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Towards cyclic, conformationally constrained, fluorine-containing β-amino acid derivatives from D-glucose

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Abstract—Novel, potentially bioactive, fluorinated branched-chain monosaccharides were obtained by reaction of diethylaminosulphur trifluoride (DAST) with a series of methyl 3-*C*-cyano-3-ethoxycarbonyl-β-D-glucopyranoside derivatives, including the 4,6-*O*-benzylidene derivative and their 3-*C*-(*N*-protected aminomethyl) reduction products, as well as the phenyl 3-*C*-cyano-3-ethoxycarbonyl-1-thio-α-D-(and β-D-)glucopyranosides. The absolute configuration at C(3) was unambiguously assigned for all compounds on the basis of X-ray crystallographic analysis of methyl 4,6-*O*-benzylidene-3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside, corroborating the previous tentative assignment by other authors for the 4,6-unprotected compound. The course of the fluorination depended on the reaction temperature and the substitution pattern of the substrate. Thus, for methyl 3-*C*-cyano-3-ethoxycarbonyl-β-D-glucopyranoside, fluorination occurred exclusively at C(6), but for the phenylthio analogue, a 2-deoxy-2-phenylthio-α-D-*manno*-configured glycosyl fluoride and its 6-fluoro derivative were obtained, resulting from the expected rearrangement reaction, whilst starting from the phenylthio α anomer, only the unrearranged 6-fluoro compound was formed. Rearrangement was also observed in the fluorination of methyl 4,6-*O*-benzylidene-3-*C*-(*N*-protected aminomethyl)-β-D-glucopyranoside, which led to the 2-*O*-methyl-α-D-mannopyranosyl fluoride derivative as the sole product. This methodology may constitute a simple route to enantiopure conformationally constrained cyclic fluorinated β-amino acids having the α carbon atom shared with a pyranose ring, although only moderate yields were achieved, particularly in the fluorination step. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

β-Amino acids are natural products of increasing interest because of their synthetic and biological applications; for instance, they are synthetic precursors of β-lactams, and diverse enantioselective syntheses have been developed.[1] Fluorine-containing β-amino acids constitute a particular class of derivatives, some of which show biological activity as enzyme inhibitors,[2–4] thus attracting the attention of many researchers.[5,6] It is also known that conformationally restricted peptides and peptide mimics show enhanced specificity on interacting with the receptor[7,8] and, for this reason, synthetic routes towards cyclic conformationally constrained α-amino acids have been developed.

These precedents led us to search for routes to β-amino acids and fluoro-β-amino acids having restricted conformational mobility. One way to achieve such conformational restriction might be to embed a moiety of the desired structure, or a synthetic precursor (such as a cyanoacetic ester in this case), into the ring of a readily available compound (for instance, pyranose), so that an atom is shared. It has been described[9] that, in the Baer–Fischer reaction of ethyl cyanoacetate with the dialdehyde **1**, (easily prepared by periodate oxidation of methyl β-D-glucopyranoside), the only product is a 3-branched-chain pyranoside **2**, characterised as its 2,4,6-triacetate **3**, to which the (3*R*) absolute configuration was tentatively assigned on the basis of the expected relative stability of the two possible *axial–equatorial* substitution patterns.

We report herein the crystalline structure of its 4,6-*O*-benzylidene derivative **4**, thus unambiguously evidencing the absolute configuration of **2** (Scheme 1). Fluorination of bioactive substances may lead to therapeutic agents of increasing lipid permeability and metabolic stability;[10] most particularly, fluorination of

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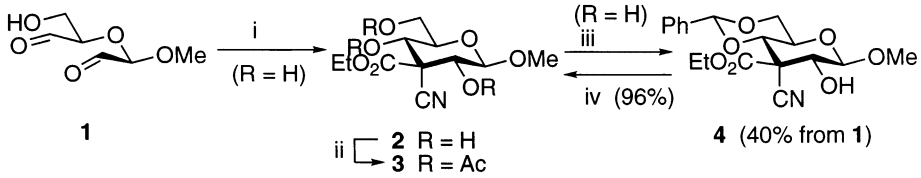


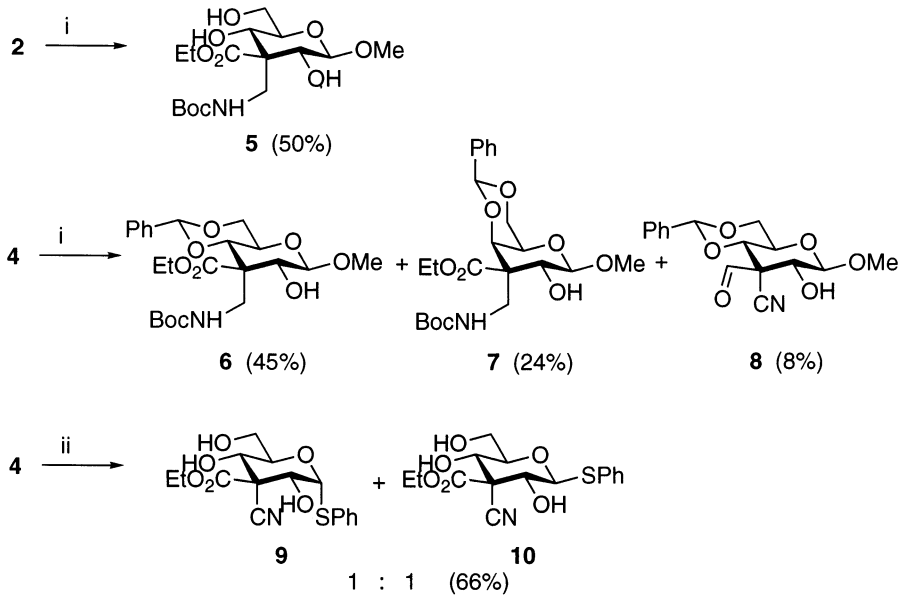
Scheme 1. (i) NC–CH_2–COOEt/piperidine; (ii) Ac_2O/pyridine (Ref. 9); (iii) PhCHO/$ZnCl_2$; (iv) TsOH.

the sugar moiety of glycosides[11] and nucleosides[12] results in considerable reinforcement of the glycosidic bond, which is perhaps one reason for the increasing number of syntheses of deoxyfluoro sugars published over the past decade.[13] Furthermore, glycosyl fluorides have been used as glycosyl donors in the synthesis[14–16] of glycosides, oligosaccharides, and nucleosides and it is well known that the presence of a phenylthio group at the 2 position of the glycosyl donor assists stereocontrol in the glycosidation reaction;[17] the required 2-phenylthio-glycosyl fluorides can be obtained from 1,2-*trans*-diequatorial phenyl 1-thio-glycopyranosides by fluorination with diethylaminosulphur trifluoride (DAST), which occurs with rearrangement.[17,18] Herein, we report the results found in the transformation of the 3-*C*-cyano-3-ethoxycarbonyl sugar derivatives **2** and **4** into conformationally constrained *N*-protected β-amino esters with the α carbon atom being C(3) of the pyranose ring, as well as into phenyl 1-thio derivatives, all of which are suitable substrates for obtaining, via reaction with DAST, novel fluorinated branched-chain monosaccharides.

2. Results and discussion

Unambiguous assignment of the (3*R*) absolute configuration of **2** was made by X-ray diffraction analysis of the crystals of 4,6-*O*-benzylidene derivative **4**, which was easily prepared from crude **2**, thus corroborating the previous tentative assignment.[9] Deprotection of **4** with *p*-toluenesulphonic acid in methanol–dioxane afforded the pure β-D-glycopyranoside **2** in near quantitative yield. The cyano group of **2** and **4** could be easily reduced with sodium borohydride–cobalt(II) chloride[19] to the aminomethyl group, which was protected by acylation with di-*tert*-butyl dicarbonate, in a one-pot procedure,[20] to afford the respective *tert*-butoxycarbonyl-aminomethyl branched-chain sugar compounds. Starting from **2**, compound **5** was obtained in 50% yield as the only product, while **4** afforded the expected compound **6** (45%), accompanied by an isomer (24%) for which the structure **7** is tentatively proposed, and a small amount of the cyano-aldehyde **8** (8%). The high excess of sodium borohydride (>20 mol/mol of substrate), used to compensate for possible losses due to the presence of free hydroxyl group(s) in the substrates and methanol as the solvent would raise the basicity and might promote partial epimerisation, not only at the benzylic position, (as observed with other 4,6-*O*-benzylidene-D-glucopyranosides[21]) but also at C(4), thus affording **7**. In turn, the aldehyde **8** might have been formed in a competitive reduction of the ester group of **4**. Molecules **5** and **6** contain a β-amino ester moiety having the α carbon atom shared with the pyranose ring, a valuable structural feature from a biological point of view. By using the method of Hanessian and Guindon,[22] slightly modified[23] to improve the desilylation process, the phenyl 1-thio-α- and β-D-glucopyranosides **9** and **10** were obtained from **4** as a 1:1 mixture in 66% yield, from which the pure α and β anomers could be separated (each 31% yield) by preparative TLC (Scheme 2).

Fluorination of the foregoing branched-chain sugar derivatives **2**, **4**–**6**, and a 0.6:1 mixture of **9** and **10** with DAST was also studied. The course of the reaction depended on the temperature and the 1,2-*cis* or *trans* substitution pattern of the substrate, but the substrates showed markedly lower reactivity than the 3-*C*-methyl-3-nitro analogues having the methyl *axially* situated instead of the cyano group.[18,24] Thus, the 4-*O*-unprotected compound **2**, treated in dichloromethane at room temperature with DAST, led to the unrearranged 6-fluoro compound **11** (39% from converted substrate), but heating under reflux for 10 h resulted in a complex mixture of products. Treatment of the 4,6-*O*-benzylidene derivative **4** with DAST in refluxing dichloromethane or in the presence of a base such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at room temperature led to the recovery of considerable amounts of unreacted substrate (56–76%), thus affording only low yields of the non-fluorinated product **12** (4–12%, corresponding to 15–29% from converted substrate), which proved to be a 2-deoxy-2-diethylamino sugar derivative. The inability of **2** and **4** to undergo the expected 1,2-rearrangement may be attributed to the presence of two electron-withdrawing groups at C(3), with the cyano group in the *axial* disposition, a structural feature absent in the analogues cited above, which had an *axial* methyl group instead. This *axial* cyano group might exert a destabilising effect on the transition state of the rearrangement reaction, in which the O–SF_2NEt_2 leaving group must adopt a *quasi-axial* orientation in a half-chair conformation of the pyranose ring, implying a strong repulsive dipolar interaction with the *vicinal* cyano group (Fig. 1). The formation of unrearranged **12**, with retained configuration at C(2), may be due to nucleophilic attack of diethylamine (from DAST decomposition). Treatment of the 4,6-*O*-unprotected-3-aminomethyl derivative **5** with DAST in dichloromethane at room temperature or under reflux resulted in a complex mixture containing 43–55% of the



Scheme 2. (i) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, $^tBuOCO–O–COO^tBu$; (ii) $PhSSiMe_3$, $ClCH_2CH_2Cl$, ZnI_2, TBAI.

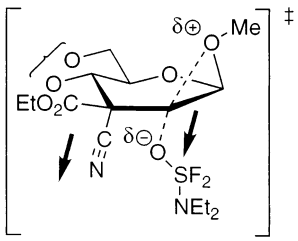
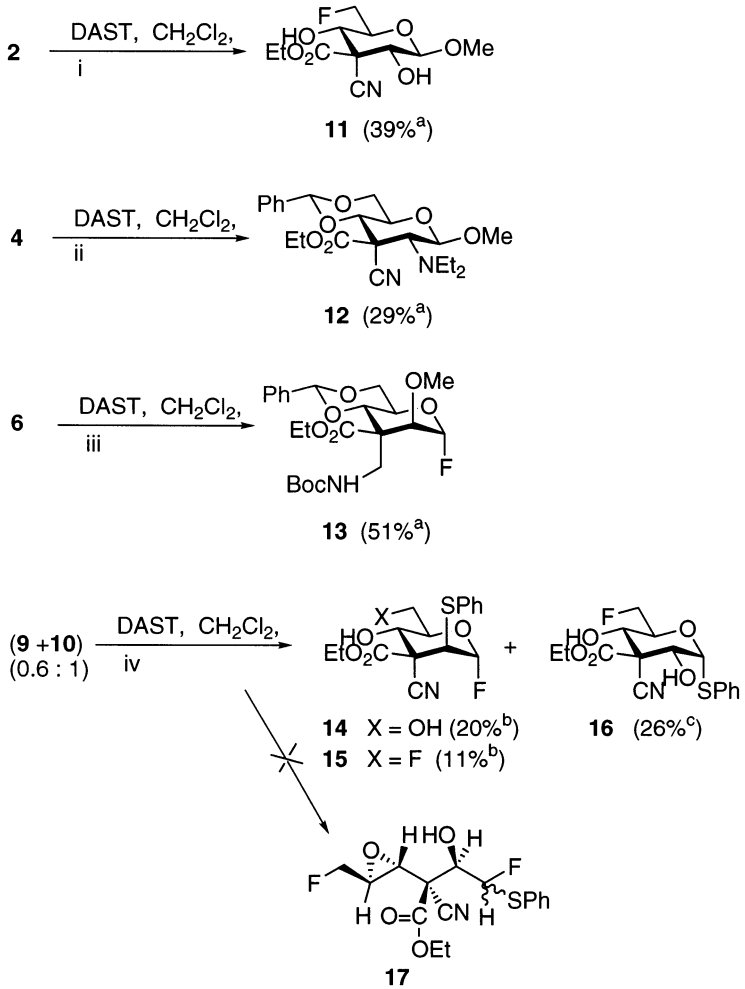


Figure 1. Destabilised transition state for the rearrangement step in the reaction of **2** and **4** with DAST.

unreacted substrate and at least three products which could not be separated. The reaction proceeded better for the 4,6-*O*-protected glycoside **6**, which underwent the expected rearrangement on treatment under reflux, to afford the α-D-*manno* configured glycosyl fluoride **13** as a monohydrate (51% yield from converted substrate). Lastly, treatment of a 0.6:1 mixture of the phenyl 1-thioglycopyranosides **9** and **10** with DAST, first at –40°C and then at room temperature, gave a mixture of the rearranged α-D-mannopyranosyl fluoride **14** and its 6-fluoro derivative **15**, in 20% and 11% yields (from converted **10**), respectively, and the non-rearranged 6-fluoro compound **16**, in 26% yield (from converted **9**). The formation of **14** and **15** from the 1,2-*trans* configured substrate **10** agrees with that expected from the precedents;[17,18] compound **10** undergoes rearrangement to α-D-mannopyranosyl fluoride derivatives **14** and **15** much more easily than the methyl glycoside analogues, **2** and **4**. This is probably a consequence of the greater volume and nucleophilicity of sulphur over oxygen. However, no 4,5-anhydro-1-fluorohexitol derivative, such as **17**, analogous to those obtained from other 4-*O*-unprotected 1,2-*cis*-configured substrates[18] similar to **9**, could be detected (Scheme 3).

The new compounds were structurally elucidated on the basis of their elemental analyses and/or high-resolution mass spectra, as well as IR and ^1H and ^{13}C NMR spectra. For the D-*gluco* configured compounds **2**, **4**–**12** and **16**, the anomeric configuration was easily assigned from the C(1)H/C(2)H coupling constant values. Thus, only the α-D-glucopyranosyl compounds **9** and **16** show for this constant a value of 6.0 Hz, low enough to agree with that expected for an *equatorial–axial* relationship between these protons, while the value observed (7.8–9.8 Hz) in the spectra of the remaining compounds **2**, **4**–**8**, and **10**–**12** indicates the C(1)H/C(2)H *trans-diaxial* disposition present in β-D-glucopyranosyl derivatives. Tentative assignment of structure **7** for the isomer of **6** isolated in the reduction of **4** is supported by its NMR spectra, where the low value of the C(4)H/C(5)H coupling constant (≈ 0) represents the most important change in comparison with that of **6**; other noteworthy changes appeared in the chemical shift values for C(4)H (4.25 and 4.06 ppm, respectively, for **7** and **6**), C(2)H (4.25 and 3.86 ppm), C(6′)H (4.17 and 3.72 ppm), C(4) (78.3 and 81.9 ppm), and C(2) (69.6 and 74.5), all of which are placed on the β-face of the pyranose ring. Furthermore, 1D NOESY experiments for **7** showed contacts of C(7)H with C(4)H and one of the two C(6) protons, and between C(1)H, C(5)H, and the *N*-methylenic protons, compatible with the proposed structure. The NMR spectra of the minor product **8** lack any signal for the ethyl and *tert*-butoxycarbonyl proton and carbon nuclei, showing instead signals for an aldehyde group (9.66 and 192.7 ppm, respectively) and for the cyano group (115.0 ppm), also confirmed by the IR band at 2259 cm^{-1}. For the α-D-mannopyranosyl fluorides **13**–**15**, having the C(1)H/C(2)H *trans-diequatorial* relationship, the coupling constant value is very low (1.1–1.5 Hz) as expected; in these three rearranged compounds, the presence of fluorine is detected in the ^1H and ^{13}C NMR spectra by the characteristic splitting of the signals of other atoms[18,25,26] located 1–3 bonds from it. Thus, for the α-D-*manno*-configured fluorides



Scheme 3. (i) rt, 5 h; (ii) DMAP, rt, 6 days; (iii) reflux, 5 h; (iv) –40°C→rt, 5 h. [a] From converted substrate; [b] from converted **10**; [c] from converted **9**.

13–**15**, the presence of the fluorine atom at position 1 is evidenced by its couplings with C(1)H (49.7, 51.8, and 51.2 Hz, respectively) and C(2)H (13.9, 4.7, and 4.2 Hz), and with C(1) (222.5, 230.0, and 232.5 Hz) and C(2) (36.5, 28.0, and 27.3 Hz). The lack of splitting of the C(3) signal corroborates the α configuration. In the case of the fluoride **15**, another fluorine atom is located at C(6) [couplings with the two C(6)H (47.0 and 48.2 Hz) and C(5)H (27.2 Hz), and with C(6) (172.6 Hz), C(5) (18.2 Hz), and C(4) (7.9 Hz)]. A similar situation was found for compounds **11** and **16**, having a single fluorine atom that also shows couplings with the two C(6) protons (47.9 and 47.7; 47.3 and 48.1; respectively) and C(5)H (26.6 and 27.5 Hz), as well as with C(6) (172.2 and 172.9 Hz), C(5) (17.6 and 17.9 Hz), and C(4) (7.5 and 7.5 Hz). In the case of **12**, the absence of any fluorine atom was evidenced from the lack of the couplings referred to above, while HRMS indicated the introduction of a further nitrogen atom and two ethyl groups, also corroborated in the NMR spectra.

2.1. X-Ray structure analysis of crystalline compound 4

A perspective PLATON view[27] of the molecule along the *c* axis, showing the relative configuration together with the atomic labelling scheme, is shown in Fig. 2. Bond lengths and torsion angles are shown in Table 1. The typical asymmetry of the endocyclic bonds for the pyranose ring [O(5)–C(1) = 1.436(3) and O(5)–C(5) = 1.422(3) Å], caused by the anomeric effect, is observed. The geometry of the pyranose ring agrees with a nearly

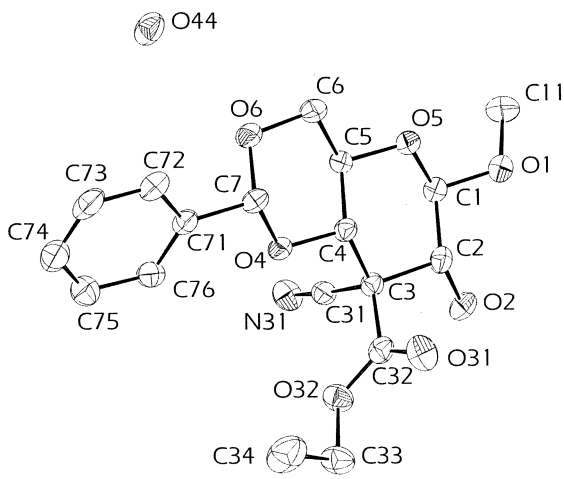


Figure 2. A PLATON view of the molecule **4** along the *c* axis.

Table 1. Selected bond distances (Å) and torsion angles (°) for **4**

Bond lengths		Torsion angles			
O1–C1	1.379(3)	C11–O1–C1–O5	−73.93(29)	C2–C3–C31–N31	−61.03(3.28)
O1–C11	1.428(4)	C11–O1–C1–C2	165.53(25)	C4–C3–C31–N31	55.96(3.29)
O2–C2	1.407(3)	C5–O5–C1–O1	−178.90(20)	C32–C3–C31–N31	176.25(3.17)
O4–C4	1.415(3)	C5–O5–C1–C2	−61.23(26)	C2–C3–C32–O31	50.98(34)
O5–C1	1.436(3)	C1–O5–C5–C4	63.58(25)	C2–C3–C32–O32	−130.12(24)
O5–C5	1.422(3)	C1–O5–C5–C6	−179.57(21)	C4–C3–C32–O31	−65.35(32)
O6–C6	1.435(3)	O1–C1–C2–O2	−66.88(28)	C4–C3–C32–O32	113.56(24)
O6–C7	1.429(3)	O1–C1–C2–C3	173.15(21)	C31–C3–C32–O31	172.94(26)
O31–C32	1.185(4)	O5–C1–C2–O2	175.33(21)	C31–C3–C32–O32	−8.16(31)
O32–C32	1.316(3)	O5–C1–C2–C3	55.36(28)	O4–C4–C5–O5	176.27(19)
O32–C33	1.465(4)	O2–C2–C3–C31	−54.85(22)	O4–C4–C5–C6	57.95(26)
N31–C31	1.139(4)	O2–C2–C3–C32	69.02(26)	C3–C4–C5–O5	−62.72(25)
C1–C2	1.518(4)	C1–C2–C3–C4	−52.03(27)	C3–C4–C5–C6	178.97(21)
C2–C3	1.546(4)	C1–C2–C3–C31	67.16(27)	O5–C5–C6–O6	−173.56(21)
C3–C4	1.532(4)	C1–C2–C3–C32	−168.97(21)	C4–C5–C6–O6	−55.99(27)
C3–C31	1.482(4)	C2–C3–C4–O4	177.64(19)	C7–O4–C4–C3	177.63(20)
C3–C32	1.537(4)	C2–C3–C4–C5	56.13(26)	C4–O4–C7–C71	179.44(21)
C4–C5	1.528(3)	C31–C3–C4–O4	59.26(26)	O4–C7–C71–C72	172.53(25)
C5–C6	1.519(4)	C32–C3–C4–O4	−63.71(25)	O6–C7–C71–C72	−67.34(33)
C7–C71	1.496(4)	C32–C3–C4–C5	174.79(20)	H1–C1–C2–H2	172.86(24)

perfect chair conformation $^4C_1$, with the C(3) atom on one side [0.697(2) Å] and the O(5) atom on the other side [0.676(2) Å] of the least-squares best plane. The ring puckering coordinates[28] and Nardelli[29] asymmetry parameters are $Q=0.59(1)$ Å, $\varphi=-70(3)°$, and $\theta=5(1)°$ for the sequence O(5), C(1), C(2), C(3), C(4), C(5), with $\Delta C_s[C2]=0.004$ and $\Delta C_2[C2–C1]=0.016$. The benzylidene ring geometry observed is also a perfect chair, with the O(4) atom on one side of the least-squares plane, at 0.656(2) Å, and the C(6) atom on the other side, at 0.687(3); the ring puckering coordinates[28] and Nardelli[29] asymmetry parameters are $Q=0.583(3)$ Å, $\varphi=107(8)°$, and $\theta=1.8(3)°$ for the sequence O(4), C(4), C(5), C(6), O(6), C(7). The molecules pack to form a compacted structure where there is a water-of-hydration molecule, accepting and donating H-bonds to symmetry-related pairs of molecules. The water molecule is involved in three H-bonds—in two as a donor and in one as an acceptor—forming a three-dimensional network which stabilises the crystal structure (Table 2).

3. Conclusion

The 3-*C*-cyano-3-ethoxycarbonyl sugar compounds **2**, **4**, **6**, **9**, and **10** used as substrates for fluorination with DAST have shown, under the conditions indicated, an apparent reactivity lower than that exhibited by the 3-*C*-methyl-3-nitro analogues previously described.[18] It is noteworthy that **2** and **4**, having the 1,2-*trans* relationship between the substituents, proved unable to undergo the expected rearrangement to α-D-mannopyranosyl fluoride derivatives; instead, they gave low yields of the unrearranged 6-fluoro compound **11** (from **2**), or the non-fluorinated 2-diethylamino derivative **12** (from **4**). The reduction of **2** and **4** to *N*-protected aminomethyl derivatives occurs with moderate yields, leading in the case of **4** to two isomers **6** and **7** in 69% combined yield and a small amount (8% yield) of a secondary product. This may be considered acceptable as a synthetic route, since the two 4,6-*O*-benzylidene isomers are easily separable. The transformation of **4** into a mixture of the phenyl 1-thioglycopyranoside anomers **9** and **10** was achieved in 66% combined yield, and led—by reaction with DAST—to two rearranged products (from the 1,2-*trans* anomer **10**, as anticipated) and another unrearranged product (from **9**), but no difluoro epoxide **17** similar to those obtained from analogues of the 3-*C*-methyl-3-nitro series.[18] In spite of the only moderate chemical yields achieved, this route may constitute a facile synthetic procedure towards enantiomerically pure, conformationally constrained β-amino acids having the α carbon atom shared with a fluorinated pyranose ring.

4. Experimental

4.1. General

Hexane and ether were distilled from sodium prior to use. TLC was performed on silica gel plates (DC-Alufolien F_{254}, E. Merck, or Alugram Sil G/UV_{254}, Macherey–Nagel), and detection of compounds was accomplished with UV light (254 nm) and by charring with H_2SO_4 or ninhydrin. Silica gel 60 (E. Merck, 230–400 mesh) was used for column chromatography. Solutions were concentrated under diminished pressure

Table 2. Hydrogen-bonding geometry (Å, °) for **4**

D–H···A	D–H	H–A	D–A	D–H···A
O44–H44A···O6^{i}	0.94	2.09	2.924(3)	148
O2–H2···O44^{i}	0.82	1.97	2.784(3)	173
O44–H44B···N31^{ii}	0.83	2.27	3.086(4)	168

Symmetry codes: ^{i} $-x+1$, $y+1/2$, $-z+1/2$; ^{ii} $x+1$, y, z.

at <40°C. Melting points were determined on a Gallenkamp MFB-595 apparatus and are uncorrected. A Perkin–Elmer 241 MC polarimeter was used for measurement of optical rotations. IR spectra (film) were obtained on a FTIR Bomem Michelson MB-120 spectrophotometer. ^{1}H NMR spectra (300 and 500 MHz) and ^{13}C NMR spectra (75.4 and 125.7 MHz) were recorded with Bruker AMX-300 or AMX-500 spectrometers; chemical shifts (δ) are expressed in ppm from TMS; coupling constants (J), in Hz. Assignments were confirmed by decoupling, homonuclear 2D COSY correlated spectra, heteronuclear 2D correlated (HETCOR) spectra, heteronuclear 1D single quantum coherence (HSQC) spectra, and 1D NOESY experiments. EI mass spectra (70 eV) were measured with a Kratos MS-80RFA instrument, with an ionising current of 100 μA, 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. HREIMS (70 eV) and HRCIMS (150 eV) experiments were performed with a Micromass AutoSpecQ instrument with a resolution of 10 000 (5% valley definition). HRFABMS was performed on a VG AutoSpec spectrometer (Fisons Instruments) (30 keV).

4.2. Methyl 4,6-*O*-benzylidene-3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside 4

Ethyl cyanoacetate (3.90 mL, 4.15 g, 36.7 mmol) and piperidine (310 μL) were successively added dropwise to a solution of crude dialdehyde **1** (5.95 g, obtained quantitatively by oxidation of methyl β-D-glucopyranoside (6.24 g, 32.2 mmol)) in 2:1 dioxane:water (81 mL). The reaction mixture was stirred at rt until the complete transformation of the substrate (24 h, TLC monitoring, ether). The mixture was concentrated to a syrup, which was dissolved in water (50 mL), the solution was extracted with ethyl acetate (4×60 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. To a solution of the syrupy residue (crude **2**) in fresh distilled benzaldehyde (44.0 mL, 45.4 g, 428 mmol) dry zinc chloride (7.10 g, 52.0 mmol) was added, and the mixture was kept at rt for 24 h (TLC monitoring, 1:1 hexane:ethyl acetate), and then poured into ice-water (≈500 mL). After separation of the two layers, the organic phase was washed with cold water (2×100 mL) and the excess of benzaldehyde evaporated under reduced pressure. Column chromatography of the residue (9:1→3:1 gradient, hexane:ethyl acetate) afforded **4** as a crystalline product (4.88 g, 40%), X-ray crystallographic analysis of which evidenced the (3*R*) configuration; mp 94–96°C; R_f=0.23 (2:1, hexane:ethyl acetate); $[\alpha]_D^{26}$ −37 (*c* 1.0, CH_2Cl_2); IR (film) ν_{max} 3504 (OH), 2260 (C≡N), 1742 (C=O), 1103 and 1030 cm^{-1} (ester C–O–C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.34 (m, 5H, Ph), 5.50 (s, 1H, C*H*-Ph), 4.63 (d, 1H, $J_{1,2}$=7.9, H-1), 4.40 (dd, 1H, $J_{5,6}$=4.5, $J_{6,6'}$=10.5, H-6), 4.33 (2q, 2H, J=7.0, CH_2-Me), 3.95 (d, 1H, $J_{4,5}$=8.3, H-4), 3.93 (dd, 1H, $J_{5,6'}\approx$0, H-5), 3.92 (d, 1H, H-2), 3.79 (d, 1H, H-6′), 3.59 (s, 3H, MeO), 2.81 (br s, 1H, HO-2), and 1.30 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 165.5 (COO), 136.3–126.3 (Ph), 114.0 (CN), 102.8 (C-1), 102.0 (*C*H-Ph), 78.4 (C-4), 72.5 (C-2), 68.6 (C-6), 66.5 (C-5), 63.9 (Me-*C*H_2), 57.6 (MeO), 55.8 (C-3), and 14.0 (*Me*-CH_2); HREIMS: m/z 363.1299 (calcd for $C_{18}H_{21}NO_7$: 363.1318). Anal. calcd for $C_{18}H_{21}NO_7\cdot H_2O$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.32; H, 6.02; N, 3.91%.

4.3. Methyl 3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside 2

p-Toluenesulphonic acid (52.2 mg, 0.274 mmol) was added to a solution of **4** (1.043 g, 2.74 mmol) in 1:1 methanol:dioxane (26 mL), The mixture was heated at 60°C for 2 h and then at 85°C for 1 h, neutralised with triethylamine and concentrated. Column chromatography of the residue (1:1→1:2 gradient, hexane:ethyl acetate) afforded **2** as a syrup (0.753 g, 96%): R_f=0.20 (1:3, hexane:ethyl acetate); $[\alpha]_D^{25}$ −14 (*c* 1.22, acetone); IR (film) ν_{max} 3455 (OH), 2255 (C≡N), 1744 (C=O), 1082 and 1032 cm^{-1} (ester C–O–C); ^{1}H NMR (500 MHz, acetone-d_6) δ 5.31 (d, 1H, $J_{4,HO}$=6.0, HO-4), 5.25 (d, 1H, $J_{2,HO}$=4.5, HO-2), 4.49 (d, 1H, $J_{1,2}$=7.9, H-1), 4.26 (2q, 2H, J=7.1, CH_2-Me), 4.08 (dd, 1H, $J_{4,5}$=9.7, H-4), 3.84 (dd, 1H, $J_{5,6}$=2.6, $J_{6,6'}$=12.0, H-6), 3.77 (dd, 1H, $J_{5,6'}$=4.5, H-6′), 3.71 (dd, 1H, H-2), 3.66 (ddd, 1H, H-5), 3.49 (s, 3H, MeO), and 1.28 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 167.7 (COO), 116.3 (CN), 103.5 (C-1), 77.3 (C-5), 72.6 (C-2), 70.3 (C-4), 63.4 (Me-*C*H_2), 61.9 (C-6), 61.4 (br, C-3), 56.9 (MeO), and 14.3 (*Me*-CH_2); HRCIMS: m/z 276.1084 (calcd for $C_{11}H_{17}NO_7$+H: 276.1083). Anal. calcd for $C_{11}H_{17}NO_7\cdot 0.5H_2O$: C, 46.48; H, 6.38; N, 4.93. Found: C, 46.73; H, 6.72; N, 4.52%.

4.4. Methyl 3-*C*-[(*tert*-butoxycarbonylamino)methyl]-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside 5

Compound **2** (0.203 g, 0.738 mmol), cobalt(II) chloride hexahydrate (0.600 g, 2.52 mmol), and di-*tert*-butyl dicarbonate (0.359 g, 1.64 mmol) were dissolved in methanol (37 mL), and sodium borohydride (0.600 g, 15.88 mmol) was gradually added (*caution!* vigorous reaction; hydrogen evolution). After stirring for 5 h at rt, the mixture was filtered and the filter cake was washed with methanol. The filtrate and washings were concentrated, the residue was dissolved in water (80 mL), the solution was shaken with ethyl acetate (4×50 mL), and the organic layer was washed with brine (2×100 mL), dried ($MgSO_4$), and concentrated to a crude product, which was purified by elution (1:3 hexane:ethyl acetate) through a short column of silica gel 60 (0.063–0.200 nm, E. Merck), to give pure **5** as a syrup (0.138 g, 50%): R_f=0.16 (1:3 hexane:ethyl acetate); $[\alpha]_D^{28}$ −7.3 (*c* 0.75, acetone); IR (film) ν_{max} 3416 (OH, NH), 1699 (C=O), 1244 (amide), 1101 and 1045 cm^{-1} (ester C–O–C); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.11 (br s, 1H, NH), 4.71 (d, 1H, $J_{4,HO}$=6.7, HO-4), 4.63 (d, 1H, $J_{2,HO}$=5.0, HO-2), 4.58 (d, 1H, $J_{1,2}$=7.9, H-1), 4.14 (q, 2H, J=7.1, CH_2-Me), 4.02 (dd, 1H, $J_{4,5}$=9.4, H-4), 3.88 (dd, 1H, J_{gem}=14.5, $J_{CH^a,NH}$=6.0, CH^a-NH), 3.78 (dd, 1H, $J_{5,6}$=2.5, $J_{6,6'}\approx$12.6, H-6),

3.78 (dd, 1H, H-2), 3.77 (dd, 1H, $J_{CH^b,NH}=5.2$, CH^b-NH), 3.69 (ddd, 1H, $J_{5,6'}=4.7$, H-5), 3.65 (dd, 1H, H-6′), 3.44 (s, 3H, MeO), 1.40 (s, 9H, Me_3C), and 1.23 (t, 3H, Me-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 173.5 (C-COO), 157.2 (N-COO), 102.6 (C-1), 79.0 (CMe$_3$), 76.0 (C-5), 74.1 (C-2), 71.4 (C-4), 63.4 (C-6), 61.5 (Me-CH$_2$), 56.6 (MeO), 56.0 (C-3), 38.6 (CH$_2$-NH), 30.0, 28.6 (Me_3C), and 14.4 (Me-CH$_2$); HRCIMS: m/z 380.1912 (calcd for $C_{16}H_{29}NO_9$+H: 380.1921).

4.5. Reduction of 4 with sodium borohydride. Preparation of methyl 4,6-*O*-(*R*)-benzylidene-3-*C*-[(*tert*-butoxycarbonylamino)methyl]-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside 6, methyl 4,6-*O*-(*S*)-benzylidene-3-*C*-[(*tert*-butoxycarbonylamino)methyl]-3-deoxy-3-ethoxycarbonyl-β-D-galactopyranoside 7, and methyl 4,6-*O*-benzylidene-3-*C*-cyano-3-deoxy-3-formyl-β-D-glucopyranoside 8

To a solution of **4** (1.335 g, 3.50 mmol), cobalt(II) chloride hexahydrate (2.85 g, 12.0 mmol), and di-*tert*-butyl dicarbonate (1.71 g, 7.81 mmol) in methanol (170 mL) was gradually (10 portions) added sodium borohydride (2.85 g, 75.4 mmol) (*caution!* vigorous reaction; hydrogen evolution). The mixture was kept at rt until **4** was completely transformed (3 h, TLC monitoring, 2:1 hexane:ethyl acetate). The insoluble salts were filtered off, the filtrate was concentrated, the solid residue was dissolved in ethyl acetate (50 mL), and the solution was successively washed with water (2×50 mL) and brine (100 mL). After drying over magnesium sulphate, the organic layer was concentrated and the residue was subjected to column chomatography (2:1→1:1 gradient, hexane:ethyl acetate) to give **6** (0.73 g, 45%), **7** (0.29 g, 24%), and **8** (0.088 g, 8%).

Compound **6**: syrup; $R_f=0.45$ (1:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ −35.5 (*c* 1.01, acetone); IR (film) ν_{max} 3443 (OH, NH), 1724, 1710 (C=O), 1248 (amide), 1099 and 1007 cm^{-1} (ester C–O–C); ^{1}H NMR (500 MHz, acetone-d_6) δ 7.48–7.31 (m, 5H, Ph), 5.83 (br s, 1H, NH), 5.56 (s, 1H, CH-Ph), 4.92 (d, 1H, $J_{2,HO}=5.1$, HO-2), 4.67 (d, 1H, $J_{1,2}=7.9$, H-1), 4.29 (dd, 1H, $J_{5,6}=5.0$, $J_{6,6'}=10.3$, H-6), 4.18 (q, 2H, $J=7.1$, CH_2-Me), 4.06 (d, 1H, $J_{4,5}=9.8$, H-4), 3.97 (ddd, 1H, $J_{5,6'}=9.8$, H-5), 3.90 (d, 2H, $J=5.6$, CH_2-NH), 3.86 (dd, 1H, H-2), 3.72 (dd, 1H, H-6′), 3.47 (s, 3H, MeO), 1.34 (s, 9H, Me_3C), and 1.22 (t, 3H, Me-CH$_2$); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 172.6 (C-COO), 156.5 (N-COO), 138.7–127.1 (Ph), 102.9 (C-1), 102.5 (CH-Ph), 81.9 (C-4), 78.7 (CMe$_3$), 74.5 (C-2), 70.8 (C-6), 65.0 (C-5), 61.8 (CH$_2$-Me), 57.1 (MeO), 54.8 (C-3), 38.4 (CH$_2$-N), 28.7, 28.6 (Me_3C), and 14.4 (Me-CH$_2$); HRCIMS: m/z 468.2235 (calcd for $C_{23}H_{33}NO_9$+H: 468.2234). Anal. calcd for $C_{23}H_{33}NO_9$: C, 59.09; H, 7.11; N, 3.00. Found: C, 59.19; H, 7.22; N, 3.10.

Compound **7**: syrup; $R_f=0.24$ (5:1, ether:hexane); $[\alpha]_D^{26}$ +26 (*c* 0.84, acetone); IR (film) ν_{max} 3420 (OH, NH), 1720 (C=O), 1248 (amide), 1234, 1172, 1108 and 1085 cm^{-1} (ester C–O–C); ^{1}H NMR (500 MHz, acetone-d_6) δ 7.41–7.30 (m, 5H, Ph), 5.93 (d, 1H, $J_{CH^a,NH}=9.1$, $J_{CH^b,NH}\approx 0$, NH), 5.60 (s, 1H, CH-Ph), 4.69 (d, 1H, $J_{2,HO}=4.1$, HO-2), 4.62 (d, 1H, $J_{1,2}=8.3$, H-1), 4.25 (m, 2H, H-4 and H-2), 4.17 (m, 2H, H-6 and H-6′), 4.12 (q, 2H, $J=7.1$, CH_2-Me), 3.88 (dd, 1H, $J_{gem}=13.9$, CH^a-N), 3.85 (m, 1H, H-5), 3.48 (s, 3H, MeO), 3.45 (d, 1H, CH^b-N), 1.40 (s, 9H, Me_3C), and 1.16 (t, 3H, Me-CH$_2$); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 171.7 (C-COO), 156.2 (N-COO), 139.5–126.8 (Ph), 103.1 (C-1), 101.3 (CH-Ph), 79.0 (CMe$_3$), 78.3 (C-4), 69.7 (C-6), 69.6 (C-2), 66.9 (C-5), 61.2 (CH$_2$-Me), 56.7 (MeO), 55.3 (C-3), 41.2 (CH$_2$-N), 28.6, 28.5 (Me_3C), and 14.5 (Me-CH$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41–7.25 (m, 5H, Ph), 5.49 (s, 1H, CH-Ph), 4.61 (d, 1H, $J_{1,2}=8.3$, H-1), 4.42 (d, 1H, H-2), 4.28 (br d, 1H, $J_{gem}=12.2$, H-6), 4.19 and 4.17 (2q, 2H, $J=7.1$, CH_2-Me), 4.13 (br s, 1H, H-4), 4.00 (br d, 1H, H-6′), 3.93 (dd, 1H, $J_{CH^a,NH}=10.4$, $J_{gem}=14.2$, CH^a-N), 3.74 (br s, 1H, H-5), 3.58 (s, 3H, MeO), 3.42 (d, 1H, $J_{CH^b,NH}\approx 0$, CH^b-N), 1.45 (s, 9H, Me_3C), and 1.20 (t, 3H, Me-CH$_2$); NOE contacts (1D NOESY): H-7, H-6′, H-4; H-1, CH^a-N, CH^b-N, H-5, MeO; ^{13}C NMR (125.7 MHz, CDCl$_3$) δ 171.9 (C-COO), 156.0 (N-COO), 137.5–126.0 (Ph), 101.4 (C-1), 101.0 (CH-Ph), 79.6 (CMe$_3$), 76.8 (C-4), 69.2 (C-6 and C-2), 66.1 (C-5), 61.4 (CH$_2$-Me), 57.0 (MeO), 54.2 (C-3), 39.8 (CH$_2$-N), 28.3 (Me_3C), and 14.1 (Me-CH$_2$); HRCIMS: m/z 468.2214 (calcd for $C_{23}H_{33}NO_9$+H: 468.2234).

Compound **8**: syrup; $R_f=0.17$ (5:1, ether:hexane); $[\alpha]_D^{26}$ −32 (*c* 0.4, acetone); IR (film) ν_{max} 3452 (OH), 2259 (C≡N), and 1719 cm^{-1} (aldehyde C=O); ^{1}H NMR (500 MHz, acetone-d_6) δ 9.66 (s, 1H, CHO), 7.44–7.35 (m, 5H, Ph), 5.69 (s, 1H, CH-Ph), 5.57 (d, 1H, $J_{2,HO}=4.5$, HO-2), 4.65 (d, 1H, $J_{1,2}=7.8$, H-1), 4.35 (m, 1H, H-6), 4.33 (d, 1H, $J_{4,5}=9.0$, H-4), 4.07 (dd, 1H, H-2), 3.89 (m, 2H, H-5 and H-6′), and 3.54 (s, 3H, MeO); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 192.7 (HCO), 138.3–127.1 (Ph), 115.0 (CN), 104.2 (C-1), 102.7 (CH-Ph), 76.1 (C-4), 70.1 (C-2), 69.1 (C-6), 67.2 (C-5), 62.6 (C-3), and 57.4 (MeO); HRCIMS: m/z 320.1125 (calcd for $C_{16}H_{17}NO_6$+H: 320.1134).

4.6. Phenyl 3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-1-thio-α-D-glucopyranoside 9 and phenyl 3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-1-thio-β-D-glucopyranoside 10

Compound **4** (1.044 g, 2.74 mmol) was dissolved under argon atmosphere in freshly distilled pyridine (9 mL) and a small amount of molecular sieves (4 Å) was added. After 45 min, hexamethyldisilazane (290 μL, 1.37 mmol) and trimethylchlorosilane (340 μL, 2.74 mmol) were successively dropped into the mixture cooled in an ice bath. The mixture was kept at rt for 5 h, then diluted with hexane (20 mL) and poured into ice-water (200 mL). The organic layer was separated, washed successively with water (4×50 mL) and brine (2×50 mL), and dried over sodium sulphate. To the amorphous per-*O*-trimethylsilyl derivative obtained by evaporation of the solvent, without further purification, was added under argon a solution of

trimethyl(phenylthio)silane (2.6 mL, 13.7 mmol) in 1,2-dichloroethane (9 mL). To this mixture was added zinc iodide (2.62 g, 8.22 mmol) and tetrabutylammonium iodide (1.01 g, 2.74 mmol) and the suspension was heated at 60°C; after 9 h, all the four reagents were replaced and the heating was maintained for 10 h, but desilylation was incomplete. The solids were filtered off and the filtrate was washed successively with saturated aqueous hydrogencarbonate (2×80 mL) and brine (4×50 mL), dried over sodium sulphate, and concentrated to a syrup, which was purified by elution (4:1 dichloromethane:acetone) through a short column of silica gel 60 (0.063–0.200 nm, E. Merck). The purified product was treated[23] with 4:2:1 dichloromethane:methanol:water (200 mL), the mixture was acidified with 10% aqueous acetic acid, and the resulting solution was heated at 60°C for 8 h and concentrated (coevaporation with toluene) to give a residue, which was subjected to column chromatography (1:1→7:1 gradient, ether:hexane) to afford a 1:1 mixture (0.643 g, 66%) of **9** and **10**. A small sample (≈15 mg) of this mixture was purified by preparative TLC (20:1 ether:hexane) to give separately **9** (≈7 mg, 31%) and **10** (≈7 mg, 31%).

Compound **9**: syrup; R_f=0.20 (20:1 ether:hexane); $[\alpha]_D^{22}$ +73 (*c* 0.43, acetone); IR (film) ν_{max} 3387 (OH), 2263 (C≡N), 1734 (C=O), 1285 and 1101 (ester C–O–C), and 692 cm^{-1} (C–S); ^1H NMR (500 MHz, acetone-d_6) δ 7.34–7.27 (m, 5H, Ph), 5.62 (d, 1H, $J_{1,2}$=6.0, H-1), 5.36 (d, 1H, $J_{4,HO}$=6.2, HO-4), 5.28 (d, 1H, $J_{2,HO}$=5.8, HO-2), 4.49 (dd, 1H, H-2), 4.28 (m, 1H, H-5), 4.28 (q, 2H, *J*=7.1, CH_2-Me), 4.17 (dd, 1H, $J_{4,5}$=9.8, H-4), 3.88 (dd, 1H, $J_{5,6}$=2.9, $J_{6,6'}$=11.9, H-6), 3.82 (dd, 1H, $J_{5,6'}$=2.8, H-6′), and 1.29 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 168.2 (COO), 137.2–128.0 (Ph), 116.5 (CN), 90.6 (C-1), 71.9 (C-2), 71.7 (C-5), 69.8 (C-4), 68.6 (C-3), 63.4 (Me-*C*H_2), 61.7 (C-6), and 13.8 (*Me*-CH_2); HRCIMS: *m*/*z* 354.1003 (calcd for $C_{16}H_{19}NO_6S$+H: 354.1011).

Compound **10**: syrup; R_f=0.35 (20:1 ether:hexane); $[\alpha]_D^{22}$ −2.4 (*c* 0.86, acetone); IR (film) ν_{max} 3380 (OH), 2253 (C≡N), 1740 (C=O), 1265 and 1099 (ester C–O–C), and 692 cm^{-1} (C–S); ^1H NMR (500 MHz, acetone-d_6) δ 7.60–7.30 (m, 5H, Ph), 5.48 (d, 1H, $J_{2,HO}$=5.8, HO-2), 5.34 (d, 1H, $J_{4,HO}$=6.0, HO-4), 4.88 (d, 1H, $J_{1,2}$=9.8, H-1), 4.25 (q, 2H, *J*=7.1, CH_2-Me), 4.13 (dd, 1H, $J_{4,5}$=9.7, H-4), 3.88 (dd, 1H, H-2), 3.84 (dd, 1H, $J_{5,6}$=3.9, $J_{6,6'}$=11.1, H-6), 3.83 (dd, 1H, $J_{5,6'}$=2.8, H-6′), 3.66 (ddd, 1H, H-5), and 1.27 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 167.6 (COO), 133.9–128.4 (Ph), 116.1 (CN), 87.6 (C-1), 80.3 (C-5), 71.7 (C-2), 69.5 (C-4), 63.5 (Me-*C*H_2), 63.0 (C-3), 61.7 (C-6), and 13.3 (*Me*-CH_2); FABHRMS: *m*/*z* 376.0833 (calcd for $C_{16}H_{19}NO_6S$+Na: 376.0831).

4.7. Methyl 3-*C*-cyano-3,6-dideoxy-3-ethoxycarbonyl-6-fluoro-β-D-glucopyranoside 11

DAST (180 μL, 1.35 mmol) was added dropwise to a solution of compound **2** (0.074 g, 0.27 mmol) in dry dichloromethane (1.5 mL) at 0°C under argon. After a few minutes, the cooling bath was removed and the mixture was allowed to warm to rt under stirring, for 5 h (TLC monitoring, 1:2 hexane:ethyl acetate). The mixture was poured onto iced saturated aqueous sodium hydrogencarbonate (100 mL) and the aqueous layer was extracted with dichloromethane (3×40 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated, to afford, after preparative TLC (1:1 hexane:ethyl acetate), unreacted starting material (0.010 g, indicating 86% of conversion) and pure compound **11** (0.025 g, 34%, corresponding to 39% yield from converted substrate); R_f=0.26 (1:1 hexane:ethyl acetate); $[\alpha]_D^{26}$ −4.9 (*c* 0.40, acetone); IR (film) ν_{max} 3451 (OH), 2274 (C≡N), 1751 (C=O), 1101 and 1074 (ester C–O–C), and 1042 cm^{-1} (CF); ^1H NMR (500 MHz, acetone-d_6) δ 5.69 (d, 1H, $J_{4,HO}$=6.5, HO-4), 5.41 (d, 1H, $J_{2,HO}$=4.5, HO-2), 4.52 (d, 1H, $J_{1,2}$=7.9, H-1), 4.70 (ddd, 1H, $J_{6,F}$=47.9, $J_{5,6}$=3.2, $J_{6,6'}$=12.5, H-6), 4.69 (ddd, 1H, $J_{6',F}$=47.7, $J_{5,6'}$=2.1, H-6′), 4.27 (q, 2H, *J*=7.2, CH_2-Me), 4.08 (dd, 1H, $J_{4,5}$=9.9, H-4), 3.83 (dddd, 1H, $J_{5,F}$=26.6, H-5), 3.72 (dd, 1H, H-2), 3.50 (s, 3H, MeO), and 1.33 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 167.4 (COO), 116.0 (CN), 103.6 (C-1), 82.5 (d, $^1J_{C,F}$=172.2, C-6), 75.7 (d, $^2J_{C,F}$=17.6, C-5), 72.5 (C-2), 69.0 (d, $^3J_{C,F}$=7.5, C-4), 63.6 (Me-*C*H_2), 61.4 (C-3), 57.0 (MeO), and 13.9 (*Me*-CH_2); HRCIMS: *m*/*z* 278.1039 (calcd for $C_{11}H_{16}FNO_6$+H: 278.1040).

4.8. Methyl 4,6-*O*-benzylidene-3-*C*-cyano-2,3-dideoxy-3-ethoxycarbonyl-2-diethylamino-β-D-glucopyranoside 12

(a) Molecular sieves (4 Å) were added to a solution of **4** (0.124 g, 0.325 mmol) in dry dichloromethane (2 mL). After 30 min, the suspension was cooled to 0°C, DAST (215 μL, 1.63 mmol) was added, and the mixture was heated under reflux. Monitoring the reaction by TLC (2:1 hexane:ethyl acetate) indicated that the reaction had stopped after 15 h, even after replacing the amount of DAST twice during this interval. The reaction mixture was then poured into cold saturated aqueous sodium hydrogen carbonate (70 mL), the aqueous layer was extracted with dichloromethane (3×50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was subjected to column chromatography (9:1→3:1 gradient, hexane:ethyl acetate) to give unreacted **4** (0.094 g, indicating 24% of conversion) and compound **12** (5 mg, 4%, corresponding to 15% yield from converted substrate).

(b) Molecular sieves (4 Å) were allowed to act over a solution of **4** (0.118 g, 0.310 mmol) in dry dichloromethane (3 mL) for 30 min and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (0.090 g, 0.68 mmol) was then added. After complete dissolution of the base, the mixture was cooled to 0°C, treated with DAST (205 μL, 1.55 mmol), and stored at rt for 6 days, replacing the amounts of DMAP and DAST three times during this interval, until the progress of the reaction stopped (TLC, 2:1 hexane:ethyl acetate). Quenching was achieved by adding methanol (3 mL) to the cold (0°C) mixture. The mixture was diluted with ether (100 mL), washed with 5% aqueous hydrochloric acid (20 mL)

and 5% aqueous sodium hydrogencarbonate (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by TLC (several plates, 3:1 hexane:ethyl acetate, half plus one runs) to afford unreacted starting substrate (0.070 g, indicating 41% of conversion) and compound **12** (0.015 g, 12%, corresponding to 29% yield from converted substrate): syrup; $R_f = 0.55$ (3:1, hexane:ethyl acetate); $[\alpha]_D^{27}$ −22.5 (*c* 0.50, acetone); IR (film) ν_{max} 2244 (C≡N), 1752 (C=O), 1259 and 1100 cm^{-1} (ester C–O–C); ^1H NMR (500 MHz, acetone-d_6) δ 7.45–7.36 (m, 5H, Ph), 5.69 (s, 1H, C*H*-Ph), 4.98 (d, 1H, $J_{1,2} = 8.5$, H-1), 4.35 (dd, 1H, $J_{5,6} = 4.8$, $J_{6,6'} = 9.9$, H-6), 4.35 (q, 2H, $J = 7.0$, O-CH_2-Me), 4.09 (d, 1H, $J_{4,5} = 9.2$, H-4), 3.88 (dd, 1H, $J_{5,6'} = 9.8$, H-6′), 3.83 (ddd, 1H, H-5), 3.55 (s, 3H, MeO), 3.13 (d, 1H, H-2), 2.95 [dq, 2H, $J_{CH^a,Me} = 7.1$, $J_{gem} = 14.0$, N(CH^a-Me)$_2$], 2.71 [dq, 2H, $J_{CH^b,Me} = 6.8$, N(CH^b-Me)$_2$], 1.29 (t, 3H, *Me*-CH_2-O), and 0.97 [dt, 6H, $J = 7.1$, (*Me*-CH_2)$_2$N]; ^{13}C NMR (125.7 MHz, acetone-d_6) δ 166.8 (C-*C*OO), 138.2–127.1 (Ph), 116.7 (CN), 103.2 (C-1), 102.1 (*C*H-Ph), 80.1 (C-4), 69.1 (C-6), 67.2 (C-2), 67.1 (C-5), 63.5 (Me-*C*H_2-O), 57.4 (C-3), 56.8 (MeO), 46.8 [(Me-*C*H_2)$_2$N], 14.7 [(*Me*-CH_2)$_2$N], and 14.4 (*Me*-CH_2-O); HREIMS: *m*/*z* 418.2106 (calcd for $C_{22}H_{30}N_2O_6$: 418.2104).

4.9. 4,6-*O*-Benzylidene-3-*C*-[(*tert*-butoxycarbonylamino)methyl]-3-deoxy-3-ethoxycarbonyl-2-*O*-methyl-α-D-mannopyranosyl fluoride 13

Molecular sieves (4 Å) were added to a solution of compound **6** (0.114 g, 0.245 mmol) in dry dichloromethane (5 mL). After 45 min, the mixture was cooled in an ice bath, DAST (160 μL, 1.23 mmol) was added, and the whole was heated under reflux until the starting substrate was consumed (5 h, TLC monitoring, 1:1 hexane:ethyl acetate). The mixture was cooled at 0°C and methanol (2 mL) was added to quench the reaction. After evaporation of the solvents, the crude residue was subjected to TLC (1:1 hexane:ethyl acetate) to give unreacted **6** (0.075 g, indicating 34% of conversion) and the sugar fluoride **13** monohydrate (0.020 g, 17%, corresponding to 51% yield from converted substrate): syrup; $R_f = 0.47$ (2:1, hexane:ethyl acetate); $[\alpha]_D^{26}$ −42 (*c* 0.50, acetone); IR (film) ν_{max} 3445 (NH), 1744 and 1721 (C=O), 1179 and 1109 (ester C–O–C), and 1097 cm^{-1} (CF); ^1H NMR (500 MHz, acetone-d_6) δ 7.50–7.38 (m, 5H, Ph), 5.76 (s, 1H, C*H*-Ph), 5.73 (dd, 1H, $J_{1,2} = 1.1$, $^2J_{1,F} = 49.7$, H-1), 5.45 (br d, 1H, $J_{CH_2,NH} = 8.9$, NH), 4.49 (d, 1H, $J_{4,5} = 10.1$, H-4), 4.32 (dd, 1H, $J_{5,6} = 4.9$, $J_{6,6'} = 10.2$, H-6), 4.17 (q, 2H, $J = 7.1$, CH_2-Me), 4.14 (ddd, 1H, $J_{5,6'} = 10.1$, H-5), 3.90 (dd, 1H, $J_{gem} = 13.9$, CH^a-NH), 3.89 (dd, 1H, H-6′), 3.66 (d, 1H, CH^b-NH), 3.66 (overlapped dd, 1H, $J_{2,F} = 13.9$, H-2), 3.44 (s, 3H, MeO), 1.34 (s, 9H, *Me*$_3$C), and 1.27 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 169.9 (C-*C*OO), 155.6 (N-*C*OO), 138.8–126.9 (Ph), 105.4 (d, $^1J_{1,F} = 222.5$, C-1), 102.7 (*C*H-Ph), 81.9 (C-4), 80.2 (d, $^2J_{2,F} = 36.5$, C-2), 78.8 (*C*Me$_3$), 69.3 (C-6), 62.5 (Me-*C*H_2), 61.3 (C-5), 59.8 (MeO), 53.1 (C-3), 41.1 (*C*H_2-NH), 28.4 (*Me*$_3$C), and 14.5 (*Me*-CH_2); HRCIMS: *m*/*z* 470.2186 (calcd for $C_{23}H_{32}FNO_8$+H: 470.2190). Anal. calcd for $C_{23}H_{32}FNO_8 \cdot H_2O$: C, 56.66; H, 7.03; N, 2.87. Found: C, 57.03; H, 6.72; N, 2.80.

4.10. 3-*C*-Cyano-2,3-dideoxy-3-ethoxycarbonyl-2-phenylthio-α-D-mannopyranosyl fluoride 14, 3-*C*-cyano-2,3,6-trideoxy-3-ethoxycarbonyl-6-fluoro-2-phenylthio-α-D-mannopyranosyl fluoride 15, and phenyl 3-*C*-cyano-3,6-dideoxy-3-ethoxycarbonyl-6-fluoro-1-thio-α-D-glucopyranoside 16

Freshly activated molecular sieves (4 Å) were added, under argon, to a solution of a 0.6:1 **9:10** mixture (0.165 g, 0.467 mmol) in dry dichloromethane (3 mL). After 45 min, the mixture was cooled to −40°C, DAST (370 μL, 2.80 mmol) was added, and the temperature was allowed to rise to 20°C and the mixture stirred for 5 h. After cooling to 0°C, the reaction was quenched via addition of methanol (2 mL). Evaporation of the solvents left a crude residue, which was purified by TLC (3:1 ether:hexane) to afford unreacted substrate (0.065 g of a 1:0.8 mixture of **9**:**10**, indicating 42% conversion for **9** and 72% conversion for **10**), rearranged monofluoro compound **14** (0.015 g, 15%, corresponding to 20% yield from converted **10**), rearranged difluoro compound **15** (0.008 g, 8%, corresponding to 11% yield from converted **10**), and compound **16** (0.011 g, 11%, corresponding to 26% yield from converted **9**).

Compound **14**: syrup; $R_f = 0.21$ (3:1 ether:hexane); $[\alpha]_D^{26}$ +39.5 (*c* 1.14, acetone); IR (film) ν_{max} 3370 (OH), 2258 (C≡N), 1743 (C=O), 1261 and 1179 (ester C–O–C), 1097 CF), and 614 cm^{-1} (C–S); ^1H NMR (500 MHz, acetone-d_6) δ 7.57–7.38 (m, 5H, Ph), 5.98 (dd, 1H, $J_{1,2} = 1.3$, $^2J_{1,F} = 51.8$, H-1), 5.36 (d, 1H, $J_{4,HO} = 5.8$, HO-4), 4.50 (dd, 1H, $J_{4,5} = 10.0$, H-4), 4.20 (q, 2H, $J = 7.1$, CH_2-Me), 4.06 (dd, 1H, $^3J_{2,F} = 4.7$, H-2), 3.98 (ddd, 1H, $J_{5,6} = J_{5,6'} = 3.1$, H-5), 3.88 (dd, 1H, $J_{6,6'} = 10.5$, H-6), 3.87 (dd, 1H, H-6′), and 1.12 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 165.1 (COO), 134.0–127.0 (Ph), 116.5 (CN), 108.3 (d, $^1J_{1,F} = 230.0$, C-1), 74.0 (C-5), 63.8 (C-4), 63.7 (Me-*C*H_2), 61.3 (C-6), 53.7 (d, $^2J_{2,F} = 28.0$, C-2), 52.6 (C-3), and 13.9 (*Me*-CH_2); HRCIMS: *m*/*z* 356.0963 (calcd for $C_{16}H_{18}FNO_5S$+H: 356.0968), 355.0892 (calcd for $C_{16}H_{18}FNO_5S$: 355.0890).

Compound **15**: syrup; $R_f = 0.32$ (1:1 ether:hexane); $[\alpha]_D^{24}$ +28 (*c* 0.54, acetone); IR (film) ν_{max} 3486 (OH), 2269 (C≡N), 1746 (C=O), 1247 and 1167 (ester C–O–C), 1106 CF), and 620 cm^{-1} (C–S); ^1H NMR (500 MHz, acetone-d_6) δ 7.58–7.41 (m, 5H, Ph), 6.04 (dd, 1H, $J_{1,2} = 1.5$, $^2J_{1,F} = 51.2$, H-1), 5.69 (d, 1H, $J_{4,HO} = 6.0$, HO-4), 4.82 (ddd, 1H, $J_{5,6} = 3.3$, $J_{6,6'} = 10.7$, $^2J_{6,F} = 47.0$, H-6), 4.72 (ddd, 1H, $J_{5,6'} = 1.7$, $^2J_{6',F} = 48.2$, H-6′), 4.49 (dd, 1H, $J_{4,5} = 10.3$, H-4), 4.21 (q, 2H, $J = 7.1$, CH_2-Me), 4.15 (dddd, 1H, $^3J_{5,F} = 27.2$, H-5), 4.13 (dd, 1H, $^3J_{2,F} = 4.2$, H-2), and 1.11 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 167.9 (COO), 135.0–129.0 (Ph), 116.1 (CN), 108.0 (d, $^1J_{1,F} = 232.5$, C-1), 82.1 (d, $^1J_{6,F} = 172.6$, C-6), 72.3 (d, $^2J_{5,F} = 18.2$, C-5), 63.9 (Me-*C*H_2), 62.7 (d, $^3J_{4,F} = 7.9$, C-4), 53.5 (d, $^2J_{2,F} = 27.3$, C-2), 52.3 (C-3), and 13.8 (*Me*-CH_2); HRCIMS: *m*/*z* 358.0925 (calcd for $C_{16}H_{17}F_2NO_4S$+H: 358.0925).

Compound **16**: syrup; $R_f=0.30$ (3:1 ether:hexane); $[\alpha]_D^{26}$ +56.5 (*c* 0.54, acetone); IR (film) ν_{max} 3393 (OH), 2253 (C≡N), 1752 (C=O), 1259 and 1155 (ester C–O–C), 1099 CF), and 615 cm^{-1} (C–S); ^1H NMR (500 MHz, acetone-d_6) δ 7.56–7.30 (m, 5H, Ph), 5.71 (d, 1H, $J_{4,HO}=6.6$, HO-4), 5.66 (d, 1H, $J_{1,2}=6.0$, H-1), 5.44 (d, 1H, $J_{2,HO}=5.6$, HO-2), 4.82 (ddd, 1H, $J_{5,6}=3.6$, $J_{6,6'}=10.5$, $^2J_{6,F}=47.3$, H-6), 4.68 (ddd, 1H, $J_{5,6'}=1.7$, $^2J_{6',F}=48.1$, H-6′), 4.47 (dddd, 1H, $J_{4,5}=10.2$, $^3J_{5,F}=27.5$, H-5), 4.28 (dd, 1H, H-2), 4.26 (q, 2H, $J=7.1$, CH_2-Me), 4.16 (dd, 1H, H-4), and 1.31 (t, 3H, *Me*-CH_2); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 167.9 (COO), 136.7–128.2 (Ph), 116.3 (CN), 90.5 (C-1), 82.7 (d, $^1J_{6,F}=172.9$, C-6), 71.7 (C-2), 70.4 (d, $^2J_{5,F}=17.9$, C-5), 68.7 (d, $^3J_{4,F}=7.5$, C-4), 63.8 (Me-CH_2), 63.7 (C-3), and 14.2 (*Me*-CH_2); HRCIMS: m/z 356.0961 (calcd for $C_{16}H_{18}FNO_5S$+H: 356.0968).

4.11. Crystallographic analysis for compound 4[†]

The compound crystallised as colourless prisms. For X-ray investigations, a crystal of approximate dimensions 0.40×0.40×0.44 mm was used, which belonged to the orthorhombic system with systematic absences consistent with the space group *P*212121, later confirmed by a successful refinement of the structure. Accurate cell dimensions and crystal orientation matrix, determined on a CAD4 Enraf–Nonius four-circle automated, graphite-monochromated, diffractometer by least-squares treatment of the setting angles of 25 independent reflections in the range $2\leq\theta\leq30°$, were $a=8.0958(13)$, $b=11.028(6)$, and $c=21.640(2)$ Å, $\alpha=\beta=\gamma=90°$, $V=1932.0(10)$ Å^3, $d_{calcd}=1.311$ g cm^{-3} for $Z=4$, $F(000)=808$ and the absorption coefficient $\mu=0.104$ mm^{-1}. Intensity data were collected at rt in the $\omega/2\theta$ scan mode, using Mo Kα radiation ($\lambda=0.71069$ Å) up to $\theta=30°$ for a total of 3181 reflections (h: 0→11, k: 0→15, l: 0→30). Intensities of three standard reflections were followed during data collection, and no significant decay was observed. Data were corrected for Lorentz and polarisation effects, extinction factors were ignored but no absorption correction was made. A total of 2158 reflections were considered observed [$I>2\sigma(I_o)$]. The structure was solved by direct methods using SIR-92[30] to locate all non-hydrogen atoms. Refinement on F^2 using SHELXL-93.[31] All H-atoms were included fixed in the later refinement in the positions calculated geometrically. The isotropic thermal parameters of each H-atom were fixed at 1.2 and 1.5 times the equivalent isotropic thermal parameters of the carrier atom. The final cycle of refinements led to a final agreement factor $R=0.044$, and $Rw(F^2)=0.127$ for $w=1/[\sigma^2(F_o^2)+(0.100P)^2]$ where $P=(F_o^2+2F_c^2)/3$ for 244 variables, $(\Delta/\sigma)_{max}=-0.029$ and $S=1.002$. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography,[32] and the remaining calculations were carried out with the X-ray system of crystallographic programs.[33] Maximum and minimum electron densities in the final difference map were 0.286 and −0.245 e Å^{-3}, respectively. The geometrical analysis was performed using PARST.[34]

[†] Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as suplementary publication number CCDC 166879. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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