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Stereoselective Synthesis of Alexine Stereoisomers from (*S*)-Pyroglutamic Acid

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Abstract: Four stereoisomers of alexine (1,7a-diepialexine (**1a**), 1,7,7a-triepialexine (**1b**), 1-epi-alexine (**30a**), and 1,7-diepialexine (**30b**)), the polyhydroxylated pyrrolizidine alkaloid, were synthesized from (*S*)-pyroglutamic acid derivative (**6**). © 1998 Elsevier Science Ltd. All rights reserved.

Alexines[1] are polyhydroxylated pyrrolizidine alkaloid with a carbon substituent at C-3 and five adjacent asymmetric carbons, and have been shown to possess interesting biological activities such as inhibitory activity toward glucosidase and antiviral activity. Alexine and its stereoisomers have been synthesized to evaluate the structural basis of biological activity from sugars as the starting materials.[2] In a continuation of our synthetic studies to utilize optically active pyroglutamic acid derivatives for natural product synthesis and asymmetric reaction, [3] we have already reported a stereocontrolled synthesis[4] of 1,7a-diepialexine **1a** and 1,7,7a-triepi-alexine **1b** *via* a none-carbohydrate based approach utilizing (*S*)-pyroglutamic acid derivative. The details of this work and further synthetic studies on alexine stereoisomers (**30a** and **30b**) are presented here.

According to our retrosynthetic analysis as shown in Scheme 1, **1a** could be obtained from **2**, which might be synthesized by alkylation of the aldehyde **3** derived from a protected 3,4-dihydroxy-2,5-dihydroxy-methylpyrrolidine derivative **4**. The polyhydroxylated pyrrolidine **4** could be in turn prepared from (*S*)-pyroglutamic acid. Since optically active 3,4-dihydroxy-2,5-dihydroxymethylpyrrolidines have interesting biological activities, the synthesis of (2*R*,3*R*,4*S*,5*R*)- and (2*R*,3*R*,4*S*,5*S*)-3,4-dihydroxy-2,5-dihydroxy-methylpyrrolidine derivatives (**13b** and **14b**) from (*S*)-pyroglutamic acid has been first examined as shown in Scheme 2. An enone **7** was obtained by the reaction of (3*R*,4*R*,5*R*)-1-(*tert*-butoxycarbonyl)-3,4-isopropylidenedioxy-5-trityloxymethyl-2-pyrrolidinone **6**,[3c] prepared from the unsaturated lactam **5** by dihydroxylation with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide followed by isopropylidenation, with vinylmagnesium bromide[5] in tetrahydrofuran (THF) at -40 - -50°C in 93% yield. Reduction of **7** with $NaBH_4$ in the presence of $CeCl_3$ in MeOH[6] gave an allylic alcohol **10** as a mixture of inseparable diastereomers in 91% yield. Ozonolysis of the allylic alcohol **10** followed by workup with $NaBH_4$ gave diols **11a** and **12a**, which were separated by column chromatography (**11a**: **12a** = 2.4:1). The both diols were converted to the corresponding *tert*-butyldimethylsilyl ethers **11b** and **12b** by *tert*-butyldimethylsilyl chloride (1.2 equiv.) and imidazole in dimethylformamide (DMF) in 48% and 19% yields from **10**, respectively. Silyl ethers **11b** and **12b** were converted to the mesylate by methanesulfonyl chloride

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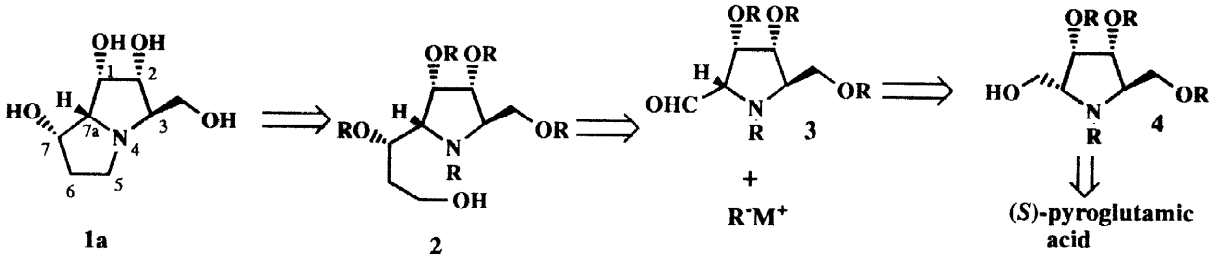
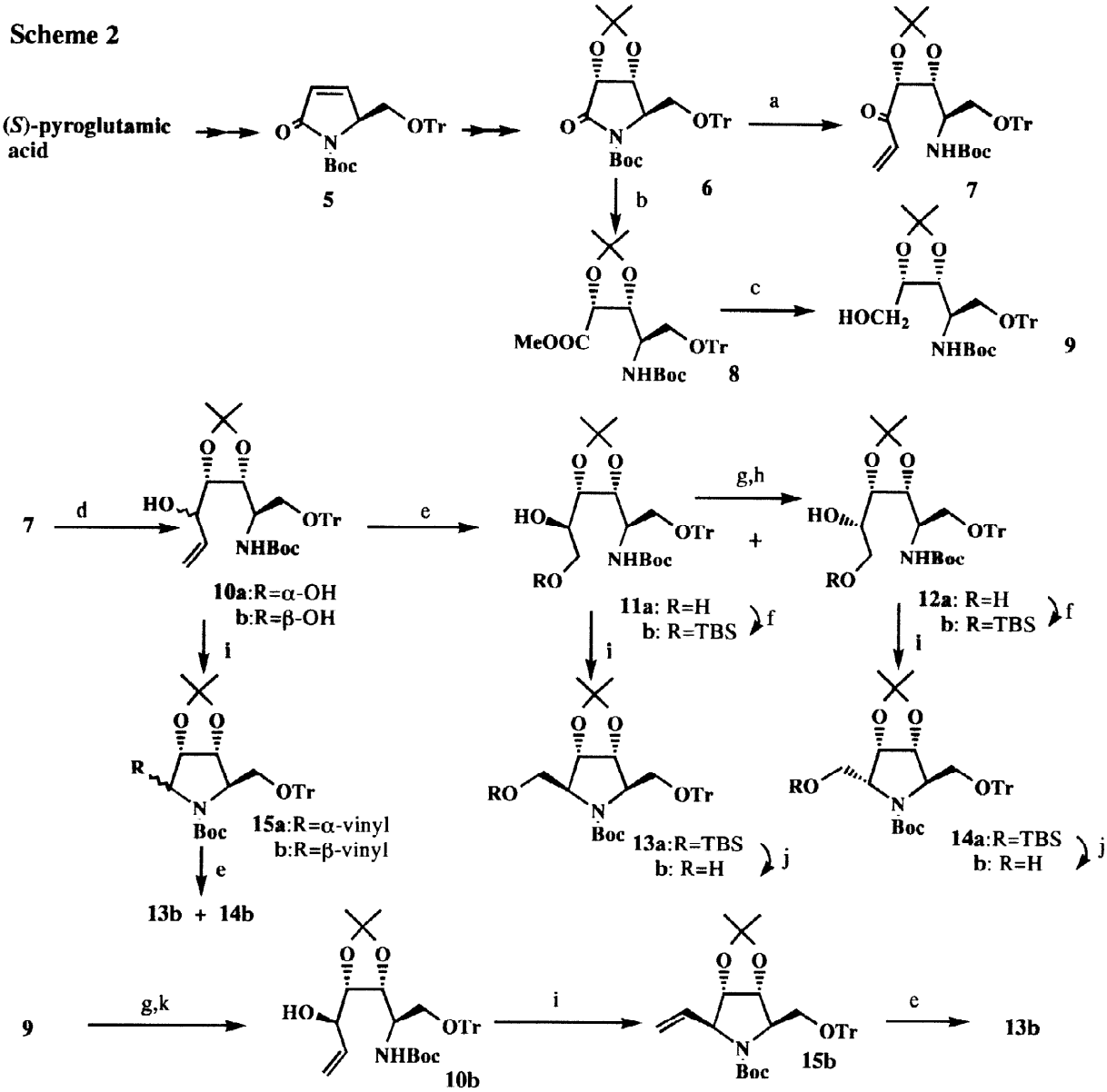
Scheme 1



Scheme 2



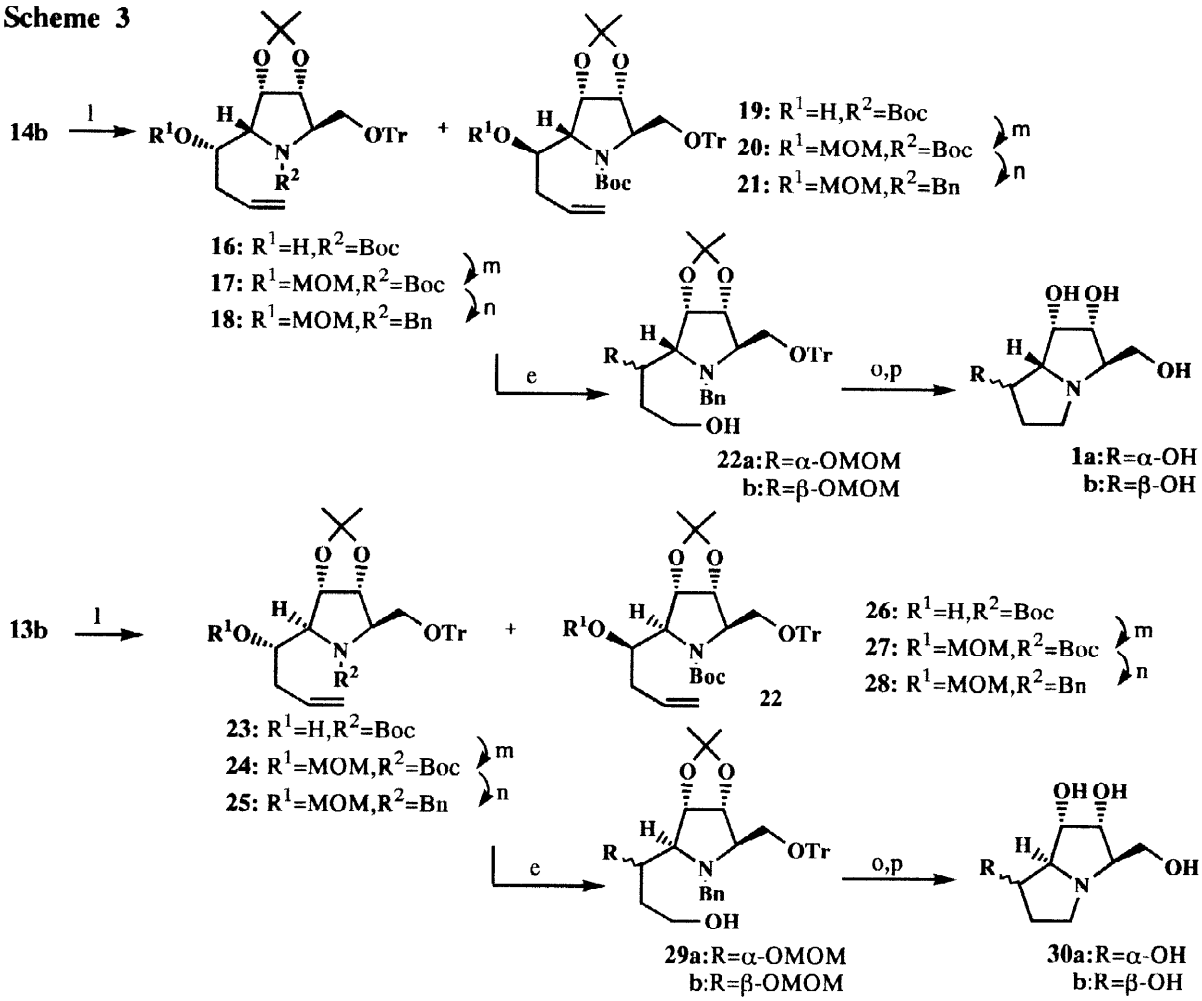
Reagents and conditions: (a) vinylmagnesium bromide, THF, -40 - -50°C; (b) aq LiOH, THF-MeOH, then CH_2N_2, ether; (c) $NaBH_4$, EtOH; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (e) O_3, CH_2Cl_2, -78°C, then $NaBH_4$, EtOH; (f) *tert*-butyldimethylsilyl chloride, imidazole, DMF, 0°C; (g) Swern oxidation, -20°C; (h) $NaBH_4$, EtOH, -78°C; (i) MsCl, TEA, CH_2Cl_2, then *tert*-BuOK, THF; (j) tetrabutylammonium fluoride, THF; (k) vinylmagnesium bromide, THF, -78°C

and triethylamine (TEA) in methylene chloride followed by cyclization with potassium *tert*-butoxide to yield the fully protected pyrrolidines **13a** and **14a** by intramolecular S_N2 displacement in 75% and 78% yields, respectively. Removal of the *tert*-butyldimethylsilyl group in **13a** and **14a** with tetrabutylammonium fluoride in THF gave the alcohols **13b** and **14b** in 78% and 82% yields, respectively. The structure of **13b** and **14b** and optical purity of **14b** were confirmed by the conversion of **13b** and **14b** into the hydrochlorides of the corresponding *meso*- and (2*R*,3*R*,4*S*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidines by acidic treatment.[3e,4] The diols **13b** and **14b** were also prepared from the allylic alcohol **10**. Mesylation of **10** followed by cyclization with potassium *tert*-butoxide in THF gave the pyrrolidine **15** as an inseparable diastereomeric mixture in 68% yield,[7] from which the diols **13b** and **14b** were isolated by treatment with ozone followed by $NaBH_4$ reduction in EtOH in 60% and 25% yields, respectively. Since (2*R*,3*R*,4*S*,5*R*)-5-hydroxymethylpyrrolidine **14b** was the desired compound for the synthesis of 1,7a-diepialexine, selective conversion of **11b** into **12b** was examined by employing oxidation-reduction procedure. Thus, oxidation of **11b** by the method of Swern [8] followed by reduction with $NaBH_4$ in EtOH at -78°C gave **12b** with very high diastereoselectivity (**12b**:**11b**=18:1) in 73% yield, which was already converted into the pyrrolidine **14b**.

On the other hand, (2*R*,3*R*,4*S*,5*S*)-5-hydroxymethylpyrrolidine **13b** was the intermediate for the preparation of 1-epialexines (**30**). Although **10b** was obtained predominantly by the reduction of enone **7**, the selective formation of **10b** was examined by vinylation of the aldehyde derived from an alcohol **9**. The lactam ring opening of **6** (aqueous lithium hydroxide in THF-MeOH) followed by esterification with diazomethane and subsequent reduction of the resulting methyl ester **8** with sodium borohydride gave the alcohol **9** in 79% yield from **6**. Swern oxidation of **9** followed by treatment with vinylmagnesium bromide in THF at -78°C gave the allylic alcohol **10b** in 71% yield, which was converted into the pyrrolidine **13b** *via* the 5-vinylpyrrolidine **15b** in 72 % yield.

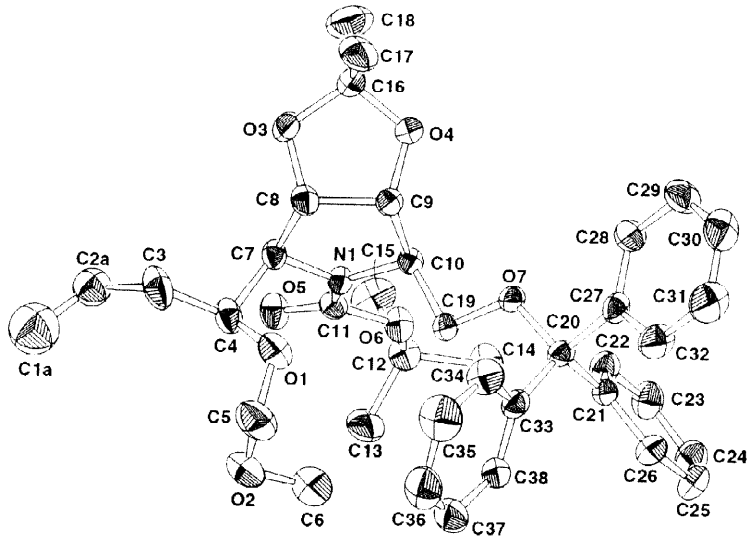
The construction of pyrrolizidine skeleton was shown in Scheme 3. The carbon unit required for the pyrrolizidine ring was introduced using a diastereoselective allylation of the aldehyde[9] derived from the alcohols **13b** and **14b**. Swern oxidation of the alcohol **14b** followed by treatment with either allylmagnesium chloride in THF or allyllithium in ether-THF at -78°C afforded **16** predominantly (allylmagnesium chloride: **16**/**19**=2.5/1, yield 84%; allyllithium: **16**/**19**=5.4/1, yield 81%; the ratio was determined by HPLC analysis (Waters, radial pak cartridge silica (10 μ), AcOEt:hexane=1:4 as eluants)).[10] The reaction of the aldehyde derived from **14b** with allyltrimethylsilane in the presence of $TiCl_4$ in methylene chloride at -78°C for 5 min afforded **16** selectively. However, the yield was very low due to the instability of the aldehyde toward strong acidic conditions. On the other hand, the aldehyde derived from **13b** was very unstable and only the trace of aldehyde was obtained after aqueous workup for Swern oxidation. Therefore, allylmagnesium chloride in THF was directly added to crude Swern oxidation mixture of **13b** in THF at -78°C[11] to afford allylic alcohols **23** and **26** in 52% and 25% yields after column chromatography, respectively. The stereochemistry of newly formed asymmetric carbon for the major isomer **23** was established to be *S* by x-ray crystallography of **23** after the conversion into its methoxymethyl ether **24** as shown in Figure 1.[12] The hydroxy group in **16** was protected as the methoxymethyl ether (chloromethyl methyl ether, *N*,*N*-diethyl-aniline, methylene chloride), and selective transformation of *N*-*tert*-butoxycarbonyl group in **17** into *N*-benzyl group by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate[13] in the presence of 2,6-lutidine followed by successive treatments with tetrabutylammonium fluoride in THF and benzyl

Scheme 3



Reagents and conditions: (l) Swern oxidation, then allylation, -78°C; (m) chloromethyl methyl ether, *N,N*-diethylaniline, CH_2Cl_2; (n) *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2, then (j), then BnBr, K_2CO_3, acetone; (o) MsCl, TEA, CH_2Cl_2, then 10% Pd-C, H_2, HCl- EtOH. (p) 10% HCl-MeOH, 70°C, then Dowex 50W-X8

Figure 1 ORTEP structure of **24**



bromide in the presence of potassium carbonate in acetone to furnish **18** in 58% yield. Ozonolysis of **18** followed by reductive workup with $NaBH_4$ gave the alcohol **22a** in 58% yield. Mesylation of **22a** gave a mesylate, which was spontaneously cyclized to give the pyrrolizidine derivative. After hydrogenation of the protected pyrrolizidine with 10% palladium on carbon in EtOH under atmospheric hydrogen in the presence of hydrogen chloride to remove *N*-benzyl group, acidic treatment with 10% HCl-MeOH (1:1) at 70°C to cleave the acetonide and trityl groups afforded the 1,7a-diepialexine **1a** ($[\alpha]_D^{20}$ +12.5° (c=0.6, H_2O), lit. $[\alpha]_D^{20}$ +12° (c=1.17, H_2O),[1c] $[\alpha]_D^{20}$ +8.5° (c=0.41, H_2O),[1d] $[\alpha]_D^{20}$ +13.3° (c=0.1, H_2O)[2c]) in 52% yield after purification by ion exchange chromatography (Dowex 50W-X8, H^+ form). Its spectral data (^1H and ^{13}C NMR) were identical with those reported for **1a**. By a parallel series of reactions, the allylic alcohols, **19**, **23**, and **26** were converted to 1,7,7a-triepialexine **1b** (oil, $[\alpha]_D^{20}$ +4.7° (c=0.5, H_2O), lit. $[\alpha]_D^{20}$ +11.7° (c=1, H_2O),[2c]), 1-epialexine **30a** ($[\alpha]_D^{20}$ +34.8° (c=0.5, H_2O), and 1,7-diepialexine **30b** ($[\alpha]_D^{20}$ +37.0° (c=0.7, H_2O), in 13-21% yields.

Since we have synthesized various optically active 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine derivatives,[3e,f] this approach utilizing (S)-pyroglutamic acid derivative could be efficient synthetic method for the preparation of the alexine stereoisomers.

Experimental

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 on a JASCO DIP-360 polarimeter. 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*R*,2*R*,3*R*)-2,3-isopropylidenedioxy-1-trityloxymethyl-5-hexen-4-onyl]carbamate (7). Vinylmagnesium bromide (4.8 ml of 0.98 M solution in THF) was added to a solution of (3*R*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3,4-isopropylidenedioxy-5-trityloxymethyl-2-pyrrolidinone (**6**, 1.74 g, 3.29 mmol) in THF (15 ml) at -40 - -50°C and the mixture was stirred at -40 - -50°C for 3 h. After addition of saturated aqueous NH_4Cl (10 ml), 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=1:3) gave the enone **7** (1.69 g, 93%) as crystals, mp 104-105°C (AcOEt-hexane), $[\alpha]_D^{20}$ -85.1° (c=0.4, $CHCl_3$); IR ν_{max} (nujol) 1700, 1240, 1170, 698, 623 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.36(12H, s, CH_3, *t*-Bu), 1.60(3H, s, CH_3), 3.16(1H, dd, *J*=9 and 3.4 Hz, CH), 3.30-3.58(1H, m, CH), 4.10-4.36(2H, m, NH, CH), 4.46-4.62(2H, m, 2xCH), 5.13(1H,dd, *J*=2 and 10.5 Hz, CH=C<u>H</u>2), 5.39(1H, dd, *J*=2 and 17 Hz, CH=C<u>H</u>2), 6.16(1H, dd, *J*=10.5 and 17 Hz, C<u>H</u>=CH2), 6.70-7.93(15H, m, aromatic protons) ^{13}C NMR δ:25.29(q), 25.73(q), 28.22(q), 61.16(d), 62.92(t), 80.16(s), 80.80(s), 84.06(s), 87.08(s), 88.40(s), 112.56(s), 114.32(t), 127.04, 127.72, and 128.46(aromatic carbons), 141.07(d), 143.36(s), 153.65 (s). *Anal.* Calcd for C_{34} $H_{39}NO_6$: C,73.22; H, 7.05; N, 2.35. Found: C, 72.98; H, 6.86; N. 2.31.

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*,4*S*)- and (1*R*,2*R*,3*S*,4*R*)-4-Hydroxy-2,3-isopropylidenedioxy-1-trityloxymethyl-5-hexenyl]carbamate(10). A mixture of **7** (1.48 g, 2.7 mmol), $CeCl_3$•$7H_2O$ (1.0 g, 2.7 mmol), and $NaBH_4$ (200 mg, 5.3 mmol) in MeOH (20 ml) was stirred at 0°C for 10 min, then at room temperature for 1 hr. After dilution with AcOEt, the mixture was washed with half-saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:3) gave an inseparable diastereomeric mixture of **10** (1.35 g, 91%) as an oil, $[\alpha]_D^{20}$ -38.5° (c=1.2, $CHCl_3$); IR ν_{max} (film) 3450, 1704, 1496, 1375, 1220, 756, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.39

(15H, s, *t*-Bu, 2xCH3), 2.35-2.50 and 2.90-3.00(1H, br s, OH), 3.00-3.25(1H, m, CH), 3.30-3.50(1H, m, CH), 3.90-4.60(4H, m, 4xCH), 4.70-5.10(1H, m, NH), 5.10-5.50(2H, m,CH=CH2), 5.77-6.16(1H, m, CH=CH2), 7.10-7.58(15H, m , aromatic protons). ^{13}C NMR δ: 24.70(q) and 25.33(q), 26.65(q) and 27.19 (q), 28.11(q), 49.89(d), 63.20(t) and 63.34(t) , 69.82(d) and 69.92(d), 75.57(d) and 76.30(d), 79.52(d) and 80.20(d), 79. 91(s), 86.30(s), 107.98(s), 115.92(t) and 116.22(t), 126.79, 127.57, and 128.40(aromatic carbons), 137.51(d) and 137.65(d), 143.70(s), 155.10(s) and 155.63(s). MS *m/z* 559 (M^+).

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-4,5-Dihydroxy-2,3-isopropylidenedioxy-1-(trityloxymethyl)pentyl]carbamate (11a and 12a). A solution of **10** (1.2 g, 2.15mmol) in CH_2Cl_2 (9 ml) was added at -78°C to 9 ml of CH_2Cl_2 saturated with ozone, and ozone was bubbled further 5 min at -78°C. Then, this solution was added to a suspension of $NaBH_4$ (570 mg, 15 mmol) in EtOH (9 ml) at 0°C. After being stirred at 0°C for 15 min, the mixture was diluted with AcOEt-benzene (1:1, 100 ml), and washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (AcOEt:hexane=3:2) to give **11a** (641 mg, 53%) and **12a** (266 mg, 22%). **11a** (polar isomer): mp 135-137°C, $[\alpha]_D^{20}$ -50.5° (c=1.1, $CHCl_3$); IR ν max (nujol) 1670, 1249, 1087, 758, 704 cm^{-1}; ^{1}H NMR($CDCl_3$) δ: 1.39(15H, br s, 2xCH3, *t*-Bu), 2.30(1H, br s, OH), 2.94(1H, br s, OH), 3.07-3.12(1H, m, CH), 3.40-3.44(1H, m, CH), 3.50-3.80 (3H, m, 3xCH), 4.13-4.40(3H, m, CH), 4.90(1H, d, *J*=10 Hz, NH), 7.15-7.40(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.85(q), 26.66(q), 28.17(q), 49.95(d), 63.20(t), 64.71(t), 68.81(d), 75.43(d), 77.24 (d), 79.87(s), 86.35(s), 108.18(s), 126.85, 127.62, and 128.45(aromatic carbons), 143.70(s).155.60(s). *Anal.* Calcd for $C_{33}H_{41}NO_7$: C,70.31; H, 7.33; N 2.49 . Found: C, 70.12 ; H, 7.56 ; N.2.38. **12a** (less polar isomer): $[\alpha]_D^{20}$ -28.9° (c=1.5, $CHCl_3$); IR ν max (film) 3429, 1699, 1450, 1375, 1220, 1057, 758, 704 cm^{-1}; ^{1}H NMR($CDCl_3$) δ: 1.38(15H, br s, 2xCH3, *t*-Bu), 2.34-2.90(2H, br s, 2xOH), 2.90-3.20(1H, m, CH), 3.26-3.51(1H, m, CH), 3.51-3.90(3H, m, 3xCH), 3.90-4.57(3H, m, CH), 5.00(1H, d, *J*=8 Hz, NH), 7.05-7.56(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.44(q), 27.53(q), 28.17(q), 50.00(d), 63.50(t), 64.32(t), 68.51(d), 76.36(d), 78.11(d), 80.31(s), 86.49(s), 108.03(s), 126.89, 127.67, and 128.50(aromatic carbons), 143.70(s), 156.23(s). MS *m/z* 563(M^+).

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-4-hydroxy-2,3-isopropylidenedioxy-5-*tert*-butyldimetylsilyloxy-1-(trityloxymethyl)pentyl]carbamate (11b and 12b). A mixture of **11a** (1.25 g, 2.2mmol), *tert*-butyldimethylsilyl chloride (435 mg, 2.9 mmol), and imidazole (635 mg, 7.2 mmol) in DMF (15 ml) was stirred at 0°C for 1 h. After dilution with AcOEt (2:1, 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=1:5) to give **11b** (1.37 g, 91%) as crystals. The compound **12b** was obtained from **12a** in 86% yield as an oil in the same manner as described above for the preparation of **11b**. **11b**: mp 54-56°C, $[\alpha]_D^{20}$ -39.8° (c=0.3, $CHCl_3$); IR ν max (nujol) 3432, 1710, 1500, 1373, 1252, 1166, 1075, 773, 702 cm^{-1} ; ^{1}H NMR($CDCl_3$) δ: 0.05(6H,s, 2xCH3), 0.88(9H, s, *t*-Bu), 1.38(15H, s, 2xCH3, *t*-Bu), 2.60(1H, br s, OH), 3.02-3.20(1H, m, CH), 3.34-3.89(4H, m, 4xCH)), 4.05-4.58(3H,m ,3xCH), 4.96(1H, d, *J*=7 Hz, NH), 7.07-7.59(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ:-5.46(q), -3.65(q), 18.18(s), 24.95(q), 25.78(q), 26.51(q), 28.21(q), 50.24(d), 63.25(t), 64.47(t), 68.95(d), 75.29(d), 75.83(d), 79.48(s), 86.30(s), 108.03(s), 126.80, 127.58, and 128.50(aromatic carbons), 143.80 (s).155.35(s). *Anal.* Calcd for $C_{39}H_{55}NSiO_7$: C,69.09; H, 8.18; N, 2.07. Found: C, 68.87; H, 8.39; N. 1.82. **12b**: $[\alpha]_D^{20}$ -28.1° (c=0.8, $CHCl_3$); IR ν max (film) 3434, 1710, 1500, 1373, 1252, 1075, 773, 702 cm^{-1}; ^{1}H NMR($CDCl_3$) δ: 0.07(6H,s, 2xCH3), 0.90(9H, s, *t*-Bu), 1.18(3H, s, CH3), 1.27(3H, s, CH3), 1.43(9H, s, *t*-Bu), 2.82(1H, br s, OH), 3.22-3.33(2H, m, 2xCH), 3.52-3.90(3H, m, 3xCH), 4.00-4.45(3H, m, 3xCH), 5.06(1H, d, *J*=7 Hz, NH), 7.10-7.62(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: -5.55(q), -3.65(q), 18.17(s), 25.49(q), 25.73(q), 27.34(q), 28.31(q), 50.29(d), 63.45(t), 64.47(t), 68.37(d), 76.78(d), 79.04(d), 86.20(s), 107.94(s), 126.65, 127.48, and 128.58(aromatic carbons), 143.85(s).155.25(s). HRMS *m/z* (M^+) calcd for $C_{39}H_{55}NSiO_7$ 677.3748, found 677.3737.

Conversion of 11b into 12b by Swern oxidation followed by reduction with $NaBH_4$. Dimethyl sulfoxide (660 mg, 8.52 mmol) was added at -78°C to a solution of oxalyl chloride (492 mg, 3.9

mmol)) in CH_2Cl_2 (12 ml). The mixture was stirred at - 78°C for 2 min, and then a solution of **11b** (1.2 g, 1.77 mmol) in CH_2Cl_2 (6 ml) was added at - 20°C over a period of 5 min. The whole was strirred at - 20 °C for 15 min, then TEA (1.24 ml, 8.86 mmol) was added and the reaction mixture was stirred at - 20°C for 5 min, then allowed to warm to room temperature. After addition of H_2O (10 ml), the aqueous layer was extracted with ether. The organic layers were washed with half-saturated aqueous NaCl. Drying followed by evaporation gave the crude ketone, which was dissolved in EtOH (4 ml) and treated with $NaBH_4$ (640 m g, 16.8 mmol) at -78°C for 20 min. 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=1:4) to give **12b** (876 mg, 73%) and **11b**(48 mg, 4%) as an oil. Physical and NMR data were identical with those of authentic samples.

(2*R*,3*R*,4*S*,5*S*)- and (2*R*,3*R*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine (13a and 14a). A mixture of **11b** (1.34 g, 1.98 mmol), methanesulfonyl chloride (300 mg, 2.64 mmol), and TEA (264 mg, 2.64 mmol) in CH_2Cl_2 (16 ml) was stirred at 0° C for 1 h. 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 (560 mg, 5 mmol) in THF (16 ml) at 0°C for 20 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 **13a** (978 mg, 75%) as an oil. The compound **14a** was obtained from **12b** in 78% yield as an oil in the same manner as described above for the preparation of **13a**. **13a**: $[\alpha]_D^{20}$ -18.9°(c=0.7, $CHCl_3$); IR ν_{max} (film) 1695, 1390, 1250, 1066, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: -0.13(6H,s, 2xCH_3), 0.76(9H, s, *t*-Bu), 1.28(12H, s, CH_3, *t*-Bu), 1.44(6H, s, 2xCH_3), 2.69-3.15(1H, m CH), 3.15-3.77(3H, m, 2xCH), 3.77-4.25(2H, m, 2xCH)), 4.61(2H,br s, 2xCH), 7.11-7.55(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: -5.51(q), 18.18(s), 25.44(q), 25.83(q), 27.29(q), 28.17(q), 62.18(t), 63.35(t), 64.37(d), 65.74(d), 79.57(s), 81.14(d), 82.40 (d), 86.49(s), 111.30(s), 126.84, 127.62, and 128.50(aromatic carbons), 143.468(s).153.89(s). HRMS *m/z* (M^+) calcd for $C_{39}H_{53}NSiO_6$ 659.3642, found 659.3613. **14a**: $[\alpha]_D^{20}$ -37.9° (c=0.5, $CHCl_3$); IR ν_{max} (film) 1697, 1375, 1084, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 0.05(6H,s, 2xCH_3), 0.88(9H, s, *t*-Bu), 1.27 (12H, s, CH_3, *t*-Bu), 1.42(3H, s, CH_3), 2.82-3.17(1H, m CH), 3.17-3.45(1H, m, CH), 3.60-4.22(4H, m, 4xCH)), 4.33-4.98(2H,m, 2xCH), 6.89-7.75(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: -5.55(q), -5.31(q), 18.13(s), 24.81(q), 25.78(q), 26.31(q), 28.21(q), 59.89(t), 63.45(t), 63.55(d), 64.81(d), 79.33(s), 80.26(d), 86.94(s), 110.52(s), 126.84, 127.67, and 128.35(aromatic carbons), 143.41(s).154.08(s). HRMS *m/z* (M^+) calcd for $C_{39}H_{53}NSiO_6$ 659.3642, found 659.3624.

(2*R*,3*R*,4*S*,5*S*)- and (2*R*,3*R*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-hydroxymethylpyrrolidine(13b and 14b). A mixture of **14a** (920 mg, 1.4 mmol) in THF (10 ml) and tetrabutylammonium fluoride (4 ml of a 1M 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=1:1) to give **14b** (630 mg, 82%) as crystals. The compound **13b** was obtained from **13a** in 78% yield as crystals after column chromatography (AcOEt : hexane= 1 : 1) in the same manner as described above for the preparation of **14b**. **14b**: mp 145°C (AcOEt-hexane), $[\alpha]_D^{20}$ -49.1° (c=1.6, $CHCl_3$); IR ν_{max} (nujol) 3376, 1674, 1060, 762, 706 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.27(3H, s, CH3), 1.33(9H,s, *t*-Bu), 1.41(3H, s, CH_3), 3.01-3.15(1H, m CH), 3.29-3.57(1H, m, CH), 3.75-4.23(4H, m, 4xCH)), 4.50(1H, d, *J*=6 Hz, CH), 4.88(1H, m, CH), 5.40(1H, br s, OH), 7.15-7.44(15H, m, aromatic protons) ; ^{13}C NMR ($CDCl_3$) δ:24.51(q), 25.88(q), 28.17(q), 62.72(t), 63.25(t), 63.54(d), 65.74(d), 80.31(d), 80.60(s), 80.70 (d), 87.13(s), 110.86(s), 126.99, 127.77, and 128.26(aromatic carbons), 143.17(s).155.49(s). *Anal.* Calcd for C_{33} $H_{39}NO_6$: C,72.63; H,7.20 , N; 2.57. Found: C,72.42 ; H, 7.41 ; N.2.31. **13b**: mp 90-92°C(AcOEt-hexane) , $[\alpha]_D^{20}$ -23.1° (c=1.1, $CHCl_3$); IR ν_{max} (nujol) 3423, 1674, 1065, 760, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.29(12H, s, *t*-Bu), 1.43(3H, s, CH_3), 3.10-3.25(2H, m CH_2), 3.50-3.70(3H, m, CH_2, OH), 3.90-4.10(2H, m, 2xCH)), 4.30-4.65(2H, m, 2xCH), 7.10-7.45(15H, m, aromatic protons);

^{13}C NMR($CDCl_3$) δ: 25.54(q), 27.48(q), 28.28(q), 63.33(t), 64.50(d), 65.32(t), 67.19(d), 80.84(d), 81.63(d), 81.83(d), 87.31(s), 111.81(s), 127.22, 127.88, and 128.70(aromatic carbons), 143.32(s), 156.16(s). Anal. calcd for $C_{33}H_{39}NO_6$: C, 72.63; H, 7.20, N; 2.57. Found: C,72.53; H, 7.48; N.2.61.

(2*R*,3*R*,4*S*,5*R*)- and (2*R*,3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-vinylpyrrolidine (15). A mixture of **10** (800 mg, 1.43 mmol), methanesulfonyl chloride (229 mg, 1.99 mmol), and TEA (202 mg, 1.99 mmol) in CH_2Cl_2 (15 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 (400 mg, 3.58 mmol) in THF (15ml) at 0°C for 15 min, then 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 =1:4) to give an inseparable diastereomeric mixture **15** (526 mg, 68%) as an oil; ^1H NMR($CDCl_3$) δ: 1.30(3H, s, CH_3), 1.40(9H, S, *t*-Bu), 1.48(3H, s, CH_3), 2.90-3.25(2H, m, CH_2), 4.20-4.65(4H, m, 4xCH), 4.65-5.30(2H, m, CH=C$\underline{H_2}$), 5.50-6.00(1H, m, C$\underline{H}$=CH_2), 7.10-7.50(15H, m, aromatic protons). ^{13}C NMR δ: 24.66(q) and 25.34(q), 25.83(q) and 27.19(q), 28.26(q), 63.06(t) and 64.03(t), 65.54(d), 67.10(d), 79.82(s), 81.57(d) and 81.87(d), 84.46(d), 86.84(s), 111.25 and 111.59(s)., 114.86 and 115.88(t), 126.89, 127.67, and 128.54(aromatic carbons), 136.69(d), 142.53(s) and 143.51(s), 154.13(s). MS *m/z* 541 (M^+).

(2*R*,3*R*,4*S*,5*S*)- and (2*R*,3*R*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-5-hydroxymethyl-2-trityloxymethylpyrrolidine (13b and 14b) from 15. The compounds **13b** (351 mg, 60%) and **14b** (146 mg, 25%) were obtained from **15** (580 mg, 1.1 mmol) as crystals after column chromatography (AcOEt : hexane= 1 : 2) in the same manner as described above for the preparation of **11a** and **12a** from **10**. Physical and NMR data were identical with those of authentic samples.

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*R*)-2,3-Isopropylidenedioxy-3-methoxycarbonyl-1-(trityloxymethyl)propyl]carbamate (8). A mixture of **6** (1.0 g, 1.89 mmol) and 2 ml of 2M solution of lithium hydroxide in 7 ml of THF-MeOH (1:1) was stirred at room temperature for 2 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 at room temperature. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (AcOEt:hexane=1: 2.5) to give **8** (954 mg, 90 %) as crystals, mp 124°C (AcOEt-hexane), $[\alpha]_D^{20}$ -46.8° (c=0.9, $CHCl_3$); IR ν_{max} (nujol) 1760, 1716, 1161, 1082, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.37(12H, s, CH_3, *t*-Bu), 1.46(3H, s, CH_3), 3.06-3.44(2H, m, CH_2), 3.66(3H, s, $COOCH_3$), 3.66-4.10(1H, m, CH), 4.45-4.83(3H, m, 2xCH, NH), 7.06-7.52(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ:25.49(q), 26.66(q),28.17(q), 50.48(d), 52.14(q), 62.72(t), 76.12(d), 76.41(d), 79.24(s), 86.25(s), 110.62(s), 126.80, 127.58, 128.40(aromatic carbons), 143.66(s)., 154.62(s), 169.48(s). *Anal.* Calcd for $C_{33}H_{39}NO_7$: C, 70.57; H, 7.00; N, 2.49. Found: C, 70.42; H, 7.25; N, 2.30.

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*)-4-hydroxy-2,3-isopropylidenedioxy-1-(trityloxymethyl)butyl]carbamate (9). A mixture of $NaBH_4$ (230 mg, 6.1 mmol) and **8** (850 mg, 1.52 mol) in EtOH (10 ml) was stirred at room temperature for 8 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=2:1) to give **9** (710 mg, 88%) as crystals, mp 100-102°C (ether-hexane), $[\alpha]_D^{20}$ -38.5° (c=0.7, $CHCl_3$); IR ν_{max} (nujol) 3432, 1707, 1498, 1167, 1045, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.35(15H, s, 2xCH_3, *t*-Bu), 2.42(1H, br s, OH), 3.05-3.09(1H, m, CH), 3.30-3.45(1H, m, CH), 3.50-3.65(1H, m, CH), 3.70-3.95(2H, m, CH2), 4.20-4.40(2H, m, 2xCH), 4.78(1H, d, *J*=9 Hz, NH),7.16-7.50(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.56(q), 27.99(q),28.29(q), 49.56(d), 61.25(t), 63.37(t), 75.43(d), 78.22(d), 80.16(s), 86.56(s), 108.41(s), 127.03, 127.79, 128.61 (aromatic carbons), 143.84(s)., 155.69(s). *Anal.* Calcd for $C_{32}H_{39}NO_6$: C, 72.02; H, 7.37; N, 2.62. Found: C, 71.82; H, 7.58; N, 2.43.

1,1-Dimethylethyl *N*-[(1*R*,2*R*,3*S*,4*R*)-4-Hydroxy-2,3-isopropylidenedioxy-1-trityloxymethyl-5-hexenyl]carbamate(10b) from 9. Swern oxidation of **9** (540 mg, 1.01 mmol) in

CH_2Cl_2 was performed in the same manner as described above for the preparation of **12b** from **11b**. The crude aldehyde was dissolved in THF (6ml). Then, vinylmagnesium bromide (2.1 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 saturated aqueous NH_4Cl and 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 **10b** (401 mg, 71%) as an oil. **10b**: $[\alpha]_D^{20}$ -39.8° (c=1.2, $CHCl_3$); IR ν max (film) 3456, 1716, 1493, 1377, 1161 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.37(15H, s, *t*-Bu, 2xCH_3), 2.36(1H, brs, OH), 3.11(1H, dd, *J*=3 and 8.5 Hz, CH), 3.42(1H, dd, *J*=2 and 8.5 Hz, CH), 3.90-4.45(4H, m, 4xCH), 4.65-4.95(1H, m , NH), 5.05-5.40(2H, m , CH=C$\underline{H}_2$), 5.65-7.05(1H, m, C$\underline{H}$=CH_2), 7.10-7.50(15H, m , aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.75(q), 26.70(q), 28.21(q), 49.95(d), 63.25(t), 69.98(d), 75.53(d), 79.58(d and s)), 86.35(s), 108.13(s), 116.03(t), 126.84, 127.62, and 128.50(aromatic carbons), 137.56(d), 143.75(s), 155.25(s). MS *m/z* 559 (M^+).

(2*R*,3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-vinylpyrrolidine (15b). This compound **15b** (306 mg, 88%) was obtained from **10b** (360 mg, 0.64 mmol) as an oil in the same manner as described above for the preparation of **13a**, $[\alpha]_D^{20}$ -51.0° (c=0.7, $CHCl_3$); IR ν max (film) 1377, 1167, 1051, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.30(3H, s, CH_3), 1.40(9H, S, *t*-Bu), 1.47(3H, s, CH_3), 2.90-3.25(2H, m, CH_2), 4.20-4.65(4H, m, 4xCH), 4.65-5.30(2H, m, CH=C$\underline{H}_2$), 5.50-6.00(1H, m, C$\underline{H}$=CH_2), 7.11-7.55(15H, m, aromatic protons) ; ^{13}C NMR($CDCl_3$) δ: 25.39(q), 27.24(q), 28.31(q), 63.11(t), 64.03(d), 67.05(d), 79.82(s), 81.91(d), 84.55(d), 86.88(s), 111.64 (s), 115.93(t), 127.20, 128.26, and 128.98(aromatic carbons), 136.73(d), 143.14(s), 153.79(s). MS *m/z* 541(M^+).

(2*R*,3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-5-hydroxymethyl-3,4-isopropylidenedioxy-2-(trityloxymethyl)pyrrolidine (13b). This compound **13b** (207 mg, 82%) was obtained from **15b** (250 mg, 0.46 mmol) as crystals after column chromatography (AcOEt : hexane= 1 : 1) in the same manner as described above for the preparation of **11a** and **12a** from **10**. Physical and NMR data were identical with those of an authentic sample.

(2*R*,3*R*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-[(1*S*)- and (1*R*)-1-hydroxy-3-butenyl]pyrrolidine(16 and 19). A) Allylation with Grignard Reagent: Swern oxidation of **14b** (800 mg, 1.47 mmol) was performed in the same manner as described above for the preparation of **12b** from **11b**. The crude aldehyde was dissolved in THF (14 ml) and treated with allylmagnesium chloride (1.7 ml of a 2 M solution in THF) at - 78°C. After being stirred at - 78°C for 1 h, the mixture was quenched with 5 ml of 10% aqueous NH_4Cl and extracted with AcOEt. The organic layers were washed with half-saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt : hexane= 1 : 4) gave **16** (516 mg, 60%) and **19** (206 mg, 24%). **16** (less polar isomer): mp 93-94°C (AcOEt-hexane), $[\alpha]_D^{20}$ -29.9° (c=1, $CHCl_3$); IR ν max (nujol) 3342, 1672, 1417, 1207, 1171, 1130, 698, 623 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.29(3H, s, CH_3), 1.34(9H,s , *t*-Bu), 1.41 (3H, s, CH_3), 2.11-2.89(2H,m, CH_2), 2.98-3.44(2H,m, 2xCH), 3.66-3.92(1H, m, CH), 3.92-4.36 (2H, m, 2xCH), 4.45-4.87(2H, m, 2xCH), 5.00-5.25(2H, m, CH=C$\underline{H}_2$), 5.76-6.34(1H,m, C$\underline{H}$=CH_2), 6.34-6.55 (1H, br s, OH), 6.90-7.61(15H, m, aromatic protons) ; ^{13}C NMR($CDCl_3$) δ: 22.05(q), 26.61(q), 28.17(q), 37.91(t), 63.11(t), 65.49(d), 67.95(d), 69.34(d), 79.57(d), 80.45(s), 80.70(d), 86.98(s), 110.06 (s), 116.32 (t), 126.99, 127.77, and 128.35(aromatic carbons), 135.37(d), 143.27(s).155.21(s). *Anal.* Calcd for $C_{36}H_{43}NO_6$: C, 73.82; H, 7.40; N, 2.39. Found: C, 73.591; H,7.62; N, 2.23. **19** (polar isomer) : $[\alpha]_D^{20}$ -57.1° (c=1, $CHCl_3$); IR ν max (film) 3435, 1680, 1403, 1243, 1081, 758, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.25(3H, s, CH_3), 1.33(9H, s , *t*-Bu), 1.47(3H, s, CH_3), 1.95-2.67(2H,m, CH_2), 2.87-3.17 (1H,m, CH), 3.43-3.65(1H, m, CH), 3.91-4.56(4H, m, 3xCH, OH), 4.73-5.34(4H, m, 4xCH), 5.69-6.18(1H, m, C$\underline{H}$=CH_2), 6.70-7.93(15H, m, aromatic protons); ^1H NMR($CDCl_3$) δ: 23.63(q), 25.24(q), 28.21(q), 37.86(t), 63.38(d), 63.59(t), 67.98(d), 69.98(d), 79.92(d), 80.70(s), 80.94(d), 87.18(s), 110.96 (s), 115.64(t), 127.09, 127.87, and 128.35(aromatic carbons), 136.64(d), 143.27(s).156.03(s). HRMS *m/z* (M^+) calcd for $C_{36}H_{43}NO_6$ 585.3090, found 585.3140.

B) Allylation with Allyllithium: 1.85 ml of allyllithium[14] (about 1 M in ether, prepared from tetraallyltin (1 equiv.) and phenyllithium (4 equv.) in ether) was added at -78°C to a solution of the crude aldehyde prepared from **14b** (500 mg, 0.92 mmol). The mixture was stirred at - 78°C for 1 h. After addition of 10% aqueous NH_4Cl (6ml), the reaction 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= 1 : 4) gave **16** (363 mg, 68%) and **19** (72 mg, 13%).

C) Allylation with Allyltrimethylsilane and $TiCl_4$: A solution of $TiCl_4$ (160 mg, 0.843 mmol) in CH_2Cl_2 (1 ml) was added to a solution of allytrimethylsilane (115 mg, 1.0 mmol) and the aldehyde prepared from **14b** (230 mg, 0.42 mmol) in CH_2Cl_2 (2.5 ml) at - 78°C over a period of 5 min. After being stirred at - 78°C for 10 min , the mixture was basified with 10% aqueous NaOH and extracted with AcOEt. The AcOEt extracts were washed with half-saturated aqueous NaCl. Drying followed by evaporation and purification of the residue by column chromatography (AcOEt:hexane=1:4) gave **16** (52 mg, 21%).

***(2R,3R,4S,5S)*-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-[(1*S*)- and (1*R*)-1-hydroxy-3-butenyl]pyrrolidine (23 and 26).** Dimethyl sulfoxide (590mg, 7.5 mmol) was added at - 78°C to a solution of oxalyl chloide (440 mg, 3.4 mmol) in THF (8 ml). The mixture was stirred at -40 - -50°C for 3 min. Then a solution of **13b** (850 mg, 1.56 mmol) in THF (3 ml) was added at -10 °C. After being stirred at -10°C for 40 min, TEA (787 mg, 7.8 mmol) was added. Then the mixture was recooled at -78°C, and vinylmagnesium bromide (7.3 ml of 1 M solution in THF) was added at -78°C. The mixture was stirred at -78°C for 30 min, and then treated with EtOH (1 ml) and saturated aqueous NH_4Cl (5 ml). 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 **23** (476 mg, 52%) and **26** (227 mg, 25%) as an oil. **23**(polar isomer): $[\alpha]_D^{20}$ -23.2° (c=1, $CHCl_3$); IR ν max (film) 3480, 1695, 1379, 1219, 1167, 1066, 758, 706 cm^{-1} ; ^1H NMR($CDCl_3$) δ: 1.29(3H, s, CH_3), 1.37(9H,s , *t*-Bu), 1.42(3H, s, CH_3), 1.96-2.40(2H,m, CH_2), 3.13-3.50(3H,m, CH_2, CH), 3.50-3.91(1H, br s, OH), 3.91-4.33(2H, m, 2xCH), 4.33-4.82(2H, m, 2xCH), 4.82-5.25(2H, m, CH=C<u>H</u>$_2$), 5.42-5.98 (1H, m, C<u>H</u>=CH_2),6.92-7.58(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.19(q), 27.14(q), 28.02 (q), 38.16(t), 62.96(t), 64.57(d), 68.37(d), 70.32(d), 79.53(d), 79.72(s), 81.87(d), 86.88(s), 111.06(s), 117.49(t), 126.75, 127.48, and 128.35(aromatic carbons), 134.05(d), 143.12(s).154.38(s). HRMS *m/z* (M^+) calcd for $C_{36}H_{43}NO_6$ 585.3090, found 585.3130. **26** (less polar isomer); $[\alpha]_D^{20}$ -20.1° (c=0.7, $CHCl_3$); IR ν max (film) 3496, 1693, 1379, 1221, 1167, 1068, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.28 (3H, s, CH_3), 1.37(9H, s, *t*-Bu), 1.43(3H, s, CH_3), 1.84-2.50(2H, m, CH_2), 3.08-3.80(4H, m, CH_2, CH, OH), 3.92-4.30(2H, m, 2xCH), 4.34-4.68(2H, m, 2xCH), 4.83-5.19(2H, m, CH=C<u>H</u>$_2$), 5.48-6.03(1H, m, C<u>H</u>=CH_2),7.00-7.57(15H, m, aromatic protons).^{13}C NMR($CDCl_3$) δ: 25.49(q), 27.39(q), 28.22(q), 38.84(t), 63.21(t), 64.96(d), 68.81(d), 73.19(d), 80.74(s), 81.96(d), 82.40(d), 87.23(s), 111.54(s), 117.54(t), 127.04, 127.77, and 128.65(aromatic carbons), 134.40(d), 143.36(s), 156.76(s). HRMS *m/z* (M^+) calcd for $C_{36}H_{43}NO_6$ 585.3090, found 585.3075.

***(2R,3R,4S,5R)*-*N*-*tert*-Butoxycarbonyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-[(1*S*)-1-methoxymethyloxy-3-butenyl]pyrrolidine(17).** A mixture of **16** (330 mg, 0.56 mmol), *N*,*N*-diethylaniline (673 mg, 4.5 mmol), and chloromethyl methy ether (363 m g, 4.5 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 40 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: 3) to give **17** (300 mg, 85%) as crystals, **17**: mp 126-127°C(AcOEt-hexane), $[\alpha]_D^{20}$ -68.5° (c=0.9, $CHCl_3$); IR ν max (nujol) 1699, 1040, 762, 706 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.28(3H, s, CH_3), 1.32(9H,s , *t*-Bu), 1.50(3H, s, CH_3), 2.15-2.84(2H, m, 2xCH), 2.99-3.24(1H, m, CH), 3.30-3.71(1H, m, CH), 3.31(3H, s, OCH_3), 3.90-4.20(3H, m, CH), 4.23-5.23(6H, m, 4xCH, CH=C<u>H</u>$_2$), 5.64-6.17(1H, m, C<u>H</u>=CH_2), 6.94-7.56(15H, m, aromatic protons) ; ^{13}C NMR($CDCl_3$) δ: 23.93(q), 25.83(q), 28.26(q), 36.21(t), 55.55(q), 63.50(d and t), 64.32(d), 80.41(s and d), 81.19(d), 87.08(s), 97.80(t), 111.11(s), 115.98(t), 126.99, 127.77, and 128.45, (aromatic carbons),

137.23 (d), 143.41(s), 154.18(s). *Anal.* Calcd for $C_{38}H_{47}NO_7$: C, 72.47; H, 7.52, N 2.22. Found: C, 72.51 ; H,7.68 ; N.2.31.

(2*R*,3*R*,4*S*,5*R*)-*N*-Benzyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-[(1*S*)-1-methoxymethyloxy-3-butenyl]pyrrolidine(18). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (370 mg, 1.4 mmol) was added at room temperature to a solution of **17** (180 mg, 0.29 mmol) and 2,6-lutidine (150 mg, 1.4 mmol) in CH_2Cl_2 (3 ml) .The mixture was stirred at room temperature for 3 h and quenched with saturated aqueous NH_4Cl solution. The product was extracted with ether and the combined ether layers were washed with half-saturated aqueous NaCl . Drying followed by evaporation gave a residue, which was dissolved in THF (2 ml) and tetrabutylammonium fluoride (1 ml of a 1M solution in THF) was added. After being stirred at room temperature for 30 min, the mixture was diluted with AcOEt and washed with half-saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was benzylated with benzyl bromide (180 mg, 1.1 mmol) in the presence of K_2CO_3 (200 mg) in acetone (3 ml) at room temperature for 2 h. Filtration followed by evaporation and purification with column chromatography (AcOEt:hexane=1: 6) gave **18** (103 mg, 58%) as an oil, $[\alpha]_D^{20}$ -60.9° (c=1.3, $CHCl_3$); IR ν_{max} (film) 1448, 1211, 1151, 1037, 740, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.35(3H, s, CH_3), 1.55(3H,s CH_3), 2.54-2.82(2H, m, 2xCH), 2.92-3.74(5H, m, 3xCH, CH_2OTr), 3.30(3H, s, OCH_3), 3.40-4.23(2H, m, 2xCH), 4.58-5.26(6H, m, 2xCH2, 2xCH), 5.68-6.14(1H, m, C<u>H</u>=CH_2), 6.86-7.763(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.41(q), 24.98(q), 36.11(t), 51.31(t), 55.75(q), 60.82(t), 64.27(d), 66.71(d), 78.65(d), 81.38(d), 81.72(d), 87.23(s), 96.58(t), 110.91(s), 116.42(t), 126.31, 126.94, and 127.72, 128.00, 128.65 (aromatic carbons), 135.30(d), 139.42(s), 143.46(s). HRMS *m/z* (M^+) calcd for $C_{40}H_{45}NO_5$ 619.3298, found 619.3282.

(2*R*,3*R*,4*R*,5*R*)-*N*-Benzyl-3,4-isopropylidenedioxy-2-trityloxymethyl-5-[(1*S*)-1-methoxymethyloxy-3-hydroxypropanyl]pyrrolidine(22a). This sample **22a** (114 mg, 58%) was obtained from **18** (195 mg, 0.31 mmol) as an oil after column chromatography (AcOEt : hexane= 1 : 4) in the same manner as described above for the preparation of **11a** and **12a** from **10**, $[\alpha]_D^{20}$ -26.9° (c=0.5, $CHCl_3$). IR ν_{max} (film) 3460, 1374,1247, 1047, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.32(3H, s, CH_3), 1.57(3H,s CH_3), 1.80-2.43 (3H, CH_2, OH), 2.89-3.27(4H,m, CH_2, 2xCH), 3.34(3H, s, OCH_3), 3.42-4.20(4H, m, 4xCH), 4.50--5.10 (5H, m, 5xCH), 6.86-7.52(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.46(q), 26.02(q), 33.97(t), 51.09(t), 55.65(q), 59.68(t), 60.52(t), 63.69(d), 66.76(d), 76.94(d), 81.33(d), 81.43(d), 87.08(s), 96.92(t), 110.76(s), 126.21, 126.80, and 127.43, 127.53, 127.87, and 128.46(aromatic carbons), 135.64(d), 143.17 (s). HRMS *m/z* (M^+) calcd for $C_{39}H_{45}NO_6$ 623.3247, found 623.3288.

1,7a-Diepialexine(1a). A mixture of **22a** (80 mg, 0.13 mmol), methanesulfonyl chloride (22 mg, 0.19 mmol), and TEA (19 mg, 0.19 mmol) in CH_2Cl_2(1.5 ml) was stirred at room temperature for 16 h. After addition of 20 ml of CH_2Cl_2, the mixture was washed with H_2O. Drying followed by evaporation gave a residue, which was hydrogenated using 10% palladium on carbon (25 mg) in EtOH (2 ml) in the presence of hydrogen chloride at room temperature for 1h under hydrogen at atmospheric pressure. The mixture was filtered and concentrated *in vacuo*, and the residue was treated with 10% aqueous HCl (1 ml) and MeOH (1 ml) 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 H_2O, and eluted with 0.6 N NH_4OH. Freeze-drying of the appropriate fractions gave 1,7a-diepialexine (**1a**, 13 mg, 52%) as an oil, $[\alpha]_D^{20}$ +12.5° (c=0.6, H_2O); ^1H NMR(D_2O) δ: 2.01(2H, m), 3.00(1H, m), 3.09(1H, m), 3.20(1H, m), 3.53(1H, dd), 3.62(1H, dd), 3.80(1H, dd), 3.91(1H, dd), 4.38(1H, m), 4.55(1H, m); ^{13}C NMR(D_2O, dioxane δ=67.40) 36.01(t), 52.92(t), 63.20(t), 67.00(d), 70.85(d), 72.80(d), 73.73(d), 75.09(d). HRMS (FAB): *m/z* $(M+H)^+$ calcd for $C_8H_{16}NO_4$ 190.1080, found 190.1088.

Physical and NMR data for 20, 21, 22b, 1b, 24, 25, and 27-30. **20**: oil, $[\alpha]_D^{20}$ -71.5° (c=0.7, $CHCl_3$); IR ν_{max} (film) 1695, 1373, 1043, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.28(3H, s, CH_3), 1.40 (9H, s, *t*-Bu), 1.51(3H, s, CH_3), 2.43-2.74(2H, m, 2xCH), 2.86-3.20(1H, m, CH), 3.30-3.70(1H, m, CH), 3.34(3H, s, OCH_3), 3.94-4.43(3H, m, 3xCH), 4.43-5.31(6H, m, 4xCH, CH=C<u>H2</u>), 5.66-6.17(1H, m,

CH=CH_2), 6.90-7.63(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.41(q), 25.19(q), 28.21(q), 36.74 (t), 55.11(q), 62.62(d), 64.86(d), 76.31(d), 79.48(d), 81.33(d), 86.88(s), 97.22(t), 110.06(s), 116.17(t), 126.89, 127.67, and 128.31, (aromatic carbons), 135.81(d), 143.36(s), 154.18(s). HRMS *m/z* (M^+) calcd for $C_{38}H_{47}NO_7$ 629.3353, found 629.3362. **21**:oil, $[\alpha]_D^{20}$ -55.9° (c=1.3, $CHCl_3$); IR ν max (film) 1488, 1215, 1153, 1038, 756, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.31(3H, s, CH_3), 1.55(3H, s, CH_3), 1.90-2.56(2H, m, 2xCH), 2.72-3.30(5H,m, 3xCH, CH_2OTr), 3.30(3H, s, OCH_3), 3.60-4.20(2H, m, 2xCH), 4.50-5.20 (6H, m, 2xCH_2, 2xCH), 5.68-6.17(1H, m, CH=C, 6.84-7.72(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.12(q), 25.88(q), 36.45(t), 51.75(t), 55.51(q), 61.11(t), 63.40(d), 68.17(d), 77.92(d), 81.33(d), 82.30 (d), 87.23(s), 96.53(t), 110.26(s), 115.88(t), 126.26, 126.94, and 127.72, 128.01, 128.60(aromatic carbons), 137.17(d), 139.12(s), 143.41(s). HRMS *m/z* (M^+) calcd for $C_{40}H_{45}NO_5$ 619.3298, found 619.3290. **22b**: oil, $[\alpha]_D^{20}$ -70.5° (c=0.5, $CHCl_3$); IR ν max (film) 3440, 1450, 1377, 1215, 1032, 756, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ: 1.29(3H, s, CH_3), 1.53(3H,s CH_3), 2.10-2.63(3H, CH_2, OH), 3.00-3.24(3H,m, CH_2, CH), 3.32(3H, s, OCH_3), 3.57-3.86(3H, m, 3xCH), 3.97-4.31(3H, m, 3xCH), 4.50-4.98(4H, m, 4xCH), 6.88-7.56(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 24.07(q), 25.92(q), 34.06(t), 51.80(t), 55.75 (q), 60.57(t), 61.16(t), 63.59(d), 67.93(d), 76.36(d), 81.48(d), 82.26(d), 87.28(s), 96.53(t), 110.96(s), 126.41, 126.99, and 127.22, 128.06, and 128.59(aromatic carbons), 138.88(d), 143.41(s). HRMS *m/z* (M^+) calcd for $C_{39}H_{45}NO_6$ 623.3247, found 623.3268. **1b**: oil, $[\alpha]_D^{20}$ +4.7° (c=0.5, H_2O); ^1H NMR(D_2O) δ: 1.83(1H,m), 2.18(1H,m), 2.81(2H, m), 3.21(1H, m), 3.34(1H,m), 3.61(1H,dd), 3.78 (1H, m), 3.88(1H, m), 4.16(1H, m), 4.53(1H, m); ^{13}C NMR(D_2O, dioxane δ=67.40) δ: 35.29(t), 53.81 (t), 62.97(t), 69.30(d), 70.81(d), 70.91(d), 73.34(d), 74.90(d). HRMS (FAB): *m/z* $(M+H)^+$ calcd for $C_8H_{16}NO_4$ 190.1080, found 190.1086. **24**: mp 118-119°C ; $[\alpha]_D^{20}$ -43.5° (c=0.7, $CHCl_3$); IR ν max (nujol) 1697, 1165, 1029, 760, 708 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.31(3H, s, CH_3), 1.35(9H, s,*t*-Bu), 1.44(3H, s, CH_3), 2.05-2.48(2H, m, 2xCH), 2.65-2.90(1H, m, CH), 3.02(3H, s, OCH_3), 3.15-3.50(1H, m, CH), 3.50-3.90(2H, m, 2xCH), 3.90-4.19(2H,m, 2xCH), 4.20-4.65(3H, m, 3xCH), 4.90-5.20(2H, m, CH=CH_2), 5.45-5.95(1H, m, CH=CH_2), 7.14-7.53(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.58(q), 27.39(q), 28.31(q), 36.69(t), 55.21(q), 63.06(t), 63.93(d), 67.35(d), 76.41(d), 78.94(d), 79.91(s), 82.40(d), 86.45(s), 96.19(t), 111.45(s), 117.68(t), 126.84, 127.72, and 128.50, (aromatic carbons), 133.72 (d), 143.95(s), 154.18(s). *Anal.* Calcd for $C_{38}H_{47}NO_7$: C, 72.47 ; H, 7.52; N, 2.22 , Found: C,72.53 ; H,7.68 ; N, 2.01. **27**: oil, $[\alpha]_D^{20}$ -30.1° (c=1.1, $CHCl_3$); IR ν max (film) 1691, 1165, 1036, 758, 706 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.29(3H, s, CH_3), 1.41(9H,s CH_3), 1.46(3H, s, CH_3), 1.78-2.28(2H, m, 2xCH), 2.88-3.13(1H, m, CH), 3.10(3H, s, OCH_3), 3.18-3.85(2H, m, 2xCH), 4.00-4.65(6H,m, CH2, 4xCH), 4.85-5.10(2H, m, CH=CH_2), 5.49-6.05(1H, m, CH=CH_2), 7.14-7.53(15H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.49(q), 27.39(q), 28.21(q), 35.18(t), 55.65(q), 63.01(t), 66.03(d), 66.42(d), 77.681(d), 79.82(d), 82.30(s), 83.52(d), 86.20(s), 95.22(t), 111.11(s), 116.86(t), 126.70., 127.58, and 128.55, (aromatic carbons), 134.59(d), 143.90(s), 155.30(s). HRMS : *m/z* (M^+) calcd for $C_{38}H_{47}NO_7$, 629.3353, found 629.3268. **25**: oil, $[\alpha]_D^{20}$ -24.2° (c=0.5, $CHCl_3$); IR ν max (film) 1446, 1377, 1215, 1036, 756, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.39(3H, s, CH_3), 1.56(3H, s, CH_3), 2.28-2.56(2H, m, 2xCH), 2.90-3.67(5H, m, CH_2, 3xCH), 3.34(3H, s, OCH_3), 3.80-4.20(2H,m, 2xCH), , 4.40-4.60(2H, m, 2xCH), 4.60-4.80 (2H,m, 2xCH), 5.00-5.30(2H, m, 2xCH), 5.52-5.69(1H, m, CH=CH_2), 7.13-7.61(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.58(q), 27.78(q), 37.13(t), 55.41(q), 58.48(t), 65.30(t), 68.17(d), 71.63 (d), 76.65(d), 80.66(d), 82.60(d), 86.50(s), 96.88(t), 111,50(s), 117.15(t), 126.75, 127.57, 128.55, 128.01, 128.54, and 129.33(aromatic carbons), 134.74(d), 138.20(s), 143.90(s). HRMS : *m/z* (M^+) calcd for $C_{40}H_{45}NO_5$, 619.3298, found 619.3308. **28**: oil, $[\alpha]_D^{20}$ +12.8° (c=0.9, $CHCl_3$); IR ν max (film) 1446, 1375, 1215, 1035, 758, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.12(3H, s, CH3), 1.29(3H,s CH_3), 1.70-2.52(2H, m, 2xCH), 2.65-3.25(5H, m, CH_2, 3xCH), 3.11(3H, s, OCH_3), 3.60 and 3.82(2H, AB*J*=13.5 Hz, CH_2Ph), 4.05-4.50(4H, m, CH_2, 2xCH), 4.50-5.00(2H,m, CH=CH_2), 5.20-5.70(1H, m, CH=CH_2), 6.83-7.43(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ: 25.54(q), 27.78(q), 34.45(t), 55.36(q), 59.16 (t), 64.66(t), 60.24(d), 70.71(d), 77.92(d), 81.87(d), 82.21(d), 86.49(s), 96.14(t), 111,50(s), 116.37(t), 126.70, 126.89, 127.53, 127.96, 128.54, and 129.13(aromatic carbons), 135.71(d), 138.68(s), 143.90(s). HRMS : *m/z* (M^+)

calcd for $C_{40}H_{45}NO_5$, 619.3298, found 619.3334. **29a**: oil, $[\alpha]_D^{20}$ -37.9° (c=1.1, $CHCl_3$); IR ν max (film) 3380, 1446,1379, 1217, 1072, 1033, 756, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.36(3H, s, CH_3), 1.42 (3H,s, CH_3), 1.50-1.75(2H, m, CH_2), 2.63(1H, br s, OH), 2.81-3.04(2H,m, 2xCH), 3.04-3.45(2H, m, 2xCH), 3.25(3H, s, OCH_3), 3.45-3.78(2H, m, 2xCH), 3.80-3.96(2H, m, CH_2), 4.22-4.70(5H, m, 5xCH), 7.04-7.52(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ:25.53(q), 27.73(q), 34.89(t), 55.65(t), 58.18(t), 59.01(t), 65.01(t), 68.07(d), 72.90(d), 79.77(d), 82.21(d), 86.55(s), 97.99(t), 116.69(s), 126.80, 127.09, 127.58, 128.55,and 129.33 (aromatic carbons), 137.81(d), 143.85(s). HRMS : *m/z* (M^+) calcd for $C_{39}H_{45}NO_6$ 623.3247, found 623.3262. **29b**: oil, $[\alpha]_D^{20}$ +11.9° (c=0.4, $CHCl_3$); IR ν max (film) 3373, 1450, 1377,1217, 1070, 1034, 757, 704 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.24(3H, s, CH_3), 1.38(3H, s, CH_3), 1.60(1H, br s, OH), 1.75-1.90(1H, m, CH), 3.00-3.13(3H,m, 3xCH), 3.18-3.30(3H, m, 3xCH), 3.23(3H, s, OCH_3), 3.40-3.50(2H, m, 2xCH), 3.60-4.00(2H, m, CH_2), 4.26-4.42(4H, m, 4xCH), 7.11-7.41(20H, m, aromatic protons); ^{13}C NMR($CDCl_3$) δ:25.66(q), 27.86(q), 32.91(t), 55.68(q), 60.36(t), 64.71(t), 69.25(d), 70.65(d), 76.97(d), 80.26(d), 81.65(d), 86.30(s), 96.41(t), 111.95(s), 126.95, 127.34, 127.74, 128.22, 128.30, 128.72, and 129.59 (aromatic carbons), 138.15(s), 143.98(s). HRMS : *m/z* (M^+) calcd for $C_{39}H_{45}NO_6$ 623.3247, found 623.3257. **1-Epialexine (30a)**: oil, $[\alpha]_D^{20}$ +34.8° (c=0.5, H_2O); IR ν max (film) 3332, 1674, 1631, 1597, 1342, 1099, 1042 cm^{-1}; ^1H NMR(D_2O) δ:1.67(1H, m), 2.06(1H,m), 2.75-3.03(2H,m), 3.09-3.40(2H,m), 3.55-3.90(3H,m), 3.90-4.20(2H, m); ^{13}C NMR(D_2O, dioxane δ= 67.40) δ 34.11(t), 46.02(t), 59.35(t), 65.54(d), 71.49(d), 73.97(d), 74.56(d), 76.95(d), HRMS (FAB): *m/z* $(M+H)^+$ calcd for $C_8H_{16}NO_4$ 190.1080, found 190.1085. **1,7-diepialexine (30b)**: oil, $[\alpha]_D^{20}$ +37.0° (c=0.7, H_2O); IR ν max (film) 3346, 1670, 1632, 1597, 1319, 1092, 1036 cm^{-1}; ^1H NMR($CDCl_3$) δ:1.89(2H, m), 3.15(2H,m), 3.38(1H,m), 3.69(1H,m), 3.72-3.94(3H,m), 4.17(1H, m), 4.41(1H,m); ^{13}C NMR(D_2O, dioxane δ=67.40) δ 35.05(t), 46.36(t), 58.99(t), 64.16(d), 69.68(d), 70.14(d), 72.28(d), 76.36(d), HRMS (FAB): *m/z* $(M+H)^+$ calcd for $C_8H_{16}NO_4$ 190.1080, found 190.1089.

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