Abietane and C_{20}-Norabietane Diterpenes from the Stem Bark of *Fraxinus sieboldiana* and Their Biological Activities

Sheng Lin, Yanling Zhang, Mingtao Liu, Sen Yang, Maoluo Gan, Jiachen Zi, Weixia Song, Xiaona Fan, Sujuan Wang, Yang Liu, Yongchun Yang, Xiaoguang Chen, Ying Guo, Wenjie Wang, and Jiangong Shi*

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College (Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education), Beijing 100050, People's Republic of China

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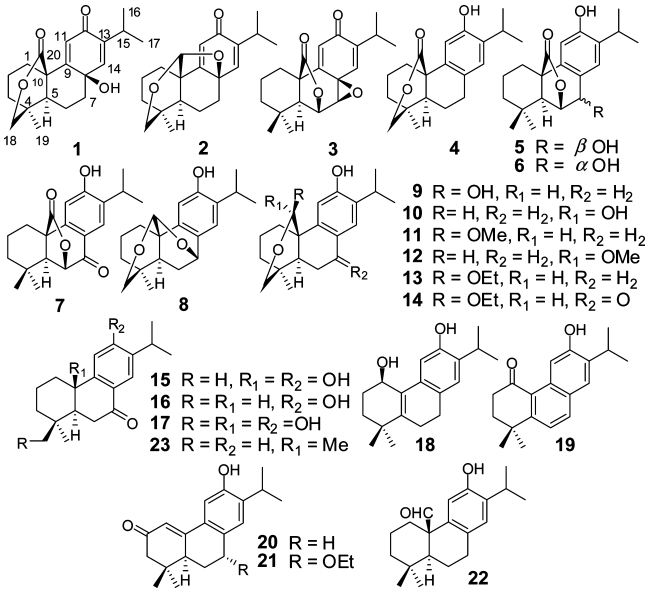
Fourteen new abietane (**1**−**14**) and seven new C_{20}-norabietane (**15**−**21**) diterpenes, together with five known analogues, have been isolated from the stem bark of *Fraxinus sieboldiana*. Their structures were elucidated by spectroscopic data analysis. In the in vitro assays, at 10^{-5} M, compounds **8**, **16**, and **22** showed inhibitory activity against the release of β-glucuronidase in rat polymorphonuclear leukocytes induced by platelet-activating factor, with 59.7 ± 4.8%, 56.1 ± 5.6%, and 65.9 ± 3.1% inhibition, respectively. Compound **23** was active against H5N1 avian influenza virus with an IC_{50} value of 4.8 μM. Compounds **3** and **5** exhibited selective cytotoxic activities against A2780 (IC_{50} 1.7 μM) and A549 (IC_{50} 6.0 μM), respectively.

The genus *Fraxinus*, a member of the Oleaceae family, is a rich source of bioactive metabolites including coumarins, lignans, secoiridoid glucosides, and phenylethanoids.[1−7] Our previous investigation of the stem bark of *Fraxinus sieboldiana* Blume (Oleaceae), a folk medicine with diuretic, antifebrile, analgesic, and antirheumatic activities, resulted in characterization of a unique norditerpene glucopyranoside and 33 aromatic glycosides from the water-soluble fraction of an ethonolic extract.[8] As part of our ongoing effort to study the chemical and biological diversity of this plant, we report herein the isolation, structure elucidation, and biological assays of 14 new abietane diterpenes (**1**−**14**), seven new C_{20}-norabietane diterpenes (**15**−**21**), and five known analogues from the EtOAc-soluble fraction of the ethonolic extract. This is the first report of the abietane and C_{20}-norabietane diterpenes from the genus *Fraxinus*.



Results and Discussion

Compound **1** was obtained as an amorphous powder with $[\alpha]_D^{20}$ −22.3 (*c* 0.11, MeOH). The presence of OH (3447 cm^{-1}) and carbonyl (1715 and 1668 cm^{-1}) groups was evident in its IR spectrum. The molecular formula ($C_{20}H_{26}O_4$), with eight degrees of unsaturation, was indicated by HREIMS. The ^1H NMR spectrum of **1** (Table 1) showed resonances for a tertiary methyl [δ_H 0.96 (H_3-19)], an isopropyl group attached to an olefinic carbon [δ_H 1.03 and 1.05 (each d, J = 7.2 Hz, H_3-16 and H_3-17) and 2.86 (hept, J = 7.2 Hz, H-15)], and two trisubstituted double bonds [δ_H 6.07 (1H, s, H-11) and 6.53 (1H, s, H-14)]. Also it displayed resonances corresponding to an isolated oxymethylene [δ_H 4.50 (1H, brd, J = 11.6 Hz, H-18a), 4.17 (1H, d, J = 11.6 Hz, H-18b)], an OH [δ_H 3.82 (exchangeable brs, O*H*-8)], an aliphatic methine [δ_H 1.59 (dd, J = 13.2 and 4.0 Hz, H-5)], and partially overlapped resonances due to five methylenes [between δ 1.34 and 2.15]. Besides proton-bearing carbon resonances corresponding to the above units, the ^{13}C NMR and DEPT spectra exhibited resonances for seven quaternary carbons consisting of a ketone, a carboxyl, two olefinic, an oxygen-bearing, and two aliphatic carbons (Table 4). The NMR data suggested that **1** was an abietane diterpene closely related to the co-occurring 8-hydroxy-12-oxo-abieta-9(11),13-dien-20-oic acid 8,20-lactone.[9] As compared with the NMR data of the known compound, the deshielded shifts of the resonance for the isolated methylene (CH_2-18) and the shielded shift of the oxygen-bearing quaternary carbon (C-8) indicated that it was 8,18-dihydroxy-12-oxo-abieta-9(11),13-dien-20-oic acid 18,20-lactone. This structure was proved by analysis of the 2D NMR data including HSQC, $^1H-^1H$ COSY, and HMBC experiments of **1**. In particular, the 8-hydroxy-18,20-lactone functionality was demonstrated by HMBC correlations for H_2-18/C-3, C-4, C-5, C-19, and C-20, H-5 and H_2-1/C-20, and O*H*/C-7 and C-8 (Supporting Information, Figure S28), combined with shifts of these protons and carbons. In the NOE difference spectrum of **1**, H-6β was enhanced upon irradiation of H-18a, and H-5 was enhanced by irradiation of H_3-19. The enhancements, together with the coupling constants between H-5 and H_2-6 ($J_{5,6\beta}$ = 13.2 Hz and $J_{5,6\alpha}$ = 4.0 Hz), revealed a *trans*-junction of the A and B rings and a *trans*-vicinal diaxial orientation of H-5 and C-18. The CD spectrum of **1** (Supporting Information, Figure S1) showed Cotton effects, negative at 248 nm ($\Delta\varepsilon$ −5.31) and positive at 219 nm ($\Delta\varepsilon$ +0.17), indicating exciton coupling between the $\pi\rightarrow\pi^*$ transition of the cross-conjugated dienone and the $n\rightarrow\pi^*$ transition of the δ-lactone chromophores. On the basis of the CD exciton chirality method, the negative chirality suggested the 8*R*,10*R* configuration for **1**.[9] In addition, the CD spectrum displayed a negative Cotton effect at 358 nm ($\Delta\varepsilon$ −0.31) corresponding to the $n\rightarrow\pi^*$ transition of the cross-conjugated dienone

* To whom correspondence should be addressed. Tel: 86-10-83154789. Fax: 86-10-63017757. E-mail: shijg@imm.ac.cn.

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Table 1. ^{1}H NMR Data (δ) for Compounds **1**−**7** in Me_2CO-d_6[a]

no.	1	2	3	4	5	6	7
1α	1.71 m	1.68 m	1.56 dd (14.0, 10.0)	1.58 m	1.57 m	1.58 m	1.75 m
1β	2.08 m	1.74 m	2.45 brdd (14.0, 2.5)	2.41 brdd (14.5, 2.0)	2.46 brd (10.5)	2.48 brd (13.6)	2.57 dd (13.0, 4.5)
2α	1.70 m	1.63 m	1.63 m	1.78 m	1.63 m	1.64 m	1.70 m
2β	1.84 m	2.10 m	1.44 m	1.76 m	1.50 m	1.55 m	1.59 m
3α	1.55 m	1.43 m	1.29 m	1.55 m	1.24 dd (14.5, 13.5, 3.0)	1.33 ddd (14.2, 13.6, 3.2)	1.34 ddd (13.5, 13.0, 3.0)
3β	1.80 m	1.73 m	1.44 m	1.81 m	1.43 brd (14.5)	1.48 dd (14.2, 4.0)	1.49 brd (13.5)
5	1.59 dd (13.2, 4.0)	1.84 dd (10.0, 8.5)	2.75 s	1.65 brd (13.0)	2.00 s	2.27 s	2.55 s
6α	1.82 m	1.73 m	5.31 d (3.5)	2.18 ddd (13.0, 2.5, 2.5)	4.78 d (2.0)	4.61 d (3.6)	4.79 s
6β	2.14 m	2.13 m		1.38 dddd (13.0, 13.0, 6.5, 6.0)			
7α	2.15 ddd (14.4, 12.0, 4.8)	2.32 dd (14.0, 9.0)	4.38 d (3.5)	2.74 m	4.74 d (2.0)		
7β	1.34 ddd (14.4, 4.8, 4.4)	1.43 m		2.75 m		4.70 dd (5.6, 3.6)	
11	6.07 s	5.82 s	6.42 s	7.05 s	6.67 s	6.70 s	6.92 s
14	6.53 s	6.71 s	6.23 d (1.0)	6.82 s	7.37 s	7.26 s	7.82 s
15	2.86 hept (7.2)	2.89 hept (7.2)	2.90 hept (7.5)	3.23 hept (7.0)	3.26 hept (7.0)	3.27 hept (7.2)	3.29 hept (7.0)
16	1.03 d (7.2)	1.01 d (7.2)	1.01 d (7.5)	1.18 d (7.0)	1.17 d (7.0)	1.18 d (7.2)	1.22 d (7.0)
17	1.05 d (7.2)	1.04 d (7.2)	1.04 d (7.5)	1.18 d (7.0)	1.19 d (7.0)	1.19 d (7.2)	1.22 d (7.0)
18a	4.50 brd (11.6)	4.13 brd (12.0)	0.88 s	4.31 brd (12.0)	0.91 s	0.90 s	0.98 s
18b	4.17 d (11.6)	3.47 d (12.0)		4.16 d (12.0)			
19	0.96 s	0.81 s	1.07 s	1.01 s	1.03 s	1.02 s	1.08 s
20		4.93 s					

[a] Data were measured for **1**−**7** at 600, 500, or 400 MHz. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on ^{1}H−^{1}H COSY, HSQC, and HMBC.

Table 2. ^{1}H NMR Data (δ) for Compounds **8**−**14** in Me_2CO-d_6[a]

no.	8	9	10	11	12	13	14
1α	1.99 m	1.39 m	1.18 m	1.38 m	1.18 m	1.39 m	1.49 m
1β	2.01 m	2.16 dd (14.0, 6.0)	2.74 dd (13.0, 6.0)	2.17 dd (14.0, 6.0)	2.64 dd (13.0, 6.0)	2.17 dd (14.0, 6.0)	2.33 m
2α	1.66 m	1.48 m	1.48 m	1.55 m	1.48 m	1.55 m	1.61 m
2β	2.45 m	2.49 m	2.64 m	2.51 m	2.57 m	2.51 m	2.55 m
3α	1.39 m	1.46 ddd (13.5, 13.0, 2.5)	1.52 m	1.45 ddd (13.5, 13.0, 2.5)	1.47 m	1.45 ddd (13.5, 13.0, 2.5)	1.49 ddd (13.5, 13.0, 6.0)
3β	1.74 dd (13.5, 4.5)	1.70 dd (13.5, 6.0)	1.71 dd (13.5, 6.0)	1.71 dd (13.5, 6.0)	1.72 dd (13.5, 6.0)	1.71 dd (13.5, 6.0)	1.75 dd (13.5, 6.5)
5	1.29 brd (12.5)	1.41 dd (13.0, 2.5)	1.53 dd (13.0, 2.5)	1.40 dd (13.0, 2.5)	1.52 dd (13.0, 2.5)	1.41 dd (13.0, 2.5)	1.98 dd (14.5, 5.5)
6α	1.52 dd (13.5, 12.0)	2.45 m	1.82 m	1.69 m	1.85 m	1.67 m	2.35 dd (16.5, 5.5)
6β	2.31 ddd (13.5, 4.5, 3.5)	1.71 m	1.90 m	2.26 m	1.90 m	2.34 m	3.14 dd (16.5, 14.5)
7α	4.83 brd (4.5)	2.65 ddd (15.5, 12.0, 6.0)	2.73 ddd (15.5,12.0, 6.0)	2.66 ddd (15.5, 12.0, 6.0)	2.72 ddd (15.5,12.0, 6.0)	2.65 ddd (16.0,12.0,6.0)	
7β		2.73 dd (15.5, 6.0)	2.76 dd (15.5, 6.0)	2.71 dd (15.5, 6.0)	2.75 dd (15.5, 6.0)	2.73 dd (16.0, 6.0)	
11	6.79 s	6.70 s	7.06 s	6.69 s	7.00 s	6.69 s	6.91 s
14	7.01 s	6.81 s	6.77 s	6.81 s	6.78 s	6.80 s	7.85 s
15	3.31 hept (7.0)	3.21 hept (7.0)	3.21 hept (7.0)	3.21 hept (7.0)	3.21 hept (7.0)	3.22 hept (7.0)	3.27 hept (7.0)
16	1.20 d (7.0)	1.17 d (7.0)	1.18 d (7.0)	1.17 d (7.0)	1.18 d (7.0)	1.18 d (7.0)	1.21 d (7.0)
17	1.21 d (7.0)	1.19 d (7.0)	1.18 d (7.0)	1.20 d (7.0)	1.18 d (7.0)	1.19 d (7.0)	1.23 d (7.0)
18a	3.97 brd (12.0)	3.95 brd (11.0)	3.76 brd (11.5)	3.71 brd (11.0)	3.76 brd (11.0)	3.76 brd (11.0)	3.86 brd (11.5)
18b	3.30 d (12.0)	3.26 d (11.0)	3.49 d (11.5)	3.21 d (11.0)	3.55 d (11.0)	3.25 d (11.0)	3.34 d (11.5)
19	0.76 s	0.78	0.78	0.91 s	0.79 s	0.77 s	0.77 s
20	4.51 s	4.99 d (4.5)	4.98 d (3.5)	4.55 s	4.55 s	4.55 s	4.60 s
OMe/OEt				3.01 s/	3.26 s/	/3.47 m, 3.06 m; 0.80 t (7.0)	/3.50 m, 3.20 m; 0.78 t (7.5)

[a] Data were measured for **8**−**14** at 600, 500, or 400 MHz. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on ^{1}H−^{1}H COSY, HSQC, and HMBC.

Table 3. ^{1}H NMR Data (δ) for Compounds **15**−**21** in Me_2CO-d_6[a]

no.	15	16	17	18	19	20	21[b]
1α	2.48 brd (14.0)	1.17 ddd (13.0, 12.0, 3.0)	2.50 dd (13.0, 3.0)	4.36 brs		6.40 d (2.0)	6.44 d (1.8)
1β	1.58 ddd (14.0, 13.2, 3.6)	2.44 dd (13.0, 3.0)	1.60 ddd (13.0, 12.0, 3.0)				
2α	1.58 m	1.69 m	1.58 m	1.86 m	2.73 t (7.2)		
2β	2.04 m	1.69 m	2.18 m	1.76 m			
3α	1.33 ddd (14.0, 13.2, 3.2)	1.30 ddd (13.0, 8.5, 4.0)	1.27 ddd (13.5, 4.5, 4.0)	1.93 brdd (13.0, 12.0)	2.06 t (7.2)	2.40 d (16.0)	2.45 d (15.6)
3β	1.52 dd (14.0, 4.0)	1.48 brd (13.0)	1.94 brd (13.5)	1.39 ddd (13.0, 4.0, 3.0)		2.15 d (16.0)	2.18 d (15.6)
5	1.81 dd (13.2, 3.2)	1.57 ddd (14.5, 11.5, 3.0)	2.02 dd (14.0, 3.5)			2.58 ddd (13.5, 3.0, 3.5)	3.10 ddd (13.2, 3.6, 3.6)
6α	2.44 dd (16.8, 3.2)	2.56 dd (16.0, 3.0)	2.49 dd (16.5, 3.5)	2.19 ddd (13.5, 6.5, 6.0)	7.41 d (8.4)	2.14 ddd (13.0, 3.0, 3.5)	2.37 ddd (13.2, 3.6, 3.6)
6β	2.88 dd (16.8, 13.2)	2.22 dd (16.0, 14.5)	2.88 dd (16.5, 14.0)	2.09 ddd (13.5, 13.0, 6.0)		1.45 ddd (13.5, 13.0, 3.5)	1.58 ddd (13.2, 13.2, 2.4)
7α				2.56 m	7.95 d (8.4)	2.76 ddd (15.5, 13.0, 3.5)	
7β				2.48 m		2.88 ddd (15.5, 3.5, 3.5)	4.47 dd (3.6, 2.4)
10		2.73 ddd (11.5, 11.5, 4.0)					
11	7.01 s	6.94 s	7.06 s	7.15 s	8.80 s	7.31 s	7.35 s
14	7.81 s	7.82 s	7.82 s	6.85 s	7.64 s	7.03 s	7.17 s
15	3.27 hept (6.8)	3.26 hept (7.0)	3.28 hept (7.0)	3.26 hept (7.0)	3.40 hept (7.2)	3.29 hept (7.0)	3.31 hept (7.2)
16	1.20 d (6.8)	1.21 d (7.0)	1.21 d (7.0)	1.18 d (7.0)	1.30 d (7.2)	1.21 d (7.0)	2.23 d (7.2)
17	1.23 d (6.8)	1.22 d (7.0)	1.22 d (7.0)	1.19 d (7.0)	1.30 d (7.2)	1.22 d (7.0)	2.24 d (7.2)
18a	1.13 s	0.95 s	3.94 d (11.5)	1.06 s	1.43 s	0.89 s	0.87 s
18b			3.39 d (11.5)				
19	0.93 s	0.96 s	0.91 s	1.06 s	1.43 s	1.18 s	1.17 s

[a] Data were measured for **15**−**21** at 600, 500, or 400 MHz. Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on ^{1}H−^{1}H COSY, HSQC, and HMBC. [b] Data of OEt for **21**: δ 3.60, 3.49 (each 1H, m), 1.13 (3H, t, J = 7.2 Hz).

chromophore. This also supported the 8*R* configuration for **1** based on the CD rule for cross-conjugated dienone derivatives.[10,11] Accordingly, **1** was determined to be (−)-(4*S*,5*S*,8*R*,10*R*)-8,18-dihydroxy-12-oxo-abieta-9(11),13-dien-20-oic acid 18,20-lactone.

Compound **2**, $C_{20}H_{26}O_3$ (HREIMS), showed spectroscopic data similar to those of **1**. Although many of the NMR resonances of **2** were significantly shifted as compared with those of **1** (Tables 1 and 4), the predominant difference was that the resonances for the ester carbonyl and O*H*-8 in **1** were replaced by those for an acetal in **2** [δ_H 4.93 (s, H-20) and δ_C 105.1 (C-20)]. This suggested that **2** was an analogue of **1** derived from acetalation of C-20 with 8,18-dihydroxy groups. The suggestion was verified by analysis of the 2D NMR data that amended the assignments of resonances in the NMR spectra of **2**. Particularly, HMBC correlations for H-11/C-8, C-10, and C-13, H-14/C-7, C-9, C-12, and C-15, and H-20/C-18 and C-5 (Supporting Information, Figure S39) in combination with their shifts confirmed the cross-conjugated dienone and acetal moieties in **2**. The configuration of **2** was supported by its CD spectrum, showing Cotton effects similar to those of **1** (Supporting Information, Figure S2). Therefore, **2** was (−)-(4*S*,5*S*,8*R*,10*R*,20*S*)-8,18-dihydroxy-12-oxo-abieta-9(11),13-dien-20-aldehyde 8,18,20-acetal.

The molecular formula $C_{20}H_{24}O_4$ of **3** (HRESIMS) had two fewer hydrogen atoms than **1**. Comparison of the NMR data between **1** and **3** (Tables 1 and 4) indicated that the resonances for three methylenes including the oxymethylene (CH_2-18) of **1** were replaced by those attributed to two vicinal oxymethines [δ_H 5.31 (d, J = 3.5 Hz) and 4.38 (d, J = 3.5 Hz); δ_C 76.6 (d) and 62.0 (d)] and a tertiary methyl [δ_H 0.88; δ_C 22.4], respectively, while the resonance of C-8 was shifted significantly from δ_C 68.7 of **1** to δ_C 55.7 of **3**. These data suggested that **3** was 7,8-epoxy-6-hydroxy-12-oxo-abieta-9(11),13-dien-20-oic acid 6,20-lactone. The suggestion was supported by 2D NMR data analysis, which verified the 1D NMR data assignments of **3** (Tables 1 and 4). In the HMBC spectrum of **3**, correlations from both H_3-18 and H_3-19 to C-3, C-4, and C-5, from H-5 to C-7, C-9, C-10, C-18, C-19, and C-20, and from H-6 to C-4, C-8, and C-20 (Supporting Information, Figure S49) combined with their shifts verified the 7,8-epoxy and 6,20-lactone groups in **3**. In the NOE difference spectrum of **3**, irradiation of H-7 enhanced H-6 and H-14, indicating that H-7 had a quasi-axial α-orientation. The CD spectrum of **3** showed Cotton effects, positive at 216 ($\Delta\varepsilon$ +3.09), 234 ($\Delta\varepsilon$ +3.21), and 293 ($\Delta\varepsilon$ +6.97) nm and negative at 255 ($\Delta\varepsilon$ −6.32) and 362 ($\Delta\varepsilon$ −0.65) nm (Supporting Information, Figure S3), indicating the 6*S*,8*R*,10*R* configuration for **3**. Thus, **3** was assigned as (+)-(5*S*,6*S*,7*S*,8*R*,10*R*)-6-hydroxy-7,8-epoxy-12-oxo-abieta-9(11),13-dien-20-oic acid 6,20-lactone.

Compound **4** ($C_{20}H_{26}O_3$) was an isomer of **2**. The NMR data of **4** (Tables 1 and 4) indicated that the resonances for the cross-conjugated dienone ring in **2** were replaced by those assignable to a tetrasubstituted benzene ring having two *para*-protons and a phenolic OH group in **4**. This suggested that the cross-conjugated dienone ring in **1** was aromatized in **4**. In addition, the NMR data indicated replacement of the resonances for the 8,18,20-acetal in **2** by those of the 18,20-lactone in **4**. Accordingly, **4** was assigned as (−)-(4*S*,5*S*,10*R*)-12,18-dihydroxyabieta-8,10,12-trien-20-oic acid 18,20-lactone. The structure and NMR data assignments of **4** were confirmed by 2D NMR data analysis (Supporting Information, Figures S58−S60). In the HMBC spectrum of **4**, correlations for O*H*/C-11, C-12, and C-13, H-11/C-8, C-9, C-10, C-12, and C-13, and H-14/C-7, C-8, C-9, C-12, C-13, and C-15 proved the location of the phenolic OH at C-12. The CD spectrum of **4** displayed Cotton effects, negative at 285 nm ($\Delta\varepsilon$ −0.16) and 226 nm ($\Delta\varepsilon$ −3.62), confirmed the 4*S*,5*S*,10*R* configuration for **4** based on the exciton chirality method and the δ-lactone rules.[10,12,13]

The spectroscopic data of compound **5** (Tables 1 and 4 and Experimental Section) indicated that it was an aromatized analogue of **3**. This was demonstrated by comparison of the NMR data

Table 4. ^{13}C NMR Data (δ) for Compounds **1**−**21** in Me_2CO-d_6[a]

no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	36.1	29.3	26.3	39.3	26.9	27.0	26.9	29.5	39.1	34.5	39.5	35.4	39.2	37.4	37.5	31.7	37.5	65.2	200.3	119.5	120.3
2	21.4	20.7	18.7	22.3	19.2	19.3	19.0	21.5	22.5	22.9	22.5	22.8	22.4	22.2	19.0	22.4	19.6	29.8	37.8	198.5	198.5
3	41.2	41.1	38.6	41.1	39.0	39.2	38.7	40.9	41.6	41.7	41.5	41.6	41.6	41.0	42.2	41.8	37.8	34.0	37.7	53.9	54.1
4	33.8	33.4	31.1	33.6	32.0	31.7	32.8	33.8	33.5	33.8	33.4	33.8	33.5	33.1	33.8	33.6	38.5	35.4	35.7	36.8	36.5
5	49.9	46.1	45.0	47.9	55.5	50.2	60.4	38.1	47.7	49.8	47.8	49.9	47.7	44.9	50.4	49.9	51.2	144.3	154.2	48.1	40.9
6	19.8	20.3	76.6	23.1	80.4	79.2	81.9	31.3	20.5	19.4	20.3	19.3	20.4	37.1	35.7	40.5	35.5	25.1	121.6	24.5	28.8
7	39.3	41.9	62.0	30.0	70.6	68.7	189.8	70.8	30.5	30.6	30.5	30.6	30.5	197.0	197.5	196.8	197.1	28.9	134.9	30.5	74.9
8	68.7	76.6	55.7	127.9	128.9	127.8	121.8	134.2	128.9	128.0	128.7	128.1	128.8	126.7	124.7	125.8	124.6	127.4	125.0	133.0	131.1
9	162.3	169.6	149.9	136.4	139.0	139.8	146.3	140.7	140.8	139.7	140.3	139.3	140.3	148.5	149.9	148.5	149.6	134.9	131.9	130.7	130.8
10	49.8	44.9	50.6	49.1	47.1	46.3	48.8	38.5	41.2	41.8	41.2	41.5	41.2	41.2	70.4	38.5	69.7	129.9	128.9	155.9	155.2
11	125.6	116.5	132.4	117.3	110.5	110.7	111.5	110.8	112.5	117.2	112.2	117.0	112.1	111.8	110.9	112.6	111.4	112.2	109.6	111.2	111.2
12	186.1	185.1	185.6	152.7	154.7	154.9	161.2	154.4	153.0	152.4	153.0	152.5	152.9	160.2	160.1	160.4	160.2	153.5	157.2	153.9	155.5
13	142.9	145.6	150.8	134.4	135.5	135.6	136.7	132.7	132.7	133.3	132.7	133.5	132.6	133.9	135.1	133.9	135.1	132.7	137.8	139.4	138.9
14	146.9	140.7	137.7	126.6	128.0	129.4	127.5	120.2	127.1	126.5	127.1	126.7	126.9	125.9	126.2	125.9	126.2	124.9	126.0	119.5	129.7
15	26.6	27.0	27.2	27.5	27.6	27.5	27.4	27.4	27.5	27.5	27.5	27.5	27.4	27.5	27.5	27.4	27.5	27.4	28.0	27.8	27.8
16	21.7	21.7	21.5	22.8	22.7	22.7	22.4	22.9	22.9	22.9	22.7	22.8	22.8	22.6	22.6	22.6	22.6	23.0	22.7	22.6	22.5
17	21.9	22.2	21.6	22.8	22.8	22.8	22.5	23.0	23.1	22.9	23.1	23.0	23.1	22.8	22.7	22.7	22.7	23.0	22.7	22.6	22.6
18	77.2	68.9	22.4	77.4	22.1	22.2	22.1	66.0	66.6	72.3	66.7	72.2	66.9	66.2	21.9	20.2	67.2	26.8	30.3	20.4	20.4
19	23.7	23.8	31.8	23.6	31.6	31.6	31.4	24.1	24.0	23.5	23.9	23.5	23.9	23.2	31.9	29.8	26.9	28.0	30.3	29.2	29.0
20	172.0	105.1	175.5	173.4	178.3	178.3	177.1	99.2	99.2	97.6	106.4	105.2	104.9	104.6							
OMe/OEt											55.1/	56.9/	/63.5, 15.2	/63.6,15.1							/64.1, 15.9

[a] ^{13}C NMR data were measured for **1**−**21** at 150 or 125 or 100 MHz. The assignments were based on DEPT, $^1H-^1H$ COSY, HSQC, and HMBC experiments.

between **3** and **5**, which indicated replacement of the resonances for the cross-conjugated dienone ring in **3** by resonances due to the aromatic ring in **5**. In the HMBC spectrum of **5**, correlations from both H-5 and H_2-1 to C-20, from H_3-18 and H_3-19 to C-3, C-4, and C-5, from H-5 to C-7, C-9, C-10, C-18, C-19, and C-20, from H-6 to C-20, and from H-14 to C-7 (Supporting Information, Figure S71) confirmed that **5** was 6,7,12-trihydroxyabieta-8,11,13-trien-20-oic acid 6,20-lactone. In the NOE difference experiment, H-7 was enhanced by irradiation of H-5, demonstrating that H-7 had a quasi-axial α-orientation. The CD spectrum of **5** showed a typical coupled Cotton effect, positive at 244 nm ($\Delta\varepsilon$ +10.49) and negative at 223 nm ($\Delta\varepsilon$ −3.96), indicating exciton coupling between the $\pi\rightarrow\pi^*$ transition of the phenol and the $n\rightarrow\pi^*$ transition of the γ-lactone chromophores. The positive chirality supported the 6*S*,10*R* configuration for **5**. Therefore, **5** was determined as (+)-(5*S*,6*S*,7*R*,10*R*)-6,7,12-trihydroxyabieta-8,11,13- trien-20-oic acid 6,20-lactone.

The spectroscopic data of compound **6** indicated that it was an isomer of **5**. Comparison of the NMR data between **5** and **6** indicated that H-5, H-6, and H-7 and C-5, C-6, and C-7 of **6** were shifted by $\Delta\delta_H$ +0.05, −0.17, and −0.04 and $\Delta\delta_C$ −5.3, −1.2, and −1.9 ppm, respectively, while the coupling constant for $J_{6,7}$ was changed from 2.0 Hz of **5** to 3.6 Hz of **6**. This suggested that **6** was the 7-epimer of **5**, which was proved by 2D NMR and CD data of **6** (Supporting Information).

Compound **7** ($C_{20}H_{24}O_4$) had two fewer hydrogen atoms than **5**. The NMR data of **7** (Tables 1 and 4) indicated that a resonance for a conjugated carbonyl (δ_C 189.8) in **7** replaced the resonances for H-7 and C-7 of **5**, while H-5, H-11, and H-14 and C-5, C-6, C-8, C-9, and C-12 of **7** were shifted significantly by $\Delta\delta_H$ +0.06, +0.25, and +0.45 and $\Delta\delta_C$ +4.9, +1.5, −7.1, +7.3, and +6.5 ppm, respectively. These data indicated that **7** was the 7-oxo derivative of **5**. This was proved by 2D NMR data analysis, particularly, by correlations of C-7 with H-5, H-6, and H-14 in the HMBC spectrum of **7**. The 5*S*,6*S*,10*R* configuration of **7** was supported by Cotton effects in the CD spectrum (Supporting Information, Figure S7). Thus, **7** was (+)-(5*S*,6*S*,10*R*)-12-hydroxy-7-oxo-abieta-8,11,13-trien-20-oic acid 6,20-lactone.

Compound **8** ($C_{20}H_{26}O_3$) was an isomer of **4**. The main differences of the NMR data between **4** and **8** (Tables 2 and 4) were the absence of the ester carbonyl resonance and the presence of resonances for an acetal methine [δ_H 4.51 (s) and δ_C 99.2] and an oxymethine [δ_H 4.83 (brd, J = 4.5 Hz) and δ_C 70.8] in **8**. This demonstrated acetal formation of C-20 with the oxymethylene (CH_2-18) and oxymethine in **8**. In the HMBC spectrum of **8**, correlation from the oxymethine proton to C-5, C-6, C-8, C-9, C-13, C-14, and C-20 and from H-20 to C-1, C-5, C-7, C-9, and C-18 (Supporting Information, Figure S100), together with their shifts, revealed the oxymethine to be C-7 and the 7,18,20-acetal in **8**. Thus, **8** was determined as (−)-(4*S*,5*S*,7*S*,10*R*,20*S*)-7,12,18-trihydroxyabieta-8,11,13-trien-20-aldehyde 7,18,20-acetal.

Compounds **9** and **10** were obtained as an inseparable mixture of two isomers in a near 2:3 ratio, as determined by the doubling of resonances in the ^1H and ^{13}C NMR spectra (Supporting Information, Figures 105 and 106). The molecular formula of **9** and **10** ($C_{20}H_{28}O_3$, HREIMS) had two more hydrogen atoms than **8**. Analysis of the NMR data of **9** or **10** revealed replacement of the resonances for the oxymethine (H-7 and C-7) in **8** by resonances for a methylene in **9** or **10**. This indicated that **9** and **10** were C-20 epimers of 12,18-dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-hemiacetal. This was verified by detailed interpretation of the 2D NMR data for **9** and **10** (Tables 2 and 4). In the NOE difference spectrum of the mixture, H-6β and O*H*-20 of **9** were enhanced upon irradiation of H-18a for **9**, whereas H-6β and H-20 of **10** were enhanced when H-18a for **10** was irradiated (Supporting Information, Figures S111 and S112). Therefore, **9** and **10** were (4*S*,5*S*,10*R*,20*R*)-12,18- dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-hemiacetal and (4*S*,5*S*,10*R*,20*S*)-12,18-dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-hemiacetal, respectively.

The spectroscopic data of compound **11** (Tables 2 and 4 and Experimental Section) indicated that it was a methoxy acetal derivative of **9**. This was confirmed by a long-range correlation from O*Me* to C-20 in the HMBC spectrum of **11** and enhancements of H-1β and H-2β upon irradiation of H-20 and enhancements of O*Me* and H-6β by irradiation of H-18a in the NOE difference experiment (Supporting Information, Figures S122 and S123).

Compound **12** was a C-20 epimer of **11**, as indicated by the spectroscopic data (Tables 2 and 4 and Experimental Section) and confirmed by its 2D NMR data and enhancements of H-6β and H-18a upon irradiation of H-20 in the NOE difference experiment of **12** (Supporting Information, Figure S132).

Compound **13** ($C_{22}H_{32}O_3$) was an analogue of **11**. Comparison of the NMR and MS data between **11** and **13** (Tables 2 and 4) demonstrated that the only difference was replacement of resonances for OMe in **11** by those for OEt in **13**.

Compound **14**, $C_{22}H_{30}O_4$ (HREIMS), displayed spectroscopic features similar to those of **13**. However, in the NMR spectra of **14**, a resonance due to a conjugated carbonyl carbon (δ_C 197.0) replaced the resonances for one methylene in **13**. The HMBC spectrum of **14** showed long-range correlations of the carbonyl carbon with H_2-6 and H-14, placing the carbonyl at C-7. Thus, **14**

was determined to be (−)-(4*S*,5*S*,10*R*,20*R*)-12,18-dihydroxy-7-oxo-abieta-8,11,13-trien-20-aldehyde 18,20-ethyl acetal.

The NMR spectroscopic data of compound **15** (Tables 3 and 4 and Experimental Section) were similar to those of **7**, except for substitution of resonances of the oxymethine (H-6 and C-6) and the quaternary carbon (C-10) in **7** by resonances due to a methylene and a hydroxy-substituted quaternary carbon in **15** (Tables 3 and 4). In addition, the ester carbonyl resonance in **7** was absent in **15**. This indicated that **15** was a C_{20}-norabietane derivative, which was supported by the molecular composition ($C_{19}H_{26}O_3$) and confirmed by 2D NMR analysis. Particularly, HMBC correlations for H_2-6/C-5, C-7, and C-10, H-11/C-8, C-10, C-12, and C-13, and H-14/C-7, C-9, C-12, and C-15 (Supporting Information, Figure S159), in combination with their shifts, verified the functionality of 10,12-dihydroxy-7-oxo in **15**. In the NOE difference experiment of **15**, irradiation of H_3-18 enhanced O*H*-10, while H_3-19, H-11, and H-14 were enhanced when H-5 was irradiated (Supporting Information, Figure S160). These enhancements demonstrated *trans* quasi-axial orientations of H-5, H_3-18, and *OH*-10 in **15**, which was supported also by $J_{5,6\beta}$ (13.2 Hz). The CD spectrum of **15** displayed a positive Cotton effect at 318 nm ($\Delta\varepsilon$ +2.72) and a negative Cotton effect at 290 nm ($\Delta\varepsilon$ −2.91), indicating a 5*S*,10*R* configuration based on the aryl ketone CD rule.[14,15] Therefore, the structure of **15** was assigned as (+)-(5*S*,10*R*)-10,12-dihydroxy-7-oxo-norabieta-8,11,13-triene.

Compound **16** was disclosed to be the 10-dehydroxy analogue of **15** from its spectroscopic data (Tables 3 and 4 and Experimental Section) and 2D NMR data analysis (Supporting Information, Figures S167 and S168). The coupling constant (11.5 Hz) between H-5 and H-10 in **16** evidenced the *trans* quasi-diaxial relationship between them. The CD spectrum of **16** showed a positive Cotton effect at 320 nm ($\Delta\varepsilon$ +3.30) and a negative Cotton effect at 297 nm ($\Delta\varepsilon$ −4.20) similar to those of **15**, demonstrating the 5*R*,10*S* configuration for **15** according to the aryl ketone CD rule.[14,15] Thus, **16** was (−)-(5*R*,10*S*)-12-hydroxy-7-oxo-20-norabieta-8,11,13-triene.

The HREIMS of compound **17** ($C_{19}H_{26}O_4$) indicated that it had one more oxygen atom than **15**. Comparison the NMR data between **15** and **17** showed that the resonances for one methyl at C-4 in **15** were replaced by those of a hydroxymethyl in **17** (Tables 3 and 4 and Experimental Section), suggesting that **17** was a 18- or 19-OH derivative of **15**. In the NOE difference spectrum of **17**, irradiation of the methyl protons at C-4 enhanced H-5 and H-6α, while H-6β was enhanced when the oxymethine protons were irradiated (Supporting Information, Figure S180). The enhancements revealed that the hydroxymethyl was β-oriented, opposite H-5. Thus, **17** was (−)-(4*S*,5*S*,10*R*)-10,12,18-trihydroxy-7-oxo-20-norabieta-8,11,13-triene. The structure and NMR data assignments of **17** were proved by the 2D NMR and CD data (Supporting Information, Figures S15 and S177−S179).

The spectroscopic data of compound **18** (Tables 3 and 4 and Experimental Section) indicated that it was an isomer of **16**. However, the NMR spectrum of **18** showed resonances attributable to an oxymethine and a tetrasubstituted double bond replacing the resonances for the carbonyl and two methines in **16**. This supported **18** as hydroxyl-20-norabieta-5(10),8,11,13-tetraen-12-ol. Cross-peaks of the vicinal coupling protons for H-1/H_2-2/H_2-3 in the ^{1}H−^{1}H COSY spectrum and long-range correlations from O*H* to C-1 and C-10, from H_2-2 to C-10, and from H_2-3 to C-1, C-4, C-5, C-18, and C-19 in the HMBC spectrum placed the OH at C-1 in **18** (Supporting Information, Figures S187 and S189). The CD spectrum of **18** exhibited a positive Cotton effect at 232 nm ($\Delta\varepsilon$ +3.57) for the allylic alcohol $\pi-\pi^*$ transition, suggesting a 1*R* configuration according to the reverse octant rule for allylic alcohols (oxygen-substituted olefins).[16] Consequently, **18** was proposed to be (+)-(1*R*)-1,12-dihydroxy-20-norabieta-5(10),8,11,13-tetraene.

HREIMS of compound **19** indicated that it had the molecular formula $C_{19}H_{22}O_2$. Comparison of the NMR data of compound **19** with those of **18** (Tables 3 and 4) indicated substitution of the oxymethine and two methylenes in **18** by a carbonyl and two vicinal coupling sp^2 methines in **19**. This suggested that **19** was a tetradehydrogenated analogue of **18**. In the HMBC spectrum of **19**, correlations from H_2-2 to C-10, from H_2-3 to C-1 and C-5, from H-6 to C-4, C-8, and C-10, from H-7 to C-5, C-9, and C-14, and from both H_3-18 and H_3-19 to C-3, C-4, and C-5 (Supporting Information, Figure S197), together their shifts, revealed the presence of the naphthalene ring system and 1-oxo group in **19**. Hence, **19** was 12-hydroxy-1-oxo-20-norabieta-5(10),6,8,11,13-pentaene; the 12-*O*-methyl derivative had been reported as a synthetic intermediate.[17]

Analysis of the spectroscopic data including 2D NMR experiments of compound **20** (Tables 3 and 4, Experimental Section, and Supporting Information, Figures 204 and 205) demonstrated that it was 12-hydroxy-2-oxo-20-norabieta-1(10),8,11,13-tetraene. The planar structure of **20** was identical to an intermediate reported in the synthesis of salvirecognine; however, neither spectroscopic data nor stereochemistry was presented for the compound in the literature.[18] On the basis of the octant rule for the cyclohexenone,[10,13] a positive Cotton effect at 319 nm ($\Delta\varepsilon$ +4.28) in the CD spectrum supported the 5*S* configuration for **20**.

The NMR data of **21** (Tables 3 and 4) resembled those of **20**, except for replacement of a methylene in **20** by an oxymethine and an *O*-ethyl in **21**. This indicated that **21** was an ethoxy-substituted analogue of **20**, which was also inferred by HRESIMS ($C_{21}H_{28}O_3$). In the HMBC spectrum of **21** (Supporting Information, Figure S213), although no correlation of C-7 or H-7 with the oxymethylene protons or carbon of the *O*-ethyl was observed due to limitation of the sample amount available, correlations from H-14 to C-7 and from H-7 to C-5 and C-14 combined with their shifts located the *O*-ethyl at C-7 in **21**. Comparing with those for H_2-6 and H_2-7 of **20**, the coupling constants for H_2-6 and H-7 [$J_{7,6a}$ (3.6 Hz) and $J_{7,6e}$ (2.4 Hz)] of **21** suggested the β quasi-equatorial orientation of H-7. A positive Cotton effect at 336 nm ($\Delta\varepsilon$ +3.17) in the CD spectrum (Supporting Information, Figure S18) supported the 5*S* configuration of **21**.[10,13] Consequently, **21** was determined to be (+)-(5*S*,7*R*)-7-ethoxy-12-hydroxy-2-oxo-20-norabieta-1(10),8,11,13-tetraene.

Because TLC detection indicated that compounds **11** and **12** could be produced in a MeOH solution of the mixture of **9** and **10** after keeping at 40 °C for 24 h, they may be artifacts generated in the isolation procedure using MeOH. This also evidenced that the ethyl unit in **13**, **14**, and **21** would be introduced in the extraction using EtOH, although the precursors of **14** and **21** were not obtained in this study.

The known compounds were identified by comparison of spectroscopic data with those reported in the literature as 8-hydroxy-12-oxoabieta-9(11),13-dien-20-oic 8,20-lactone,[9] (+)-pisiferic acid,[9,19] (+)-pisiferal (**22**),[20,21] 6β-hydroxyferruginol,[22] and 7-dehydroabietanone (**23**).[23]

In the cytotoxic assay against human cancer cell lines including ovary (A 2780), colon (HCT-8), hepatoma (Bel-7402), stomach (BGC-823), and lung (A549), compounds **3** and **5** exhibited selective cytotoxic activities against A2780 (IC_{50} 1.7 μM) and A549 (IC_{50} 6.0 μM), respectively, while the positive control camptothecin gave IC_{50} values of 0.2 and 3.6 μM, respectively. The other compounds were inactive to all tested cell lines (IC_{50} > 10 μM). Compounds **8**, **16**, and **22** showed inhibitory activities against the release of β-glucuronidase in rat polymorphonuclear leukocytes (PMNs) induced by platelet-activating factor (PAF), with inhibitory rates of 59.7 ± 4.8%, 56.1 ± 5.6%, and 65.9 ± 3.1% at 10^{-5} M [the positive control ginkgolide B (BN52021) gave an inhibitory rate of 82.8 ± 5.3% at the same concentration], respectively. Compound **23** demonstrated inhibitory activity against H5N1 avian influenza virus with an IC_{50} value of 4.8 μM [the positive control

zidovudine gave an IC_{50} value of 0.048 μM], and the other compounds were inactive (IC_{50} > 10 μM).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. IR spectra were recorded as KBr disks on a Nicolet Impact 400 FT-IR spectrophotometer. NMR spectra were obtained at 600, 500, or 400 MHz for ^{1}H and 150, 125, or 100 MHz for ^{13}C, respectively, on Inova 600, 500, and 400 MHz spectrometers in Me_2CO-d_6 with solvent peaks being used as references. EIMS and HREIMS were measured with a Micromass Autospec-Ultima ETOF spectrometer. ESIMS were measured with a Q-Trap LC/MS/MS (Turbo ionspray source) spectrometer. Column chromatography (CC) was performed using silica gel (200−300 mesh, Qingdao Marine Chemical Inc., China) and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala Sweden). HPLC separation was performed using a Waters 600 pump, a Waters 2487 dual λ absorbance detector, and an Alltima (250 × 10 mm) preparative column packed with C_{18} (5 μm). TLC was carried out on precoated silica gel GF_{254} plates. Spots were visualized under UV light (254 or 356 nm) or by spraying with 7% H_2SO_4 in 95% EtOH followed by heating.

Plant Material. See ref 8.

Extraction and Isolation. For extraction and partition separation of the extract, see ref 8. The EtOAc fraction (133 g) was chromatographed over silica gel (1500 g), eluting with increasing amounts of Me_2CO (0−100%) in petroleum ether, to afford fractions (F_1−F_{10}) based on TLC analysis. F_3 (5.12 g) was separated by reversed-phase flash chromatography over C-18 silica gel eluting with a step gradient from 20% to 95% MeOH in H_2O to give four subfractions, $F_{3\text{-}1}$−$F_{3\text{-}4}$. Separation of $F_{3\text{-}2}$ (1.08 g) over Sephadex LH-20 using petroleum ether−$CHCl_3$−MeOH (5:5:1) gave $F_{3\text{-}1\text{-}1}$−$F_{3\text{-}1\text{-}5}$. $F_{3\text{-}1\text{-}2}$ (0.11 g) and $F_{3\text{-}1\text{-}3}$ (53 mg) were separately purified by CC over silica gel, eluting with $CHCl_3$−MeOH (25:1), to give **1** (18.4 mg) and **7** (9.5 mg), respectively. $F_{3\text{-}1\text{-}4}$ (95 mg) was purified by reversed-phase preparative HPLC (RP_{18}, 5 μm, 254 nm, MeOH−H_2O, 75:25) to afford **4** (2.5 mg) and **8** (19.5 mg). $F_{3\text{-}3}$ (1.15 g) was further fractionated via silica gel CC, eluting with a gradient of increasing MeOH (4−10%) in $CHCl_3$, to yield $F_{3\text{-}3\text{-}1}$−$F_{3\text{-}3\text{-}4}$). Fraction $F_{3\text{-}3\text{-}2}$ (0.29 g) was separated by CC over Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5:5:1) and then purified by reversed-phase preparative HPLC (RP_{18}, 5 μm, 254 nm, MeOH−H_2O, 87:13) to give **11** (12.4 mg), **12** (25.5 mg), and **13** (10.7 mg). Fraction $F_{3\text{-}3\text{-}3}$ (0.22 g) was purified using the same protocol, but eluting the HPLC system with 15% H_2O−MeOH, to afford **20** (8.8 mg) and **21** (1.6 mg). Fraction $F_{3\text{-}3\text{-}4}$ (0.32 g) was subjected to CC over silica gel, eluting with a gradient of increasing MeOH (4−10%) in $CHCl_3$, to give $F_{3\text{-}3\text{-}4\text{-}1}$−$F_{3\text{-}3\text{-}4\text{-}3}$, of which $F_{3\text{-}3\text{-}4\text{-}2}$ (69 mg) and $F_{3\text{-}3\text{-}4\text{-}3}$ (108 mg) were separately isolated by reversed-phase preparative HPLC (RP_{18}, 5 μm, 254 nm, MeOH−H_2O, 85:15) to yield **2** (2.0 mg), **3** (2.2 mg), **14** (3.5 mg), and **19** (1.8 mg). Fraction F_4 (4.80 g) was separated by reversed-phase flash chromatography over C-18 silica gel, eluting with a step gradient from 20% to 95% MeOH in H_2O, to give four fractions ($F_{4\text{-}1}$−$F_{4\text{-}4}$). Separation of $F_{4\text{-}1}$ (0.35 g) over Sephadex LH-20 with $CHCl_3$−MeOH (1:1) gave $F_{4\text{-}1\text{-}1}$−$F_{4\text{-}1\text{-}4}$. Fraction $F_{4\text{-}1\text{-}2}$ (32 mg) was purified by reversed-phase preparative HPLC (RP_{18}, 5 μm, 254 nm, MeOH−H_2O, 80:20) to give **18** (2.1 mg). Using the same HPLC system, from $F_{4\text{-}1\text{-}3}$ (56 mg) and $F_{4\text{-}1\text{-}4}$ (0.10 g), yielded **5** (6.8 mg), **6** (11.7 mg), and a mixture of **9** and **10**. Successive separation of $F_{4\text{-}2}$ (1.75 g) over Sephadex LH-20 eluting with CH_3Cl−MeOH (1:1) and by reversed-phase preparative HPLC (RP_{18}, 5 μm, 254 nm, MeOH−H_2O, 78:22) yielded **15** (9.8 mg), **16** (2.2 mg), and **17** (2.4 mg). Using the same procedure as described above for the isolation of **18**, compounds **22** (3.6 mg) and **23** (11.3 mg) were obtained from $F_{4\text{-}3}$ (1.28 g).

(−)-(4*S*,5*S*,8*R*,10*R*)-8,18-Dihydroxy-12-oxo-abieta-9(11),13-dien-20-oic acid 18,20-lactone (1): white powder; $[\alpha]_D^{20}$ −22.3 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε) 240 (3.9) nm; CD (MeOH) 358 ($\Delta\varepsilon$ −0.31), 248 ($\Delta\varepsilon$ −5.31), 219 ($\Delta\varepsilon$ +0.17) nm; IR (KBr) ν_{max} 3447, 2957, 2874, 1715, 1668, 1636, 1465, 1381, 1153, 1045 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 100 MHz) data, see Tables 1 and 4; ESIMS *m*/*z* 353 $[M + Na]^+$, 369 $[M + K]^+$; EIMS *m*/*z* 330 $[M]^{+\cdot}$; HREIMS *m*/*z* 330.1826 $[M]^{+\cdot}$ (calcd for $C_{20}H_{26}O_4$, 330.1831).

(−)-(4*S*,5*S*,8*R*,10*R*,20*S*)-8,18-Dihydroxy-12-oxo-abieta-9(11),13-dien-20-aldehyde 8,18,20-acetal (2): white powder; $[\alpha]_D^{20}$ −103.5 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.2), 229 (1.1), 271 (0.5) nm; CD (MeOH) 354 ($\Delta\varepsilon$ −1.50), 244 ($\Delta\varepsilon$ −13.68), 218 ($\Delta\varepsilon$ +4.02) nm; IR (KBr) ν_{max} 2996, 2927, 2871, 2849, 1684, 1634, 1620, 1464, 1383, 1334, 1306, 1245, 1220, 1177, 1142, 1031, 1006 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 600 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 1 and 4; EIMS *m*/*z* 314 $[M]^{+\cdot}$; HREIMS *m*/*z* 314.1882 $[M]^{+\cdot}$ (calcd for $C_{20}H_{26}O_3$, 314.1882).

(+)-(5*S*,6*S*,7*S*,8*R*,10*R*)-6-Hydroxy-7,8-epoxy-12-oxo-abieta-9(11),13-dien-20-oic acid 6,20-lactone (3): white powder; $[\alpha]_D^{20}$ +27.3 (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.1), 247 (1.1), 259 (sh), 288 (0.3) nm; CD (MeOH) 362 ($\Delta\varepsilon$ −0.65), 293 ($\Delta\varepsilon$ +6.97), 255 ($\Delta\varepsilon$ −6.32), 234 ($\Delta\varepsilon$ +3.21), 216 ($\Delta\varepsilon$ +3.09) nm; IR (KBr) ν_{max} 3360, 2958, 2870, 1771, 1696, 1658, 1638, 1603, 1459, 1392, 1326, 1302, 1273, 1226, 1172, 1111, 1086, 1047, 1032 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 600 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 1 and 4; ESIMS *m*/*z* 329 $[M + H]^+$, 679 $[2\ M + Na]^+$, 1007 $[3\ M + Na]^+$; HRESIMS *m*/*z* 329.1800 $[M + H]^+$ (calcd for $C_{20}H_{25}O_4$, 329.1753).

(−)-(4*S*,5*S*,10*R*)-12,18-Dihydroxyabieta-8,10,12-trien-20-oic acid 18,20-lactone (4): white powder; $[\alpha]_D^{20}$ −128.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.3), 223 (sh), 285 (0.9) nm; CD (MeOH) 285 ($\Delta\varepsilon$ −0.16), 226 ($\Delta\varepsilon$ −3.62), 211 ($\Delta\varepsilon$ −0.90) nm; IR (KBr) ν_{max} 3416, 2951, 2923, 2867, 1699, 1619, 1515, 1462, 1420, 1325, 1220, 1186, 1159, 1032 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 1 and 4; EIMS *m*/*z* 314 $[M]^{+\cdot}$; HREIMS 314.1870 $[M]^{+\cdot}$ (calcd for $C_{20}H_{26}O_3$, 314.1882).

(+)-(5*S*,6*S*,7*R*,10*R*)-6,7,12-Trihydroxyabieta-8,11,13-trien-20-oic acid 6,20-lactone (5): white powder; $[\alpha]_D^{20}$ +77.4 (*c* 0.50, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.2), 239 (sh), 286 (1.2) nm; CD (MeOH) 281 ($\Delta\varepsilon$ +0.73), 244 ($\Delta\varepsilon$ +10.49), 223 ($\Delta\varepsilon$ −3.96) nm; IR (KBr) ν_{max} 3359, 2957, 2932, 2871, 1756, 1701, 1614, 1503, 1458, 1424, 1362, 1333, 1280, 1252, 1174, 1084, 1049 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 1 and 4; EIMS *m*/*z* 330 $[M]^{+\cdot}$; HREIMS *m*/*z* 330.1823 $[M]^{+\cdot}$ (calcd for $C_{20}H_{26}O_4$, 330.1831).

(−)-(5*S*,6*S*,7*S*,10*R*)-6,7,12-Trihydroxyabieta-8,11,13-trien-20-oic acid 6,20-lactone (6): white powder; $[\alpha]_D^{20}$ −3.7 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.2), 237 (sh), 285 (1.1) nm; CD (MeOH) 241 ($\Delta\varepsilon$ +4.58), 219 ($\Delta\varepsilon$ −2.91) nm; IR (KBr) ν_{max} 3373, 2957, 2871, 1754, 1616, 1507, 1459, 1175, 1045 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 400 MHz) and ^{13}C NMR (Me_2CO-d_6, 100 MHz) data, see Tables 1 and 4; EIMS *m*/*z* 330 $[M]^{+\cdot}$; HREIMS *m*/*z* 330.1827 $[M]^{+\cdot}$ (calcd for $C_{20}H_{26}O_4$, 330.1831).

(+)-(5*S*,6*S*,10*R*)-12-Hydroxy-7-oxo-abieta-8,11,13-trien-20-oic acid 6,20-lactone (7): white powder; $[\alpha]_D^{20}$ +64.9 (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 208 (3.9), 246 (4.3), 297 (3.5) nm; CD (MeOH) 338 ($\Delta\varepsilon$ −0.62), 308 ($\Delta\varepsilon$ +3.74), 247 ($\Delta\varepsilon$ +2.12), 227 ($\Delta\varepsilon$ −10.53); IR (KBr) ν_{max} 3332, 2957, 2931, 2871, 1785, 1694, 1598, 1578, 1498, 1461, 1372, 1322, 1298, 1271, 1175, 1100, 1043, 1008 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 1 and 4; EIMS *m*/*z* 328 $[M]^{+\cdot}$; HREIMS *m*/*z* 328.1658 $[M]^{+\cdot}$ (calcd for $C_{20}H_{24}O_4$, 328.1675).

(−)-(4*S*,5*S*,7*S*,10*R*,20*S*)-7,12,18-Trihydroxyabieta-8,11,13-trien-20-aldehyde 7,18,20-acetal (8): white powder; $[\alpha]_D^{20}$ −52.1(*c* 0.52, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.1), 223 (1.2), 281 (0.9) nm; CD (MeOH) 278 ($\Delta\varepsilon$ −0.59), 229 ($\Delta\varepsilon$ −1.98), 210 ($\Delta\varepsilon$ −2.78); IR (KBr) ν_{max} 3386, 2958, 2902, 2869, 1622, 1594, 1504, 1438, 1377, 1360, 1337, 1288, 1271, 1228, 1167, 1109, 1080, 1054, 1008 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 2 and 4; EIMS *m*/*z* 314 $[M]^{+\cdot}$; HREIMS *m*/*z* 314.1870 $[M]^{+\cdot}$ (calcd for $C_{20}H_{26}O_3$, 314.1882).

Mixture of (4*S*,5*S*,10*R*,20*R*)-12,18-Dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-hemiacetal (9) and (4*S*,5*S*,10*R*,20*S*)-12,18-dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-hemiacetal (10): white powder; IR (KBr) ν_{max} 3364, 2957, 2870, 1617, 1511, 1462, 1420, 1372, 1332, 1269, 1222, 1188, 1163, 1101, 1074, 1032 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 2 and 4; EIMS *m*/*z* 316 $[M]^{+\cdot}$; HREIMS *m*/*z* 316.2056 $[M]^{+\cdot}$ (calcd for $C_{20}H_{28}O_3$, 316.2038).

(−)-(4*S*,5*S*,10*R*,20*R*)-12,18-Dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-methyl acetal (11): white powder; $[\alpha]_D^{20}$ −10.0 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.2), 224 (1.3), 283 (1.2) nm; CD (MeOH) 294 ($\Delta\varepsilon$ −0.52), 266 ($\Delta\varepsilon$ +0.99), 207 ($\Delta\varepsilon$ +11.2); IR (KBr) ν_{max} 3379, 2959, 2870, 1618, 1512, 1462, 1420, 1112, 1050 cm^{-1};

^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 2 and 4; EIMS *m/z* 330 $[M]^{+\cdot}$; HREIMS *m/z* 330.2216 $[M]^{+\cdot}$ (calcd for $C_{21}H_{30}O_3$, 330.2195).

(−)-(4*S*,5*S*,10*R*,20*S*)-12,18-Dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-methyl acetal (12): white powder; $[\alpha]_D^{20}$ −19.9 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.1), 230 (1.1), 278 (0.9) nm; CD (MeOH) 296 ($\Delta\varepsilon$ −0.75), 256 ($\Delta\varepsilon$ −1.01), 213 ($\Delta\varepsilon$ −4.72), 202 ($\Delta\varepsilon$ +10.7); IR (KBr) ν_{max} 3392, 2955, 2870, 1617, 1509, 1462, 1419, 1125, 1075, 994 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 2 and 4; EIMS *m/z* 330 $[M]^{+\cdot}$; HREIMS *m/z* 330.2216 $[M]^{+\cdot}$ (calcd for $C_{21}H_{30}O_3$, 330.2195).

(−)-(4*S*,5*S*,10*R*,20*R*)-12,18-Dihydroxyabieta-8,11,13-trien-20-aldehyde 18,20-ethyl acetal (13): white powder; $[\alpha]_D^{20}$ −12.5 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 205 (4.0), 232 (1.4), 283 (2.2) nm; CD (MeOH) 295 ($\Delta\varepsilon$ −1.02), 266 ($\Delta\varepsilon$ +1.05), 206 ($\Delta\varepsilon$ +9.81); IR (KBr) ν_{max} 3374, 2960, 2871, 1618, 1512, 1462, 1420, 1111, 1034, 983 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 2 and 4; ESIMS *m/z* 367 $[M + Na]^+$; EIMS *m/z* 298 $[M - EtO]^{+\cdot}$.

(−)-(4*S*,5*S*,10*R*,20*R*)-12,18-Dihydroxy-7-oxo-abieta-8,11,13-trien-20-aldehyde 18,20-ethyl acetal (14): white powder; $[\alpha]_D^{20}$ −110.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 208 (4.3), 234 (3.8), 281 (3.0) nm; CD (MeOH) 319 ($\Delta\varepsilon$ +3.29), 295 ($\Delta\varepsilon$ −2.16); IR (KBr) ν_{max} 3331, 2962, 2930, 2870, 1652, 1594, 1575, 1510, 1460, 1379, 1304, 1290, 1264, 1173, 1109, 1058, 1034 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 2 and 4; EIMS *m/z* 358 $[M]^{+\cdot}$; HREIMS 358.2155 $[M]^{+\cdot}$ (calcd for $C_{22}H_{30}O_4$, 358.2144).

(+)-(5*S*,10*R*)-10,12-Dihydroxy-7-oxo-20-norabieta-8,11,13-triene (15): white powder; $[\alpha]_D^{20}$ +1.9 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.1), 230 (3.3), 285 (2.9) nm; CD (MeOH) 318 ($\Delta\varepsilon$ +2.72), 290 ($\Delta\varepsilon$ −2.91) nm; IR (KBr) ν_{max} 3247, 2961, 1656, 1591, 1520, 1459, 1305, 1270, 1169, 1036 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 400 MHz) and ^{13}C NMR (Me_2CO-d_6, 100 MHz) data, see Tables 2 and 4; EIMS *m/z* 302 $[M]^{+\cdot}$; HREIMS *m/z* 302.1856 $[M]^{+\cdot}$ (calcd for $C_{19}H_{26}O_3$, 302.1882).

(−)-(5*R*,10*S*)-12-Hydroxy-7-oxo-20-norabieta-8,11,13-triene (16): white powder; $[\alpha]_D^{20}$ −19.5 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 207 (4.1), 232 (2.8), 281 (2.7) nm; CD (MeOH) 320 ($\Delta\varepsilon$ +3.30), 297 ($\Delta\varepsilon$ −4.20) nm; IR (KBr) ν_{max} 3326, 2963, 2932, 2869, 1657, 1597, 1574, 1508, 1460, 1365, 1303, 1265, 1177, 1122, 1021 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 3 and 4; EIMS *m/z* 286 $[M]^{+\cdot}$; HREIMS *m/z* 286.1924 $[M]^{+\cdot}$ (calcd for $C_{19}H_{26}O_2$, 286.1933).

(−)-(4*S*,5*S*,10*R*)-10,12,18-Trihydroxy-7-oxo-20-norabieta-8,11,13-triene (17): white powder; $[\alpha]_D^{20}$ −29.3 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 207 (4.2), 231 (3.9), 287 (3.6) nm; CD (MeOH) 321 ($\Delta\varepsilon$ +3.29), 294 ($\Delta\varepsilon$ −3.43) nm; IR (KBr) ν_{max} 3235, 2960, 2931, 2873, 1656, 1595, 1504, 1462, 1381, 1303, 1270, 1174, 1054 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 3 and 4; EIMS *m/z* 318 $[M]^{+\cdot}$; HREIMS *m/z* 318.1844 $[M]^{+\cdot}$ (calcd for $C_{19}H_{26}O_4$, 318.1831).

(+)-(1*R*)-1,12-Dihydroxy-20-norabieta-5(10),8,11,13-tetraene (18): white powder; $[\alpha]_D^{20}$ +7.4 (*c* 0.03, MeOH); UV (MeOH) λ_{max} (log ε) 230 (3.6), 265 (1.1), 303 (0.8) nm; CD (MeOH) 268 ($\Delta\varepsilon$ +1.31), 232 ($\Delta\varepsilon$ +3.57), 211 ($\Delta\varepsilon$ −1.20); IR (KBr) ν_{max} 3327, 2958, 2930, 2868, 1616, 1507, 1457, 1424, 1360, 1318, 1277, 1234, 1193, 1168, 1116, 1060, 1037 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 3 and 4; EIMS *m/z* 286 $[M]^{+\cdot}$; HREIMS *m/z* 286.1941 $[M]^{+\cdot}$ (calcd for $C_{19}H_{26}O_2$, 286.1933).

12-Hydroxy-1-oxo-20-norabieta-5(10),6,8,11,13-pentaene (19): colorless oil; UV (MeOH) λ_{max} (log ε) 225 (4.1), 266 (sh), 359 (1.1) nm; IR (KBr) ν_{max} 3329, 2958, 2926, 2868, 1731, 1631, 1589, 1522, 1460, 1413, 1388, 1334, 1248, 1176, 1119, 1041 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 3 and 4; EIMS *m/z* 282 $[M]^{+\cdot}$; HREIMS *m/z* 282.1608 $[M]^{+\cdot}$ (calcd for $C_{19}H_{22}O_2$, 282.1620).

(+)-(5*S*)-12-Hydroxy-2-oxo-20-norabieta-1(10),8,11,13-tetraene (20): colorless plate (acetone); mp 182−184 °C; $[\alpha]_D^{20}$ +77.6 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 204 (3.8), 225 (3.5), 237 (sh), 308 (3.8), 350 (2.7) nm; CD (MeOH) 319 nm ($\Delta\varepsilon$ +4.28), 297 ($\Delta\varepsilon$ −1.11); IR (KBr) ν_{max} 3381, 2958, 2867, 1637, 1581, 1501, 1427, 1368, 1257 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 3 and 4; EIMS *m/z* 284 $[M]^{+\cdot}$.

(+)-(5*S*,7*R*)-7-Ethoxy-12-hydroxy-2-oxo-20-norabieta-1(10),8,11,13-tetraene (21): colorless solid; $[\alpha]_D^{20}$ +44.8 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 212 (3.7), 237 (sh), 309 (1.9) nm; CD (MeOH) 336 ($\Delta\varepsilon$ +3.17), 242 ($\Delta\varepsilon$ −1.06), 226 ($\Delta\varepsilon$ −1.38) nm; IR (KBr) ν_{max} 3358, 2960, 2927, 2871, 1730, 1643, 1590, 1510, 1435, 1370, 1334, 1302, 1240, 1164, 1117, 1079 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 500 MHz) and ^{13}C NMR (Me_2CO-d_6, 125 MHz) data, see Tables 3 and 4; ESIMS *m/z* 329 $[M + H]^+$, 679 $[2\ M + Na]^+$, 1007 $[3\ M + Na]^+$; HRESIMS *m/z* 329.2165 $[M + H]^+$ (calcd for $C_{21}H_{29}O_3$, 329.2117).

Anti-inflammatory Activity Assay. See ref 24.

Cells, Culture Conditions, and Cell Proliferation Assay. See refs 25−27.

Production of HA/HIV Pseudovirions. Human embryonic kidney 293T cells were transiently co-transected with 8 μg of hemagglutinin [A/Viet Nam/1203/2004 (H5N1)] envelope expression plasmid with 0.5 μg of NA [A/PR/8/34 influenza virus (H1N1)] and 10 μg of Env-deficient HIV vector (pNL4-3-Luc-R$^-$E$^-$) in 100 mm plates by a standard $Ca_3(PO_4)_2$ protocol. Sixteen hours post-transfection, cells were washed by PBS w/o Ca^{2+}, Mg^{2+}; then 10 mL of fresh medium was added into each plate. Forty-eight hours post-transfection, the supernatants were collected and filtered through a 0.45 μm pore size filter. A549 cells were seeded in a 24-well plate with 5×10^4 cells/well density. Compounds were incubated with A549 cells 15 min prior to adding the HA/HIV pseudovirions (0.5 mL/well). Cells were lysed by lysis buffer (Promega) 48 h post-infection. The luciferase activity was measured with substrate (Promega) and an FB15 luminometer (Berthold detection system) according to the supplier's protocols.[28,29]

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Supporting Information Available: The MS, IR, 1D and 2D NMR, UV, and CD spectra of **1**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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