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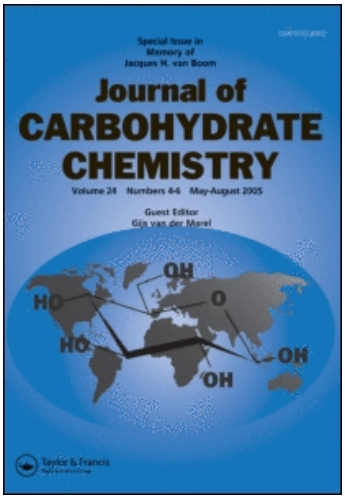

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Synthesis of Amino-Dideoxy-Dl-Pentopyranoses and Their Ureido Derivatives

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SYNTHESIS OF AMINO-DIDEOXY-DL-PENTOPYRANOSES AND THEIR UREIDO DERIVATIVES

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ABSTRACT

Various 4-deoxy-α or β -erythro or threo-pentopyranoses aminated on position 1 (**6** and **19**), 2 (**38**) or 3 (**9**, **22**, **23**, **24**, **32** and **35**) were synthesised from 2-methoxy-5,6-dihydro-2H-pyran (**1**) and methyl 2,3-anhydro-4-deoxy-α and β -DL-erythro-pentopyranoside (**11**). Different reactions were investigated including azidation, cis-oxyamination, epimine formation and oxirane aminolysis. All these amino sugars were converted into their chloroethylureido derivatives.

INTRODUCTION

Over the past few years we have been engaged in the synthesis of various azidodeoxypentopyranosylnucleosides.[1,2,3] In connection with this synthetic program, we have been interested in preparing chloroethylureas derived from the same glycosidic skeleton for biological studies of their corresponding nitrosoureas.[4] In this report we describe the synthesis and the structure of new azido- and aminodeoxypentopyranoses and the preparation of their ureido derivatives.

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RESULTS AND DISCUSSION

Compounds were prepared starting from 2-methoxy-5,6-dihydro-2H-pyran (**1**)[5] or methyl 2,3-anhydro-4-deoxy α and β -DL-erythro-pentopyranoside (**11**)[6] by the sequence outlined in Schemes 1, 2 and 3. The final ureas (Tables 1 and 2) were obtained by reaction of the corresponding amino sugars with 2-chloroethyl isocyanate in N,N'-dimethylformamide. The amino sugars **6**, **19** and **32** were prepared from the corresponding azides by catalytic hydrogenation. Oxyamination of **1** gave the aminosugar **9**. Aminolysis of the oxirane **11** gave **22**, **23** and **24**. Hydrolysis of the aziridine intermediate **36** yielded the amino sugar **38**.

The glycosyl azides **5** and **15** were synthesised by the reaction of azidotrimethylsilane with the respective per-O-acetylated sugars **4** and **14** in the presence of the Lewis acid stannic chloride. This method has been reported to give products with N_3 - I and AcO-2 trans.[7,8,9] This is in agreement with the result that **14** gave, for the most part, the α anomer **15** as assigned by NMR spectroscopy ($J_{1a,2a}$ = 7.7 Hz, $J_{2a,3a}$ = 8.4 Hz, $J_{3a,4a}$ = 10.1 Hz, $J_{3a,4e}$ = 4.9 Hz). Only trace amounts of the β anomer could be detected. In contrast, **4** gave a mixture of anomeric azides **5**β and **5** α in the ratio 4:1. On the basis of these results, the presence of a participating ester group at C-2 does not necessarily lead to the stereoselective formation of a 1,2-trans -azide suggesting that the 1,2-acyloxonium ion is not the only intermediate to be considered. Compound **4** and **14** resulted from the acetylation of the triols **3** and **13**[10] in acetic anhydride with sodium acetate. Only the β isomer of **4** was formed whereas both α- and β -anomers of **14** were obtained in the ratio 7:3 respectively. The triols **3** and **13** were obtained by acid hydrolysis of **2** and **12**.[10] A previous synthesis [11] of **2** involved three steps starting from **11**. We now report a one step synthesis of this diol from **1** which involves cis-dihydroxylation with osmium tetraoxide / N-methylmorpholine N-oxide. In contrast, the α-isomer had been obtained by other authors[5] using potassium permanganate as the oxidizing reagent.

Reduction of the azide **15** does not afford the corresponding amine, but rather the acetamide **16** which is formed through a O-2 → N-1 acetyl migration. It was not possible to obtain the free amine by the removal of the N-acetyl group. However, a facile synthesis was achieved starting from **15** by the following steps: (i) O-deacetylation to produce **17**, (ii) protection of the hydroxyls as tert-butyldimethylsilyl ethers to give **18**, (iii) reduction

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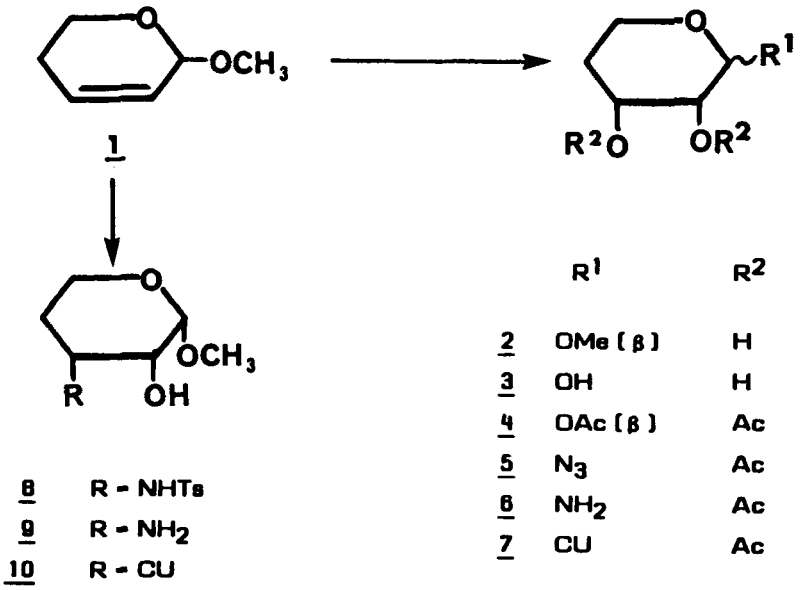

CU = - NH CO NH (CH_2)$_2$ Cl

SCHEME 1

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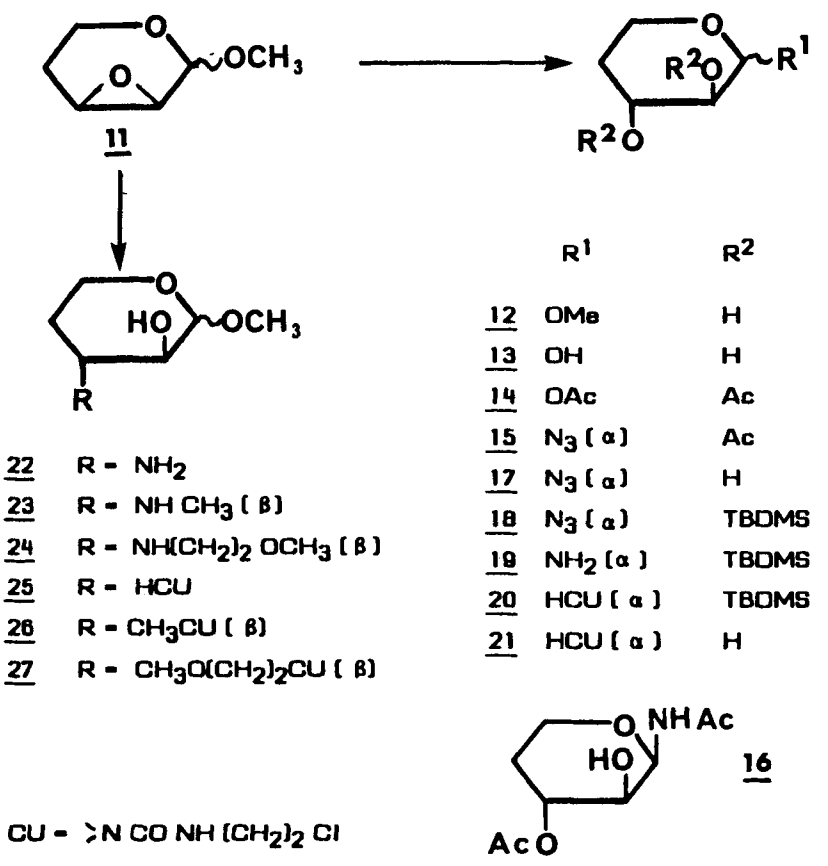
of the azido group to furnish the amine **19**. The urea **20** was prepared from **19** in the usual way and its deprotection into **21** was performed by treatment with methanolic hydrochloric acid.

The amino sugar **9**, previously prepared in four steps from **11**,[12] was derived directly from **1** through a cis-oxyamination reaction with Chloramine-T, catalyzed with osmium tetraoxide in the presence of benzyltriethylammonium chloride as a phase-transfer catalyst.[13] Cleavage of the tosyl group of the vicinal hydroxy-p-toluenesulfonamide **8** required mild conditions involving sodium-liquid ammonia as used in similar reactions with tosylamino peptides.[14] Compound **9** was compared to its β -isomer **32**[12] prepared from the C-2 O-trifluoromethanesulfonate **29**[15,16] by hydrolysis[17] with sodium acetate in aqueous 2-methoxyethanol followed by the catalytic hydrogenation of the azide **31**.[2]



SCHEME 2

The amino sugar **38**,[17] recently prepared through an N-allyl aziridinium intermediate,[18] was obtained by opening the aziridine ring of **36** using trifluoroacetic anhydride and subsequent N-detrifluoroacetylation of the intermediate **37** with methanolic ammonia. The aziridine **36**[17] was generated during reduction of the α-isomer of **30** with lithium aluminium hydride. No formation of an epimine was found to occur on similar treatment of the corresponding β-isomer. The erythro configuration of **36** was indicated by the magnitude[19] of $J_{1,2}$ coupling (4 Hz) observed on the N-benzoyl derivative. The formation of this aziridine was also attempted by reaction of the azide **28** with triphenylphosphine. The cleavage of the resulting phosphinimine α or β **34** by trifluoroacetic anhydride afforded the amino sugar **35** having its N-trifluoroacetyl group

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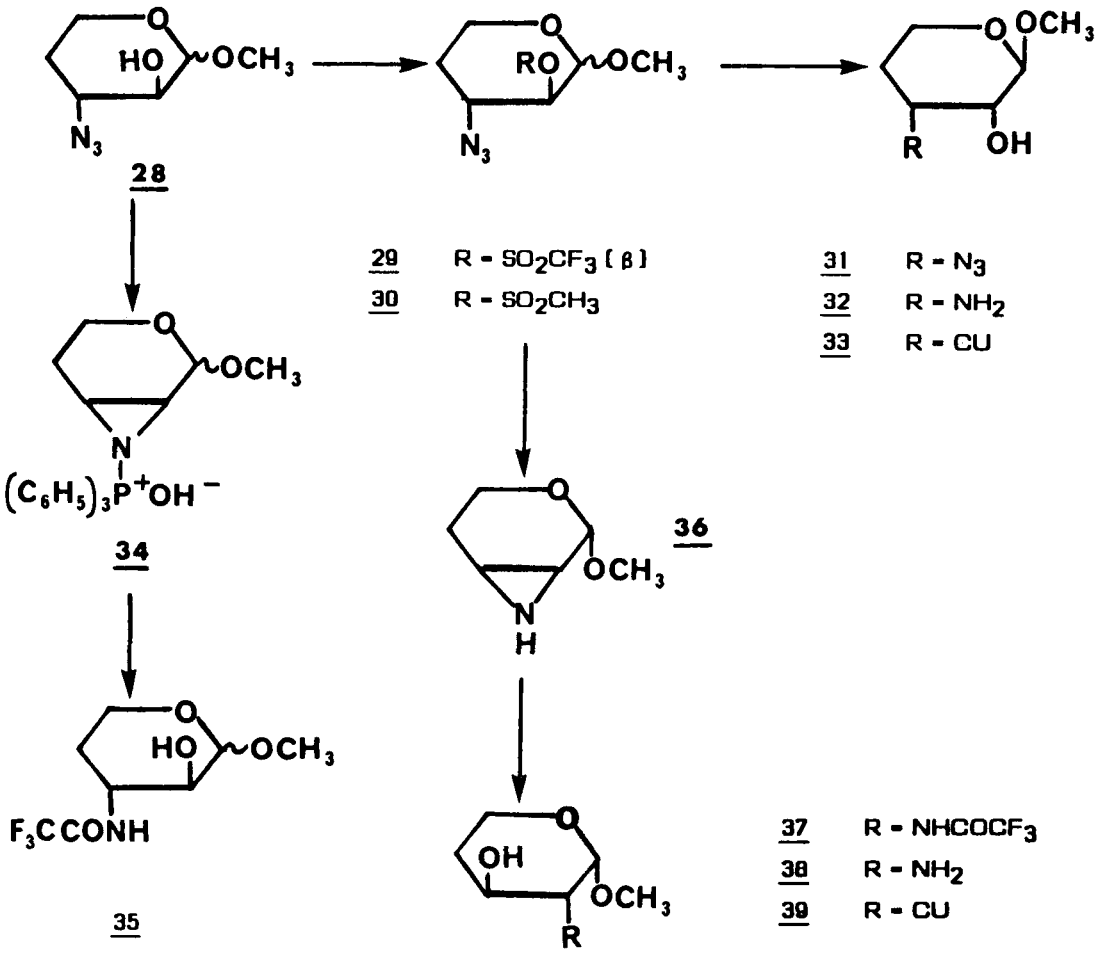

SCHEME 3

at C-3. The electron-impact and chemical-ionization mass spectra of the peracetylated glycosides derived from **35** and **38** enabled complete structural elucidation of this series of aminodideoxypentoses.[20]

In conclusion, the present study shows various synthetic approaches to known or new amino-deoxy-DL-pentopyranoses. A convenient access to these compounds was necessary for preparation of the corresponding ureas and nitroso derivatives which were tested as antitumor compounds[4]. This

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study allowed us to establish some relationships between the biological activity of these compounds and their stereochemistry.

EXPERIMENTAL

General methods. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Column chromatography was performed on Merck Silica Gel F_{254} (70-230 mesh, ASTM) and TLC on Silica Gel F_{254} aluminium sheets: substances were visualized by spraying the plates with the phosphomolybdic acid reagent followed by heating at 120 °C. IR spectra were recorded with a Beckman Acculab-4 instrument. ^1H NMR spectra were measured at 80 MHz using a Brucker WP-80 spectrometer or at 350 MHz with a Cameca spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as internal standard. Elemental analyses were performed by the Service Central d'Analyse du CNRS.

Methyl 4-deoxy- β -DL-erythro-pentopyranoside (2).

a) With $KMnO_4$. To a solution of **1** (5 g, 0.044 mol) in methanol (80 mL) was added 9 g (0.057 mol) of $KMnO_4$ dissolved in 100 mL of water, over a period of 2 h. After the addition was finished, the brown precipitate was removed by filtration. The filtrate was rendered neutral with 0.1 N hydrochloric acid, and then concentrated and extracted with a mixture of chloroform-methanol 1:1. The organic phase was evaporated and the resulting oil was purified by silica gel column chromatography using 1:1 chloroform-methanol as eluent to give **2** (2.2 g, 34 %) as a colourless oil.

b) With OsO_4. To a stirred solution of N-methylmorpholine N-oxide (3.41 g, 25 mmol as dihydrate) and OsO_4 (5 mmol in 12.5 mL of tert-butyl-alcohol) in water (12.5 mL) under N_2 atmosphere was added a solution of **1** (2.85 g, 25 mmol) in tert-butyl alcohol (12.5 mL). The resulting black mixture was quickly brought to 85-90 °C. After 1 h at this temperature, the reaction mixture was concentrated to a black syrup from which portions of toluene (4 x 50 mL) were evaporated to remove N-methylmorpholine. The residue was dissolved in water (15 mL). After addition of sodium hydrosulfite (0.25 g), the suspension was stirred for 15 min and filtered. The filtrate was concentrated to dryness leaving a black syrup that was chromatographed on a column of silica gel. Elution with chloroform-methanol (3:1) gave 1.81 g (49 %) of **2**: Rf 0.65 (chloroform-methanol 3:1); IR (film) 3480-3360 (OH), 2950 (C-H), 1150 (C-O-C) and 1050 cm^{-1} (CH_2O).

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Compound **2** was characterised as its 2',3'-di-O-acetyl derivative prepared according to procedure as noted below: Rf 0.53 (ethyl acetate-hexane 1:1); mp 79 °C; IR (KBr) 1750 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 5.33-5.00 (m, 1, H-3, $J_{2,3}$ = 2.8 Hz, $J_{3,4e}$ = 5.1 Hz, $J_{3,4a}$ = 10.5 Hz); 4.95 (dd, 1, H-2); 4.60 (d, 1, H-1, $J_{1,2}$ = 2.8 Hz); 3.95-3.60 (m, 2, 2 H5); 3.40 (s, 3, OCH_3); 2.10 and 2.0 (2s, 6, 2 OAc).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.90. Found: C, 51.90; H, 7.06.

General procedure for the peracetylation of 3 and 13. A mixture of **3** or **13** (5 g, 34 mmol) (each of which was prepared according to the procedure previously described[10]), melted sodium acetate (2.8 g, 33 mmol) and acetic anhydride (28 mL, 254 mmol) was heated at 100 °C for 1 h and then cooled. The excess anhydride was destroyed by adding ice and the mixture was extracted into dichloromethane. The organic phase was washed with a saturated solution of sodium hydrogen carbonate and water, dried and concentrated. The crude product was purified by column chromatography and eluted with 1:1 ethyl acetate-hexane to give an oil which crystallized rapidly at room temperature.

1,2,3-tri-O-acetyl-4-deoxy- β -DL-erythro-pentopyranose (**4**): yield 65 % (5.7 g); Rf 0.45 (ethyl acetate-hexane 1:1); mp 72 °C; IR (KBr) 1750 (CO) and 1240 cm^{-1} (OAc); ^1H NMR (350 MHz, $CDCl_3$) δ 6.25 (d, 1, H-1, $J_{1,2}$ = 3.3 Hz); 5.30 (m, 1, H-3), $J_{3,4a}$ = 9.16 Hz, $J_{3,4e}$ = 5.3 Hz); 5.05 (dd, 1, H-2, $J_{2,3}$ = 3.6 Hz); 4;10-3.80 (m, 2, 2 H-5); 2.20-1.60 (m, 2, 2 H-4); 2.15 and 2.05 (2s, 6, 2 OAc).

Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.15. Found: C, 51.05; H, 6.22.

1,2,3-tri-O-acetyl-4-deoxy- α - and β -DL-threo-pentopyranose (**14**): yield 65 % (5.7 g); Rf 0.70 (ethyl acetate-hexane 1:1); mp (mixture) 52 °C; IR (KBr) 1750 (CO) and 1240 cm^{-1} (OAc); ^1H NMR ($CDCl_3$) δ 6.33 (d, 1, H-1 β $J_{1,2}$ = 3.30 Hz); 5.77 (d, 1, H-1 α , $J_{1,2}$ = 6.7 Hz); 5.35-4.75 (m, 2, H-2 and H-3); 4.25-3.45 (m, 2, 2 H-5); 2.07 and 1.98 (2s, 6, 2 OAc); 2.30-1.50 (m, 2, 2 H-4).

Anal. (mixture) Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.15. Found: C, 50.82; H, 6.26.

Procedure for the synthesis of 5 and 15 by azidation of 4 and 14, respectively. To a mixture of **4** or **14** (5 mmol) in dichloromethane (5 mL) and trimethylsilyl azide (0.8 mL) was added a solution of stannic chloride (0.7 mL)

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in anhydrous dichloromethane (26 mL). The mixture was stirred at room temperature for 4 h, washed with water (30 mL), saturated aqueous hydrogen carbonate (26 mL) and water (26 mL), dried ($MgSO_4$) and concentrated. The resulting yellow syrup was purified by column chromatography to yield **5** or **15** as a colourless oil.

2,3-di-O-acetyl-4-deoxy- α and β -DL-erythro-pentopyranosyl azide (**5**): yield 83 % (1.01 g); Rf 0.8 (ethyl acetate-hexane 1:1); IR (film) 2125 (N_3) and 1750 cm^{-1} (CO); ^1H NMR (350 MHz, $CDCl_3$) **5α** δ5.27 (dd, 1, H-2, $J_{2,1}$ = 1.5 Hz, $J_{2,3}$ = 3.1 Hz); 5.04 (m, 1, H-3, $J_{3,4a}$ = 7.0 Hz, $J_{3,4e}$ = 4.5 Hz); 4.68 (d, 1, H-1); 4.18 and 3.64 (2m, 2, 2 H-5, $J_{5e,5a}$ = 12.6 Hz, $J_{5e,4a}$ = $J_{5e,4e}$ = 4.2 Hz, $J_{5a,4a}$ = 10.5 Hz); 2.21 and 2.00 (2s, 6, 2 OAc); 1.95-1.90 and 1.75-1.70 (2m, 2, 2 H-4). **5** β δ 5.27 (m, 1, H-3, $J_{3,2}$ = 3.5 Hz, $J_{3,4a}$ = 8.4 Hz, $J_{3,4e}$ = 4.2 Hz); 5.19 (d, 1, H-1, $J_{1,2}$ = 4.3 Hz); 4.87 (t, 1, H-2); 4.00 (m, 1, H-5a, $J_{5a,5e}$ = 12.6 Hz, $J_{5a,4a}$ = 8.4 Hz, $J_{5a,4e}$ = 3.1 Hz); 3.90 (m, 1, H-5e, $J_{5e,4e}$ = 4.2 Hz, $J_{5e,4a}$ = 5.6 Hz); 2.14 and 2.05 (2s, 6, 2 OAc); 2.05-2.0 and 1.88-1.80 (2m, 2, 2 H-4).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.56; H, 5.25; N, 17.28. Found: C, 44.78; H, 5.41; N, 17.18.

2,3-di-O-acetyl-4-deoxy- α -DL-threo-pentopyranosyl azide (**15**): yield 90 % (1.09 g); Rf 0.77 (ethyl acetate-hexane 1:1); mp 57 °C (cyclohexane-diethyl ether); IR (KBr) 2140 (N_3) and 1740 cm^{-1} (CO). ^1H NMR (350 MHz, $CDCl_3$) δ 4.95 (m, 1, H-3, $J_{3,2}$ = 8.4 Hz, $J_{3,4e}$ = 4.9 Hz, $J_{3,4a}$ = 10.1 Hz); 4.82 (dd, 1, H-2); 4.55 (d, 1, H-1, $J_{1,2}$ = 7.7 Hz); 4.12 (m, 1, H-5e, $J_{5e,5a}$ = 11.9 Hz, $J_{5e,4a}$ = 4.2 Hz, $J_{5e,4e}$ = 2.8 Hz); 3.62 (m, 1, H-5a, $J_{5a,4a}$ = 11.7 Hz, $J_{5a,4e}$ = 2.8 Hz); 2.12 and 2.05 (2s, 6, 2 OAc); 2.13 and 1.80 (2m, 2, 2 H-4).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.56; H, 5.25; N, 17.28. Found: C, 44.44; H, 5.35; N, 17.28.

Procedure for the synthesis of 6, 19 and 32[12] by reduction of 5, 18 and 31, respectively. Compound **5**, **18** or **31** (8.2 mmol) in methanol (200 mL) was reduced with hydrogen under atmospheric pressure at room temperature in the presence of Adam's catalyst (0.2 g). The hydrogenation was conducted for 8 h, until no azide absorption at 2100 cm^{-1} was observed in the reaction mixture IR spectrum. The catalyst was then filtered off through Celite, and the filtrate concentrated to an oil which was purified by column chromatography on silica gel.

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2,3-di-O-acetyl-4-deoxy- β -DL-erythro-pentopyranosylamine (6β): yield 87 % (1.55 g); Rf 0.62 (chloroform-methanol 5:1); IR (film) 3330 (NH_2) and 1730 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 5.10 (d, 1, H-1, $J_{1,2}$ = 1.5 Hz); 4.92 (s, 2, NH_2); 3.90-3.0 (m, 4, H-2, H-3 and 2 H-5); 2.0 and 1.9 (2s, 6, 2 OAc); 2.10-1.70 (m, 2, 2 H-4).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.77; H, 6.91; N, 6.45. Found: C, 49.50; H, 6.67; N, 6.60.

2,3-di-O-t. butyldimethylsilyl-4-deoxy- α -DL-threo-pentopyranosylamine (19): yield 70 % (2.07 g); Rf 0.80 (chloroform); IR (film) 3400 (NH_2) and 2980-2860 cm^{-1} (TBDMS); ^1H NMR ($CDCl_3$) δ 4.45 (d, 1, H-1, $J_{1,2}$ = 1.25 Hz); 3.90 (m, 1, H-3); 3.75 (m, 2, H-2 and H-5e); 3.45 (m, 1, H-5a); 1.95 (s, 2, NH_2); 1.90-1.15 (m, 2, 2 H-4); 0.90 (s, 18, 2 t-C_4H_9Si); 0.10 (s, 12, 2 $Si(CH_3)_2$).

Anal. Calcd for $C_{17}H_{39}NO_3Si_2$: C, 56.51; H, 10.80; N, 3.88. Found: C, 56.77; H, 11.09; N, 3.58.

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Methyl 3,4-dideoxy-3-p-toluenesulfonamido- α -DL-erythro-pentopyranoside (8). To a stirred solution of compound **1** (5 g, 43.8 mmol) in chloroform (220 mL) were successively added a solution of osmium tetraoxide (55 mg, 0.2 mmol) in tert-butyl alcohol (11 mL), chloramine T trihydrate (15.5 g, 55 mmol), benzyltriethylammonium chloride (0.5 g, 2.2 mmol) and distilled water (220 mL). The mixture was heated at 60 °C. The progress of the reaction was monitored by following the disappearance of olefin by TLC. When the reaction was completed after 4 h, sodium bisulfite (4.6 g, 44 mmol) was added. The mixture was refluxed for 8 h and then stirred overnight at room temperature. The two phases were separated. The organic phase was washed with saturated brine containing 1 % sodium hydroxyde (200 mL) and then with saturated brine (300 mL) and water (100 mL). The organic layer was dried ($MgSO_4$) and concentrated. The resulting brown oil was purified by column chromatography using 10:4:1 ethyl acetate-chloroform-methanol to give **8** as an oil which crystallizes from cold methanol: yield 68 % (9 g); Rf 0.44 (chloroform-methanol 9:1); mp 156 °C; IR (KBr) 3520 (OH), 3200 (NH), 1600 (C_6H_4) and 1440 cm^{-1} (SO_2); ^1H NMR (350 MHz, DMSO-d_6) δ 7.85 and 7.40 (2d, 4, C_6H_4); 6.75 (d, 1, NH); 4.52 (d, 1, OH); 4.45 (d, 1, H-1, $J_{1,2}$ = 1.5 Hz); 3.60-3.30 (m, 4, H-2, 3, 5); 3.25 (s, 3, OCH_3); 2.42 (s, 3, $ArCH_3$); 1.95-1.75 (m, 1, H-4e); 1.35-1.15 (m,1, H-4a).

Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.83; H, 6.31; N, 4.65; S, 10:63. Found: C, 51.88; H, 6.37; N, 4.46; S, 10.64.

Methyl 3-amino-3,4-dideoxy- α -DL-erythro-pentopyranoside (9). To a solution of **8** (340 mg, 1.1 mmol) in anhydrous liquid ammonia (15 mL) was added sodium metal in thin slices until a green color developed. Solid ammonium acetate was added until the green color disappeared. After evaporation of ammonia under a rapid stream of nitrogen, the dry white residue was taken up in water (6 mL). The aqueous solution was extracted with ether and the ether extract separated and concentrated. The residue was dissolved in a minimum amount of methanol and the precipitated salts were filtered. The filtrate was concentrated to dryness leaving pure **9** (91 mg, 56 %), the characteristics of which were in agreement with those described in the literature.[12]

3-O-Acetyl-4-deoxy- β -DL-threo-pentopyranosyl acetamide (16). Compound **15** (1.7 g, 7 mmol) in N,N-dimethylformamide (50 mL) was hydrogenated under atmospheric pressure with 5 % palladium-on-carbon (0.3 g) as the catalyst for 24 h at 25 °C. After removal of the catalyst and solvent, the resultant oil was applied to a column of silica gel with 5:1 (v/v) chloroform-methanol as eluent to afford pure **16** which crystallized from diether ether (1.06 g, 70 %); Rf 0.73 (chloroform-methanol 5:1); mp 102 °C ; IR (KBr) 3420 (OH), 3350 (NH), 1740 (CO), 1680 (NHCO) and 1240 cm^{-1} (acetyl C-O); ^1H NMR (350 MHz, DMSO-d_6) δ 7.25 (d, 1, NH, $J_{NH,1}$ = 9.1 Hz); 5.36 (d, 1, H-1, $J_{1,2}$ = 1.1 Hz); 5.05 (m, 1, H-3, $J_{3,2}$ = 2.8 Hz, $J_{3,4e}$ = $J_{3,4a}$ = 2.5 Hz); 4.20 (m, 1, OH); 3.85 (m, 2, 2 H-5); 3.60 (dd, 1, H-2); 2.15 (m, 1, H-4a, $J_{4a,4e}$ = 14.7 Hz); 2.10 and 2.05 (2s, 6, Ac); 1.57 (m, 1, H-4e).

Anal. Calcd for $C_9H_{15}NO_5$:C, 49.77; H, 6.91; N, 6.45. Found: C, 49.81; H, 6.90; N, 6.46.

4-Deoxy- α -DL-threo-pentopyranosyl azide (17). A solution of **15** (1g, 4.1 mmol) in methanol (22 mL) was heated with triethylamine (11 mL) at 75 °C for 6 h. Upon removal of the solvent, the resulting hygroscopic oil was subjected to column chromatography (eluent 3:1 chloroform-methanol) to yield pure **17** (0.49 g, 75 %) which was directly used in the further step.

Anal. Calcd for $C_5H_8N_3O_3$: C, 37.74; H, 5.66; N, 26.41. Found: C, 37.94; H, 5.67; N, 26.25.

2,3-Di-O-t-butyldimethylsilyl-4-deoxy- α -DL-threo-pentopyranosyl azide (18). To a stirred solution containing **17** (0.45 g, 2.80 mmol) and imidazole (1.5 g, 22 mmol) in dry N,N-dimethylformamide (5 mL) was added

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tert-butyldimethylsilyl chloride (1.35 g, 9 mmol) under a nitrogen atmosphere. The reaction was monitored by TLC. After stirring the reaction mixture at room temperature for 15 h, water was added. The aqueous phase was extracted with diethyl ether. The combined ether extracts were dried and concentrated leaving an oil which was chromatographed on a column with chloroform as eluent giving 1.07 g (98 %) of **18** as a colourless oil; Rf 0.85 (chloroform); IR (film) 2980-2860 (TBDMS) and 2125 cm^{-1} (N_3). ^1H NMR ($CDCl_3$) δ 4.80 (d, 1, H-1, $J_{1,2}$ = 6.5 Hz); 4.07-3.63 (m, 3, H-3 and 2 H-5); 3.43 (dd, 1, H-2, $J_{2,3}$ = 6.8 Hz); 2.31-1.62 (m, 2, 2 H-4); 0.90 (s, 18, 2-tert-C_4H_9Si); 0.10 (s, 12, 2 $Si(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{37}N_3O_3Si_2$: C, 52.71; H, 9.56; N, 10.85. Found: C, 52.95; H, 9.78; N, 10.73.

Procedure for the synthesis of 23 and 24. A mixture of cis oxiran **11**[6] (1.3 g, 10 mmol) and the appropriate amine (109 mL of 35 % methylamine in water or 50 mL 2-methoxyethylamine in 50 mL of methanol respectively) was stirred and heated at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure affording a yellow oil which crystallized at room temperature as an amorphous powder in nearly quantitative yield and was used in the next step without any purification.

Methyl 3,4-dideoxy-3 methylamino- β-DL-threo-pentopyranoside (23): yield 88 % (1.42 g); Rf 0.3 (chloroform-methanol 5:1); mp 81 °C; IR (KBr) 3400 (OH) and 3320 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 4.72 (d, 1, H-1, $J_{1,2}$ = 3.3 Hz); 3.70-3.30 (m, 4, H-2, H-3 and 2 H-5); 3.42 (s, 3, OCH_3); 2.94 (s, 2, OH and NH); 2.43 (s, 3, NCH_3); 1.90-1.20 (m, 2, 2 H-4).

Methyl 3,4-dideoxy-3-(2-methoxyethyl) amino- β -DL-threo-pentopyranoside (24): yield 81 % (1.7 g); Rf 0.5 (chloroform-methanol 5:1); IR (film) 3400 (OH) and 3300 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 4.76 (d, 1, H-1, $J_{1,2}$ = 3.3 Hz); 3.80-3.30 (m, 6, H-2, H-3, 2 H-5 and CH_2O); 3.41 and 3.35 (2s, 6, OCH_3); 3.26 (s, 2, OH and NH); 2.90-2.60 (m, 2,NCH_2); 1.90-1.30 (m, 2, 2 H-4).

Methyl 3-azido-3,4-dideoxy- β -DL-erythro-pentopyranoside (31). A solution of **29**[15,16] (0.8 g, 2.5 mmol) and sodium acetate (1.3 g) in 20 % aqueous methoxyethanol (50 mL) was heated at 100 °C for 2 h and then cooled. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using 1:1 ethyl acetate-hexane to give **31** (0.3 g, 72 %) as an oil identical with an authentic sample prepared by a different route.[2]

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Procedure for the methanesulfonylation of 28α and 28 β . To a stirred solution of **28** α or β [1] (1.5 g, 8.7 mmol) and triethylamine (1.95 mL) in dichloromethane (45 mL) was added dropwise, at -5 °C, freshly distilled mesyl chloride (0.9 mL, 11.6 mmol). The mixture was stirred at room temperature for 4h and then poured into ice-water. The organic layer was separated, washed with aqueous sodium hydrogen carbonate (30 mL) and water (20 mL), dried ($MgSO_4$) and concentrated yielding semicrystalline solids which were purified by recrystallization.

Methyl 3-azido-3,4-dideoxy-2-O-methylsulfonyl- α -DL-threo-pentopyranoside (30 α). Yield 79 % (1.7 g); Rf 0.40 (ethyl acetate-hexane 1:1); mp 70 °C (diethyl ether); IR (KBr) 2140 (N_3), 1350 and 1180 cm^{-1} (SO_3); ^1H NMR ($CDCl_3$) δ 4.31 (s, 1, H-1, $J_{1,2}$ = 6.4 Hz); 4.22 (d, 1, H-2, $J_{2,3}$ = 8.4 Hz); 4.17-3.86 (m, 1, H-3); 3.70-3.30 (m, 2, 2 H-5); 3.50 (s, 3, OCH_3); 3.12 (s, 3, SO_2CH_3); 2.30-1.50 (m, 2, 2 H-4).

Anal. Calcd for $C_7H_{13}N_3O_5S$: C, 33.46; H, 5.16; N, 16.73; S, 12.75. Found: C, 33.45; H, 5.26; N, 16.77; S, 12.62.

Methyl 3-azido-3,4-dideoxy-2-O-methylsulfonyl- β -DL-threo-pentopyranoside (30 β). Yield 1.1 g, 51 %; Rf 0.52 (ethyl acetate-hexane 1:1); mp 76 °C (ethyl acetate-hexane); IR (KBr) 3080-2800 (CH), 2120 (N_3), 1360 and 1170 cm^{-1} (SO_3); ^1H NMR ($CDCl_3$) δ 4.92 (d, 1, H-1, $J_{1,2}$ = 3 Hz); 4.40 (dd, 1, H-2, $J_{2,3}$ = 9.5 Hz); 4.08 (m, 1, H-3, $J_{3,4a}$ = 10 Hz); 3.70 (m, 2, 2 H5); 3.45 (s, 3, OCH_3); 3.25 (s,3, SO_2CH_3); 2.30-1.50 (m, 2, 2 H-4).

Anal. Calcd for $C_7H_{13}N_3O_5S$: C, 33.46; H, 5.18; N, 16.73; S, 12.75. Found: C, 33.31; H, 5.15; N, 16.64; S, 12.62.

Methyl 2,3-epimino-2,3,4-trideoxy- α-DL-erythro-pentopyranoside (36). A solution of **30 α** (1g, 39 mmol) in diethyl ether (250 mL) was added dropwise, at 0 °C, to a suspension of $LiAlH_4$ (0.27 g, 7 mmol) in diethyl ether (100 mL). After the reaction was shown to be complete by TLC, excess hydride was decomposed by the addition of water. The solution was filtered and concentrated and the residual oil was subjected to column chromatography (eluent 3:1 chloroform-methanol) to afford pure **36** (0.35 g, 69 %), characterised by its N-benzoyl derivative prepared according to the following process. To a stirred solution containing **36** (60 mg, 0.5 mmol) and triethylamine (0.35 mL) in chloroform (5 mL) was added at 0 °C benzoyl chloride (0.05 mL, 0.5 mmol). Stirring was continued for 2 h at 0 °C. The reaction mixture was poured into ice-water and extracted with chloroform. The extract was concentrated.

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The salts were precipitated with diethyl ether and collected by filtration. The filtrate was concentrated to dryness and the residue was eluted from a silica gel column using 1:1 ethyl acetate-hexane to give the syrupy N-benzoyl derivative of **36** (60 mg, 55 %); Rf 0.45 (ethyl acetate-hexane 1:1); IR (film) 1725 (N-CO), 1600 and 1520 cm^{-1} (C_6H_5); ^1H NMR ($CDCl_3$)δ8.35-8.00 and 7.55-7.25 (2m, 5, Ar); 5.00 (d, 1, H-1, $J_{1,2}$ = 4 Hz); 4.25-3.30 (m, 2, 2 H-5); 3.15 (dd, 1, H-2, $J_{2,3}$ = 6.5 Hz);3.05-2.80 (m, 1, H-3); 2.20-1.85 (m, 2, 2 H-4).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.43; N, 6.01. Found: C, 67.22; H, 6.20; N, 6.24.

Methyl 2,4-dideoxy-2-trifluoroacetamido- β -DL-threo-pentopyranoside (37). To an ice-cold solution of **36** (0.62 g, 4.8 mmol) in dichloromethane (43 mL) was added dropwise a solution of trifluoroacetic anhydride (0.9 mL, 6.05 mmol) in dichloromethane (4.5 mL) and the mixture was stirred overnight at room temperature. After addition of a saturated solution of sodium hydrogen carbonate (22 mL) at 0 °C, the mixture was stirred for a further 4 h at room temperature. The organic phase was separated, the aqueous phase was back extracted with dichloromethane (22 mL), and the combined organic layers were concentrated. The residue was applied to a column of silica gel and eluted with 2:1 ethyl acetate-hexane affording solid **37** which was recyrstallized from the mixed solvent ethyl acetate-hexane: yield 61 % (0.67 g); Rf 0.58 (ethyl acetate-hexane 2:1); mp 110 °C (ethyl acetate-hexane); IR (KBr) 3390 (OH), 3320 (NH), 1710 (CO) and 1560 cm^{-1} (NHCO); ^1H NMR (DMSOd_6) δ 9.30 (d,1, NH, $J_{NH,2}$ = 9.5 Hz); 4.85 (d, 1, OH, $J_{OH,3}$ = 7 Hz); 4.66 (d, 1, H-1, $J_{1,2}$ = 2.8 Hz); 3.90-3.79 (m, 1, H-3, $J_{2,3}$ = 9.8 Hz, $J_{3,4a}$ = 9.8 Hz, $J_{3,4e}$ = 5.6 Hz); 3.65 (q, 1, H-2); 3.62-3.50 (m, 2, 2 H-5); 3.22 (s, 3, OCH_3); 1.88-1.52 (m, 2, 2 H-4).

Anal. Calcd. for $C_8H_{12}O_4F_3$: C, 39.55; H, 4.94; N, 5.77; F, 23.36. Found: C, 39.66; H, 4.88; N, 5.69; F, 23.25.

Methyl 2-amino-2,4-dideoxy- β -DL-threo-pentopyranoside (38). A solution of **37** (0.82 g, 3.6 mmol) in methanolic ammonia (saturated at 0 °C, 50 mL) was stirred for 3 days at room temperature in a stoppered flask and then concentrated to dryness in vacuo to afford pure **38** (0.44 g, 92 %), the physical data of which were in agreement with those reported in the literature.[18]

Methyl 2,3,4-trideoxy-2,3-N-triphenylphosphonioepimino α -erythro or β -threo-DL-pentopyranoside hydroxide (34 α) or (34 β). To a solution

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of triphenylphosphine (0.76 g, 2.89 mmol) in dry diethyl ether (15 mL) was added the azide **28** α or **28** β (0.5 g, 2.89 mmol). The mixture was protected from moisture and stirred overnight at room temperature. Compound **34** α was obtained pure as an oil by evaporating the solvent and coevaporating the residue with dry diethyl ether. **34** β was isolated by concentrating the solution to deposit crystals which were filtered off, washed with cold ether and dried over P_2O_5 in a vacuum dessicator.

34 α : yield 69 % (0.81 g); IR (film) 3600-3390 (OH), 1440 and 750-700 cm^{-1} (Ar); ^1H NMR ($CDCl_3$) δ 8.0-7.5 (m, 15, Ar); 4.21 (d, 1, H-1, $J_{1,2}$ = 7.3 Hz); 3.90-3.10 (m, 5, H-2, H-3, 2 H-5 and OH); 3.60 (s, 3, OCH_3); 2.01.40 (m, 2, 2 H-4).

34 β : yield 80 % (0.94 g); mp 190 °C; IR (KBr) 3500-3400 (OH), 1430 and 740-700 cm^{-1} (Ar); ^1H NMR ($CDCl_3$) δ 7.90-7.40 (m, 15, Ar); 4.85 (d, 1, H-1, $J_{1,2}$ = 3.8 Hz); 3.75-3.40 (m, 4, H-2, H-3, 2 H-5 and OH); 3.36 (s, 3, OCH_3); 1.90-1.40 (m, 2, 2 H-4).

Anal. Calcd for $C_{24}H_{26}NO_3P$: C, 70.76; H, 6.39; N, 3.44; P, 7.62. Found: C, 70.82;H, 6.45; N, 3.42; P, 7.54.

Methyl 3,4-dideoxy-3-trifluoroacetamido- α or β -DL-threo-pentopyranoside (**35** α) or (**35** β). These compounds were prepared form **34** α or **34** β according to the procedure described for the synthesis of **37**.

35 α (90 %): mp 109 °C; IR (KBr) 3420 (OH), 3300 (NH), 1700 (CO) and 1560 cm^{-1} (NHCO); ^1H NMR (DMSO-d_6) δ 9.30 (d, 1, NH, $J_{NH,3}$ = 8 Hz); 5.35 (d, 1, OH, $J_{OH,2}$ = 5 Hz); 4.15 (d, 1, H-1, $J_{1,2}$ = 6.6 Hz); 4.10-3.70 (m, 4, H-2, H-3 and 2 H-5); 3.45 (s, 3, OCH_3); 2.00-1.65 (m, 2, 2 H-4).

Anal. Calcd for $C_8H_{12}O_4F_3$: C, 39.55; H, 4.94; N, 5.77; F, 23.36. Found: C, 39.30; H, 5.01; N, 5.73; F, 23.27.

35 β (71 %): mp 152 °C; IR (KBr) 3440 (OH), 3310 (NH), 1700 (CO) and 1560 cm^{-1} (NHCO); ^1H (350 MHz, DMSO-d_6) δ 8.95 (d, 1, NH, $J_{NH,2}$ = 7.5 Hz); 4.80 (d, 1, OH, $J_{OH,3}$ = 5.6 Hz); 4.59 (d, 1, H-1, $J_{1,2}$ = 3.5 Hz); 3.99 (m, 1, H-3, $J_{3,4a}$ = 10.5 Hz, $J_{3,4e}$ = 4.4 Hz); 3.64-3.50 (m, 2, 2 H-5); 3.49 (dd, 1, H-2, $J_{2,3}$ = 8.8 Hz); 3.29 (s, 3, OCH_3); 1.70-1.50 (m, 2, 2 H-4).

Anal. Calcd for $C_8H_{12}O_4F_3$: C, 39.55; H, 4.94; N, 5.77; F, 23.36. Found: C, 39.77; H, 4.79; N, 5.73; F, 23.25

Procedure for the preparation of the ureas 7, 10, 20, 25, 26, 27, 33 and 39. To a stirred solution of each amine **6, 9, 19, 22, 23, 24, 32** and **38** (15 mmol) in dry N,N-dimethylformamide (60 mL) was added dropwise at

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TABLE 1

Element Analysis of the Ureas **7**, **10**, **20**, **25**, **26**, **27**, **33** and **39**

N°	Anal. for	Calcd				Found			
		C	H	N	Cl	C	H	N	Cl
7	$C_{12}H_{19}N_2O_6Cl$	44.65	5.89	8.68	11.01	44.96	5.91	9.03	11.46
10	$C_9H_{17}N_2O_4Cl$	42.85	6.74	11.11	14.07	42.80	6.94	10.97	14.36
20	$C_{20}H_{43}N_2O_4ClSi_2$	51.23	9.18	5.98	7.58	51.40	9.11	6.12	7.88
25α	$C_9H_{17}N_2O_4Cl$	42.85	6.74	11.11	14.07	42.56	6.59	11.15	13.88
25β	$C_9H_{17}N_2O_4Cl$	42.85	6.74	11.11	14.07	42.92	6.46	10.97	14.07
26	$C_{10}H_{19}N_2O_4Cl$	45.03	7.13	10.51	13.32	45.23	7.05	10.75	13.64
27	$C_{12}H_{23}N_2O_5Cl$	46.38	7.41	9.02	11.43	46.26	7.66	8.84	11.11
33	$C_9H_{17}N_2O_4Cl$	42.85	6.74	11.11	14.07	43.04	6.70	11.06	13.72
39	$C_9H_{17}N_2O_4Cl$	42.85	6.74	11.11	14.07	42.64	6.82	11.00	13.88

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0 °C a solution of chloroethylisocyanate (1.4 mL, 16.5 mmol) in dry DMF (3.3 mL). The mixture was stirred for 1h at 0 °C and set aside overnight at room temperature. After removal of the solvent, the residue was coevaporated with n-butanol and purified by column chromatography on silica gel using chloroform-methanol as eluent. The urea obtained was crystallized from the solvent indicated in the Table 2.

1-(2-Chloroethyl)-3-(4-deoxy- α -DL-threo-pentopyranosyl)-urea (**21**). The urea **20** (0.35 g, 0.75 mmol) was treated with 0.1 N methanolic hydrochloric acid (7 mL) for 90 min at room temperature. After removal of the solvent, the residue was coevaporated with methanol and purified by column chromatography (eluent 7:3, v/v chloroform-methanol) to yield **21** (0.13 g, 73 %), the physical data of which are summarized in the Table 2.

TABLE 2

Physical Data of the Ureas 7, 10, 20, 21, 25, 26, 27, 33 and 39

Educt	Product	Yield %	R_f	mp (°C)	IR(KBr): ν cm^{-1}	^{1}H NMR (DMSO-d_6): δ ppm
6	7	70	0.59[a]	136 (ether)	3480 and 3300 (NH), 1730 (CH_3COO) 1640 (urea C=O) and 1550 (NHCO)	8.31 (d, 1, NH), 7.50 (t, 1, NH), 5.22 (d, 1, H-1), 5.10-4.90 (m, 2, H-2 and H-3), 4.10-3.15 (m, 6, H-5 and $2CH_2$), 1.95 and 1.85 (2s, 6, $2CH_3$), 2.2-1.6 (m, 2, 2 H-4).
9	10	73	0.28[a]	125 ($CHCl_3$-MeOH)	3400 and 3180 (OH, NH), 1660(CO) and 1590 (NHCO)	8.40 (t, 1, NH), 6.15 (d, 1, NH), 5.20 (d, 1, OH), 4.50 (s, 1, H-1), 3.45 (s, 1, H-2), 3.82 (m, 1, H-3), 3.27 (s, 3, OCH_3), 3.64-3.52 and 3.34-3.28 (2m,6, 2H-5 and 2 CH_2), 1.69 and 1.36 (2m, 2, 2 H-4)
19	20	75	0.70[b]	160 (acetone-hexane)	3300 (NH), 2980-2860 (TBDMS), 1650 (CO) and 1580 (NHCO)	5.47 (t,1, NH), 5.20 (s,2,NH and H-1), 4.06-3.33(m,6,H-2,3,5 and CH_2), 2.36-1.66 (m,2,H-4), 0.95(s,18,2 t[C_4H_9Si), 0.15 (s, 12,2 Si[$CH_3)_2$)
20	21	73	0.68[c]	oil	3400 (OH, NH), 1650 (CO) and 1550 (NHCO)	6.53 (d,1,NH), 5.98 (t,1,NH), 5.23(d,1,H-1), 4.10-3.30 (m, 8, H-2,3,5 and CH_2), 2.30-1.70 (m, 2, 2 H-4)
22 α	25 α	65	0.58[a]	155 (acetone-hexane)	3440 (OH), 3380 and 3320(NH), 1630 (CO)and 1590 (NHCO)	6.30 (t, 1,NH), 6.10 (d,1,NH), 5.15 (s,1,OH), 4.10(d,1,H-1), 4.0-2.7 (m,8,H-2,3,5 and CH_2), 3.40 (s,3,OCH_3), 2.10-1.65 and 1.60-0.90 (2m, 2, 2 H-4).
22 β	25 β	67	0.53[a]	140 (acetone-hexane)	3360 (OH), 3220 (NH), 1630 (CO) and 1570 (NHCO)	6.30 (t, 1, NH), 6.10 (d,1,NH), 4.80 (s,1,OH), 4.61 (d,1,H-1), 4.0-3.45 (m,8,H-2,3,5 and CH_2), 3.31 (s,3,OCH_3), 2.0-1.30 (m, 2,2 H-4).
23	26	68	0.65[a]	122 (MeOH-ether)	3360 (OH), 3260 (NH), 1670 (CO) and 1590 (NHCO)	6.55 (t,1,NH), 4.77 (d,1,OH), 4.62 (d,1,H-1), 4.10-3.30 (m, 8, H-2,3,5 and CH_2), 3.35 (s,3,OCH_3), 2.71 (s,3,NCH_3), 2.20-1.30 (m,2,2 H-4).
24	27	62	0.60[a]	86 (MeOH-ether)	3500 (OH), 3340 (NH), 1640 (CO) and 1560 (NHCO)	6.55 (t,1,NH), 4.63 (d, 1,H-1), 4.55 (d, 1,OH), 4.10-3.0 (m,12, H-2,3,5 and CH_2), 3.47 and 3.38 (2s,6,OCH_3), 2.0-1.40(m,2,2H-4).
32	33	71	0.25[a]	137 (acetone-hexane)	3480 (OH), 3380 and 3340 (NH) 1630 (CO) and 1590 (NHCO)	6.35 (t,1,NH), 6.10 (d,1,NH), 5.15(d,1,OH), 4.10 (d,1,H-1), 3.38 (s,3,OCH_3), 3.70-3.20 (m,8,H-2,3,5 and $2CH_2$), 2.0-1.6 and 1.50-1.10 (2m, 2, 2 H-4)
38	39	68	0.54[a]	136 (acetone-hexane)	3360 (OH), 3200 (NH), 1650 (CO) and 1580 (NHCO)	6.40 (t,1,NH), 5.98 (d,1,NH), 4.78 (s,1,OH), 4.60(d,1, H-1), 3.75-3.40 (m,8,H-2,3,5 and CH_2), 3.30 (s,3,OCH_3), 2.0-1.30 (m, 2,2H-4).

[a] Chloroform-methanol 5:1 [b] Chloroform-methanol 2.5 % [c] Chloroform-methanol 7:3

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