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TETRAHEDRON

Stereoselective Synthesis of α, α' -Bridged bis(α -Alanine) Derivatives.

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Abstract: Stereoselective syntheses of α, α' -dimethylated C₂-C₄ alkylene-bridged bis(glycine) methyl esters are described. The products were further converted into *N*-Fmoc-protected bis(amino acids). © 1998 Elsevier Science Ltd. All rights reserved.

The preparation of rigidified α -amino acids to effect conformational constraints in peptides has assumed an important role in drug design and development.¹ Isosteric structures may be envisaged to replace cystine in peptoid bioorganics when cycstine exerts mainly a structural skeletal function. We have recently reported syntheses of several bridged bis(glycines) in which the -CH₂SSCH₂- bridge between the two glycine units in cyctine has been replaced by substituted even-numbered carbon bridges with special emphasis on C4-rigidified bridges as cystine substitutes with reduced conformational freedom.² C3-bridges, especially halogenated bridges and α -hydroxymethyl derivatives, have received considerable attention.³



In an alternative approach to affect conformational preferences, the α -hydrogen in α -amino acids can be replaced by a carbosubstituent as exemplified by simple α -methyl and higher α -alkyl amino acid derivatives.⁴ We have further increased the rigidity of α -aminoid acid structures by incorporation of the α amino acid carbon into cyclic structures.⁵ In this report we describe work on α, α' -dimethyl derivatives of bridged bis(glycines).

The chiral auxiliary to be used as pro-alanine was the 5-methylated derivative of (2R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**1b**, Scheme 1). The latter is available by methylation of the lithiated bislactim ether **1a** or by *O*-methylation of the cyclic dipeptide prepared from (*R*)-valine and racemic alanine.⁶ The stereochemistry at C-5 in substrate **1b** is of little importance since this stereochemistry is lost on metalation before the second C-5 alkylation. Stereoselectivity in the second alkylation step is trans with respect to the isopropyl group. In monoalkylations diastereomeric excess (d.e.) in the first alkylation is variable. In most dialkylations, however, the diastereoselectivity is often high with **1a** as the original substrate.^{5,6} Stereochemistry at C-5 is controlled either by the stereochemistry of the isopropyl group at C-2, *ie*. the configuration of valine used for the bislactim ether, or by the order of the alkylation reactions using the same chiral auxiliary. In this work our efforts have been directed towards producing bis(alanines) with (*S*)configuration at the stereogenic centers using **1b** as the substrate.

Alkylations were effected by initial lithiation by n-butyllithium at -78 °C followed by addition of the alkylating agent, an α,ω -dibromoalkane. For the C₂-bridge, however, this approach may cause problems since vicinal dihalides are also agents used for halogenation at anionic carbon.⁷ A trial with 1,2-dibromoethane for alkylation confirmed extensive halogenation and elimination reactions. This problem was largely overcome when the second halogen atom was chlorine, the reagent being either 1-bromo-2-chloroethane or 1-chloro-2-iodoethane. 1-Bromo-2-chloroethane was the better reagent. When the alkylation of lithiated **1b** was run at -78 °C in THF in the presence of 1,3-dimethyl-2-imidazolidinone (DMEU) with excess 1-bromo-2-chloroethane to yield the chloroethyl product **2**.

Prior to the second alkylation for the preparation of 4a, halogen exchange was effected by warming the chloride 2 with either sodium bromide or iodide in DMF. Coupling of either the bromide 3a or the iodide 3b yielded the bridged structure 4a which was isolated in 60% (d.e.96%) after flash chromatography which removes any diastereomeric product coming from the wrong stereoisomer of the alkylating agent 3a. Coupling reactions with the other α, ω -dibromalkanes proceeded in high yields and were characterized by high diastereoselectivity. It is noteworthy that the high stereoselectivity results after two separate alkylation steps where in principle two different alkylating agents are involved in the formation of the product 4. When present, the second isomer was readily removed by flash chromatograpy or recrystallization of the product from acetonitrile. The products in this report all contain more than one stereochemical center. The main stereochemical information on the homogeneity of a product formed, is based ¹³C and ¹H NMR spectroscopy (vide infra). Additional information is provided by chromatography (capillary GLC).

For the hydrolytic cleavage of the bislactim ether unit in 4 to furnish the bridged amino acid esters 5, the mild acid conditions were used; 0.25 M HCl in aqueous acetonitrile. The second product in this reaction, viz. value methyl ester was removed form the crude hydrolysates by slow bulb-to-bulb distillation at 35 °C/0.05 torr.



For subsequent use as reactants in solid phase peptide synthesis the amino acid esters 5 were *N*-protected and the ester groups hydrolyzed. A solution of the amino acid ester in dioxane was treated with a 50% excess 9-fluorenylmethyloxycarbonyl chloride (Fmoc-Cl) and aqueous sodium bicarbonate. Fmoc-*N*-acylated amino functions are resistant towards acid hydrolysis. Concequently, HCl in dioxane was used to effect selective ester hydrolysis with formation of the *N*-protected amino acids 7 in high yields.



Scheme 3

EXPERIMENTAL

¹H NMR spectra were recorded at 300 MHz and ¹³C at 75 MHz on a Varian Unit 300 The mass spectra under electron impact conditions were recorded at 70 eV ionizing potential. The mass spectra are given as m/z(% rel. int.). IR spectra were recorded in chloroform. Analytical GLC was by a Shimadzu gas chromatograph, GC-14A (FID detector) equipped with a SPMTM-1, Silica capillar column, 30 m, 0.25 mm ID. IR spectra were recorded in chloroform.

The products were purified by flash chromatography on silica gel 60 (0.063 mm, 230-400 mesh ASTM).

(2*R*.5*S*)-5-(2-Chloroethyl)-2.5-dihydro-3.6-dimethoxy-2-isopropyl-5-methylpyrazine (2). 1-Bromo-2-chloroethane (6.33 g, 44.15 mmol) in THF (30 ml) was added with stirring to a solution prepared from (2*R*,5*S*/*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (3.5 g, 17.66 mmol), THF (200 ml), n-butyllithium (1.6 N, 14.14 ml, 19.43 mmol) and DMEU (4.03 g, 35.31 mmol) under argon at -78 °C. Stirring was continued at -78 °C for 18 h. The excess of 1-bromo-2-chloroethane was removed from the crude mixture by evaporation at 40 °C/0.01 torr. The product was isolated after flash chromatography on silica gel using hexane:Et₂O 20:1; yield 2.44 g (53%), d.e. 90% (capillary GLC). HRMS: *M* 260.1291. Calc. for $C_{12}H_{21}N_2O_2Cl$ 260.1284. IR: v 1690 cm⁻¹ (C=N). ¹H NMR (CDCl₃): δ 0.68 and 1.06 (2 d, *J* 7.7 Hz, 6H, -CH(CH₃)₂), 1.34 (s, 3H, 2-CH₃), 1.97-2.37 (m, 3H, -CH₂-CH₂Cl and -CH(CH₃)₂), 3.21-3.38 (m, 2H, -CH₂-CH₂Cl), 3.66 and 3.67 (2 s, 6H, -OCH₃), 3.95 (d, *J* 3.7 Hz 1H, H-2). ¹³C NMR (CDCl₃): δ 16.91 and 19.30 (-CH(CH₃)₂), 28.65 (2-CH₃), 31.00 (-CH(CH₃)₂), 40.51 (-CH₂-CH₂-Cl), 43.72 (-CH₂-CH₂-Cl), 52.19 and 52.32 (-OCH₃), 57.29 (C-2), 61.08 (C-5), 162.49 and 164.31 (C=N).

(2*R*,5*S*)-5-(2-Bromoethyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (**3a**). (2*R*,5*S*)-5-(2-Chloroethyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-2-methylpyrazine (1.0 g, 3.83 mmol) and NaBr (0.47 g, 4.60 mmol) in DMF (30 ml) was stirred at 70 °C for 12 h. The solvent was removed at 40 °C/0.01 torr and the product purified by flash chromatography on silica gel 60 using hexane:Et₂O 20:1; yield 1.03 g (88%). HRMS:*M*: 304.0786. Calc. for C₁₂H₂₁N₂O₂Br: 304.0782. IR: v 1690 cm⁻¹ (C=N). ¹H NMR (CDCl₃): δ 0.68 and 1.06 (2 d, *J* 7.7 Hz, 6H, -CH(C<u>H</u>₃)₂), 1.34 (s, 3H, 2-CH₃), 1.97-2.37 (m, 3H, -CH₂-C<u>H₂Cl and -CH(CH₃)₂), 3.21-3.38 (m, 2H, -CH₂-C<u>H₂Cl</u>), 3.66 and 3.67 (2 s, 6H, -OCH₃), 3.95 (d, *J* 3.7 Hz, 1H; H-2). ¹³C NMR (CDCl₃): δ 16.91 and 19.30 (-CH(<u>C</u>H₃)₂), 28.65 (2-CH₃), 31.00 (-<u>C</u>H(CH₃)₂), 40.51 (-C<u>H</u>₂-CH₂-Cl), 43.72 (-CH₂-Cl), 52.19 and 52.32 (-OCH₃), 57.29 (C-2), 61.08 (C-5), 162.49 and 164.31 (C=N).</u>

(2*R*.5*S*)-2.5-Dihydro-3.6-dimethoxy-5-(2-iodoethyl)-2-isopropyl-5-methylpyrazine (**3b**) was prepared in 88% yield by the above procedure using sodium iodide for the halogen exchange. HRMS: *M*: 352.0649. Calc. for C₁₂H₂₁N₂O₂I: 352.0647. IR: v 1690 cm⁻¹ (C=N). ¹H NMR (CDCl₃): δ 0.66 and 1.05 (2 d, *J* 7.7 Hz, 6H; -CH(CH₃)₂), 1.30 (s, 3H, 2-CH₃), 2.12-2.49 (m, 3H, -CH₂-CH₂I and -CH(CH₃)₂), 2.76-2.98 (m, 2H, -CH₂-CH₂I), 3.65 and 3.66 (2 s, 6H;,-OCH₃), 3.93 (d, *J* 4.0 Hz, 1 H, H-2). ¹³C NMR (CDCl₃): δ 0.92 (-CH₂-CH₂-I), 16.89 and 19.30 (-CH(CH₃)₂), 28.30 (2-CH₃), 31.00 (-CH(CH₃)₂), 45.65 (-CH₂-CH₂-I), 52.23 and 52.36 (-OCH₃), 59.77 (C-2), 61.16 (C-5), 162.59 and 163.96 (C=N).

1.2-Bis[(2*R*, 5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]ethane (**4a**). (2*R*,5*S*)-5-Bromoethyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (2.18 g, 10.08. mmol) in THF (30 ml) was added with stirring to a solution prepared from (2*R*,5*S*/*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (2.0 g, 10.08 mmol), THF (70 ml), n-butyllithium (1.6 N, 6.94 ml, 11.1 mmol) and DMEU (2.30 g, 20.16 mmol) at -78 °C under argon. Stirring was continued at -78 °C for 18 h. The product was isolated after flash chromatography on silica gel 60 using hexane:Et₂O 20:1; yield 2.44 g (62%), mp 96 °C (MeNO₂). Capillary GLC: d.e. 96%. Found: C, 62.48; H, 9.10; N, 13.30. Calc for C₂₂H₃₈N₄O₄: C, 62.53; H, 9.06; N 13.26. HRMS: *M*: 422.2893. Calc. for C₂₂H₃₈N₄O₄: 422.2883. IR: v 1690 cm⁻¹ (C=N). ¹H NMR (CDCl₃): δ 0.65 and 1.05 (2 d, *J* 7.7 Hz, 6 H, -CH(CH₃)₂), 1.28 (s, 3H, 2-CH₃), 1.38 -1.80 (m, 4H, -CH₂-CH₂-), 2.24 (dsp, *J*₁ 7.7 Hz, *J*₂ 3.7 Hz, 1 H, -CH(CH₃)₂), 3.63 (s, 6H, -OCH₃), 3.90 (d, *J* 3.7 Hz, 1 H, H-2). ¹³C NMR (DMSO): δ 16.72 and 19.30 (-CH(CH₃)₂), 24.36 (-CH₂-CH₂-), 28.61 (2-CH₃), 30.87 (-CH(CH₃)₂), 52.00 and 52.02 (-OCH₃), 58.31 (C-2), 61.01 (C-5), 161.62 and 165.32 (C=N).

General procedure for direct formation of bridged structures (4b, 4c). A solution of n-butyllithium in hexane (1.60 M solution in hexane; 3.44 ml, 5.5 mmol) was injected into a solution of (2R,5S/R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (5 mmol) and DMEU (10 mmol) in THF (50 ml). Stirring was continued for 15 - 20 min to complete the formation of the aza-enolate. A solution of α,ω -dibromoalkane (2.5 mmol) in THF (10 ml) was added and stirring was continued for 18 h at -78 °C. Phosphate buffer (pH 7.4) was then added, the reaction mixture allowed to warm to ambient temperature, the solvent evaporated at reduced pressure and the residual material shaken with water (30 ml) and diethyl ether (50 ml). The layers were allowed to separate, the water layer extracted twice with diethyl ether (50 ml), the combined ether extracts dried (MgSO4) and the ether distilled off. The crude product was purified by bulb-to-bulb distillation. Final purification was by flash chromatography on silica gel 60 using hexane:Et₂O 20:1. The diastereomeric ratio of the crude product was determined by capillary GLC.

1,3-Bis[(2R, 5S)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]propane (**4b**) was obtained in 75% yield, mp. 65 °C (MeNO₂). Capillary GLC: d.e. 88%. Found: C, 63.25; H 9.30; N, 12.78. Calc. for C₂₃H₄₀N₄O₄: C, 63.27; H, 9.23; N, 12.83. HRMS: *M*: 436.3049. Calc. for C₂₃H₄₀N₄O₄: 436.3039. IR: v 1690 cm⁻¹ (C=N). ¹H NMR (CDCl₃): δ 0.66 and 1.05 (2 d, *J* 7.7 Hz, 6H, -CH(C<u>H</u>₃)₂), 0.71 - 0.82 (m, 2H, -CH₂-CH₂-CH₂-), 1.27 (s, 3H, 2-CH₃), 1.32-1.81 (m, 2H, -C<u>H</u>₂-CH₂-CH₂-), 2.20 (dsp, *J*₁ 7.7 Hz, *J*₂ 4.0 Hz, 1 H, -C<u>H</u>(CH₃)₂), 3.61 (s, 6H, -OCH₃), 3.87 (d, *J* 4.0 Hz, 1 H, H-2). ¹³C NMR (CDCl₃): δ 16.87 and 19.28 (-CH(<u>C</u>H₃)₂), 19.09 (-CH₂-<u>C</u>H₂-CH₂-), 28.58 (2-CH₃), 30.97 (-<u>C</u>H(CH₃)₂), 41.31 (-<u>C</u>H₂-CH₂-CH₂-CH₂-), 51.97 and 51.93 (-OCH₃), 58.31 (C-2), 61.01 (C-5), 161.71 and 165.26 (C=N).

1,4-Bis[(2*R*, 5*S*)-2.5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]butane (4c) was obtained in 82% yield, mp. 57 °C (MeNO₂). Capillary GLC: d.e. 88 %. Found: C, 63.94; H 9.42; N, 12.40. Calc. for C₂₄H₄₂N₄O₄: C, 63.97; H, 9.39; N, 12.43. HRMS: *M* 450.3206 Calc. for C₂₄H₄₂N₄O₄: 450.3196. IR: v 1690 cm⁻¹ (C=N). ¹H NMR (CDCl₃): δ 0.66 and 1.04 (2 d, *J* 6.9 Hz, 6H; -CH(C<u>H</u>₃)₂), 0.89-1.07 (m, 4H, -CH₂-C<u>H</u>₂-C<u>H</u>₂-CH₂-), 1.29 (s, 3H, 2-CH₃), 1.38-1.90 (m, 4H; -C<u>H</u>₂-CH₂-C<u>H</u>₂-), 2.25 (dsp.*J*₁ 6.9 Hz, *J*₂ 3.4 Hz, 1H, -C<u>H</u>(CH₃)₂), 3.64 (s, 6H, -OCH₃), 3.91 (d, *J* 3.4 Hz, 1 H, H-2). ¹³C NMR (CDCl₃): δ

16.81 and 19.38 (-CH(<u>C</u>H₃)₂), 24.44 (-CH₂-<u>C</u>H₂-<u>C</u>H₂-CH₂-), 28.67 (2-CH₃), 30.95 (-<u>C</u>H(CH₃)₂), 41.39 (-<u>C</u>H₂-CH₂-CH₂-<u>C</u>H₂-), 52.11 (-OCH₃), 58.40 (C-2), 61.10 (C-5), 161.71 and 165.41 (C=N).

General procedure for the preparation of (S.S)- $\alpha.\omega$ -diamino- $\alpha.\omega$ -dimethylalkanedioc acid dimethyl esters (5). and subsequently (S.S)- $\alpha.\omega$ -bis(9-fluorenylmethyloxycarbonylamino)- $\alpha.\omega$ -dimethylalkanedioc acid dimethyl esters (6). The $\alpha.\omega$ -bis((2R, 5S)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]alkane (4) (2.00 mmol) was dissolved in acetonitrile (24 ml) and 0.5 M HCl (24.0 ml) was added dropwise. The solution was stirred at ambient temperature for 12 h. Aqueous ammonia was subsequently added until pH 11, the mixture extracted (3x) with chloroform (20 ml), the chloroform solution dried (MgSO4), evaporated and the valine methyl ester removed from the residual product by slow bulb-to-bulb distillation at 35 °C/0.05 torr. 9-Fluorenylmethyloxycarbonyl chloride (3.66 mmol) and 1 M NaHCO3 (3.7 ml) were added gradually together with stirring to a solution of the crude (S.S)- $\alpha.\omega$ -diamino- $\alpha.\omega$ -dimethylalkanedioic acid dimethyl ester (1.22 mmol) in dioxane (30 ml). The mixture was stirred at ambient temperature for 20 h before the dioxane was removed by distillation. The residue was extracted (3x) with chloroform (20 ml), the chloroform solution washed, dried (MgSO4), the solvent distilled off and the product isolated from the residual material after flash chromatography using hexane:AcOMe from 4:1 to 2:1.

(S.S)-2,5-Bis(9-fluoromethyloxycarbonylamino)-2,5-dimethylhexanedioic acid dimethyl ester (6a). Acid hydrolysis of 1,2-bis[(2R, 5S)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]ethane gave the intermediate amino acid ester (S.S)-2,5-diamino-2,5-dimethylhexanedioic acid dimethyl ester (5a) in 91% yield as a non-solid material. IR: v 1731 cm⁻¹ (C=O). ¹H NMR (CDCl₃): δ 1.08-1.24 (m, 1H, CH₂), 1.30 (s, 3H, -CH₃), 1.42-1.76 (m, 1H, CH₂, -NH₂), 3.69 (s, 3H, -OCH₃).

The crude amino acid ester **5a** was acylated to yield the title compound **6a** in 75% yield as a non-solid. Found: C, 71.02; H, 6.26. Calc. for C₄₀H₄₀N₂O₈: C, 70.99; H, 5.96. IR: v 1738, 1719 cm⁻¹ (C=O). ¹H NMR (CDCl₃): δ 1.56 (s, 3H, -CH₃), 1.03, 1.24, 1.73 and 2.11 (br s, 4 H, -C<u>H₂-CH₂-), 3.74 (s, 3H, -OCH₃), 4.22 (t, *J* 6.2 Hz, 1H, -Fmoc), 4.37 (br s, 2H, -C<u>H₂-Fmoc), 5.59 (br s, 1H, -NH</u>-Fmoc), 7.23-7.81 (m, 8H, Fmoc). ¹³C NMR (CDCl₃): δ 23.36, 23.90, 36.57, 47.21, 52.68, 59.88, 66.32, 119.90, 124.94, 126.97, 127.90, 141.27, 143.87, 174.66.</u>

(S.S)-2.6-Bis(9-fluoromethyloxycarbonylamino)-2.6-dimethylheptanedioic acid dimethyl ester (6b). Acid hydrolysis of 1,3-bis[(2*R*, 5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]propane gave the intermediate amino acid ester (S.S)-2,6-Diamino-2,6-dimethylheptanedioic acid dimethyl ester (5b) in 91% as a non-solid material. IR: v 1731 cm⁻¹ (C=O). ¹H NMR (CDCl₃): δ 1.02-1.34 (m, 2H, CH₂), 1.30 (s, 3H, -CH₃), 1.34-1.82 (m, 4H, NH₂, CH₂), 3.69 (s, 3H, OCH₃).

The crude amino acid ester **5b** was acylated to yield the title compound **6b** in 75% yield as a non-solid. IR: v 1737, 1706 cm⁻¹ (C=O). ¹H NMR (DMSO-*d*₆): δ 1.56 (s, 3H, -CH₃), 1.03, 1.24, 1.73 and 2.11 (br s, 6H, -CH₂-CH₂-CH₂-), 3.74 (s, 3H, -OCH₃), 4.22 (t, *J* 6.2 Hz, 1H, -Fmoc), 4.37 (br s, 2H, -CH₂-Fmoc), 5.59 (s, 1H, -NH), 7.23-7.81 (m, 8H, Fmoc). ¹³C NMR (DMSO-*d*₆): δ 23.36, 36.31, 47.16, 52.66, 59.66, 66.43, 119.93, 124.94, 127.02, 127.63, 141.26, 143.85, 171.51.

(S.S)-2.7-Bis(9-fluoromethyloxycarbonylamino)-2.7-dimethyloctanedioic acid dimethyl ester (6c). Acid hydrolysis of 1,4-bis[(2R, 5S)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazin-5-yl]butane gave the intermediate amino acid ester (S.S)-2,7-Diamino-2,7-dimethyloctanedioic acid dimethyl ester (5c) in 92% yield as a non-solid material. IR: v 1730 cm⁻¹ (C=O). ¹H NMR (CDCl₃): δ 1.02-1.28 (m, 2H, CH₂), 1.29 (s, 3H, -CH₃) 1.42-1.85 (m, 4H, -NH₂, CH₂), 3.69 (s, 3H, -OCH₃). ¹³C NMR (CDCl₃): δ 24.36 (-CH₂CH₂-), 26.27 (-CH₃), 40.90 (-CH₂CH₂-), 52.05 (-OCH₃), 57.65 (-CNH₂), 178 (-C=O).

The crude amino acid ester **5c** was acylated to yield the title compound **6c** in 88% yield as a non-solid. IR: v 1738, 1707 cm⁻¹ (C=O). ¹H NMR (CDCl₃) : δ 1.59 (s, 3H, -CH₃), 1.02, 1.55 1.75 and 2.12 (br s, 4H; -C<u>H₂-CH₂-</u>), 3.74 (s, 3H, -OCH₃), 4.21 (t, *J* 6.2 Hz, 1H, -Fmoc), 4.37 (br s, 2H, -C<u>H₂-Fmoc</u>), 5.59 (br s, 1H, -NH), 7.21-7.79 (m, 8H, Fmoc). ¹³C NMR (CDCl₃): δ 23.36, 23.90, 36.56, 47.20, 52.68, 59.87, 66.32, 119.90, 124.93, 126.96, 127.59, 141.26, 143.86, 174.65.

General procedure for the preparation of $(S,S)-\alpha,\omega$ -bis(9-fluorenylmethyloxycarbonylamino)- α,ω dimethylalkanedioc acids (7). A solution of $(S,S)-\alpha,\omega$ -bis(9-fluorenylmethyloxycarbonylamino)- α,ω dimethylalkanedioic acid dimethyl ester (1.00 mmol) in dioxane (10 ml) and 6 M HCl (0.67 ml, 4.00 mmol) was heated at 90 °C for 24 h. The dioxane was then distilled off at reduced pressure, the residue extracted with chloroform (2x20 ml), the solution dried (MgSO4), evaporated and the residual material subjected to flash chromatography using hexane:AcOEt:AcOH (1:1:0.1). Fractions containing the product were pooled, concentrated to a small volume at reduced pressure and dried overnight to give the title compound as a white powder in high vaccum.

(*S*.*S*)-2,5-Bis(9-fluorenylmethyloxycarbonylamino)-2,5-dimethylhexanedioc acid (**7a**) was obtained from (*S*,*S*)-2,5-bis(9-fluorenylmethyloxycarbonylamino)-2,5-dimethylhexanedioic acid dimethyl ester in 71% yield of a non-crystalline solid. Found: C, 70.47; H, 5.58. Calc. for C38H36N2O8: C, 70.36; H, 5.59. ¹H NMR (DMSO-*d*₆): δ 1.13 (s (br), 1 H, -CH₂-CH₂-CH₂-), 1.30 (s, 3H, -CH₃), 1.68 (s (br), 1H, -CH₂-CH₂-), 4.22 (m, 3H, -Fmoc), 7.21-7.96 (m, 9H, -Fmoc and -N<u>H</u>), 12.40 (s (br), 1H, -COOH). ¹³C NMR (DMSO-*d*₆): δ 22.97, 23.98, 37.09, 44.00, 47.17, 58.76, 65.59, 120.46, 125.63, 127.44, 127.98, 141.10, 144.27, 155.01, 175.71.

(*S*,*S*)-2,6-Bis(9-fluorenylmethyloxycarbonylamino)-2,6-dimethylheptanedioc acid (**7b**) was obtained from (*S*,*S*)-2,6-bis(9-fluorenylmethyloxycarbonylamino)-2,6-dimethylheptanedioic acid dimethyl ester in 88% yield of a non-crystalline solid. Found: C, 70.56; H, 5.80. Calc. for C39H38N2O8: C, 70.68; H, 5.78. ¹H NMR (DMSO-*d*₆): δ 1.16 (s (br), 2 H, -CH₂-CH₂-), 1.30 (s, 3H, -CH₃), 1.68 (s (br), 2 H (-CH₂-CH₂-CH₂-), 4.22 (m, 3H, -Fmoc), 7.21- 7.98 (m, 9 H, -Fmoc and -NH), 12.14 (s (br), 1H, -COOH). ¹³C NMR (DMSO-*d*₆): δ 21.47, 22.95, 23.98, 37.10, 47.16, 58.75, 65.60, 120.46, 125.65, 127.45, 128.00, 141.10, 144.27, 155.06, 172.99, 175.70.

(S,S)-2,7-Bis(9-fluorenylmethyloxycarbonylamino)-2,7-dimethyloctanedioc acid (7c) was obtained from (S,S)-2,7-bis(9-fluorenylmethyloxycarbonylamino)-2,7-dimethyloctanedioic acid dimethyl ester in 88% yield of a non-crystalline solid. Found: C, 70.97; H, 6.07. Calc. for C40H40N2O8 : C, 70.99; H, 5.96. ¹H NMR (DMSO-d6): δ 1.16 (s (br), 2H, -CH₂-CH₂-), 1.30 (s, 3H, -CH₃), 1.68 (s (br); 2H, -CH₂-CH₂-CH₂-), 4.22

(m, 3H, -Fmoc), 7.21 - 7.98 (m, 9 H, -Fmoc and -N<u>H</u>), 12.14 (s (br), 1H, -COOH). ¹³C NMR (DMSO-d6): δ 21.47, 22.95, 23.98, 37.10, 47.16, 58.75, 65.60, 120.46, 125.65, 127.45, 128.00, 141.10, 144.27, 155.06, 172.99, 175.70.

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