Synthesis of Enantiopure ω-Functionalized C15 α-Amino Carboxylates

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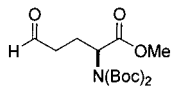
Abstract: An efficient route for the synthesis of enantiopure ω-hydroxy, ω-carboxy, ω-oxo, and ω-amino α-amino acids and bis-α-amino acids was developed. The synthesis of ω-trityloxy δ,ϵ-unsaturated α-amino acids was based on the Wittig reaction of methyl (2*S*)-2-[bis(*tert*-butoxycarbonyl)-amino]-5-oxopentanoate with ω-trityloxy alkylidene triphenylphosphoranes. After hydrogenation, the ω-hydroxy α-amino acid was used as starting material for the synthesis of other ω-functionalized α-amino acids. The length of the side chain of α-amino acids or bis-α-amino acids depends on the starting alkanediol or dibromide used to prepare the phosphoranes.

In the past decade, the field of amino acids and peptides has gained enormous popularity and relevance, particularly with the emergence of unnatural analogues as components of compounds with therapeutic potential.[1] The need to replace natural amino acids in peptides with nonproteinogenic counterparts in order to obtain new medicinal agents, exhibiting better binding to specific receptors and more potent inhibition of target enzymes, has stimulated a great deal of innovation on synthetic methods. Recent developments in new bioorganic methodologies such as site-directed mutagenesis using expanded genetic codes, total- or semi-synthesis of enzymes, and protein splicing have enabled incorporation of unnatural amino acids into the framework of native proteins.[2]

A variety of methods for the stereoselective synthesis of α-amino acids and the construction of chiral molecules using amino acids have been developed.[3] Approaches using regioselective functionalization of readily available chiral building blocks, e.g., aldehydes obtained from amino acids, are especially attractive for the synthesis of unnatural amino acids. Rapoport and Lubell have used configurationally stable *N*-(9-(9-phenylfluorenyl))-L-alaninal for the synthesis of amino acid analogues,[4] whereas Reetz has employed *N*,*N*-dibenzylamino aldehydes for a variety of stereoselective reactions.[5] Protected enantiopure aldehydes obtained from serine, such as Gamrner's aldehyde[6] as well as L-aspartic acid β-semialdehydes,[7] have also found interesting synthetic applications. We have illustrated the use of methyl (2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxopentanoate (**1**) for the synthesis of unsaturated lipidic α-amino acids.[8] This paper reports an efficient method to prepare ω-functionalized enantiopure α-amino acids using the protected glutamic acid γ-aldehyde **1** as the key intermediate compound. We have focused our attention on long chain derivatives, because long chain α-amino acids are of great importance for the synthesis of drug delivery systems and bioactive lipid mimetics.[9,10]



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Methyl (2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxopentanoate (**1**) was obtained by selective reduction of dimethyl *N*,*N*-di-Boc glutamate with DIBALH as previously described.[8] The Wittig olefination of aldehyde **1** with oxido, carboxy, or amino ylides may directly lead to α-amino acids containing a free functional group in the side chain. Maryanoff[11] has studied the reaction of hexanal and benzaldehyde with triphenylphosphonium ylides containing anionic nucleophilic groups in their side chain. Following Maryanoff's procedure the reactions of **1** with the ylides generated from phosphonium salts of 10-bromodecan-1-ol and 11-bromoundecanoic acid were tested. In each case, the desired product was not obtained. Thus, we decided to use an ylide containing an ω-protected hydroxy group.

To prepare such ylides, α,ω-alkane diols **2a**,**b** were treated with TrtCl and DMAP in pyridine to produce monoprotected diols **3a**,**b** (Scheme 1). The free hydroxy group of **3a**,**b** was activated by conversion to mesylate, and the methanesulfonyloxy group was replaced by iodide ion. Iodides **4a**,**b** were treated with PPh_3 in MeCN under reflux to produce triphenylphosphonium salts **5a**,**b**.

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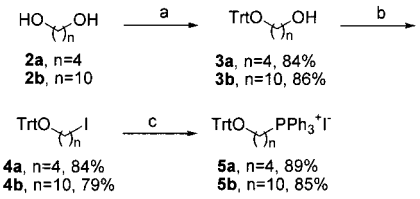
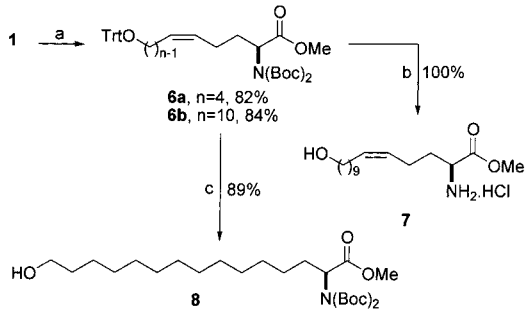
Scheme 1. Synthesis of Triphenylphosphonium Salts 5a,b[a]



[a] Reagents and conditions: (a) TrtCl, DMAP, pyridine; (b) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaI, acetone; (c) PPh_3, MeCN.

Scheme 2. Synthesis of ω-Hydroxy α-Amino Acid Derivatives[a]



[a] Reagents and conditions: (a) **5a** or **5b**, KHMDS, toluene; (b) 4 N HCl/THF; (c) H_2, 10% Pd/C, MeOH.

Aldehyde **1** reacted with the ylides generated by treatment of **5a**,**b** with KHMDS in toluene at 0 °C (Scheme 2). The reactions were carried out at −78 °C, and the protected amino acids **6a**,**b** were produced in high yields. Both compounds were identified as *Z*-olefins, after ^{1}H NMR analysis, as was expected.[12,13] Methyl ester of amino acid **7** was obtained almost quantitatively by treatment of **6b** with HCl in THF. To check the enantiomeric purity of protected amino acids **6**, methyl ester of amino acid **7** was converted into the corresponding Mosher amides[14] and studied by ^{19}F NMR analysis. Coupling of **7** with (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as a condensing agent in the presence of 1-hydroxybenzotriazole (HOBt) produced the corresponding MTP amides. An enantiomeric excess > 95% was indicated for **7** by the absence of any diastereomeric signal in the ^{19}F NMR spectrum of each MTP amide.

Catalytic hydrogenation of **6b** produced the saturated ω-hydroxy α-amino acid **8** (Scheme 2). This derivative was chosen as a model compound and was converted to ω-carboxy, ω-oxo, and ω-amino α-amino acids as depicted in Scheme 3. Oxidation of **8** using 2.5 equiv of NaOCl in the presence of 4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy free radical (AcNH-TEMPO)[15] and Aliquat 336[16] produced the ω-carboxy amino acid **9**. In the absence of the phase-transfer catalyst and using 1.1 equiv of NaOCl[17] the ω-oxo derivative **10** was isolated. To prepare diamino acids, the hydroxy group of **8** was activated as its methanesulfonate and was converted directly into azide **11** by treatment with sodium azide in DMF at 60 °C in high yield. Catalytic hydrogenation of **11** produced the free ω-amino functionalized derivative **12**, whereas in the presence of *N*-(9- fluorenylmethoxycarbonyloxy)succinimide the selectively protected derivative **13** was isolated.

In recent years there is an increasing interest in the development of synthetic routes to enantiopure bis-α-amino acids, not only because of their synthetic usefulness[18,19] but also for their ability to function as substrate-based inhibitors[20] and ligands for self-assembly.[21] Aldehyde **1** may also be used as starting material for the synthesis of bis-α-amino acids. Bis(triphenylphosphonium salt) $Br^-Ph_3P^+(CH_2)_8PPh_3^+Br^-$ was prepared by treatment of the corresponding α,ω-dibromoalkane with PPh_3 in MeCN under reflux. Bis(phosphonium ylide) generated from the corresponding bis(triphenylphosphonium salt) with KHMDS in toluene at 0 °C, reacted with aldehyde **1** under the conditions described for the synthesis of **6a**,**b** to produce bis-α-amino acid **14** in high yield (Scheme 4). The geometry of the double bonds was *Z*, based on NMR data. Saponification of the methyl esters, after removal of the Boc protecting groups under acidic conditions, produced the free bis-α-amino acid **15** in high yield.

In conclusion, we have developed an efficient route for the synthesis of enantiopure ω-hydroxy, ω-carboxy, α-amino α-amino acids and bis-α-amino acids. The length of the side chain depends on the starting alkanediol or dibromide used to prepare the phosphonium salts. Both enantiomers of ω-functionalized α-amino acids may be prepared, since the chirality of the product depends on the chirality of the key intermediate glutamic acid γ-aldehyde **1** obtained from the inexpensive and available in both enantiomeric forms Glu.

Experimental Section

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on polarimeter using a 10 cm cell. NMR spectra were recorded on a 200 or a 300 MHz spectrometer. Where applicable, structural assignments were based on DEPT, COSY, and HETCOR experiments. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70−230 or 230−400 mesh) for column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin both in ethanol stain. THF was passed through a column of aluminum oxide, distilled over CaH_2, and stored over molecular sieves. Toluene was distilled and stored over Na. DMF was distilled under reduced pressure and stored over molecular sieves. MeCN was of HPLC grade whereas all other solvents and chemicals were of reagent grade and used without further purification. Compound **1** was prepared as described in the literature.[8]

General Procedure for the Wittig Reaction (compounds 6a,b, 14). To a stirred suspension of phosphonium salt **5a**,**b** (9.60 mmol) or $Br^-Ph_3P^+(CH_2)_8PPh_3^+Br^-$ (4.00 mmol, 3.19 g) in dry toluene (54 mL) was added a 0.5 M solution of KHMDS (17.6 mL or 16.0 mL, respectively) in toluene dropwise over a period of 5 min at 0 °C under N_2. The bright red solution was stirred for another 15 min and cooled to −78 °C, and a solution of the

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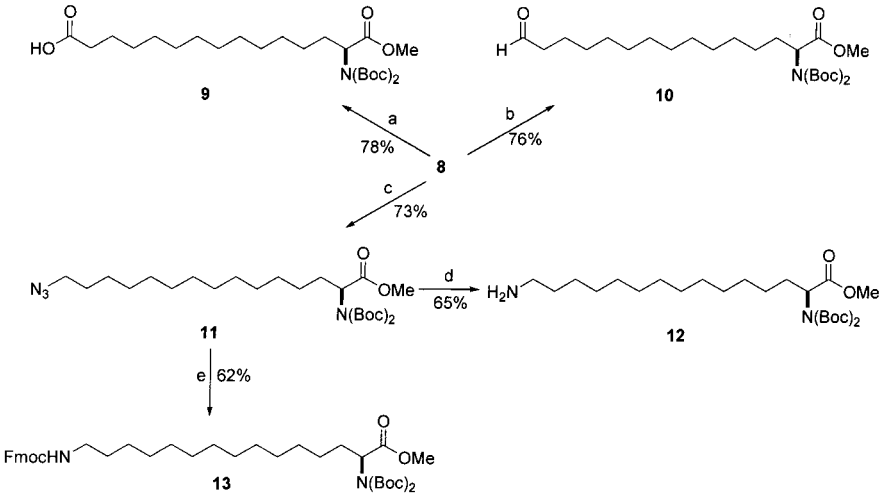
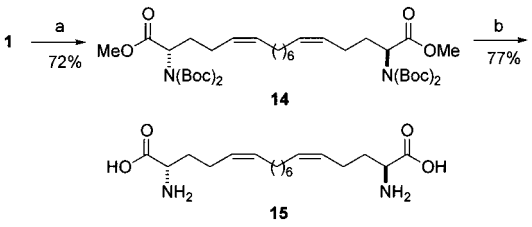
Scheme 3. Synthesis of Protected ω-Functionalized α-amino Acids[a]



[a] Reagents and conditions: (a) NaOCl, AcNH-TEMPO, Aliquat, KBr, $NaHCO_3$, CH_2Cl_2, H_2O; (b)NaOCl, AcNH-TEMPO, NaBr, $NaHCO_3$, EtOAc, toluene, H_2O; (c) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaN_3, DMF; (d) H_2, 10% Pd/C, MeOH; (e) H_2, 10% Pd/C, Fmoc-OSu, CH_2Cl_2.

Scheme 4. Synthesis of Bis-α-amino Acid[a]



[a] Reagents and conditions: (a) $Br^-Ph_3P^+(CH_2)_8PPh_3^+Br^-$, KHMDS, toluene; (b) (i) 4 N HC1/THF, (ii) 1 N NaOH, MeOH.

aldehyde **1** (8.00 mmol, 2.76 g) in dry toluene (8 mL) was added in one portion. The light yellow mixture was stirred at room temperature for 20 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (70 mL) and extracted with Et_2O (3 × 16 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed, and the residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:9 (compounds **6a**,**b)** or $CHCl_3$ (compound **14)** as eluent.

Methyl (2*S*,5*Z*)-2-[bis(*tert*-butoxycarbonyl)amino]-9-trityloxynon-5-enoate (6a): yield 82%; colorless oil; $[\alpha]^{23}_D$ −24.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 [br s, 18H, 2 × $C(CH_3)_3$], 1.67−1.75 (m, 2H, CH_2CH_2O), 1.80−2.22 (m, 6H, CH_2CHCO, $CH_2CH{=}CHCH_2$), 3.08 (t, 2H, *J* = 6.6 Hz, CH_2O), 3.71 (s, 3H, OMe), 4.88 (dd, 1H, *J* = 5.0, 8.6 Hz, CHCO), 5.32−5.43 (m, 2H, CH=CH), 7.18−7.37 and 7.41−7.51 (m, 15H, CPh_3); ^{13}C NMR (50 MHz, CDC_{13}) δ 24.1, 27.9 (6C), 28.1 (2C), 30.1, 52.1, 57.6, 63.2, 83.0 (2C), 86.2, 126.7 (3C), 127.6 (6C), 128.5 (6C), 128.9, 130.5, 144.5 (3C), 152.1 (2C), 171.4. Anal. Calcd for $C_{39}H_{49}NO_7$ (643.82): C, 72.76; H, 7.67; N, 2.18. Found: C, 73.02; H, 7.49; N, 2.32.

Methyl (2*S*,5*Z*)-2-[bis(*tert*-butoxycarbonyl)amino]-15-trityloxypentadec-5-enoate (6b): yield 84%; colorless oil; $[\alpha]^{23}_D$ −20.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 [br s, 12H, $(CH_2)_6$], 1.50 [br s, 18H, 2 × $C(CH_3)_3$], 1.56−1.70 (m, 2H, CH_2CH_2O), 1.82−2.27 (m, 6H, CH_2CHCO, $CH_2CH{=}CHCH_2$), 3.04 (t, 2H, *J* = 6.6 Hz, CH_2O), 3.71 (s, 3H, OMe), 4.88 (dd, 1H, *J* = 5.0, 8.6 Hz, CHCO), 5.30−5.52 (m, 2H, CH=CH), 7.18−7.37 and 7.41−7.51 (m, 15H, CPh_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0 (CH_2), 26.2 (CH_2), 27.2 (CH_2), 27.9 (6 × CH_3), 29.3 (CH_2), 29.5 (3 × CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 52.1 (CH_3), 57.7 (CH), 63.6 (CH_2), 83.0 (2 × C), 86.2 (C), 126.7 (3 × CH), 127.6 (6 × CH), 128.0 (CH), 128.6 (6 × CH), 131.2 (CH), 144.5 (3 × C), 152.0 (2 × C), 171.4 (C). Anal. Calcd for $C_{45}H_{61}NO_7$ (727.98): C, 74.25; H, 8.45; N, 1.92. Found: C, 74.19; H, 8.62; N, 2.21.

Dimethyl (2*S*,5*Z*,13*Z*,17*S*)-2,17-{bis[di(*tert*-butoxycarbonyl)amino}-octadeca-5,13-dienedioate (14): yield 72%; colorless oil; $[\alpha]^{23}_D$ −1.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 [br s, 8H, $(CH_2)_4$], 1.50 [br s, 36H, 4 × $C(CH_3)_3$], 1.82−2.27 (m, 12H, 2 × $CH_2CH{=}CHCH_2$, 2 × CH_2CHCO), 3.71 (s, 6H, 2 × OMe), 4.88 (dd, 2H, *J* = 5.0, 8.6 Hz, 2 × CHCO), 5.28−5.50 (m, 4H, 2 × CH=CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0 (2 × CH_2), 27.2 (2 × CH_2), 27.9 [4 × $C(CH_3)_3$], 29.3 (2 × CH_2), 29.6 (2 × CH_2), 30.1 (2 × CH_2), 52.1 (2 × OCH_3), 57.7 (2 × CHCO), 83.0 (4 × C), 128.1 (2 × CH=CH), 131.2 (2 × CH=CH), 152.0 (4 × CO), 171.4 (2 × CO). TOF MS *m*/*z* (%): 791 (M^+ + Na, 52), 691 (5), 579 (9), 569 (17), 469 (100), 413 (99), 369 (32). Anal. Calcd for $C_{40}H_{68}N_2O_{12}$ (768.99): C, 62.48; H, 8.91; N, 3.64. Found: C, 62.57; H, 8.64; N, 3.51.

Methyl (2*S*,5*Z*)-2-Amino-15-hydroxypentadec-5-enoate Hydrochloride (7). The *tert*-butoxycarbonyl group of **6b** (1.00 mmol, 728 mg) was removed by treatment with 4 N HCl in THF (12.5 mL) at room temperature for 30 min. After evaporation, the residue was purified by column chromatography using a mixture of $CHCl_3$:MeOH 9:1 as eluent. Yield >95%; yellow oil; $[\alpha]^{23}_D$ +7.6 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (br s, 12H), 1.52−1.94 (m, 4H), 1.96−2.22 (m, 4H), 3.43−3.78 (m, 6H), 5.26−5.50 (m, 2H). FAB MS *m*/*z* (%): 286 (M^+ + 1 − HCl, 100), 226 (50). Anal. Calcd for $C_{16}ClH_{32}NO_3{\cdot}H_2O$ (339.90): C, 56.54; H, 10.08; N, 4.12. Found: C, 56.63; H, 10.17; N, 4.15.

General Procedure for the Catalytic Hydrogenation (compounds 8, 12). To a solution of **6b** or **11** (5.00 mmol) in MeOH (50 mL) was added 10% Pd/C (300 mg), and the reaction mixture was stirred under H2 (1 atm) at room temperature for 16 h (compound **8)** or 45 min (compound **12).** After filtration through a pad of Celite, the solvent was removed and the product was purified by column chromatography using a mixture of $CHCl_3$:MeOH 9:1 as eluent.

Methyl (2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-15-hydroxypentadecanoate (8): yield 89%; colorless oil; $[\alpha]^{23}_D$ −9.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 [br s, 20H, $(CH_2)_{10}(CH_2)_2O$], 1.40−1.62 [m, 20H, CH_2CH_2O, 2 × $C(CH_3)_3$], 1.78−1.96 (m, 1H, CHHCHCO), 1.98−2.17 (m, 1H, CHHCHCO), 3.58−3.73 (m, 5H, OMe, CH_2O), 4.84 (dd, 1H, *J* = 5.2, 9.6 Hz, CHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8 (CH_2), 26.3 (CH_2), 28.0 (6 × CH_3), 28.1 (2 × CH_2), 29.4 (CH_2), 29.5 (2 × CH_2), 29.7 (3 × CH_2), 29.9 (CH_2), 32.9 (CH_2), 52.2 (CH_3), 58.0 (CH), 63.1 (CH_2), 83.0 (2 × C), 152.1 (2 × C), 171.5 (C). FAB MS *m*/*z* (%): 510 (M^+ + Na, 19), 410 (8), 288 (100). Anal. Calcd for $C_{26}H_{49}NO_7$ (487.68): C, 64.04; H, 10.13; N, 2.87. Found: C, 63.77; H, 10.38; N, 2.74.

Methyl (2*S*)-15-amino-2-[bis(*tert*-butoxycarbonyl)amino]pentadecanoate (12): yield 65%; colorless oil; $[\alpha]^{23}_D$ −22.0 (*c* 0.85, $CHCl_3$); ^{1}H NMR (200 MHz, $CDC1_3$) δ 1.23 [br s, 20H, $(CH_2)_{10}(CH_2)_2NH_2$], 1.48 [br s, 18H, 2 × $C(CH_3)_3$], 1.61−1.96 (m, 3H, $CH_2CH_2NH_2$, CHHCHCO), 9 1.98−2.16 (m, 1H, CHH-CHCO), 2.86−3.00 (m, 2H, CH_2NH_2), 3.69 (s, 3H, OMe), 4.83 (dd, 1H, *J* = 5.2, 9.8 Hz, CHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ

26.2, 26.6, 28.0 (6C), 28.1 (2C), 29.1, 29.3, 29.5 (2C), 29.6 (2C), 29.7 (2C), 40.2, 52.1, 58.0, 83.0 (2C), 152.2 (2C), 171.7. FAB MS *m*/*z* (%): 509 ($M^+ + Na$, 6), 487 ($M^+ + 1$, 76), 409 (6), 387 (26), 309 (10), 287 (100). Anal. Calcd for $C_{26}H_{50}N_2O_6$ (486.69): C, 64.16; H, 10.36; N, 5.76. Found: C, 64.33; H, 10.47; N, 5.51.

(14*S*)-14-[Bis(*tert*-butoxycarbonyl)amino]-15-methoxy-15-oxopentadecanoic Acid (9). To a cold (0 °C), rapidly stirred solution of **8** (1.60 mmol, 780 mg) in CH_2Cl_2 (2 mL) were added a solution of 4-acetamido-TEMPO free radical (0.016 mmol, 3 mg) in CH_2Cl_2 (1 mL), a solution of Aliquat 336 (0.080 mmol, 32 mg) in CH_2Cl_2 (l mL), an aqueous solution (0.32 mL) of KBr (0.160 mmol, 19 mg), and an aqueous solution (11.4 mL) of NaOCl (4.00 mmol) containing $NaHCO_3$ (4.64 mmnol, 390 mg). After 15 min, the mixture was acidified with 10% aqueous $KHSO_4$ and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 3:7 as eluent. Yield 78%; colorless oil; $[\alpha]^{23}_D$ −25.4 (*c* 0.7, C*H*Cl_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 [br s, 18H, (C*H*$_2$)$_9$(CH$_2$)$_2$CO], 1.48 [br s, 18H, 2 × C(C*H*$_3$)$_3$], 1.52−1.71 (m, 2H, C*H*$_2$CH$_2$CO), 1.75−1.97 (m, 1H, C*H*HCHCO), 1.98−2.18 (m, 1H, CH*H*CHCO), 2.33 (t, 2H, *J* = 7.4 Hz, CH$_2$CO), 3.69 (s, 3H, OMe), 4.84 (dd, 1H, *J* = 5.2, 9.6 Hz, CHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.7, 26.2, 28.0 (6C), 28.1 (2C), 29.1, 29.3, 29.4 (2C), 29.6 (2C), 29.9, 34.0, 52.2, 58.1, 83.0 (2C), 152.2 (2C), 171.7, 179.6. FAB MS *m*/*z* (%): 524 ($M^+ + Na$, 100), 446 (8), 424 (57), 324 (32), 302 (74). Anal. Calcd for $C_{26}H_{47}NO_8$ (501.66): C, 62.25; H, 9.44; N, 2.79. Found: C, 62.19; H, 9.26; N, 2.82.

Methyl (2*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-15-oxopentadecanoate (10). To a cold (−6 °C), rapidly stirred biphasic mixture of **8** (1.00 mmol, 488 mg), 4-acetamido-TEMPO free radical (0.020 mmol, 4 mg), NaBr (1.00 mmol, 103 mg), toluene (3 mL), EtOAc (3 mL), and water (0.5 mL) was added an aqueous solution (3.14 mL) of NaOCl (1.10 mmol) containing $NaHCO_3$ (2.90 mmol, 244 mg) dropwise over a period of 1 h. The aqueous layer was separated and washed with EtOAc (5 mL). The combined organic phases were washed consecutively with a solution of KI (8 mg) dissolved in 10% aqueous $KHSO_4$ (2 mL), 5% aq sodium thiosulfate (2 mL), and brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 2:8 as eluent. Yield 76%; colorless oil; $[\alpha]^{23}_D$ −23.6 (*c* 1, C*H*Cl_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 [br s, 18H, (C*H*$_2$)$_9$(CH$_2$)$_2$CO], 1.48 [br s, 18H, 2 × C(C*H*$_3$)$_3$], 1.52−1.72 (m, 2H, C*H*$_2$CH$_2$CO), 1.73−1.97 (m, 1H, C*H*HCHCO), 1.99−2.18 (m, 1H, CH*H*CHCO), 2.40 (td, 2H, *J* = 2.0, 7.4 Hz, CH$_2$CO), 3.69 (s, 3H, OMe), 4.83 (dd, 1H, *J* = 5.2, 9.6 Hz, CHCO), 9.79 (t, 1H, *J* = 2.0 Hz, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1, 26.2, 28.0 (6C), 28.1 (2C), 29.3, 29.5 (2C), 29.6 (3C), 29.9, 44.0, 52.2, 58.0, 83.0 (2C), 152.2 (2C), 171.6, 203.0. FAB MS *m*/*z* (%): 508 ($M^+ + Na$, 72), 429 (6), 408 (50), 308 (16), 286 (100). Anal. Calcd for $C_{26}H_{47}NO_7$ (485.66): C, 64.30; H, 9.75; N, 2.88. Found: C, 64.51; H, 9.69; N, 2.59.

Methyl (2*S*)-15-Azido-2-[bis(*tert*-butoxycarbonyl)amino]-pentadecanoate (11). To a stirred solution of **8** (1.60 mmol, 780 mg) in CH_2Cl_2 (3 mL) were added triethylamine (2.40 mmol, 0.34 mL) and methanesulfonyl chloride (2.40 mmol, 0.19 mL) portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aq $NaHCO_3$, and brine and dried (Na_2SO_4), and the solvent was removed. The mesylate was dissolved in DMF (5 mL). Sodium azide (4.80 mmol, 312 mg) was added, and the mixture was heated at 60 °C for 6 h. The solvent was removed, and the residue was taken up in EtOAc (3 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography using a mixture of EtOAc:petroleum ether 1:9 as eluent. Yield 73%; colorless oil; $[\alpha]^{23}_D$ −23.4 (*c* 0.5, C*H*Cl_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 [br s, 20H, (C*H*$_2$)$_{10}$(CH$_2$)$_2$N$_3$], 1.49 [br s, 18H, 2 × C(C*H*$_3$)$_3$], 1.50−1.65 (m, 2H, C*H*$_2$CH$_2$N$_3$), 1.71−1.95 (m, lH, C*H*HCHCO), 1.97−2.16 (m, 1H, CH*H*CHCO), 3.23 (t, 2H, *J* = 6.9 Hz, CH$_2$N$_3$), 3.68 (s, 3H, OMe), 4.82 (dd, lH, *J* = 5.2, 9.8 Hz, CHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.1, 26.7, 27.8 (2C), 28.0 (6C), 28.8, 29.1, 29.2, 29.4 (2C), 29.5 (2C), 29.8, 51.4, 52.1, 58.0, 82.9 (2C), 152.1 (2C), 171.5. FAB MS *m*/*z* 11 (%): 487 (3), 313 (61). Anal. Calcd for $C_{26}H_{48}N_4O_6$ (512.69): C, 60.91; H, 9.44; N, 10.93. Found: C, 61.20; H, 9.51; N, 10.89.

Methyl (2*S*)-2-[Bis(*tert*-butoxycarbonyl)amino]-15-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}pentadecanoate (13). To a solution of **11** (1.00 mmol, 513 mg) in CH_2Cl_2 (10 mL) were added 10% Pd/C (60 mg) and Fmoc-OSu (1.50 mmol, 506 mg). The reaction mixture was stirred under H_2 at room temperature for 16 h. After filtration through a pad of Celite, the solvent was removed and the product was purified by column chromatography using a mixture of EtOAc:petroleum ether 2:8 as eluent. Yield 62%; colorless oil; $[\alpha]^{23}_D$ −15.3 (*c* 0.75, C*H*Cl_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 [br s, 20H, (C*H*$_2$)$_{10}$(CH$_2$)$_2$N], 1.49 [br s, 18H, 2 × C(C*H*$_3$)$_3$], 1.52−1.68 (m, 2H, C*H*$_2$CH$_2$N), 1.78−1.97 (m, 1H, C*H*HCHCO), 1.98−2.17 (m, 1H, CH*H*CHCO), 3.07−3.23 (m, 2H, CH$_2$N), 3.70 (s, 3H, OMe), 4.14−4.28 (m, 1H, CHCH$_2$O), 4.39 (d, 2H, *J* = 6.8 Hz, CH$_2$O), 4.69−4.79 (m, 1H, NH), 4.85 (dd, 1H, *J* = 5.2, 9.8 Hz, CHCO), 7.23−7.45 (m, 4H, Fmoc), 7.59 (d, 2H, *J* = 6.8 Hz, Fmoc), 7.76 (d, 2H, *J* = 6.8 Hz, Fmoc); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.1, 26.7, 27.9 (6C), 28.0 (2C), 29.3 (2C), 29.4 (2C), 29.6 (4C), 41.1, 47.1, 52.1, 58.1, 66.5, 82.9 (2C), 119.8 (2C), 125.1 (2C), 127.8 (4C), 141.3 (2C), 144.0 (2C), 152.1 (2C), 156.4, 171.6. FAB MS *m*/*z* (%): 731 ($M^+ + Na$, 100), 631 (61), 531 (24), 509 (75). Anal. Calcd for $C_{41}H_{60}N_2O_8$ (708.94): C, 69.46; H, 8.53; N, 3.95. Found: C, 69.31; H, 8.49; N, 4.13.

(2*S*,5*Z*,13*Z*,17*S*)-2,17-Diaminooctadeca-5,13-dienedioic Acid (15). The *tert*-butoxycarbonyl group of **14** (1.00 mmol, 769 mg) was removed by treatment with 4 N HCl in THF (25 mL) at room temperature for 30 min. After evaporation, the residue was dissolved in MeOH (4 mL) and treated with 1 N aqueous NaOH (5.60 mL) under vigorous stirring at room temperature for 1.5 h. The organic solvent was removed, and the aqueous residue was carefully neutralized with 1 N aqueous HCl. The product was filtered and washed with water and Et_2O. Yield 77%; white solid; mp 243 °C (decomp); $[\alpha]^{23}_D$ +25.7 (*c* 0.3, AcOH); ^{1}H NMR (200 MHz, CD_3COOD) δ 1.15−1.47 [m, 8H, CHCH$_2$-(C*H*$_2$)$_4$CH$_2$CH], 1.83−2.30 (m, 12H, 2 × C*H*$_2$CHCO, 2 × C*H*$_2$-CH=CHC*H*$_2$), 4.02−4.22 (br, 1H, 12 2 × CHCO), 5.26−5.52 (m, 2H, 2 × CH=CH). TOF MS *m*/*z* (%): 339 ($M^+ - 1$, 100), 279 (57). Anal. Calcd for $C_{18}H_{32}N_2O_4 \cdot 1.5H_2O$ (367.49): C, 58.83; H, 9.60; N, 7.62. Found: C, 59.10; H, 9.52; N, 7.44.

General Procedure for the Preparation of Mosher Amides of ω-Hydroxy Amino Ester 7. To a stirred solution of amino ester **7** (0.25 mmol, 80 mg) in CH_2Cl_2 (2.5 mL) were added Et_3N (0.60 mmol, 0.08 mL), (*R*)-(+)- or (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.30 mmol, 70 mg), HOBt (0.30 mmol, 41 mg), and EDC (0.30 mmol, 58 mg) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature overnight. After removal of the solvent, the product was directly used for ^{19}F NMR analysis.

Characteristic NMR Chemical Shifts (in ppm). Methyl (2*S*,5*Z*)-2-amino-15-hydroxypentadec-5-enoate (*R*)-Mosher amide: ^{19}F NMR (188 MHz, $CDCl_3$, reference with external TFA) δ 8.79 (s).

Methyl (2*S*,5*Z*)-2-amino-15-hydroxypentadec-5-enoate (*S*)-Mosher amide: ^{19}F NMR (188 MHz, $CDCl_3$, reference with external TFA) δ 9.18 (s).

Supporting Information Available: Experimental procedures and analytical data for compounds **3a**,**b**, **4a**,**b**, and **5a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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