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TETRAHEDRON: *ASYMMETRY*

Synthesis of orthogonally protected hydroxylated azalkene-α,α′-bridged bis(α-glycine) and dihydroxylysine derivatives

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Abstract

Stereoselective syntheses of hydroxylated azalkene-α,α′- bridged bis(α-glycine) derivatives and lysine derivatives are described. The bridge was formed as a secondary amine by a reductive dimerization process of two azide molecules upon hydrogenolysis over 5% palladium-on-charcoal. Lysine derivatives were formed by reduction of the azide function to a primary amine. In the target amino acids the vicinal dihydroxy functions were protected as acetonides, the *N′*-amino group as a Z-derivative and the α-amino groups as Fmoc-derivatives.

1. Introduction

From our program on the stereoselective preparation of α,α′-bridged bis(amino acid) derivatives,[1,2] we herein describe work leading to hydroxylated bridges coupled together *via* an amino nitrogen atom in the bridge. The coupling reaction is based on our newly discovered reductive dimerization reaction of azides upon hydrogenolysis over palladium-on-charcoal. Symmetrical secondary amine bridges are formed in this reaction (Scheme 1).[3]

2. Results and discussion

The bridge in the present work was to carry hydroxy groups with known stereochemistry. For C_4-bridges we have previously used as substrates the enantiomeric pairs of the sugar alcohols threitol and

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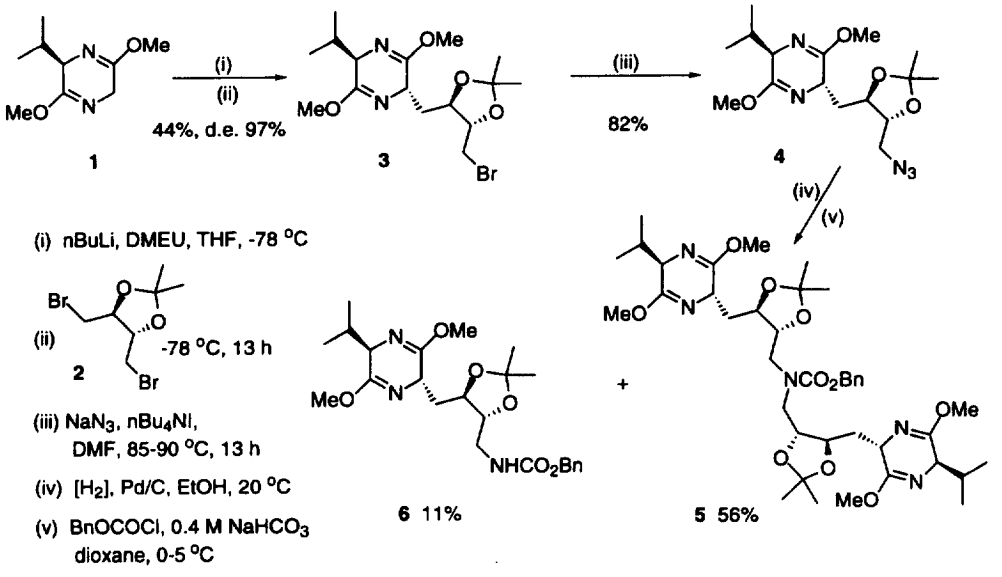


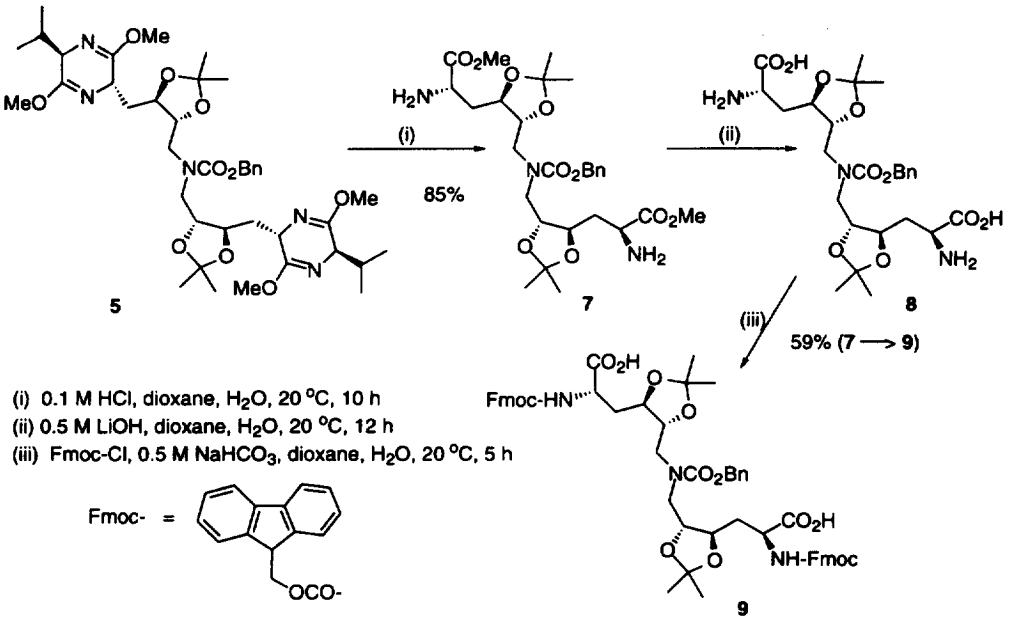
Scheme 1.

the *meso* form, erythritol. In this work (2*R*,3*R*)-threitol, as its 2,3-acetonide, was converted into the 1,4-dibromide using bromine and triphenylphosphine.[1] For alkylation at both termini of this reagent, a large excess of the metallated bislactim ether (2*R*)-3,6-dimethoxy-2,5-dihydro-2-isopropylpyrazine was used.[1] In this work equimolar amounts of reactants were used to favour monoalkylation. The reaction was run at −78°C in the presence of 1,3-dimethyl-2-pyrrolidinone (DMEU). The desired product **3** was isolated in 44% yield, d.e. 97%. Both the bislactim ether **1** and the alkylating agent **2** are sterically crowded reactants and hence showed low reactivity. The reactivity of the monoalkylated product was further decreased. Any bridge product from dialkylation was readily removed by flash chromatography. Conversion of the bromide **3** to the azide **4** was effected with sodium azide in the presence of tetrabutylammonium iodide in DMF at 85–90°C.

Reductive coupling of the azide **4** resulted from hydrogenolysis over palladium-on-charcoal in ethanol solution with hydrogen at atmospheric pressure. The major product **5** from the reaction was isolated in 56% yield after acylation of the intermediate amine with benzyloxycarbonyl chloride. The minor product was the corresponding primary amine which was isolated as structure **6** after acylation. The primary amine would correspond to the normal amine product to be expected from metal catalyzed hydrogenolysis of an azide,[4] and as an acylated derivative **6** it was isolated in 11% yield. If desireable, the latter is available by other reduction techniques.[4] The products **5** and **6** were obtained in pure form after flash chromatography (Scheme 2).

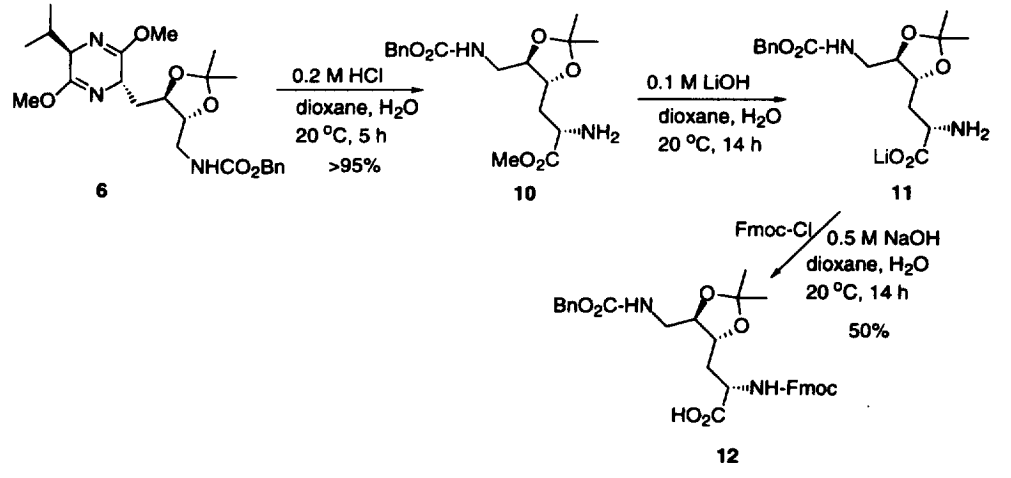
Formation of the dimeric secondary amine structure **5** may be rationalized as follows.[3] Palladium is presumably activated by some form of coordination to the bislactim ether which may allow the reaction to take a different course from the common pathway for reduction of azides to primary amines. In this reaction an imine is probably an intermediate, and it is formed by expulsion of nitrogen after an α-hydrogen shift. The imine may subsequently add hydrogen to form a primary amine. The latter may add to another imine molecule with formation of an aminal. Subsequent loss of ammonia followed by hydrogen addition gives the observed secondary amine. Secondary amines can also be prepared from azides by another route. In the latter case, *N*-substitution is effected by transfer of a carbosubstituent from a borane to an azide nitrogen which subsequently loses nitrogen to become a secondary amine.[5,6]

The monomer **6** is a potential, protected precursor for a dihydroxylysine derivative (*vide infra*)



Scheme 2.

(Scheme 3). The dimeric structure **5** is a precursor for a bridged amino acid series and has been converted into a suitable bridge building block for peptide synthesis. For this purpose the bislactim ether ring in bridge structure **5** was cleaved under mildly acidic conditions using 0.1 M HCl at ambient temperature. This left the acetal groups intact in the amino acid dimethyl ester **7** which was obtained in 85% yield. The dimethyl ester **7** was subsequently hydrolysed using 0.5 M LiOH in dioxane at ambient temperature. For solid phase peptide coupling reactions the amino groups in the amino acid **8** were protected as fluorenylmethoxycarbonyl (Fmoc) derivatives. The protection was effected by the reaction with the Fmoc–Cl in dioxane and with 0.5 M sodium hydrogen carbonate as base. The overall yield was 59% from the ester **7** to the Fmoc-protected amino acid **9**.



Scheme 3.

The preparation of an orthogonally protected dihydroxylysine is illustrated with structure **12.** The bislactim ether **6** was chemoselectively cleaved under mild acidic conditions to the amino acid ester **10**

in close to quantitative yield. Clean chemoselective cleavage of the methyl ester function in the presence of the benzylurethane functionality was effected with lithium hydroxide. The lithium salt of the acid **11** in solution was subsequently reacted further with benzyloxycarbonyl chloride in aqueous dioxane in the presence of an equimolar amount of sodium hydroxide to form the orthogonally protected hydroxylated lysine derivative **12**.

The products **9** and **12** carry protecting groups compatible with solid phase peptide synthesis. The protocol for solid phase peptide synthesis has been reported in part;[7] a full report is planned for publication elsewhere.

3. Experimental

3.1. (2S,3R)-1-Bromo-4-((2R,5S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)-2,3-(isopropylidenedioxy)butane (3)

A solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (3.24 g, 17.36 mmol) and DMEU (7.8 ml, 34.72 mmol) in anhydrous THF (60 ml) was cooled to −78°C and 1.6 M n-butyllithium in hexane (10.35 ml, 17.36 mmol) added. The mixture was stirred for 30 min at this temperature before a solution of (2*S*,3*S*)-1,4-dibromo-2,3-(isopropylidenedioxy)butane[1] (5.0 g, 17.36 mmol) in THF (10 ml) was added dropwise. The mixture was allowed to reach ambient temperature overnight before being poured into a phosphate buffer (150 ml). The resultant mixture was extracted (3×) with diethyl ether, the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed at reduced pressure. The crude monoalkylated product was purified by flash chromatography using hexane:EtOAc (9:1); yield 3.00 g (44%), d.e. 97% (capillary GLC), of a non-solid material. FAB-MS signal at *m/z* 391.2 (72), 141.1 (100). Calc. for ($C_{16}H_{27}N_2O_4Br$+*H*): 391.22. IR: ν 1690 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.70, 1.04 (2 d, *J* 7 Hz, 6H, $CH(CH_3)_2$), 1.40, 1.41 (2 s, 6H, $(CHO)_2C(CH_3)_2$), 1.95–2.30 (m, 3H, $CH(CH_3)_2$ and $CH_2(CHO)_2CH_2Br$), 3.40–3.58 (m, 2H, $(CHO)_2CH_2Br$), 3.68, 3.70 (2 s, 6H, OCH_3), 3.97 (d, *J* 3 Hz, 1H, H-5), 4.03–4.20 (m, 3H, H-2 and $(CHO)_2C(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 16.74, 19.03 ($CH(CH_3)_2$), 27.29, 27.46, 32.66, 37.83 ($CH_2(CHO)_2CH_2Br$), 31.88 ($CH(CH_3)_2$), 52.40, 52.42 (OCH_3), 52.55 (C-2), 60.76 (C-5), 79.80 ($(CHO)_2C(CH_3)_2$), 109.22 ($(CHO)_2C(CH_3)_2$), 163.21, 163.69 (C=N).

3.2. (2R,3R)-1-Azido-4-((2R,5S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)-2,3-(isopropylidenedioxy)butane (4)

Sodium azide (2.93 g, 45.0 mmol) and tetrabutylammonium iodide (0.1 g) were added to a solution of (2*R*,3*R*)-1-bromo-4-((2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)-2,3-(isopropylidenedioxy)butane (5.51 g, 14.09 mmol) in DMF (40 ml) and the mixture heated with stirring at 85–90°C for 13 h before being poured into water (50 ml). The mixture was extracted with chloroform (3×20 ml), the combined organic extracts washed with brine, dried ($MgSO_4$) and the solvent distilled off at reduced pressure. The product was isolated after flash chromatograpy of the residual material using hexane:EtOAc (7:3); yield 4.10 g (82%) of a non-solid material. Found: C, 54.12; H, 7.35; N, 19.72. Calc. for $C_{16}H_{27}N_5O_4$: C, 54.38; H, 7.70; N, 19.82%. FAB-MS signal at *m/z* 354.3 (100). Calc. for ($C_{16}H_{27}N_5O_4$+*H*) 354.22. IR: ν 2080 cm^{-1} (N_3) and 1680 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.68, 1.03 (2 d, *J* 7 Hz, 6H, $CH(CH_3)_2$), 1.40, 1.42 (2 s, 6H, $(CHO)_2C(CH_3)_2$), 1.95–2.30 (m, 3H, $CH(CH_3)_2$ and $CH_2(CHO)_2CH_2Br$), 3.20–3.80 (m; 2H, $(CHO)_2CH_2Br$), 3.65, 3.68 (2 s, 6H; OCH_3), 3.95 (d, *J* 3 Hz, 1H, 5-H), 4.00–4.15 (m, 3H, H-2 and $(CHO)_2C(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 16.72, 19.02

($CH(CH_3)_2$), 26.92, 27.27, 37.52, 52.10 ($CH_2(CHO)_2CH_2N_3$), 31.85 ($CH(CH_3)_2$), 52.36, 52.41 (OCH_3), 52.47 (C-2), 60.70 (C-5), 79.64 ($(CHO)_2C(CH_3)_2$), 109.13 ($(CHO)_2C(CH_3)_2$), 163.50, 164.00 (C=N).

3.3. N,N-*Bis[4-((2R,5S)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl)-(2R,3R)-2,3-(isopropylidenedioxy)butyl]*-N-*benzyloxycarbonylamine* (5) *and* (2R,5S)-5-[4-*benzyloxycarbonylamino*-(2R,3R)-2,3-*(isopropylidenedioxy)butyl]*-2,5-*dihydro*-3,6-*dimethoxy*-2-*isopropylpyrazine* (6)

A solution of (2*R*,3*R*)-1-azido-4-((2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)-2,3-(isopropylidenedioxy)butane (3.57 g, 10.08 mmol) in ethanol (66.0 ml) containing the catalyst 5% palladium-on-charcoal (1.30 g) was purged with nitrogen. Hydrogen was bubbled through the solution and the stirred mixture kept under hydrogen at atmospheric pressure (balloon) overnight. After removal of hydrogen, the mixture was filtered through a pad of Celite, and the filtrate was evaporated at reduced pressure. The residue was dissolved in dioxane (30 ml) and benzyloxycarbonyl chloride (1.84 ml, 13.0 mmol) was added to the dioxane solution at 0°C followed by dropwise addition of 1 M $NaHCO_3$ (15.0 ml, 15.0 mmol). The mixture was stirred for 4 h, diluted with water and extracted with chloroform (4×25 ml). The combined organic layers were dried ($MgSO_4$), the solvents removed at reduced pressure and the residual material subjected to flash chromatography using hexane:Et_2O (4:1). The monomeric product **6** was first eluted; yield 0.17 g (11%) of an oil (TLC; R_F 0.44). The dialkylamine **5** was the second product eluted; yield 1.12 g (56%) of an oily material.

3.4. N,N-*Bis[4-[(2R,5S)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl]-(2R,3R)-2,3-(isopropylidenedioxy)butyl]*-N-*benzyloxycarbonylamine* (5)

FAB-MS signal at *m/z* 638.4 (M+H−134). Calc. for $C_{40}H_{61}N_5O_{10}$+*H*: 772.45. IR: ν 1680 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.69, 1.03 (2 d, *J* 7 Hz, 12H, $CH(CH_3)_2$), 1.33, 1.36 (2 s, 12H, $(CHO)_2C(CH_3)_2$), 1.80–2.40 (m, 6H, $CH(CH_3)_2$ and $CH_2(CHO)_2CH_2NCO$), 3.20–3.50 (m, 2H, $(CHO)_2CH_2NCO$), 3.64 (s, 2H, $(CHO)_2CH_2NCO$), 3.66, 3.68 (2 s, 12H, OCH_3), 3.80–4.25 (m, 8H, 5-H, 2H and $(CHO)_2C(CH_3)_2$), 5.10 (s, 2H, CH_2–C_6H_5), 7.20–7.40 (m, 5H, CH_2–C_6H_5). ^{13}C NMR ($CDCl_3$): δ 16.72, 19.07 ($CH(CH_3)_2$), 27.20, 37.90 ($CH_2(CHO)_2CH_2NCO$), 31.73 ($CH(CH_3)_2$), 50.69 (OCH_3), 51.06 (C-2), 60.50 (C-5), 67.24 (CH_2–C_6H_5), 75.51, 75.83 ($(CHO)_2C(CH_3)_2$), 80.65, 81.18 ($(CHO)_2C(CH_3)_2$), 108.89 ($(CHO)_2C(CH_3)_2$), 127.66, 127.98, 128.42, 136.50 (CH_2–C_6H_5), 155.92 (NHCO), 163.69 (C=N).

3.5. (2R,5S)-5-((2R,3R)-*[4-Benzyloxycarbonylamino-2,3-(isopropylidenedioxy)butyl]*-2,5-*dihydro*-3,6-*dimethoxy*-2-*isopropylpyrazine* (6)

Found: C, 62.99; H, 7.67; N 8.77. Calc. for $C_{24}H_{35}N_3O_6$: C, 62.45; H 7.64; N 9.10%. FAB-MS signal at *m/z* 462.3 (56), 141.1 (47), 91.0 (100). Calc. for $C_{24}H_{35}N_3O_6$+*H*: 462.27. ^1H NMR ($CDCl_3$): δ 0.67, 1.03 (2 d, *J* 7 Hz, 6H, $CH(CH_3)_2$), 1.35, 1.38 (2 s, 6H, $(CHO)_2C(CH_3)_2$), 1.90–2.05 (m, 1H), 210–230 (m, 2H), 3.30–3.55 (m, 2H), 3.64, 3.68 (2 s, 6H, OCH_3), 3.92–4.15 (m, 4H), 5.09 (s, 2H), 7.26–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.70, 19.05, 27.17, 31.83, 37.69, 42.94, 52.26, 52.41, 52.52, 60.65. 66.72, 75.69, 79.41, 108.61, 128.02, 128.07, 128.47, 136.54, 156.40, 163.24, 164.11 (C=N).

3.6. N,N-*Bis[methyl (2S,4R,5R)-2-amino-4,5-(isopropylidenedioxy)hexanoate-6-yl]*-N-*benzyloxycarbonylamine (7)*

1 M HCl (4.47 ml, 4.47 mmol) was added dropwise to a solution of *N,N*-bis[4-((2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazin-5-yl)-(2*R*,3*R*)-2,3-(isopropylidenedioxy)butyl]-*N*-benzyloxycarbonylamine (0.69 g, 0.89 mmol) in dioxane (4.47 ml) and the solution stirred at ambient temperature for 10 h. Aqueous ammonia was then added until pH 9 and the mixture extracted with chloroform (3×25 ml). The combined organic layers were dried ($MgSO_4$), the solvent and the valine methyl ester distilled off at reduced pressure by bulb-to-bulb distillation (50°C, 0.02 torr); yield: 0.44 g (85%). ^{1}H NMR ($CDCl_3$): δ 1.32, 1.33, 1.35 (3 s, 12H, $(CHO)_2C(CH_3)_2$), 1.55 (s, 4H, NH_2), 1.55–2.20 (m, 4H, $CH_2(CHO)_2CH_2NCO$), 3.28–3.56 (m, 2H, C–H), 3.69, 3.71 (s, 6H, OCH_3), 3.70–4.00 (m, 8H, $CH_2(CHO)_2CH_2NCO$), 5.10 (t, *J* 3 Hz, 2H, CH_2–C_6H_5), 7.33 (s, 5H, CH_2–C_6H_5). ^{13}C NMR ($CDCl_3$): δ 27.03, 37.68 ($CH_2(CHO)_2CH_2NCO$), 50.35 (OCH_3), 52.34, 52.57 (C–H), 67.52 (CH_2–C_6H_5), 76.25, 76.43 ($(CHO)_2C(CH_3)_2$), 80.70, 81.07 ($(CHO)_2C(CH_3)_2$), 109.18, 109.31 ($(CHO)_2C(CH_3)_2$), 128.10, 128.17, 128.46, 136.29 (CH_2–C_6H_5), 155.92 (NHCO), 175.51 (C=O).

3.7. N,N-*Bis[(2S,4R,5R)-2-fluorenylmethoxycarbonylamino-4,5-(isopropylidenedioxy)hexanoic acid-6-yl]*-N-*benzyloxycarbonylamine (9)*

2 M LiOH (0.756 ml, 1.512 mmol) was added to a solution of *N,N*-bis[methyl (2*S*,4*R*,5*R*)-2-amino-4,5-(isopropylidenedioxy)hexanoate-6-yl]-*N*-benzyloxycarbonylamine (0.44 g, 0.756 mmol) in dioxane (3 ml) and the mixture stirred at ambient temperature for 12 h to effect complete hydrolysis of the methyl ester groups. The solution was then cooled to 0°C and 1 M $NaHCO_3$ (2.5 ml, 2.5 mmol) added. A solution of 9-fluorenylmethoxycarbonyl chloride (0.62 g, 2.4 mmol) in dioxane (2.5 ml) was added dropwise to the cold solution and the resultant solution stirred at ambient temperature for 5 h. The solution was then acidified by addition of $KHSO_4$, and the aqueous layer extracted with chloroform (3×50 ml). The combined organic extracts were washed, dried ($MgSO_4$) and the solvent distilled off at reduced pressure. The residual product was purified by flash chromatography using hexane:Et_2O:AcOH (7:4:1); yield 0.45 g (59%) (TLC; R_F 0.15). Found: C, 67.32; H, 6.17; N, 4.37. Calc. for $C_{56}H_{59}N_3O_{14}$: C, 67.25; H, 6.15; N, 4.20%. ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 12H, $(CHO)_2C(CH_3)_2$), 1.60–2.00 (s, 4H, $CH_2(CHO)_2CH_2NCO$), 3.28 (m, 2H, C–H), 3.50 (m, 2H, C–H(Fmoc)), 3.75 (m, 4H, $CH_2(CHO)_2CH_2NCO$), 4.14 (m, 8H, $CH_2(CHO)_2CH_2NCO$ and CH_2–$C_{13}H_9$), 4.98 (t, *J* 6 Hz, CH_2–C_6H_5), 7.20–7.80 (m, 21H, CH_2–C_6H_5). ^{13}C NMR ($CDCl_3$): δ 27.52, 35.62, 47.41, 50.52, ($CH_2(CHO)_2CH_2NCO$), 52.35 (C–H), 66.50 (CH_2–$C_{13}H_9$), 67.42, (CH_2–C_6H_5), 76.51 ($(CHO)_2C(CH_3)_2$), 80.09, 80.39 ($(CHO)_2C(CH_3)_2$), 109.32 ($(CHO)_2C(CH_3)_2$), 120.86, 125.91, 127.94, 128.38, 128.56, 128.70, 129.16, 137.30, 141.44, 144.38, 144.46 (CH_2–C_6H_5 and CH_2–$C_{13}H_9$), 156.36, 156.69, 156.94 (NHCO), 175.32 (C=O).

3.8. *(2S,4R,5R)-2-*N′*-Benzyloxycarbonyl-4,5-(isopropylidenedioxy)lysine methyl ester (10)*

(2*R*,5*S*)-5-((2*R*,3*R*)-(4-Benzyloxycarbonylamino-2,3-(isopropylidenedioxy)butyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (0.5 g, 1.08 mmol) was dissolved in dioxane (5 ml) and 0.5 M HCl (4.20 ml, 2.10 mmol) was added dropwise. The mixture was stirred under argon at ambient temperature for 5 h. Aqueous ammonia was then added until pH=9 and the mixture was extracted with chloroform (3×25 ml). The combined organic layers were dried ($MgSO_4$), the solvent and the valine methyl ester distilled off at reduced pressure by bulb-to-bulb distillation (25°C, 0.05 torr); yield: 0.40 g (>95%). ^{1}H

NMR ($CDCl_3$): δ 1.35 (s, 6H), 1.70–2.20 (m, 4H), 3.20–3.60 (m, 3H), 3.70 (s, 3H), 3.73–3.90 (m, 2H), 5.09 (s, 2H), 5.32 (m, 1H), 7.26–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 27.01, 27.05, 37.56, 42.11, 51.99, 52.38, 66.79, 75.79, 79.82, 108.99, 128.00, 128.44, 136.39, 156.46, 175.30.

3.9. (2S,4R,5R)-2-N′-Benzyloxycarbonyl-N-(9-fluorenylmethoxycarbonyl)-4,5-(isopropylidenedioxy)-lysine (12)

(2*S*,4*R*,5*R*)-2-*N*′-Benzyloxycarbonyl-4,5-(isopropylidenedioxy)lysine methyl ester (0.40 g, 1.08 mmol) was dissolved in water (3.5 ml) and dioxane (4 ml), the solution cooled to 0°C, 2 M LiOH (0.54 ml, 1.08 mmol) added and the solution stirred under nitrogen at ambient temperature overnight. The product was the lithium salt of (2*S*,4*R*,5*R*)-2-*N*′-benzyloxycarbonyl-*N*-(9-fluorenylmethoxycarbonyl)-4,5-(isopropylidenedioxy)lysine (**11**). The solution was used in the subsequent acylation reaction without isolation of the acid from its salt **11**.

1 M NaOH (2.5 ml, 2.5 mmol) was added to the above solution and this was followed by a solution of 9-fluorenylmethoxycarbonyl chloride (0.518 g, 2.00 mmol) in dioxane (3 ml). The resultant mixture was stirred under argon at ambient temperature overnight. The solution was then adjusted to pH 2 by addition of $KHSO_4$ solution, extracted with ethyl acetate, dried ($MgSO_4$), the solution evaporated and the product isolated from the residual material after flash chromatography using chloroform:MeOH (8:2); yield 310 mg (50%) of a non-solid material. Found: N, 5.03. Calc. for $C_{32}H_{34}N_2O_8$: N, 4.88%. FAB-MS signal at *m/z* 497.1 (3), 429.1 (4), 91.0 (64). Calc. for $C_{32}H_{34}N_2O_8$+*H*: 497.23. ^1H NMR (DMSO-d_6/D_2O): δ 1.19 (s, 3H), 1.22 (s, 3H), 1.60–2.10 (m, 2H), 2.90–3.30 (m, 2H), 3.50–4.00 (m, 3H), 4.00–4.40 (m, 3H), 4.95 (s, 2H), 7.20–8.00 (m, 13H). ^{13}C NMR (DMSO-d_6/D_2O): δ 27.59, 27.81, 37.14, 43.15, 53.94, 65.92, 66.01, 76.98, 80.16, 108.40, 120.61, 125.67, 125.79, 127.66, 128.16, 128.22, 128.32, 128.89, 137.55, 141.18, 144.36, 156.14, 156.87, 176.09.

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