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Stereoselective synthesis of 1,2-*cis*- and 2-deoxyglycofuranosyl azides from glycosyl halides

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Abstract

Protected 1,2-*cis* glycofuranosyl azides with α-D-ribo, β-D-arabino and 2-deoxy-2-fluoro-β-D-arabino configurations were efficiently prepared from the appropriate 1,2-*trans* glycosyl halides bearing non-participating O-2 substituent by inversion with sodium azide under phase transfer catalytic conditions (80–85% yields, 90–96% de). The same method failed to result in sufficiently good β-selectivity starting from 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**5α**) (40% de). The selectivity in favour of the protected 2-deoxy-β-D-*erythro*-pentofuranosyl azides was greatly improved (74–80% de) by treating **5α** and its *p*-chlorobenzoyl analog **6α** with cesium or potassium azide in dimethylsulfoxide at room temperature (83–85% yields).

Keywords: 1,2-*cis* Glycofuranosyl azides; 2-Deoxyglycofuranosyl azides; Glycosyl halides, azide displacement; Phase transfer catalysis

1. Introduction

Glycosyl azides are frequently applied carbohydrate building blocks, especially as precursors to glycosylamines and 1,2,3-triazole nucleosides [1]. As a part of our programme directed towards a linear synthesis of 1,2,3-triazolo[4,5-*c*]pyridine nucleosides via the 1,2,3-triazole nucleosides [2], several glycofuranosyl azides were required as starting materials. While those with the 1,2-trans configuration were conveniently prepared by the stannic chloride catalysed reaction of trimethylsilyl azide with glycosyl esters possessing a participating 2-*O*-acyl group [3], the synthesis of 1,2-*cis* and 2-deoxypentofuranosyl azides requires a fundamentally different approach. Displacement of protected pyranosyl halides with sodium azide in dipolar aprotic solvents [1], with sodium azide in a liquid two phase system in combination with a phase transfer catalyst [1,4,5] as well as with tetrabutylammonium azide [6] or *N*,*N*,*N*′,*N*′-tetramethylguanidinium azide (TMGA) [7], were known to be stereospecific and always occurred with complete inversion of the anomeric configuration. With this in mind, we chose to study the synthetic route to the selected glycofuranosyl azides with α-D-ribo, β-D-arabino and 2-deoxy-2-fluoro-β-D-arabino configurations, as well as 2-deoxy-β-D-*erythro*-pentofuranosyl azides starting from the corresponding readily available 1,2-*trans* glycosyl and 2-deoxy-α-D-*erythro*-pentofuranosyl halides, respectively.

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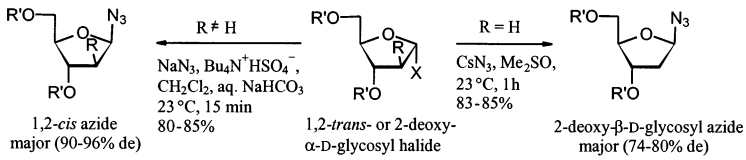
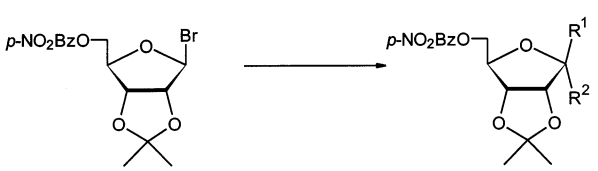
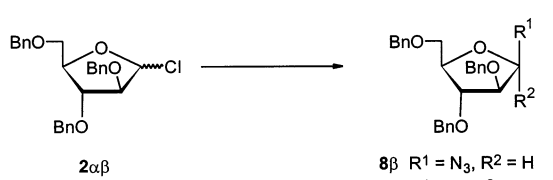
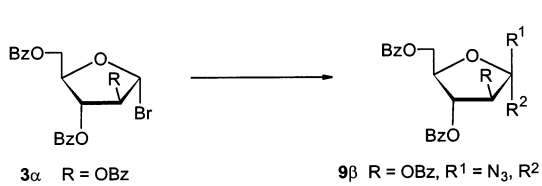


2. Results and discussion

1,2-cis *Glycofuranosyl azides.*—Several methods for the synthesis of 1,2-*cis* azides were examined in order to find the optimal conditions for inversion of 1,2-*trans* glycosyl halides **1β**, **2αβ**, **3α**, and **4α** by the azide ion. As shown in Table 1, the best selectivities (90–96% de) and yields in favour of 1,2-*cis* azides **7α**, **8β**, and **10β** were achieved by using the phase transfer catalytic (PTC) method of Roy and coworkers [5] using sodium azide (5 equivalents) and tetrabutylammonium hydrogensulfate (1 equivalent) in a two-phase system of dichloromethane and saturated aqueous sodium hydrogencarbonate solution (Method A). Under these conditions furanosyl halides reacted much faster (reaction time less than 15 min at room temperature) as compared with their pyranosyl counterparts (1–2 h) [5].







The first two examples in Table 1 indicate that the PTC substitution predominantly follows the S_N2 mechanism. For illustration, the reaction of the freshly prepared mixture of arabinosyl halides **2αβ** (α:β = 19:1) resulted in a mixture of azides **8α** and **8β** in exactly the opposite anomeric ratio (α:β = 1:19). A deviation from the clean inversion was noticed with substrates **3α** and **4α**, both being prone to generate oxonium intermediates. The formation of the α-azide **10α** from the pure starting 2-deoxy-2-fluoroarabinofuranosyl bromide **4α** points to the partial involvement of furanoxonium and/or 1,5-benzoxonium ions, as described previously [8]. On the other hand, reaction of the pure arabinosyl bromide **3α**, by Method A, was entirely non-selective (β:α = ~ 1:1), a fact, which may be readily explained by the competitive participation of the neighbouring 2-*O*-benzoyl group.

Nevertheless, the PTC method appeared substantially more selective in comparison with reactions of glycosyl halides with azide ion in polar aprotic solvents, like the treatment of **1β** with sodium azide in hexamethylphosphoric triamide (Method B; β:α = 17:3) [3a], the treatment of **2αβ** with sodium azide in boiling acetonitrile (β:α = 4:1) [9], as well as the homogeneous one-phase reactions of **4α** with TMGA in acetonitrile (Method C1; β:α = 4:1) or in dichloromethane (Method C2; β:α = 17:3).

The structures of previously unknown azides **10β** and **10α** were confirmed by X-ray analysis of the former (details will be given in a separate publication) and ^{13}C NMR spectroscopy. In particular, the magnitude of C(1)–F coupling constants in ^{13}C NMR spectra of **10α** ($J_{C(1)-F}$ 35.3 Hz) and **10β** ($J_{C(1)-F}$ 17.1 Hz) was in excellent agreement with the typical values for 2′-deoxy-2′-fluoro-α-arabinofuranosides (35–36 Hz) and the corresponding β anomers (16–17 Hz) [10].

*2-Deoxy-β-*D-erythro-*pentofuranosyl azides.*—2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-

Table 1
Synthesis of 1,2-*cis*- and 2-deoxyglycofuranosyl azides from the corresponding halides

Entry	Substrate	Method [a]	Product(s)	Yield (%) [b]	β:α [c]	$[\alpha]_D^{25}$ (*c* in $CHCl_3$) (°)
1	**1β**	A	**7β**	0.6	1:49	−162 (0.40)
			7α	80		+12.8 (1.00)
		B	**7β**	9	3:17	−165 (1.00)
			7α	73		+11.5 (1.00)
2	**2αβ** [d]	A	**8β**	83	19:1	−116 (1.0) [e]
			8α	3.2		+115 (1.0) [f]
3	**3α**	A	**9β**	35	1.3:1	−135 (4.00)
			9α	41		+71 (4.00)
4	**4α**	A	**10β**	85	19:1	−68 (2.00)
		C1	**10β**	71	4:1	
			10α	19		+225 (1.00)
		C2	**10β**+**10α**	87	17:3	
5	**5α**	A	**11β**+**11α**		7:3	
		D	**11β**	83	9:1	−93 (1.00)
			11α	8		+213 (1.00)
6	**6α**	D	**12β**	85	87:13	−83 (1.00)
			12α	4		+208 (1.00)

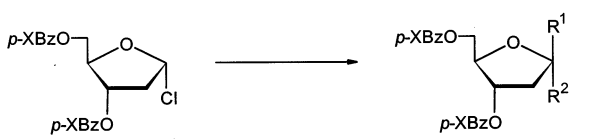
[a] Method A: NaN_3 (5 equiv), tetrabutylammonium hydrogensulfate (1 equiv), CH_2Cl_2, satd aq $NaHCO_3$, rt, 15 min; Method B: NaN_3 (~3 equiv), $(Me_2N)_3PO$, 0 °C, 1 h (see lit. [3a]); Method C: TMGA (1 equiv), rt, 15 min, (1) in CH_3CN, (2) in CH_2Cl_2; Method D: CsN_3 (1.5 equiv), Me_2SO, rt, 1 h.
[b] Isolated yields.
[c] Anomeric ratio determined from the ^1H NMR spectrum of the crude product mixture.
[d] α:β = 19:1.
[e] Lit. $[\alpha]_D^{25}$ −118.2° (*c* 1.0, $CHCl_3$) [9].
[f] Lit. $[\alpha]_D^{25}$ +111.5° (*c* 1.0, $CHCl_3$) [9].

pentofuranosyl chloride (**5α**) and its *p*-chlorobenzoyl analog **6α** are traditional substrates for the synthesis of 2′-deoxyribonucleosides, which are readily available in anomerically pure, crystalline forms, were selected as convenient starting materials for the β-selective synthesis of the title azides. Glycosylation of **5α** was reported to occur with inversion at the anomeric position and competing concomitant anomerisation to the more reactive β-chloride. The latter process apparently reduced the selectivity of glycosylation and was especially sensitive to solvent effects [11]. Therefore, a number of displacement experiments of **5α** with different azide donors were carried out in order to find proper inversion conditions.

The aforementioned PTC reaction of **5α** resulted in a disappointingly low β-selectivity (entry 5; β:α = 7:3). Conditions were modified by addition of compound **5α** to a solution or saturated suspension of an azide donor (5 equivalents) in various anhydrous solvents (4 mL per mmol of **5α**) at room temperature. 15-Crown-5 (~ 0.35 equivalents) was used occasionally as an additive in combination with sodium azide for conducting the reaction in solvents of lower dielectric constant. A practically useful β:α ratio of 4:1 was achieved with sodium azide in acetonitrile, sodium azide in combination with 15-crown-5 in benzene, lithium azide in dimethylsulfoxide and tetrabutylammonium azide in carbon tetrachloride, while at the other extreme, systems of lithium azide in tetrahydrofuran, acetonitrile, 1,4-dioxane or acetone as well as tetrabutylammonium azide in 1,2-dichloroethane produced almost equal proportions of both anomeric azides. Since the compound **5α** was reported to resist anomerisation in benzene and pyridine [11], a relatively poor selectivity observed in these solvents under different conditions (β:α = 1.6–4:1) appeared particularly unrewarding.

In a single case, a dramatic increase in the β:α ratio (9:1) was noticed when cesium azide in dimethylsulfoxide was used. We succeeded to optimise this procedure only with respect to the economy of reagents (1.5 equivalents of cesium azide and 1 mL of dimethylsulfoxide per mmol of **5α**) without increasing the β:α ratio. In separate experiments, using the optimal ratio of reagents, cesium azide was compared with the other two azide donors. While TMGA proved to be much inferior (β:α = 4:1), the use of potassium azide afforded the identical β:α ratio (9:1).

The reaction of the *p*-chlorobenzoate **6α** in dimethylsulfoxide in the optimal ratio of reactants previously used on **5α**, gave the β:α ratios of 7:3 for lithium and sodium azide and 22:3 for potassium and cesium azide. The latter two azide donors are obviously the best and equivalent alternatives among those examined for the β-selective displacement of chlorides **5α** and **6α** by the azide ion. Preparative reactions using cesium azide furnished β-azides **11β** and **12β** in 83 and 85% yields along with minor amounts of α isomers **11α** and **12α** in 8 and 4% yields, respectively, though after rather tedious chromatographic purification.



5α X = Me
6α X = Cl

11β X = Me, $R^1 = N_3$, R^2 = H
11α X = Me, R^1 = H, $R^2 = N_3$
12β X = Cl, $R^1 = N_3$, R^2 = H
12α X = Cl, R^1 = H, $R^2 = N_3$

The anomeric configuration of products was determined by ^{1}H NMR spectroscopy in a similar way as described for 2′-deoxyribonucleosides, i.e., from the splitting pattern of the anomeric proton [12] as well as by the characteristic difference in chemical shifts for protons H-4, H-5a and H-5b of 3,5-di-*O*-acyl derivatives [13]. Thus, the 'pseudotriplet' was observed for the anomeric proton of **11β** and **12β** due to nearly equal couplings to H-2α and H-2β (~ 5 Hz), while the well resolved doublet of doublets were observed for the corresponding α anomers due to unequal couplings to the adjacent protons. In addition, α anomers exhibit a large chemical shift difference between the H-4, H-5a and H-5b resonances compared to their near coincidence in β anomers. An additional support for the configurational assignment may be found in the optical rotation values for individual anomers. As generally holds true, the β-D-anomers display more negative values than the appropriate α-D-anomers (see Table 1).

3. Experimental

General procedures.—Flash column chromatography was carried out on Silica Gel 60 (E. Merck, 40–63 μm) and thin-layer chromatography on Silica Gel 60 F_{254} (E. Merck) with detection by UV light. Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter for solutions in $CHCl_3$ at 25 °C. IR spectra were recorded with a Bio-Rad FTS 15/18 spectrometer and mass spectra with a VG Analytical Autospec Q spectrometer. ^{1}H (299.9 MHz, internal Me_4Si), ^{13}C (75.4 MHz), and ^{19}F NMR (282.2 MHz, internal $CFCl_3$) spectra were recorded with a Varian VXR-300 instrument for solutions in $CDCl_3$ (δ_C 77.00 ppm).

Materials.—2,3-*O*-Isopropylidene-5-*O*-(4-nitrobenzoyl)-β-D-ribofuranosyl bromide (**1β**) [14], tri-*O*-benzyl-α,β-D-arabinofuranosyl chloride (**2αβ**) [15], tri-*O*-benzoyl-α-D-arabinofuranosyl bromide (**3α**) [16], 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**4α**) [8], LiN_3, KN_3, and CsN_3 [17], TMGA [18], and tetrabutylammonium azide [19] were prepared following the reported procedures. 2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**5α**) [20] and 2-deoxy-3,5-di-*O*-(4-chlorobenzoyl)-α-D-*erythro*-pentofuranosyl chloride (**6α**) [21] were synthesised as crude crystalline solids (the latter was contaminated with ~ 10% of the methyl α,β-D-glycosides, from which it was prepared) and used without further purification. Both materials were kept in vacuum desiccator over P_4O_{10} and NaOH for several months without observable decomposition.

*General procedure for the PTC synthesis of 1,2-*cis *glycosyl azides (Method A).*—To a solution of glycosyl halide (1 equiv) in CH_2Cl_2 (10 mL/g of halide) was added a solution of

tetrabutylammonium hydrogensulfate (1 equiv) and NaN_3 (5 equiv) in satd aq $NaHCO_3$ (10 mL/g of halide). The two-phase mixture was vigorously stirred at rt for 15 min, followed by addition of EtOAc (ten times the volume of CH_2Cl_2). The organic phase was separated, successively washed with satd aq $NaHCO_3$, water (3 ×), and brine, and dried (Na_2SO_4). Evaporation under reduced pressure afforded a mixture of products, which were separated and purified as described for individual preparations.

2,3-O-Isopropylidene-5-O-(4-nitrobenzoyl)-β- (**7β**) *and -α-D-ribofuranosyl azide* (**7α**).—The reaction of **1β** (3.92 g, 9.75 mmol) by Method A afforded the crude product mixture (β:α = 1:49) as a yellow solid. Four crystallisations from *tert*-butyl methyl ether yielded pure **7α** (1.90 g, 54%) with mp 101–102 °C, lit. mp 100–101 °C [3a]. The residue, obtained after concentration of the mother liquor, was chromatographed with 1:4:10 CH_2Cl_2–Et_2O–pentane, followed by ether to give, first, **7β** (23 mg, 0.6%) as light yellow plates with mp 122.5–123.5 °C after crystallisation from EtOH, lit. mp 121–121.5 °C [3a], and **7α** (0.94 g, 26%) with mp 101.5–102.5 °C. Both compounds were identical with products obtained by treatment of **1β** with NaN_3 in $(Me_2N)_3PO$ (Method B [3a]).

Tri-O-benzyl-β- (**8β**) *and -α-D-arabinofuranosyl azide* (**8α**).—The reaction of **2αβ** (α:β = 19:1), freshly prepared from 2,3,5-tri-*O*-benzyl-1-*O*-(4-nitrobenzoyl)-D-arabinofuranose (50.1 g, 88 mmol) [15], by Method A afforded the crude product mixture (38.5 g, 98%; β:α = 19:1), which was resolved by chromatography (15:2 petroleum ether–Et_2O). Both products were isolated as colourless liquids.

α-Azide **8α**: 1.24 g (3.2%); R_f 0.49 (4:1 petroleum ether–Et_2O); IR (film): ν 2107 (N_3), 1241, 1097, 1027, 740, and 699 cm^{-1}; ^1H NMR: δ 3.60 (d, 2 H, J 4.9 Hz, H-5a,5b), 3.90 (dd, 1 H, H-2), 3.97 (dd, 1 H, H-3), 4.36 (pseudo q, 1 H, J 5.1 Hz, H-4), 4.43 and 4.51 (2 d, each 1 H, J_{gem} 11.8 Hz, CH_2Ph), 4.48 and 4.53 (2 d, each 1 H, J_{gem} 12.2 Hz, CH_2Ph), 4.55 (s, 2 H, CH_2Ph), 5.41 (br d, 1 H, H-1), 7.22-7.38 (m, 15 H, Ph–H), $J_{1,2}$ 1.6, $J_{2,3}$ 2.6, $J_{3,4}$ 5.5 Hz; ^{13}C NMR: δ 69.39 (C-5), 72.01, 72.12, and 73.37 (3 *C*H_2Ph), 82.96 and 83.03 (C-3,4), 87.34 (C-2), 94.45 (C-1), 127.6–128.5, 136.96, 137.39, and 137.82 (Ph–C); CIMS (NH_3): m/z 463 ($[M + NH_4]^+$, < 1%), 418 ($[MH - N_2]^+$, 8), 91 ($[PhCH_2]^+$, 100). Anal. Calcd for $C_{26}H_{27}N_3O_4$ (445.52): C, 70.10; H, 6.11; N, 9.43. Found: C, 70.27; H, 6.11; N, 9.56.

β-Azide **8β**: 32.4 g (83%); R_f 0.33; IR (film): ν 2117 (N_3), 1251, 1115, 1084, 1071, 740, and 698 cm^{-1}; ^1H NMR: δ 3.59 (d, 2 H, J 5.6 Hz, H-5a,5b), 4.04–4.15 (m, 3 H, H-2,3,4), 4.54 and 4.63 (2 d, each 1 H, J_{gem} 11.8 Hz, CH_2Ph), 4.56 and 4.60 (2 d, each 1 H, J_{gem} 10.1 Hz, CH_2Ph), 4.55 (s, 2 H, CH_2Ph), 5.19 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 7.2–7.4 (m, 15 H, Ph–H); ^{13}C NMR: δ 70.73 (C-5), 72.27, 72.75, and 73.37 (3 *C*H_2Ph), 80.89, 81.87, and 83.61 (C-2,3,4), 90.13 (C-1), 127.6–128.5, 137.05, 137.61, and 137.86 (Ph–C); CIMS (NH_3): m/z 463 ($[M + NH_4]^+$, 1%), 418 ($[MH - N_2]^+$, 22), 91 ($[PhCH_2]^+$, 100). Anal. Calcd for $C_{26}H_{27}N_3O_4$ (445.52): C, 70.10; H, 6.11; N, 9.43. Found: C, 70.27; H, 5.97; N, 9.45.

Tri-O-benzoyl-β- (**9β**) *and -α-D-arabinofuranosyl azide* (**9α**).—The reaction of **3α** (8.6 g, 16.4 mmol) by Method A afforded the crude product mixture (β:α = 14:11), which was resolved by chromatography (8:1:1 petroleum ether–Et_2O–CH_2Cl_2). Both products were isolated as colourless oils which crystallised from MeOH.

α-Azide **9α**: 3.30 g (41%); R_f 0.35 (eluent); mp 88–90.5 °C (colourless crystals); IR (film): ν 2114 (N_3), 1725 (C=O), 1267 (C–O, benzoate), 1108, 1072, and 710 cm^{-1} (benzoate); ^1H NMR: δ 4.70 (dd, 1 H, H-5a), 4.74–4.78 (m, 1 H, H-4), 4.85 (dd, 1 H, H-5b), 5.43 (dd, 1 H, H-2), 5.62 (ddd, 1 H, H-3), 5.74 (dd, 1 H, H-1), 7.30–7.65 and 7.98–8.12 (2 m, 15 H, Ph–H); $J_{1,2}$ 0.6, $J_{1,3}$ 0.9, $J_{2,3}$ 1.2, $J_{3,4}$ 4.3, $J_{4,5a}$ 5.1, $J_{4,5b}$ 3.0, $J_{5a,5b}$ 11.0 Hz; ^{13}C NMR: δ 63.41 (C-5), 77.53 (C-3), 81.76 (C-2), 83.00 (C-4), 94.57 (C-1), 128.3–129.9, 133.13, 133.71, and 133.73 (Ph–C), 165.28, 165.57, and 166.10 (3 CO); EIMS: m/z 445 ($[M - N_3]^+$, 7%), 105 ($[PhCO]^+$, 100), 77 (Ph^+, 48). Anal. Calcd for $C_{26}H_{21}N_3O_7$ (487.47): C, 64.06; H, 4.34; N, 8.62. Found: C, 64.15; H, 4.38; N, 8.59.

β-Azide **9β**: 2.75 g (35%); R_f 0.24; mp 78–80 °C (colourless needles); IR (film): ν 2117

(N_3), 1724 (C=O), 1267 (C–O, benzoate), 1110, 1099, 1073, and 710 cm^{-1} (benzoate); ^1H NMR: δ 4.53 (ddd, 1 H, H-4), 4.69 (dd, 1 H, H-5a), 4.81 (dd, 1 H, H-5b), 5.63 (dd, 1 H, H-2), 5.87–5.90 (m, 2 H, H-1,3), 7.36–7.63 and 8.01–8.12 (2 m, 15 H, Ph–H); $J_{1,2} \sim 5$, $J_{2,3} \sim 6$, $J_{4,5a}$ 6.1, $J_{4,5b}$ 4.4, $J_{5a,5b}$ 11.8 Hz; ^{13}C NMR: δ 64.43 (C-5), 75.67 (C-3), 76.58 (C-2), 79.50 (C-4), 89.95 (C-1), 128.3–130.0, 133.10, 133.69, and 133.75 (Ph–C), 165.52, 165.57, and 166.12 (3 CO); EIMS: m/z 445 ($[M - N_3]^+$, 22%), 105 ($[PhCO]^+$, 100), 77 (Ph^+, 17). Anal. Calcd for $C_{26}H_{21}N_3O_7$ (487.47): C, 64.06; H, 4.34; N, 8.62. Found: C, 64.21; H, 4.45; N, 8.62.

*3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-* (**10β**) *and -α-*D*-arabinofuranosyl azide* (**10α**)

Under PTC conditions (Method A). The reaction of **4α** (47.7 g, 113 mmol) afforded the crude product mixture (β:α = 19:1) in a quantitative yield. Crystallisation from MeOH yielded pure β-azide **10β** (37.04 g, 85%) as white needles with mp 89–90.5 °C; IR (film): ν 2123 (N_3), 1726 (C=O), 1272 (C–O, benzoate), 1112, 1070, and 710 cm^{-1} (benzoate); ^1H NMR: δ 4.44 (ddd, 1 H, H-4), 4.65 (ddd, 1 H, H-5a), 4.73 (ddd, 1 H, H-5b), 5.23 (ddd, 1 H, H-2), 5.34 (m, 1 H, H-1), 5.69 (dm, 1 H, H-3), 7.4–7.65 and 8.0–8.12 (2 m, 10 H, Ph–H); $J_{1,2}$ and $J_{2,3} \sim 3.5$, $J_{2,F}$ 46.9, $J_{4,5a}$ 5.4, $J_{4,5b}$ 4.4, $J_{5a,F}$ and $J_{5b,F}$ 0.7, $J_{5a,5b}$ 12.0 Hz; ^{13}C NMR: δ 63.87 (C-5), 76.07 (d, $J_{3,F}$ 27.2 Hz, C-3), 80.15 (d, $J_{4,F}$ 3.5 Hz, C-4), 89.30 (d, $J_{1,F}$ 17.1 Hz, C-1), 93.82 (d, $J_{2,F}$ 196.9 Hz, C-2), 128.4–129.8, 133.15, and 133.87 (Ph–C), 165.17 and 166.11 (2 CO); ^{19}F NMR: δ −202.5 (m); EIMS: m/z 343 ($[M - N_3]^+$, 31%), 122 ($[PhCO_2H]^+$, 10), 105 ($[PhCO]^+$, 100); CIMS (NH_3): m/z 403 ($[M + NH_4]^+$, 2), 386 (MH^+, 1), 358 ($[MH - N_2]^+$, 13), 343 ($[M - N_3]^+$, 21), 122 ($[PhCO_2H]^+$, 23), 105 ($[PhCO]^+$, 100). Anal. Calcd for $C_{19}H_{16}FN_3O_5$ (385.36): C, 59.22; H, 4.19; N, 10.90. Found: C, 59.14; H, 4.23; N, 10.82.

With TMGA (Method C). To a solution of **4α** (2.11 g, 5 mmol) in dry MeCN (5 mL) was added TMGA (0.79 g, 5 mmol), the resulting solution was stirred at rt for 15 min and then concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), washed with water (2 × 5 mL) and dried (Na_2SO_4). Evaporation afforded a mixture of anomers (1.85 g, 96%; β:α = 4:1), which was resolved by chromatography (2:1 petroleum ether–1% AcOH in EtOAc) to give, first, **10α** (372 mg, 19%), R_f 0.27 (eluent), and **10β** (1.38 g, 71%), R_f 0.14, both as colourless oils.

α-Azide **10α**: IR (film): ν 2115 (N_3), 1723 (C=O), 1268 (C–O, benzoate), 1109, 1096, 1073, and 710 cm^{-1} (benzoate); ^1H NMR: δ 4.64 (dd, 1 H, H-5a), 4.71 (ddd, 1 H, H-4), 4.76 (dd, 1 H, H-5b), 5.05 (d, 1 H, H-2), 5.54 (dd, 1 H, H-3), 5.75 (d, 1 H, H-1), 7.4–7.64 and 8.04–8.1 (2 m, 10 H, Ph–H); $J_{1,F}$ 12.5, $J_{2,F}$ 48.8, $J_{3,4}$ 3.7, $J_{3,F}$ 20.5, $J_{4,5a}$ 3.9, $J_{4,5b}$ 3.2, $J_{5a,5b}$ 10.7 Hz; ^{13}C NMR: δ 63.31 (C-5), 77.12 (d, $J_{3,F}$ 30.7 Hz, C-3), 83.32 (C-4), 93.82 (d, $J_{1,F}$ 35.3 Hz, C-1), 97.68 (d, $J_{2,F}$ 184.3 Hz, C-2), 128.4–129.9, 133.18, and 133.82 (Ph–C), 165.43 and 166.10 (2 CO); ^{19}F NMR: δ −187.57 (ddd, J 49.0, 20.5, 12.6 Hz); FABMS: m/z 386 (MH^+, 7%), 358 ($[MH - N_2]^+$, 2), 343 ($[M - N_3]^+$, 30), 105 ($[PhCO]^+$, 100). Anal. Calcd for $C_{19}H_{16}FN_3O_5$ (385.36): C, 59.22; H, 4.19; N, 10.90. Found: C, 59.14; H, 4.18; N, 10.83.

The above reaction carried out in CH_2Cl_2 afforded both products (β:α = 17:3) in 87% combined yield.

*2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-* (**11β**) *and -α-*D*-erythro-pentofuranosyl azide* (**11α**).—To a mixture of CsN_3 (11.8 g, 67.5 mmol) in dry Me_2SO (45 mL), previously stirred at rt for 30 min, was added chloride **5α** (17.50 g, 45 mmol). The mixture was vigorously stirred for 1 h at 16–18 °C in an inert atmosphere and then diluted with EtOAc (200 mL). The insoluble material was filtered and washed with EtOAc (100 mL). The filtrate was washed with water (2 × 200 mL), brine (150 mL) and dried (Na_2SO_4). Evaporation afforded the crude product mixture (17.30 g, 97%; β:α = 9:1), which was resolved by chromatography using 25:2 and 100:9 mixtures of petroleum ether–1% AcOH in EtOAc.

β-Azide **11β**: 14.74 g (83%); R_f 0.17 (10:1 hexane–1% AcOH in EtOAc); mp 72.5–73 °C (needles from EtOH); IR (film): ν 2113 (N_3), 1722 (C=O), 1612, 1272 (C–O, toluate), 1180, 1103, and 754 cm^{-1} (*p*-toluoyl); ^1H NMR: δ 2.396 and 2.407 (2 s, each 3 H, 2 Ar–CH_3),

2.414 (m, 2 H, H-2α,2β), 4.48–4.64 (m, 3 H, H-4,5a,5b), 5.57 (m, 1 H, H-3), 5.72 (pseudo t, 1 H, $J_{1,2\alpha}$ and $J_{1,2\beta} \sim 5.1$ Hz, H-1), 7.23 and 7.24 (2 m, 4 H, H-3,5 of *p*-toluoyl), 7.90 and 7.98 (2 m, 4 H, H-2,6 of *p*-toluoyl); ^{13}C NMR: δ 21.64 (2 Ar–*C*H$_3$), 38.61 (C-2), 64.15 (C-5), 74.84 (C-3), 82.64 (C-4), 92.05 (C-1), 126.49 and 126.88 (C-1 of *p*-toluoyl), 129.09 and 129.14 (C-3,5 of *p*-toluoyl), 129.67 and 129.70 (C-2,6 of *p*-toluoyl), 143.82 and 144.24 (C-4 of *p*-toluoyl), 165.87 and 166.22 (2 CO); EIMS: *m*/*z* 353 ([M − N$_3$]$^+$, 14%), 119 ([*p*-MePhCO]$^+$, 100), 91 ([*p*-MePh]$^+$, 42). Anal. Calcd for $C_{21}H_{21}N_3O_5$ (395.42): C, 63.79; H, 5.35; N, 10.63. Found: C, 63.87; H, 5.36; N, 10.58.

α-Azide **11α**: 1.44 g (8%); R_f 0.12; mp 88–88.5 °C (needles from EtOH); IR (film): *v* 2110 (N$_3$), 1721 (C=O), 1272 (C–O, ester), 1611, 1179, 1103, and 752 cm^{-1} (*p*-toluoyl); ^{1}H NMR: δ 2.23 (ddd, 1 H, H-2α), 2.405 and 2.414 (2 s, each 3 H, 2 Ar–CH$_3$), 2.55 (ddd, 1 H, H-2β), 4.52 (dd, 1 H, H-5a), 4.62 (dd, 1 H, H-5b), 4.71 (ddd, 1 H, H-4), 5.50 (ddd, 1 H, H-3), 5.71 (dd, 1 H, H-1), 7.23 and 7.25 (2 m, 4 H, H-3,5 of *p*-toluoyl), 7.91 and 7.96 (2 m, 4 H, H-2,6 of *p*-toluoyl); $J_{1,2\alpha}$ 1.2, $J_{1,2\beta}$ 6.4, $J_{2\alpha,2\beta}$ 14.7, $J_{2\alpha,3}$ 1.5, $J_{2\beta,3}$ 7.3, $J_{3,4}$ 2.7, $J_{4,5a}$ 4.4, $J_{4,5b}$ 3.4, $J_{5a,5b}$ 12.0 Hz; ^{13}C NMR: δ 21.62 and 21.65 (2 Ar–*C*H$_3$), 38.78 (C-2), 63.93 (C-5), 74.52 (C-3), 83.52 (C-4), 91.98 (C-1), 126.62 and 126.80 (C-1 of *p*-toluoyl), 129.15 (C-3,5 of *p*-toluoyl), 129.61 and 129.77 (C-2,6 of *p*-toluoyl), 143.94 and 144.17 (C-4 of *p*-toluoyl), 166.07 and 166.22 (2 CO); CIMS (NH$_3$): *m*/*z* 413 ([M + NH$_4$]$^+$, 1.3%), 368 ([MH − N$_2$]$^+$, 1.7), 353 ([M − N$_3$]$^+$, 14), 136 ([*p*-MePhCO$_2$H]$^+$, 46), 119 ([*p*-MePhCO]$^+$, 100), 91 ([*p*-MePh]$^+$, 50). Anal. Calcd for $C_{21}H_{21}N_3O_5$ (395.42): C, 63.79; H, 5.35; N, 10.63. Found: C, 63.69; H, 5.37; N, 10.55.

3,5-Di-O-*(4-chlorobenzoyl)-2-deoxy-β*- (**12β**) *and* -α-D-erythro-*pentofuranosyl azide* (**12α**). —The reaction of the chloride **6α** (15.0 g, containing 13.2 mmol of the pure material), as described for **5α**, afforded the crude product mixture (14.84 g, β:α = 87:13, containing also ∼10% of methyl 3,5-di-*O*-(4-chlorobenzoyl)-2-deoxy-α,β-D-*erythro*-pentofuranoside), which was resolved by chromatography using 25:2, 100:9, and 10:1 mixtures of petroleum ether–1% AcOH in EtOAc. Compounds were eluted in the following order: β-azide **12β** (R_f 0.21, 10:1 petroleum ether–1% AcOH in EtOAc), α,β-glycoside (R_f 0.17), α-azide **12α** (R_f 0.14) and β,α-glycoside (R_f 0.10).

β-Azide **12β**: 11.29 g (85%); mp 86.5–87 °C (EtOH); IR (film): *v* 2114 (N$_3$), 1724 (C=O), 1595, 1270 (C–O, ester), 1240, 1095, and 758 cm^{-1}; ^{1}H NMR: δ 2.42 (m, 2 H, H-2α,2β), 4.51–4.65 (m, 3 H, H-4,5a,5b), 5.58 (dt, 1 H, *J* 5.6, 5.6, and 2.7 Hz, H-3), 5.74 (pseudo t, 1 H, $J_{1,2\alpha}$ and $J_{1,2\beta} \sim 5$ Hz, H-1), 7.41 and 7.42 (2 m, 4 H, H-3,5 of aroyl), 7.94 and 8.02 (2 m, 4 H, H-2,6 of aroyl); ^{13}C NMR: δ 38.50 (C-2), 64.39 (C-5), 75.14 (C-3), 82.46 (C-4), 92.06 (C-1), 127.59 and 128.04 (C-1 of aroyl), 128.76 and 128.83 (C-3,5 of aroyl), 131.00 and 131.05 (C-2,6 of aroyl), 139.66 and 140.04 (C-4 of aroyl), 164.95 and 165.26 (2 CO); CIMS (NH$_3$): *m*/*z* 453 ([M + NH$_4$]$^+$, 27%), 393 ([M − N$_3$]$^+$, 29), 156 ([*p*-ClPhCO$_2$H]$^+$, 53), 139 ([*p*-ClPhCO]$^+$, 100). Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_5$ (436.26): C, 52.31; H, 3.47; N, 9.63. Found: C, 52.43; H, 3.53; N, 9.62.

α-Azide **12α**: 0.52 g (4%); mp 97.5–98.5 °C (needles from EtOH); IR (film): *v* 2111 (N$_3$), 1723 (C=O), 1595, 1269 (C–O, ester), 1240, 1093, and 758 cm^{-1}; ^{1}H NMR: δ 2.24 (ddd, 1 H, H-2α), 2.53 (ddd, 1 H, H-2β), 4.53 (dd, 1 H, H-5a), 4.62 (dd, 1 H, H-5b), 4.70 (ddd, 1 H, H-4), 5.48 (ddd, 1 H, H-3), 5.73 (dd, 1 H, H-1), 7.42 and 7.44 (2 m, 4 H, H-3,5 of aroyl), 7.96 and 8.00 (2 m, 4 H, H-2,6 of aroyl); $J_{1,2\alpha}$ 1.0, $J_{1,2\beta}$ 6.2, $J_{2\alpha,2\beta}$ 14.7, $J_{2\alpha,3}$ 1.3, $J_{2\beta,3}$ 7.3, $J_{3,4}$ 2.7, $J_{4,5a}$ 4.6, $J_{4,5b}$ 3.9, $J_{5a,5b}$ 12.0 Hz; ^{13}C NMR: δ 38.65 (C-2), 64.17 (C-5), 74.81 (C-3), 83.22 (C-4), 91.97 (C-1), 127.72 and 127.94 (C-1 of aroyl), 128.84 and 128.86 (C-3,5 of aroyl), 130.98 and 131.14 (C-2,6 of aroyl), 139.78 and 140.02 (C-4 of aroyl), 165.18 and 165.30 (2 CO); CIMS (NH$_3$): *m*/*z* 453 ([M + NH$_4$]$^+$, 0.8%), 393 ([M − N$_3$]$^+$, 5), 156 ([*p*-ClPh-CO$_2$H]$^+$, 70), 139 ([*p*-ClPhCO]$^+$, 100). Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_5$ (436.26): C, 52.31; H, 3.47; N, 9.63. Found: C, 52.46; H, 3.53; N, 9.46.

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