Synthesis of (2*R*,3*S*,4*S*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine and Polyoxamic Acid Derivatives from (*S*)-Pyroglutamic Acid[1)]

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(2*R*,3*S*,4*S*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine (6) and polyoxamic acid (20) were synthesized from (*S*)-pyroglutamic acid derivatives (1 and 7). The key reactions are the selective mono-*O*-benzylation of 1 and 7, and subsequent Mitsunobu reaction to invert the stereochemistry of the free hydroxy group of 3 and 11.

Keywords chiral synthesis; (*S*)-pyroglutamic acid; (2*R*,3*S*,4*S*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine; polyoxamic acid; selective mono-*O*-benzylation; Mitsunobu reaction

We have already reported the synthesis of polyhydroxylated indolizidines and related compounds from (*S*)- or (*R*)-pyroglutamic acid.[2)] In a continuation of our work on the utility of optically active pyroglutamic acid derivatives for natural products synthesis and for asymmetric reactions,[3)] we report here the synthesis of (2*R*,3*S*,4*S*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine derivatives (**5** and **6**) and polyoxamic acid derivatives (**18**—**21**) from (*S*)-pyroglutamic acid. Polyoxamic acid is a component of the polyoxin family of antifungal antibiotics[4a)] and has been synthesized previously from sugars,[4b)] L-tartaric acid,[4c–e)] and D-serine.[4f)]

Compounds **1**[2a)] and **7**,[2d)] prepared by *cis*-dihydroxylation of the corresponding α,β-unsaturated lactams with OsO_4, were mono-*O*-benzylated by Ohno's procedure[5)] to afford **2a** and **2b** (**2a**:**2b**=6:1), and **8**, respectively. Compound **2a**, isolated by column chromatography, was treated with borane-dimethyl sulfide in tetrahydrofuran (THF) to provide the pyrrolidine **3** in 59% yield from **1**. The Mitsunobu reaction[6)] of **3** to invert the stereochemistry of the unprotected secondary hydroxy group gave **4** in 72% yield. (2*R*,3*S*,4*S*)-3,4-Dibenzyloxy-2-hydroxymethyl-*N*-benzylpyrrolidine (**5**) was obtained in 53% yield from **4** by exchange of the benzoyl group to a benzyl group (NaOMe in MeOH, then NaH, benzyl bromide in THF–DMF (*N*,*N*-dimethylformamide)) followed by cleavage of the methoxymethyl group by acidic hydrolysis. Catalytic hydrogenation of **5** with palladium on carbon in EtOH in the presence of hydrogen chloride provided the hydrochloride of (2*R*,3*S*,4*S*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine (**6**, mp 116—118 °C; $[\alpha]_D^{20}$ +9.8° (*c*=0.6, H_2O), lit.[7)] $[\alpha]_D^{20}$ +12° (H_2O)) in 81% yield. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of the hydrochloride of **6** was identical with that reported.[7)]

Compound **8** was converted to a dihydroxy derivative **10** in 62% yield by hydrolysis with aqueous lithium hydroxide followed by esterification with diazomethane and subsequent reduction with $NaBH_4$. After protection of the primary hydroxy group in **10** as a *tert*-butyldimethylsilyl ether, the Mitsunobu reaction of **11** followed by the exchange of the secondary hydroxy protecting groups to an isopropylidene group ((i) debenzoylation with aqueous NaOH, (ii) debenzylation by catalytic hydrogenation with palladium black, (iii) isopropylidenation with 1,1-dimethoxypropane) gave **14** in 34% yield from **10**. The configurations of **14** were confirmed by the conversion into the

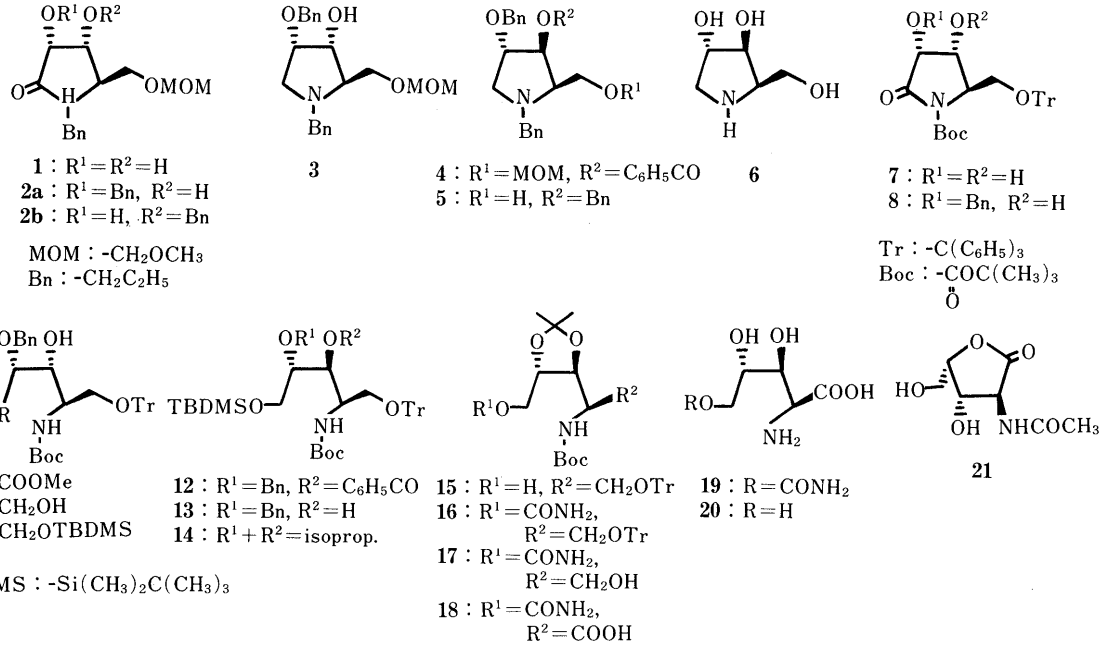

Chart 1

known polyoxamic acid derivative **18**. After removal of the *tert*-butyldimethylsilyl group with tetrabutylammonium floride in THF, carbamoylation of **15** (4-nitrophenyl chloroformate in THF–ether, then NH_3–MeOH) followed by selective cleavage of the trityl group in **16** under acidic conditions (concentrated HCl : MeOH = 1 : 50, room temperature, 30 min) furnished the alcohol **17**, which was oxidized with a catalytic amount of $RuCl_3$ and $NaIO_4$[8] to give the protected 5-*O*-carbamoylpolyoxamic acid **18** in 44% yield from **14**, $[\alpha]_D^{20}$ +0.9° (*c* = 3, acetone), lit.[4d] $[\alpha]_D^{26}$ +0.3° (*c* = 1.5, acetone). 5-*O*-Carbamoylpolyoxamic acid **19**, polyoxamic acid **20**, and *N*-acetylpolyoxaminolactone **21** were obtained from **18** by the reported procedures.[4d] Physical data (melting point and specific optical rotation) of **19**, **20** and **21** were identical with those reported (see the experimental section). Thus, the selective mono-*O*-benzylation of the diols **1** and **7** followed by inversion of configuration of the free hydroxy group resulted in the facile synthesis of polyhydroxylated α-amino acid derivatives such as polyoxamic acid. Further syntheses utilizing the hydroxylated pyrrolidinone derivatives are in progress.

Experimental[9]

(3*R*,4*R*,5*R*)-1-Benzyl-3-benzyloxy-4-hydroxy-5-(methoxymethoxy)methyl-2-pyrrolidinone (2a) A mixture of (3*R*,4*R*,5*R*)-1-benzyl-3,4-dihydroxy-5-(methoxymethoxy)methyl-2-pyrrolidinone (**1**, 1.41 g, 5 mmol) and dibutyltin oxide (1.25 g, 5 mmol) in 25 ml of toluene was heated under azeotropic conditions for 2 h, and then the solution was evaporated to dryness *in vacuo*. Cesium fluoride (1.54 g, 10 mmol) was added and the mixture was dried *in vacuo* over P_2O_5 for 1 h, and benzylated with benzyl bromide (1.78 ml, 15 mmol) in 20 ml of DMF at room temperature for 2 h. After dilution with AcOEt–benzene (2 : 1, 200 ml), the mixture was washed with H_2O and saturated aqueous NaCl. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 2) afforded **2a** (1.38 g, 74% yield) and **2b** (0.23 g, 12% yield). **2a**: Oil, $[\alpha]_D^{20}$ +103.6° (*c* = 0.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3434, 1688. ^{1}H-NMR ($CDCl_3$): 3.08 (1H, br s, OH), 3.19 (3H, s, OCH_3), 3.47 (3H, s, CH_2OMOM, CH), 4.0—4.5 (5H, m, 3 × CH, OCH_2O), 4.16 and 4.85 (2H, AB, *J* = 15 Hz, NCH_2Ph), 4.80 and 5.08 (2H, AB, *J* = 12 Hz, OCH_2Ph), 7.20—7.40 (10H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 44.05 (t), 55.02 (q), 62.28 (d), 64.18 (t), 68.37 (d), 72.85 (t), 75.92 (d), 95.95 (t), 127.19, 127.53, 127.77, 127.87, 128.16, 135.27 (s), 136.74 (s), 171.24 (s). MS *m/z*: 371 (M^+). **2b**: Oil, $[\alpha]_D^{20}$ +82.6° (*c* = 0.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3432, 1693. ^{1}H-NMR ($CDCl_3$): 3.25 (3H, s, OCH_3), 3.49 (4H, br s, OH, CH_2OMOM, CH), 4.0—4.12 (1H, m, CH), 4.10 and 4.96 (2H, AB, *J* = 15 Hz, NCH_2Ph), 4.35—4.62 (5H, m, 2 × OCH_2, CH), 7.26 (10H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 44.54 (t), 55.46 (q), 59.94 (d), 64.71 (t), 70.51 (d), 72.17 (t), 76.51 (d), 96.34 (t), 127.58, 127.77, 127.92, 128.35, 128.65, 135.42 (s), 137.03 (s), 173.48 (s). MS *m/z*: 371 (M^+).

(2*R*,3*R*,4*S*)-4-Benzyloxy-3-hydroxy-2-hydroxymethyl-*N*-benzylpyrrolidine (3) A mixture of **2a** (1.13 g, 3.05 mmol) and borane–dimethyl sulfide (1 ml) in 15 ml of THF was stirred at 70 °C for 90 min. After cooling to room temperature, the solution was acidified with 10% aqueous HCl and heated at 70 °C for 5 min. After cooling to room temperature, the mixture was basified with 10% aqueous NaOH and extracted with AcOEt. The organic extracts were washed with H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 2 : 1) gave **3** (870 mg, 80% yield) as an oil. $[\alpha]_D^{20}$ −23° (*c* = 0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3446. ^{1}H-NMR ($CDCl_3$): 2.51 (1H, dd, *J* = 7, 9 Hz, C_5-H), 2.75—2.80 (2H, m, OH, C_2-H), 3.15 (1H, dd, *J* = 6, 9 Hz, C_5-H), 3.32 (3H, s, OCH_3), 3.53—3.58 (2H, m, CH_2OMOM), 3.54 and 3.99 (2H, AB, *J* = 13.5 Hz, NCH_2Ph), 3.8—4.12 (2H, m, 2 × CH), 4.51 and 4.60 (2 × 2H, 2 × s, 2 × OCH_2), 7.28 (10H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 54.82 (q), 55.50 (t), 59.11 (t), 67.78 (t), 69.15 (d), 71.58 (t), 72.32 (d), 76.36 (d), 96.29 (t), 126.60, 127.33, 127.48, 127.81, 128.09, 128.07, 137.23 (s), 138.44 (s). MS *m/z*: 356 ($(M-1)^+$), 357 (M^+).

(2*R*,3*S*,4*S*)-3-Benzoyloxy-4-benzyloxy-2-(methoxymethoxy)methyl-*N*-benzylpyrrolidine (4) A mixture of **3** (800 mg, 2.24 mmol), triphenylphosphine (2.15 g, 5.6 mmol), benzoic acid (685 mg, 5.6 mmol), and diethyl azodicarboxylate (975 mg, 5.6 mmol) in 20 ml of THF was stirred at room temperature for 14 h. After dilution with AcOEt, the mixture was washed with saturated aqueous $NaHCO_3$ and H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 5) gave **4** (740 mg, 72% yield) as an oil. $[\alpha]_D^{20}$ −32.1° (*c* = 0.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$): 2.43 (1H, dd, *J* = 5.4, 10.5 Hz, C_5-H), 3.20 (3H, s, OCH_3), 3.21—3.78 (4H, m, CH_2OMOM, C_2- and C_5-H), 3.56 and 4.09 (2H, AB, *J* = 13 Hz, NCH_2Ph), 4.49 (2H, s, OCH_2), 4.49—4.81 (4H, m, 2 × OCH_2), 6.63 (1H, dd, *J* = 2.3, 6 Hz, C_3-H), 7.10—8.20 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.06 (q), 57.65 (t), 59.06 (t), 64.23 (d), 66.37 (t), 71.44 (t), 78.07 (d), 81.13 (d), 96.58 (t), 126.83, 127.63, 128.33, 128.5, 128.9, 130.3, 131.4, 132.96 (d), 137.81 (s), 138.44 (s), 165.9 (s). MS *m/z*: 461 (M^+).

(2*R*,3*S*,4*S*)-3,4-Dibenzyloxy-2-hydroxymethyl-*N*-benzylpyrrolidine (5) A mixture of **4** (600 mg, 1.3 mmol) and sodium methoxide (140 mg, 2.6 mmol) in 10 ml of methanol was stirred at room temperature for 3 h. After dilution with AcOEt, the mixture was washed with H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : $CHCl_3$ = 2 : 3) gave (2*R*,3*S*,4*S*)-4-benzyloxy-3-hydroxy-2-(methoxymethoxy)methyl-*N*-benzylpyrrolidine (344 mg, 74% yield, $[\alpha]_D^{20}$ −68.3° (*c* = 0.8, $CHCl_3$)): IR ν_{max}^{film} cm^{-1}: 3450: ^{1}H-NMR ($CDCl_3$): 2.27 (1H, dd, *J* = 6.1, 10 Hz, C_5-H), 2.87 (1H, br s, OH), 2.8—3.04 (1H, m, C_2-H), 3.26 (1H, m, C_5-H), 3.37 (3H, s, OCH_3), 3.44 and 3.95 (2H, AB, *J* = 13.5 Hz, NCH_2Ph), 3.70—4.06 (3H, m, CH_2OMOM, C_3-H), 4.27 (1H, m, C_4-H), 4.51 and 4.57 (2H, AB, *J* = 12 Hz, OCH_2), 4.63 (2H, s, OCH_2), 7.10—7.25 (10H, m, aromatic protons): ^{13}C-NMR ($CDCl_3$): 55.06 (q), 57.65 (t), 59.06 (t), 64.23 (d), 66.37 (t), 71.44 (t), 78.07 (d), 81.13 (d), 96.58 (t), 126.83, 127.63, 128.33, 128.5, 128.9, 130.3, 131.4, 132.96 (d), 137.81 (s), 138.44 (s), 165.90 (s): MS *m/z*: 357 (M^+)) as an oil, which was treated with sodium hydride (78 mg, 60% oil suspension, 1.96 mmol, washed with hexane) in 7 ml of THF–DMF (1 : 1) at room temperature for 30 min. After addition of 0.25 ml of benzyl bromide, the mixture was stirred at room temperature for 1 h, diluted with AcOEt, and washed with H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 3) gave (2*R*,3*S*,4*S*)-3,4-dibenzyloxy-2-(methoxymethoxy)methyl-*N*-benzylpyrrolidine (336 mg, 80% yield, $[\alpha]_D^{20}$ −31.2° (*c* = 0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.32 (1H, dd, *J* = 6, 10 Hz, C_5-H), 3.0—3.30 (2H, m, C_5- and C_2-H), 3.33 (3H, s, OCH_3), 3.50 and 4.07 (2H, AB, *J* = 13.5 Hz, NCH_2Ph), 3.66—3.89 (2H, m, CH_2OMOM), 3.95—4.11 (2H, m, 2 × CH), 4.42, 4.58, and 4.61 (3 × 2H, 3 × s, 3 × OCH_2), 7.28—7.30 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.11 (q), 56.92 (t), 59.16 (t), 64.91 (d), 66.66 (t), 71.24 (t), 71.88 (t), 81.72 (d), 83.33 (d), 96.63 (t), 126.70, 127.33, 127.53, 127.96, 128.65, 128.06, 137.90 (s), 138.68 (s). MS *m/z*: 447 (M^+), 446 ($(M-1)^+$) as an oil. A mixture of the above fully protected pyrrolidine (250 mg, 0.56 mmol), 3 ml of 10% aqueous HCl, and 3 ml of methanol was heated at 70 °C for 1 h. The resulting reaction mixture was basified with 10% aqueous NaOH and extracted with AcOEt. The organic layers washed with H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 2) gave **5** (203 mg, 90% yield) as an oil. $[\alpha]_D^{20}$ −34° (*c* = 0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3452. ^{1}H-NMR ($CDCl_3$): 2.29 (1H, dd, *J* = 6.5, 10 Hz, C_5-H), 2.43 (1H, br s, OH), 2.80—3.02 (1H, m, C_2-H), 3.20—3.30 (1H, m, C_5-H), 3.44 and 3.85 (2H, AB, *J* = 13 Hz, NCH_2Ph), 3.73 (2H, d, *J* = 4.1 Hz, OCH_2), 3.99—4.20 (2H, m, 2 × CH), 4.46 (2H, s, OCH_2Ph), 4.64 and 4.80 (2H, AB, *J* = 12 Hz, OCH_2Ph), 7.28 (15H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 55.80 (t), 59.62 (t), 59.89 (t), 62.20 (d), 71.88 (t), 72.07 (t), 82.26 (d), 84.50 (d), 127.14, 127.62, 127.72, 128.31, 128.45, 128.98, 137.81 (s), 138.01 (s). MS *m/z*: 403 (M^+).

(2*R*,3*S*,4*S*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine Hydrochloride (Hydrochloride of 6) A solution of **5** (160 mg, 0.4 mmol) in 5 ml of EtOH in the presence of 10% palladium on carbon (30 mg) and hydrogen chloride (about 3 mmol) was stirred under hydrogen at atmospheric pressure for 13 h and then filtered. The filtrate was concentrated *in vacuo* to give a residue, which was crystallized from MeOH–ether to provide the hydrochloride of **6** (55 mg, 81% yield) as needles, mp 116—118 °C. $[\alpha]_D^{20}$ +9.8° (*c* = 0.6, H_2O). ^{1}H-NMR (D_2O, internal standard: dioxane δ = 3.7): 3.2—3.36 (1H, m), 3.59—3.78 (1H, m), 3.85—4.10 (2H, m), 4.26—4.46 (2H, m). ^{13}C-NMR (D_2O, internal standard: dioxane δ = 67.4): 51.41 (t), 58.14 (t), 63.88 (d), 75.19 (2 × d). *Anal.* Calcd for $C_5H_{12}ClNO_3$: C, 35.41; H, 7.13; N, 8.26. Found: C, 35.03; H, 7.31; N, 7.98.

(3*R*,4*R*,5*R*)-3-Benzyloxy-1-[(*tert*-butoxy)carbonyl]-4-hydroxy-5-(trityloxy)methyl-2-pyrrolidinone (8) Compound **8** (4.26 g, 90% yield) was obtained from **7** (4 g, 8.18 mmol) in the manner described above for the preparation of **2a**. $[\alpha]_D^{20}$ +45.0° (*c* = 1.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3460, 1786, 1716. ^{1}H-NMR ($CDCl_3$): 1.46 (9H, s, $(CH_3)_3CO$), 2.79 (1H, br s, OH), 2.98 (1H, dd, *J* = 2, 10 Hz, CH_2OTr), 3.66 (1H, dd, *J* = 3, 10 Hz, CH_2OTr),

3.90 (1H, m, CH), 4.05 (1H, m, CH), 4.57 (1H, m, CH), 4.73 and 5.03 (2H, AB, J = 12 Hz, OCH_2Ph), 7.0—7.7 (20H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 27.48 (q), 61.11 (t), 62.18 (d), 68.42 (d), 72.95 (t), 77.00 (d), 82.74 (s), 86.79 (s), 126.75, 127.48, 127.92, 128.06, 136.25 (s), 142.58 (s), 149.12 (s), 171.38 (s). MS m/z: 578 ($(M-1)^+$).

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*)-3-Benzyloxy-2,4-dihydroxy-1-[(trityloxy)methyl]butyl]carbamate (10) A mixture of **8** (8.1 g, 14 mmol) and 16 ml of 2 N aqueous LiOH in 65 ml of THF was stirred at room temperature for 2 h. The reaction mixture was acidified with aqueous citric acid and extracted with AcOEt. The organic layers were washed with H_2O. Drying followed by evaporation gave a crude acid, which was treated with ethereal diazomethane to afford the methyl ester **9** after purification by column chromatography (AcOEt : hexane = 1 : 1) (6.48 g, 76% yield, $[\alpha]_D^{20}$ +11.5° (c = 0.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3440, 1741, 1708. ^{1}H-NMR ($CDCl_3$): 1.50 (9H, s, $(CH_3)_3CO$), 3.10—4.30 (6H, m, CH_2OTr, 2 × CH, OH, CH_2Ph), 3.68 (3H, s, OCH_3), 4.45 (1H, AB, J = 11.5 Hz, OCH_2Ph), 4.5—4.65 (1H, m, CH), 5.23 (1H, d, J = 7.1 Hz, NH), 6.90—7.70 (20H, m, aromatic protons).^{13}C-NMR ($CDCl_3$): 28.31 (q), 51.50 and 52.00 (d or q), 63.25 (t), 72.56 (t), 73.24 (d), 79.53 (s and d), 86.79 (s), 127.14, 127.92, 128.26, 128.40, 136.54 (s), 143.21 (s), 171.09 (s)) as an oil, which was reduced with $NaBH_4$ (1.0 g, 26.4 mmol) in EtOH (40 ml) at room temperature for 2 h. After neutralization with 10% aqueous HCl, the mixture was diluted with AcOEt and washed with saturated aqueous NaCl. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 2 : 1) gave **10** (5.06 g, 82% yield) as crystals, mp 73 °C (AcOEt–hexane). $[\alpha]_D^{20}$ +14.9° (c = 0.4, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1690. ^{1}H-NMR ($CDCl_3$): 1.42 (9H, s, $(CH_3)_3CO$), 2.5 (1H, br s, OH), 2.9—4.1 (8H, m, 2 × CH_2, 3 × CH, OH), 4.07 and 4.44 (2H, AB, J = 11.5 Hz, OCH_2Ph), 5.35 (1H, d, J = 8 Hz, NH), 6.9—7.6 (20H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 28.31 (q), 51.56 (d), 63.91 (t), 63.30 (t), 71.54 (t), 73.34 (d), 79.24 (d), 87.13 (s), 127.13, 127.62, 127.87, 128.35, 137.47 (s), 143.21 (s). *Anal.* Calcd for $C_{36}H_{41}NO_6 \cdot H_2O$: C, 71.85; H, 7.20; N, 2.33. Found: C, 71.72; H, 7.25; N, 2.29.

1,1-Dimethylethyl *N*-[(1*R*,2*S*,3*S*)-2-Benzoyloxy-3-benzyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-1-[(trityloxy)methyl]butyl]carbamate (12) A mixture of **10** (3.58 g, 6.0 mmol), *tert*-butyldimethylsilyl chloride (975 mg, 6.45 mmol) and imidazole (1.05 g, 15.4 mmol) in 40 ml of DMF was stirred at 0 °C for 5 h. After dilution with AcOEt–benzene (1 : 1, 100 ml), the mixture was washed with H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 3) gave **11** (3.82 g, 92% yield, $[\alpha]_D^{20}$ +5.3° (c = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3446, 1708, 1074. ^{1}H-NMR ($CDCl_3$): 0.02 (6H, s, $(CH_3)_2Si$), 0.87 (9H, s, $(CH_3)_3CSi$), 1.45 (9H, s, $(CH_3)_3CO$), 2.98—4.2 (8H, m), 4.02 and 4.51 (2H, AB, J = 11.5 Hz, OCH_2Ph), 5.39 (1H, d, J = 9 Hz, NH), 6.9—7.6 (20H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): −5.60 (q), 18.08 (s), 25.78 (q), 28.36 (q), 51.26 (d), 63.30 (t), 63.50 (t), 72.12 (t), 72.85 (d), 79.14 (d), 80.06 (d), 86.98 (s), 126.99, 127.28, 127.43, 127.81, 128.06, 128.40, 138.10 (s), 143.31 (s), 155.45 (s)) as an oil, which was subjected to the Mitsunobu reaction (three equivalents of the reagents used) as described above for the preparation of **4**. Purification by column chromatography (silica gel, AcOEt : hexane = 1 : 10) gave **12** (2.63 g, 60% yield) as an oil. $[\alpha]_D^{20}$ −23° (c = 3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1720, 1710, 1080. ^{1}H-NMR ($CDCl_3$): −0.04—0.04 (6H, m, $(CH_3)_2Si$), 0.86 (9H, m, $(CH_3)_3CSi$), 1.28 (9H, s, $(CH_3)_3CO$), 2.80—3.90 (5H, m, CH, 2 × CH_2), 4.1—4.4 (1H, m, CH), 4.10 and 4.49 (2H, AB, J = 11.5 Hz, OCH_2Ph), 5.15 (1H, d, J = 10 Hz, NH), 5.79 (1H, m, CHOBz), 6.99—8.14 (25H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): −5.70 (q), 17.98 (s), 25.68 (q), 28.12 (q), 51.26 (d), 61.79 (t), 62.77 (t), 72.27 (t), 72.66 (t), 78.02 (d), 78.99 (d), 86.35 (s), 126.80, 127.23, 127.48, 127.62, 128.06, 128.50, 132.69 (s), 138.01 (s), 143.31 (s), 155.30 (s), 166.12 (s). MS m/z: 801 (M^+).

1,1-Dimethylethyl *N*-[(1*R*,2*S*,3*S*)-3-Benzyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-1-[(trityloxy)methyl]butyl]carbamate (13) A mixture of **12** (1.8 g, 2.25 mmol) and 4 ml of 2 N aqueous NaOH in 30 ml of MeOH–THF (5 : 1) was stirred at room temperature for 7 h, then diluted with AcOEt and washed with H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 8) gave **13** (1.21 g, 77% yield) as crystals, mp 109 °C (AcOEt–hexane). $[\alpha]_D^{20}$ −10.6° (c = 0.5, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1716, 1040. ^{1}H-NMR ($CDCl_3$): −0.05 (6H, s, $(CH_3)_2Si$), 0.88 (9H, s, $(CH_3)_3CSi$), 1.40 (9H, s, $(CH_3)_3CO$), 2.69 (1H, br s, OH), 2.94—4.05 (7H, m), 4.40 and 4.66 (2H, AB, J = 12 Hz, OCH_2), 5.00 (1H, d, J = 7 Hz, NH), 6.99—7.53 (20H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): −5.51 (q), 18.18 (s), 25.83 (q), 28.31 (q), 51.80 (d), 62.42 (t), 63.93 (t), 70.22 (d), 72.85 (d), 79.09 (s), 79.92 (d), 86.49 (s), 126.84, 127.67, 127.76, 128.26, 128.55, 138.10 (s), 143.66 (s), 155.40 (s). *Anal.* Calcd for $C_{42}H_{55}NO_6Si$: C, 72.27; H, 7.94; N, 2.01. Found: C, 72.01; H, 7.99; N, 1.82.

1,1-Dimethylethyl *N*-[(1*R*,2*S*,3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-[(isopropylidene)dioxy]-1-[(trityloxy)methyl]butyl]carbamate (14) A solution of **13** (1.06 g, 1.5 mmol) in 24 ml of EtOH in the presence of palladium black (240 mg) was stirred under hydrogen at room temperature for 2 h and then filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 2) to provide the dihydroxy derivative (850 mg, 92% yield, $[\alpha]_D^{20}$ −12.8° (c = 2, $CHCl_3$)). IR ν_{max}^{film} cm^{-1}: 3440, 1700, 1082. ^{1}H-NMR ($CDCl_3$): 0.08 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.43 (9H, s, $(CH_3)_3CO$), 2.91 and 3.14 (2 × 1H, 2 × br s), 2 × OH), 3.14—4.0 (6H, m), 5.10 (1H, d, J = 9 Hz, NH), 7.10—7.56 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): −5.56 (q), 18.08 (s), 22.47 (q), 25.73 (q), 51.51 (d), 63.79 (t), 63.93 (t), 70.85 (d), 71.78 (d), 79.24 (s), 86.59 (s), 126.84, 127.62, 128.40, 143.51 (s), 155.79 (s)) as an oil, which was treated with 6 ml of 1,1-dimethoxypropane in 6 ml of acetone in the presence of a catalytic amount of *p*-TsOH at room temperature for 20 min. After dilution with AcOEt, the mixture was washed with saturated aqueous $NaHCO_3$ and H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 4) gave **14** (790 mg, 87% yield) as an oil. $[\alpha]_D^{20}$ −17° (c = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1714, 1086. ^{1}H-NMR ($CDCl_3$): 0.10 (6H, s, $(CH_3)_2Si$), 0.92 (9H, s, $(CH_3)_3CSi$), 1.37 (6H, s, $(CH_3)_2C$), 1.43 (9H, s, $(CH_3)_3CO$), 3.10—3.25 (2H, m, CH_2), 3.62—4.4 (5H, m, 3 × CH, CH_2), 4.92 (1H, d, J = 9 Hz, NH), 7.00—7.60 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): −5.36 (q), 18.42 (s), 26.02 (q), 26.85 (q), 27.11 (q), 28.41 (q), 49.61 (d), 62.62 (t), 64.27 (t), 76.75 (d), 77.72 (d), 79.24 (s), 86.59 (d), 108.77 (s), 126.89, 127.67, 128.70, 143.90 (s), 155.55 (s). MS m/z: 404 ($(M-Tr)^+$).

1,1-Dimethylethyl-*N*-[(1*R*,2*S*,3*S*)-4-[(Aminocarbonyl)oxy]-2,3-[(isopropylidene)dioxy]-1-[(trityloxy)methyl]butyl]carbamate (16) A mixture of **14** (760 mg, 1.18 mmol) and 2.5 ml of tetrabutylammonium fluoride in THF (1 M solution) was stirred at 0 °C for 5 min, diluted with AcOEt and washed with H_2O. Drying followed by evaporation and purification by column chromatography (AcOEt : hexane = 1 : 1) gave **15** (620 mg, 93% yield, $[\alpha]_D^{20}$ −13° (c = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3444, 1709, 1086. ^{1}H-NMR ($CDCl_3$): 1.36 (6H, s, $(CH_3)_2$), 1.41 (9H, s, $(CH_3)_3CO$), 2.42 (1H, br s, OH), 3.17—3.25 (2H, d, J = 6 Hz, CH_2), 3.5—4.3 (5H, m, 3 × CH, CH_2), 4.82 (1H, d, J = 9 Hz, NH), 7.00—7.55 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 26.90 (q), 28.26 (q), 49.80 (d), 61.50 (t), 64.32 (t), 76.75 (d), 77.43 (d), 79.58 (s), 86.55 (d), 108.91 (s), 126.84, 127.67, 128.55, 143.66 (s), 155.88 (s)) as an oil, which was treated with pyridine (0.62 ml), triethylamine (0.2 ml), and 4-nitrophenyl chloroformate (280 mg, 1.4 mmol) in 6 ml of THF–Et_2O (1 : 5) at 0 °C for 13 h. After dilution with AcOEt, the mixture was washed with 0.1 N H_2SO_4, saturated aqueous $NaHCO_3$, and H_2O. Drying followed by evaporation gave a residue, which was dissolved in 15 ml of ether and treated with 8 ml of saturated NH_3–MeOH solution at 0 °C for 30 min. After removal of the methanol *in vacuo*, the residue was dissolved in AcOEt and washed with saturated aqueous $NaHCO_3$ and H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 2 : 1) gave **16** (510 mg, 82% yield) as an oil. $[\alpha]_D^{20}$ −22° (c = 1.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1734, 1790. ^{1}H-NMR ($CDCl_3$): 1.38 (6H, s, $(CH_3)_2$), 1.44 (9H, s, $(CH_3)_3CO$), 3.1—3.3 (2H, m, CH_2), 3.85—4.34 (5H, m, 3 × CH, CH_2), 4.90 (1H, d, J = 10 Hz, NH), 5.28 (2H, br s, NH_2), 7.00—7.6 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 26.66 (q), 28.12 (q), 49.46 (d), 64.03 (t), 75.05 (d), 77.13 (d), 79.28 (s), 86.45 (d), 109.16 (s), 126.75, 127.53, 128.40, 143.51 (s), 155.40 (s), 156.42 (s). MS m/z: 576 (M^+).

(3*S*,4*S*)-5-[(Aminocarbonyl)oxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-3,4-[(isopropylidene)dioxy]-L-norvaline (18) A mixture of **16** (485 mg, 0.86 mmol) and 10 ml of concentrated HCl–MeOH solution (1 : 50) was stirred at room temperature for 30 min, diluted with AcOEt, and washed with saturated aqueous $NaHCO_3$ and H_2O. Drying followed by evaporation and purification by column chromatography (silica gel, AcOEt : hexane = 5 : 1) gave **17** (200 mg, 72% yield, $[\alpha]_D^{20}$ −10.3° (c = 1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3448, 1724, 1706. ^{1}H-NMR ($CDCl_3$): 1.36 (15H, s, 5 × CH_3), 2.73 (1H, br s, OH), 3.4—4.3 (7H, m, 3 × CH, 2 × CH_2), 5.11 (1H, d, J = 9 Hz, NH), 5.45 (2H, br s, NH_2). ^{13}C-NMR ($CDCl_3$): 26.66 (q), 28.12 (q), 50.92 (d), 63.25 (t), 63.98 (t), 75.09 (d), 77.38 (d), 79.77 (s), 109.45 (s), 155.98 (s), 156.76 (s). MS m/z: 335 (M^+)) as an oil, which was treated with $NaIO_4$ (360 mg, 1.86 mmol), 1.2 ml of CH_3CN, 1.2 ml of CCl_4, and 1.8 ml of H_2O at room temperature for 5 min. After addition of $RuCl_3$ (6 mg), the mixture was stirred at room temperature for 40 min, diluted with H_2O (5 ml), and extracted with ether. The organic layers were washed with saturated aqueous NaCl. Drying followed by evaporation and purification

by column chromatography (silica gel, AcOEt : MeOH = 10 : 1) gave **18** (170 mg, 81% yield) as an oil. $[\alpha]_D^{20}$ +0.9° (c = 3, acetone). IR ν_{max}^{film} cm^{-1}: 2596, 1737, 1709. ^{1}H-NMR ($CDCl_3$): 1.41 (15H, s, 5 × CH_3), 3.73—4.65 (5H, m, 3 × CH, CH_2), 5.37 (1H, d, J = 9 Hz, NH), 5.55 (2H, br s, NH_2), 9.37 (1H, br s, COOH). ^{13}C-NMR ($CDCl_3$): 26.61 (q), 28.07 (q), 52.78 (d), 63.93 (t), 74.75 (d), 77.92 (d), 80.55 (s), 109.98 (s), 155.98 (s), 157.44 (s), 172.84 (s). MS m/z: 348 (M^+).

5-*O*-Carbamoylpolyoxamic Acid (19), Polyoxamic Acid (20), and *N*-Acetylpolyoxaminolactone (21) Compounds **19**, **20**, and **21** were obtained from **18** in the manner described previously.[4d] **19**: mp 222—225 °C (dec.), $[\alpha]_D^{20}$ +3.2° (c = 1.6, H_2O), lit. mp 226—232 °C (dec.),[4d] $[\alpha]_D^{20}$ +4° (c = 1.1, H_2O).[4b] ^{1}H-NMR (D_2O, internal standard: dioxane δ = 3.7): 3.52—3.97 (1H, m), 3.97—4.20 (3H, m), 4.20—4.31 (1H, m). ^{13}C-NMR (D_2O, internal standard: dioxane δ = 67.4): 58.77 (d), 66.37 (t), 68.81 (d), 71.68 (d), 159.93 (s), 173.43 (s). **20**: mp 160—170 °C (dec.), $[\alpha]_D^{20}$ +2.1° (c = 2, H_2O), lit.[4d] mp 162—178 °C (dec.), $[\alpha]_D^{20}$ +2.1° (c = 1, H_2O). ^{1}H-NMR (D_2O, internal standard: dioxane δ = 3.7): 3.48—3.74 (2H, m), 3.74—3.97 (2H, m), 4.08—4.23 (1H, m). ^{13}C-NMR (D_2O, internal standard: dioxane δ = 67.4): 58.82 (d), 63.30 (t), 69.39 (d), 73.92 (d), 174.35 (s). **21**: mp 141—142 °C (MeOH–$CHCl_3$), $[\alpha]_D^{20}$ −99.7° (c = 2, MeOH), lit.[4d] mp 146—150 °C. ^{1}H-NMR (20% $CD_3OD/CDCl_3$): 2.04 (3H, s, CH_3CO), 3.80—4.01 (2H, m, 2 × CH), 4.40—4.77 (3H, m, CHN, CH_2). ^{13}C-NMR (20% $CD_3OD/CDCl_3$): 22.28 (q), 57.27 (d), 60.09 (t), 72.42 (d), 82.22 (d), 173.71 (s), 174.85 (s). *Anal.* Calcd for $C_7H_{11}NO_5$: C, 44.44; H, 5.86; N, 7.40. Found: C, 44.28; H, 5.86; N, 7.20.

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References and Notes

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9) Melting points were measured on a hot stage apparatus and are uncorrected. Infrared (IR) spectral measurements were performed with a JASCO IRA-1 grating infrared spectrometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were measured with a JNM FX-100 (100 MHz) spectrometer. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane unless otherwise described. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a JASCO DIP-360. Mass spectra (MS) was recorded with a JEOL JMS-D302 mass spectrometer. The organic solvents were dried over $MgSO_4$ before vacuum evaporation.