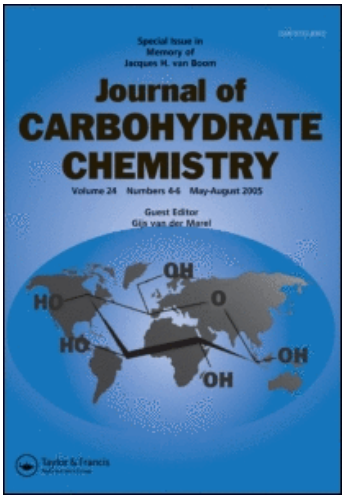

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A NEW SYNTHESIS OF METHYL 3-AMINO-3,4-DIDEOXY-β-D-*XYLO*-HEXOPYRANOSIDE

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ABSTRACT

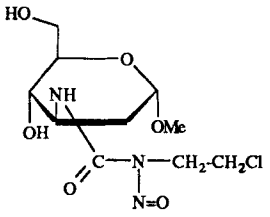
Benzylidenation of methyl β-D-glucopyranoside, followed by selective 3-*O*-tosylation, reductive acetal opening, chlorination, radical deoxygenation and transesterification, afforded methyl 2,3-anhydro-6-*O*-benzyl-4-deoxy-β-D-*ribo*-hexopyranoside **8**. Subsequent epoxide opening with NaN_3 and catalytic hydrogenation led to the title compound.

INTRODUCTION

During the last decade, many efforts have been devoted to the development of new analogues of known anticancer drugs, including nitrosourea derivatives,[1] in an effort to reduce side-effects and increase therapeutic differences. In our laboratories, methyl 3[3-(2-chloroethyl)-3-nitrosoureido]-2,3-dideoxy-α–D-*arabino*-hexopyranoside (**1**)(CY 233, NSC 609224) was synthesized[2] and found to be very potent in mice, not only against murine tumors such as L 1210 leukemia, B 16 melanoma, but also advanced colon 38

adenocarcinoma, known for its resistance to nitrosoureas.[3,4] Moreover, this compound is very effective against human colon and melanoma xenografts.[5]

In search of new analogues, we were especially interested in the synthesis of methyl 3-[3-(2-chloroethyl)-3-nitrosoureido]-3,4-dideoxy-α- and β-D-*xylo*-hexopyranoside (**2a** and **2b**).



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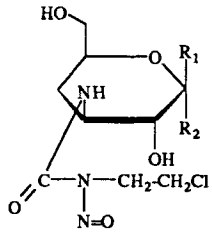


2a $R_1 = H$ $R_2 = OMe$

2b $R_1 = OMe$ $R_2 = H$

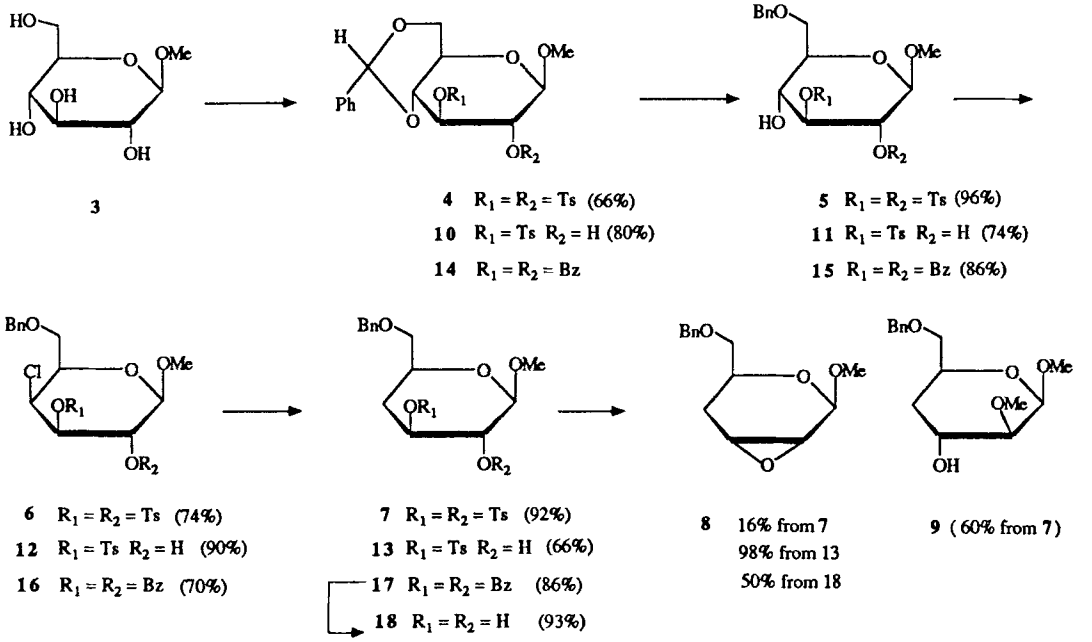
With respect to these considerations, syntheses of the sugar moiety of these new drugs have been undertaken and, as a result, we have recently reported[6] the synthesis of α- and β-anomers of methyl 3-amino-3,4-dideoxy-α- and β-D-*xylo*-hexopyranosides from 3-azido-3-deoxy-D-glucose. Since preliminary biological results[7] have indicated that β–anomer **2b** was the most active of all against advanced colon 38 adenocarcinoma, it became urgent to develop a more practical and stereoselective synthesis of the sugar moiety, namely the methyl 3-amino-3,4-dideoxy-β-D-*xylo*-hexopyranoside.

Methyl β-D-glucopyranoside **3** was therefore used as starting material and classically converted[8] into the benzylidene derivative **4** (66% overall yield) by 4,6-*O*-benzylidenation and ditosylation. Reductive opening of the acetal ring with sodium cyanoborohydride-hydrogen chloride[9] then afforded, in an almost quantitative yield, the 6-*O*-benzyl ether **5**. Further treatment of **5** with sulfuryl chloride led to **6** (74% yield) which was in turn treated under radical reduction conditions (Bu_3SnH, AIBN, toluene) to give the 4-deoxy derivative **7** in 92% yield. Unexpected difficulties occurred during the conversion of **7** into the anhydro-sugar of D-*ribo*-configuration **8** using standard methods such as 1M or 2 M sodium methoxide in methanol (rt or 50 °C for 5 days), 2 M sodium methoxide in methanol with chloroform, or 1,2-dichloroethane as co-solvents. Finally, treatment of **7** with 2N NaOMe in MeOH and toluene (45 °C for 19 h) seemed to be the best procedure although 60% of 2-*O*-methyl derivative **9** was obtained along with the expected epoxide **8** (≈ 16%).

In order to improve the yield for obtaining the *ribo* epoxide **8**, two other routes were alternatively developed. In the first methyl β-D-glucopyranoside **3** was transformed

into the 3-*O*-tosyl derivative **10**.[10] Therefore, the same sequence of reactions, including reductive opening of the benzylidene acetal, chlorination and radical dehalogenation afforded successively the monobenzyl ether **11** (74%), the 4-chloro derivative **12** (90 %) and the 4-deoxy derivative **13** (66%). In this case, the anhydro-sugar **8** was formed in an almost quantitative yield (≈ 98%) by treatment of **13** with 1M sodium methoxide in MeOH.

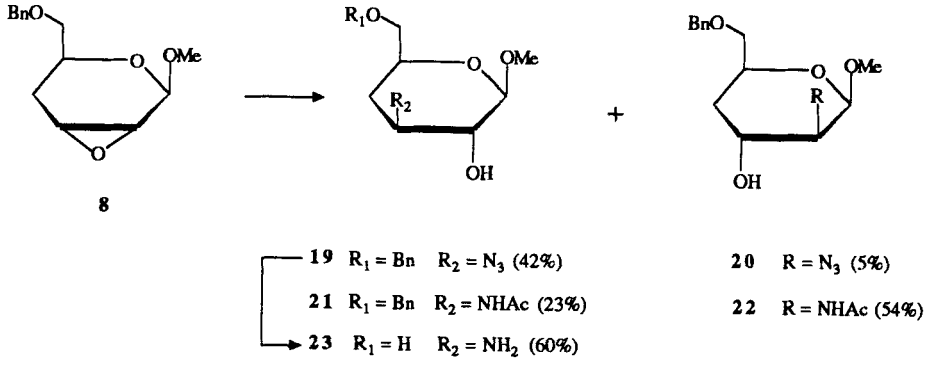
The second route involved methyl 2,3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-glucopyranoside[11] (**14**) as starting material. This was readily converted into the 4-deoxy-*xylo*-hexopyranoside **17** via reductive opening of the acetal ring, chlorination and deoxygenation (**14** -> **15** -> **16** -> **17**, 51.5% overall yield).



After transesterification of **17** to afford **18** (93%), treatment with tributylphosphine in the presence of diethyl azodicarboxylate[12] readily gave **8** in 50% yield after purification. In a subsequent step, the desired 3-azidosugar **19** was stereoselectively obtained along with its 2-isomer **20** (ratio **19/20** ≈ 66:33) by reacting **8** with 4 eq of NaN_3 in 2-methoxyethanol in the presence of a large excess (≈ 20 eq mol) of NH_4Cl. After purification by column chromatography, hydrogenation of **19** (isolated in 42% yield) in EtOH in the presence of 10% Pd-C and a small amount of acetic acid, led to the title aminosugar **23** in 60% yield along with side products which were not analyzed further.

In contrast with the result obtained with NaN_3, ring opening of the epoxide **8** with NH_3 in EtOH, followed by acetylation of the crude product, stereoselectively

afforded the 2-acetamido sugar **22** (54% yield) whereas the corresponding 3-acetamido isomer **21** became the minor product (23% yield).



In conclusion, the synthesis of the title compound was successfully achieved in seven steps from methyl β-D-glucopyranoside, but in an overall yield not exceeding 10%. This relatively low yield was partly due to the low stereoselectivity of the epoxide opening **8** towards the formation of 3-azido- and 3-aminosugars **19** and **23**. This was rather unexpected, since it has previously been reported[13] that the corresponding ethyl or benzyl 2,3-anhydro-4-deoxy-β-DL-*ribo*-hexopyranosides gave 3'-substituted derivatives with NH_3 or $NHMe_2$. Nevertheless, this new route could be considered competitive with the previous twelve-step one[6] from diacetone-glucose in an overall yield of 18%.

EXPERIMENTAL

General methods. Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer IR 1710 spectrophotometer calibrated against polystyrene film and are expressed in cm^{-1}. ^1H NMR spectra at 250 MHz were obtained on a Bruker AC 250 spectrometer in $CDCl_3$, except when indicated. Chemical shifts are expressed in ppm downfield from internal Me_4Si with the notations indicating the multiplicity of the signal (s, singlet; d, doublet; t, triplet; m, multiplet), Table 1. Coupling constants are expressed as *J* values in units of Hertz, Table 2. Mass spectra (DCI/NH_3) were recorded on a Nermag R10-10C. Column and flash chromatographies were performed with Merck silica gel H 60 n°7736 and 60 n°9385. Analytical thin-layer chromatographies were performed on Merck silica gel 60 F 254. Microanalyses were carried out by the "Laboratoire de Microanalyse du CNRS" in Lyon.

Table 1. ^{1}H-NMR data for compounds 5-9, 11-13, 15-22. Chemical shifts (δ)[a].

Compounds	*H-1*	*H-2*	*H-3*	*H-4a*	*H-4e*	*H-5*	*H-6a*	*H-6b*	*OCH_3*	*CH_2Ph*	*Others*
5	4.10 (d)	4.36 (dd)	4.61 (t)	3.76 (m)		3.36 (m)	3.73 (dd)	3.63 (dd)	3.00 (s)	4.50 (AB)	7.87 and 7.68 (2d, OTs),7.33-7.18 (Ar), 2.44 and 2.41 (2s, 2 CH_3)
6	4.21 (d)	4.72 (t)	4.65 (t)		4.62 (m)	3.78 (m)	<-----3.64-----> (m)		3.14 (s)	4.52 (s)	7.81 and 7.75 (2d, OTs),7.38-7.26 (Ar), 2.44 and 2.42 (2s, 2 CH_3)
7	4.10 (d)	4.37 (dd)	4.57 (m)	1.78 (m)	2.45 (m)	<--------3.60-3.45--------> (m)			3.08 (s)	4.53 (s)	7.85 and 7.73 (2d, OTs),7.37-7.24 (Ar), 2.44 and 2.43 (2s, 2 CH_3)
8	4.71 (s)	3.10 (d)	3.32 (m)	1.78 (ddd)	1.97 (ddd)	3.62 (m)	<-----3.43-----> (m)		3.52 (s)	4.53 (s)	7.30 (s, Ar)
9	4.62 (d)	3.69 (dd)	3.62 (m)	1.82 (ddd)	1.67 (ddd)	3.98 (m)	<-----3.54-----> (m)		3.38 (s) 3.54 (s)	4.59 (AB)	7.30 (s, Ar)
11	4.20 (d)	3.80-3.72 (m)	4.52 (t)	<----------3.80--372----------> (m)			<-----3.52-----> (m)		3.52 (s)	4.58 (AB)	7.85 and 7.29 (2d, OTs), 7.32 (s, Ar), 2.44 (s, CH_3)
12	4.21 (d)	3.85 (m)	4.63 (dd)		4.48 (dd)	3.85 (m)	<-----3.68-----> (m)		3.53 (s)	4.55 (s)	7.85 and 7.29 (2d, OTs), 7.32 (s, Ar), 2.44 (s, CH_3)
13	4.12 (d)	3.75-3.35 (m)	4.54 (m)	1.71 (ddd)	2.17 (ddd)	<---------3.75-3.35--------> (m)			3.51 (s)	4.55 (s)	7.85 and 7.29 (2d, OTs), 7.32 (s, Ar), 2.43 (s, CH_3)
15[b]	4.38 (d)	<---5.50-5.40---> (m)		3.80 (m)		3.47 (dt)	<-----3.67-----> (d)		3.30 (s)	4.43 (AB)	7.92 (4H, Ar), 7.25-7.03 (m, 11H, Ar)
16	4.64 (d)	5.78 (dd)	5.45 (dd)		4.78 (dd)	4.11 (m)	<-----3.80-----> (m)		3.55 (s)	4.61 (s)	8.03-7.97 (4H, Ar), 7.60-7.30 (m, 11H, Ar)
17	4.55 (d)	<---5.38-5.35---> (m)		1.78 (m)	2.40 (m)	3.90 (m)	<---3.71-3.56---> (m)		3.52 (s)	4.61 (s)	8.00-7.96 (4H, Ar), 7.50-7.30 (m, 11H, Ar)
18	4.12 (d)	3.25 (dd)	3.80-3.50 (m)	1.48 (ddd)	2.02 (ddd)	<--------3.80-3.50--------> (m)			3.55 (s)	4.58 (AB)	7.38 (s, Ar), 2.31 (bs, 2 OH)
19	4.16 (d)	3.35 (dd)	3.67-3.50 (m)	1.51 (ddd)	2.07 (ddd)	3.80-3.70 (m)	<---3.67-3.60---> (m)		3.55 (s)	4.57 (s)	7.33 (s, Ar), 2.50 (bs, OH)
20	4.82 (d)	3.40 (dd)	3.62 (m)	1.88 (ddd)	1.64 (ddd)	4.20-4.08 (m)	<---3.63-3.55---> (m)		3.55 (s)	4.57 (AB)	7.33 (s, Ar), 4.15 (bs, OH)
21	4.21 (d)	3.24 (dd)	3.70 (m)[c]	1.38 (ddd)	2.05 (m)	3.90 (m)[c]	<---3.56-3.49---> (m)		3.55 (s)	4.56 (AB)	7.32-7.25 (m, 5H, Ar), 6.10 (bd, NH), 2.95 (bs, OH)
22	4.85 (d)	<---4.20-3.90---> (m)		1.77 (ddd)	1.60 (ddd)	4.20-3.90 (m)	<-----3.55------> (m)		3.48 (s)	4.57 (s)	7.35-7.29 (m, 5H, Ar), 6.19 (bd, NH), 2.95 (bs, OH)

a. in $CDCl_3$; TMS = δ 0. b. in $CDCl_3$-C_6D_6 (1:1). c. interchangeable or inverse.

Table 2. ^{1}H NMR for compounds **5-9**, **11-13**, **15-20**, and **22**, **23**. Coupling constants in Hz.

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4a}$	$J_{3,4e}$	$J_{4a,4e}$	$J_{4a,5}$	$J_{4e,5}$	$J_{5,6a}$	$J_{5,6b}$	CH_2Bn
5	8	9.5	9.5	-	-	9.5	-	2.5	5	12
6	7	7	-	4	-	-	4	6	-	-
7	7.5	9	6	-	12	6	-	-	-	-
8		4.5	1.5	2.5	14.5	10	2.5	-	-	-
9	1.5	4	3	3	14	10	3	-	-	11
11	8	10	10	-	-	-	-	-	-	11
12	7	10	-	4	-	-	≃1			-
13	7.5	-	10	1.5*	12	10	5.5*	-	-	-
15	8	-	10	-	-	10	-	4.5	-	11
16	8	10	-	3.5	-	-	-	-	-	-
17	8	-	-	-	12	-	-	-	-	-
18	8	9	9	5*	12	10	2*	-	-	12
19	8	10	9	7*	12	10	2*	-	-	-
20	2	3	3	4	12	10	4	-	-	12
21	7.5	9	9	-	11	9	-	-	-	11
22	2	-	3	4	12	10	4	-	-	-

* interchangeable.

Methyl 6-*O*-Benzyl-2,3-di-*O*-tosyl-β-D-glucopyranoside (5). Hydrogen chloride in ether (≈ 200 mL) was added dropwise to a solution of **4** (17 g, 28.8 mmol) and sodium cyanoborohydride (18.7 g, 297 mmol) in THF (350 mL) containing 4 Å molecular sieves until the evolution of gas ceased (≈ 30 min). The mixture was diluted with dichloromethane (600 mL) and water (50 mL), then filtered. The organic layer was separated, washed with H_2O, saturated aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the resulting syrup, using dichloromethane-MeOH (99:1) as eluent, afforded 16.4 g (96%) of pure **5** as a crystalline compound: mp 97 °C; $[\alpha]_D^{20}$ -9° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3513 (OH), 2937, 1599 cm^{-1}, MS (d.c.i.) *m/z* 610 $(M + NH_4)^+$.

Anal. Calcd for $C_{28}H_{32}O_{10}S_2$: C, 56.74; H, 5.44; S, 10.82. Found: C, 56.94; H, 5.49; S, 10.61.

Methyl 6-*O*-Benzyl-4-chloro-4-deoxy-2,3-di-*O*-tosyl-β-D-galactopyranoside (6). Sulfuryl chloride (19.25 mL, 239 mmol) was added dropwise to a cooled (≈ 0 °C) solution of **5** (7.4 g, 12.5 mmol) in pyridine (200 mL). Additional stirring was maintained at 0 °C for 18 h and then at room temperature for 2 h. The resulting mixture was poured into ice-water (300 mL) and extracted with dichloromethane. The organic layer was separated, washed with 5% aqueous H_2SO_4, saturated aqueous $NaHCO_3$ and brine before drying ($MgSO_4$). Flash chromatography with CH_2Cl_2 as eluent afforded 5.64 g (74%) of **6** as a crystalline compound: mp 93 °C (MeOH); $[\alpha]_D^{20}$ +18° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 2956, 1600, 1375, 1249 cm^{-1}, MS (d.c.i.) *m/z* 630 and 628 $(M + NH_4)^+$.

Anal. Calcd for $C_{28}H_{31}ClO_9S_2$: C, 55.07; H, 5.12; Cl, 5.73; S, 10.49. Found: C, 55.70; H, 4.90; Cl, 5.76; S, 10.66.

Methyl 6-*O*-Benzyl-4-deoxy-2,3-di-*O*-tosyl-β-D-*xylo*-hexopyranoside (7). A solution of **6** (3.72 g, 6.09 mmol) in dry toluene (150 mL) was heated at 80 °C for 24 h in the presence in tributyltin hydride (9.24 mL, 34 mmol) and a catalytic amount of AIBN. After cooling the mixture, the toluene was removed by evaporation under reduced pressure and the residue dissolved in ether (950 mL) before stirring 1.5 h in the presence of 10% aqueous KF (465 mL). Filtration, followed by decantation, drying of the ether layer ($MgSO_4$) and concentration under reduced pressure gave 12.7 g of the residue. Flash chromatography with dichloromethane as eluent afforded 3.23 g (92%) of pure **7** as a syrup: $[\alpha]_D^{20}$ -0.5° (*c* 2, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1600, 1371, 1192, 1179 cm^{-1}, MS (d.c.i.) *m/z* 594 $(M + NH_4)^+$, 440.

Anal. Calcd for $C_{28}H_{32}O_9S_2$: C, 58.32; H, 5.59; S, 11.12. Found: C, 58.86; H, 5.69; S, 11.08.

Methyl 2,3-Anhydro-6-*O*-benzyl-4-deoxy-β-D-*ribo*-hexopyranoside (8) and **Methyl 6-*O*-Benzyl-4-deoxy-2-*O*-methyl-β-D-*arabino*-hexopyrano-**

side (9). To a solution of **7** (2.3 g) in anhydrous toluene (29 mL), a 2 M solution of sodium methoxide in MeOH (18 mL) was added and stirring was maintained for 20 h at 45 °C. After bubbling CO_2 through the reaction mixture, filtration and concentration afforded a crude residue mixture (1.22 g) of **8** and **9** in a 2:8 ratio, as shown by ^1H NMR analysis. Flash chromatography with cyclohexane-EtOAc (7:3) as eluent led to the isolation of 150 mg (16%) of **8** and 740 mg (60%) of **9**.

For compound **8** (syrup): $[\alpha]_D^{20}$ -60° (*c* 1.6, $CHCl_3$); MS (d.c.i.) *m/z* 268 $(M + NH_4)^+$.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.77; H, 6.97.

For compound **9** (syrup) : $[\alpha]_D^{20}$ -70.5° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3575 cm^{-1} (OH); MS (d.c.i.) *m/z* 300 $(M + NH_4)^+$, 268.

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.54; H, 8.01.

Methyl 6-*O*-Benzyl-3-*O*-tosyl-β-D-glucopyranoside (11). 1.27 g (74%) was obtained from monotosylate **10** (1.7 g) according to the procedure used for preparing **5**.

For compound **11** (syrup) : $[\alpha]_D^{20}$ -3.5° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3600 and 2956 cm^{-1} (OH); MS (d.c.i.) *m/z* 456 $(M + NH_4)^+$, 424, 302 and 284.

Anal. Calcd for $C_{21}H_{26}O_8S$: C, 57.52; H, 5.98; S, 7.31. Found: C, 57.36; H, 6.00; S, 7.50.

Methyl 6-*O*-Benzyl-4-chloro-4-deoxy-3-*O*-tosyl-β-D-galactopyranoside (12) was obtained (1.19 g, 90%) from **11** (1.25 g) according to the procedure described for preparing **6**.

For compound **12** (syrup): $[\alpha]_D^{20}$ +24° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3603 cm^{-1} (OH); MS (d.c.i.) *m/z* 476 and 474 $(M + NH_4)^+$, 150, 148 and 114.

Anal. Calcd for $C_{21}H_{25}ClO_7S$: C, 55.20; H, 5.51. Found: C, 55.06; H, 5.46.

Methyl 6-*O*-Benzyl-4-deoxy-3-*O*-tosyl-β-D-*xylo*-hexopyranoside (13). It was obtained (0.73 g, 66%) from **12** (1.2 g) according to the procedure described for preparation of **7**, followed by flash chromatography with dichloromethane-MeOH (98:2) and crystallization from cyclohexane: m.p 103 °C; $[\alpha]_D^{20}$ +7° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3599 cm^{-1} (OH); MS (d.c.i.) *m/z* 440 $(M + NH_4)^+$, 268.

Anal. Calcd for $C_{21}H_{26}O_7S$: C, 59.70; H, 6.20; S, 7.59. Found: C, 59.70; H, 6.01; S, 7.36.

Methyl 6-*O*-Benzyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (15). See the preparation of **5** and **11**. Thus, 3.3 g of **14**, after flash chromatography with dichloromethane-MeOH (90:10, then 99:1), gave 2.88 g (86%) of **15**, as a syrup:$[\alpha]_D^{20}$ +59° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3483 (OH), 1730 and 1249 cm^{-1} (CO ester); MS (d.c.i.) *m/z* 510 $(M + NH_4)^+$, 493 $(M + H)^+$, 461 $(M + H - CH_3OH)^+$.

Anal. Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.73. Found: C, 67.85; H, 5.58.

Methyl 6-*O*-Benzyl-2,3-di-*O*-benzoyl-4-chloro-4-deoxy-β-D-galactopyranoside (16). Treatment of **15** (2.88 g) as already mentioned for preparation of **6** and **12** afforded **16** in 70% (2.10 g) after flash chromatography with dichloromethane as eluent and crystallization from pentane: mp 94 °C; $[\alpha]_D^{20}$ +69° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1729 and 1249 cm^{-1} (CO ester); MS (d.c.i.) *m/z* 530 and 528 $(M + NH_4)^+$, 513 and 511 $(M + H)^+$, 498, 479.

Anal. Calcd for $C_{28}H_{27}ClO_7$: C, 65.82; H, 5.33; Cl, 6.94. Found: C, 65.25; H, 5.38; Cl, 7.27.

Methyl 6-*O*-Benzyl-2,3-di-*O*-benzoyl-4-deoxy-β-D-*xylo*-hexopyranoside (17). Treatment of **16** (1.45 g) as already described for **7** and **13**, led to **17** as a syrup (1.15 g, 86%) after flash chromatography using dichloromethane-MeOH (98:2) as eluent:$[\alpha]_D^{20}$ +59° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1724 and 1249 cm^{-1} (CO ester); MS (d.c.i.) *m/z* 494 $(M + NH_4)^+$, 445 $(M + H - MeOH)^+$.

Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.58; H, 5.92. Found: C, 70.52; H, 5.81.

Methyl 6-*O*-Benzyl-4-deoxy-β-D-*xylo*-hexopyranoside (18). After addition of 1 M sodium methoxide in methanol (2 mL) to a solution of **17** (1.05 g, 2.2 mmol) in MeOH and stirring at rt for 2 h, filtration through amberlite IR50S and concentration under reduced pressure afforded a crude product (0.98 g). Flash chromatography with ethyl acetate gave 0.55 g (93%) of a crystalline compound: mp72 °C; $[\alpha]_D^{20}$ -49° (*c* 1, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3598 cm^{-1} (OH); MS (d.c.i.) *m/z* 286 $(M + NH_4)^+$, 254 $(M + NH_4 - MeOH)^+$, 237 $(M + H - MeOH)^+$.

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.87; H, 7.54.

Methyl 2,3-Anhydro-6-*O*-benzyl-4-deoxy-β-D-*ribo*-hexopyranoside (8).

1) *From* **13.** Stirring a methanol solution (25 mL) of **13** (588 mg, 1.4. mmol) in the presence of 1 M NaOMe-MeOH (2.8 mL) afforded, after the usual work-up, 350 mg (98%) of anhydro-sugar (**8**).

2) *From* **18.** Compound **18** (106 mg, 0.4 mmol) was stirred in dry toluene (2 mL) containing 4 Å molecular sieves, for 2 h at rt, and then for 8 h at 50 °C in the presence of tributylphosphine (0.11 mL, 0.44 mmol) and diethylazodicarboxylate (0.07 mL, 0.44 mmol). The mixture was cooled and extracted with ether, washed with 5% HCl and treated in the usual manner. After concentration under reduced pressure, flash chromatography of the residue with cyclohexane/EtOAc (70:30) afforded 50 mg (50%) of pure **8**.

Methyl 3-Azido-6-*O*-benzyl-3,4-dideoxy-β-D-*xylo*-hexopyranoside (19) and Methyl 2-Azido-6-*O*-benzyl-2,4-dideoxy-β-D-*arabino*-hexopyranoside (20). To a solution of anhydro-sugar **8** (200 mg, 0.8 mmol) in 2-

methoxyethanol (4 mL), were added sodium azide (212 mg, 3.2 mmol) and NH_4Cl (846 mg, 15.8 mmol). After stirring under reflux for 4.5 h, concentration under reduced pressure, followed by extraction of the crude residue with dichloromethane, washings with water, drying over $MgSO_4$ and concentration, led to 220 mg of a syrup. Flash chromatography with cyclohexane/EtOAc (70:30) gave 192 mg (82%) of a mixture of **19** and **20**. A second chromatography with CH_2Cl_2-MeOH (99:1) afforded successively **19** (103 mg, 42%), a mixture of **19** and **20** (74 mg), and **20** (13 mg, 5%).

For compound **19** (syrup): $[\alpha]_D^{20}$ -25° (*c* 0.7, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3599 (OH), 2105 cm^{-1} (N_3); MS (d.c.i.) *m/z* 311 $(M + NH_4)^+$.

Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.55; H, 6.61; N, 14.27.

For compound **20** (syrup): $[\alpha]_D^{20}$ -127° (*c* 0.75, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3613 and 3468 (OH), 2110 cm^{-1} (N_3); MS (d.c.i.) *m/z* 311 $(M + NH_4)^+$.

Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.20; H, 6.63; N, 13.68.

Methyl 3-amino-3,4-dideoxy-β-D-*xylo*-hexopyranoside (23). A solution of **19** (120 mg, 0.41 mmol) in ethanol (5 mL) was stirred under H_2 atm (1 atm) in the presence of 10% Pd-on-charcoal (35 mg) and AcOH (0.5 mL). Filtration of the mixture to remove the catalyst, followed by concentration under reduced pressure ($t < 40$ °C), flash chromatography (CH_2Cl_2/MeOH sat. NH_3 85:15) led to ≈ 35 mg (60%) of a crystalline **23**: mp 152 °C; IR, MS and NMR results were in agreement with our previous findings.[6]

Methyl 3-Acetamido-6-*O*-benzyl-3,4-dideoxy-β-D-*xylo*-hexopyranoside (21) and **Methyl 2-Acetamido-6-*O*-benzyl-2,4-dideoxy-β-D-*arabino*-hexopyranoside (22).** A solution of **8** (186 mg) in methanol saturated with NH_3 (8 mL) was heated at 150 °C for 5 h in an autoclave. Concentration of the solution under reduced pressure afforded a crude residue which was dissolved in MeOH (6 mL) and stirred at rt overnight in the presence of Ac_2O (1 mL). Then concentration *in vacuo*, followed by dilution with a sat. aq. solution of sodium hydrogenocarbonate, extraction with EtOAc, gave 227 mg of a mixture of **21** and **22**. Column chromatography with CH_2Cl_2-MeOH (95:5) led successively to 124 mg (54%) of **22**, 17 mg of **21** and **22**, and finally 53 mg (23%) of **21**.

For compound **21** (mp 169 °C): $[\alpha]_D^{20}$ -35° (*c* 0.8, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3612, 1667 cm^{-1} (NHAc); MS (d.c.i.) *m/z* 327 $(M + NH_4)^+$, 310 $(M + H)^+$, 278 $(M + H - MeOH)^+$.

For compound **22** (syrup): $[\alpha]_D^{20}$ -39° (*c* 0.85, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3612, 1667 cm^{-1} (NHAc); MS (d.c.i.) *m/z* 327 $(M + NH_4)^+$, 310 $(M + H)^+$, 278 (M + H - MeOH)$^+$.

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