A SYNTHESIS OF THE POLYHYDROXYLATED PYRROLIDINES : SYNTHESIS OF 1,4-DIDEOXY-1,4-IMINO-D-LYXITOL AND *N*-BENZYL-4-*EPI*-(-)-ANISOMYCIN

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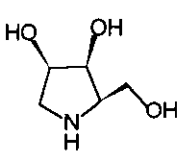
Abstract- A synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol and *N*-benzyl-4-*epi*-(-)-anisomycin was described

Polyhydroxylated pyrrolidines and piperidines provide an extensive class of powerful and specific glycosidase inhibitors [1] 1,4-Dideoxy-1,4-imino-D-lyxitol (**1**) was reported as a potent competitive inhibitor of α-galactodase [2] (-)-Swainsonine (**2**) has potential activity for the prevention of metastasis of cancer [3] (-)-Anisomycin (**3**) possesses strong and selective activities against pathogenic protozoa and fungi, and has been used successfully in the clinic for the treatment of amebic dysenetry and trichomonas vaginitis.[4]



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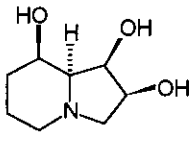

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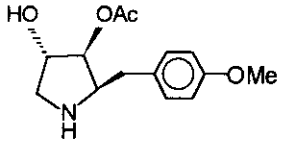

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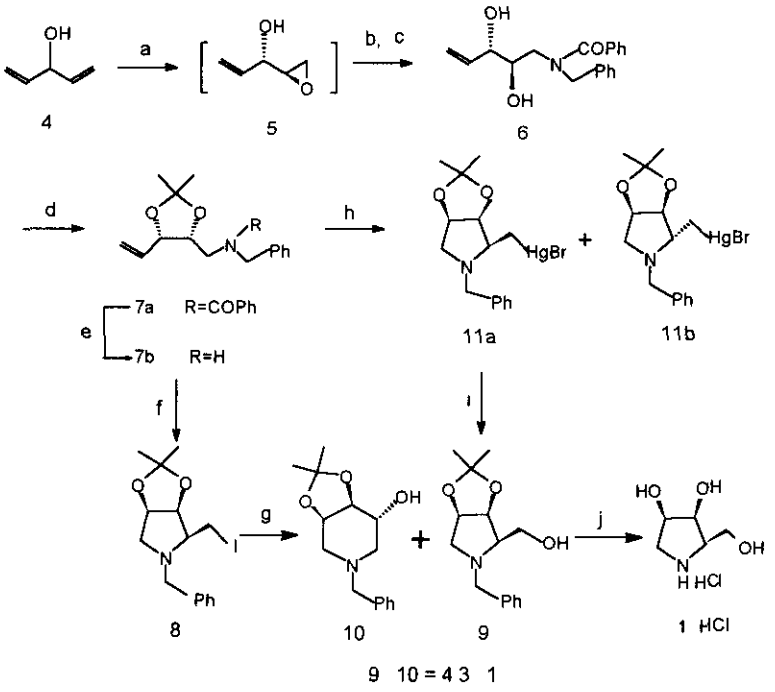
A survey of literature suggested that polyhydroxylated pyrrolidines and piperidines, such as compounds (**1~3**) were mostly synthesized from natural sugars[5] although a number of chiral synthesis of **1**[6] and **3**[7] have been reported by using different approachs. The formation of the pyrrolidine ring has been achieved by many ways, such as an intramolecular nucleophilic displacement with amine nitrogen,[5h-j,5l] anodic cyclization of δ-alkenylamine,[7a] or a Dieckmann cyclization of aminodiester.[5m] Being interested in the remarkable physiological effects of these compounds, and as a continuation of our work on the utility of optically active 1,2-epoxy-4-penten-3-ol (**5**) for the asymmetric synthesis of natural products,[8] we

think the product (**7a**) generated by one-pot aminolysis of **5**[8a] can act as a chiral building block to synthesize some polyhydroxylated pyrrolidines and piperidines. So we describe here the facile chiral synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol (**1**) and *N*-benzyl-4-*epi*-(-)-anisomycin (**20**).

The synthesis of **1**·HCl was outlined in Scheme 1. *(2R,3S)*-**5** was conveniently prepared from the divinylcarbinol (**4**) *via* Sharpless asymmetric epoxidation [TBHP, L-(+)-DIPT, $Ti[OCH(CH_3)_2]_4$, molecule sieves(4Å)] at -20 °C for 2 days.[9] One pot aminolysis of the oxirane (**5**) with phenylamine promoted by $Ti[OCH(CH_3)_2]_4$ and followed by benzoylation of the ring opening product to give **6** in 63.1% yield based on **4**.[8a] Protection of the diol group in **6** as an isopropylideneketal gave



Scheme 1

Reagents and conditions: (a) L-(+)-DIPT, TBHP, $Ti[OCH(CH_3)_2]_4$, CH_2Cl_2, 4 Å sieves, -20 °C, 2 days. b) $PhCH_2NH_2$, 1.5 eq. $Ti[OCH(CH_3)_2]_4$, room temperature. (c) PhCOCl, $NaHCO_3$, acetone, room temperature, 63.1% from **4**. (d) dimethoxypropane, CH_2Cl_2, *p*-TsOH, room temperature, 92.1%. (e) DIBAL-H, THF, -78°C. (f) I_2, $NaHCO_3$, DME-H_2O=4.1, 0°C. (g) 4N aq. NaOH, $[CH_3(CH_2)_3]_4N^+I^-$, room temperature, 55.9% from **7a**. (h) $Hg(OCOCF_3)_2$/THF, then sat. aq. $NaHCO_3$, sat. aq. KBr (i)O_2/ $NaBH_4$/ DMF, room temperature, 54.4% from **7a**. (j) H_2/ $Pd(OH)_2$/ MeOH, then 2N aq. HCl/ MeOH, room temperature, 68.1% from **9**

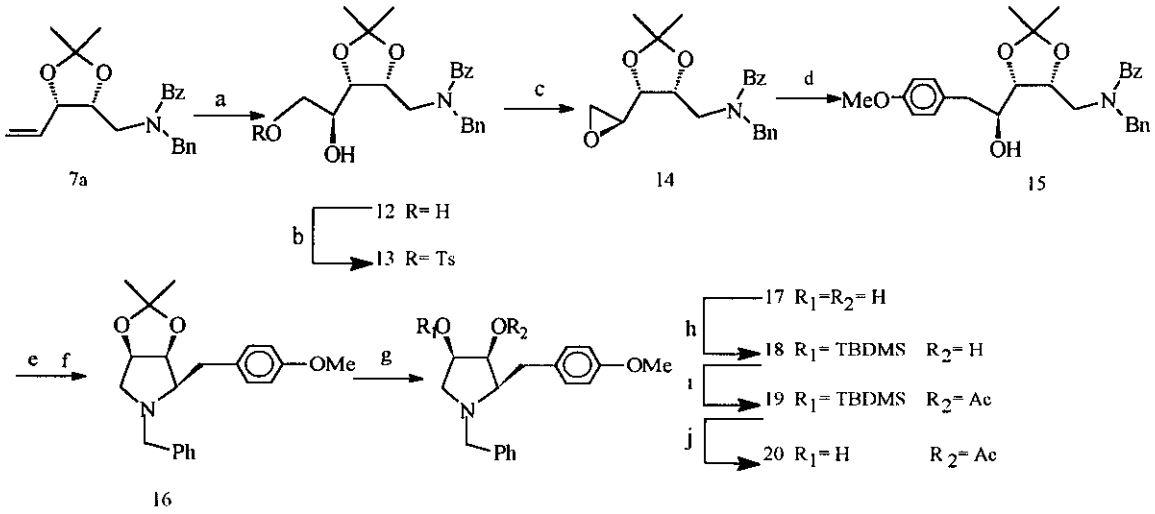
7a in 92.1% yield. Removal of the benzoyl group in **7a** with DIBAL-H afforded the crude **7b**, which was immediately subjected to iodoamidation with $I_2/NaHCO_3$ in DME - H_2O. The resultant mixture was hydrolyzed with 4N aq. NaOH

in the presence of phase transfer catalyst ($[CH_3(CH_2)_3]_4N^+I^-$) to produce **9** and the undesired six-membered ring product **10** in a ratio of 4.3 : 1, which can be separated by flash column chromatography. The isolated yield of **9** from **7a** is 55.9%. **9** and **10** were charactrized by ^1H nmr, ms , ir, and ^1H-^1H COSY. The difference of ^1H nmr between **9** and **10** lies clearly in the ^1H nmr signals of the benzylic protons which show an AB peak in **9** (4.04 and 3 22 ppm, J=13 4 Hz) and a singlet peak in **10** (s, 3 56 ppm) The stereochemistry of the newly introduced chiral center in **9** was proved by coupling constant (J= 4 9 Hz) between H-2 and H-3, which is similiar in magnititude to that of analogue of **9** in literature[10] indicating a *syn* relation between these two protons. By comparison, the corresponding *anti* protons reported in literature are coupled by 7-8 Hz [11] This assignment of stereochemistry was also confirmed by the spectral data of the target product which is in accordance with literature.[12] In the event, **9** was easily converted to 1,4-dideoxy-1,4-imino-D-lyxitol in crystalline form by hydrogenation with $H_2/Pd(OH)_2$ in methanol, followed by deprotection of the hydroxyl groups with 2N aq. HCl. The overall yield of **1**·HCl from **4** was 17%.

As an improvement, amidomercuration ($Hg(OCOCF_3)_2$/THF) of **7b** offered **11a** and its epimer (**11b**) in a ratio of 6 : 1. Reductive oxygenation of **11a** with oxygen and $NaBH_4$ in DMF afforded **9** as a single product. **9** was easily turned to hydrochloride salt of **1** in the same way as mentioned above in 21.5% overall yield based on **4** Since **9** has been reported as an intermediate for the synthesis of (-)-swainsonine (**2**),[13] a formal synthesis of (-)-swainsonine from divinylcarbinol was thus completed

4-*epi*-(-)-Anisomycin was also prepared from **7a** as shown in Scheme 2 Direct epoxidation of **7a** under various conditions failed Finally, the osmium tetraoxide dihydroxylation of **7a** with $K_3[Fe(CN)_6]_2$ as cooxidant in *tert*-butyl alcohol and water provided dihydroxyl compound (**12**) and its epimer in a 4.6 . 1 ratio in 91% yield. The stereochemistry of the newly introduced chiral center in the major diastereoisomer (**12**) is established according to Kishi's empirical rule that the relative stereochemistry between the preexisting hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product in all cases is ***erythro*** in the OsO_4 dihydroxylated reaction [14] **12** was tosylated at 0°C with *p*-TsCl and the resultant tosylate was treated with K_2CO_3 to yield oxirane **14** Ring opening of **14** by 4-methoxyphenyl magnesium bromide gave **15.** Removal of the benzoyl group in **15** with DIBAL-H, followed by cyclization with PPh_3/DEAD afforded the crucial five-membered ring intermediate **16** The cyclization involved a S_N2 displacement of hydroxyl group in Mitsunobu reaction [15] The coupling constant of 4.92 Hz for H2-H3 indicates a *cis* configuration of these two protons since the corresponding coupling constant of (-)-anisomycin was reported to be 4.9 Hz [5l] The ketal group of **16** was then hydrolyzed with 2N aq. HCl to yield **17.** Selective protection of one hydroxyl group of **17** with TBDMS-Cl afforded **18** . Acetylation of **18** , followed by removal of TBDMS group gave *N*-benzyl-4-*epi*-(-)-anisomycin (**20**) The overall yield of **20** from **7a** was 15.8%

In summary, we synthesized the 1,4-dideoxy-1,4-imino-D-lyxitol and *N*-benzyl-4-*epi*-(-)-anisomycin using *(2R,3S)*-**5** as the versatile material. The present syntheses represent an efficient strategy for the preparation of some polyhydroxylated pyrrolidines and piperidines.



Scheme 2

Reagents and conditions: (a) OsO_4 / $K_3[Fe(CN)_6]_2$ / K_2CO_3, *tert*-butyl alcohol -H_2O =1:1, room temperature, 91% yield d r =10 1 (b) TsCl, Et_3N, CH_2Cl_2, 0°C. (c) K_2CO_3, MeOH, room temperature, 85.2% from **12** (d) 4-methoxy phenyl magnesium bromide , CuI(5% mol), THF, -10°C, 86% yield (e) DIBAL-H, THF, -78°C (f) PPh_3/ DEAD/ THF, room temperature, 43% yield from **15** (g) 2N aq HCl/THF, room temperature, 80%. (h) TBDMS-Cl, DMF, room temperature, 89% (i) Ac_2O/ pyridine, room temperature , 92% (j) n-$Bu_4N^+F^-$/ THF, 0°C, 84% yield

EXPERIMENTAL:

Melting points were measured with a Büchi 535 spectrometer and uncorrected. ^1H Nmr and ^{13}C nmr spectra were obtained on Bruker AM-300 (300 MHz) spectrometer, using TMS as an internal standard Ir spectra were taken on a Shimadzu IR-440 spectrophotometer and main absorption frequencies were given in cm^{-1}. EI and HR mass spectra were recorded with Finnigan 4021 spectrometer. Optical rotations were mesaured on Perkin-Elemer 241 polarimeter at the sodium D line and 25°C. Microanalysis was taken by Analytical Department of Shanghai Institute of Organic Chemistry Flash column chromatography was carried out using silica gel (200-300 mesh, made in Shanghai, China)

Synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol.

Preparation of (2*R*, 3*S*)-*N*-benzyl-*N*-benzoyl-2,3-dihydroxy-4-ene-pentylamine(6): To a mixture of 3 g of molecular sieves (4Å) and 75 ml of dried CH_2Cl_2 , was added subsequently 1.0 ml of L-(+)-DIPT (4 75 mmol), 7.5 ml of TBHP (6 7

M in CH_2Cl_2) and 1 5 ml of $Ti[OCH(CH_3)_2]_4$ (5.0 mmol) at -20°C under positive N_2 pressure After stirring for 0 5 h, 3 ml of **4** (31 0 mmol) was added *via* syringe. The mixture was kept in refrigerator at -20°C for 10 days. 2 5 ml of $P(OEt)_3$ (14.6 mmol) was then added at -20°C, stirring was continued for 0.5 h followed by the addition of 12 ml of $Ti[OCH(CH_3)_2]_4$ (40.0 mmol) together with 5 ml of benzylamine (45 8 mmol). The mixture was stirred overnight at room temperature. Then 120 ml of $CHCl_3$ and 30 ml of 10% NaOH in brine were added. The stirring was kept for 5 h The mixture was filtered through a pad of celite, and the organic layer was dried over anhydrous Na_2SO_4 Removal of solvent gave a yellow oil, which was dissolved in 30 ml of acetone Then 120 ml of sat aq. $NaHCO_3$ and 8 ml of benzoyl chloride (68 9 mmol) were added The mixture was stirred at room temperature for 3 h, extracted with ethyl acetate after removal of acetone. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent gave a residue which was subjected to flash column chromatography (silica gel, petroleum ether ethyl acetate = 1 : 3) to give 5.36 g of **6** (5.36 g ,55 6% yield from **4**) as white solid. $[\alpha]_D^{25}$ -65.8° (c= 1.0, CH_2Cl_2) Ir (KBr) cm^{-1} 3450; 1730; 1640, 1450. ^1H Nmr ($CDCl_3$) δ 2 50 (br, 2H, 2-OH), 3 40 (m, 1H, H5); 3 75 (m, 1H, H5'); 4.00 (m, 1H, H4); 4.10 (m, 1H, H3); 4.62 (s, 2H, C$\underline{H_2}$Ph); 5 23 (d, J=12 Hz, 1H, H1), 5 35 (d, J=18 Hz, 1H, H1'); 5 80 (m, 1H, H2); 7.15-7.40 (m, 10H, 2 x Ph) Ms: m/z 312 (M^++1), 311(M^+); 105 (-COPh), 91 (-Bn) HRms: exact mass 311.1551 (calcd for $C_{19}H_{21}NO_3$ 311 1522) Anal Calcd for $C_{19}H_{21}NO_3$: C, 73 29; H, 6.80; N, 4.50. Found: C, 72.72; H, 6.78, N, 4.25.

Preparation of (2*R*,3*S*)-*N*-benzyl-*N*-benzoyl-2,3-*O*-isopropylidene-4-ene-pentylamine (7a). To a solution of 350 mg of **6**(1.13 mmol) in 40 ml of CH_2Cl_2, 21.5 mg of PTS (0.113 mmol) and 0 4 ml of dimethoxypropane (3 25 mmol) were added under positive N_2 pressure. 200 mg of $NaHCO_3$ (2 38 mmol) was added to quench the reaction after completion of reaction monitored by tlc, and then 20 ml of water was poured into the bottle The organic layer was separated and the water layer was extracted with CH_2Cl_2 3 times The organic layer was combined and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 *in vacuo* gave a residue which was purified by column chromatrography (silica gel, petroleum ether · ethyl acetate = 4 . 1) to obtain 360 mg of **7a** as a pale oil (91 1 % yield) $[\alpha]_D^{25}$ +96.33° (c=1.84 , $CHCl_3$). Ir (neat) cm^{-1} 3050, 1730, 1650, 1450 ^1H Nmr ($CDCl_3$) δ 1 40 (s, 3H, CH_3); 1 51 (s, 3H, CH_3), 2.90 (m, 1H, H5); 3 20 (m, 1H, H5'), 4.00 (m, 1H, H4), 4.30 (m, 1H, H3), 4.70 (s, 2H, C$\underline{H_2}$Ph); 5 25-5.40 (m, 2H, H1 and H1'), 5.78 (m, 1H, H2); 7.40 (m, 10H, 2 x Ph). Ms. m/z 352 (M^++1); 105 (-COPh); 91 (-Bn).

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3,4-*O*-isopropylidene-2-hydroxymethylpyrrolidine (9). To a solution of 915 mg of **7a** (2 61 mmol) in 20 ml of THF, 10 ml of DIBAL (1.0 M in toluene) was added at -78°C. 20 ml of water was added to quench the reaction after completion of reaction monitored by tlc. The mixture was stirred for 10 min and filtered through a pad of silica gel, then extracted with EtOAc 4 times. The organic layer was dried over anhydrous Na_2SO_4 Removal of EtOAc *in vacuo* gave a viscous oil Immidiately, 20 ml of DME, 10 ml of water and 500 mg of $NaHCO_3$ were added to the

viscous oil, then 1.1 g of I_2 (4.3 mmol) was added at 0°C The mixture was stirred overnight. Then, 6 ml of sat aq. $Na_2S_2O_3$ was added to quench the reaction. A viscous yellow oil was obtained after usual workup. To the yellow oil, 28 ml of THF, 27 ml of 4N aq. NaOH and 0 5 g of $[CH_3(CH_2)_3]_4N^+I^-$ were added The mixture was stirred at room temperature for 2 days THF was removed under reduced pressure and the water layer was extracted with EtOAc 4 times. The EtOAc layer was combined, washed with sat. aq. NaCl and dried over anhydrous Na_2SO_4 Removal of EtOAc gave a residue which was purified by column chromatography (silica gel, petroleum ether : ethyl acetate = 4 : 1) to produce **9** (307 mg, 44.8 % yield from **7a**) and **10** (76 mg , 11.1% yield from 7a) as pale viscous oil **9** $[\alpha]_D^{25}$ -76° (c=2.4, CH_2Cl_2). Ir (neat) cm^{-1}: 3450, 1380; 1240. ^1H Nmr ($CDCl_3$) δ: 1.32 (s, 3H, CH_3); 1.55 (s, 3H, CH_3); 2.13 (dd, $J_{5,5'}$=11 1 Hz, $J_{5,4}$= 4.7 Hz, 1H, H5); 2.37 (m, 1H, H2), 2.70 (br, 1H, -OH); 3.08 (d, $J_{5,5'}$=11 1 Hz, 1H, H5'); 3.95 (m, 2H, C<u>H</u>$_2$OH); 3.22 and 4 04 (AB, J=13 4 Hz, 2H, C<u>H</u>$_2$Ph); 4.59 (dd, $J_{3,4}$=6 4 Hz, $J_{4,5}$=4.7 Hz, 1H, H4); 4 72 (dd, $J_{3,4}$=6.3 Hz, $J_{2,3}$=4 9 Hz, 1H, H3); 7.31 (s, 5H, -Ph). Ms· m/z 263 (M^+), 232 (M-CH_2OH); 91 (base). **10**: $[\alpha]_D^{25}$ +9 1° (c=1.6, CH_2Cl_2). Ir (neat) cm^{-1}: 3450; 3050; 1500, 1380, 1240 ^1H Nmr ($CDCl_3$) δ· 1.37 (s, 3H, CH_3), 1.56 (s, 3H, CH_3); 2 37 (dd, $J_{2,2'}$=11.8 Hz, $J_{2,3}$= 4.2 Hz, 1H, H2); 2 44 (dd, $J_{6,6'}$=11.9 Hz, $J_{6,5}$=6 5 Hz, H6), 2.60 (dd, $J_{6,6'}$=11 9 Hz, $J_{6',5}$= 4.2 Hz, H6'); 2 74 (dd, $J_{2,2'}$=11.8 Hz, $J_{2',3}$= 5 9 Hz, 1H, H2'); 3.56 (s, 2H, C<u>H</u>$_2$Ph), 3.88 (m, 1H, H5), 4 22 (m, 2H, H2 and H3); 7.31 (s, 5H, -Ph) Ms: m/z 263 (M^+, 5.2), 232 (M-CH_2OH, 15); 91 (CH_2Ph, base).

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3,4-*O*-isopropylidene-2-bromomercuriumpyrrolidine (11a). 4 ml of DIBAL (1.0 M in toluene) was added at -78°C under N_2 to a solution of 182 mg of **7a** (0.52 mmol) in 20 ml of THF. The same procedure was taken as before to obtain a pale viscous oil **7b**, which was dissloved in 6 ml of THF. 500 mg of $Hg(OCOCF_3)_2$ (1.17 mmol) was then added to the solution at room temperature. The mixture was stirred overnight 20 ml of sat. aq. $NaHCO_3$ was added and the resultant mixture was stirred for 0.5 h, then 20 ml of sat aq. KBr was added to the mixture. The stirring was continued for 2 h. After usual workup, the mixture was subjected to column chromatography (silica gel, petroleum ether : ethyl acetate = 15 · 1) to afford **11a** (145 mg, 46.9 % yield from **7a**) and **11b** (24 mg, 7 8% yield from **7a**) as pale viscous oil. **11a**. $[\alpha]_D^{25}$ -14.6° (c = 2 6, CH_2Cl_2) Ir (neat) cm^{-1}· 3050; 1500, 1380, 1200 ^1H Nmr($CDCl_3$) δ: 1.42 (s, 3H, CH_3), 1 60 (s, 3H, CH_3); 1.99 (d, $J_{6,6'}$=12.7 Hz, 1H, C<u>H</u>$_2$HgBr), 2 10 (dd, $J_{6,6'}$=12.7 Hz, $J_{2,6}$=5.4 Hz, 1H, C<u>H</u>$_2$HgBr); 2.23 (dd, $J_{5,5'}$=11 3 Hz, $J_{4,5}$=4.9 Hz, 1H, H5); 2 75 (m, 1H, H2); 3 09 (d, $J_{5,5'}$=11.3 Hz, 1H, H5'); 3.20 and 3.90 (AB, J=13.3 Hz, 2H, C<u>H</u>$_2$Ph); 4.48 (m, 1H, H4); 4.58 (m, 1H, H3), 7 33 (s, 5H, -Ph). Ms. m/z 528 (M^++1); 527 (M^+); 246 (M-HgBr); 232 (M-CH_2HgBr), 91(-CH2Ph). HRms· (fragment M-HgBr) exact mass 246.1512 (calcd for $C_{15}H_{20}NO_2$ 246.1494). **11b**. $[\alpha]_D^{25}$ -5.2° (c = 1.2, CH_2Cl_2) Ir (neat) cm^{-1}: 3050, 2990; 1500; 1380; 1200. ^1H Nmr($CDCl_3$) δ: 1.34 (s, 3H, CH_3); 1 52 (s, 3H, CH_3); 2.20 (dd, $J_{6,6'}$=11.2 Hz, $J_{2,6}$=5.6 Hz, 1H, C<u>H</u>$_2$HgBr); 2.39 (d, $J_{6,6'}$=11.2 Hz, 1H, C<u>H</u>$_2$HgBr); 2.52 (m, 1H, H5); 2.97 (m, 1H, H2), 3 31 (m, 1H, H5'); 3.42 and 3.95 (AB,

J=12.6 Hz, 2H, C$\underline{H}_2$Ph), 4.09 (m, 1H, H4); 4.65 (m, 1H, H3), 7 31 (s, 5H, -Ph). Ms: m/z 528 (M^++1); 526 (M^+-1), 246 (M-HgBr); 232 (M-CH_2HgBr); 91(-CH2Ph)

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3,4-*O*-isopropylidene-2-hydroxymethylpyrrolidine(9) from 11a. In a 50 ml flask, oxygen was bubbled to the suspension of 11 mg of $NaBH_4$ (0.29 mmol) in 4 ml of DMF for 0.5 h 100 mg of **11a** (0.19 mmol) in 10 ml of DMF was added dropwise in 0.5 h Oxygen was bubbled contiunously for 0 5 h The mixture was filtered through a pad of celite Removal of DMF *in vacuo* gave a mixture, which was purified by column chromatography (silica gel, petroleum ether ethyl acetate = 4 · 1) give **9** (34 mg , 68 % yield) as a pale viscous oil .

Preparation of hydrochloride of 1,4-dideoxy-1,4-imino-D-lyxitol(1·HCl). 50 mg of **9** (0.19 mmol) was dissolved in 12 ml of MeOH, 80 mg of $Pd(OH)_2$ (0.57 mmol) was added and the resultant mixture was stirred under H_2 atomsphere at room temperature The mixture was filtered and 2.5 ml of 2 N aq. HCl was added The stirring was contiuned for 1 h The MeOH and water were removed *in vacuo* gave a residue which was washed with Et_2O and cooled MeOH to obtain 1·HCl (22 mg , 68.1% yield) as a white solid. mp 156.5-158.0°C (G.N Austin, P.D Baird, G.W.J.Fleet, J M Peach, P.W.Smith, and D J.Watkin, *Tetrahedron*, 1987, **43**, 3095 157-159°C).

Synthesis of *N*-benzyl-4-*epi*-(-)-anisomycin.

Preparation of (2*S*,3*R*,4*S*)-*N*-benzyl-*N*-benzoyl-2,3-*O*-isopropylidene-4.5-dihydroxypentylamine (12). 1.1 g of **7a** (3.1 mmol) was dissolved in 30 ml of *tert*-Butyl alcohol and 30 ml of water, then 3 4 g of $K_3Fe(CN)_6$ (10.3 mmol) and 1 43 g of K_2CO_3 (10.3 mmol) were added. 3 ml of 0.05 M solution of OsO_4 in *tert*-Butyl alcohol was added to the reaction *via* syringe. The mixture was stirred at room temperature and the reaction was monitored by the disappearance of **7a** with tlc. After the completion of the reaction, 3 g of $Na_2S_2O_3$ (19 0 mmol) was added and the mixture was stirred for 2 h Removal of tert-Butyl alcohol gave a residue which was extracted with EtOAc 4 times. After usual workup and column chromatography (silica gel, petroleum ether ethyl acetate = 2 1), **12** (985 mg , 74.9 % yield) as a white solid and epimer of **12**(212 mg , 16.1 % yield) as a viscous oil were obtained **12** mp 48 0-49.5°C. $[\alpha]_D^{25}$ +82 1° (c=0.81, CH_2Cl_2) Ir (KBr) cm^{-1}: 3350; 1610, 1380, 1240. ^{1}H Nmr ($CDCl_3$) δ 1 35 (s, 3H, CH_3); 1.40 (s, 3H, CH_3); 3.18-4.00 (m, 6H, C$\underline{H}_2$NC$\underline{H}_2$Ph and 2-OH); 4.18 (m, 2H, HOC$\underline{H}_2$-), 4.70-4.82 (m, 3H, 3-C$\underline{H}$OH), 7.28-7.50 (m, 10H, 2-Ph). Ms: m/z 386 (M^++1); 385 (M^+), 280 (M-COPh); 105 (-COPh); 91 (-CH_2Ph) HRms: exact mass 385.1895 (calcd for $C_{22}H_{27}NO_5$ 385.1890). epimer of **12:** $[\alpha]_D^{25}$ +17 8° (c=0.41, CH_2Cl_2). Ir (film) cm^{-1}. 3340; 1610, 1240. ^{1}H Nmr ($CDCl_3$) δ· 1 33 (s, 3H, CH_3), 1.41 (s, 3H, CH_3); 3.15-3 98 (m, 6H, C$\underline{H}_2$NC$\underline{H}_2$Ph and 2-OH); 4.11 (m, 2H, HOC$\underline{H}_2$-), 4.70-4.80 (m, 3H, 3-C$\underline{H}$OH); 7 25-7 52 (m, 10H, 2-Ph) Ms: m/z 386 (M^++1); 385(M^+), 280(M-COPh); 105(-COPh), 91(-CH_2Ph)

Preparation of (3*S*,4*R*,5*S*)-*N*-benzyl-*N*-benzoyl-3,4-*O*-isopropylidene-5,6-epoxypentylamine(14). 750 mg of **12** (1.9 mmol) was dissolved in 15 ml of CH_2Cl_2. 7 ml of Et_3N (50.3 mmol) and 1.8 g of *p*-TsCl (9.5 mmol) were added at

0°C under positive N_2 pressure. After the completion of the reaction monitored by tlc, the reaction mixture was diluted with 150 ml of CH_2Cl_2, then was successively washed with 50 ml of 5% aq. HCl , 50 ml of sat. aq. $NaHCO_3$ and 100 ml of sat. aq. NaCl. Removal of CH_2Cl_2 gave a crude monotosylate, which was then dissolved in 20 ml of MeOH. 500 mg of K_2CO_3 (3 6 mmol) was added to the mixture and the resultant mixture was stirred for 20 min, then 40 ml of water was added and MeOH was removed *in vacuo*. The mixture was extracted with EtOAc 4 times. The EtOAc layer was combined, washed with 200 ml of sat. aq. NaCl 2 times and dried over anhydrous Na_2SO_4. Removal of the solvent gave a residue which was purified by flash column chromatography (silica gel , petroleum ether · ethyl acetate = 5 · 1) to give 350 mg of pure epoxide (**14**) as a pale viscous oil with 85.2% yield from **12**. $[\alpha]_D^{25}$ + 69.2° (c = 0.15, CH_2Cl_2). Ir (neat) cm^{-1}: 3030; 1630; 1380, 1240. ^1H Nmr ($CDCl_3$) δ: 1 37 (s, 3H, CH_3), 1.48 (s, 3H, CH_3); 2 63 (m, 1H, H2), 2.79 (m, 1H, H2'), 2.93 and 3 25 (m, 2H, H6); 3 58 and 4.35 (AB, J=12.7 Hz, 2H, CH_2Ph); 3 78 (m, 1H, H5); 4 65-4 81 (m, 2H, H3 and H4), 7.20-7.46 (m, 10H, 2-Ph). Ms. m/z 368 (M^++1); 367 (M^+); 262 (M-COPh); 105 (-COPh); 91 (-Bn). HRms: exact mass 367.17825 (calcd for $C_{22}H_{25}NO_4$ 367.17853).

(3*S*,4*R*,5*S*)-*N*-benzyl-*N*-benzoyl-3,4-*O*-isopropylidene-5-hydroxy-6-(4-methoxyphenyl)pentylamine(15). To a solution of 400 mg of **14** (1.1 mmol) in 10 ml of THF, 80 mg of CuI (0 4 mmol) was added 6 ml of (4-methoxyphenyl)magnesium bromide (prepared with 0 5 g of Mg (20 8 mmol), 2.5 ml of 4-bromoanisole in 18 ml of THF) was added dropwise at -10°C. After completion of the reaction monitored by tlc , 20 ml of sat aq NH_4Cl was added to quench the reaction THF was removed *in vacuo* and the mixture was extracted with Et_2O 4 times The etheral layer was combined, washed with sat. aq. NaCl and dried over anhydrous Na_2SO_4. After column chromatography (silica gel, petroleum ether : ethyl acetate = 6 : 1) , 440 mg of pure **15** was obtained as a white solid. (85.2% yield). mp 38.0-39.0°C. $[\alpha]_D^{25}$ +57.8° (c =0.43, CH_2Cl_2). Ir (KBr) cm^{-1}: 3320; 1620; 1460; 1240. ^1H Nmr ($CDCl_3$) δ: 1.37 (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 2.62 (m, 1H, C$\underline{H}_2$N); 3 04 (d, J=11.4 Hz, 1H, C$\underline{H}_2$N); 3.20 and 3.90 (m, 2H, MeOPhC$\underline{H}_2$-); 3 79 (s, 3H, -OMe), 3.40 and 4.25 (AB, J=14.4 Hz, 2H, C$\underline{H}_2$Ph); 4.61 (m, 1H, -C$\underline{H}$OH); 4.70-4.73 (m, 2H, 2-C$\underline{H}$O-); 6.82 (d, J=7 5 Hz, 2H, 2H of MeOPh), 7.15 (d, J=7.6Hz, 2H, 2H of MeOPh), 7.35-7 42 (m, 10H, 2-Ph).Ms: m/z 476 (M^++1); 354 (M-CH_2PhOMe); 105 (-COPh), 91 (-Bn). Anal. Calcd for $C_{29}H_{33}NO_5$· C, 73.26; H, 2.95; N, 6.95. Found. C, 73.40; H, 2.75; N, 6.92.

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3,4-*O*-iisopropylidene-2-(4-methoxybenzyl)pyrrolidine(16). 100 mg of **15** (0.2 mmol) was dissolved in 3 ml of THF 1 ml of DIBAL (1.0 M in toluene) was added at -78°C *via* syringe under N_2 atomsphere The mixture was stirred at -78°C for 3 h until the completion of the reaction monitored by tlc. 2 ml of water was added to quench the reaction and the mixture was filtered through a pad of silica gel then extracted with EtOAc, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give a crude debenzoyl product as an oil, which was dissolved in 4 ml

of CH_2Cl_2 immediately 120 mg of PPh_3 (0.46 mmol) and 0.07 ml of DEAD (0.44 mmol) were added under N_2 atomsphere The mixture was stirred at room temperature overnight and the reaction was monitored by tlc. 2 ml of water was added when the reaction completed. After removal of CH_2Cl_2, the mixture was extracted with Et_2O 3 times After usual workup, the residue was subjected to column chromatography (silica gel , petroleum ether : ethyl acetate = 10 . 1) to give 32 mg of pure **16** as a pale viscous oil with 43 % yield. $[\alpha]_D^{25}$ -24 5° (c = 1.74 , CH_2Cl_2). Ir (neat) cm^{-1}· 3030; 1460, 1380; 1240 ^1H Nmr ($CDCl_3$) δ: 1.30 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 2 30 (dd, $J_{5,5'}$=12.9 Hz, $J_{4,5}$=1 74 Hz, 1H, H5); 2 58 (dd, $J_{6,6'}$=14 2 Hz, $J_{2,6}$=8.4 Hz, 1H, H6); 2.84 (dd, $J_{6,6'}$=14 2 Hz, $J_{2,6'}$=2 3 Hz, 1H, H6'), 3.00 (dd, $J_{5,5'}$=12.9 Hz, $J_{4,5'}$=12 8 Hz); 3.18 (m, 1H, H2); 3.82 (s, 3H, OMe), 3.24 and 3.86 (AB, J=12 9 Hz, 2H, C<u>H</u>$_2$Ph); 3.98 (m, 1H, H3); 4.42 (m, 1H, H4), 6 85 (d, J=8 75 Hz, 2H, 2H of *p*-MeOPh-); 7 15 (d, J=8.64 Hz, 2H, 2H of *p*-MeOPh-), 7 25 (m, 5H, Ph). Ms: m/z 354 (M^++1), 353 (M^+); 233 (M-PhOMe); 91 (-Bn). HRms: exact mass 353.19936 calcd for $C_{22}H_{27}NO_3$ 353 19932

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3,4-dihydroxy-2-(4-methoxybenzyl)pyrrolidine(17). To a solution of 120 mg of **16**(0.34 mmol) in 2 ml of THF, was added 4 ml of 2N aq. HCl . The mixture was stirred overnight and 5 ml of sat. aq $NaHCO_3$ was added Removal of THF gave a residue, which was extracted with EtOAc 4 times. The EtOAc layer was washed with sat. aq. NaCl, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* 84.6 mg of pure **17** was obtained as a pale viscous oil with 80.0 % yield after purification with column chromatography on silica gel (petroleum ether · ethyl acetate = 1 · 5). $[\alpha]_D^{25}$ +5.36° (c =0.88, CH_2Cl_2). Ir (neat) cm^{-1}: 3350, 1460; 1380; 1240. ^1H Nmr ($CDCl_3$) δ: 2.49 (dd, $J_{5,5'}$=11.1 Hz, $J_{4,5}$=6 7 Hz, 1H, H5); 2.71 (d, $J_{5,5'}$=11 2 Hz, 1H, H5'), 2 82-3.01 (m and br, 4H, H6, H6' and 2 x OH), 3 79 (s, 3H, -OMe); 3 91 (m, 1H, H2); 3 27 and 4.07 (AB, J=13.1 Hz, 2H, C<u>H</u>$_2$Ph); 4.07 (m, 2H, H3 and H4); 6 85 (d, J=8 5 Hz, 2H, 2H of *p*-MeOPh-); 7 25 (d, J=8 31 Hz, 2H, 2H of *p*-MeOPh-), 7.31 (s, 5H, Ph) Ms. m/z 313 (M^+); 121 (-CH_2PhOMe), 91(-Bn).

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3-hydroxy-2-(4-methoxybenzyl)-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine (18). To a solution of 25 mg of **17** (0.08 mmol) in 0.5 ml of DMF, was added 25 mg of imidazole (0 37 mmol) and 30 mg of *tert*-butyldimethylsilyl chloride (0.20 mmol), and the mixture was stirred at room temperature for 50 min The reaction mixture was chromatographed on silica gel (petroleum ether . ethyl acetate = 12 · 1) to give 30.4 mg of **18** in 89% yield as a colorless oil. $[\alpha]_D^{25}$ -2.3° (c = 0 85 , CH_2Cl_2). Ir (neat) cm^{-1}: 3400, 1460; 1380 ^1H Nmr ($CDCl_3$) δ· 0.00 (s, 6H, 2 x CH_3); 0.86 (s, 9H, 3 x CH_3), 2.49 (m. 1H, H5); 2.72 (m, 1H, H5'); 2.85 (br, 2H, H6 and -OH); 3.10 (dd, $J_{6,6'}$=12 8 Hz, $J_{6',2}$=9.95 Hz, 1H, H6'); 3.76 (s, 3H, OMe); 3 79 (dd, $J_{2,6'}$=9 90 Hz, $J_{2,3}$=4.55 Hz, 1H, H2), 3 40 and 4 04 (AB, J=13 5 Hz, 2H, C<u>H</u>$_2$Ph); 3 85 (m, 1H, H3); 4.17 (dd, $J_{4,5}$=12.0 Hz, $J_{3,4}$=5.06 Hz, 1H, H4), 6.83 (d, J=8.43 Hz, 2H), 7 24 (d, J=8.45 Hz, 2H); 7.33 (m, 5H, Ph). Ms. m/z 427 (M^+); 312 (M-TBDMS).

(2*R*,3*S*,4*R*)-*N*-benzyl-3-acetoxy-2-(4-methoxybenzyl)-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine (19). A mixture of 18 mg of **18** (0 04 mmol) and 0.1 ml of acetic anhydride (1.05 mmol) in 0.8 ml of pyridine was stirred at room temperature for 2 days. Concentration *in vacuo* followed by chromatography on a silica gel column (petroleum ether : ethyl acetate = 16 · 1) gave 18 mg of **19** with 92% yield as a colorless oil. $[\alpha]_D^{25}$ +19 2° (c = 0.55 , CH_2Cl_2). Ir (neat) cm^{-1}: 3030; 1710; 1460; 1380. ^1H Nmr ($CDCl_3$) δ -0.39 (s, 3H, CH_3), -0.08 (s, 3H, CH_3); 0 81 (s, 9H, 3 x CH_3), 2 09(s, 3H, -OCOC$\underline{H}_3$), 2 53 (dd, $J_{6,6'}$=13.6 Hz, $J_{2,6}$=8.4 Hz, 1H, H6); 2 73 (dd, $J_{6,6'}$=13 6 Hz, $J_{2,6'}$=4.1 Hz, 1H, H6'); 2.83 (m, 2H, H5 and H5'), 3.80 (s, 3H, OMe); 3.50 and 3.84 (AB, J=13.7 Hz, 2H, C$\underline{H}_2$Ph), 3.88 (m, 1H, H2), 4.98 (dd, $J_{3,4}$=5 3 Hz, $J_{2,3}$=2 6 Hz, 1H, H3); 5.46 (m, 1H, H4), 6 80 (d, J=8 7 Hz, 2H); 7.00 (d, J=8.6 Hz, 2H), 7.35 (m, 5H, Ph) ^{13}C Nmr δ: 20.9 (Si$\underline{C}$H$_3$); 21.3 (CO$\underline{C}$H$_3$), 25.9 (SiC($\underline{C}$H$_3$)$_3$), 29.8 (C6); 39.2 (N$\underline{C}$H$_2$Ph); 55.3 (O$\underline{C}$H$_3$); 59.2 (C5), 70 9 (C2), 74 1 (C3), 75.4 (C4). Ms· m/z 469 (M^+); 426 (M-Ac), 91 (-Bn).

Preparation of (2*R*,3*S*,4*R*)-*N*-benzyl-3-acetoxy-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine (20). To a stirred solution of 15 mg of **19** (0.03 mmol) in 2 ml of THF at 0°C was added 0.01 ml of 1 M solution of *tetra*-n-butylammonium fluoride After stirring at 0°C for 30 min, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether · ethyl acetate = 2 : 1) to give 9.5 mg of **20** with 84% yield as a colorless oil. $[\alpha]_D^{25}$ +19 2° (c = 0.15, CH_2Cl_2). Ir (neat) cm^{-1}: 3350; 1710; 1460; 1380. ^1H Nmr ($CDCl_3$) δ 2 06 (s, 3H, OCOC$\underline{H}_3$); 2.77 (dd, $J_{6,6'}$=13.5 Hz, $J_{2,6}$=7.2 Hz, 1H, H6), 2.82 (d, $J_{4,5}$=6.4 Hz, 2H, H5 and H5'); 2.91 (dd, $J_{6,6'}$=13 5 Hz, $J_{2,6'}$=4.1 Hz, 1H, H6'), 3 64 (s, 2H, C$\underline{H}_2$Ph), 3.71 (dd, $J_{2,6}$=7.1 Hz, $J_{2,3}$=4.9 Hz, 1H, H2); 3 76 (s, 3H, OMe), 4.75 (dd, $J_{4,5}$=11 4 Hz, $J_{3,4}$=6.5 Hz, 1H, H4); 4.91 (dd, $J_{3,4}$=6.4 Hz, $J_{2,3}$=4.9 Hz, 1H, H3); 6.78 (d, J=8.6 Hz, 2H); 7 04 (d, J=8.6 Hz, 2H); 7 34 (m, 5H, -Ph). Ms. m/z 356 (M^++1), 355 (M^+), 91 (-Bn).

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