Acta Chemica Scandinavica, 1994: 48: 511–516
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Synthesis of Amino Acids with Modified Principal Properties 2:† Amino Acids with Polar Side Chains

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Larsson, U. and Carlson, R., 1994. Synthesis of Amino Acids with Modified Principal Properties 2: Amino Acids with Polar Side Chains. – Acta Chem. Scand. 48: 511–516 © Acta Chemica Scandinavica 1994.

The synthesis and characterization of five new homochiral amino acids derived from L-serine are presented. In the modified amino acids, the side chain of serine has been elongated by the introduction of one or more ethyleneoxy moieties and the new compounds contain either a terminal hydroxy group or a terminal amino group. Full experimental details are given for the synthesis of the following amino acids: (2*S*)-2-amino-6-hydroxy-4-oxahexanoic acid, (2*S*)-2-amino-9-hydroxy-4,7-dioxanonanoic acid, (2*S*)-2-amino-12-hydroxy-4,7,10-trioxadodecanoic acid, (2*S*)-2,9-diamino-4,7-dioxanonanoic acid, and (2*S*)-2,12-diamino-4,7,10-trioxadodecanoic acid.

These compounds were prepared with a view to obtaining amino acids which possess physical and chemical properties such that their principal properties would be different from previously known amino acids. The structural modifications were made with the objective of altering the principal properties related both to lipophilicity and to size. The principal properties are determined as latent variables in the principal component analysis of molecular property descriptors. Three new amino acids, (2*S*)-2-amino-9-hydroxy-4,7-dioxanonanoic acid, (2*S*)-2-amino-12-hydroxy-4,7,10-trioxadodecanoic acid and (2*S*)-2,12-diamino-4,7,10-trioxadodecanoic acid were found to have principal properties which are clearly different from those of previously known amino acids. The principal properties as measured by the principal component scores are given.

In recent years peptides and peptide-like compounds have attracted considerable interest from a pharmacological point of view. In this context, different approaches have been taken to synthesize such compounds. One approach is to synthesize isosteric compounds in which, for instance, one or more peptide bonds are replaced by moieties which resemble the amide linkage with respect to bond distances and bond angles but that are resistant to degradation by proteolytic enzymes. Another approach to peptide modification is to incorporate non-natural amino acids into the peptide framework. For this purpose, a number of modified amino acids have been described.

Quantitative structure–activity relationships (QSARs) are powerful tools for optimizing the pharmacological properties of compounds. It has been clearly demonstrated that the pharmacological action of peptides can very efficiently be quantitatively related to the principal properties of their amino acid constituents through PLS modelling.[2] This indicates that the properties of the individual amino acids in a peptide will exert an influence on the pharmacological properties of the peptide. One way to obtain peptides with new and possibly unique properties would therefore be to incorporate new amino acids for which the principal properties are different to hitherto known amino acids. A general discussion of the concept of principal properties is given in Ref. 3 and we will not go into details here. Thorough discussions of peptide QSAR through PLS modelling from principal properties of amino acids are given in Ref. 4.

In the preceding paper[1] in this series we discussed how the principal component model used to determine the principal properties of the amino acids, can be used to elucidate the type of structural modifications necessary to yield amino acids for which the principal properties have been altered in the desired directions. In Ref. 1, which reported the synthesis and the characterization of polyfluoro substituted analogs of norvaline and norleucine, it was found that by increasing the number of fluoro substituents, the corresponding amino acid was projected with an expected displacement along the principal property axis related to the lipophilic–hydrophilic properties of the amino acids. Some of the new amino acids were indeed found to be projected outside the range of variation previously known for amino acids.

† For Part 1, see Ref. 1.
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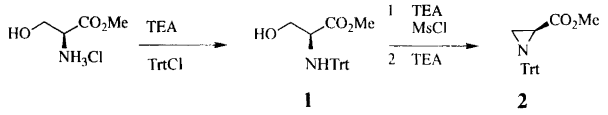
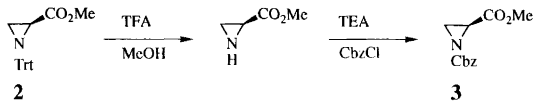
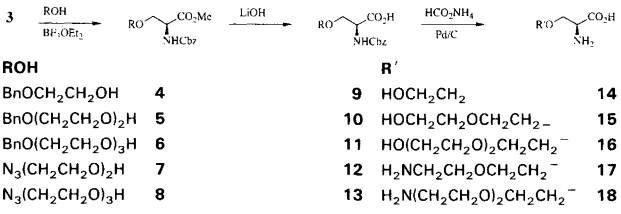


Scheme 1.



Scheme 2.



Scheme 3.

In this paper, we report the synthesis and the characterization of some amino acids related to lysine and serine. The structural modifications were made by incorporating one or more ethyleneoxy moieties into the side chains. Our intentions were to obtain amino acids with polar side chains which can act as hydrogen-bond acceptors and thereby be solvated in aqueous solution. Elongation of the side chains by appending ethyleneoxy groups was expected to yield amino acids which would be projected with clear displacements along the principal property axis related to 'size'. Whether or not such structural modification also would yield displacements along the principal property axis related to hydrophilic–lipophilic properties was an open question. The amino acids were prepared in homochiral form (L-amino acids) which in this case correspond to the 2*S* configuration by using natural L-serine as the starting material.

Methods and results

Synthesis of amino acids. The syntheses of the amino acids are summarized in Schemes 1–3.

L-Serine methyl ester was converted into the trityl-substituted aziridine derivative, **2**, by the sequence shown in Scheme 1.[5] The acid-labile trityl group was replaced by the more stable and less crowded benzyloxycarbonyl group (Cbz) to yield **3** through the sequence shown in Scheme 2. The side-chain precursors, ω′-functionalized ethylene glycol or oligoethylene glycols, were affixed to the aziridine moiety by a Lewis acid catalyzed (BF_3–diethyl ether) nucleophilic (S_N2) ring-opening procedure described by Nakajima *et al.*,[6] see Scheme 3. The side chain precursors of the ω-hydroxy amino acids were the monobenzylated ethylene glycol or the corresponding oligoethylene glycol which was prepared from benzyl chloride and the corresponding glycol.[7] The side chain precursor of the ω-amino amino acids were 2-(2-azidoethoxy)ethanol and 2-[2-(2-azidoethoxy)ethoxy]ethanol which were prepared in excellent yields from the corresponding chloro analogs and sodium azide under phase-transfer conditions.[8]

Alkaline hydrolysis of the methyl ester group was easily achieved by using lithium hydroxide in a mixture of tetrahydrofuran and water (Scheme 3). The free amino acids were obtained by subsequent catalytic hydrogenation using ammonium formate and a palladium catalyst (Pd/C)[9] which removed the Cbz protecting group, and either cleaved the benzyl protection of the ω-hydroxy group or reduced the azido group to yield the terminal amino group (Scheme 3).

The yields of the amino acids and intermediate products are given in the Experimental section.

Multivariate characterization for determining the principal properties of the amino acids. The new amino acids were characterized by the descriptors summarized in Table 1. The principal properties are measured by the principal component scores, t_1–t_3, obtained by projecting the descriptor data in Table 1 down to the principal component model determined from data set comprising 55 previously characterized amino acids in Ref. 10.

Table 1. Descriptors and principal property scores of the amino acids.

	Descriptor[a]												Principal property scores		
Amino acid	1	2	3	4	5	6	7	8	9	10	11	12[b]	t_1	t_2	t_3
14	65	21	40	14	51	26	48	42.4	149.1	4.20	3.92	–	−0.58	0.68	−0.34
15	64	17	47	16	57	28	67	66.6	193.2	4.20	3.91	–	0.30	0.88	0.84
16	60	15	53	17	65	33	85	90.8	237.3	4.15	3.91	–	1.19	0.88	2.12
17	2	7	13	2	16	10	4	69.1	192.2	4.13	3.93	–	−3.48	1.97	2.38
18	3	6	17	2	18	9	13	93.3	236.3	4.20	3.91	–	−2.81	2.55	3.48

[a] The descriptors were the same as were used for characterizing the fluorinated amino acids described in Ref. 1. The descriptors are: 1–7, R_f values determined by TLC from a test battery of seven eluents;[10] 8, van der Waal's volume ($cm^3\ mol^{-1}$) of the side chain; 9, molar mass ($g\ mol^{-1}$); 10–12, ^1H NMR shifts of the α-proton as determined in deuterium oxide at different pD; 10, (pD 2.0). 11, (pD 7.0); 11, (pD 12.5), respectively. [b] The chemical shift of the α proton could not be determined owing to overlapping signals in the spectrum.

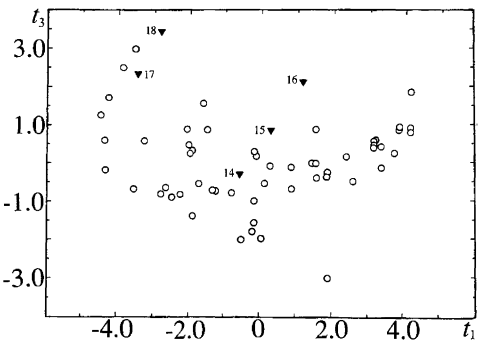


Fig. 1. Principal component score plot displaying the variations of the principal properties related to lipophilicity, t_1, and to size, t_3: ○, the position of the projected amino acids described in Ref. 10; ▼, the position of the projected amino acids described in this paper.

Score plots showing the positions of the new amino acids in the principal property map are shown in Fig. 1.

Discussion

It is seen in Fig. 1 how the structural modifications of the amino acid side chains influence the positions of the amino acids in the score plot displaying the variation of the principal properties.

As expected, elongation of the side chain by incorporation ethyleneoxy moieties causes very clear and regular displacements in the positive direction along the t_3 axis. The principal component corresponding to this axis is largely described by descriptors of molecular properties related to the 'size' of the side chain.

The displacements along the other principal property axes are less pronounced but they also show regular behaviour. An interesting pattern is found in the variation along the t_1 axis which largely portrays the variation in lipophilic–hydrophilic properties. The change along the t_1 axis going from serine to homoserine estimates the increase in lipophilicity caused by the inclusion of an extra methylene group in the side chain. It is seen in Fig. 1 that inclusion of extra ethyleneoxy groups causes a much smaller change in the lipophilic–hydrophilic properties. The ether group thus counteracts and partially compensates for the increase in lipophilicity caused by the extra methylene groups in the side chain.

Three new amino acids; *(2S)-2-amino-9-hydroxy-4,7-dioxanonanoic acid* (**15**), *(2S)-2-amino-12-hydroxy-4,7,10-trioxadodecanoic acid* (**16**) and *(2S)-2,12-diamino-4,7,10-trioxadodecanoic acid* (**18**), are projected into previously empty areas of the principal property map and these amino acids can therefore be considered to possess new principal properties.

Experimental

Experimental techniques. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC80, ACP250 or AC500 instrument, using deuteriochloroform as the solvent and TMS (tetramethylsilane) as an internal reference except for the free amino acids which were dissolved in deuterium oxide and for which sodium 2,2-dimethyl-2-silapentane-5-sulfonate, DSS was used as internal reference. Electron impact (EI) mass spectra were obtained on an HP GC/MSD 5830/5970 system. Mass spectra are reported as follows: *m/z* (% relative abundance) [assignment]. IR spectra were recorded on a Perkin-Elmer 681 spectrometer and are reported in cm^{-1}. The optical rotation was measured on a Perkin-Elmer 141 or 241 polarimeter using chloroform as the solvent unless otherwise stated. The course of the reactions was monitored by HPLC using a Merck–Hitachi L-6250 chromatograph equipped with a 4.0 mm × 25 cm LiChrosorb 10 μ silica 60 column using heptane–ethyl acetate 1:1 (v:v) as the eluent. Flash chromatography[11] was carried out with using silica gel 60 (230–400 mesh).

Chemicals. Starting materials, reagents and solvents were of *pro analysi* grade and were supplied by Aldrich, Merck or Jansen. Tetrahydrofuran (THF) was dried by distillation from sodium–potassium amalgam. Dichloromethane was distilled from diphosphorus pentoxide and stored over 3 Å molecular sieves. Triethylamine (TEA) was distilled and stored over solid potassium hydroxide. Chloroform and trifluoroacetic acid were used as delivered.

*(2S)-Methyl 3-hydroxy-2-(tritylamino)propanoate (**1**).*[5] To a solution of L-serine methyl ester hydrochloride (25.00 g, 0.161 mol) and TEA (32.52 g, 0.322 mol) in 110 ml of dichloromethane at 0 °C, was added in one portion a solution of chloro(triphenyl)methane (44.80 g, 0.161 mol) in 85 ml of dichloromethane. The mixture was allowed to stand at 0 °C for 24 h under a protective atmosphere of argon, whereon it was successively washed with 10% aqueous citric acid, water and finally dried over magnesium sulfate. Evaporation of the solvent yielded **1** as a pale yellow crystalline solid in quantitative yield, 58.55 g. TLC on silica 60 using heptane–ethyl acetate 1:1 as eluents afforded $R_f = 0.52$. The product was used for the next step without further purification.

*(2R)-1-Tritylaziridine-2-carboxylic acid methyl ester (**2**).* The crude crystalline material **1** (58.20 g, 0.161 mol) from the above procedure was dissolved in 400 ml of dichloromethane and cooled to 0 °C under argon. Freshly distilled methanesulfonyl chloride (20.53 g, 0.179 mol, 1.1 equiv.) was added to the cooled solution, followed by the dropwise addition of TEA (24.39 g, 1.5 equiv.). The resulting solution was allowed to stand at 0 °C for 30 min. It was then shaken with 10% aqueous citric acid followed by water. After drying ($MgSO_4$) and evaporation of the solvent the crude mesylate ($R_f = 0.57$ on TLC, silica 60; hexane–ethyl acetate 1:1) was dissolved in 110 ml of THF and TEA (32.52 g, 0.322 mol, 2 equiv.) was added. The reaction mixture was heated to reflux and

maintained at this temperature for 25 h under a protective atmosphere of argon. After cooling, the mixture was washed consecutively with 10% aqueous citric acid, saturated aqueous sodium hydrogen carbonate and finally with distilled water. Drying ($MgSO_4$) and evaporation of the solvent afforded a crude crystalline material, which after recrystallization in two crops from hexane–ethyl acetate yielded 36.47 g of pure **2**. Work-up of the mother liquors and purification by flash chromatography (heptane–ethyl acetate 5:1) afforded an additional crop of pure **2**, 12.65 g. The total yield of **2** was 49.12 g (89% calculated from L-serine methyl ester hydrochloride). ^{1}H NMR (80.13 MHz): δ 7.57–7.14 (m, 15 H), 3.73 (s, 3 H), 2.25 (dd, 1 H, *J* 2.8 Hz, 1.7 Hz), 1.89 (dd, 1 H, *J* 6.1, 2.7 Hz), 1.40 (dd, 1 H, *J* 6.1, 1.7 Hz). ^{13}C NMR (20.15 MHz): δ 171.8, 143.6, 129.3, 127.6, 126.9, 74.4, 52.0, 31.7, 28.6. IR (KBr): 3030–3000, 2970, 1745, 1600, 1490, 1450, 1400, 1240, 1200, 1180, 750, 710.

*(2R)-(−)-1-(Benzyloxycarbonyl)aziridine-2-carboxylic acid methyl ester (**3**).* To a solution of **2** (48.67 g, 0.142 mol) in 120 ml of methanol and 120 ml of chloroform at 0°C were added 200 ml of trifluoroacetic acid. The resulting mixture was allowed to stand at 0°C for 2 h after which time the solvents were removed by evaporation under reduced pressure. The remaining oil was partitioned between water and ether. The ether layer was collected. The aqueous layer was made alkaline by the addition of solid sodium hydrogen carbonate, saturated with sodium chloride and then transferred to an apparatus for continuous ether extraction. Extraction with diethyl ether was allowed to proceed overnight. The combined ether extracts were dried ($MgSO_4$) and the ether was removed by distillation. The remaining crude (2*S*)-aziridine-2-carboxylic acid methyl ester was dissolved in 400 ml of dichloromethane and TEA (15.77 g, 0.156 mol, 1.1 equiv.) was added. The mixture was cooled to 0°C and a solution of benzyl chloroformate (26.43 g, 0.155 mol) in 100 ml of dichloromethane was added dropwise. The reaction mixture was allowed to stand at room temperature overnight and was then washed successively with 10% aqueous potassium hydrogensulfate, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and the solvent was removed by evaporation. The crude product was purified by flash chromatography (Silica gel 60; heptane–ethyl acetate, 2:1) to yield **3** (14.33 g, 46% from **2**). The purity of the product was 90%. It was contaminated with benzyl alcohol which was not possible to remove by flash chromatography. ^{1}H NMR (80.13 MHz): δ 7.31 (m, 5 H), 5.10 (s, 2 H), 3.68 (s, 3 H), 3.06 (dd, 1 H, *J* 3.2 and 5.3 Hz), 2.53 (dd, 1 H, *J* 1.2 and 3.2 Hz), 2.40 (dd, 1 H, *J* 1.2 and 5.4 Hz). ^{13}C NMR (20.15 MHz): δ 168.7, 160.7, 135.4, 128.5, 68.6, 52.7, 34.8, 31.4. MS (EI): 176 (1), 129 (10), 107 (31), 91 (100). IR (neat film): 3100–3000, 2990–2820, 1750, 1730, 1325, 1295, 1225, 1190, 750, 700. $[\alpha]_D^{25} = -47.3°$ (*c* 0.25).

*(2S)-(+)-Methyl 2-(N-benzyloxycarbonylamino)-6-benzyloxy-4-oxahexanoate (**4**). General method for BF_3–OEt_2-catalyzed nucleophilic ring-opening of (**3**).*[6] To a solution of **3** (1.00 g, 3.83 mmol) and 2-benzyloxyethanol (the nucleophile) (2.90 g, 5 equiv.) in 20 ml of dichloromethane at room temperature were added six drops of boron trifluoride–diethyl ether ($BF_3 \cdot OEt_2$). The reaction mixture was allowed to stand for 3 h and then quenched with saturated aqueous sodium hydrogencarbonate and extracted with several portions of ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash chromatography (Silica gel 60; heptane–ethyl acetate 7:4) to yield 1.14 g (77%) of **4**. ^{1}H NMR (500 MHz): δ 7.28 (m, 10 H), 5.98 (d, 1 H, *J* 8.4 Hz), 5.11 (s, 2 H), 4.50 (dd, 1 H, *J* 3.1), 4.49 (s, 2 H), 3.82 (dd, 1 H, *J* 9.7 and 3.1 Hz), 3.71 (dd, 1 H, *J* 9.7 and 3.1 Hz), 3.67 (m, 3 H), 3.59 (m, 2 H), 3.54 (m, 2 H). ^{13}C NMR (125.71 MHz): δ 170.8, 156.1, 138.2, 136.5, 128.4, 128.3, 128.0, 128.0, 127.6, 73.1, 71.0, 69.2, 66.8, 54.6, 52.3. IR (neat film): 3500–3200, 3100–3000, 2990–2850, 1750, 1725, 1520, 1210, 1100, 740, 700. $[\alpha]_D^{25} = 7.7°$ (*c* 0.25).

*(2S)-(+)-Methyl 2-(N-benzyloxycarbonylamino)-9-benzyloxy-4,7-dioxanonanoate (**5**).* Following the general procedure given above using **3** (1.00 g, 3.83 mmol) and 2-(2-benzyloxyethoxy)ethanol (5 equiv.) as nucleophile afforded 1.37 g (83%) of **5** after purification of the crude product by flash chromatography (Silica gel 60; heptane–ethyl acetate 5:4). ^{1}H NMR (500 MHz): δ 7.26 (m, 10 H), 5.91 (d, *J* 8.3 Hz), 5.09 (s, 2 H), 4.50 (s, 2 H), 4.46 (dd, 1 H, *J* 8.1 and 3.8 Hz), 3.92 (dd, 1 H, *J* 9.6 and 3.1 Hz), 3.70 (1 H, *J* 9.6 and 3.1 Hz), 3.68 (m, 3 H), 3.56 (m, 8 H). ^{13}C NMR (125.71 MHz): δ 170.8, 156.1, 138.3, 136.4, 128.4, 128.3, 128.1, 128.0, 127.6, 127.5, 73.1, 71.0, 70.6, 70.4, 69.4, 66.8, 54.6, 52.3. IR (neat film): 3450–3250, 3100–3000, 2980–2820, 1750, 1730, 1520, 1210, 1100, 740, 700. $[\alpha]_D^{25} = 5.7°$ (*c* 0.25).

*(2S)-(+)-Methyl 2-(N-benzyloxycarbonylamino)-12-benzyloxy-4,7,10-trioxadodecanoate (**6**).* Using 2-[2-(2-benzyloxyethoxy)ethoxy]ethanol (5 equiv.) as the nucleophile **3** (1 g, 3.83 mmol) in the general procedure followed by purification by flash chromatography (Silica gel 60; heptane–ethyl acetate 2:3) yielded 1.46 g (80%) of **6**. ^{1}H NMR (250.13 MHz): δ 7.29 (m, 10 H), 5.89 (d, *J* 8.5 Hz), 5.10 (s, 2 H), 4.53 (s, 2 H), 4.46 (dd, 1 H, *J* 8.6 and 3.8 Hz), 3.93 (dd, 1 H, *J* 9.8 and 3.4 Hz), 3.71 (s, 3 H), 3.68 (dd, 1 H), 3.61 (m, 12 H). ^{13}C NMR (62.89 MHz): δ 170.8, 156.1, 138.3, 136.3, 128.4, 128.3, 128.0, 127.7, 127.5, 73.1, 71.0, 70.6, 70.3, 69.4, 66.9, 54.5, 52.4. IR (neat film): 3450–3250, 3100–3000, 2980–2800, 1750, 1730, 1520, 1210, 1100, 740, 700. $[\alpha]_D^{25} = 4.2°$ (*c* 0.25).

*(2S)-(+)-Methyl 9-azido-2-(N-benzyloxycarbonylamino)-4,7-dioxanonanoate (**7**).* By the general procedure using 2-(2-azidoethoxy)ethanol (5 equiv.) and 2.00 g (7.66 mol)

of **3**, 2.19 g (78%) of **7** was obtained after purification of the crude product by flash chromatography (Silica gel 60; heptane–ethyl acetate 3:1). ^{1}H NMR (250.13 MHz): δ 7.32 (s, 5 H), 5.92 (d, 1 H, *J* 8.5 Hz), 5.11 (s, 2 H), 4.48 (m, 1 H, *J* 8.8 and 3.9 Hz), 3.94 (dd, 1 H, *J* 9.6 and 3.2 Hz), 3.73 (s, 3 H), 3.71 (dd, 1 H, *J* 3.6 Hz), 3.61 (m, 6 H), 3.30 (t, 2 H). ^{13}C NMR (62.89 MHz): δ 170.6, 156.1, 136.4, 128.5, 128.1, 71.1, 71.0, 70.4, 70.1, 66.9, 54.5, 52.5, 50.6. IR (neat film): 3480–3230, 3100–3000, 2980–2820, 2105, 1750, 1730, 1520, 1300, 1210, 1120, 740, 700. $[\alpha]_D^{25} = 6.4°$ (*c* 0.25).

*(2S)-(+)-Methyl 12-azido-2-(*N*-benzyloxycarbonylamino)-4,7,10-trioxadodecanoate (***8***).* 2-[2-(2-Azidoethoxy)ethoxy]ethanol (5 equiv.) was reacted with **3** (1.5 g, 5.75 mmol) according to the general procedure. Purification by flash chromatography (Silica gel 60; heptane–ethyl acetate 2:3) gave 1.78 g (76%) of **8**. ^{1}H NMR (250.13 MHz): δ 7.31 (m, 5 H), 5.98 (d, 1 H, *J* 8.5 Hz), 5.10 (s, 2 H), 4.47 (m, 1 H, *J* 8.7 and 3.9 Hz), 3.93 (dd, 1 H, *J* 9.7 and 3.3 Hz), 3.72 (s, 3 H), 3.70 (dd, 1 H, *J* 3.5 Hz), 3.58 (s, 12 H), 3.30 (t, 2 H). ^{13}C NMR (62.89 MHz): δ 170.8, 158.1, 136.4, 128.5, 128.1, 70.9, 70.6, 70.5, 70.4, 70.0, 66.6, 54.5, 52.4, 50.5. IR (neat film): 3450–3230, 3100–3000, 2980–2870, 2105, 1750, 1730, 1520, 1300, 1210, 1125, 740, 700. $[\alpha]_D^{25} = 6.2°$ (*c* 0.25).

Procedure for the hydrolysis of methyl esters with lithium hydroxide. The *N*-protected amino acid ester was dissolved in tetrahydrofuran–water (3:1) (v:v) to yield a 0.1–0.2 M solution. Solid lithium hydroxide (1.1 equiv.) was added in one portion. The reaction mixture was allowed to stand at room temperature for 1–2 h after which time the hydrolysis was complete. The reaction was monitored by TLC. The tetrahydrofuran was evaporated off and the remaining alkaline water solution was extracted with diethyl ether to remove traces of unchanged starting material and was then acidified by the addition of solid potassium hydrogen sulfate to pH 1–2. The acidic aqueous layer was extracted with several portions of diethyl ether. The combined ether layers were dried ($MgSO_4$). The *N*-protected amino acid was obtained in 90–95% yield after evaporation of the ether.

*(+)-(2S)-6-Benzyloxy-2-(*N*-benzyloxycarbonylamino)-4-oxahexanoic acid (***9***).* ^{1}H NMR (250.13 MHz): δ 10.3 (s, 1 H), 7.24 (m, 10 H), 5.92 (d, 1 H, *J* 8.45 Hz), 5.11 (s, 2 H), 4.49 (m, 3 H), 3.97 (dd, 1 H, *J* 9.8 and 3.0 Hz), 3.69 (dd, 1 H, *J* 9.8 and 3.6 Hz), 3.60 (m, 4 H). ^{13}C NMR (62.89 MHz): δ 173.8, 156.4, 137.7, 136.2, 128.4, 128.1, 127.8, 73.1, 70.8, 69.0, 67.2, 54.2. IR (neat film): 3400–3300, 3100–3000, 2980–2830, 2700–2330, 1725, 1520, 1215, 1090, 740, 700. $[\alpha]_D^{25} = 8.0°$ (*c* 0.25).

*(+)-(2S)-9-Benzyloxy-2-(*N*-benzyloxycarbonylamino)-4,7-dioxanonanoic acid (***10***).* ^{1}H NMR (250.13 MHz): δ 10.1 (s, 1 H), 7.27 (m, 10 H), 5.95 (d, 1 H, *J* 8.4 Hz), 5.10 (s, 2 H), 4.51 (s, 3 H), 4.50 (m, 1 H), 3.97 (dd, 1 H, *J* 9.9 and 3.1 Hz), 3.72 (dd, 1 H, *J* 9.8 and 3.5 Hz), 3.62 (m, 8 H). ^{13}C NMR (62.89 MHz): δ 173.3, 156.4, 137.9, 136.2, 128.5, 128.4, 128.1, 127.8, 127.7, 73.2, 70.8, 70.5, 70.3, 69.3, 67.1, 65.9, 54.3. IR (neat film): 3500–3200, 3100–3000, 2980–2820, 2800–2400, 1725, 1520, 1210, 1190, 740, 700. $[\alpha]_D^{25} = 8.9°$ (*c* 0.25).

*(+)-(2S)-12-Benzyloxy-2-(*N*-benzyloxycarbonylamino)-4,7,10-trioxadodecanoic acid (***11***).* ^{1}H NMR (250.13 MHz): δ 10.3 (s, 1 H), 7.29 (m, 10 H), 5.97 (d, *J* 8.4 Hz), 5.10 (s, 2 H), 4.53 (s, 2 H), 4.47 (m, 1 H, *J* 8.3 and 3.2 Hz), 3.95 (dd, 1 H, *J* 9.6 and 3.0 Hz), 3.70 (dd, 1 H, *J* 9.6 and 3.0), 3.60 (m, 12 H). ^{13}C NMR (62.89 MHz): δ 172.6, 156.2, 137.8, 136.2, 128.4, 128.3, 128.0, 127.8, 127.7, 73.1, 70.8, 70.5, 70.3, 70.0, 69.2, 67.0, 54.3. IR (neat film): 3500–3200, 3100–3000, 2980–2800, 2800–2400, 1725, 1520, 1210, 1100, 740, 700. $[\alpha]_D^{25} = 15.2°$ (*c* 0.25).

*(+)-(2S)-9-Azido-2-(*N*-benzyloxycarbonylamino)-4,7-dioxanonanoic acid (***12***).* ^{1}H NMR (250.13 MHz): δ 11.1 (s, 1 H), 7.31 (m, 5 H), 6.01 (d, 1 H, *J* 8.6 Hz), 5.12 (s, 2 H), 4.52 (m, 1 H, *J* 8.5 and 3.7 Hz), 3.99 (dd, *J* 9.6 and 2.8 Hz), 3.71 (*J* 9.8 and 3.1 Hz), 3.61 (m, 6 H), 3.30 (t, 2 H). ^{13}C NMR (62.89 Hz): δ 174.1, 156.4, 136.1, 128.5, 128.2, 128.1, 70.9, 70.8, 70.2, 70.0, 67.1, 54.2, 50.5. IR (neat film): 3500–3200, 3100–3000, 2980–2800, 2800–2450, 2100, 1725, 1510, 1210, 1100, 740, 700. $[\alpha]_D^{25} = 7.4°$ (*c* 0.25).

*(+)-(2S)-12-Azido-2-(*N*-benzyloxycarbonylamino)-4,7,10-trioxadodecanoic acid (***13***).* ^{1}H NMR (250.13 MHz): δ 10.2 (s, 1 H), 7.30 (m, 5 H), 6.16 (d, 1 H, *J* 8.4 Hz), 5.11 (s, 2 H), 4.47 (m, 1 H, *J* 8.4 and 3.8 Hz), 3.97 (dd, 1 H, *J* 9.7 and 3.1 Hz), 3.71 (dd, 1 H, *J* 9.8 and 3.2 Hz), 3.60 (m, 10 H), 3.31 (t, 2 H). ^{13}C NMR (62.89 Hz): δ 172.8, 156.5, 136.3, 128.5, 128.2, 128.1, 70.8, 70.7, 70.5, 70.3, 69.9, 67.0, 54.3, 50.5. IR (neat film): 3450–3200, 3100–3000, 2980–2800, 2800–2400, 2105, 1725, 1510, 1210, 1100, 740, 700. $[\alpha]_D^{25} = 10.9°$ (*c* 0.25).

General procedure for deprotection by catalytic phase-transfer hydrogenation.[8] *(2S)-2-Amino-6-hydroxy-4-oxahexanoic acid (***14***).* To a solution of **9** (0.66 g, 1.77 mmol) and ammonium formate (0.89 g, 8 equiv.) in 20 ml of methanol were added 700 mg 10% Pd–C. The reaction mixture was heated at 60°C overnight under an atmosphere of argon. The catalyst was removed by filtration and the solvent was evaporated off to afford the amino acid which was purified by ion exchange chromatography on an Amberlite CG-120 column using 0.2 M aqueous ammonia as the eluent to yield 0.25 g (96%) of **14** as a white solid. ^{1}H NMR (250.13 MHz): δ 3.92 (m, 3 H), 3.72 (m, 2 H), 3.65 (m, 2 H). ^{13}C NMR (62.89 MHz): δ 174, 74.6, 71.3, 63.1, 57.4. IR (KBr): 3600–3000, 2990–2800, 2650, 2100, 1630, 1600, 1510, 1110, 1060. $[\alpha]_D^{25} = -6.8°$ (*c* 0.02, H_2O).

(−)-(2S)-2-Amino-9-hydroxy-4,7-dioxanonanoic acid (**15**). Deprotection of **10** (1.25 g, 2.99 mmol) by the general procedure yielded 0.50 g (87%) of **15** as an amorphous, very hygroscopic, solid. ^{1}H NMR (250 MHz): δ 3.91 (m, 3 H), 3.68 (m, 8 H). ^{13}C NMR (62.89 MHz): δ 174, 74.4, 72.6, 72.2, 71.5, 63.0, 57.4. IR (KBr): 3340, 2900, 2100, 1623, 1496, 1112. $[\alpha]_D^{25} = -2.6°$ ($c = 0.027$, H_2O).

(−)-(2S)-2-Amino-12-hydroxy-4,7,10-trioxadodecanoic acid (**16**). Deprotection of **11** (1.37 g, 2.97 mmol) afforded 0.60 g (85%) of **16** as amorphous, very hygroscopic, solid. ^{1}H NMR (250.13 MHz): δ 3.91 (m, 3 H), 3.66 (m, 12 H). ^{13}C NMR (62.89 MHz): δ 174, 74.1, 72.3, 72.1, 71.8, 71.2, 62.8, 57.6. IR (KBr): 3340, 2890, 2100, 1621, 1492, 1110. $[\alpha]_D^{25} = -11.0$ ($c = 0.01$, H_2O).

(+)-(2S)-2,9-Diamino-4,7-dioxanonanoic acid (**17**). Deprotection of **12** (1.84 g, 5.22 mmol) by the general procedure yielded 0.84 g (84%) of **17** as an amorphous solid. A reaction time of 1–2 h was sufficient with this substrate. ^{1}H NMR (250.13 MHz): δ 3.74 (m, 9 H), 3.10 (t, 2 H). ^{13}C NMR (62.89 MHz): δ 179.5, 74.2, 72.0, 70.2, 57.7, 41.7. IR (KBr): 3330, 2950, 1621, 1487, 1110. $[\alpha]_D^{25} = 2.5°$ ($c = 0.02$, H_2O).

(+)-(2S)-2,12-Diamino-4,7,10-trioxadodecanoic acid (**18**). Use of the same procedure as above for **13** (1.63 g, 4.11 mmol) afforded 0.83 g (86%) of **18** as an amorphous solid. ^{1}H NMR (250.13 MHz): δ 3.70 (m, 13 H), 3.12 (t, 2 H). ^{13}C NMR (62.89 MHz): δ 178.9, 73.9, 72.2, 72.1, 71.9, 69.9, 57.6, 41.7. IR (KBr): 3340, 2960, 2050, 1620, 1495, 1110. $[\alpha]_D^{25} = 1°$, $[\alpha]_{302}^{25} = 22.3°$ ($c = 0.03$, H_2O).

Acknowledgements. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged. We also thank Dr. Åke Nordahl for help in the computational work in determining the principal properties of the new amino acids and Dr. Peter Kaufmann for linguistic assistance.

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Received January 4, 1994.