SYNTHESIS OF (2*R*,3*R*,4*R*,5*R*)-3,4-DIHYDROXY-2,5-DI-HYDROXYMETHYLPYRROLIDINE AND (-)-ANISOMYCIN DERIVATIVE FROM (*S*)-PYROGLUTAMIC ACID DERIVATIVE

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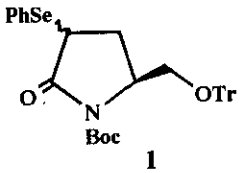
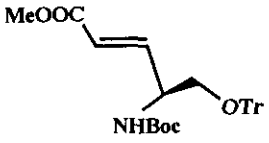
Abstract —Double asymmetric dihydroxylation of (*E*)-α,β-unsaturated ester (**2**) with a catalytic amount of potassium osmate and chiral ligand gave dihydroxy compounds (**3a** and **4a**) selectively. Polyhydroxylated pyrrolidines (**10** and **14**) were synthesized from corresponding methoxymethy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

Polyhydroxylated pyrrolidines show interesting biological activities, and their synthesis including stereo-isomers and biological evaluation have been extensively studied.[1] In a previous paper,[2] 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 OsO_4 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[3c] with chiral ligand,[3a,b] and the facile synthesis of (2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-dihydroxymethyl-pyrrolidines (**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 hydro-quinidine 9-phenanthryl ether (0.15 equiv.) as a chiral ligand[3a] in the presence of $K_3Fe(CN)_6$ (3 equiv.) and K_2CO_3 (3 equiv.) in *tert*-BuOH-H_2O (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.[4] The ratio of



1



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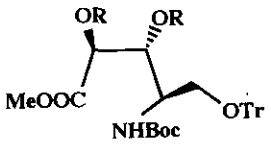
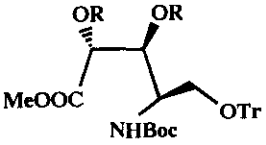
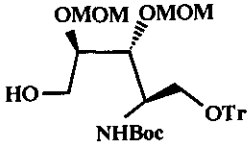


3a: R=H
b: R=Ac
c: R=MOM
d: R=TBS



4a: R=H
b: R=Ac
c: R=MOM
d: R=TBS



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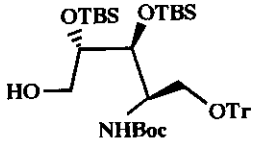

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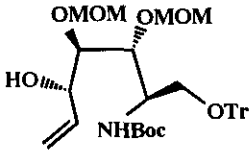

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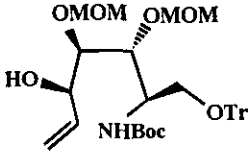

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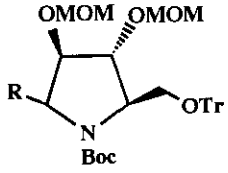
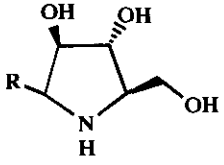
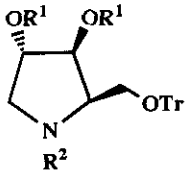


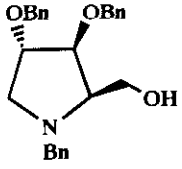
9a: R= α-vinyl
b: R= α-CH_2OH
c: R= β-vinyl
d: R= β-CH_2OH



10a: R= α-CH_2OH
b: R= β-CH_2OH



11a: R^1=TBS, R^2=Boc
b: R^1=H, R^2=Boc
c: R^1=Bn, R^2=Boc
d: R^1=R^2=Bn



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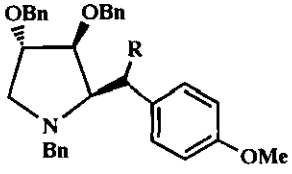
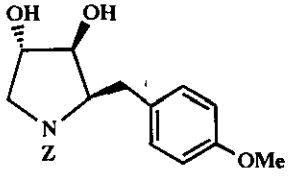


13a: R=OH
b: R=H



14

Boc: -COOt-Bu
MOM: -CH_2OMe
TBS: -$SiMe_2$t-Bu
Bn: -$CH_2C_6H_5$
Z: -$COOCH_2C_6H_5$

3a and **4a** was determined by high performance liquid chhromatographic (hplc) analysis after conversion of **3a** and **4a** into the coresponding diacetate (**3b** and **4b**) (pyridinc, acetic anhydridc). The polyhydroxylatcd 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 hydroquinidinc 9-phenanthryl ether, was converted into the MOM ether (MOM chloride, *N*,*N*-diethylaniline, CH_2Cl_2) and the major diasteromer (**3c**) was isolated by recrystallization from AcOEt-hexane in 78% yield. Then, **3c** was treated with $NaBH_4$ in EtOH to give an alcohol (**5**) in 85% yield. Swern oxidation[5b] 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 chloridc (MsCl), triethylamine (TEA), CH_2Cl_2) 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 $NaBH_4$ afforded the alcohol (**9b**) in 93% yield. The compound (**9b**) could bc 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, $[\alpha]_D$ +54.0° (c=1, H_2O), lit.,[7b] mp 116-118°C, $[\alpha]_D$ +54.3° (c=1.2, H_2O)) in 77% yield after treatment with ion exchange column (Dowex 50W-X8, H^+ form). In the same reaction sequence, (2*R*,3*R*,4*R*,5*S*)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidinc (**10b**) (mp 133-136°C, $[\alpha]_D$ +26.3° (c=0.8,MeOH), lit.,[8] mp 139-142.5°C, $[\alpha]_D$ +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 hydroquinine 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 $LiBH_4$ in the presence of lithium triethylboro-hydride[9] in ether to provide an alcohol (**6**), which was then converted to the pyrrolidine derivative (**11a**) *via* mesylate (MsCl, TEA, CH_2Cl_2; 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 K_2CO_3 in acetone gave **12** in 32% yield. Oxidation of **12** by the method of Swern followed by reaction with 4-methoxyphenylmagnesium bromide in ether gave **13a** as a sole diastereomer, which was then treated with triethylsilane[11] in the presence of trifluoroacetic acid and trifluoromethansulfonic acid in CH_2Cl_2 to afford **13b** in 31% yield. In this reaction, **13b** was not obtained without addition of trifluoromethansulfonic acid. *N*-Benzyloxycarbonyl-3,4-dihydroxy-2-(4-methoxyphenyl)-pyrrolidine (**14**) [12] (mp 123-126°C, $[\alpha]_D$ -8.7° (MeOH), lit.,[12c] mp 127-129°C, $[\alpha]_D$ -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, Na_2CO_3, CH_2Cl_2). ^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 (2*R*,3*R*,4*R*)- and (2*R*,3*S*,4*S*)-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 ^{13}C 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 $CHCl_3$ solution at 20°C on a JASCO DIP-360 polarimeter unless otherwise mentioned. The organic solvents were dried over $MgSO_4$ before vacuum evaporation and a column chromatography was carried out with silica gel (Wakogel C-200).

1,1-Dimethylethyl *N*-[(1*S*)-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 ($CDCl_3$): 1.38 (9H, s, t-Bu), 1.58-2.33 (2H, m, CH_2), 2.84-3.22 (2H, m, CH_2OTr), 3.56 and 3.58 (3H, each s, OCH_3), 3.45-4.20 (2H, m, 2xCH), 4.40-4.70 (1H, m, NH), 6.80-7.61 (20H, m, aromatic protons); ^{13}C-nmr ($CDCl_3$): 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% H_2O_2 (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 H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1: 3) to give **2** (1.35g, 89%) as crystals, mp 88 °C (AcOEt-hexane), $[\alpha]_D$ -11.9°(c=1.3) ; ir ν_{max} (nujol) 1707, 1656, 1513 cm^{-1}; ^1H nmr ($CDCl_3$): 1.44(9H, s, t-Bu), 3.25(2H, m, CH_2), 3.70(3H, s, $COOCH_3$), 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); ^{13}C nmr ($CDCl_3$): 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. Calcd for $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87. Found: C, 73.66; H, 7.03; N, 2.67.

Double asymmmetric 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), $K_3Fe(CN)_6$ (506 mg, 1.54 mmol), and K_2CO_3 (212 mg, 1.54 mmol) in a *tert*-BuOH-H_2O (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, Na_2SO_3 (1 g) was added and the mixture was stirred for 30 min, and extracted with AcOEt. The organic extracts were washed with 5% aqueous H_2SO_4, H_2O, saturated aqueous $NaHCO_3$, 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, $[\alpha]_D$ +45.5°(c=0.7); ^1H nmr ($CDCl_3$): 1.38(9H, s, t-Bu), 1.75 and 2.11 (2x3H, each s, 2-CH_3), 3.10-3.20 (2H, m, CH_2), 3.69(3H, s, $COOCH_3$), 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); ^{13}C nmr ($CDCl_3$): 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), $[\alpha]_D$ -32.2°(c=0.5), ^1H nmr ($CDCl_3$): 1.41(9H, s, t-Bu), 1.97 and 2.04 (2x3H, each s, 2-CH_3), 2.90-3.30(2H, m, CH_2), 3.69(3H, s, $COOCH_3$), 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); ^{13}C nmr ($CDCl_3$): 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. Calcd for $C_{34}H_{39}NO_9$: C, 67.42; H, 6.49; N, 2.31. Found: C, 67.55; H, 6.64; N, 2.20.

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*)-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*-diethylaniline (2.3 g, 15.5 mmol), and chloromethyl methy ether (1.24 g, 15.5 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 30 h. After addition of AcOEt (100 ml), the mixture was washed with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and H_2O. 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 cystals, mp 73-74 °C (AcOEt-hexane), $[\alpha]_D$ -49.1° (c=1) ; ir ν_{max} (nujol)

1755, 1714 cm^{-1}; ^1H nmr ($CDCl_3$): 1.41(9H, s, t-Bu), 3.10-3.40(2H, m, CH_2), 3.20 and 3.24 (2x3H, each s, 2xOCH_3), 3.72(3H, s, $COOCH_3$), 4.11-4.36(3H, m, 3xCH), 4.44-4.69(4H, m, 2xCH_2), 5.22 (1H, d, J=8 Hz, NH), 7.10-7.49 (15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 28.06(q), 50.49(t), 51.65 (d), 55.89(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 $C_{34}H_{43}NO_9$: C, 66.97; H, 7.11; N, 2.30. Found: C, 66.71; H, 7.33; N, 2.11.

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*R*)-2,3-Bis(methoxymethyloxy)-4-hydroxy-1-trityloxymethylbutyl]carbamate (5) A mixture of $NaBH_4$ (500 m g, 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, $[\alpha]_D$ -19.7° (c=1) ; ir ν_{max} (neat) 3440, 1710, 1026 cm^{-1}; ^1H nmr ($CDCl_3$): 1.43(9H, s, t-Bu), 2.94-3.40(2H, m, CH_2), 3.25 and 3.31(2x3H, each s, 2xOCH_3), 3.40-4.36(6H, m, 3xCH, CH_2, OH), 4.40-4.15(4H, m, 2xCH_2), 5.18(1H, d, J=10 Hz, NH), 7.01-7.62(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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*-[(1*R*,2*R*,3*R*,4*R*)- and (1*R*,2*R*,3*R*,4*S*)-2,3-Bis(methoxymethoxy)-4-hydroxy-1-trityloxymethyl-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 strred 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 NH_4Cl (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**: $[\alpha]_D$ -15.3° (c=1) ; ir ν_{max} (neat) 3434, 1705 cm^{-1}; ^1H nmr ($CDCl_3$): 1.40(9H, s, t-Bu), 3.10-3.40(2H, m, CH_2), 3.27 (6H, s, 2xOCH_3), 3.40-4.70(9H, m, 4 x CH, 2xCH_2, OH), 5.10-5.50 (3H, m, NH, CH_2=CH), 5.74-6.20(1H, m, CH_2=CH), 7.10-7.50(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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**: $[\alpha]_D$ -22.0° (c=1) ; ir ν_{max} (neat) 3436, 1705 cm^{-1}; ^1H nmr ($CDCl_3$): 1.41(9H, s, t-Bu), 3.00-3.50(2H, m, CH_2), 3.24 and 3.34(2x3H, each s, 2x OCH_3), 3.69-4.72(9H, m, 4xCH, 2xCH_2, OH), 5.10-5.58 (3H, m, NH, CH_2=CH), 5.65-6.09(1H, m, CH_2=CH), 6.98-7.51(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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).

(2*R*,3*R*,4*R*,5*R*)-*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 CH_2Cl_2 (4 ml) was stirred at 0° C for 30 min. After dilution with AcOEt, the mixture was washed with H_2O, saturated aqueous $NaHCO_3$, and H_2O. Drying followed by evaporation gave a residue, which was treated with potassium *tert*-butoxide(56 mg, 0.5 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, $[\alpha]_D$ -16.5°(c=1) ; ir ν_{max} (neat) 1699, 1600, 1040 cm^{-1}; ^1H nmr ($CDCl_3$): 1.24 and 1.33 (9H, each s, t-Bu), 2.87-3.52(2H, m, CH_2), 3.20 and 3.42 (2x3H, each s, 2xOCH_3), 3.92(1H, m, CH), 4.00-4.61(5H, m, 3xCH, CH_2), 4.73(2H, m, CH_2), 4.93-5.30(2H, m, CH_2=CH), 5.60-6.05(1H, m, CH_2=CH), 7.08-7.57(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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^+-Tr).

(2*R*,3*R*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-bis(methoxymethyloxy)-5-hydroxymethyl-2-trityloxymethylpyrrolidine (9b) A solution of **9a** (110 mg, 0.19 mmol) in CH_2Cl_2 (6 ml) was added at -78°C to 6 ml of CH_2Cl_2 saturated with ozone, then ozone was bubbled further 5 min at -78°C. Then, this solution was added to a suspension of $NaBH_4$ (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, $[\alpha]_D$ -34.6°(c=1) ; ir ν_{max} (neat) 3378, 1672, 1038 cm^{-1}; ^1H nmr ($CDCl_3$): 1.25 (9H, each s, t-Bu), 2.90-3.20(2H, m, CH_2), 3.22 and 3.42 (2x3H, each s, 2xOCH_3), 3.40-3.60(2H, m, CH_2), 3.60-4.40(7H, m, 4xCH, CH_2, OH), 4.73(2H, s CH_2), 7.04-7.58(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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)

(2*R*,3*R*,4*R*,5*R*)-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 filterd off, and the filtrate was placed on a Dowex 50W-X8 (H^+ form) column (15 ml), washed with 30 ml of H_2O, and eluted with 0.6 N NH_4OH. Freeze-drying of the appopriate fractions gave a residue, which was crystallized from MeOH-ether to give **10a** (17 mg, 77 %) as crystals, mp 113-114°C, $[\alpha]_D$ +54.0° (c=1, H_2O); ^1H nmr (D_2O, DHO: δ=4.70) : 2.90-3.10(2H, m), 3.45-3.72(4H, m), 3.72-3.82(2H, m); ^{13}C nmr (D_2O, internal standard: dioxane δ =67.4): 62.09(t), 62.53(d), 78.03(d). Anal. Calcd for $C_6H_{13}NO_4$: 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: $[\alpha]_D$ -24.8°(c=1) ; ir ν_{max} (neat) 1698, 1600, 1038 cm^{-1}; ^1H nmr ($CDCl_3$): 1.35(9H, s, t-Bu),

3.10-3.40(2H, m, CH_2), 3.24 and 3.27 (6H, each s, 2xOCH_3), 3 .77-4.10(2H, m, 2xCH), 4.10-4.90 (6H, m, 2xCH, 2xCH_2), 5.04-5.33(2H, m, CH_2=CH), 5.61-6.04(1H, m, CH_2=CH), 7.09-7.52(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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), 154.62(s). **9d**: $[\alpha]_D$ +9.2°(c=0.8) ; ir ν_{max} (neat) 3376, 1675, 1040 cm^{-1}; ^1H nmr($CDCl_3$): 1.34 (9H, each s, t-Bu), 3.00-3.50(2H, m, CH_2), 3.22 and 3.35 (2x3H, each s, 2xOCH_3), 3.50-3.80(2H, m, CH_2), 3.80-4.80(7H, m, 4xCH, CH_2, OH), 4.68(2H, s, CH_2), 7.69-7.55(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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, $[\alpha]_D$ +26.3° (c=0.8, MeOH); ^1H nmr (D_2O, DHO: δ=4.70), 2.90-3.12(1H, m), 3.18-3.42(1H, m), 3.502-3.87(5H, m), 3.88-4.11 (1H, m); ^{13}C nmr (D_2O, 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*-[(1*R*,2*R*,3*S*)- and (1*R*,2*S*,3*R*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-3-methoxycarbonyl-1-trityloxymethylpropanyl]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 (x5). Drying 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**: $[\alpha]_D$ -28.1°(c=1) ; ir ν_{max} (neat) 1761, 1711 cm^{-1}; ^1H nmr ($CDCl_3$): -0.36, -0.08, 0.00, and 0.07(12H, each s, 4xCH_3), 0.82(18H, s, 2xt-Bu), 1.35(9H, s, t-Bu), 2.60-2.83 (1H, m, $C\underline{H}_2O$), 3.40-3.60(1H, m, $C\underline{H}_2O$), 3.65(3H, s, $COOCH_3$), 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). ^{13}C nmr($CDCl_3$): -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), 73.14(d), 78.07(s), 86.20(s), 126.80, 127.58 and 128.35(aromatic carbons), 143.41 (s), 155.55(s), 171.67(s); ms *m/z* 750 (M^++1). **4d**: $[\alpha]_D$ -29.0°(c=0.9) ; ir ν_{max} (neat) 1753, 1714 cm^{-1}; ^1H nmr ($CDCl_3$): -0.29, -0.22, 0.05 and 0.11(12H, each s, 4xCH_3), 0.77, 0.85, 0.94 and 1.00 (18H, each s, 2xt-Bu), 1.41 and 1.46(9H, each s, t-Bu), 2.62-2.96(1H, m, $C\underline{H}_2O$), 3.13-3.37(1H, m, $C\underline{H}_2O$), 3.67(3H, s, OCH_3), 4.11-4.82(3H, m, 2xCH, NH), 7.13-7.57 (15H, m, aromatic protons). ^{13}C nmr ($CDCl_3$): -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*-[(1*R*,2*S*,3*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-1-trityloxymethylbutyl]carbamate (6) $LiBH_4$ (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 $LiBHEt_3$ (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 H_2SO_4 and diluted with ether. After washings with H_2O, saturated aqueous $NaHCO_3$, 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, $[\alpha]_D$ -25.8°(c=0.9) ; ir ν_{max} (neat) 3442, 1701, 1105 cm^{-1}; ^1H nmr ($CDCl_3$): -0.33, -0.02 and 0.10(12H, each s, 4xCH_3), 0.70 and 0.90(18H, each s, 2xt-Bu), 1.41 (9H, s, t-Bu), 1.72(1H, br s, OH), 2.60-3.16(2H, m, CH_2OTr), 3.30-4.00(4H, m, 2xCH, CH_2O), 4.17-4.77(2H, m, CH, NH), 6.97-7.58(15H, m, aromatic protons); ^{13}C-nmr ($CDCl_3$): -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^+).

(2*R*,3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-bis(*tert*-butyldimethylsilyloxy)-2-trityloxymethylpyrrolidine (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**, $[\alpha]_D$ +7.2° (c=0.6) ; ir ν_{max} (neat) 1691 cm^{-1} ; ^1H nmr ($CDCl_3$): -0.12, -0.04, -0.02 and 0.06(12H, each s, 4xCH_3), 0.68, 0.74 and 0.87(18H, each s, 2xt-Bu), 1.25 and 1.45(9H, s, t-Bu), 2.89-3.55(3H, m, CH_2, CH), 3.55-4.23 (3H, m, 3xCH), 4.50-4.78(1H, m, CH), 6.89-7.50(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): -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).

(2*R*,3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dihydroxy-2-trityloxymethylpyrrolidine (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, $[\alpha]_D$ -22.0°(c=0.5) ; ir ν_{max} (nujol) 3430, 1680, 1074 cm^{-1}; ^1H nmr ($CDCl_3$): 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); ^{13}C nmr ($CDCl_3$): 28.36 (q), 51.31(t), 58.48(d), 61.60(t), 74.36d), 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 $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95. Found: C, 72.98; H, 7.25; N, 2.81.

(2*R*,3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dibenzyloxy-2-trityloxymethylpyrrolidine (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 att 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, $[\alpha]_D$ +5.93°(c=0.5) ; ir ν_{max} (neat) 1691 cm^{-1}; ^1H nmr ($CDCl_3$): 1.25 and 1.44(9H, each br s, t-Bu), 2.98-3.58(3H, m, CH_2, CH), 3.58-3.88(1H, m, CH), 3.88-4.36(2H, m, 2xCH), 4.36-4.80(5H, m, 2xOCH_2Ph,CH), 6.89-7.50(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 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), 87.13(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^+-1), 412(M^+-Tr).

(2R,3S,4S)-*N*-Benzyl-3,4-bis(benzyloxy)-2-hydroxymethylpyrrolidine (12)

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 H_2O. Drying followed by evaporation gave a residue, which was benzylated with benzyl bromide (190 mg, 1.12 mmol) in the presence of K_2CO_3 (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), $[\alpha]_D$ -35.8°(c=0.4) (lit.,[10] $[\alpha]_D$ -34.0°(c=0.6)) ; ^{13}C-nmr ($CDCl_3$): 55.78(t), 59.58(t), 59.86(t), 62.16(d), 71.85t), 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 $C_{26}H_{29}NO_3$: C,77.39 ; H,7.24 ; N, 3.47. Found: C, 77.15; H, 7.48; N, 3.59.

(2*R*,3*S*,4*S*)-*N*-Benzyl-3,4-bis(benzyloxy)-1-hydroxy-2-(4-methoxyphenyl) mehtyl-pyrrolidine (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 CH_2Cl_2, -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 4-methoxyphenylmagnesium bromide (1.3 ml of 0.8 M solution in ether). After being stirred at reflux temperature for 1h, the mixture was quenched with 1 ml of 10% aqueous NH_4Cl, and diluted with AcOEt. Washing with half-saturated aqueous NaCl followed by drying and evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:4) to give **13a** (83 mg, 51 % yield) as an oil, $[\alpha]_D$ +16.4° (c=1.2) ; ir $\nu_{max.}$ (neat) 3463, 1608, 1107 cm^{-1}; ^{1}H nmr ($CDCl_3$): 2.39(1H, dd, J=6.5 and 10.3 Hz, CH), 3.09-3.68(4H, m, 2xCH, OH, NC<u>H</u>$_2$Ph), 3.73(3H, s, OMe), 3.98-4.20(3H, m, 2xCH, NC<u>H</u>$_2$Ph), 4.47(2H, s, OCH_2Ph), 4.48 and 4.66(2H, AB, J=12Hz, OCH_2Ph), 4.94(1H, d, J=2.8 Hz, CH), 6.80(2H, d, J=9 Hz, aromatic protones), 7.09-7.36(17H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 54.43(t), 55.07(q), 61.40(t), 68.95(d), 70.07(d), 71.88(t), 72.71(t), 81.48(d), 83.62(d), 113.45(d), 126.80-128.65(aromatic carbons), 135.86(s), 137.90(s), 138.15(s); ms *m/z* 510(M^++1), 508(M^+-1).

(2*R*,3*S*,4*S*)-*N*-Benzyl-3,4-bis(benzyloxy)-2-(4-methoxybenzyl)pyrrolidine (13b) Trifluoroacetic acid (57mg, 0.5 mmol) was added to a solution of **13a** (53 mg, 0.11 mmol) and triethylsilane (28 mg, 0.25 mmol) in CH_2Cl_2 (3 ml) at 0°C followed by addition of trifluoromethanesulfonic acid (15 mg, 0.1 mmol). After being stirred at 0°C for 2 h, the mixture was diluted with AcOEt and washed with 1N NaOH, H_2O, and saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=1:2.5) to give **13b** (32 mg, 60 %, $[\alpha]_D$ -74.1°(c=0.4) ; ir ν_{max} (neat) 1614, 1508 cm^{-1}; ^{1}H nmr ($CDCl_3$): 2.10-2.34(1H, m, CH), 2.70-3.02 (2H, m, CH_2), 3.18-3.36 (2H, m, CH, NC<u>H</u>$_2$Ph), 3.60-3.72(1H, m, CH), 3.70(3H, s, OMe), 3.72-4.15(2H, m, CH, NC<u>H</u>$_2$Ph), 4.31(2H, s, OCH_2Ph), 4.28 and 4.41(2H, AB, J=12 Hz, OCH_2Ph), 6.70(2H, d, J=9 Hz, aromatic protons), 7.05 (2H, d, J=9 Hz, aromatic protons), 6.95-7.20(15H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 32.89(t), 55.16 (q), 57.89(t), 58.87(t), 68.22(d), 71.19(t), 71.58 (t), 81.13(d), 83.43(d), 113.54(d), 126.80-131.96 (aromatic carbons), 139.97(s), 138.68(s); ms *m/z* 492(M^+-1), 372(M^+-$MeOC_6H_4CH_2$)) and a small amount of a monobenzyl hydroxy compound ((2*R*,3*S*,4*S*)-*N*-benzyl-3- or 4-benzyloxy-4- or 3-hydroxy-2-(4-methoxybenzyl)pyrrolidine, 6 mg; ^{1}H nmr ($CDCl_3$): 2.39(1H, dd, J=3 and 12 Hz, CH), 2.75-3.10(4H, m, CH_2, CH, OH), 3.30-3.95(3H, m, 3x

CH), 3.55 and 4.10(2H, AB, J=13 Hz, NCH_2Ph), 3.74(3H, s, OMe), 4.40(2H, s, OCH_2Ph), 6.78 (2H, d, J=9 Hz, aromatic protons), 7.00-7.35(12H, m, aromatic protons); ^{13}C nmr ($CDCl_3$): 31.92(t), 55.16(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).

(2*R*,3*S*,4*S*)-*N*-Benzyloxycarbony-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 N_2 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 CH_2Cl_2 (4 ml) and aqueous 5% Na_2CO_3 (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), $[\alpha]_D$ -8.7°(c=0.5, MeOH) ; ^1H nmr ($CDCl_3$): 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, OCH_3), 3.80-4.30(3H, m, 3xCH), 5.15(2H, s, OCH_2Ph), 6.78(2H, d, J=8.3 Hz), 6.90-7.45(10H, m, aromatic protons). Anal. Calcd for $C_{20}H_{23}NO_5$: 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

1. a) G. W. J. Fleet, S. J. Nicholas, P. W. Smith, S. V. Evans, L. E. Fellows, and R. J. Nash, *Tetrahedron Lett.*, 1985, **26**, 3127; b) G. W. J. Fleet and P. W. Smith, *Tetrahedron*, 1987, **43**, 971.
2. N. Ikota and A. Hanaki, *Heterocycles*, 1987, **26**, 2369.
3. a) K. B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lubben, E. Manoury, Y. Ogino, T. Shibata, and T. Ukita, *J. Org. Chem.*, 1991, **56**, 4585; b) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K-S. Jeong, H.-L. Kwong, K. Morikawa, Z-M. Wang, D. Xu, and X-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768; c) K. Morikawa and K. B. Sharpless, *Tetrahedron Lett.*, 1993, **34**, 5575.
4. The reaction of **2** with AD-mix-β in the presence of methanesulfonamide (1 equiv.) in *tert*-BuOH-H_2O (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.
5. a) A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480; b) R. E. Ireland and

D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198.
6. N. Ikota, *Tetrahedron Lett.*, 1992, **33**, 2553.
7. a) A. Welter, J. Jadot, G. Dardenne, M. Marlier, and J. Casimir, *Phytochemistry*, 1976, **15**, 747; b) S. V. Evans, L. E. Fellows, T. K. M. Shing, and G. W. J. Fleet, *Phytochemistry*, 1985, **24**, 1953.
8. A. B. Reitz and E. W. Baxter, *Tetrahedron Lett.*, 1990, **31**, 6770.
9. H. C. Brown and S. Narasimhan, *J. Org. Chem.*, 1982, **47**, 1604.
10. N. Ikota, *Chem. Pharm. Bull.*, 1989, **37**, 3399.
11. D. N. Kursanov, Z. N. Parnes, and N. M. Loin, *Synthesis*, **1974**, 633.
12. Some representative synthesis of (-)-anisomycin : a) C. M. Wong, J. Buccini, I. Chang, J. T. Raa, and K. Schwenk, *Can. J. Chem.*, 1969, **47**, 2421; b) I. Felner and K. Shenke, *Helv. Chim. Acta*, 1970, **53**, 754; c) A. Iida, N. Yamazaki, and C. Kibayashi, *J. Org. Chem.*, 1986, **51**, 1069 ; d) T.Shono and N. Kise, *Chem. Lett.*, **1987**, 697; e) A. I. Meyers, B. Dupre, *Heterocycles*, 1987, **25**, 113; f) H. H. Baer and M. Zamkanei, *J. Org. Chem.*, 1988, **53**, 4786; g) S. Jegham and B. C. Das, *Tetrahedron Lett.*, 1989, **30**, 4419; h) R. Ballini, E. Marcantoni, and M. Petrini, *J. Org. Chem.*, 1992, **57**, 1316.
13. V. S. Rao and A. S. Perlin, *Carbohydro. Res.*, 1980, **83**, 175.

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