Betulinic Acid Derivatives: A New Class of Specific Inhibitors of Human Immunodeficiency Virus Type 1 Entry

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A novel series of ω-aminoalkanoic acid derivatives of betulinic acid were synthesized and evaluated for their activity against human immunodeficiency virus (HIV). The anti-HIV-1 activity of several members of this new series was found to be in the nanomolar range in CEM 4 and MT-4 cell cultures. The optimization of the ω-aminoalkanoic acid side chain is described. The presence of an amide function within the side chain was found important for optimal activity. RPR 103611 (**14g**), a statine derivative, was found to be inactive against HIV-1 protease, reverse transcriptase, and integrase as well as on gp120/CD4 binding. "Time of addition" experiments suggested interaction with an early step of HIV-1 replication. As syncytium formation, but not virus−cell binding, seems to be affected, betulinic acid derivatives are assumed to interact with the postbinding virus−cell fusion process.

Several triterpenes have been described as weak antiviral compounds. Glycyrrhetinic acids display some limited activity against a whole range of viruses including human immunodeficiency virus type 1 (HIV-1).[1] Salaspermic acid[2] and suberol[3] inhibit HIV-1 in H9 cells in the upper micromolar range. Furthermore, bile acid derivatives were found slightly active (at 10^{-4} M) against HIV-1 in MT-4 cells.[4] We have previously described new derivatives of betulinic acid as potent inhibitors of the cytopathicity of HIV-1 in CEM 4 and MT-4 cells without affecting HIV-1 reverse transcriptase (RT) or protease activity.[5] Even minor modifications on the lupane backbone (ring A, isopropylidene) strongly affect potency. In the present report we describe the synthesis and structure−activity relationship for this class of compounds obtained by modifying the alkanoic acid side chain. RPR 103611 (**14g**), a statine derivative, was selected for further investigations.

Chemistry

Betulinic acid **1a** is the common starting material for the synthesis of the described molecules. After protection of the hydroxyl group in the 3 position as an acetate, the carboxylic acid function in position 17 was activated as its acid chloride. Reaction of 3β-acetoxylup-20(29)-en-28-oyl chloride (**1b**) with an alkyl ester of an ω-aminoalkanoic acid (**2a**−**l**) in the presence of triethylamine afforded the resulting diesters **4a**−**l** with yields ranging from 39% to 91%. Saponification of diesters **4a**−**l** with aqueous sodium hydroxide in a methanol/THF mixture, at room temperature, resulted in the concomitant cleavage of the terminal ester function and the regeneration of the free hydroxyl group in position 3, yielding the corresponding ω-aminoalkanoic acid amide of betulinic acids **5a**−**l** (Scheme 1). Alternatively, reacting 3β-acetoxylup-20(29)-en-28-oyl chloride (**1b**) with an ω-aminoalkanoic acid trimethylsilyl ester, followed by aqueous workup, allowed isolation of intermediates **6a**−**g** (Scheme 1).

The intermediate diesters **7a**−**j** obtained by coupling acids **6a**−**g** with an ester of an ω-aminoalkanoic acid in the presence of EDCI/HOBT gave access, after saponification, to compounds **8a**−**j** with yields ranging from 23% to 100% (Scheme 2). *N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoic acid (**6g**) was used as the common precursor for the synthesis of α-amino acid derivatives **11a**−**j** (Scheme 3), β-amino acids **14a**−**f,** as well as γ-amino acids **14g**−**j** (Scheme 4), and derivatives of amino benzoic acids (Scheme 5).

N-[3β-Acetoxylup-20(29)-en-28-oyl]-1,7-diaminoheptane (**17**) is the key intermediate for the synthesis of compounds **19a**−**f,** containing an inverted amide function in the lateral chain (Scheme 6). Intermediate **17** was obtained in 85% yield by reacting acid chloride **1b** with an excess of 1,7-diaminoheptane. The reaction of **17** with a variety of dicarboxylic acid monoesters in the presence of HOBT/EDCI led to the corresponding esters **18a**−**c,e,f**, except in the case of the phthalic acid derivative which led to the phthalimido compound **18d**. Alkaline hydrolysis of **18a**−**f** gave the desired "reversed amides" **19a**−**f**.

Results and Discussions

The structure−activity relationship for this series of betulinic acid derivatives was investigated by evaluating the inhibition of HIV-1 infection in CEM 4 and MT-4 cell cultures (Tables 1−3). Fifty percent cell culture inhibitory concentrations (IC_{50}) are defined as those which inhibit HIV-1-induced cytopathicity by 50%. Viral cytopathicity is assessed by the number of viable cells, following staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.[5d] First, a systematic study was undertaken in order to determine the optimal chain length (Table 1, compounds **5a**−**l**). Incremental lengthening of the chain showed that significant activity was observed for the compounds positioned between the (betulinylamino)octanoic and (betulinyl-

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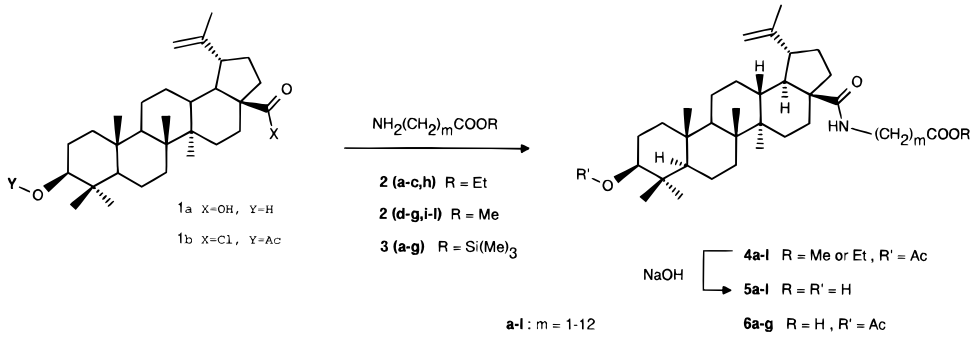
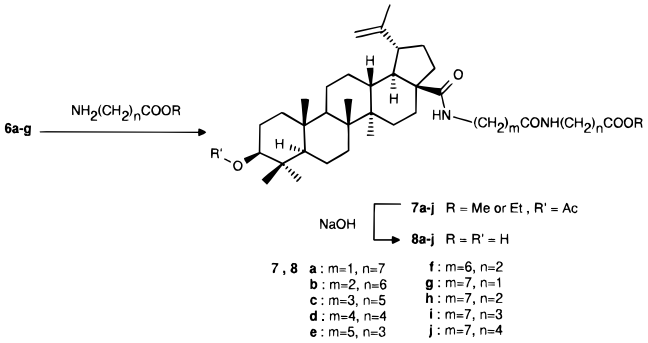
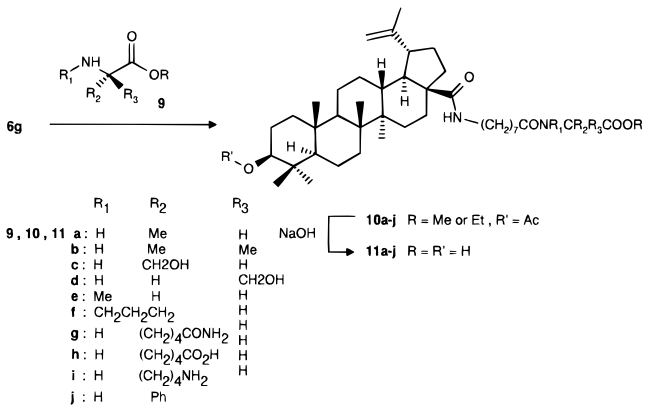
Scheme 1



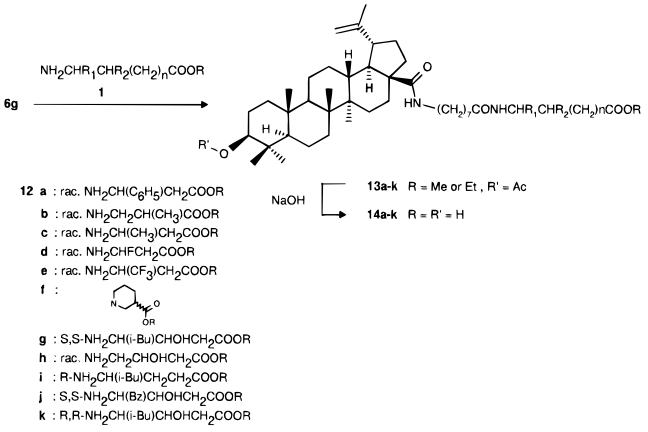
Scheme 2



Scheme 3



Scheme 4

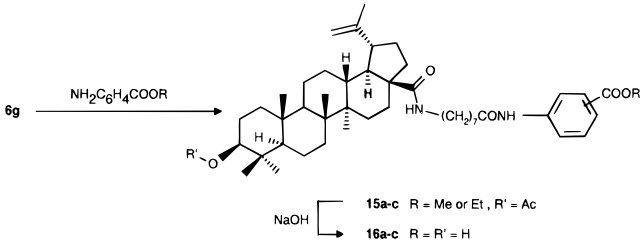


amino)dodecanoic acids **5g**−**k**. The most potent compound was found to be the undecylic acid derivative **5j**.

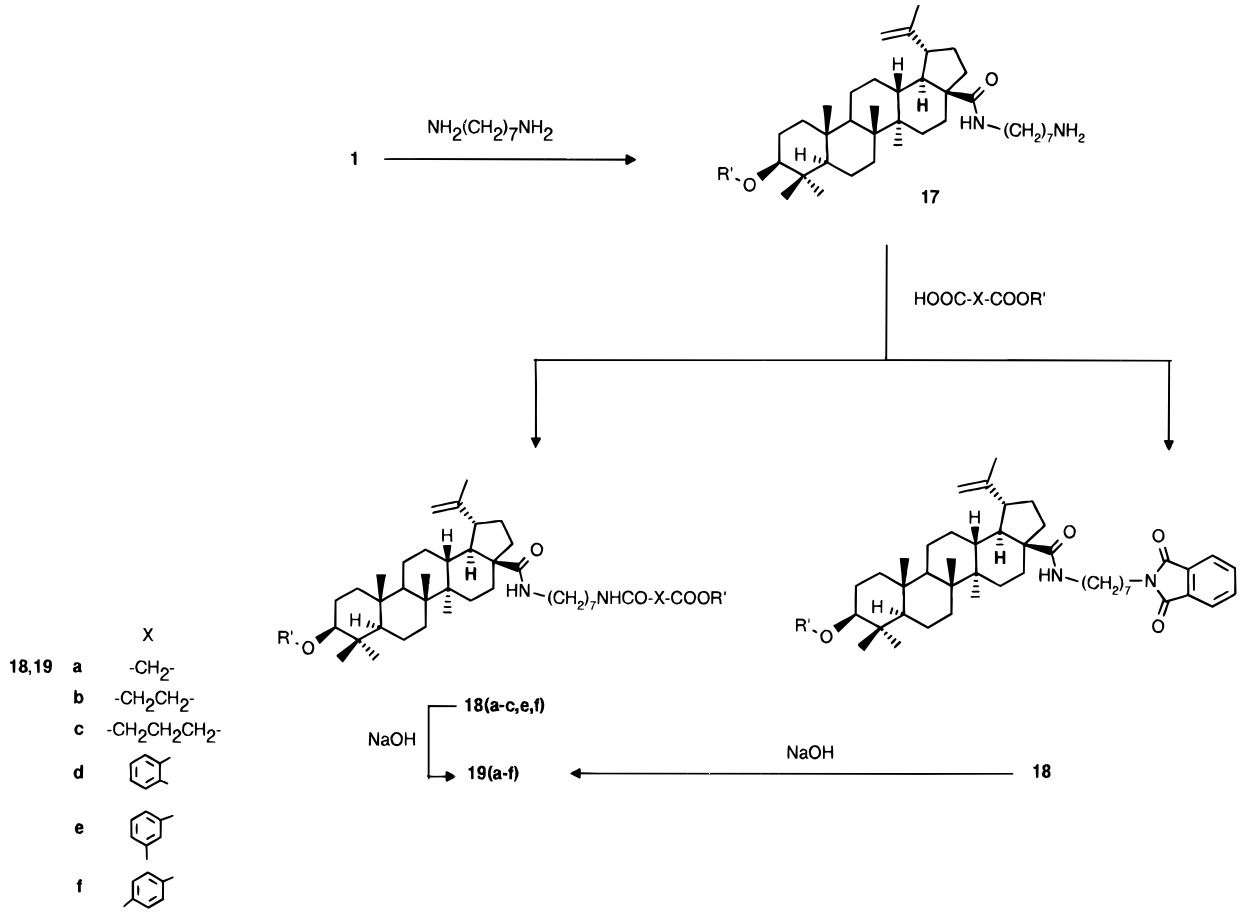
The successive condensation of betulinic acid with two aminoalkanoic acids results in the introduction of an amide moiety at different positions within the lateral chain (compounds **8a**−**j**, Table 1). Compounds **8a**−**f** were found to be considerably less active than the undecylic acid lead compound **5j**. This result is not unexpected as these compounds are in fact amides of the poorly active or inactive molecules **5a**−**f**. However, compound **8g,** the glycine amide of the active octanoic acid derivative **5g**, was found to be more potent than both the lead compound and the parent compound **5g**. Replacement of the glycine by β-alanine (**8h**), 3-aminopropionic acid (**8i**), or 4-aminobutyric acid (**8j**) resulted in very potent derivatives with an IC_{50} around 100 nM. Inverting the amide moiety within the chain led to compounds **19a**−**c** which were found to be somewhat more potent than the latter molecules with IC_{50} values ranging between 20 and 95 nM. (Betulinylamino)-octanoic acid amides of small α-amino acids such as the alanine derivative **11a** and derivative **11b** displayed improved activity compared to the parent glycine derivative **8g** (Table 2). This indicates the presence of a small lipophilic space accommodating one or two methyl groups. Indeed, the presence of more bulky groups such as in compounds **11g**−**j** leads to only poorly active molecules. The presence of an amide (asparagine derivative **11g**) or an amine (lysine derivative **11i**) is particularly unfavorable and leads to virtually inactive molecules.

A difference was observed between the L- and D-serine derivatives **11c**,**d**. Compared to **11a**,**b**, a 2−3-fold drop in activity was observed for the L-serine derivative (IC_{50} = 250 nM), whereas a 20-fold drop was observed for the D-serine derivative (IC_{50} = 1900 nM). The sarcosine derivative **11e** and the proline derivative **11f** retained a relatively good level of activity. This result contrasts with the complete loss of activity observed upon *N*-methylation of the amide moiety at position 19 of the triterpene.[5] For the β-amino acids, small substituents in the α or β position (compounds **14b**−**e**) or even the more bulky phenyl substituent in the β position (compound **14a**) did not significantly influence activity. In all these cases IC_{50} values around 100 nM were observed, which is identical with the activity of the parent β-alanine derivative **8h**. The cyclic compound **14f** was

Scheme 5



Scheme 6



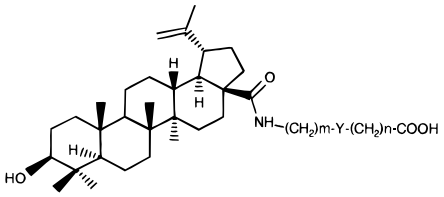
found somewhat less active (IC_{50} = 185 nM) than the latter compounds.

As observed for β-amino acids, substituents on the γ-amino acid side chain modulated anti-HIV-1 potency only to a slight extent. The statine derivative **14g** was found to display the best overall activity with an IC_{50} of 50 ± 26 nM (CEM 4) and 40 ± 19 nM (MT-4). However, the virtually equipotent monosubstituted derivatives **14h**,**i** and parent compound **8i** demonstrate the very limited influence of substituents at least on the screening values. Nevirapine, tested under the same conditions, displayed an IC_{50} value of 84 ± 21 nM (CEM 4). As exemplified by compounds **14a**,**j**, a good level of activity was observed for molecules containing a substituted phenyl moiety. We therefore synthesized derivatives of *o*-, *m*-, and *p*-aminobenzoic acids (compounds **16a**—**c**; Table 3). The ortho aminobenzoic acid derivative **16a** was found inactive, probably due to steric hindrance as observed for the phenylalanine derivative **11j**. The activities of the meta- and para-substituted derivatives **16b,c** were found in the same range as for the best compounds **14g**,**l**,**k** and **19a**—**c**. A similar result was obtained for the reversed amides obtained from benzenedicarboxylic acids (compounds **19d**—**f**).

Selectivity index (CC_{50}) for **14g** was in excess of 100. The precise assessment of cytotoxic concentrations for many betulinic acid derivatives was hampered by the limited solubility of these compounds above 10 μM (formation of gels). For the routine assessment of activity, the highest concentration used was generally 3 μM. At this highest concentration, most of our derivatives displayed no or marginal cytotoxicity except for **14a**, the aminobenzoic acid derivatives **16b,c**, and the benzenedicarboxylic acid derivatives **19e,f**. The selectivity index for **14a**, **16b**,**c**, and **19e**,**f** was respectively 70, 37, 14, 5, and 27 on CEM 4 cells. Most of the reported derivatives were tested against HIV-2 (ROD) and found inactive. Surprisingly, specificity turned out to be even higher than that for the "non nucleoside" RT inhibitors such as TIBO or nevirapine, as much less activity or even no activity was observed with **14g** against NDK and ELI, two HIV-1 isolates of African origin. No inhibition was noted with **14g** against RT, integrase, or protease at concentrations well above IC_{50} concentrations in cellular assays (data not shown).

Compound **14g** (RPR 103611) was used for further mechanistic studies. Details are reported elsewhere.[5d] Delaying the addition of compounds after the exposure of MT-4 cells to HIV-1 ("time of addition" experiment) for more than 1 h was sufficient to lose activity. This suggests the interference with an early step of the virus life cycle. Several experiments ruled out an interference with the binding of gp120 to the CD4 molecule, as shown either by biochemical assays (ELISA or BIAcore) or in a cellular context (FACS analysis). Moreover, betulinic acid derivatives were able to block efficiently syncytium formation of CD4 cells mediated by the HIV-1 envelope glycoproteins. This observation was made in many systems involving different cell lines (lymphoid or fibroblastic) either with the whole virus or by vectors expressing only the HIV-1 envelope (gp120 and gp41) at its surface. Thus, betulinic acid derivatives may be postulated to interfere with the virus—cell fusion process required for virus entry into the cells.

Table 1



no.	*m*	*n*	Y	mp, °C	anal.[a]	formula	anti-HIV-1 activity IC_{50} (nM) CEM cells	anti-HIV-1 activity IC_{50} (nM) MT-4 cells
5a	1	0	–	260 dec	C,H,[f]N	$C_{32}H_{51}NO_4$	na	nt
5b	2	0	–	204	C,H,N	$C_{33}H_{53}NO_4$	na	nt
5c	3	0	–	180	C,[b]H,N	$C_{34}H_{55}NO_4$	na	nt
5d	4	0	–	160	C,H,N	$C_{35}H_{57}NO_4$	46%[k]	nt
5e	5	0	–	135	C,[c]H,N	$C_{36}H_{59}NO_4$	2300	2400
5f	6	0	–	134	C,H,N	$C_{37}H_{61}NO_4$	12 000	4300
5g	7	0	–	140	C,H,N	$C_{38}H_{63}NO_4$	750	465
5h	8	0	–	162	C,H,[g]N	$C_{39}H_{65}NO_4$	420	3400
5i	9	0	–	100	C,H,N	$C_{40}H_{67}NO_4$	600	420
5j	10	0	–	115	C,H,N	$C_{41}H_{69}NO_4$	230	443
5k	11	0	–	182–185	C,[d]H,[h]N	$C_{42}H_{71}NO_4$	550	250
5l	12	0	–	168	C,H,N	$C_{43}H_{73}NO_4$	35%[k]	nt
8a	1	7	CONH	130	C,H,N	$C_{40}H_{66}N_2O_5$	30%[k]	nt
8b	2	6	CONH	130	C,H,N	$C_{40}H_{66}N_2O_5$	20%[l]	nt
8c	3	5	CONH	140–145	C,H,[i]N	$C_{40}H_{66}N_2O_5$	5500	nt
8d	4	4	CONH	132	C,H,N	$C_{40}H_{66}N_2O_5$	4500	nt
8e	5	3	CONH	206	C,H,[j]N	$C_{40}H_{66}N_2O_5$	3000	nt
8f	6	2	CONH	194	C,H,N	$C_{40}H_{66}N_2O_5$	4500	nt
8g	7	1	CONH	132	C,H,N	$C_{40}H_{66}N_2O_5$	150	156
8h	7	2	CONH	138	C,H,N	$C_{41}H_{68}N_2O_5$	100	94
8i	7	3	CONH	168	C,[e]H,N	$C_{42}H_{70}N_2O_5$	44	129
8j	7	4	CONH	152	C,H,N	$C_{43}H_{72}N_2O_5$	61	nt
19a	7	1	NHCO	140	C,H,N	$C_{40}H_{66}N_2O_5$	50	34
19b	7	2	NHCO	128	C,H,N	$C_{41}H_{68}N_2O_5$	95	53
19c	7	3	NHCO	170	C,H,N	$C_{42}H_{70}N_2O_5$	20	nt

[a] Elemental analyses were within 0.4% of theory unless otherwise noted. [b] C: calcd, 75.37; found, 76.5. [c] C: calcd, 75.88; found, 75.4. [d] C: calcd, 77.13; found, 76.4. [e] C: calcd, 73.86; found, 73.4. [f] H: calcd, 10.01; found, 10.6. [g] C: calcd, 10.71; found, 10.2. [h] H: calcd, 10.94; found, 11.4. [i] H: calcd, 10.16; found, 10.7. [j] H: calcd, 10.16; found, 10.7. [k] Inhibition at 1 μM, does not reach IC_{50}. [l] Inhibition at 0.2 μM, does not reach IC_{50}. na: not active. nt: not tested.

In conclusion, this new class of anti-HIV-1 compounds seems to block a postbinding event involved in the virus–cell fusion step. Betulinic acid derivatives represent the first low molecular weight compounds to be suggested as fusion inhibitors. To date, only very few fusion inhibitors have been described.[6] Further studies are underway in order to determine the precise target within the viral envelope for RPR 103611. Current synthetic efforts are focused toward the synthesis of derivatives with improved oral bioavailability.

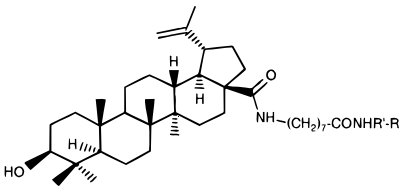
Experimental Section

Melting points were recorded on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were obtained on a Brucker WM (250 MHz), AC (400 MHz), or AM (400 MHz) spectrometer, and proton chemical shifts are relative to tetramethylsilane as an internal standard. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, dt = double triplet, b = broad. Mass spectra were recorded on a Finnigan 3300 spectrometer (EI at 70 eV), a Nermag R 10.10B instrument (DCI, using NH_3 as a reactant gas), or a Kratos MS50 instrument (FAB or LSIMS). Where elementary analyses are reported only by symbols of the elements in the tables, results were within 0.4% of the theoretical values. All reactions, as well as column chromatography, were monitored routinely with the aid of thin layer chromatography with precoated silica gel 60 F_{256} from Merck. Visualization was achieved with color response upon spraying with a solution of *p*-anisaldehyde, sulfuric acid, and acetic acid in ethanol (5:7:2:200, v/v). High-performance liquid chromatography (HPLC) was performed on reverse-phase column Bondapack C18.

General Procedure for 4a-l: Methyl *N*-[3β-Acetoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (4j). To a solution of methyl 11-aminoundecanoate[7] (580 mg, 2.7 mmol) and 3β-acetoxylup-20(29)-en-28-oyl chloride (**1b**)[8] (1.03 g, 2 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (0.62 mL, 4.4 mmol). After further stirring for 12 h at room temperature, the mixture was concentrated to dryness under reduced pressure. Column chromatography on SiO_2, eluting with *i*-Pr_2O, afforded 1.29 g (91%) of the ester **4j** (R_f = 0.31, eluent: 15% ethyl acetate in cycloxane).

General Procedure for 5a–l: *N*-[3β-Hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5j). To a solution of **4j** (1.29 g, 1.8 mmol) in methanol (8 mL) and THF (13 mL) was added 4.5 mL of aqueous NaOH (4 N). The reaction mixture was stirred overnight at room temperature, concentrated to dryness under reduced pressure, diluted with distilled water (60 mL), and then acidified to pH = 2 with 5 N hydrochloric acid. After further stirring for 20 min, the solid was collected and washed with distilled water to afford 1.2 g (95%) of **5j** as a white solid: mp 115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (b, J = 9 Hz, 1H, -*H* in 5), 0.76 (s, 3H, -CH_3), 0.82 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 0.98 (s, 6H, -CH_3), 1.56 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.70 (s, 3H, -CH_3 in 29), 2.36 (t, J = 7.5 Hz, 2H, -CH_2-COO-), 2.44 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 3.14 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.10–3.25 and 3.31 (2m, 1H each, -CONH-CH_2-), 3.20 (dd, J = 11, 5 Hz, 1H, -C*H* in 3), 4.59 and 4.74 (2bs, 1H each, =CH_2), 5.60 (t, J = 5.5 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3390, 3250–2250, 3075, 2925, 2855, 1710, 1640, 1515, 1465, 1450, 1385, 1375, 1045, 1035, 88; MS (EI) 639, 624, 611, 596, 81 (base).

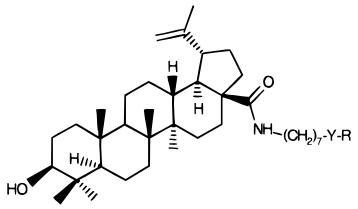
Table 2



					anti-HIV-1 activity IC_{50} (nM)	
no.	RNHR′	mp, °C	formula	anal.[a]	CEM cells	MT-4 cells
11a	Ala	120	$C_{41}H_{68}N_2O_5$	C,H,[h]N	92	62
11b	$NH_2C(Me)_2COOH$	140	$C_{42}H_{70}N_2O_5$	C,H,[i]N	133	89
11c	Ser	>260	$C_{41}H_{68}N_2O_6$	C,H,N	250	250
11d	D-Ser	252	$C_{41}H_{68}N_2O_6$	C,H,[j]N	1900	nt
11e	sarcosine	120	$C_{41}H_{68}N_2O_6$	C,H,N	250	333
11f	Pro	142	$C_{43}H_{70}N_2O_5$	C,[b]H,N	640	58
11g	Asp	140	$C_{42}H_{68}N_2O_7$	C,[c]H,[k]N	18 000	nt
11h	Asn	120	$C_{42}H_{69}N_3O_6$	C,[d]H,N	950	nt
11i	Lys	hygrosc	$C_{44}H_{75}N_3O_5$	C,[e]H,[e]N[e]	10 000	nt
11j	Phe	116	$C_{47}H_{72}N_2O_5$	C,H,N	2000	nt
14a	*rac*$NH_2CH(C_6H_5)CH_2COOH$	135−140	$C_{47}H_{72}N_2O_5$	C,H,N	85	47
14b	*rac*$NH_2CH_2CH(CH_3)COOH$	130	$C_{42}H_{70}N_2O_5$	C,H,N	130	nt
14c	*rac*$NH_2CH(CH_3)CH_2COOH$	134	$C_{42}H_{70}N_2O_5$	C,[f]H,[l]N	130	nt
14d	*rac*NH_2CHFCH_2COOH	132	$C_{41}H_{67}FN_2O_5$	C,[g]H,[m]N	95	nt
14e	*rac*$NH_2CH(CF_3)CH_2COOH$	140	$C_{42}H_{67}F_3N_2O_5$	C,H,N	155	nt
14f		184	$C_{44}H_{72}N_2O_5$	C,H,N	185	nt
14g	(*S*,*S*)-$NH_2CH(i\text{-Bu})CHOHCH_2COOH$	158	$C_{46}H_{78}N_2O_6$	C,H,[n]N	50	40
14h	*rac*$NH_2CH_2CHOHCH2COOH$	130	$C_{42}H_{70}N_2O_6$	C,H,N	200	33
14i	(*R*)-$NH_2CH(i.Bu)CH_2CH_2COOH$	116	$C_{46}H_{78}N_2O_5$	C,H,N	52	85
14j	(*S*,*S*)-$NH_2CH(Bz)CHOHCH_2COOH$	138	$C_{49}H_{76}N_2O_6$	C,H,N	130	33
14k	(3*R*,4*S*)-$NH_2CH(i\text{-Bu})CHOHCH2COOH$	130	$C_{46}H_{78}N_2O_6$	C,H,N	50	44
nevirapine					84	

[a] Elemental analyses were within 0.4% of theory unless otherwise noted. [b] C: calcd, 71.89; found, 68.8. [c] C: calcd, 70.75; found, 70.1. [d] C: calcd, 70.85; found, 61.7. [e] Deliquescent. [f] C: calcd, 73.86; found, 74.9. [g] C: calcd, 71.68; found, 71.1. [h] H: calcd, 10.25; found, 10.9. [i] H: calcd, 10.33; found, 10.8. [j] H: calcd, 10.25; found, 11.0. [k] H: calcd, 9.61; found, 10.3. [l] H: calcd, 10.33; found, 11.0. [m] H: calcd, 9.83; found, 10.6. [n] H: calcd, 10.41; found, 11.1. nt: not tested.

Table 3



						anti-HIV-1 activity IC_{50} (nM)	
no.	Y	R-	mp, °C	formula	anal.	CEM cells	MT-4 cells
16a	CONH	o-$COOHC_6H_4$	116	$C_{45}H_{68}N_2O_5$	C,H,N	na	nt
19d	NHCO	*o*-$COOHC_6H_4$	156	$C_{45}H_{68}N_2O_5$	C,H,N	1800	nt
16b	CONH	*m*-$COOHC_6H_4$	160 dec	$C_{45}H_{68}N_2O_5$	C,H,N	80	nt
19e	NHCO	*m*-$COOHC_6H_4$	154	$C_{45}H_{68}N_2O_5$	C,H,N	105	40
16c	CONH	*p*-$COOHC_6H_4$	167	$C_{45}H_{68}N_2O_5$	C,H,N	70	26
19f	NHCO	*p*-$COOHC_6H_4$	190	$C_{45}H_{68}N_2O_5$	C,H,N	110	22

Ethyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]glycinate (4a). Following the procedure described for **4j**, **1b** (2.1 g, 4 mmol) was reacted with ethyl glycinate hydrochloride (5.60 g, 40 mmol). The crude product was purified by column chromatography eluting with 18% CH_2Cl_2 in diisopropyl ether to yield 900 mg (38.8%) of **4a** as a white powder: mp 120 °C (R_f = 0.40, eluent: 25% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]glycine (5a).** Following the procedure described for **5j**, **4a** (870 mg, 1.5 mmol) led to 460 mg (59.7%) of **5a** as a beige powder: mp 260 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (bd, J = 9 Hz, 1H, -*H* in 5), 0.78 (s, 3H, -CH_3), 0.84 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 0.98 (s, 3H, -CH_3), 1.00 (s, 3H, -CH_3), 1.61 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.70 (s, 3H, -CH_3 in 29), 2.42 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 3.09 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.21 (dd, J = 10, 5 Hz, 1H, -C*H* in 3), 3.3 (b, 1H, -O*H* in 3), 4.07 (limit ab, J = 18, 5 Hz, 1H, *N*-CH_2-COO-), 4.61 and 4.75 (2bs, 1H each, =CH_2), 6.14 (t, J = 5 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3420, 3075, 2940, 2870, 1635, 1605, 1510, 1450, 1400, 1375, 1045, 1030, 880; MS (FAB) 557, 536.

Ethyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-3-aminopropanoate (4b). Following the procedure described for **4j**, **1b** (1 g, 2 mmol) was reacted with ethyl 3-aminopropanoate hydrochloride (340 mg, 2.2 mmol) and triethylamine (0.62 mL, 4.4 mmol). The crude product was purified by column chromatography eluting with 25% ethyl acetate in cyclohexane to yield 1 g (83%) of **4b** as a white meringue (R_f = 0.32, eluent: 30% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-3-aminopropanoic Acid (5b).** Following the procedure described for **5j**, **4b** (1 g 1.6 mmol) led to 800 mg (95%) of **5b** as a white powder: mp 204 °C; IR (KBr, cm^{-1}) ν 3430, 3200−2250, 3090, 1720, 1640, 1515, 1380, 1375, 1045, 880; MS (EI) 528, 203, 189 (base), 175, 159, 119.

Ethyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-4-aminobutyrate (4c). Following the procedure described for **4j**, **1b** (1.38 g, 2.68 mmol) was reacted with ethyl 4-aminobutyrate hydrochloride (520 mg, 3.1 mmol) and triethylamine (0.87 mL, 6.2 mmol). The crude product was purified by column chromatography eluting with diisopropyl ether to yield 1 g (61%) of **4c** as a white meringue (R_f = 0.46, eluent: diisopropyl ether).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-4-aminobutyric Acid (5c).** Following the procedure described for **5j**, **4c** (1 g, 1.63 mmol) led to 870 mg (98.5%) of **5c** as a white powder: mp 180 °C (R_f = 0.34 eluent: 10% methanol in chloroform); IR (KBr, cm^{-1}) ν 3425, 3200−2250, 3080, 2950, 2870, 1720, 1640, 1515, 1380, 1375, 1045, 880; MS (DCI) 542 (base); MS (EI) 203, 189, 159, 119, 105, 81, 69 (base).

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-5-aminopentanoate (4d). Following the procedure described for **4j**, acid chloride **1b** (1.71 g, 3.3 mmol) was reacted with methyl 5-aminopentanoate hydrochloride[9] (650 mg, 3.8 mmol) and triethylamine (1.07 mL, 7.6 mmol). The crude product was purified by column chromatography eluting with diisopropyl ether to yield 1.1 g (54%) of **4d** as a white meringue (R_f = 0.35, eluent:diisopropyl ether).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-5-aminopentanoic Acid (5d).** Following the procedure described for **5j**, ester **4d** (1.1 g, 1.8 mmol) led to 820 mg (82%) of **5d** as a white powder: mp 160 °C (R_f = 0.42, eluent: 10% methanol in chloroform); IR (KBr, cm^{-1}) ν 3400, 3200−2250, 3090, 2940, 2870, 1710, 1640, 1515, 1380, 1375, 1045, 885; MS (EI) 555, 540, 527, 512, 411, 334, 237, 203, 189 (base), 175, 119, 95.

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-6-aminohexanoate (4e). Following the procedure described for **4j**, acid chloride **1b** (1.03 g, 2 mmol) was reacted with methyl 6-aminohexanoate hydrochloride (380 mg, 2.1 mmol) and triethylamine (0.53 mL, 3.8 mmol). The crude product was purified by preparative HPLC eluting with $CH_3CN-THF-H_2O$ (75:15:10) to yield 834 mg (82%) of **4e** as a white meringue (R_f = 0.28, eluent: 20% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-6-aminohexanoic Acid (5e).** Following the procedure described for **5j**, ester **4e** (800 mg, 1.3 mmol) led to 750 mg (100%) of **5e** as a white powder: mp 135 °C; IR (KBr, cm^{-1}) ν 3410, 3100−2250, 3075, 2945, 2870, 1715, 1640, 1530, 1455, 1390, 1380, 1045, 1035, 885; MS (EI) 569, 541, 526, 411, 189 (base).

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptanoate (4f). Following the procedure described for **4j**, acid chloride **1b** (1.03 g, 2.0 mmol) was reacted with methyl 7-aminoheptanoate hydrochloride[10] (320 mg, 2.2 mmol) and triethylamine (0.62 mL, 4.4 mmol). The crude product was purified by column chromatography eluting with 20% ethyl acetate in cyclohexane to yield 930 mg (73%) of **4f** as a white meringue (R_f = 0.28, eluent: 20% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptanoic Acid (5f).** Following the procedure described for **5j**, ester **4f** (930 mg, 1.4 mmol) led to 740 mg (90%) of **5f** as a white powder: mp 134 °C (R_f = 0.33, eluent: 20% ethyl acetate in cyclohexane); IR (KBr, cm^{-1}) ν 3400, 3200−2250, 3080, 2950, 2870, 1720, 1640, 1515, 1380, 1375, 1045, 880.

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoate (4g). To a solution of 8-aminooctanoic acid[11] (1 g, 6.2 mmol) in methanol (40 mL) cooled to −20 °C was added thionyl chloride (0.7 mL, 9.5 mmol), and stirring was maintained for 12 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 1.29 g (100%) of methyl 8-aminooctanoate hydrochloride as a white powder used without purification in the next step.

Following the procedure described for **4j**, acid chloride **1b** (1.03 g, 2.0 mmol) was reacted with methyl 8-aminooctanoate hydrochloride (490 mg, 2.1 mmol) and triethylamine (0.53 mL, 3.8 mmol). The crude product was purified by preparative HPLC eluting with $CH_3CN-THF-H_2O$ (70:15:15) to yield 750 mg (79%) of **4g** as a white meringue (R_f = 0.34, eluent: 20% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoic Acid (5g).** Following the procedure described for **5j**, ester **4g** (800 mg, 1.3 mmol) led to 750 mg (100%) of **5g** as a white powder: mp 135 °C; IR (KBr, cm^{-1}) ν 3400, 3125−2250, 3075, 2930, 2860, 1710, 1640, 1515, 1465, 1455, 1390, 1375, 1045, 1035, 885; MS (EI) 597, 569, 554, 411, 135 (base).

Ethyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-9-aminononanoate (4h). Following the prodecure described for **4j**, acid chloride **1b** (1.03 g, 2 mmol) was reacted with ethyl 9-aminononanoate[11] (442 mg, 2.2 mmol). The crude product was purified by column chromatography eluting with 20% ethyl acetate in cyclohexane to yield 810 mg (59%) of **4h** as a white meringue (R_f = 0.30, eluent: 20% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroylup-20(29)-en-28-oyl]-9-aminononanoic Acid (5h).** Following the procedure described for **5j**, ester **4h** (680 mg, 1 mmol) led to 290 mg (47%) of **5h** as a white solid: mp 162 °C; IR (KBr, cm^{-1}) ν 3420, 3125−2250, 3070, 2940, 2860, 1710, 1640, 1520, 1465, 1455, 1390, 1375, 1045, 1035, 885; MS (DCI) 612 (base).

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-10-aminodecanoate (4i). Following the procedure described for **4j**, acid chloride **1b** (570 mg, 1.1 mmol) was reacted with methyl 10-aminodecanoate hydrochloride[12] (310 mg, 1.26 mmol) and triethylamine (0.35 mL, 2.5 mmol). The crude product was purified by column chromatography eluting with 30% ethyl acetate in cyclohexane to yield 600 mg (80%) of **4i** as a white meringue (R_f = 0.74, eluent: 40% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-10-aminodecanoate (5i).** Following the procedure described for **5j**, ester **4i** (600 mg, 0.87mmol) led to 530 mg (98%) of **5i** as a white meringue: mp 100 °C; IR (KBr, cm^{-1}) ν 3400, 3125−2250, 3075, 2935, 2860, 1710, 1640, 1525, 1465, 1455, 1390, 1375, 1045, 1035, 885; MS (EI) 625, 610, 597, 582, 411, 69 (base).

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-12-aminododecanoate (4k). Following the procedure described for **4j**, acid chloride **1b** (660 mg, 1.27 mmol) was reacted with methyl 12-aminododecanoate hydrochloride[13] (374 mg, 1.4 mmol) and triethylamine (0.40 mL, 2.8 mmol). The crude product was purified by column chromatography eluting with 20% ethyl acetate in cyclohexane to yield 647 mg (71%) of **4k** as a white meringue (R_f = 0.32, eluent: 20% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-12-aminododecanoic Acid (5k).** Following the procedure described for **5j**, ester **4k** (525 mg, 0.8 mmol) led to 466 mg (88.8%) of **5k** as a white meringue: mp 182 °C; IR (KBr, cm^{-1}) ν 3385, 3200−2250, 3075, 2925, 2855, 1720, 1640, 1530, 1465, 1455, 1390, 1375, 1045, 1030, 885; MS (EI) 654, 653, 626, 611, 410, 189 (base).

Methyl *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-13-aminotridecanoate (4l). To a solution of 13-aminotridecanoic acid[14] (330 mg, 1.24 mmol) in methanol (15 mL) cooled to −20 °C, was added thionyl chloride (0.14 mL, 1.86 mmol), and stirring was maintained for 12 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 285 mg (71%) of methyl 13-aminotridecanoate as a white powder used without purification in the next step.

Following the procedure described for **4j**, acid chloride **1b** (447 mg, 0.86 mmol) was reacted with methyl 13-aminotridecanoate hydrochloride (265 mg, 0.95 mmol) and triethylamine (0.27 mL, 1.9 mmol). The crude product was purified by column chromatography eluting with 20% ethyl acetate in cyclohexane to yield 567 mg (90%) of **4l** as a white meringue (R_f = 0.35, eluent: 20% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-12-aminotridecanoic Acid (5l).** Following the procedure described for **5j**, ester **4l** (530 mg, 0.73 mmol) led to 470 mg (92%) of **5l** as a white meringue: mp 168 °C; IR (KBr, cm^{-1}) ν 3450, 3375, 3070, 2925, 2850, 1640, 1525, 1465, 1455, 1390, 1375, 1045,

1030, 885; MS (EI) 649, 639, 624, 410, 349, 189, 135, 121, 95, 81, 69, 43 (base).

General Procedure: *N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoic Acid (6g). A mixture of 8-aminooctanoic acid (12.92 g, 81 mmol) and trimethylsilyl chloride (14.34 g, 13.2 mmol) in CH_2Cl_2 (835 mL) was heated at reflux for 4 h and cooled to room temperature. Then were added successively a solution of acid chloride **1** (32 g, 61.9 mmol) in CH_2Cl_2 (450 mL), over 15 min, and triethylamine (37.1 mL), over 10 min. After further strirring for 12 h, the solvent was evaporated to dryness under reduced pressure and purified by column chromatography on silica gel eluting with 17% CH_2Cl_2 and 25% ethyl acetate in cyclohexane to afford 21 g (62%) of the acid **6g** as a white meringue (R_f = 0.30, eluent: 40% ethyl acetate in cyclohexane).

General Procedure: Methyl *N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]glycinate (7g). A solution of **6g** (1.13 g, 1.8 mmol) in CH_2Cl_2 (100 mL) was treated successively with methyl glycinate hydrochloride (0.25 g, 2 mmol), 1-hydroxybenzotriazole (0.24 g, 1.8 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.69 g, 3.6 mmol), and triethylamine (0.5 mL). After further stirring for 15 h at room temperature, distilled water (100 mL) was added. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 30% cyclohexane in ethyl acetate as eluent to yield 1.2 g (93%) of the ester **7g** as a white meringue (R_f = 0.30, eluent: 50% ethyl acetate in cyclohexane).

General Procedure: *N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]glycine (8g). A solution of **7g** (1.2 g, 1.17 mmol) in methanol (17 mL) and THF (8.5 mL) was treated with aqueous NaOH (4 N, 2.1 mL). The reaction mixture was stirred overnight at room temperature, concentrated to dryness under reduced pressure, diluted with methanol (10 mL) and water (40 mL), and acidified with hydrochloric acid (5 N, 2.5 mL). After further stirring for 30 min, the solid was collected and washed with distilled water to afford 1.03 g (93%) of **8g** as a white solid: mp 132 °C; ^{1}H NMR ($CDCl_3$ with a few drops of CD_3COOD-d_4, 400 MHz) δ 0.63 (b, J = 9 Hz, 1H, -*H* in 5), 0.70 (s, 3H, -C*H*$_3$), 0.77 (s, 3H, -C*H*$_3$), 0.88 (s, 3H, -C*H*$_3$), 0.91 (s, 3H, -C*H*$_3$), 0.94 (s, 3H, -C*H*$_3$), 1.54 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.65 (s, 3H, -C*H*$_3$ in 29), 2.24 (t, J = 7.5 Hz, 2H, -C*H*$_2$-CONH-), 2.36 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 3.02 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.05−3.25 (m, 2H, -CONH-C*H*$_2$-), 3.20 (m, 1H, -C*H* in 3), 4.05 (s, 2H, -CONH-C*H*$_2$-COO-), 4.53 and 4.67 (2bs, 1H each, =C*H*$_2$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.05 (d, J = 5 Hz, 2H, -CONH-C*H*$_2$-COO-), 5.80 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.65 (t, J = 5 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3420, 3130−2200, 3070, 2940, 2860, 1730, 1635, 1525, 1460, 1450, 1385 and 1370, 1040 and 1030, 880; MS (EI) 654, 639, 626, 611, 410, 189, 55 (base).

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]glycine (6a).** Following the procedure described for **6g**, acid chloride **1b** (5.17 g, 11.0 mmol) was reacted with glycine (0.83 g, 11.0 mmol). The crude product was purified by column chromatography eluting with 10% methanol in CH_2Cl_2 to yield 3.49 g (62.9%) of **6a** as a white solid (R_f = 0.50, eluent: 10% methanol in CH_2Cl_2).

Methyl *N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-2-aminoacetyl]-8-aminooctanoate (7a). Following the procedure described for **7g**, **6a** (1.0 g, 1.8 mmol) was reacted with methyl 8-aminooctanoate hydrochloride (0.41 g, 2.0 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 1.2 g (93%) of **7a** as a white meringue (R_f = 0.33, eluent: 10% methanol in CH_2Cl_2).

***N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-2-aminoacetyl]-8-aminooctanoic Acid (8a).** Following the procedure described for **8g**, ester **7a** (1.2 g, 1.7 mmol) led to 880 mg (79.5%) of **8a** as a white solid: mp 130 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.65 (m, 1H, -*H* in 5), 0.66 (s, 3H, -C*H*$_3$), 0.76 (s, 3H, -C*H*$_3$), 0.83 (s, 3H, -C*H*$_3$), 0.90 (s, 3H, -C*H*$_3$), 0.94 (s, 3H, -C*H*$_3$), 1.45 (m, 1H, -C*H* in 18), 1.65 (s, 3H, -C*H*$_3$ in 29), 2.19 (t, J = 7.5 Hz, 2H, -C*H*$_2$-COO-), 2.53 (m, 1H, -C*H* in 13), 2.90−3.10 (m, 4H, -CONH-C*H*$_2$-, -C*H* in 3, -C*H* in 19), 3.57 (limit ab, 2H, -CONH-C*H*$_2$-CONH-), 4.28 (b, 1H, -O*H* in 3), 4.53 and 4.65 (2bs, 1H each, =C*H*$_2$), 7.55 (t, J = 6 Hz, 1H, -CON*H*-), 7.93 (t, J = 6 Hz, 1H, -CON*H*- in 17), 12 (b, 1H, -COO*H*); IR (KBr, cm^{-1}) ν 3450, 3150−2300, 3075, 2940, 2865, 1710, 1640, 1515, 1470, 1455, 1390, 1380, 1045, 1035, 885; MS (EI) 654, 452, 410, 217, 189, 160, 113 (base), 95.

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-*β*-alanine (6b).** Following the procedure described for **6g**, acid chloride **1b** (1.1 g, 2.2 mmol) was reacted with *β*-alanine (0.23 g, 2.6 mmol). The crude product was purified by column chromatography eluting with 2% methanol in CH_2Cl_2 to yield 800 mg (64%) of **6b** as a white meringue (R_f = 0.26, eluent: 5% methanol in CH_2Cl_2).

Methyl *N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-3-aminopropanoyl]-7-aminoheptanoate (7b). Following the procedure described for **7g**, **6b** (0.8 g, 1.4 mmol) was reacted with methyl 7-aminoheptanoate hydrochloride (0.32 g, 1.62 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 900 mg (90%) of **7b** as a white meringue (R_f = 0.18, eluent: cyclohexane).

***N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-3-aminopropanoyl]-7-aminoheptanoic Acid (8b).** Following the procedure described for **8g**, ester **7b** (0.85 g, 1.19 mmol) led to 720 mg (92%) of **8b** as a white powder: mp 130 °C; IR (KBr, cm^{-1}) ν 3420, 3150−2250, 3075, 2940, 2870, 1715, 1640, 1520, 1465, 1455, 1390, 1375, 1045, 1030, 885; MS (DCI) 655 (base).

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-4-aminobutyric Acid (6c).** Following the procedure described for **6g**, acid chloride **1b (**2.1 g, 4.0 mmol) was reacted with 4-aminobutyric acid (470 mg, 4.4 mmol). The crude product was purified by column chromatography eluting with 5% methanol in CH_2Cl_2 to yield 1.3 g (55.6%) of **6c** as a white meringue (R_f = 0.20, eluent: 5% methanol in CH_2Cl_2).

Methyl *N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-4-aminobutanoyl]-6-aminohexanoate (7c). Following the procedure described for **7g**, acid **6c** (1.3 g, 2.2 mmol) was reacted with methyl 6-aminohexanoate hydrochloride (0.44 g, 2.44 mmol). The crude product was purified by column chromatography on silica gel eluting with 2% ethyl acetate in CH_2Cl_2 followed by 50% ethyl acetate in CH_2Cl_2 to yield 1.17 g (75%) of **7c** as a white meringue (R_f = 0.61, eluent: 10% methanol in CH_2Cl_2).

***N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-4-aminobutanoyl]-6-aminohexanoic Acid (8c).** Following the procedure described for **8g**, ester **7c** (1.1 g, 1.54 mmol) led to 1.0 g (100%) of **8c** as a white solid: mp 140−145 °C; IR (KBr, cm^{-1}) ν 3400, 3150−2300, 3075, 2940, 2865, 1710, 1635, 1530, 1450, 1390, 1375, 1040, 1030, 880; MS (EI) 626, 217, 200, 114 (base).

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-5-aminopentanoic Acid (6d).** Following the procedure described for **6g**, acid chloride **1b** (2.1 g, 4.0 mmol) was reacted with 5-aminopentanoic acid (530 mg, 4.4 mmol). The crude product was purified by column chromatography eluting with 5% methanol in CH_2Cl_2 to yield 1.1 g (46%) of **6d** as a white meringue (R_f = 0.24, eluent: 5% methanol in CH_2Cl_2).

Methyl *N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-5-aminopentanoyl]-5-aminopentanoate (7d). Following the procedure described for **7g**, acid **6d** (1.1 g, 1.8 mmol) was reacted with methyl 5-aminopentanoate hydrochloride (330 mg, 2.0 mmol). The crude product was purified by column chromatography on silica gel eluting with 2% ethyl acetate in CH_2Cl_2 followed by 50% ethyl acetate in CH_2Cl_2 to yield 1.0 g (86%) of **7d** as a white meringue (R_f = 0.61, eluent: 10% methanol in CH_2Cl_2).

***N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-5-aminopentanoyl]-5-aminopentanoic Acid (8d).** Following the procedure described for **8g**, ester **7d** (1.0 g, 1.4 mmol) led to 780 mg (85%) of **8d** as a white solid: mp 132 °C; IR (KBr, cm^{-1}) ν 3400, 3150−2300, 3075, 2940, 2865, 1710, 1635, 1530, 1450, 1390, 1375, 1040, 1030, 880; MS (DCI) 655 (base).

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-6-aminohexanoic Acid (6e).** Following the procedure described for **6g**, acid chloride **1b** (1.54 g, 3.0 mmol) was reacted with 6-aminohexanoic acid (440 mg, 3.3 mmol). The crude product was purified by column chromatography eluting with 40% ethyl acetate in cyclohexane to yield 1.1 g (61%) of **6e** as a white meringue (R_f = 0.20, eluent: 40% ethyl acetate in cyclohexane).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-6-aminohexanoyl]-4-aminobutyrate (7e). Following the procedure described for **7g**, acid **6e** (1.1 g, 1.8 mmol) was reacted with methyl 4-aminobutyrate hydrochloride (300 mg, 1.98 mmol). The resulting product (1.7 g, 100%) was used without further purification in the next step (R_f = 0.41, eluent: 40% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-6-aminohexanoyl]-4-aminobutyric Acid (8e).** Following the procedure described for **8g**, ester **7e** (1.7 g, 1.8 mmol) led to 1.36 g of crude **8e** which was purified by column chromatography on silica gel eluting with 3% methanol in ethyl acetate, yielding 3.6 g (31%) of pure **8e** as a white solid: mp 206 °C; IR (KBr, cm^{-1}) ν 3400, 3150−2250, 3075, 2940, 2865, 1715, 1640, 1450, 1390, 1375, 1045, 1035, 885; MS (DCI) 655 (base); MS (EI) 189, 95, 44 (base).

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptanoic Acid (6f).** Following the procedure described for **6g**, acid chloride **1b** (1.54 g, 3.0 mmol) was reacted with 7-aminoheptanoic acid (480 mg, 3.3 mmol). The crude product was purified by column chromatography eluting with 40% ethyl acetate in cyclohexane to yield 1.08 g (58%) of **6f** as a white meringue (R_f = 0.26, eluent: 40% ethyl acetate in cyclohexane).

Ethyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptanoyl]-3-aminopropionate (7f). Following the procedure described for **7g**, acid **6f** (1.08 g, 1.7 mmol) was reacted with ethyl *β*-alaninate hydrochloride (290 mg, 1.9 mmol). The crude product was purified by column chromatography on silica gel eluting with 20% ethyl acetate in CH_2Cl_2 to yield 470 mg (45%) of **7f** as a white solid (R_f = 0.40, eluent: 50% ethyl acetate in CH_2Cl_2).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptanoyl]-3-aminopropionic Acid (8f).** Following the procedure described for **8g**, ester **7f** (0.47 g, 0.65 mmol) led to 150 mg (36%) of **8f** as a white solid: mp 194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (b, J = 9 Hz, 1H, -*H* in 5), 0.77 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 0.97 (s, 6H, -CH_3), 1.60 (t, J = 12 Hz, 1H, -C*H* in 18), 1.68 (s, 3H, -CH_3 in 29), 2.20 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.40 (dt, J = 12, 3 Hz, 1H, -C*H* in 13), 2.64 (t, J = 6 Hz, 2H, -CH_2-COO-), 3.07 (dt, J = 12, 4 Hz, 1H, -C*H* in 19), 3.18 (dd, J = 11, 5 Hz, 1H, -C*H* in 3), 3.15−3.35 (m, 2H, -CONH-CH_2- in 17), 3.53 (q, J = 6 Hz, 2H, -CONH-CH_2-), 4.60 and 4.73 (2bs, 1H each, =CH_2), 5.84 (t, J = 6 Hz, 1H, -CON*H*- in 17), 6.27 (t, J = 6 Hz: 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3400, 3150 to 2250, 3075, 2940, 2865, 1725, 1640, 1530, 1460, 1450, 1390, 1375, 1045, 1035, 885. MS(DCI) 655 (base).

Ethyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminopropanoate (7h). Following the procedure described for **7g**, acid **6g** (900 mg, 1.4 mmol) was reacted with ethyl *β*-alaninate hydrochloride (250 mg, 1.6 mmol). The crude product was purified by column chromatography on silica gel eluting with 2% methanol in CH_2Cl_2 to yield 810 mg (78%) of **7h** as a white meringue (R_f = 0.21, eluent: 50% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminopropanoic Acid (8h).** Following the procedure described for **8g**, ester **7h** (810 mg, 1.1 mmol) led to 660 mg of crude **8h** which was purified by column chromatography on silica gel eluting with 10% methanol in CH_2Cl_2, yielding 370 mg (50.7%) of pure **8h** as a white powder: mp 138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (bd, J = 9 Hz, 1H, -*H* in 5), 0.77 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 0.98 (s, 6H, -CH_3), 1.59 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.70 (s, 3H, -CH_3 in 29), 2.19 (t, J = 7.5 Hz, 2H, -CH_2-CO-*N*-), 2.40 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.61 (t, J = 6 Hz, 2H, -CH_2-COO-), 3.10 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.10−3.25 (m, 3H, -CONH-CH_2- in 17, -C*H* in 3), 3.53 (m, 2H, -CONH-CH_2-), 4.60 and 4.74 (2bs, 1H each, =CH_2), 5.82 (t, J = 6 Hz, 1H, -CON*H*- in 17), 6.31 (t, J = 6 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3400, 3070, 2940, 2860, 2750−2250, 1715, 1635, 1530, 1450, 1390, 1375, 1045, 1035, 885; MS (EI) 668, 640, 410, 350, 189, 119, 95, 69 (base).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-aminobutyrate (7i). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl 4-aminobutyrate hydrochloride (140 mg, 0.93 mmol). The resulting product (410 mg, 72%) was used without further purification in the next step (R_f = 0.74, eluent: ethyl acetate).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-aminobutyric Acid (8i).** Following the procedure described for **8g**, ester **7i** (400 mg, 0.58 mmol) led to 370 mg of crude **8i** which was purified by column chromatography on silica gel eluting with 30% cyclohexane in ethyl acetate, yielding 90 mg (23%) of pure **8i** as a white solid: mp 168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66 (bd, J = 9 Hz, 1H, -*H* in 5), 0.74 (s, 3H, -CH_3), 0.82 (s, 3H, -CH_3), 0.92 (s, 3H, -CH_3), 0.96 (s, 6H, -CH_3), 1.58 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.70 (s, 3H, -CH_3in 29), 2.19 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.39 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.44 (t, J = 7 Hz, 2H, -CH_2-COO-), 3.08 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.10−3.35 (m, 2H, -CONH-CH_2- in 17), 3.18 (dd, J = 10, 5 Hz, 1H, -C*H* in 3), 3.35 (m, 2H, -CONH-CH_2-), 4.58 and 4.72 (2bs, 1H each, =CH_2), 5.72 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.28 (b, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3380, 3075, 2935, 2865, 2750−2250, 1715, 1635, 1535, 1450, 1390, 1375, 1040, 1030, 885; MS (LSIMS) 683 (base).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-5-aminopentanoate (7j). Following the procedure described for **7g**, acid **6g** (2.0 g, 3.1 mmol) was reacted with methyl 5-aminopentanoate hydrochloride (630 mg, 3.7 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 500 mg (21%) of **7j** as a white solid (R_f = 0.14, eluent: 50% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-5-aminopentanoic Acid (8j).** Following the procedure described for **8g**, ester **7j** (480 mg, 0.64 mmol) led to 178 mg (40%) of **8j** as a white solid: mp 152 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.65 (m, 1H, -*H* in 5), 0.67 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3), 0.90 (s, 3H, -CH_3), 0.95 (s, 3H, -CH_3), 1.45 (m, 1H, -C*H* in 18), 1.65 (s, 3H, -CH_3 in 29), 2.05 (t, J = 7.5 Hz: -CH_2-CONH-), 2.22 (t, J = 7.5 Hz: -CH_2-COO-), 2.57 (m, 1H, -C*H* in 13), 2.85−3.20 (m, 4H, -CONH-CH_2- in 17, -C*H* in 3 and -C*H* in 19), 3.04 (m, 2H, -CH_2-NHCO-), 4.30 (b, 1H, -O*H* in 3), 4.56 and 4.67 (2bs, 1H each, =CH_2), 7.55 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 7.76 (t, J = 6 Hz, 1H, -CON*H*-); MS (LSIMS) 677, 655 (base), 637, 611.

Benzyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-alaninate 10a. Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with benzyl L-alaninate hydrochloride (200 mg, 0.92 mmol). The crude product was purified by column chromatography on silica gel eluting with 30% ethyl acetate in cyclohexane followed by 45% ethyl acetate in cyclohexane to yield 550 mg (87%) of **10a** as a white meringue (R_f = 0.48, eluent: 50% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-alanine (11a).** Following the procedure described for **8g**, **10a** (520 mg, 0.65 mmol) led to 380 mg of crude **11a** which was purified by column chromatography on silica gel eluting with 20% methanol in ethyl acetate, yielding 150 mg (34.5%) of pure **11a** as a white solid: mp 120 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.65 (m, 1H, -*H* in 5), 0.68 (s, 3H, -CH_3), 0.79 (s, 3H, -CH_3), 0.86 (s, 3H, -CH_3), 0.90 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 1.25 (d, J = 7.5 Hz, 3H, CH-CH_3), 1.47 (t, J = 11.5 Hz, 1H, -C*H* in 13), 1.66 (s, 3H, -CH_3 in 29), 2.10 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.58 (bt, J = 11.5 Hz, 1H, -C*H* in 13), 2.85−3.05 and 3.10 (2m, 1H each, -CONH-CH_2-), 2.98 (m, 1H, -C*H* in 3), 3.03 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 4.15 (quintuplet, J = 7.5 Hz, 1H, CH-COO-), 4.29 (b, 1H, -O*H*), 4.55 and 4.67 (2bs, 1H each, =CH_2), 7.56 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 8.00 (d, J = 7.5 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3410, 3120−2250, 3070, 2940 and 2870, 1730, 1640, 1525, 1455, 1390 and 1375, 1045 and 1035, 880; MS (DCI) 726, 708 (base).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-2-aminoisobutyrate (10b). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl 2-aminoisobutyrate hydrochloride[15] (125 mg, 0.8 mmol). The crude product was purified by column chroma-

tography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 310 mg (54%) of **10b** as a white meringue (R_f = 0.3, eluent: 50% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-2-aminoisobutyric Acid (11b).** Following the procedure described for **8g**, ester **10b** (300 mg, 0.4 mmol) led to 270 mg (99%) of **11b** as a white solid: mp 140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (bd, J = 9 Hz, 1H, -*H* in 5), 0.78 (s, 3H, -CH_3), 0.84 (s, 3H, -CH_3), 0.96 (s, 3H, -CH_3), 0.99 (s, 6H, -CH_3), 1.59 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.60 [s, 6H, C(CH_3)$_2$], 1.70 (s, 3H, -CH_3 in 29), 2.19 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.43 (dt, J = 11.5, 3.5 Hz, 1H, -C*H* in 13), 3.14 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.10−3.20 and 3.28 (2m, 1H each, -CONH-CH_2-), 3.20 (dd, J = 11, 5 Hz, 1H, -C*H* in 3), 4.60 and 4.74 (2bs, 1H each, =CH_2), 5.67 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.17 (s, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3400, 3125−2250, 3070, 2940 and 2865, 1730, 1640, 1525, 1455, 1390 and 1375, 1045 and 1030, 885; MS (DCI) 683 (base), 665.

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-serinate (10c). Following the procedure described for **7g**, acid **6g** (1.5 g, 2.4 mmol) was reacted with methyl L-serinate hydrochloride (440 mg, 2.8 mmol). The resulting solid (1.58 g, mp 132 °C) was used without further purification in the next step.

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-serine (11c).** Following the procedure described for **8g**, ester **10c** (1.58 g, 2.13 mmol) led to 1.2 g of crude **11c** which was purified by column chromatography on silica gel eluting with 50% cyclohexane in ethyl acetate, yielding 210 mg (14%) of pure **11c** as a white meringue: mp >260 °C (R_f = 0.10, eluent: $CHCl_3$−MeOH−20% ammonia, 24:6:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.62 (m, 1H, -*H* in 5), 0.64 (s, 3H, -CH_3), 0.76 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3), 0.91 (s, 3H, -CH_3), 1.43 (t, J = 12.5 Hz, 1H, -C*H* in 18), 1.62 (s, 3H, -CH_3 in 29), 2.13 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.55 (bt, J = 12.5 Hz, 1H, -C*H* in 13), 2.85−3.00 and 3.09 (2m, 1H each, -CONH-CH_2-), 2.96 (m, 1H, -C*H* in 3), 3.02 (dt, J = 12.5, 4 Hz, 1H, -C*H* in 19), 3.58 and 3.67 (2dd, J = 12, 5 Hz, 1H each, -CH_2-O-), 4.25 (dt, J = 8, 5 Hz, 1H, -CONH-C*H*-), 4.52 and 4.64 (2bs, 1H each, =CH_2), 7.53 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 8.03 (d, J = 8 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3415, 3125−2250, 3075, 2940, 2865, 1735, 1635, 1530, 1465, 1455, 1390, 1375, 1045, 1035, 885; MS (DCI) 685, 667, 623, 597 (base).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-D-serinate (10d). Following the procedure described for **7g**, acid **6g** (1.0 g, 1.56 mmol) was reacted with methyl D-serinate hydrochloride (290 mg, 1.87 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 760 mg (66%) of **10d** as a white solid (R_f = 0.11, eluent: 50% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-D-serine (11d).** Following the procedure described for **8g**, ester **10d** (750 mg, 1.01 mmol) led to crude **11d** which was purified by column chromatography on silica gel eluting with 50% cyclohexane in ethyl acetate, yielding 53 mg (8%) of pure **11d** as a white solid: mp 252 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.64 (m, 1H, -*H* in 5), 0.66 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3), 0.89 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 1.43 (t, J = 12 Hz, 1H, -C*H* in 18), 1.64 (s, 3H, -CH_3 in 29), 2.14 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.55 (m, 1H, -C*H* in 13), 2.85−3.00 and 3.10 (2m, 1H each, -CONH-CH_2-), 2.85−3.05 (m, 1H, -C*H* in 3), 3.03 (dt, J = 12, 4 Hz, 1H, -C*H* in 19), 3.45 and 3.61 (2dd, J = 11, 6 Hz, 1H each, -CH_2-O-), 4.04 (dt, J = 7, 6 Hz, 1H, -CONH-C*H*-), 4.28 (d, J = 5 Hz, 1H, -O*H* in 3), 4.55 and 4.67 (2bs, 1H each, =CH_2), 7.57 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 7.64 (d, J = 7 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3425, 3130−2250, 3075, 2940, 2870, 1735, 1640, 1525, 1465, 1455, 1390, 1375, 1045, 1035, 880; MS (DCI) 669 (base).

Ethyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]sarcosinate (10e). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with ethyl sarcosinate hydrochloride (120 mg, 0.78 mmol). The crude product was purified by column chromatography on silica gel eluting with 15% ethyl acetate in CH_2Cl_2 to yield 510 mg (88%) of **10e** as a white meringue (R_f = 0.29, eluent: 15% ethyl acetate in CH_2Cl_2).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]sarcosine (11e).** Following the procedure described for **8g**, ester **10e** (490 mg, 0.66 mmol) led to 420 mg (95%) of **11e** as a white solid: mp 120 °C; ^{1}H NMR (DMSO-d_6, at temperature of 373 K, 400 MHz) δ 0.67 (m, 1H, -*H* in 5), 0.71 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.92 (s, 6H, -CH_3), 0.95 (s, 3H, -CH_3), 1.49 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.67 (s, 3H, -CH_3 in 29), 2.29 (b, 2H, -CH_2-CON-), 2.62 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.8−3.10 (b, 3H, *N*-CH_3), 2.85−3.10 and 3.13 (2m, 1H each, -CONH-CH_2-), 2.90−3.10 (m, 2H, -C*H* in 3, -C*H* in 19), 4.00 (s, 1H, *N*-CH_2-COO-), 4.56 and 4.68 (2bs, 1H each, =CH_2), 7.07 (t, J = 5.5 Hz, 1H, -CON*H*- in 17); IR (KBr, cm^{-1}) ν 3420, 3150, 2250, 3075, 2945, 2870, 1740, 1640, 1525, 1450, 1390, 1365, 1045, 1035, 880; MS (LSIMS) 695 (base).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-prolinate (10f). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl L-prolinate hydrochloride (150 mg, 0.86 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 600 mg (100%) of **10f** as a white meringue (R_f = 0.32, eluent: 50% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-proline (11f).** Following the procedure described for **8g**, ester **10f** (630 mg, 0.84 mmol) led to 422 mg (72%) of **11f** as a white solid: mp 142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (bd, J = 9 Hz, 1H, -*H* in 5), 0.76 (s, 3H, -CH_3), 0.82 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 0.96 (s, 6H, -CH_3), 1.56 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.69 (s, 3H, -CH_3 in 29), 2.02 (m, 2H, -CH_2-), 2.37 (limit ab, 2H, -CH_2-CON), 2.45 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 3.14 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.15 and 3.27 (2m, 1H each, -CONH-CH_2-), 3.19 (dd, J = 11, 5 Hz, 1H, -C*H* in 3), 3.48 and 3.59 (2m, 1H each, *N*-CH_2-), 4.60 (m, 1H, C*H*-COO-), 4.60 and 4.74 (2bs, 1H each, =CH_2), 5.67 (t, J = 5.5 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3425, 3120 to 2250, 3075, 2940, 2865, 1720, 1640, 1525, 1465, 1455, 1390, 1375, 1045, 1035, 880; MS (DCI) 685, 598 (base).

Dibenzyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-aspartate (10g). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with dibenzyl L-aspartate *p*-toluenesulfonate (410 mg, 0.85 mmol). The crude product was purified by column chromatography on silica gel eluting with 10% ethyl acetate in CH_2Cl_2 to yield 580 mg (79%) of **10g** as a colorless glaze (R_f = 0.40, eluent: 10% ethyl acetate in CH_2Cl_2).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-aspartic Acid (11g).** Following the procedure described for **8g**, **10g** (580 mg, 0.62 mmol) led to 263 mg (60%) of **11g** as a white solid: mp 140 °C; ^{1}H NMR (DMSO-d_6 with a few drops of CD_3COOD-d_4, 400 MHz) δ 0.63 (m, 1H, -*H* in 5), 0.66 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3), 0.86 (s, 3H, -CH_3), 0.89 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 1.62 (s, 3H, -CH_3 in 29), 2.11 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.55 (m, 1H, -C*H* in 13), 2.59 (dd, J = 16, 7 Hz, 1H, -*H* of -CH_2-COO-), 2.70 (dd, J = 16, 6 Hz, 1H, the other -*H* of -CH_2-COO-), 2.85−3.00 and 3.10 (2m, 1H each, -CONH-CH_2-), 2.97 (dd, J = 10, 7 Hz, 1H, -C*H* in 3), 3.02 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 4.54 (m, 1H, -CONH-C*H*-), 4.52 and 4.66 (2bs, 1H each, =CH_2), 7.49 (t, J = 5.5 Hz, -CON*H*- in 17), 8.10 (residual d, J = 8 Hz, -CON*H*-); IR (KBr, cm^{-1}) ν 3420, 3125−2250, 3075, 2940, 2865, 1730, 1640, 1525, 1465, 1450, 1390, 1375, 1045, 1030, 880; MS (DCI) 713, 695 (base).

***p*-Nitrophenyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-asparaginate (10h).** Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with *p*-nitrophenyl asparaginate hydrobromide (300 mg, 0.86 mmol). The crude product was triturated with isopropyl oxide to yield 660 mg (95%) of **10h** as a white solid (R_f = 0.20, eluent: ethyl acetate).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-asparagine (11h).** Following the procedure described for **8g**, **10h** (590 mg, 0.66 mmol) led to 170 mg (36%) of **11h** as a white solid: mp 120 °C (softening); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.65 (m, 1H, -*H* in 5), 0.67 (s, 3H, -CH_3),

0.79 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3), 0.90 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 1.48 (m, 1H, -C*H* in 18), 1.65 (s, 3H, -CH_3 in 29), 2.10 (t, J = 7 Hz, 2H, -CH_2-CONH-), 2.42 (dd, J = 16, 7 Hz, 1H, 1H of -CH_2-CONH$_2$), 2.58 (m, 1H, -C*H* in 13), 2.85−3.20 (m, 2H, -CONH-CH_2-), 2.98 (m, 1H, -C*H* in 3), 3.03 (dt, J = 12, 4 Hz, 1H, -C*H* in 19), 4.39 (d, J = 6 Hz, 1H, -O*H* in 3), 4.49 (q, J = 7 Hz, 1H, -CONH-C*H*-), 4.55 and 4.67 (2bs, 1H each, =CH_2), 6.9 and 7.4 (2bs, 1H each, -CONH$_2$), 7.57 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 8.09 (d, J = 7 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3420, 3100−2250, 3070, 2940, 2870, 1730, 1645, 1520, 1465, 1450, 1390, 1375, 1045, 1035, 885; MS (DCI) 694 (base), 597.

Methyl *N*′$^{\epsilon}$-(Trifluoroacetyl)-*N*′$^{\alpha}$-[*N*-[3*β*-acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-lysinate (10i). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl N$^{\epsilon}$-(trifluoroacetyl)lysinate hydrochloride (275 mg, 0.94 mmol). The crude product was purified by column chromatography on silica gel eluting with 20% cyclohexane in ethyl acetate to yield 430 mg (71%) of **10i** as a white meringue (R_f = 0.67, eluent: 20% cyclohexane in ethyl acetate).

***N*′$^{\alpha}$-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-lysine (11i).** Following the procedure described for **8g**, **10i** (420 mg, 0.48 mmol) led to 80 mg (23%) of **11i** as a white solid: mp 180 °C; IR (KBr, cm^{-1}) ν 3400, 3150−2250, 3070, 2940, 2865, 1715, 1640, 1525, 1465, 1450, 1390, 1375, 1045, 1035, 885; MS (LSIMS) 726, 255 (base).

Methyl *N*′-[*N*-[3*β*-acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-phenylalaninate (10j). Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl L-phenylalaninate hydrochloride (180 mg, 0.86 mmol). The crude product was purified by column chromatography on silica gel eluting with 35% ethyl acetate in cyclohexane to yield 660 mg (100%) of **10j** as a colorless glaze (R_f = 0.68, eluent: 50% ethyl acetate in cyclohexane).

***N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-L-phenylalanine (11j).** Following the procedure described for **8g**, ester **10j** (660 mg, 0.82 mmol) led to 400 mg (65.5%) of **11j** as a white solid: mp 116 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.68 (bd, J = 9 Hz, 1H, -*H* in 5), 0.76 (s, 3H, -CH_3), 0.82 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 0.97 (s, 6H, -CH_3), 1.58 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.68 (s, 3H, -CH_3 in 29), 2.18 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.43 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 3.05−3.20 (m, 1H, -C*H* in 19), 3.05−3.20 and 3.25 (2m, 1H each, -CONH-CH_2-), 3.12 and 3.22 (2dd, J = 15, 7 Hz, 1H each, -CH_2-C$_6$H$_5$), 3.20 (dd, J = 10, 5 Hz, 1H, -C*H* in 3), 4.59 and 4.74 (2bs, 1H each, =CH_2), 4.88 (q, J = 7 Hz, 1H, C*H*-COO-), 5.77 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.20 (d, J = 7 Hz, 1H, -CON*H*-), 7.10−7.35 (m, 5H, aromatics); IR (KBr, cm^{-1}) ν 3425, 3150−2250, 3070, 3030, 2940, 2865, 1740, 1640, 1520, 1495, 1455, 1390, 1375, 885, 740, 700; MS (LSIMS) 745 (base), 727.

Ethyl (3*R*,*S*)-*N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-3-phenylpropionate (13a). Following the procedure described for **7g**, acid **6g** (960 mg, 1.5 mmol) was reacted with ethyl (*R*,*S*)-3-amino-3-phenylpropionate hydrochloride[16] (410 mg, 1.8 mmol). The crude product was purified by column chromatography on silica gel eluting with 20% ethyl acetate in CH_2Cl_2 to yield 1.02 g (83.6%) of **13a** as a white meringue (R_f = 0.76, eluent: 20% ethyl acetate in CH_2Cl_2).

(3*R*,*S*)-*N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-3-phenylpropionic Acid (14a). Following the procedure described for **8g**, ester **13a** (980 mg, 1.2 mmol) led to 820 mg (92%) of **14a** as a white solid: mp 135 °C; ^{1}H NMR (CDCl$_3$, 400 MHz), mixture of diastereoisomers = 50/50) δ 0.68 (bd, J = 9 Hz, 1H, -*H* in 5), 0.78 (s, 3H, -CH_3), 0.81 and 0.84 (2s, 3H, -CH_3), 0.92 and 0.94 (2s, 3H, -CH_3), 1.00 (s, 6H, -CH_3), 1.60 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.69 (s, 3H, -CH_3 in 29), 2.23 (m, 2H, -CH_2-CONH-), 2.39 (m, 1H, -C*H* in 13), 2.88 and 3.03 (2dd, J = 16, 6.5 Hz, 1H each, -CH_2-C$_6$H$_5$), 3.08 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.10−3.35 (m, 2H, -CONH-CH_2-), 3.18 (dd, J = 10, 5 Hz, 1H, -C*H* in 3), 4.60 and 4.73 (2bs, 1H each, =CH_2), 5.45 (m, 1H, -CONH-C*H*), 5.79 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.78 (d, J = 8 Hz, 1H, -CON*H*-), 7.20−7.40 (m, 5H, aromatics); IR (KBr, cm^{-1}) ν 3400, 2750−2250, 3070, 3030, 2940, 2865, 1720, 1640, 1640, 1515, 1390, 1375, 1040, 1030, 885; 700; MS (LSIMS) 705, 683 (base), 665.

Methyl (3*R*,*S*)-*N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminoisobutyrate (13b). Following the procedure described for **7g**, acid **6g** (1.0 g, 1.56 mmol) was reacted with methyl (*R*,*S*)-3-aminoisobutyrate hydrochloride[17] (240 mg, 1.56 mmol). The crude product was purified by column chromatography on silica gel eluting with 40% cyclohexane in ethyl acetate to yield 1.06 g (92%) of **13b** as a white meringue (R_f = 0.5, eluent: 40% cyclohexane in ethyl acetate).

(3*R*,*S*)- *N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-isobutyric Acid (14b). Following the procedure described for **8g**, ester **13b** (1.04 g, 1.4 mmol) led to 940 mg (98%) of **14b** as a white solid: mp 130 °C; ^{1}H NMR (CDCl$_3$ with a few drops of CD$_3$COOD-d_4, 400 MHz) δ 0.63 (bd, J = 9 Hz, 1H, -*H* in 5), 0.71 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3), 0.88 (s, 3H, -CH_3), 0.90 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 1.16 (d, J = 7 Hz, 3H, CH-CH_3), 1.55 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.64 (s, 3H, -CH_3 in 29), 2.18 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.35 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.71 (m, 1H, C*H*-COO-), 3.03 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.05−3.30 (m, 2H, -CONH-CH_2- in 17), 3.20 (m, 1H, -C*H* in 3), 3.20 and 3.38 (2m, 1H each, -CONH-CH_2-), 4.53 and 4.67 (2bs, 1H each, =CH_2), 5.92 (residual t, J = 5.5 Hz: -CON*H*- in 17), 6.55 (residual m, -CON*H*-); IR (KBr, cm^{-1}) ν 3400, 2750−2250, 3075, 2945, 2870, 1715, 1640, 1530, 1465, 1455, 1390, 1375, 1040, 1035, 885; MS (LSIMS) 705, 683 (base), 665.

Methyl (3*R*,*S*)-*N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminobutyrate (13c). Following the procedure described for **7g**, acid **6g** (1.0 g, 1.6 mmol) was reacted with methyl (*R*,*S*)-3-aminobutyrate hydrochloride[18] (250 mg, 1.6 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 660 mg (56%) of **13c** as a colorless glaze (R_f = 0.16, eluent: 50% ethyl acetate in cyclohexane).

(3*R*,*S*)- *N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminobutyric Acid (14c). Following the procedure described for **8g**, ester **13c** (660 mg, 0.90 mmol) led to 521 mg (85%) of **14c** as a white solid: mp 134 °C; ^{1}H NMR (CDCl$_3$ with a few drops of CD$_3$COOD-d_4, 400 MHz) δ 0.60 (bd, J = 9 Hz, 1H, -*H* in 5), 0.65 (s, 3H, -CH_3), 0.73 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.85 (s, 3H, -CH_3), 0.89 (s, 3H, -CH_3), 1.16 (d, J = 7 Hz, 3H, CH-CH_3), 1.50 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.60 (s, 3H, -CH_3 in 29), 2.12 (t, J = 7 Hz, 2H, -CH_2-CONH-), 2.33 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.48 (limit ab, 2H, -CH_2-COO-), 2.99 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.00−3.25 (m, 2H, -CONH-CH_2-), 3.16 (dd, J = 10, 6 Hz, 1H, -C*H* in 3), 4.28 (m, 1H, -CONH-C*H*-), 4.49 and 4.62 (2bs, 1H each, =CH_2), 6.10 (residual t, J = 5.5 Hz: -CON*H*- in 17), 6.70 (residual d, J = 8 Hz, -CON*H*-); IR (KBr, cm^{-1}) ν 3375, 3075, 2945, 2870, 2700−2250, 1715, 1635, 1535, 1455, 1390, 1375, 1045, 1035, 880; MS (LSIMS) 683 (base), 245.

Methyl (3*R*,*S*)-*N*′-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-3-fluoropropionate (13d). To a solution of (*R*,*S*)-3-amino-3-fluoropropanoic acid (300 mg, 2.1 mmol) in methanol (20 mL) cooled to −20 °C was added thionyl chloride (0.23 mL, 3.1 mmol), and stirring was maintained for 12 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 360 mg (100%) of methyl (*R*,*S*)-3-amino-3-fluoropropionate hydrochloride as a white powder used without purification in the next step.

Following the procedure described for **7g**, acid **6g** (1.0 g, 1.6 mmol) was reacted with (*R*,*S*)-methyl 3-amino-3-fluoropropionate hydrochloride (250 mg, 1.6 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 1.08 g (91%) of **13d** as a white meringue (R_f = 0.26, eluent: 50% ethyl acetate in cyclohexane).

(3*R*,*S*)- *N*′-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-3-fluoropropionic Acid (14d). Following the procedure described for **8g**, ester **13d** (500 mg, 0.70 mmol) led to 400 mg (100%) of **14d** as a white solid: mp 132 °C; ^{1}H NMR (CDCl$_3$ with a few drops of CD$_3$COOD-d_4, 300 MHz) δ 0.59 (bd, J = 9 Hz, 1H, -*H* in 5), 0.65 (s, 3H, -CH_3), 0.73 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.85 (s, 3H, -CH_3), 0.88

(s, 3H, -CH_3), 1.45 (t, J = 12 Hz, 1H, -C*H* in 18), 1.58 (s, 3H, -CH_3 in 29), 2.14 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.30 (dt, J = 12, 3 Hz, 1H, -C*H* in 13), 2.95 (dt, J = 12, 4 Hz, 1H, -C*H* in 19), 3.00−3.25 (m, 2H, -CONH-CH_2- in 17), 3.13 (dd, J = 10, 6.5 Hz, 1H, -C*H* in 3), 3.50−3.85 (m, 2H, -CONH-CH_2-), 4.48 and 4.62 (2bs, 1H each, =CH_2), 4.98 (dt, J = 48, 10 Hz, 1H, C*H*-F), 5.85 (residual t, J = 5.5 Hz, -CON*H*- in 17), 6.43 (residual m, -CON*H*-); IR (KBr, cm^{-1}) ν 3450, 3390, 3200−2250, 3075, 2940, 2865, 1745, 1637, 1525, 1380, 1375, 1040, 880.

Methyl (3*R*,*S*)-*N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-4,4,4-trifluorobutyrate (13e). To a solution of (*R*,*S*)-3-amino-4,4,4-trifluorobutyric acid (1.57 g, 10 mmol) in methanol (15 mL) cooled to −20 °C was added thionyl chloride (3 mL), and stirring was maintained for 15 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 2.0 g (96.6%) of methyl (*R*,*S*)-3-amino-4,4,4-trifluorobutyrate hydrochloride as a white powder: mp 104 °C.

To a solution of acid **6g** (960 mg, 1.5 mmol) and triethylamine (0.21 mL) in THF (4.5 mL) was added dropwise at −7 °C isobutyl chloroformate (0.2 mL, 1.54 mmol). After further stirring at −7 °C for 30 min, a solution of methyl (*R*,*S*)-3-amino-4,4,4-trifluorobutyrate hydrochloride (0.32 g, 1.54 mmol) and triethylamine (0.22 mL) in a mixture of dioxane (4.5 mL) and water (1.5 mL) was added. After further stirring for 15 h at room temperature, the solvent was evaporated to dryness under reduced pressure. The residue was diluted with CH_2Cl_2, and the resulting solution was washed with distilled water, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 15% ethyl acetate in CH_2Cl_2 to yield 560 mg (46.7%) of **13e** as a white meringue (R_f = 0.36, eluent: 15% ethyl acetate in CH_2Cl_2).

(3*R*,*S*)- *N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-amino-4,4,4-trifluorobutyric Acid (14e). Following the procedure described for **8g**, ester **13e** (910 mg, 1.14 mmol) led to 734 mg (87%) of **14e** as a white solid: mp 140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.63 (m, 1H, -*H* in 5), 0.65 (s, 3H, -CH_3), 0.77 (s, 3H, -CH_3), 0.86 (s, 3H, -CH_3), 0.89 (s, 3H, -CH_3), 0.92 (s, 3H, -CH_3), 1.474 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.63 (s, 3H, -CH_3 in 29), 2.11 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.52 (m, 1H, 1H of -CH_2-COO-), 2.57 (m, 1H, -C*H* in 13), 2.73 (dd, J = 17, 4 Hz, 1H, the other H of -CH_2-COO-), 2.85−3.00 and 3.15 (2m, 1H each, -CONH-CH_2- in 17), 2.85−3.00 (m, 1H, -C*H* in 3), 3.03 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 4.28 (b, 1H, -O*H* in 3), 4.53 and 4.65 (2bs, 1H each, =CH_2), 4.89 (m, 1H, -CONH-C*H*), 7.56 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 8.42 (d, J = 9 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3440, 3200−2250, 3075, 2940, 2870, 1730, 1670, 1637, 1520, 1380, 1375, 1180, 1130, 1040, 885; MS (EI) 736, 708, 649, 418, 299, 189 (base).

Methyl *N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]nipecotate (13f). Following the procedure described for **7g**, acid **6g** (3.0 g, 4.69 mmol) was reacted with methyl nipecotate hydrochloride[19] (1.0 g, 5.6 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 2.65 g (76%) of **13f** as a white solid: mp 108 °C.

***N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]nipecotic Acid (14f).** Following the procedure described for **8g**, ester **13f** (2.5 g, 3.2 mmol) led to 2.35 g of crude **14f** which was purified by column chromatography on silica gel eluting with ethyl acetate, yielding 800 mg (78%) of pure **14f** as a white solid: mp 184 °C; ^{1}H NMR ($CDCl_3$, at temperature of 333 K, 400 MHz) δ 0.72 (bd, J = 9 Hz, 1H, -*H* in 5), 0.80 (s, 3H, -CH_3), 0.88 (s, 3H, -CH_3), 0.98 (s, 3H, -CH_3), 1.02 (s, 6H, -CH_3), 1.60 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.73 (s, 3H, -CH_3 in 29), 1.90−2.20 (m, 2H, -CH_2-CON-), 2.30−2.70 (m, 1H, C*H*-COO-), 2.34 and 2.54 (2m, 1H each, 1H of the *N*-CH_2-), 2.47 (bt, J = 11.5 Hz, 1H, -C*H* in 13), 3.13 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.15−3.35 (m, 2H, -CONH-CH_2-), 3.20 (dd, J = 11, 6 Hz, 1H, -C*H* in 3), 3.65−3.95 (b, 2H, the other H of *N*-CH_2-), 4.38 (b, 1H, -O*H*), 4.60 and 4.75 (2bs, 1H each, =CH_2), 5.64 (m, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3400, 3200−2250, 3075, 2940, 2860, 1730, 1637, 1525, 1385, 1375, 1040, 880; MS (LSIMS) 709 (base), 691.

Methyl (3*S*,4*S*)-*N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-3-hydroxy-6-methylheptanoate (13g). Following the procedure described for **7g**, acid **6g** (0.5 g, 0.78 mmol) was reacted with methyl (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoate hydrochloride[20] (210 mg, 0.93 mmol). The resulting product (570 mg, 90%) was used without further purification in the next step (R_f = 0.2, eluent: 50% ethyl acetate in cyclohexane).

(3*S*,4*S*)-*N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-3-hydroxy-6-methylheptanoic Acid (14g). Following the procedure described for **8g**, 3*S*,4*S* ester **13g** (550 mg, 0.68 mmol) led to 280 mg (56%) of **14g** as a white solid: mp 158 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.65 (m, 1H, -*H* in 5), 0.67 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3), 0.83 and 0.89 [2d, J = 6.5 Hz, 3H each, -CH-(CH_3)$_2$], 0.87 (s, 3H, -CH_3), 0.89 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 1.46 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.65 (s, 3H, -CH_3 in 29), 2.10 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.14 (dd, J = 15, 9 Hz, 1H, 1H of -CH_2-COO-), 2.30 (dd, J = 15, 4.5 Hz, 1H, 1H of -CH_2-COO-), 2.55 (m, 1H, -C*H* in 13), 2.85−3.00 and 3.11 (2m, 1H each, -CONH-CH_2-), 2.98 (dd, J = 10, 6 Hz, 1H, -C*H* in 3), 3.03 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.85 (m, 2H, -CONH-C*H*-C*H*-O-), 4.30 (b, 1H, -O*H* in 3), 4.55 and 4.67 (2bs, 1H each, =CH_2), 4.90 (b, 1H, -O*H*), 7.38 (d, J = 7.5 Hz, 1H, -CON*H*-), 7.55 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 12.00 (b, 1H, -COO*H*-); IR (KBr, cm^{-1}) ν 3605, 3450, 3425, 3375−3225, 2945, 2870, 1785, 1675, 1525, 1380, 1375, 1040, 885; MS (LSIMS) 755 (base) 737.

Methyl (3*R*,*S*)-*N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-3-hydroxybutyrate (13h). To a solution of (*R*,*S*)-4-amino-3-hydroxybutyric acid (1.19 g, 10 mmol) in methanol (25 mL) cooled to −20 °C was added thionyl chloride (1.0 mL, 13.9 mmol), and stirring was maintained for 12 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 1.69 g (100%) of (R,S) methyl 4-amino-3-hydroxybutyrate hydrochloride as a white powder used without purification in the next step.

Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl (*R*,*S*)-4-amino-3-hydroxybutyrate hydrochloride (135 mg, 0.8 mmol). The crude product was purified by column chromatography on silica gel eluting with ethyl acetate to yield 520 mg (88%) of **13h** as a white meringue (R_f = 0.35, eluent: ethyl acetate).

(3*R*,*S*)- *N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-3-hydroxybutyric Acid (14h). Following the procedure described for **8g**, ester **13h** (50 g, 0.66 mmol) led to 460 mg (100%) of **14h** as a white solid: mp 130 °C; ^{1}H NMR ($CDCl_3$ with a few drops of CD_3COOD-d_4, 400 MHz) δ 0.67 (bd, J = 9 Hz, 1H, -*H* in 5), 0.75 (s, 3H, -CH_3), 0.84 (s, 3H, -CH_3), 0.95 (s, 3H, -CH_3), 1.01 (s, 6H, -CH_3), 1.60 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.69 (s, 3H, -CH_3 in 29), 2.25 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.40 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.54 (dd, J = 17, 8 Hz, 1H, 1H of -CH_2-COO-), 2.60 (dd, J = 17, 5 Hz, 1H, the other H of -CH_2-COO-), 3.08 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.10−3.35 (m, 2H, -CONH-CH_2- in 17), 3.22 (dd, J = 11, 6 Hz, 1H, -C*H* in 3), 3.29 (dd, J = 15, 7 Hz, 2H, 1H of -CONH-CH_2-), 3.52 (dd, J = 15, 3 Hz, 2H, the other H of -CONH-CH_2-), 4.17 (m, J = 8, 7, 5, 3 Hz, 1H, C*H*-O-), 4.59 and 4.73 (2bs, 1H each, =CH_2), 5.80 (residual t, J = 5.5 Hz, -CON*H*- in 17), 6.70 (residual t, J = 6.5 Hz, -CON*H*-); IR (KBr, cm^{-1}) ν 3420, 3200−2250, 3075, 2945, 2870, 1717, 1637, 1537, 1380, 1375, 1040, 880; MS (LSIMS) 699 (base), 681, 598, 580.

Methyl (4*R*)-*N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-6-methylheptanoate (13i). To a solution of (4*R*)-4-amino-6-methylheptanoic acid[21] (490 mg, 2.5 mmol) in methanol (8 mL) cooled to −70 °C was added thionyl chloride (0.22 mL, 3.0 mmol), and stirring was maintained for 5 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 520 mg (99%) of methyl (4*R*)-4-amino-6-methylheptanoate hydrochloride as a white powder: mp 134 °C.

Following the procedure described for **7g**, acid **6g** (1.2 g, 2.0 mmol) was reacted with methyl (4*R*)-4-amino-6-methylheptanoate hydrochloride (510 mg, 2.44 mmol). The crude product

was purified by column chromatography on silica gel eluting with 40% ethyl acetate in cyclohexane to yield 1.5 g (93%) of **13i** as a white meringue (R_f = 0.42, eluent: 50% ethyl acetate in cyclohexane).

(4*R*)-*N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-6-methylheptanoic Acid (14i). Following the procedure described for **8g**, ester **13i** (1.45 g, 1.8 mmol) led to 1.2 g (90%) of **14i** as a white solid: mp 120 °C (softening); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (bd, J = 9 Hz, 1H, -*H* in 5), 0.76 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.92 [d, J = 7 Hz, 6H, -CH(CH_3)$_2$], 0.96 (s, 3H, -CH_3), 0.99 (s, 6H, -CH_3), 1.58 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.68 (s, 3H, -CH_3 in 29), 2.20 (m, 2H, -CH_2-CONH-), 2.40 (m, 3H, -C*H* in 13, -CH_2-COO-), 3.10−3.35 (m, 2H, -CONH-CH_2-), 3.12 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.18 (m, 1H, -C*H* in 3), 4.03 (m, 1H, -CONH-C*H*), 4.59 and 4.73 (2bs, 1H each, =CH_2), 5.70 (d, J = 9 Hz, -CON*H*-), 5.76 (t, J = 5.5 Hz, -CON*H*- in 17); IR (KBr, cm^{-1}) ν 3425, 3200−2250, 3075, 2940, 2870, 1715, 1637, 1530, 1380, 1375, 1040, 880; MS (DCI) 739 (base), 721.

Methyl (3*S*,4*S*)-*N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-4-benzyl-3-hydroxybutyrate (13j). To a solution of (3*S*,4*S*)-4-[[(*tert*-butyloxy)carbonyl]-amino]-4-benzyl-3-hydroxybutyric acid (0.5 g, 1.6 mmol) in methanol (20 mL) cooled to −20 °C was added thionyl chloride (0.19 mL, 2.4 mmol), and stirring was maintained for 12 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 0.42 g (100%) of methyl (3*S*,4*S*)-4-amino-4-benzyl-3-hydroxybutyrate hydrochloride as a white powder used without purification in the next step.

Following the procedure described for **7g**, acid **6g** (500 mg, 0.78 mmol) was reacted with methyl (3*S*,4*S*)-4-amino-4-benzyl-3-hydroxybutyrate hydrochloride (420 mg, 1.6 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 600 mg (91%) of **13j** as a white meringue (R_f = 0.38, eluent: 50% ethyl acetate in cyclohexane).

(3*S*,4*S*)-*N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-4-benzyl-3-hydroxybutyric Acid (14j). A solution of **13j** (600 mg, 0.71 mmol) in methanol (7 mL) and THF (3.5 mL) was treated with aqueous LiOH (1 N, 3.6 mL). The reaction mixture was stirred overnight at room temperature, acidified with hydrochloric acid (5 N, 1.5 mL), and concentrated to dryness under reduced pressure. The residue was washed with water to afford 550 mg (100%) of **14j** as a white solid: mp 138 °C; ^{1}H NMR ($CDCl_3$ with a few drops of CD_3COOD-d_4, 400 MHz) δ 0.66 (bd, J = 9 Hz, 1H, -*H* in 5), 0.74 (s, 3H, -CH_3), 0.80 (s, 3H, -CH_3), 0.90 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 0.97 (s, 3H, -CH_3), 1.53 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.68 (s, 3H, -CH_3 in 29), 2.18 (limit ab, 2H, -CH_2-CONH-), 2.39 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.50 (dd, J = 17, 4.5 Hz, 1H, 1H of -CH_2-COO-), 2.54 (dd, J = 17, 8 Hz, 1H, the other H of -CH_2-COO-), 2.85 and 2.90 (2dd, J = 14, 8 Hz, 1H each, -CH_2-C$_6$H$_5$), 3.07 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.17 and 3.24 (2m, 1H each, -CONH-CH_2-), 3.22 (m, 1H, -C*H* in 3), 4.08 (m, 1H, C*H*-O-), 4.21 (m, 1H, -CONH-C*H*), 4.57 and 4.71 (2bs, 1H each, =CH_2), 5.93 (residual t, J = 5.5 Hz, -CON*H*- in 17), 6.70 (residual d, J = 9 Hz, -CON*H*-), 7.15−7.35 (m, 5H, aromatics); IR (KBr, cm^{-1}) ν 3425, 3200−2250, 3070, 2940, 2870, 1720, 1637, 1525, 1380, 1375, 1040, 880, 750, 700; MS (DCI) 789, 771, 728 (base).

(3*R*,4*S*)-Methyl *N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-3-hydroxy-6-methylheptanoate (13k). To a solution of (3*R*,4*S*)-4-[[(*tert*-butyloxy)-carbonyl]amino]-3-hydroxy-6-methylheptanoic acid (400 mg, 1.45 mmol) in methanol (8 mL) cooled to −20 °C was added thionyl chloride (0.16 mL, 2.18 mmol), and stirring was maintained for 12 h at room temperature. The mixture was concentrated to dryness under reduced pressure to yield 330 mg (100%) of methyl (3*R*,4*S*)-4-amino-3-hydroxy-6-methylheptanoate hydrochloride as a white powder used without purification in the next step.

Following the procedure described for **7g**, acid **6g** (900 mg, 1.4 mmol) was reacted with methyl (3*R*,4*S*)-4-amino-3-hydroxy-6-methylheptanoate hydrochloride (320 mg, 1.4 mmol). The crude product was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to yield 960 mg (85%) of **13k** as a white meringue (R_f = 0.25, eluent: 50% ethyl acetate in cyclohexane).

(3*R*,4*S*)-*N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-amino-3-hydroxy-6-methylheptanoic Acid (14k). Following the procedure described for **8g**, ester **13k** (940 mg, 1.16 mmol) led to 875 mg (91%) of **14k** as a white solid: mp 130 °C; ^{1}H NMR ($CDCl_3$ with a few drops of CD_3COOD-d_4, 400 MHz) δ 0.65 (bd, J = 9 Hz, 1H, -*H* in 5), 0.72 (s, 3H, -CH_3), 0.80 (s, 3H, -CH_3), 0.85 and 0.90 [2d, J = 7 Hz, 3H each, -CH(CH_3)$_2$], 0.90 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 0.96 (s, 3H, -CH_3), 1.55 (t, J = 12 Hz, 1H, -C*H* in 18), 1.64 (s, 3H, -CH_3 in 29), 2.20 (t, J = 7.5 Hz, 2H, -CH_2-CONH-), 2.37 (dt, J = 12, 3 Hz, 1H, -C*H* in 13), 2.50 (limit ab, 2H, -CH_2-COO-), 3.04 (dt, J = 12, 4 Hz, 1H, -C*H* in 19), 3.10−3.30 (m, 2H, -CONH-CH_2-), 3.20 (m, 1H, -C*H* in 3), 4.00−4.15 (m, 2H, -CONH-C*H*-C*H*-O-), 4.55 and 4.69 (2bs, 1H each, =CH_2), 5.87 (residual t, J = 5.5 Hz, -CON*H*- in 17), 6.50 (residual d, J = 9 Hz, -CON*H*-); IR (KBr, cm^{-1}) ν 3375, 3200−2250, 3075, 2940 and 2870, 1720, 1637, 1530, 1380 and 1375, 1040, 880; MS (LSIMS) 777, 755 (base), 737.

Methyl *N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-2-aminobenzoate (15a). To a solution of acid **6g** (1.0 g, 1.5 mmol) in CH_2Cl_2 (30 mL) was added thionyl chloride (0.150 mL, 2 mmol). After further stirring for 12 h at room temperature, the reaction medium was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (30 mL) and methyl anthranilate (0.4 mL, 3 mmol) and stirred for 12 h at room temperature. The reaction medium was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), the solution was filtered, and the filtrate was concentrated to dryness under reduced pressure. Column chromatography on SiO_2, eluting with 5% ethyl acetate in CH_2Cl_2, afforded 1.15 g (65%) of the ester **15a** as a white meringue (R_f = 0.37, eluent: 5% ethyl acetate in CH_2Cl_2).

***N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-2-aminobenzoic Acid (16a).** Following the procedure described for **5j**, ester **15a** (750 mg, 0.97 mmol) led to 650 mg (93.5%) of **16a** as a white powder: mp 116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.68 (bd, J = 9 Hz, 1H, -*H* in 5), 0.77 (s, 3H, -CH_3), 0.80 (s, 3H, -CH_3), 0.92 (s, 3H, -CH_3), 0.97 (s, 3H, -CH_3), 0.99 (s, 3H, -CH_3), 1.62 (t, J = 11.5 Hz, 1H, -*H* in 18), 1.70 (s, 3H, -CH_3 in 29), 2.41 (dt, J = 11.5, 3 Hz, 1H, -*H* in 13), 2.47 (t, J = 7 Hz, 2H, -CH_2-CONH-), 3.10 (dt, J = 11.5, 4 Hz, 1H, -*H* in 19), 3.20 (dd, J = 11, 5 Hz, 1H, -*H* in 3), 3.20−3.40 (m, 2H, -CONH-CH_2-), 4.61 and 4.77 (2bs, 1H each, =CH_2), 5.79 (t, J = 6 Hz, 1H, -CON*H*-), 7.11 (bt, J = 8.5 Hz, 1H, -*H* aromatic in 5), 7.56 (bt, J = 8.5 Hz, 1H, -*H* aromatic in 4), 8.11 (bd, J = 8.5 Hz, 1H, -*H* aromatic in 3), 8.64 (bd, J = 8.5 Hz, 1H, -*H* aromatic in 6), 11.29 (s, 1H, -CON*H*-Ar); IR (KBr, cm^{-1}) ν 3450, 3400, 3200−2250, 3075, 2940, 2870, 1690, 1640, 1595, 1525, 1380, 1375, 1045, 880, 760; MS (EI) 716, 698, 670, 410, 380, 287, 261, 203, 189, 136 (base), 119, 93.

Ethyl *N*′-[*N*-[3β-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminobenzoate (15b). A solution of acid **6g** (640 mg, 1 mmol) in CH_2Cl_2 (25 mL) was treated successively with ethyl 3-aminobenzoate (200 mg, 1.2 mmol), 1-hydroxybenzotriazole (150 mg, 1 mmol), 1-[3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (390 mg, 2 mmol), and triethylamine (0.28 mL, 2 mmol). After further stirring for 19 h at room temperature, water (50 mL) was added. The aqueous layer was extracted using CH_2Cl_2 (60 mL). The combined organic layers were washed with an aqueous methanesulfonic acid solution (0.1 *N*, 20 mL) and then with distilled water (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in CH_2Cl_2 as eluent to yield 400 mg (51%) of the ester **15b** as a white meringue (R_f = 0.26, eluent: 5% ethyl acetate in CH_2Cl_2.

***N*′-[*N*-[3β-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-3-aminobenzoic Acid (16b).** Following the procedure described for **5j**, ester **15b** (340 mg, 0.43 mmol) led to 248 mg (80.5%) of **16b** as a white powder: mp 160 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.65 (b, J = 9 Hz, 1H, -*H* in 5), 0.68 (s, 3H, -CH_3), 0.81 (s, 3H, -CH_3), 0.89 (s, 6H, -CH_3), 0.95 (s, 3H, -CH_3), ca. 1.45 (m, 1H, -*H* in 18), 1.69 (s, 3H, -CH_3 in 29), 2.61

(bt, J = 11.5 Hz, 1H, -*H* in 13), 2.34 (t, J = 7 Hz, 2H, -CH_2-CONH-), 2.61 (bt, J = 11.5 Hz, 1H, -*H* in 13), 2.90−3.10 and 3.18 (2m, 1H each, -CONH-CH_2-), 3.00 (b, 1H, - *H* in 3), 3.08 (dt, J = 11.5, 4 Hz, 1H, -*H* in 19), 4.30 (b, 1H, -O*H* in 3), 4.57 and 4.70 (2bs, 1H each, =CH_2), 7.44 (bt, J = 8.5 Hz, 1H, -*H* aromatic in 5), 7.59 (t, J = 5.5 Hz, 1H, -CON*H*-), 7.63 (bd, J = 8.5 Hz, 1H, -*H* aromatic in 4), 7.87 (bd, J = 8.5 Hz, 1H, -*H* aromatic in 6), 8.27 (bs, 1H, -*H* aromatic in 2), 11.10 (s, 1H, -CON*H*-Ar), 12.50−13.40 (b, 1H, -COO*H*); IR (KBr, cm^{-1}) ν 3425, 3200−2250, 3070, 2945, 2865, 1700, 1675, 1640, 1595, 1550, 1380, 1375, 1045, 880, 760; MS (DCI) 717 (base).

Methyl *N′*-[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-aminobenzoate (15c). A solution of acid **6g** (1 g, 1.6 mmol) in CH_2Cl_2 (100 mL) was treated successively with methyl 4-aminobenzoate hydrochloride (330 mg, 1.76 mmol), 1-hydroxybenzotriazole (240 mg, 2.8mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (610 mg, 3.2 mmol), and triethylamine (0.67 mL, 4.8 mmol). After further stirring for 12 h at room temperature, water (50 mL) was added. The aqueous layer was extracted using ethyl acetate (125 mL). The combined organic layers were washed with distilled water (20 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 5% ethyl acetate in CH_2Cl_2 as eluent to yield 940 mg (76%) of the ester **15c** as a white meringue (R_f = 0.41, eluent: 40% ethyl acetate in cyclohexane).

***N′*-[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-8-aminooctanoyl]-4-aminobenzoic Acid (16c).** Following the procedure described for **5j**, ester **15c** (940 mg, 0.1.2 mmol) led to 758 mg (87%) of **16c** as a white powder: mp 167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.58 (m, 1H, -*H* in 5), 0.60 (s, 3H, -CH_3), 0.73 (s, 3H, -CH_3), 0.82 (s, 6H, -CH_3), 0.87 (s, 3H, -CH_3), ca. 1.45 (m, 1H, -*H* in 18), 1.59 (s, 3H, -CH_3 in 29), 2.31 (t, J = 7.5 Hz, 2H, -CH_2-COO-), 2.54 (m, 1H, -*H* in 13), 2.80−3.00 (m, 2H, 1H of -CONH-CH_2-, -*H* in 3), 2.99 (dt, J = 11.5, 4 Hz, 1H, -*H* in 19), 3.10 (m, 1H, the other H of -CONH-CH_2-), 4.23 (d, J = 5 Hz, 1H, -O*H* in 3), 4.51 and 4.63 (2bs, 1H each, =CH_2), 7.50 (t, J = 5.5 Hz, 1H, -CON*H*-), 7.67 (bd, J = 8.5 Hz, 2H, -*H* aromatics in ortho of -COOH), 7.84 (bd, J = 8.5 Hz, 2H, -*H* aromatics in meta of -COOH), 10.14 (s, 1H, -CON*H*-Ar); IR (KBr, cm^{-1}) ν 3425, 3200−2250, 3075, 2940, 2870, 1690, 1640, 1595, 1525, 1385, 1375, 1040, 880, 775; MS (DCI) 717 (base), 699; MS (EI) 411, 398, 279, 223, 189, 137 (base).

***N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-1,7-diaminoheptane (17).** A solution of acid chloride **1b** (31 g, 60 mmol) in CH_2Cl_2 (1000 mL) was added over 10 h to 1,7-diaminoheptane (46.8 g, 36 mmol) in CH_2Cl_2 (120 mL). After further stirring for 15 h at room temperature, the mixture was concentrated to dryness under reduced pressure. Distilled water (2000 mL) was added. The solid was filtered, washed with distilled water (200 mL), and dissolved in ethanol (500 mL). Insoluble material was filtered; then the solution was concentrated to dryness under reduced pressure. The solid residue was purified by column chromatography on SiO_2, eluting with a mixture of chloroform−methanol−ammoniac (24:6:1) to afford 28 g (85%) of **17** as a white meringue (R_f = 0.25, eluent $CHCl_3$−MeOH−ammoniac, 24:6:1).

Ethyl [[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]acetate (18a). To a solution of malonic acid monomethyl ester (133 mg, 1 mmol), 1-hydroxybenzotriazole (153 mg, 1 mmol), and **17** (560 mg, 0.92 mmol) in CH_2Cl_2 (25 mL) was added a solution of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (500 mg, 2.6 mmol) and triethylamine (0.52 mL, 3.7 mmol) in CH_2Cl_2 (5 mL). After stirring for 12 h at room temperature, water (15 mL) was added. The organic layer was separated, washed with distilled water (30 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 25% ethyl acetate in cyclohexane as eluent to yield 350 mg (52%) of the ester **18a** as a white meringue (R_f = 0.38, eluent: 5% CH_3OH in CH_2Cl_2).

[[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]acetic Acid (19a). Following the procedure described for **5j**, ester **18a** (350 mg, 0.48 mmol) led to 305 mg (92.5%) of **19a** as a white meringue: (mp 140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.63 (m, 1H, -*H* in 5), 0.65 (s, 3H, -CH_3), 0.75 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3), 0.92 (s, 3H, -CH_3), 1.42 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.61 (s, 3H, -CH_3 in 29), 2.57 (m, 1H, -C*H* in 13), 2.85−3.15 (m, 4H, -CONH-CH_2- in 17, -C*H* in 3, -C*H* in 19), 3.04 (m, 2H, -CH_2-NHCO-), 3.09 (s, 2H, -NHCO-CH_2-COO-), 4.18 (b, 1H, -O*H* in 3), 4.53 and 4.65 (2bs, 1H each, =CH_2), 7.55 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 8.05 (t, J = 6 Hz, 1H, -CON*H*-); MS (LSIMS) 677, 655 (base), 611.

Methyl [[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]propanoate (18b). To a solution of succinic acid monomethyl ester (420 mg, 3 mmol), 1-hydroxybenzotriazole (510 mg, 3.3 mmol), and **17** (1.8 g, 2.9 mmol) in CH_2Cl_2 (60 mL) was added a solution of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (1.4g, 7.3 mmol) and triethylamine (1.75 mL, 12 mmol) in CH_2Cl_2 (20 mL). After stirring for 3 h at room temperature, distilled water (150 mL) was added. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 1% CH_3OH in CH_2Cl_2 as eluent to yield 1.38 g (65%) of the ester **18b** as a white meringue (R_f = 0.38, eluent: 5% CH_3OH in CH_2Cl_2).

[[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]propanoic Acid (19b). Following the procedure described for **5j**, ester **18b** (1.38 g 1.8 mmol) led to 1.10 g (84.8%) of **19b** as a white solid: mp 128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (bd, J = 9 Hz, 1H, -*H* in 5), 0.78 (s, 3H, -CH_3), 0.84 (s, 3H, -CH_3), 0.95 (s, 3H, -CH_3), 0.99 (s, 6H, -CH_3), 1.60 (t, J = 11.5 Hz, 1H, -C*H* in 18), 1.70 (s, 3H, -CH_3in 29), 2.42 (dt, J = 11.5, 3 Hz, 1H, -C*H* in 13), 2.54 and 2.72 (2t, J = 6.5 Hz, 2H each, -NHCO-CH_2-CH_2-COO-), 3.10 (dt, J = 11.5, 4 Hz, 1H, -C*H* in 19), 3.15−3.45 (m, 3H, -CONH-CH_2- in 17, -C*H* in 3), 3.30 (q, J = 6 Hz, 2H, -CH_2-NHCO-), 4.62 and 4.75 (2bs, 1H each, =CH_2), 5.78 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.27 (t, J = 6 Hz, 1H, -CON*H*-); IR (KBr, cm^{-1}) ν 3400, 3200−2250, 3075, 2940, 2865, 1725, 1637, 1530, 1380, 1375, 1040, 880; MS (LSIMS) 669 (base); MS (EI) 650, 622, 553, 410, 332, 189, 121, 56 (base).

Methyl [[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]butanoate (18c). A solution of **17** (1.81 g, 2.96 mmol) in CH_2Cl_2 (80 mL) was treated successively with glutaric acid monomethyl ester[22] (397 mg, 2.72 mmol), 1-hydroxybenzotriazole (540 mg, 3.3 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (1.41g, 7.23 mmol), and triethylamine (1.77 mL, 12.7 mmol). After further stirring for 8 h at room temperature, distilled water (80 mL) was added. The organic layer was separated, washed with distilled water (20 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in cyclohexane as eluent to yield 1.70 g (85%) of the ester **18c** as a colorless meringue (R_f = 0.52, eluent: CH_2Cl_2−MeOH−ammoniac 24:12:1).

[[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]butanoic Acid (19c). Following the procedure described for **5j**, ester **18c** (1.44 g, 1.95 mmol) led to 770 mg (58%) of **19c** as a white solid: mp 170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (b, J = 9 Hz, 1H, -*H* in 5), 0.79 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 0.98 (s, 6H, -CH_3), 1.57 (t, J = 11.5 Hz, 1H, -*H* in 18), 1.69 (s, 3H, -CH_3 in 29), 1.99 (m, 2H, -CH_2-), 2.31 and 2.44 (2 t, J = 7.5 Hz, 2H each, -NHCO-CH_2-CH$_2$-CH_2-COO-), 2.42 (dt, J = 11.5, 3 Hz, 1H, -*H* in 13), 3.10−3.35 (m, 2H, -CONH-CH_2- in 17), 3.13 (t, J = 11.5, 4 Hz, 1H, -*H* in 19), 3.20 (dd, J = 11, 5 Hz, 1H, - *H* in 3), 3.28 (bq, J = 7 Hz, 2H, -CH_2-NHCO-), 4.60 and 4.75 (2bs, 1H each, =CH_2), 5.72 (t, J = 6 Hz, 1H, -CON*H*- in 17), 5.92 (t, J = 7 Hz, 1H, -N*H*-CO-); IR (KBr, cm^{-1}) ν 3450, 3375, 3200−2250, 3075, 2940, 2870, 1720, 1640, 1530, 1380, 1375, 1040, 880; MS (LSIMS) 683 (base), 569.

2-[7-[[3*β*-Acetoxylup-20(29)-en-28-oyl]amino]heptyl]-phthalimide (18d). A solution of **17** (1.83 g, 3 mmol) in CH_2Cl_2 (100 mL) was treated successively with isophthalic acid monomethyl ester (540 mg, 3 mmol), 1-hydroxybenzotriazole (560 mg, 3.3 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.41 g, 7 mmol), and triethylamine

(1.85 mL, 13 mmol). After further stirring for 2 h at room temperature, the mixture was concentrated to dryness under reduced pressure. Ethyl acetate (100 mL) and distilled water (100 mL) were added to the residue. The organic layer was separated, washed with distilled water (100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 40% ethyl acetate in cyclohexane as eluent to yield 2.0 g (90%) of **18d** as a white meringue (R_f = 0.57, eluent: 30% ethyl acetate in cyclohexane).

2-[[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptyl]-carbamoyl]benzoic Acid (19d). To a solution of **18d** (2.0 g, 2.7 mmol) in methanol (60 mL) and THF (60 mL) was added 10.8 mL of NaOH (5 N). The reaction mixture was stirred for 12 h at room temperature and then diluted with distilled water (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with distilled water (200 mL), dried over sodium sulfate, and evaporated under reduced pressure to afford 1.4 g of **19d** (72%) as a beige solid: mp 156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.66 (b, J = 9 Hz, 1H, -*H* in 5), 0.75 (s, 3H, -C*H*$_3$), 0.79 (s, 3H, -C*H*$_3$), 0.93 (s, 3H, -C*H*$_3$), 0.96 (s, 6H, -C*H*$_3$), 1.57 (t, J = 11.5 Hz, 1H, -*H* in 18), 1.68 (s, 3H, -C*H*$_3$ in 29), 2.43 (dt, J = 11.5, 3 Hz, 1H, -*H* in 13), 3.05−3.35 (m, 2H, -CONH-C*H*$_2$- in 17), 3.12 (t, J = 11.5, 4 Hz, 1H, -*H* in 19), 3.17 (dd, J = 11, 5 Hz, 1H, - *H* in 3), 3.45 (bq, J = 7 Hz, 2H, -C*H*$_2$-NHCO-), 4.57 and 4.72 (2bs, 1H each, =C*H*$_2$), 5.85 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.90 (t, J = 7 Hz, 1H, -N*H*-CO-), 7.51 (t, J = 8 Hz, 1H, -*H* aromatic in 5), 8.08 (bd, J = 8 Hz, 1H, -*H* aromatic in 4), 8.18 (bd, J = 8 Hz, 1H, -*H* aromatic in 6), 8.46 (bs, 1H, -*H* aromatic in 6); IR (KBr, cm^{-1}) ν 3430, 3200−2250, 3075, 2940 and 2870, 1720, 1640, 1600, 1525, 1385 and 1375, 1040, 880, 750; MS (LSIMS) 739, 717 (base), 569, 279, 261.

Methyl 3-[[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]benzoate (18e). A solution of **17** (1.83 g, 3 mmol) in CH_2Cl_2 (100 mL) was treated successively with isophthalic acid monomethyl ester (540 mg, 3 mmol), 1-hydroxybenzotriazole (560 mg, 3.3 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (1.41 g, 7 mmol), and triethylamine (1.85 mL, 13 mmol). After further stirring for 2 h at room temperature, ethyl acetate (100 mL) and distilled water (100 mL) were added to the residue. The organic layer was separated, washed with distilled water (100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 40% ethyl acetate in cyclohexane as eluent to yield 1.88 g (81%) of the ester **18e** as a colorless meringue (R_f = 0.36, eluent: 40% ethyl acetate in cyclohexane).

3-[[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptyl]-carbamoyl]benzoic Acid (19e). Following the procedure described for **5j**, ester **18e** (1.88 g, 2.4 mmol) led to 1.0 g (58%) of **19e** as a white solid: mp 154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.66 (b, J = 9 Hz, 1H, -*H* in 5), 0.75 (s, 3H, -C*H*$_3$), 0.79 (s, 3H, -C*H*$_3$), 0.93 (s, 3H, -C*H*$_3$), 0.96 (s, 6H, -C*H*$_3$), 1.57 (t, J = 11.5 Hz, 1H, -*H* in 18), 1.68 (s, 3H, -C*H*$_3$ in 29), 2.43 (dt, J = 11.5, 3 Hz, 1H, -*H* in 13), 3.05−3.35 (m, 2H, -CONH-C*H*$_2$- in 17), 3.12 (t, J = 11.5, 4 Hz, 1H, -*H* in 19), 3.17 (dd, J = 11, 5 Hz, 1H, - *H* in 3), 3.45 (bq, J = 7 Hz, 2H, -C*H*$_2$-NHCO-), 4.57 and 4.72 (2bs, 1H each, =C*H*$_2$), 5.85 (t, J = 5.5 Hz, 1H, -CON*H*- in 17), 6.90 (t, J = 7 Hz, 1H, -N*H*-CO-), 7.51 (t, J = 8 Hz, 1H, -*H* aromatic in 5), 8.08 (bd, J = 8 Hz, 1H, -*H* aromatic in 4), 8.18 (bd, J = 8 Hz, 1H, -*H* aromatic in 6), 8.46 (bs, 1H, -*H* aromatic in 6); IR (KBr, cm^{-1}) ν 3430, 3200−2250, 3075, 2940, 2870, 1720, 1640, 1600, 1525, 1385, 1375, 1040, 880, 735; MS (EI) 716, 688, 398, 305, 279, 224, 189, 166, 149 (base).

Methyl 4-[[*N*-[3*β*-Acetoxylup-20(29)-en-28-oyl]-7-aminoheptyl]carbamoyl]benzoate (18f). A solution of **17** (1.83 g, 3 mmol) in CH_2Cl_2 (100 mL) was treated successively with terephthalic acid monomethyl ester (540 mg, 3 mmol), 1-hydroxybenzotriazole (560 mg, 3.3 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (1.41 g, 7 mmol), and triethylamine (1.85 mL, 13 mmol). After further stirring for 2 h at room temperature, the mixture was concentrated to dryness under reduced pressure. To the residue were added ethyl acetate (100 mL) and distilled water (100 mL). The organic layer was separated, washed with distilled water (100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 40% ethyl acetate in cyclohexane as eluent to yield 2.06 g (89%) of the ester **18f** as a colorless meringue (R_f = 0.39, eluent: 40% ethyl acetate in cyclohexane).

4-[[*N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-7-aminoheptyl]-carbamoyl]benzoic Acid (19f). Following the procedure described for **5j**, ester **18f** (2.06 g, 2.7 mmol) led to 1.62 g (83%) of **19f** as a white solid: mp 190 °C; ^{1}H NMR ($CDCl_3$ with a few drops of CD_3OD-d_4, 400 MHz) δ 0.52 (b, J = 9 Hz, 1H, -*H* in 5), 0.59 (s, 3H, -C*H*$_3$), 0.67 (s, 3H, -C*H*$_3$), 0.78 (s, 3H, -C*H*$_3$), 0.80 (s, 3H, -C*H*$_3$), 0.83 (s, 3H, -C*H*$_3$), 1.43 (t, J = 11.5 Hz, 1H, -*H* in 18), 1.56 (s, 3H, -C*H*$_3$ in 29), 2.30 (dt, J = 11.5, 3 Hz, 1H, -*H* in 13), 2.90−3.05 (m, 2H, 1H of -CONH-C*H*$_2$- in 17, -*H* in 3), 2.96 (t, J = 11.5, 4 Hz, 1H, -*H* in 19), 3.10 (m, 1H, the other H of -CONH-C*H*$_2$- in 17), 3.28 (bq, J = 7 Hz, 2H, -C*H*$_2$-NHCO-), 4.43 and 4.57 (2bs, 1H each, =C*H*$_2$), 6.21 (t, J = 6 Hz, 1H, -CON*H*- in 17), 7.63 (t, J = 7 Hz, 1H, -N*H*-CO-), 7.70 (bd, J = 8.5 Hz, 2H, -*H* aromatics in meta of -COO-), 7.95 (bd, J = 8.5 Hz, 2H, -*H* aromatics in ortho of -COO-); IR (KBr, cm^{-1}) ν 3400, 3200−2250, 3075, 2940 and 2865, 1730, 1637, 1530, 1380 and 1375, 1040, 880; MS (EI) 716, 398, 279, 189, 149 (base), 119.

Biological Methods. Antiviral assays were done according to ref 5a for CEM 4 cells and to ref 23 for MT-4 cells

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Supporting Information Available: NMR data for compounds **5b**−**i**,**k**,**l**, **8b**−**e**, and **11i** (5 pages). Ordering information can be found on any current masthead page.

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