A (1.5 kg) was subjected to silica gel CC eluted with a gradient of petroleum ether−EtOAc (1:0−0:1), to obtain six major fractions (Fr.A-1 to Fr.A-6). Fr.A-2 (130 g) was further chromatographed over silica gel using petroleum ether−EtOAc (150:1−100:1) to yield 1-hydroxy-2-methyl-9,10-anthraquinone (15 mg) and 2-carbomethoxy-9,10-anthraquinone (2 mg). Fr.A-3 (70 g) gave **23** (28 mg) and lanosta-9(11),24-dien-3-one (40 mg) after repeated chromatography over Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) and silica gel (petroleum ether−Me$_2$CO, 70:1). Ursolic acid (131 mg) and β-sitosterol (120 mg) were obtained by recrystallization in CHCl$_3$ from Fr.A-4 directly. Fr.A-5 (78 g) was applied to silica gel eluting with CHCl$_3$−MeOH (50:1−20:1) and was then separated over Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) and then a RP-18 column using MeOH−H$_2$O (80−100%), to yield four subfractions (Fr.A-5-1 to Fr.A-5-4). Fr.A-5-2 (270 mg) was separated by semipreparative HPLC (ACN−H$_2$O, 90%) to obtain compounds **2** (5 mg), **3** (4 mg), **4** (11 mg), and **17** (9 mg). Fr.A-5-4 (1 g) was further purified on Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) and then applied to silica gel (CHCl$_3$−Me$_2$CO, 20:1) to give parkeol (44 mg).

The remainder of the cyclopeptide-containing fraction after the isolation of all cyclic hexapeptides[14,15] was combined and named Fr.B (500 g). Fr.B was chromatographed on a silica gel column eluted with CHCl$_3$−MeOH (30:1−8:2) to afford five fractions (Fr.B-1 to Fr.B-5). Fr.B-1 (50 g) was separated by silica gel CC (petroleum ether−Me$_2$CO, 10:1−1:1) and then by Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) to give **13** (5 mg), **21** (24 mg), rubianthraquinone (42 mg), 2-hydroxymethyl-9,10-anthraquinone (2 mg), 6-*cis*-docosenamide (28 mg), and squalene (8 mg). Fr.B-2 (156 g) was chromatographed over silica gel using petroleum ether−Me$_2$CO (5:1−0:1) and then Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) to give three subfractions (Fr.B-2-1 to Fr.B-2-3). Fr.B-2-1 (11 g) was purified by repeated silica gel CC (CHCl$_3$−MeOH, 30:1) to obtain **16** (12 mg), **19** (1.3 g), rubiarbonone C (32 mg), and 1-*O*-hexadecanolenin (17 mg). Fr.B-2-2 (33 g) was separated by RP-18 gel (MeOH−H$_2$O, 60−80%) and silica gel (CHCl$_3$−Me$_2$CO, 5:1) to yield **20** (899 mg), xanthopurpurin (28 mg), 1,6-dihydroxy-2-methyl-9,10-anthraquinone (5 mg), rubiadin (10 mg), and 5,7,2′-trihydroxy-6-methoxyflavone (15 mg). Fr.B-2-3 (68 g) was further subjected to passage over RP-18 gel (MeOH−H$_2$O, 50−80%), followed by repeated silica gel CC (CHCl$_3$−MeOH, 20:1), to give **18** (9 mg), rubianol-e (74 mg), rubiarbonone B (11 mg), 4-epihederagenin (18 mg), maslinic acid (25 mg), spathodic acid (7 mg), and two mixtures. Compound **1** (10 mg) and rubianol-c (7 mg) were purified by semipreparative HPLC (ACN−H$_2$O, 60%) from one mixture, and compound **6** (18 mg) and rubiarbonone A (38 mg) were purified by semipreparative HPLC (ACN−H$_2$O, 65%) from the other mixture. Fr.B-3 (65 g) was subjected to RP-18 gel CC eluting with MeOH−H$_2$O (40−80%), followed by column chromatography over Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) and silica gel (CHCl$_3$−Me$_2$CO, 3:1), to give **5** (15 mg), rubiarbonol A (594 mg), (+)-lariciresinol (85 mg), (+)-isolariciresinol (63 mg), (−)-secoisolariciresinol (100 mg), (+)-pinoresinol (34 mg), and a mixture. The mixture was finally purified by semipreparative HPLC (MeOH−H$_2$O, 60%) to yield **7** (4 mg) and rubiarbonone E (25 mg). Fr.B-4 (89 g) was further separated by Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) and then silica gel CC (CHCl$_3$−MeOH, 15:1) to obtain rubiarbonol F (52 mg), rubianol-d (2 mg), (2S,3S,4R,9E)-1,3,4-trihydroxy-2-[(2′R)-2′-hydroxytetracosanoylamino]-9-octadecene (20 mg), vladinol D (6 mg), and 4-hydroxy-3-prenylbenzoic acid (6 mg). Fr.B-5 (52 g) was subjected to RP-18 gel (MeOH−H$_2$O, 40−60%) and Sephadex LH-20 (CHCl$_3$−MeOH, 1:1) column chromatography to provide three fractions (Fr.B-5-1 to Fr.B-5-3). Compound **15** (13 mg) was purified from Fr.B-5-2 by passage over a RP-18 column (MeOH−H$_2$O, 50%). Compound **8** (39 mg), rubiarboside C (300 mg), daucosterol (210 mg), and a mixture were obtained from Fr.B-5-3 by purification over RP-18 (MeOH−H$_2$O, 40−50%) and silica gel (CHCl$_3$−MeOH, 10:1) columns. The mixture was further separated by semipreparative HPLC

(CH₃CN−H₂O, 48%) and yielded rubianoside I (60 mg) and rubianoside A (8 mg).

The *n*-BuOH layer (8 kg), named Fr.C, was separated using a macroporous adsorption resin D101 and eluted with a gradient of MeOH−H₂O (0−60%). The fractions eluted with MeOH−H₂O (20−60%, 1.3 kg) were combined and subjected to silica gel CC. Gradient elution with CHCl₃−MeOH−H₂O (9:1:0.1−7:3:0.3) gave Fr.C-1 through Fr.C-5. Fr.C-2 (270 g) was further chromatographed over a silica gel column using EtOAc−MeOH (9:1−8:2), followed by passage over RP-18 gel (MeOH−H₂O, 10−60%), to furnish four subfractions (Fr.C-2-1 to Fr. C-2-4). Subfractions Fr.C-2-2 (35 g) and Fr.C-2-4 (23 g) were respectively separated over RP-18 gel (MeOH−H₂O, 30−60%) followed by Sephadex LH-20 eluted with CHCl₃−MeOH (1:1) and then purified by semipreparative HPLC (40% MeOH and 35% CH₃CN) to yield **14** (9 mg) and 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(6′-*O*-acetyl)-β-ᴅ-glucopyranoside (140 mg), and **9** (48 mg) and **10** (29 mg), respectively. Fr.C-4 (85 g) was also chromatographed over RP-18 (MeOH−H₂O, 20%−50%) and Sephadex LH-20 (CHCl₃−MeOH, 1:1) to give subfractions Fr.C-4-1 to Fr.C-4-5. Compounds **11** (30 mg) and **12** (15 mg) were isolated from Fr.C-4-1 by semipreparative HPLC (CH₃CN−H₂O, 30−33%). 1,3,6-Trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(6′-*O*-acetyl)-β-ᴅ-xylopyranosyl-(1→2)-β-ᴅ-glucopyranoside (22 mg) and 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-(3′-*O*-acetyl)-α-ʟ-rhamnopyranosyl-(1→2)-β-ᴅ-glucopyranoside (15 mg) were purified from Fr.C-4-3 by semipreparative HPLC (MeOH−H₂O, 30−35%). Fr.C-5 (35 g) was applied to a silica gel column, eluting with EtOAc−MeOH (8:2−7:3), and then to RP-18 (MeOH-H₂O, 20−30%) and Sephadex LH-20 (MeOH) columns to obtain **22** (140 mg), 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-*O*-α-ʟ-rhamnopyranosyl-(1→2)-β-ᴅ-glucopyranoside (90 mg), and rubiarboside G (120 mg).

*Rubiarbonol A 7-acetate (**1**):* white powder; $[\alpha]_D^{23}$ +1.7 (*c* 0.22, MeOH); UV (MeOH) λ_{max} (log ε) 203 (3.74) nm; IR (KBr) ν_{max} 3423, 2971, 2951, 2870, 1728, 1641, 1460, 1444, 1377, 1248, 1209, 1028 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; positive-mode ESIMS *m/z* 539 [M + Na]⁺; positive-mode HRESIMS *m/z* 539.3707 [M + Na]⁺ (calcd for C₃₂H₅₂O₅Na, 539.3712).

*Rubiyunnanol A (**2**):* white powder; $[\alpha]_D^{16}$ +23.2 (*c* 0.27, CHCl₃); UV (MeOH) λ_{max} (log ε) 244 (3.97) nm; IR (KBr) ν_{max} 3440, 2930, 2886, 2867, 1637, 1470, 1452, 1382, 1374, 1087, 1037, 990 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; positive-mode ESIMS *m/z* 463 [M + Na]⁺; positive-mode HRESIMS *m/z* 463.3540 [M + Na]⁺ (calcd for C₃₀H₄₈O₂Na, 463.3552).

*Rubiyunnanol B (**3**):* white needles (CHCl₃); mp 247−248 °C; $[\alpha]_D^{16}$ +25.8 (*c* 0.32, CHCl₃); UV (MeOH) λ_{max} (log ε) 251 (3.03), 256 (3.06) nm; IR (KBr) ν_{max} 3431, 2968, 2939, 2872, 2831, 1639, 1471, 1453, 1375, 1095, 1077, 1027, 809 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; positive-mode ESIMS *m/z* 463 [M + Na]⁺; positive-mode HRESIMS *m/z* 463.3544 [M + Na]⁺ (calcd for C₃₀H₄₈O₂Na, 463.3552).

*19,28-Didehydroxyrubiarbonol A (**4**):* white powder; $[\alpha]_D^{16}$ +39.7 (*c* 0.28, CHCl₃); UV (MeOH) λ_{max} (log ε) 250 (2.59), 255 (2.60) nm; IR (KBr) ν_{max} 3423, 2941, 2886, 2869, 1639, 1470, 1454, 1380, 1373, 1031 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; positive-mode ESIMS *m/z* 465 [M + Na]⁺; positive-mode HRESIMS *m/z* 465.3710 [M + Na]⁺ (calcd for C₃₀H₅₀O₂Na, 465.3708).

*Rubiyunnanol C (**5**):* white powder; $[\alpha]_D^{18}$ −28.9 (*c* 0.35, MeOH); UV (MeOH) λ_{max} (log ε) 251 (3.74) nm; IR (KBr) ν_{max} 3440, 2954, 2935, 2871, 1656, 1651, 1379, 1025 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; negative-mode FABMS *m/z* 487 (100) [M − H]⁻; negative-mode HRESIMS *m/z* 487.3419 [M − H]⁻ (calcd for C₃₀H₄₇O₅, 487.3423).

*Rubiarbonone E 19-acetate (**6**):* white crystals (CHCl₃); mp 259−260 °C; $[\alpha]_D^{23}$ −4.6 (*c* 0.14, MeOH); UV (MeOH) λ_{max} (log ε) 225

(4.04) nm; IR (KBr) ν_{max} 3547, 3519, 2975, 2954, 2926, 2900, 1706, 1658, 1377, 1272, 1025, 842 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; positive-mode FABMS *m/z* 513 (13) [M + H]⁺; positive-mode HRESIMS *m/z* 535.3397 [M + Na]⁺ (calcd for C₃₂H₄₈O₅Na, 535.3399).

*2-Hydroxyrubiarbonone E (**7**):* white powder; $[\alpha]_D^{23}$ +19.7 (*c* 0.19, MeOH); UV (MeOH) λ_{max} (log ε) 257 (3.65), 262 (3.66), 324 (3.28) nm; IR (KBr) ν_{max} 3441, 2952, 2933, 1676, 1641, 1631, 1383, 1209, 1060 cm⁻¹; ¹H and ¹³C NMR data, see Tables 1 and 2; positive-mode ESIMS *m/z* 509 [M + Na]⁺; positive-mode HRESIMS *m/z* 509.3247 [M + Na]⁺ (calcd for C₃₀H₄₆O₅Na, 509.3242).

*Rubianol-e 3-O-(6′-O-acetyl)-β-ᴅ-glucopyranoside (**8**):* white powder; $[\alpha]_D^{25}$ −25.2 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 203 (3.68) nm; IR (KBr) ν_{max} 3449, 3445, 2971, 2952, 2874, 1726, 1371, 1255, 1082, 1039, 888 cm⁻¹; ¹H and ¹³C NMR data, see Tables 3 and 2; negative-mode FABMS *m/z* 777 (100) [M − H]⁻; negative-mode HRESIMS *m/z* 777.4425 [M − H]⁻ (calcd for C₄₂H₆₅O₁₃, 777.4425).

*Rubiarboside G 28-acetate (**9**):* white powder; $[\alpha]_D^{16}$ −21.7 (*c* 0.36, MeOH); UV (MeOH) λ_{max} (log ε) 250 (3.56), 256 (3.59), 261 (3.45) nm; IR (KBr) ν_{max} 3426, 2942, 2872, 1737, 1631, 1373, 1245, 1078, 1038, 535 cm⁻¹; ¹H and ¹³C NMR data, see Tables 3 and 2; negative-mode FABMS *m/z* 840 (100) [M]⁻; negative-mode HRESIMS *m/z* 839.4799 [M − H]⁻ (calcd for C₄₄H₇₁O₁₅, 839.4792).

*2α-Acetoxy-28-acetylrubiarboside G (**10**):* white powder; $[\alpha]_D^{16}$ −27.9 (*c* 0.32, MeOH); UV (MeOH) λ_{max} (log ε) 250 (3.37), 256 (3.39) nm; IR (KBr) ν_{max} 3427, 2947, 2935, 1722, 1639, 1631, 1373, 1258, 1077, 1041 cm⁻¹; ¹H and ¹³C NMR data, see Tables 3 and 2; negative-mode FABMS *m/z* 897 (48) [M − H]⁻; negative-mode HRESIMS *m/z* 933.4635 [M + Cl]⁻ (calcd for C₄₆H₇₄O₁₇Cl, 933.4614).

*Rubiarboside G 28-al (**11**):* white powder; $[\alpha]_D^{16}$ −41.7 (*c* 0.31, MeOH); UV (MeOH) λ_{max} (log ε) 257 (3.74), 261 (3.74) nm; IR (KBr) ν_{max} 3427, 2948, 2874, 1703, 1639, 1345, 1075, 1039, 535 cm⁻¹; ¹H and ¹³C NMR data, see Tables 3 and 2; negative-mode FABMS *m/z* 795 (100) [M − H]⁻; negative-mode HRESIMS *m/z* 795.4513 [M − H]⁻ (calcd for C₄₂H₆₇O₁₄, 795.4530).

*Rubiarbonol A 3-O-β-ᴅ-glucopyranosyl-(1→2)-β-ᴅ-glucopyranoside (**12**):* white powder; $[\alpha]_D^{16}$ −9.0 (*c* 0.34, MeOH); UV (MeOH) λ_{max} (log ε) 251 (3.42), 256 (3.46), 261 (3.31) nm; IR (KBr) ν_{max} 3425, 2944, 2873, 1637, 1373, 1079, 1037, 591 cm⁻¹; ¹H and ¹³C NMR data, see Tables 3 and 2; negative-mode FABMS *m/z* 797 (100) [M − H]⁻; negative-mode HRESIMS *m/z* 797.4706 [M − H]⁻ (calcd for C₄₂H₆₉O₁₄, 797.4687).

*1,3-Dihydroxy-6-methoxy-2-methyl-9,10-anthraquinone (**13**):* yellowish needles (CHCl₃); mp 250−251 °C; UV (MeOH) λ_{max} (log ε) 276 (4.42), 337 (3.73), 415 (3.70) nm; IR (KBr) ν_{max} 3409, 2923, 1659, 1621, 1593, 1433, 1370, 1323, 1229, 1123, 1016, 757, 586 cm⁻¹; ¹H and ¹³C NMR data, see Table 4 ; EIMS *m/z* 284 (100) [M]⁺; positive-mode HRESIMS *m/z* 307.0578 [M + Na]⁺ (calcd for C₁₆H₁₂O₅Na, 307.0582).

*1,3,6-Trihydroxy-2-hydroxymethyl-9,10-anthraquinone-3-O-(6′-O-acetyl)-β-ᴅ-glucopyranoside (**14**):* pale yellow powder; $[\alpha]_D^{25}$ −50.8 (*c* 0.08, DMSO); UV (MeOH) λ_{max} (log ε) 219 (4.29), 275 (4.40), 302 (4.01), 427 (3.60) nm; IR (KBr) ν_{max} 3525, 3417, 2922, 1712, 1624, 1598, 1580, 1478, 1378, 1306, 1282, 1122, 1082 cm⁻¹; ¹H and ¹³C NMR data, see Table 4; negative-mode ESIMS *m/z* 489 [M − H]⁻; negative-mode HRESIMS *m/z* 489.1021 [M − H]⁻ (calcd for C₂₃H₂₁O₁₂, 489.1033).

*Rubinaphthin A methyl ester (**15**):* pale yellow powder; $[\alpha]_D^{15}$ −73.0 (*c* 0.34, MeOH); UV (MeOH) λ_{max} (log ε) 260 (4.32), 276 (3.44), 312 (3.46), 357 (3.71) nm; IR (KBr) ν_{max} 3422, 2928, 1670, 1637, 1602, 1454, 1442, 1379, 1345, 1248, 1094, 1075, 771 cm⁻¹; ¹H and ¹³C NMR data, see Table 4; negative-mode FABMS *m/z* 379 (77) [M − H]⁻; negative-mode HRESIMS *m/z* 379.1030 [M − H]⁻ (calcd for C₁₈H₁₉O₉, 379.1029).

*4R′S′,4′R′S′-Dihydroxy-2R′S′,2′R′S′-binaphthalene-1,1′-dione (**16**):* white powder; $[\alpha]_D^{23}$ −38.6 (*c* 0.24, pyridine); UV (MeOH) λ_{max} (log ε) 251 (4.46), 287 (3.65) nm; IR (KBr) ν_{max} 3351, 2865, 1683, 1600, 1468,

1456, 1342, 1268, 1224, 1076, 1045, 1018, 970, 773, 764, 707 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 4; positive-mode ESIMS m/z 345 [M + Na]$^+$; positive-mode HRESIMS m/z 345.1111 [M + Na]$^+$ (calcd for $C_{20}H_{18}O_4Na$, 345.1102).

Acid Hydrolysis of Compounds 8−12, 14, and 15. Compounds **8−12** (6 mg) and **14** and **15** (4 mg) were hydrolyzed with 2 M HCl in 1,4-dioxane (1:1, 4 mL) under reflux at 80 °C for 6 h, respectively. Each reaction mixture was extracted with $CHCl_3$ three times (2 mL × 3). The aqueous layer was neutralized with 2 M NaOH and then dried to give one or more monosaccharides. The dried powders were dissolved in pyridine (2 mL), L-cysteine methyl ester hydrochloride (1.5 mg) was added, and the mixture was heated at 60 °C for 1 h. Thereafter, trimethylsilylimidazole (1.5 mL) was added to the reaction mixture in ice-cold water and kept at 60 °C for another 30 min. An aliquot (4 μL) of the supernatant was directly subjected to GC analysis under the following conditions: column temperature 180−280 °C; programmed increase, 3 °C/min; carrier gas N_2 (1 mL/min); injector and detector temperature 250 °C, split ratio 1:50. The configurations of D-glucose for **8−12**, **14**, and **15** were determined by comparing the retention times with the derivatives of authentic samples (D-glucose: 18.20 min, L-glucose: 18.79 min).

Cytotoxicity Assays. The cytotoxicity of the test compounds against the A549 (human lung adenocarcinoma), HeLa (human cervical carcinoma), and SMMC-7721 (human hepatocellular carcinoma) cancer cell lines was measured using a sulforhodamine B (SRB) assay as described in the literature.[42] Paclitaxel and camptothecin were used as positive controls. Briefly, cells were plated in 96-well culture plates for 24 h and then treated with serial dilutions of all compounds, with a maximum concentration of 20 μg/mL. After being incubated for 48 h under a humidified atmosphere of 5% CO_2 at 37 °C, cells were fixed with 25 μL of ice-cold 50% trichloroacetic acid and incubated at 4 °C for 1 h. After washing with distilled water and air-drying, the plate was stained for 15 min with 100 μL of 0.4% SRB (Sigma) in 1% glacial acetic acid. The plates were washed with 1% acetic acid and air-dried. For reading the plate, the protein-bound dye was dissolved in 100 μL of 10 mM Tris base. The absorbance was measured at 560 nm on a microplate spectrophotometer (Molecular Devices SpectraMax 340, MWG-Biotech, Inc., Sunnyvale, CA, USA). All tests were performed in triplicate, and results are expressed as IC_{50} values.

Antimicrobial Assay. Test compounds were evaluated for their antibacterial activity against the Gram-positive *Staphylococcus aureus* CGMCC1.2465 and for antifungal activity against *Candida albicans* CGMCC 2.2086 using a turbidimetric method as described in the literature.[41] All organisms were obtained from China General Microbiological Culture Collection Center (CGMCC). Ampicillin and miconazole nitrate were used as positive controls for antibacterial and antifungal activities, respectively. Inocula were prepared by correcting the OD_{620} of microbe suspensions in incubation broth to McFarland standard 0.5 and diluted with medium to 1×10^6 cfu/mL. Inocula were plated in 96-well U-bottomed culture plates and then treated with serial dilutions of all compounds with the maximum concentration of 25 μg/mL. The *S. aureus* was incubated in Mueller-Hinton broth at 37 °C for 24 h, while the *C. albicans* in potato dextrose agar broth at 25 °C for 24 h. The absorbance was measured at 620 nm on a microplate spectrophotometer. All tests were performed in triplicate, and results are expressed as MIC_{50} values.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Copies of 1D and 2D NMR spectra and physical data of compounds **1−18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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