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Branched-chain fluoro nitro D- and L-sugars from glucose

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Abstract

Mixed crystals of methyl 3-deoxy-3-*C*-methyl-3-nitro-α-D- and β-L-glucopyranosides (1:1), easily available from D-glucose by means of the Baer reaction, were completely characterised by X-ray diffraction analysis. These diastereomeric components, separation of which could be achieved through their 4,6-*O*-benzylidene derivatives, were selectively fluorinated at position 6 by treatment with DAST and stereoselectively transformed into phenyl 3-deoxy-3-*C*-methyl-3-nitro-1-thio-β-D-glucopyranoside and phenyl 3-deoxy-3-*C*-methyl-3-nitro-1-thio-β-L-glucopyranoside, respectively. Fluorination with DAST of each pure enantiomer afforded, depending on the conditions, the corresponding enantiomeric phenyl 3,6-dideoxy-6-fluoro-3-*C*-methyl-3-nitro-1-thio-β-D- and β-L-glucopyranosides or the respective rearranged 2,3,6-trideoxy-6-fluoro-3-*C*-methyl-3-nitro-2-phenylthio-α-D- and α-L-mannopyranosyl fluorides. This route constitutes a simple method for obtaining fair-to-good yields of 6-fluorinated branched-chain D- and L-sugar derivatives, potentially useful as glycosyl donors, starting from D-glucose.

1. Introduction

Diverse branched-chain nitro sugars are constituents of glycosidic antibiotics.[1] D-Rubranitrose **1** and L-evernitrose **2**, the sugar moieties of rubradirin and everninomicin, respectively, are representative examples of the D- and L-series of sugars, for which various syntheses have been reported.[2,3] There has been an increased interest in fluoro sugars in the last two decades.[4–7] This may be attributed in part to the observation that the glycosidic bond of pharmacologically active glycosides and nucleosides is reinforced by the introduction of a fluorine atom at certain positions of the sugar moiety, a feature that consequently

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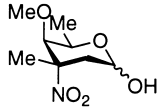
enhances their therapeutic effect.[8,9] Biologically active fluoro sugar derivatives of both D-series[10] and L-series, for example 2-deoxy-2,2-difluoro-L-ribofuranosyl adenine,[11] have been synthesised. The utility of glycosyl fluorides as glycosyl donors in the synthesis of glycosides, oligosaccharides and nucleosides is well established.[7,12,13] Moreover, when a phenylthio group is located at the 2 position of this glycosyl donor, a good stereocontrol in the formation of the glycoside bond can be achieved,[14] with subsequent reductive desulphuration of the product affording the corresponding 2-deoxy-glycosidic compound.[14] On the other hand, phenyl 1-thioglycosides are quite versatile intermediates in oligosaccharide synthesis because of their possible usage as glycosyl donors, as well as glycosyl acceptors, particularly in the Nicolaou two-stage procedure for glycoside bond formation.[13] In this paper we propose the synthesis of 6-fluorinated branched-chain nitro sugars having a fluorine atom or a phenylthio group at the anomeric position, or rearranged 2-phenylthio-glycosyl fluorides, which might be used as synthons for pharmaceuticals of enhanced activity. The proposed methodology for obtaining this kind of compound involves the selective fluorination of nitro sugars having several free OH groups by diethylaminosulphur trifluoride (DAST),[4,15] which in most cases occurs with inversion of configuration (S_N2 mechanism). Taking advantage of the easy access to sugars of D- or L-configurations starting from D-glucose by means of the Baer reaction,[16] the synthesis of new D- and L-branched-chain fluoro nitro monosaccharides was carried out, and is reported herein.



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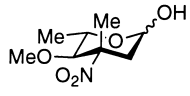

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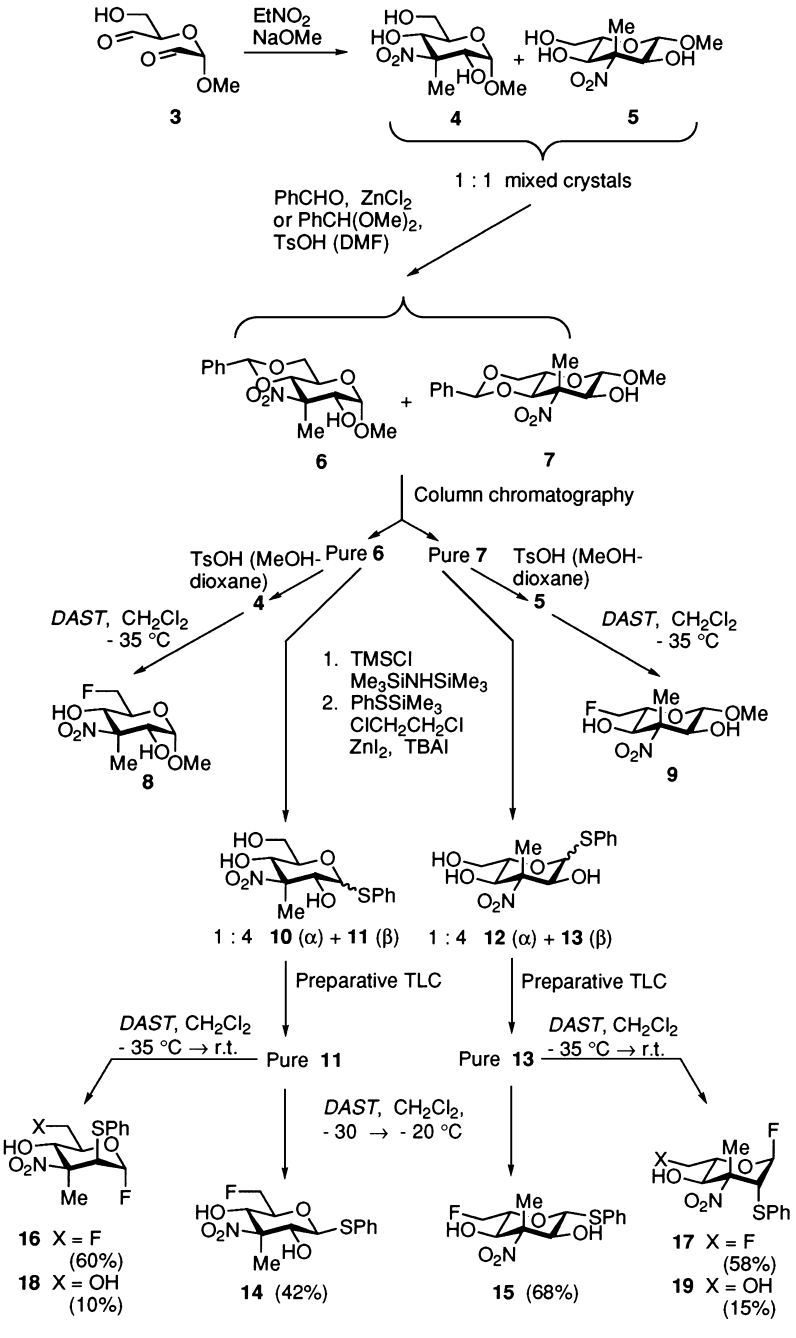
2. Results and discussion

Complete characterisation of the crystalline product obtained in the Baer reaction of dialdehyde **3** with nitroethane (Scheme 1) was achieved. Baer had concluded[16] that this product was an equimolecular mixture of an α-D- and a β-L-*gluco*-(or *allo*-)hexopyranosides, but no configurational assignment for C-3 was made. We could carry out the X-ray diffraction analysis of the crystals, thus elucidating the absolute configuration of the nitro-substituted centre (C-3). A perspective PLATON[17] view of the asymmetric unit enclosing one molecule of each of the two isomers, methyl 3-deoxy-3-*C*-methyl-3-nitro-α-D-*gluco*-hexopyranoside **4** and methyl 3-deoxy-3-*C*-methyl-3-nitro-β-L-*gluco*-hexopyranoside **5**, is given in Fig. 1, where the atomic numbering scheme is also shown. The crystal cohesion is governed by intra- and intermolecular H-bonds (Fig. 2), the two molecules being connected by a complex system of H-bonds forming a three-dimensional network which stabilises the crystal structure. To separate the mixture, it was treated with benzaldehyde–zinc chloride to afford a mixture of the respective 4,6-*O*-benzylidene derivatives **6** and **7**, which could be separated by column chromatography to yield 36% of **6** and 35% of **7**; alternatively, the use of benzaldehyde dimethylacetal in *N*,*N*-dimethylformamide led, after chromatography, to 42% of **6** and 47% of **7**. Separate treatment of **6** and **7** with *p*-toluenesulphonic acid in methanol–dioxane quantitatively yielded the respective deprotected methyl glycosides **4** and **5**. From these two pairs of separated branched-chain nitro sugars we carried out diverse parallel transformations focused on the preparation of novel fluoro and phenylthio-fluoro derivatives belonging to the D- or L-series of monosaccharides. First, **4** and **5** were separately treated with the DAST reagent in dichloromethane at −35°C; under these conditions, the reaction proceeded regioselectively on position 6, to give only the respective 6-monofluoro derivative in good yield (77% of **8** and 64% of **9**, respectively, after column chromatography), which is a model for more complex branched-chain glycosides with

enhanced resistance to chemical and enzymatic cleavage. Application of the method of Hanessian and Guindon[18] for preparing phenyl 1-thioglycosides to each pure benzylidene compound (**6**, **7**) provoked its debenzylidenation and stereoselectively led, after a first purification by column chromatography, to a 1:4 α/β mixture of the branched-chain phenyl 1-thioglycosides **10** and **11** (67% from **6**) or **12** and **13** (64% from **7**). The mixtures were resolved by preparative thin-layer chromatography on silica gel. The pure β enantiomers **11** and **13** were then separately allowed to react with DAST to give monofluoro and difluoro sugars having the phenylthio group at position 1 or 2. Thus, starting from **11**, treatment at −30°C for 3 h [(**A**) conditions] yielded 42% of the 6-deoxy-6-fluoro-1-thio-β-D-*gluco*-hexopyranosyl derivative **14** and 11% of unreacted **11**, while the rearranged 1,6-di- and 1-monofluoro-2-phenylthio-α-D-*manno*-hexopyranosyl derivatives **16** and **18** were obtained in 60% and 10% yields, respectively, by treatment of **11** first at −35°C and then allowing the reaction mixture to rise to room temperature for 90 min [(**B**) conditions]. Starting from **13**, under (**A**) conditions the 6-fluoro-1-thio sugar **15**, enantiomer of **14**, was isolated in 68% yield, whereas under (**B**) conditions the reaction led to the 1,6-difluoro sugar **17** (58%) and the sugar fluoride **19** (15%), enantiomers of **16** and **18**, respectively.

With regard to the characterisation of the new compounds, the elemental analyses and/or the high-resolution mass spectra were in agreement with the respective molecular formulae; all the compounds were optically active and the characteristic IR bands confirmed the presence of the nitro group and other functional groups in each particular case. The assignment of anomeric configuration was straightforward for the *gluco*-configured compounds (**4**–**15**); thus, the ^{1}H NMR spectra of all the α-D-*gluco*-isomers (**4**, **6**, **8**, and **10**) and the α-L-*gluco*-isomer **12** showed H-1/H-2 coupling constants of lower value (4.3–6.3 Hz) than those of their respective β-L-*gluco*-isomers (**5**, **7**, **9**, **13**) and the β-D-*gluco*-isomer **11** (7.5–10.0 Hz), as expected. The presence of one fluorine atom at C-6 of the methyl glycosides **8** and **9** was evidenced by the following data: (i) the ^{1}H–^{19}F coupling constant values, measured on the H-6 and H-6′ signals (each of them ddd), are 47.3 and 47.6 Hz, in agreement with a geminal-fluorine atom;[19] (ii) the C-6 signal in the ^{13}C NMR spectrum is a doublet, the high values of the coupling constant (172.2 and 176 Hz) corresponding[19] to a ^{1}J (^{13}C–^{19}F). Also in agreement with that expected, the anomeric proton of the enantiomeric phenyl 6-fluoro-1-thio-β-D- and -β-L-*gluco*-pyranosides **14** and **15** gave rise to a doublet showing the value 9.9 Hz for the H-1/H-2 coupling. For these enantiomers **14** and **15**, the ^{1}H–^{19}F coupling constant values (47.5 and 47.2 Hz), measured on the H-6 and H-6′ signals (each of them ddd), as well as the high value (176 Hz) of the coupling constant ^{1}J (^{13}C–^{19}F), measured at the C-6 signal, evidenced the fluorine substituent at this position; moreover, their preferred conformation in chloroformic solution is that which has the fluorine atom and the H-5 in the *anti*-periplanar disposition, as shown by the corresponding coupling constant value (24.8 Hz), in the range 21–30 Hz observed for other pyranose derivatives.[19] The α-anomeric configuration was assigned for the D- and L-*manno*-pyranosyl fluorides **16**–**19**, also on the basis of ^{1}H–^{19}F or ^{13}C–^{19}F coupling constants;[19] thus, the presence of one fluorine atom at position 1 is shown by the coupling constant (233.8, 233.4 Hz) observed for C-1, and by the anomeric proton signal, which is now a double doublet with a high-value ^{1}H–^{19}F geminal-coupling constant (53.2, 53.3 Hz). The low-value H-1/H-2 coupling constant (1.3 Hz) agrees with a *trans*-diequatorial relationship, corroborated by the absence of splitting of the C-3 signal [^{3}J (^{13}C–^{19}F)≈0 Hz], indicative of a *syn*-relationship between C-3 and F around the C-2/C-1 bond. Interestingly, the methyl proton signal and the methyl carbon signal appear as doublets with ^{5}J (^{1}H–^{19}F) 2.3 and ^{4}J (^{13}C–^{19}F) 7.8–7.6 Hz, respectively, similar to those found for a related compound also showing the 1-fluoro-3-methyl-*syn*-diaxial pattern.[20] NOE experiments (1D NOESY), carried out for **17**, showed contacts of the methyl group with H-2 and H-5, but not with H-1, a fact congruent only with the α-anomer. The second fluorine atom of **16** and **17** is located at C-6, as shown by the splitting of the H-6 and H-6′ signals (each



Scheme 1.

of them ddd) and the C-6 one (d), and the corresponding coupling constant values, as in the case of **8**, **9**, **14** and **15**.

The formation of compounds **16**–**19** can be considered a new case of the known 1,2-rearrangement that occurs in the fluorination of related sugars,[14,20,21] and therefore may be explained in terms of a mechanism similar to that proposed by other authors.[22,23]

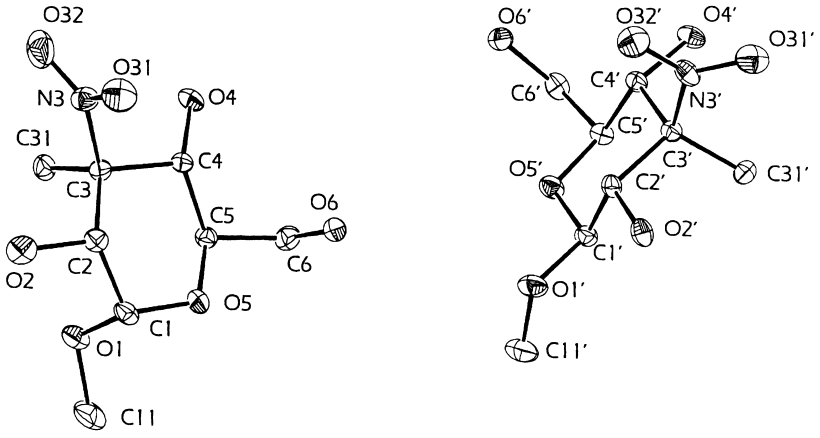


Figure 1. A PLATON view of the unit cell of the mixed crystal of **4** and **5** along the *z*-axis

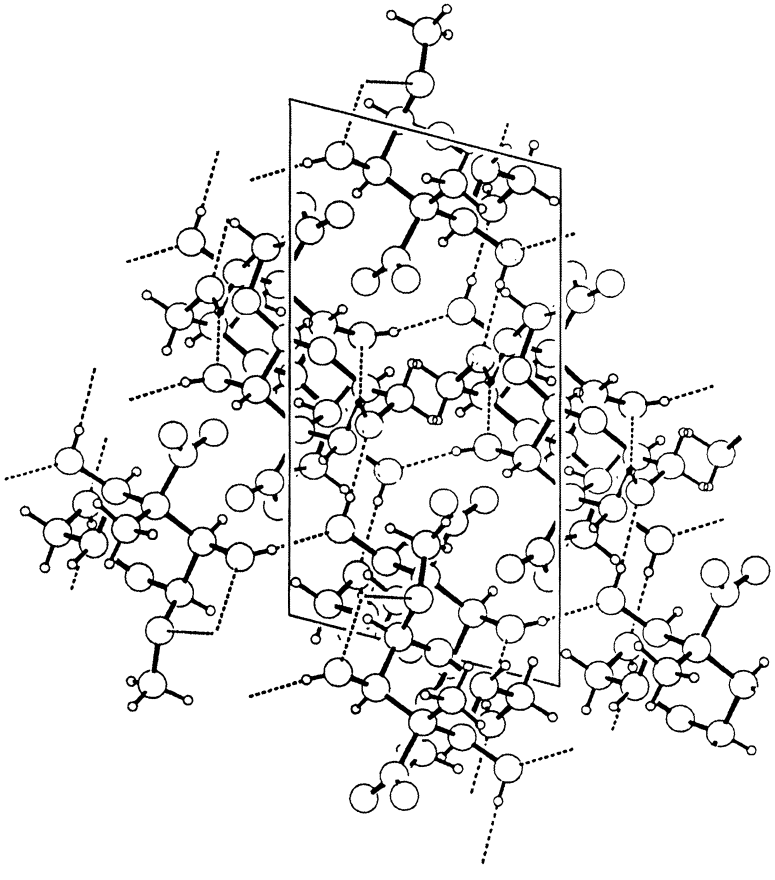


Figure 2. A perspective PLUTON drawing of the packing arrangement viewed along the *y*-axis, with dashed lines indicating H-bonds

2.1. X-Ray structure analysis of 1:1 mixed crystals of **4**+**5**

A perspective PLATON view[17] of the asymmetric unit (two molecules: **4** and **5**) in the solid state, showing the relative configuration and the atomic numbering scheme, is given in Fig. 1. Bond lengths and torsion angles are shown in Table 1. The pyranose endocyclic bond lengths O5–C1=1.409(3) Å and O5–C5=1.429(3) Å, and O5′–C1′=1.419(3) Å and O5′–C5′=1.429(3) Å shows the characteristic anomeric effects. The two α-D- and β-L-pyranose rings show chair conformations, $^4C_1$ and $^1C_4$, respectively, with Cremer and Pople[24] parameters: θ=172(1)°, Q=0.57(2) Å, φ=−23(2)°, and θ′=7(1)°, Q′=0.60(2) Å, φ′=−0.36(2)°, and Nardelli[25] asymmetry parameters: ΔC_s[C1]=0.014, ΔC_2[C1–O5]=0.008, and ΔC_s[C1′]=0.024, ΔC_2[C1′–O5′]=0.036, respectively. For the α-D-pyranose molecule, the substituents O1 and C31 are in axial positions and the O2, N3, O4, and C6 in equatorial positions. For the β-L-molecule, the substituents O1′, O2′, N3′, O4′, and C6′ are in equatorial and the C31′ in axial position. The crystal cohesion is governed by intra- and intermolecular H-bonds (Fig. 2 and Table 2). The α-D- and β-L-molecules are linked to each other by two oxygen–oxygen H-bonds; moreover, they are connected by a complicated system of H-bonds forming a three-dimensional network which stabilises the crystal structure.

3. Conclusion

In conclusion, the described chemical transformations constitute a convenient route to 6-fluorinated branched-chain D- and L-sugar derivatives starting from D-glucose. In particular, the methyl glycosides **6** and **7**, the phenyl 1-thioglycosides **14** and **15**, and the glycosyl fluorides **16** and **17** (the latter two carrying a phenylthio group at C-2), were prepared in fair-to-good yields. It is noteworthy that the application of the Hanessian and Guindon procedure to the methyl glycosides **6** (α-D) and **7** (β-L) preferentially afforded, in both cases, the β-anomer [D (**11**) and L (**13**)], thus opening access to enantiomeric pairs of derivatives (**14**/**15**, **16**/**17**, **18**/**19**). These findings are expected to enhance the availability of fluoro nitro branched-chain sugars, directly useful as synthons for pharmaceuticals through stereocontrolled glycosidation processes.

Extension of this methodology and its application to the synthesis of oligosaccharides and nucleosides of potential biological activity, especially 2-deoxy glycosides structurally related to compounds **1** and **2**, are in progress.

4. Experimental

4.1. General

TLC was performed on silica gel 60 plates (DC-Alufolien F_{254}, E. Merck, or Alugram Sil G/UV_{254}, Macherey–Nagel), and preparative TLC on Kieselgel 60 F_{254} DC-Platten 105715 HR, with detection by UV light (254 nm) or by charring with H_2SO_4. Silica gel 60 (E. Merck) was used for column chromatography. Solutions were concentrated under diminished pressure at <40°C. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. IR spectra (films or films on KBr discs) were recorded with an FTIR Bomem Michelson MB-120 spectrophotometer. ^{1}H NMR spectra (500 or 300 MHz) and ^{13}C NMR spectra (125.7 or 75.5 MHz) were recorded with a Bruker AMX-500 or a Bruker AMX-300 spectrometer. Assignments were confirmed by decoupling and/or homonuclear

Table 1
Bond distances (Å) and torsion angles (°) for **4**+**5**

Bond lengths		Torsion angles			
O1'-C1'	1.393(3)	C11'-O1'-C1'-O5'	81.1(2)	C11-O1-C1-O5	71.7(3)
O1'-C11'	1.418(3)	C11'-O1'-C1'-C2'	-161.6(2)	C11-O1-C1-C2	-163.7(2)
O2'-C2'	1.416(3)	C5'-O5'-C1'-O1'	-178.5(2)	C5-O5-C1-O1	69.4(2)
O4'-C4'	1.422(3)	C5'-O5'-C1'-C2'	64.8(2)	C5-O5-C1-C2	-54.7(2)
O5'-C1'	1.419(3)	C1'-O5'-C5'-C4'	-58.6(2)	C1-O5-C5-C4	58.1(2)
O5'-C5'	1.429(3)	C1'-O5'-C5'-C6'	-179.9(2)	C1-O5-C5-C6	179.5(2)
O6'-C6'	1.422(3)	O31'-N3'-C3'-C2'	133.6(2)	O31-N3-C3-C2	48.7(3)
O31'-N3'	1.213(3)	O31'-N3'-C3'-C4'	-111.4(2)	O31-N3-C3-C4	-65.0(3)
O32'-N3'	1.214(3)	O31'-N3'-C3'-C31'	11.1(3)	O31-N3-C3-C31	172.6(2)
N3'-C3'	1.552(2)	O32'-N3'-C3'-C2'	-48.4(2)	O32-N3-C3-C2	-133.1(2)
C1'-C2'	1.529(3)	O32'-N3'-C3'-C4'	66.5(2)	O32-N3-C3-C4	113.3(2)
C2'-C3'	1.535(3)	O32'-N3'-C3'-C31'	-171.0(2)	O32-N3-C3-C31	-9.2(3)
C3'-C4'	1.537(3)	O1'-C1'-C2'-O2'	59.3(2)	O1-C1-C2-O2	50.7(2)
C3'-C31'	1.518(3)	O1'-C1'-C2'-C3'	179.6(2)	O1-C1-C2-C3	-72.9(2)
C4'-C5'	1.538(3)	O5'-C1'-C2'-O2'	175.9(2)	O5-C1-C2-O2	176.6(2)
C5'-C6'	1.515(3)	O5'-C1'-C2'-C3'	-63.7(2)	O5-C1-C2-C3	53.0(2)
O1-C1	1.393(3)	O2'-C2'-C3'-N3'	-67.3(2)	O2-C2-C3-N3	67.8(2)
O1-C11	1.421(3)	O2'-C2'-C3'-C4'	179.8(2)	O2-C2-C3-C4	179.9(2)
O2-C2	1.416(3)	O2'-C2'-C3'-C31'	51.8(2)	O2-C2-C3-C31	-51.4(2)
O4-C4	1.419(3)	C1'-C2'-C3'-N3'	171.5(2)	C1-C2-C3-N3	-168.2(2)
O5-C1	1.409(3)	C1'-C2'-C3'-C4'	58.7(2)	C1-C2-C3-C4	-56.1(2)
O5-C5	1.429(3)	C1'-C2'-C3'-C31'	-69.4(2)	C1-C2-C3-C31	72.6(2)
O6-C6	1.412(3)	N3'-C3'-C4'-O4'	74.6(2)	N3-C3-C4-O4	-70.2(2)
O31-N3	1.218(3)	N3'-C3'-C4'-C5'	-167.0(2)	N3-C3-C4-C5	170.4(2)
O32-N3	1.210(4)	C2'-C3'-C4'-O4'	-172.0(2)	C2-C3-C4-O4	177.9(2)
N3-C3	1.550(3)	C2'-C3'-C4'-C5'	-53.7(2)	C2-C3-C4-C5	58.5(2)
C1-C2	1.528(3)	C31'-C3'-C4'-O4'	-44.2(2)	C31-C3-C4-O4	48.5(2)
C2-C3	1.530(3)	C31'-C3'-C4'-C5'	74.2(2)	C31-C3-C4-C5	-70.9(2)
C3-C4	1.542(3)	O4'-C4'-C5'-O5'	174.1(2)	O4-C4-C5-O5	179.9(2)
C3-C31	1.512(3)	O4'-C4'-C5'-C6'	-67.4(2)	O4-C4-C5-C6	62.7(2)
C4-C5	1.533(3)	C3'-C4'-C5'-O5'	52.4(2)	C3-C4-C5-O5	-58.5(2)
C5-C6	1.519(3)	C3'-C4'-C5'-C6'	170.9(2)	C3-C4-C5-C6	-175.7(2)
		O5'-C5'-C6'-O6'	65.1(2)	O5-C5-C6-O6	-61.0(2)
		C4'-C5'-C6'-O6'	-55.8(2)	C4-C5-C6-O6	58.7(2)

Table 2
Hydrogen-bonding geometry

Intermolecular				
D-H...A(Å)	D-H	H-A	D-A	D-H...A
O6'-H6'...O2'(2)	0.82(2)	2.056(2)	2.841(2)	160(1)
O2'-H2'...O4'(1)	0.82(1)	1.945(1)	2.752(2)	169(1)
O4'-H4...O6(0)	0.82(1)	1.868(2)	2.665(2)	163(1)
O4-H4...O6'(0)	0.82(1)	1.920(2)	2.726(2)	167(1)
O2-H2...O4(3)	0.82(1)	1.960(1)	2.766(2)	168(1)
O6-H6...O2(4)	0.82(2)	2.258(2)	2.992(3)	149(1)
C11-H110...O31'(5)	0.96(3)	2.960(2)	3.283(4)	108(1)
C31-H310...O5(6)	0.96(2)	2.416(2)	3.241(3)	144(1)
Intramolecular				
C31'...O4'	0.96(0)	2.645(2)	2.873(3)	93(1)
C31...O1	0.96(0)	2.404(2)	3.008(3)	121(1)
C2'...O32'	0.98(0)	2.427(2)	2.771(3)	100(1)

Symmetry code:

(0) x, y, z
(1) x, y, z+1
(2) -x+1, y+1/2, -z+2
(3) x, y, z-1
(4) -x+2, y-1/2, -z+1
(5) -x+2, y+1/2, -z+2
(6) -x+2, y+1/2, -z+1

2D COSY, 1D NOESY, and heteronuclear 2D correlated (HETCOR) experiments. HR-EI mass spectra (70 eV) were measured with a Kratos MS-80RFA instrument, with an ionising current of 100 mA, an accelerating voltage of 4 kV, and a resolution of 10 000 (10% valley definition). Fast-atom bombardment mass spectrometry (FABMS) was performed on the same instrument; ions were produced by a beam of xenon atoms (6–7 keV) using a matrix consisting of *m*-nitrobenzyl alcohol or thioglycerol and NaI as salt. FAB-HRMS was performed on a VG Autospec spectrometer (Fisons Instruments) (30 keV). Desorption chemical ionisation (DCI) HRMS (methane) was performed on an AutospecQ instrument (Micromass).

*4.2. Preparation of mixed crystals of methyl 3-deoxy-3-*C*-methyl-3-nitro-α-*D*-glucopyranoside **4** and methyl 3-deoxy-3-*C*-methyl-3-nitro-β-*L*-glucopyranoside **5***[16]

Nitroethane (2.7 mL, 3.00 g, 0.04 mol) and abs. methanol (37.5 mL) were added to a sample of crude dialdehyde **3** obtained by quantitative oxidation of methyl α-D-glucopyranoside (7.74 g, 0.04 mol).[26] After **3** was totally dissolved, 1.3 M methanolic NaOMe (29 mL) was gradually added, the mixture was kept at room temperature for 3 h and water (50 mL) was then added. Sodium ions were exchanged by shaking the mixture with Amberlite IR-120 H resin until pH≈5. The resin was filtered off and washed with distilled water. The filtrate and washings were joined and concentrated at reduced pressure, and the residue was coevaporated with abs. ethanol (3×20 mL). Addition of a final amount of abs. ethanol (25 mL) to the dry residue and cooling at 5°C afforded, after 1 h, a crystalline product, X-ray crystallographic

analysis of which evidenced that it consisted of mixed crystals formed by a 1:1 mixture of **4** and **5** (1.46 g, 15%); mp 183–185°C, $[\alpha]_D^{30}$ +73.4 (*c* 1.45, H_2O). Anal. calcd for $C_8H_{15}NO_7$: C, 40.52; H, 6.37; N, 5.91. Found: C, 40.28; H, 6.11; N, 6.07; lit.[16], mp 191–193°C, $[\alpha]_D^{23}$ +79.3 (*c* 1.45, H_2O). The residue obtained (7.28 g) by evaporation of the mother liquor contained α-D-isomer **4** (50% by ^{1}H NMR) and minor amounts of other diastereomers.

*4.3. Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-3-nitro-α-*D*-glucopyranoside **6** and methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-3-nitro-β-*L*-glucopyranoside **7***

(a) Dry zinc chloride (0.97 g, 7.11 mmol) was added to a solution of mixed crystals of **4** and **5** (1.00 g, 4.22 mmol) in freshly distilled benzaldehyde (6 mL, 6.27 g, 59.10 mmol). The solution was kept at room temperature for 24 h and then poured into ice-water. After separation of the two layers, the organic phase was washed with water. Hexane was added to the organic phase to afford, after cooling and scratching, a solid which was filtered and washed with hexane portions to eliminate the excess of benzaldehyde. The solid was subjected to column chromatography (1:2, ether:hexane) to give, separately, **6** (0.488 g, 36%) and **7** (0.486 g, 35%).

(b) Benzaldehyde dimethylacetal (475 μL, 3.16 mmol) and *p*-toluenesulphonic acid (3 mg) were added to a solution of mixed crystals of **4** and **5** (0.50 g, 2.11 mmol) in *N*,*N*-dimethylformamide (3 mL). The solution was kept at room temperature and reduced pressure for 8 h in order to eliminate the MeOH evolved. It was necessary to replace the benzaldehyde dimethylacetal partially evaporated during the process. The reaction mixture was then neutralised with saturated aqueous sodium hydrogencarbonate and concentrated at reduced pressure. The residue was treated with dichloromethane (3×10 mL) and the extract was concentrated to a colourless syrup, which was subjected to column chromatography (same system) to give, separately, **6** (0.291 g, 42%) and **7** (0.321 g, 47%). Compound **6**: mp 162–164°C; R_F=0.35 in 2:1 ether:hexane; $[\alpha]_D^{20}$ +84 (*c* 1, CH_2Cl_2); IR (film) ν_{max} 3507 (OH), 1545 and 1394 cm^{-1} (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.33 (m, 5H, Ph), 5.53 (s, 1H, C*H*–Ph), 4.85 (d, 1H, $J_{1,2}$=4.4, H-1), 4.45 (dd, 1H, $J_{2,OH}$=11.0, H-2), 4.36 (dd, 1H, $J_{5,6}$=5.5, $J_{6,6'}$=9.5, H-6), 4.33 (dd, 1H, $J_{4,5}$=9.1, H-4), 3.79 (m, 2H, H-5 and H-6′), 3.46 (s, 3H, MeO), 2.48 (d, 1H, HO-2), and 1.79 (s, 3H, Me-3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 136.4, 129.1, 128.1 and 126.0 (Ph), 101.3 (*C*H–Ph), 99.3 (C-1), 92.9 (C-3), 79.8 (C-4), 72.1 (C-2), 68.9 (C-6), 60.8 (C-5), 56.1 (MeO), and 11.3 (Me-3); FABMS: *m/z* 348 (100, $[M+Na]^+$). Anal. calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.89; N, 4.30. Found: C, 55.16; H, 6.13; N, 4.54. Compound **7**: mp 154–156°C; R_F=0.46 in 2:1 ether:hexane; $[\alpha]_D^{25}$ +69 (*c* 0.75, CH_2Cl_2); IR (film) ν_{max} 3437 (OH), 1563 and 1388 cm^{-1} (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.33 (m, 5H, Ph), 5.53 (s, 1H, C*H*–Ph), 4.42 (dd, 1H, $J_{5,6}$=5.0, $J_{6,6'}$=10.6, H-6), 4.36 (d, 1H, $J_{1,2}$=7.5, H-1), 4.30 (d, 1H, $J_{4,5}$=9.5, H-4), 4.20 (dd, 1H, H-2), 3.83 (dd, 1H, $J_{5,6'}\approx$10.0, H-6′), 3.61 (ddd, 1H, H-5), 3.59 (s, 3H, MeO), 2.56 (brs, 1H, HO-2), and 1.77 (s, 3H, Me-3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 136.2, 129.2, 128.2 and 125.9 (Ph), 102.8 (C-1), 101.4 (*C*H–Ph), 91.9 (C-3), 80.4 (C-4), 74.0 (C-2), 68.8 (C-6), 65.7 (C-5), 57.6 (MeO), and 10.3 (Me-3); FABMS: *m/z* 348 (100, $[M+Na]^+$). Anal. calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.89; N, 4.30. Found: C, 55.35; H, 6.06; N, 4.17.

*4.4. Methyl 3-deoxy-3-*C*-methyl-3-nitro-α-*D*-glucopyranoside **4***

p-Toluenesulphonic acid (19 mg, 0.1 mmol) was added to a solution of **6** (0.325 g, 1 mmol) in 1:1 methanol:dioxane (10 mL). The mixture was heated at 60°C for 2 h and then at 85°C for 1 h, neutralised with Et_3N and concentrated at reduced pressure. Treatment of the residue with hexane gave a white solid which was collected and washed thoroughly with hexane to yield the title product **4**: 0.237 g, 99%;

R_F=0.27 (ether); mp 156–158°C; $[\alpha]_D^{28}$ +124 (*c* 1.0, methanol); IR (film) ν_{max} 3325 (OH), 1553 and 1418 cm^{-1} (NO_2); ^1H NMR (500 MHz, CD_3OD): δ 4.74 (d, 1H, $J_{1,2}$=4.3, H-1), 4.28 (d, 1H, H-2), 4.19 (d, 1H, $J_{4,5}$=10.1, H-4), 3.81 (dd, 1H, $J_{5,6}$=2.4, $J_{6,6'}$=12.0, H-6), 3.71 (dd, 1H, $J_{5,6'}$=5.1, H-6′), 3.53 (ddd, 1H, H-5), 3.40 (s, 3H, MeO), and 1.66 (s, 3H, Me-3); ^{13}C NMR (125.7 MHz, CD_3OD): δ 101.0 (C-1), 98.2 (C-3), 73.3 (C-2), 71.9 (C-5), 71.7 (C-4), 62.5 (C-6), 56.1 (OMe) and 11.8 (Me-3); CIHRMS: *m/z* 238.0928 (calcd for $C_8H_{15}NO_7$ [M^++1]: 238.0927).

*4.5. Methyl 3-deoxy-3-*C*-methyl-3-nitro-β-*L*-glucopyranoside **5***

Treatment of compound **7** (0.325 g, 1 mmol) as indicated above for compound **6** gave the title product **5**: 0.235 g, 99%; R_F=0.38 (ether); mp 102–104°C; $[\alpha]_D^{23}$ +13 (*c* 1.0, methanol); IR (film) ν_{max} 3341 (OH), 1553 and 1410 cm^{-1} (NO_2); ^1H NMR (500 MHz, CD_3OD): δ 4.31 (d, 1H, $J_{1,2}$=8.0, H-1), 4.15 (d, 1H, $J_{4,5}$=10.0, H-4), 3.94 (d, 1H, H-2), 3.86 (dd, 1H, $J_{5,6}$=2.1, $J_{6,6'}$=12.0, H-6), 3.68 (dd, 1H, $J_{5,6'}$=5.1, H-6′), 3.53 (s, 3H, MeO), 3.42 (ddd, 1H, H-5), and 1.60 (s, 3H, Me-3); ^{13}C NMR (125.7 MHz, CD_3OD): δ 103.7 (C-1), 97.5 (C-3), 76.9 (C-5), 72.0 (C-2), 68.1 (C-4), 62.7 (C-6), 57.3 (OMe) and 10.3 (Me-3); CIHRMS: *m/z* 238.0933 (calcd for $C_8H_{15}NO_7$ [M^++1]: 238.0927).

*4.6. Methyl 3,6-dideoxy-6-fluoro-3-*C*-methyl-3-nitro-α-*D*-glucopyranoside **8***

A suspension of compound **4** (0.80 g, 3.36 mmol) in dry dichloromethane (13.6 mL), cooled at −35°C under argon, was treated with DAST (2.5 mL, 20 mmol). The cooling bath was removed and the mixture was kept stirring at room temperature for 1.5 h. The mixture was cooled to −10°C, quenched via addition of methanol (6.8 mL), and then concentrated at reduced pressure. Column chromatography of the residue (2:1, hexane:ethyl acetate) afforded **8** as a syrup: 0.62 g, 77%; R_F=0.25 (same system); $[\alpha]_D^{23}$ +10.1 (*c* 0.9, methanol); IR (film) ν_{max} 3436 (OH), 1553 and 1347 (NO_2), 1045 (CF) cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 4.75 (d, 1H, $J_{1,2}$=4.3, H-1), 4.64 (ddd, 1H, $J_{6,F}$=47.3, $J_{6,6'}$=10.3, $J_{5,6}$=3.8, H-6), 4.59 (ddd, 1H, $J_{6',F}$=47.9, $J_{5,6}$=1.7, H-6′), 4.28 (d, 1H, H-2), 4.24 (d, 1H, $J_{4,5}$=10.4, H-4), 3.66 (dddd, 1H, $J_{5,F}$=26.5, H-5), 3.40 (s, 3H, MeO), and 1.68 (s, 3H, Me-3); ^{13}C NMR (125.7 MHz, CD_3OD): δ 101.1 (s, C-1), 98.0 (s, C-3), 83.3 (d, $J_{C\text{-}6,F}$=172.2, C-6), 73.2 (s, C-2), 70.6 (d, $J_{C\text{-}5,F}$=24.5, C-5), 70.5 (s, C-4), 56.2 (s, MeO), and 11.7 (s, Me-3). FABMS: *m/z* 262 (58, [M+Na]$^+$); EIHRMS: *m/z* 208.0608 (calcd for $C_8H_{14}FNO_6$−OMe: 208.0621). Anal. calcd for $C_8H_{14}FNO_6$: C, 40.16; H, 5.90; N, 5.85. Found: C, 40.32; H, 5.85; N, 5.80.

*4.7. Methyl 3,6-dideoxy-6-fluoro-3-*C*-methyl-3-nitro-β-*L*-glucopyranoside **9***

Compound **5** (0.284 g, 1.2 mmol), dissolved in dichloromethane (5 mL) at −35°C, was treated with DAST (900 μL, 7.15 mmol) as indicated for the preparation of **6**. The mixture was processed as stated above, and the residue was subjected to column chromatography (4:1, hexane:ethyl acetate) to give **9**: 183 mg, 64%; R_F=0.21 (2:1, hexane:ethyl acetate); $[\alpha]_D^{25}$ +14.0 (*c* 1, methanol); IR (film) ν_{max} 3412 (OH), 1553 and 1355 (NO_2), 1045 (CF) cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 4.80 (dd, 2H, $J_{6,F}$=47.6, $J_{5,6}$=2.4, H-6 and H-6′), 4.54 (d, 1H, $J_{1,2}$=8.0, H-1), 4.39 (d, 1H, $J_{4,5}$=10.1, H-4), 4.12 (d, 1H, H-2), 3.80 (ddt, 1H, $J_{5,F}$=25.6, H-5), 3.71 (s, 3H, MeO), and 1.79 (s, 3H, Me-3); ^{13}C NMR (125.7 MHz, CD_3OD): δ 103.7 (s, C-1), 97.2 (s, C-3), 83.2 (d, $J_{C\text{-}6,F}$=176.0, C-6), 75.4 (d, $J_{C\text{-}5,F}$=25.1, C-5), 74.8 (s, C-2), 70.9 (d, $J_{C\text{-}4,F}$=7.5, C-4), 57.3 (s, MeO), and 10.1 (s, Me-3). FABHRMS: *m/z* 262.0686 (93, [M+Na]$^+$; calcd for $C_8H_{14}FNO_6$+Na: 262.0703). CIHRMS: *m/z* 238.0724 ([M−1]$^+$; calcd for $C_8H_{14}FNO_6$−H: 238.0730);

208.0622 (calcd for $C_8H_{14}FNO_6$−OMe: 208.0621). Anal. calcd for $C_8H_{14}FNO_6$: C, 40.16; H, 5.90; N, 5.85. Found: C, 40.40; H, 5.24; N, 5.97.

*4.8. Phenyl 3-deoxy-3-*C*-methyl-3-nitro-1-thio-α-*D*-glucopyranoside **10** and phenyl 3-deoxy-3-*C*-methyl-3-nitro-1-thio-β-*D*-glucopyranoside **11***

Into a solution of compound **6** (0.60 g, 1.85 mmol) in freshly distilled pyridine (5.5 mL), kept under argon atmosphere, were dropped successively hexamethyldisilazane (193 μL, 0.92 mmol) and trimethylchlorosilane (234 μL, 1.85 mmol). After 2 h at room temperature, the mixture was diluted with hexane (~35 mL) and poured into a large excess of ice-water. The organic layer was separated, washed several times with water and brine, and dried over sodium sulphate. Evaporation of the solvent yielded the per-*O*-trimethylsilyl derivative, to which, without further purification, was added under argon a solution of trimethyl(phenylthio)silane (1.75 mL, 9.26 mmol) in 1,2-dichloroethane (9 mL). To this mixture were added zinc iodide (1.77 g, 5.55 mmol) and tetrabutylammonium iodide (0.69 g, 1.85 mmol), and the resulting suspension was heated at 60°C with stirring for 8 h. The solids were filtered off and the filtrate was washed with saturated aqueous sodium hydrogencarbonate. The organic phase was shaken with brine, dried over sodium sulphate, and concentrated at reduced pressure to give a syrup which was purified by column chromatography (9:1, dichloromethane:acetone). The product (0.39 g, 67%) was a 1:4 mixture of the anomeric thioglycosides **10** and **11**, respectively. Anal. calcd for $C_{13}H_{17}NO_6S$: C, 49.51; H, 5.43; N, 4.44. Found: C, 49.75; H, 5.62; N, 4.02. Separation of the two anomers could be achieved by preparative TLC (22:1, dichloromethane:methanol). α-Anomer **10**: R_F=0.21 (20:1, dichloromethane:methanol); $[\alpha]_D^{25}$ +220.7 (*c* 0.58, $CHCl_3$); IR (film) ν_{max} 3444 (OH), 1545 and 1348 (NO_2), 606 (CS) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.35 (m, 5H, Ph), 5.61 (d, 1H, $J_{1,2}$=6.3, H-1), 4.70 (dd, 1H, $J_{2,OH}$=8.0, H-2), 4.50 (dd, 1H, $J_{4,5}$=9.8, H-4), 4.06 (dt, 1H, $J_{5,6}$=$J_{5,6'}$=3.3, H-5), 3.95 (brs, 2H, H-6, and H-6′), 3.11 (brs, 1H, HO-4), 2.83 (d, 1H, HO-2), 1.99 (brs, 1H, HO-6), and 1.82 (s, 3H, Me-3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 133.6, 132.3, 129.3 and 128.3 (Ph), 95.5 (C-3), 90.2 (C-1), 71.2 (C-2), 70.4 (C-5), 69.7 (C-4), 62.0 (C-6), and 12.1 (Me-3); FABMS: *m/z* 338 (46, $[M+Na]^+$); CIHRMS: *m/z* 315.0789 ($[M^+]$; calcd for $C_{13}H_{17}NO_6S$: 315.0776). β-Anomer **11**: R_F=0.43 (20:1, dichloromethane:methanol); $[\alpha]_D^{25}$ −39 (*c* 1, $CHCl_3$); IR (film) ν_{max} 2880 (OH), 1547 and 1340 (NO_2), 574 (CS) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.50–7.34 (m, 5H, Ph), 4.61 (d, 1H, $J_{1,2}$=10.0, H-1), 4.06 (dd, 1H, $J_{2,OH}$=2.7, H-2), 4.30 (dd, 1H, $J_{4,OH}$=3.4, $J_{4,5}$=9.7, H-4), 3.46 (dt, 1H, $J_{5,6}$=$J_{5,6'}$=3.4, H-5), 3.90 (dd, 1H, $J_{6,6'}$=11.9, H-6), 3.82 (dd, 1H, H-6′), 3.32 (brs, 1H, HO-4), 2.79 (d, 1H, HO-2), 2.33 (brs, 1H, HO-6), and 1.68 (s, 3H, Me-3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 133.2, 130.8, 129.3 and 128.8 (Ph), 95.3 (C-3), 87.2 (C-1), 77.4 (C-5), 71.7 (C-2), 70.1 (C-4), 62.2 (C-6), and 9.6 (Me-3); FABMS: *m/z* 338 (17, $[M+Na]^+$). CIHRMS: *m/z* 315.0771 ($[M^+]$; calcd for $C_{13}H_{17}NO_6S$: 315.0776).

*4.9. Phenyl 3-deoxy-3-*C*-methyl-3-nitro-1-thio-α-*L*-glucopyranoside **12** and phenyl 3-deoxy-3-*C*-methyl-3-nitro-1-thio-β-*L*-glucopyranoside **13***

Treatment of compound **7** (0.80 g, 2.46 mmol), under the above conditions, with hexamethyldisilazane (256 μL, 1.23 mmol) and trimethylchlorosilane (310 μL, 2.46 mmol), and subsequently with trimethyl(phenylthio)silane (2.32 mL, 12.3 mmol) gave, after a similar workup, a syrup, which was purified by column chromatography (11:1, dichloromethane:acetone). The product (0.50 g, 64%) was a 1:4 mixture of the anomeric thioglycosides **12** and **13**, respectively. FABMS: *m/z* 338 (48, $[M+Na]^+$). Anal. calcd for $C_{13}H_{17}NO_6S$: C, 49.51; H, 5.43; N, 4.44. Found: C, 49.26; H, 5.34; N, 4.39. Separation of the

two anomers could be achieved by preparative TLC (22:1, dichloromethane:methanol). α-Anomer **12**: $[\alpha]_D^{25}$ −215.5 (*c* 0.58, $CHCl_3$); CIHRMS: *m/z* 315.0777 ([M^+]; calcd for $C_{13}H_{17}NO_6S$: 315.0776); this product showed IR and NMR spectra identical to those of its enantiomer **10**. β-Anomer **13**: $[\alpha]_D^{25}$ +38 (*c* 1, $CHCl_3$); CIHRMS: *m/z* 315.0785 ([M^+]; calcd for $C_{13}H_{17}NO_6S$: 315.0776); this product showed IR and NMR spectra identical to those of its enantiomer **11**.

*4.10. Phenyl 3,6-dideoxy-6-fluoro-3-*C*-methyl-3-nitro-1-thio-β-*D*-glucopyranoside **14***

A suspension of compound **11** (100 mg, 0.32 mmol) in dry dichloromethane (2 mL), cooled at −35°C under argon, was treated with DAST (250 μL, 1.91 mmol). The mixture was stirred at −30°C for 3 h; then the temperature was allowed to rise to −20°C and the reaction was quenched via addition of methanol (600 μL). After evaporation of the solvents under reduced pressure, column chromatography of the residue (gradient 60:1 to 10:1, dichloromethane:acetone) afforded pure **14** (42 mg, 26%) [unreacted **11** (11 mg, 11%) was recovered]. Compound **14** had $[\alpha]_D^{27}$ −22.4 (*c* 1.0, $CHCl_3$); EIHRMS: *m/z* 317.0727 (calcd for $C_{13}H_{16}FNO_5S$ [M^+]: 317.0733); this product showed IR and NMR spectra identical to those of its enantiomer **15**.

*4.11. 2,3,6-Trideoxy-6-fluoro-3-*C*-methyl-3-nitro-2-phenylthio-α-*D*-mannopyranosyl fluoride **16** and 2,3-dideoxy-3-*C*-methyl-3-nitro-2-phenylthio-α-*D*-mannopyranosyl fluoride **18***

DAST (305 μL, 2.30 mmol) was added to a solution of compound **11** (120 mg, 0.38 mmol) in dry dichloromethane (2 mL), cooled at −35°C under argon. The mixture was allowed to warm to room temperature for 90 min and the reaction was then quenched at −10°C by adding methanol (0.75 mL). After evaporation of the solvents, the residue was subjected to column chromatography (gradient 1:3 to 1:1, ether:hexane) to afford 73 mg (60%) of **16** and 10 mg (10%) of **18**, both as syrups. Compound **16** had $[\alpha]_D^{28}$ −14.8 (*c* 0.80, $CHCl_3$); EIHRMS: *m/z* 319.0688 ([M^+]; calcd for $C_{13}H_{15}F_2NO_4S$: 319.0690); this product showed identical IR and NMR spectra to those of its enantiomer **17**. Compound **18** showed IR and NMR spectra identical to those of its enantiomer **19**.

*4.12. Phenyl 3,6-dideoxy-6-fluoro-3-*C*-methyl-3-nitro-1-thio-β-*L*-glucopyranoside **15***

A suspension of compound **13** (70 mg, 0.23 mmol) in dry dichloromethane (2 mL), cooled at −35°C under argon, was treated with DAST (179 μL, 1.38 mmol) for 3 h under the conditions indicated above for the preparation of **14**, followed by a similar workup (460 μL of methanol used for quenching), to afford after column chromatography (same system) 47 mg (68%) of **15** as a syrup [unreacted **13** (16 mg, 22%) was recovered]; R_F=0.57 (2:1, ether:hexane); $[\alpha]_D^{27}$ +23.6 (*c* 0.55, $CHCl_3$); IR (film) ν_{max} 1551 and 1344 (NO_2), 1096 (CF) cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.56–7.35 (m, 5H, Ph), 4.57 (d, 1H, $J_{1,2}$=9.9, H-1), 4.70 (ddd, 1H, $J_{6,F}$=47.5, $J_{6,6'}$=10.3, $J_{5,6}$=2.3, H-6), 4.67 (ddd, 1H, $J_{6',F}$=47.2, $J_{5,6}$=3.2, H-6′), 4.31 (d, 1H, $J_{4,5}$=10.0, H-4), 4.02 (d, 1H, H-2), 3.56 (dddd, 1H, $J_{5,F}$=24.8, H-5), 2.64 and 2.54 (each brs, each 1H, HO-2 and HO-4), and 1.70 (s, 3H, Me-3); ^{13}C NMR (125.7 MHz, CD_3OD): δ 133.6, 130.3, 129.2 and 128.9 (each s, Ph), 95.0 (s, C-3), 86.9 (s, C-1), 81.9 (d, $J_{C-6,F}$=176.0, C-6), 76.4 (d, $J_{C-5,F}$=18.4, C-5), 71.2 (s, C-2), 69.2 (d, $J_{C-4,F}$=7.5, C-4), and 9.7 (s, Me-3); FABMS: *m/z* 340 (30, [M+Na]$^+$); CIHRMS: *m/z* 317.0740 ([M^+]; calcd for $C_{13}H_{16}FNO_5S$: 317.0733); EIHRMS: *m/z* 317.0727 ([M^+]; calcd for $C_{13}H_{16}FNO_5S$: 317.0733).

4.13. 2,3,6-Trideoxy-6-fluoro-3-C-methyl-3-nitro-2-phenylthio-α-L-mannopyranosyl fluoride **17** and 2,3-dideoxy-3-C-methyl-3-nitro-2-phenylthio-α-D-mannopyranosyl fluoride **19**

Treatment of compound **13** (58 mg, 0.18 mmol) in dry dichloromethane (1.2 mL) with DAST (146 μL, 1.11 mmol) under the conditions stated above for the preparation of **16** and **18**, followed by a similar workup (0.40 mL of methanol used for quenching), afforded after column chromatography (same system) 34 mg (58%) of **17** and 8.5 mg (15%) of **19**, both as syrups. Compound **17**: R_F=0.53 (1:1, ether:hexane); $[\alpha]_D^{30}$ +14.9 (*c* 0.80, $CHCl_3$); IR (film) ν_{max} 3579 (OH), 1553 and 1394 (NO_2), 1097 (CF) and 665 (CS) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.34 (m, 5H, Ph), 5.98 (dd, 1H, $J_{1,F}$=53.2, $J_{1,2}$=1.3, H-1), 4.82 (ddd, 1H, $J_{6,F}$=46.0, $J_{6,6'}$=10.3, $J_{5,6}$=3.3, H-6), 4.72 (ddd, 1H, $J_{6',F}$=45.4, $J_{5,6}$=1.7, H-6′), 4.67 (d, 1H, $J_{4,5}$=10.2, H-4), 3.94 (dddd, 1H, $J_{5,F}$=25.7, H-5), 3.73 (dd, 1H, $J_{2,F}$=3.4, H-2), 2.97 (brs, 1H, HO-4), and 1.91 (d, 3H, $J_{Me,F}$=2.3, Me-3); NOE contacts (1D NOESY): Me-3, H-2, H-5; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 133.2, 133.0, 129.6 and 129.2 (each s, Ph), 108.6 (d, $J_{C\text{-}1,F}$=233.8, C-1), 91.8 (s, C-3), 81.3 (d, $J_{C\text{-}6,F}$=174.7, C-6), 71.6 (d, $J_{C\text{-}5,F}$=18.9, C-5), 64.3 (d, $J_{C\text{-}4,F}$=7.5, C-4), 56.4 (d, $J_{C\text{-}2,F}$=23.9, C-2), and 20.2 (d, $J_{Me,F}$=7.8, Me-3); EIHRMS: *m/z* 319.0688 ([M^+]; calcd for $C_{13}H_{15}F_2NO_4S$: 319.0690). Anal. calcd for $C_{13}H_{15}F_2NO_4S$: C, 48.90; H, 4.73; N, 4.39; S, 10.04. Found: C, 49.24; H, 4.50; N, 4.78; S, 9.55. Compound **19**: R_F=0.21 (2:1, ether:hexane); $[\alpha]_D^{29}$ +16.2 (*c* 0.80, $CHCl_3$); IR (film) ν_{max} 3542 (OH), 1545 and 1386 (NO_2), 1085 (CF) and 653 (CS) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.35 (m, 5H, Ph), 5.97 (dd, 1H, $J_{1,F}$=53.3, $J_{1,2}$=1.3, H-1), 4.69 (d, 1H, $J_{4,5}$=9.9, H-4), 3.99 (d, 2H, $J_{5,6}\approx J_{5,6'}$=3.2, H-6 and H-6′), 3.87 (dt, 1H, H-5), 3.73 (dd, 1H, $J_{2,F}$=3.5, H-2), and 1.92 (d, 3H, $J_{Me,F}$=2.3, Me-3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 133.2, 132.8, 129.5 and 129.1 (each s, Ph), 108.4 (d, $J_{C\text{-}1,F}$=233.4, C-1), 91.8 (s, C-3), 72.4 (s, C-5), 64.9 (s, C-4), 61.5 (s, C-6), 56.4 (d, $J_{C\text{-}2,F}$=25.0, C-2), and 20.2 (d, $J_{Me,F}$=7.6, Me-3); EIHRMS: *m/z* 317.0732 ([M^+]; calcd for $C_{13}H_{16}FNO_5S$: 317.0733).

4.14. Crystallographic analysis for mixed crystals of **4**+**5**[†]

The compound crystallised as colourless monoclinic prisms. A crystal of dimensions 0.20×0.28×0.40 mm was mounted on a CAD4 Enraf–Nonius automated diffractometer; it belonged to the monoclinic system, space group $P2_1$. Accurate cell dimensions and crystal orientation matrix, determined by least-squares treatment of the setting angles of 25 independent reflections in the range $2<\theta<30°$ using Mo-Kα radiation (λ=0.71069 Å), were *a*=12.713(2), *b*=12.557(3), and *c*=6.708(1) Å, β=104.07(1)°, *V*=1038.7(3) $Å^3$, d_{calc}=1.52 g cm^{-3} for *Z*=2, *F*(000)=504 and the absorption coefficient μ=0.13 mm^{-1}. Data (3148 reflections) were collected at room temperature, using ω/2θ scan mode to a maximum 2θ value of 60°. The intensities of two standard reflections were measured every 100 reflections, and as the intensities of these reflections showed less than 5% variation, corrections for decomposition were deemed unnecessary. Intensities were corrected for Lorentz and polarisation effects, but no absorption correction was made. A total of 2547 reflections were considered observed [$I>2\sigma(I_0)$]. The structure was solved by direct methods using SIR92[27] to locate all non-hydrogen atoms. Refinement on F^2 was performed using SHELXL93.[28] All H-atoms were located by difference Fourier, but not refined. The final cycle of refinements led to a final agreement factor *R*=0.0374, and $wR(F^2)$=0.0918 for $w=1/[\sigma^2(F_0^2)+(0.0602P)^2+0.0000P]$ where $P=(F_0^2+2F_c^2)/3$ for 197 variables. Atomic scattering factors were taken from the *International Tables for X-Ray Crystallography*,[29] maximum and minimum residual

[†] Lists of the atomic coordinates, hydrogen coordinates, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

densities in the final difference map 0.30 and −0.23 eÅ^{-3}, respectively. The geometrical analysis was performed using PARST.[30]

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