SYNTHESIS OF (2R,3S,4R)-3,4-DIHYDROXY-2-HYDROXYMETHYL-PYRROLIDINE AND (2S,3R,4S,5S)-3,4-DIHYDROXY-2,5-DI-HYDROXYMETHYLPYRROLIDINE FROM (R)-SERINE AND D-RIBONO-LACTONE

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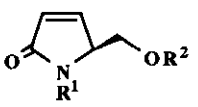
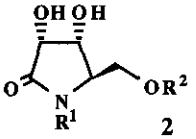
Abstract ——(2R,3S,4R)-3,4-Dihydroxy-2-hydroxymethyl-pyrrolidine derivative (9, 10) and (2S,3R,4S,5S)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine derivatives (16, 17) were synthesized stereoselectively from (R)-serine and D-ribonolactone, respectively.

Polyhydroxylated pyrrolidines are potent competitive inhibitors of glycosidases and have potential therapeutic utility in the treatment of various diseases such as viral infections.[1] Therefore, the synthesis of polyhydroxylated pyrrolidines has been the subject of considerable recent research.[2] In connection with our studies[3] on the synthesis of polyhydroxylated pyrrolidines, piperidines, indolizidine alkaloids, and pyrrolizidine alkaloids, we describe here the synthesis of (2R,3S,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine derivatives (9, 10), (2S,3R,4S,5S)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine derivatives (16, 17), and (2R,3R,4S)-3,4-dihydroxyproline (18b) from (R)-serine and D-ribonolactone derivative, respectively.[4]

We have reporetd that cis-dihydroxylation of α,β-unsaturated lactam (1),



1



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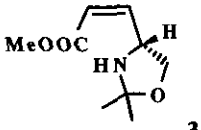

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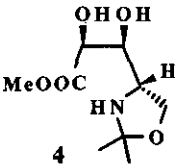

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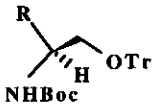
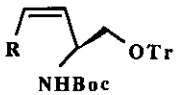
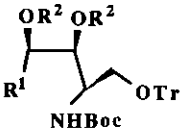


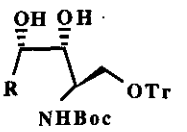
5a: R=COOMe
b: R=CH_2OH



6a: R=COOMe
b: R=CH_2OH
c: R=CH_2OTBS

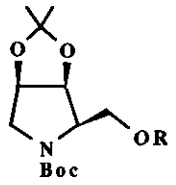


7a: R^1=COOMe,R^2=H
b: R^1=CH_2OTBS,R^2=H
c: R^1=COOMe,R^2+R^2=isoprop.
d: R^1=CH_2OTBS,R^2+R^2=isoprop.
e: R^1=CH_2OH,R^2+R^2=isoprop.

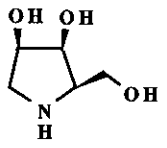


8a: R=COOMe
b: R=CH_2OTBS

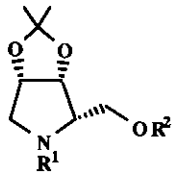
Tr: -$C(C_6H_5)_3$
MOM: -CH_2OMe
Boc: -$COOCMe_3$
TBS:-$SiMe_2CMe_3$



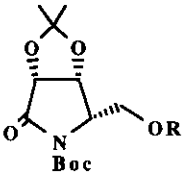
9a: R=Tr
b: R=H



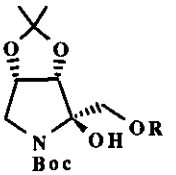
HCl
10



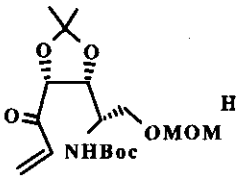
11a: R^1=H,R^2=Tr
b: R^1=Boc,R^2=Tr
c: R^1=Boc,R^2=H
d: R^1=Boc,R^2=TBS
e: R^1=Boc,R^2=MOM



12a: R=Tr
b: R=TBS
c: R=MOM



13a: R=Tr
b: R=TBS
c: R=MOM



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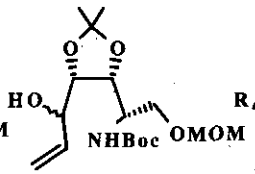

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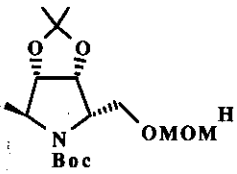
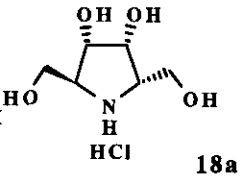


16a: R=vinyl
b: R=CH_2OH



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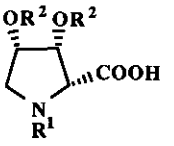

18a: R^1=Boc,
R^2+R^2=isoprop.
b: R^1=R^2=H

prepared from (S)-pyroglutaminol, gave a diol (2) predominantly.[3a] On the other hand, the steric course of cis-dihydroxylation of the Z-olefin (6) derived from (R)-serine might be different from the case of the α,β-unsaturated lactam (1) due to the allylic strain.[5] Recently, Koskinen et al.[6] reported that cis-dihydroxylation of Z-olefin (3) derived from (S)-serine with a catalytic amount of OsO_4 gave a diol (4) selectively.

The Z-olefin (6a) was prepared from N-tert-butoxycarbonyl-O-trityl-(R)-serine methyl ester (5a) by reduction with diisobutylaluminum hydride (DIBALH) followed by Z-selective Horner-Emmons reaction[7,8] in 65% yield. The olefin (6c) was obtained from 6a by DIBALH reduction followed by tert-butyldimethylsilylation using standard procedure[9] in 75% yield. In contrast with the result by Koskinen, cis-dihydroxylation of 6a and 6c with OsO_4 (0.15 eq.) in the presence of N-methylmorpholine N-oxide in acetone-H_2O gave 7a and 7b predominantly. Thus, the reaction of 6a at 0 °C gave 7a and 8a in a 2.2:1 ratio (the ratio was determined by ^1H nmr analysis) in 83% yield, while a higher diastereoselectivity was observed in the reaction of 6c at -10 °C (7b:8b=4.2:1, 65% yield). The structures of the major products (7a) and (7b) were confirmed by derivation to the known compound (10). Protection of the diol (7a) with isopropylidene group (2,2-dimethoxypropane, acetone, p-TsOH) followed by reduction of 7c with $NaBH_4$ in EtOH gave an alcohol (7e) in 57% yield. After protection of the diol of 7b with isopropylidene group, removal of the silyl group of 7d with tetrabutylammonium fluoride in tetrahydrofuran (THF) afforded the alcohol (7e) in 79% yield. Mesylation of 7e (methanesulfonyl chloride, triethylamine, methylene chloride) followed by cyclization with potassium tert-butoxide in THF furnished the pyrrolidine (9a), which was transformed to the hydrochloride of (2R,3S,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine (10, mp 155-156 °C, $[\alpha]_D$ +20.6° (H_2O), lit.,[2a] mp 157-159 °C, $[\alpha]_D$ +18.8° (H_2O)) by hydrolysis (MeOH-10% HCl, 70 °C) in 71% yield. Selective removal of the trityl group of 9a (MeOH:concentrated HCl=40:1) gave the alcohol (9b), useful intermediate for the synthesis of (-)-swainsonine, in 68% yield. Optically active 3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine derivatives were used for asymmetric reaction as chiral catalyst ligand[10] and for the synthesis of stereoisomer of alexine.[3e] Synthesis of (2S,3R,4S,5S)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine derivatives (16b, 17) was examined by employing (2S,3R,4S)-3,4-dihydroxy-2-hydroxymethylpyrrolidine

derivative (11a), prepared from O-trityl-D-ribonolactone[11] in the same manner as previously reported,[3d] with the use of similar strategy to prepare (2R,3R,4S,5R)-derivative.[3e] After N-tert-butoxycarbonylation of 11a with di-tert-butyl dicarbonate and triethylamine, oxidation of 11b with RuO_2 in the presence of $NaIO_4$[12] gave the lactam (12a) in quite low yield (6%) with the formation of hydroxy compound (13a, 5%) and 80% recovery of 11b. Therefore, the trityl group was exchanged by methoxymethyl and tert-butyldimethylsilyl group after selective cleavage of the trityl group of 11b. Oxidation of 11d with RuO_2 in the presence of $NaIO_4$ gave mostly 13b in 65% yield with 7% yield of the lactam (12b), while the reaction of 11e gave an inseparable mixture of 12c and 13c (about 1:1), which was reacted with vinylmagnesium bromide[13] in THF at -50 °C to afford the enone (14) in 37% yield after column chromatography on silica gel. Then, the enone (14) was reduced with $NaBH_4$ in the presence of $CeCl_3$[14] in EtOH to give allylic alcohol (15) as a single isomer (the configuration of the new chiral center was not determined). Mesylation of the alcohol (15) followed by cyclization with potassium tert-butoxide in THF gave 5-vinylpyrrolidine (16a) in 74 % yield from 14. This cyclization may proceed via the allylic cation derived from mesylate to afford the pyrrolidine (16a), which might be thermodynamically stable isomer. Ozonolysis of 16a followed by reductive workup with $NaBH_4$ gave the alcohol (16b) in 87% yield, which could be useful for the preparation of 1,3-diepialexine. The structure of 16b was confirmed by the conversion of 16b into the hydrochloride of (2S,3R,4S,5S)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine (17, mp 191-192 °C, $[\alpha]_D$ -51.3° (H_2O), lit. for (2R,3S,4R,5R)-derivative,[3e] mp 190-192 °C, $[\alpha]_D$ +51.5° (H_2O)) by acidic hydrolysis (MeOH-10% HCl, 70 °C).

(2R,3R,4S)-3,4-Dihydroxyproline (18b),[15] which has not yet been synthesized, was also obtained from 11c by oxidation using the method of Sharpless[16] (cat. $RuCl_3$, $NaIO_4$, MeCN-CCl_4-H_2O) followed by removal of the protecting groups of 18a with aqueous trifluoroacetic acid in 50% yield.

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. ^{1}H and ^{13}C nmr spectra were recorded on a JEOL JNM-FX100 (100 MHz) spectrometer in $CDCl_3$. 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 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-[(1S)-3-Methoxycarbonyl-1-trityloxymethyl-2(Z)-propenyl]carbamate (6a) DIBALH (2.7 ml of a 1.5 M solution in toluene) was added to a solution of N-tert-butoxycarbonyl-O-trityl-(R)-serine methyl ester (5a, 922 mg, 2 mmol) in ether (10 ml) at -78 °C. After being stirred at -78 °C for 40 min, MeOH (1 ml) was added, followed by ether (30 ml) and saturated aqueous sodium tartarate (40 ml). The organic layer was separated and washed with saturated aqueous NaCl. Drying followed by evaporation gave a crude aldehyde, which was reacted with the Clark Still phosphonate[7] using potassium bis(trimethylsilyl)amide as the base to give 6a (633 mg, 65%) after column chromatography (AcOEt:hexane=1:4 as an eluent) as an oil, $[\alpha]_D^{20}$ +13.0°(c=1.6); ir ν_{max}(neat) 1716, 1660, 1600 cm^{-1}; ^{1}H nmr: 1.41(9H, s, t-Bu), 3.33(2H, m, CH_2), 3.64(3H, s, $COOCH_3$), 5.09-5.52 (2H, m, CH, NH), 5.83(1H, d, J=11.5 Hz, CH=), 6.29(1H, dd, J=8.0, 11.5 Hz, CH=), 7.10-7.52(15H, m, ArH); ^{13}C nmr: 28.17(q), 49.46(d), 51.12(q), 65.44(t), 79.83(s), 86.64(s), 119.93(d), 143.36(s), 148.87(d), 155.10(s), 165.63(s); ms m/z 487 (M^+).

1,1-Dimethylethyl N-[(1S)-4-tert-Butyldimetylsilyloxy-1-trityloxymethyl-2(Z)-butenyl]carbamate (6c) DIBALH (0.9 ml of 1.5 M solution in toluene) was added to a solution of 6a (300 mg, 0.62 mmol) in methylene chloride (5 ml) at -78 °C. After being stirred at -78 °C for 30 min, the mixture was

quenched with 10% aqueous NH_4Cl (5 ml), and then extracted with methylene chloride. The oaganic layer was washed with H_2O. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt: hexane=1:1) gave the alcohol 6b (226 mg, 80%) as an oil, $[\alpha]_D^{20}$ +14.1°(c= 1.5); ir ν_{max} (neat) 3353, 1693, 1045 cm^{-1}; ^1H nmr: 1.40(9H, s, t-Bu), 3.17(2H, m, CH_2), 3.42(1H, br s, OH), 3.70-4.65(3H, m, CH_2, CH), 4.94(1H, d, J=8.0 Hz, NH), 5.45-5.99(2H, m, CH=CH), 7.04-7.52(15H, m, ArH); ^{13}C nmr: 28.26(q), 47.80(d), 57.60(q), 65.20(t), 79.82(s), 86.64(s), and 126.99-128.40(ArC), 129.87(d), 130.93(d), 143.41(s), 155.49(s); ms m/z 533(M^+), 518(M^+-CH_3). 6c was obtained in 94% yield as an oil after column chromatography (AcOEt:hexane=1:4) according to the reported procedure.[9] $[\alpha]_D^{20}$ -9.3°(c=1); ir ν_{max} (neat) 1710, 1600 cm^{-1}; ^1H nmr: 0.03(6H, s, 2xCH_3), 0.86(9H, s, t-Bu), 1.42(9H, s, t-Bu), 3.10(2H, m, CH_2), 4.26(2H, m, CH_2), 4.50(1H, m, CH), 4.76(1H, d, J=8 Hz, NH), 5.30-5.80(2H, m, CH=CH), 7.05-7.57(15H, m, ArH); ^{13}C nmr: -5.21(q), 18.23(s), 25.88(q), 28.36(q), 48.58(d), 59.55(q), 65.93(t), 79.24(s), 86.45(s), 126.94-128.55 (ArC), 127.92(d), 132.59(d), 143.66(s), 154.91(s); ms m/z 516 (M^+-t-Bu).

cis-Dihydroxylation of 6a and 6c with OsO_4. A mixture of 6a (400 mg, 0.82 mmol), OsO_4 (31 mg, 0.12 mmol) and NMO monohydrate (144 mg, 1.1 mmol) in acetone-H_2O (2:1, 5 ml) was stirred at 0 °C for 13 h. After addition of sodium hydrosulfite (300 mg), the mixture was diluted with AcOEt and washed with half-saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane= 2:1) gave 7a (239 mg, 56%) and 8a (116 mg, 27%) as an oil. 7a: $[\alpha]_D^{20}$ +4.9° (c=1); ir ν_{max} (neat) 3442, 1737, 1080 cm^{-1}; ^1H nmr: 1.43(9H, s, t-Bu), 3.14-3.49(3H, m, CH_2, OH), 3.75(3H, s, OCH_3), 3.86-4.19(3H, m, 3xCH), 4.47(1H, br s, OH), 5.04(1H, d, J=9.0 Hz, NH), 7.05-7.50(15H, m, ArH); ^{13}C nmr: 28.17(q), 50.39(d), 52.43(q), 64.18(t), 71.00(d), 72.85(d), 80.31(s), 86.98(s), 127.04-128.35(ArC), 143.21(s), 157.01(s), 173.38(s); ms m/z 520 (M^+-1). 8a: $[\alpha]_D^{20}$ -21.2°(c=0.8); ^1H nmr: 1.40(9H, s, t-Bu), 2.77(1H, s,

OH), 2.90-3.18(2H, m, CH_2), 3.73(3H, s, OCH_3), 3.70-4.36(4H, m, 3xCH, OH), 4.79(1H, d, J=9.0 Hz, NH), 7.07-7.50(15H, m, ArH); ^{13}C nmr: 28.36(q), 51.26(d), 52.34(q), 62.52(t), 72.95(d), 80.26(s), 86.79(s), 127.07-128.40 (ArC), 143.36(s), 155.98(s), 172.31(s); ms m/z 520 (M^+-1).

cis-Dihydroxylation of 6c (300 mg, 0.52 mmol) was performed at -10 °C for 15 h in the similar manner described above for the preparation of 7a to afford 7b (182 mg, 52%) and 8b (42 mg, 13%) after column chromatography (AcOEt:hexane=1:3). 7b: mp 130 °C(ether-hexane); $[\alpha]_D^{20}$ -10.0°(c=1, MeOH); ir ν_{max}(nujol) 3351, 1781, 1070 cm^{-1}; ^1H nmr: 0.05(6H, s, 2xCH_3), 0.92(9H, s, t-Bu), 1.43(9H, s, t-Bu), 3.07-3.58(4H, m), 3.58-3.91(4H, m), 3.95-4.20(1H, m, CH), 4.95(1H, d, J=9.0 Hz, NH), 6.92-7.52(15H, m, ArH); ^{13}C nmr: -5.56(q), 18.18(s), 25.83(q), 28.31(q), 50.70(d), 65.93(t), 69.49(t and d), 74.66(d), 79.96(s), 86.76(s), 127.04-128.50(ArC), 143.46(s), 155.45(s). Anal. Calcd for $C_{35}H_{49}NO_6Si$: C, 69.16; H, 8.13; N, 2.30. Found: C, 68.89; H, 8.10; N, 2.08. 8b: $[\alpha]_D^{20}$ -6.5°(c=1); ir ν_{max}(neat) 3445, 1706, 1060 cm^{-1}; ^1H nmr: 0.06(6H, s, 2xCH_3), 0.88(9H, s, t-Bu), 1.46(9H, s, t-Bu), 2.61(1H, br s, OH), 3.02-3.48(3H, m, CH_2, OH), 3.48-4.58(5H, m, CH_2, 3xCH), 5.30(1H, d, J=10.0 Hz, NH), 7.15-7.59(15H, m, ArH); ^{13}C nmr: -5.51(q), 18.18(s), 25.73(q), 28.31(q), 51.46(d), 63.35(t), 64.03(t), 71.34(d), 73.68(d), 79.48(s), 87.18(s), 127.14-128.40(ArC), 143.27(s), 155.59(s); ms m/z 607 (M^+), 550 (M^+-CH_3).

1,1-Dimethylethyl N-[(1R,2S,3R)-4-Hydroxy-2,3-isopropylidenedioxy-1-trityloxymethylbutyl]carbonate (7e) A mixture of 7a (200 mg, 0.38 mmol) and 2,2-dimethoxypropane (2 ml, 16 mmol) in acetone (2 ml) was stirred in the presence of a catalytic amount of p-TsOH at room temperature for 1 h. After dilution with AcOEt, the mixture was washed with saturated aqueous $NaHCO_3$ and H_2O. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:3) gave 7c (151 mg, 71%) as an oil; $[\alpha]_D^{20}$ -14.9°(c=0.8); ir ν_{max} (neat) 1750, 1690 cm^{-1}; ^1H nmr: 1.30(3H, s, CH_3), 1.37(9H, s, t-Bu), 1.54(3H, s, CH_3), 2.86-3.20(2H, m,

CH_2), 3.69(3H, s, OCH_3), 4.17(1H, m, CH), 4.43-4.86(3H, m, NH, 3xCH), 7.00-7.51(15H, m, ArH); ^{13}C nmr: 24.71(q), 26.41(q), 28.31(q), 48.39(d), 52.14(q), 64.13(t), 74.85(d), 75.87(d), 79.33(s), 86.55(s), 110.03(s), 126.84-128.59(ArC), 143.70(s), 154.77(s), 169.78(s). A mixture of 7c (120 mg, 0.21 mmol) and $NaBH_4$ (80 mg, 2.1 mmol) in EtOH (3 ml) was stirred at room temperature for 2 h, and then diluted with AcOEt. After washing with half-saturated aqueous NaCl, drying followed by evaporation and purification of the residue by column chromatography (AcOEt;hexane=2:3) gave 7e (89 mg, 80%) as crystals, mp 83-84°C(AcOEt-hexane), $[\alpha]_D^{20}$ -18.0° (c=1.8); ir ν_{max} (nujol) 3355, 1716, 1070 cm^{-1}; ^1H nmr: 1.29(3H, s, CH_3), 1.41(12H, s, t-Bu, CH_3), 2.68(1H, br s, OH), 3.10(2H, d, J=6 Hz, CH_2), 3.52-3.75(2H, m, CH_2), 3.75-4.45(3H, m, 3xCH), 4.83(1H, d, J=10 Hz, NH), 7.08-7.51(15H, m, ArH); ^{13}C nmr: 24.66(q), 27.24(q), 28.31(q), 48.58(d), 61.35(t), 64.96 (t), 74.75(d), 77.63(d), 79.92(s), 86.55(s), 108.03(s), 126.89-128.58 (ArC), 143.66(s), 155.86(s). Anal. Calcd for $C_{32}H_{39}NO_6$: C, 72.02; H, 7.37; N, 2.62. Found: C, 71.77; H, 7.45; N, 2.28.

1,1-Dimethylethyl N-[(1R,2S,3R)-4-tert-Butyldimethylsilyloxy-2,3-isopropylidenedioxy-1-trityloxymethylbutyl]carbonate (7d) This sample (374 mg, 90%) was obtained from 7b (390 mg, 0.65 mmol) after column chromatography AcOEt:hexane=1:4) in the similar manner as described in the preparation of 7c, $[\alpha]_D^{20}$ -26.2° (c=0.6); ir ν_{max} (neat) 1714 cm^{-1}; ^1H nmr: 0.02 (6H, s, 2xCH_3), 0.85(9H, s, t-Bu), 1.28(3H, s, CH_3), 1.39(12H, s, t-Bu, CH_3), 3.09(2H, d, J=6.0 Hz, CH_2), 3.68(2H, d, J=6.5 Hz, CH_2), 3.88-4.46 (3H, m, 3xCH), 4.81(1H, d, J=9.0 Hz, NH), 6.92-7.52(15H, m, ArH); ^{13}C nmr: -5.36(q), 18.27(s), 24.46(q), 25.88(q), 27.00(q), 28.36(q), 48.88(d), 62.28(t), 64.51(t), 75.19(d), 78.10(d), 79.04(s), 86.40(s), and 107.79(s), 126.80-128.59(ArC), 143.85(s), 154.71(s); ms m/z 640 (M^++1).

Preparation of 7e from 7d A mixture of 7d (350 mg, 0.56 mmol) in THF (2 ml) and tetrabutylammonium fluoride (1 ml of a 1 M solution in THF) was stirred at 0°C for 15 min, diluted with AcOEt and washed with H_2O. Drying

followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=2:3) gave 7e (235 mg, 88%) as crystals, mp 83-84 °C (AcOEt-hexane), $[\alpha]_D^{20}$ -17.6°(c=1). Spectral data (^{1}H and ^{13}C nmr) were identical with those obtained from 7a.

(2R,3S,4R)-N-tert-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethylpyrrolidine (9a) A mixture of 7e (230 mg, 0.43 mmol), methanesulfonyl chloride (64 mg, 0.55 mmol), and triethylamine (57 mg, 0.56 mmol) in methylene chloride (3 ml) was stirred at 0 °C for 30 min, and then diluted with AcOEt. After washing with saturated aqueous $NaHCO_3$ and H_2O, drying followed by evaporation gave a crude mesylate, which was dissolved in THF (4 ml). Potassium tert-butoxide (74 mg, 0.64 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 30 min. After dilution with AcOEt, the mixture was washed with half-saturatwd aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatagraphy (AcOEt:hexane=1:4) gave 9a (180 mg, 81%) as an oil, $[\alpha]_D^{20}$ -32.0° (c=1); ir ν_{max} (neat) 1687, 1217 cm^{-1}; ^{1}H nmr: 1.24(3H, s, CH_3), 1.27(3H, s, CH_3), 1.38(9H, s, t-Bu), 3.00-3.36(3H, m, CH, CH_2), 3.90(1H, m, CH), 4.27(1H, m, CH), 4.18-4.40(2H, m, 2xCH), 7.01-7.66(15H, m, ArH); ^{13}C nmr: 25.00(q), 26.17(q), 28.21(q), 49.90(d), 58.28(q), 61.35(t), 77.53(d), 79.48(d), 79.67(s), 86.50(s), 112.76(s), 126.65-128.65(ArC), 143.99(s), 153.89(s); ms m/z 515(M^+).

(2R,3S,4R)-N-tert-Butoxycarbonyl-5-hydroxymethyl-3,4-isopropylidenedioxypyrrolidine (9b) A mixture of 9a (120 mg, 0.23 mmol) and 2 ml of concentrated HCl-MeOH (1:40) was stirred at 0 °C for 30 min. After addition of 10% aqueous NaOH (1.5 ml), the mixture was diluted with AcOEt-benzene (3:1, 100 ml) and washed with saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:1) gave 9b (43 mg, 68%) as an oil, $[\alpha]_D^{20}$ -43.2°(c=1); ir ν_{max} (neat) 3417, 1681, 1049 cm^{-1}; ^{1}H nmr: 1.37(3H, s, CH_3), 1.50(9H, s, t-Bu), 1.53 (3H, s, CH_3), 3.45-3.70(2H, m, CH_2), 3.70-3.75(3H, m), 4.61-

4.97(3H, m); ^{13}C nmr: 24.71(q), 26.22(q), 28.26(q), 51.56(d), 61.38(t), 77.43(d), 80.35(d), 80.60(s), 112.28(s); ms m/z 273 (M^+).

Hydrochloride of (2R,3S,4R)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine (10) A mixture of 9a (50 mg, 0.1 mmol), 10% aqueous HCl (0.4 ml), and MeOH (0.4 ml) was stirred at 70 °C for 1 h. After removal of the methanol in vacuo, the aqueous layer was washed with AcOEt (x2), and then evaporated in vacuo to dryness. The residue was triturated with MeOH-ether to give 10 (12 mg, 75%) as crystals, mp 155-156 °C, $[\alpha]_D^{20}$ +20.6° (c=0.7, H_2O). Spectral data (^{1}H and ^{13}C nmr) were identical with those of the authentic sample.[2a,3a]

(2S,3R,4S)-3,4-Isopropylidenedioxy-5-trityloxymethylpyrrolidine (11a) This sample (multigrams) was obtained in 32% yield from O-trityl-D-ribonolactone by the similar procedure previously reported[3d] in the preparation of (2R,3S,4R)-derivative, mp 96-97 °C (AcOEt-hexane), $[\alpha]_D^{20}$ +35.2° (c=1). Spectral data (^{1}H and ^{13}C nmr) were identical with those of (2R,3S,4R)-derivative.

(2S,3R,4S)-N-tert-Butoxycarbonyl-3,4-isopropylidenedioxy-5-trityloxymethylpyrrolidine (11b) This sample was obtained in 88% yield after column chromatography (AcOEt:hexane=1:4) by treatment of 11a with di-tert-butyl dicarbonate and triethylamine in methylene chloride at room temperature for 1 h, $[\alpha]_D^{20}$ +33.1° (c=2). Spectral data (^{1}H and ^{13}C nmr) were identical with those of 9a.

(2S,3R,4S)-N-tert-Butoxycarbonyl-5-hydroxymethyl-3,4-isopropylidenedioxypyrrolidine (11c) This sample was obtained in 65% yield from 11b in the similar manner as described above for the preparation of 9b, $[\alpha]_D^{20}$ +44.1° (c=1).

(2S,3R,4S)-N-tert-Butoxycarbonyl-3,4-isopropylidenedioxy-5-methoxymethoxymethylpyrrolidine (11e) A mixture of 11c (900 mg, 3.3 mmol), N,N-diethylaniline (1.6 ml, 9.9 mmol) and chloromethyl methyl ether (800 mg, 9.9 mmol) in methylene chloride (10 ml) was stirred at room temperature for 24 h. After dilution with AcOEt, the mixture was washed with 5% aque-

ous HCl and saturated aqueous NaCl. Drying followed by evaporation and purificatipn of the residue by column chromatography gave 11e (816 mg, 78%) as an oil, $[\alpha]_D^{20}$ +54.3°(c=2), lit. for (2R,3S,4R)-derivative,[3d] $[\alpha]_D^{20}$ -53.8°(c=1.9). Spectral data (^{1}H and ^{13}C nmr) were identical with those of (2R,3S,4R)-derivative.

Oxidation of 11e with RuO_2 in the presence of $NaIO_4$ A mixture of 11e (800 mg, 2.53 mmol), RuO_2 hydrate (19 mg, 0.14 mmol), 10% aqueous $NaIO_4$ (20 ml), and AcOEt (10 ml) was stirred at room temperature for 2 h. After addition of AcOEt (80 ml), the organic layer was separated and treated with isopropanol (0.5 ml), and then washed with H_2O. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:1) gave a mixture of 12c and 13c (770 mg, about 1:1) as an oil.

1,1-Dimethylethyl N-[(1S,2R,3R)-2,3-isopropylidenedioxy-1-methoxymethoxymethyl-5-hexen-4-onyl]carbamate (14) Vinylmagnesium bromide (3.2 ml of 0.98 M solution in THF) was added to a solution of the mixture of 12c and 13c (0.77 g) in THF (5 ml) at -50 °C and the mixture was stirred at -50 °C for 2 h. After addition of saturated aqueous NH_4Cl, the mixture was diluted with AcOEt. The organic layer was washed with half-saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:4) gave 14 (335 mg, 37%) and 13c (402 mg, 47%) as an oil. 14: $[\alpha]_D^{20}$ +58.8°(c=0.6); ir ν_{max}(neat) 1718, 1612 cm^{-1}; ^{1}H nmr: 1.40(12H, s, t-Bu, CH_3), 1.66(3H, s, CH_3), 3.37(3H, s, OCH_3), 3.14-4.11(3H, m), 4.63(2H, s, OCH_2O), 4.26-4.91(3H, m), 5.68(1H, m, CH=), 6.06-6.40(1H, m, CH=), 6.60-7.11(1H, m, CH=); ^{13}C nmr: 23.68(q), 26.17(q), 28.26(q), 47.61(d), 55.16(q), 66.61(t), 76.94(d), 79.38(s), 79.72(s), 96.14(t), 109.50(s), 128.66(t), 131.04(d), 154.08(s). Anal. Calcd for $C_{17}H_{29}NO_7$: C, 56.81; H, 8.13; N, 3.90. Found: C, 56.46; H, 8.33; N, 3.68. 13c: $[\alpha]_D^{20}$ +4.0°(c=1.5, MeOH); ir ν_{max} (neat) 3432, 1707, 1167 cm^{-1}; ^{1}H nmr: 1.38(3H, s, CH_3), 1.49(9H, s, t-Bu), 1.52(3H, s, CH_3), 3.45(3H, s,

OCH_3), 3.34-3.94(3H, m, CH_2, OH), 4.00-5.26(2H, m), 5.31-5.91(3H, m), 4.76(2H, s, OCH_2O); ^{13}C nmr: 25.00(q), 26.56(q), 28.22(q), 53.51(t), 55.36(q), 70.22(t), 75.48(d), 80.94(s), 86.55(s), 87.10(d), 91.97(s), 97.41(t), 111.83(s), 154.94(s). Anal. Calcd for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.02. Found: C, 53.60; H, 8.29; N, 3.70.

Physical and spectral data of 12a, 13a, 11d, 12b, and 13b **12a**: mp 69-72 °C (AcOEt-hexane), $[\alpha]_D^{20}$ +20.9° (c=0.9); ir ν_{max} (nujol) 1768, 1713 cm^{-1}; ^1H nmr: 1.26(9H, s, t-Bu), 1.29(3H, s, CH_3), 1.39(3H, s, CH_3), 3.43(1H, dd, J=8.0, 10 Hz, CH_2O), 3.68(1H, dd, J=4.0, 8.0 Hz, CH_2O), 4.13(1H, m, CH), 4.59(1H, d, J=6.1 Hz, CH), 4.88(1H, m, CH), 7.10-7.59(15H, m, ArH); ^{13}C nmr: 25.97(q), 26.90(q), 27.68(q), 57.26(d), 60.33(t), 72.02(d), 76.94(d), 83.67(s), 86.88(s), 112.47(s), 126.99-128.70(ArC), 148.92(s), 171.48(s). **13a**: $[\alpha]_D^{20}$ -0.46° (c=3); ^1H nmr: 1.29(15H, s, 2xCH_3, t-Bu), 3.30-4.05(5H, m, 2xCH_2, OH), 4.59-4.84(2H, m, 2xCH), 7.07-7.64(15H, m, ArH); ^{13}C nmr: 25.24(q), 26.66(q), 28.26(q), 53.51(t), 65.15(t), 74.99(d), 80.74(s), 86.84(s and d), 91.95(s), 111.88(s), 126.84-128.79(ArC), 143.90(s), 154.57(s). **11d**: $[\alpha]_D^{20}$ +56.0° (c=0.3); ir ν_{max} (neat) 1699 cm^{-1}; ^1H nmr: 0.02(6H, s, 2xCH_3), 0.85(9H, s, t-Bu), 1.38(6H, s, 2xCH_3), 1.46(9H, s, t-Bu), 3.21(1H, dd, J=5.0, 12.0 Hz, CH), 3.57-4.10(4H, m, CH_2, 3xCH), 4.48-4.79(2H, m, 2xCH); ^{13}C nmr: -5.6(q), 18.12(s), 25.00(q), 25.68(q), 26.80(q), 28.17(q), 51.61(t), 60.08(t), 60.43(d), 76.99(d), 79.53(s and d), 84.79(s), 112.08(s), 146.48(s), 154.23(s). **12b**: mp 114-115 °C(hexane); $[\alpha]_D^{20}$ +12.0° (c=1); ir ν_{max} (nujol) 1790, 1714 cm^{-1}; ^1H nmr: 0.02(6H, s, 2xCH_3), 0.84(9H, s, t-Bu), 1.31(3H, s, CH_3), 1.39(3H, s, CH_3), 1.47(9H, s, t-Bu), 3.60-4.40(3H, m, CH_2, CH), 4.56-4.85(2H, m, 2xCH); ^{13}C nmr: -5.60(q), 18.33(s), 25.68(q), 26.95(q), 27.92(q), 58.28(d), 59.50(t), 71.63(d), 76.40(d), 83.77(s), 112.47(s), 149.65(s), 170.63(s). **13b**: $[\alpha]_D^{20}$ -17.0 (c=0.4); ir ν_{max} (neat) 3471, 1700, 1164 cm^{-1}; ^1H nmr: 0.02(6H, s, 2xCH_3), 0.82(9H, s, t-Bu), 1.37(6H, s, CH_3), 1.44(9H, s, t-Bu), 3.10-3.93(4H, m, 2xCH_2), 4.25-4.73(3H, m, 2xCH, OH); ^{13}C nmr: -5.40, -5.60(q), 18.18(s),

24.95(q), 25.73(q), 26.66(q), 28.21(q), 54.09(t), 63.74(t), 74.95(d), 80.45(s), 84.99(s), 86.25(d), 92.34(s), 111.54(s), 154.62(s).

1,1-Dimethylethyl N-[(1S,2R,3S)-4-Hydroxy-2,3-isopropylidenedioxy-1-methoxymethoxymethyl-5-hexenyl]carbamate (15) A mixture of 14 (300 mg, 0.84 mmol), $CeCl_3 \cdot 7H_2O$ (310 mg, 0.84 mmol), and $NaBH_4$ (63 mg, 1.65 mmol) in EtOH (6 ml) was stirred at 0 ℃ for 10 min, and then diluted with AcOEt. After washing with half-saturated aqueous NaCl, drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:2) gave 15 (285 mg, 95%) as an oil, $[\alpha]_D^{20}$ +25.1° (c=0.7); ir ν_{max} (neat) 3456, 1716, 1161 cm^{-1}; ^1H nmr: 1.40(3H, s, CH_3), 1.46(9H, s, t-Bu), 1.56(9H, s, CH_3), 2.55(1H, br s, OH), 3.36(3H, s, OCH_3), 3.48 (2H, m, CH_2), 3.81-4.47(4H, m, 4xCH), 4.62(2H, s, OCH_2O), 4.90(1H, d, J=8 Hz, NH), 5.25-6.10(3H, m, vinyl protons); ^{13}C nmr: 24.37(q), 26.61(q), 28.21(q), 48.34(d), 55.21(q), 67.54(t), 70.61(d), 74.02(d), 79.67(s and d), 96.35(t), 107.99(s), 119.34(t), 135.86(d), 154.86(s); ms m/z 362 (M^++1).

(2S,3R,4S,5S)-N-tert-Butoxycarbonyl-3,4-isopropylidenedioxy-2-methoxymethoxymethyl-5-vinylpyrrolidine (16a) This sample (147 mg, 78%) was obtained from 15 (200 mg, 0.55 mmol) after column chromatography (AcOEt:hexane=1:3) in the similar manner as described above in the preparation of 9a, $[\alpha]_D^{20}$ +69.7° (c=1.1); ir ν_{max} (neat) 1681 cm^{-1}; ^1H nmr: 1.37 (3H, s, CH_3), 1.45(9H, s, t-Bu), 1.55(3H, s, CH_3), 3.41(3H, s, OCH_3), 3.73-4.02(2H, m, CH_2), 4.27-4.60(3H, m, 3xCH), 4.69(2H, s, OCH_2O), 4.80(1H, m, CH), 5.03-5.30(2H, m, CH=), 5.49-6.03(1H, m, CH=); ^{13}C nmr: 24.85(q), 26.12(q), 28.17(q), 55.11(q), 60.04((d), 65.05(t), 66.03(d), 79.43(d), 80.02(s), 82.35(d), 96.78(t), 111.54(s), 115.69(t), 134.64(d). HR-ms m/z: Calcd for $C_{17}H_{30}NO_6$ (M^++1): 344.2072. Found: 344.2062.

(2S,3R,4S,5S)-N-tert-Butoxycarbonyl-5-hydroxymethyl-3,4-isopropylidenedioxy-2-methoxymethoxymethylpyrrolidine (16b) Ozone was bubbled to methylene chloride (5 ml) at -78 ℃, then a solution of 16a (125 mg, 0.36

mmol) in methylene chloride (3 ml) was added. Ozone was bubbled further 5 min at -78 °C. Then this solution was added to a solution of $NaBH_4$ (100 mg, 2.63 mmol) in EtOH (8 ml) at °0 C. The mixture was stirred at °0 C for 30 min, and then diluted with AcOEt-benzene (1:1, 100 ml). After washing with half-saturated aqueous NaCl, drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=2:1) gave 16b (110 mg, 87%) as an oil, $[\alpha]_D^{20}$ +54.1°(c=1.1); ir ν_{max}(neat) 3452, 1695, 1047 cm^{-1}; ^1H nmr: 1.32(3H, s, CH_3), 1.43(9H, s, t-Bu), 1.48(3H, s, CH_3), 3.34(3H, s, OCH_3), 3.57-4.33(7H, m, 2xCH_2, OH, 2xCH), 4.40-4.90(2H, m, 2xCH); ^{13}C nmr: 24.85(q), 26.17(q), 28.17(q), 55.02(q), 60.62(d), 62.38(t), 64.86(t), 65.15(d), 78.75(d), 80.45(s), 80.79(d), 96.49(t), 111.83(s), 154.47(s); ms m/z 348 (M^++1).

(2S,3R,4S,5S)-3,4-Dihydroxy-2,5-dihydroxymethylpyrrolidine Hydrochloride (17) This sample was prepared from 16b in 80% yield in the similar manner as described above in the preparation of 10; mp 191-192°C, $[\alpha]_D^{20}$ -51.3°(c=0.8, H_2O). Spectral data (^1H and ^{13}C nmr) were identical with those of the enantiomer of 17.[3e]

(2R,3R,4S)-3,4-Dihydroxyproline (18b) $RuCl_3$ (10 mg, 0.05 mmol) was added to a solution of 11c (100 mg, 0.37 mmol), $NaIO_4$ (320 mg, 1.5 mmol), 0.8 ml of MeCN, 0.8 ml of CCl_4, and 1.1 ml of H_2O. The mixture was stirred at room temperature for 30 min, and diluted with H_2O and ether. The organic layer was washed with saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:MeOH=7:1) gave 18a (75 mg, 72%) as crystals, mp 185-187°C(AcOEt-hexane); $[\alpha]_D^{20}$ +53.1°(c=0.25); ir ν_{max} (nujol) 2638, 1733, 1633 cm^{-1}; ^1H nmr: 1.28 (3H, s, CH_3), 1.33(9H, s, t-Bu), 1.41(3H, s, CH_3), 3.61-3.87(2H, m, CH_2), 4.46(1H, d, J=8.0 Hz, CH), 4.69-5.04(2H, m, 2xCH), 9.75(1H, br s, COOH); ^{13}C nmr: 24.80(q), 25.92(q), 28.02(q), 50.87(t), 63.15(d), 78.21(d), 79.19(d), 80.74(s), 113.44(s), 153.79(s), 173.77(s). Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.88. Found: C, 54.11; H, 7.51; N, 4.60.

18b (17 mg, 69%) was obtained by hydrolysis of 18a (50 mg, 0.17 mmol) with 3 ml of 80% aqueous trifluoroacetic acid,[15b] followed by purification by ion exchange chromatography (Dowex 50W-X8, H^+ form, eluted with 1N aqueous NH_4OH), mp 230-235 °C(decomp.), $[\alpha]_D^{20}$ +55.9° (c=0.6, H_2O), lit. for (2S,3S,4R)-derivative,[15a] mp above 220 °C(decomp.), $[\alpha]_D^{20}$ -56.8° (c=0.16, H_2O). Spectral data (^1H and ^{13}C nmr) were identical with those of (2S,3S,4R)-derivative reported.

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