SYNTHESIS OF (2R,3R,4R,SR)-3,4-DIHYDROXY-2,5-DIHYDROXYMETHYL PYRROLIDINE AND (-)-ANISOMYCIN DERIVATIVE FROM (S)-PYROGLUTAMIC ACID DERIVATIVE

Nobuo Ikota

National Institute of Radiological Sciences, 9-1, Anagawa-4-chome, Inage-ku, Chiba 263, Japan

Abstract — Double asymmetric dihydroxylation of (E)-α,β-unsaturated ester (2) with a catalytic amount of potassium osmate and chiral ligand gave dihydroxy compounds (3a and 4a) selectively. Polyhydroxylated pyrrolidines (10 and 14) were synthesized from corresponding methoxymethy ether (3c) and tert-butyl-dimethylsilyl ether (4d), respectively.

Polyhydroxylated pyrrolidines show interesting biological activities, and their synthesis including stereoisomers and biological evaluation have been extensively studied. In a previous report, we have reported the synthesis of 1-deoxynojirimycin from (S)-pyroglutamic acid derivative, in which a diastereoselection of dihydroxylation of (E)-α,β-unsaturated ester (2) with a catalytic amount of OsO₄ was not high. In connection with our studies on the synthesis of chiral polyhydroxylated amines, we describe here the improvement of stereoselectivity of dihydroxylation of 2 employing double asymmetric dihydroxylation with chiral ligand, and the facile synthesis of (2R,3R,4R,SR)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidines (10a) and (-)-anisomycin derivative (14) from (S)-pyroglutamic acid derivative.

Dihydroxylation of 2, prepared from 1 in 80% yield, with potassium osmate (0.04 equiv.) using hydroquinidine 9-phenanthryl ether (0.15 equiv.) as a chiral ligand in the presence of K₂Fe(CN)₆ (3 equiv.) and K₂CO₃ (3 equiv.) in tert-BuOH-H₂O (1:1) at 0°C for 24 h gave 3a and 4a in a ratio of 93:7 in 71% yield, while 19:81 ratio was obtained using hydroquinine 9-phenanthryl ether in 76% yield. The ratio of
3a and 4a was determined by high performance liquid chromatographic (hplc) analysis after conversion of 3a and 4a into the corresponding diacetate (3b and 4b) (pyridine, acetic anhydride). The polyhydroxylated pyrrolidines (10 and 14) were synthesized starting from the methoxymethy (MOM) ether (3c) and tert-butyldimethylsilyl (TBS) ether (4d), respectively.

A mixture of 3a and 4a, obtained by dihydroxylation using hydroquinidine 9-phenanthryl ether, was converted into the MOM ether (MOM chloride, N,N-diethylaniline, CH2Cl2) and the major diastereomer (3c) was isolated by recrystallization from AcOEt-hexane in 78% yield. Then, 3c was treated with NaBH4 in EtOH to give an alcohol (5) in 85% yield. Swern oxidation5b of 5 followed by reaction of the corresponding aldehyde with vinylmagnesium bromide in THF at -78°C gave 7 and 8 in a ratio of 9:1 in 59% yield. The predominant formation of 7 may be rationalized by cyclic chelate formation between magnesium and α-alkoxy carbonyl. The major isomer (7) was converted to a mesylate (methanesulfonyl chloride (MsCl), triethylamine (TEA), CH2Cl2) followed by cyclization with potassium tert-butoxide in tetrahydrofuran (THF) to give the 5-vinylpyrrolidine (9a) in 78% yield. Ozonolysis of 9a followed by reductive work-up with NaBH4 afforded the alcohol (9b) in 93% yield. The compound (9b) could be useful intermediate for the synthesis of stereoisomes of alexine.6 Hydrolysis of 9b with MeOH-10% HCl (1:1) at 70°C gave 10a (mp 113-114°C, [α]D +54.0° (c=1, H2O), lit.,7b mp 116-118°C, [α]D +54.3° (c=1.2, H2O)) in 77% yield after treatment with ion exchange column (Dowex 50W-X8, H+ form). In the same reaction sequence, (2R,3R,4R,5S)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine (10b) (mp 133-136°C, [α]D +26.3° (c=0.8,MeOH), lit.,8 mp 139-142.5°C, [α]D +27.6°(c=1.3, MeOH)) was obtained from 8 in 45% yield. Nmr spectral data of 10a and 10b were identical with those reported.1b,7a,8

A mixture of 3a and 4a obtained by dihydroxylation using hydroquinidine 9-phenanthryl ether was converted into the corresponding TBS ether (TBS chloride, imidazole, dimethylformamide (DMF)) and the diastereoisomers (3d and 4d) were separated by column chromatography in 17% and 68% yields, respectively. The major isomer (4d) was reduced with LiBH4 in the presence of lithium triethylborohydride9 in ether to provide an alcohol (6), which was then converted to the pyrrolidine derivative (11a) via mesylate (MsCl, TEA, CH2Cl2; then tert-BuOK, THF) in 40% yield. The configurations of 11a was confirmed by converting 11a into the known pyrrolidine derivative (12).10 Thus, a removal of TBS group in 11a with tetrabutylammonium fluoride in THF followed by di-O-benzylation (NaH, DMF-THF, then BnBr) of 11b gave 11c in 65% yield. Cleavage of tert-butoxycarbonyl and trityl group in 11c
with acidic conditions (MeOH:10% HCl=1:1, 70°C) followed by N-benzylation with benzyl bromide in the presence of K2CO3 in acetone gave 12 in 32% yield. Oxidation of 12 by the method of Swern followed by reaction with 4-methoxyphenylmagnesium bromide in the presence of K2CO3 in acetone gave 13a as a sole diastereomer, which was then treated with triethylsilane11 in the presence of trifluoroacetic acid and trifluoromethanesulfonic acid in CH2Cl2 to afford 13b in 31% yield. In this reaction, 13b was not obtained without addition of trifluoromethanesulfonic acid. N-Benzylxocarbonyl-3,4-dihydroxy-2-(4-methoxyphenyl)-pyrrolidine (14)12 (mp 123-126°C, [α]D -8.7° (MeOH), lit.,12c mp 127-129°C, [α]D -8.2°(MeOH)) was obtained in 60% yield after debenzylation of 13a (10% palladium carbon, 99% HCOOH, EtOH)13 followed by N-benzyloxycarbonylation (benzyl chloroformate, Na2CO3, CH2Cl2). 1H Nmr spectral data was identical with that reported.12c

Thus, the selective formation of 3a and 4a from 2 by double asymmetric dihydroxylation provided the facile approach for the synthesis of (2R,3R,4R)- and (2R,3S,4S)-polyhydroxylated pyrrolidines.

EXPERIMENTAL

General methods.—Melting points were determined on a hot stage apparatus and are uncorrected. Ir spectra were measured with a JEOL JIR-110 FT-IR spectrophotometer. 1H and 13C nmr spectra were recorded on a JEOL JNM-FX100 (100 Mz) spectrometer. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane. Mass spectra were taken on a JEOL JMS-D302 spectrometer. Optical rotations were measured in CHC13 solution at 25°C on a JASCO DIP-360 polarimeter unless otherwise mentioned. The organic solvents were dried over MgSO4 before vacuum evaporation and a column chromatography was carried out with silica gel (Wakogel C-200).

1,1-Dimethylethyl N-[(1S)-3-Methoxycarbonyl-1-trityloxymethyl-2-(E)-propenyl] carbamate (2) A mixture of 1 (3.0 g, 4.9 mmol) and 5 ml of 2N solution of lithium hydroxide in 15 ml of THF-MeOH (1:1) was stirred at room temperature for 1 h. After removal of the solvents in vacuo, the aqueous layer was acidified with 10% aqueous citric acid and extracted with AcOEt. The AcOEt extracts were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was treated with ethereal diazomethane. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (AcOEt:hexane=1:4) to give α-phenylseleno ester (2.83 g, 90%) as an oil, 1H nmr (CDCl3): 1.38 (9H, s, t-Bu), 1.58-2.33 (2H, m, CH2), 2.84-3.22 (2H, m, CH2OTr), 3.56 and 3.58 (3H, each s, OCH3), 3.45-4.20 (2H, m, 2xCH), 4.40-4.70 (1H, m, NH), 6.80-7.61 (20H, m, aromatic protons); 13C-nmr (CDCl3): 28.07(q), 33.87 and 34.65 (t), 38.74 and 40.15(d), 49.17 and 49.70(d), 51.70(q), 64.91 and 65.30(t), 78.85(s), 86.10(s), 126.65, 127.48, 127.92, 128.20 and 128.59(aromatic carbons), 135.86(d), 143.31(s), 154.96(s), 172.45(s), 173.29 (s)). A mixture of α-phenylseleno ester (2.0 g, 3.1 mmol) and 30% H2O2 (5 ml) in AcOEt (20 ml) was stirred at room temperature for 15 min. After addition of AcOEt (60 ml), the organic layer was separated and washed...
with H₂O, saturated aqueous NaHCO₃, and saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:3) to give 2 (1.35 g, 89%) as crystals, mp 88 °C (AcOEt-hexane), [α]D 11.9° (c=1.3); ir νmax (nujol) 1707, 1656, 1513 cm⁻¹; ¹H nmr (CDCl₃): 1.44(9H, s, t-Bu), 3.25(2H, m, CH₂), 3.70(3H, s, COOCH₃), 4.51(H, m, CH), 5.26(1H, d, J=9 Hz, NH), 6.00(1H, d, J=15.8 Hz, CH=CH), 6.95(1H, dd, J=4.9 and 15.8 Hz, CH=CH), 7.10-7.60(15H, m, aromatic protons); ¹³C nmr (CDCl₃): 27.97(q), 51.17(d), 59.93(q), 64.71(t), 79.38(s), 86.45(s), 120.99(t), 126.80, 127.48 and 128.20(aromatic carbons), 143.07(s), 146.33(d), 154.82(s), 166.07(s). Anal. Calc. for C₃₀H₃₅NO₅: C, 73.90; H, 6.82; N, 2.87. Found: C, 73.66; H, 7.03; N, 2.67.

**Double asymmetric reaction of 2 using chiral ligand.** Potassium osmate dihydrate (7.6 mg, 0.02 mmol) was added to a mixture of hydroquinidine 9-phenanthryl ether or hydroquinine 9-phenanthryl ether (38.7 mg, 0.077 mmol), K₃Fe(CN)₆ (506 mg, 1.54 mmol), and K₂CO₃ (212 mg, 1.54 mmol) in a tert-BuOH-H₂O (1:1, 7 ml) at room temperature. Then, 2 (250 mg, 0.51 mmol) was added at 0°C. After being stirred at 0°C for 24 h, Na₂SO₃ (1 g) was added and the mixture was stirred for 30 min, and extracted with AcOEt. The organic extracts were washed with 5% aqueous H₂SO₄, H₂O, saturated aqueous NaHCO₃, and saturated aqueous NaCl. Drying followed by evaporation gave a residue. A half portion was used for purification by column chromatography (AcOEt:hexane=1:3) to determine the chemical yields and other half was converted to the corresponding diacetate (excess pyridine, acetic anhydride, room temperature, 13 h). The ratio of 3b and 4b was determined by hplc analysis (Waters, Radial pak cartridge, silica gel(10µ), AcOEt:hexane=1:4 as the eluent). 3b: oil, [α]D +45.5° (c=0.7); ¹H nmr (CDCl₃): 1.38(9H, s, t-Bu), 1.75 and 2.11 (2x3H, each s, 2-CH₃), 3.10-3.20 (2H, m, CH₂), 3.69(3H, s, COOCH₃), 4.12(1H, m, CH), 4.90(1H, d, J=11 Hz, NH), 5.22(1H, m, CH), 5.51(1H, dd, J=1.7 and 10 Hz, CH), 7.09-7.64(15H, m, aromatic protons); ¹³C nmr (CDCl₃): 20.27(q), 20.47(q), 28.21(q), 49.17(d), 52.53(q), 61.35(t), 69.98(d), 79.96(s), 86.69(s), 127.09, 127.77 and 128.59(aromatic carbons), 143.02(s), 154.77(s), 168.43(s), 169.29(s), 170.14(s). 4b: mp 152-153°C (AcOEt-hexane), [α]D -32.2° (c=0.5); ¹H nmr (CDCl₃): 1.41(9H, s, t-Bu), 1.97 and 2.04 (2x3H, each s, 2-CH₃), 2.90-3.30(2H, m, CH₂), 3.69(3H, s, COOCH₃), 3.95-4.10 (1H,m, CH), 4.80-5.00(2H, m, NH, CH), 5.62-5.75(1H, m, CH), 7.05-7.50(15H, m, aromatic protons); ¹³C nmr (CDCl₃): 20.17(q), 20.32(q), 28.17(q), 50.87(d), 2.48(q), 62.47(t), 70.46(d), 79.57(s), 86.64(s), 126.99, 127.72 and 128.31(aromatic carbons), 143.07(s), 55.06(s), 67.34(s), 69.38(s), 69.82(s). Anal. Calc. for C₃₄H₃₉NO₅: C, 76.42; H, 6.49; N, 2.31. Found: C, 76.55; H, 6.64; N, 2.20.

**1,1-Dimethylethyl N-[(1R,2R,3S)-2,3-Bis(methoxymethyloxy)-3-methoxycarbonyl-1-trityloxymethylpropanyl]carbamate (3c)** A mixture of 3a and 4a (1.0 g, 1.92 mmol), prepared from 2 by dihydroxylation using hydroquinine 9-phenanthryl ether, N,N-dietylaniline (2.3 g, 15.5 mmol), and chloromethyl methy ether (1.24 g, 15.5 mmol) in CH₂Cl₂ (15 ml) was stirred at room temperature for 30 h. After addition of AcOEt (100 ml), the mixture was washed with 5% aqueous HCl, H₂O, saturated aqueous NaHCO₃, and H₂O. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:4) followed by recrystallization from AcOEt-hexane to give 3b (0.99 g, 78%) as crystals, mp 73-74 °C (AcOEt-hexane), [α]D -49.1° (c=1); ir νmax (nujol)
The organic layers were washed with half-saturated aqueous (aromatic carbons), 77.92(d), (3H, 3.24 and 3.34(2x3H, each s, 2xOCH3), 3.72(3H, s, COOCH3), 4.11-4.36(3H, m, 3xCH), 4.44-4.69(4H, m, 2xCH2), 5.22 (1H, d, J=8 Hz, NH), 7.10-7.49 (15H, m, aromatic protons); 13C nmr (CDCl3): 28.06(q), 50.49(t), 51.65(d), 55.80(q), 56.43(q), 62.33(t), 75.38(d), 77.38(d), 78.99(s), 86.30(s), 96.78(t), 97.02(t), 126.80, 127.53 and 128.13(aromatic carbons), 143.12(s), 155.16(s), 170.46(s). Anal. Calcd for C34H43NOg: C, 66.97; H, 7.11; N, 2.30. Found: C, 66.71; H, 7.33; N, 2.11.

1,1-Dimethylethyl N-[(1R,2R,3R)-2,3-Bis(methoxymethyloxy)-4-hydroxy-1-trityloxy-methylbutyl]carbamate (5) A mixture of NaBH4 (500 mg, 13.2 mmol) and 3c (1.7 g, 2.79 mol) in EtOH (20 ml) was stirred at room temperature for 13 h. After addition of AcOEt (100 ml), the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:1) to give 5 (1.38 g, 85%) as an oil, [α]D -19.7° (c=1); ir ν max (neat) 3440, 1710, 1026 cm⁻¹; 1H nmr (CDCl3): 1.43(9H, s, t-Bu), 2.94-3.40(2H, m, CH2), 3.25 and 3.31(2x3H, each s, 2xOCH3), 3.40-4.36(6H, m, 3xCH, CH2, OH), 4.40-4.15(4H, m, 2xCH2), 5.18(1H, d, J=10 Hz, NH), 7.01-7.62(15H, m, aromatic protons); 13C nmr (CDCl3): 28.36(q), 50.29(d), 55.70(q), 56.09(q), 62.08(t), 62.76(t), 77.53(d), 79.24(s), 81.09(d), 86.45(s), 97.85(t), 98.09(t), 26.94, 127.62 and 128.45(aromatic carbons), 143.17(s), 155.16(s); ms m/z 338 (M+−Tr).

1,1-Dimethylethyl N-[(1R,2R,3R,4R)- and (1R,2R,3R,4S)-2,3-Bis(methoxymethoxy)-4-hydroxy-1-trityloxy-5-hexenyl]carbamate (7 and 8) Dimethyl sulfoxide (455mg, 5.8 mmol) was added at -78°C to a solution of oxalyl chloride (460 mg, 3.62 mmol) in THF (8 ml). The mixture was stirred at -40 -50°C for 3 min. Then a solution of 5 (850 mg, 1.46 mmol) in THF (3 ml) was added at -10°C. After being stirred at -10°C for 40 min, TEA (730 mg, 7.3 mmol) was added, and the mixture was recooled at -78°C, and vinylmagnesium bromide (7.3 ml of 1 M solution in THF) was added at -78°C. After being stirred at -78°C for 30 min, the mixture was treated with EtOH (0.5 ml) and saturated aqueous NH4Cl (3 ml), and then extracted with AcOEt. The organic layers were washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:2) to give 7 (466 mg, 53%) and 8 (52 mg, 6%) as an oil. 7: [α]D -15.3° (c=1); ir ν max (neat) 3434, 1705 cm⁻¹; 1H nmr (CDCl3): 1.40(9H, s, t-Bu), 3.10-3.40(2H, m, CH2), 3.27(6H, s, 2xOCH3), 3.40-4.70(9H, m, 4x CH, 2xCH2, OH), 5.10-5.50(3H, m, NH, CH2=CH), 5.74-6.20(1H, m, CH2=CH ), 7.10-7.50(15H, m, aromatic protons); 13C nmr (CDCl3): 28.31(q), 50.58(d), 55.80(q), 56.23(q), 62.23(t), 71.93(d), 77.92(d), 79.19(s), 81.67(d), 86.55(s), 97.95(t), 98.09(t), 116.12(t), 126.99, 127.72 and 128.50 (aromatic carbons), 137.17(d), 143.27(s), 155.21(s); ms m/z 606(M+), 364(M+−Tr). 8: [α]D -22.0° (c=1); ir ν max (neat) 3436, 1705 cm⁻¹; 1H nmr (CDCl3): 1.41(9H, s, t-Bu), 3.00-3.50(2H, m, CH2), 3.24 and 3.34(2x3H, each s, 2xOCH3), 3.69-4.72(9H, m, 4x CH, 2xCH2, OH), 5.10-5.58 (3H, m, NH, CH2=CH), 5.65-6.09(1H, m, CH2=CH ), 6.98-7.51(15H, m, aromatic protons); 13C nmr (CDCl3): 28.31(q), 50.58(q), 55.80(q), 56.28(q), 62.23(t), 71.93(d), 77.92(d), 79.19(s), 81.67(d), 86.55(s), 97.95(t), 98.09(t), 116.12(t), 126.99, 127.72 and 128.50(aromatic carbons), 137.17(d), 143.27(s), 155.21(s); ms m/z 607(M+−1), 364(M+−Tr).
(2R,3R,4R,5R)-N-tert-Butoxycarbonyl-3,4-bis(methoxymethoxy)-2-trityloxymethyl-5-vinylpyrrolidine (9a) A mixture of 7 (200 mg, 0.33 mmol), methanesulfonyl chloride (75 mg, 0.66 mmol), and TEA (66 mg, 0.66 mmol) in CH₂Cl₂ (4 ml) was stirred at 0°C for 30 min. After dilution with AcOEt, the mixture was washed with H₂O, saturated aqueous NaHCO₃, and H₂O. Drying followed by evaporation gave a residue, which was treated with potassium tert-butoxide (56 mg, 0.55 mmol) in THF (4 ml) at 0°C for 15 min. After dilution with AcOEt, the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane = 1:4) to give 9a (150 mg, 78%) as an oil, [α]D -16.5° (c=1); ir ν max (neat) 1699, 1600, 1040 cm⁻¹; 1H nmr (CDCl₃): 1.24 and 1.33 (9H, each s, t-Bu), 2.87-3.52 (2H, m, CH₂), 3.20 and 3.42 (2x3H, each s, 2xOCH₃), 3.92 (1H, m, CH), 4.00-4.61 (5H, m, 3xCH, CH₂), 4.73 (2H, m, CH₂), 4.93-5.30 (2H, m, CH₂=CH), 5.60-6.05 (1H, m, CH₂=CH), 7.08-7.57 (15H, m, aromatic protons); 13C nmr (CDCl₃): 28.17 (q), 55.26 (q), 55.41 (q), 61.16 and 61.50 (each t), 63.69 and 63.98 (each d), 66.90 and 67.64 (each d), 79.38 (s), 79.63 (d), 83.33 (d), 86.45 (s), 94.44 (t), 94.93 (t), 115.88 (t), 126.80, 127.58 and 128.55 (aromatic carbons), 136.54 (d), 143.80 (s), 153.45 (s); ms m/z 588 (M⁺-1), 346 (M⁺-Try).

(2R,3R,4R,5R)-N-tert-Butoxycarbonyl-3,4-bis(methoxymethoxy)-5-hydroxymethyl-2-trityloxymethylpyrrolidine (9b) A solution of 9a (110 mg, 0.19 mmol) in CH₂Cl₂ (6 ml) was added at -78°C to 6 ml of CH₂Cl₂ saturated with ozone, then ozone was bubbled further 5 min at -78°C. Then, this solution was added to a suspension of NaBH₄ (43 mg, 1.13 mmol) in EtOH (6 ml) at 0°C. After being stirred at 0°C for 15 min, the mixture was diluted with AcOEt-benzene (1:1, 50 ml) and washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane = 2:1) to give 9b (99 mg, 93%) as an oil, [α]D -34.6° (c=1); ir ν max (neat) 3378, 1672, 1038 cm⁻¹; 1H nmr (CDCl₃): 1.25 (9H, each s, t-Bu), 2.90-3.20 (2H, m, CH₂), 3.22 and 3.42 (2x3H, each s, 2xOCH₃), 3.40-3.60 (2H, m, CH₂=CH), 4.73 (2H, s, CH₂), 7.04-7.58 (15H, m, aromatic protons); 13C nmr (CDCl₃): 28.12 (q), 55.36 (q), 55.55 (q), 61.06 (t), 64.23 (t), 64.52 (d), 66.81 (d), 79.04 (d), 80.55 (s and d), 86.40 (s), 94.49 (t), 94.97 (t), 126.84, 127.58 and 128.50 (aromatic carbons), 143.71 (s), 155.25 (s); ms m/z 594 (M⁺+1).

(2R,3R,4R,5R)-3,4-Dihydroxy-2,5-dihydroxymethylpyrrolidine (10a) A mixture of 9b (80 mg, 0.13 mmol), 10% aqueous HCl (2 ml), and MeOH (2 ml) was stirred at 70°C for 1 h. After removal of the methanol in vacuo, the insoluble materials were filtered off, and the filtrate was placed on a Dowex 50W-X8 (H⁺ form) column (15 ml), washed with 30 ml of H₂O, and eluted with 0.6 N NH₄OH. Freeze-drying of the appropriate fractions gave a residue, which was crystallized from MeOH-ether to give 10a (17 mg, 77%) as crystals, mp 113-114°C, [α]D +54.0° (c=1, H₂O); 1H nmr (D₂O, DHO): δ=4.70: 2.90-3.10 (2H, m), 3.45-3.72 (4H, m), 3.72-3.82 (2H, m); 13C nmr (D₂O, internal standard: dioxane δ =67.4): 62.09 (t), 62.53 (d), 78.03 (d). Anal. Calcd for C₆H₁₃NO₄: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.50; H, 7.85; N, 8.44.

Physical and spectral data of 9c, 9d and 10b
9c: [α]D -24.8° (c=1); ir ν max (neat) 1698, 1600, 1038 cm⁻¹; 1H nmr (CDCl₃): 1.35 (9H, s, t-Bu),
3.10-3.40(2H, m, CH2), 3.24 and 3.27 (6H, each s, 2xOCH3), 3.77-4.10(2H, m, 2xCH), 4.10-4.90 (6H, m, 2xCH, 2xCH2), 5.04-5.33(2H, m, CH2=CH), 5.61-6.04(1H, m, CH2=CH ), 7.09-7.52(15H, m, aromatic protons); 13C nmr (CDCl3): 28.26(q), 55.36(q), 55.75(q), 62.47(t), 62.18(d), 78.94(d), 79.77(s), 80.21(d), 86.45(s), 95.51 and 95.61(t), 117.20(t), 126.75, 127.58 and 128.65 (aromatic carbons), 135.17(d), 143.80(s), 154.52(s).

9d: [a]D +9.2°(c=0.8) ; ir ν max (neat) 3376, 1675, 1040 cm⁻¹; 1H nmr (CDCl3): 1.34 (9H, each s, t-Bu), 3.00-3.50(2H, m, CH2), 3.22 and 3.35 (2x3H, each s, 2xOCH3), 3.50-3.80(2H, m, CH2), 3.80-4.80(7H, m, CH, 2xCH2, OH), 4.68(2H, s, CH2), 7.69-7.55(15H, m, aromatic protons); 13C nmr (CDCl3): 28.26(q), 55.50(q), 55.94(q), 61.79(t), 63.01(t and d), 64.13(d), 77.14(d), 80.11(d), 80.80(s), 86.49(s), 95.46(t), 126.94, 127.67 and 128.59 (aromatic carbons), 143.60(s), 154.80(s).

10b: mp 133-136°C, [a]D +26.3° (c=0.8, MeOH); 1H nmr (D2O, DOH: δ=4.70), 2.90-3.12(1H, m), 3.18-3.42(1H, m), 3.50-3.87(5H, m), 3.88-4.11 (1H, m); 13C nmr (D2O, internal standard:dioxane δ=67.4): 60.52(t), 61.40(d), 62.62(t), 65.39(d), 77.72(d), 79.53(d).

1,1-Dimethylethyl N-[[(1R,2R,3S)- and (1R,2S,3R)-2,3-Bis(tert-butyldimethylsilyloxy)-3-methoxycarbonyl-1-trityloxyethylpropanoyl]carbamate (3d and 4d)

A mixture of 3a and 4a (1.0 g, 1.92 mmol), prepared from 2 by dihydroxylation using hydroquinine 9-phenanthryl ether, tert-butyldimethylsilyl chloride (1.64 g, 9.6 mmol), and imidazole (1.22 g, 17.9 mmol) in DMF (10 ml) was stirred at room temperature for 40 h. After dilution with AcOEt-benzene (2:1, 150 ml), the mixture was washed with half-saturated aqueous NaCl, dried followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane:1=8) to give 3d (0.24 g, 17%) and 4d (0.98 g, 68%) as an oil. 3d: [a]D -28.1°(c=1); ir ν max (neat) 1761, 1711 cm⁻¹; 1H nmr (CDCl3): -0.36, -0.08, 0.00, and 0.07(12H, each s, 4xCH3), 0.82(18H, s, t-Bu), 1.35(9H, s, t-Bu), 2.60-2.83 (1H, m, CH2O), 3.40-3.60(1H, m, CH2O), 3.65(3H, s, COOCH3), 3.90-4.29(2H, m, 2xCH), 4.48-4.58(1H, m, CH), 5.74(1H, d, J=10 Hz, NH), 7.10-7.50(15H, m, aromatic protons). 13C nmr (CDCl3): -5.60, -5.27 and -4.73(q), 17.64 and 17.84(s), 25.34(q), 25.53(q), 28.12(q), 51.36(q), 54.04(d), 63.01(d), 70.46(d), 78.07(s), 86.20(s), 126.90, 127.58 and 128.35 (aromatic carbons), 143.41(s), 155.55(s), 171.67(s); ms m/z 750 (M⁺+1). 4d: [a]D -29.0°(c=0.9); ir ν max (neat) 1753, 1714 cm⁻¹; 1H nmr (CDCl3): -0.29, -0.22, 0.05 and 0.11(12H, each s, 4xCH3), 0.77, 0.85, 0.94 and 1.00 (18H, each s, 2x-t-Bu), 1.41 and 1.46(9H, each s, t-Bu), 2.62-2.96(1H, m, CH2O), 3.13-3.37(1H, m, CH2O), 3.67(3H, s, OCH3), 4.11-4.82(3H, m, 2xCH, NH), 7.13-7.57 (15H, m, aromatic protons). 13C nmr (CDCl3): -5.36, -5.11 and -4.68(q), 17.79 and 18.13(s), 25.54(q), 28.17(q), 28.36(q), 49.71 and 49.80(d), 51.31 and 51.65(q), 62.72 and 63.15(t), 71.68 and 71.97(d), 72.51 and 72.71(d), 78.75(s), 79.48(s), 86.40(s), 126.80, 127.57 and 128.50 (aromatic carbons), 143.75(s), 154.52(s), 155.66(s), 171.63(s); ms m/z 750 (M⁺+1).

1,1-Dimethylethyl N-[[(1R,2S,3S)-2,3-Bis(tert-butyldimethylsilyloxy)-4-hydroxy-1-trityloxyethylbutyl]carbamate (6)

LiBH4 (30 mg, 1.43 mmol) was added to a solution of 4d (300 mg, 0.4 mmol) in ether (6 ml) at room temperature, and then LiBH3Et3 (0.3 ml of 1 M solution in THF) was added. After being stirred at room temperature for 15 min, the mixture was quenched with 0.9 ml of 1N H2SO4 and diluted with ether. After washings with H2O, saturated aqueous NaHCO3, and saturated aqueous NaCl, drying followed by evaporation gave a residue, which was purified by column...
chromatography (AcOEt:hexane=1:6) to give 6 (147 mg, 52%) as an oil, [α]D -25.8° (c=0.9); ir νmax (neat) 3442, 1701, 1105 cm⁻¹; 1H nmr (CDCl₃): -0.33, -0.02 and 0.10 (12H, each s, 4xCH₃), 0.70 and 0.90 (18H, each s, 2x-t-Bu), 1.41 (9H, s, t-Bu), 1.72 (1H, br s, OH), 2.60-3.16 (2H, m, CH₂OTr), 3.30-4.00 (4H, m, 2xCH₂, CH₂O), 4.17-4.77 (2H, m, CH, NH), 6.97-7.58 (15H, m, aromatic protons); 13C nmr (CDCl₃): -5.12, -4.53 and -4.39 (q), 17.79 (s), 25.63 (q), 25.78 (q), 28.36 (q), 48.24 and 49.12 (d), 63.06 and 64.66 (t), 1.49 and 72.27 (d), 74.95 (d), 79.04 and 79.67 (s), 86.64 (s), 126.84, 127.62 and 128.59 (aromatic carbons), 143.75 (s), 154.82 (s); ms m/z 721 (M⁺).

(2R,3S,4S)-N-tert-Butoxycarbonyl-3,4-bis(tert-butylidimethylsilyloxy)-2-trityloxyethylpyrrolidine (11a) This sample was obtained from 6 in 76% yield after column chromatography (AcOEt:hexane=7:1) in the similar manner as described above in the preparation of 9a, [α]D +7.2° (c=0.6); ir νmax (neat) 1691 cm⁻¹; 1H nmr (CDCl₃): -0.12, -0.04, -0.02 and 0.06 (12H, each s, 4xCH₃), 0.68, 0.74 and 0.87 (18H, each s, 2x-t-Bu), 1.25 and 1.45 (9H, s, t-Bu), 2.89-3.55 (3H, m, CH₂, CH), 3.55-4.23 (3H, m, 3xCH), 4.50-4.78 (1H, m, CH), 6.89-7.50 (15H, m, aromatic protons); 13C nmr (CDCl₃): -4.92, -4.63, -4.53 and -4.39 (q), 14.08 (s), 25.83 (q), 28.36 and 28.50 (q), 50.92 and 51.12 (t), 57.94 and 58.72 (t), 60.13 and 60.28 (t), 74.60 and 75.34 (d), 77.58 (d), 79.33 and 79.24 (s), 87.03 and 87.13 (s), 126.70, 127.58 and 128.74 (aromatic carbons), 143.95 (s), 154.04 (s).

(2R,3S,4S)-N-tert-Butoxycarbonyl-3,4-dihydroxy-2-trityloxyethylpyrrolidine (11b) A mixture of 11a (360 mg, 0.51 mmol) in THF (7 ml) and tetrabutylammonium fluoride (1.5 ml of a 1 M solution in THF) was stirred at room temperature for 30 min. After dilution with AcOEt, the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue which was purified by column chromatography (AcOEt:hexane=1:2) to give 11b (198 mg, 81%) as crystals, mp 86-87°C, [α]D -22.0° (c=0.5); ir νmax (nujol) 3430, 1680, 1074 cm⁻¹; 1H nmr (CDCl₃): 1.32 (9H, br s, t-Bu), 2.40-3.05 (2H, m), 3.10-3.80 (4H, m), 3.90-4.45 (3H, m), 6.89-7.50 (15H, m, aromatic protons); 13C nmr (CDCl₃): 28.36 (q), 51.31 (t), 58.48 (d), 61.60 (t), 74.36 (d), 77.77 (d), 79.82 (s), 87.33 (s), 127.19, 127.96 and 128.20 (aromatic carbons), 143.21 (s), 154.67 (s). Anal. Calcd for C₂₉H₃₃NO₅S: C, 73.24; H, 6.99; N, 2.95. Found: C, 72.98; H, 7.25; N, 2.81.

(2R,3S,4S)-N-tert-Butoxycarbonyl-3,4-dibenzyloxy-2-trityloxyethylpyrrolidine (11c) A suspension of NaH (75 mg, 1.89 mmol, 60% oil suspension) in THF (2 ml) was added at 0°C to a solution of 11b (300 mg, 0.16 mmol) in DMF (2 ml). After being stirred at room temperature for 30 min, benzyl bromide (360 mg, 2.1 mmol) was added and the mixture was stirred at room temperature for 1.5 h. After dilution with AcOEt-benzene (1:1, 100 ml), the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue which was purified by column chromatography (AcOEt:hexane=1:4) to give 11c (330 mg, 80%) as an oil, [α]D +5.93° (c=0.5); ir νmax (neat) 1691 cm⁻¹; 1H nmr (CDCl₃): 1.25 and 1.44 (9H, each br s, t-Bu), 2.98-3.58 (3H, m, CH₂, CH), 3.58-3.88 (1H, m, CH), 3.88-4.36 (2H, m, 2xCH₂), 4.36-4.80 (5H, m, 2xOCH₂Ph,CH), 6.89-7.50 (15H, m, aromatic protons); 13C nmr (CDCl₃): 28.36 (q), 49.36 (t), 57.02 and 57.84 (d), 60.57 (t), 72.02 (t), 72.80 (t), 79.47 (s), 79.48 (d), 79.96 (d), 82.49 (s), 85.13 (s), 126.70, 127.58, 128.16 and 128.35 (aromatic carbons), 138.05 (s), 143.95 (s), 153.93 (s); ms m/z 654 (M⁺-Tr), 412 (M⁺-Ph).
A mixture of 11c (295 mg, 0.45 mmol), 10% aqueous HCl (3 ml), and MeOH (3 ml) was stirred at 70°C for 1 h, then basified with 2N NaOH and extracted with AcOEt. AcOEt extracts were washed with H2O. Drying followed by evaporation gave a residue, which was benzylated with benzyl bromide (190 mg, 1.12 mmol) in the presence of K2CO3 (190 mg, 1.40 mmol) in acetone (3 ml) at room temperature for 1.5 h. Then, filtration followed by evaporation and purification with column chromatography (AcOEt: hexane=1: 2) gave 12 (59 mg, 32%) as crystals, mp 53-54°C (ether-hexane), [a]D -35.8° (c=0.4) (lit.,10 [a]D -34.0° (c=0.6)); 13C-nmr (CDCl3): 55.78(t), 59.86(t), 62.16(d), 71.85(t), 72.07(t), 82.22(d), 84.45(d), 127.12, 127.60, 127.70, 128.30, 128.43 and 128.96(aromatic carbons), 137.81(s) 138.01(s). Anal. Calcd for C26H29N03: C, 77.15; H, 7.48; N, 3.59.

(2R,3S,4S)-N-Benzyl-3,4-bis(benzyloxy)-1-hydroxy-2-(4-methoxyphenyl) methylypyrrolidine (13a) 12 (120 mg, 0.30 mmol) was oxidized by the method of Swern 5a (82 mg (0.64 mmol) of oxalyl chloride, 112 mg (1.42 mmol) of DMSO, 2 ml of CH2Cl2, -10°C, 20 min, then 150 mg (1.48 mmol) of TEA). The crude aldehyde in ether (2 ml) was added at -10°C to a solution of 12a (53 mg, 0.11 mmol) and 3.18-3.36(4H, m, CH), 6.80(2H, d, J=12 Hz, aromatic protons), 7.05-7.36(17H, m, aromatic carbons), 135.86(s), 137.90(s), 138.15(s); ms m/z 510(M+1), 508(M+1).
CH), 3.55 and 4.10 (2H, AB, J=13 Hz, NCH2Ph), 3.74 (3H, s, OMe), 4.40 (2H, s, OCH2Ph), 6.78 (2H, d, J=9 Hz, aromatic protons), 7.00-7.35 (12H, m, aromatic protons); 13C nmr (CDCl3): 31.92 (t), 55.18 (q), 57.99 (t), 58.33 (t), 69.30 (d), 71.39 (t), 75.05 (d), 82.40 (d), 113.88 (d), 127.61, 128.47, 129.33, 130.18, 137.62 and 137.05 (aromatic carbons).

(2R,3S,4S)-N-Benzylxycarbonyl-3,4-dihydroxy-2-(4-methoxybenzyl)pyrrolidine (14)
A mixture of 13a (28 mg, 0.06 mmol), 10% palladium carbon (50 mg), 99% formic acid (0.5 ml) in EtOH (2 ml) under N2 was placed in an ultrasonic bath. After sonification for 2 h at 45-55°C, the catalyst was filtered off and washed with EtOH. The filtrate was evaporated in vacuo to give a residue, which was reacted with benzyl chloroformate (20 mg, 0.12 mmol) in CH2Cl2 (4 ml) and aqueous 5% Na2C03 (0.24 ml) at room temperature for 1 h. After dilution with AcOEt, the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:1) to give 14 (12 mg, 60%) as crystals, mp 123-126°C (ether-hexane), [a]D -8.7°(c=0.5, MeOH); 1H nmr (CDCl3): 1.90-2.30 (2H, 2xOH), 2.89 (1H, dd, J=13.7 and 8.5 Hz), 3.00-3.46 (2H, m, 2xCH), 3.60 (1H, dd, J=11.9 and 5.4 Hz), 3.77 (3H, s, OCH3), 3.80-4.30 (3H, m, 3xCH), 5.15 (2H, s, OCH2Ph), 6.78 (2H, d, J=8.3 Hz), 6.90-7.45 (10H, m, aromatic protons). Anal. Calcd for C20H23N05: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.03; H, 6.70; N, 4.11.

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REFERENCES AND NOTES
4. The reaction of 2 with AD-mix-β in the presence of methanesulfonamide (1 equiv.) in tert-BuOH-H2O (1:1) 3b at 0°C for 30 h gave 3a predominantly (>98% de). However, the chemical yield was 22%. In the case of AD-mix-α, 28:72 ratio of 3a:4a was obtained in only 5% yield.


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