STEREOSPECIFIC SYNTHESIS OF A RIBOSYL-DIAZEPANONE DERIVATIVE; A SYNTHETIC APPROACH FOR ELUCIDATION OF THE STEREOCHEMISTRY OF A LIPID NUCLEOSIDE ANTIBIOTIC LIPOSIDOMYCIN B

Marianne R. Spada[1], Makoto Ubukata,* and Kiyoshi Isono[2]

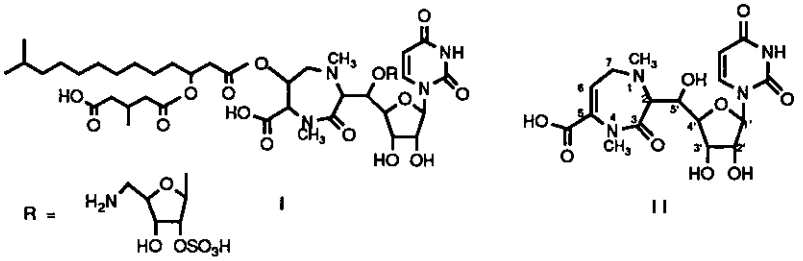
Antibiotics Laboratory
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351-01, Japan

Abstract - A new type of ribosyl-diazepanone derivative (**23**), the core ribosyl 7-membered heterocycle of the nucleoside antibiotic liposidomycin B has been synthesized using a chiral synthetic route that could offer accessibility to any of possible stereoisomers of **23**. Starting from readily available *cis*-1,4-butenediol and β-D-ribose, epoxides (**4**) and (**14**) were obtained. Regioselective nucleophillic ring opening of these epoxides subsequently to the several reaction steps afforded key intermediates amine (**9**) and azido acid (**19**) which were ultimately coupled to furnish amide (**20**). During hydrogenolysis of azido aldehyde (**22**) an intramolecular Schiff base formation occurred yielding the desired product (**23**).

Recently, we reported the isolation and structure determination of the nucleoside antibiotic liposidomycin B (**I**; Figure 1), a bacterial peptidoglycan synthesis inhibitor.[3,4] This novel lipid nucleoside of unusual complexity possesses a branched fatty acid side chain attached to a substituted diazepanone ring containing three chiral centers, one of which is linked *via* an intervening asymmetric carbon to the nucleoside, uridine. It was found that degradation of **I** by acid hydrolysis gave the diazepanone nucleoside subunit (**II**).[4] Examination of the

coupling constants from nmr and the NOE difference spectra suggested a (1'*R*, 2'*R*, 3'*S*, 4'*R*, 5'*S*, 2*S*) configuration for **II**.[5,6]

Figure 1.



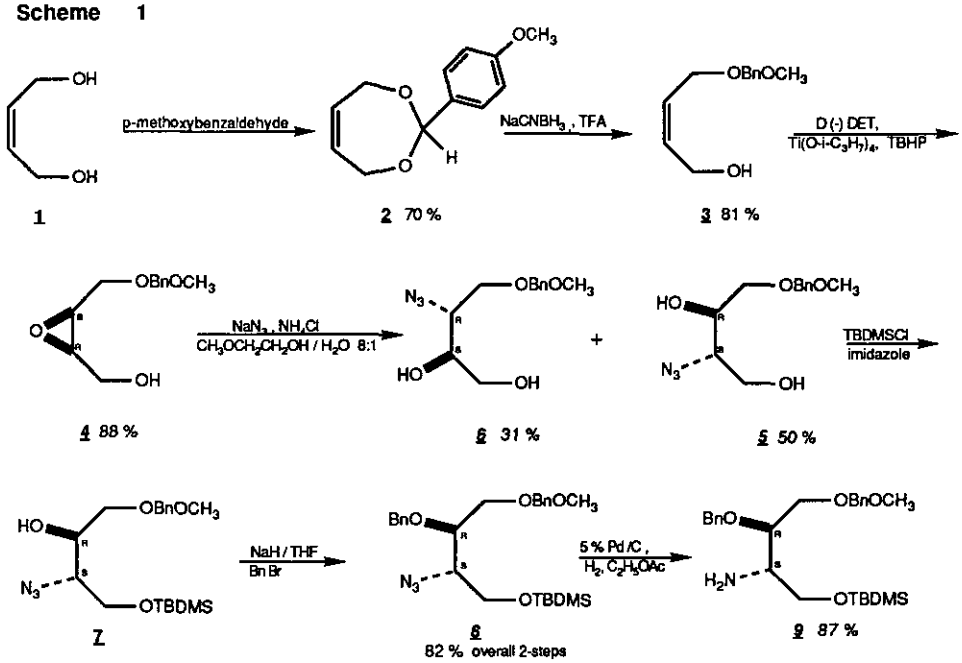
Unfortunately the nmr data did not provide conclusive evidence regarding the configurations of the three asymmetric carbons in the 7-membered ring and at ribosyl C-5'. In addition, low productivity of liposidomycins by *Streptomyces griseosporeus* and difficulty encountered in separation of pure liposidomycin B from the closely related components, limited the availability of pure liposidomycin B. Limited quantities also made stereochemical elucidation difficult by degradative methods. The present goal of this study is to develop a chiral synthesis that will help to establish the stereochemistry of liposidomycin B. First, our efforts were directed towards the synthesis of ribosyl-diazepanone subunit of liposidomycin B. Since four of the configurations of the asymmetric centers are speculatively assigned, emphasis was given to a synthetic plan that could offer access to any specific stereoisomer desired. Compound (**23**) was selected as our initial target since the stereochemistries at C2 and C5' correspond to that tentatively assigned to the liposidomycin subunit (**II**).[7]

In this paper we report a stereospecific synthesis for **23**, a new type of ribosyl-diazepanone derivative. The approach undertaken is amenable to the synthesis of each of the stereoisomers of the liposidomycin fragment. The construction of the diazepanone subunit of **23** is based on reductive cyclization of azide (**22**). Compound (**20**) was obtained *via* coupling of key intermediate amine (**9**) with azido acid (**19**) (Scheme 3) The Sharpless catalytic asymmetric epoxidation method[8] proved to be a valuable and versatile tool in controlling the stereochemistry of epoxides (**4**) and (**14**) (Schemes 1 and 2). Regioselective nucleophilic ring opening of these epoxides afforded alcohols (**5**) and (**15**) of the desired

stereochemistry. Protecting groups for hydroxyl functions were chosen on the basis of their stability and lability under the given reaction conditions.

Scheme 1 depicts the synthesis of **9** *via* a 7-step reaction sequence from readily available *cis*-2-butene-1,4-diol (**1**). Reaction of **1** with *p*-methoxybenzaldehyde gave benzylidene derivative (**2**) which was subsequently converted to allylic alcohol (**3**) by reduction with sodium cyanoborohydride.[9] Catalytic asymmetric epoxidation[8] of **3** using D-(-)-(DET), Ti(O-i-Pr)$_4$, TBHP and 3Å molecular sieves provided **4** having the expected 2*R*,3*S* configuration. Epoxide ring opening with sodium azide[10] afforded a mixture of regioisomeric azido diols (**5**) and (**6**), which was separated by silica gel chromatography (50 and 31% yield, respectively). ^{1}H Nmr analysis of *O*-diacetate of **5** showed a quartet at δ 5.12 ppm (J = 5.1 Hz) for the proton at C3 which coupled with C-4 methylene protons at δ 3.59 and 3.56 ppm (each dd, each J = 5.1 Hz and 10 Hz, each 1H), whereas the C-3 azido diacetate derived from **6** had a doublet of triplet at δ 5.24 ppm (C-2H, J = 4.4 and 6.1 Hz) which coupled with C-1 methylene protons at δ 4.31 ppm (dd, J = 4.4 and 12.1 Hz) and 4.12 ppm (dd, J = 6.1 and 12.1 Hz).

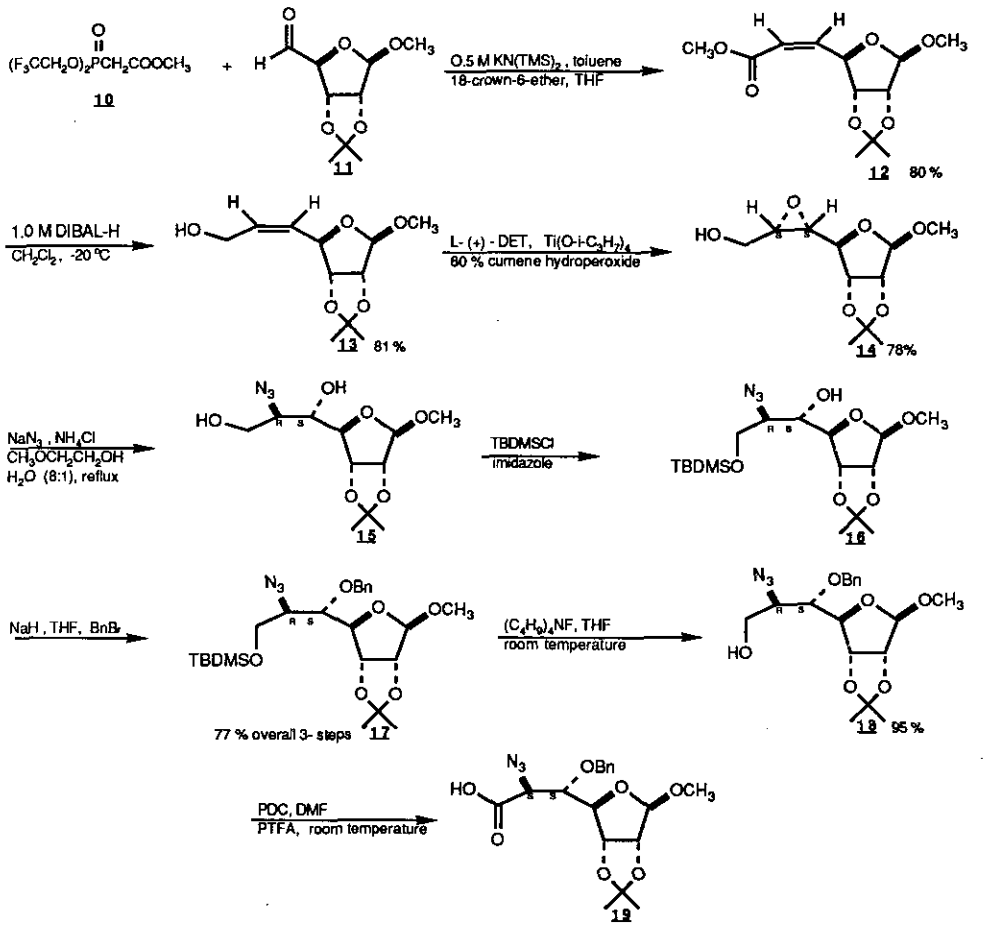
Scheme 1



Although compound (**5**) was selected for this synthetic sequence, compound (**6**) with a different chirality would be available if needed for future stereochemical studies of **I**.

Sequential protection of the primary and secondary hydroxyl functions of **5**, t-butyldimethylsilylation followed by benzylation provided **8**. Selective hydrogenation of azide (**8**) to amine (**9**) was accomplished without cleavage of the benzyl ether function at 1 atm using 5% Pd/C in ethyl acetate.

Scheme 2

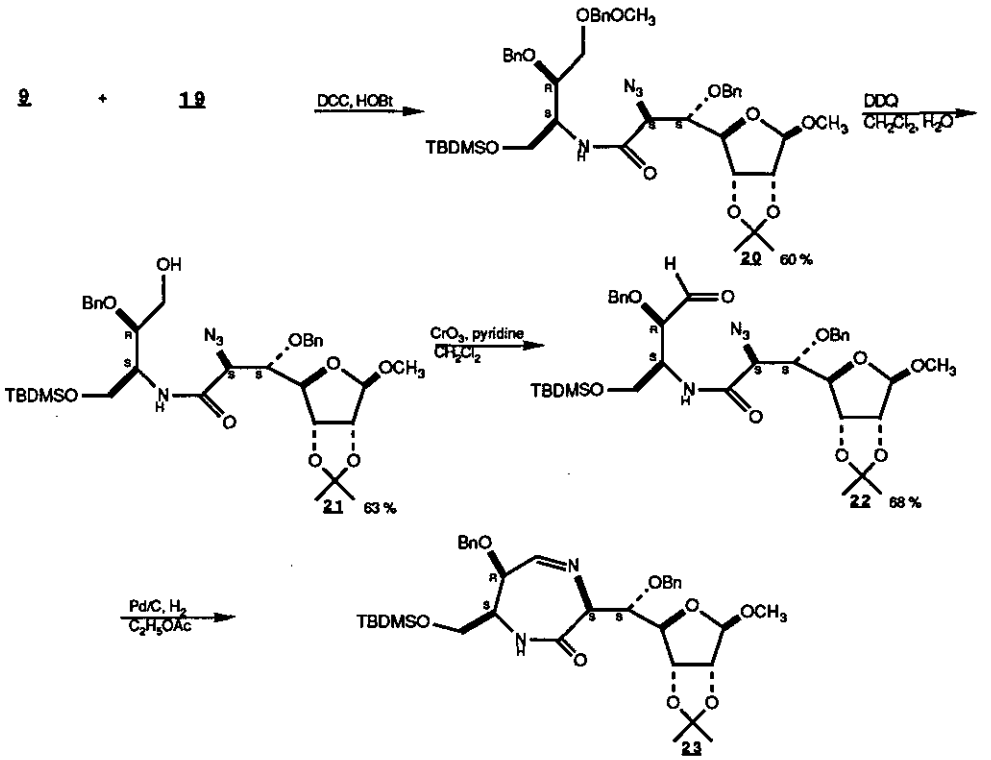


Preparation of key azido acid (**19**) is described in Scheme 2. Sugar aldehyde (**11**)[11] prepared by oxidation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside was reacted with bis(2,2,2-trifluoroethyl)methoxycarbonylmethyl phosphonate (**10**)[12] to give the *cis*-α,β-unsaturated ester (**12**). DIBAL-H reduction[13] of **12** afforded allylic alcohol (**13**) which was epoxidized to **14** by Sharpless procedure using 80% cumene hydroperoxide instead of TBHP.[8,14] Treating **14** with azide ion gave the regioselective ring opened C-6 azide (**15**)

in high yield (C-6 azide : C-5 azide of >95 : 5). Unequivocal confirmation of the regio- and stereochemistry was made by X-ray crystallography.[15] With the desired azido diol (**15**) in hand, our attention was again focused on protecting group chemistry. The TBDMS and Bn ether were chosen as candidates for this purpose. Sequential protection of the primary hydroxyl function with TBDMSCl and the secondary function with BnBr afforded the protected diol (**17**). Removal of the TBDMS group with tetra-*n*-butylammonium fluoride gave alcohol (**18**) which was then subjected to oxidation with PDC in DMF to furnish α-azido acid (**19**).[16,17] Coupling of key intermediates (**9**) and (**19**) (Scheme 3) was accomplished by treatment of acid (**19**) with HOBt/DCC[18] in DMF followed by addition of **9** to furnish amide (**20**). DDQ[19] provided a useful method for removal of the *p*-methoxybenzyl group without disturbing the benzyl ether affording alcohol (**21**). Oxidation of **21** with chromium trioxide/pyridine in methylene chloride gave the desired aldehyde (**22**) which underwent an intramolecular Schiff base formation during hydrogenation of the azido function furnishing imine (**23**). The structure and stereochemistry of **23** were confirmed by nmr, ^{1}H-^{1}H COSY, NOE spectroscopy and FDms. The difference NOE spectra data for **23**, (3.2 % NOE H-2 and H-5, 7.74% NOE H-7 and H-5, 4.8% NOE H-7 and H-6, 4.5% NOE H-2 and H-7, 6.2% NOE H-7 and H-2) support the 7-membered diazepine ring structure. Hydrogenation of imine followed by *N*-methylation would afford a diazepanone derivative, whose nmr data could be compared with those of the natural product.

In conclusion, the ribosyl substituted diazepanone derivative (**23**), a precursor of the ribosyl subunit of liposidomycin B and other structurally related liposidomycins has been synthesized. This synthetic approach can be adapted to generate other stereoisomers of **23**, thereby establishing the stereochemistry of liposidomycin B. Also, these intermediates as themselves or as nucleosides may prove to be interesting candidates for biological evaluation and structure-activity relationship studies.

Scheme 3



EXPERIMENTAL SECTION

Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected. Ir spectra were recorded with a 27 Grating spectrophotometer in cm^{-1} and calibrated at 1601 and 1028 with polystyrene film. ^1H Nmr spectra were measured with a JEOL GX400 or GSX500 spectrometer. $CDCl_3$ was used as solvent unless otherwise indicated with TMS as internal standard. Chemical shifts are given in δ (ppm) and coupling constants in hertz (Hz). NOE difference, decoupling and COSY experiments were performed on a JEOL GX400 spectrometer. ^{13}C Nmr spectra were measured with a JEOL FX100 spectrometer. Mass spectra were recorded on a Hitachi M80 instrument with the sample heater set at 200 °C, and a current of 20 eV. Optical rotations were measured with a Perkin-Elmer 241MC polarimeter at 23 °C. X-Ray diffraction data were collected on Rigaku automated four-circle diffractometer with graphite-monochromatized Mo *Kα* radiation. Crystallographic calculations were performed on a FACOM M-380 computer using UNICS III program system. Tlc analyses were carried out on Merck silica gel 60 F-254 (0.25mm).

Preparative tlc separations were performed on Merck silica gel 60 F-254 (0.50mm) 20x20 silica plates. Column chromatographic separations were carried out using Merck silica 60 (70-230 mesh). All commercial chemicals and reagents were used as received, unless stated otherwise. All solvents were distilled and dried over appropriate drying agents. Evaporations were performed under reduced pressure on rotary evaporators. Elemental analyses were performed at this Institute.

4,7-Dihydro-2-(4-methoxyphenyl)-1,3-dioxepin (2).

A round bottom flask equipped with a Dean-Stark trap was charged with *cis*-2-butene-1, 4-diol (**1**) (95 %, 5.00 g, 53.9 mmol) in benzene (100 ml). To the solution were added *p*-methoxybenzaldehyde (98 %, 7.70 g, 55.4 mmol) and 3 drops of trifluoroacetic acid. The reaction mixture was refluxed overnight,[20] allowed to cool and most of the benzene was evaporated. To the residue was added methylene chloride and the solution was successively washed with saturated sodium bisulfite, saturated sodium bicarbonate and water. After drying (Na_2SO_4) and evaporation of solvent, the crude material was purified by silica gel chromatography (hexane/ethyl acetate 8 : 2 v/v) to afford a syrup, 7.80 g (70%) of **2**; R_f = 0.70 (hexane/ethyl acetate 1 : 1 v/v); ir (NaCl) 2930, 2885, 2850, 1610, 1585, 1510, 1455, 1440, 1335, 1290, 1235, 1200, 1160, 1110, 1095, 1065, 1025, 810, 665 cm^{-1}; ^1H nmr δ 7.47 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.85 (s, 1H), 5.78 (s, 2H), 4.48 (d, J = 14 Hz, 2H), 4.25 (d, J = 14 Hz, 2H), 3.80 (s, 3H); Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.84; H, 6.86.

***cis*-4-*O*-(4-Methoxybenzyl)-2-butene-1,4-diol (3).**

Using a modified procedure of Johansson,[9] sodium cyanoborohydride (95 %, 3.66 g, 55.3 mmol) and trifluoroacetic acid (7.5 ml, 96.0 mmol) in 30 ml of DMF was added to a solution containing **2** (4.00 g, 19.4 mmol) in 60 ml of DMF. The reaction mixture was stirred at room temperature for 0.5 h, then carefully quenched with 0.1 *N* NaOH until pH 7. Solvent was evaporated under reduced pressure and the residue was dissolved in methylene chloride and washed with water. Purification by silica gel column chromatography (hexane/ethyl acetate 1 : 1 v/v) gave 3.27 g (81%) of **3**; R_f = 0.42 (hexane/ethyl acetate 1 : 1

v/v); ir (NaCl) 3380, 2930, 2855, 1610, 1585, 1510, 1460, 1290, 1235, 1165, 1060, 1025, 810 cm^{-1}; ^1H nmr (500 MHz) δ 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.78 (m, 1H), 5.69 (m, 1H), 4.44 (s, 3H), 4.14 (d, J = 6.7 Hz, 2H), 4.05 (d, J = 6.4 Hz, 2H) 3.79 (s, 3H); ^{13}C nmr 158.9, 132.5, 129.5, 129.4, 127.8, 113.8, 72.0, 65.3, 58.3, 55.1. Anal. Calcd for $C_{12}H_{16}O_3 \cdot 0.2H_2O$: C, 68.04; H, 7.80. Found: C, 68.01; H, 7.68.

(2*R*,3*S*)-2,3-Epoxy-4-*O*-(4-methoxybenzyl)butan-1,4-diol (4).

A dried flask was charged with 0.5 g of activated 3Å molecular sieves (powdered and heated at 160 °C overnight) and 25 ml of dry methylene chloride under nitrogen. To the mixture were added *via* a syringe D-(-)-diethyl tartarate (98%, 0.2 ml, 14 mol %), and titanium isopropoxide (97%, 0.3 ml, 10 mol %). The flask was cooled between -15 °C and -20 °C in an ethylene glycol/dry ice bath, and to the resulting solution was added *tert* -butyl hydroperoxide in 2,2,4-trimethyl pentane (3.0 *M*, 6.4 ml, 19.2 mmol). After constant stirring for 30 min, allylic alcohol (**3**) (2.00 g, 9.60 mmol) dried over activated 3Å molecular sieves in 25 ml of methylene chloride for 30 min was added *via* a cannula under a positive nitrogen pressure, then the molecular sieves were rinsed with methylene chloride (2 x 15 ml) and the washings were added to the above reaction mixture *via* a cannula. The reaction vessel was then placed in a refrigerator at -2 °C overnight. The reaction was quenched with 30 ml of water and the mixture was stirred vigorously for 30 min, then 10 ml of 30% aqueous NaOH saturated with NH_4Cl was added and stirring was continued for an additional 30 min. The mixture was filtered through a glass wool plug and the filtrate was extracted with methylene chloride (2 x 200 ml). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified on a silica gel column (hexane/ethyl acetate 1 : 1 v/v) to give 1.90 g (88%) of **4** which eventually solidified on standing to a waxy white solid, mp 95-96 °C; R_f = 0.28 (hexane/ethyl acetate 1 : 1 v/v); $[\alpha]_D$ +23.0° (c 1.0, $CHCl_3$); ir (NaCl) 3400 br, 2900, 1610, 1510, 1455, 1240, 1168, 1080, 1030, 820 cm^{-1}; ^1H nmr δ 7.26 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.54 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H), 3.68-3.77 (m, 3H), 3.61 (dd, J = 5.1 and 11.0 Hz, 1H), 3.28 (m, 1H), 3.21 (m, 1H), 2.13 (t, J = 6.0 Hz, 1H); ^{13}C nmr 159.5, 129.5, 113.8, 73.0, 67.7, 60.5, 55.8, 55.2, 54.8; Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.22.

(2*S*,3*R*)-2-Azido-4-*O*-(4-methoxybenzyl)butan-1,3,4-triol (5) and (2*S*, 3*R*)-3-azido-4-*O*-(4-methoxybenzyl)butan-1,2,4-triol (6).

To **4** (4.00 g, 17.8 mmol) were added 80 ml of methoxyethanol/water (8 : 1), sodium azide (5.80 g, 89.2 mmol) and ammonium chloride (2.00 g, 37.4 mmol). The mixture was refluxed for 3.5 h, allowed to cool and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with water. The aqueous layer was back-extracted with methylene chloride, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to give a crude material that was purified on a silica gel column (hexane/ethyl acetate 1 : 1 v/v). Fractions containing products (tlc, uv) were collected and concentrated to give 2.40 g (50%) of **5** and 1.46 g (31%) of **6** as syrups; **5** R_f = 0.40 (hexane/ethyl acetate 1 : 1 v/v); $[\alpha]_D$ +25.5^0 (c 0.86, $CHC1_3$); ir (NaCl) 3410 br, 2950, 2850, 2100, 1610, 1590, 1512, 1461, 1358, 1298, 1170, 1100, 1030, 815 cm^{-1}; ^{1}H nmr δ 7.26 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H). 4.50 (s, 2H), 3.96 (dt, J = 5.6 and 10.2 Hz, 1H), 3.81 (s, 3H), 3.75-3.90 (m, 2H), 3.50-3.60 (m, 3H), 2.51 (d, J = 5.1 Hz, 1H), 2.30 (t, J = 6.6 Hz, 1H); ^{13}C nmr 159.5, 129.5, 113.9, 73.2, 70.9, 70.7, 64.2, 62.8, 55.2; *O*-Diacetylation of **5** with acetic anhydride in pyridine at room temperature, ^{1}H nmr δ 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.12 (q, J = 5.1 Hz, 1H), 4.48 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.26 (dd, J = 4.2 and 11.7 Hz, 1H), 4.12 (dd, J = 7.8 and 11.7 Hz, 1H), 3.97 (ddd, J = 4.2, 5.1 and 7.8 Hz, 1H), 3.59 (dd, J = 5.1 and 10.0 Hz, 1H), 3.56 (dd, J = 5.1 and 10.0 Hz, 1H); **6** R_f = 0.32 (hexane/ethyl acetate 1 : 2 v/v); $[\alpha]_D$ -29.1^0 (c 0.93, $CHC1_3$); ^{1}H nmr δ 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H). 4.52 (s, 2H), 3.81(s, 3H), 3.80 (m, 1H), 3.74 (dd, J = 0.78 and 5.1 Hz, 1H), 3.68 (m, 1H), 3.67 (m, 1H), 3.62 (br dd, J = 5.2 and 9.7 Hz, 1H), 2.64 (br d, J = 5.4 Hz, 1H), 2.14 (t, J = 6.4 Hz, 1H); *O*-Diacetylation of **6**, ^{1}H nmr δ 7.26 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 5.24 (dt, J = 4.4 and 6.1 Hz, 1H), 4.48 (s, 3H), 4.31 (dd, J = 4.4 and 12.1 Hz, 1H), 4.12 (dd, J = 6.1 and 12.1 Hz, 1H), 3.72 (dt, J = 4.4 and 7.2 Hz, 1H), 3.63 (dd, J = 4.5 and 9.8 Hz, 1H), 3.57 (dd, J = 7.5 and 9.8 Hz, 1H), 2.06 (s, 3H), 2,05 (s, 3H); Anal. Calcd for a mixture of **5** and **6**, $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41. Found: C, 53.82; H, 6.45.

(2*S*, 3*R*)-2-Azido-1-*O*-(*tert*-butyldimethylsilyl)-4-*O*-(4-methoxybenzyl)butane-1, 3, 4-triol (7).

To **5** (1.24 g, 4.64 mmol) dissolved in dry DMF (40 ml) were added imidazole (0.37 g, 5.44 mmol) and *tert* -butyldimethylsilyl chloride (0.85 g, 5.47 mmol). The reaction mixture was stirred under nitrogen for 2 h at room temperature. Evaporation of the DMF gave a residue to which methylene chloride (150 ml) was added. The solution was washed with water (100 ml) and the organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to afford pure **7** (1.77 g, 100 % yield) as a syrup; R_f = 0.38 (hexane/ethyl acetate 2.5 : 0.7 v/v); $[\alpha]_D$ + 42.1^0 (c 1.0, $CHC1_3$); ir (NaCl) 3430 br, 2945, 2915, 2850, 2060, 1610, 1510, 1460, 1240, 1165, 1090, 1030, 826, 770 cm^{-1}; ^{1}H nmr δ 7.27 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.50 (s, 2H), 3.82-3.9 (m, 3H), 3.81 (m, 3H), 3.48-3.55 (m, 3H), 2.58 (br s, 1H), 0.86 (s, 9H), 0.09 (s, 6H); ^{13}C nmr 159.5, 129.9, 129.5, 114.0, 73.2, 70.9, 70.3, 64.2, 63.9, 55.3, 25.9, 18.2, -5.50. Anal. Calcd for $C_{18}H_{31}N_3O_4Si$: C, 56.66; H, 8.19; N, 11.01. Found: C, 56.51; H, 8.11; N, 10.83.

(2*S*, 3*R*)-2-Azido-3-*O*-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-*O*-(4-methoxybenzyl)butane-1, 3, 4-triol (8).

Alcohol (**7**) (1.77 g, 4.64 mmol) dissolved in dry THF (20 ml) was added *via* syringe to a suspension of sodium hydride (60% mineral oil dispersion prewashed with hexane, 260 mg, 6.49 mmol) in THF (10 ml). The mixture was allowed to stir for 1 h after which benzyl bromide (98%, 0.77 ml, 6.49 mmol) was added and stirring was continued for an additional 2.5 h. After this period the reaction was carefully quenched with water (1 ml), then methylene chloride (150 ml) was added and the resulting solution was washed with water (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude product that was purified by silica gel chromatography (hexane/ethyl acetate 8 : 1 v/v) furnishing 1.75 g of **8** as a gum (80% overall 2-steps from **5**); R_f = 0.83 (hexane/ethyl acetate 3 : 1 v/v); $[\alpha]_D$ + 60.3^0 (c 1.0, $CHC1_3$); ir (NaCl) 2945, 2915, 2850, 2070, 1610, 1510, 1460, 1240, 1090, 1030, 828, 770, 688 cm^{-1}; ^{1}H nmr δ 7.23-7.36 (m, 5H), 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.69 (d, J = 11.8 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.81 (m, 3H), 3.68-3.74 (m, 3H), 3.55-3.64 (m, 3H), 0.87 (s, 9H), 0.09 (s, 6H); ^{13}C nmr

159.5, 138.2, 130.0, 129.3, 128.3, 127.8. 127.7. 113.8, 76.8, 73.1, 73.0, 69.1, 64.1, 63.1, 55.2, 25.8, 18.2, -5.56. Anal. Calcd for $C_{25}H_{37}N_3O_4Si$: C, 63.66; H, 7.91; N, 8.91. Found: C, 63.55; H, 7.90; N, 8.78.

(2*S*, 3*R*)-2-Amino-3-O-benzyl-1-*O*-(*tert*-butyldimethylsilyl)-4-*O*-(4-methoxybenzyl)butane-1, 3, 4-triol (9),

Into a 100 ml round bottom flask containing ethyl acetate (30 ml) were added **8** (1.10 g, 2.33 mmol) and 5% Pd/C (500 mg). The stirred suspension was degassed and purged with hydrogen three times then kept under a hydrogen balloon with occasional degassing overnight. The mixture was filtered through a celite pad and the solid was rinsed with several portions of ethyl acetate. The combined filtrates were evaporated to afford 0.90 g (87%) of **9**, as a tacky gum which slowly solidified on standing; R_f = 0.25 (hexane/ethyl acetate 1 : 1 v/v), streaking, positive to ninhydrin spray; $[\alpha]_D$ + 11.0^0 (c 1.3, $CHCl_3$); ir (NaCl) 2950, 2930, 2850, 1610, 1510, 1460, 1250, 1090, 1030, 810, 690, 660 cm^{-1}; ^{1}H nmr δ 7.25-7.35 (m, 5H), 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.74 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.47 (br s, 2H), 3.81 (s, 3H), 3.60-3.69 (m, 3H), 3.59 (dd, J = 5.6 and 9.7 Hz, 1H), 3.50 (dd, J = 6.4 and 9.7 Hz, 1H), 2.95 (m, 1H), 1.55 (m, 2H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C nmr 159.7, 137.7, 130.3, 129.2, 128.2, 127.7, 127.4, 113.7, 78.2, 72.9, 70.4, 65.0, 55.2, 54.3, 25.8, 18.2, -5.50. Anal. Calcd for $C_{25}H_{39}NO_4Si$: C, 67.38; H, 8.82; N, 3.14. Found: C, 67.16; H, 8.76; N, 3.05.

Methyl [methyl (*Z*)-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranosid]uronate (12).

To a magnetically stirred solution of dry THF (80 ml) were added bis(2,2,2-trifluoroethyl) methoxycarbonylmethylphosphonate (**10**) (95%, 1.66 g, 5.55 mmol), 18-crown-6-ether (6.50 g, 24.7 mmol) and potassium bis(trimethylsilyl)amide (0.5 *M* in toluene, 10 ml, 5 mmol) at -78 ^{o}C (acetone/dry ice bath) under a nitrogen atmosphere. Aldo-ribose (**11**)[11] (1.00 g, 4.95 mmol) dissolved in 10 ml of methylene chloride was added *via* a syringe to the reaction mixture and the resulting mixture was stirred for 40 min. After this period the mixture was carefully quenched with 180 ml of saturated NH_4Cl solution and warmed to room

temperature. The mixture was then extracted with ethyl ether (2 x 250 ml). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and evaporated to give 3.26 g of crude product Purification by column chromatography on silica gel (methylene chloride/hexane 8 : 2 v/v) gave 1.00 g (78%) of **12** as a syrup; R_f = 0.78 (hexane/ethyl acetate, 1 : 1 v/v); ir (NaCl) 2980, 2940, 2830, 1722, 1645, 1432, 1385, 1370, 1360, 1265, 1192, 1158, 1100, 1090, 1055, 1030, 989, 950, 860, 810, 768 cm^{-1}; ^1H nmr δ 6.33 (dd, J = 9 and 10 Hz, 1H), 5.85 (d, J = 11 Hz, 1H), 5.70 (d, J = 9.0 Hz, 1H), 5.10 (s, 1H), 4.65 (d, J = 6.2 Hz, 1H) 4.59 (dd, J = 0.9, 6.2 Hz, 1H), 3.75 (s, 3H), 3.40 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H); ^{13}C nmr 165.9, 149.9, 119.9, 112.3, 110.5, 86.3, 85.1, 84.8, 54.8, 51.5, 26.4, 25.1. Anal. Calcd for $C_{12}H_{18}O_6 \cdot 0.2H_2O$: C, 55.05; H, 7.08. Found: C, 55.17; H, 6.97.

Methyl (*Z*)-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranoside (13).

To a solution of **12** (4.50 g, 17.4 mmol) in 50 ml of dry methylene chloride was added diisobutylaluminum hydride (1.0 *M* in hexane, 52.3 ml, 52.3 mmol) at a temperature range from -20 °C to -10 °C (ethylene glycol/dry ice bath) under a nitrogen atmosphere. The reaction mixture was stirred for 1.5 h, then carefully quenched with a saturated NH_4Cl solution. The mixture was then filtered through a glass wool plug, the solid was rinsed several times with methylene chloride and the filtrates were transferred into a separatory funnel. The layers were then separated and the aqueous phase was extracted with methylene chloride. After separation the organic fractions were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to give a crude material that was purified on a silica gel column (hexane/ethyl acetate 1 : 1 v/v) to afford 3.25 g (81%) of **13** as a colorless syrup; R_f = 0.38 (hexane/ethyl acetate 1 : 1 v/v); ir (NaCl) 3445 br, 2990, 2950, 2850, 2340, 1455, 1375, 1365, 1265, 1200, 1155, 1100, 1080, 1020, 950, 860, 770 cm^{-1}; ^1H nmr δ 5.75 (ddt, J = 1.5, 6.8 and 11.6 Hz, 1H), 5.63 (ddt, J = 1.5, 9.0 and 11.6 Hz, 1H), 4.98 (s, 1H), 4.96.(br d, J = 9.0 Hz, 1H), 4.64 (d, J = 6.1 Hz, 1H), 4.59 (dd, J = 0.9 and 6.1 Hz, 1H), 4.34 (ddd, J = 1.5, 6.8 and 13.4 Hz, 1H), 4.25 (ddd, J = 1.5, 6.8 and 13.4 Hz, 1H), 3.32 (s, 3H), 1.66 (br s, 1H), 1.50 (s, 3H), 1.31 (s, 3H); ^{13}C nmr 131.9, 130.9, 112.5, 109.2, 85.6, 85.2, 82.7, 58.2, 54.6, 26.5, 25.0. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.33; H, 7.92.

Methyl 5,6-anhydro-2,3-*O*-isopropylidene-β-L-*glycero*-L-*talo*-heptofuranoside (14).

A dried flask was charged with 1 g of activated 3Å molecular sieves (powdered and heated 160 °C overnight) and 50 ml of dry methylene chloride under nitrogen. To the mixture were added *via* syringe L-(+)-diethyl tartarate (0.9 ml, 36 mol%), and $Ti(O\text{-}i\text{-}Pr)_4$ (1.0 ml, 24 mol%). The stirred mixture was cooled between -15 °C and -20 °C (ethylene glycol/dry ice bath) and 80% cumene hydroperoxide (8.2 ml, 42.6 mmol) stored prior to use overnight over activated 3Å molecular sieves, was added. After a 40 min aging period, allylic alcohol (**13**) (3.25 g, 14.2 mmol) pre-treated with activated 3Å sieves in 25 ml of methylene chloride 30 min prior to use was added *via* a cannula under a positive nitrogen pressure. The molecular sieves were then rinsed with (2 x 25 ml) portions of dry methylene chloride and the organic washings were added to the reaction mixture *via* cannula. The reaction mixture was allowed to stir until the temperature rose to -2 °C and either put into a freezer at -2 °C or stirred at 5 °C in a cold room for 24 h. The mixture was quenched with 30 ml of water and stirred vigorously for 30 min, then 10 ml of 30% aqueous NaOH saturated with NH_4Cl was added and stirring was continued for an additional 30 min. The mixture was transferred into a separatory funnel and the lower organic phase was removed. The milky sieve-containing aqueous phases were extracted with 250 ml of methlyene chloride. The organic fractions were then combined, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified on a silica gel column (hexane/ethyl acetate 1 : 1 v/v) to furnish 2.67 g (77%) of **14** as a white wax-like solid, mp 84.5-85.5 °C; R_f = 0.37 (hexane/ethyl acetate 1 : 1 v/v); $[\alpha]_D$ -45.9 ° (c 2.4, $CHC1_3$); ir (KBr) 3220, 2965, 2920, 2815, 1455, 1450, 1436, 1372, 1360, 1262, 1235, 1195, 1185, 1155, 1080, 1020, 1000, 930, 910, 860, 840, 780, 740, 575, 480 cm^{-1}; ^1H nmr δ 5.06 (s, 1H), 4.73 (dd, J = 1.9 and 5.9 Hz, 1H), 4,63 (d, J = 5.9 Hz, 1H), 4.07 (dd, J = 1.9 and 9.0 Hz, 1H), 3.85 (m, 2H), 3.43 (s, 3H), 3.23 (m, 1H), 3.14 (dd, J = 4.6 and 9.0 Hz, 1H), 1.48 (s, 3H), 1.33 (s, 3H); ^{13}C nmr 113.0, 109.0, 86.1, 85.1, 82.1, 60.3, 57.9, 56.1, 54.9, 26.4, 25.9. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.64; H, 7.43.

Methyl 6-azido-6-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-L-*talo*-hepto-furanoside (15).

Epoxide (**14**) (1.40 g, 5.68 mmol) was dissolved in 75 ml of 2-methoxyethanol/water (8 : 1 v/v) followed by the addition of sodium azide (1.85 g, 28.4 mmol) and ammonium chloride (0.61 g, 11.36 mmol). The reaction mixture was refluxed for 7 h and allowed to cool to room temperature. The solvents were removed under vacuum, and the resulting residue was dissolved in methylene chloride (125 ml) and water (75 ml). The aqueous layer was separated and extracted with methylene chloride (2 x 100 ml). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and evaporated to afford **15** (1.46 g, 89%) which was used for next reaction without further purification. Recrystallization from hexane/ethanol gave rod like crystals mp 91-92°C; X-ray crystallographic analysis confirmed the C-6*R* C-5*S* configuration.[15] Hplc (Senshu-Pak silica gel, 4.6 x 250 mm, CH_2Cl_2/MeOH 50 : 50 v/v) showed one major component >95%; R_f = 0.53 (hexane/ethyl acetate 1 : 2 v/v); $[\alpha]_D$ -40.7 ^{0} (c 2.3, $CHC1_3$); ir (KBr) 3450, 3360, 2960, 2905, 2150, 2110, 1425, 1380, 1300, 1275, 1240, 1210, 1160, 1130, 1110, 1095, 1080, 1065, 1010, 985, 958, 875, 855, 815, 690 , 630, 585, 460 cm^{-1}; ^1H nmr δ 5.01 (s, 1H), 4.85 (br d, J = 5.9 Hz, 1H), 4.61 (br d, J = 6.1 Hz, 1H), 4.53 (br d, J = 2.2 Hz, 1H), 3.82 (dd, J = 3.9 and 11.3 Hz, 1H), 3.75 (m, 1H), 3.50 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H); ^{13}C nmr 112.5, 110.6, 88.2, 85.3, 82.3, 72.2, 66.5, 62.1, 56.3, 26.4, 24.7. Anal. Calcd for $C_{11}H_{19}N_3O_6$: C, 45.67; H, 6.62; N, 14.52. Found: C, 45.74; H, 6.61; N, 14.16. A small sample of **15** was acetylated with acetic anhydride in pyridine to give the diacetate, ^1H nmr δ 5.13 (dd, J = 4.6 and 6.7 Hz, 1H), 5.0 (br s, 1H), 4.54 (br d, J = 6.2 Hz, 1H), 4.40 (dd, J = 2.1 and 6.2 Hz, 1H), 4.38 (dd, J = 4.1 and 12.3 Hz, 1H), 4.17 (dd, J = 8.4 and 12.3 Hz, 1H), 3.90 (m, 1H), 3.35 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.50 (s, 3H) 1.30 (s, 3H).

Methyl 6-azido-7-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranoside (16).

This compound was obtained according to the procedure described for the preparation of **7** in 98% yield. Analytically pure **16** was isolated using silica gel chromatography (hexane/ethyl acetate 3 : 1 v/v); R_f = 0.51 (hexane/ethyl acetate 3 : 1 v/v); $[\alpha]_D$ -43.1^0 (c 1.0, $CHC1_3$); ir

(NaCl) 3400, 2950, 2920, 2850, 2075, 1460, 1450, 1370, 1360, 1245, 1200, 1150, 1090, 1055, 1005, 950, 850, 830, 770 cm^{-1}; ^1H nmr (500 MHz) δ 4.99 (s, 1H), 4.83 (br d, J = 6.2 Hz, 1H), 4,59 (d, J = 6.2 Hz, 1H), 4.49 (d, J = 2.9 Hz, 1H), 3.84 (dd, J = 4.4 and 11.0 Hz, 1H), 3.81 (dd, J = 5.5 and 11.0 Hz, 1H), 3.71 (ddd, J = 2.9, 6.2 and 10.8 Hz, 1H), 3.54 (d, J= 10.9 Hz, 1H), 3.47 (s, 3H), 3.36 (dt, J = 4.4 and ~5.5 Hz, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C nmr 112.5, 110.6, 88.6, 85.4, 82.4, 70.8, 65.8, 63.3, 56.2, 26.4, 25.9, 24.7, 18.2, -5.5. Anal. Calcd for $C_{17}H_{33}N_3O_6Si \cdot 0.2H_2O$: C, 49.93; H, 8.28; N, 10.28. Found: C, 50.09; H, 8.25; N, 9.96.

Methyl 6-azido-5-*O*-benzyl-7-*O*-(*tert*-butyldimethylsily)-6-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranoside (17).

To a suspension of sodium hydride [60% mineral oil dispersion prewashed with hexane (2 x 5ml), 266 mg, 6.66 mmol] in dry THF (20 ml) was added crude **16** (2.00 g, 4.96 mmol) in dry THF (20 ml). The mixture was stirred for 15 min at room temperature. Benzyl bromide (98%, 0.81 ml, 6.66 mmol) was then added and the reaction mixture was stirred for 4.5 h. The excess sodium hydride was quenched by carefully dropwise addition of water (2 ml). The mixture was transferred to a separatory funnel containing water (50 ml) and the product was extracted with methylene chloride (150 ml). After separation, the organic layer was dried (Na_2SO_4), filtered and evaporated to afford 2.16 g of **17** [77% overall 3-steps from epoxide (**14**)] after purification by column chromatography (hexane/ethyl acetate 8 : 1 v/v) ; R_f = 0.83 (hexane/ethyl acetate 3 : 1 v/v); $[\alpha]_D$ -37.4 ^{0} (c 1.0, $CHC1_3$); ir (NaCl) 2910, 2850, 2075, 1460, 1370, 1360, 1240, 1200, 1100, 830, 770 cm^{-1}; ^1H nmr δ 7.37-7.40 (m, 5H), 5.00 (s, 1H), 4.77 (d, J = 11.6 Hz, 1H), 4.73 (dd, J = 2.4 and 6.1 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 6.1 Hz, 1H), 4.40 (dd, J = 2.4 and 6.4 Hz, 1H), 3.83 (dd, J = 7.3 and 10.4 Hz, 1H), 3.77 (dd, J = 4.6 and 10.4 Hz, 1H), 3.66 (m, 1H,), 3.61 (dd, J= 4.0 and 6.4 Hz, 1H), 3.40 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C nmr 138.3, 128.4, 127.8, 112.8, 110.3, 87.1, 85.3, 81.0, 78.3, 73.9, 63.5, 55.8, 26.9, 25.8, 25.2, 18.2, -5.50. Anal. Calcd for $C_{24}H_{39}N_3O_6Si$: C, 58.46; H, 7.97; N, 8.52. Found: C, 58.32; H, 7.98; N, 8.38.

Methyl 6-azido-5-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranoside (18).

To a solution containing **17** (1.90 g, 3.85 mmol) in dry DMF (40 ml) was added tetrabutylammonium fluoride (1.0 *M* in THF, 4.23 ml, 4.23 mmol). The mixture was stirred at room temperature for 15 min. The solvent was evaporated and the residue was dissolved in methylene chloride (150 ml), washed with water (50 ml), the organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated to give 1.69 g of crude product. Purification by silica gel chromatography (hexane/ethyl acetate 1 : 1 v/v) afforded 1.35 g (95%) of **18**; R_f = 0.40 (hexane/ethyl acetate 1 : 1 v/v); $[\alpha]_D$ -50.1° (c 1.23, $CHC1_3$); ir (NaCl) *3450, 2980, 2930, 2080, 1450, 1370, 1360, 1255, 1200, 1095, 1070, 860, 730, 690* cm^{-1}; ^1H nmr δ 7.35 (m, 5H), 5.02 (s, 1H), 4.75 (s, 2H), 4.65 (dd, J = 2.4 and 6.1 Hz, 1H), 4.54 (d, J = 6.1 Hz, 1H), 4.42 (dd, J = 2.4 and 5.5 Hz, 1H), 3.82 (m, 2H), 3.72 (dd, J = 5.0 and 10.0 Hz, 1H), 3.72 (m, 1H), 3.64 (dd, J = 5.0 and 5.5 Hz, 1H), 3.41 (s, 3H), 2.0 (bt, J = Hz, 1H), 1.50 (s, 3H), 1.29 (s, 3H); ^{13}C nmr 137.8, 128.5, 127.9, 112.9, 110.5, 86.6, 85.2, 81.2, 78.8, 73.9, 63.2, 62.1, 55.9, 26.9, 25.2. Anal. Calcd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08. Found: C, 56.91; H, 6.67; N, 10.92.

Methyl 6-azido-5-*O*-benzyl-*N*-[(1*S*, 2*R*)-2-benzyloxy-1-(*tert*-butyldimethylsilyl)oxymethyl]-3-(4-methoxybenzyloxy)propyl]-6-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranosiduronamide (20).

To a magnetically stirred solution of azido alcohol (**18**) (0.56 g,1.48 mmol) in dry DMF (30 ml) under a nitrogen atmosphere was added pyridinium dichromate (98%, 4.00 g, 10.6 mmol) in two equal portions over 14 h. After this period, 1.5 g of pyridinium trifluoroacetate was added and stirring was continued for an additional 2 h. Water was then added to the reaction mixture which was then extracted with ethyl ether (3 x 250 ml). The ether layers were separated, combined, dried (Na_2SO_4) and evaporated *in vacuo* to afford a crude product to which several portions of toluene were added for azeotropic removal of pyridine. Removal of the solvent afforded 0.56 g of a impure material containing mainly azido acid (**19**), unreacted starting material (**18**) and minor unidentified components (tlc). An analytical sample was purified by preparative tlc (0.5mm, 20 x 20 cm, CH_2Cl_2, MeOH 9.5 : 0.5 v/v); ^1H nmr δ 7.23-

7.37 (m, 5H), 4.95 (s, 1H). 4.77 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 5.3 Hz, 1H), 4.45 (d, J = 5.3 Hz, 1H), 4.43 (d, J = 5.3 Hz, 1H), 4.03 (br s, 1H), 3.94 (m, 1H), 3.30 (s, 3H), 1.45 (s, 3H), 1.31 (s, 3H). Without purification the crude **19** was dissolved in THF (30 ml), to the solution were added DCC (293 mg, 1.42 mmol) and 1-hydroxybenzotriazole (680 mg, 1.52 mmol). The reaction mixture was stirred at room temperature and added amine (**19**). After 2 h the mixture was evaporated and the resulting residue was partitioned between ethyl acetate and water. Evaporation of the organic layer gave a crude gum that was purified by silica gel chromatography (hexane/ethyl acetate 4 : 1) to give 0.70 g of **20** (60%) as a tacky gum and ~150 mg of starting material (**18**); R_f = 0.41 (hexane/ethyl acetate 4 : 1 v/v); $[\alpha]_D$ -10.2 ^{0} (c 1.1, $CHCl_3$); ir (NaCl) 2950, 2920, 2850, 2100, 1680, 1610, 1510, 1460, 1450, 1370, 1360, 1240, 1090, 830, 770, 730, 690 cm^{-1}; ^1H nmr δ 7.24-7.37 (m, 12H), 6.88 (dd, J = 8.9 Hz, overlapping 3H), 5.02 (s, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.74 (dd, J = 2.5 and 6.1 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 6.1 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.40 (dd, J = 2.5 and 6.7 Hz, 1H), 4.18 (m, 1H), 4.12 (m, overlapping, 1H), 4.09 (br dd, J = 2.93 Hz overlapping, 1H), 4.03 (br dt, J = 2 Hz, 4.2 Hz, 1H) 3.82 (s, 3H), 3.53-3.61 (m, 3H), 3.44 (t, J = 9.1 Hz, 1H), 3.40 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 0.88 (s, 9H), -0.04 (s, 3H), -0.02 (s, 3H); ^{13}C nmr 167.8, 159.4, 138.6, 138.0, 130.2, 129.4, 128.4, 127.5, 127.7, 113.8, 113.1, 110.2, 87.4, 85.3, 80.7, 80.0, 75.1, 74.5, 73.1, 70.4, 64.9, 61.0, 55.9, 55.3, 52.0, 26.9, 25.9, 25.3, 18.0, -5.4. Anal. Calcd for $C_{43}H_{60}N_4O_{10}Si$: C, 62.90; H, 7.37. Found: C, 62.76 ; H, 7.44.

Methyl 6-azido-5-*O*-benzyl-*N*-[(1*S*, 2*R*)-2-benzyloxy-1-(*tert*-butyldimethylsilyl)-oxymethyl-3-hydroxypropyl]-6-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranosiduronamide (21).

To a solution of **20** (270 mg, 0.328 mmol) in 19 ml of methylene chloride and water (18 : 1 v/v) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (98%, 111.7 mg, 0.492 mmol). The reaction mixture was stirred at room temperature during which time reduced DDQ became visible as a white precipitate. After a period of 2.5 h, the mixture was then filtered through a celite pad and the solid was rinsed with a small portion of methylene chloride. The filtrates were transferred into a separatory funnel and washed with water, dried (Na_2SO_4), filtered and

evaporated *in vacuo*. The crude product was chromatographed on a silica gel column and eluted with a solvent system (hexane/ethyl acetate 2 : 1 v/v). The fractions (tlc) containing product were combined and evaporated to afford 145 mg (63%) of **21** as a gum; R_f = 0.32 (hexane/ethyl acetate 2 : 1 v/v); $[\alpha]_D$ = -27.5° (c 1.05, $CHCl_3$); ir (NaCl) 3400, 2950, 2920, 2850, 2100, 1680, 1610, 1510, 1460, 1450, 1370, 1360, 1240, 1100, 1090, 830, 770, 730, 690 cm^{-1}; ^1H nmr δ 7.24 - 7.37 (m, 10H), 6.82 (d, J = 8.9 Hz, 1H), 5.03 (s, 1H), 4.74 (dd, J = 2.8 and 6.1 Hz, 1H), 4.71 (d, J = 11.3 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 6.1 Hz, 1H), 4.42 (dd, J = 2.8 and 7.3 Hz, 1H), 4.18 - 4.23 (m, 1H), 4.21 (d, J = 3.1 Hz, 1H), 4.11 (dd, J = 3.1 and 7.3 Hz, 1H), 3.85 (dt, J =2.5 and 5.8 Hz, 1H), 3.68 - 3.65 (m, 2H), 3.51 - 3.55 (m, 2H), 3.39 (s, 3H), 2.68 (t, J = 7 Hz, 1H), 1.5 (s, 3H), 1.3 (s, 3H), 0.88 (s, 9H). 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C nmr 168.5, 138.1, 137.7, 128.5, 128.3, 127.7, 127.5, 113.1, 110.0, 87.3, 85.1, 80.6, 79.9, 77.0, 74.5, 73.0, 64.5, 61.3, 61.0, 55.8, 51.2, 26.8, 25.7, 25.1, 18.0, -5.5. Anal. Calcd for $C_{35}H_{52}N_4O_9Si$: C, 59.98; H, 7.48; N, 7.99. Found: C, 59.85 ; H, 7.55; N, 7.61.

Methyl 6-azido-5-*O*-benzyl-*N*-[(1*S*, 2*R*)-2-benzyloxy-1-(*tert*-butyldimethyl-silyl)oxymethyl-2-formylethyl]-6-deoxy-2,3,-*O*-isopropylidene-β-D-*glycero*-L-*talo*-heptofuranosiduronamide (22).

A solution containing chromium trioxide (239 mg, 2.39 mmol) and pyridine (0.39 ml, 4.78 mmol) in 5 ml of methylene chloride was stirred at room temperature for 20 min under a nitrogen atmosphere. Using a syringe, alcohol (**21**) (210 mg, 0.30 mmol) dissolved in 5 ml of dry methylene chloride was added and the reaction mixture was stirred for 10 min. Ethyl ether (2 x 10 ml) portions were added to the reaction vessel and the residue was sonicated for several minutes. The ether extracts were then transferred to a separatory funnel and washed with 10 ml of water. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered through a celite pad and the solid was rinsed with a small amount of ether. Azeotropic removal of pyridine from the combined organic solution with toluene gave 180 mg of crude product. Purification by passing through a short silica column (hexane/ethyl acetate 2 : 1 v/v) gave 140 mg (67%) of **21**; R_f = 0.32 (hexane/ethyl acetate 3 : 1 v/v); $[\alpha]_D$ = -20.3° (c, 0.87, $CHCl_3$); ir (NaCl) 3400, 2950, 2920, 2850, 2100, 1725, 1680, 1505, 1455, 1365, 1240,

1090, 830, 770, 730, 690 cm^{-1}; ^1H nmr δ 9.64 (d, J = 1.2 Hz, 1H), 7.25-7.38 (m, 10H), 6.98 (d, J = 8.9 Hz, 1H), 5.04 (s, 1H), 4.76 (dd, J = 2.7 and 6.1 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 6.1 Hz, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.41 (dd, J = 2.7 and 7.3 Hz, 1H), 4.38 (m, 1H), 4.18 (d, J = 3.1 Hz, 1H), 4.11 (dd, J = 3.1 and 7.3 Hz, 1H), 4.10 (dd, J = 1.3 and 2.5 Hz, 1H), 3.81 (dd, J = 3.2 and 9.8 Hz, 1H), 3.43 (dd, J = 6.1 and 9.8 Hz, 1H), 3.40 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 0.86 (s, 9H), 0.02(s, 3H), -0.01 (s, 3H); ^{13}C nmr 201.5, 168.0, 137.9, 137.1, 128.6, 128.3, 128.1, 127.8, 127.6, 113.2, 110.2, 87.3, 85.2, 80.7, 80.6, 74.6, 73.2, 64.7, 56.0, 51.8, 26.9, 25.8, 25.3, 18.0, -5.4, -5.6; Elms m/z 683 $(M - CH_3)^+$, 669 $(M - CHO)^+$. 653 $(M-CH_3 \times 2)^+$, 641 $(M-C_4H_9)^+$.

Methyl (5*S*)-5-*O*-benzyl-5-*C*-[(2*S*, 5*S*, 6*R*)-6-(benzyloxy)-5-[(*tert*-butyldimethylsilyl)oxymethyl]-3,4,5,6-tetrahydro-3-oxo-2*H*-1,4-diazepin-2-yl]-2,3,-*O*-isopropylidene-β-D-ribofuranoside (23).

Into a 50 ml round bottom flask containing 2 ml of ethyl acetate were added **22** (21 mg, 0.030 mmol) and 5 % Pd/C (22 mg). The mixture was stirred under a hydrogen balloon for 48 h with occasional degassing and then filtered through a celite pad and the solid was washed with a small amount of ethyl acetate. The combined filtrates were evaporated to give 17 mg of a crude mixture which was applied to a preparative tlc plate (0.25 mm 20 x 20 cm, hexane/ethyl acetate 1.5 : 3.0). The major product showed uv positive band was isolated to provide 7 mg (36%) of imine (**23**); mp > 176 °C, R_f= 0.29 (hexane/ethyl acetate 1 : 1 v/v); $[\alpha]_D$ = 13.6° (c 0.52, $CHCl_3$); ^1H nmr δ 7.45 (s, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.10 - 7.33 (m, 10 H), 4.99 (s, 1H), 4.97 (d, J = 11.5 Hz, 1H), 4.87 (d, J = 11.5 Hz, 1H), 4.64 (dd, J = 2.9 and 5.7 Hz, 1 H), 4.59 (d, J = 11.5 Hz, 1H), 4.51 (d, J = 5.7 Hz, 1H), 4.51 (br s, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.13 (m, 1H), 4.06 (dd, J = 2.9 and 9.0 Hz, 1H), 3.98 (s, 1H), 3.97 (dd, J = 2.9 and 9.0 Hz, 1H), 3.46 (dd, J = 4.9 and 9.0 Hz, 1H), 3.38 (s, 3H), 3.25 (dd, J = 9.0 and 9.4 Hz, 1H), 1.37 (s, 3H), 1.25 (s, 3H), 0.81 (s, 9H), -0.05 (s, 3H), -0.01 (s, 3H); NOE [3.2% H_7 and H_2, 7.74% H_7 and H_5 , 4.8% H_7 and H_6 , 4.5% H_2 and H_7 , 6.2% H_2 and H_5]; ^{13}C nmr 170.6, 167.2, 138.8, 128.2, 128.0, 127.5, 127.1, 126.4, 113.2, 108.6, 88.2, 85.0, 81.8, 80.6, 75.2, 74.8, 73.9, 72.4, 59.4, 55.7, 51.9, 27.0, 25.9, 24.4, 18.1, -5.4; FDms m/z 654 M^+, 597$(M - C_4H_9)^+$.

ACKNOWLEDGEMENT

We are grateful to Ms. K. Kobayashi for performing the X-ray crystallographic study and Dr. M. Uramoto for recording mass spectra. The technical assistance of Mr. M. Seya and Mr. X.-C. Chen is also appreciated.

REFERENCES AND NOTES

1 An awardee of Science and Technology Agency Fellowship.
Present address: Research Biochemicals Incorporated, One Strathmore Road, Natick, MA 01760 U. S. A.

2 Present address: Department of Marine Science, School of Marine Science and Technology, Tokai University, 3-20-1, Shimizu, Shizuoka 424, Japan.

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7 Facile elimination of fatty acid from **I** under mild alkaline conditions and the coupling constant of 4.9 Hz between H-5 and H-6 in **III** suggested the *erythro* configuration at C-5 and C-6. The absolute configurations of H-5 and H-6 could not be assigned. However the (5*R*, 6*S*)configuration was tentatively given, on the bases of steric factor consideration, namely NOE network data interpretation on the assumption

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15 $C_{11}H_{19}N_3O_6$, M_W = 1157.17, orthorhombic, $P2_12_12_1$, a = 9.252 (1), b = 24.734 (4), c 5.979 (2) Å, U = 1368.2 (5) Å^3, Z = 4, λ (Mo $K\alpha$) = 0.71073 A, Final R = 5.3, Rw = 5.1 % for 945 unique reflections.

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20 Reaction was complete after 4 h as indicated by tlc (uv).

Received, 5th February, 1992