Anti-HIV Agents Derived from the *ent*-Kaurane Diterpenoid Linearol

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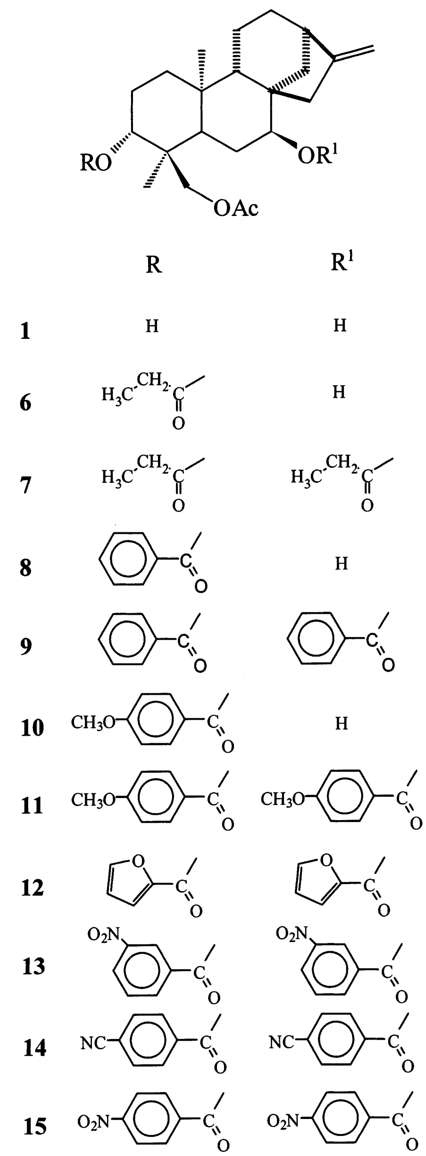
Twenty-six semisynthetic *ent*-kaurane derivatives of linearol (**1**) have been investigated for their anti-HIV effects. Five compounds (**4**, **7**, **11**, **25**, and **26**) showed significant activity against HIV replication in H9 lymphocyte cells with EC_{50} values in the range <0.1−3.11 μg/mL. With TI values of 163 and 184, compounds **4** and **25** are especially promising for further development as potential anti-HIV agents.

ent-Kauranes are diterpenoids isolated from several plant families, including the Asteraceae and Lamiaceae, and have been largely investigated for their biological effects such as potential antitumor and antibacterial properties.[1] Some of these compounds have also shown interesting activity against HIV replication in H9 lymphocyte cells.[2−4]



Results and Discussion

Recently, we studied several species of *Sideritis* (family Lamiaceae) from Turkey, which provided large amounts of linearol (**1**).[5] We then designed a systematic structure−activity relationship study by modifying different functional groups of the *ent*-kaurane skeleton in order to determinate their importance in eliciting the anti-HIV activity of these compounds. The antifeedant activity of some of these derivatives has already been reported in a previous paper.[6]

In the present paper, the anti-HIV activity has been evaluated for linearol (**1**) and 26 of its semisynthetic *ent*-kaurane derivatives (**2**−**27**). Compounds **2**−**15** were synthesized previously and their physical and spectroscopic properties reported.[6]

Treating linearol (**1**) with 2-methoxybenzoyl chloride, triethylamine (TEA), and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 gave its 3-mono- (**16**) and 3,7-di(2-methoxybenzoyl) (**17**) esters. In the same way, the 3-mono and 3,7-diester derivatives (**18**−**25**) were prepared using various acyl chlorides (4-thiomethoxybenzoyl, 4-fluorobenzoyl, 4-chlorobenzoyl, and piperonyl). However, with toluoyl chloride and pyrazinoyl chloride, the same synthetic procedure gave only the 3,7-diesters (**26** and **27**); the 3-monoacyl derivatives were not obtained. In addition, no 7-monoacyl derivatives were formed with any of the acyl chlorides.

The effects of **1**−**27** on HIV replication in H9 lymphocyte cells were tested, and the results are reported in Table 1. Although linearol (**1**) did not inhibit virus replication, five of its derivatives (**4**, **7**, **11**, **25**, and **26**) showed significant activity. The results indicate that the presence of ester moieties at both the C-3 and C-7 positions is necessary for anti-HIV activity. Among these diester derivatives, an electron donor effect seems to enhance the resultant biological effects. Notably, compounds **4** and **25** are promising leads for future development with good TI values of 163 and 184, respectively.

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Experimental Section

General Experimental Procedures. ^{1}H NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC 250 E apparatus at 250 MHz, and chemical shifts are reported with respect to residual $CHCl_3$ (δ 7.27). ^{13}C NMR spectra were recorded in $CDCl_3$ on the same instrument at 62.7 MHz, and chemical shifts were reported with respect to solvent signals

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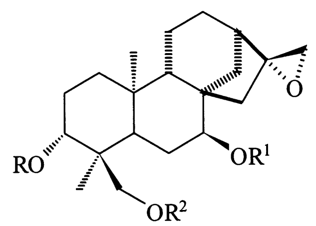
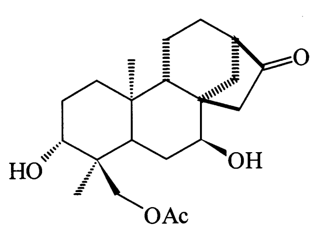


	R	R1	R2
2	H	H	Ac
3	Ac	H	H
4	Ac	Ac	Ac



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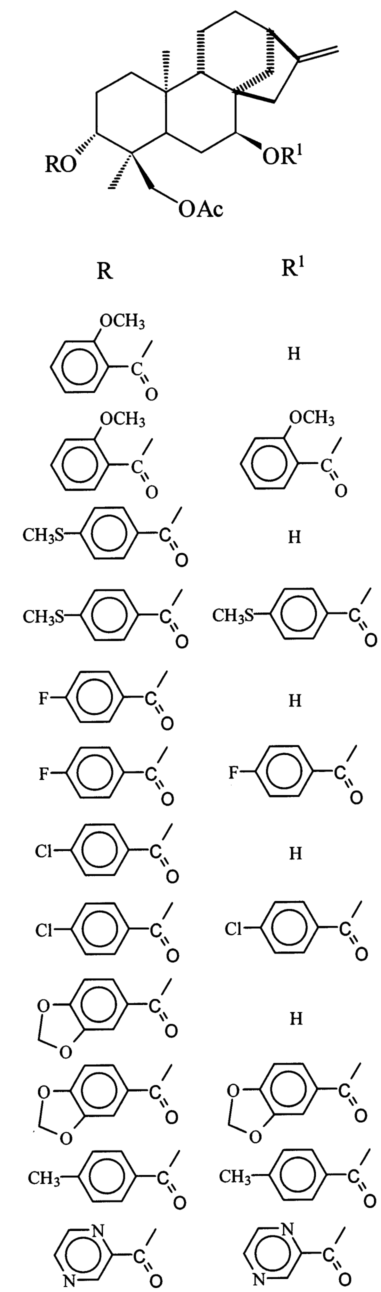

(δ_{CDCl_3} 77.0). ^{13}C NMR assignments were determined by DEPT spectra. MS were recorded on a Finnigan TSQ70 instrument (70 eV, direct inlet). Elemental analysis was carried out with a Perkin-Elmer 240 apparatus. Merck Si gel no. 7734 (70−230 mesh) deactivated with 15% H_2O w/v was used for column chromatography. Linearol (**1**) was isolated from the following species: *Sideritis akmanii* Aytac, Ekici and Donmez, *S. niveotomentosa* Hub.-Mor., *S. brevidens* P. H. Davis, *S. rubriflora* Hub.-Mor., and *S. gulendamii* H. Duman and Karavel.[5] CH_2Cl_2 was dried by distillation over calcium hydride.

General Esterification Procedure. Linearol (**1**, 150 mg) was solubilized in 10 mL of dry CH_2Cl_2 and added to 1 equiv of DMAP (56 mg), 25 equiv of TEA (1.5 mL), and the appropriate acyl chloride (4 equiv) at room temperature under an argon atmosphere. After stirring overnight, the reaction was subjected to the usual workup by adding H_2O and extracting with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Generally, the residue was purified by column chromatography (Si gel, 4:1 petroleum ether−EtOAc as eluent). This procedure gave the following ester derivatives.

Compounds 16 and 17. Treatment of **1** with 2-methoxybenzoyl chloride gave a mixture of two compounds, which were separated by column chromatography (Si gel, 4:1 petroleum ether−EtOAc as eluent), giving 25 mg of **16** and 149 mg of **17**.

Compound 16: amorphous solid; ^{1}H NMR ($CDCl_3$) δ 5.11 (1H, dd, J = 11.3 and 4.6 Hz, H-3β), 3.61 (1H, t, J = 3.8 Hz, H-7α), 2.70 (1H, m, H-13), 2.28 (2H, br s, H-15), 4.83 (1H, br s, H_A-17), 4.80 (1H, br s, H_B-17), 4.22 (1H, d, J = 11.7 Hz, H_A-18), 3.69 (1H, d, J = 11.7 Hz, H_B-18), 0.95 (3H, s, Me-19), 1.12 (3H, s, Me-20), 2.07 (3H, s, OAc), 7.79 (1H, dd, J = 8.0 and 1.8 Hz, H-6′), 7.45 (1H, dt, J = 1.8 and 8.0 Hz, H-4′), 6.95−7.01 (2H, m, H-3′ and H-5′), 3.89 (3H, s, OCH_3); ^{13}C NMR, see Table 2; EIMS m/z 478 $[M - H_2O]^+$ (2), 344 $[M - CH_3OC_6H_4COOH]^+$ (10), 284 $[M - CH_3OC_6H_4COOH - AcOH]^+$ (5), 266 $[M - CH_3OC_6H_4COOH - AcOH - H_2O]^+$ (20), 153 (22), 135 (100); *anal.* C 72.61%, H 8.06%, calcd for $C_{30}H_{40}O_6$ C 72.55%, H 8.12%.

Compound 17: amorphous solid; ^{1}H NMR ($CDCl_3$) δ 5.01 (1H, dd, J = 12.1 and 4.9 Hz, H-3β), 5.07 (1H, t, J = 3.8 Hz, H-7α), 2.74 (1H, m, H-13), 2.29 (2H, br s, H-15), 4.83 (1H, br s, H_A-17), 4.76 (1H, br s, H_B-17), 3.86 (1H, d, J = 11.7 Hz, H_A-18), 3.65 (1H, d, J = 11.7 Hz, H_B-18), 0.95 (3H, s, Me-19), 1.19 (3H, s, Me-20), 1.27 (3H, s, OAc), 7.90 (1H, dd, J = 8.0 and 1.8 Hz, H-6′), 7.48 (1H, dt, J = 1.8 and 8.0 Hz, H-4′), 7.72 (1H, dd, J = 8.0 and 1.8 Hz, H-6″), 7.44 (1H, dt, J = 1.8 and 8.0 Hz, H-4″), 6.92−7.05 (4H, m, H-3′, H-5′, H-3″, and H-5″), 3.86 (3H, s, OCH_3), 3.94 (3H, s, OCH_3); ^{13}C NMR, see Table 2; EIMS m/z 478 $[M - CH_3OC_6H_4COOH]^+$ (5), 326 $[M - 2 \times CH_3OC_6H_4COOH]^+$ (28), 266 $[M - 2 \times CH_3OC_6H_4COOH - AcOH]^+$ (20), 153 (18), 135 (100); *anal.* C 72.29%, H 7.40%, calcd for $C_{38}H_{46}O_8$ C 72.36%, H 7.35%.

Compounds 18 and 19. Similar treatment of **1** with 4-thiomethoxybenzoyl chloride gave 36 mg of **18** and 178 mg of **19**.

Compound 18: amorphous solid; ^{1}H NMR ($CDCl_3$) δ 5.10 (1H, dd, J = 11.4 and 4.8 Hz, H-3β), 3.62 (1H, br t, J = 3.8 Hz, H-7α), 2.70 (1H, m, H-13), 2.29 (2H, br s, H-15), 4.84 (1H, br s, H_A-17), 4.81 (1H, br s, H_B-17), 4.29 (1H, d, J = 11.7 Hz, H_A-18), 3.57 (1H, d, J = 11.7 Hz, H_B-18), 0.99 (3H, s, Me-19), 1.14 (3H, s, Me-20), 2.06 (3H, s, OAc), 7.91 (2H, d, J = 8.6 Hz, H-2′ and H-6′), 7.25 (2H, d, J = 8.6 Hz, H-3′ and H-5′), 2.52 (3H, s, SCH_3); ^{13}C NMR, see Table 2; EIMS m/z 512 $[M]^+$ (2), 326 $[M - CH_3SC_6H_4COOH - H_2O]^+$ (1), 266 $[M - CH_3SC_6H_4COOH - AcOH - H_2O]^+$ (10), 168 (30), 151 (100), 79 (20); *anal.* C 70.38%, H 7.80%, calcd for $C_{30}H_{40}O_5S$ C 70.34%, H 7.86%.

Table 1. Data from Anti-HIV Evaluation of **1**−**27**

compound	EC_{50} (μg/mL)	IC_{50} (μg/mL)	therapeutic index
1	N.S.[a]	56.5	N.S.
2	N.S.	>100	N.S.
3	N.S.	>100	N.S.
4	0.13	20.6	163
5	N.S.	>100	N.S.
6	N.S.	22.2	N.S.
7	2.63	16.0	6.10
8	N.S.	1.8	N.S.
9	N.S.	2.2	N.S.
10	N.S.	2.0	N.S.
11	<0.1	1.9	>19.2
12	3.11	10.8	3.49
13	N.S.	21.4	N.S.
14	N.S.	>100	N.S.
15	N.S.	>100	N.S.
16	N.S.	5.4	N.S.
17	N.S.	6.0	N.S.
18	N.S.	5.3	N.S.
19	N.S.	59.8	N.S.
20	N.S.	57.7	N.S.
21	N.S.	41.1	N.S.
22	N.S.	54.0	N.S.
23	N.S.	60.1	N.S.
24	N.S.	5.3	N.S.
25	0.27	50.6	184
26	1.05	52.5	50.1
27	N.S.	5.6	N.S.

[a] N.S. = no suppression.

Table 2. ^{13}C NMR Chemical Shift Values for Compounds **16**−**21** in $CDCl_3$

carbon	**16**	**17**	**18**	**19**	**20**	**21**
1	38.4 t[a]	38.0 t	38.5 t[a]	38.0 t	38.4 t[a]	38.0 t
2	23.1 t	23.1 t	23.2 t	23.1 t	23.1 t	23.1 t
3	75.2 d	74.8 d	75.1 d	74.4 d	75.4 d	74.6 d
4	40.8 s	40.4 s	40.9 s	40.5 s	40.8 s	40.5 s
5	38.1 d	39.7 d	38.2 d	39.7 d	38.2 d	39.7 d
6	27.1 t	24.2 t	27.1 t	24.1 t	27.1 t	24.1 t
7	76.8 d	79.4 d	76.7 d	79.8 d	76.6 d	80.2 d
8	48.0 s	47.2 s	48.0 s	47.2 s	48.0 s	47.1 s
9	50.1 d	51.2 d	50.1 d	51.5 d	50.1 d	51.5 d
10	38.7 s	38.7 s	38.7 s	38.7 s	38.7 s	38.7 s
11	17.9 t	18.0 t	17.9 t	18.0 t	17.9 t	17.9 t
12	33.5 t	33.3 t	33.5 t	33.3 t	33.5 t	33.3 t
13	43.7 d	43.6 d	43.6 d	43.5 d	43.6 d	43.4 d
14	37.9 t[a]	38.0 t	37.8 t[a]	38.0 t	37.8 t[a]	38.0 t
15	45.0 t	45.3 t	45.0 t	45.3 t	45.0 t	45.3 t
16	154.9 s	154.3 s	154.8 s	153.9 s	154.8 s	153.7 s
17	103.6 t	103.7 t	103.7 t	104.0 t	103.6 t	104.1 t
18	64.9 t	65.1 t	65.0 t	64.9 t	65.0 t	64.8 t
19	13.3 q	13.3 q	13.3 q	13.3 q	13.3 q	13.3 q
20	17.9 q	18.0 q	17.9 q	18.0 q	17.9 q	17.9 q
OAc	171.6 s	170.5 s	171.5 s	170.7 s	171.5 s	170.6 s
	21.2 q	19.7 q	21.1 q	19.7 q	21.1 q	19.6 q
C=O′	165.9 s	166.0 s	165.6 s	165.6 s	164.9 s	164.9 s
C=O″		165.0 s		165.1 s		164.4 s
1′	127.4 s	128.3 s	126.8 s	126.9 s	126.8 s[b]	127.0 s[b]
2′	159.1 s	159.7 s	129.8 d	129.9 d	132.0 d[c]	132.1 d[c]
3′	112.0 d	112.1 d	125.1 d	125.1 d	115.5 d[d]	115.6 d[d]
4′	133.4 d	133.7 d	145.4 s	145.6 s	165.7 s[e]	165.8 s[e]
5′	120.1 d	120.2 d	125.1 d	125.1 d	115.5 d[d]	115.6 d[d]
6′	131.7 d	132.2 d	129.8 d	129.9 d	132.0 d[c]	132.1 d[c]
1″		127.5 s		126.6 s		126.7 s[b]
2″		159.6 s		129.8 d		132.0 d[c]
3″		111.9 d		125.0 d		115.4 d[d]
4″		133.2 d		145.4 s		165.7 s[e]
5″		120.1 d		125.0 d		115.4 d[d]
6″		131.5 d		129.8 d		132.0 d[c]
CH_3′	55.8 q	55.9 q	14.9 q	14.9 q		
CH_3″		55.7 q		14.9 q		

[a] Assignments within the same column may be reversed. [b] J_{C-F} = 2.0 Hz. [c] J_{C-F} = 9.2 Hz. [d] J_{C-F} = 22.0 Hz. [e] J_{C-F} = 253.8 Hz.

Compound 19: amorphous solid; ^1H NMR ($CDCl_3$) δ 4.98 (1H, dd, J = 11.0 and 4.9 Hz, H-3β), 5.01 (1H, t, J = 3.8 Hz, H-7α), 2.75 (1H, m, H-13), 2.32 (1H, br d, J = 17.2 Hz, H_A-15), 2.22 (1H, dt, J = 17.2 and 2.4 Hz, H_B-15), 4.83 (1H, br s, H_A-17), 4.76 (1H, br s, H_B-17), 3.79 (1H, d, J = 11.8 Hz, H_A-18), 3.61 (1H, d, J = 11.8 Hz, H_B-18), 0.98 (3H, s, Me-19), 1.20 (3H, s, Me-20), 1.21 (3H, s, OAc), 7.96 (2H, d, J = 8.5 Hz, H-2′ and H-6′), 7.86 (2H, d, J = 8.5 Hz, H-2″ and H-6″), 7.28 (2H, d, J = 8.5 Hz, H-3′ and H-5′), 7.22 (2H, d, J = 8.5 Hz, H-3″ and H-5″), 2.52 (3H, s, SCH_3), 2.50 (3H, s, SCH_3); ^{13}C NMR, see Table 2; EIMS m/z 326 [M − 2 × $CH_3SC_6H_4COOH$]$^+$ (15), 266 [M − 2 × $CH_3SC_6H_4COOH$ − AcOH]$^+$ (20), 251 (15), 168 (22), 151 (100), 43 (20); *anal.* C 68.98%, H 6.93%, calcd for $C_{38}H_{46}O_6S_2$ C 68.93%, H 7.00%.

Compounds 20 and 21. Treatment of **1** with 4-fluorobenzoyl chloride gave 60 mg of **20** and 141 mg of **21**.

Compound 20: amorphous solid; ^1H NMR ($CDCl_3$) δ 5.11 (1H, dd, J = 11.4 and 5.5 Hz, H-3β), 3.61 (1H, br t, J = 3.8 Hz, H-7α), 2.70 (1H, m, H-13), 2.28 (2H, br s, H-15), 4.83 (1H, br s, H_A-17), 4.81 (1H, br s, H_B-17), 4.17 (1H, d, J = 11.6 Hz, H_A-18), 3.57 (1H, d, J = 11.6 Hz, H_B-18), 0.98 (3H, s, Me-19), 1.13 (3H, s, Me-20), 2.05 (3H, s, OAc), 8.01 (2H, dd, J = 8.5, $J_{H,F}$ = 5.3, Hz, H-2′ and H-6′), 7.10 (2H, t, J = 8.5 Hz, $J_{H,F}$ = 8.5, H-3′ and H-5′); ^{13}C NMR, see Table 2; EIMS m/z 466 [M − H_2O]$^+$ (3), 344 [M − FC_6H_4COOH]$^+$ (7), 326 [M − FC_6H_4COOH − H_2O]$^+$ (85), 284 [M − FC_6H_4COOH − AcOH]$^+$ (22), 266 [M − FC_6H_4COOH − AcOH − H_2O]$^+$ (100), 253 (30), 123 (50), 83 (15); *anal.* C 71.88%, H 7.70%, calcd for $C_{29}H_{37}O_5F$ C 71.83%, H 7.77%.

Compound 21: amorphous solid; ^1H NMR ($CDCl_3$) δ 4.99 (1H, dd, J = 11.4 and 5.0 Hz, H-3β), 5.00 (1H, t, J = 3.8 Hz, H-7α), 2.75 (1H, m, H-13), 2.30 (1H, dt, J = 17.0 and 2.4 Hz, HA-15), 2.20 (1H, dt, J = 17.0 and 2.4 Hz, H_B-15), 4.84 (1H, br s, H_A-17), 4.77 (1H, br s, H_B-17), 3.81 (1H, d, J = 11.8 Hz, H_A-18), 3.58 (1H, d, J = 11.8 Hz, H_B-18), 0.98 (3H, s, Me-19), 1.20 (3H, s, Me-20), 1.20 (3H, s, OAc), 8.07 (2H, dd, J = 8.5, $J_{H,F}$ = 5.3, Hz, H-2′ and H-6′), 7.97 (2H, dd, J = 8.5, $J_{H,F}$ = 5.3, Hz, H-2″ and H-6″), 7.15 (2H, t, J = 8.5 Hz, $J_{H,F}$ = 8.5, H-3′ and H-5′), 7.07 (2H, t, J = 8.5 Hz, $J_{H,F}$ = 8.5, H-3″ and H-5″); ^{13}C NMR, see Table 2; EIMS m/z 466 [M − FC_6H_4COOH]$^+$ (7), 406 [M − FC_6H_4COOH − AcOH]$^+$ (2), 326 [M − 2 × FC_6H_4COOH]$^+$ (90), 266 [M − 2 × FC_6H_4COOH − AcOH]$^+$ (95), 251 (38), 185 (25), 123 (100); *anal.* C 71.21%, H 6.73%, calcd for $C_{36}H_{40}O_6F_2$ C 71.26%, H 6.65%.

Compounds 22 and 23. Treatment of **1** with 4-chlorobenzoyl chloride gave 31 mg of **22** and 164 mg of **23**.

Compound 22: amorphous solid; ^1H NMR ($CDCl_3$) δ 5.11 (1H, dd, J = 11.5 and 4.6 Hz, H-3β), 3.61 (1H, br t, J = 3.8 Hz, H-7α), 2.70 (1H, m, H-13), 2.28 (2H, br s, H-15), 4.84 (1H, br s, H_A-17), 4.81 (1H, br s, H_B-17), 4.18 (1H, d, J = 11.7 Hz, H_A-18), 3.56 (1H, d, J = 11.7 Hz, H_B-18), 0.98 (3H, s, Me-19), 1.14 (3H, s, Me-20), 2.06 (3H, s, OAc), 7.94 (2H, d, J = 8.4 Hz, H-2′ and H-6′), 7.41 (2H, d, J = 8.4 Hz, H-3′ and H-5′); ^{13}C NMR, see Table 3; EIMS m/z 482 [M − H_2O]$^+$ (3), 326 [M − ClC_6H_4COOH − H_2O]$^+$ (85), 266 [M − ClC_6H_4COOH − AcOH − H_2O]$^+$ (100), 251 (28), 185 (10), 139 (40); *anal.* C 69.46%, H 7.48%, calcd for $C_{29}H_{37}O_5Cl$ C 69.52%, H 7.44%.

Compound 23: amorphous solid; ^1H NMR ($CDCl_3$) δ 5.00 (1H, dd, J = 11.4 and 5.0 Hz, H-3β), 5.01 (1H, t, J = 3.8 Hz, H-7α), 2.76 (1H, m, H-13), 2.32 (1H, br d, J = 17.0 Hz, H_A-15), 2.20 (1H, br d, J = 17.0 Hz, H_B-15), 4.85 (1H, br s, H_A-17), 4.77 (1H, br s, H_B-17), 3.81 (1H, d, J = 11.9 Hz, H_A-18), 3.59 (1H, d, J = 11.9 Hz, H_B-18), 0.98 (3H, s, Me-19), 1.21 (3H, s, Me-20), 1.22 (3H, s, OAc), 7.99 (2H, d, J = 8.5, Hz, H-2′ and H-6′), 7.89 (2H, d, J = 8.5, Hz, H-2″ and H-6″), 7.45 (2H, d, J = 8.7 Hz, H-3′ and H-5′), 7.38 (2H, d, J = 8.7 Hz, H-3″ and H-5″); ^{13}C NMR, see Table 3; EIMS m/z 482 [M − ClC_6H_4COOH]$^+$ (2), 422 [M − ClC_6H_4COOH − AcOH]$^+$ (2), 326 [M − 2 × ClC_6H_4COOH]$^+$ (75), 266 [M − 2 × ClC_6H_4COOH − AcOH]$^+$ (100), 251 (32), 185 (25), 139 (78); *anal.* C 67.61%, H 6.24%, calcd for $C_{36}H_{40}O_6Cl_2$ C 67.57%, H 6.30%.

Compounds 24 and 25. Treatment of **1** with piperonyl chloride gave 53 mg of **24** and 196 mg of **25**.

Compound 24: amorphous solid; ^1H NMR ($CDCl_3$) δ 5.08 (1H, dd, J = 11.5 and 4.6 Hz, H-3β), 3.62 (1H, br t, J = 3.8 Hz, H-7α), 2.70 (1H, m, H-13), 2.29 (2H, br s, H-15), 4.84 (1H,

Table 3. ^{13}C NMR Chemical Shift Values for Compounds **22**−**27** in $CDCl_3$

C	22	23	24	25	26	27
1	38.4 t[a]	38.0 t	38.4 t[a]	38.0 t	38.0 t	38.0 t[a]
2	23.1 t	23.1 t	23.1 t	23.1 t	23.1 t	23.0 t
3	75.6 d	74.7 d	75.1 d	74.4 d	74.3 d	75.9 d
4	40.9 s	40.5 s	40.9 s	40.5 s	40.5 s	40.7 s
5	38.2 d	39.8 d	38.2 d	39.7 d	39.7 d	39.8 d
6	27.1 t	24.1 t	27.1 t	24.1 t	24.1 t	24.2 t
7	76.7 d	80.4 d	76.7 d	79.9 d	79.7 d	81.6 d
8	48.0 s	47.1 s	48.0 s	47.2 s	47.2 s	47.0 s
9	50.1 d	51.5 d	50.1 d	51.5 d	51.5 d	51.1 d
10	38.7 s	38.7 s	38.7 s	38.7 s	38.7 s	38.7 s
11	17.9 t	17.9 t	17.9 t	18.0 t	18.0 t	18.0 t
12	33.5 t	33.2 t	33.5 t	33.3 t	33.3 t	33.2 t
13	43.6 d	43.4 d	43.6 d	43.5 d	43.5 d	43.4 d
14	37.8 t[a]	38.0 t	37.8 t[a]	38.0 t	38.0 t	37.8 t[a]
15	45.0 t	45.3 t	45.0 t	45.3 t	45.3 t	45.2 t
16	154.8 s	153.6 s	154.8 s	153.9 s	153.9 s	153.4 s
17	103.7 t	104.1 t	103.6 t	104.0 t	103.9 t	104.3 t
18	65.0 t	64.8 t	65.0 t	64.9 t	64.9 t	64.6 t
19	13.3 q	13.3 q	13.3 q	13.4 q	13.3 q	13.1 q
20	17.9 q	17.9 q	17.9 q	18.0 q	18.0 q	18.0 q
OAc	171.5 s	170.5 s	171.5 s	170.8 s	170.7 s	170.2 s
	21.1 q	19.7 q	21.1 q	19.8 q	19.5 q	19.9 q
C=O′	165.0 s	165.0 s	165.2 s	165.2 s	165.9 s	163.2 s
C=O″		164.5 s		164.8 s	165.4 s	162.8 s
1′	129.1 s	129.2 s	124.7 s	124.8 s	128.1 s	
2′	130.9 d	130.9 d	109.4 d	109.5 d	129.6 d	144.0 s
3′	128.7 d	128.9 d	147.7 s	147.8 s	129.1 d	146.1 d
4′	139.3 s	139.5 s	151.5 s	151.7 s	143.6 s	
5′	128.7 d	128.9 d	108.0 d	108.1 d	129.1 d	147.5 d
6′	130.9 d	130.9 d	125.2 d	125.3 d	129.6 d	144.7 d
1″		128.9 s		124.5 s	127.8 s	
2″		130.8 d		109.4 d	129.5 d	143.7 s
3″		128.7 d		147.7 s	129.0 d	146.0 d
4″		139.3 s		151.6 s	143.4 s	
5″		128.7 d		108.0 d	129.0 d	147.4 d
6″		130.8 d		125.2 d	129.5 d	144.6 d
CH_3′					21.6 q	
CH_3″					21.6 q	
OCH_2O′			101.7 t	101.8 t		
OCH_2O″				101.7 t		

[a] Assignments within the same column may be reversed.

br s, H_A-17), 4.81 (1H, br s, H_B-17), 4.19 (1H, d, $J = 11.7$ Hz, H_A-18), 3.57 (1H, d, $J = 11.7$ Hz, H_B-18), 0.97 (3H, s, Me-19), 1.13 (3H, s, Me-20), 2.10 (3H, s, OAc), 7.62 (1H, dd, $J = 8.2$ and 1.4 Hz, H-2′), 7.43 (1H, d, $J = 1.6$ Hz, H-6′), 6.84 (1H, d, $J = 8.2$, H-3′), 6.05 (2H, s, OCH_2O); ^{13}C NMR, see Table 3; EIMS *m/z* 510 $[M]^+$ (2), 344 $[M - C_7H_5O_2COOH]^+$ (1), 326 $[M - C_7H_5O_2COOH - H_2O]^+$ (10), 266 $[M - C_7H_5O_2COOH - AcOH - H_2O]^+$ (25), 251 (20), 166 (40), 149 (100); *anal.* C 70.59%, H 7.44%, calcd for $C_{30}H_{38}O_7$ C 70.56%, H 7.50%.

Compound 25: amorphous solid; ^1H NMR ($CDCl_3$) δ 4.97 (1H, dd, $J = 11.1$ and 5.0 Hz, H-3β), 4.98 (1H, t, $J = 3.8$ Hz, H-7α), 2.75 (1H, m, H-13), 2.31 (1H, br d, $J = 17.0$ Hz, H_A-15), 2.19 (1H, br d, $J = 17.0$ Hz, H_B-15), 4.85 (1H, br s, H_A-17), 4.78 (1H, br s, H_B-17), 3.82 (1H, d, $J = 11.8$ Hz, H_A-18), 3.60 (1H, d, $J = 11.8$ Hz, H_B-18), 0.99 (3H, s, Me-19), 1.21 (3H, s, Me-20), 1.32 (3H, s, OAc), 7.68 (1H, dd, $J = 8.1$ and 1.6 Hz, H-2′), 7.59 (1H, dd, $J = 8.1$ and 1.6 Hz, H-2″), 7.48 (1H, d, $J = 1.6$ Hz, H-6′), 7.39 (1H, d, $J = 1.6$ Hz, H-6″), 6.88 (1H, d, $J = 8.1$, H-3′), 6.81 (1H, d, $J = 8.1$, H-3″), 6.06 (2H, s, OCH_2O), 6.02 (2H, s, OCH_2O); ^{13}C NMR, see Table 3; EIMS *m/z* 492 $[M - C_7H_5O_2COOH]^+$ (1), 326 $[M - 2 \times C_7H_5O_2COOH]^+$ (20), 266 $[M - 2 \times C_7H_5O_2COOH - AcOH]^+$ (30), 251 (20), 149 (100), 119 (10); *anal.* C 69.23%, H 6.49%, calcd for $C_{38}H_{42}O_{10}$ C 69.28%, H 6.43%.

Compound 26. Treatment of **1** with 4-toluoyl chloride gave 180 mg of **26**: amorphous solid; ^1H NMR ($CDCl_3$) δ 5.00 (1H, dd, $J = 11.4$ and 5.0 Hz, H-3β), 5.01 (1H, t, $J = 3.8$ Hz, H-7α), 2.75 (1H, m, H-13), 2.33 (1H, br d, $J = 17.3$ Hz, H_A-15), 2.19 (1H, br d, $J = 17.3$ Hz, H_B-15), 4.83 (1H, br s, H_A-17), 4.75 (1H, br s, H_B-17), 3.78 (1H, d, $J = 11.8$ Hz, H_A-18), 3.60 (1H, d, $J = 11.8$ Hz, H_B-18), 0.98 (3H, s, Me-19), 1.20 (3H, s, Me-20), 1.16 (3H, s, OAc), 7.94 (2H, d, $J = 8.1$, Hz H-2′ and H-6′), 7.84 (2H, d, $J = 8.1$, Hz, H-2″ and H-6″), 7.26 (2H, d, $J = 8.1$ Hz, H-3′ and H-5′), 7.19 (2H, d, $J = 8.1$ Hz, H-3″ and H-5″), 2.41 (3H, s, CH_3), 2.38 (3H, s, CH_3); ^{13}C NMR see Table 3; EIMS *m/z* 462 $[M - CH_3C_6H_4COOH]^+$ (7), 326 $[M - 2 \times CH_3C_6H_4COOH]^+$ (62), 266 $[M - 2 \times CH_3C_6H_4COOH - AcOH]^+$ (60), 251 (20), 185 (10), 119 (100); *anal.* C 76.20%, H 7.80%, calcd for $C_{38}H_{46}O_6$ C 76.22%, H 7.74%.

Compound 27. Treatment of **1** with pirazinoyl chloride gave 166 mg of **27**: amorphous solid; ^1H NMR ($CDCl_3$) δ 5.10 (1H, dd, $J = 12.0$ and 5.4 Hz, H-3β), 5.16 (1H, t, $J = 3.8$ Hz, H-7α), 2.76 (1H, m, H-13), 2.36 (1H, br d, $J = 17.1$ Hz, H_A-15), 2.22 (1H, br d, $J = 17.1$ Hz, H_B-15), 4.84 (1H, br s, H_A-17), 4.76 (1H, br s, H_B-17), 3.94 (1H, d, $J = 11.9$ Hz, H_A-18), 3.58 (1H, d, $J = 11.9$ Hz, H_B-18), 1.02 (3H, s, Me-19), 1.22 (3H, s, Me-20), 1.27 (3H, s, OAc), 9.32 (1H, br s. H-3′), 9.20 (1H, br s. H-3″), 8.78 (2H, br s, H-5′ and H-5″), 8.73 (1H, br s, H-6′), 8.71 (1H, br s, H-6″); ^{13}C NMR, see Table 3; EIMS *m/z* 450 $[M - C_4H_3N_2COOH]^+$ (1), 326 $[M - 2 \times C_4H_3N_2COOH]^+$ (28), 266 $[M - 2 \times C_4H_3N_2COOH - AcOH]^+$ (78), 251 (45), 185 (42), 107 (78), 79 (93), 43 (100); *anal.* C 66.92%, H 6.73%, N 9.69%, calcd for $C_{32}H_{38}O_6N_4$ C 66.88%, H 6.67%, N 9.75%.

Anti-HIV Assay. The biological tests have been carried out following the already described protocol.[7]

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