Diastereoselective Alkylation of Schiff Bases for the Synthesis of Lipidic Unnatural Fmoc-Protected α-Amino Acids

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Peptides with increased lipophilicity can cross cell membranes more easily and have longer half-life times. For these reasons, the synthesis of enantiomerically pure Fmoc-protected lipidic α-amino acids is a relevant goal. Schiff bases originating from the reaction between the two enantiomers of 2-hydroxypinan-3-one with Gly-O*t*Bu were alkylated with a series of long alkyl halides. Diastereomeric excesses were determined by reversed-phase HPLC, under conditions carefully chosen for such lipophilic substrates.

Introduction

The therapeutic use of many potentially bioactive peptides is limited by their insufficient bio-availability, which is related mainly to their poor membrane solubility. As a potential means of overcoming this difficulty, lipoconjugates prepared by the introduction of a lipophilic moiety into the peptide sequence have been demonstrated to increase the overall hydrophobicity of the peptide efficiently. In this respect, particular attention has been focused on lipidic α-amino acids (Laas). These unnatural α-amino acids containing long hydrocarbon side chains have an amphiphilic nature that influences their physical properties.[1] Poor oral absorption of peptides is a significant obstacle to their use as drugs, whereas peptides conjugated with Laas show increased permeability through cell membranes and increased biological stability,[2,3] both of which are essential properties for good drug delivery. Moreover, lipoconjugated peptides show better resistance towards proteolytic enzymes than the unmodified sequences.[4−6] We have previously demonstrated[4] that lipo derivatives of MBP peptide epitope GpMBP(83-99) were not degraded by lysosomal peptides, while the native epitope was very quickly destroyed. The degree of the lipidic character of the Laa system can be modified to allow selection of a drug−Laa conjugate possessing optimal lipophilicity for oral absorption and biological stability. The large-scale and stereoselective synthesis of Laas protected for solid-phase peptide synthesis by the Fmoc/*t*Bu strategy therefore represents an important goal.

To the best of our knowledge, Fmoc-protected L- or D-Laas have previously been obtained only by enzymatic resolution.[1,7−12] In earlier studies, we developed the large-scale synthesis of (±)-Fmoc-2-aminohexadecanoic acid [(±)-Fmoc-Ahd-OH], which was introduced into lipopeptides. The products were obtained as diastereomeric mixtures that could be separated by HPLC only in favourable cases.[3] This amphiphilic amino acid required the preparation of a soluble intermediate, such as a benzyl or *tert*-butyl ester, for N^{α}-protection with Fmoc-OSu.

Results and Discussion

The enantiomerically pure lipophilic building blocks were prepared by Yamada's alkylation method (Scheme 1).[13] Thus, the enantiomeric Schiff base substrates (+)-**1** or (−)-**1**, prepared from *tert*-butyl glycinate and (+)- or (−)-2-hydroxypinan-3-one, respectively, were treated with LDA (2.2 equiv.) to form the dianion, which was then allowed to react with the appropriate bromo- or iodoalkane to yield products containing side chains with twelve (**2**), fourteen (**3**) or sixteen carbon atoms (**4**). As shown in Table 1, iodoalkanes were more reactive and gave higher diastereoselectivities than bromoalkanes. Moreover, addition of DMPU did not improve the reactivity or the diastereoselectivity. Flash chromatography of the crude products afforded the major diastereomeric Schiff bases in pure form.

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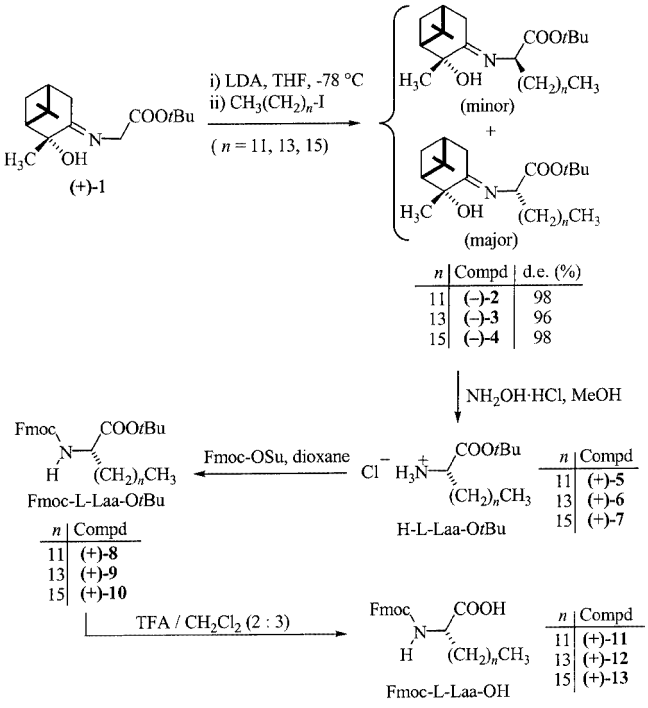

Scheme 1

Hydrolysis of compounds **2**−**4** with hydroxylamine hydrochloride gave 85−90% yields of the soluble amino acids as *tert*-butyl esters, ready for protection of the α-amino group. Compounds **5**−**7** were treated with Fmoc-OSu in dioxane, and the α-carboxy group was then deprotected with TFA in CH_2Cl_2. The enantiomerically pure Fmoc-protected L-Laas 2-aminotetradecanoic (**11**), 2-aminohexadecanoic (**12**) and 2-aminooctadecanoic (**13**) acid were obtained in good yields (80−95%) when starting from (+)-(1*R*,2*R*,5*R*)-2-hydroxypinan-3-one. The analogous procedure from the Schiff bases of (−)-(1*S*,2*S*,5*S*)-2-hydroxypinan-3-one and *tert*-butyl glycinate afforded the D-amino acids.

The assignment of the configurations of the two enantiomers of Fmoc-Ahd-OH was based on $[\alpha]_D$ measurements and comparison with reported literature data for these amino acids obtained after enzymatic resolution.[7] By the synthetic pathway described here, it was possible to obtain the (+)-amino acids, corresponding to the L enantiomers, from (+)-2-hydroxypinan-3-one, and the (−)-D enantiomers from (−)-2-hydroxypinan-3-one. Correlation with the new Fmoc-protected amino acids was performed as predicted by Yamada's model and confirmed by other authors for amino acids without heteroatom-containing side chains.[14−17] Moreover, it was observed that the $[\alpha]_D^{20}$ values of the two enantiomers of Fmoc-Ahd-OH both inverted their sign in DMF, as previously reported for the same products obtained independently by enzymatic resolution.[7]

Conclusion

The method described represents a convenient synthesis of enantiomerically pure Fmoc-protected lipophilic amino acids containing alkyl side chains of variable length (C_{12}, C_{14} and C_{16}). This highly diastereoselective pathway does not require expensive chiral auxiliaries. Moreover, we have demonstrated that the synthesis could easily be scaled up, up to 10 g in our experience, as we have been able to demonstrate in the case of Fmoc-Ahd-OH. Extensive application of the pure enantiomers of these lipophilic amino acids in peptide synthesis is in progress in our laboratories.

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian spectrometer at a frequency of 200 MHz. Chemical shifts are reported in ppm relative to TMS, and coupling constants (*J*) in Hz. FT-IR spectra were obtained with a Perkin−Elmer Spectrum BX II apparatus. Melting points were determined with a Büchi 510 apparatus. Elemental analyses were performed with a Perkin−Elmer 2400 Series II CHN Analyzer. The polarized light rotation angles were measured in a thermostatted 1-dm cell with a Perkin−Elmer model 343 polarimeter. Diastereomeric excesses were evaluated by RP-HPLC on a Phenomenex Jupiter C18 (5 μm,

Table 1. Alkylation reactions of the enantiomeric Schiff bases

R−X	(−)-2-Hydroxypinanone Compd.	Yield (%)[a]	*de* (%)[a]	(+)-2-Hydroxypinanone Compd.	Yield (%)[a]	*de* (%)[a]
$nC_{12}H_{25}I$	(+)-**2**	64	99	(−)-**2**	52	98
$nC_{14}H_{29}I$	(+)-**3**	66	99	(−)-**3**	43	96
$nC_{16}H_{33}I$	(+)-**4**	67	98	(−)-**4**	44	98
$nC_{12}H_{25}Br$	(+)-**2**	53	86			
$nC_{14}H_{29}Br$	(+)-**3**	24	83			
$nC_{16}H_{33}Br$	(+)-**4**	54	91			
$nC_{12}H_{25}Br$[b]	(+)-**2**	41	86	(−)-**2**	43	89
$nC_{14}H_{29}Br$[b]	(+)-**3**	40	90	(−)-**3**	45	88
$nC_{16}H_{33}Br$[b]	(+)-**4**	28	91	(−)-**4**	24	79

[a] Determined by HPLC analysis of the raw materials after quenching of the reaction mixtures. [b] DMPU added.

300 Å, 250 × 4.6 mm) column with a Beckman System Gold apparatus at 215 nm. Isocratic analyses with 100% HPLC grade CH_3CN (Carlo Erba, Italy) were performed at 1 mL/min flow rates. The products were lyophilized with an Edwards apparatus, model Modulyo. Flash column chromatography (FCC) was accomplished on SiO_2 (ICN; 32−63 μm, 60 Å). Thin layer chromatography (TLC) was carried out on SiO_2 (Merck; 60 Å, F_{254}). Dry solvents were distilled immediately before use.

Synthesis of Schiff Bases (−)-1 and (+)-1. General Procedure: 2-Hydroxypinan-3-one (15 mmol) was added to GlyO*t*Bu (30 mmol) dissolved in benzene (25 mL) in a Dean−Stark apparatus. $BF_3{\cdot}Et_2O$ (50 μL) was added, and the mixture was heated under reflux for 2 h until all the ketone had reacted. Purification was accomplished by distillation under reduced pressure.

***tert*-Butyl {[(1*S*,2*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylidene]amino}acetate [(−)-1] from (1*S*,2*S*,5*S*)-(−)-2-Hydroxypinan-3-one:** Yield 76% (3.2 g); b.p.$_{0.2\ Torr}$ 124−125 °C (ref.[13] 120−122 °C). IR (KBr): $\tilde{\nu}$ = 3540 (OH), 1736 (C=O), 1650 cm^{-1}(C=N). ^1H NMR ($CDCl_3$): δ = 0.85 (m, 6 H, 16-H_3 and 2′-CH_3), 1.31 (s, 3 H, 6′-CH_3), 1.46 [s, 9 H, $C(CH_3)_3$], 1.50 (s, 3 H, 6′-CH_3), 1.54 (d, 1 H, 7′-H), 2.05 (m, 2 H, 1′-H and 5′-H), 2.30 (m, 1 H, 7′-H), 2.46 (m, 2 H, 4′-H_2), 4.06 (s, 2 H, α-H_2) ppm.

***tert*-Butyl {[(1*R*,2*R*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}acetate [(+)-1] from (1*R*,2*R*,5*R*)-(+)-2-Hydroxypinan-3-one:** Yield 85% (3.58 g). IR and ^1H NMR spectra are in agreement with those of compound **(−)-1**.

Alkylation of Schiff Bases (−)-1 and (+)-1; General Procedure: The Schiff base (1 mmol) in THF (2 mL) was added to LDA (2.2 mmol) and kept at −78 °C in dry THF (2 mL) under argon. After 30 min, the iodo- or bromoalkane [2 mmol; in the case of bromoalkanes, DMPU (0.24 mL, 2 mmol) was added 15 min before addition of the electrophile] was added to the stirred mixture. After 2 h, the mixture was allowed to come slowly to room temperature and stirred overnight. The reaction was quenched by addition of 15% aqueous citric acid to the mixture at 0 °C. This was then extracted with benzene, and the organic layer was washed with brine. The solvent was removed under reduced pressure, and the diastereomeric Schiff bases were separated and purified by FCC.

***tert*-Butyl (2*R*)-2-{[(1*S*,2*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}tetradecanoate [(+)-2] from 1-Iodododecane:** Yield 64% (0.29 g); R_f (EtOAc/petroleum ether, 1:6) = 0.4; *de* = 99%. HPLC: t_R = 14.46 min. $[\alpha]_D^{25}$ = +55.9 (*c* = 4.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3438 (br, OH), 2925 and 2855 (CH_2), 1730 (C=O), 1649 cm^{-1}(C=N). ^1H NMR: δ = 0.83 (s, 3 H, 2′-CH_3) 0.85 (pt, 3 H, 14-H_3), 1.22 [br m, 20 H, $(CH_2)_{10}$], 1.30 (s, 3 H, 6′-CH_3), 1.41 [s, 9 H, $C(CH_3)_3$], 1.46 (s, 3 H, 6′-CH_3), 1.53 (d, 1 H, 7′-H), 1.83 (m, 2 H, β-H_2), 2.03 (m, 2 H, 1′-H and 5′-H), 2.30 (m, 1 H, 7′-H), 2.53 (m, 2 H, 4′-H_2), 4.02 (dd, *J* = 5.4, *J* = 8.3 Hz, 1 H, α-H) ppm. ^{13}C NMR: δ = 14.0 (C-14), 22.6 (6′-CH_3), 22.8 (2′-CH_3), 25.8 (C-13), 27.2 (6′-CH_3), 27.9 (C-7′), 28.0 [$C(CH_3)_3$], 28.2 (C-13), 29.2−29.5 [$(CH_2)_7$], 31.8 (C-γ), 32.9 (C-β), 33.2 (C-4′), 38.1 (C-6′), 38.3 (C-5′), 49.9 (C-1′), 62.7 (C-α), 76.3 (C-2′), 80.8 (CMe_3), 170.8 (C=N), 177.5 (COO*t*Bu) ppm. $C_{28}H_{51}NO_3$ (449.71): calcd. C 74.78, H 11.43, N 3.11; found C 74.75, H 11.61, N 2.97.

***tert*-Butyl (2*S*)-2-{[(1*R*,2*R*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}tetradecanoate [(−)-2] from 1-Iodododecane:** Yield 47% (0.22 g); R_f (EtOAc/petroleum ether, 1:6) = 0.5; *de* = 96%. HPLC: t_R = 13.34 min. $[\alpha]_D^{20}$ = −65.0 (*c* = 0.55, $CHCl_3$). IR: in accordance with (+)-**2**. ^1H NMR: δ = 0.83 (s, 3 H, 2′-CH_3), 0.85 (pt, 3 H, 14-H_3), 1.22 [m, 20 H, $(CH_2)_{10}$], 1.30 (s, 3 H, 6′-CH_3), 1.42 [s, 9 H, $C(CH_3)_3$], 1.46 (s, 3 H, 6′-CH_3), 1.53 (d, 1 H, 7′-H), 1.83 (m, 2 H, β-H_2), 2.03 (m, 2 H, 1′-H and 5′-H), 2.28 (m, 1 H, 7′-H), 2.53 (m, 2 H, 4′-H_2), 4.03 (dd, *J* = 5.1, *J* = 8.1 Hz, 1 H, α-H) ppm. ^{13}C NMR: δ = 14.0 (C-14), 22.6 (6′-CH_3), 22.8 (2′-CH_3), 25.8 (C-13), 27.2 (6′-CH_3), 27.9 [$C(CH_3)_3$ and C-7′], 28.2 (C-13), 29.2−29.5 [$(CH_2)_7$], 31.8 (C-γ), 32.9 (C-β), 33.2 (C-4′), 38.1 (C-6′), 38.3 (C-5′), 49.9 (C-1′), 62.7 (C-α), 76.3 (C-2′), 80.8 (CMe_3), 170.8 (C=N), 177.5 (COO*t*Bu) ppm. $C_{28}H_{51}NO_3$ (449.71): calcd. C 74.78, H 11.43, N 3.11; found C 74.43, H 11.65, N 2.94.

***tert*-Butyl (2*R*)-2-{[(1*S*,2*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}hexadecanoate [(+)-3] from 1-Iodotetradecane:** Yield 66% (0.315 g); R_f (EtOAc/petroleum ether, 1:7) = 0.4; *de* = 99%; t_R = 17.86 min. $[\alpha]_D^{25}$ = +67.3 (*c* = 0.7, CCl_4). IR (KBr): $\tilde{\nu}$ = 3438 (br, OH), 2925−2855 (CH_2), 1730 (C=O), 1649 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 0.85 (s, 3 H, 2′-CH_3), 0.87 (pt, 3 H, 16-H_3), 1.23 [br m, 24 H, $(CH_2)_{12}$], 1.33 (s, 3 H, 6′-CH_3), 1.42 [s, 9 H, $C(CH_3)_3$], 1.48 (s, 3 H, 6′-CH_3), 1.58 (d, 1 H, 7′-H), 1.84 (m, 2 H, β-H_2), 2.02 (m, 2 H, 1′-H and 5′-H), 2.30 [m, 1 H, 7′-H], 2.53 (m, 2 H, 4′-H_2), 2.66 (br, 1 H, OH), 4.03 (dd, *J* = 5.3, *J* = 8.2 Hz, 1 H, α-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (C-16), 22.6 (6′-C), 22.8 (2′-C), 25.8 (C-15), 27.2 (6′-C), 27.9 [$C(CH_3)_3$ and C-7′], 28.2 (C-14), 29.2−29.5 [$(CH_2)_9$], 31.8 (C-γ), 32.9 (C-β), 33.2 (C-4′), 38.3 (C-6′), 38.4 (C-5′), 50.1 (C-1′), 62.8 (C-α), 76.3 (C-2′), 81.0 (CMe_3), 171.0 (C=N), 177.6 (COO*t*Bu) ppm. $C_{30}H_{55}NO_3$ (477.76): calcd. C 75.42, H 11.60, N 2.93; found C 75.40, H 11.95, N 2.64.

***tert*-Butyl (2*S*)-2-{[(1*R*,2*R*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}hexadecanoate [(−)-3] from 1-Iodotetradecane:** Yield 43% (0.205 g); R_f (EtOAc/petroleum ether, 1:6) = 0.28; *de* = 96%; t_R = 18.56 min. $[\alpha]_D^{25}$ = −53.4 (*c* = 1.0, CCl_4). IR (KBr): $\tilde{\nu}$ = 3438 (br. OH), 2925−2855 (CH_2), 1730 (C=O), 1649 cm^{-1} (C=N). ^1H NMR: δ = 0.83 (s, 3 H, 2′-CH_3), 0.86 (pt, 3 H, 16-H_3), 1.23 [br m, 24 H, $(CH_2)_{12}$], 1.31 (s, 3 H, 6′-CH_3), 1.42 [s, 9 H, $C(CH_3)_3$], 1.47 (s, 3 H, 6′-CH_3), 1.54 (d, 1 H, 7′-H), 1.83 (m, 2 H, β-H_2), 2.04 (m, 2 H, 1′-H and 5′-H), 2.29 (m, 1 H, 7′-H), 2.53 (m, 2 H, 4′-H_2), 4.03 (dd, *J* = 5, *J* = 8.2 Hz, 1 H, α-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5 (C-16), 22.1 (6′-CH_3), 22.3 (2′-C), 25.3 (C-15), 26.7 (6′-CH_3), 27.5 [$C(CH_3)_3$ and C-7′], 27.7 (C-14), 28.9−29.1 [$(CH_2)_9$], 31.3 (C-γ), 32.5 (C-β), 32.7 (C-4′), 37.6 (C-6′), 37.8 (C-5′), 49.5 (C-1′), 62.2 (C-α), 75.8 (C-2′), 80.4 (CMe_3), 170.4 (C=N), 177.0 (COO*t*Bu) ppm. $C_{30}H_{55}NO_3$ (477.76): calcd. C 75.42, H 11.60, N 2.93; found C 75.67, H 11.76, N 2.85.

***tert*-Butyl (2*R*)-2-{[(1*S*,2*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}octadecanoate [(+)-4] from 1-Iodohexadecane:** Yield 67% (0.34 g); R_f (EtOAc/petroleum ether, 1:7) = 0.3; *de* = 98%; t_R = 27.56 min. $[\alpha]_D^{25}$ = +31.7 (*c* = 0.7, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3438 (br. OH), 2925 and 2855 (CH_2), 1730 (C=O), 1649 cm^{-1} (C=N). ^1H NMR: δ = 0.83 (s, 3 H, 2′-CH_3), 0.86 (pt, 3 H, 18-H_3), 1.23 [br m, 28 H, $(CH_2)_{14}$], 1.30 (s, 3 H, 6′-CH_3), 1.42 [s, 9 H, $C(CH_3)_3$], 1.47 (s, 3 H, 6′-CH_3), 1.55 (d, 1 H, 7′-H), 1.83 (m, 2 H, β-H_2), 2.04 (m, 2 H, 1′-H and 5′-H), 2.29 (m, 1 H, 7′-H), 2.51 (m, 2 H, 4′-H_2), 4.03 (dd, *J* = 5.2, *J* = 8 Hz, 1 H, α-H) ppm. ^{13}C NMR: δ = 14.1 (C-18), 22.7 (6′-CH_3), 22.9 (2′-CH_3), 25.9 (C-17), 27.3 (6′-CH_3), 28.0 (C-7′), 28.1 [$C(CH_3)_3$], 28.3 (C-16), 29.3−29.7 [$(CH_2)_{11}$], 31.9 (C-γ), 33.1 (C-β), 33.3 (C-4′), 38.2 (C-6′), 38.4 (C-5′), 50.1 (C-1′), 62.8 (C-α), 76.4 (C-2′), 80.9 (CMe_3), 170.9 (C=N), 177.7 (COO*t*Bu) ppm. $C_{32}H_{59}NO_3$ (505.82): calcd. C 75.99, H 11.75, N 2.78; found C 75.66, H 11.99, N 2.62.

***tert*-Butyl (2*S*)-2-{[(1*R*,2*R*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo-[3.1.1]hept-3-ylidene]amino}octadecanoate [(−)-4] from 1-Iodohexadecane:** Yield 44% (0.22 g); R_f (EtOAc/petroleum ether, 1:7) = 0.3;

de = 98%; t_R = 26.28 min. $[\alpha]_D^{25} = -40.6$ (*c* = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3438 (br, OH), 2925 and 2855 (CH_2), 1730 (C=O), 1649 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 0.82 (s, 3 H, 2′-CH_3), 0.86 (pt, 3 H, 18-H_3), 1.23 [br. m, 28 H, $(CH_2)_{14}$], 1.31 (s, 3 H, 6′-CH_3), 1.42 (s, 9 H, *t*Bu), 1.47 (s, 3 H, 6′-CH_3), 1.55 (d, 1 H, 7′-H), 1.83 (m, 2 H, β-H_2), 2.06 (m, 2 H, 1′-H and 5′-H), 2.30 (m, 1 H, 7′-H), 2.54 (m, 2 H, 4′-H_2), 4.03 (dd, *J* = 5.2, *J* = 8 Hz, 1 H, α-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-18), 22.7 (6′-CH_3), 22.9 (2′-CH_3), 25.9 (C-17), 27.3 (C-7′ and 6′-CH_3), 28.0 [C(CH_3)$_3$], 28.3 (C-16), 29.3−29.7 [$(CH_2)_{11}$], 31.9 (C-γ), 33.1 (C-β), 33.3 (C-4′), 38.23 (C-6′), 38.4 (C-5′), 50.1 (C-1′), 62.8 (C-α), 76.4 (C-2′), 80.9 (CMe_3), 170.9 (C=N), 177.6 (COO*t*Bu) ppm. $C_{32}H_{59}NO_3$ (505.82): calcd. C 75.99, H 11.75, N 2.78; found C 75.97, H 11.62, N 2.68.

Hydrolysis of Schiff Bases. General Procedure: A solution of $NH_2OH{\cdot}HCl$ in MeOH (0.5 M, 12 mL) was added to a solution of the Schiff bases (−)- or (+)-**2**−**4** (1.7 mmol) in MeOH (6 mL), and the solution was stirred overnight at room temperature. Finally, water was added and the white crystalline product was filtered off. The residue was washed with MeOH/water and dried to provide the enantiomerically pure hydrochlorides **5**−**7**.

***tert*-Butyl D-2-Aminotetradecanoate Hydrochloride [(*R*)-(−)-5]:** Yield 91% (0.52 g); m.p. 103−105 °C (MeOH/water). $[\alpha]_D^{20} = -6.47$ (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3334 (NH), 2919−2878 (CH_2), 1730 (C=O), 1480 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.84 (pt, 3 H, 14-H_3), 1.20 [m, 20 H, $(CH_2)_{10}$], 1.46 [s, 9 H, C(CH_3)$_3$], 1.99 (m, 2 H, β-H_2), 3.84 (m, 1 H, α-H), 8.13 (m, 3 H, NH_3^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-14), 22.5−30.7 [$(CH_2)_{10}$], 29.6 [C(CH_3)$_3$], 31.9 (C-β), 53.6 (C-α), 83.8 (CMe_3), 167.9 (COO*t*Bu) ppm. $C_{18}H_{38}ClNO_2$ (335.95): calcd. C 64.35, H 11.40, N 4.17; found C 64.68, H 11.54, N 4.07.

***tert*-Butyl L-2-Aminotetradecanoate Hydrochloride [(*S*)-(+)-5]:** Yield 88% (0.5 g); m.p. 102−103 °C (MeOH/water). $[\alpha]_D^{20} = +6.47$ (*c* = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, 14-H_3), 1.22 [m, 20 H, $(CH_2)_{10}$], 1.47 [s, 9 H, C(CH_3)$_3$], 1.96 (pq, 2 H, β-H_2), 3.84 (pt, 1 H, α-H), 8.8 (br. m, NH_3^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-14), 22.7−30.6 [$(CH_2)_{10}$], 29.7 [C(CH_3)$_3$], 31.9 (C-β), 53.6 (C-α), 83.8 (CMe_3), 167.8 (COO*t*Bu) ppm. $C_{18}H_{38}ClNO_2$ (335.95): calcd. C 64.35, H 11.40, N 4.17; found C 64.64, H 11.37, N 4.20.

***tert*-Butyl D-2-Aminohexadecanoate Hydrochloride [(*R*)-(−)-6]:** Yield 89% (0.55 g); m.p. 103.5−104.5 °C (MeOH/water). $[\alpha]_D^{25} = -11.3$ (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3440 (NH), 2920 and 2850 (CH_2), 1736 (C=O), 1467 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.86 (pt, 3 H, 16-H_3), 1.23 [m, 24 H, $(CH_2)_{12}$], 1.48 [s, 9 H, C(CH_3)$_3$], 1.96 (m, 2 H, β-H_2), 3.84 (m, 1 H, α-H), 8.77 (m, 3 H, NH_3^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-16), 22.7−29.7 [$(CH_2)_{12}$], 30.6 [C(CH_3)$_3$], 31.9 (C-β), 53.6 (C-α), 83.8 (CMe_3), 167.8 (COO*t*Bu) ppm. $C_{20}H_{42}ClNO_2$ (364.01): calcd. C 65.99, H 11.63, N 3.85; found C 65.86, H 11.63, N 3.65.

***tert*-Butyl L-2-Aminohexadecanoate Hydrochloride [(*S*)-(+)-6]:** Yield 90% (0.56 g); m.p. 102−103 °C (MeOH/water). $[\alpha]_D^{25} = +10.5$ (*c* = 0.94, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.86 (pt, 3 H, 16-H_3), 1.23 (m, 24 H, $(CH_2)_{12}$], 1.48 [s, 9 H, C(CH_3)$_3$], 1.98 (pq, 2 H, β-H_2), 3.84 (pt, 1 H, α-H), 8.76 (br. m, NH_3^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-16), 22.7−30.7 [$(CH_2)_{12}$], 29.7 [C(CH_3)$_3$], 32 (C-β), 53.6 (C-α), 83.9 (CMe_3), 167.8 (COO*t*Bu) ppm. $C_{20}H_{42}ClNO_2$ (364.01): calcd. C 65.99, H 11.63, N 3.85; found C 65.66, H 11.64, N 3.88.

***tert*-Butyl D-2-Aminooctadecanoate Hydrochloride [(*R*)-(−)-7]:** Yield 91% (0.61 g); m.p. 97−98 °C (MeOH/water). $[\alpha]_D^{20} = -8.3$ (*c* = 1.44, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3448 (NH), 2918 and 2850 (CH_2), 1730 (C=O), 1471 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.84 (pt, 3 H, 18-H_3), 1.21 [m, 28 H, $(CH_2)_{14}$], 1.46 [s, 9 H, C(CH_3)$_3$], 1.94 (m, 2 H, β-H_2), 3.85 (m, 1 H, α-H), 8.71 (m, 3 H, NH_3^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-18), 22.7−31.9 [$(CH_2)_{14}$], 30.7 [C(CH_3)$_3$], 31.94 (C-β), 53.58 (C-α), 83.77 (CMe_3), 167.8 (COO*t*Bu) ppm. $C_{22}H_{46}ClNO_2$ (392.06): calcd. C 67.40, H 11.83, N 3.57; found C 67.40, H 12.06, N 3.42.

***tert*-Butyl L-2-Aminooctadecanoate Hydrochloride [(*S*)-(+)-7]:** Yield 89% (0.59 g); m.p. 94−95 °C (MeOH/water). $[\alpha]_D^{20} = +7.6$ (*c* = 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.84 (pt, 3 H, 18-H_3), 1.21 [m, 28 H, $(CH_2)_{14}$], 1.46 [s, 9 H, C(CH_3)$_3$], 1.94 (pq, 2 H, β-H_2), 3.85 (pt, 1 H, α-H), 8.73 (br. m, NH_3^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-18), 22.7−30.6 [$(CH_2)_{14}$], 29.7 [C(CH_3)$_3$], 31.9 (C-β), 53.8 (C-α), 83.8 (CMe_3), 167.8 (COO*t*Bu) ppm. $C_{22}H_{46}ClNO_2$ (392.06): calcd. C 67.40, H 11.83, N 3.57; found C 67.32, H 11.64, N 3.44.

Protection of Amino Esters. General Procedure: Fmoc-OSu (1 mmol) in dioxane (10 mL) was added at 40 °C to the enantiomerically pure hydrochloride **5**−**7** (0.9 mmol), dissolved in dioxane (10 mL). NaOH (1 M) was then added dropwise until pH = 8−9 was reached. The reaction was stopped by addition of water (20 mL) and HCl (1 M) until pH = 3 was reached. Extraction with CH_2Cl_2, washing of the organic layer with water and concentration under reduced pressure afforded an oil that was crystallised from MeOH/H_2O to afford compounds **8**−**10**.

***tert*-Butyl D-2-[(9-Fluorenylmethoxycarbonyl)amino]tetradecanoate [Fmoc-D-Atd-O*t*Bu, (*R*)-(−)-8]:** Yield 71% (0.333 g); m.p. 38−39 °C (MeOH/water); R_f (EtOAc/petroleum ether, 1:2) = 0.73. $[\alpha]_D^{20} = -7.6$ (*c* = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3353 (NH), 2928 and 2851 (CH_2), 1729 (COO*t*Bu), 1694 (CONH), 1449 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, 14-H_3), 1.23 [m, 20 H, $(CH_2)_{10}$], 1.45 [s, 9 H, C(CH_3)$_3$], 1.66−1.76 (m, 2 H, β-H_2), 4.22 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.25 (d, *J* = 8 Hz, NH, 1 H), 7.33 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.58 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.75 (d, *J* = 7 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (C-14), 22.7−31.9 [$(CH_2)_{10}$], 28.1 [C(CH_3)$_3$], 32.9 (C-β), 47.2 (fluorenyl C-9), 54.3 (C-α), 66.9 (CH_2−O), 81.9 (CMe_3), 119.9 (fluorenyl C-4 and C-5), 125.1 (fluorenyl C-1 and C-8), 127.0 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141 and 143.8 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.7 (CONH), 171.7 (COO*t*Bu) ppm. $C_{33}H_{47}NO_4$ (521.73): calcd. C 75.97, H 9.08, N 2.68; found C 76.13, H 9.15, N 2.70.

***tert*-Butyl L-2-[(9-Fluorenylmethoxycarbonyl)amino]tetradecanoate [Fmoc-L-Atd-O*t*Bu, (*S*)-(+)-8]:** Yield 75% (0.35 g); m.p. 37−39 °C (MeOH/water); R_f (EtOAc/petroleum ether, 1:2) = 0.73. $[\alpha]_D^{20} = +7.3$ (*c* = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, 14-H_3), 1.23 [m, 20 H, $(CH_2)_{10}$], 1.45 (s, 9 H, [C(CH_3)$_3$], 1.64−1.76 (m, 2 H, β-H_2), 4.23 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.28 (d, *J* = 7 Hz, 1 H, NH), 7.4 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.59 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.75 (d, *J* = 7 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-14), 22.7−31.9 [$(CH_2)_{10}$], 28.1 [C(CH_3)$_3$], 32.9 (C-β), 47.3 (fluorenyl C-9), 54.3 (C-α), 66.9 (CH_2−O), 81.9 (CMe_3), 119.9 and 120.1 (fluorenyl C-4 and C-5), 127.4 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 125.1 (fluorenyl C-1 and C-8), 141.2 and 143.8 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.7 (CONH), 171.7 (COO*t*Bu) ppm. $C_{33}H_{47}NO_4$ (521.73): calcd. C 75.97, H 9.08, N 2.68; found C 76.12, H 9.13, N 2.53.

***tert*-Butyl D-2[(9-Fluorenylmethoxycarbonyl)amino]hexadecanoate [Fmoc-D-Ahd-O*t*Bu, (*R*)-(−)-9]:** Yield 84% (0.42 g); m.p. 47−48 °C

(MeOH/water); R_f (EtOAc/petroleum ether, 1:2) = 0.76. $[\alpha]_D^{20}$ = −5.7 (*c* = 0.28, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3340 (NH), 2920 and 2850 (CH_2), 1736 (COO*t*Bu), 1696 (CONH), 1467 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.86 (pt, 3 H, 16-H_3), 1.23 [m, 24 H, $(CH_2)_{12}$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.56−1.76 (m, 2 H, β-H_2), 4.21 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.27 (d, *J* = 8.4 Hz, 1 H, NH), 7.35 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.58 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.76 (d, *J* = 7.2 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (C-16), 22.7−31.9 [$(CH_2)_{12}$], 28.0 [$C(CH_3)_3$], 32.8 (C-β), 47.2 (fluorenyl C-9), 54.3 (C-α), 66.9 (CH_2−O), 81.9 (CMe_3), 119.9 (fluorenyl C-4 and C-5), 125.0 (fluorenyl C-1 and C-8), 126.9 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2 and 143.8 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.7 (CONH), 171.7 (COO*t*Bu) ppm. $C_{35}H_{51}NO_4$ (549.78): calcd. C 76.46, H 9.35, N 2.55; found C 76.45, H 9.44, N 2.44.

***tert*-Butyl L-2-[(9-Fluorenylmethoxycarbonyl)amino]hexadecanoate [Fmoc-L-Ahd-O*t*Bu, (*S*)-(+)-9]:** Yield 83% (0.41 g); m.p. 47−48 °C (MeOH/water); R_f (EtOAc/petroleum ether, 1:2) = 0.72. $[\alpha]_D^{20}$ = +5.9 (*c* = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.86 (pt, 3 H, 16-H_3), 1.23 [m, 24 H, $(CH_2)_{12}$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.53−1.77 (m, 2 H, β-CH_2), 4.21 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.27 (d, *J* = 8.6 Hz, 1 H, NH), 7.33 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.58 (d, *J* = 7.4 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 6.6 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (C-16), 22.7−31.9 [$(CH_2)_{12}$], 28.1 [$C(CH_3)_3$], 32.9 (C-β), 47.2 (fluorenyl C-9), 54.4 (C-α), 66.9 (CH_2−O), 81.9 (CMe_3), 119.9 (fluorenyl C-4 and C-5), 125.1 (fluorenyl C-1 and C-8), 126.9 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2 and 143.8 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.7 (CONH), 171.7 (COO*t*Bu) ppm. $C_{35}H_{51}NO_4$ (549.78): calcd. C 76.46, H 9.35, N 2.55; found C 76.12, H 9.38, N 2.31.

***tert*-Butyl D-2-[(9-Fluorenylmethoxycarbonyl)amino]octadecanoate [Fmoc-D-Aod-O*t*Bu, (*R*)-(−)-10]:** Yield 76% (0.395 g); m.p. 49−50 °C (MeOH/water); R_f (EtOAc/petroleum ether, 1:2) = 0.65. $[\alpha]_D^{20}$ = −6.6 (*c* = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3340 (NH), 2919 and 2850 (CH_2), 1736 (COO*t*Bu), 1694 (CONH), 1467 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, 18-H_3), 1.23 [m, 28 H, $(CH_2)_{14}$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.65−1.76 (m, 2 H, β-H_2), 4.23 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.27 (d, *J* = 7.6 Hz, 1 H, NH), 7.35 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.58 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7.4 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (C-18), 22.7−31.9 [$(CH_2)_{14}$], 28.0 [$C(CH_3)_3$], 32.8 (C-β), 47.2 (fluorenyl C-9), 54.3 (C-α), 66.9 (CH_2−O), 81.9 (CMe_3), 119.9 (fluorenyl C-4 and C-5), 125.1 (fluorenyl C-1 and C-8), 127.0 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.3 and 143.9 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.8 (CONH), 171.8 (COO*t*Bu) ppm. $C_{37}H_{55}NO_4$ (577.84): calcd. C 76.91, H 9.59, N 2.42; found C 76.90, H 9.71, N 2.40.

***tert*-Butyl L-2-[(9-Fluorenylmethoxycarbonyl)amino]octadecanoate [Fmoc-L-Aod-O*t*Bu, (*S*)-(+)-10]:** Yield 80% (0.42 g); m.p. 52−53 °C (MeOH/water); R_f (EtOAc/petroleum ether, 1:2) = 0.77. $[\alpha]_D^{20}$ = +6.4 (*c* = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, 18-H_3), 1.23 [m, 28 H, $(CH_2)_{14}$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.64−1.76 (m, 2 H, β-H_2), 4.22 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.27 (d, *J* = 8 Hz, 1 H, NH), 7.35 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.58 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7.2 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (C-18), 22.7−31.9 [$(CH_2)_{14}$], 28.1 [$C(CH_3)_3$], 32.9 (C-β), 47.2 (fluorenyl C-9), 54.4 (C-α), 66.9 (CH_2−O), 81.9 (CMe_3), 119.9 (fluorenyl C-4 and C-5), 125.1 (fluorenyl C-1 and C-8), 127.1 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2 and 143.8 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.8 (CONH), 171.7 (COO*t*Bu) ppm. $C_{37}H_{55}NO_4$ (577.84): calcd. C 76.91, H 9.59, N 2.42; found C 76.83, H 9.83, N 2.62.

Hydrolysis of Amino Esters. General Procedure: The Fmoc-protected amino ester **8**−**10** (0.5 mmol) was treated with 40% TFA in DCM (10 mL) at room temperature for 1.5 h. The solvent was removed, and the residue was crystallised from hexane and subsequently lyophilized to provide compounds **11**−**13**.

D-2-[(9-Fluorenylmethoxycarbonyl)amino]tetradecanoic Acid [Fmoc-D-Atd-OH), (*R*)-(−)-11]: Yield 97% (0.226 g); m.p. 102−103 °C (hexane); R_f (EtOAc/petroleum ether, 1:2) = 0.33. $[\alpha]_D^{20}$ = −4.7 (*c* = 0.36, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3600−2500 (br, OH), 3320 (NH), 2920 and 2851 (CH_2), 1729 (CONH), 1697 (COOH), 1449 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, CH_3), 1.22 [m, 20 H, $(CH_2)_{10}$], 1.63−1.83 (m, 2 H, β-H_2), 4.18 (m, 2 H, α-H and fluorenyl 9-H), 4.36 (m, 2 H, CH_2−O), 5.32 (d, *J* = 8.2 Hz, 1 H, NH), 7.31 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.55 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.72 (d, *J* = 7.4 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 22.7−31.9 [$(CH_2)_{10}$], 32.1 (C-β), 47.1 (fluorenyl C-9), 54.1 (C-α), 67.6 (CH_2−O), 119.9 (fluorenyl C-4 and C-5), 125.1 (fluorenyl C-1 and C-8), 127.0 and 127.7 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.3 and 143.7 (fluorenyl C-4a and C-4b and C-8a and C-9a), 156.2 (CONH), 171.2 (COOH) ppm. $C_{29}H_{39}NO_4$ (465.62): calcd. C 74.81, H 8.44, N 3.01; found C 75.14, H 8.58, N 3.09.

L-2-[(9-Fluorenylmethoxycarbonyl)amino]tetradecanoic Acid [Fmoc-L-Atd-OH, (*S*)-(+)-11]: Yield 80% (0.186 g); m.p. 100−101 °C (hexane); R_f (EtOAc/petroleum ether, 1:2) = 0.33. $[\alpha]_D^{20}$ = +5.3 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, CH_3), 1.23 [m, 20 H, $(CH_2)_{10}$], 1.65−1.85 (m, 2 H, β-H_2), 4.2 (m, 2 H, α-H and fluorenyl 9-H), 4.4 (m, 2 H, CH_2−O), 5.22 (d, *J* = 8.4 Hz, 1 H, NH), 7.35 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.57 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6 (CH_3), 22.7−31.9 [$(CH_2)_{10}$], 32.3 (C-β), 47.1 (fluorenyl C-9), 53.8 (C-α), 67.1 (CH_2−O), 119.9 (fluorenyl C-4 and C-5), 124.9 (fluorenyl C-1 and C-8), 126.9 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2, 143.6 and 143.7 (fluorenyl C-4a and C-4b and C-8a and C-9a), 156.0 (CONH), 177.6 (COOH) ppm. $C_{29}H_{39}NO_4$ (465.62): calcd. C 74.81, H 8.44, N 3.01; found C 75.10, H 8.67, N 2.88.

D-2-[(9-Fluorenylmethoxycarbonyl)amino]hexadecanoic Acid [Fmoc-D-Ahd-OH, (*R*)-(−)-12]: Yield 83% (0.204 g); m.p. 96−97 °C (hexane); R_f (EtOAc/petroleum ether, 1:2) = 0.5. $[\alpha]_D^{20}$ = −4.92 (*c* = 0.95, $CHCl_3$), −1.0 (*c* = 1.1, CH_2Cl_2), +9.3 (*c* = 1.1, DMF). IR (KBr): $\tilde{\nu}$ = 3600−2500 (br, OH), 3319 (NH), 2918 and 2849 (CH_2), 1753 (CONH), 1698 (COOH), 1468 cm^{-1} (CH_2). ^1H NMR ($CDCl_3$): δ = 0.86 (pt, 3 H, CH_3), 1.23 [m, 24 H, $(CH_2)_{12}$], 1.7−1.88 (m, 2 H, β-H_2), 4.21 (m, 2 H, α-H and fluorenyl 9-H), 4.4 (m, 2 H, CH_2−O), 5.2 (d, *J* = 8 Hz, 1 H, NH), 7.34 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.57 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.7−31.9 [$(CH_2)_{12}$], 32.4 (C-β), 47.1 (fluorenyl C-9), 53.8 (C-α), 67.0 (CH_2−O), 119.9 (fluorenyl C-4 and C-5), 125.1 (fluorenyl C-1 and C-8), 126.9 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2 and 143.6 (fluorenyl C-4a and C-4b and C-8a and C-9a), 156.0 (CONH), 176.4 (COOH) ppm. $C_{31}H_{43}NO_4$ (493.68): calcd. C 75.42, H 8.78, N 2.84; found C 75.03, H 8.90, N 3.03.

L-2-[(9-Fluorenylmethoxycarbonyl)amino]hexadecanoic Acid [Fmoc-L-Ahd-OH, (*S*)-(+)-12]: Yield 98% (0.24 g); m.p. 95 °C (hexane); R_f (EtOAc/petroleum ether, 1:2) = 0.48. $[\alpha]_D^{20}$ = +5.17 (*c* = 1.1, $CHCl_3$), +3.7 (*c* = 0.9, CH_2Cl_2), −8.8 (*c* = 1.2, DMF). ^{1}H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, CH_3), 1.23 [m, 24 H, $(CH_2)_{12}$], 1.7−1.85 (m, 2 H, β-H_2), 4.21 (m, 2 H, α-H and fluorenyl 9-H), 4.4 (m, 2 H, CH_2−O), 5.22 (d, *J* = 8.2 Hz, 1 H, NH), 7.33 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.57 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.7−31.9 [$(CH_2)_{12}$], 32.4 (C-β), 47.1 (fluorenyl C-9), 53.8 (C-α), 67.1 (CH_2−O), 119.9 (fluorenyl C-4 and C-5), 124.9 (fluorenyl C-1 and C-8), 126.9 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2, 143.6 and 143.7 (fluorenyl C-4a and C-4b and C-8a and C-9a), 156.0 (CONH), 176.9 (COOH) ppm. $C_{31}H_{43}NO_4$ (493.68): calcd. C 75.42, H 8.78, N 2.84; found C 75.43, H 9.21, N 2.11.

D-2-[(9-Fluorenylmethoxycarbonyl)amino]octadecanoic Acid [Fmoc-D-Aod-OH, (*R*)-(−)-13]: Yield 96% (0.25 g); m.p. 88−89 °C (hexane); R_f (EtOAc/petroleum ether, 1:2) = 0.3. $[\alpha]_D^{20}$ = −4.5 (*c* = 0.95, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3600−2500 (br, OH), 3317 (NH), 2918 and 2849 (CH_2), 1750 (CONH), 1697 (COOH), 1541 cm^{-1} (CH_2). ^{1}H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, CH_3), 1.22 [m, 28 H, $(CH_2)_{14}$], 1.63−1.83 (m, 2 H, β-H_2), 4.2 (m, 2 H, α-H and fluorenyl 9-H), 4.4 (m, 2 H, CH_2−O), 5.23 (d, *J* = 8.2 Hz, 1 H, NH), 7.34 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.57 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7.2 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.7−31.9 [$(CH_2)_{14}$], 32.4 (C-β), 47.1 (fluorenyl C-9), 53.8 (C-α), 67.1 (CH_2−O), 119.9 (fluorenyl C-4 and C-5), 124.7 (fluorenyl C-1 and C-8), 126.9 and 127.6 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.2 and 143.7 (fluorenyl C-4a and C-4b and C-8a and C-9a), 156.0 (CONH), 171.2 (COOH) ppm. $C_{33}H_{47}NO_4$ (521.73): calcd. C 75.97, H 9.08, N 2.68; found C 75.72, H 9.42, N 2.61.

L-2-[(9-Fluorenylmethoxycarbonyl)amino]octadecanoic Acid [Fmoc-L-Aod-OH, (*S*)-(+)-13]: Yield 97% (0.253 g); m.p. 88−89 °C (hexane); R_f (EtOAc/petroleum ether, 1:2) = 0.25. $[\alpha]_D^{20}$ = +4.44 (*c* = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.85 (pt, 3 H, CH_3), 1.23 [m, 28 H, $(CH_2)_{14}$], 1.65−1.85 (m, 2 H, β-H_2), 4.2 (m, 2 H, α-H and fluorenyl 9-H), 4.4 (m, 2 H, CH_2−O), 5.2 (d, *J* = 8, 1 H, NH), 7.33 (m, 4 H, fluorenyl 2-H and 7-H and 3-H and 6-H), 7.57 (d, *J* = 7 Hz, 2 H, fluorenyl 1-H and 8-H), 7.74 (d, *J* = 7 Hz, 2 H, fluorenyl 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 22.7−31.9 [$(CH_2)_{14}$], 32.4 (C-β), 47.2 (fluorenyl C-9), 53.8 (C-α), 67.1 (CH_2−O), 119.9 (fluorenyl C-4 and C-5), 125.0 (fluorenyl C-1 and C-8), 127.0 and 127.7 (fluorenyl C-2 and C-7 and C-3 and C-6), 141.3 and 143.6 (fluorenyl C-4a and C-4b and C-8a and C-9a), 155.0 (CONH), 171.2 (COOH) ppm. $C_{33}H_{47}NO_4$ (521.73): calcd. C 75.97, H 9.08, N 2.68; found C 76.01, H 9.41, N 2.34.

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