Chemical Constituents of *Heteroplexis micocephala*

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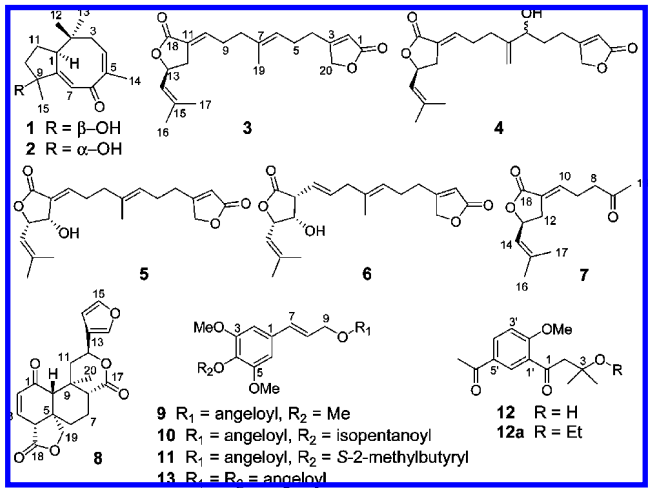
Eleven new compounds including two sesquiterpenes with an unusual 2,2,5,9-tetramethylbicyclo[6.3.0]undecane carbon skeleton (**1** and **2**), five phytane-type diterpene dilactones (**3**−**7**), an *ent*-clerodane diterpene dilactone (**8**), and three phenylpropenol esters (**9**−**11**), together with a diacylphenol (**12**) and 38 known compounds, have been isolated from an ethanolic extract of *Heteroplexis micocephala*. Their structures including absolute configurations were elucidated by spectroscopic and chemical analyses. In the *in vitro* assays, compound **6** showed a selective cytotoxic activity against A2780 with an IC_{50} value of 4.37 μM, while sinapyl diangelate (**13**) showed a potent activity inhibiting HIV-1 replication with an IC_{50} value of 4.04 μM.

Heteroplexis (Compositae) is a unique genus consisting of five species found in the limestone terrains of Longzhou and Yangshuo, Guangxi Province, mainland China. *H. micocephala* Y. L. Chen is planted and used as a folk medicine for treatment of indigestion and dropsy.[1] However, nothing is known about the chemical constituents of the genus. As part of a program to assess the chemical and biological diversity of several traditional Chinese medicines,[2] an ethanolic extract of *H. micocephala* has been investigated. We report herein the isolation, structural elucidation, and *in vitro* bioassays of 11 new compounds including two sesquiterpenes with an unusual 2,2,5,9-tetramethylbicyclo[6.3.0]-undecane carbon skeleton (**1** and **2**), five phytane-type diterpene dilactones (**3**−**7**), an *ent*-clerodane diterpene dilactone (**8**), and three phenylpropenol esters (**9**−**11**), together with a diacylphenol (**12**) and 38 known compounds. Although derivatives with the 2,2,5,9-tetramethylbicyclo[6.3.0]undecane carbon skeleton were semisynthesized by the acid-catalyzed transannular cyclization of zerumbol and zerumbone epoxide,[3] compounds **1** and **2** are the first examples of natural products with this skeleton.



Results and Discussion

Compound **1** was obtained as a yellowish oil, $[\alpha]^{20}_D$ −84.0 (*c* 0.16, MeOH), and the presence of hydroxy (3424 cm^{-1}) and conjugated ketone (1730, 1714, 1650, 1623, and 1601 cm^{-1}) groups was indicated by its IR spectrum. The EIMS of **1** gave a molecular ion peak at *m/z* 234 $[M]^{+\bullet}$, and the molecular formula $C_{15}H_{22}O_2$ (calcd for $C_{15}H_{22}O_2$, 234.1620) with five degrees of unsaturation was indicated by HREIMS at *m/z* 234.1623 $[M]^{+\bullet}$. The ^1H NMR spectrum of **1** in acetone-d_6 showed signals attributed to three tertiary methyls at δ 0.91 (s, H_3-12), 1.07 (s, H_3-13), and 1.31 (s, H_3-15) and an olefinic methyl at δ 1.84 (d, J = 1.5 Hz, H_3-14). Signals attributed to olefinic protons at δ 6.21 (ddq, J = 12.0, 12.0, 1.5 Hz, H-4) and 6.39 (d, J = 2.0 Hz, H-7) indicated the presence of two trisubstituted double bonds. An exchangeable singlet at δ 4.00 (O*H*-9) suggested the presence of a hydroxy group attached at a quaternary carbon. A double doublet at δ 2.92 (dd, J = 6.5 and 2.0 Hz, H-1) and a broadened triplet at δ 2.34 (brt, J = 12.0 Hz, H-3a), together with partially overlapped multiplets integrating for five protons between δ 1.63 and 1.96 (see Table 1), suggested the presence of a methine and three methylenes in **1**. The ^{13}C NMR and DEPT spectra showed carbon signals corresponding to the above protonated units and five quaternary carbons (Table 2). On the basis of chemical shifts, the quaternary carbons were differentiated to be a carbonyl carbon, two olefinic carbons, an oxygen-bearing carbon, and an aliphatic carbon. These spectroscopic data suggested that **1** was an unusual bicyclic sesquiterpene containing crossed conjugated dienone and hydroxy functional groups.

The structure was further elucidated by the 2D NMR spectroscopic data of **1**. Analysis of $^1H-^1H$ COSY and HSQC spectra provided unambiguous assignments of proton and carbon signals. In the HMBC spectrum, long-range correlations from H-1 to C-8, C-10, and C-11, from both HO-9 and H_3-15 to C-8, C-9, and C-10, and from HO-9 to C-15, in combination with chemical shifts and coupling patterns of these protons and carbons, indicated the presence of a 9-hydroxy-9-methylcyclopentane moiety. HMBC correlations from H-4 to C-6 and C-14, from H-7 to C-1, C-5, and C-8, from both H_3-12 and H_3-13 to C-1, C-2, and C-3, and from H_3-14 to C-4, C-5, and C-6, together with chemical shifts and coupling patterns of these protons and carbons, indicated unequivocally that there was an unusual 2,2,5-trimethylcycloocta-4,7-dien-6-one moiety in **1**. Accordingly, the planar structure of **1** was assigned as 9-hydroxy-2,2,5,9-tetramethylbicyclo[6.3.0]undeca-4,7-dien-6-one. The configuration of **1** was elucidated by an analysis of the NOE difference experiment and CD data. Irradiation of H-1 enhanced H_3-13 and H_3-15, and in turn irradiation of H_3-15 enhanced H-1 and H-7. This indicated that H-1, H_3-13, and H_3-15 were cofacially oriented. The CD spectrum of **1** showed negative Cotton effects at 354 ($\Delta\varepsilon$ −1.1) and 257 nm ($\Delta\varepsilon$ −5.88). Molecular modeling using the MM2 program indicated that the cross-conjugated octadienone ring of 1*S*,9*S*- or 1*R*,9*R*-9-hydroxy-2,2,5,9-tetramethylbicyclo[6.3.0]undeca-4,7-dien-6-one possessed a slightly twisted boat conformation for the lowest energy conformation (Figure S1, Supporting Information). On the basis of the octant

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Table 1. ^{1}H NMR Spectroscopic Data (δ) of Compounds **1**−**8**[a]

position	1	2	3	4	5	6	7	8
1	2.92 dd (6.5, 2.0)	3.04 td (6.0, 2.5)						
2			5.84 s	5.84 t (2.0)	5.84 s	5.85 s		6.14 dd (10.0, 3.0)
3a	2.34 t (12.0)	2.27 t (12.0)						6.58 dd (10.0, 3.0)
3b	1.72 t (12.0)	1.75 dd (12.0, 8.5)						
4	6.21 ddq (12.0, 12.0, 1.5)	6.19 ddq (12.0, 8.5, 1.0)	2.45 t (7.0)	2.55 m	2.53 m	2.53 m		3.37 t (3.0)
5a			2.31 dt (14.0, 7.0)	1.91 m	2.36 m	2.35 m		
5b				1.82 m				
6a			5.13 t (7.0)	4.17 dt (7.0, 5.0)	5.26 t (6.5)	5.26 td (7.0, 1.0)		2.03 m
6b								1.75 m
7a	6.39 d (2.0)	6.40 d (2.5)						2.10 m
7b								1.75 m
8a			2.16 t (7.0)	2.33 dt (15.0, 7.5)	2.22 m	2.75 d (7.0)	2.70 t (7.2)	2.54 dd (11.5, 3.0)
8b				2.22 dt (15.0, 7.5)				
9			2.26 dt (14.0, 7.0)	2.42 m	2.53 m	5.70 dt (15.0, 7.0)	2.37 q (7.2)	
10a	1.89 m	1.85 m	6.66 m	6.57 m	6.71 td (7.5, 1.0)	5.57 dd (15.0, 8.5)	6.49 m	3.01 s
10b	1.66 m	1.75 m						
11a	1.93 m	1.90 m				3.49 dd (8.5, 4.5)		3.00 dd (12.0, 5.0)
11b	1.65 m	1.70 m						1.95 t (12.0)
12a	0.91 s	0.81 s	3.03 dd (17.0, 5.0)	3.15 dd (16.5, 3.5)	4.93 dd (6.0, 5.0)	4.41 ddd (4.5, 4.5, 2.0)	3.18 dd (18.4, 7.2)	5.60 dd (12.0, 5.0)
12b			2.48 m	2.52 m			2.55 m	
13	1.07 s	1.05 s	5.21 dt (7.0, 4.0)	5.26 m	5.10 dd (9.0, 5.0)	5.15 dd (9.0, 4.5)	5.25 m	
14	1.84 d (1.5)	1.84 brs	5.22 d (4.0)	5.26 m	5.47 d (9.0)	5.47 d (9.0)	5.25 m	6.56 brs
15	1.31 s	1.38 s						7.64 brs
16			1.75 s	1.75 s	1.75 s	1.75 s	1.75 s	7.54 brs
17			1.77 s	1.75 s	1.79 s	1.76 s	1.75 s	
19a			1.63 s	5.12 brs	1.67 s	1.64 s	2.11 s	4.60 d (9.5)
19b				4.88 brs				4.11 d (9.5)
20			4.73 s	4.83 d (2.0)	4.81 s	4.81 d (2.0)		1.16 s
OH	4.00 s	3.87 s		4.05 d (5.0)	4.40 d (6.0)	4.44 d (2.0)		

[a] Data (δ) were measured in $CDCl_3$ for **3** and in acetone-d_6 for **1**, **2**, and **4**−**8** at 500 MHz. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT, ^{1}H−^{1}H COSY, HSQC, and HMBC experiments.

Table 2. ^{13}C NMR Spectroscopic Data (δ) of Compounds **1**−**8**[a]

position	1	2	3	4	5	6	7	8
1	49.8	49.9	174.0	174.3	174.3	173.5		197.0
2	44.5	43.9	115.7	115.2	115.5	115.6		132.6
3	41.1	41.3	169.9	172.5	172.0	172.0		139.4
4	133.7	133.2	28.5	25.4	29.0	29.1		53.2
5	140.8	141.1	25.7	33.8	26.3	26.4		43.7
6	195.9	196.1	123.2	74.2	124.5	124.5		35.0
7	130.4	130.1	135.8	151.9	136.3	136.2	206.8	19.1
8	169.4	170.2	37.8	30.4	38.8	43.5	41.6	50.9
9	80.9	80.8	28.4	29.1	28.5	134.9	24.6	36.1
10	41.1	41.2	139.3	130.2	144.6	124.2	138.4	56.7
11	24.6	24.3	126.9	128.5	132.7	51.5	128.8	43.0
12	25.6	25.7	32.4	32.9	68.1	74.2	32.8	72.1
13	26.0	25.9	74.3	74.6	79.7	80.1	74.7	127.2
14	20.1	20.2	123.6	125.2	119.2	119.4	125.2	109.7
15	30.4	26.6	139.6	130.2	140.4	140.3	139.2	144.6
16			18.4	18.3	18.6	18.6	18.2	140.9
17			25.6	25.7	26.1	26.0	25.7	171.3
18			170.8	170.8	170.3	176.7	170.8	173.6
19			16.0	110.3	16.0	16.2	30.2	72.4
20			73.1	73.7	73.7	73.7		14.6

[a] Data (δ) were measured in $CDCl_3$ for **3** at 125 MHz and in acetone-d_6 for **1**, **2**, and **4**−**8** at 125 or 150 MHz. The assignments were based on DEPT, ^{1}H−^{1}H COSY, HSQC, and HMBC experiments.

rule for cross-conjugated dienones,[4] negative Cotton effects were predicted by the octant projection diagram of the 1*S*,9*S*-enantiomer, whereas positive Cotton effects were predicted for the 1*R*,9*R*-enantiomer. Therefore, the structure of **1** was determined as (−)-1*S*,9*S*-9-hydroxy-2,2,5,9-tetramethylbicyclo[6.3.0]undeca-4,7-dien-6-one.

Compound **2** was obtained as a yellowish gum, $[\alpha]^{20}_D$ −55.3 (*c* 0.53, MeOH). Its IR, EIMS, and NMR spectroscopic features were similar to those of **1** (see Tables 1 and 2 and Experimental Section), indicating that **2** is an isomer of **1**. Analysis of the 2D NMR spectroscopic data of **2** further confirmed that it had a planar structure identical to that of **1**. However, the NMR resonances assignable to H-1, H_3-15, and C-8 of **2** (Tables 1 and 2) were deshielded by $\Delta\delta_H$ +0.12, +0.07 and $\Delta\delta_C$ +0.8 ppm, respectively, compared to those of **1**. Meanwhile, the resonances due to H-3a, H_3-12, and C-15 of **2** were shielded by $\Delta\delta_H$ −0.07, −0.10 and $\Delta\delta_C$ −3.8 ppm, respectively. These differences suggested that **2** was a C-1 or C-9 epimer of **1**. The C-9 epimeric relationship was confirmed by the NOE difference experiment of **2** that showed enhancements of HO-9 and H_3-13 by irradiation of H-1 and an enhancement of H_3-12 by irradiation of H_3-15. This was supported by the molecular modeling and the octant projection diagrams of the C-1 and C-9 epimers of **1** (Figure S2, Supporting Information). Therefore, the structure of **2** was determined as (−)-1*S*,9*R*-9-hydroxy-2,2,5,9-tetramethylbicyclo[6.3.0]undeca-4,7-dien-6-one.

Compound **3**, a yellowish oil, $[\alpha]^{20}_D$ +31.3 (*c* 1.38, MeOH), showed IR absorptions (1778, 1748, 1678, and 1637 cm^{-1}) consistent with the presence of both an exo- and an endocyclic unsaturated γ-lactone functionality. The EIMS of **3** gave a molecular ion peak at *m*/*z* 330 $[M]^{+\bullet}$, and the HREIMS at *m*/*z* 330.1859 $[M]^{+\bullet}$

indicated that the molecular formula of **3** was $C_{20}H_{26}O_4$. The ^{1}H NMR spectrum of **3** displayed signals attributed to three olefinic tertiary methyls at δ 1.63 (s, H_3-19), 1.75 (s, H_3-16), and 1.77 (s, H_3-17) and signals assignable to five olefinic and/or oxygen-bearing methines at δ 6.66 (m, H-10), 5.84 (s, H-2), 5.22 (d, J = 4.0 Hz, H-14), 5.21 (dt, J = 7.0, 4.0 Hz, H-13), and 5.13 (t, J = 7.0 Hz, H-6). In addition, it showed signals due to a deshielded oxymethylene and five aliphatic methylenes (Table 1). The ^{13}C NMR spectrum of **3** showed 20 carbon resonances corresponding to the above protonated units and six quaternary carbons including two ester carbonyls and four olefinic carbons (Table 2). The above spectroscopic data indicated that **3** is a dilactonized acyclic diterpene. The protonated carbons and their bonded protons (see Tables 1 and 2) were assigned unambiguously by the HSQC data. In the ^{1}H−^{1}H COSY spectrum of **3**, homonuclear vicinal coupling correlation between H_2-5 and both H_2-4 and H-6, and between H_2-9 and both H_2-8 and H-10, in combination with the chemical shifts and coupling patterns of these protons, indicated unambiguously the presence of the two structural fragments from C-4 to C-6 and from C-8 to C-10 in **3**. Vicinal coupling correlations of H-13 with both H_2-12 and H-14, together with the chemical shifts and coupling patterns of these protons, established the fragment from C-12 to C-14 in **3**. In the HMBC spectrum of **3**, two- and three-bond heteronuclear correlations from H-6 to C-4, C-5, C-8, and C-19, from H_2-8 to C-6, C-7, C-9, C-10, and C-19, and from H_3-19 to C-6, C-7, and C-8 indicated unequivocally that the two former fragments were connected through C-7 to form a linear central moiety and that one of the methyls was located at C-7 in **3**. HMBC correlations from H-2 to C-1, C-3, C-4, and C-20, from H_2-4 to C-2, C-3, C-5, C-6, and C-20, and from H_2-20 to C-1, C-2, and C-3, in combination with chemical shifts of these protons and carbons, indicated the presence of the eastern α,β-unsaturated γ-lactone ring fragment connecting to the central moiety through a single bond between C-3 and C-4. HMBC correlations from H_2-9 to C-11, from H-10 to C-12 and C-18, and from H-12a to C-11, C-13, C-14, and C-18, along with the chemical shifts of these protons and carbons, indicated the presence of the western γ-lactone ring fragment connecting to the central moiety through a double bond between C-10 and C-11. In addition, HMBC correlations from H-14 to C-16 and C-17 and from both H_3-16 and H_3-17 to C-14 and C-15, together with chemical shifts of these protons and carbons, established the connection of C-15 with C-14, C-16, and C-17. In the NOE difference experiment of **3**, irradiation of H-6 caused an enhancement of H_2-8, while H_2-9 was enhanced by irradiation of H-12a. These NOE data indicated an *E* geometric configuration for the double bonds between C-6 and C-7 and between C-10 and C-11. On the basis of the specific rotations reported for γ-substituted α-methylene-γ-lactones,[5] the positive specific rotation of **3** indicated that it had 13*S*-configuration. Thus, the structure of **3** was determined and assigned the trivial name heteroplexisolide A.

Compound **4**, a yellowish oil, $[\alpha]^{20}_D$ +31.4 (*c* 0.50, MeOH), exhibited a quasimolecular ion peak at *m*/*z* 369 $[M + Na]^+$ in its positive ESIMS. The molecular formula $C_{20}H_{26}O_5$ (calcd for $C_{20}H_{26}O_5Na$, 369.1678) of **4**, with one oxygen more than that of **3**, was indicated from the HRESIMS at *m*/*z* 369.1688 $[M + Na]^+$. The IR and NMR spectroscopic features of **4** showed some similarities to those of **3** (see Tables 1 and 2 and Experimental Section). However, the IR spectrum of **4** showed the presence of hydroxy group(s) (3463 cm^{-1}). The ^{1}H NMR spectrum of **4** showed that the signals of the olefinic methyl (*CH*$_3$-19) and methine (*CH*-6) of **3** were replaced respectively by signals attributable to an olefinic methylene [δ_H 5.12 and 4.88 (brs each, H-19a and H-19b) and δ_C 110.3] and an oxymethine [δ_H 4.17 (dt, J = 7.0 and 5.0 Hz, H-6) and 4.05 (d, J = 5.0 Hz, exchangeable, HO-6) and δ_C 74.2]. This suggested that **4** was a derivative of **3** containing a double bond between C-7 and C-19 and a hydroxy group at C-6. This suggestion was supported by changes of the chemical shifts and coupling patterns of the central moiety of **4** as compared with those of **3** (Tables 1 and 2). It was further confirmed by the 2D NMR spectroscopic data of **4**, which permitted unambiguous assignment of the NMR data (Tables 1 and 2). In particular, in the HMBC spectrum of **4**, long-range heteronuclear correlations from H_2-19 to C-6, C-7, and C-8 and from HO-6 to C-5 and C-6, together with chemical shifts and coupling patterns of these protons and carbons, proved the location of the double bond between C-7 and C-19 and the hydroxy group at C-6 in **4**. The CD data of **4** (Experimental Section) were similar to those of **3**. This suggested that **4** also possessed *S* absolute configuration at C-13. Therefore, the structure of **4** was proposed for heteroplexisolide B. The determination of the absolute configuration at C-6 of **4** by using the Mosher's method failed due to a limitation of the sample amount.

Compound **5** was obtained as a yellowish oil, $[\alpha]^{20}_D$ +67.0 (*c* 2.08, MeOH). The IR and HRESIMS data of **5** (Experimental Section) indicated that it is an isomer of **4**. However, the NMR data of **5** (Tables 1 and 2) indicated that it possessed a central linear moiety and an eastern α,β-unsaturated γ-lactone ring identical to those of **3**. A further analysis of the ^{1}H NMR spectrum of **5** demonstrated that the chemical shifts and coupling patterns assignable to the western γ-lactone moiety [δ_H 4.40 (d, J = 6.0 Hz, exchangeable, O*H*-12), 4.93 (dd, J = 6.0 and 5.0 Hz, H-12), 5.10 (dd, J = 9.0 and 5.0 Hz, H-13), and 5.47 (d, J = 9.0 Hz, H-14)] were significantly different from those of **3** and **4**. These data suggested that the hydroxy group is located at C-12 in **5** instead of C-6 in **4**. This suggestion was supported by the ^{13}C NMR (Table 2) and 2D NMR data of **5**. In particular, it was proved by two- and three-bond correlations from HO-12 to C-11, C-12, and C-13 and from H-12 to C-10, C-11, C-13, and C-18 in the HMBC spectrum. In the NOE difference spectrum of **5**, irradiation of HO-12 enhanced H-14, while irradiation of H-12 caused enhancements of H_2-9 and H-13. This indicated a *cis*-orientation of H-12 and H-13 and an *E* geometric configuration of the double bond between C-10 and C-11 for **5**. On the basis of comparison of the specific rotation of **5** with those of the closely related analogues, such as 3-epilitsenolides D_1 and D_2,[6] the absolute configuration of **5** was proposed to be 12*S*,13*S*. Therefore, the structure of **5** was determined for heteroplexisolide C.

The spectroscopic data of **6** (Tables 1 and 2 and Experimental Section) indicated that it is also an isomer of **4**. Comparison of the NMR data of **5** and **6** indicated that they had the same eastern α,β-unsaturated γ-lactone ring. However, the signals assigned to H_2-9 and H-10 of **5** were replaced by resonances attributed to an *E*-double bond [δ 5.70 (dt, J = 15.0, 7.0 Hz, H-9) and 5.57 (dd, J = 15.0, 8.5 Hz, H-10)] and a deshielded methine [3.49 (dd, J = 8.5, 4.5 Hz, H-11)] for **6**. This suggested that the double bond between C-10 and C-11 in **5** shifted to between C-9 and C-10 in **6**. The suggestion was supported by a shielded shift of H-12 ($\Delta\delta$ −0.52 ppm) for **6** compared with **5**. The elucidation was further verified by the ^{13}C NMR (Table 2) and 2D NMR data of **6**. Although the C-1 resonance was not clearly observable in the ^{13}C NMR spectrum of **6**, the HMBC spectrum (Supporting Information) indicated that there was a carbon resonance at δ_C 173.5 correlating with H_2-20. HMBC correlations from H-9 to C-8, C-10, and C-11, from H-10 to C-8, C-9, and C-11, from H-11 to C-9, C-10, and C-18, and from H-13 to C-15, together with the chemical shifts and coupling constants of these protons and carbons, confirmed the location of the double bond between C-9 and C-10 and the hydroxy group at C-12 in **6**. In the NOE spectrum, irradiation of H-11 enhanced H-12 and H-13; in turn irradiation of H-13 enhanced H-11 and H-12. These data indicated that H-11, H-12, and H-13 are oriented on the same side of the western lactone ring in **6**. The positive specific rotation suggested that **6** had an 11*R*,12*S*,13*S* configuration.[6] Therefore, the structure of **6** was determined for heteroplexisolide D.

Compound **7** was obtained as a yellowish oil, $[\alpha]^{20}_D$ +15.6 (*c* 0.27, MeOH). Its IR spectrum showed the presence of conjugated lactone (1752 and 1679 cm^{-1}) and carbonyl (1715 cm^{-1}) groups.

Table 3. NMR Spectroscopic Data (δ) for Compounds **9**−**11**[a]

	9		**10**		**11**	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		133.0		135.7		135.6
2	6.79 s	105.0	6.85 s	104.2	6.85 s	104.3
3		154.5		153.4		153.4
4		139.4		129.7		129.6
5		154.5		153.4		153.4
6	6.79 s	105.0	6.85 s	104.2	6.85 s	104.3
7	6.65 d (16.0)	134.6	6.69 d (15.5)	134.2	6.70 d (15.5)	134.2
8	6.36 dt (16.0, 6.5)	123.9	6.45 dt (15.5, 6.0)	125.1	6.44 dt (15.5, 6.0)	125.0
9	4.77 dd (6.5, 1.0)	65.1	4.79 dd (6.0, 1.0)	65.0	4.79 dd (6.0, 1.0)	65.0
1′		167.8		167.7		167.8
2′		133.0		128.7		128.7
3′	6.10 qd (7.0, 1.0)	138.2	6.11 qd (7.0, 1.5)	138.3	6.11 qd (7.0, 1.5)	138.3
4′	1.96 dd (7.0, 1.0)	15.9	1.96 dd (7.0, 1.5)	15.9	1.96 dd (7.0, 1.5)	15.9
5′	1.88 brs	20.7	1.88 t (1.5)	20.7	1.88 t (1.5)	20.7
1″				170.5		174.2
2″			2.40 d (7.0)	43.3	2.62 q (7.0)	41.6
3″a			2.18 m	26.7	1.77 m	27.6
3″b					1.59 m	
4″			1.04 d (6.5)	22.6	1.01 t (7.0)	11.7
5″			1.04 d (6.5)	22.6	1.23 d (7.0)	17.2
OMe-3	3.83 s	56.4	3.81 s	56.4	3.81 s	56.6
OMe-4	3.71 s	60.5				
OMe-5	3.83 s	56.4	3.81 s	56.4	3.81 s	56.6

[a] Data (δ) were measured in acetone-d_6 for **9**, **10**, and **11** at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT and HMBC experiments.

The EIMS gave a molecular ion peak at *m/z* 222 $[M]^{+\bullet}$, and the HREIMS at *m/z* 222.1249 $[M]^{+\bullet}$ indicated the molecular formula $C_{13}H_{18}O_3$ (calcd for $C_{13}H_{18}O_3$, 222.1256). The NMR spectra resembled those of **3** except for the absence of resonances attributed to the eastern side moiety at C-7 of **3** (Tables 1 and 2). In addition, in the NMR spectra of **7**, the resonance corresponding to C-7 of **3** appeared to be a carbonyl at δ_C 206.8, while resonances corresponding to H_2-8 and H_3-19 and C-8 and C-19 of **7** were deshielded, respectiveyly, by $\Delta\delta_H$ +0.54 and +0.48 ppm and $\Delta\delta_C$ +3.8 and +14.2 ppm, as compared with those of **3**. The above data indicated that compound **7** was a 7-oxo analogue of **3** eliminating the eastern side moiety on C-7. This was confirmed by the HMBC experiment of **7** that showed correlations from H_2-8, H_2-9, and H_3-19 to C-7. The positive specific rotation of **7** indicated that it had a 13*S* configuration.[5] Thus, the structure of **7** was determined for heteroplexisolide E.

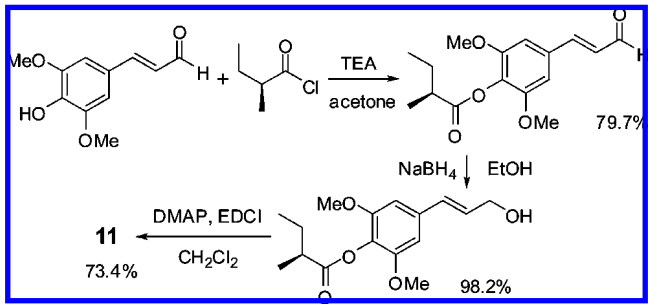
Compound **8**, a white amorphous powder, $[\alpha]^{20}_D$ −22.8 (*c* 0.26, MeOH), showed IR absorption bands for lactone (1783 and 1670 cm^{-1}) and conjugated carbonyl (1668 cm^{-1}) functional groups. Its EIMS exhibited a molecular ion peak at *m/z* 356 $[M]^{+\bullet}$, and the HREIMS at *m/z* 356.1241 $[M]^{+\bullet}$ suggested a molecular formula of $C_{20}H_{20}O_6$ (calcd for $C_{20}H_{20}O_6$, 356.1260). The NMR data of **8** displayed characteristic signals of a β-substituted furan ring at δ 7.64 (brs, H-15), 7.54 (brs, H-16) and 6.56 (brs, H-14),[7] which were in accordance with the IR absorption for a furan ring (ν_{max} 3154, 1509, and 875 cm^{-1}). A group of signals at δ 6.14 (dd, J = 10.0, 3.0 Hz, H-2), 6.58 (dd, J = 10.0, 3.0 Hz, H-3), and 3.37 (t, J = 3.0 Hz, H-4) were assignable to a *cis* −CH═CH−CH− unit. An ABX spin system at δ 3.00 (dd, J = 12.0, 5.0 Hz, H-11a), 1.95 (t, J = 12.0 Hz, H-11b), and 5.60 (dd, J = 12.0, 5.0 Hz, H-12) revealed the presence of a $-CH_2CH-O-$ unit. An AB spin system at δ 4.60 and 4.11 (d each, J = 9.5 Hz, H-19a and H-19b) indicated the presence of an isolated oxymethylene. In addition, the NMR spectrum showed signals due to an isolated methine at δ 3.01 (s, H-10), a tertiary methyl at δ 1.16 (s, H_3-20), and signals due to two vicinal coupled methylenes attached to another methine (Table 1). The ^{13}C NMR and DEPT spectra showed 20 carbon resonances corresponding to the above structural units, two ester carbonyls (C-17 and C-18), and two quaternary carbons (C-5 and C-9) (Table 2). These spectroscopic data are similar to those of rhynchosperin A reported from *Rhynchospermum verticullatum*.[8] A comprehensive analysis of the 2D NMR data of **8** confirmed that it is a stereoisomer of rhynchosperin A. In the NOE spectrum of **8**, H-10 was enhanced by irradiation of H-4 or H-8, while H-12 and H_2-19 were enhanced by irradiation of H_3-20. These NOE enhancements indicated unambiguously that **8** was a C-8 epimer of rhynchosperin A.[8] Therefore, the structure of **8** was determined and given the trivial name 8-epirhynchosperin A.

Compound **9** had the molecular formula $C_{17}H_{22}O_5$ (cacld for $C_{17}H_{22}O_5$, *m/z* 306.1467) indicated from the HREIMS at *m/z* 306.1455 $[M]^{+\bullet}$. The IR spectrum of **9** displayed absorption bands for a conjugated ester carbonyl (1670 cm^{-1}) and an aromatic ring (1582 and 1508 cm^{-1}). The ^{1}H NMR spectrum of **9** (Table 3) showed characteristic signals of an (*E*)-3,4,5-trimethoxyphenylpropenyloxy moiety at δ 6.79 (s, H-2 and H-6), 6.65 (d, J = 16.0 Hz, H-7), 6.36 (dt, J = 16.0, 6.5 Hz, H-8), 4.77 (dd, J = 6.5, 1.0 Hz, H_2-9), 3.83 (s, O*Me*-3 and O*Me*-5), and 3.71 (s, O*Me*-4). In addition, it showed characteristic signals for an angeloyl unit at δ 6.10 (qd, J = 7.0, 1.0 Hz, H-3′), 1.96 (dd, J = 7.0, 1.0 Hz, H_3-4′), and 1.88 (brs, H_3-5′).[9] On the basis of the above spectroscopic data, the structure of **9** was determined as (*E*)-3,4,5-trimethoxyphenylpropenyl angelate, which was confirmed by the ^{13}C NMR and HMBC data (Table 3 and Supporting Information).

The molecular formula of compound **10**, $C_{21}H_{28}O_6$, was indicated from the HREIMS at *m/z* 376.1885 $[M]^{+\bullet}$. The UV, IR, and NMR spectroscopic data of **10** were similar to those of **9** (Table 3 and Experimental Section) except that the C-4 *O*-methyl resonance in **9** was replaced by a group of signals reminiscent of an isopentanoyl unit in **10**. In addition, the chemical shift of C-4 was shielded by $\Delta\delta_C$ −9.7 ppm compared with that of **9**. These data suggested that the *O*-methyl group at C-4 of **9** was replaced by an isopentanoyloxy in **10**. This was confirmed by the HMBC data of **10** (Supporting Information). Thus, **10** was determined to be (*E*)-3,5-dimethoxy-4-isopentanoyloxyphenylpropenyl angelate.

The spectroscopic data of **11** (Table 3 and Experimental Section) indicated that it was an isomer of **10**. Comparison of the NMR data of **10** and **11** indicated that the resonances due to the isopentanoyl group of **10** were replaced by those attributed to a 2-methylbutyryl moiety in **11**. Therefore, **11** was determined as (*E*)-3,5-dimethoxy-4-(2-methylbutyryloxy)phenylpropenyl angelate. The *S*-configuration at the stereogenic center of **11** was determined by synthesis of **11** (Scheme 1). The synthetic product gave

Scheme 1. Synthesis of **11**



spectroscopic data and specific rotation identical to those of the natural product (Experimental Section).

Compound **12** was determined as 1-(5′-acetyl-2′-methoxyphenyl)-3-hydroxy-3-methylbutan-1-one by its spectroscopic data (Experimental Section). Although **12** was synthesized as an intermediate in a preparation of 1-(2′-alkoxy-5′-carboxyphenyl)-α,β-unsaturated ketones,[10] it has not yet been obtained as natural product before. In addition, the ethyl ether of **12** was also obtained in the isolation procedure (**12a**); however, it is considered an artifact because of a production of **12a** by keeping **12** in ethanol at 40 °C for 24 h. The spectroscopic data of **12** and **12a** were included in the Experimental Section due to their absence in the literature.

The known compounds were identified by comparison of spectroscopic data with those reported in the literature as (−)-bornyl ferulate,[11] 1β-hydroxy-α-cyperone,[12] α-rotunol,[13] 10α-hydroxycadin-4-en-15-al,[14] 10α-hydroxyisodauc-3-en-15-al,[15] germacrene B,[16] mandassidione,[17] loliolide,[18] 12-*epi*-bacchotricuneatin A,[7] cleroinermin,[19] desoxyarticulin,[20] andydroolearin,[21] friedelin,[22] ursolic acid,[23] obtusalin,[24] α-spinasterol,[25] 6-hydroxystigmasta-4,22-dien-6β-ol-3-one,[26] 3-*O*-β-D-glucopyranosyl spinasterol,[27] scopoletin,[28] umbelliferone,[29] ayapin,[30] 3,3′-dimethylquercetin,[31] 3-methoxy-5,7,3′,4′-tetrahydroxyflavone,[32] 5-hydroxy-7,4′-dimethoxyflavone,[33] isosakuranetin,[34] 7-methoxy-4′,5,6-trihydroxyflavone,[35] acacetin,[36] morinin B,[9a] sinapyl diangelate (**13**),[9b] viscidone,[37] espeleton,[38] 6-methoxy-4-methyl-1-tetralone,[39] 4-hydroxy-2,3-dimethyl-2-nonen-4-olide,[40] 1-eicosanyl 3,4-dihydroxycinnamate, 2,4-diacetylanisole, isovanillin, salicylic acid, and ferulic acid.

In the *in vitro* bioassays, **6** showed a selective cytotoxic activity against A2780 with an IC_{50} value of 4.37 μM [the positive control camptothecin (CPT), IC_{50} 0.28 μM], and **13** showed activity against HIV-1 replication with an IC_{50} value of 4.04 μM [the positive control zidovudine (AZT), IC_{50} 0.048 μM]. However other compounds were inactive. In addition, the isolates were also assessed for their activities against the release of β-glucuronidase in rat polymorphonuclear leukocytes (PMNs) induced by platelet-activating factor (PAF),[41] neuroprotective activity against glutamate-induced neurotoxicity in cultures of PC12 cells,[2] the antioxidant activity in Fe^{2+}-cystine-induced rat liver microsomal lipid peroxidation,[42] and the inhibitory activity against protein tyrosine phosphatase 1B (PTP1B),[43] but were inactive at concentrations of 10^{-5} M.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a PE model 343 polarimeter. UV spectra were measured on a Cary 300 spectrometer. CD spectra were recorded on a JASCO-815 CD spectrometer. IR spectra were recorded on a Nicolet 5700 FT-IR microscope spectrometer (FT-IR microscope transmission). 1D- and 2D-NMR spectra were obtained at 500 or 600 MHz for ^1H, and 125 or 150 MHz for ^{13}C, respectively, on INOVA 500 MHz or SYS 600 MHz spectrometers in acetone-d_6 or $CDCl_3$, with solvent peaks as references. EIMS and HREIMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. ESIMS data were measured with a Q-Trap LC/MS/MS (Turbo Ionspray source) spectrometer. HRESIMS data were measured using a JMS-T100CS AccuToF CS spectrometer. Column chromatography was performed with silica gel (200−300 mesh, Qingdao Marine Chemical Inc. Qingdao, People's Republic of China) and Pharmadex LH-20 (Amersham Biosciences Inc. Shanghai, People's Republic of China). Preparative TLC separation was preformed with high-performance silica gel preparative TLC plates ($HSGF_{254}$, glass precoated, Yantai Jiangyou Silica Gel Development Co. Ltd. Yantai, People's Republic of China). HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector, with a Prevail (250 × 10 mm i.d.) column packed with C_{18} (5 μm). TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV light or by spraying with 7% H_2SO_4 in 95% EtOH followed by heating. Unless otherwise noted, all chemicals were obtained from commercially available sources and were used without further purification.

Plant Material. The herbs of *H. micocephala* were collected at Dayao mountain, Guangxi Province, People's Republic of China, in 2003. The plant was identified by Mr. Guang-Ri Long (Guangxi Forest Administration, Guangxi 545005, China). A voucher specimen (no. YG 01025) was deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica.

Extraction and Isolation. The air-dried plant material of *H. micocephala* (2.56 kg) was powdered and extracted with 95% EtOH at room temperature. The EtOH extract was evaporated under reduced pressure below 40 °C to yield a dark green residue (270.0 g). The residue was suspended in H_2O (1500 mL) and then partitioned with EtOAc (4 × 1500 mL). After removal of solvent, the EtOAc extract (125.0 g) was applied to a normal-phase silica gel column. Successive elution of the column with a gradient of increasing EtOAc (2−100%) in petroleum ether afforded 12 fractions (A1−A12) on the basis of TLC analysis. Fraction A5 (15.3 g), eluted by 20% EtOAc in petroleum ether, was chromatographed over Pharmadex LH-20 with $CHCl_3$−MeOH (2:1) as mobile phase to give four subfractions (A5-1−A5-4). Fraction A5-3 (2.3 g) was purified by reversed-phase preparative HPLC, using a mobile phase of 40% CH_3CN in H_2O, to yield **1** (2.0 mg) and **2** (6.4 mg). Fraction A5-4 (5.4 g) was separated by reverse-phase preparative HPLC using 46% MeOH in H_2O as a mobile phase to yield **9** (23.3 mg), **10** (6.1 mg), **11** (7.3 mg), **12** (4.5 mg), and **12a** (2.3 mg). Fraction A7 (30.2 g), eluted by 60% EtOAc in petroleum ether, was subjected to CC over normal-phase silica gel with a gradient of increasing MeOH (0−100%) in $CHCl_3$, to yield eight subfractions (A7-1−A7-8). A7-4 (12.5 g) was separated by reversed-phase preparative HPLC, using a mobile phase of 45% MeOH in H_2O, to yield **3** (1237.7 mg), **4** (2.1 mg), **5** (2683.5 mg), **6** (7.5 mg), **7** (5.4 mg), and **8** (13.4 mg).

(−)-1*S*,9*S*-9-Hydroxy-2,2,5,9-tetramethylbicyclo[6.3.0]undeca-4,7-dien-6-one (1): yellowish oil; $[\alpha]^{20}_D$ −84.0 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.62), 262 (3.76) nm; CD (MeOH) 354 (Δε −1.1), 257 (Δε −5.88) nm; IR ν_{max} 3424, 2961, 2925, 1730, 1714, 1650, 1623, 1601 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 2; EIMS *m/z* 234 $[M]^{+\bullet}$; HREIMS *m/z* 234.1623 $[M]^{+\bullet}$ (calcd for $C_{15}H_{22}O_2$, 234.1620).

(−)-1*S*,9*R*-9-Hydroxy-2,2,5,9-tetramethylbicyclo[6.3.0]undeca-4,7-dien-6-one (2): yellowish gum; $[\alpha]^{20}_D$ −55.3 (*c* 0.53, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.52), 259 (3.69) nm; CD (MeOH) 358 (Δε −1.23), 248 (Δε −3.87) nm; IR ν_{max} 3420, 2960, 2925, 1732, 1715, 1648, 1621, 1601 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 2; EIMS *m/z* 234 $[M]^{+\bullet}$; HREIMS *m/z* 234.1613 $[M]^{+\bullet}$ (calcd for $C_{15}H_{22}O_2$, 234.1620).

Heteroplexisolide A (3): yellowish oil; $[\alpha]^{20}_D$ +31.3 (*c* 1.38, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.30) nm; CD (MeOH) 210 (Δε +1.67) nm; IR ν_{max} 2933, 1778, 1748, 1678, 1637, 1444, 1322, 1199, 1181, 1022, 971, 888 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; EIMS *m/z* 330 $[M]^{+\bullet}$; HREIMS *m/z* 330.1859 $[M]^{+\bullet}$ (calcd for $C_{20}H_{26}O_4$, 330.1831).

Heteroplexisolide B (4): yellowish oil; $[\alpha]^{20}_D$ +31.4 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ε) 208 (4.52) nm; CD (MeOH) 219 (Δε +1.44) nm; IR ν_{max} 3463, 2931, 1778, 1746, 1678, 1637, 1443, 1322, 1205, 1180, 1020, 970, 893 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 2; ESIMS *m/z* 369 $[M + Na]^+$ and 385 $[M + K]^+$; HRESIMS *m/z* 369.1688 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_5Na$, 369.1678).

Heteroplexisolide C (5): yellowish oil; $[\alpha]^{20}_D$ +67.0 (*c* 2.08, MeOH); UV (MeOH) λ_{max} (log ε) 208 (4.35) nm; IR ν_{max} 3431, 2927, 1747, 1679, 1636, 1446, 1322, 1181, 1037, 965, 889, 846 cm^{-1}; ^1H

NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 2; ESIMS *m/z* 369 $[M + Na]^+$ and 385 $[M + K]^+$; HRESIMS *m/z* 369.1680 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_5Na$, 369.1678).

Heteroplexisolide D (6): yellowish gum; $[\alpha]^{20}_D$ +4.9 (*c* 0.24, MeOH); UV (MeOH) λ_{max} (log ε) 205 (4.28) nm; IR ν_{max} 3429, 2933, 1743, 1637, 1445, 1379, 1177, 1032, 977, 896, 861 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 150 MHz) data, see Table 2; ESIMS *m/z* 369 $[M + Na]^+$ and 385 $[M + K]^+$; HRESIMS *m/z* 369.1687 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_5Na$, 369.1678).

Heteroplexisolide E (7): yellowish oil; $[\alpha]^{20}_D$ +15.6 (*c* 0.27, MeOH); IR ν_{max} 2970, 2920, 1752, 1715, 1679 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 150 MHz) data, see Table 2; EIMS *m/z* 222 $[M]^{+\bullet}$; HREIMS *m/z* 222.1249 $[M]^{+\bullet}$ (calcd for $C_{13}H_{18}O_3$, 222.1256).

8-Epirhynchosperin A (8): white, amorphous powder; $[\alpha]^{20}_D$ −22.8 (*c* 0.26, MeOH); IR ν_{max} 3154, 1783, 1730, 1670, 1668, 1509, 1380, 1147, 1022, 875 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) data, see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 2; EIMS *m/z* 356 $[M]^{+\bullet}$; HREIMS *m/z* 356.1241 $[M]^{+\bullet}$ (calcd for $C_{20}H_{20}O_6$, 356.1260).

(*E*)-3,4,5-Trimethoxyphenylpropenyl angelate (9): yellowish oil; IR ν_{max} 2941, 1700, 1670, 1582, 1508, 1420, 1246, 1127 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 3; EIMS *m/z* 306 $[M]^{+\bullet}$; HREIMS *m/z* 306.1455 $[M]^{+\bullet}$ (calcd for $C_{17}H_{22}O_5$, 306.1467).

(*E*)-3,5-Dimethoxy-4-isopentanoyloxyphenylpropenyl angelate (10). yellowish oil; IR ν_{max} 2961, 1760, 1715, 1598, 1462, 1338, 1233, 1134 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 3; EIMS *m/z* 376 $[M]^{+\bullet}$; HREIMS *m/z* 376.1885 $[M]^{+\bullet}$ (calcd for $C_{21}H_{28}O_6$, 376.1886).

(*E*)-3,5-Dimethoxy-4-(*S*-2-methylbutyryloxy)phenylpropenyl angelate (11): yellowish gum; $[\alpha]^{20}_D$ +6.5 (*c* 0.63, MeOH); UV (MeOH) λ_{max} (log ε) 196 (4.35), 220 (4.69), 265 (4.29) nm; IR ν_{max} 2969, 2939, 2878, 1758, 1715, 1597, 1460, 1231, 1133 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) and ^{13}C NMR (acetone-d_6, 125 MHz) data, see Table 3; EIMS *m/z* 376 $[M]^{+\bullet}$; HREIMS *m/z* 376.1868 $[M]^{+\bullet}$ (calcd for $C_{21}H_{28}O_6$, 376.1886).

Synthesis of 11. *S*-2-Methylbutyric acid (220 μL) was added into $SOCl_2$ (5 mL). The mixture was refluxed for 2 h, and then the excess $SOCl_2$ was removed by evaporation under reduced pressure. The residue was dissolved in dried acetone (10 mL) and cooled in an ice bath. (*E*)-3,5-Dimethoxy-4-hydroxyphenylpropenaldehyde (104.0 mg) and triethylamine (TEA, 0.50 μL) were added, and the mixture was stirred for 0.5 h at 0 °C and 8 h at room temperature. After the solvent was removed under reduced pressure the residue was dissolved in H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was separated by preparative TLC (petroleum ether−acetone, 2:1) to give (*E*)-3,5-dimethoxy-4-(*S*-2-methylbutyryloxy)phenylpropenaldehyde (116.4 mg, 79.7%) as a yellowish gum: $[\alpha]^{20}_D$ +25.3 (*c* 0.13, MeOH); ^{1}H NMR (acetone-d_6, 600 MHz) δ 9.70 (1H, d, J = 7.8 Hz, H-9), 7.63 (1H, d, J = 15.6 Hz, H-7), 7.17 (2H, s, H-2 and H-6), 6.81 (1H, dd, J = 15.6, 7.8 Hz, H-8), 3.87 (6H, s, *OMe*-3 and *OMe*-5), 2.65 (1H, m, H-2′), 1.79 (1H, m, H-3′a), 1.61 (1H, m, H-3′b), 1.26 (3H, d, J = 7.2 Hz, H_3-5′), 1.02 (3H, t, J = 7.2 Hz, H_3-4′); EIMS *m/z* 292 $[M]^{+\bullet}$.

(*E*)-3,5-Dimethoxy-4-(*S*-2-methylbutyryloxy)phenylpropenaldehyde (102.2 mg) was reduced by $NaBH_4$ (20.0 mg) in EtOH (5 mL) for 30 min at room temperature. After the solution was acidified by 1 M HCl to pH 2.0, the solvent was removed under reduced pressure. Water (15 mL) was added to the residue, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was dried over $MgSO_4$ and evaporated to yield (*E*)-3,5-dimethoxy-4-(*S*-2-methylbutyryloxy)-phenylpropenol (101.0 mg, 98.2%) as a yellowish gum: $[\alpha]^{20}_D$ +18.0 (*c* 0.14, MeOH); ^{1}H NMR (acetone-d_6, 600 MHz) δ 6.78 (2H, s, H-2 and H-6), 6.57 (1H, d, J = 15.6 Hz, H-7), 6.40 (1H, dt, J = 15.6, 4.8 Hz, H-8), 4.23 (2H, m, H_2-9), 3.84 (1H, m, *OH*-9), 3.81 (6H, s, *OMe*-3 and *OMe*-5), 2.61 (1H, m, H-2′), 1.77 (1H, m, H-3′a), 1.59 (1H, m, H-3′b), 1.24 (3H, d, J = 7.2 Hz, H_3-5′), 1.01 (3H, t, J = 7.2 Hz, H_3-4′); EIMS *m/z* 294 $[M]^{+\bullet}$.

Angelic acid (80.0 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 176.2 mg), and DMAP (277.2 mg) were added to a solution of (*E*)-3,5-dimethoxy-4-(*S*-2-methylbutyryloxy)phenylpropenol (58.8 mg) in dry CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 12 h at 0 °C and then extracted with H_2O (3 × 15 mL). After the organic layer was concentrated, the residue was separated by preparative TLC (petroleum ether−acetone, 2:1) to give **11** (55.2 mg, 73.4%) as a yellowish gum: $[\alpha]^{20}_D$ +11.4 (*c* 1.26, MeOH). Its ^{1}H NMR (acetone-d_6, 500 MHz), ^{13}C NMR (acetone-d_6, 125 MHz), and EIMS data were identical to those of the natural product.

1-(5′-Acetyl-2′-methoxyphenyl)-3-hydroxy-3-methylbutan-1-one (12): yellowish, amorphous powder; UV (MeOH) λ_{max} (log ε) 208 (4.02), 240 (4.27), 268 (4.09) nm; IR ν_{max} 3493, 2973, 2937, 1680, 1597 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.15 (1H, d, J = 2.0 Hz, H-6′), 8.13 (1H, dd, J = 8.5, 2.0 Hz, H-4′), 7.25 (1H, d, J = 8.5 Hz, H-3′), 4.03 (3H, s, *OMe*-2′), 3.84 (1H, s, *OH*-3), 3.18 (2H, s, H_2-2), 2.54 (3H, s, *Me*-Ac), 1.25 (6H, s, H_3-4 and H_3-5); ^{13}C NMR (acetone-d_6, 125 MHz) 203.4 (C-1), 196.1 (*CO*-Ac), 162.4 (C-2′), 134.2 (C-4′), 131.0 (C-1′), 130.8 (C-6′), 130.5 (C-5′), 112.8 (C-3′), 70.3 (C-3), 56.6 (*OMe*-2′), 55.5 (C-2), 30.3 (C-4 and C-5), 26.4 (*Me*-Ac); EIMS *m/z* 250 $[M]^{+\bullet}$; HREIMS *m/z* 250.1200 $[M]^{+\bullet}$ (calcd for $C_{14}H_{18}O_4$, 250.1205).

12a: yellowish oil; UV (MeOH) λ_{max} (log ε) 209 (3.86), 240 (4.01), 268 (3.90) nm; IR ν_{max} 2974, 2933, 1681, 1597, 1262 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.10 (1H, dd, J = 8.5, 2.0 Hz, H-4′), 8.03 (1H, d, J = 2.0 Hz, H-6′), 7.22 (1H, d, J = 8.5 Hz, H-3′), 4.02 (3H, s, *OMe*-2′), 3.34 (2H, q, J = 7.0 Hz, CH_2-OEt), 3.18 (2H, s, H_2-2), 2.53 (3H, s, *Me*-Ac), 1.23 (6H, s, H_3-4 and H_3-5), 0.91 (3H, t, J = 7.0 Hz, *Me*-OEt); ^{13}C NMR (acetone-d_6, 125 MHz) δ 201.8 (C-1), 196.1 (*CO*-Ac), 161.9 (C-2′), 133.6 (C-4′), 131.9 (C-1′), 131.0 (C-5′), 130.6 (C-6′), 112.5 (C-3′), 75.0 (C-3), 57.0 (CH_2-OEt), 56.5 (*OMe*-2′), 53.3 (C-2), 26.4 (*Me*-Ac), 26.3 (C-4 and C-5), 16.2 (*Me*-OEt); EIMS *m/z* 278 $[M]^{+\bullet}$; HREIMS *m/z* 278.1501 $[M]^{+\bullet}$ (calcd for $C_{16}H_{22}O_4$, 278.1518).

Cells, Culture Conditions, and Cell Proliferation Assay. See ref 44.

Anti-HIV Activity Assay. A cell-based VSVG/HIV-1 pseudotyping system was used for evaluating a compound's anti-HIV replication activity as described previously.[45] Briefly, vesicular stomatitis virus glycoprotein (VSV-G) plasmid was cotransfected with env-deficient HIV-1 vector, pNL4-3.luc.R$^-$E$^-$,[46] into 293T cells by using a modified $Ca_3(PO_4)_2$ method.[47] Sixteen hours post-transfection, plates were washed by PBS, and fresh media DMEM with 10% FBS was added into the plates. Forty eight hours post-transfection, supernatant, which contained VSVG/HIV-1 virions, was harvested and filtered through a 0.45 μm filter. VSVG/HIV-1 pseudotyped virions were quantified by p24 concentrations, which were detected by ELISA (ZeptoMetrix, Cat.: 0801111), then diluted to 0.2 ng p24/mL, which can be used directly or stored at −80 °C.

For the infection assay, 293T cells were plated on 24-well plates at the density of 6 × 10^4 cells per well one day prior to infection. Compounds were incubated with target cells for 15 min prior to adding VSVG/HIV-1. The same amount of solvent alone was used as blank control. After postinfection for 48 h, cells were lysed in 50 μL Cell Lysis Reagent (Promega). Luciferase activity of the cell lysate was measured by a FB15 luminometer (Berthold Detection System) according to the manufacture's instructions.

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Supporting Information Available: . MS, ^{1}H and ^{13}C NMR, HMBC, and NOE spectra of compounds **1**−**12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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