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Note

Cyclic sulfates in the regioselective synthesis of 5- and 6-amino and 5- and 6-fluorohexofuranoses

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Abstract

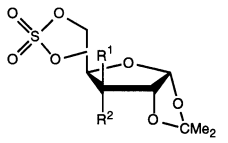
Cyclic sulfates of 5,6- and 3,5-D-glucofuranose were used to prepare 6- and 5-azido (amino) and 6- and 5-fluoro derivatives of 1,2-*O*-isopropylidenehexofuranoses (D-*gluco* and L-*ido* configurations). The reactions were completely regioselective and, in the case of stereogenic centers (substitution at C-5), completely stereoselective.

Keywords: Cyclic sulfates; Amino sugars; Azido sugars; Fluoro sugars

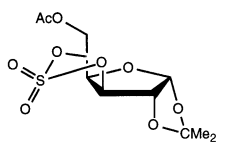
The cyclic sulfates of *vic*-diols are synthetic equivalents of epoxides and cyclic sulfites which have been widely used in organic synthesis [1,2]. However, their applications in carbohydrate chemistry are limited [1,3–11].

In a recent letter [12], we have communicated the preliminary results on the use of glucofuranose cyclic sulfates in the preparation of 6- and 5-azido(fluoro) aldofuranose derivatives. In this paper, we go further into the preparation of 5,6- and 3,5-glucofuranose cyclic sulfates and the nucleophilic opening of the ester rings with sodium azide and different fluoronucleophiles.

The previously described [3] D-glucofuranose (**1**, **2**) and D-allofuranose (**4**) 5,6-cyclic sulfates and the new D-glucofuranose 5,6- (**3**) and 3,5- (**5**) cyclic sulfates were used as starting materials. Compounds **3** and **5** were prepared from the corresponding diols [13,14] through the cyclic sulfites, which were obtained as mixtures of diastereomers that were directly oxidized [2] with the reagent sodium periodate–ruthenium trichloride hydrate.



	R^1	R^2
1	OAc	H
2	OBn	H
3	OMs	H
4	H	N_3



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The nucleophilic opening of the sulfate ring of compounds **1**–**4** with sodium azide produced the 6-azido-6-deoxy-D-glucofuranose derivatives **6**–**9** in high yields in a completely regioselective manner. In the case of the 3-*O*-mesyl derivative **8**, no displacement of the mesyloxy group at C-3 was observed under the conditions used for the ring opening of the cyclic sulfate **3**; this mesyloxy group was stable even on treatment of **3** or **8** with sodium azide at 105 °C in DMF for 6 h. The nucle-

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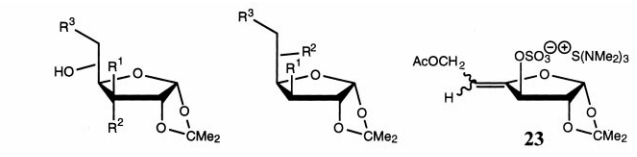
ophilic sulfate ring opening of the non-vicinal cyclic sulfate **5**, using the same work-up as for the preparation of **6**–**9**, produced exclusively the 5-azido-5-deoxy-L-idofuranose derivative **11**, as seen from the downfield shift of the H-5 and C-5 resonances.



	R^1	R^2	R^3
6	OAc	H	N_3
7	OBn	H	N_3
8	OMs	H	N_3
9	H	N_3	N_3
10	OH	H	N_3
13	OMs	H	NH_2
14	H	NH_2	NH_2
16	OAc	H	F
17	OBn	H	F
18	OMs	H	F
19	H	N_3	F
20	H	NH_2	F

	R^1	R^2	R^3
11	OH	N_3	OAc
12	OH	N_3	OH
15	OH	NH_2	OH
21	$(Me_2N)_3S^+OSO^-_3$	F	OAc
22	OH	F	OAc

Conventional Zemplén deacetylation of **6** and **11** afforded the known azido sugar derivatives **10** and **12**, respectively [15].

Catalytic (10% Pd–C) hydrogenation of the azidoglycofuranose derivatives **8**, **9**, and **12** yielded quantitatively the 6-amino-D-glucofuranose (**13**), the 3,6-diamino-D-allofuranose (**14**), and the 5-amino-L-idofuranose (**15**) derivatives, respectively.

This method to introduce an azido or amino function into a sugar molecule through a cyclic sulfate is a valuable option for the synthesis of 6-amino sugars. It is particularly interesting in the case of 5-amino-5-deoxyfuranoses because there are no problems of mixtures of epimers, as in the reduction of oxime derivatives [16], or of competition between elimination and substitution, as in methods based on inversion of the C-5 configuration [15], and the number of steps from the diol derivative is only three, with high overall yields.

The 6-fluoro-6-deoxy-D-gluco-furanose (**16**–**18**) and D-allo-furanose (**19**) were prepared analogously by sulfate ring opening of **1**–**4** using tetraethylammonium fluoride dihydrate as a nucleophile. Subsequent reduction of the 3-azido-6-fluoro-D-allofuranoside **19** gave the amino-fluoro derivative **20** in a high yield.

The reaction of the cyclic sulfate **5** with tetraethylammonium fluoride dihydrate led to complex mixtures of decomposition products. In the case of anhydrous tetrabutylammonium fluoride, the reaction was strongly dependent on the nucleophile/starting material ratio, on temperature, and on reaction time. Both ^{1}H and ^{13}C NMR spectra showed the formation of **21** as a minor product, and a major elimination compound for which the ^{1}H NMR spectrum [6.04 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.42 (s, 1 H, H-3), 5.17 (dd, 1 H, $J_{5,6a}$ 9.7, $J_{5,6b}$ 6.5, H-5), 5.05 (d, 1 H, H-2), 4.81 (dd, 1 H, $J_{6a,6b}$ 12.5, H-6a), 4.70 (dd, 1 H, H-6b)] and reported data on related eliminations [10] suggest structure **23**. The best ratio (**23**:**21**, 5:3) of substitution product was obtained when the reaction was conducted in DMF at 0 °C for 40 h. When tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TAS-F) was used as a nucleophile, practically only the 5-fluoroderivative **21** was formed (**23**:**21** ratio, measured by digital integration of the ^{1}H NMR signals, $\approx$1:100). Treatment of **21** with sulfuric acid in THF produced quantitatively the 5-fluoro-L-idofuranose derivative **22**.

The NMR spectra of the 6-fluoroglycofuranose derivatives **16**–**20** had the signals for H-6a and H-6b at 4.51–4.71 ppm ($^2J_{H,F} \approx 47$ Hz) and for C-6 at 83.2–85.0 ppm ($^1J_{C,F} \approx 169$ Hz) in agreement with the presence of a fluorine atom. In the case of the 5-fluoro-L-idofuranoses **21** and **22**, the resonances for H-5 and C-5 appeared at low field (4.90 and 90.3 ppm, respectively) and the values for $^2J_{H5,F}$ and $^1J_{C5,F}$ were $\approx$90.4 and $\approx$175 Hz, respectively, also supporting the introduction of the fluorine atom.

In conclusion, we describe a new, short and inexpensive method for the regio- and stereoselective preparation of 6- and 5-azido, 6- and 5-amino, and 6- and 5-fluoro glycofuranoses. The method is especially useful in the case of the 5-substituted-L-*ido* derivatives.

1. Experimental

General methods.—Melting points are uncorrected. Optical rotations were measured at 24 $\pm$ 4 °C in 1 cm cells. FTIR spectra were

recorded for KBr discs. ^{1}H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ or MeOH-d_4. Assignments were confirmed by homonuclear 2D COSY and heteronuclear 2D correlated experiments. FAB mass spectra were recorded with a Kratos MS-80RFA instrument with a resolution of 1000 (10% valley definition). HREIMS (70 eV), HRCIMS (150 eV) experiments were performed with a Micromass AutoSpecQ instrument with a resolution of 10,000 (5% valley definition). Ions were produced by a beam of xenon atoms (6–7 keV) using a matrix consisting of thioglycerol or 3-nitrobenzyl alcohol and NaI as salt. TLC was performed on Silica Gel HF_{254}, with detection by UV light or charring with H_2SO_4. Silica Gel 60 (E. Merck, 230–400 mesh) was used for preparative chromatography.

Preparation of cyclic sulfates **3** *and* **5**.—To an ice-cooled and magnetically stirred solution of the corresponding diol [11,12] (1 mmol) and pyridine (4.08 mmol) in dry CH_2Cl_2 (5 mL), a solution of thionyl chloride (2 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise over a period of 10 min. Stirring was continued at 0 °C until TLC analysis showed complete conversion of the starting material into cyclic sulfite. The mixture was diluted with CH_2Cl_2 (15 mL), washed three times with water, dried ($MgSO_4$), and concentrated. To a solution (7 mL) of the residue in (2:2:3) CH_2Cl_2–MeCN–water, $NaIO_4$ (2 equiv) and $RuCl_3{\cdot}H_2O$ (2 mg) were added. The resulting mixture was stirred for 20–60 min at rt. After dilution with CH_2Cl_2 (15 mL), the organic layer was separated and washed with water, dried ($MgSO_4$), and concentrated. The corresponding cyclic sulfates were purified by column chromatography.

1,2-O-*Isopropylidene-3*-O-*mesyl-α*-D-*gluco-furanose-5,6-cyclic sulfate* (**3**). Column chromatography (1:1 Et_2O–light petroleum ether) of the residue gave **3** as a solid (252 mg, 70%) which crystallized from Et_2O–light petroleum ether: mp 154–157 °C; $[\alpha]_D^{21} = -40°$ (*c* 1.0, CH_2Cl_2); IR ν_{max} 1385, 1215, 1175, 1094, 1026 and 980 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.09 (d, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 5.06 (m, 1 H, H-5), 4.78 (d, 1 H, H-2), 4.85 (dd, 1 H, $J_{5,6a}$ 6.3, $J_{6a,6b}$ 9.3 Hz, H-6a), 4.78 (dd, 1 H, $J_{5,6b}$ 5.5 Hz, H-6b), 4.58 (dd, 1 H, $J_{4,5}$ 8.4 Hz, H-4), 3.12 (s, 3 H, Ms), 1.53, 1.34 (2 s, each 3 H, CMe_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 113.5 (*C*Me_2), 105.3 (C-1), 83.4 (C-2), 80.8 (C-3), 77.1 (C-4), 76.2 (C-5), 70.3 (C-6), 38.2 (OMs), 26.6, 26.0 (C*Me*$_2$) ppm; FABMS *m*/*z* 383 ([M + Na]$^+$). Anal. Calcd for $C_{10}H_{16}O_{10}S_2$: C, 33.33; H, 4.47. Found: C, 33.22; H, 4.39.

6-O-*Acetyl-1,2*-O-*isopropylidene-α*-D-*gluco-furanose 3,5-cyclic sulfate* (**5**). Column chromatography (3:1 Et_2O–light petroleum ether) of the residue gave **5** as a solid (292 mg, 90%), which crystallized from Et_2O–light petroleum ether: mp 116–118 °C (dec); $[\alpha]_D^{24} = +38°$ (*c* 1.0, CH_2Cl_2); IR ν_{max} 1753, 1398, 1254, 1204, 1094, 1042 and 866 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.06 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.19 (d, 1 H, $J_{3,4}$ 2.5 Hz, H-3), 5.00 (t d, 1 H, $J_{4,5}$ 2.5, $J_{5,6a} = J_{5,6b}$ 6.4 Hz, H-5), 4.79 (d, 1 H, H-2), 4.57 (m, 1 H, H-6a), 4.54 (m, 1 H, H-6b), 4.35 (t, 1 H, H-4), 2.13 (s, 3 H, COCH_3), 1.53, 1.36 (2 s, each 3 H, CMe_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 169.9 (CO), 113.2 (*C*Me_2), 104.8 (C-1), 85.1 (C-3), 82.9 (C-5), 82.5 (C-2), 71.7 (C-4), 61.5 (C-6), 26.5, 26.0, (C*Me*$_2$), 20.4 (CO*C*H$_3$) ppm; FABMS: *m*/*z* 347 ([M + Na]$^+$). Anal. Calcd for $C_{11}H_{16}O_9S$: C, 40.74; H, 4.97. Found: C, 40.78; H, 5.09.

General procedure for the preparation of azido derivatives **6**–**12**.—A solution of the corresponding cyclic sulfate **1**–**5** (1 mmol) and sodium azide (2 mmol) in DMF (5 mL) at 50 °C was stirred for 10–60 min until total consumption of the starting material, monitoring by TLC, then the mixture was concentrated and dissolved in THF (5 mL). Concd H_2SO_4 (50 μL) and water (18 μL) were added and the mixture was stirred for 20–60 min at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat aq $NaHCO_3$. The organic layer was separated, washed three times with water, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by column chromatography (1:2 Et_2O–light petroleum ether) to give **6**–**9** or **11** (1:1 to 3:1 Et_2O–light petroleum ether), respectively. Zemplén deacetylation of **9** and **11** yielded **10** and **12**.

3-O-*Acetyl*-*6*-*azido*-*6*-*deoxy*-*1,2*-O-*isopropylidene*-α-D-*glucofuranose* (**6**).—Syrup (238 mg, 83%); $[\alpha]_D^{23} + 9°$ (*c* 0.8, CH_2Cl_2); IR ν_{max} 3472, 2104, 1742, 1375, 1228, 1084, 1024 and 864 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.89 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.27 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-3), 4.58 (d, 1 H, H-2), 4.17 (dd, 1 H, $J_{4,5}$ 9.2 Hz, H-4), 3.72 (ddd, 1 H, $J_{5,6a}$ 2.7, $J_{5,6b}$ 6.4 Hz, H-5), 3.58 (dd, 1 H, $J_{6a,6b}$ 12.7 Hz, H-6a), 3.47 (dd, 1 H, H-6b), 2.16 (s, 3 H, COCH_3), 1.53, 1.32 (2 s, each 3 H, CMe_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.2 (CO), 112.4 (*C*Me_2), 104.7 (C-1), 83.0 (C-2), 79.3 (C-4), 76.4 (C-3), 67.5 (C-5), 53.9 (C-6), 26.5, 26.1 (CMe_2), 20.6 (CO*C*H_3) ppm; FABMS: *m*/*z* 310 ($[M + Na]^+$). Anal. Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.96; N, 14.63. Found: C, 46.24; H, 5.58; N, 14.28.

6-*Azido*-*3*-O-*benzyl*-*6*-*deoxy*-*1,2*-O-*isopropylidene*-α-D-*glucofuranose* (**7**).—Syrup (265 mg, 79%); $[\alpha]_D^{28} - 54°$ (*c* 1.1, CH_2Cl_2); IR ν_{max} 3493, 2104, 1080 and 1022 cm^{-1}; lit. [17] 3500(OH) and 2100(N_3); ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.33 (m, 5 H, Ar), 5.93 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.75 (d, 1 H, $J_{H,H}$ 11.8 Hz, C*H*HPh), 4.64 (d, 1 H, H-2), 4.53 (d, 1 H, C*H*HPh), 4.09 (m, 3 H, H-3, H-4, and H-5), 3.54 (m, 1 H, H-6a), 3.42 (dd, 1 H, $J_{5,6b}$ 5.4, $J_{6a,6b}$ 12.5 Hz, H-6b), 2.28 (d, 1 H, $J_{5,OH}$ 4.2 Hz, OH), 1.49, 1.33 (2 s, each 3 H, CMe_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 136.8–127.9 (6 C, Ar), 111.9 (*C*Me_2), 105.1 (C-1), 81.9 (C-2), 81.4 (C-3*), 79.8 (C-4*), 71.9 (*C*H_2Ph) 68.3 (C-5), 54.3 (C-6), 26.7, 26.2 (CMe_2) ppm; HREIMS *m*/*z* obsd 320.1243, calcd for $C_{15}H_{18}N_3O_5$ 320.1246 ($[M - CH_3]^+$).

6-*Azido*-*6*-*deoxy*-*1,2*-O-*isopropylidene*-*3*-O-*methanesulfonyl*-α-D-*glucofuranose* (**8**).—Syrup (284 mg, 88%); $[\alpha]_D^{21} - 27°$ (*c* 1.1, CH_2Cl_2) IR ν_{max} 3528, 2106, 1360, 1171, 1088, 1020, 943 and 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.14 (d, 1 H, $J_{3,4}$ 2.7 Hz, H-3), 4.75 (d, 1 H, H-2), 4.22 (dd, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.97 (ddd, 1 H, $J_{5,6a}$ 2.8, $J_{5,6b}$ 6.0 Hz, H-5), 3.64 (dd, 1 H, $J_{6a,6b}$ 12.7 Hz, H-6a), 3.52 (dd, 1 H, H-6b), 3.15 (s, 3 H, Ms), 1.52, 1.33 (2 s, each 3 H, CMe_2) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 112.8 (*C*Me_2), 104.9 (C-1), 83.1 (C-2), 81.1 (C-3), 78.7 (C-4), 67.3 (C-5), 54.0 (C-6), 38.0 (OMs), 26.5, 26.1 (CMe_2) ppm; FABMS: *m*/*z* 346 ($[M + Na]^+$). HREIMS: *m*/*z* obsd 308.0548, calcd for $C_9H_{14}N_3O_7S$ 308.0552 ($[M - CH_3]^+$). Anal. Calcd for $C_{10}H_{17}O_7N_3S$: C, 37.14; H, 5.30; N, 13.00; S, 9.92. Found: C, 37.32; H, 5.23; N, 12.66; S, 10.14.

3,6-*Diazido*-*3,6*-*dideoxy*-*1,2*-O-*isopropylidene*-α-D-*allofuranose* (**9**).—Amorphous solid (216 mg, 80%); $[\alpha]_D^{26} + 128°$ (*c* 1.0, CH_2Cl_2); IR ν_{max} 2108, 1379, 1262, 1107, 1026, and 872 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.80 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.77 (dd, 1 H, $J_{2,3}$ 4.7 Hz, H-2), 4.08-4.05 (m, 1 H, H-4), 4.07–4.03 (m, 1 H, H-5), 3.58 (dd, 1 H, $J_{3,4}$ 8.9 Hz, H-3), 3.54 (dd, 1 H, $J_{5,6a}$ 7.6, $J_{6a,6b}$ 12.7 Hz, H-6a), 3.45 (dd, 1 H, $J_{5,6b}$ 3.7 Hz, H-6b), 2.37 (d, 1 H, $J_{5,OH}$ 3.5 Hz, OH), 1.59, 1.38 (2 s, each 3 H, CMe_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 113.4 (*C*Me_2), 104.1 (C-1), 80.6 (C-2), 77.7 (C-4), 70.3 (C-5), 60.2 (C-3), 52.7 (C-6), 26.4 (2C, CMe_2) ppm; FABMS: *m*/*z* 293 ($[M + Na]^+$). Anal. Calcd for $C_9H_{14}N_6O_4$: C, 40.00; H, 5.22; N, 31.10. Found: C, 40.18; H, 4.93; N, 30.75.

6-*Azido*-*6*-*deoxy*-*1,2*-O-*isopropylidene*-α-D-*glucofuranose* (**10**).—$[\alpha]_D^{27} + 1°$ (*c* 0.6, Me_2CO); lit. [15] $[\alpha]_D^{27} + 2.48°$ (Me_2CO).

6-O-*Acetyl*-*5*-*azido*-*5*-*deoxy*-*1,2*-O-*isopropylidene*-β-L-*idofuranose* (**11**).—Solid (201 mg, 70%); mp 72–74 °C (Et_2O–light petroleum ether); $[\alpha]_D^{26} = -57°$ (*c* 1.0, CH_2Cl_2); IR ν_{max} 3443, 2104, 1740, 1373, 1260, 1082 and 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.98 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.53 (d, 1 H, H-2), 4.32 (dd, 1 H, $J_{6a,6b}$ 11.7 Hz, H-6a), 4.22 (m, 1 H, H-3), 4.14 (dd, 1 H, H-6b), 4.13 (dd, 1 H, $J_{3,4}$ 2.5 Hz, H-4), 3.94 (t d, 1 H, $J_{4,5}$ 7.6, $J_{5,6a}$ 3.4, $J_{5,6b}$ 7.6, Hz H-5), 2.66 (d, 1 H, OH), 2.13 (s, 3 H, COCH_3), 1.50, 1.32 (2 s, each 3 H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.9 (CO), 112.0 (*C*Me_2), 104.5 (C-1), 85.2 (C-2), 79.6 (C-4), 75.2 (C-3), 63.8 (C-6), 59.8 (C-5), 26.7, 26.1 (CMe_2), 20.6 (CO*C*H_3); FABMS: *m*/*z* 310 ($[M + Na]^+$). Anal. Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.96; N, 14.63. Found: C, 46.04; H, 5.94; N, 14.77.

5-*Azido*-*5*-*deoxy*-*1,2*-O-*isopropylidene*-β-L-*idofuranose* (**12**).—$[\alpha]_D^{21} - 77°$ (*c* 1.2, MeOH); lit. [15] $[\alpha]_D^{20} - 77.0$ (*c* 2.6, MeOH).

General procedure for the preparation of amino derivatives **13**–**15**.—A mixture of the

corresponding azidoderivative **8**, **9** or **12** (1 mmol) and 10% Pd–C (20% for **9**) in MeOH (26 mL) was hydrogenated at rt for 45–90 min followed by filtration and evaporation to dryness to give **13**–**15**, respectively.

6-Amino-6-deoxy-1,2-O-*isopropylidene-3*-O-*methanesulfonyl-α*-D-*glucofuranose* (**13**). Isolated as an amorphous solid (297 mg, 100%) after column chromatography (4:1 CH_2Cl_2–MeOH); $[\alpha]_D^{24} - 44°$ (*c* 1.0, CH_2Cl_2); IR ν_{max} 3368, 3304, 1348, 1171, 1086, 1018, and 959 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.87 (d, 1 H, $J_{1,2}$ 3.7, Hz, H-1), 5.02 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 4.70 (d, 1 H, H-2), 4.02 (dd, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.72 (m, 1 H, H-5), 3.15 (s, 3 H, Ms), 3.05 (bd, 1 H, $J_{6a,6b}$ 12.7 Hz, H-6a), 2.84 (dd, 1 H, $J_{5,6b}$ 6.0 Hz, H-6b), 1.50, 1.32 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 112.5 (*C*Me$_2$), 105.0 (C-1), 83.5 (C-2), 82.3 (C-3), 79.6 (C-4), 67.4 (C-5), 43.8 (C-6), 38.0 (1C, OMs), 26.5, 26.1 (C*Me*$_2$) ppm; FABMS: *m/z* 298 ($[M+H]^+$); HRCIMS: *m/z* obsd 298.095089; calcd for $C_{10}H_{20}NO_7S$ 298.096049 ($[M+H]^+$).

3,6-Diamino-3,6-dideoxy-1,2-O-*isopropylidene-α*-D-*allofuranose* (**14**). Isolated as an amorphous solid (218 mg, 100%). $[\alpha]_D^{24} + 50°$ (*c* 1.0, MeOH); IR ν_{max} 3372, 3304, 1589, 1377, 1217, 1098, 1017 and 874 cm^{-1}; ^1H NMR (500 MHz, MeOD): δ 5.75 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.56 (dd, 1 H, $J_{2,3}$ 4.8 Hz, H-2), 3.65–3.62 (m, 1 H, H-5), 3.59 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 6.1 Hz, H-4), 3.10 (dd, 1 H, H-3), 2.84 (dd, 1 H, $J_{5,6a}$ 3.7, $J_{6a,6b}$ 13.3 Hz, H-6a), 2.69 (dd, 1 H, $J_{5,6b}$ 6.8 Hz, H-6b), 1.51, 1.32 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, MeOD): δ 113.2 (*C*Me$_2$), 105.7 (C-1), 82.2 (C-2), 83.2 (C-4), 74.7 (C-5), 58.2 (C-3), 45.6 (C-6), 26.9, 26.6 (C*Me*$_2$) ppm; FABMS: *m/z* 219 ($[M+H]^+$); HREIMS: *m/z* obsd 203.1030, calcd for $C_8H_{15}N_2O_4$ 203.1032 ($[M-CH_3]^+$); HRCIMS: *m/z* obsd 219.1345; calcd for $C_9H_{19}N_2O_4$ 219.1345 ($[M+H]^+$).

5-Amino-5-deoxy-1,2-O-*isopropylidene-β*-L-*idofuranose* (**15**). Crystallized from EtOH: mp 179–183 °C, $[\alpha]_D^{24} - 6°$ (*c* 0.6, MeOH); lit. [17] mp 184–185 °C, $[\alpha]_D^{20} = -3.7°$ (*c* 1.1, MeOH); lit. [18] mp 178 °C, $[\alpha]_D^{25} = -3.0°$ (*c* 0.9, MeOH); lit. [19] mp 176–179 °C, $[\alpha]_D^{20} = -3.4°$ (*c* 1.0, MeOH);.^1H NMR (500 MHz, MeOD): δ 5.89 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.46 (d, 1 H, H-2), 4.12 (d, 1 H, $J_{3,4}$ 2.9 Hz, H-3), 4.05 (dd, 1 H, $J_{4,5}$ 6.2 Hz, H-4), 3.62 (dd, 1 H, $J_{5,6a}$ 5.3, $J_{6a,6b}$ 10.9 Hz, H-6a), 3.52 (dd, 1 H, $J_{5,6b}$ 6.0 Hz, H-6b), 3.14 (m, 1 H, H-5), 1.43, 1.28 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, MeOD): δ 115.1 (*C*Me$_2$), 108.4 (C-1), 89.6 (C-2), 83.8 (C-4), 79.2 (C-3), 67.0 (C-6), 55.8 (C-5), 29.5, 28.9 (C*Me*$_2$) ppm; FABMS: *m/z* 220 ($[M+H]^+$).

General procedure for the preparation of fluoro derivatives **16**–**19**.—To a solution of the corresponding cyclic sulfate **1**–**4** (1 mmol) in Me_2CO (5 mL), tetraethylammonium fluoride dihydrate (1.5 mmol) was added, and the mixture was stirred at rt until the TLC analysis (3:1 Et_2O–light petroleum ether) showed complete conversion of the cyclic sulfate into baseline material. The mixture was concentrated, and dissolved in THF (5 mL). Concd H_2SO_4 (50 μL) and water (18 μL) were added and the mixture was stirred for 15–45 min at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat aq $NaHCO_3$. The organic layer was separated, washed three times with water, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by column chromatography.

3-O-*Acetyl-6-deoxy-6-fluoro-1,2*-O-*isopropylidene-α*-D-*glucofuranose* (**16**). Isolated as a syrup (227 mg, 86%) after column chromatography (1:1 Et_2O–light petroleum ether); $[\alpha]_D^{23} + 11°$ (*c* 1.1, CH_2Cl_2); IR ν_{max} 3489, 1742, 1460, 1425, 1379, 1088 and 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.90 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.31 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-3), 4.67 (ddd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 9.6, $J_{6a,F}$ 47.4 Hz, H-6a), 4.57 (ddd, 1 H, $J_{5,6b}$ 5.3, $J_{6b,F}$ 47.3 Hz, H-6b), 4.56 (d, 1 H, H-2), 4.22 (dd, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 3.85 (m, 1 H, H-5), 2.15 (s, 3 H, COCH_3), 1.52, 1.32 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.6 (CO), 112.4 (*C*Me$_2$), 104.8 (C-1), 84.5 (d, $J_{C,F}$ 169.7 Hz, C-6), 83.0 (C-2), 77.8 (d, $J_{C,F}$ 7.5 Hz, C-4), 76.3 (C-3), 67.5 (d, $J_{C,F}$ 18.8 Hz, C-5), 26.5, 26.1 (C*Me*$_2$), 20.6 (CO*C*H$_3$) ppm; FABMS: *m/z* 287 ($[M+Na]^+$). HREIMS: *m/z* obsd 249.0780, calcd for $C_{10}H_{14}FO_6$ 249.0774 ($[M-CH_3]^+$). Anal. Calcd for $C_{11}H_{17}FO_6$: C, 50.00; H, 6.48. Found: C, 49.62; H, 6.38.

3-O-Benzyl-6-deoxy-6-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (**17**). Isolated as a syrup (218 mg, 70%) after column chromatography (1:2 Et_2O–light petroleum ether); $[\alpha]_D^{20} - 38°$ (*c* 0.9, CH_2Cl_2); IR ν_{max} 3474, 1456, 1379, 1217, 1082 and 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.34 (m, 5 H, Ar), 5.95 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.73 (d, 1 H, $J_{H,H}$ 11.6 Hz, C*H*HPh), 4.71–4.57 (m, 1 H, H-6a), 4.64 (d, 1 H, H-2), 4.58 (d, 1 H, CH*H*Ph), 4.60–4.48 (m, 1 H, H-6b), 4.19 (m, 1 H, H-5), 4.17 (m, 1 H, H-4), 4.14 (m, 1 H, H-3), 1.50, 1.33 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 137.0–127.8 (6C, Ar), 111.9 (*C*Me$_2$), 105.1 (C-1), 85.0 (d, $J_{C,F}$ 168.4 Hz, C-6), 82.0, 81.9 (C-2,3), 78.6 (d, $J_{C,F}$ 6.3 Hz, C-4), 72.2 (*C*H$_2$Ph), 68.3 (d, $J_{C,F}$ 17.6 Hz, C-5), 26.7, 26.2 (C*Me*$_2$) ppm; FABMS: *m/z* 335 ($[M + Na]^+$). HREIMS: *m/z* obsd 312.1362, calcd for $C_{16}H_{21}FO_5$ 312.1373. Anal. Calcd for $C_{16}H_{21}FO_5$: C, 61.53; H, 6.78. Found: C, 61.26; H, 6.79.

6-Fluoro-6-deoxy-1,2-O-isopropylidene-3-O-mesyl-α-D-glucofuranose (**18**). Isolated as a syrup (258 mg, 86%) after column chromatography (2:1 Et_2O–light petroleum ether); $[\alpha]_D^{21} - 28°$ (*c* 1.0, CH_2Cl_2); IR ν_{max} 3528, 1362, 1173, 1090, 1026 and 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.95 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.13 (d, 1 H, $J_{3,4}$ 2.7 Hz, H-3), 4.78 (d, 1 H, H-2), 4.67 (ddd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 9.8, $J_{6a,F}$ 47.5 Hz, H-6a), 4.59 (ddd, 1 H, $J_{5,6b}$ 4.7, $J_{6b,F}$ 47.2 Hz, H-6b), 4.28 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.01 (dddd, 1 H, $J_{5,F}$ 21 Hz, H-5), 3.15 (s, 3 H, Ms), 1.51, 1.33 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 112.8 (*C*Me$_2$), 105.0 (C-1), 84.4 (d, $J_{C,F}$ 168.4 Hz, C-6), 83.2 (C-2), 81.7 (C-3), 77.3 (d, $J_{C,F}$ 7.0 Hz, C-4), 67.4 (d, $J_{C,F}$ 18.8 Hz, C-5), 38.0 (1C, OMs), 26.5, 26.1 (C*Me*$_2$) ppm; FABMS: *m/z* 323 ($[M + Na]^+$). HREIMS: *m/z* obsd 285.0438, calcd for $C_9H_{14}FO_7S$ 285.0444 ($[M - CH_3]^+$). Anal. Calcd for $C_{10}H_{17}FO_7S$: C, 40.00; H, 5.71; S, 10.68. Found: C, 39.99; H, 6.11; S, 11.01.

3-Azido-3,6-dideoxy-6-fluoro-1,2-O-isopropylidene-α-D-allofuranose (**19**). Isolated as a syrup (198 mg, 80%) after column chromatography (2:1 Et_2O–light petroleum ether); $[\alpha]_D^{25} + 107°$ (*c* 1.1, CH_2Cl_2); IR ν_{max} 3472, 2112, 1379, 1258, 1111, 1026 and 874 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.82 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.77 (dd, 1 H, $J_{2,3}$ 4.8 Hz, H-2), 4.58 (ddd, 1 H, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 9.7, $J_{6a,F}$ 46.6 Hz, H-6a), 4.54 (ddd, 1 H, $J_{5,6b}$ 6.3, $J_{6b,F}$ 47.4 Hz, H-6b), 4.17 (m, 1 H, H-5), 4.12 (dd, 1 H, $J_{4,5}$ 4.6 Hz, H-4), 3.63 (dd, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 2.38 (d, 1 H, $J_{5,OH}$ 4.3 Hz, OH), 1.58, 1.37 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 113.4 (*C*Me$_2$), 104.1 (C-1), 83.2 (d, $J_{C,F}$ 169.7 Hz, C-6), 80.5 (C-2), 76.8 (d, $J_{C,F}$ 7.3 Hz, C-4), 70.1 (d, $J_{C,F}$ 20.1 Hz, C-5), 60.6 (C-3), 26.4 (2C, C*Me*$_2$) ppm; FABMS: *m/z* 270 ($[M + Na]^+$). Anal. Calcd for $C_9H_{14}FN_3O_4$: C, 43.72; H, 5.71; N, 17.00. Found: C, 44.10; H, 5.44; N, 16.81.

3-Amino-3,6-dideoxy-6-fluoro-1,2-O-isopropylidene-α-D-allofuranose (**20**).—Prepared following the general procedure described above for **13**–**15**. Column chromatography (20:1 CH_2Cl_2–MeOH) of the residue gave **20** as a syrup (221 mg, 83%); $[\alpha]_D^{25} + 53°$ (*c* 1.3, CH_2Cl_2); IR ν_{max} 3381, 3312, 1377, 1219, 1099, 1013 and 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.59 (ddd, 1 H, $J_{5,6a}$ 2.6, $J_{6a,6b}$ 9.9, $J_{6a,F}$ 47.4 Hz, H-6a), 4.51 (ddd, 1 H, $J_{5,6b}$ 4.9, $J_{6b,F}$ 47.6 Hz, H-6b), 4.46 (dd, 1 H, $J_{2,3}$ 4.6 Hz, H-2), 3.95 (dddd, 1 H, $J_{5,F}$ 23.2 Hz, H-5), 3.65 (dd, 1 H, $J_{4,5}$ 7.9 Hz, H-4), 3.20 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 2.35 (bs, 1 H, OH), 1.55, 1.35 (2 s, each 3 H, C*Me*$_2$) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 112.3 (*C*Me$_2$), 104.5 (C-1), 84.1 (d, $J_{C,F}$ 170.4 Hz, C-6), 80.1 (C-2), 76.1 (d, $J_{C,F}$ 7.5 Hz, C-4), 73.2 (d, $J_{C,F}$ 18.1, C-5), 58.6 (C-3), 26.4, 26.3 (C*Me*$_2$) ppm; FABMS: *m/z* 222 ($[M + Na]^+$). Anal. Calcd for $C_9H_{16}FNO_4$: C, 48.86; H, 7.29; N, 6.33. Found: C, 49.16; H, 7.14; N, 6.18.

6-O-Acetyl-5-fluoro-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose (**22**).—A solution of TAS-F (100 mg) in CH_2Cl_2 (1.5 mL) was added dropwise, at −10 °C, to a stirred solution of the cyclic sulfate **5** (35 mg). After 24 h, the reaction mixture was warmed to 35 °C, and kept at this temperature for a further 72 h. The solvent was evaporated under diminished pressure, and the crude was purified by column chromatography using 2:1 CH_2Cl_2–Me_2CO as eluent to give tris(dimethylamino)sulfonium 6-*O*-acetyl-5-fluoro-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose-3-sulfate (**21**) (29 mg, 53%) as a syrup. ^1H NMR (500 MHz, $CDCl_3$): δ 5.98 (d, 1 H, $J_{1,2}$ 3.6,

H-1), 5.01 (m, 1 H, H-2), 5.02-4.89 (m, 1 H, H-5), 4.80 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 4.58 (m, 1 H, H-6a), 4.48–4.43 (m, 1 H, H-4), 4.48–4.39 (m, 1 H, H-6b), 2.97 (s, 18 H, NMe_2), 2.10 (s, 3 H, COCH_3), 1.49, 1.30 (2 s, each 3 H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.4 (CO), 112.0 (*C*Me$_2$), 105.0 (C-1), 90.3 (d, $J_{C,F}$ 174.7 Hz, C-5), 83.5 (C-2), 79.3 (d, $J_{C,F}$ 7.5 Hz, C-3), 78.2 (d, $J_{C,F}$ 20.1 Hz, C-4), 63.2 (d, $J_{C,F}$ 20.1 Hz, C-6), 38.6 (NMe_2), 26.8, 26.3 (CMe_2), 20.7 (CO*C*H$_3$). Compound **21** (29 mg) was dissolved in THF (0.4 mL) and a catalytic amount of H_2SO_4 was added. The mixture was stirred for 30 min at rt and then diluted with EtOAc (5 mL) and washed with sat aq $NaCO_3H$. The organic layer was separated, washed three times with water, dried ($MgSO_4$), and concentrated to dryness to yield **22** (15 mg, 100%) as a syrup. $[\alpha]_D^{24} - 28°$ (*c* 0.8, CH_2Cl_2); IR ν_{max} 3455, 1742, 1377, 1260, 1084, 1020 and 799 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.90 (dtd, 1 H, $J_{5,6a}$ 2.6, $J_{5,6b}$ 6.3, $J_{5,F}$ 49.4 Hz, H-5), 4.46 (m, 1 H, H-2), 4.37 (ddd, 1 H, $J_{6a,6b}$ 12.7, $J_{6a,F}$ 27.0 Hz, H-6a), 4.21 (m, 1 H, H-3), 4.22 (ddd, $J_{3,4}$ 2.9, $J_{4,5}$ 6.3, $J_{4,F}$ 17.1 Hz, 1 H, H-4), 4.29 (ddd, 1 H, $J_{6b,F}$ 23.6 Hz, H-6b), 2.06 (s, 3 H, COCH_3), 1.43, 1.26 (2 s, each 3 H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.9 (CO), 112.1 (*C*Me$_2$), 104.8 (C-1), 90.5 (d, $J_{C,F}$ 176.0 Hz, C-5), 85.3 (C-2), 78.6 (d, $J_{C,F}$ 17.6 Hz, C-4), 75.5 (d, $J_{C,F}$ 5.7 Hz, C-3), 63.6 (d, $J_{C,F}$ 22.6 Hz, C-6), 26.7, 26.2 (CMe_2), 20.6 (CO*C*H$_3$); FABMS: m/z 287 ($[M + Na]^+$). HRCIMS: m/z obsd 265.1073, calcd for $C_{11}H_{18}FO_6$ 265.1087 ($[M + H]^+$).

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References

[1] (a) H.C. Kolb, M.S. VanNieuwenhze, K.B. Sharpless, *Chem. Rev.*, 94 (1994) 2483–2547. (b) B.B. Lohray, *Synthesis*, (1992) 1035–1052.
[2] Y. Gao, K.B. Sharpless, *J. Am. Chem. Soc.*, 110 (1988) 7538–7539.
[3] F.G. Calvo-Flores, P. García-Mendoza, F. Hernández-Mateo, J. Isac-García, F. Santoyo-González, *J. Org. Chem.*, 67 (1997) 3944–3961.
[4] P.M. Vanhessche, K.B. Sharpless, *Chem. Eur. J.*, 3 (1997) 517–522.
[5] M.S. Berridge, M.P. Franceschini, E. Rosenfeld, T.J. Tewson, *J. Org. Chem.*, 55 (1990) 1211–1217.
[6] R. Oi, K.B. Sharpless, *Tetrahedron Lett.*, 32 (1991) 999–1002.
[7] (a) P.A.M. Van der Klein, W. Filemon, G.H. Veeman, G.A. Van der Marel, J.H. Van Boom, *J. Carbohydr. Chem.*, 11 (1992) 837–848. (b) P.A.M. Van der Klein, J.H. Van Boom, *Carbohydr. Res.*, 224 (1992) 193–200. (c) A.M. Gómez, S. Valverde, B. Fraser Reid, *J. Chem. Soc., Chem. Commun.*, (1991) 1207–1208.
[8] K. Vanhessche, E. Van der Eycken, M. Vandewalle, H. Roper, *Tetrahedron Lett.*, 31 (1990) 2337–2340.
[9] T. Tsuchiya, *Adv. Carbohydr. Chem. Biochem.*, 48 (1990) 91–277.
[10] (a) Y. Mori, K. Harada, N. Morishima, S. Zen, *Chem. Pharm. Bull.*, 41 (1993) 755–757. (b) Y. Mori, N. Morishima, *Bull. Chem. Soc. Jpn.*, 67 (1994) 236–241.
[11] R. Albert, K. Dax, S. Seidl, H. Sterk, A.E. Stütz, *J. Carbohydr. Chem.*, 4 (1985) 513–520.
[12] J. Fuentes, M. Angulo, M.A. Pradera, *Tetrahedron Lett.*, 39 (1998) 7149–7152.
[13] T. Netscher, I. Gautshi, *Liebig Ann. Chem.*, (1992) 543–546.
[14] W. Szeja, *Carbohydr. Res.*, 158 (1986) 245–248.
[15] K. Dax, B. Gaigg, V. Grassberger, B. Koblinger, A.E. Stütz, *J. Carbohydr. Chem.*, 9 (1990) 479–499.
[16] G. Legler, E. Julich, *Carbohydr. Res.*, 128 (1984) 61–72.
[17] H. Saeki, E. Ohki, *Chem. Pharm. Bull.*, 16 (1968) 2471–2476.
[18] R.E. Gramera, R.M. Bruce, S. Hirase, R.L. Whistler, *J. Org. Chem.*, 38 (1963) 1401–1403.
[19] H. Paulsen, K. Todt, *Chem. Ber.*, (1966) 3450–3460.