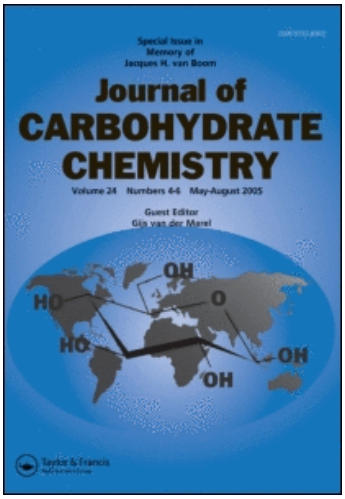


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of (*Z*)-3-Deoxy-3-(1,2,3,6-Tetradeoxy-3,6-Imino-L-*Arabino*-Hexitol-1-*C*-Ylidene)-D-*Xylo*-Hexose Derivatives. First Examples Of Homo-(1→3)-*C*-Linked Iminodisaccharides.

Francesca Cardona; Inmaculada Robina; Pierre Vogel

To cite this Article Cardona, Francesca , Robina, Inmaculada and Vogel, Pierre(2000) 'Synthesis of (*Z*)-3-Deoxy-3-(1,2,3,6-Tetradeoxy-3,6-Imino-L-*Arabino*-Hexitol-1-*C*-Ylidene)-D-*Xylo*-Hexose Derivatives. First Examples Of Homo-(1→3)-*C*-Linked Iminodisaccharides.', Journal of Carbohydrate Chemistry, 19: 4, 555 — 571

To link to this Article: DOI: 10.1080/07328300008544099

URL: http://dx.doi.org/10.1080/07328300008544099

J. CARBOHYDRATE CHEMISTRY, 19(4&5), 555–571 (2000)

SYNTHESIS OF (*Z*)-3-DEOXY-3-(1,2,3,6-TETRADEOXY-3,6-IMINO-L-*arabino*-HEXITOL-1-*C*-YLIDENE)-D-*xylo*-HEXOSE DERIVATIVES. FIRST EXAMPLES OF HOMO-(1→3)-*C*-LINKED IMINODISACCHARIDES.[1]

Francesca Cardona,[a] Inmaculada Robina[b] and Pierre Vogel[a]*

[a] Section de Chimie de l'Université de Lausanne, BCH, CH-1015-Lausanne-Dorigny, Switzerland
[b] Departamento de Química Orgánica, Universidad de Sevilla, Apartado 557, E-41071 Sevilla, Spain

Received September 13, 1999 - Final Form January 19, 2000

ABSTRACT

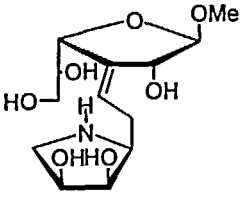
Cross-aldolisation of 3,6-[(*tert*-butoxy)carbonyl]imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexose (**10**) with 1,6-anhydro-2-*O*-benzyl-3-deoxy-β-D-*erythro*-hexopyrano-4-ulose (**6**) generates, after water elimination, a single enone **11** that is reduced selectively into an allylic alcohol **12**, deprotection of which affords methyl (*Z*)-3-deoxy-3-(1,2,3,6-tetradeoxy-3,6-imino-L-*arabino*-hexitol-1-*C*-ylidene)-β-D-*xylo*-hexofuranoside (**1**) and (*Z*)-1,6-anhydro-3-deoxy-3-(1,2,3,6-tetradeoxy-3,6-imino-L-*arabino*-hexitol-1-*C*-ylidene)-β-D-*xylo*-hexopyranose (**14**).

INTRODUCTION

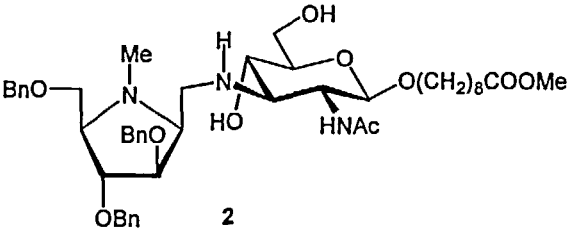
Glycosidase and glycosyltransferases are key enzymes in the biosynthesis and processing of glycoproteins, which are molecules involved in recognition (cell-cell, host-pathogen interactions) and in control of biological mechanisms and structures.[2] Thus, substances able to inhibit these enzymes have become potential antibacterial, antiviral,

antimetastatic, antidiabetes, antihyperglycemic, antiadhesive, or immunostimulatory agents.[3] A new class of selective glycosidase inhibitors has emerged, namely *C*-linked imino disaccharides (aza-*C*-disaccharides),[4,5] which contains not only the steric and charge information of the glycosyl moiety liberated during the enzyme-catalyzed hydrolysis, but also that of the aglycon. The first example of a *C*-linked imino disaccharide (1,5-dideoxy-1,5-imino-D-mannitol linked at C(6) of D-galactose through a CH_2 unit) was prepared by Johnson and co-workers.[6] Other examples of "linear" *C*-linked imino disaccharides were obtained by the groups of Martin[7] and van Boom.[8] We have prepared the first examples of "branched" disaccharides.[4,9] Further examples were reported by Johnson and coworkers[5] and by our group.[10,11] Brandi and co-workers[12] have obtained the first examples of (1→2)-linked pseudo imino-*C*-disaccharides in which a 2,3-dihydroxypyrrolidine or a 2-hydroxypyrrolidine is linked at C-2 of D-glucose via a single C-C bond.

In the mechanism of the glycosidase-catalyzed hydrolysis of an *O*-disaccharide, the distance between the liberated glycosyl cation intermediate and its "aglycone" partner might be larger than that between the corresponding monosaccharides in the substrate. It is thus possible that homo-*C*-linked iminodisaccharides, in which iminoalditols are linked to monosaccharides through a two-carbon chain, are better glycosidase inhibitors than the corresponding *C*-linked iminodisaccharides in which iminoalditols are linked by one carbon linker to monosaccharides. The latter are substrate mimetics rather than transition state mimetics. We report here our preliminary efforts toward the synthesis of a homo-(1→3)-*C*-linked imino-disaccharide **1** in which a 3,4-dihydroxypyrrolidine is tethered at C-2 to C-3 of a hexose derivative by a two-carbon linker. To our knowledge such a system has never been reported. Wong and co-workers[13] have prepared compound **2** that can be considered as an analogue with an azaethano linker.



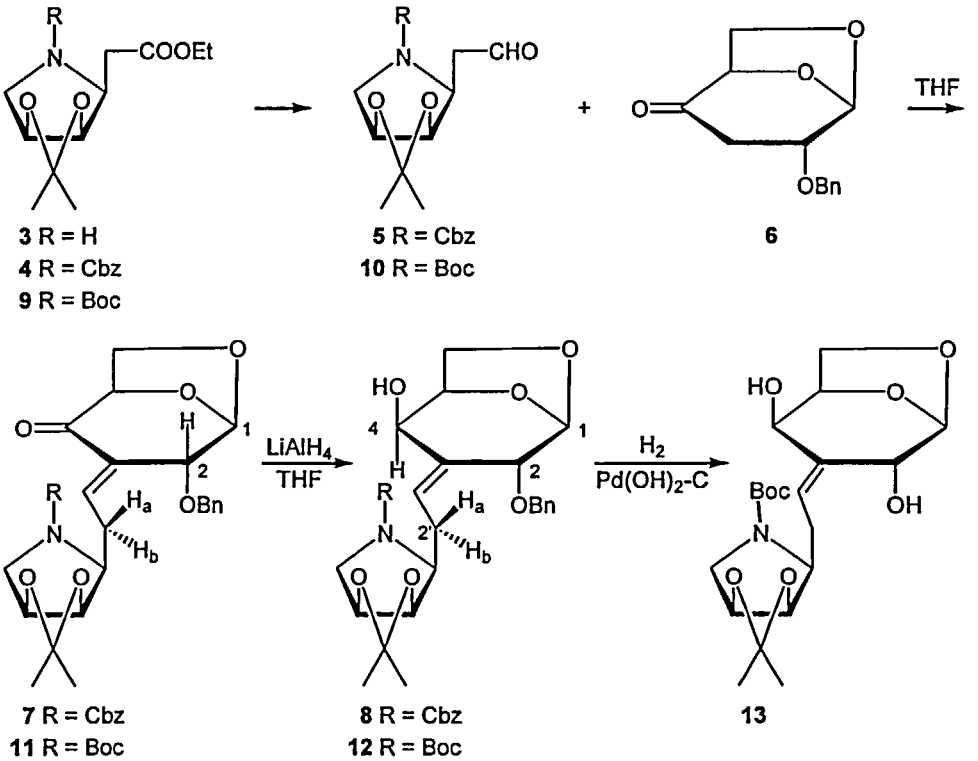
1



2

RESULTS AND DISCUSSION

Our first approach to **1** and analogues (Scheme 1) relied on the cross-aldolisation of ketone **6** (product of conjugate addition of benzyl alcohol to isolevoglucosenone)[10] and aldehyde **5** derived from ethyl 2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexonate (**3**).[14] Protection of amine **3** as a benzylcarbamate **4** (88% yield) was performed under standard conditions[15] (CbzCl/$NaHCO_3$/EtOH/H_2O, 20 °C, 3 h). Reduction of **4** with 1.2 equivalent of $(i\text{-Bu})_2AlH$ in CH_2Cl_2 at -78 °C provided **5** in 54% yield, with 37% of recovered **4**. The lithium enolate of **6** was added to aldehyde **5** and gave a major aldol that could not be isolated because of its instability.[16] The mixture was thus treated with CF_3COOH (-78 °C) and allowed to stand with silica gel at 20 °C overnight. This produced enone **7** in 94% yield. Reduction of enone **7** with $LiAlH_4$ in THF at -78 °C was highly chemo- and stereoselective affording allylic alcohol **8** as a single product in 85%



3 R = H
4 R = Cbz
9 R = Boc

5 R = Cbz
10 R = Boc

6

7 R = Cbz
11 R = Boc

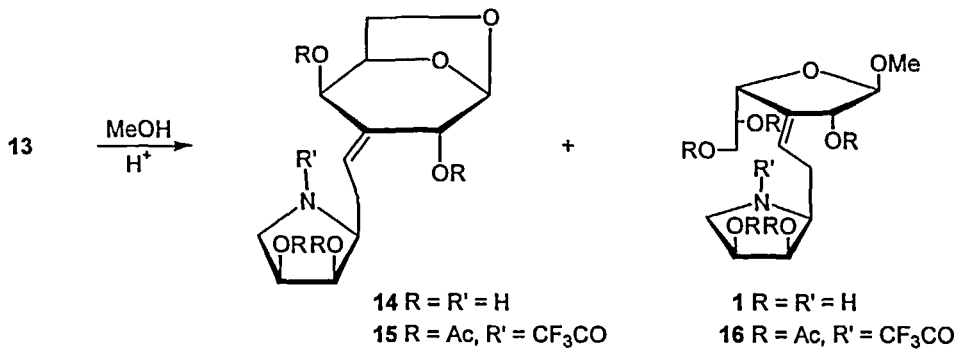
8 R = Cbz
12 R = Boc

13

Scheme 1

yield. Its *xylo* configuration was suggested by the 2D NOESY ^{1}H NMR spectrum that did not show any NOE between signals at δ 4.63 (H-4) and 3.79 ppm (H*endo*-6). It was confirmed by the structure of **16**, see below. The (*Z*) configuration of the alkene moiety of **8** was given by the observation of a NOE between signals at δ 4.24 (H-2) and 2.86 ppm (Ha-2').

Debenzylation of benzylcarbamate **8** led to intractable mixtures, probably arising from reactions of the free pyrrolidine moiety. We thus decided to protect the amine with a Boc group. This was done by treating **4** with H_2/$Pd(OH)_2$ in MeOH containing $(Boc)_2O$, a reaction that led to the *tert*-butyl carbamate **9** in quantitative yield. Its reduction with $(i\text{-Bu})_2AlH$ (CH_2Cl_2, -78 °C) provided aldehyde **10** (83% yield). Condensation of **10** with the lithium enolate of **6** produced a major aldol that eliminated H_2O (CF_3COOH/SiO_2) to afford pure enone **11** (78% yield). Its reduction with $LiAlH_4$/THF gave allylic alcohol **12** (89% yield). Hydrogenolysis of **12** (H_2, $Pd(OH)_2/C$) in MeOH was a clean reaction giving diol **13** in 92% yield, without hydrogenation of the alkene. The structure of **13** was revealed from its spectral data. In particular, the 2D NOESY ^{1}H NMR spectrum of **13** showed a cross-peak for the signal pair at δ 4.44 (H-2) and 2.92 ppm (Ha-2') proving the (*Z*) configuration of the allylic diol.



14 R = R' = H
15 R = Ac, R' = CF_3CO

1 R = R' = H
16 R = Ac, R' = CF_3CO

Scheme 2

Methanolysis of the anhydro-pyranose moiety of **13** proved more difficult than expected.[10,11] Heating **13** in anhydrous MeOH saturated with gaseous HCl for 18 h led to an inseparable 1:1 mixture (72% yield) of the deprotected 1,6-anhydro homo-C-linked iminodisaccharide **14** and methyl β-*xylo*-hexofuranoside **1**. Prolonged reaction time led

to higher proportions of **1** but with lower yields. Higher reaction temperatures induced fast decomposition. Treatment of **13** with CF_3COOH/H_2O at 85 °C afforded pure **14** in 71% yield, with no hydrolysis of the anhydrohexose moiety.[17] Protection of the pyrrolidine moieties of the 1:1 mixture of **14** + **1** as trifluoroacetamides [$(CF_3CO)_2O$/pyridine, 20 °C, 15 h), followed by methanolysis ($MeOH/NH_3$ (catalyst)][18] and acetylation (Ac_2O/pyridine, 20 °C, 15 h) produced a 1:1 mixture of **15** and **16** that could be separated by flash chromatography on silica gel in 33% and 30% yield, respectively. The spectral data from **15** and **16** confirmed their structures and those of their synthetic precursors. In particular, the 2D NOESY ^1H NMR spectrum of methyl furanoside **16** displayed cross-peaks between signal pairs at δ 5.48 (H-2) and 4.61 ppm (H-4), on one hand, and at δ 4.61 ppm (H-4) and 3.34 ppm (MeO-C(1)), on the other hand, proving the β-furanoside structure and the *cis*-relative configuration of H-C(2) and H-C(4) (*xylo* configuration). Additionally, NOE's between signals at δ 5.48 (H-2) and 2.85 ppm (Ha-2'), and between signals at δ 5.79 (H-1') and 5.37 ppm (H-5), were observed.

CONCLUSION

The synthesis of two derivatives of (*Z*)-3-deoxy-3-(1,2,3,6-tetradeoxy-3,6-imino-L-*arabino*-1-*C*-ylidene)-D-*xylo*-hexose derivatives (**1**, **14**) has been realized. They represent the first examples of homo-(1→3)-*C*-linked iminodisaccharides. The synthetic approach is convergent and highly stereoselective and should allow one to generate a large variety of analogues.[19]

EXPERIMENTAL

General methods. Most procedures were not optimized. All solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and pyridine form CaH_2; MeOH from Mg. Solutions after reactions and extractions were concentrated on a rotatory evaporator under reduced pressure. Liquid/solid flash chromatography (FC): columns of silica gel (0.040–0.64 μm, Merck No. 9385 silica gel 60, 240-400 mesh) or Lobar columns (Merck SiO_2, or RP-8). Thin-layer chromatography (TLC) for reaction

monitoring: Merck silica gel 60 F_{254} plates; detection by UV light. Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O), or $KMnO_4$. Reagents were from Fluka or Aldrich and used without purification. Melting points are reported uncorrected; Tottoli (Büchi SMP-20) apparatus. Optical rotations: Jasco-DIP-370 polarimeter. UV/VIS spectra: Kontron-Uvikon-811 or Hewlett-Packard-HP8450 A spectrometer; λ in nm (ε [$dm^3mol^{-1}cm^{-1}$]). IR spectra: Perkin-Elmer-1420 or Beckman-IR4230 spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H NMR spectra: Bruker-DPX-400, or Bruker-ARX-400 spectrometer, δ in ppm rel to internal Me_4Si (0.00 ppm) or to the solvent's residual ^1H-signals ($CHCl_3$, δ 7.27; C_6HD_5, δ 7.16; CHD_2COCD_3, δ 1.95; CD_2HCN, δ 2.50; CHD_2SOCD_3, δ 2.50; CHD_2OD, δ 3.31) as internal reference; in D_2O, internal reference $Me_3SiCH_2CH_2CH_2SO_3Na$ (δ(Me_3Si) 0), all ^1H-signal assignments were confirmed by double irradiation experiments or by 2D COSY-DQF or COSY-45 spectra. ^{13}C NMR spectra: same instruments as above (100.61 MHz); δ in ppm rel to internal Me_4Si (0.00 ppm) or to the solvent's C-signal ($CDCl_3$, δ 77.0; C_6D_6, δ 128.4; $(CD_3)_2CO$, δ 29.8; CD_3CN, δ 1.3; $(CD_3)_2SO$, δ 39.5; CD_3OD, δ 49.2) as internal reference, coupling constants J in Hz (±0.5 Hz). MS (Nermag R-10-10C, chemical ionization (NH_3) mode, *m/z* (amu) (% rel. base peak (100%)). Elemental analysis: Ilse Beetz, D-96301 Kronach, Germany.

Ethyl 3,6-[(Benzyloxy)carbonyl]imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexonate (4). A mixture of ethyl 2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexonate (**3**,[14] 1.51 g, 6.59 mmol), BnOCOCl (CbzCl, 1 mL, 7.25 mmol) and $NaHCO_3$ (730 mg) in 1:1 EtOH/H_2O (16 mL) was stirred at 20 °C for 3 h. The mixture was then diluted with CH_2Cl_2 and H_2O. The organic phase was dried ($MgSO_4$). Solvent evaporation, flash chromatography on silica gel (1:3 EtOAc/light petroleum ether) afforded **4** (R_f 0.4, 2.1 g, 5.80 mmol, 88%) as a colorless oil. $[\alpha]_{589}^{25}$ +52°, $[\alpha]_{577}^{25}$ +54°, $[\alpha]_{546}^{25}$ +61°, $[\alpha]_{435}^{25}$ +100°, $[\alpha]_{405}^{25}$ +119° (*c* 0.4, $CHCl_3$); UV (CH_3CN) 207 (7100), 195 (8400); IR (film) 2985, 1705, 1410, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 333 K) δ 7.38-7.29 (m, 5H arom.), 5.17-5.10 (m, 2H, CH_2(Cbz)), 4.83 (t, $J_{4,3} = J_{4,5} = 6.5$ Hz, 1H, H-4), 4.74 (td, $J_{5,4} = J_{5,6a} = 6.5$ Hz, $J_{5,6b} = 3.3$ Hz, 1H, H-5), 4.38 (ddd, J = 11.0 Hz, $J_{3,4} = 6.5$ Hz, J = 5.0 Hz, 1H, H-3), 4.15 (q, J = 7.1 Hz, 2H, CH_2 Et), 3.77 (dd, $J_{6a,6b} = 12.5$ Hz, $J_{6a,5} = 6.5$ Hz, 1H, Ha-6), 3.53 (dd, $J_{6b,6a} = 12.5$ Hz, $J_{6b,5} = 3.2$ Hz, 1H, Hb-6), 3.05 (dd, $J_{2a,2b} = 16.4$ Hz,

J = 4.3 Hz, 1H, Ha-2), 2.66 (dd, $J_{2b,2a}$ = 16.4 Hz, J = 9.8 Hz, 1H, Hb-2), 1.51, 1.34 (2s, 6H, Me_2C), 1.26 (t, J = 7.1 Hz, 3H, CH_3(Et)); ^{13}C NMR ($CDCl_3$, 333 K) δ 171.3 (s, C-1), 154.8 (s, C=O(Cbz)), 136.7 (s, C arom.), 128.5, 128.0, 127.9 (3d, C arom.), 112.7 (s, Me_2C), 79.9 (d, C-4), 77.8 (d, C-5), 67.0 (t, CH_2-Cbz), 60.1 (t, CH_2(Et)), 57.2 (d, C-3), 50.9 (t, C-6), 34.5 (t, C-2), 26.2, 25.0 (2q, Me_2C), 14.1 (q, CH_3(Et)); CI-MS (NH_3): 363 (M^+, 3), 348 (11), 305 (6), 288 (14), 244 (12), 170 (13), 124 (10), 91 (100).

Anal. Calcd for $C_{19}H_{25}NO_6$ (363.41): C, 62.80; H, 6.93; N, 3.85. Found: C, 62.93; H, 6.94; N, 3.86.

3,6-[(Benzyloxy)carbonyl]imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexose (5). 1 M (*i*-Bu)$_2$AlH in CH_2Cl_2 (2 mL) was added dropwise under an argon atmosphere to a solution of **4** (633 mg, 1.74 mmol) in dry CH_2Cl_2 (3 mL) cooled to -78°C. After stirring at -78°C for 2 h, MeOH (0.5 mL) was added, and the cooling bath was removed. Once at 0°C, 1 M aq HCl (4 mL) was added. The mixture was extracted with CH_2Cl_2 (40 mL, 4 times). The organic phase was washed with a sat aq solution of $NaHCO_3$ (10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography on silica gel (1:3 EtOAc/light petroleum ether) afforded **4** (R_f 0.4, 232 mg, 0.639 mmol, 37%) and **5** (R_f 0.3, 300 mg, 0.94 mmol, 54%) as a colorless oil. $[\alpha]_{589}^{27}$ +64°, $[\alpha]_{577}^{27}$ +65°, $[\alpha]_{546}^{27}$ +85°, $[\alpha]_{435}^{27}$ +147°, $[\alpha]_{405}^{27}$ +179° (*c* 0.9, $CHCl_3$); UV (CH_3CN) 204 (14400), 196 (16000); IR (film) 3065, 3035, 2985, 2940, 1705, 1410, 1340, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 333 K) δ 9.78 (s, 1H, H-1), 7.38-7.29 (m, 5H arom.), 5.16-5.09 (m, 2H, CH_2(Cbz)), 4.81 (t, $J_{4,3}$ = $J_{4,5}$ = 6.4 Hz, 1H, H-4), 4.75 (td, $J_{5,6a}$ = $J_{5,4}$ = 6.4 Hz, $J_{5,6b}$ = 3.2 Hz, 1H, H-5), 4.39-4.34 (m, 1H, H-3), 3.74 (dd, $J_{6a,6b}$ = 12.5 Hz, $J_{6a,5}$ = 6.4 Hz, 1H, Ha-6), 3.56 (dd, $J_{6b,6a}$ = 12.5 Hz, $J_{6b,5}$ = 3.2 Hz, 1H, Hb-6), 3.09-3.06 (m, 1H, Ha-2), 2.89 (ddd, $J_{2b,2a}$ = 17.4 Hz, J = 8.3 Hz, J = 1.0 Hz, 1H, Hb-2), 1.50, 1.33 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 333 K) δ 199.5 (d, C-1), 154.9 (s, C=O(Cbz)), 136.5 (s, C arom.), 128.5, 128.1, 128.0 (3d, C arom.), 112.7 (s, Me_2C), 79.8 (d, C-4), 77.7 (d, C-5), 67.1 (t, CH_2(Cbz)), 56.3 (d, C-3), 51.3 (t, C-6), 43.6 (t, C-2), 26.3, 24.9 (2q, Me_2C); CI-MS (NH_3): 319 (M^+, 3), 304 (10), 276 (3), 228 (5), 200 (4), 184 (17), 170 (5), 142 (11), 91 (100).

Anal. Calcd for $C_{17}H_{21}NO_5$ (319.36): C, 63.94; H, 6.63; N, 4.39. Found: C, 63.86; H, 6.49; N, 4.24.

(*E*)-1,6-Anhydro-2-*O*-benzyl-3-{3',6'-[(benzyloxy)carbonyl]imino-1',2',3',6'-tetradeoxy-4',5'-*O*-isopropylidene-L-*arabino*-hexitol-1'-*C*-ylidene}-3-deoxy-β-D-*ery*-

***thro*-hexopyran-4-ulose (7).** 1.6 M of BuLi in hexane (91 μL, 0.146 mmol) was added to a stirred solution of $(Me_3Si)_2NH$ (31 μL, 0.146 mmol) in anhydrous THF (0.23 mL) at -10°C. After stirring at -10 C for 30 min, the mixture was cooled to -78°C and a solution of 1,6-anhydro-2-*O*-benzyl-3-deoxy-D-*erythro*-hexopyran-4-ulose (**6**,[10] 28.5 mg, 0.122 mmol) in dry THF (0.25 mL) was added dropwise over a period of 5-10 min. At the end of the addition, the mixture was left at -78 °C for 2 h and then cooled to -100 °C. A solution of **5** (58.4 mg, 0.183 mmol) in dry THF (0.4 mL) was added dropwise over 5-10 min. The mixture was stirred at -100 °C for 30 min and left for 15 h at -60 °C. The mixture was then poured into a 10% solution of AcOH in THF (6 mL) previously cooled to -78 °C. After warming up to 0 °C, the mixture was neutralized with a sat aq solution of $NaHCO_3$ (13 mL) and extracted with CH_2Cl_2 (20 mL, 3 times). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was then dissolved in CH_2Cl_2 (15 mL) and stirred in the presence of silica gel (800 mg) at 20 °C for 15 h. Flash chromatography on silica gel (1:2 EtOAc/light petroleum ether) afforded **7** (R_f 0.26, 61.2 mg, 0.114 mmol, 94%) as a white foam. $[\alpha]_{589}^{25}$ +109°, $[\alpha]_{577}^{25}$ +122°, $[\alpha]_{546}^{25}$ +152°, $[\alpha]_{435}^{25}$ +247°, $[\alpha]_{405}^{25}$ +274° (*c* 0.4, $CHCl_3$); UV (CH_3CN) 241 (16300), 206 (35500), 196 (42600); IR (film) 3395, 3035, 2960, 2895, 1705, 1620, 1415, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 333 K) δ 7.37-7.25 (m, 11H, 10H arom., H-1'), 5.70 (s, 1H, H-1), 5.15-5.09 (m, 2H, CH_2(Cbz)), 4.74-4.51 (m, 5 H, CH_2(Bn), H-5, H-4', H-5'), 4.38 (br s, 1H, H-2), 4.04-3.91 (m, 1H, H-3'), 3.88-3.84 (m, 3H, Ha-6', H_{endo}-6, H_{exo}-6), 3.44 (dd, $J_{6'b,6'a}$ = 12.7 Hz, $J_{6'b,5}$ = 3.5 Hz, 1H, Hb-6'), 2.85-2.81 (m, 1H, Ha-2'), 2.70 (ddd, $J_{2'b,2'a}$ = 13.8 Hz, J = 8.2 Hz, J = 5.4 Hz, 1H, Hb-2'), 1.44, 1.33 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 333 K) δ 199.4 (s, C-4), 154.8 (s, C=O(Cbz)), 149.2 (d, C-1'), 138.0, 136.6, 131.6 (s, 3C, 2C arom., C-3), 128.6-127.8 (d, 10C, CH arom.), 113.3 (s, Me_2C), 101.7 (d, C-1), 79.8 (d), 78.6 (d, C-5), 78.0 (d), 74.8 (d, C-2), 70.6 (t, CH_2(Bn)), 67.3 (t, 2C, CH_2(Cbz)), C-6), 59.3 (d, C-3'), 50.9 (t, C-6'), 29.2 (t, C-2'), 26.4, 25.0 (2q, Me_2C); CI-MS (NH_3): 535 (M^+, 1), 428 (28), 353 (5), 232 (6), 91 (100).

Anal. Calcd for $C_{30}H_{33}NO_8$ (535.59): C, 67.28; H, 6.21; N, 2.62. Found: C, 66.89; H, 5.98; N, 2.71.

(*Z*)-1,6-Anhydro-2-*O*-benzyl-3-{3',6'-[(benzyloxy)carbonyl]imino-1',2',3',6'-tetradeoxy-4',5'-*O*-isopropylidene-L-*arabino*-hexitol-1'-*C*-ylidene}-3-deoxy-β-D-*xylo*-hexopyranose (8). 1 M $LiAlH_4$ in THF (2 eq, 0.912 mL) was added dropwise to a stirred

solution of 7 (244 mg, 0.456 mmol) in dry THF (8.6 mL) cooled to -78 °C, under an argon atmosphere. After stirring at -78 °C for 3 h, Et_2O (1 mL) and two drops of H_2O were added dropwise. The mixture was acidified with 1 M HCl. Extraction with CH_2Cl_2 (20 mL, 3 times), drying of the organic phases ($MgSO_4$), solvent evaporation and flash chromatography on silica gel (3:2 EtOAc/light petroleum ether) afforded **8** (R_f 0.23, 208 mg, 0.387 mmol, 85%) as a white solid, mp 52-53 °C. $[\alpha]_{589}^{25}$ +69°, $[\alpha]_{577}^{25}$ +72°, $[\alpha]_{546}^{25}$ +82°, $[\alpha]_{435}^{25}$ +140°, $[\alpha]_{405}^{25}$ +169° (*c* 0.5, $CHCl_3$). UV (CH_3CN) 257 (3200), 194 (36900); IR (KBr) 3445, 3065, 3030, 2960, 2895, 1670, 1455, 1420, 1375, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 333 K) δ 7.40-7.23 (m, 10H arom.), 6.13-6.09 (m, 1H, H-1'), 5.40 (s, 1H, H-1), 5.16-5.02 (m, 2H, CH_2(Cbz)), 4.76-4.73 (m, 2H, H-4', H-5'), 4.63 (br s, 1H, H-4), 4.55 (d, J = 11.7 Hz, 1H, CH_2(Bn)), 4.43 (t, $J_{5,4} = J_{5,6exo} = 4.6$ Hz, 1H, H-5), 4.40 (d, J = 11.7 Hz, 1H, CH_2(Bn)), 4.24 (br s, 1H, H-2), 4.15-3.97 (m, 1H, H-3'), 3.94-3.84 (m, 1H, Ha-6'), 3.79 (d, $J_{6endo,6exo} = 7.2$ Hz, 1H, H_{endo}-6), 3.56 (dd, $J_{6exo,6endo} = 7.2$ Hz, $J_{6exo,5} = 4.6$ Hz, 1H, H_{exo}-6), 3.40 (dd, $J_{6'b,6'a} = 12.1$ Hz, $J_{6'b,5'} = 3.5$ Hz, 1H, Hb-6'), 2.89-2.82 (m, 1H, Ha-2'), 2.48-2.41 (m, 1H, Hb-2'), 1.52, 1.36 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 333 K) δ 155.1 (s, C=O(Cbz)), 138.6, 136.6, 134.9 (s, 3C, 2C arom., C-3), 128.6-127.2 (d, 11C, CH arom., C-1'), 113.2 (s, Me_2C), 101.5 (d, C-1), 79.9, 78.0 (d, 2C, C-4', C-5'), 76.6 (d, C-5), 73.9 (d, C-2), 70.5 (t, CH_2(Bn)), 68.7 (d, C-4), 67.2 (t, CH_2(Cbz)), 63.4 (t, C-6), 60.6 (d, C-3'), 50.7 (t, C-6'), 27.9 (t, C-2'), 26.6, 25.2 (2q, Me_2C); CI-MS (NH_3): 555 (M^++18, 5), 537 (M^+, 8), 430 (18), 322 (95), 278 (7), 91 (100).

Anal. Calcd for $C_{30}H_{35}NO_8$ (537.61): C, 67.02; H, 6.56; N, 2.61. Found: C, 67.15; H, 6.46; N, 2.64.

Ethyl 3,6-[(*tert*-Butoxy)carbonyl]imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexonate (9). A degassed mixture of **4** (1.43 g, 3.95 mmol), $(Boc)_2O$ (949 mg, 4.35 mmol), 20% $Pd(OH)_2$ on charcoal (1.40 g) and MeOH (100 mL) was stirred under an H_2 atmosphere at 20 °C for 1 h. The catalyst was filtered off and the solvent evaporated *in vacuo* to obtain 1.44 g of the crude **9**, pure enough to be used in the next step. An analytically pure sample (colorless oil) was obtained upon purification by flash chromatography on silica gel (1:3 EtOAc/light petroleum ether, R_f 0.5). $[\alpha]_{589}^{26}$ +62°, $[\alpha]_{577}^{26}$ +69°, $[\alpha]_{546}^{26}$ +75°, $[\alpha]_{435}^{26}$ +123°, $[\alpha]_{405}^{26}$ +149° (*c* 0.6, $CHCl_3$); UV (CH_3CN) 197 (1500); IR (film) 3580, 2980, 2940, 1735, 1700, 1395, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 333 K) δ 4.81 (t, $J_{4,3} = J_{4,5} = 6.6$ Hz, 1H, H-4), 4.71 (td, $J_{5,4} = J_{5,6a} = 6.6$ Hz, $J_{5,6b} = 3.3$ Hz,

1H, H-5), 4.29 (ddd, J = 10.5 Hz, $J_{3,4}$ = 6.6 Hz, J = 4.6 Hz, 1H, H-3), 4.15 (q, J = 7.1 Hz, 2H, CH_2(Et)), 3.70 (dd, $J_{6a,6b}$ = 12.5 Hz, $J_{6a,5}$ = 6.6 Hz, 1H, Ha-6), 3.41 (dd, $J_{6b,6a}$ = 12.5 Hz, $J_{6b,5}$ = 3.3 Hz, 1H, Hb-6), 2.99 (dd, $J_{2a,2b}$ = 16.3 Hz, J = 4.1 Hz, 1H, Ha-2), 2.61 (dd, $J_{2b,2a}$ = 16.3 Hz, J = 10.1 Hz, 1H, Hb-2), 1.45 (s, 9H, Boc), 1.50, 1.32 (2s, 6H, Me_2C), 1.25 (t, J = 7.1 Hz, 3H, CH_3(Et)); ^{13}C NMR ($CDCl_3$, 333 K) δ 171.4 (s, C-1), 154.3 (s, C=O Boc), 112.6 (s, Me_2C), 80.1 (s, Boc), 79.9 (d, C-4), 77.9 (d, C-5), 60.0 (t, CH_2(Et)), 56.9 (d, C-3), 50.8 (t, C-6), 34.7 (t, C-2), 28.4 (q, 3C, Boc), 26.2, 25.0 (2q, Me_2C), 14.1 (q, CH_3(Et)); CI-MS (NH_3): 330 (M^++1, 60), 329 (M^+, 6), 314 (18), 274 (45), 256 (11), 230 (100), 191 (4), 171 (15), 154 (52), 129 (24).

Anal. Calcd for $C_{16}H_{27}NO_6$ (329.39): C, 58.34; H, 8.26; N, 4.25. Found: C, 58.31; H, 8.23; N, 4.32.

3,6-[(*tert*-Butoxy)carbonyl]imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexose (10). 1 M (*i*-Bu)$_2$AlH in CH_2Cl_2 (11.85 mL, 11.85 mmol) was added dropwise under an argon atmosphere to a solution (-78 °C) of crude **9** (1.44 g. 3.95 mmol) in dry CH_2Cl_2 (20 mL). After stirring at -78 °C for 3.5 h, MeOH (5 mL) was added, and the mixture slowly warmed up to 20 °C. Then, in an ice-cold bath, 1 M aq HCl (15 mL) was added. The aq phase was extracted with CH_2Cl_2 (100 mL, 4 times). The combined organic phases were washed with a sat aq solution of $NaHCO_3$ (20 mL) and dried ($MgSO_4$). Solvent evaporation, flash chromatography on silica gel (1:3 EtOAc/light petroleum ether) afforded **10** (R_f 0.28, 934 mg, 3.28 mmol, 83%) as a colorless oil. $[\alpha]_{589}^{26}$ +73°, $[\alpha]_{577}^{26}$ +78°, $[\alpha]_{546}^{26}$ +88°, $[\alpha]_{435}^{26}$ +154°, $[\alpha]_{405}^{26}$ +191° (*c* 0.6, $CHCl_3$); UV (CH_3CN) 196 (3800); IR (film) 2980, 2935, 1725, 1695, 1395, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$, 333 K) δ 9.79 (t, $J_{1,2}$ = 1.3 Hz, 1H, H-1), 4.79 (t, $J_{4,3}$ = $J_{4,5}$ = 6.4 Hz, 1H, H-4), 4.72 (td, $J_{5,6a}$ = $J_{5,4}$ = 6.4 Hz, $J_{5,6b}$ = 3.3 Hz, 1H, H-5), 4.29 (ddd, J = 7.9 Hz, $J_{3,4}$ = 6.4 Hz, J = 6.2 Hz, 1H, H-3), 3.68 (dd, $J_{6a,6b}$ = 12.5 Hz, $J_{6a,5}$ = 6.4 Hz, 1H, Ha-6), 3.44 (dd, $J_{6b,6a}$ = 12.5 Hz, $J_{6b,5}$ = 3.3 Hz, 1H, Hb-6), 2.98 (dd, $J_{2b,2a}$ = 17.3 Hz, J = 4.1 Hz, 1H, Ha-2), 2.86 (ddd, $J_{2b,2a}$ = 17.3 Hz, J = 8.2 Hz, J = 1.1 Hz, 1H, Hb-2), 1.45 (s, 9H, Boc), 1.49, 1.32 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 333 K) δ 199.9 (d, C-1), 154.4 (s, C=O Boc), 112.7 (s, Me_2C), 80.4 (s, Boc), 79.9 (d, C-4), 77.8 (d, C-5), 56.0 (d, C-3), 51.2 (t, C-6), 43.9 (t, C-2), 28.4 (q, 3C, Boc), 26.3, 25.0 (2q, Me_2C); CI-MS (NH_3): 286 (M^++1, 69), 285 (M^+, 1), 270 (8), 247 (19), 230 (100), 214 (20), 186 (8), 110 (25).

Anal. Calcd for $C_{14}H_{23}NO_5$ (285.34): C, 58.93; H, 8.12; N, 4.91. Found: C, 58.80; H, 8.22; N, 4.97.

(*E*)-1,6-Anhydro-2-*O*-benzyl-3-{3',6'-[(*tert*-butoxy)carbonyl]imino-1',2',3',6'-tetradeoxy-4',5'-*O*-isopropylidene-L-*arabino*-hexitol-1'-*C*-ylidene}-3-deoxy-β-D-*eryt-hro*-hexopyran-4-ulose (11). 1.6 M BuLi in hexane (1.65 mL, 2.65 mmol) was added to a stirred solution of $(Me_3Si)_2NH$ (0.55 mL, 2.65 mmol) in anhydrous THF (3.9 mL) at -10 °C. After stirring at -10 °C for 30 min, the mixture was cooled to -78 °C and a solution of **6** (516 mg, 2.20 mmol) in dry THF (4.4 mL) was added dropwise over a period of 20 min. At the end of the addition, the mixture was left at -78 °C for 2 h and then cooled to -100 °C. A solution of **10** (934 mg, 3.28 mmol) in dry THF (7.6 mL) was added dropwise during 10-15 min. The mixture was stirred at -100 °C for 30 min and left for 15 h at -60 °C. The mixture was then poured into a 10% solution of AcOH in THF (44 mL) previously cooled to -78 °C. After warming up to 0 °C, the mixture was neutralized with a sat aq solution of $NaHCO_3$ (83 mL) and extracted with CH_2Cl_2 (150 mL, 3 times). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was then dissolved in CH_2Cl_2 (50 mL) and stirred with silica gel (6 g) at 20 °C for 15 min. Flash chromatography on silica gel (1:3 EtOAc/light petroleum ether) afforded unreacted **10** (R_f 0.28, 295 mg, 1.04 mmol, 0.47 eq); following the elution with 1:2 EtOAc/light petroleum ether afforded **11** (R_f 0.3, 862 mg, 1.72 mmol, 78%) as a white foam. $[\alpha]_{589}^{26}$ +99°, $[\alpha]_{577}^{26}$ +104°, $[\alpha]_{546}^{26}$ +118°, $[\alpha]_{435}^{26}$ +202°, $[\alpha]_{405}^{26}$ +236° (*c* 0.9, $CHCl_3$); UV (CH_3CN) 207 (6300), 193 (13000), 201 (7200); IR (film) 2980, 2940, 2895, 1695, 1620, 1395, 1370 cm^{-1}; ^1H NMR ($CDCl_3$, 333 K) δ 7.41-7.26 (m, 6H, 5H arom., H-1'), 5.73 (s, 1H, H-1), 4.75 (d, J = 11.3 Hz, 1H, CH_2(Bn)), 4.72-4.69 (m, 2H, H-4', H-5'), 4.67 (d, J = 11.3 Hz, 1H, CH_2(Bn)), 4.64 (t, $J_{5,6endo} = J_{5,6exo}$ =3.1 Hz, 1H, H-5), 4.43 (br s, 1H, H-2), 4.00 (q, $J_{3',2'a} = J_{3',2'b} = J_{3',4'}$ = 6.5 Hz, 1H, H-3'), 3.89-3.82 (m, 3H, H_{endo}-6, H_{exo}-6, Ha-6'), 3.33 (dd, $J_{6'b,6'a}$ = 12.5 Hz, $J_{6'b,5}$ = 3.4 Hz, 1H, Hb-6'), 2.84-2.76 (m, 1H, Ha-2'), 2.73-2.66 (m, 1H, Hb-2'), 1.45 (s, 9H, Boc), 1.44, 1.33 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 333 K) δ 192.3 (s, C-4), 154.2 (s, C=O Boc), 149.9 (d, C-1'), 138.1, 131.2 (s, 2C, C arom., C-3), 128.5-127.7 (d, 5C, CH arom.), 113.2 (s, Me_2C), 101.7 (d, C-1), 80.3 (s, Boc), 79.9 (d), 78.6 (d, C-5), 78.0 (d), 74.9 (d, C-2), 70.7 (t, CH_2(Bn)), 67.2 (t, C-6), 58.8 (d, C-3'), 50.5 (t, C-6'), 29.4 (t, C-2'), 28.4 (q, 3C, Boc), 26.3, 25.0 (2q, Me_2C); CI-MS (NH_3): 519 (M^++18, 18), 502 (M^++1, 54), 501 (M^+, 7), 446 (17), 402 (87), 338 (32), 91 (100).

Anal. Calcd for $C_{27}H_{35}NO_8$ (501.58): C, 64.66; H, 7.03; N, 2.79. Found: C, 64.55; H, 7.10; N, 2.82.

(*Z*)-1,6-Anhydro-2-*O*-benzyl-3-{3',6'-[(*tert*-butoxy)carbonyl]imino-1',2',3',6'-tetradeoxy-4',5'-*O*-isopropylidene-L-*arabino*-hexitol-1'-*C*-ylidene}-3-deoxy-β-D-*xylo*-hexopyranose (12). 1 M $LiAlH_4$ in THF (2 eq, 1.66 mL) was added dropwise cooled to -78 °C to a stirred solution (-78 °C) of **11** (415 mg, 0.828 mmol) in dry THF (17 mL) under an argon atmosphere. After stirring at -78 °C for 3 h, Et_2O (5 mL) and then 3 drops of H_2O were added dropwise. The mixture was acidified with 1 M HCl. Extraction with CH_2Cl_2 (10 mL, 3 times), drying the organic phases ($MgSO_4$), solvent evaporation and flash chromatography on silica gel (3:2 EtOAc/light petroleum ether) afforded **12** (R_f 0.4, 370 mg, 0.736 mmol, 89%) as a white solid, mp 45-47 °C. $[\alpha]_{589}^{26}$ +55°, $[\alpha]_{577}^{26}$ +57°, $[\alpha]_{546}^{26}$ +64°, $[\alpha]_{435}^{26}$ +110°, $[\alpha]_{405}^{26}$ +134° (*c* 0.9, $CHCl_3$); UV (CH_3CN) 204 (16100); IR (film) 3450, 2980, 2935, 1690, 1370 cm^{-1}; ^1H NMR ($CDCl_3$, 333 K) δ 7.37-7.24 (m, 5H arom.), 6.13 (ddd, $J_{1',2'a}$ = 8.6 Hz, $J_{1',2'b}$ = 6.1 Hz, J = 2.0 Hz, 1H, H-1'), 5.46 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.74-4.68 (m, 3H, H-4, H-4', H-5'), 4.64, 4.49 (2d, J = 11.8 Hz, 2H, CH_2(Bn)), 4.46 (t, $J_{5,4} = J_{5,6exo}$ = 4.8 Hz, 1H, H-5), 4.36 (d, $J_{2,1}$ = 2.0 Hz, 1H, H-2), 3.94-3.89 (m, 1H, H-3'), 3.85 (d, $J_{6endo,6exo}$ = 7.2 Hz, 1H, H_{endo}-6), 3.86-3.82 (m, 1H, Ha-6'), 3.61 (dd, $J_{6exo,6endo}$ = 7.2 Hz, $J_{6exo,5}$ = 4.8 Hz, 1H, H_{exo}-6), 3.32 (dd, $J_{6'b,6'a}$ = 12.9 Hz, $J_{6'b,5'}$ = 4.0 Hz, 1H, Hb-6'), 2.85 (ddd, $J_{2'a,2'b}$ = 14.3 Hz, J = 8.3 Hz, J = 6.0 Hz, 1H, Ha-2'), 2.45 (dddd, $J_{2'b,2'a}$ = 14.3 Hz, J = 8.5 Hz, J = 6.1 Hz, J = 2.2 Hz, 1H, Hb-2'), 1.46 (s, 9H, Boc), 1.52, 1.36 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 298 K) δ 154.5 (s, C=O Boc), 138.6, 134.5 (s, 2C, C arom., C-3), 128.4-127.4 (d, 6C, CH arom., C-1'), 113.0 (s, Me_2C), 101.6 (d, C-1), 80.1 (s, Boc), 80.0, 78.0 (d, 2C, C-4', C-5'), 76.6 (d, C-5), 73.9 (d, C-2), 70.5 (t, CH_2(Bn)), 68.7 (d, C-4), 63.5 (t, C-6), 60.3 (d, C-3'), 50.7 (t, C-6'), 28.5 (q, 3C, Boc), 27.9 (t, C-2'), 26.7, 25.3 (2q, Me_2C); CI-MS (NH_3): 504 (M^++1, 54), 503 (M^+, 25), 430 (11), 404 (53), 340 (33), 312 (19), 252 (17), 142 (27), 91 (100).

Anal. Calcd for $C_{27}H_{37}NO_8$ (503.59): C, 64.40; H, 7.41; N, 2.78. Found: C, 64.41; H, 7.56; N, 2.75.

(*Z*)-1,6-Anhydro-3-{3',6'-[(*tert*-butoxy)carbonyl]imino-1',2',3',6'-tetradeoxy-4',5'-*O*-isopropylidene-L-*arabino*-hexitol-1'-*C*-ylidene}-3-deoxy-β-D-*xylo*-hexopyranose (13). A degassed mixture of **12** (212 mg, 0.421 mmol), 20% $Pd(OH)_2$ on charcoal (210 mg), and MeOH (33 mL) was stirred under an H_2 atmosphere at 20 °C for 30 min. The catalyst was filtered off and the solvent evaporated *in vacuo* to afford **13** (160 mg, 0.387 mmol, 92%) as a white solid pure enough to be used in the next step. An analytical

sample (white solid) was obtained by flash chromatography on silica gel (3:1 EtOAc/light petroleum ether, R_f 0.2) or by recrystallization (EtOH/H_2O or ethyl EtOAc/light petroleum ether), mp 183-184 °C. $[\alpha]_{589}^{26}$ +57°, $[\alpha]_{577}^{26}$ +60°, $[\alpha]_{546}^{26}$ +71°, $[\alpha]_{435}^{26}$ +123°, $[\alpha]_{405}^{26}$ +154° (*c* 0.4, $CHCl_3$); UV (CH_3CN) 201 (11300); IR (KBr) 3410, 2975, 2935, 1670, 1480, 1455, 1410, 1170, 1125, 1080, 1040 cm^{-1}; ^1H NMR (CD_3OD, 333 K) δ 6.07 (td, $J_{1',2'a} = J_{1',2'b} = 8.2$ Hz, J = 2.3 Hz, 1H, H-1'), 5.32 (d, $J_{1,2} = 2.0$ Hz, 1H, H-1), 4.82-4.76 (m, 2H, H-4', H-5'), 4.59 (br s, H-4), 4.44 (d, $J_{2,1} = 2.0$ Hz, 1H, H-2), 4.40 (t, $J_{5,4} = J_{5,6exo} = 4.3$ Hz, 1H, H-5), 3.90 (dd, $J_{6endo,6exo} = 7.2$ Hz, $J_{6endo,5} = 0.8$ Hz, 1H, H_{endo}-6), 3.85 (ddd, J = 10.2 Hz, J = 5.3 Hz, J = 5.2 Hz, 1H, H-3'), 3.78 (dd, $J_{6'a,6'b} = 12.2$ Hz, $J_{6'a,5'} = 6.8$ Hz, 1H, Ha-6'), 3.60-3.53 (m, 1H, H_{exo}-6), 3.32 (dd, $J_{6'b,6'a} = 12.2$ Hz, $J_{6'b,5'} = 3.4$ Hz, 1H, Hb-6'), 2.92 (dddd, $J_{2'a,2'b} = 13.5$ Hz, J = 8.4 Hz, J = 4.9 Hz, J = 1.3 Hz, 1H, Ha-2'), 2.52 (dddd, $J_{2'b,2'a} = 13.5$ Hz, J = 9.4 Hz, J = 7.3 Hz, J = 1.9 Hz, 1H, Hb-2'), 1.52 (s, 9H, Boc), 1.56, 1.39 (2s, 6H, Me_2C); ^{13}C NMR ($CDCl_3$, 298 K) δ 154.9 (s, C=O Boc), 137.8 (s, C-3), 125.9 (d, C-1'), 112.7 (s, Me_2C), 102.1 (d, C-1), 80.5 (d), 80.4 (s, Boc), 77.5 (d), 75.9 (d, C-5), 67.7 (d), 66.7 (d, C-2), 63.1 (t, C-6), 59.8 (d, C-3'), 51.8 (t, C-6'), 28.4 (q, 3C, Boc), 26.8 (t, C-2'), 26.9, 25.4 (2q, Me_2C). CI-MS (NH_3): 414 (M^++1, 6), 413 (M^+, 0.2), 398 (25), 358 (7), 340 (100), 314 (45), 265 (74), 142 (72).

Anal. Calcd for $C_{20}H_{31}NO_8$ (413.47): C, 58.10; H, 7.56; N, 3.39. Found: C, 58.04; H, 7.60; N, 3.38.

(*Z*)-1,6-Anhydro-3-deoxy-3-(1',2',3',6'-tetradeoxy-3',6'-imino-L-*arabino*-hexitol-1'-*C*-ylidene)-β-D-*xylo*-hexopyranose (14). CF_3COOH (1 mL) was added dropwise to a suspension of **13** (29.1 mg, 0.071 mmol) in H_2O (3 mL). The mixture was then heated to 85 °C for 2.5 h. After cooling, the solution was poured onto a column (1 cm diameter, 8 cm length) of Dowex 50WX8 (100-200 mesh). The column was washed sequentially with MeOH (30 mL), H_2O (10 mL) and 6% $NH_3 \cdot H_2O$ (50 mL). The fractions containing product **14** were concentrated *in vacuo* and purified by flash chromatography on silica gel (2:3:0.5 CH_2Cl_2/MeOH/12% $NH_3 \cdot H_2O$) to afford **14** (R_f 0.2, 13.7 mg, 0.051 mmol, 71%), colourless oil. $[\alpha]_{589}^{26}$ +41°, $[\alpha]_{577}^{26}$ +33°, $[\alpha]_{546}^{26}$ +54°, $[\alpha]_{435}^{26}$ +70° (*c* 0.2, H_2O); UV (CH_3CN) 193 (5600); IR (KBr) 3420, 1635, 1385, 1130, 1040 cm^{-1}; ^1H NMR (D_2O, 298 K) δ 5.94 (td, $J_{1',2'a} = J_{1',2'b} = 7.7$ Hz, J = 1.9 Hz, 1H, H-1'), 5.48 (d, $J_{1,2} = 1.8$ Hz, 1H, H-1), 4.66-4.64 (m, 1H, H-4), 4.62 (t, $J_{5,4} = J_{5,6exo} = 4.8$ Hz,

1H, H-5), 4.47 (br s, 1H, H-2), 4.44 (ddd, $J_{5',6'b} = J_{5',4'} = 7.7$ Hz, $J_{5',6'a} = 5.3$ Hz, 1H, H-5'), 4.17-4.11 (m, 1H, H-4'), 3.91 (d, $J_{6endo,6exo} = 7.7$ Hz, 1H, H_{endo}-6), 3.71 (dd, $J_{6exo,6endo} = 7.7$ Hz, $J_{6exo,5} = 4.8$ Hz, 1H, H_{exo}-6), 3.38-3.30 (m, 2H, H-3', Ha-6'), 2.99 (dd, $J_{6'b,6'a} = 11.7$ Hz, $J_{6'b,5'} = 7.7$ Hz, 1H, Hb-6'), 2.58 (t, $J_{2',1'} = J_{2',3'} = 7.7$ Hz, 2H, Ha-2', Hb-2'); ^{13}C NMR (D_2O, 298 K) δ 136.4 (s, C-3), 126.7 (d, C-1') 102.0 (d, C-1), 76.0 (d, C-5), 71.5 (d, C-5'), 71.4 (d, C-4'), 67.2 (d, C-4), 66.3 (d, C-2), 63.5 (t, C-6), 61.5 (d, C-3'), 48.0 (t, C-6'), 25.6 (t, C-2'); CI-MS (NH_3): 274 (M^++1, 6), 273 (M^+, 0.4), 212 (2), 102 (100).

Anal. Calcd for $C_{12}H_{19}NO_6$ (273.29): C, 52.74; H, 7.01; N, 5.13. Found: C, 52.47; H, 7.34; N, 5.51.

Mixture of methyl (*Z*)-3-Deoxy-3-(1',2',3',6'-tetradeoxy-3',6'-imino-L-*arabino*-hexitol-1'-*C*-ylidene)-β-D-*xylo*-hexofuranoside (1) and of 14. A mixture of **13** (24.2 mg, 0.059 mmol) and anhydrous MeOH sat with gaseous HCl (2 mL) was heated under reflux and an argon atmosphere for 18 h. After cooling to 20 °C, the solution was poured onto a column (1 cm diameter, 6 cm length) of Dowex 50WX8 (100-200 mesh). The column was washed sequentially with MeOH (30 mL), H_2O (10 mL) and 6% $NH_3 \cdot H_2O$ (50 mL). The fractions containing products **1** and **14** were concentrated *in vacuo* (1:1 ratio by ^{1}H NMR analysis) and purified by flash chromatography on silica gel (2:3:0.5 CH_2Cl_2/MeOH/12% $NH_3 \cdot H_2O$) to afford a 1:1 mixture (^{1}H NMR analysis) of **14** and **1** (R_f 0.2, 12.2 mg, 72%). ^{13}C NMR (D_2O, 298 K) δ (detected signals for **1**) 140.7 (s, C-3), 124.9 (d, C-1'), 108.4 (d, C-1), 80.1 (d), 73.4 (d), 72.1 (d), 71.2 (d), 62.9 (t, C-6), 61.3 (d), 54.7 (q, OMe), 48.1 (t, C-6'), 28.3 (t, C-2).

(*Z*)-2,4-Di-*O*-acetyl-3-{4',5'-*O*-diacetyl-1',2',3',6'-tetradeoxy-3',6'-{[(trifluoromethyl)carbonyl]imino}-L-*arabino*-hexitol-1'-*C*-ylidene}-1,6-anhydro-3-deoxy-β-D-*xylo*-hexopyranose (15) and Methyl (Z)-2,5,6-Tri-*O*-acetyl-3-{4',5'-di-*O*-acetyl-1',2',3',6'-tetradeoxy-3',6'-{[(trifluoromethyl)carbonyl]imino}-L-*arabino*-hexitol-1'-*C*-ylidene}-3-deoxy-β-D-*xylo*-hexofuranoside (16). The inseparable 1:1 mixture of **1** and **14** (8.3 mg, 0.004 mmol of **1** and 0.004 mmol of **14**) was dissolved in pyridine (0.5 mL) and an excess of trifluoroacetic anhydride (0.2 mL) was added. After stirring at 20 °C for 15 h, the solvents were evaporated *in vacuo*, H_2O and CH_2Cl_2 were added and the phases separated. The aq phase was extracted with CH_2Cl_2 (10 mL, twice). The combined organic phases were dried ($MgSO_4$). Solvent evaporation afforded a brown oil

that was dissolved in MeOH (2.5 mL). A few drops of 12% aq NH_3 were added and the mixture was stirred at 20 °C for 3 h. After concentration under reduced pressure, the crude product was dissolved in pyridine (0.3 mL) and Ac_2O (0.2 mL). After stirring at 20 °C for 15 h, the mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel (1:2 EtOAc/light petroleum ether) to afford **15** (R_f 0.2, 2.54 mg, 33%) and **16** (R_f 0.1, 2.63 mg, 30%).

Data for **15:** $[\alpha]_{589}^{26}$ +7°, $[\alpha]_{577}^{26}$ +7°, $[\alpha]_{546}^{26}$ +9°, $[\alpha]_{435}^{26}$ +14°, $[\alpha]_{405}^{26}$ +17° (*c* 0.4, $CHCl_3$); UV (CH_3CN) 200 (9300); IR (film) 2965, 1745, 1695, 1445, 1370, 1230, 1135 cm^{-1}; ^1H NMR ($CDCl_3$, 298 K) δ 5.72 (ddd, $J_{1',2'}$ = 9.0 Hz, $J_{1',2'}$ = 6.1 Hz , J = 2.2 Hz, 1H, H-1'), 5.66 (br s, H-4), 5.52 (d, $J_{2,1}$ = 2.2 Hz, 1H, H-2), 5.50-5.48 (m, 1H, H-5'), 5.45 (d, $J_{1,2}$ = 2.2 Hz, 1H, H-1), 5.33 (dd, $J_{4',3'}$ = 7.3 Hz, $J_{4',5'}$ = 5.1 Hz, 1H, H-4'), 4.58 (q, $J_{3'a,2'a}$ = $J_{3'a,2'b}$ = $J_{3'a,4'}$ = 7.3 Hz, 1H, H-3'), 4.55 (dd, $J_{5,4}$ = $J_{5,6exo}$ = 4.6 Hz, 1H, H-5), 4.10 (dd, $J_{6'a,6'b}$ = 12.7 Hz, $J_{6'a,5'}$ = 5.0 Hz, 1H, Ha-6'), 3.92 (d, $J_{6endo,6exo}$ = 7.7 Hz, 1H, H_{endo}-6), 3.80 (dd, $J_{6'b,6'a}$ = 12.7 Hz, $J_{6'b,5'}$ = 3.7 Hz, 1H, Hb-6'), 3.66 (dd, $J_{6exo,6endo}$ = 7.7 Hz, $J_{6exo,5}$ = 4.6 Hz, 1H, H_{exo}-6), 3.20-3.09 (m, 1H, Ha -2'), 2.43 (dddd, $J_{2'b,2'a}$ = 12.6 Hz, J = 6.3 Hz, J = 6.2 Hz, J = 2.6 Hz, 1H, Hb-2'), 2.19, 2.18, 2.14, 2.11 (4s, 4 x 3H, 4Ac); ^{19}F-NMR ($CDCl_3$, 298 K) δ -76.2; ^{13}C NMR ($CDCl_3$, 298 K) δ 169.9, 169.7, 169.7, 169.5 (4s, 4C=O(Ac)), 156.5 (q, J_{C-F} = 37.1 Hz, CF_3), 129.2 (s, C-3), 128.2 (d, C-1'), 100.1 (d, C-1), 73.9 (d, C-5), 70.0 (d, C-5'), 69.6 (d, C-4'), 69.2 (d, C-4), 68.0 (d, C-2), 64.4 (t, C-6), 58.4 (d, C-3'), 49.4 (t, C-6'), 26.7 (t, C-2'), 21.0, 20.8, 20.6, 20.4 (4q, Ac); CI-MS (NH_3): 555 (M^++18, 96), 538 (M^++1, 1), 502 (12), 478 (M^+-CH_3COO, 76), 435 (45), 402 (73), 84 (100).

Anal. Calcd for $C_{22}H_{26}NF_3O_{11}$ (537.44): C, 49.17; H, 4.88; N, 2.61. Found: C, 49.07; H, 4.88; N, 2.52.

Data for **16:** $[\alpha]_{589}^{26}$ -27°, $[\alpha]_{577}^{26}$ -32°, $[\alpha]_{546}^{26}$ -33°, $[\alpha]_{435}^{26}$ -50°, $[\alpha]_{405}^{26}$ -49° (*c* 0.2, $CHCl_3$); UV (CH_3CN) 199 (3400); IR (film) 2980, 1745, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 298 K) δ 5.81-5.78 (m, 1H, H-1'), 5.50-5.46 (m, 2H, H-2, H-5'), 5.38-5.32 (m, 2H, H-5, H-4'), 4.94 (s, 1H, H-1), 4.61 (br s, 1H, H-4), 4.55-4.50 (m, 1H, H-3'), 4.41 (dd, $J_{6a,6b}$ = 12.0 Hz, $J_{6a,5}$ = 3.4 Hz, 1H, Ha-6), 4.18 (dd, $J_{6b,6a}$ = 12.0 Hz, $J_{6b,5}$ = 8.0 Hz, 1H, Hb-6), 4.12 (dd, $J_{6'a,6'b}$ = 12.5 Hz, $J_{6'a,5'}$ = 6.4 Hz, 1H, Ha-6'), 3.78 (dd, $J_{6'b,6'a}$ = 12.5 Hz, $J_{6'b,5'}$ = 4.0 Hz, 1H, Hb-6'), 3.34 (s, 3H, OMe), 2.90-2.81 (m, 1H, Ha-2'), 2.55 (dddd, $J_{2'b,2'a}$ = 14.9 Hz, J = 5.9 Hz, J = 5.8 Hz, J = 2.0 Hz, 1H, Hb-2'), 2.16, 2.14, 2.12, 2.11, 2.08 (5s, 5

x 3H, Ac); ^{19}F-NMR ($CDCl_3$, 298 K) δ -76.3; ^{13}C NMR ($CDCl_3$, 298 K) δ 170.7, 170.1, 169.8, 169.8, 169.5 (5s, 5 C=O(Ac)), 136.0 (s, C-3), 127.9 (d, C-1'), 106.1 (d, C-1), 78.1 (d, C-4), 73.9 (d), 71.4 (d), 69.8 (d), 69.6 (d), 62.9 (t, C-6), 58.0 (d, C-3'), 54.5 (q, OMe), 49.3 (t, C-6'), 29.3 (t, C-2'), 21.0, 20.9, 20.8, 20.5, 20.4 (5q, 5Ac); CI-MS (NH_3): 629 (M^++18, 100), 611 (M^+, 0.4), 580 (M^+-OMe, 60), 552 (M^+-CH_3COO, 11), 491 (35), 406 (45).

Anal. Calcd for $C_{25}H_{32}NF_3O_{13}$ (611.52): C, 49.10; H, 5.27; N, 2.29. Found: C, 49.00; H, 5.25; N, 2.18.

ACKNOWLEDGMENTS

We thank the Swiss National Science Foundation, the Fonds Herbette (Lausanne) and the Dirección General de Enseñanza Superior e Investigación Cientifica (Spain) (Grant Number PB 97-0730) for financial support, and the European COST D13 program (project D13/0001/99) for encouragements.

REFERENCES AND NOTES

1. Presented as a poster at the *First EuroConference on Carbohydrates in Drug Research*, Stintino, Sardinia, Italy, Sept. 16-19, 1999.
2. See e.g.: a) R. Schauer, *Adv. Carbohydr. Chem. Biochem.*, **40**, 131 (1982). b) A. E. Stütz, *Angew. Chem., Int. Ed. Engl.*, **35**, 1926 (1996). c) T. W. Rademacher, R. B. Parekh and R. A. Dwek, *Annu. Rev. Biochem.*, **57**, 785 (1988). d) O. Hindsgaul, D. P. Khare, D. P. Bach and R. U. Lemieux, *Can. J. Chem.*, **63**, 2653 (1985). e) T. Feizi, *Carbohydrate Recognition in Cellular Function*, Ciba Geigy Symposium 145; Wiley: Chichester 1989, p 62. f) R. Kornfeld and S. Kornfeld, *Annu. Rev. Biochem.*, **54**, 631 (1985). g) K. W. Moremen, R. B. Trimble and A. Herscovics, *Glycobiology*, **4**, 113 (1994). h) G. E. Rice and M. P. Bevilacqua, *Science*, **246**, 1303 (1989). i) C. A. Smith, T. Davis, D. Anderson, L. Solam, M. P. Beckmann, R. Jerzy, S. K. Dower, D. Cosman and R. G. Goodwin, *Science*, **248**, 1019 (1990). j) A. Varki, *Glycobiology*, **3**, 97 (1993). k) R. A. Dwek, *Chem. Rev.*, **96**, 683 (1996).
3. See e.g.: a) B. Ganem, *Acc. Chem. Res.*, **29**, 340 (1996) and references cited therein. b) L. A. G. M. van de Broek, D. J. Vermaas, B. M. Heskamp, C. A. A. van Boeckel, M. C. A. A. Tan, J. G. M. Bolscher, H. L. Ploegh, F. J. van Kemenade, R. E. Y. de Goede and F. Miedema, *Recl. Trav. Chim. Pays-Bas*, **112**, 82 (1993). c) G. C. Look, C. H. Fotsch and C.-H. Wong, *Acc. Chem. Res.*, **26**, 182 (1993). d) B. Winchester and G. W. J. Fleet, *Glycobiology*, **2**, 199 (1992). e) Y. Zheng, Y. T. Pan, N. Asano, R. J. Nash and A. D. Elbein, *Glycobiology*, **7**, 297 (1997) and references cited therein. f) R. Pal, G. M. Hoke and M. G.

Samgadharan, *Proc. Natl. Acad. Sci. U.S.A.*, **86**, 3384 (1989). g) V. A. Johnson, B. Walker, M. A. Barlow, T. J. Paradis, T. C. Chou and M. S. Hirsch, *Antimicrob. Agents Chemother.*, **33**, 53 (1989). h) A. Mehta, X. Lu, T. M. Block, B. S. Blumberg and R. A. Dwek, *Proc. Natl. Acad. Sci. U.S.A.*, **94**, 1822 (1997). i) P. B. Fischer, G. B. Karlsson, R. A. Dwek and F. M. Platt, *J. Virol.*, **70**, 7153 (1996). j) E. Fenouillet, M. J. Papandreou and I. M. Jones, *Virology*, **231**, 89 (1997). k) S. L. White, T. Nagai, S. K. Akijama, E. J. Reeves, K. Grzegorzewski and K. Olden, *Cancer Commun.*, **3**, 83 (1991). l) K. Olden, P. Breton, K. Grzegorzewski, Y. Yasuda, B. L. Gause, O. A. Oredipe, S. A. Newton and S. L. White, *Pharmacol. Ther.*, **50**, 285 (1991). m) P. E. Goss, J. Baptiste, B. Fernandez, M. Baker and J. W. Dennis, *Cancer Res.*, **54**, 1450 (1994).

4. a) K. Kraehenbuehl, S. Picasso and P. Vogel, *Bioorg. Med. Chem. Lett.*, **7**, 893 (1997). b) *idem*, *Helv. Chim. Acta*, **81**, 1439 (1998).
5. B. A. Johns, Y. T. Pan, A. D. Elbein and C. R. Johnson, *J. Am. Chem. Soc.*, **119**, 4856 (1997).
6. C. R. Johnson, M. W. Miller, A. Golebiowski, H. Sundram and M. B. Ksebati, *Tetrahedron Lett.*, **35**, 8991 (1994).
7. O. R. Martin, L. Liu and F. Yang, *Tetrahedron Lett.*, **37**, 1991 (1996).
8. M. A. Leeuwenburgh, S. Picasso, H. S. Overkleeft, G. A. van der Marel, P. Vogel and J. H. Van Boom, *Eur. J. Org. Chem.*, 1185 (1999).
9. a) A. Baudat and P. Vogel, *Tetrahedron Lett.*, **37**, 483 (1996). b) E. Frérot, C. Marquis and P. Vogel, *Tetrahedron Lett.*, **37**, 2023 (1996). c) A. Baudat and P. Vogel, *J. Org. Chem.*, **62**, 6252 (1997).
10. Y. H. Zhu and P. Vogel, *J. Org. Chem.*, **64**, 666 (1999).
11. C. Marquis, S. Picasso and P. Vogel, *Synthesis*, 1441 (1999).
12. F. Cardona, S. Valenza, S. Picasso, A. Goti and A. Brandi, *J. Org. Chem.*, **63**, 7311 (1998).
13. C.-H. Wong, L. Provencher, J. A. Porco, Jr., S.-H. Jung, Y.-F. Wang, L. Chen, R. Wang and D. H. Steepsma, *J. Org. Chem.*, **60**, 1492 (1995).
14. D. K. Thompson, C. N. Hubert and R. H. Wightman, *Tetrahedron*, **49**, 3827 (1993); see also: I. Robina, R. P. Gearing, J. G. Buchanan and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 2622 (1990).
15. J. G. Buchanan, V. B. Jigajinni, G. Singh and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 2377 (1987).
16. Attempts to reduce the aldol at low temperature with $LiAlH_4$, L-Selectride or $LiBH_4$ all failed to give the expected diol; only decomposition was observed.
17. Other conditions (e.g.: CF_3SO_3H, (+)-camphor-10-sulfonic acid, H_2SO_4, CH_3COOH/Ac_2O, gaseous HBr) for the methanolysis of **13** led to decomposition only.
18. X.-Y. Chen, T. M. Link and V. L. Schramm, *J. Am. Chem. Soc.*, **118**, 3067 (1996).
19. Evaluation of **1** and **14** as potential glycosidase inhibitiors will be reported in a forthcoming report.