# Betulinic Acid Derivatives: A New Class of Human Immunodeficiency Virus Type 1 Specific Inhibitors with a New Mode of Action

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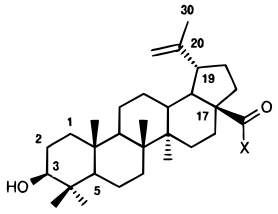
A series of $\omega$-undecanoic amides of lup-20(29)-en-28-oic acid derivatives were synthesized and evaluated for activity in CEM 4 and MT-4 cell cultures against human immunodeficiency virus type 1 (HIV-1) strain $III_B$/LAI. The potent HIV inhibitors which emerged, compounds **5a, 16a**, and **17b**, were all derivatives of betulinic acid (3$\beta$-hydroxylup-20(29)-en-28-oic acid). No activity was found against HIV-2 strain ROD. Compound **5a** showed no inhibition of HIV-1 reverse transcriptase activity with poly(C)·oligo(dG) as template/primer, nor did it inhibit HIV-1 protease. Additional mechanistic studies revealed that this class of compounds interfere with HIV-1 entry in the cells at a postbinding step.

The only approved drugs for the treatment of human immunodeficiency virus (HIV) infections are the nucleoside analogs 3′-azido-3′-deoxythymidine (AZT),[1] 2′,3′-dideoxyinosine (ddI),[2] and 2′,3′-dideoxycytidine (ddC).[3] They act through the inhibition of the HIV reverse transcriptase (RT) activity and/or by a mechanism of oligonucleotide chain termination. This noncurative treatment suffers from important limitations such as toxic side effects and the emergence of drug-resistant strains. Other approaches currently under clinical investigations include allosteric HIV-1 RT inhibitors represented by TIBO,[4a] HEPT,[4b] nevirapine,[4c] and various others (for a review, see ref 5) and HIV protease inhibitors such as Ro 31-8959[6] and A 80987,[7] as well as the TAT inhibitor Ro 24-7429[8]which was recently dropped from development. The rapid appearance of HIV-1 resistance to allosteric RT inhibitors[9] (for a commentary, see ref 9b) and the poor oral bioavailability of the first-generation HIV protease inhibitors hamper the development of these drugs. Drugs with a new mode of action are urgently needed to overcome the limitations of the current approaches.

Our discovery that *N*-[3$\beta$-hydroxylup-20(29)-en-28-oyl]glycine (betulinylglycine, **1b**) displays a weak inhibition of the HIV-1 protease (data not shown) led us to synthesize analogs of **1b** in order to improve its activity against the viral protease. No significant improvement of the antiprotease activity was achieved. However, *N*-[3$\beta$-hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoic acid ((betulinylamino)undecanoic acid, **5a**), although devoid of any activity against HIV-1 protease, was found to inhibit the cytopathogenicity of HIV-1 in CEM 4 cells at a concentration of 300 nM. From this lead, we started a program to optimize the anti-HIV-1 activity (in cell culture) by systematic alterations of the backbone of betulinic acid as well as the chain attached to carbon 28. This report deals with variations in the triterpene moiety.




**1(a-c)**

**a:** X = OH
**b:** X = $NHCH_2COOH$
**c :** X = $OCH_3$

## Chemistry

The starting materials for the synthesis of **5a**,**b** are the corresponding 3$\beta$-acetoxylup-20(29)-en-28-oic acid[10] **(2a)** and 3$\alpha$-acetoxylup-20(29)-en-28-oic acid (**2b**) obtained respectively from 3$\beta$-betulinic acid and 3$\alpha$-betulinic acid[11] (Scheme 1). Treatment with oxalyl chloride afforded acid chlorides **3a,**[12]**b**. Condensation of methyl 11-aminoundecanoate[13] with **3a**,**b** followed by saponification of the resulting esters **4a,b** gave the two stereoisomers **5a** (3$\beta$-OH) and **5b** (3$\alpha$-OH). Compounds **5e**,**f** were obtained in a similar way using methyl 11-hydroxyundecanoate[14] and methyl 11-(methylamino)-undecanoate,[15] respectively.

Betulonic acid **2c**[16] was directly converted into its acid chloride **3c** using oxalyl chloride in $CH_2Cl_2$ at room temperature. Compound **3c** led to **5c** by the same pathway as described for **5a**,**b**. The synthesis of methyl ether **5d** was achieved using **2d** as starting material. The synthesis of **2d** is described in the Experimental Section. Saponification of **4c** followed by Wolf−Kishner reduction in a mixture of *n*-BuOH/ethylene glycol (1:5) at reflux led to **5g** in 16% yield. Reductive amination of **4c** ($NH_2OH$·HCl/$NaBH_3CN$−$TiCl_3$) followed by saponification gave the 3$\beta$ amino derivative **5g**.

The two-step tosylation−elimination reaction of betulinic acid **2a** led to the 2,3-dehydro acid **6** (Scheme 2). The latter was used as starting material for the synthesis of **7b** as described above for molecule **5c**.

The synthesis of **9b** and **10b** is outlined in Scheme 3. The common starting acid **8**[17] was first treated with

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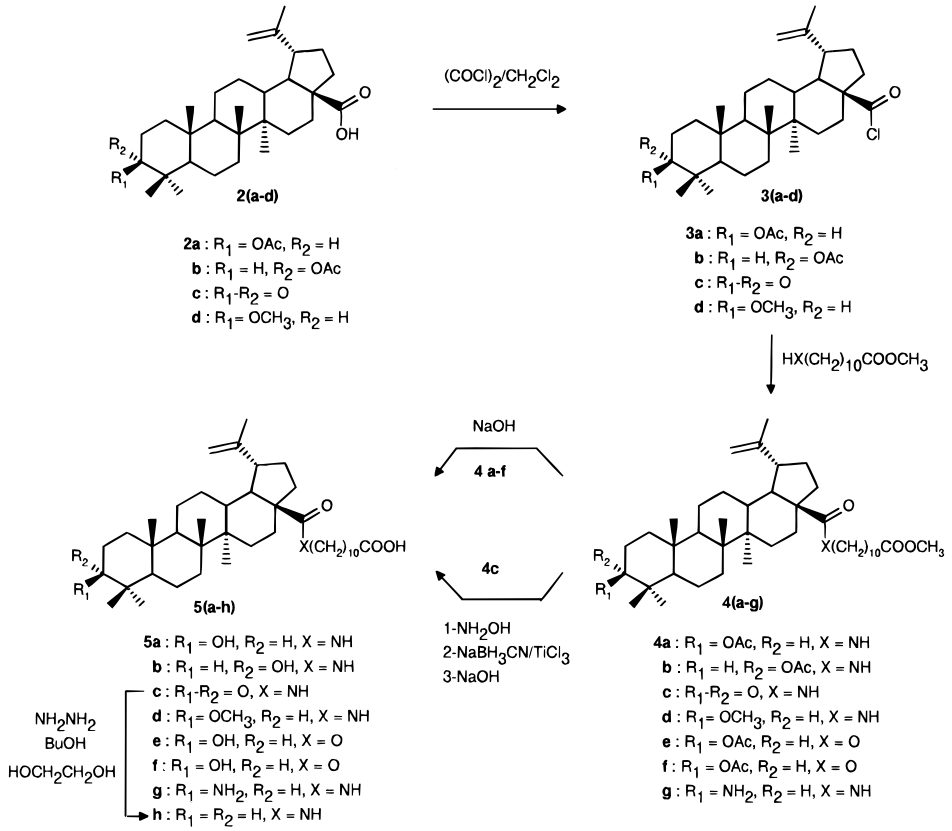
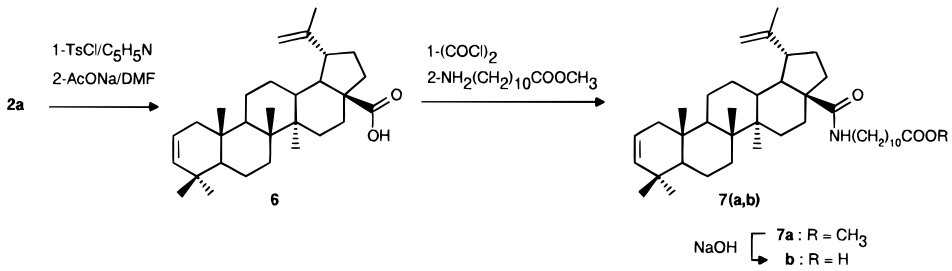
**Scheme 1**




**Scheme 2**




oxalyl chloride, and the crude acid chloride was reacted with methyl 11-aminoundecanoate to yield the ester **9a**. Saponification of **9a** gave **9b**. Further reduction of the ketone **9a** by $NaBH_3CN$ led, after saponification, to **10b**.

Scheme 4 describes the palladium-catalyzed hydrogenation of the isopropylidene moiety in **4a**. The ester **11a** was further reacted with aqueous NaOH to afford **11b** in 74% yield.

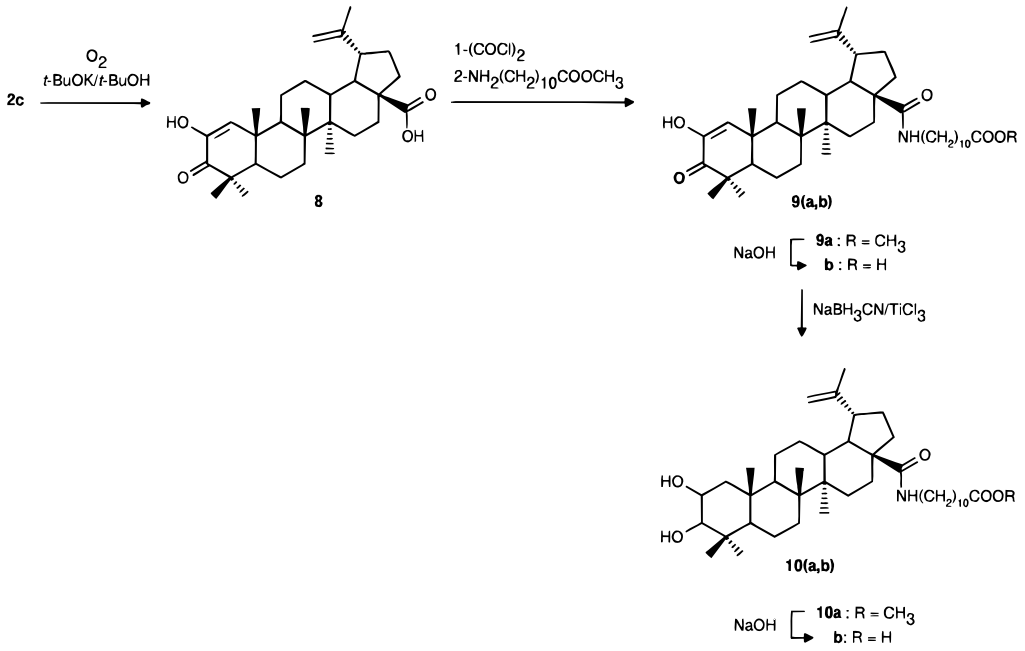
The methyl keto derivative **12** was prepared by ozonolysis of **2a** according to Vistrcil[18] and transformed as described for **2a** into the undecylic acid derivative **13b** via ester **13a.** Haloform degradation ($NaOH/Br_2$ at 5 °C) of the latter afforded the diacid **13c** (Scheme 5).

The 30-bromo compound **14**, a key intermediate for the synthesis of isopropylidene-substituted compounds depicted in Scheme 6, was obtained in quantitative yield by vinylic bromination of **4a** using *N*-bromosuccinimide in $CCl_4$. Various sulfur and nitrogen nucleophiles were introduced via the Trost—Tsuji $\pi$-allylpalladium procedure[19] leading, after saponification of the intermediate esters **15a**—**g**, to 30-substituted acids **16a**—**g**. Reaction of silver acetate with bromo compound **14**, in the presence of a catalytic amount of $Bu_4N^+Br_3^-$ in refluxing toluene, gave diacetoxy ester **17a**, which was transformed into the hydroxy acid **17b** on saponification (Scheme 6).

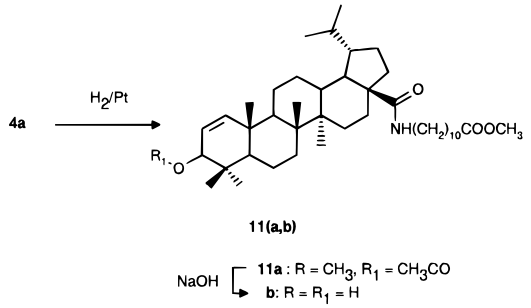
The introduction of a free amino group and an acetylamino group at position 30 was achieved via the phthalimide intermediate **18** which could be obtained from **14** and potassium phthalimide (Scheme 7). Treatment of **18** with 1.5 equiv of hydrazine in methanol at room temperature led to 30-amino diester **19a**. Saponification of **19a** gave 30-amino acid **19b** in 36% yield, whereas prior treatment with acetyl chloride followed by alkaline cleavage of both ester functions led to 30-acetylamino acid **19c**.

Modifications of the carboxyl function are described in Scheme 8. Acid chloride **3a** was treated with $NH_3$; the crude amide obtained was then reacted with iodosobenzene diacetate leading to the intermediate isocyanate **20**.[12] This isocyanate was the starting material for the synthesis of molecules **21b** and **22b**. Acidic hydrolysis of isocyanate **20** led to the corresponding amino derivative which was then reacted with methyl 11-(chloroformyl)undecanoate[20] to afford the corresponding methyl ester **21a**. Reaction of **20** with methyl 10-aminodecanoate[21] yielded the ureido compound **22a**.

**Scheme 3**




**Scheme 4**



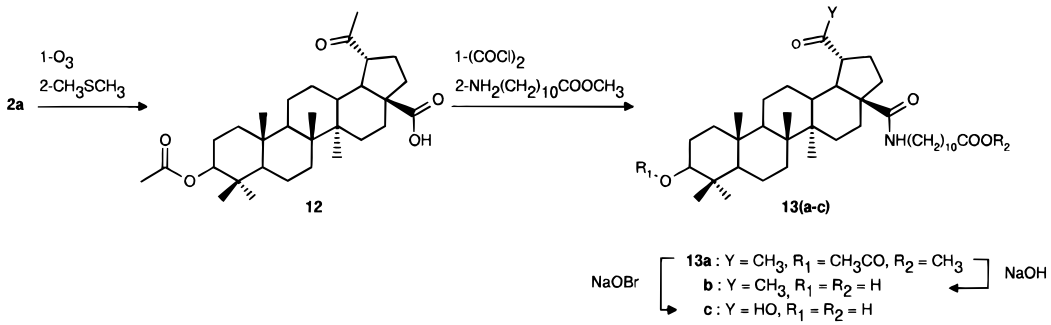

Saponification of esters **21a** and **22a** using aqueous sodium hydroxide gave the acids **21b** and **22b**. As outlined in Scheme 9, molecules **26b**,**c** were obtained from methyl betulinate (**1c**). Protection of the 3-hydroxy function of the latter as its dimethyl *tert*-butylsilyl ether followed by lithium aluminum hydride reduction gave the betulinol derivative **24** in a quantitative yield. Swern oxidation of **24** led to the aldehyde **25**. Reductive amination of the latter with methyl 11-aminoundecanoate hydrochloride and sodium cyanoborohydride afforded the dimethyl *tert*-butylsilyl-protected compound **26a.** Deprotection of the 3-hydroxy group using standard ferric chloride in a 1:1 $CH_3CN-THF$ mixture followed by saponification of the methyl ester led to **26c**.

## Results and Discussion

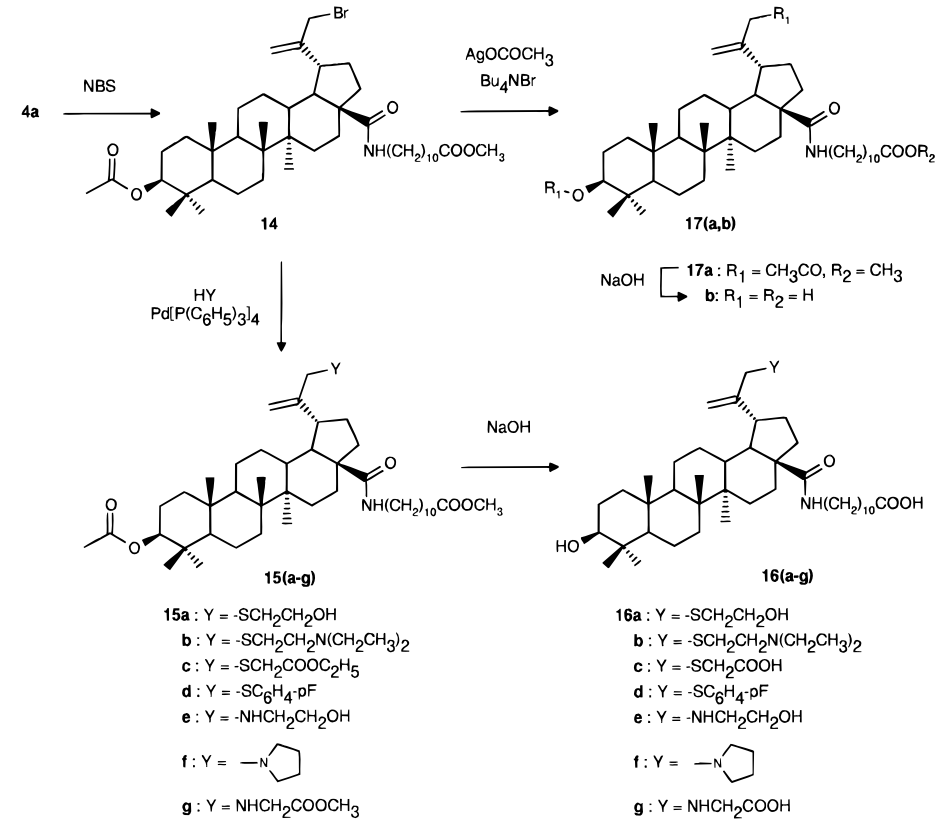
The anti-HIV-1 activity of reported triterpenes was assessed in CEM 4 and MT-4 cells, and the results are presented in Tables 1 and 2. The concentration that produced 50% protection against the cytopathogenicity ($IC_{50}$) as stated was the mean for at least two experiments. Structural variations in cycle A of the triterpene highlight the importance of the 3$\beta$-hydroxy substituent. Changing the hydroxy position from 3$\beta$ (**5a**) to 3$\alpha$ (**5b**) led to a 10-fold drop in activity. The 3-keto derivative **5c** was found of intermediate activity, whereas the 3-deoxy derivative **5g** displayed no activity at all. This points to a critical hydrogen bond interaction involving the oxygen at the 3 position, which preferentially occurs in the 3$\beta$ position (Figure 1). The 3$\beta$-methoxy (**5d**) and the 3$\beta$-amino (**5h**) derivatives were found inactive. The inactivity of **5d** might be explained by a steric hindrance due to the presence of the methyl groups at the 4 position combined to the presence of the methyl substituent on the oxygen. The introduction of a second hydroxyl at the 2 position (compound **10**) led to a complete loss of activity. Furthermore, the antiviral activities of the diketone **9b** and the 2,3-dehydro derivative **7b** were rather low. Thus, almost all chemical modifications in ring A led to considerable loss in activity.

The isopropylidene could be substituted at position

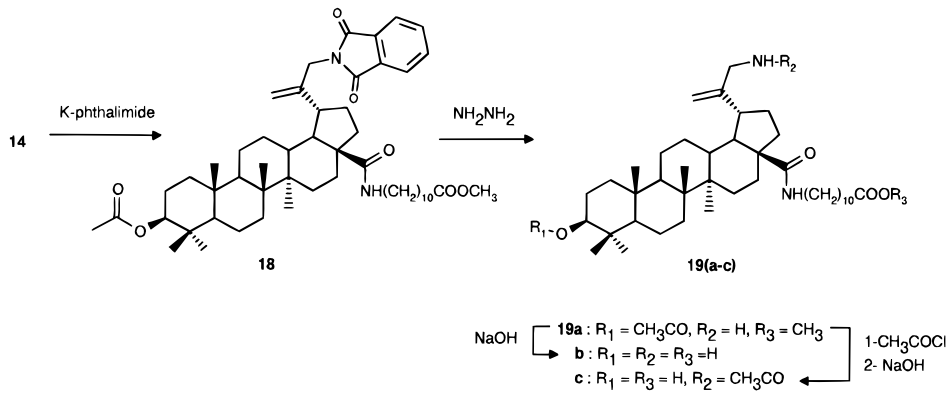
**Scheme 5**



**Scheme 6**



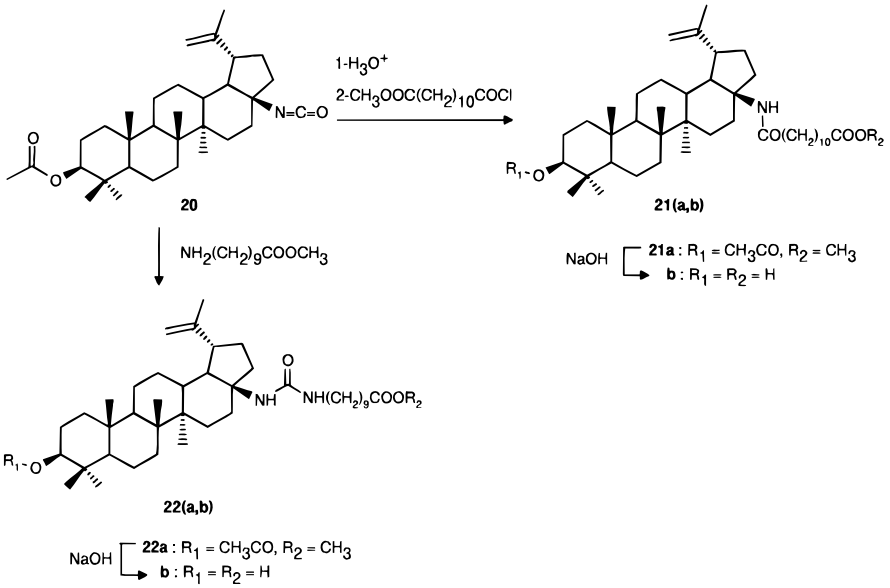

**Scheme 7**



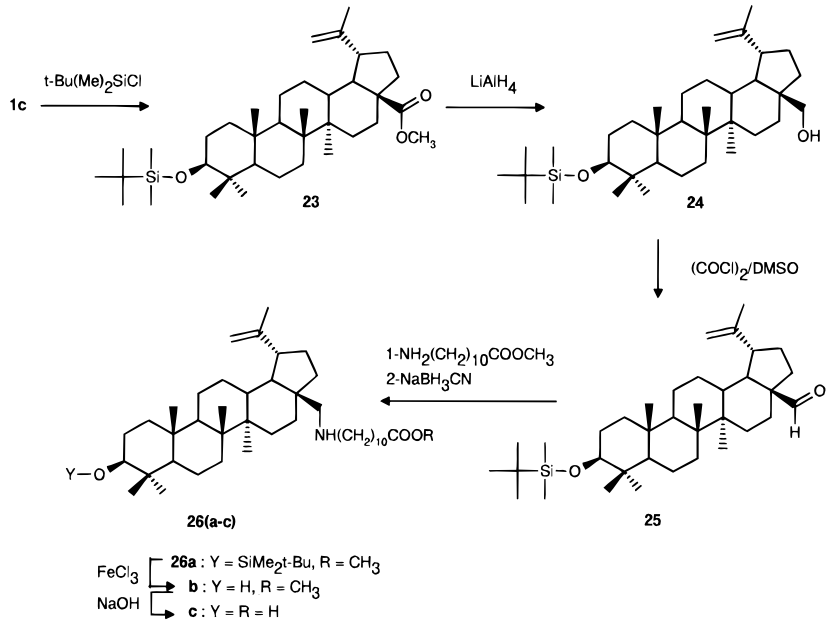

30 by different substituents. The antiviral activity of the 30-(hydroxyethyl)thio (**16a**), 30-[2-(diethylamino)-ethyl]thio (**16b**), 30-(1-pyrrolidine) (**16f**), and 30-hydroxy (**17b**) derivatives remained high but was not better than that of the unsubstituted derivative **5a**. This illustrates a lack of steric requirements by the HIV-1 molecular target for groups at position 30. However, an acidic substituent such as 30-(carboxymethyl)thio (**16c**) was clearly detrimental to potency. A similar drop of activity was observed when a secondary nitrogen was directly attached at position 30 (compounds **16e** and **19c**). The combination of a free carboxyl and a secondary amine as well as an unsubstituted amino moiety (compounds **16g** and **19b**) led to complete inactivation. An aromatic substituent (**16d**) also led to a significant drop in activity. Hydrogenation of the double bond (compound **11b**) reduced activity by 2−5-fold, and replacement of the isopropylidene at position 19 by an acetyl or a carboxyl group (compounds **13b**,**c**) led to virtually inactive molecules. In conclusion, the isopropylidene seems important for optimal activity, probably due to binding to a hydrophobic pocket. A certain lack of steric hindrance accommodates a variety of substituents without improvement of activity. However, unfavorable interactions are observed for primary and secondary amines as well as for the free carboxylic acid function.

Variations at the C28 carboxyl such as N-methylation of the amide moiety in **5f**, replacement of the amide by an ester in **5e**, and replacement of the carbonyl by a methylene in **24b** led to a complete loss of activity. Figure 2 clearly indicates that the interactions of the amide moiety with neighboring protons restrain the free rotation of the carbonyl group, predetermining its spatial orientation. The importance of a hydrogen-donating NH group is higlighted by the fact that the corresponding ester **5e** is completly inactive. This was further corroborated by the lack of biological activity of the reversed amide **21b** and the urea derivative **22b**, in which the NH group occupies a different spatial position. Furthermore, 11-aminoundecanoic amides of

**Scheme 8**




**Scheme 9**



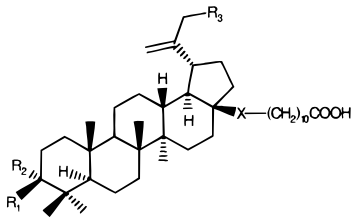

other triterpenes, such as oleanic acid and hederagine, proved to be devoid of any activity in the cellular screen (data not shown). The dramatic loss of activity for most of the modifications on the triterpene skeleton suggests a stringent specificity for these compounds.

No activity was found for the most potent inhibitors of HIV-1, namely, **5a**, **16a**, and **17b**, against the HIV-2 strain ROD. Furthermore, compound **5a** showed no inhibition in an in vitro HIV-1 RT assay using poly(C)•-olifo(dG) template/primer and did not inhibit HIV-1 protease[22] at concentrations compatible with cellular activity, suggesting a new mode of anti-HIV action for these triterpenes. From their activity pattern following addition at different times and their inhibitory effect on HIV-1-induced syncytium formation (combined with the lack of virus−cell binding inhibition), it was inferred that these compounds interfere with virus entry in the cells at a postbinding fusion step.[22]

## Experimental Section

Melting points were recorded on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were obtained on either a Brucker WM (250 MHz), a Brucker AC (300 MHz), or a Brucker AM (400 MHz) spectrometer, and proton chemical shifts are relative to tetramethylsilane as internal standard. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quadruplet, br = broad, m = multiplet. The compounds were analyzed by electronic impact (EI) on a Finnigan 3300 spectrometer at 70 eV, or by desorption chemical ionization (DCI) on a Nermag R 10.10B spectrometer using $NH_3$ as reactant gas, or by liquid secondary ion mass spectrometry (LISIMS) on a Kratos MS50 spectrometer. 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. The 3D structures were built using the X-ray structure of 19α-lupeol methyl ether[23] as registered in the Cambridge Structural database.

**Table 1.** Anti-HIV-1 Activity in CEM and MT-4 Cells




| | | | | | | | | anti-HIV-1 activity $IC_{50}$ ($\mu$M) | |
|---|---|---|---|---|---|---|---|---|---|
| no. | $R_1$ | $R_2$ | $R_3$ | X | mp, °C | formula | anal.[a] | CEM cells | MT-4 cells |
| **5a** | OH | H | H | CONH | 115 | $C_{41}H_{69}NO_4$ | C,H,N | 0.23 | 0.44 |
| **5b** | H | OH | H | CONH | 182 | $C_{41}H_{69}NO_4$ | C,H,N | 3.0 | 2.52 |
| **5c** | =O | | H | CONH | 90 | $C_{41}H_{67}NO_4$ | C,[b]H,N | 1.2 | 0.33 |
| **5d** | OMe | H | H | CONH | 100 | $C_{42}H_{71}NO_4$ | C,H,N | na | na |
| **5e** | OH | H | H | COO | 122 | $C_{41}H_{68}O_5$ | C,H,N | na | na |
| **5f** | OH | H | H | CONMe | 154 | $C_{42}H_{71}NO_4$ | C,H,[i]N | na | na |
| **5g** | H | H | H | CONH | 85 | $C_{41}H_{69}NO_3$ | C,H,N | na | nt |
| **5h** | $NH_2$ | H | H | CONH | 145 | $C_{41}H_{70}N_2O_3$ | C,[c]H,N | na | nt |
| **16a** | OH | H | $SCH_2CH_2OH$ | CONH | 180 | $C_{43}H_{73}NO_5S$ | C,[d]H,N | 0.29 | 0.27 |
| **16b** | OH | H | $SCH_2CH_2N(Et)_2$ | CONH | 145 | $C_{47}H_{82}N_2O_4S$ | C,H,N | 1.0 | 0.63 |
| **16c** | OH | H | $SCH_2COOH$ | CONH | 194 | $C_{43}H_{71}NO_6S$ | C,H,N | na | 1.61 |
| **16d** | OH | H | $SC_6H_4$-*p*-F | CONH | 146 | $C_{47}H_{72}FNO_4S$ | C,H,N | 2.0 | 1.37 |
| **16e** | OH | H | $NHCH_2CH_2OH$ | CONH | 214 | $C_{43}H_{74}N_2O_5$ | C,H,N | 5.75 | 2.0 |
| **16f** | OH | H | 1-pyrrolidinyl | CONH | 146 | $C_{45}H_{76}N_2O_4$ | C,H,[j]N | 1.0 | 0.42 |
| **16g** | OH | H | $NHCH_2COOH$ | CONH | 220 | $C_{43}H_{72}N_2O_6$ | C,H,N | na | nt |
| **17b** | OH | H | OH | CONH | 174 | $C_{41}H_{69}NO_5$ | C,[e]H,N | 0.20 | 0.38 |
| **19b** | OH | H | $NH_2$ | CONH | 220 | $C_{41}H_{70}N_2O_4$ | C,H,[k]N | na | nt |
| **19c** | OH | H | NHCOMe | CONH | 160 | $C_{43}H_{72}N_2O_5$ | C,H,[l]N | 1.25 | 0.26 |
| **21b** | OH | H | H | NHCO | 130 | $C_{41}H_{69}NO_4$ | C,[f]H,[m]N | na | na |
| **22b** | OH | H | H | NHCONH | 225 | $C_{40}H_{68}N_2O_4$ | C,[g]H,N | na | na |
| **26c** | OH | H | H | $CH_2NH$ | 182 | $C_{41}H_{71}NO_3$ | C,[h]H,[n]N | na | nt |

[a] Elemental analyses were within 0.4% of theory unless otherwise noted. [b] C: calcd, 77.19; found, 77.9. [c] C: calcd, 77.06; found, 73.4. H: calcd, 11.04; found, 11.1. N: calcd, 4.38; found, 4.0. This sample was partially a sodium salt. [d] C: calcd, 72.12; found, 71.1. [e] C: calcd, 75.07; found, 73.4. [f] C: calcd, 76.95; found, 76.3. [g] C: calcd, 74.95; found, 74.3. [h] C: calcd, 78.66; found, variable results due to incomplete combustion. [i] H: calcd, 10.94; found, 11.3. [j] H: calcd, 10.80; found, 11.6. [k] H: calcd, 10.77; found, 11.9. [l] H: calcd, 10.41; found, 11.5. [m] H: calcd, 10.87; found, 11.4. [n] H: calcd, 11.43; found, 10.7. na: not active. nt: not tested.

**Table 2.** Other Compounds

| | | | | anti-HIV-1 activity $IC_{50}$ ($\mu$M) | |
|---|---|---|---|---|---|
| no. | mp,°C | formula | anal.[a] | CEM cells | MT4 cells |
| **7b** | 82 | $C_{41}H_{67}NO_3$ | C,H,N | 1.8 | 2.6 |
| **9b** | 90 | $C_{41}H_{65}NO_5$ | C,H,N | 3.0 | nt |
| **10b** | 102 | $C_{41}H_{69}NO_5$ | C,H,N | na | nt |
| **11b** | 110−115 | $C_{41}H_{71}NO_4$ | C,H,[c]N | 1.5 | 0.58 |
| **13b** | 150 | $C_{40}H_{67}NO_5$ | C,[b]H,[d]N | 12.0 | nt |
| **13c** | 160 | $C_{39}H_{65}NO_6$ | C,H,N | 50.0 | 9.0 |

[a] Elemental analyses were within 0.4% of theory unless otherwise noted. [b] C: calcd, 74.84; found, 74.3. [c] H: calcd, 11.5; found, 12.2. [d] H: calcd, 10.52; found, 11.2.

After modifications of the structure to fit with the different derivatives, energy minimization using Chem-X (Chemical Design Ltd., Oxford) and/or Insight (Biosym Technologies Inc., San Diego) was performed.

**General Procedure: Methyl *N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoate (4a).** To a solution of 3*β*-acetoxylup-20(29)-en-28-oyl chloride[12] (**3a**) (1.03 g, 2 mmol) in $CH_2Cl_2$ (30 mL) at room temperature was added dropwise a solution of methyl 11-aminoundecanoate hydrochloride (0.58 g, 2.3 mmol) in $CH_2Cl_2$ (30 mL), followed by triethylamine (0.62 mL, 4.45 mmol). The resulting solution was stirred for 16 h, diluted with $CH_2Cl_2$ (50 mL), washed twice with water, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with diisopropyl oxide to give 1.29 g (98.6%) of **4a** as a white meringue ($R_f$ = 0.31, eluent 15% ethyl acetate in cyclohexane).

**General Procedure: *N*-[3*β*-Hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5a).** To a solution of methyl *N*-[3*β*−hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoate (**4a**) (1.28 g, 1.96 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (20 mL) was added aqueous NaOH (4 N, 4.5 mL). After stirring for 24 h and concentrating the solution in vacuo, the residue was suspended in distilled water (60 mL). The suspension was treated with aqueous 5 N hydrochloric acid (3.6 mL). After 20 min, the suspension was filtered, washed with distilled water to pH 7, and dried to yield 1.2 g (98%) of **5a** as a white solid: mp 115 °C; $^1$H-NMR ($CDCl_3$, 400 MHz) (ppm) 0.67 (br d, $J$ = 9 Hz, 1H, -*H* in 5), 0.76 (s, 3H, -C$H_3$),

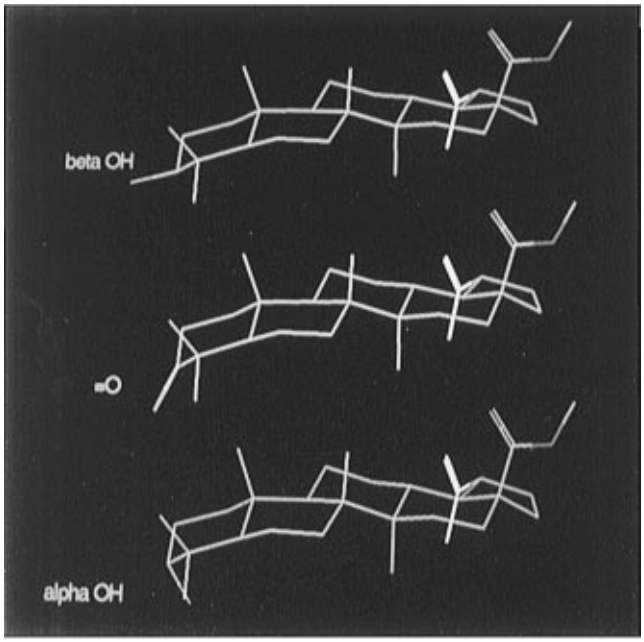



**Figure 1.** Three-dimensional structure of methyl 3*β*-hydroxy- and methyl 3α-hydroxybetulinate and methyl betulonate.

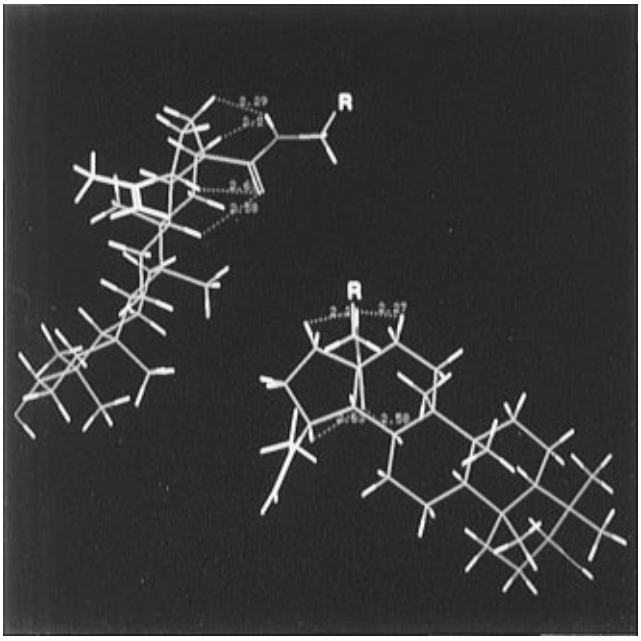


**Figure 2.** Molecular models of the interactions between the 28-amide moiety and neighboring protons.

0.82 (s, 3H, -C$H_3$), 0.93 (s, 3H, -C$H_3$), 0.98 (s, 6H, -C$H_3$), 1.56 (t, $J$ = 11.5 Hz, 1H, C$H$ in 18), 1.70 (s, 3H, -C$H_3$ in 29), 2.36 (t, $J$ = 7.5 Hz, 2H, -C$H_2$-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-C$H_2$-), 3.20 (dd, $J$ = 11, 5 Hz, 1H, C$H$ in 3), 4.59 and 4.74 (2br s, 1H each, =C$H_2$), 5.60 (t, $J$ = 5.5 Hz, 1H, -CON$H$-); IR (KBr, cm$^{-1}$) $\nu$ 3390, 3250−2250, 3075, 2925, 2855, 1710, 1640, 1515, 1465, 1450, 1385, 1045, 1035, 808; MS(EI) 639, 611, 596, 203, 189, 81 (base).

**Methyl *N*-[3α-Acetoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (4b).** A solution of 3α-acetoxylup-20(29)-en-28-oic acid **(2b)**[11] (437 mg, 0.97 mmol) in $CHCl_3$ (14 mL) and oxalyl chloride (0.184 mL, 2.10 mmol) was stirred at room temperature for 18 h. The mixture was concentrated in vacuo, cyclohexane (20 mL) was added to the residue, and the mixture was evaporated under reduced pressure. This was repeated twice to yield 453 mg of crude 3α-acetoxylup-20(29)-en-28-oyl chloride (**3b)** which was reacted with methyl 11-aminoundecanoate hydrochloride as described for **4a**. The residue was purified by column chromatography on silica gel eluting with 15% ethyl acetate in cyclohexane to give 810 mg (98.5%) of **4b** as a white meringue ($R_f$ = 0.25, eluent 15% ethyl acetate in cyclohexane).

***N*-[3α-Hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5b).** To a solution of methyl *N*-[3α-acetoxylup-20-(29)-en-28-oyl]-11-aminoundecanoate **(4b)** (400 mg, 0.575 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (10.5 mL) was added aqueous NaOH (4 N, 4.8 mL). After the solution was stirred for 24 h and concentrated in vacuo, the residue was suspended in distilled water (35 mL). The suspension was treated with aqueous hydrochloric acid (4 N, 6.8 mL), and after 20 min, the suspension was filtered, washed with distilled water to pH 7, and dried to yield 290 mg (78%) of **5b** as a white solid: mp 182 °C; IR (KBr, cm$^{-1}$) $\nu$ 3400, 3200−2250, 3075, 2940, 2860, 1710 ($\nu_{CO}$ acid), 1525, 1455, 1065, 885; MS(EI) 639 (base), 624, 611, 596, 203, 189.

**Methyl *N*-[3-Oxolup-20(29)-en-28-oyl]-11-aminoundecanoate (4c).** 3-Oxolup-20(29)-en-28-oyl chloride (**3c**), prepared from 3-oxolup-20(29)-en-28-oic acid[16] (**2c**) (1g, 2.2 mmol) and oxalyl chloride (0.290 mL, 3.3 mmol), was treated with methyl 11-aminoundecanoate hydrochloride (553 mg, 2.2 mmol) as described for **4a**. The residue was purified by two subsequent chromatographies on silica gel using respectively 2% methanol in $CH_2Cl_2$ and 10% ethyl acetate in $CH_2Cl_2$ as eluents to yield 600 mg (60%) of **4c** as a white meringue ($R_f$ = 0.77, eluent 2% methanol in $CH_2Cl_2$).

***N*-[3-Oxolup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5c).** Following the procedure described for **5a**, methyl *N*-[3-oxolup-20(29)-en-28-oyl]-11-aminoundecanoate (**4c**) (600 mg, 0.92 mmol) led to a gummy solid which was extracted twice with ethyl acetate (25 mL). The organic solution was washed with distilled water, dried over sodium sulfate, filtered, and concentrated in vacuo to yield 340 mg (58%) of **5c** as a white powder: mp 90 °C; IR (KBr, cm$^{-1}$) $\nu$ 3400, 3200−2250, 3075, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1640, 1525, 1460, 885; MS(EI) 637, 609, 594, 409, 189, 69 (base).

**3β-Methoxylup-20(29)-en-28-oic Acid (2d).** To a solution of betulinic acid (**1a**) (0.8 g, 1.75 mmol) in dry THF (30 mL) was added portionwise a 60% slurry of NaH in mineral oil (0.3 g, 7.5 mmol). The resulting mixture was stirred at room temperature for 1 h and then heated at reflux for 1 h. After cooling to 40 °C, $CH_3I$ (1.2 mL, 19 mmol) was added, and the resulting solution was heated at reflux for 16 h. After cooling to room temperature, an additional portion of NaH in oil (0.3 g) and $CH_3I$ (3 mL) was added and the mixture heated at reflux for an additional 24 h. At this point, the reaction was complete. Distilled water (10 mL) was added dropwise, and the solvent was removed. The residue was then dissolved in $CH_2Cl_2$ (100 mL), and the solution was washed with distilled water (5 × 40 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with $CH_2Cl_2$ to give 0.82 g (97%) of methyl 3β-methoxylup-20(29)-en-28-oate as a white solid melting at 198 °C.

A solution of methyl 3β-methoxylup-20(29)-en-28-oate (1 g, 2.06 mmol) and dry LiI (4 g) in collidine (160 mL) was heated at reflux under nitrogen during 7 h. The collidine was concentrated in vacuo, and the residue was treated with distilled water (150 mL). The pH was adjusted to 2 using aqueous HCl (5 N), and the product was extracted with ethyl acetate (3 × 100 mL). The organic phase was washed with distilled water, dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a semisolid orange residue which was purified by column chromatography eluting with $CH_2Cl_2$ to yield 800 mg of **2d** (82%) as a white meringue: mp 300 °C.

**Methyl *N*-[3β-Methoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (4d).** 3β-Methoxylup-20(29)-en-28-oyl chloride (**3d**), prepared from 3β-methoxylup-20(29)-en-28-oic acid (**2d)** (900 mg, 1.91 mmol) and thionyl chloride (0.7 mL) in $CH_2Cl_2$, was treated with methyl 11-aminoundecanoate hydrochloride (600 mg, 2 mmol) in the presence of triethylamine (0.67 mL) as described for **4a**. The residue was purified by column chromatography on silica gel using $CH_2Cl_2$ as eluent to yield 1.3 g (100%) of **4d** as a resin ($R_f$ = 0.49, 20% ethyl acetate in cyclohexane).

***N*-[3β-Methoxylup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5d).** Following the procedure described for **5a**, methyl *N*-[3β-methoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (**4d**) (1.1g, 1.64 mmol) led to 950 mg (88.2%) of **5d** as a white powder: mp 100 °C; IR (KBr, cm$^{-1}$) $\nu$ 3400, 3125−2250, 3075, 2935, 2860, 2825, 1710 ($\nu_{CO}$ acid), 1640 ($\nu_{CO}$ amide), 1525, 1465, 1455, 1390, 1375, 885; MS(DCI) 654, 121, 119, 69 (base).

**Methyl 11-[[3β-Acetoxylup-20(29)-en-28-oyl]oxy]undecanoate (4e).** Crude acid chloride[12] **3a**, prepared from 3β-acetoxylup-20(29)-en-28-oic acid (**2a**) (920 mg, 1.8 mmol) and oxalyl chloride (0.2 mL, 2.2 mmol), was treated with methyl 11-hydroxyundecanoate[14] as described for **4a**. The residue was purified by column chromatography on silica gel using 1% ethyl acetate in $CH_2Cl_2$ as eluent to yield 550 mg (44%) of **4e** as a colorless oil ($R_f$ = 0.35, 1% ethyl acetate in $CH_2Cl_2$).

**11-[3β-Hydroxylup-20(29)-en-28-oyl]oxy]undecanoic Acid (5e).** Following the procedure described for **5a**, methyl 11-[[3β-acetoxylup-20(29)-en-28-oyl]oxy]undecanoate **(4e)** (500 mg, 0.72 mmol) led to 420 mg (91%) of **5e** as a white solid: mp 122 °C; IR (KBr, cm$^{-1}$) $\nu$ 3430, 3075, 2940, 2855, 2750, 1725 ($\nu_{CO}$ acid), 1640, 1465, 1455, 1390, 1375, 1045, 1035, 885; MS(DCI) 658 (base), 641; MS(EI) 623, 411, 203, 189 (base).

**Methyl *N*-[3β-Acetoxylup-20(29)-en-28-oyl]-*N*-methyl-11-aminoundecanoate (4f).** Following the procedure described for **4a**, crude acid chloride[12] **3a** (1 g, 2 mmol) was reacted with methyl 11-(methylamino)undecanoate[15] (0.54 g, 2 mmol) and triethylamine (0.8 mL) to yield an oil (1.2 g). The crude oil was purified by two subsequent column chromatog-

raphies on silica gel eluting with 10% ethyl acetate in cyclohexane followed by 1% ethyl acetate in $CH_2Cl_2$ for the second column yielding 250 mg (18%) of **4f** as a colorless oil ($R_f$ = 0.5, eluent 10% ethyl acetate in cyclohexane).

***N*-[3$\beta$-Hydroxylup-20(29)-en-28-oyl]-*N*-methyl-11-aminoundecanoic Acid (5f).** Following the procedure described for **5a**, methyl *N*-[3$\beta$-acetoxylup-20(29)-en-28-oyl]-*N*-methyl-11-aminoundecanoate **(4f)** (230 mg, 0.32 mmol) led to 200 mg (94.3%) of **5f** as a white powder: mp 154 °C; IR (KBr, $cm^{-1}$) $\nu$ 3430, 3070, 2930, 2855, 2750−2250, 1710 ($\nu_{CO}$ acid), 1630, 1610 ($\nu_{CO}$ amide), 1465, 1455, 1390, 1375, 1040, 880; MS(EI) 653 (base), 638, 625, 411, 189.

**Methyl *N*-[3$\beta$-Aminolup-20(29)-en-28-oyl]-11-aminoundecanoate (4g).** A solution of methyl *N*-[3-oxolup-20(29)-en-28-oyl]-11-aminoundecanoate (**4c**) (500 mg, 0.77 mmol) in pyridine (10 mL) and hydroxylamine hydrochloride (110 mg, 1,54 mmol) was heated for 45 min at 112 °C. After cooling to room temperature, distilled water (125 mL) was added and the residue extracted with ethyl acetate (4 × 35 mL). The combined organic layers were washed with distilled water (3 × 35 mL), dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 20% ethyl acetate in cyclohexane to yield to 200 mg (39%) of the corresponding oxime.

A solution of the crude oxime (190 mg, 0.28 mmol) and ammonium acetate (216 mg, 4 mmol) in $CH_3OH$ (25 mL) was treated with solid sodium cyanoborohydride (250 mg, 4 mmol). The medium was cooled to 10 °C, 15% aqueous titanium trichloride (0.86 mL, 0.84 mmol) was added dropwise over 5 min, and the mixture was left at room temprature for 12 h. Aqueous sodium hydroxide was added until pH = 10, followed by addition of $CH_2Cl_2$ (180 mL). The organic layer was washed to neutrality with distilled water, dried over magnesium sulfate, filtered, and evaporated in vacuo to give 160 mg (88%) of **4g** as a white meringue which was used in the next step without further purification.

***N*-[3$\beta$-Aminolup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5g).** A solution of methyl *N*-[3$\beta$-aminolup-20(29)-en-28-oyl]-*N*-methyl-11-aminoundecanoate (**4g**) (150 mg, 0.23 mmol) and aqueous sodium hydroxide (5 N, 0.05 mL) in $C_2H_5OH$ (11 mL) was stirred at room temperature for 15 h. The solution was evaporated under reduced pressure and the residue triturated with distilled water (3 mL). The solid was filtered, washed with distilled water (5 × 2 mL), dried, and washed with ethyl acetate (2 × 2 mL) to yield 110 mg (73%) of **5g** as a white powder: mp 145 °C; IR (KBr, $cm^{-1}$) $\nu$ 3400, 3100 to 2250, 3075, 2930, 2865, 1710 ($\nu_{CO}$ acid), 1640, 1525, 1465, 1455, 1385, 1375, 885; MS (LSIMS/glycerol) 639 (base), 622.

***N*-[Lup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (5h).** To a solution of *N*-[3-oxolup-20(29)-en-28-oyl]-11-aminoundecanoic acid (**5c**) (480 mg, 0.75 mmol) in a mixture of *n*-butanol (10 mL) and ethylene glycol (50 mL) was added hydrazine hydrate (0.36 mL, 0.75 mmol). The mixture was heated at 130 °C for 3h and allowed to cool to room temperature. Potassium hydroxide (3.4 g, 61 mmol) was added. *n*-Butanol was distilled off; then the medium was heated at 210 °C for 3h. The medium was allowed to cool to room temperature; distilled water (20 mL) was added under stirring followed by acidification to pH = 1 using aqueous hydrochloric acid (4 N, 10 mL). The solid obtained was filtered, dried, and purified by column chromatography on silica gel using 35% ethyl acetate in cyclohexane to yield crude **5g** which was triturated in a mixture of $C_2H_5OH$ and distilled water to yield 123 mg of **5h** (27%) as a white powder: mp 85 °C; IR (KBr, $cm^{-1}$) $\nu$ 3390, 3200−2250, 3070, 2930, 2855, 1640 ($\nu_{CO}$ acid), 1540, 1470, 1455, 1390, 1375, 885; MS(DCI) 623 (base).

**Lupa-2(3),20(29)-dien-28-oic Acid (6).** To a solution of betulinic acid[1a] (5 g, 10.9 mmol) in pyridine (50 mL) was added *p*-toluenesulfonyl chloride (4.6 g, 24 mmol), and the yellow solution was stirred for 24 h at room temperature. An additional amount of *p*-toluensulfonyl chloride (2.3 g, 12 mmol) was added. After additional stirring for 24 h at room temperature, water (150 mL) was added. The white solid (7.33 g) that precipitated was collected by filtration and used in the next step without further purification.

Sodium acetate was added to a solution of this white solid in DMF (360 mL), and the mixture was heated at 120 °C for 6 h. The solvent was evaporated in vacuo, and the creamy residue was treated with water (200 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate in cyclohexane to yield 3.45 g (71%) of **6**: mp 225 °C.

**Methyl *N*-[Lupa-2(3),20(29)-dien-28-oyl]-11-aminoundecanoate (7a).** Lupa-2(3),20(29)-dien-28-oyl chloride, prepared from lupa-2(3),20(29)-dien-28-oic acid (**6**) (500 mg, 1.14 mmol) and oxalyl chloride (0.2 mL), was treated with 11-aminoundecanoate hydrochloride (0.33 g, 1.31 mmol) and triethylamine (0.38 mL) as described for **4a**. The residue was purified by column chromatography on silica gel using 2% ethyl acetate in $CH_2Cl_2$ as eluent to yield 0.58 g (80%) of **7a** as a white gum ($R_f$ = 0.46, eluent 2% ethyl acetate in $CH_2Cl_2$).

***N*-[Lupa-2(3),20(29)-dien-28-oyl]-11-aminoundecanoic Acid (7b).** Following the procedure described for **5a**, methyl *N*-[lupa-2(3),20(29)-dien-28-oyl]-11-aminoundecanoate **(7a)** (470 mg, 0.74 mmol) led to 460 mg of crude **7b** which was purified by column chromatography on silica gel eluting with 35% ethyl acetate in cyclohexane yielding 430 mg (89%) of **7b** as a white solid: mp 82 °C; IR (KBr, $cm^{-1}$) $\nu$ 3420, 3125−2500, 3070, 2940, 2875, 1750 ($\nu_{CO}$ acid), 1650 ($\nu_{CO}$ amide), 1530, 1465, 1450, 1390, 1375, 890; MS(DCI) 622(base); MS(EI) 607, 594, 579, 393, 189 (base).

**2,3-Dioxolup-20(29)-en-28-oic Acid (8).** Oxygen was passed through a solution of 3-oxolup-20(29)-en-28-oic acid (**2c**) (5.27 g, 11.6 mmol) and potassium *tert*-butylate (3.48 g, 31 mmol) in *tert*-butyl alcohol (248 mL) at room temperature during 1 h. Then aqueous HCl (0.1 N, 31 mL) was added. After stirring for 15 min, the insoluble material was filtered off and the filtrate was concentrated in vacuo. The residue was treated three times with cyclohexane (50 mL) and concentrated in vacuo to dryness. The residue was purified by column chromatography on silica gel eluting with 20% ethyl acetate in cyclohexane to yield 3.3 g (61%) of **8** as a yellow meringue ($R_f$ = 0.35, eluent 20% ethyl acetate in cyclohexane).

**Methyl *N*-[2,3-Dioxolup-20(29)-en-28-oyl]-11-aminoundecanoate (9a).** 2,3-Dioxolup-20(29)-en-28-oyl chloride, prepared from 2,3-dioxolup-20(29)-en-28-oic acid (**8**) (2 g, 4.26 mmol) and oxalyl chloride (0.72 mL, 8.4 mmol), was treated with 11-aminoundecanoate hydrochloride (1.16 g, 4.6 mmol) and triethylamine (1.3 mL) as described for **4a**. The residue was purified by column chromatography on silica gel using 3% ethyl acetate in $CH_2Cl_2$ as eluent to yield 0.94 g (33.1%) of **9a** as a white gum ($R_f$ = 0.74, eluent 10% ethyl acetate in $CH_2Cl_2$).

***N*-[2,3-Dioxolupa-20(29)-en-28-oyl]-11-aminoundecanoic Acid (9b).** Following the procedure described for **5a**, methyl *N*-[2,3-dioxolup-20(29)-en-28-oyl]-11-aminoundecanoate (**9a**) (470 mg, 0.7 mmol) led to 420 mg of crude **9b** which was purified by column chromatography on silica gel using 5% methanol in chloroform yielding 234 mg (51%) of **9b** as a white meringue: mp 90 °C; IR (KBr, $cm^{-1}$) $\nu$ 3455, 3325−2375, 3070, 2930, 2850, 1710 ($\nu_{CO}$ acid), 1650, 1500, 1455, 1380, 1235, 890; MS(EI) 651, 636, 624, 189, 121 (base).

**Methyl *N*-[2$\beta$,3$\beta$-Dihydroxylup-20(29)-en-28-oyl]-11-aminoundecanoate (10a).** To a solution of methyl *N*-[2,3-dioxolup-20(29)-en-28-oyl]-11-aminoundecanoate (**9a**) (400 mg, 0.6 mmol) in methanol (50 mL) were added $NaBH_3CN$ (280 mg, 4.45 mmol) and $TiCl_4$ (3.8 mL, 4.47 mmol). The resulting dark blue solution was stirred at room temperature for 48 h. Water (100 mL) and ethyl acetate (150 mL) were added, and the organic phase was washed with water, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 33% ethyl acetate in $CH_2Cl_2$ yieding 130 mg (32.3%) of **10a** as a white meringue ($R_f$ = 0.13, eluent cyclohexane−ethyl acetate−dichloromethane, 7:2:1).

***N*-[2*β*,3*β*-Dihydroxylup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (10b).** Following the procedure described for **5a**, methyl *N*-[2*β*,3*β*-dihydroxylup-20(29)-en-28-oyl]-11-aminoundecanoate (**10a**) (120 mg, 0.179 mmol) led to 87 mg (74%) of **10b** as a white powder: mp 102 °C; IR(KBr, $cm^{-1}$) $\nu$ 3415, 3150, 2250, 3075, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1635 ($\nu_{CO}$ amide), 1520, 1460, 1390, 1375, 1055, 1045, 885; MS(DCI) 656 (base); MS(EI) 641, 627 (base), 612, 427, 203, 121, 119.

**Methyl *N*-(3*β*-Acetoxylupan-28-oyl)-11-aminoundecanoate (11a).** A solution of methyl *N*-[3*β*-hydroxylup-20(29)-en-28-oyl]-11-aminoundecanoate (**4a)** (1 g, 1.44 mmol) in methanol (50 mL) was hydrogenated at 1 atm and room temperature over 0.1 g of Pd/C. After 2 h, the catalyst was filtered off and the solution concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 10% $CH_2Cl_2$ and 10% ethyl acetate in cyclohexane to yield 600 mg (59.7%) of **11a** as a colorless syrup ($R_f$ = 0.51, eluent 20% ethyl acetate in cyclohexane).

***N*-(3*β*-Hydroxylupan-28-oyl)-11-aminoundecanoate (11b).** Following the procedure described for **5a**, methyl *N*-(3*β*-acetoxylupan-28-oyl)-11-aminoundecanoate (**4a)** (600 mg, 0.859 mmol) led to 410 mg (74%) of **11b** as a white solid: mp 110−115 °C; IR (KBr, $cm^{-1}$) $\nu$ 3400, 3150−2125, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1640 ($\nu_{CO}$ amide), 1520, 1465−1450, 1380, 1370, 1045; MS(EI) 641, 626 (base), 420.

**3*β*-Acetoxy-30-nor-20-oxolupan-28-oic Acid (12).**[18] Ozonized oxygen was passed in a solution of 3*β*-acetoxylup-20-(29)-en-28-oic acid (**2a**) (5 g, 10 mmol) and methanol (0.6 mL, 15 mmol) in $CH_2Cl_2$ (200 mL) and cooled to −60 °C until the characteristic blue color of Ozone appeared. After stirring for 30 min at −60 °C, dimethyl sulfide (3.0 mL, 41 mmol) was added and the resulting solution was allowed to slowly warm to room temperature. After stirring for 12 h at room temperature, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 25% ethyl acetate in cyclohexane to give 3.9 g of crude **12**. Triturating with diisopropyl ether (25 mL) yielded 3.3 g (66%) of **12** as a white solid: mp >250 °C.

**Methyl *N*-(3*β*-Acetoxy-30-nor-20-oxolupan-28-oyl)-11-aminoundecanoate (13a).** 3*β*-Acetoxy-30-nor-20-oxolupan-28-oyl chloride, prepared from 3*β*-acetoxy-30-nor-20-oxolupan-28-oic acid **(12)**[18] (3.5 g, 6.96 mmol) and oxalyl chloride (1.5 mL), was treated with methyl 11-aminoundecanoate hydrochloride (1.94 g, 7.7 mmol) and triethylamine (2.2 mL) as described for **4a**. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in cyclohexane as eluent to yield 4.75 g (98%) of **13a** as a white meringue ($R_f$ = 0.28, eluent 5% MeOH in $CH_2Cl_2$).

***N*-(3*β*-Hydroxy-30-nor-20-oxolupan-28-oyl)-11-aminoundecanoic Acid (13b).** Following the procedure described for **5a**, methyl *N*-(3*β*-acetoxy-30-nor-20-oxolupan-28-oyl)-11-aminoundecanoate (**13a**) (700 mg, 1 mmol) led to 650 mg of crude **13b** which was purified by column chromatography on silica gel eluting with 50% ethyl acetate in cyclohexane to give an oily residue. Triturating with a mixture of THF (3 mL) and isopropyl oxide (16.5 mL) led to 500 mg (78%) of **13b** as a white solid: mp 150 °C; IR (KBr, $cm^{-1}$) $\nu$ 3400, 3125, 2250, 2930, 2855, 1710 ($\nu_{CO}$ acid), 1630, 1640 ($\nu_{CO}$ amide), 1530, 1465, 1455, 1390, 1375, 1045; MS(EI) 641, 599, 582, 189, 81, 43 (base).

***N*-(19-Carboxy-3*β*-hydroxy-20,29,30-trinorlupan-28-oyl)-11-aminoundecanoic Acid (13c).** To a solution of methyl *N*-(3*β*-acetoxy-30-nor-20-oxolupan-28-oyl)-11-aminoundecanoate (**13a)** (2.3 g, 3.3 mmol) in dioxane (50 mL) cooled to 10 °C was added dropwise in 10 min a solution of sodium hypobromide obtained by mixing sodium hydroxide (2.6 g, 64 mmol), bromine (0.7 mL, 13 mmol), dioxane (12 mL), and distilled water (18 mL) at 5 °C. After stiring for 12 h at room temperature, sodium sulfite (500 mg, 4.85 mmol) in distilled water (5 mL) was added. The mixture was acidified to pH = 1 with aqueous hydrochloric acid (4 N) and diluted with distilled water (50 mL). The precipitate was filtered, washed successively with distilled water (50 mL), dioxane (2 mL), and diethyl ether (10 mL), and then dried to yield 800 mg (38%) of **13c** as a white solid: mp 160 °C; IR(KBr, $cm^{-1}$) $\nu$ 3400, 3250−2250, 2930, 2855, 1710 ($\nu_{CO}$ acid), 1640 ($\nu_{CO}$ amide), 1525, 1465, 1455, 1390, 1375, 1045, 1030; MS(EI) 643, 328, 610, 189 (base), 81, 69.

**Methyl *N*-[3*β*-Acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (14).** A suspension of methyl *N*-[3*β*-acetoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (**4a**) (10.4 g, 15 mmol) and *N*-bromosuccinimide (5.3 g, 30 mmol) in $CCl_4$ (300 mL) was stirred for 72 h at room temperature. The solid was filtered, and the filtrate was concentrated in vacuo to yield 11.7 g (100%) of **14** as a white meringue contaminated with 5−10% of the corresponding bromovinylic compounds ($R_f$ = 0.32, eluent 20% ethyl acetate in cyclohexane). This was used without further purification.

**General Procedure: Methyl *N*-[3*β*-Acetoxy-30-[(2′-hydroxyethyl)thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (15a).** To a solution of palladium acetate (180 mg, 0.8 mmol) and triphenylphosphine (840 mg, 3.2 mmol) in THF (25 mL) was added triethylamine (0.112 mL, 0.8 mmol). After stirring at room temperature for 30 min, the yellow-orange resulting suspension was added to a solution of methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (3.2 g, 4 mmol) and 2-mercaptoethanol (0.56 mL, 8 mmol) in THF (100 mL). After heating at reflux for 144 h, the mixture was allowed to cool to room temperature, and $CH_2Cl_2$ (200 mL) was added. The organic phase was washed with distilled water (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in cyclohexane as eluent to yield 1.85 g (60%) of **15a** as a white meringue ($R_f$ = 0.68, eluent 40% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxy-30-[(2′-hydroxyethyl)thio]lup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (16a).** Aqueous NaOH (5 N, 23 mL) was added to a solution of methyl *N*-[3*β*b-acetoxy-30-[(2′-hydroxyethyl)thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (**15a)** (1.80 g, 2.33 mmol) in a 1:1 mixture of $CH_3OH$ and THF (140 mL). After stirring for 24 h, the mixture was acidified to pH = 2 by aqueous hydrochloric acid (4 N). Distilled water (500 mL) was added. After stirring at room temperature for 2 h, the solid was filtered, washed with distilled water (6 × 30 mL), and recrystallized from a 3:7 mixture of distilled water and $CH_3OH$ (50 mL) to yield 1.30 g (78%) of **16a** as white crystals: mp 180 °C; IR (KBr, $cm^{-1}$) $\nu$ 3390, 3125−2250, 3075, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1630 ($\nu_{CO}$ amide), 1535, 1470, 1450, 1390, 1375, 1040, 1030, 900; MS-(DCI) 716 (base), 698, 640; MS(EI) 638, 203, 189, 44 (base).

**Methyl *N*-[3*β*-Acetoxy-30-[[(2,2-diethylamino)ethyl]-thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (15b).** Following the procedure described for **15a**, methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (1.0 g, 1.3 mmol) and (2,2-diethylamino)ethanethiol (0.39 mL, 2.6 mmol) led to a residue which was purified by column chromatography on silica gel using 5% $CH_3OH$ in $CH_2Cl_2$ as eluent to yield 600 mg (60%) of **15b** as a white meringue ($R_f$ = 0.21, eluent 5% MeOH in $CH_2Cl_2$).

***N*-[3*β*-Hydroxy-30-[[(2,2-diethylamino)ethyl]thio]lup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (16b).** Aqueous NaOH (5 N, 3.6 mL) was added to a solution of methyl *N*-[3*β*-acetoxy-30-[[(2,2-diethylamino)ethyl]thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (**15b**) (600 mg, 0.72 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (30 mL). After stirring for 72 h at room temperature, the solution was concentrated in vacuo. Distilled water (25 mL) was added to the residue; the suspension was acidified to pH = 2 by aqueous hydrochloric acid (4 N) and extracted with $CH_2Cl_2$ (4 × 20 mL). The organic layer was washed with distilled water (5 × 10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with diisopropyl ether (15 mL) to yield 350 mg of **16b** (63%) as a white solid: mp 145 °C; IR (KBr, $cm^{-1}$) $\nu$ 3415, 3125− 2250, 3075, 2930, 2860, 1720 ($\nu_{CO}$ acid), 1635 ($\nu_{CO}$ amide), 1525, 1465, 1455, 1390, 1375, 1045, 890; MS(FAB, *p*-nitrobenzyl alchohol) 771 (base), 638, 542.

**Methyl *N*-[3*β*-Acetoxy-30-[[(ethoxycarbonyl)methyl]-thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (15c).** Following the procedure described for **15a**, methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundeca-

noate (**14**) (1 g, 1.3 mmol) and ethyl 2-mercaptoacetate (0.23 mL, 2 mmol) led to a crude solid which was purified by column chromatography on silica gel using 20% ethyl acetate in cyclohexane as eluent to yield 580 mg (55%) of **15c** as a colorless gum ($R_f$ = 0.52, eluent 30% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxy-30-[(carboxymethyl)thio]lup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (16c).** Following the procedure described for **16a**, methyl *N*-[3*β*-acetoxy-30-[[(ethyloxycarbonyl)methyl]thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (**15c**) (540 mg, 0.67 mmol) led to a solid which was first triturated with $CH_3CN$ (10 mL) and recrystallized from a 3:7 mixture of water and $CH_3OH$ (4 mL) to yield 350 mg (88%) of **16c** as white crystals: mp 194 °C; IR (KBr, $cm^{-1}$) $\nu$ 3405, 3125−2250, 3075, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1635 ($\nu_{CO}$ amide), 1535, 1470, 1450, 1390, 1375, 1040, 1030, 900; MS-(LSIMS/glycerol) 730 (base), 712, 638.

**Methyl *N*-[3*β*-Acetoxy-30-[(4′-fluorophenyl)thio]lup-20-(29)-en-28-oyl]-11-aminoundecanoate (15d).** Following the procedure described for **15a**, methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (1 g, 1.3 mmol) and 4-fluorothiophenol (0.28 mL, 2.6 mmol) led to a residue which was purified by column chromatography on silica gel using $CH_2Cl_2$ as eluent to yield 700 mg (66%) of **15d** as a white glass ($R_f$ = 0.15, eluent 10% ethyl acetate in cyclohexane).

***N*-[3*β*-Hydroxy-30-[(4′-fluorophenyl)thio]lup-20(29)-en-28-oyl]-11-aminoundecanic Acid (16d).** Following the procedure described for **16b**, methyl *N*-[3*β*-acetoxy-30-[(4′-fluorophenyl)thio]lup-20(29)-en-28-oyl]-11-aminoundecanoate (**15d**) (700 mg, 0.85 mmol) led to a residue which was recrystallized from $CH_3CN$ (10 mL) to yield 250 mg (38%) of **16d** as a white solid: mp 146 °C; IR (KBr, $cm^{-1}$) $\nu$ 3415, 3125−2250, 3075, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1635 ($\nu_{CO}$ amide), 1465, 1450, 1390, 1375, 1045, 1030, 890; MS(DCI) 766 (base).

**Methyl *N*-[3*β*-Acetoxy-30-[(2′-hydroxyethyl)amino]lup-20(29)-en-28-oyl]-11-aminoundecanoate (15e).** Following the procedure described for **15a**, methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (1 g, 1.3 mmol) and ethanolamine (0.24 mL, 3.9 mmol) led to a residue which was purified by column chromatography on silica gel using 10% $CH_3OH$ in $CH_2Cl_2$ as eluent to yield 450 mg (45%) of **15e** as a white glass ($R_f$ = 0.4, eluent 10% MeOH in $CH_2Cl_2$).

***N*-[3*β*-Hydroxy-30-[(2′-hydroxyethyl)amino]lup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (16e).** To a solution of methyl *N*-[3*β*-acetoxy-30-[(2′-hydroxyethyl)amino]lup-20-(29)-en-28-oyl]-11-aminoundecanoate (**15d**) (700 mg, 0.85 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (15 mL) was added aqueous NaOH (5 N, 2.4 mL). After stirring for 12 h at room temperature, the medium was acidified to pH = 4 with solid citric acid, diluted with distilled water (100 mL), and extracted with $CHCl_3$ (4 × 30 mL). The organic layers were collected, washed with distilled water (2 × 20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using $CHCl_3$−$CH_3OH$−$NH_3$ (24:6:1) as eluent. Trituration of the solid obtained with $CH_3CN$ (10 mL) yielded 230 mg (56%) of **16e** as a white solid: mp 214 C; $^1$H-NMR (DMSO-$d_6$, 400 MHz) (ppm) 0.62 (m, 1H, -*H* in 5), 0.64 (s, 3H, -C*H*$_3$), 0.76 (s, 3H, -C*H*$_3$), 0.83 (s, 3H, -C*H*$_3$), 0.86 (s, 3H, -C*H*$_3$), 0.92 (s, 3H, -C*H*$_3$), 1.53 (m, 1H, -*H* in 18), 2.13 (t, $J$ = 7.5 Hz, 2H, -C*H*$_2$-COO-), 2.52 (m, 1H, -*H* in 13), 2.56 (t, $J$ = 6 Hz, 2H, -NH-C*H*$_2$-CH$_2$-), 2.80−3.00 (m, 3H, 1H of -CONH-C*H*$_2$-*H* in 3 and -*H* in 19), 3.08 (limit ab, $J$ = 16 Hz, 12, -C*H*$_2$-NH-), 3.12 (m, 1H, the other H of -CONH-C*H*$_2$-), 3.45 (t, $J$ = 6 Hz, 2H, -C*H*$_2$O-), 4.75 and 4.80 (2 br s, 1H each, =C*H*$_2$), 7.52 (t, $J$ = 5.5 Hz, 1H, -CON*H*-); IR (KBr, $cm^{-1}$) $\nu$ 3410, 3125−2250, 3080, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1630 ($\nu_{CO}$ amide), 1530, 1465, 1455, 1385, 1045, 895; MS(DCI) 699 (base); MS(EI) 668, 471, 410.

**Methyl *N*-[3*β*-Acetoxy-30-pyrrolidinolup-20(29)-en-28-oyl]-11-aminoundecanoate (15f).** Following the procedure described for **15a**, methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (1 g, 1.3 mmol) and pyrrolidine (0.33 mL, 3.9 mmol) were stirred for 12 h at room temperature. The residue was purified by column chromatography on silica gel using 5% $CH_3OH$ in $CH_2Cl_2$ as eluent to yield 650 mg (65%) of **15f** as a white solid ($R_f$ = 0.23, eluent 5% MeOH in $CH_2Cl_2$).

***N*-[3*β*-Hydroxy-30-pyrrolidinolup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (16f).** To a solution of methyl *N*-[3*β*-acetoxy-30-pyrrolidinolup-20(29)-en-28-oyl]-11-aminoundecanoate (**15f**) (650 mg, 0.85 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (15 mL) was added aqueous NaOH (5 N, 3.4 mL). After stirring for 12 h at room temperature, the medium was concentrated under reduced pressure, the residue was suspended in distilled water (10 mL), and the solid was filtered. The residue was dissolved in a mixture of dioxane (20 mL) and distilled water (5 mL), acidified to pH = 4 with solid citric acid, and extracted with $CHCl_3$ (5 × 40 mL). The organic layers were collected, washed with distilled water (3 x 20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using $CHCl_3$−$CH_3OH$−20% ammonia (24:6:1) as eluent. The resulting solid was triturated with $CH_3CN$ (10 mL) to yield 240 mg (40%) of **16f** as a white solid: mp 146 °C; IR (KBr, $cm^{-1}$) $\nu$ 3425, 3125−2250, 3075, 2930, 2860, 2795, 1715 ($\nu_{CO}$ acid), 1640 ($\nu_{CO}$ amide), 1520, 1465, 1455, 1390, 1375, 1045, 1035, 900; MS(DCI) 709 (base); MS(EI) 648, 410, 84 (base).

**Methyl *N*-[3*β*-Acetoxy-30-[[(methoxycarbonyl)methyl]-amino]-20(29)-en-28-oyl]-11-aminoundecanoate (15g).** Following the procedure described for **15a**, methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (1 g, 1.3 mmol) and methyl glycinate hydrochloride (490 mg, 3.9 mmol) yielded a residue which was purified by column chromatography on silica gel using 50% ethyl acetate in cyclohexane as eluent to yield 180 mg (18%) of **15g** as a white solid ($R_f$ = 0.41, eluent 5% MeOH in $CH_2Cl_2$).

***N*-[3*β*-Hydroxy-30-[[(hydroxycarbonyl)methyl]amino]-20(29)-en-28-oyl]-11-aminoundecanic Acid (16g).** To a solution of methyl *N*-[3*β*-acetoxy-30-[[(methoxycarbonyl)-methyl]amino]-20(29)-en-28-oyl]-11-aminoundecanoate (**15g**) (650 mg, 0.85 mmol) in a 1:2 mixture of $CH_3OH$ and THF (11 mL) was added aqueous NaOH (1 N, 1.14 mL). After stirring for 48 h at room temperature, the medium was diluted with distilled water (15 mL) and then acidified to pH = 4 with solid citric acid. After stirring for 30 min at room temperature, the solid was filtered and dissolved in dioxane (5 mL). To the solution was added distilled water (45 mL). The solid obtained was filtered to yield 100 mg (74%) of **16g** as a white solid: mp 220 °C; IR (KBr, $cm^{-1}$) $\nu$ 3415, 3125−2250, 3075, 2930, 2860, 1715 ($\nu_{CO}$ acid), 1630 ($\nu_{CO}$ amide), 1530, 1465, 1455, 1390, 1375, 1045, 910; MS(LSIMS/glycerol) 713 (base).

**Methyl *N*-[3*β*,30-Diacetoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (17a).** A suspension of methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (5.1 g, 6.6 mmol), silver acetate (1.65 g, 9.9 mmol), and tetrabutylammonium bromide (250 mg) in toluene (130 mL) was refluxed for 2 h. The solids were filtered and washed with toluene (25 mL). The filtrate was concentrated under reduced pressure to give 5.5 g (100%) of **17a** as a glaze ($R_f$ = 0.15, eluent 20% ethyl acetate in cyclohexane).

***N*-[3*β*,30-Dihydroxylup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (17b).** Following the procedure described for **5a**, methyl *N*-[3*β*,30-diacetoxylup-20(29)-en-28-oyl]-11-aminoundecanoate (**17a**) (650 mg, 0.86 mmol) led to **17b** as a white solid: mp 174 °C; $^1$H-NMR ($CDCl_3$, 400 MHz) (ppm) 0.69 (br d, $J$ = 9 Hz, 1H, -*H* in 5), 0.78 (s, 3H, -C*H*$_3$), 0.83 (s, 3H, -C*H*$_3$), 0.93 (s, 3H, -C*H*$_3$), 0.96 (s, 3H, -C*H*$_3$), 0.97 (s, 3H, -C*H*$_3$), 1.67 (t, $J$ = 11.5 Hz, 1H, -*H* in 18), 2.37 (t, $J$ = 7.5 Hz, 2H, -C*H*$_2$-COO-), 2.43 (dt, $J$ = 11.5, 3 Hz, 1H, -*H* in 13), 3.03 (dt, $J$ = 11.5, 4 Hz, 1H, -*H* in 19), 3.18 and 3.28 (2m, 1H each, -CONH-C*H*$_2$-), 3.20 (dd, $J$ = 11, 5 Hz, 1H, -*H* in 3), 4.13 (limit ab, 2H, -C*H*$_2$O-), 4.91 and 4.96 (2br s, 1H each, =C*H*$_2$), 5.62 (t, $J$ = 5.5 Hz, 1H, -CON*H*-); IR (KBr, $cm^{-1}$) $\nu$ 3400, 3100−2250, 3075, 2925, 2850, 1710 ($\nu_{CO}$ acid), 1635 ($\nu_{CO}$ amide), 1520, 1465, 1450, 1385, 1370, 1045, 1025, 880; MS(EI) 655, 640, 637, 409, 187 (base).

**Methyl *N*-[3*β*-Acetoxy-30-phthalimidolup-20(29)-en-28-oyl]-11-aminoundecanoate (18).** To a solution of methyl *N*-[3*β*-acetoxy-30-bromolup-20(29)-en-28-oyl]-11-aminoundecanoate (**14**) (2 g, 2.58 mmol) in toluene (70 mL) at room

temperature were added potassium phthalimide (0.56 g, 3 mmol) and 18-crown-6 ether (0.68 g, 2.58 mmol). The resulting suspension was heated for 8 h at 85 °C and then allowed to cool to room temperature. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The pink oil obtained was purified by column chromatography on silica gel using 30% ethyl acetate in cyclohexane as eluent to yield 1.60 g (73%) of **18** as a white meringue ($R_f = 0.8$, eluent 5% MeOH in $CH_2Cl_2$).

**Methyl *N*-[3*β*-Acetoxy-30-aminolup-20(29)-en-28-oyl]-11-aminoundecanoate (19a).** A solution of methyl *N*-[3*β*-acetoxy-30-phthalimidolup-20(29)-en-28-oyl]-11-aminoundecanoate (**18**) (1.6 g, 2.06 mmol) and hydrazine hydrate (98%, 0.12 mL, 2.5 mmol) in methanol (50 mL) was stirred for 48 h at room temperature, acidified under stirring to pH = 2 with etheral hydrochloric acid (13 N), and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 10% methanol in $CH_2Cl_2$ to give 700 mg (47%) of **19a** as a white solid directly used without further purification in the next step.

***N*-[3*β*-Hydroxy-30-aminolup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (19b).** Aqueous NaOH (1 N, 1.7 mL) was added to a solution of methyl *N*-[3*β*-acetoxy-30-aminolup-20(29)-en-28-oyl]-11-aminoundecanoate (**19a)** (300 mg, 0.42 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (20 mL). After stirring for 12 h at room temperature and concentrating the solution in vacuo, the residue was suspended in distilled water (30 mL). The medium was acidified to pH = 4 with solid citric acid, and the solid obtained was filtered, washed with distilled water (2 × 2 mL), dried, and then purified by column chromatography on silica gel eluting with a mixture of $CHCl_3$−$CH_3OH$−20% ammonia (24:6:1) to yield 100 mg (36%) of **19b** as a white solid: mp 220 °C; IR (KBr, $cm^{-1}$) $\nu$ 3420, 3125−2250, 3080, 2930, 2860, 1710 ($\nu_{CO}$ acid), 1640 ($\nu_{CO}$ amide), 1525, 1465, 1455, 1390, 1375, 1045, 1035, 880; MS(DCI) 655 (base); MS(EI) 426, 409, 189, 187, 121, 119, 69 (base).

***N*-[3*β*-Hydroxy-30-(acetylamino)lup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (19c).** Acetyl chloride (0.036 mL, 0.5 mmol) and triethylamine (0.07 mL, 0.5 mmol) in $CH_2Cl_2$ (1 mL) was added at room temperature to a solution of methyl *N*-[3*β*-acetoxy-30-aminolup-20(29)-en-28-oyl]-11-aminoundecanoate (**19a)** (300 mg, 0.42 mmol) in $CH_2Cl_2$ (15 mL). The resulting solution was stirred for 12 h , washed with distilled water (3 × 10 mL), dried over magnesium sulfate, and concentrated in vacuo. The resulting solid (300 mg, 95%) was used without further purification in the next step.

Following the procedure described for **5a**, methyl *N*-[3*β*-acetoxy-30-(acetylamino)lup-20(29)-en-28-oyl]-11-aminoundecanoate (300 mg, 0.43 mmol) led to 150 mg (53%) of **19c** as a white solid: mp 160 °C; IR (KBr, $cm^{-1}$) $\nu$ 3400, 3135−2250, 3080, 2930, 2860, 1715 ($\nu_{CO}$ acid), 1630 ($\nu_{CO}$ amide), 1530, 1465, 1450, 1390, 1375, 1045, 1030, 880; MS(DCI) 697 (base).

**Methyl 11-[[3*β*-Acetoxy-28-norlup-20(29)-en-17-yl]carbamoyl]undecanoate (21a).** Distilled water (10 mL) and hydrochloric acid in diethyl ether solution (5 N, 40 mL) were added to a solution of 3*β*-acetoxy-17*β*-isocyanato-28-norlup-20(29)-ene (**20**)[12] (1.89 g, 3.8 mmol) in $CH_2Cl_2$ (47 mL). The biphasic mixture was stirred for 24 h at room temperature and then concentrated under reduced pressure. The resulting solid (2.1 g) was purified by two subsequent column chromatographies on silica gel using $CH_2Cl_2$ and 50% methanol in $CH_2Cl_2$ as eluent to yield 1.60 g (85%) of crude 3*β*-acetoxy-17*β*-amino-28-norlup-20(29)-ene as a white solid ($R_f = 0.53$, eluent 10% methanol in $CH_2Cl_2$) which was used without further purification in the next step.

A solution of this 3*β*-acetoxy-17*β*-amino-28-norlup-20(29)-ene in THF (10 mL) and a solution of methyl (chloroformyl)-undecanoate,[20] prepared from 11-(methoxycarbonyl)undecanoic acid (526 mg, 2 mmol) and thionyl chloride in $CHCl_3$ (20 mL), were stirred at room temperature, and triethylamine (0.56 mL, 4 mmol) was added dropwise within 10 min. After stirring for 12 h at room temperature, $CH_3OH$ (5 mL) was added, stirring was maintained for 1 h, and distilled water (40 mL) was added. The mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The organic layers were collected, washed with distilled water (3 × 25 mL), dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 10% $CH_2Cl_2$ in diisopropyl ether as eluent to yield 330 mg (36%) of **21a** as colorless gum ($R_f = 0.76$, eluent 10% $CH_2Cl_2$ in diisopropyl ether).

**11-[[3*β*-Acetoxy-28-norlup-20(29)-en-17-yl]carbamoyl]-undecanoic Acid (21b).** Aqueous NaOH (4 N, 3.3 mL) was added to a solution of methyl 11-[[3*β*-acetoxy-28-norlup-20-(29)-en-17-yl]carbamoyl]undecanoate (**21a)** (330 mg, 0.47 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (5 mL). After stiring for 12 h at room temperature, distilled water was added (22 mL), and the medium was acidified to pH = 2 with aqueous hydrochloric acid (4 N, 4.5 mL). The suspension was stirred for 1 h at room temperature and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic layers were collected, washed with distilled water (3 × 15 mL), dried over sodium sulfate, and concentrated in vacuo. The solid was purified by column chromatography on silica gel using 10% $CH_3OH$ in $CH_2Cl_2$ as eluent to yield 130 mg (43%) of **21b** as a white solid: mp 130 °C; IR (KBr, $cm^{-1}$) $\nu$ 3450, 3075, 2930, 2855, 2700−2250, 1710 ($\nu_{CO}$ acid), 1645 ($\nu_{CO}$ amide), 1510, 1470, 1455, 1390, 1375, 1045, 885; MS(DCI) 640 (base); MS(EI) 410, 230, 212 (base).

**Methyl *N*-[3*β*-Acetoxy-28-norlup-20(29)-en-28-oyl]-11-aminoundecanoate (22a).** A solution of 3*β*-acetoxy-17*β*-isocyanato-28-norlup-20(29)-ene (**20**)[12] (500 mg, 1 mmol), methyl 10-aminodecanoate hydrochloride[21] (276 mg, 1.1 mmol), and triethylamine (0.18 mL, 1.28 mmol) in $CHCl_3$ (15 mL) was stirred for 16 h at room temperature. Then $CHCl_3$ (25 mL) and aqueous hydrochloric acid (0.1 N, 25 mL) were added. The mixture was stirred for an additional 30 min, and the aqueous phase was extracted with $CHCl_3$ (25 mL). The combined organic phase was mixed, washed with distilled water (3 × 25 mL), dried over magnesium sulfate, and evaporated under reduced pressure to give a solid which was purified by column chromatography eluting with 10% ethyl acetate in $CH_2Cl_2$ to yield 430 mg (61%) of **22a** as a white meringue ($R_f = 0.26$, eluent 10% ethyl acetate in $CH_2Cl_2$).

***N*-[3*β*-Hydroxy-28-norlup-20(29)-en-28-oyl]-11-aminoundecanoic Acid (22b).** Following the procedure described for **5a**, methyl *N*-[3*β*-acetoxy-28-norlup-20(29)-en-28-oyl]-11-aminoundecanoate (**22a**) (420 mg, 0.6 mmol) led to 345 mg (89%) of **22b** as a white powder: mp 225 °C; IR (KBr, $cm^{-1}$) $\nu$ 3410, 3075, 2925, 2855, 2750−2250, 1715 ($\nu_{CO}$ acid), 1640, 1625 ($\nu_{CO}$ urea), 1555, 1465, 1455, 1390, 1375, 1040, 885; MS(DCI) 641 (base); MS(EI) 410, 189, 187, 81, 69 (base).

**Methyl 3*β*-[(Dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-oate (23).** To a solution of methyl betulinate (**1c**) (6.5 g, 13.8 mmol) in DMF (165 mL) were added imidazole (2.82 g, 41.4 mmol) and *tert*-butyldimethylsilyl chloride (4.25 g, 27.6 mmol). After 35 min at room temperature, the suspension turned to a yellowish solution. After an additional 25 min of stirring, a white solid appeared. The resulting suspension was stirred for 40 h at room temperature, and distilled water (1500 mL) was added. The white solid was filtered, washed with distilled water (5 × 250 mL), and dried over KOH in vacuo to yield 8.1 g (100%) of methyl 3*β*-[(dimethyl-*tert*-butylsilyl)oxy]-lup-20(29)-en-28-oate (**23**) as a white solid: mp 190 °C.

**3*β*-[(Dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-ol (24).** To a solution of methyl 3*β*-[(dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-oate (**23**) (8.4 g, 14.5 mmol) in THF (46 mL) was added lithium aluminum hydride (1.65 g, 42.9 mmol) portionwise in 45 min. The resulting mixture was stirred at room temperature for 16 h. At this point, the reaction was complete and water (1.9 mL) was added under stirring. Then aqueous sodium hydroxide (5 N 1.4 mL) and distilled water (6.4 mL) were added. The resulting suspension was stirred at room temperature for 1 h and filtered. The solid was washed with $CH_2Cl_2$ (6 × 50 mL). The organic layers were collected, dried over magnesium sulfate, and concentrated in vacuo to give 8.0 g (100%) of **24** as a white meringue ($R_f = 0.43$, eluent 20% ethyl acetate in cyclohexane).

**3*β*-[(Dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-al (25).** A solution of DMSO (0.34 mL, 4.4 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise to a −60 °C cooled solution of oxalyl chloride (0.2 mL, 2.2 mmol) in $CH_2Cl_2$ (5 mL). After 5 min of stirring at −60 °C, a solution of 3*β*-[(dimethyl-*tert*-terbutylsilyl)oxy]lup-20(29)-en-28-ol (**24)** (1.1 g, 2 mmol) in $CH_2Cl_2$ (10

mL) was added dropwise. After additional stirring (15 min) at −60 °C, triethylamine (1.4 mL, 10 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 72 h; then, it was diluted with $CH_2Cl_2$ (50 mL). The organic layer was washed with distilled water (4 × 50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to give 1.1 g (100%) of **25** as an oil which was used without further purification ($R_f$ = 0.36, eluent 10% ethyl acetate in cyclohexane).

**Methyl 11-[[[3β-[(Dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-yl]methyl]amino]undecanoate (26a).** A solution of methyl 11-aminoundecanoate hydrochloride (5.43 g, 21.6 mmol) in MeOH (150 mL) was added dropwise to a solution of 3β-[(dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-al (**25**) (2.0 g, 3.6 mmol) in $CH_2Cl_2$ (40 mL). The resulting solution was heated for 60 h at 55 °C. The suspension was cooled at room temperature, and solid sodium cyanoborohydride (330 mg, 5.25 mmol) was added. After additional stirring for 48 h at room temperature, distilled water was added (100 mL) and the medium was extracted with $CH_2Cl_2$ (3 × 100 mL). The organic layers were collected, washed with distilled water (3 × 50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue (1.92 g) was purified by column chromatography on silica gel using 30% ethyl acetate in cyclohexane as eluent to yield 530 mg (23%) of **26a** as a white meringue ($R_f$ = 0.84, eluent 15% ethyl acetate in cyclohexane).

**Methyl 11-[[[3β-Hydroxylup-20(29)-en-28-yl]methyl]amino]undecanoate (26b).** Solid anhydrous ferric chloride (215 mg, 1.32 mmol) was added to a solution of methyl 11-[[[3β-[(dimethyl-*tert*-butylsilyl)oxy]lup-20(29)-en-28-ylmethyl]-amino]undecanoate (**26a**) (500 mg, 0.66 mmol) in a 1:1 mixture of $CH_3CN$ and THF (20 mL), and the reaction mixture was stirred at room temperature for 12 h. Distilled water (15 mL) and $CH_2Cl_2$ (15 mL) were added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL); the organic phase was collected, washed with distilled water (3 × 50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The oily residue was triturated with 15% ethyl acetate in cyclohexane (5 mL), yielding 160 mg (38%) of **26b** as a beige solid ($R_f$ = 0.42, eluent 10% methanol in $CH_2Cl_2$).

**11-[[[3β-Hydroxylup-20(29)-en-28-yl]methyl]amino]undecanoic Acid (26c).** To a solution of methyl *N*-[[3β-hydroxylup-20(29)-en-28-yl]methyl]-11-aminoundecanoate (**26b**) (150 mg, 0.2 mmol) in a 1:1.5 mixture of $CH_3OH$ and THF (3.30 mL) was added aqueous NaOH (4 N, 2.15 mL). After stirring for 60 h at room temperature, distilled water (10 mL) was added and the medium acidified to pH = 4.3 using 4 N aqueous hydrochloric acid. After stirring for 2 h at room temperature, the medium was extracted using $CH_2Cl_2$ (3 × 50 mL). The organic layers were collected, washed with distilled water (3 × 50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residual solid was triturated with $CH_2Cl_2$ (3 mL) to yield 56 mg (45%) of **26c** as beige crystals: mp 182 °C; IR (KBr, $cm^{-1}$) $\nu$ 3400, 3075, 2935, 2860, 2750−2250, 1710 ($\nu_{CO}$ acid), 1640 ($\nu_{CO}$ amide), 1525, 1455, 1390, 1375, 1065, 880; MS(EI) 624, 551, 523, 214 (base).

**Biological Methods**. **Antiviral Assay in CEM 4 Cells. Cells:** The CEM 4, a subclone enriched in $CD_4$ receptors, was obtained from the CEM T-lymphoblastoid tumor cell line. This was originally isolated from a child with acute lymphoblastic leukemia. Cells were grown at 37 °C in a $CO_2$ incubator (5%) in RPMI 1640 medium, supplemented with 10% heat-inactivated fetal calf serum, penicillin (100 IU/mL), glutamine (100 μg/mL), streptomycin (100 μg/mL) and polybrene (Sigma; 2 μg/mL).

**Virus:** The $III_B$/LAI strain of HIV-1 was used. Virus stocks were obtained from filtered (0.45 μm pore size) supernatants of infected CEM cl11 cells (PMsv, Marne la Coquette, France). The titers of the HIV-1 preparations were around $10^4$ $CCID_{50}$ (50% cell culture infective doses/mL).

**Assay:** Compounds were tested for their ability to inhibit the cytopathic effect induced by HIV-1 infection. These assays were carried out in 96-well culture plates. In the routine microplate test, 25 μL of each compound dilution or phosphate-buffered saline (PBS) alone was distributed in each well. A CEM 4 cell suspension (125 μL of 5 × $10^4$ cells/mL) was then added, and cultures were incubated for 1 h at 37 °C (5% $CO_2$). Cells were infected with 100 μL of virus suspension (100−200 $CCID_{50}$) and cultured for at least 5 days. Mock-infected cultures were carried out in parallel to determine the cytotoxicity of the compounds. To assess cell viability, a solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (10 μL at 7 mg/mL in PBS) was added to 100 μL of cell suspension. After 3-h incubation at 37 °C, most of the supernatant was removed and the formazan precipitate was dissolved in 100 μL of 0.04 M HCl in 2-propanol. The absorbance at 540 nm was measured with a Biotek EL-311 microplate reader. The concentration that produced 50% inhibition ($IC_{50}$) was estimated as the mean for at least two experiments.

**Antiviral Assay in MT-4 Cells.** Compounds were tested according to the MTT method, as described by Pauwels et al.[24]

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**Supporting Information Available:** NMR data of compounds **5b**−**h**, **7b**, **9b**, **10b**, **11b**, **13b,c**, **16a**−**g**, **19b,c**, **21b**, **22b**, and **26c** (7 pages). Ordering information can be found on any current masthead page.

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