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Efficient Preparation of a Valuable Intermediate in the Synthesis of (−)-Swainsonine

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The preparation of the octahydropyrano[3,2-*b*]pyridine-6,7,8-triol derivative **22**, a highly valuable intermediate in the synthesis of (−)-swainsonine, has been achieved by application of a fifteen-step sequence starting from D-mannose with 20% overall yield.

During the last seven years a considerable effort has been made towards the synthesis of (−)-swainsonine **1** (Fig. 1). Several enantioselective synthesis of the natural alkaloid have been reported; most of them utilize either D-mannose or D-glucose as valuable synthons.[1-6] Other contributions use *R*-glutamic[7] and D-tartaric[8] acids. Furthermore, a short synthesis has appeared starting from 2,3-*O*-isopropylidene-D-erythrose which claimed to be enable to large scale preparation.[9] Finally, the iterative use of enantioselective epoxidation[10] and the intramolecular cycloaddition of azides with ω-chloroalkenes[11] proved to be well suited for the synthesis of this interesting compound.

Among those which make use of D-mannose as the appropriate starting material, chain elongation at C-6 by means of the Wittig reaction and intramolecular reductive amination constitute the two main problems encountered in the pioneering work.[3,4]

We now wish to report the nucleophilic displacement of a tosyl derivative of D-mannose **5** as a valuable alternative to the synthesis of the secondary amine **22**, intermediate of interest in the synthesis of (−)-swainsonine in previously reported methods.[3]

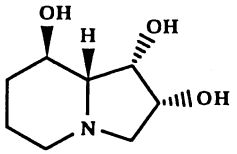

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Fig. 1.

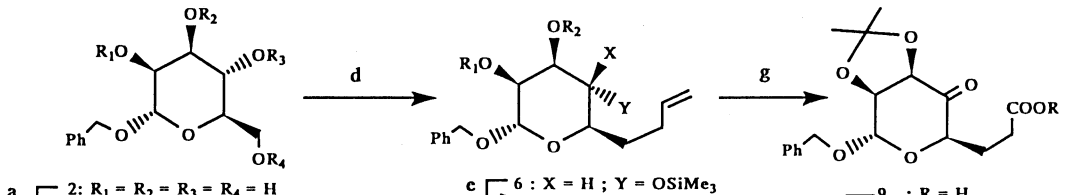
Results and Discussion

Preparation of the *p*-toluenesulfonate **5** (Scheme 1) from D-mannose, has been achieved by application of a four-step sequence (55% overall yield).

Treatment of benzyl-α-D-mannopyranoside **2**[12] with *p*-toluenesulfonyl chloride and pyridine led to a crude product, from which the *p*-toluenesulfonate **3** was isolated by flash chromatography (75% yield).

Acetonation of **3** followed by silylation of the C-4 hydroxyl by treatment of **4** with trimethylsilyl chloride (1.1 equiv) and triethylamine led quantitatively to the *p*-toluenesulfonate **5** (mp 64—65 °C). Correct assignment of the chemical shifts in the ^{13}C NMR spectrum of **5** was possible by the use of a 2D-δH/δC NMR experiment.

Nucleophilic displacement of *p*-toluenesulfonate **5** with 3 equiv of allylmagnesium chloride[13] in refluxing ether led to a crude product from which the olefinic silyl ether **6** was isolated by flash chromatography (88% yield). The presence of an ABX system centered at δ values between 5 and 6 ppm in the ^{1}H NMR spectrum of **6**, together with the appearance of two signals at δ=114.61 (CH_2) and 138.47 (CH) in the ^{13}C NMR spec-



a: 2: $R_1 = R_2 = R_3 = R_4 = H$
b: 3: $R_1 = R_2 = R_3 = H$; R_4 = Tos
c: 4: R_1, $R_2 = CMe_2$; R_3 = H ; R_4 = Tos
5: R_1, $R_2 = CMe_2$; $R_3 = SiMe_3$; R_4 = Tos
c: 6 : X = H ; Y = $OSiMe_3$
f: 7 : X = H ; Y = OH
8 : X , Y = O
h: 9 : R = H
10 : R = CH_3

a: TsCl (3 eq.), pyr, rt, 75%; b: $CH_3C(OCH_3)_2$ (3 eq.), NSA (cat.), CH_3COCH_3, rt, 94%; c: TMSCl (1.1 eq.); Et_3N, THF, rt, 94%; d: allylMgBr (3 eq.), ether, 88%; e: $(nBu)_4NF\ 3H_2O$ (1.1 eq.), THF, rt, 98%; f: $(COCl)_2$, $(CH_3)_2SO$, Et_3N, CH_2Cl_2, -60°C, 95%; g: $NaIO_4$, $RuO_2 \cdot xH_2O$, CCl_4, CH_3CN, H_2O, rt, 15h, 96%; h: CH_2N_2, 100%.

Scheme 1.

trum, confirmed the structure of the new olefinic mannose denvative.

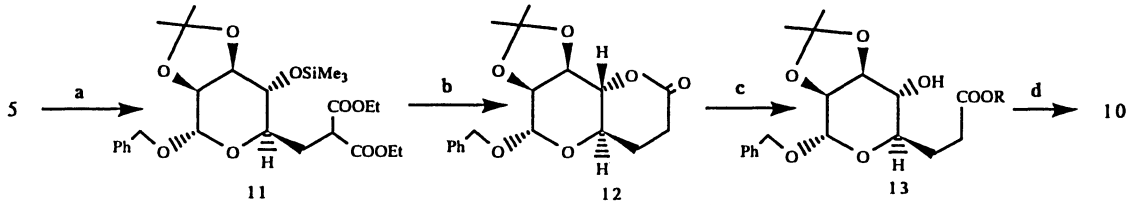
Desilylation of **6** was followed by Swem oxidation to give the intermediate olefinic ketone **8** (93% yield from **6**). The appearance of five signals at δ=203.89, 96.06, 78.57, 75.79, and 73.19 assignable to the carbonyl group and the four methine carbons of the pyranoside ring, corroborated the structure of the oxidation product **8.**

Olefinic degradation of **8** under the Lemieux–Johnson conditions[14] led to the crude uronic acid **9** (yields up to 96 %, were obtained from 2 g of **9**) which was further treated with ethereal diazomethane to give the uronate **10** (78% from **5**) after flash chromatography. The ^{1}H NMR spectrum of **10** exhibited a signal at δ=3.64 (3H) which, together with the two absorptions at δ=203.31 and 172.96 in the ^{13}C NMR spectrum, confirmed the presence of the keto and ester moieties in the new oxidation product.

An alternative route to the preparation of **10** was achieved by application of a five-step sequence starting from *p*-toluenesulfonate **5** (Scheme 2). S_N2 displacement of **5** with sodium diethylmalonate in refluxing toluene[15] led to the diester **11** (87 %). Treatment of **11** with dimethyl sulfoxide and water containing NaCl at 145 °C led to the δ-lactone **12** (70 %). Saponification of the lactone **12** was followed by esterification of the acid with ethereal diazomethane to give the hydroxy ester **13** which after PCC oxidation gave the uronate **10** (56% overall yield from **5**).

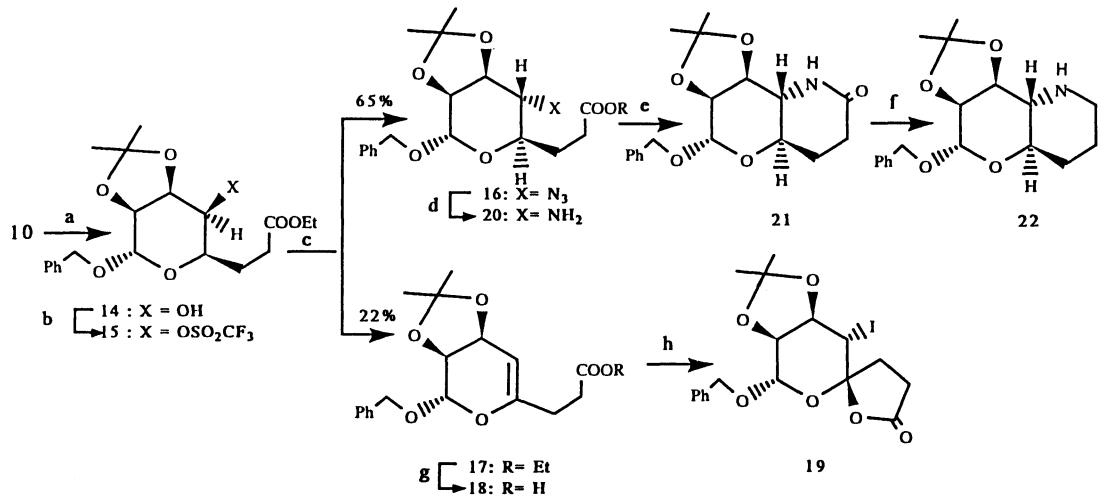
$NaBH_4$ reduction of **10** in ethanol took place from the α side as previously reported[3] to give **14** (97%) which was further transformed into the ester **15** (88%) by treatment with trifluoromethanesulfonic anhydride and pyridine (Scheme 3). The diamagnetic shift of the ^{1}H NMR signal assignable to 4-H from δ=3.80 (1H, $J_{4,5}$= 4.2 Hz) in **14** to 4.90 (1H, $J_{4,5}$=1.8 Hz) in **15** confirmed the presence of the triflate function with the stereochemistry shown.

The S_N2 displacement of **15** with sodium azide in dimethylformamide afforded the azido ester **16** (65 %). The IR spectrum of **16** exhibited bands at ν=2080 and 1740 cm^{-1} which corroborated the presence of the azido and the ester functionalities respectively. The nucleophilic displacement afforded up to 22% yield of the elimination product **17** whose structure was confirmed by olefinic cyclization to the iodospirolactone **19** (79% yield from **17**). The correct stereochemistry of the cyclization product has been possible thanks to the



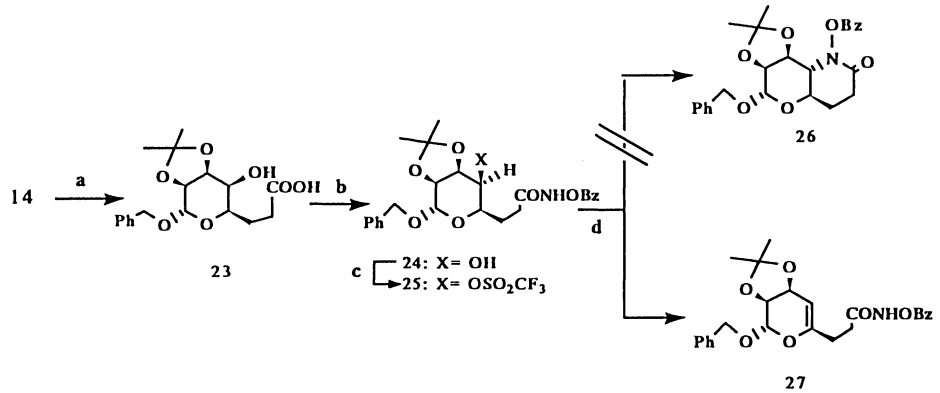
a: $NaCH(COOEt)_2$ (5 eq.), tol, reflux, 87%; b: $(CH_3)_2SO$, NaCl, H_2O, 145°C, 15h, 70%; c: 1MKOH, CH_3OH, rt, 96%; d: PCC (2 eq.), CH_2Cl_2, 15h, rt, 95%.

Scheme 2.



a: $NaBH_4$, EtOH, rt, 97%; b: $(CF_3SO_2)_2O$ (1.5 eq.), pyr, 15h,-20°C, 88%; c: NaN_3 (2 eq.), DMF, 15 h, rt, 97%; d: Pd black, H_2 (1 atm), rt, 6 h, e: tol, reflux, 1h, 97% (from 16); f: LAH (2 eq.), THF, rt, 15 h, 89%; g: 1M KOH, 2.5 h, rt, 86% h: I_2, $NaHCO_3$, $CHCl_3$, 0°C, 92%.

Scheme 3.



a: 1M NaOH, CH_3OH, rt, 15 h, 95%; b: DCC, $PhCH_2ON$, THF, 20 h, rt, 85%; c: $(CF_3SO_2)_2O$ (1.1 eq.), pyr (1.2 eq.), CH_2Cl_2, 15 h, -20°C, 85%; d: K_2CO_3, CH_3COCH_3, reflux, 1h (85%).

Scheme 4.

spectroscopic properties obtained for **19**. Irradiation experiments allowed us to unequivocally assign the ^{1}H NMR signal centered at δ=5.21 (d, J=2.5 Hz) to the H-4, what immediately led to the stereochemistry shown based on the stereospecificity of the iodolactonization process. Correct asignment of the signals in the ^{13}C NMR spectrum was possible by the use of a 2D δH/δC NMR experiment.

Pd black hydrogenation of the azide **16** in methanol led a crude amino ester **20** which led smoothly to the lactam **21** (97% from **16**) in refluxing toluene. The presence of bands at ν_{max} 3300 and 1660 cm^{-1} in the IR spectrum together with the appearance of a signal at δ=5.89 in the ^{1}H NMR spectrum assignable to the amide proton and an absorption at δ=170.5 in the ^{13}C NMR spectrum confirmed the existence of the lactam moiety.

LAH reduction of **21** in THF at room temperature for 15 h led to the secondary amine **22** (89%) which has been previously described as a valuable intermediate in the synthesis of (−)-swainsonine. Structural evidence for **22** was obtained by comparison with the spectral data of the octahydropyrano[3,2-*b*]pyridine-6,7,8-triol derivative in reported procedures.[3]

Alternatively, we tried the cyclization of the hydroxamate **25** to the *O*-benzyl-*N*-hydroxylactam **26** which, from the synthetic point of view, can be considered a precursor of **22**. Transformation of **14** into the hydroxamate **25** was achieved by application of a three-step sequence with 65% overall yield (Scheme 4). Unfortunately, treatment of **25** with K_2CO_3 in refluxing acetone for 1 h, led instead to the glycal **27** (85%) after flash chromatography of the crude.

Conclusion

The nucleophilic displacement of the tosyl derivative **5** by allylmagnesium chloride and sodium diethylmalonate is shown as a valuable alternative to other chain elongation methods which make use of the D-mannose as the starting material for the synthesis of (−)-swainsonine.[16] The preparation of *p*-toluenesulfonate **5** from D-mannose has been achieved by application of a four-step synthetic sequence with 55% overall yield and two different routes have been developed for the preparation of the keto ester **10** starting from the *p*-toluenesulfonate **5** (Scheme 1, 78%; Scheme 2, 56%). The transformation of **10** into the piperidine mannose-derivative **22** (6 steps, 48%) has been accomplished and the detailed description of all the synthetic intermediates has been reported.[16] The preparation of **22** led us to the natural alkaloid (−)-swainsonine **1** following previously reported methods.[3]

Experimental

Organic extracts were dried with commercially dried Na_2SO_4 and evaporated under reduced pressure below 40 °C. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were determined on a digital Perkin-Elmer 241 polarimeter in a 1-dm cell. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 and 50.3 MHz respectively. Mass spectra were recorded on a VG TS-250 spectrometer. The IR spectra were determined on a Beckman 33-IR spectrophotometer as indicated in each case. Microanalyses were performed using a Carlo Erba 1106 elemental analyser. All compounds discussed in this paper were obtained in a chromatographically homogeneous state.

Benzyl 6-*O*-*p*-Tolylsulfonyl-α-D-mannopyranoside (3). A solution of *p*-toluenesulfonyl chloride (63 g, 0.3 mol) in 220 ml of dichloromethane was dropwise added at room temperature and under nitrogen atmosphere into a flask containing benzyl α-mannopyranoside **2**[12,3b] (47 g, 0.174 mol), 45 ml of pyridine and 100 ml of dichloromethane.

The reaction mixture was stirred for 2 h at the same temperature, and then 100 ml of cold water was added. The organic layer was washed with an aqueous 2 M (1 M=1 mol dm^{-3}) HCl solution and brine and dried over Na_2SO_4. The evaporation of the solvent afforded 75 g of a crude product which was fractioned by flash chromatography on silica gel. Hexane–AcOEt (1 : 1) to give a yellow oil **2** (76.5 g,

75.0 %); $[\alpha]_D^{20}$ +26.4° (*c* 2.8, $CHCl_3$). Calcd for $C_{20}H_{24}O_8S$ (MW 424): C, 56.60; H 5.66; S, 7.54%. Found: C, 56.59; H, 5.68; S, 7.56%.

^{1}H NMR ($CDCl_3$) δ=2.39 (s, 3H, Ar$\underline{CH_3}$), 3.7—4.4 (m, 6H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.5 (AB system, *J*=12 Hz, 2H, CH_2OAr), 4.83 (s, 1H, 1-H); 7.26 (m, 5H, Ar); 7.5 (AB system, *J*=8 Hz, 4H, $ArSO_2O$).

^{13}C NMR ($CDCl_3$) δ= 21.31 (q), 66.99 (d), 69.09 (t), 69.63 (t), 70.45 (d), 71.57 (d), 99.08 (d), 127.78 (d), 127.79 (d), 129.22 (d), 129.67 (d), 129.66 (d), 132.76 (s), 136.89 (s), 144.69 (s).

Benzyl 2,3-*O*-Isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (4). 2,2-Dimethoxypropane (40.6 ml, 0.3 mol) and 2-naphthalenesulfonic acid (20 mg) were added to a solution of **3** (46.8 g, 0.1 mol) in 220 ml of acetone. The mixture was stirred for 8 h at room temperature and under nitrogen atmosphere. The organic solvent was evaporated at reduced pressure, and then the residue was solved in AcOEt and washed with aqueous sodium hydrogencarbonate. The organic layer was washed with brine and dried over Na_2SO_4 to give after evaporation of the solvent a colorless oil **4** (51.5 g, 94.3%); $[\alpha]_D^{20}$ +25.3° (*c* 1.09, $CHCl_3$). Calcd for $C_{23}H_{28}O_8S$ (MW 464): C, 59.48; H, 6.03; S, 6.89%. Found: C, 59.46; H, 6.05; S, 6.90%.

^{1}H NMR ($CDCl_3$) δ=1.30 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.42 (s, 3H, $ArCH_3$), 3.61 (dd, 1H, $J_{4,5}$=9.5 Hz, $J_{3,4}$=9.5 Hz, 4-H), 3.82 (m, 1H, H-5), 4.12 (dd, 1H, $J_{3,4}$=9.5 Hz, $J_{2,3}$= 6 Hz, 3-H), 4.14 (d, 1H, *J*=6 Hz, 2-H), 4.26 (m, 2H, H-6), 4.53 (AB system, *J*=12 Hz, $ArCH_2$), 5.01 (s, 1H, 1-H), 7.29 (m, 5H, Ar), 7.55 (AB system, 4H, *J*=8 Hz, Tos).

^{13}C NMR ($CDCl_3$) δ=21.38 (q), 25.69 (q), 27.68 (q), 68.39 (d), 68.84 (d), 69.18 (t), 75.50 (d), 78.21 (d), 96.23 (d), 109.58 (s), 127.83 (d), 127.84 (d), 128.18 (d), 128.34 (d), 129.67 (d), 133.14 (s), 136.61 (s), 144.68 (s).

Benzyl 2,3-*O*-Isopropylidene-6-*O*-*p*-tolylsulfonyl-4-*O*-trimethylsilyl-α-D-mannopyranoside (5). To a solution of **4** (51.5 g, 0.1 mol) in 150 ml of anhydrous THF were succesively added triethylamine (77.3 ml, 0.5 ml), and trimethylsilyl chloride (21.1 ml, 0.16 mol) at 0 °C and under nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature. Filtration of the white solid was followed by evaporation of the organic solvent at reduced pressure to give a white solid (56 g, 94%); mp 64—65 °C (hexane). Calcd for $C_{26}H_{36}O_8SSi$ (MW 536): C, 58.20; H, 6.71; S, 5.97%. Found: C, 58.18; H, 6.70; S, 5.93%.

^{1}H NMR ($CDCl_3$) δ=0.09 (s, 9H, $SiMe_3$), 1.29m (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.42 (s, 3H, $ArCH_3$), 3.49 (dd, 1H, $J_{3,4}$= 10 Hz, $J_{4,5}$=10 Hz, 4-H), 3.73 (m, 1H, 5-H), 3,98 (dd, 1H, $J_{3,4}$=10 Hz; $J_{2,3}$=6 Hz, 3-H), 4.10 (d, 1H, *J*=6 Hz, 2-H), 4.14 (m, 2H, 6-H), 4.49 (AB system, 2H, *J*=12 Hz, $ArCH_2$), 4.98 (s, 1H, 1-H), 7.30 (m, 5H, Ar), 7.55 (AB system, 4H, *J*=8 Hz, $ArSO_2O$).

^{13}C NMR ($CDCl_3$) δ=0.10 (q), 21.42 (q), 26.14 (q), 27.66 (q), 68.22 (d), 69.00 (t), 69.15 (t), 70.30 (d), 75.79 (d), 78.85 (d), 96.12 (d), 109.17 (s), 127.68 (d), 127.69 (d),128.25 (d), 128.26 (d), 129.63 (d), 133.27 (s), 136.77 (s), 144.55 (s).

MS(EI) (*m*/*z*, %) 537 ($M+H^+$, 5), 521 (10), 429 (15), 359 (60), 230 (70), 170 (70), 130 (90), 97 (100).

Benzyl, 2,3-*O*-Isopropylidene-6,7,8,9-tetradeoxy-4-*O*-trimethylsilyl-α-D-*manno*-8-nonenopyranoside (6). To a suspension of Mg (0.78 g, 32 mmol) in anhydrous ether (50 ml) allyl chloride (2.4 ml, 30 mmol) was dropwise added without stirring at room temperature and under nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred overnight under reflux. Then, a solution of **5** (5.4 g 10 mmol) in 25 ml of ether was cautiously added and the reaction mixture was refluxed for 2 h. Filtration of the unreacted Mg was followed by addition of 25 ml of aqueous sat. NH_4Cl solution and extraction with ether. The combined organic layers were washed with brine, dried on Na_2SO_4 and evaporated to afford a crude product which was fractioned by flash chromatography on silica gel. Hexane–AcOEt (95 : 5), to give a colorless oil **6** (3.6 g, 88%); $[\alpha]_D^{20}$ +41.29° (*c* 2.76, $CHCl_3$). Calcd for $C_{22}H_{34}O_5Si$ (MW 406): C, 65.02; H, 8.37%. Found: C, 65.00; H, 8.36%.

^{1}H NMR ($CDCl_3$) δ=0.18 (s, 9H, $SiMe_3$), 1.35 (s, 3H), 1.53 (s, 3H), 3.43 (dd, 1H $J_{3,4}$=10 Hz, $J_{4,5}$=10 Hz, 4-H), 3.61 (dt, 1H, $J_{4,5}$=10 Hz, $J_{5,6}$=7 Hz, 5-H), 4.05 (dd, 1H, $J_{3,4}$=10 Hz, $J_{2,3}$=6 Hz, 3-H), 4.18 (d, 1H, $J_{2,3}$=6 Hz, 2-H), 4.62 (AB system, 2H, *J*=12 Hz, $ArCH_2$), 5.05 (ddd, 2H, J_1=2 Hz, J_2=10 Hz, J_3= 17 Hz, 9-H and 9′-H), 5.08 (s, 1H, 1-H), 5.90 (m, 1H, 8-H), 7.35 (m. 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=0.46 (q), 26.40 (q), 28.11 (q), 29.76 (t), 30.85 (t), 68.92 (t), 69.27 (d), 74.75 (d), 76.14 (d), 79.20 (d), 96.24 (d), 108.99 (s), 114.61 (t), 127.88 (d), 128.12 (d), 128.46 (d), 137.19 (s), 138.47 (d).

Benzyl 2,3-*O*-Isopropylidene-6,7,8,9-tetradeoxy-α-D-*manno*-8-nonenopyranoside (7). A solution of $(n\text{Bu})_4NF \cdot 3H_2O$ (2.8 g, 9 mmol) in 5 ml of THF was dropwise added to a solution of **6** (3.5 g, 8.6 mmol) in 15 ml of THF at room temperature. The reaction was followed by TLC. Evaporation of the solvent gave a crude product which after filtration on silca-gel afforded a colorless oil **7** (2.8 g, 98%); $[\alpha]_D^{20}$ +59.0° (*c* 1.33, $CHCl_3$). Calcd for $C_{19}H_{26}O_5Si$ (MW 334): C, 68.26; H, 7.78%. Found: C, 68.24; H, 7.79%.

^{1}H NMR ($CDCl_3$) δ=1.35 (s, 3H, CH_3) 1.53 (s, 3H, CH_3), 3.46 (dd, 1H, $J_{3,4}$=10 Hz, $J_{4,5}$=10 Hz, 4-H), 3.65 (dt, 1H, $J_{4,5}$=10 Hz, $J_{5,6}$=7 Hz, 5-H), 4.13 (dd, 1H, $J_{3,4}$=10 Hz, $J_{2,3}$= 6 Hz, 3-H), 4.19 (d, 1H, $J_{2,3}$=6 Hz, 2-H), 4.62 (AB system, 2H, *J*=12 Hz, $ArCH_2$), 5.07 (ddd, 2H, J_1= 2 Hz, J_2=10 Hz, J_3= 17 Hz, 9-H and 9′-H), 5.09 (s, 1H, 1-H), 5.87 (m, 1H, 8-H), 7.35 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=26.06 (q), 27.90 (q), 29.52 (t), 30.68 (t), 68.94 (t), 69.13 (d), 72.93 (d), 75.73 (d), 78.72 (d), 96.10 (d), 109.31 (s), 114.72 (t), 127.83 (d), 128.01 (d), 128.40 (d), 136.95 (s), 138.28 (d).

Benzyl 6,7,8,9-Tetradeoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-8-nonen-4-ulopyranoside (8). In a 250 ml flask equipped with a magnetic stirrer and nitrogen inlet was placed a solution containing oxalyl chloride (1.42 ml, 16.35 mmol) in dichloromethane (10 ml). The reaction mixture was chilled to −60 °C and dimethyl sulfoxide (2.33 ml, 32.8 mmol) was dropwise added. After 5 min of stirring, a solution containing **7** (2.5 g, 7.5 mmol) in 10 ml of dichloromethane was carefully added. After 15 min of stirring at the same temperature triethylamine (10.4 ml, 75 mmol), was cautiously added. After 5 min the reaction mixture was allowed to warm to room temperature, and then water (15 ml) was added and the reaction was extracted with dichloromethane, washed with brine and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude which was fractioned by flash chromatography on silica gel. Hexane–AcOEt (7 : 3) to give a colorless product **8** (2.35 g, 95%); $[\alpha]_D^{20}$ +11.24° (*c* 0.92, $CHCl_3$). Calcd for $C_{19}H_{24}O_7$ (MW 332): C, 68.67; H, 7.22%. Found: C, 68.64; H, 7.24%.

^{1}H NMR ($CDCl_3$) δ=1.27 (s, 3H), 1.40 (s, 3H), 1.85 (m, 2H,6-H), 2.20 (m, 2H, 7-H), 4.10 (dd, 1H, $J_{5,6}$=5 Hz; $J_{5,6'}$= 8

Hz, 5-H), 4.36 (AB system, J=6.6 Hz, 2-H+3-H), 4.58 (AB system, J=11.8 Hz, $ArCH_2$), 4.94 (dd, 1H, J_1=2 Hz; J_2=2 Hz, 9-H), 4.96 (s, 1H, 1-H), 5.00 (dd, 1H, J_1=2 Hz; J_2= 17 Hz, 9′-H), 5.74 (m, 1H, 8-H), 7.25 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=25.26 (q), 26.53 (q), 29.31 (t), 29.93 (t), 69.81 (t), 73.19 (d), 75.79 (d), 78.57 (d), 96.06 (d), 111.31 (s), 115.29 (t), 127.90 (d), 127.91 (d), 128.44 (d), 136.43 (s), 137.46 (d), 203.89 (s).

Methyl (Benzyl 6,7-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-4-octulopyranosid)uronate (10). To a solution of **8** (2.35 g, 5.5 mmol) in acetonitrile (10 ml) were successively added carbon tetrachloride (10 ml), sodium periodate (9.7 g, 45.4 mmol), water (15 ml) and Rutenium tetraoxide (0.032 g, 0.24 mmol). The reaction mixture was stirred vigorously for 15 h at room temperature, and then 20 ml of dichloromethane were added. The water phase was acidulated to pH 5 with 1 M HCl and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give **9** (2.38 g, 96%). Treatment of **9** (2.2 g, 6.2 mmol) with an ethereal diazomethane solution and evaporation of the solvent afforded **10** (2.2 g, 100%); $[\alpha]_D^{20}$ +85.6° (*c* 1.1, $CHCl_3$). Calcd for $C_{19}H_{24}O_7$ (MW 364): C, 62.63; H, 6.59%. Found: C, 62.65; H, 6.60%.

IR (film) ν_{max} 1735, 1600, 1500, 1450, 1430, 1375, 1365, 1065, 840, 740, 730, 690 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ=1.33 (s, 3H), 1.45 (s, 3H), 2.15 (m, 2H, 6-H), 2.49 (t, 1H, J=7 Hz, 7-H), 3.54 (s, 3H, $COOCH_3$), 4.26 (dd, 1H, $J_{5,6}$= 5 Hz, $J_{5,6'}$= 8 Hz, 5-H), 4.43 (AB system, J=11.8 Hz, $ArCH_2$), 5.04 (s, 1H, 1-H), 7.32 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=25.22 (t), 25.23 (q), 26.46 (q), 29.26 (t), 51.29 (q), 69.66 (t), 71.96 (d), 75.61 (d), 78.50 (d), 95.75 (d), 111.02 (s), 127.88 (d), 127.89 (d), 128.34 (d), 136.14 (s), 172.97 (s), 203.31 (s).

Ethyl (Benzyl 6,7-dideoxy-7-ethoxycarbonyl-2,3-*O*-isopropylidene-4-*O*-trimethylsilyl-α-D-*manno*-octopyranosid)uronate (11). Sodium (1 g, 46.6 mmol) was added to a solution of diethyl malonate (7 ml, 46 mmol) in toluene (25 ml), and the mixture was refluxed until the metal was dissolved, and then the reaction was allowed to cool to room temperature and a solution of the *p*-toluenesulfonate **5** (5 g, 9.3 mmol) in toluene (15 ml) was added. The reaction was refluxed overnight then, cooled to room temperature and after the addition of saturated ammonium chloride solution (25 ml), extracted with ethyl acetate. The combined organic layers were washed with water and brine; dried on Na_2SO_4 and evaporated to give a colorless oil **11** (4.24 g, 87%); $[\alpha]_D^{20}$ +44.3° (*c* 1.12, $CHCl_3$). Calcd for $C_{26}H_{40}O_9Si$ (MW 524): C, 59.54; H, 5.62%. Found: C, 59.56; H, 5.60%.

^{1}H NMR ($CDCl_3$) δ=0.09 (s, 9H, $SiMe_3$), 1.10 (t, J=7 Hz, $CH_2\underline{CH_3}$), 1.16 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$), 1.22 (s, 3H), 1.41 (s, 3H), 1.89 (m, 2H, 6-H), 2.42 (m, 1H,7-H), 3.33 (dd, 1H, $J_{3,4}$=10 Hz, $J_{4,5}$=10 Hz, 4-H), 3.55 (m, 1H, 5-H), 3.93 (dd, 1H, $J_{3,4}$=10 Hz, $J_{2,3}$= 6 Hz, 3-H), 3.97—4.16 (m, J=7 Hz, 4H, $\underline{CH_2}CH_3$), 4.04 (d, 1H, $J_{2,3}$= 6 Hz, 2-H), 4.49 (AB system, 2H, J=12 Hz, $ArCH_2$), 4.94 (s,1H, 1-H), 7.21 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=0.29 (q), 13.66 (q), 26.24 (q), 27.95 (q), 31.23 (t), 48.79 (d), 61.15 (t), 61.16 (t), 67.61 (d), 68.96 (t), 74.83 (d), 75.93 (d), 78.76 (d), 96.12 (d), 106.94 (s), 127.70 (d), 127.85 (d), 128.29 (d), 137.15 (s), 166.67 (s), 169.26 (s).

(1*R*,6*R*,8*S*,9*S*,10*S*)-8-Benzyloxy-9,10-isopropylidenedioxy-2,7-dioxabicyclo[4.4.0]decan-3-one (12). A suspension of **11** (4 g, 7.6 mmol), dimethyl sulfoxide (1.08 ml, 15.2 mmol), sodium chloride (0.88 g, 15.2 mmol) and water (0.27 g, 15.2 mmol) was heated for 145 °C for 15 h under nitrogen atmosphere. Then the reaction was allowed to cool to room temperature and diluted with ethyl acetate (5 ml), and water (3 ml). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to give a residue which was purified by flash chromatography [hexane–AcOEt (1 : 1)] to give a colorless oil **12** (1.78 g, 70%); $[\alpha]_D^{20}$ +52.16° (*c* 0.25, $CHCl_3$). Calcd for $C_{18}H_{22}O_6$ (MW 334): C, 64.67; H, 6.58%. Found: C, 64.65; H, 6.56%.

^{1}H NMR ($CDCl_3$) δ=1.33 (s, 3H), 1.50 (s, 3H), 2.00 (m, 2H, 5-H), 2.65 (m, 2H,4-H), 3.76 (dt, 1H, J_1=10 Hz J_2=6 Hz, 6-H), 4.03 (dd, 1H, $J_{1,10}$=10 Hz; $J_{1,6}$=10 Hz, 4-H), 4.21 (d, 1H, $J_{9,10}$=6 Hz, 9-H), 4.62 (AB system, J=12 Hz, $ArCH_2$), 5.12 (s, 1H, 8-H), 7.32 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=24.27 (t), 26.07 (q), 28.00 (t), 28.01 (q), 62.18 (d), 69.92 (t), 75.33 (d), 75.75 (d), 80.30 (d), 97.37 (d), 109.95 (s), 126.96 (d), 128.12 (d), 128.58 (d), 136.88 (s), 169.36 (s).

Methyl (Benzyl 6,7-dideoxy-2,3-*O*-isopropylidene-α-D-*manno*-octopyranosid)uronate (13). Lactone **12** (1 g, 2.99 mmol) was dissolved in methanol (5 ml) and aqueous 1 M KOH (10 ml) was added. The reaction was stirred overnight at room temperature, and the methanol was evaporated and water (5 ml) was added, and then the aqueous solution was acidulated to pH 5 by addition of 1 M HCl and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4 to give 1g of a residue which was treated with an ethereal diazomethane solution to give, after evaporation of the solvent, a colorless oil **13** (1.04 g, 96%); $[\alpha]_D^{20}$ +42.6° (*c* 1.12, $CHCl_3$). Calcd for $C_{19}H_{26}O_7$ (MW 366): C, 62.29; H, 7.10%. Found: C, 62.30; H, 7.09%.

IR ν_{max} 3440, 1750, 1500, 1460, 1380, 1240, 1080, 860, 740, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ=1.31 (s, 3H), 1.48 (s, 3H), 2.50 (m, 2H, 7-H), 3.40 (dd, 1H, $J_{3,4}$=6.5 Hz, $J_{4,5}$= 9.6 Hz, 4-H), 3.62 (dt, 1H, $J_{4,5}$=9.6 Hz, $J_{5,6}$= 3 Hz, 5-H), 3.63 (s, 3H, $COOCH_3$), 4.08 (dd, 1H, $J_{3,4}$=6.5 Hz, $J_{2,3}$=5.7 Hz, 3-H), 4.14 (d, 1H, $J_{2,3}$=5.7 Hz, 2-H), 4.57 (AB system, J=12 Hz, $ArCH_2$), 5.03 (s, 1H, 1-H), 7.31 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=26.13 (q), 26.63 (t), 27.98 (q), 29.66 (t), 51.53 (d), 68.90 (d), 69.22 (t), 72.79 (d), 75.92 (d), 78.53 (d), 96.54 (d), 109.49 (s), 127.94 (d), 128.07 (d), 128.51 (d), 137.13 (s), 174.02 (s).

Methyl (Benzyl 6,7-dideoxy-2,3-isopropylidene-α-D-*lyxo*-4-octulopyranosid)uronate (10); (from 13). Pyridinium chlorochromate (1.16 g, 5.4 mmol) was added to a solution of **13** (1 g, 2.73 mmol) in dichloromethane (5 ml). The reaction mixture was stirred overnight at room temperature, and then hexane–ether (1 : 1) was added. Filtration of the solid followed by evaporation of the solvent gave a crude which after purification by flash chromatography [hexane–AcOEt (8 : 2)] gave a colorless oil **10** (0.94 g, 95%) with identical spectroscopic properties to those described above.

Ethyl (Benzyl 6,7-dideoxy-2,3-*O*-isopropylidene-α-D-*talo*-octopyranosid)uronate (14). Sodium borohydride (0.41 g, 11 mmol) was added to a solution of **10** (5.49 mmol) in ethanol (25 ml) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min, and then 5 ml of aqueous sat. NH_4Cl was added. The methanol was evaporated and the reaction mixture was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and evaporated to give 2.01 g (97%) of a colorless oil **14**; $[\alpha]_D^{20}$

+58.63°(*c* 1.09, $CHCl_3$). Calcd for $C_{20}H_{28}O_7$ (MW 380): C, 63.15; H, 7.36%. Found: C, 63.12; H, 7.37%.

IR (film) ν_{max} 3500, 2950, 1730, 1500, 1450, 1380, 1210, 1060, 850, 690 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.19 (t, 3H, *J*=7 Hz, $COOC\underline{H}_3$), 1.34 (s, 3H), 1.55 (s, 3H), 2.2 (m, 2H, 6-H), 2.49 (t, 2H, *J*=7 Hz, 7-H), 3.59 (m, 1H,5-H), 3.80 (dd, 1H, $J_{3,4}$=5.2 Hz; $J_{4,5}$=4.2 Hz, 4-H), 4.08 (q, 2H, *J*=7 Hz, $COO\underline{CH}_2CH_3$), 4.09 (d, 1H, *J*=6.2 Hz, 2-H), 4.21 (dd, 1H, $J_{2,3}$= 6.2 Hz, $J_{3,4}$=5.2 Hz, 3-H), 4.62 (AB system, *J*=11.8 Hz, $ArCH_2$) 5.13 (s, 1H, 1-H), 7.32 (m, Ar).

^{13}C NMR ($CDCl_3$) δ=13.90 (q), 25.08 (q), 25.65 (q), 26.13 (t), 30.28 (t), 60.15 (t), 65.75 (d), 67.47 (d), 69.20 (t), 72.55 (d), 73.47 (d), 96.58 (d), 109.13 (s), 127.77 (d), 127.89 (d), 128.29 (d), 136.90 (s), 172.98 (s).

Ethyl (Benzyl 6,7-dideoxy-2,3-*O*-isopropylidene-4-*O*-trifluoromethylsulfonyl-α-D-*talo*-octopyranosid)uronate (15). Trifluoromethanesulfonic anhydride (0.53 ml, 3.19 mmol) was added dropwise to a solution of **14** (1.1 g, 2.9 mmol) in dichloromethane (15 ml) and pyridine (0.44 ml, 5.4 mmol) at −20 °C. The solution was stirred for 15 h and quenched by the addition of saturated sodium hydrogencarbonate solution (10 ml), allowed to warm to room temperature, stirred for 30 min and diluted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated to give 1.2 g (88%) of a crude triflate. An analytical sample of the triflate was obtained by purification of the crude by flash chromatography [hexane–AcOEt (8 : 2)] to give a colorless oil **15**.

^1H NMR ($CDCl_3$) δ=1.18 (t, 3H, *J*=7 Hz, $COOCH_2\underline{CH}_3$), 1.34 (s, 3H), 1.55 (s, 3H), 2.02 (m, 2H, 6-H), 2.54 (t, 2H, *J*=7 Hz, 7-H), 4.00 (m, 1H, 5-H), 4.07 (q, 2H, *J*=7 Hz, $COO\underline{CH}_2CH_3$), 4.14 (d, 1H, *J*=6.8 Hz, 2-H), 4.40 (t, 1H, *J*=6 Hz, 3-H), 4.60 (AB system, *J*=11.6 Hz, $ArCH_2$), 4.90 (dd, 1H, $J_{3,4}$=6 Hz, $J_{4,5}$=1.8 Hz, 4-H), 5.10 (s, 1H, 1-H), 7.31 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=14.15 (q), 24.73 (q), 25.60 (q), 26.34 (t), 30.16 (t), 60.57 (t), 65.92 (d), 70.01 (d), 70.02 (t), 73.41 (d), 81.00 (d), 97.30 (d), 110.84 (s), 128.05 (d), 128.50 (d), 128.58 (d), 136.90 (s), 172.52 (s).

Ethyl (Benzyl 4-azido-4,6,7-trideoxy-2,3-*O*-isopropylidene-α-D-*manno*-octopyranosid)uronate (16). Sodium azide (0.26 g, 4 mmol) was added to a solution of the triflate **15** (1.02 g, 2.1 mmol) in dimethylformamide (10 ml). The reaction mixture was stirred for 15 h at room temperature, then the solvent was evaporated at reduced pressure, and the residue was dissolved in ether. The organic layer was washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent afforded 2.2 g of residue which was fractioned by flash chromatography on silica-gel [hexane–AcOEt (95 : 5)] to give a colorless oil **16** (0.56 g, 65%); $[\alpha]_D^{20}$ +52.89° (*c* 1.28, $CHCl_3$). Calcd for $C_{20}H_{27}O_6N_3$ (MW 405): C, 59.26; H, 6.66; N, 10.37%. Found: C, 59.27; H, 6.64; N, 10.34%.

IR(film) ν_{max} 2950, 2080, 1725, 1500, 1450, 910, 840, 800, 760, 740, 675 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.22 (t, 3H, *J*=7 Hz, $COOCH_2\underline{CH}_3$), 1.34 (s, 3H), 1.53 (s, 3H), 2.20 (m, 2H,6-H), 2.46 (t, 2H, *J*=7 Hz, 7-H), 3.23 (dd, 1H, $J_{3,4}$=7.8 Hz, $J_{4,5}$=10 Hz, 4-H), 3.53 (dt, 1H, J_1=3.2 Hz, J_2=10 Hz, 6-H), 4.10 (d, 1H, $J_{2,3}$=5.2 Hz, H-2), 4.12 (q, 2H, *J*=7 Hz, $COO\underline{CH}_2CH_3$), 4.20 (dd, 1H, $J_{2,3}$=5.2 Hz, $J_{3,4}$=7.8 Hz, 3-H), 4.55 (AB system, *J*=11.6 Hz, $ArCH_2$), 5.08 (s, 1H, 1-H), 7.31 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=14.04 (q), 26.06 (q) 27.14 (t), 27.97 (q), 29.83 (t), 60.22 (t), 64.93 (d), 66.94 (d), 69.08 (t), 74.96 (d), 76.63 (d), 95.88 (d), 109.74 (s), 127.68 (d), 127.69 (d), 128.36 (d), 138.65 (s), 172.64 (s).

Elution with hexane–AcOEt (9 : 1) afforded a colorless oil **17** (0.169 g, 22%); $[\alpha]_D^{20}$ +144.42° (*c* 1.04, $CHCl_3$). Calcd for $C_{20}H_{26}O_6$ (MW 362): C, 66.29; H, 7.18%. Found: C, 66.31; H, 7.15%.

IR (film)ν_{max} 3020, 3010, 1740, 1680, 1500, 1460, 1380, 900, 870, 740, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.23 (t, 3H, *J*=7Hz, $COOCH_2\underline{CH}_3$), 1.32 (s, 6H), 2.45 (m, 2H, 6-H), 3.98 (t, 1H, *J*=6.4 Hz, 3-H), 4.11 (q, 2H, *J*=7 Hz, $COO\underline{CH}_2CH_3$), 4.51 (dd, 1H, $J_{1,2}$=4 Hz, $J_{2,3}$=6.4 Hz, 2-H), 4.65 (d, 1H, $J_{3,4}$=6.4 Hz, 4-H), 4.78 (AB system, *J*=12.2 Hz, $ArCH_2$), 4.87 (d, 1H, $J_{1,2}$=4 Hz), 7.45 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=14.11 (q), 25.83 (q), 27.97 (q), 28.89 (t), 31.37 (t), 60.31 (t), 69.39 (d), 70.72 (t), 73.37 (d), 96.81 (d), 98.23 (d), 108.88 (s), 127.78 (d), 127.94 (d), 128.29 (d), 137.02 (s), 153.30 (s), 172.30 (s).

Benzyl (4,6,7-Trideoxy-2,3-isopropylidene-L-*erythro*-oct-4-enopyranosid)uronic Acid (18) and 7-Benzyloxy-10-iodo-8,9-isopropylidenedioxy-1,6-dioxaspiro[4.5]-decan-2-one (19). To a solution of **17** (0.108 g, 0.3 mmol) in methanol (1 ml) were added 0.4 ml of an aqueous 1 M KOH solution. The reaction was stirred for 2.5 h at room temperature. Evaporation of the methanol was followed by addition of water (2 ml) and acidulation to pH 5 with 1 M HCl. The aqueous solution was extracted with dichloromethane and the combined layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave a colorless oil **18** (85.2 mg, 86%). The crude uronic acid **18** was dissolved in chloroform (2 ml), then water (1 ml) and sodium hydrogencarbonate (42 mg, 0.5 mmol) were added. The reaction mixture was chilled at 0 °C and iodine (137 mg, 0.5 mmol) was added.

After 30 min of stirring, the reaction mixture was diluted with chloroform, the two phases were separated and the organic layer was repeatedly washed with sodium thiosulfate solution, water and brine, dried over Na_2SO_4 and evaporated to give **19** (0.107 g, 92%); $[\alpha]_D^{20}$ +7.5° (*c* 1.06, $CHCl_3$). Calcd for $C_{18}HO_6I$ (MW 460): C, 46.96; H, 4.56%. Found: C, 46.93; H, 4.53%.

IR (film) ν_{max} 2980, 2920, 1780, 1500,1450, 1380, 910, 750, 690 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.34 (s, 3H), 1.48 (s, 3H), 2.5 (m, 2H,4-H), 2.7 (m, 1H,3-H), 3.10 (m, 1H, 3′-H), 4.20 (d, 1H, $J_{8,9}$=7.78 Hz, 8-H), 4.48 (d, 1H, *J*=11.4 Hz, $ArCH_2$), 4.69 (dd, 1H, $J_{8,9}$=7.78 Hz, $J_{9,10}$=2.5 Hz, 9-H), 4.90 (s, 1H, 7-H), 4.91 (d, 1H, *J*=11.4 Hz, $ArCH_2$), 5.2 (d, 1H, $J_{9,10}$=2.5 Hz, 10-H), 7.33 (m, 5H, Ar).

^{13}C NMR δ=24.27 (q), 26.18 (q), 26.19 (d), 28.95 (t), 37.46 (t), 70.59 (t), 75.29 (d), 76.62 (d), 97.97 (d), 106.75 (s), 110.44 (s), 128.35 (d), 128.76 (d), 128.77 (d), 136.66 (s), 174.98 (s).

(1*R*,3*S*,4*S*,5*S*,6*R*)-3-Benzyloxy-4,5-isopropylidenedioxy-2-oxa-7-azabicyclo[4.4.0]decan-8-one (21). The azide uronate **16** (0.81 g, 2 mmol) was dissolved in methanol (15 ml) and added to a suspension of pre-reduced palladium black (0.150 g) in methanol (5 ml) under hydrogen at room temperature. The reaction mixture was stirred for 6 h, and then the catalyst was removed by filtration and the methanol was evaporated to give 0.74 g of crude **20** which was dissolved in toluene and heated to reflux for 1 h to give **21** (0.65 g, 97%); $[\alpha]_D^{20}$ +46.38° (*c* 1.05, $CHCl_3$). Calcd for $C_{18}H_{23}O_5N$ (MW 333): C 64.86; H, 6.90; N, 4.20%. Found: C, 64.88; H, 6.92; N, 4.18%.

IR (film) ν_{max} 3300, 1730, 1670, 1480, 1450, 1380, 920, 900,

840, 820, 770, 740, 680 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.32 (s, 3H), 1.47 (s, 3H), 1.85 (m, 2H, 5-H), 2.40 (m, 2H,4-H), 3.23 (t, 1H, J=9.2 Hz, 1-H), 3.66 (m, 1H, 6-H), 4.01 (dd, 1H, $J_{9,10}$=5.3 Hz, $J_{1,10}$=9.2 Hz, 10-H), 4.14 (d, 1H, $J_{9,10}$=5.3 Hz, 9-H), 5.16 (s, 1H,8-H), 5.86 (s, 1H, NH), 7.32 (m, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=25.93 (t), 26.24 (q), 28.09 (q), 29.48 (t), 57.44 (d), 64.00 (d), 69.66 (t), 74.80 (d), 76.36 (d), 97.34 (d), 109.96 (s), 128.05 (d), 128.06 (d), 128.51 (d), 137.01 (s), 170.62 (s).

(1*R*,3*S*,4*S*,5*S*,6*R*)-3-Benzyloxy-4,5-isopropylidenedioxy-2-oxa-7-azabicyclo[4.4.0]decan (22). To a suspension of LAH (0.148 g, 3.9 mmol) in freshly distilled tetrahydrofuran (2.5ml) a solution of **21** (0.65 g, 1.95 mmol) in THF (2.5 ml) was added. The reaction mixture was stirred overnight at room temperature and under nitrogen atmosphere. Then, $Na_2SO_4 \cdot 10\ H_2O$ (100 mg) were added and stirring was continued for 5 h. Collection by filtration of the white solid was followed by evaporation of the organic solvent to give a crude which was purified by flash chromatography [$CHCl_3$: CH_3OH (92 : 8)] to give a colorless oil **22** (0.55 g, 89%); $[\alpha]_D^{20}$ +42.61° (*c* 2.9, CH_3OH). Calcd for $C_{18}H_{25}O_4N$ (MW 319): C, 67.71; H, 7.83; N, 4.39%. Found: C, 67.73; H, 7.86; N, 4.36%.

^1H NMR ($CDCl_3$) δ=1.31 (s, 3H), 1.44 (m, 2H, 9-H), 1.50 (s, 3H), 1.70 (m, 1H, 10-H), 1.99 (m, 2H, 10-H), 2.43 (dd, 1H, J_1=8.4 Hz, J_2=9.6 Hz, 8-H), 2.59 (dt, 1H, J_1=2.8 Hz, J_2=11.6 Hz, 8-H), 2.99 (br d, 1H, 6-H), 3.39 (dt, 1H, J_1=4.8 Hz, J_2=10 Hz, 1-H), 3.98 (dd, 1H, $J_{4,5}$=5.4 Hz, $J_{5,6}$=8.4 Hz, 5-H), 4.10 (d, 1H, $J_{4,5}$=5.4 Hz, 4-H), 4.58 (AB system, J=11.8 Hz, Ar CH_2), 5.09 (s, 1H, 3-H), 7.31 (m, 5H, ArH).

^{13}C NMR ($CDCl_3$) δ=25.01 (t), 26.31 (q), 28.16 (q), 30.10 (t), 46.19 (t), 62.04 (d), 66.50 (d), 68.93 (t), 74.96 (d), 76.34 (d), 96.64 (d), 109.06 (s), 127.70 (d), 127.90 (d), 128.34 (d), 137.37 (s).

Benzyl 6,7-Dideoxy-2,3-*O*-isopropylidene-α-D-*talo*-octopyranosiduronic Acid (23). 1 M Sodium hydroxide (5.5 ml) was added to a solution of uronate **14** (2 g, 5.3 mmol) in ethanol. The reaction mixture was stirred for 15 h at room temperature under argon atmosphere. Evaporation of the solvent and addition of aqueous sat. NH_4Cl (15 ml) was followed by extraction with chloroform to yield, after evaporation of the organic solvent at reduced pressure, a colorless oil **23** (1.75 g, 95%); $[\alpha]_D^{20}$ +56.5° (*c* 1.05, $CHCl_3$). Calcd for $C_{18}H_{24}O_7$ (MW 352): C, 61.36; H, 31.82%. Found: C, 61.31; H, 31.79%.

IR (film) ν_{max} 3500, 3000, 1720, 1480, 1460, 1200, 1100, 1000 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.35 (s, 3H), 1.55 (s, 3H), 1.90 (m, 1H, 6-H), 2.20 (m, 1H, 6′-H), 2.53 (t, J=7 Hz, 2H, 7-H), 3.61 (dd, 1H, $J_{3,4}$=4.8 Hz, $J_{4,5}$=1.5 Hz, H-4), 3.81 (ddd, 1H, $J_{4,5}$=1.5 Hz, $J_{5,6}$=4.5 Hz, $J_{5,6}$=9.4 Hz, H-5), 4.08 (d, 1 H, $J_{2,3}$=6.2 Hz, H-2), 4.22 (dd, 1H, $J_{2,3}$=6.2 Hz, $J_{3,4}$=4.8 Hz, H-3), 4.65 (AB system, J=11.8 Hz, $ArCH_2$), 5.14 (s, 3H, H-1), 7.30 (s, 5H, Ar).

^{13}C NMR ($CDCl_3$) δ=25.18 (q), 25.62 (q), 26.37 (t), 30.09 (t), 65.89 (d), 67.59 (d), 69.53 (t), 72.66 (d), 73.64 (d), 96.83 (d), 109.38 (s), 128.00 (d), 128.06 (d), 128.45 (d), 137.01 (s), 178.19 (s).

Hydroxamate 24. A solution of DCC (0.9 g, 4.6 mmol) in 1 ml of dry THF was added dropwise under argon atmosphere to a solution containing the uronic acid **23** (1.5 g, 4.2 mmol) and *O*-benzylhydroxylamine (0.8 g, 1.5 equiv) in 3 ml of dry THF. The reaction mixture was stirred for 20 h at room temperature. Filtration of the urea was followed by evaporation of the organic solvent to give a crude which, after purification by flash chromatography (hexane : AcOEt=4 : 6) afforded 1.65 g (85%) of a white solid **24;** mp 112—114 °C (ether); $[\alpha]_D^{20}$ +45.8° (*c* 0.7, $CHCl_3$). Calcd for $C_{25}H_{31}O_7N$ (MW 457): C, 65.65; H, 6.78; N, 3.06%. Found: C, 65.61; H, 6.71; N, 3.02%.

IR ($CHCl_3$) ν_{max} 3500, 3200, 1660, 1480, 1450, 1370, 900, 840 cm^{-1}.

^1H NMR ($CDCl_3$) δ=1.35 (s, CH_3),1.54 (s, CH_3), 1.9 (m, 2H, H-6), 2.15 (m, 2H, 7-H), 2.25 (d, 1H, J=5.6 Hz, OH), 3.59 (t, 1H, J=5.6 Hz, 4-H), 3.77 (m, 1H, 5-H), 4.06 (d, 1H, $J_{2,3}$=6.1 Hz, 2-H), 4.19 (dd, 1H, $J_{2,3}$=6.1 Hz, $J_{3,4}$=5.6 Hz, 3-H), 4.53 (AB system, J=11.8 Hz, $ArCH_2$), 4.83 (m, 2H, $ArCH_2$), 5.10 (s, 3H, 1-H), 7.30 (s, 5H, Ar), 7.32 (s, 5H, Ar).

^{13}C NMR (CD_3OD) δ=25.72 (q), 26.21 (q), 27.61 (t), 30.12 (t), 66.61 (d), 69.91 (d), 70.56 (t), 74.60 (d), 75.31 (d), 78.97 (t), 98.34 (d), 110.60 (s), 128.79 (d), 129.11 (d), 129.39 (d), 130.14 (d), 136.99 (s), 138.88 (s), 172.53 (s).

Glycal 27. Trifluoromethanesulfonic anhydride (0.4 ml, 2.4 mmol) was added dropwise to a solution of **24** (1 g, 2.18 mmol) in dichloromethane (20 ml) and pyridine (0.20 ml, 2.5 mmol) at −20 °C. The solution was stirred for 15 h and quenched by addition of sat. sodium bicarbonate solution (25 ml), allowed to warm to room temperature, stirred for 30 min and diluted with dichloromethane (10 ml). The organic layer was dried over Na_2SO_4 and evaporated to give 1 g (85%) of the crude triflate **25.**

A solution of the crude triflate **25** (1 g, 1.2 mmol) in 10 ml of acetone was added to a slurry of powdered K_2CO_3 (0.5 g, 3.6 mmol) in 35 ml of refluxing acetone and stirred for 1 h. The thick slurry was filtered through Celite, and the solids were washed with ethyl acetate (3×15 ml). The resulting solution was concentrated and rediluted with 25 ml of ethyl acetate. After being washed with brine, the organic solution was dried over $MgSO_4$ and concentrated to afford 0.7 g of a crude which was fractioned by flash chromatography.

Elution with hexane–AcOEt (1 : 1) gave 0.6 g (85%) of glycal **27**; $[\alpha]_D^{20}$ +146.5 ° (*c* 1.05, $CHCl_3$). Calcd for $C_{25}H_{29}O_6N$ (MW 439): C, 68.33; H, 6.50; N, 3.18%. Found: C, 68.30; H, 6.56; N, 3.12%.

^1H NMR ($CDCl_3$) δ=1.32 (s, 6H), 2.5 (m, 4H, 6-H+ 7-H), 3.98 (t, 1H, J=6.2 Hz, 3-H), 4.52 (dd, 1H, $J_{2,3}$=6.2 Hz, $J_{1,2}$=3.8 Hz, 2-H), 4.66 (d, 1H, $J_{3,4}$=6.2 Hz, 4-H), 4.78 (AB system, J=11.8 Hz, $ArCH_2O$), 4.83 (m, 2H, $ArCH_2ON$), 4.88 (d, $J_{1,2}$=3.8 Hz, 1-H), 7.31 (m, 10H, Ar).

^{13}C NMR ($CDCl_3$) δ=25.70 (q), 26.20 (q), 30.10 (t), 69.51 (d), 70.60 (t), 73.42 (d), 78.97 (t), 96.64 (d), 98.19 (d), 108.91 (s), 127.68 (d), 128.01 (d), 128.36 (d), 128.97 (d), 129.29 (d), 129.66 (d), 131.85 (d), 132.99 (s), 136.39 (s), 150.12 (s), 170.92 (s).

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16) The present synthetic route avoids the problem of stability of the 6-oxo-mannose derivatives undergoing chain elongation at C-6 by means of the Wittig reaction. None of the intermediates obtained by this route exhibited problems of stability after their isolation.