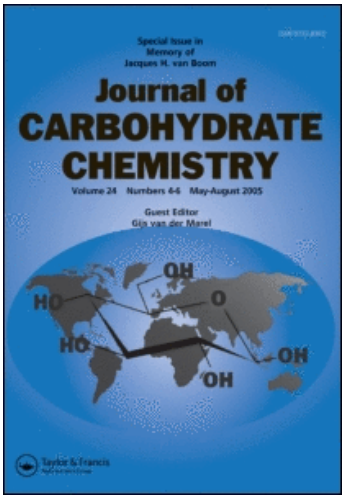

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SYNTHESIS OF METHYL 3-AMINO-3,4-DIDEOXY-α AND ß-D-XYLO-HEXOPYRANOSIDES

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ABSTRACT

3-Azido-3-deoxy-D-glucose was used as starting material for the syntheses of methyl 3-amino-3,4-dideoxy- ß and α-D-*xylo*-hexopyranoside 9 and 15 and methyl 3-amino-4-chloro-3,4-dideoxy- ß and α-D-galactopyranoside 11 and 17. The ß-D-anomers 9 and 11 were stereoselectively obtained using Koenigs-Knorr conditions for the glycosidation step with the bromo derivative 3 as intermediate.

INTRODUCTION

We have recently shown[1] that a series of nitrosoureido derivatives of methyl 3-amino-2,3-dideoxy- and 3-amino-2,3,6-trideoxy-α-D-*arabino*-hexopyranosides exhibits a very significant activity against L1210 leukemia, B16 melanocarcinoma and Lewis lung carcinoma. The influence of the hydroxyl substitution pattern, the configuration at the anomeric center and the absolute configuration of the sugar moiety have been studied in this series. In particular, it has been demonstrated that the presence of two hydroxyl substituents on the sugar component was optimal for biological activity bringing at the same time an about 10 fold increase in water solubility compared to that of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), used as reference,[2] which is of considerable importance for clinical use.

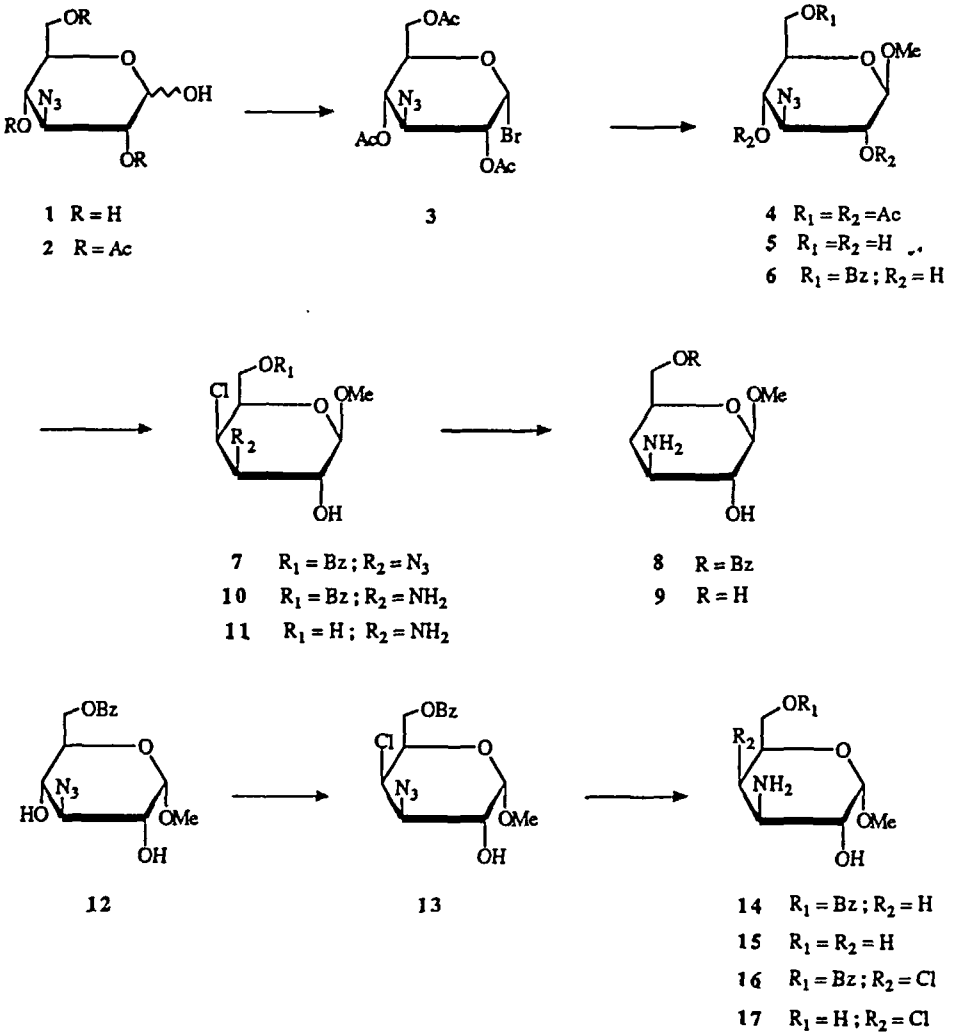
As an extension of this rationale for the synthesis of highly active antitumor nitrosoureidosugars, our next aim was the preparation of the 3-amino-3,4-dideoxy-sugar analogs, namely the title compounds, in order to prepare subsequently the corresponding nitrosoureas. These hexoses represent an important class of natural sugars and several macrolide antibiotics have been found to contain, for example, 3-amino-3,4,6-trideoxy-D-*xylo*-hexose or D-desosamine[3] as their carbohydrate component.

RESULTS AND DISCUSSION

As it has been already reported during the synthesis of methyl-D-desosaminide,[4] 3-azido-3-deoxy-D-glucose 1 was used as starting material. According to the first and stereoselective route (Scheme 1), the corresponding peracetyl derivative 2 was treated with titanium bromide to give in an almost quantitative yield the bromo compound 3. Exclusive formation of the ß-anomer of methyl glucoside 4 occurred when glycosidation of 3 was carried out under Koenigs-Knorr conditions (HgO, $HgBr_2$, molecular sieves 4Å) at room temperature for 18 h. Zemplen deacetylation of 4 led to 5. Compound 5 was obtained alternatively in a one step reaction from 3 according to the method of Austin[5] by using sodium methoxide-methanol (85% yield). Treatment of 5 with bis(dibutyltin) oxide and subsequent addition of benzoyl chloride, regiospecifically afforded the 6-*O*-benzoyl ester derivative 6. Treatment of 6 with sulfuryl chloride in pyridine gave 7 (80% yield) which was converted to 8 by reduction with tributyltin hydride in the presence of azobisisobutyronitrile and debenzoylation of 8 gave methyl 3-amino-3,4-dideoxy-ß-D-*xylo*-hexopyranoside 9 . Alternatively, selective reduction of the azido function as present in 7 was achieved by catalytic hydrogenation in the presence of triethylamine and the 3-amino-4-chloro-3,4-dideoxy-ß-D-*galacto*-hexopyranoside 11 was subsequently obtained by transesterification of the resulting aminosugar, 10.

When 3-azido-3-deoxy-D-glucose 1 was refluxed in the presence of HCl and MeOH, and the resulting crude mixture treated with bis(dibutyltin) oxide and benzoyl chloride, the methyl 6-*O*-benzoyl-ß and α-D-glucosides 6 and 12 were formed and separated by column chromatography in an approximately 1:1 ratio and 50% overall yield. The α-anomer 12 was treated as previously indicated for 6 by : i) chlorination with SO_2Cl_2 in pyridine at 0 °C ; ii) radical reduction with Bu_3SnH ; iii) transesterification with MeONa-MeOH in order to give successively 13, 14 and 15 (40% overall yield). Alternatively, catalytic hydrogenation of 13 followed by transesterification of the corresponding amino derivative 16 led to methyl 3-amino-4-chloro-3,4-dideoxy-α-D-galactopyranoside 17.

Scheme 1.



1 R = H
2 R = Ac

3

4 $R_1 = R_2$ = Ac
5 $R_1 = R_2$ = H
6 R_1 = Bz; R_2 = H

7 R_1 = Bz; $R_2 = N_3$
10 R_1 = Bz; $R_2 = NH_2$
11 R_1 = H; $R_2 = NH_2$

8 R = Bz
9 R = H

12

13

14 R_1 = Bz; R_2 = H
15 $R_1 = R_2$ = H
16 R_1 = Bz; R_2 = Cl
17 R_1 = H; R_2 = Cl

Preparation of the (chloro-2-ethyl)-3-nitroso-3-ureido-derivatives of 9, 11, 15 and 17 will be reported elsewhere as well as their preliminary biological evaluation.

EXPERIMENTAL

General Methods. Melting temperatures were determined in capillary tubes heated in a Totoli apparatus or on a Kofler hot stage microscope and were uncorrected. IR spectra were recorded on a Perkin-Elmer Model 289 spectro-

photometer, calibrated against polystyrene film, and were expressed in cm^{-1}. ^1H NMR spectra at 270 MHz were obtained on a Bruker HX 270 instrument in $CDCl_3$ except when indicated. Chemical shifts were expressed in ppm downfield from internal Me_4Si with the notations indicating the multiplicity of the signal (s, singlet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet). The coupling constants are expressed as J values in units of Hertz. Optical rotations were measured at 20 °C with a Perkin-Elmer Model 241 polarimeter on 1% solutions. Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254}. Microanalyses (C, H, N) were carried out on a Perkin-Elmer Model 240 elemental analyzer. Mass spectra [c.i. (ammonia)] were recorded on a Nermag R 1010 instrument.

2,4,6-Tri-O-acetyl-3-azido-3-deoxy-α-D-glucopyranosyl Bromide (3).

To a stirred solution of 2 (13 g, 34.8 mmol)[4] in dichloromethane (300 mL) under N_2 atmosphere and in the dark was added titanium bromide (25 g, 68 mmol). After stirring overnight, additional $TiBr_4$ (12 g, 32.6 mmol) was added and stirring was maintained for 6 days at room temperature. The reaction mixture was diluted with dichloromethane (200 mL) and poured onto crushed ice (500 g). The organic layer was separated and usual work-up afforded 3 (14.5 g) pure enough for the next steps.

An analytical sample was obtained by chromatography on silica gel using hexane-acetone (3:1) as eluent : syrup ; $[\alpha]_D$ = +164°5 (c 1.66, $CHCl_3$) ; IR (film) : 2100 (N_3), 1800-1700 cm^{-1} (ester).

Anal. Calcd for $C_{12}H_{16}BrN_3O_7$ (394.2). C : 36.5 ; H : 4.1 ; N : 10.6. Found : C : 36.6 ; H : 4.2 ; N : 10.4.

Methyl 2,4,6-Tri-O-acetyl-3-azido-3-deoxy-ß-D-glucopyranoside (4).

To a suspension of yellow HgO (18 g, 83 mmol), $HgBr_2$ (1.5 g, 4 mmol) and dry molecular sieves 4Å (60 g) in anhydrous dichloromethane (450 mL) were added methanol (12 mL, 297 mmol) and then a solution of 3 (14.5 g, 36 mmol) in anhydrous dichloromethane (50 mL). After stirring for 18 h at room temperature, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. This afforded 13.5 g (86%) of 4 as a syrup from which an analytical sample was obtained by chromatography on silica gel using hexane-acetone (4:1) as eluent : syrup ; $[\alpha]_D$ = -18.5° (c 1.2, chloroform) ; IR (film) : 2100 (N_3), 1800-1700 cm^{-1} (ester).

Anal. Calcd for $C_{13}H_{19}N_3O_8$ (345.3). C : 45.2 ; H : 5.5 ; N : 12.2. Found : C : 45.1 ; H : 5.3 ; N : 12.0.

Methyl 3-Azido-3-deoxy-ß-D-glucopyranoside (5).

Method A : A methanolic solution (100 mL) of 4 (13 g, 37 mmol) was stirred for 2 h in the presence of sodium methoxide (1M, 10 mL). Neutralization by filtration over Amberlite IR-50(H^+) ion-exchange resin followed by concentration afforded 5 (6.2 g, 77% overall yield from 3) as a syrup, $[\alpha]_D$ = -13°.0 (c 2.4, methanol) ; IR (film) : 2100 cm^{-1} (azide).

Anal. Calcd for $C_7H_{13}N_3O_5$ (219.2). C : 38.4 ; H : 6.0 ; N : 19.2. Found : C : 38.2 ; H : 6.0 ; N : 19.0.

Method B : A methanolic solution (400 mL) of 3 (17 g, 43 mmol) was stirred for 1 h in the presence of sodium methoxide (1.7 M, 125 mL). Neutralization by filtration over Amberlite IR-50 (H^+) ion-exchange resin followed by concentration and chromatography on silica gel using dichloromethane-methanol (9:1) as eluent afforded 5 (8 g, 85% overall yield from 3) as a syrup which has physical data in agreement with those previously reported using method A.

Methyl 3-Azido-6-O-benzoyl-3-deoxy-ß-D-glucopyranoside (6).

A solution of 5 (6 g, 27.4 mmol) in methanol (250 mL) was refluxed for 3 h in the presence of bis(tributyltin) oxide (21 mL, 41.2 mmol) and then concentrated under reduced pressure. The residue was dissolved in toluene (150 mL) and after cooling to -30 °C, benzoyl chloride (9 mL, 77.5 mmol) was added dropwise. Stirring was maintained at -15 °C for 18 h and excess of benzoyl chloride was destroyed by addition of methanol (10 mL) and stirring for 2 h at room temperature. Concentration under reduced pressure followed by column chromatography (dichloromethane-MeOH, 98:2) yielded 6 (7.54g, 85%) as a syrup, $[\alpha]_D \doteq$ -3.5° (c 0.8, chloroform) ; IR (film) : 3450 (OH), 2100 (azide) and 1710 cm^{-1}(ester) ; ^1H NMR, δ 8.05(d) and 7.65-7.31(m) (5H, Ar) ; 4.72 (dd, 1H, J=13, J'=3) and 4.50 (d, J=13) (CH_2-6), 4.23 (d, 1H, J=6.5, H-1), 3.64-3.26 (m, 4H, H-2, H-3, H-4, H-5), 3.53 (s, OMe).

Anal. Calcd for $C_{14}H_{17}N_3O_6$ (323.3). C : 52.0 ; H : 5.3 ; N : 13.0. Found : C : 51.7 ; H : 5.5 ; N : 12.8.

Methyl 3-Azido-6-O-benzoyl-4-chloro-3,4-dideoxy-ß-D-galactopyranoside (7).

Sulfuryl chloride (12.5 mL, 150 mmol) was added dropwise to a cooled (0 - 5 °C) solution of 6 (4.8 g, 5 mmol) in anhydrous pyridine (250 mL). The solution was stirred for 18 h at +5 °C and then allowed to reach room temperature for 2 h. The crude mixture was poured onto crushed ice (500 g) and extracted three times (3x300 mL) with dichloromethane.

The organic layer was successively washed with 1N aqueous H_2SO_4 solution, with H_2O and a saturated solution of sodium hydrogenocarbonate. After drying, concentration under reduced pressure gave a syrup which was chromatographed on

silica gel using hexane-EtOAc (8:2) as eluent. **7** was isolated as a crystalline compound, mp 84-86 °C ; $[\alpha]_D$ = +2°.0 (c 0.9, chloroform) ; IR (KBr) : 3400 (OH), 2100 (azide), 1720 cm^{-1} (ester). ^1H NMR : δ 7.96 (J=7) and 7.59-7.34(m)(5H, Ar) ; 4.75 (m, 1H, OH), 4.56 (m, 2H, CH_2-6), 4.33 (dd, 1H, J=3.5, J'=1.5, H-4), 4.24 (d, 1H, J=7.5, H-1), 4.04 (m, 1H, J=J'=6, J"=1.5, H-5), 3.89 (dd, 1H, J=10, J'=7.5, H-2), 3.67 (dd, 1H, J=10, J'=3.5, H-3), 3.55 (s, 3H, OMe).

Anal. Calcd for $C_{14}H_{16}ClN_3O_5$ (341.7). C : 49.2 ; H : 4.7 ; N : 12.3. Found : C : 49.3 ; H : 4.7 ; N : 12.0.

Methyl 3-Amino-6-O-benzoyl-3,4-dideoxy-ß-D-xylo-hexopyranoside (8).

To a solution of **7** (4 g, 12 mmol) in toluene (200 mL) under nitrogen atmosphere were added azobisisobutyronitrile (700 mg, 4.27 mmol) and tributyltin hydride (12.6 mL, 47 mmol). The mixture was refluxed for 2 h and concentrated under reduced pressure. Chromatography of the residue on silica gel using dichloromethane-MeOH/NH_3 (9:1) allowed isolation of **8** (3 g, 90%) as crystals, mp 116-117 °C ; $[\alpha]_D$ = -13°.6 (c 0.3, MeOH) ; IR (KBr) : 1720 cm^{-1} ; ^1H NMR ; δ 7.96 (d, J=3) and 7.52-7.32(m) (5H, Ar), 4.33 (m, 2H, CH_2-6), 4.13 (d, 1H, J=7.5, H-1), 3.50 (s, 3H, OMe), 3.15 (dd, 1H, J=9, J'=7.5, H-2), 2.98 (m, 1H, H-5), 2.00 (m, 1H, J=12, J'=3, J"<0.5, H-4e), 1.47 (m, 1H, J=12, J'=J"=10, H-4a).

Anal. Calcd for $C_{14}H_{19}NO_5$ (281.3). C : 59.8 ; H : 6.8 ; N : 5.0. Found : C : 59.7 ; H : 6.9 ; N : 5.1.

Methyl 3-Amino-3,4-dideoxy-ß-D-xylo-hexopyranoside (9).

A methanolic solution of **8** (3g, 10.7 mmol) was treated as described above (cf. preparation of **5**) with 5 mL of 1M sodium methoxide to afford, after chromatography on silica gel using dichloromethane-MeOH/NH_3 (17:3) as eluent, 1.5 g (79%) of **9**. Recrystallisation from acetonitrile gave : mp 155-158 °C ; $[\alpha]_D$ = -43.5° (c, 0.74, MeOH) ; ^1H NMR (DMSO-d_6) : δ 3.91 (d, 1H, J=7.5, H-1), 3.43-2.19 (m, 2H, H-3, H-5) ; 2.68 (dd, 1H, J=8, J'=7,5, H-2), 2.46 (m, 2H, CH_2-5) ; 1.67 (m, 1H, J=12, J'=4, J"<1, H-4e) ; 1.00 (m, 1H, J=12, J'=J"=10, H-4a).

Anal. Calcd for $C_7H_{15}NO_5$ (193.2). C : 43.5 ; H : 7.8 ; N : 7.2. Found : C : 43.3 ; H : 7.9 ; N : 7.0.

Methyl 3-Amino-6-O-benzoyl-4-chloro-3,4-dideoxy-ß-D-galactopyranoside (10).

A solution of **7** (3 g, 8.8 mmol) in EtOH (100 mL) was stirred under H_2 atmosphere in the presence of 10% palladium-on-charcoal (500 mg) and Et_3N (2 mL) for 24 h. Catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. Crystallization from ether gave **10** (2.27 g, 82%) : mp 160-162 °C; $[\alpha]_D$ = -11°.0 (c 0.85, chloroform). SM : m/z 316 and 318 ($M+H^+$)

Anal. Calcd for $C_{14}H_{18}ClNO_5$ (315.5). C : 53.2 ; H : 5.7 ; N : 4.4. Found : C : 53.1 ; H : 5.9 ; N : 4.3.

Methyl 3-Amino-4-chloro-3,4-dideoxy-ß-D-galactopyranoside (11).

Compound **11** was obtained from **10** by similar treatment as described for preparation of **5** and **9** with sodium methoxide. Crystallization from methanol ; mp 158-162 °C, $[\alpha]_D$ = -4.0° (c 0.84, chloroform). ^1H NMR : δ 5.24 (bs, 1H, exch D_2O), 4.88 (bs, 1H, exch. D_2O), 4.32 (d, 1H, J=2.5, H-4), 4.11 (d, 1H, J=7, H-1), 3.57-3.21 (m, 3H, H-5, CH_2-6) ; 3.39 (s, 3H, OMe), 3.09 (t, 1H, J=J'=8, H-2), 2.84 (dd, 1H, J=8, J'=3, H-3) ; SM (DCI/NH_3) : m/z 212 and 214 ($M+H^+$).

Anal.Calcd for $C_7H_{14}ClNO_4$ (211.5). C : 39.7 ; H : 6.6 ; N : 6.6. Found : C : 39.4 ; H : 6.8 ; N : 6.4.

Methyl 3-Azido-6-O-benzoyl-3-deoxy-α-D-glucopyranoside (12).

A solution of **1** (29 g) in 1N HCl-MeOH (600 mL) was refluxed for 2 h and then concentrated to dryness under reduced pressure. The residue was dissolved in dichloromethane, the organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. To the crude product (31 g) dissolved in anhydrous toluene (250 mL) were added 90 mL of bis(tributyltin) oxide and after reflux for 3 h, the solution was cooled to -15 °C before dropwise addition of benzoyl chloride (40 mL) diluted in dichloromethane (200 mL). After the mixture was stirred for 24 h, concentration to dryness followed by a column chromatography with CH_2Cl_2-MeOH (98:2) as eluent gave 7.5 g of **6** and then 7.5 g of **12** as a syrup ; $[\alpha]_D$ = +102°.0 (c 1.14, CH_2Cl_2) ; ^1H NMR : δ 8.00 (d) and 7.55-7.31 (m, 5H, Ar), 4.76 (dd, 1H, J=10, J'=3) and 4.37 (dd, 1H, J=10, J'=2.5) (CH_2-6), 4.74 (d, 1H, J=3, H-1), 3.83-3.71 (m, 3H, H-2, H-3, H-5), 3.32 (t, 1H, J=J'=10, H-4), 3.29 (s, 3H, OMe).

Anal. Calcd for $C_{14}H_{17}N_3O_6$ (323.3). C : 52.0 ; H : 5.3 ; N : 13.0. Found : C : 51.7 ; H : 5.6 ; N : 12.7.

Methyl 3-Azido-6-O-benzoyl-4-chloro-3,4-dideoxy-α-D-galactopyranoside (13).

Sulfuryl chloride (12.5 mL, 15 mmol) was added dropwise to a cold solution (0 °C) of **12** (4.8 g, 150 mmol) in anhydrous pyridine (250 mL). Stirring was maintained for 18 h at 0 °C and then the mixture was allowed to reach room temperature for 3 h. The crude mixture was poured onto crushed ice and extracted with dichloromethane and the organic layer was washed with cold 1N H_2SO_4 and water. Concentration under reduced pressure afforded a syrup which was purified by column chromatography with hexane-EtOAc (4:1) as eluent. This gave 4.05 g (80%) of pure **13** as white crystals : mp 104-106 °C; $[\alpha]_D$ = +145°.0 (c 1.3, $CHCl_3$) : MS (IE): m/z 341 (10%), 239 (15%), 203 (15%), 105 (100%). ^1H NMR : δ 7.95 (d) and 7.54-7.35 (m, 5H, Ar), 4.85 (d, 1H, J=3, H-1), 4.43 (m, 3H, CH_2-6 and H-3), 4.28 (bs,

1H, H-4), 4.21 (dd, 1H, J=7, J'=3, H-2), 3.97 (m, 1H, H-5), 3.29 (s, 3H, OMe) ; SM (DCI/NH_3), m/z : 212 and 214 ($M+H^+$).

Anal. Calcd for $C_{14}H_{16}ClN_3O_5$ (341.7). C : 49.2 ; H : 4.7 ; N : 12.3. Found : C : 48.9 ; H : 4.9 ; N : 12.1.

Methyl 3-Amino-6-O-benzoyl-3,4-dideoxy-α-D-xylo-hexopyranoside (14).

A solution of **13** (4.05 g, 12 mmol) in anhydrous toluene (200 mL) was refluxed for 2 h in the presence of azobisisobutyronitrile (700 mg, 4.27 mmol) and tributyltin hydride (12.6 mL, 47 mmol). The mixture was then concentrated under reduced pressure and the residue chromatographed on silica gel with dichloromethane-methanol/NH_3, 19:1 to afford 3 g (90%) of **14** as white crystals : mp 112-117 °C ; ^1H NMR : δ 7.98-7.94 and 7.53-7.34 (m, 5H, Ar), 4.76 (d, 1H, J=3, H-1), 4.50-4.35 (m, 2H, CH_2-6), 4.23 (m, 2H, H-3 and H-5), 3.45 (m, 1H, H-2), 3.28 (s, 3H, OMe), 1.90-1.70 (m, 2H, CH_2-4).

Anal. Calcd for $C_{14}H_{18}ClNO_5$ (315.7). C : 53.3 ; H : 5.8 ; N : 4.4. Found : C : 53.4 ; H : 5.8 ; N : 4.3.

Methyl 3-Amino-3,4-dideoxy-α-D-xylo-hexopyranoside (15).

A methanolic solution of **14** (3 g) was treated as described above (cf. preparation of **5**) with 5 mL of 1M sodium methoxide to afford after chromatography on silica gel using dichloromethane-MeOH/NH_3 (17:3), 1.5 g (79%) of **15** as a crystalline compound : mp 130-134 °C ; $[\alpha]_D$ = +163°.0 (c 0.9, chloroform).

Anal. Calcd for $C_7H_{15}NO_5$ (193.2). C : 43.5 ; H : 7.8 ; N : 7.2. Found : C : 43.5 ; H : 7.9 ; N : 7.1.

Methyl 13-Amino-6-O-benzoyl-4-chloro-3,4-dideoxy-α-D-galactopyranoside (16).

A solution of **13** (3 g) in ethanol (100 mL) was treated as described above (cf. preparation of **10**) to give 2.9 g of **16** which was crystallized from ethyl ether : mp 161-164 °C ; $[\alpha]_D$ = +118.5° (c 1.25, chloroform).

Anal. Calcd for $C_{14}H_{18}ClNO_5$ (315.5). C : 53.2 ; H : 5.7 ; N : 4.4. Found : C : 53.5 ; H : 5.9 ; N : 4.2.

Methyl 3-Amino-4-chloro-3,4-dideoxy-α-D-galactopyranoside (17).

Treatment of **16** as described above (cf. preparation of **5** and **15**) gave **17** quantitatively as crystals : mp 135-138 °C ; $[\alpha]_D$ = +184° (c 0.92, MeOH).

Anal. Calcd for $C_7H_{14}ClNO_4$ (211.6). C : 39.7 ; H : 6.6 ; N : 6.6. Found : C : 39.6 ; H : 6.8 ; N : 6.4.

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