An Efficient Method for the Synthesis of Enantiopure ω-Amino Acids with Proteinogenic Side Chains

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Abstract: An efficient method for the synthesis of enantiopure ω-amino acids with proteinogenic side chains, starting from the corresponding natural α-amino acids, was developed. *N*-Protected amino aldehydes, obtained from the corresponding amino alcohols by oxidation with NaOCl in the presence of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-yloxy free radical (AcNH-TEMPO), reacted with the ylides generated from $TrO(CH_2)_nP^+Ph_3I^-$. Catalytic hydrogenation produced *N*-protected ω-amino alcohols. Boc-Protected ω-amino acids were obtained in high yields by the oxidation of these alcohols using NaOCl in the presence of a catalytic amount of AcNH–TEMPO and $Bu_4N^+HSO_4^-$. The present route to ω-amino acids permits the insertion of any chain length between the amino and carboxy functionalities depending on the chain length of the starting ylide used for the Wittig olefination reaction.

Key words: amino acids, amino alcohols, amino aldehydes, Wittig reactions, ylides

Non-proteinogenic amino acids play an important role in the design and synthesis of pharmacologically relevant molecules, peptide mimetics and enzyme inhibitors.[1] In consequence, a large effort has been devoted to the preparation of enantiopure amino acids, a subject already covered by general reviews.[2] It is of special interest that oligopeptides containing unnatural amino acids are able to form well-defined secondary structures. Recent investigations by Seebach,[3,4] Gellman[5] and Hanessian[6,7] have shown that peptides constructed from β- and γ-amino acids can adopt helix, sheet or reverse turn conformations in solution or in the solid state as evidenced by NMR, CD, X-ray and modeling studies. The surprising difference between the natural α-, and the analogous β- and γ-peptides is that the helix stability increases upon homologation of the residues.[4] The complete stability of β- and γ-peptides against common proteases[8] is of considerable importance as it suggests that β- and γ-peptides may be suitable for pharmaceutical applications.

Methods for the enantioselective synthesis of β-amino acids have been reviewed.[9] γ-Amino acids may be prepared either by modification of glutamic acid or by homologation of α-amino acids.[4,10–12] The aim of this work was to develop an efficient method for the synthesis of enantiopure ω-substituted ω-amino acids with proteinogenic side chains starting from α-amino acids.

In recent years, *N*-protected amino alcohols, which are easily obtained from α-amino acids,[13,14] have been used for the synthesis of a variety of optically active compounds, for example α-amino aldehydes,[15] triamines,[16] or peptide nucleic acids.[17] Our strategy to synthesize ω-amino acids was based on a Wittig-type olefination reaction of *N*-protected α-amino aldehydes, leading to chain homologation. Wittig olefination of *N*-protected α-amino aldehydes with non-functionalized ylides has been reported.[18,19] *N*-Protected α-amino aldehydes may be prepared either by reduction of a carboxy derivative of amino acids or by oxidation of 2-amino alcohols.[15] It was decided to prepare α-amino aldehydes by oxidation of 2-amino alcohols, using NaOCl in the presence of a catalytic amount of a 2,2,6,6-tetramethylpiperidine-1-yloxy free radical (TEMPO) derivative, a method which appears superior to the reductive methods in terms of preservation of the enantiomeric purity.[20]

N-tert-Butoxycarbonyl-L-phenylalanine and γ-methyl *N-tert*-butoxycarbonyl-L-glutamate were converted into alcohols **1a,b** by reduction with $NaBH_4$ via either their corresponding mixed anhydrides[13] or via their corresponding acyl fluorides,[14] as previously described by the authors. Alcohols **1a,b** were oxidized to the corresponding aldehydes (Scheme, Table 1) by NaOCl in the presence of a catalytic amount of 4-acetamido-TEMPO.[21] The aldehydes were directly used for the Wittig-type reaction, without any purification. The Wittig olefination of *N*-protected α-amino aldehydes with carboxy ylides may directly lead to ω-amino acids. The reaction of hexanal and benzaldehyde with triphenylphosphonium ylides containing anionic nucleophilic groups in their side chain has been studied.[22] Following the procedure proposed by that study the reaction of the aldehyde obtained from **1a** with the ylide generated from the phosphonium salt of 10-bromodecan-1-ol was tested. However, the desired product **2a** was only obtained in very low yield (17%). Thus, it was decided to use ylides containing an ω-protected hydroxy group in subsequent procedures. Monotrityl 1,4-butanediol and 1,10-decanediol[23] were converted into the corresponding iodides and subsequently into triphenylphosphonium salts by treatment with PPh_3 in MeCN under reflux.

Boc-Protected amino aldehydes, prepared by the oxidation of **1a,b**, reacted at –78 °C with the ylides, that were generated by treatment of $TrtO(CH_2)_nP^+Ph_3I^-$ (n = 4, 10) with KHMDS in toluene at 0 °C (Scheme 1). Compounds

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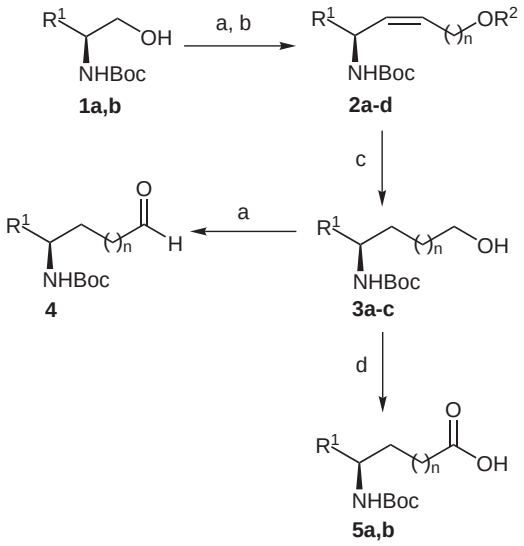

Scheme 1 Reagents and conditions: (a) AcNH–TEMPO, NaOCl, $NaHCO_3$, NaBr, H_2O/EtOAc/$PhCH_3$, –5 °C; (b) $R^2O(CH_2)_{n+1}P^+Ph_3I^-$/KHMDS, $PhCH_3$, –78 °C; (c) H_2, 10% Pd/C; (d) AcNH-TEMPO, NaOCl, $NaHCO_3$, NaBr, $Bu_4N^+HSO_4^-$, H_2O/CH_2Cl_2, 0 °C

2b–**d** were identified as *Z*-olefins according to ^{1}H NMR analysis as was expected. The use of KHMDS under such experimental conditions for the generation of nonstabilized ylides is known to lead to high *Z*-selectivity.[24] Catalytic hydrogenation of the double bond of **2b**–**d** with simultaneous removal of the trityl group produced the *N*-protected amino alcohols **3a**–**c**. Oxidation of **3a** with 1.1 equivalent of NaOCl in the presence of AcNH–TEMPO led to ω-amino aldehyde **4**. However, using 2.5 equivalents of NaOCl in the presence of AcNH-TEMPO and tetrabutylammonium hydrogensulfate as a phase transfer catalyst, the ω-substituted ω-amino acids **5a**,**b** were obtained in high yield.

Table 1

	R^1	n	R^2
1a	CH_2Ph		
1b	$(CH_2)_2CO_2Me$		
2a	CH_2Ph	9	H
2b	CH_2Ph	9	Trt
2c	$(CH_2)_2CO_2Me$	9	Trt
2d	CH_2Ph	3	Trt
3a	CH_2Ph	9	
3b	$(CH_2)_2CO_2Me$	9	
3c	CH_2Ph	3	
4	CH_2Ph	9	
5a	CH_2Ph	9	
5b	$(CH_2)_2CO_2Me$	9	

It should be noticed that in the ^{1}H NMR ($CDCl_3$) spectra of Boc-protected amino acids **5a**,**b**, two signals correspond to the carbamate NH proton, attributed to the existence of rotamers. As it has been proposed for α-amino acid carbamate derivatives,[25] the high field peak corresponds to *anti*-rotamer **6a** and the low field peak corresponds to *syn*-rotamer **6b**. The *syn*-rotamer is possibly stabilized by the formation of intermolecular H-bond complexes with another carboxylic acid moiety, as is shown in the Figure 1.

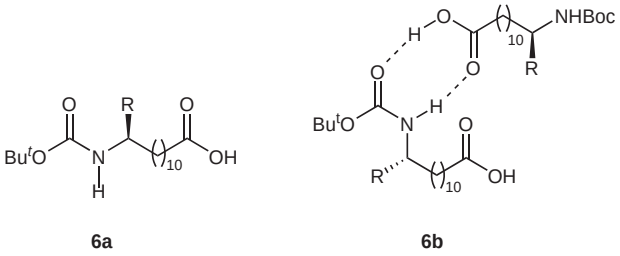

Figure 1

It is known that *N*-protected α-amino aldehydes present a high tendency for racemization. The enantiomeric purity of the final products depends on the conditions used for both the preparation of α-amino aldehydes and the Wittig reaction. To confirm if any racemization had occurred to the stereogenic center, compounds **2b**,**c** were deprotected and converted almost quantitatively into MTPA amides by coupling with (*S*)-(–)- and (*R*)-(+)-α-methoxy-α-trifluoromethyl phenylacetic acid (MTPA)[26] using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride as a condensing agent in the presence of 1-hydroxybenzotriazole. ^{1}H and ^{19}F NMR analysis of Mosher amides indicated an enantiomeric excess >95%. Furthermore, compounds **2b**,**c** were deprotected and converted quantitatively into fluorenylmethoxycarbonyl (Fmoc) derivatives. HPLC analysis of the Fmoc derivatives, using a ChiraDex® column, confirmed that the enantiomeric purity was at least 95%. Thus, the production of α-amino aldehydes by NaOCl/TEMPO oxidation, in combination with the generation of ylide by KHMDS, leads to products of high enantiomeric purity.

In conclusion, a simple and efficient method for the synthesis of enantiopure ω-amino acids with proteinogenic side chains from the corresponding natural α-amino acids was developed. The present route permits the insertion of any chain length between the amino and carboxy functionalities depending on the chain length of the starting ylide used for the Wittig olefination reaction. In addition, ω-amino alcohols and aldehydes, which are useful chiral intermediates, may be prepared.

Mps were determined on a mp apparatus and are uncorrected. Specific rotations were measured at 25 °C on a polarimeter using a 10 cm cell. NMR spectra were recorded on a 200 MHz spectrometer. All amino acid derivatives were of L-configuration and were purchased from Fluka Chemical Co. 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 EtOH stain. THF, toluene, and Et_2O were dried by standard procedures and stored over molecular sieves or Na. All other solvents and chemicals were of reagent grade and were used without further purification. The phosphonium salt $HO(CH_2)_{10}P^+Ph_3Br^-$ was prepared by refluxing PPh_3 and bromodecan-1-ol in EtOH and was used in the Wittig reaction without purification.

Compounds 2a–d; General Procedure

To a solution of *N*-protected 2-amino alcohol **1a,b** (2.00 mmol) in a mixture of toluene–EtOAc (1:1; 12 mL) were added a solution of NaBr (0.22 g, 2.1 mmol) in H_2O (1 mL) and subsequently AcNH-TEMPO (4 mg, 0.02 mmol). To the resulting biphasic system, which was cooled to –5 °C, an aq solution of NaOCl (0.35 M; 6.3 mL, 2.2 mmol) containing $NaHCO_3$ (0.50 g, 6 mmol) was added under vigorous stirring, dropwise at –5 °C over 1 h. After the mixture was stirred for an additional 15 min at 0 °C, EtOAc (12 mL) and H_2O (4 mL) were added. The aq layer was separated and washed with EtOAc (12 mL). The combined organic layers were washed with aq citric acid (5%; 12 mL) containing KI (0.07 g), aq $Na_2S_2O_3$ (10%; 12 mL) and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the obtained crude aldehyde was immediately used in the next step.

To a stirred suspension of the phosphonium salt (2.40 mmol) in anhyd toluene (12 mL) was added a solution of KHMDS (0.5 M; 4.80 mL, 2.40 mmol) 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, when the solution of the aldehyde in anhyd toluene (4 mL) was instantly added, and the temperature was left to rise from –78 °C to r.t. The light yellow mixture was stirred at r.t. for 20 h. The reaction mixture was quenched with sat. aq NH_4Cl (20 mL) and extracted with Et_2O (3 × 6 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 [EtOAc–petroleum ether (bp 40–60 °C), 1:9].

(10*Z*,12*S*)-12-[(*tert*-Butoxycarbonyl)amino]-13-phenyltridec-10-en-1-ol (2a)

Yield: 0.13 g (17%); oil; $[\alpha]_D^{25}$ –1.7 (*c* 0.9, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02–1.48 [m, 21 H, $C(CH_3)_3$, $(CH_2)_9$], 1.48–1.62 (m, 2 H, CH_2CH_2OH), 1.80–2.04 (m, 2 H, CH=CHCH_2), 2.65–2.97 (m, 2 H, $CH_2C_6H_5$), 3.64 (t, *J* = 6.6 Hz, 2 H, CH_2OH), 4.30–4.65 (m, 2 H, CH, NH), 5.18 (m, 1 H, CHC*H*=CH), 5.40 (m, 1 H, CH=C*H*CH_2), 7.15–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7, 27.7, 28.3, 29.1, 29.2, 29.3, 29.4, 32.8, 42.1, 49.3, 63.0, 79.2, 126.2, 128.1, 128.9, 129.7, 132.8, 137.7, 155.0.

FAB MS: *m*/*z* (%) = 390 (M^+ + H, 5), 334 (10), 290 (4), 288 (16), 198 (93), 91 (46) 57 (100).

(2*S*,3*Z*)-13-Trityloxy-*N*-(*tert*-butoxycarbonyl)-1-phenyltridec-3-en-2-amine (2b)

Yield: 0.97 g (77%); oil; $[\alpha]_D^{25}$ –1.2 (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12–1.40 [m, 12 H, CH=CHCH_2(CH_2)$_6$], 1.44 [s, 9 H, $C(CH_3)_3$], 1.56–1.66 (m, 2 H, CH_2CH_2O), 1.80–2.00 (m, 2 H, CH=CHCH_2), 2.65–3.02 (m, 2 H, $CH_2C_6H_5$), 3.06 (t, *J* = 6.6 Hz, 2 H, CH_2O), 4.38–4.65 (m, 2 H, CH, NH), 5.18 (m, 1 H, CHC*H*=CH), 5.41 (m, 1 H, CH=C*H*CH_2), 7.15–7.50 (m, 20 H, 4 × C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 26.3, 27.7, 28.3, 29.2, 29.3, 29.4, 29.5, 30.0, 42.2, 49.5, 63.7, 79.2, 86.2, 126.7, 127.7, 128.7, 129.7, 133.0, 137.7, 144.5, 155.0.

FAB MS: *m*/*z* (%) = 654 (M^+ + Na, 20), 316 (47), 243 (100).

Anal. Calcd. for $C_{43}H_{53}NO_3$: C, 81.73; H, 8.45; N, 2.22. Found: C, 81.59; H, 8.62; N, 2.30.

Methyl (4*S*,5*Z*)-15-Trityloxy-4-[(*tert*-butoxycarbonyl)amino]-pentadec-5-enoate (2c)

Yield: 0.64 g (51%); oil; $[\alpha]_D^{25}$ + 5.6 (*c* 1.9, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21–1.39 [m, 12 H, $CHCH_2(CH_2)_6$], 1.43 [s, 9H, $C(CH_3)_3$], 1.50–1.69 (m, 2 H, CH_2CH_2O), 1.69–1.92 (m, 2 H, $COCH_2CH_2$), 1.98–2.21 (m, 2 H, CH=CHCH_2), 2.31–2.38 (m, 2 H, $COCH_2CH_2$), 3.04 (t, *J* = 6.6 Hz, 2 H, CH_2O), 3.66 (s, 3 H, CH_3O), 4.22–4.53 (m, 2 H, CH, NH), 5.16 (m, 1 H, CHC*H*=CH), 5.48 (m, 1 H, CH=C*H*CH_2), 7.18–7.47 (m, 15 H, 3 × C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.2, 27.8, 28.3, 29.3, 29.5, 30.0, 30.5, 31.1, 47.6, 51.6, 63.6, 79.3, 86.2, 126.7, 127.6, 128.7, 129.3, 133.0, 144.5, 155.1, 173.8.

FAB MS: *m*/*z* (%) = 650 (M^+ + Na, 55), 406 (4), 243 (100), 165 (37), 57 (75).

Anal. Calcd. for $C_{40}H_{53}NO_5$: C, 76.52; H, 8.51; N, 2.23. Found: C, 76.39; H, 8.68; N, 2.11.

(2*S*,3*Z*)-7-Trityloxy-*N*-(*tert*-butoxycarbonyl)-1-phenylhept-3-en-2-amine (2d)

Yield: 0.59 g (54%); oil; $[\alpha]_D^{25}$ –1.0 (*c* 3.6, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38–1.65 [m, 11 H, $C(CH_3)_3$, CH_2CH_2O], 1.90–2.16 (m, 2 H, CH=CHCH_2), 2.60–3.05 (m, 4 H, $C_6H_5CH_2$, CH_2O), 4.40–4.60 (m, 2 H, CH, NH), 5.17 (m, 1 H, CHC*H*=CH), 5.39 (m, 1 H, CH=C*H*CH_2), 7.11–7.48 (m, 20 H, 4 × C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.5, 28.3, 29.7, 41.9, 49.4, 63.0, 79.3, 86.3, 126.7, 127.7, 128.6, 129.5, 131.8, 137.6, 144.8, 155.0.

FAB MS: *m*/*z* (%) = 570 (M^+ + Na, 40), 243 (100), 165 (23), 91 (5), 57 (56).

Anal. Calcd. for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.01; H, 7.62; N, 2.64.

Compounds 3a–c; General Procedure

To a solution of **2b–d** (1.00 mmol) in MeOH (10.0 mL), 10% Pd/C (10 mg, 0.009 mmol) was added. The reaction mixture was stirred under H_2 for 3 days. The catalyst was removed by filtration through a pad of Celite and the organic solvent was evaporated under reduced pressure. The product was purified by column chromatography (EtOAc–petroleum ether, 1:1).

(12*R*)-12-[(*tert*-Butoxycarbonyl)amino]-13-phenyltridecan-1-ol (3a)

Yield: 0.36 g (92%); white solid; mp 58–59 °C; $[\alpha]_D^{25}$ 10.7 (*c* 1.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.70 [m, 29 H, $C(CH_3)_3$, $(CH_2)_{10}$], 2.76 (d, *J* = 6.0 Hz, 2 H, $CH_2C_6H_5$), 3.64 (t, *J* = 6.6 Hz, 2 H, CH_2OH), 3.80 (m, 1 H, CH), 4.30 (d, *J* = 7.8, 1 H, NH), 7.15–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7, 25.9, 28.3, 29.4, 29.5, 32.8, 34.2, 41.3, 51.5, 63.0, 79.0, 126.0, 128.2, 129.5, 138.3, 155.5.

FAB MS: *m*/*z* (%) = 392 (M^+ + H, 7), 336 (26), 318 (8), 292 (52), 200 (63), 91 (38), 57 (95).

Anal. Calcd for $C_{24}H_{41}NO$: C, 73.61; H, 10.55; N, 3.58. Found: C, 73.54; H, 10.78; N, 3.52.

Methyl (4*R*)-15-Hydroxy-4-[(*tert*-butoxycarbonyl)amino]pentadecanoate (3b)

Yield 0.26 g (68%); oil; $[\alpha]_D^{25}$ +2.5 (*c* 0.8 $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22–1.94 [m, 31 H, $C(CH_3)_3$, $(CH_2)_{10}$, $CHCH_2CH_2COO$], 2.38 (t, *J* = 7.2 Hz, 2 H, CH_2COO), 3.46–3.70 (m, 6 H, CH, CH_2OH, OCH_3), 4.27 (d, *J* = 9.4 Hz, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7, 25.8, 28.3, 29.3, 29.4, 30.6, 30.8, 32.8, 35.8, 50.3, 51.6, 63.0, 79.0, 155.7, 174.2.

FAB MS: *m*/*z* (%) = 388 (M^+ + H, 4), 332 (4), 302 (22), 288 (69), 57 (100).

Anal. Calcd for $C_{21}H_{41}NO_5$: C, 65.08; H, 10.66; N, 3.61. Found: C, 65.13; H, 10.39; N, 3.77.

(6*R*)-6-[(*tert*-Butoxycarbonyl)amino]-7-phenylheptan-1-ol (3c)

Yield: 0.22 g (71%); white solid; mp 55–57 °C; $[\alpha]_D^{25}$ 11.8 (*c* 1.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25–1.62 [m, 15 H, $C(CH_3)_3$, $(CH_2)_4$], 1.62–1.83 (m, 2 H, CH_2), 2.76 (d, *J* = 6.4 Hz, 2 H, $CH_2C_6H_5$), 3.61 (t, *J* = 6.4 Hz, 2 H, CH_2OH), 3.84 (m, 1 H, CH), 4.33 (d, *J* = 8.6 Hz, 1 H, NH), 7.15–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.2, 25.5, 28.3, 32.5, 34.3, 41.5, 51.1, 62.5, 79.1, 126.2, 128.3, 129.5, 138.2, 155.6.

FAB MS: *m*/*z* (%) = 308 (M^+ + 1, 12), 252 (76), 208 (88), 160 (68), 116 (70), 91 (38), 57 (95).

Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.41; H, 9.58; N, 4.47.

(12*R*)-12-[(*tert*-Butoxycarbonyl)amino]-13-phenyltridecanal (4)

Boc-Protected 12-amino alcohol **3a** was converted into the aldehyde **4** as described above and was purified by column chromatography (EtOAc–petroleum ether, 1:4).

Yield: 0.58 g (74%); white solid; mp 48–50 °C; $[\alpha]_D^{25}$ 10.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15–1.46 [m, 25 H, $C(CH_3)_3$, $(CH_2)_8$], 1.46–1.65 (m, 2 H, CH_2CH_2CHO), 2.40 (dt, *J* = 7.4, 1.6 Hz, 2 H, CH_2CHO), 2.73 (d, *J* = 6.2 Hz, 2 H, $CH_2C_6H_5$), 3.76 (br, 1 H, CH), 4.27 (d, *J* = 9.0 Hz, 1 H, NH), 7.13–7.32 (m, 5 H, C_6H_5), 9.74 (t, *J* = 1.8 Hz, 1 H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0, 25.9, 28.3, 29.1, 29.3, 29.4, 29.5, 34.2, 41.4, 43.9, 51.5, 79.0, 126.2, 128.4, 129.5, 138.4, 155.5, 203.0.

FAB MS: *m*/*z* (%) = 390 (M^+ + H, 5), 334 (48), 316 (44), 290 (30), 198 (92), 91 (73), 57 (100).

Anal. Calcd for $C_{24}H_{39}NO_3$: C, 73.99; H, 10.09; N, 3.59. Found: C, 73.85; H, 9.94; N, 3.76.

Boc-Protected ω-Amino Acids (5a,b); General Procedure

To a 0 °C, rapidly stirred solution of **3a**,**b** (1 mmol) in CH_2Cl_2 (2.5 mL) and H_2O (0.5 mL) were subsequently added AcNH-TEMPO (2 mg, 0.01 mmol), $[CH_3(CH_2)_3]_4N^+HSO_4^-$ (85 mg, 0.25 mmol) and NaBr (10 mg, 0.1 mmol). Then, aq NaOCl (0.35 M; 7.1 mL, 2.5 mmol), containing $NaHCO_3$ (355 mg) was added and the mixture was stirred vigorously for 20 min. The organic solvent was evaporated under reduced pressure, and the residue was taken up with EtOAc (20 mL) and aq citric acid (10%; 10 mL) containing KI (60 mg). The aqueous phase was re-extracted with EtOAc (10 mL) and the combined organic phases were washed with aq $Na_2S_2O_3$ (10%; 10 mL) and brine and dried ($MgSO_4$). The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography ($CHCl_3$–MeOH, 98:2).

(12*R*)-12-[(*tert*-Butoxycarbonyl)amino]-13-phenyltridecanoic Acid (5a)

Yield: 0.37 g (91%); white solid; mp 60–62 °C; $[\alpha]_D^{25}$ + 3.3 (*c* 1.6, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08–1.57 [m, 25 H, $C(CH_3)_3$, $(CH_2)_8$], 1.57–1.78 (m, 2 H, CH_2), 2.35 (t, *J* = 7.2 Hz, 2 H, CH_2COOH), 2.76 (d, *J* = 6.0 Hz, 2 H, $CH_2C_6H_5$), 3.75 (br, 1 H, CH), 4.32 (d, *J* = 8.2 Hz, 2/3 H, NH), 5.92 (m, 1/3 H, NH), 7.15–7.34 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.7, 25.9, 28.3, 29.4, 29.7, 34.2, 41.3, 51.1, 79.0, 126.0, 128.1, 129.6, 138.3, 155.5, 179.2.

FAB MS: *m*/*z* (%) = 428 (M^+ + Na, 12), 406 (M^+ + 1, 3), 350 (30), 306 (100), 271 (23), 214 (58), 91 (45), 57 (92).

Anal. Calcd for $C_{24}H_{39}NO_4$: C, 71.07; H, 9.69; N, 3.45. Found: C, 70.98; H, 9.77; N, 3.21.

(12*R*)-12-[(*tert*-Butoxycarbonyl)amino]-15-methoxy-15-oxopentadecanoic Acid (5b)

Yield 0.31 g (77%); oil; $[\alpha]_D^{25}$ + 0.8 (*c* 1.0 $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.38 [m, 14 H, $CHCH_2(CH_2)_7$], 1.43 [s, 9 H, $C(CH_3)_3$], 1.52–1.71 (m, 4 H, $CHCH_2$, $CH_2CH_2CO_2H$), 1.72–2.00 (m, 2 H, CH_2CH), 2.27–2.46 (m, 4 H, 2 × CH_2CO), 3.52 (m, 1 H, CH), 3.67 (s, 3 H, OCH_3), 4.30 (d, *J* = 9.8 Hz, 3/4 H, NH), 5.55 (m, 1/4 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.6, 25.8, 28.3, 29.0, 29.1, 29.4, 30.5, 30.8, 33.9, 35.8, 50.4, 51.6, 79.1, 155.7, 174.3, 179.0.

FAB MS: *m*/*z* (%) = 402 (M^+ + 1, 12), 370 (5), 346 (22), 302 (90), 252 (15), 214 (13), 116 (32), 57 (100).

Anal. Calcd for $C_{21}H_{39}NO_6$: C, 62.81; H, 9.79; N, 3.49. Found: C, 62.96; H, 9.63; N, 3.56.

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