CSIRO PUBLISHING

Rapid Communication

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2004**, *57*, 345–353

The Fluorination (at C5) of Some Derivatives of D-Glucose

Brian W. Skelton,[A] *Robert V. Stick*,[A,B] *Keith A. Stubbs*,[A] *Andrew G. Watts*,[A] *and Allan H. White*[A]

[A] Chemistry, School of Biomedical and Chemical Sciences M313, University of Western Australia, Crawley WA 6009, Australia.

[B] Author to whom correspondence should be addressed (e-mail: rvs@chem.uwa.edu.au).

The photobromination of various per-esters of β-D-glucopyranose and α- and β-D-glucopyranosyl fluoride has yielded 5-bromo derivatives capable of conversion into the corresponding 5-fluorides. The best reagent for this conversion was found to be silver tetrafluoroborate in ether/dichloromethane. The single-crystal X-ray structure determination of penta-*O*-benzoyl-5-fluoro-α-L-idopyranose is presented.

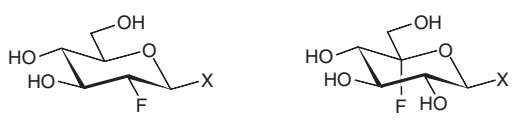
As well, various approaches to 5-fluoro glycopyranosides have been developed. The photobromination of phenyl tetra-*O*-acetyl-β-D-glucopyranoside, followed by fluorination and protecting group removal gave phenyl 5-fluoro-β-D-glucopyranoside. The photobromination of penta-*O*-acetyl-β-D-glucopyranose, followed by hydrolysis and treatment with methanol, gave a hemiacetal that was converted via treatment with diethylaminosulfur trifluoride followed by protecting group removal into methyl 5-fluoro-β-D-glucopyranoside. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α- and -β-D-*xylo*-hex-5-enosides were converted into their corresponding epoxides with either dimethyldioxirane or 3-chloroperbenzoic acid; subsequent treatment with hydrogen fluoride/pyridine then generated the 5-fluoro glycopyranosides as the major products. A single-crystal X-ray structure determination of 1,6-anhydro-2,3,4-tri-*O*-benzyl-5-hydroxy-β-L-idose is presented.

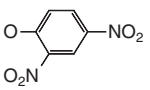
Manuscript received: 31 October 2003.
Final version: 3 January 2004.

The pioneering work of Withers has resulted in the design and synthesis of fluoro sugars as potent, mechanism-based inhibitors of various glycosidases and glycanases.[1] For example, the 2-deoxy-2-fluoro-β-D-glucoside **1**, 2-deoxy-2-fluoro-β-D-glucopyranosyl fluoride **2**, and 5-fluoro-β-D-glucopyranosyl fluoride **3** (Scheme 1) have been used to inhibit the action of β-glucosidases isolated from *Alcaligenes faecalis* and *Agrobacterium* sp. and a xylanase/glucanase from *Cellulomonas fimi*. In several cases, a fluoro sugar has been used to label the catalytic nucleophile of various retaining glycosidases.

There seemed a need for better synthetic routes to the 5-fluoro glycopyranoses. As well, it occurred to us that it may be advantageous to develop methods for the synthesis of 5-fluoro glycopyranosides to allow answers to several questions. For example, the dinitrophenyl β-D-glucoside **1** is a better inhibitor of the β-glucosidase from *Aspergillus faecalis* than the β-D-glucosyl fluoride **2** (K_i 0.05 mM for **1**, K_i 0.4 mM for **2**).[2,3] Would, then, the phenyl β-D-glucoside **4** be as good an inhibitor of retaining β-glucosidases as the β-D-glucosyl fluoride **3**? Would the methyl β-D-glucoside **5** be capable of acting as an inhibitor of β-glucosidases at all? We thus set about a synthesis of some of these molecules.

The obvious route to these 5-fluoro derivatives involves a bromination at C5, followed by halogen (fluorine) exchange. In the initial stages, we decided to apprentice ourselves with some simple 'photobrominations', that excellent reaction discovered (somewhat serendipitously) by Ferrier and Furneaux in the mid-1970s.[4,5] Thus, bromination of penta-*O*-acetyl-β-D-glucopyranose gave the bromide **6** (Scheme 2),



1 X = 

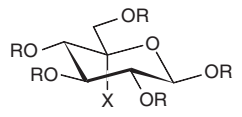
2 F

3 X = F

4 OPh

5 OMe

Scheme 1.



6 R = Ac X = Br

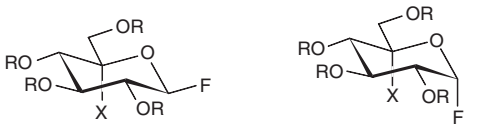
7 Bz Br

8 4-BrC_6H_4CO Br

9 4-$O_2NC_6H_4CO$ H

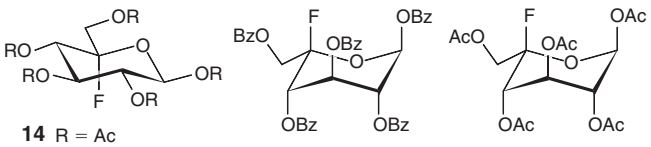
Scheme 2.

10.1071/CH03288 0004-9425/04/040345



10 R = Ac X = Br **11** R = Ac X = Br
12 Bz Br **13** Bz Br
19 Ac F **20** Ac F
21 Bz F

Scheme 3.



14 R = Ac
15 Bz
17 4-BrC$_6$H$_4$CO

16 **18**

Scheme 4.

a relatively stable molecule when crystalline but very prone to decomposition when impure or as an oil.[6] A much more stable product **7** was obtained when the comparable bromination was performed on the much less reactive penta-benzoate,[7] and the trend continued with the penta-4-bromobenzoate (the bromide **8**). Even though we could prepare the crude penta-4-nitrobenzoate **9**, the product had the characteristics of granite and we were unable to investigate the product(s) of its photobromination.

Bromination of the β- and α-anomers of tetra-*O*-acetyl-D-glucopyranosyl fluoride gave the known bromo fluorides **10** and **11** (Scheme 3), respectively.[8,9] The comparable reactions in the benzoyl series were again much slower: photobromination of tetra-*O*-benzoyl-β-D-glucopyranosyl fluoride gave the bromo fluoride **12** in good yield. However, irradiation of tetra-*O*-benzoyl-α-D-glucopyranosyl fluoride never gave a clean conversion into the bromide **13**. After 48 h at reflux in carbon tetrachloride in the presence of bromine and calcium carbonate, large amounts of starting material, as well as numerous by-products, were observed. The lack of reactivity of the α-fluoride is most likely a result of the additive effects of the deactivating benzoyl groups and the axial anomeric substituent. For the latter, the fluorine atom has an electron-withdrawing effect on the non-bonding electrons of O5 (the anomeric effect) that are required for the necessary stabilization of the intermediate free-radical generated at C5 during the photobromination step.

Having seemingly mastered the art of photobromination, we next decided to try our hand at fluorination of the bromides so prepared. Thus, treatment of the bromide **6** with silver tetrafluoroborate in ether gave the fluoride **14** (Scheme 4) in 61% yield, a result superior to the comparable reaction in toluene.[8] Treatment of the less reactive bromide **7** with silver tetrafluoroborate in ether/dichloromethane gave the fluoride **15** in excellent yield (85%). A minor by-product in this reaction was the L-*ido* epimer **16**—a single crystal X-ray structure determination of **16** showed the molecule to exist in a $^1C_4$

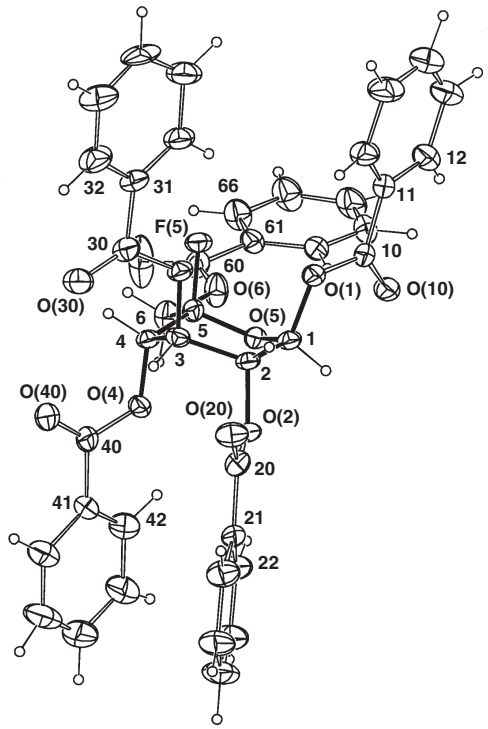


Fig. 1. Molecular projection of **16**.

conformation in the solid state (Fig. 1), also corroborated in solution by ^{1}H NMR spectroscopy (small values for $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$); substantial differences are found within the pairs of exocyclic angles at each ring carbon (Table 1). The bromide **8** furnished the fluoride **17** in 80% yield when treated with silver tetrafluoroborate in ether/dichloromethane.

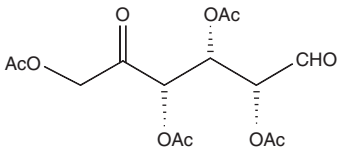
Treatment of the bromide **6** with silver fluoride in acetonitrile resulted in the virtually exclusive formation of the L-*ido* fluoride **18**. The assignment of the L-*ido* configuration to **18** was based mainly on the value of $J_{4,F}$ (11.1 Hz), significantly smaller than the corresponding value (22.7 Hz) in the D-*gluco* fluoride **14**. This difference was consistent across all of the fluorides studied here and greatly aided in the assignment of configuration [D-*gluco* ($J_{4,F}$ 22.5–23.6 Hz) versus L-*ido* ($J_{4,F}$ 6.0–14.2 Hz)]. Somewhat surprisingly, a similar treatment of the bromide **7** gave the D-*gluco* fluoride **15** in 79% yield.

Any attempt to rationalize the stereochemical outcome of the above fluorination reactions, namely retention or inversion of configuration at C5, seems fraught with danger. However, the reactions with silver tetrafluoroborate must proceed in solution by abstraction of a bromide ion (to form silver bromide) and so generate a planar carbenium ion, perhaps solvated (with ether) on the *Re* face and associated with a counter ion (tetrafluoroborate) on the *Si* face—further reaction of this salt produces the thermodynamically favoured (axial) fluoride. For the reactions with silver fluoride, the abstraction of a bromide ion at the surface of the insoluble reagent again generates a planar carbenium ion but now only the *Re* face is available for nucleophilic attack by fluoride ion in solution, to form the equatorial fluoride; alternatively, the solvent (acetonitrile) may intercept the carbenium ion from

Table 1. Selected non-hydrogen geometries of compounds 16 and 40

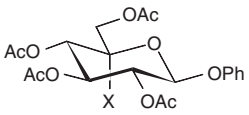
Atoms	16	40[A]
	Interbond angles [°][B]	
C(2)–C(1)–O(5)	**114.8(5)**	**108.7(3)**
C(2)–C(1)–O(1)	105.8(5)	111.1(3)
O(1)–C(1)–O(5)	109.5(5)	106.0(4)
C(1)–C(2)–C(3)	**114.8(6)**	**110.9(4)**
C(1)–C(2)–O(2)	104.0(6)	109.3(4)
C(3)–C(2)–O(2)	108.4(9)	108.6(4)
C(2)–C(3)–C(4)	**112.9(7)**	**114.1(4)**
C(2)–C(3)–O(3)	105.6(9)	104.2(4)
C(4)–C(3)–O(3)	110.3(8)	112.4(5)
C(3)–C(4)–C(5)	**113.1(9)**	**112.2(5)**
C(3)–C(4)–O(4)	110.4(8)	106.2(4)
C(5)–C(4)–O(4)	102.6(7)	111.1(4)
C(4)–C(5)–O(5)	**111.0(7)**	**108.2(4)**
C(4)–C(5)–F(5)/O(50)	105.8(7)	113.6(5)
O(5)–C(5)–F(5)/O(50)	108.0(9)	109.3(4)
C(5)–O(5)–C(1)	**120.5(6)**	**102.0(4)**
	Ring torsion angles [°]	
O(5)–C(1)–C(2)–C(3)	−36(1)	58.0(5)
C(1)–C(2)–C(3)–C(4)	39(1)	−34.3(6)
C(2)–C(3)–C(4)–C(5)	−46(1)	33.1(6)
C(3)–C(4)–C(5)–O(5)	50(1)	−53.6(6)
C(4)–C(5)–O(5)–C(1)	−51(1)	75.7(5)
C(5)–O(5)–C(1)–C(2)	44(1)	−78.5(4)

[A] C(1)–O(1)–C(6), O(1)–C(6)–C(5) are 106.9(5), 103.4(4); C(6)–C(5)–C(4), O(5,50) are 113.8(4), 101.4(5), 109.8(4)°. C(1)–O(1)–C(6)–C(5) is −7.6(4); O(1)–C(6)–C(5)–C(4), O(5,50) are −84.2(5), 31.8(4), 147.3(3), and C(6)–O(1)–C(1)–C(2), O(5) are 97.5(4), −20.3(4)°.
[B] Ring angles are in **bold**.



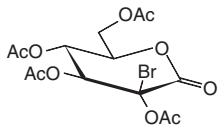
22

Scheme 5.



23 X = H
24 Br
25 F

Scheme 6.



26

Scheme 7.

27 R = Bz X = OH
28 Bz OMe
30 Ac OMe
29 R = Bz
31 Ac

Scheme 8.

the *Si* face (in so doing generating an α-nitrilium ion), forcing the approach of fluoride ion again from the *Re* face. We have absolutely no idea for the mechanism of formation of the axial fluoride **15** from the axial bromide **7** with silver fluoride in acetonitrile, although participation by an adjacent benzoyloxy group cannot be excluded. In fact, such neighbouring group participation may well offer an alternative explanation for the formation of some of the above fluorides.

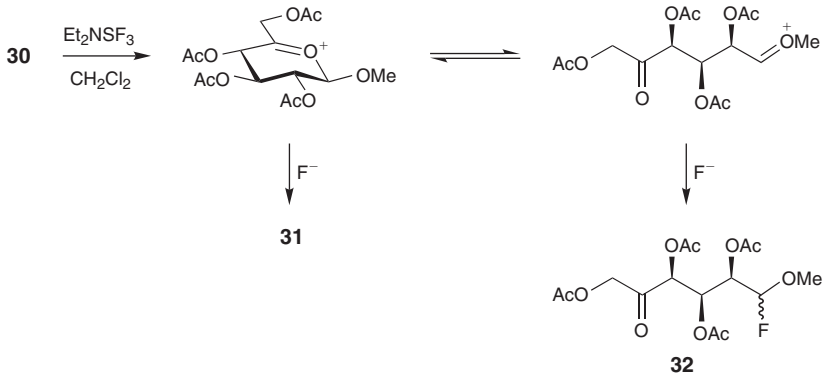
Finally, treatment of the bromides **10**, **11**, and **12** with silver tetrafluoroborate in ether/dichloromethane gave the fluorides **19**, **20**, and **21** in good yield (55, 53, and 80%, respectively), a significant improvement (for **19** and **20**) over the reported method.[8]

A somewhat unrelated quirk of these molecules is that halogenation at C5 prevents selective transformations at C1: treatment of the fluoride **14** with ammonium carbonate in dimethylformamide gave (not unexpectedly) the hexosulose **22** (Scheme 5),[8,10] while treatment of the fluoride **15** with hydrogen bromide in glacial acetic acid gave only the bromide **7**!

These last results were typical of many reactions reported here. A molecule such as **15** essentially has *two* anomeric carbon atoms (C1 and C5), with the C5—F bond being particularly strong owing to the anomeric effect. Any attempt at generating a carbenium ion at C1, for example by treatment of **15** with hydrogen bromide, is doomed to failure—a lone pair of electrons on O5, necessary to stabilize the carbenium ion, is 'lost' to the fluorine atom at C5 ($n \rightarrow \sigma^*$ interaction). Instead, a slow halogen exchange (F to Br) ensues with the excess reagent present, to produce the bromide **7**.

We now turned to the synthesis of the 5-fluoro glycopyranosides. Photobromination of the phenyl β-D-glucoside **23** (Scheme 6) gave the bromide **24** in good yield.[11] Treatment of **24** with silver tetrafluoroborate in ether then gave the fluoride **25**, and deprotection with ammonia in methanol gave the desired **4** (Scheme 1). Synthesis of the methyl β-D-glucoside **5**, by way of the 5-bromo compound, was unlikely to succeed since Ferrier and Haines have shown that standard photobromination conditions convert methyl tetra-*O*-acetyl-β-D-glucopyranoside into the bromo lactone **26** (Scheme 7).[12]

Initially, we adopted a rather indirect approach to the methyl β-D-glucoside **5**. Hydrolysis of the 5-bromo derivative **7** (Scheme 2) gave the diol **27** (Scheme 8).[7] The treatment



Scheme 9.

of **27** with methanol gave the hemiacetal **28**,[7] and a subsequent treatment with diethylaminosulfur trifluoride (DAST) gave the 5-fluoro-β-D-glucoside **29**. Although such fluorinations generally proceed with inversion of configuration, the anomeric effect probably predominates here and ensures formation of the more stable (axial) fluoride.

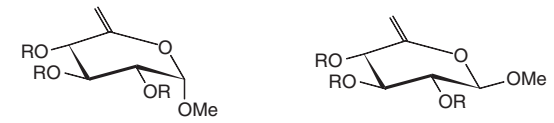
Unfortunately, the attempted debenzoylation of **29** with sodium methoxide in methanol was not successful. So, in a parallel sequence, the 5-bromo derivative **6** (Scheme 2) gave the rather unstable hemiacetal **30**. Treatment of **30** with DAST gave the desired 5-fluoro-β-D-glucoside **31**, together with substantial amounts of what appeared to be two acyclic fluorides **32** (Scheme 9). The deprotection of **31** proceeded smoothly to give the methyl β-D-glucoside **5**.

We now considered other routes to 5-fluoro glycopyranosides, and the intermediacy of glycos-5-enes and their derived epoxides seemed an attractive alternative. Thus, the alkenes **33** and **34** (Scheme 10) were prepared according to known and related methods.[13] Treatment of **33** with iodine in aqueous acetonitrile[14] indeed gave a desired iodohydrin but of structure **35** where loss of the aglycon was obvious (Scheme 11).

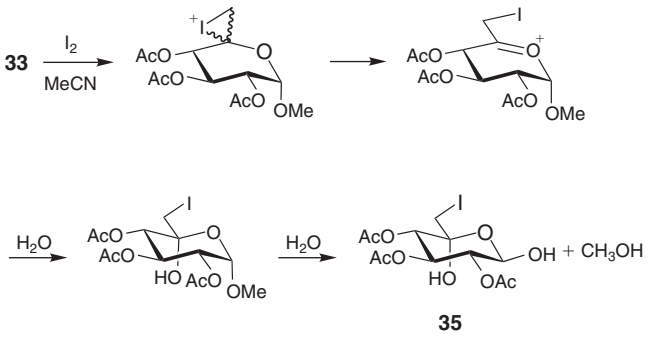
Initial attempts to epoxidize **33** and **34** using dimethyldioxirane (DMDO) were unsuccessful, so it was decided to convert the alkenes into their benzyl ether counterparts **36** and **37**. Treatment of the alkene **36** with DMDO gave the L-*ido* epoxide **38** (Scheme 12), the stereochemistry of which was assigned from a ^{1}H NMR NOESY spectrum that showed an interaction between the protons of the methyl group and a proton at C6. The approach of the reagent, DMDO, to the *Re* face of the alkene **36** is to be expected in view of the axial methoxy group at C1.

Treatment of the alkene **37** with DMDO gave, as expected, a mixture of epoxides **39**. From a comparison of the ^{1}H NMR spectrum of this mixture with that of the L-*ido* epoxide **38**, the D-*gluco* to L-*ido* ratio was determined to be 1 : 2. The epoxides **38** and **39** were rather unstable and were used in subsequent reactions without purification.

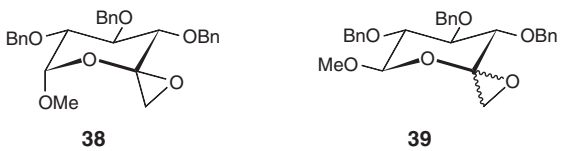
Treatment of the epoxide **38** with silver tetrafluoroborate in ether/dichloromethane gave, after workup, only the bridged hexosulose **40** (Scheme 13), whose structure was assigned from a single-crystal X-ray structure determination (Fig. 2). In potentially a better method of fluorination, the epoxide **38** was treated with hydrogen fluoride/pyridine. The



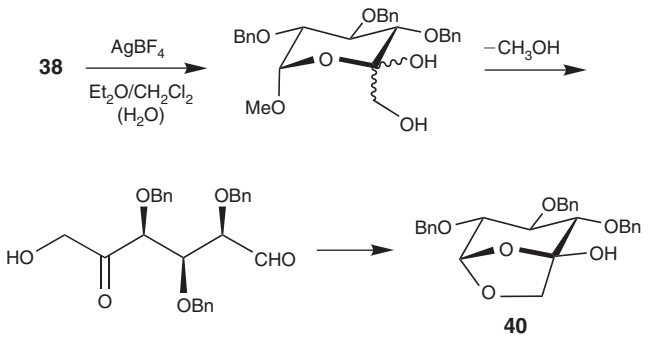
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

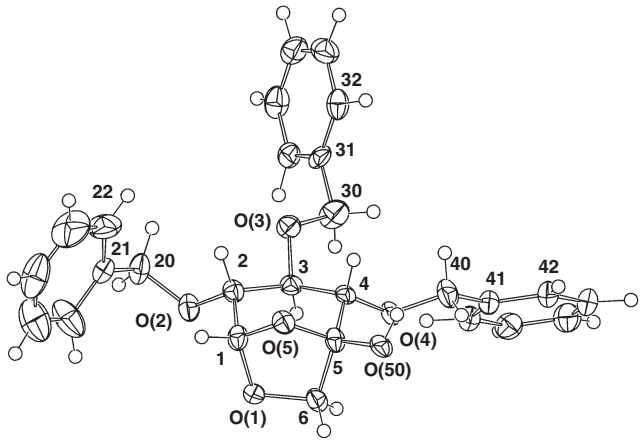
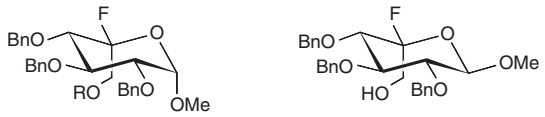


Fig. 2. Molecular projection of **40**.



41 R = H
42 Ac

43

Scheme 14.

fluoride **41** (Scheme 14) was the sole product, characterized as the acetate **42**. In the ^{1}H NMR spectrum of **42**, the value for $J_{4,F}$ (11.0 Hz) ruled out a D-*gluco* configuration but was commensurate with the L-*ido* configuration.

Treatment of the epoxides **39** with the same reagent gave just one product, the fluoride **43**—in the ^{1}H NMR spectrum, the value for $J_{4,F}$ (14.2 Hz) again suggested the L-*ido* configuration. Thus, it appears that the treatment of epoxides with hydrogen fluoride/pyridine is a viable method for the synthesis of 5-fluoro glycosides, but the reasons for the dominant formation of the L-*ido* isomers here remain obscure.

During the course of this work, a report appeared on the generation of epoxides from glycos-5-enes and their subsequent treatment with hydrogen fluoride/pyridine at low temperature.[15] Here, the alkenes **36** and **37** were separately treated with 3-chloroperbenzoic acid, presumably to generate (mixtures of) epoxides, and these were treated with hydrogen fluoride/pyridine at –78°C, to generate the 5-fluoro L-idosides **41** and **43**, respectively, but accompanied in each case by an amount of the D-*gluco* isomer.

Experimental

General experimental procedures have been given previously.[13] Irradiation of reaction mixtures was effected using two 150-W lamps at 5 cm from the reaction vessel. ^{19}F NMR spectra were recorded using C_6F_6 as an external reference.

Penta-O-*(4-bromobenzoyl)-β-D-glucopyranose*

D-Glucose (1.2 g, 6.7 mmol) was dissolved in dry pyridine (20 mL) by heating the mixture on a steam bath. Upon cooling the solution, 4-bromobenzoyl chloride (10.0 g, 45.6 mmol) was added and the mixture held at 60°C (3 h). The mixture was quenched by the addition of water and left to stir (15 min), then poured into ice-water, and the resultant gum triturated (EtOAc) to give a fine, colourless powder. Recrystallization of the powder (three times) gave the penta-4-bromobenzoate as a colourless, microcrystalline powder (5.1 g, 70%), mp 125–128°C (EtOAc; lit.[17] 123°C), $[\alpha]_D$ +83.0° (lit.[17] +81°).

5-Bromo-penta-O-*(4-bromobenzoyl)-β-D-glucopyranose* ***8***

A suspension of penta-*O*-(4-bromobenzoyl)-β-D-glucopyranose (1.0 g, 0.92 mmol) and $CaCO_3$ (1 g) in CCl_4 (40 mL) containing Br_2 (0.25 mL, 4.8 mmol) was irradiated at reflux until TLC showed complete consumption of the starting material (5 h). The mixture was allowed to cool, and was then filtered through Celite. The filtrate was concentrated to give a light yellow oil that crystallized. Recrystallization yielded the *bromide* **8** as a fine, colourless powder (0.89 g, 83%), mp 223–226°C (EtOAc), $[\alpha]_D$ −13.5° (Found: C 41.9, H 2.4. $C_{41}H_{26}Br_6O_{11}$ requires C 41.9, H 2.2%). δ_H (300 MHz) 7.89–7.39 (20H, m, Ar), 6.70 (d, $J_{1,2}$ 8.5, H1), 6.24 (t, $J_{2,3} \approx J_{3,4}$ 9.8, H3), 5.91 (dd, H2), 5.84 (d, $J_{3,4}$ 9.8, H4), 4.90, 4.67 (ABq, 2H, J 13.5, H6). δ_C (75.5 MHz) 164.59, 164.47, 164.38, 163.92, 163.38 (5C, C=O), 132.09–126.72 (Ar), 96.00 (C5), 92.37 (C1), 71.48, 70.02, 69.56 (C2, C3, C4), 66.61 (C6). m/z (FAB) 1172.6615 [(M + H)$^{+\bullet}$ requires 1172.6613].

Tetra-O-*benzoyl-5-bromo-β-D-glucopyranosyl Fluoride* ***12***

Tetra-*O*-benzoyl-β-D-glucopyranosyl fluoride[18] (500 mg, 0.74 mmol), $CaCO_3$ (400 mg), and Br_2 (0.20 mL, 3.7 mmol) in CCl_4 (40 mL) were irradiated at reflux until ^{1}H NMR analysis showed complete consumption of the starting material (5 h). The mixture was allowed to cool, then filtered. Dichloromethane was added and the mixture washed with 1 M aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, and then dried and concentrated to give a colourless foam. Crystallization gave the *bromide* **12** as a microcrystalline solid (420 mg, 84%), mp 160–162°C (Et_2O), $[\alpha]_D$ +23.5° (Found: C 60.2, H 4.0. $C_{34}H_{26}BrFO_9$ requires C 60.3, H 3.9%). δ_H (300 MHz) 8.19–7.28 (20H, m, Ph), 6.20 (br t, $J_{2,3} \approx J_{3,4}$ 9.7, H3), 5.99 (dd, $J_{1,2}$ 7.1, $J_{1,F}$ 51.0, H1), 5.95 (d, H4), 5.78 (ddd, $J_{2,F}$ 5.5, H2), 5.01, 4.67 (ABq, 2H, J 12.3, H6). δ_C (75.5 MHz) 165.36, 165.17, 164.91, 164.49 (4C, C=O), 133.93–128.00 (Ph), 106.95 (d, $J_{1,F}$ 225, C1), 75.55 (d, $J_{5,F}$ 6.0, C5), 71.19–70.78 (2d, C2, C3), 69.11 (C4), 66.36 (C6). m/z (FAB) 677.0843 [(M + H)$^{+\bullet}$ requires 677.0822].

Penta-O-*acetyl-5-fluoro-β-D-glucopyranose* ***14***

(*a*) Silver tetrafluoroborate (47 mg, 0.24 mmol) in dry Et_2O (5 mL) was added dropwise to the bromide **6** (92 mg, 0.20 mmol) in Et_2O (5 mL) with stirring. The solution was left to stir (5 min), and a precipitate (AgBr) formed immediately. The resultant mixture was filtered through a plug of silica, the filtrate concentrated, and the residue purified by flash chromatography (30% EtOAc/petrol) to give a colourless oil that crystallized. Recrystallisation gave the *fluoride* **14** as a fine powder (49 mg, 61%), mp 86–90°C (EtOAc/petrol), $[\alpha]_D$ −41.6° (Found: C 46.9, H 5.0. $C_{16}H_{21}FO_{11}$ requires C 47.1, H 5.2%). δ_H (300 MHz) 6.18 (d, $J_{1,2}$ 8.3, H1), 5.48 (dd, $J_{2,3}$ 9.3, $J_{3,4}$ 9.5, H3), 5.30 (dd, $J_{4,F}$ 22.7, H4), 5.22 (dd, H2), 4.38 (dd, $J_{6,6}$ 12.0, $J_{6,F}$ 7.0, H6), 3.99 (dd, $J_{6,F}$ 4.1, H6), 2.13, 2.10, 2.08, 2.05, 2.01 (5s, 15H, Me). δ_C (125.8 MHz) 169.70, 169.66, 169.33, 169.22 (5C, C=O), 109.50 (d, $J_{5,F}$ 253, C5), 88.59 (d, $J_{1,F}$ 5.7, C1), 69.76–61.27 (C2, C3, C4), 61.52 (d, $J_{6,F}$ 38.0, C6), 20.69, 20.51, 20.46, 20.39 (5C, Me). δ_F (282.4 MHz) −131.66 (ddd, $J_{4,F}$ 22.7, $J_{6,F}$ 4.1, 7.0, F5).

(*b*) Silver tetrafluoroborate (55 mg, 2.8 mmol) was added to the bromide **6** (110 mg, 0.23 mmol) in dry toluene (10 mL). The mixture was left to stir (30 min), and a precipitate formed immediately. The mixture was then processed as in (*a*) to give the fluoride **14** as a colourless powder (16 mg, 17%). The spectroscopic data (^{1}H and ^{13}C NMR) were consistent with those observed above.

Penta-O-*benzoyl-5-fluoro-β-D-glucopyranose* ***15***

(*a*) Silver tetrafluoroborate (100 mg, 0.54 mmol) in dry Et_2O (5 mL) was added dropwise to the bromide **7** (350 mg, 0.45 mmol) in Et_2O/CH_2Cl_2 (1 : 1, 5 mL) with stirring. The mixture was treated as in (*a*) above to

give, after flash chromatography (15% EtOAc/petrol), the *fluoride* **15** as a colourless oil (275 mg, 85%), $[\alpha]_D$ +13° (Found: C 68.6, H 4.4. $C_{41}H_{31}FO_{11}$ requires C 68.5, H, 4.3%). δ_H (300 MHz) 8.13–7.22 (25H, m, Ph), 6.75 (d, $J_{1,2}$ 7.8, H1), 6.27 (t, $J_{2,3}$ 8.8, $J_{3,4}$ 8.9, H3), 6.12 (dd, $J_{4,F}$ 22.6, H4), 5.97 (dd, H2), 4.63 (dd, $J_{6,6}$ 12.0, $J_{6,F}$ 6.5, H6), 4.54 (dd, $J_{6,F}$ 6.7, H6). δ_C (75.5 MHz) 165.27, 164.97, 164.03 (5C, C=O), 133.94–128.17 (Ar), 109.87 (d, $J_{5,F}$ 230, C5), 89.73 (d, $J_{1,F}$ 3.0, C1), 70.45, 69.74 (C2, C3), 69.02 (d, $J_{4,F}$ 24.0, C4), 62.60 (d, $J_{6,F}$ 37.0, C6). m/z (FAB) 699.1893 [$(M-F)^{+\bullet}$ requires 699.1866].

Also isolated was the L-*ido* isomer **16** as colourless plates (25 mg, 8%). δ_H (500 MHz) 8.12–7.37 (25H, m, Ph), 6.73–6.72 (m, H1), 6.05 (dd, $J_{3,4}$ 4.7, $J_{4,F}$ 6.0, H4), 5.89 (br dd, $J_{2,3}$ 4.5, H3), 5.77 (dd, $J_{1,2}$ 2.4, H2), 4.78 (dd, $J_{6,6}$ 12.0, $J_{6,F}$ 10.4, H6), 4.67 (dd, $J_{6,F}$ 20.7, H6).

(*b*) Silver tetrafluoroborate (54 mg, 2.8 mmol) was added to the bromide **7** (180 mg, 0.23 mmol) in dry toluene (10 mL). The mixture was treated as in (*a*) for the preparation of **14** to give the fluoride **15** as a colourless oil (124 mg, 75%). The spectroscopic data (^{1}H and ^{13}C NMR) were consistent with those observed above.

(*c*) Silver fluoride (76 mg, 0.60 mmol) was added to the bromide **7** (235 mg, 0.30 mmol) in dry MeCN (5 mL). The mixture was treated as in (*a*) for the preparation of **14** to give the fluoride **15** as a colourless oil (170 mg, 79%). The spectroscopic data (^{1}H and ^{13}C NMR) were consistent with those observed above.

Penta-O-*(4-bromobenzoyl)-5-fluoro-β-D-glucopyranose* ***17***

Silver tetrafluoroborate (40 mg, 0.21 mmol) in dry Et_2O (2 mL) was added dropwise to the bromide **8** (190 mg, 0.16 mmol) in Et_2O/CH_2Cl_2 (1 : 1, 4 mL) with stirring. The mixture was treated as in (*a*) for the preparation of **14** to give, after flash chromatography (15% EtOAc/petrol), a colourless oil that crystallized. Recrystallization gave the *fluoride* **17** as fine needles (144 mg, 80%), mp 231–233°C (AcOH), $[\alpha]_D$ −15° (Found: C 44.2, H 2.5. $C_{41}H_{26}Br_5FO_{11}$ requires C 44.3, H 2.3%). δ_H (300 MHz) 7.73–7.30 (20H, m, Ar), 6.49 (d, $J_{1,2}$ 7.8, H1), 5.98 (t, $J_{2,3}$ 8.7, $J_{3,4}$ 9.8, H3), 5.85 (dd, $J_{4,F}$ 22.5, H4), 5.72 (dd, H2), 4.45 (dd, $J_{6,6}$ 12.2, $J_{6,F}$ 7.4, H6), 4.34 (dd, $J_{6,F}$ 6.9, H6). δ_C (75.5 MHz) 165.34, 165.29, 165.03, 164.97, 164.04 (5C, C=O), 133.96–128.12 (Ar), 109.87 (d, $J_{5,F}$ 231, C5), 89.73 (d, $J_{1,F}$ 4.3, C1), 70.43, 69.72 (C2, C3), 69.00 (d, $J_{4,F}$ 24.4, C4), 62.60 (d, $J_{6,F}$ 39.4, C6).

Penta-O-*acetyl-5-fluoro-α-L-idopyranose* ***18***

Silver fluoride (53 mg, 0.42 mmol) was added to the bromide **6** (130 mg, 0.28 mmol) in dry MeCN (5 mL). The mixture was treated as in (*a*) for the preparation of **14** to give, after flash chromatography (35% EtOAc/petrol), the fluoride **18** as a colourless oil (87 mg, 76%). δ_H (300 MHz) 6.11 (dd, $J_{1,2}$ 3.1, $J_{1,F}$ 1.4, H1), 5.47 (dd, $J_{3,4}$ 6.0, $J_{4,F}$ 11.1, H4), 5.32–5.22 (m, H2,3), 4.31 (dd, $J_{6,6}$ 11.9, $J_{6,F}$ 15.2, H6), 4.24 (dd, $J_{6,F}$ 23.0, H6), 2.12, 2.10, 2.08, 2.07, 2.03 (15H, 5s, Me).

Tetra-O-*acetyl-5-fluoro-β-D-glucopyranosyl Fluoride* ***19***

Silver tetrafluoroborate (130 mg, 0.66 mmol) in Et_2O (15 mL) was added dropwise to the bromide **10** (235 mg, 0.55 mmol) in Et_2O (5 mL) with stirring. The mixture was treated as in (*a*) for the preparation of **14** to give, after flash chromatography (35% EtOAc/petrol), the fluoride **19** as a colourless oil (111 mg, 55%). δ_H (300 MHz)[19] 5.65 (dd, $J_{1,F}$ 49.0, H1), 5.45 (dd, $J_{4,F}$ 22.1, H4), 5.40 (dd, $J_{3,4}$ 9.2, H3), 5.20 (ddd, $J_{1,2}$ 6.0, $J_{2,3}$ 8.0, $J_{2,F}$ 9.0, H2), 4.34 (dd, $J_{F,6}$ 7.1, H6), 4.08 (dd, $J_{F,6}$ 4.6, $J_{6,6}$ 12.0, H6), 2.15, 2.13, 2.09, 2.01 (12H, 4s, Me). δ_F (470.6 MHz) −143.1 (ddd, F1), −128.3 (m, F5).

Tetra-O-*acetyl-5-fluoro-α-D-glucopyranosyl Fluoride* ***20***

Silver tetrafluoroborate (195 mg, 1.00 mmol) in Et_2O (15 mL) was added dropwise to the bromide **11** (350 mg, 0.82 mmol) in Et_2O (10 mL) with stirring. The mixture was treated as in (*a*) for the preparation of **14** to give, after flash chromatography (35% EtOAc/petrol), the fluoride **20** as a colourless oil (160 mg, 53%). δ_H (300 MHz)[19] 5.81 (dd, $J_{1,F}$ 53.5, H1), 5.70 (dd, $J_{2,3} \approx J_{3,4}$ 9.8, H3), 5.30 (dd, $J_{4,F}$ 22.0, H4), 5.00 (ddd, $J_{1,2}$ 3.0, $J_{2,F}$ 24.0, H2), 4.25 (dd, $J_{F,6}$ 6.5, H6), 4.01 (dd, $J_{F,6}$ 3.0, $J_{6,6}$ 12.0, H6), 2.13, 2.10, 2.03, 1.98 (12H, 4s, Me), δ_F (470.6 MHz) −138.2 (ddd, F1), −123.0 (m, F5).

Tetra-O-*benzoyl-5-fluoro-β-D-glucopyranosyl Fluoride* ***21***

Silver tetrafluoroborate (35 mg, 0.18 mmol) was added to the bromide **12** (100 mg, 0.15 mmol) in Et_2O/CH_2Cl_2 (1 : 1, 10 mL) with stirring. The mixture was treated as in (*a*) for the preparation of **14** to give, after flash chromatography (35% EtOAc/petrol), the *fluoride* **21** as a colourless oil (75 mg, 81%), $[\alpha]_D$ +33.4° (Found: C 66.1, H 4.2. $C_{34}H_{26}F_2O_9$ requires C 66.1, H 4.2%). δ_H (300 MHz) 8.10–7.21 (20H, m, Ar), 6.24–5.88 (m, H1,3,4), 5.74 (ddd, $J_{1,2}$ 5.3, $J_{2,3}$ 6.6, $J_{2,F}$ 9.8, H2), 4.68 (dd, $J_{6,6}$ 12.0, $J_{6,F5}$ 6.6, H6), 4.57 (dd, $J_{6,F5}$ 6.4, H6). δ_C (75.5 MHz) 165.35, 165.27, 164.81 (4C, C=O), 133.79–128.15 (Ar), 109.73 (dd, $J_{5,F5}$ 231, $J_{5,F1}$ 5.5, C5), 104.42 (d, $J_{1,F1}$ 222, C1), 71.23, 69.48, 68.16 (C2, C3, C4), 62.25 (d, $J_{6,F5}$ 39.2, C6). δ_F (282.4 MHz) −127.67 (dddd, $J_{4,F5}$ 23.1, $J_{6,F5}$ 6.4, 6.6, $J_{F1,F5}$ 10.2, F5), −139.78 (ddd, $J_{1,F1}$ 52.0, $J_{2,F1}$ 9.8, $J_{F1,F5}$ 10.2, F1). m/z (FAB) 617.1676 [$(M+H)^{+\bullet}$ requires 617.1623].

Treatment of ***15*** *with Hydrogen Bromide*

The fluoride **15** (540 mg) in HBr/HOAc (30% w/w; 4 mL) was kept at room temperature (3 days). Usual workup (CH_2Cl_2) gave a colourless oil that crystallized on standing. Recrystallization (EtOAc/petrol) gave the bromide **7** as a fine powder (455 mg, 78%). The spectroscopic data (^{1}H and ^{13}C NMR) were consistent with those reported.[7]

Phenyl Tetra-O-*acetyl-5-fluoro-β-D-glucopyranoside* ***25***

Silver tetrafluoroborate (300 mg, 1.50 mmol) in Et_2O (15 mL) was added dropwise to the bromide **24**[12] (500 mg, 1.00 mmol) in Et_2O (10 mL) at room temperature. A precipitate formed immediately and stirring was continued (5 min). The mixture was then filtered through a plug of silica, subjected to a usual workup (Et_2O), and purified by flash chromatography (40% EtOAc/petrol) to give the *fluoride* **25** as a colourless oil (256 mg, 58%), $[\alpha]_D$ +18° (Found: C 54.3, H 5.2. $C_{20}H_{23}FO_{10}$ requires C 54.3, H 5.2%). δ_H (300 MHz) 7.34–6.99 (20H, m, Ph), 5.60 (d, $J_{1,2}$ 7.7, H1), 5.54 (br dd, $J_{2,3}$ 9.3, $J_{3,4}$ 9.8, $J_{3,F}$ 0.6, H3), 5.41 (dd, $J_{4,F}$ 22.7, H4), 5.39 (dd, H2), 4.38 (dd, $J_{6,6}$ 11.9, $J_{6,F}$ 8.3, H6), 4.07 (dd, $J_{6,F}$ 4.9, H6), 2.09, 2.08, 2.03, 2.01 (12H, 4s, Me). δ_C (75.5 MHz) 169.80, 169.76, 169.30, 169.22 (4C, C=O), 156.46, 129.63, 123.50, 116.59 (Ph), 109.64 (d, $J_{5,F}$ 229, C5), 95.77 (d, $J_{1,F}$ 4.5, C1), 70.35, 69.34 (C2, C3), 68.02 (d, $J_{4,F}$ 24.0, C4), 61.78 (d, $J_{6,F}$ 40.0, C6), 20.59, 20.48, 20.41, 20.37 (4C, Me).

Phenyl 5-Fluoro-β-D-glucopyranoside ***4***

Ammonia was passed over a stirred solution of the fluoride **25** (200 mg) in dry MeOH (5 mL) at 0°C (5 min) and the solution kept at this temperature (1 h). The solution was then concentrated and the residue purified by flash chromatography (EtOH/EtOAc/H_2O, 1 : 6 : 0.5) to give the *β-D-glucoside* **4** as a colourless oil (98 mg, 79%) (Found: C 52.4, H 5.5. $C_{12}H_{13}FO_6$ requires C 52.6, H 5.5%). δ_H (300 MHz) 7.31–6.95 (m, Ph), 5.31 (d, $J_{1,2}$ 8.0, H1), 4.58–3.58 (5H, m, H2, H3, H4, H6). δ_C (75.5 MHz) 158.57, 130.28, 123.21, 117.24 (Ph), 113.76 (d, $J_{5,F}$ 226, C5), 99.07 (d, $J_{1,F}$ 4.6, C1), 74.10, 73.47 (C2, C3), 70.84 (d, $J_{4,F}$ 28.0, C4), 62.85 (d, $J_{6,F}$ 34.0, C6).

Methyl Tetra-O-*benzoyl-5-fluoro-β-D-glucopyranoside* ***29***

Diethylaminosulfur trifluoride (0.5 mL, 4 mmol) was added to the methyl β-D-glucoside **28**[11] (780 mg, 1.25 mmol) in CH_2Cl_2 (10 mL) at −10°C and the solution kept at this temperature (20 min). Usual workup (CH_2Cl_2) followed by flash chromatography (25% EtOAc/petrol) gave the *fluoride* **29** as fine needles (320 mg, 41%), mp 138–139°C (MeOH), $[\alpha]_D$ +25° (Found: C 66.7, H 4.6. $C_{35}H_{29}FO_{10}$ requires C 66.9, H 4.7%). δ_H (300 MHz) 8.00–7.19 (20H, m, Ph), 6.15 (t, $J_{2,3}$ 9.5, $J_{3,4}$ 9.9, H3), 5.97 (dd, $J_{4,F}$ 22.5, H4), 5.66 (dd, $J_{1,2}$ 7.8, H2), 5.24 (d, H1), 4.63 (dd, $J_{6,6}$ 12.0, $J_{6,F}$ 7.6, H6), 4.53 (dd, $J_{6,F}$ 7.9, H6), 3.59 (s, OMe). δ_C (75.5 MHz) 165.52, 165.45, 165.05, 165.01 (4C, C=O), 133.63–128.28 (Ph), 109.35 (d, $J_{5,F}$ 229, C5), 99.15 (d, $J_{1,F}$ 2.0, C1), 71.16,

69.57 (C2, C3), 69.48 (d, $J_{4,F}$ 25.0, C4), 62.95 (d, $J_{6,F}$ 36.0, C6), 57.54 (OMe). m/z (FAB) 629.1832 [$(M+H)^{+\bullet}$ requires 629.1823].

Methyl Tetra-O-*acetyl-5-hydroxy-β-D-glucopyranoside* ***30***

The hydrate of 2,3,4,6-tetra-*O*-acetyl-hexos-5-ulose[20] (1.60 g) was stirred at 40°C in dry MeOH (30 mL; 2 h). The solution was then concentrated to give the methyl β-D-*glucoside* **30** as a pale yellow oil (1.74 g), which was used without purification. δ_H (300 MHz) 5.45 (t, $J_{2,3}$ 9.9, $J_{3,4}$ 7.1, H3), 5.21 (d, $J_{1,2}$ 7.1, H1), 5.13 (d, H4), 4.91 (dd, H2), 4.08, 3.94 (2H, ABq, *J* 11.8, H6), 3.40 (s, OMe), 2.09, 2.00, 1.98, 1.91 (12H, 4s, Me). δ_C (75.5 MHz) 170.92, 170.35, 170.05, 169.68 (4C, C=O), 95.10 (C5), 90.50 (C1), 73.10, 69.78, 69.64 (C2, C3, C4), 64.89 (C6), 56.54 (OMe), 20.55, 20.41 (4C, Me). m/z (FAB) 361.1156 [$(M-OH)^{+\bullet}$ requires 361.1135].

Methyl Tetra-O-*acetyl-5-fluoro-β-D-glucopyranoside* ***31***

Diethylaminosulfur trifluoride (0.3 mL, 2 mmol) was added to the β-D-glucoside **30** (0.4 g, 1 mmol) in dry CH_2Cl_2 (15 mL) at 0°C. The solution was kept at this temperature (5 min), then subjected to a usual workup (CH_2Cl_2), and the residue purified by flash chromatography (30% EtOAc/petrol). First to elute was the β-D-*glucoside* **31** as a colourless oil (165 mg, 43%) (Found: C 47.4, H 5.6. $C_{15}H_{21}FO_{10}$ requires C 47.4, H 5.6%). δ_H (300 MHz) 5.43 (t, $J_{2,3}$ 9.9, $J_{3,4}$ 9.9, H3), 5.31 (dd, $J_{4,F}$ 22.8, H4), 5.10 (dd, $J_{1,2}$ 8.0, H2), 4.90 (d, H1), 4.33 (dd, $J_{6,6}$ 11.9, $J_{6,F}$ 7.2, H6), 4.03 (dd, $J_{6,F}$ 4.9, H6), 3.52 (s, OMe), 2.09, 2.07, 2.06, 1.99 (12H, 4s, Me). δ_C (125.8 MHz) 169.84, 169.34, 169.32 (4C, C=O), 109.21 (d, $J_{5,F}$ 227, C5), 98.59 (d, $J_{1,F}$ 5.0, C1), 70.55, 69.40 (C2, C3), 68.17 (d, $J_{4,F}$ 25.0, C4), 61.89 (d, $J_{6,F}$ 38.0, C6), 57.44 (OMe), 20.59, 20.54, 20.48, 20.40 (4C, Me). δ_F (470.5 MHz) −130.85 (ddd, $J_{4,F}$ 22.8, $J_{6,F}$ 4.9, 7.2, F5). m/z (FAB) 381.1193 [$(M+H)^{+\bullet}$ requires 381.1197].

Next to elute were the hex-5-uloses **32** as an inseparable mixture (1 : 1.3) (165 mg, 40%). δ_H (300 MHz) 5.78 (dd, $J_{2,3}$ 6.7, H3), 5.72 (dd, $J_{2,3}$ 6.7, H3), 5.50 (d, $J_{3,4}$ 3.1, H4), 5.44 (d, $J_{3,4}$ 3.1, H4), 5.27–5.18 (m, H2), 5.22 (dd, $J_{1,2}$ 2.5, $J_{1,F}$ 66.0, H1), 5.16 (dd, $J_{1,2}$ 4.0, $J_{1,F}$ 66.0, H1), 4.85, 4.83, 4.73, 4.71 (2H, 2ABq, *J* 17.3, H6), 3.57 (d, $J_{OMe,F}$ 1.2, OMe), 3.51 (d, $J_{OMe,F}$ 1.2, OMe), 2.19, 2.15, 2.08 (12C, 3s, Me). δ_C (75.5 MHz) 197.36, 197.28 (C5), 169.67, 169.56, 169.38 (4C, C=O), 110.19, 109.81 (2d, $J_{1,F}$ 223, C1), 70.23, 69.90 (2d, $J_{2,F}$ 25.0, 29.0, C2), 74.55, 67.62, 67.56 (C3, C4), 66.63, 66.59 (C6), 57.79, 57.49 (OMe), 20.44, 20.39, 20.27 (4C, Me). δ_F (470.5 MHz) −135.9 (br dd, $J_{1,F}$ 66.0, $J_{2,F}$ 8.0, F1), −143.17 (br dd, $J_{1,F}$ 66.0, $J_{2,F}$ 16.0, F1). m/z (FAB) 361.1156 [$(M-F)^{+\bullet}$ requires 361.1135].

Methyl 5-Fluoro-β-D-glucopyranoside ***5***

Ammonia was bubbled through a solution of **31** (62 mg) in dry MeOH (5 mL) at 0°C (5 min) and the solution held at this temperature (30 min). The solution was then concentrated and the residue purified by flash chromatography (EtOH/EtOAc/H_2O, 1 : 6 : 0.5) to give the β-D-*glucoside* **5** as a colourless oil (26 mg, 74%) (Found: C 39.5, H 6.3. $C_7H_{13}FO_6$ requires C 39.6, H 6.2%). δ_H (300 MHz) 4.98 (d, $J_{1,2}$ 8.2, H1), 4.01–3.55 (5H, m, H2, H3, H4, H6), 3.45 (s, OMe). δ_C (75.5 MHz) 111.45 (d, $J_{5,F}$ 229, C5), 99.28 (d, $J_{1,F}$ 4.6, C1), 74.58, 74.46 (C2, C3), 71.87 (d, $J_{4,F}$ 29.0, C4), 62.65 (d, $J_{6,F}$ 35.0, C6), 57.82 (OMe).

Methyl Tri-O-*acetyl-6-deoxy-6-iodo-β-D-glucopyranoside*

Triphenylphosphine (24.3 g, 92.8 mmol), imidazole (6.32 g, 92.8 mmol), and I_2 (19.6 g, 77.3 mmol) were added to a suspension of methyl β-D-glucopyranoside (15.0 g, 77.3 mmol) in toluene (200 mL) with vigorous stirring. The mixture was held at 70°C (2 h), then quenched with water, and stirring continued (30 min). The mixture was concentrated, and then taken up in pyridine (100 mL) and Ac_2O (100 mL). The solution was left to stand at room temperature (4 h), and then concentrated. Usual workup (EtOAc) followed by flash chromatography (20% EtOAc/petrol) gave the title iodide as fine needles (23.6 g, 71%), mp 112–113°C (Pr^i_2O/petrol; lit.[21] 114–115°C), $[\alpha]_D$ +2.0° (lit.[21] +1.0°). δ_H (300 MHz) 5.19 (t, $J_{2,3}$ 9.4, $J_{3,4}$ 9.4, H3), 4.97 (dd, $J_{1,2}$ 8.0, H2), 4.88 (t, $J_{4,5}$ 9.4, H4), 4.44 (d, H1), 3.57 (s, OMe), 3.56–3.49 (m, H5), 3.29 (dd, $J_{5,6}$ 2.7, $J_{6,6}$ 10.9, H6), 3.15 (dd, $J_{5,6}$ 8.5, H6), 2.08, 2.06, 1.95 (9H, Me). δ_C (75.5 MHz) 169.99, 169.38 (3C, C=O), 101.34 (C1), 73.38, 72.41, 72.25, 71.46 (C2, C3, C4, C5), 57.14 (OMe), 20.69, 20.57 (3C, Me), 2.93 (C6).

Methyl Tri-O-*acetyl-6-deoxy-β-D*-xylo-*hex-5-enopyranoside* ***34***

1,8-Diazabicyclo[5.4.0]undec-7-ene (13.0 mL, 87.2 mmol) was added to the above iodide (7.50 g, 17.4 mmol) in THF (60 mL), and the solution heated at reflux (2 h). The mixture was then concentrated, subjected to a usual workup (EtOAc), and purified by flash chromatography (40% EtOAc/petrol) to give the alkene **34** as a colourless oil (3.63 g, 69%), $[\alpha]_D$ −34.6° (lit.[22] −34.8°). δ_H (300 MHz) 5.68 (dt, $J_{3,4}$ 8.9, $J_{4,6}$ 1.8, 1.8, H4), 5.08 (dd, $J_{2,3}$ 5.6, H3), 5.00 (dd, $J_{1,2}$ 4.4, H2), 4.74 (t, $J_{6,6}$ 1.8, H6), 4.65 (d, H1), 4.47 (t, H6), 3.51 (OMe), 2.16, 2.09, 2.02 (9H, Me). δ_C (75.5) 170.14, 169.69, 169.64 (3C, C=O), 150.93 (C5), 101.26 (C1), 94.70 (C6), 72.48, 72.22, 68.46 (C2, C3, C4), 56.73 (OMe), 20.97 (3C, Me).

Tri-O-*acetyl-6-deoxy-5-hydroxy-6-iodo-β-D-glucopyranose* ***35***

Iodine (508 mg, 2.00 mmol) was added to the alkene **33**[13] (300 mg, 1.0 mmol) in MeCN/H_2O (30 mL; 2 : 1) at −15°C and the solution left to stir at this temperature (30 min). The solution was then concentrated, subjected to a usual workup (CH_2Cl_2), and the residue purified by flash chromatography (50% EtOAc/petrol) to give the *diol* **35** as colourless cubes (360 mg, 84%), mp 132–138°C (EtOH), $[\alpha]_D$ +23° (Found: C 33.4, H 4.1. $C_{12}H_{17}IO_9$ requires C 33.4, H 4.0%). δ_H (500 MHz) 7.28 (d, OH), 7.26 (s, OH), 5.55 (dd, $J_{2,3}$ 9.9, $J_{3,4}$ 9.8, H3), 5.38 (d, H4), 5.31 (dd, $J_{1,OH}$ 7.8, $J_{1,2}$ 8.0, H1), 5.03 (dd, H2), 3.59 (s, OMe), 3.56, 3.47 (2H, ABq, *J* 10.9, H6), 2.26, 2.24, 2.18 (9H, Me). δ_C (75.5 MHz) 167.60, 167.38, 167.19 (3C, C=O), 91.97 (C5), 88.48 (C1), 71.29, 69.00, 68.94 (C2, C3, C4), 18.82, 18.63 (3C, Me), 8.17 (C6). m/z (FAB) 414.9914 [$(M-OH)^{+\bullet}$ requires 414.9890].

Methyl Tri-O-*benzyl-6-deoxy-β-D*-xylo-*hex-5-enopyranoside* ***37***

The alkene **34** (7.20 g, 23.8 mmol) in MeOH (50 mL) was treated with Na (3 mg) and the solution kept at room temperature (30 min). Concentration of the mixture then gave a pale yellow oil that was dissolved in DMF (100 mL) and treated with NaH (3.8 g, 95 mmol; 60% suspension in oil) with vigorous stirring (30 min). Benzyl bromide (8.76 mL, 73.8 mmol) was added dropwise and stirring continued (2 h). Water (10 mL) was then added dropwise to the mixture and stirring continued (2 h). Concentration of the mixture, followed by usual workup (EtOAc) and flash chromatography (10% EtOAc/petrol), gave the alkene **37** as a colourless oil (9.46 g, 89%), $[\alpha]_D$ −10.8°. δ_H (300 MHz) 7.40–7.29 (15H, m, Ph), 4.84–4.67 (8H, m, H6,CH_2Ph), 4.65 (d, $J_{1,2}$ 6.1, H1), 4.10 (dt, $J_{4,6} \approx J_{4,6}$ 1.4, $J_{3,4}$ 7.5, H4), 3.67 (dd, $J_{2,3}$ 6.9, H3), 3.60 (s, OMe), 3.59 (dd, H2). δ_C (75.5 MHz) 153.84 (C5), 138.23–127.67 (Ph), 103.99 (C6), 94.61 (C1), 82.87, 81.45, 78.28 (C2, C3, C4), 74.27, 73.86, 73.04 (3C, *C*H_2Ph), 56.90 (OMe). m/z (FAB) 447.2154 [$(M+H)^{+\bullet}$ requires 447.2171].

Methyl 5,6-Epoxy-tri-O-*benzyl-β-L-idopyranoside* ***38***

DMDO in acetone (100 mL of 0.1 M) was added to the alkene **36**[13] (780 mg, 1.75 mmol) in CH_2Cl_2 (20 mL) at room temperature and the mixture kept (10 min). Concentration of the mixture gave the epoxide **38** as a colourless oil (795 mg). δ_H (500 MHz) 7.45–7.38 (15H, m, Ph), 4.93–4.64 (7H, m, H1, CH_2Ph), 4.08 (t, $J_{2,3}$ 9.6, $J_{3,4}$ 9.7, H3), 3.87 (d, H4), 3.69 (dd, $J_{1,2}$ 3.7, H2), 3.46 (s, OMe). δ_C (75.5 MHz) 138.48–127.55 (Ph), 99.26 (C1), 81.43 (C5), 79.85, 78.99, 77.30 (C2, C3, C4), 75.83, 74.89, 73.63 (3C, *C*H_2Ph), 56.80 (OMe), 50.09 (C6). The epoxide **38** was used without purification.

Methyl 5,6-Epoxy-tri-O-*benzyl-α-L-idopyranoside and Methyl 5,6-Epoxy-tri*-O-*benzyl-β-D-glucopyranoside*

DMDO in acetone (100 mL of 0.1 M) was added to the alkene **37** (500 mg, 1.12 mmol) in CH_2Cl_2 (20 mL) at room temperature and

the mixture kept (10 min). Concentration of the mixture gave the epoxides **39** as an inseparable mixture (D-*gluco*/L-*ido* 1 : 2; 480 mg). δ_H (300 MHz) D-*gluco*: 7.39–7.28 (15H, m, Ph), 4.95–4.69 (6H, m, CH_2Ph), 4.68 (d, $J_{1,2}$ 8.3, H1), 3.99 (d, $J_{3,4}$ 9.3, H4), 3.92 (dd, $J_{2,3}$ 8.5, H3), 3.59 (dd, H2), 3.52 (s, OMe), 2.97, 2.89 (2H, ABq, J 5.5, H6); L-*ido*: 7.39–7.28 (15H, m, Ph), 4.97–4.63 (6H, m, CH_2Ph), 4.56 (d, $J_{1,2}$ 6.2, H1), 3.99 (d, $J_{3,4}$ 9.0, H4), 3.73 (dd, $J_{2,3}$ 8.3, H3), 3.64 (dd, H2), 3.54 (s, OMe), 3.13, 2.87 (2H, ABq, J 5.2, H6).

1,6-Anhydro-tri-O-*benzyl-5-hydroxy-β-L-idopyranose* ***40***

The epoxide **38** (460 mg, 1.00 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of $AgBF_4$ (195 mg, 1.00 mmol) in Et_2O (30 mL) and stirring continued (10 min). The mixture was then filtered through a plug of silica and the filtrate treated with cation-exchange resin (Amberlite IR-120, H^+). The mixture was filtered and the filtrate concentrated to give a pale yellow solid. Recrystallization then gave the *hexosulose* **40** as fine needles (383 mg, 85%), mp 137–141°C (Et_2O), $[\alpha]_D$ +43° (Found: C 72.4, H 6.1. $C_{27}H_{28}O_6$ requires C 72.3, H 6.3%). δ_H (500 MHz) 7.36–7.27 (15H, m, Ph), 5.28 (d, $J_{1,2}$ 1.9, H1), 4.86, 4.83 (ABq, J 11.0, CH_2Ph), 4.88, 4.79 (ABq, J 11.5, CH_2Ph), 4.72, 4.67 (ABq, J 11.8, CH_2Ph), 4.21 (d, $J_{6,6}$ 8.1, H6), 3.80 (t, $J_{2,3}$ 7.8, $J_{3,4}$ 8.1, H3), 3.69 (dd, H4), 3.56 (dd, H2), 3.34 (dd, $J_{4,6}$ 1.9, H6). δ_C (125.8 MHz) 138.36–127.66 (Ph), 103.36 (C5), 98.44 (C1), 82.57 (C2), 82.05 (C3), 81.92 (C4), 75.53, 74.69, 73.00 (3C, CH$_2$Ph), 68.61 (C6). m/z (FAB) 447.1790 [$(M-H)^{+\bullet}$ requires 447.1807].

Methyl 2,3,4-Tri-O-*benzyl-5-fluoro-β-L-idopyranoside* ***41***

Hydrogen fluoride/pyridine (0.7 mL) was added to a stirred solution of the epoxide **38** (240 mg) in CH_2Cl_2 (50 mL) at 0°C. The solution was kept at this temperature (5 min), then poured into cold water, and subjected to a usual workup (CH_2Cl_2). Flash chromatography (20% EtOAc/petrol) then gave the fluoride **41** as a colourless oil (210 mg, 88%). δ_H (300 MHz) 4.85 (d, $J_{1,2}$ 3.1, H1), 4.81–4.68 (6H, m, CH_2Ph), 4.05–3.80 (5H, m, H2,3,4,6), 3.52 (s, OMe), 2.56 (br m, OH). δ_C (75.5 MHz) 138.00–127.67 (Ph), 113.31 (d, $J_{5,F}$ 218, C5), 98.25 (d, $J_{1,F}$ 4.4, C1), 80.05 (d, $J_{4,F}$ 32.0, C4;), 77.76 (d, $J_{3,F}$ 6.0, C3), 77.63 (C2), 74.07, 73.82, 73.54 (3C, CH$_2$Ph), 64.00 (d, $J_{6,F}$ 30.6, C6), 56.86 (OMe).

Methyl 6-O-*Acetyl-tri*-O-*benzyl-5-fluoro-β-L-idopyranoside* ***42***

Acetic anhydride (1 mL) was added to the fluoride **41** (130 mg) in CH_2Cl_2 (10 mL) and pyridine (2 mL) at room temperature and the mixture kept (20 min). Concentration of the mixture, followed by flash chromatography (25% EtOAc/petrol) of the residue, gave the acetate **42** as a colourless oil (112 mg, 79%). δ_H (300 MHz) 7.43–7.25 (15H, m, Ph), 4.93, 4.53 (ABq, J 12.1, CH_2Ph), 4.83 (d, $J_{1,2}$ 3.0, H1), 4.81, 4.69 (ABq, J 11.3, CH_2Ph), 4.62 (s, CH_2Ph), 4.56 (dd, $J_{6,6}$ 12.2, $J_{6,F}$ 16.6, H6), 4.30 (dd, $J_{6,F}$ 21.0, H6), 3.95 (dd, $J_{2,3}$ 7.8, $J_{3,4}$ 5.1, H3), 3.82 (dd, $J_{1,2}$ 3.0, H2), 3.76 (dd, $J_{4,F}$ 11.0, H4), 3.48 (s, OMe), 2.08 (s, Me). δ_C (75.5 MHz) 170.17 (C=O), 138.02–127.75 (Ph), 112.07 (d, $J_{5,F}$ 218, C5), 98.32 (d, $J_{1,F}$ 4.4, C1), 77.43 (d, $J_{4,F}$ 32.0, C4), 77.32 (C2), 77.11 (d, $J_{3,F}$ 4.7, C3), 74.15, 73.60, 73.42 (3C, CH$_2$Ph), 64.20 (d, $J_{6,F}$ 25.9, C6), 56.70 (OMe), 20.69 (Me).

Methyl 2,3,4-Tri-O-*benzyl-5-fluoro-α-L-idopyranoside* ***43***

Hydrogen fluoride/pyridine (0.8 mL) was added to the epoxides **39** (ratio of D-*gluco* to L-*ido* 1 : 2; 310 mg) in CH_2Cl_2 (50 mL) at 0°C. The solution was kept (5 min), then poured into cold water, and subjected to a usual workup (CH_2Cl_2). Flash chromatography (20% EtOAc/petrol) then gave the fluoride **43** as a colourless oil (278 mg, 84%). δ_H (300 MHz) 7.39–7.28 (15H, m, Ph), 4.88 (br dd, $J_{1,2}$ 2.1, $J_{1,F}$ 2.0, H1), 4.80–4.56 (6H, m, CH_2Ph), 4.27 (dd, $J_{3,4}$ 8.9, $J_{4,F}$ 14.2, H4), 3.95 (br dd, $J_{6,6}$ 12.1, $J_{6,F}$ 9.0, H6), 3.88 (dd, $J_{2,3}$ 5.0, H3), 3.82–3.73 (m, H2,6), 3.52 (s, OMe), 2.34 (br s, OH). δ_C (75.5 MHz) 138.12–127.71 (Ph), 112.56 (d, $J_{5,F}$ 231, C5), 102.32 (C1), 82.32, 79.73 (C2, C3), 79.40 (d, $J_{4,F}$ 26.0, C4), 74.78, 73.76, 73.02 (3C, CH$_2$Ph), 63.05 (d, $J_{6,F}$ 38.0, C6), 56.21 (OMe).

Methyl 2,3,4-Tri-O-*benzyl-5-fluoro-β-L-idopyranoside* ***41*** *and Methyl 2,3,4-Tri*-O-*benzyl-5-fluoro-α-D-glucopyranoside*

(*a*) 3-Chloroperbenzoic acid (170 mg, 1.0 mmol) was added to the alkene **36** (460 mg, 1.0 mmol) in a mixture of CH_2Cl_2 (10 mL) and 0.5 M $NaHCO_3$ solution (10 mL), and the mixture stirred at room temperature (5 min). Separation of the organic phase followed by evaporation of the solvent gave the epoxide **38** as an inseparable mixture (2 : 1, ^{1}H NMR) with methyl 5,6-anhydro-tri-*O*-benzyl-β-D-glucopyranoside (480 mg).

(*b*) Hydrogen fluoride/pyridine (0.5 mL) was added to the above mixture of epoxides (480 mg) in CH_2Cl_2 (5 mL) at −78°C, and the solution stirred (10 min). Water was added and the usual workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol; 1 : 4) furnished the β-L-idoside **41** as a colourless oil (123 mg, 24%), $[\alpha]_D$ +13.5°. m/z 481.2037 [$(M-H)^{+\bullet}$ requires 481.2026].

Next to elute was *methyl 2,3,4-tri*-O-*benzyl-5-fluoro-α-D-glucopyranoside* as a colourless oil (250 mg, 50%), $[\alpha]_D$ +8.8° (Found: C 69.9, H 6.6. $C_{28}H_{31}FO_6$ requires C 69.7, H 6.5%). δ_H (600 MHz) 7.38–7.29 (15H, m, Ph), 5.02–4.68 (6H, m, CH_2Ph), 4.72 (d, $J_{1,2}$ 3.7, H1), 4.34 (dd, $J_{2,3}$ 9.7, $J_{3,4}$ 9.7, H3), 3.70 (dd, $J_{4,F}$ 23.0, H4), 3.58–3.50 (3H, m, H2,6), 3.44 (s, OMe), 2.44 (br s, OH). δ_C (150.8 MHz) 138.47–127.71 (Ph), 112.15 (d, $J_{5,F}$ 232, C5), 99.77 (C1), 79.07, 77.72 (C2, C3), 76.53 (d, $J_{4,F}$ 25.0, C4), 75.95, 75.35, 74.46 (3C, CH$_2$Ph), 62.90 (d, $J_{6,F}$ 38.0, C6), 56.09 (OMe). m/z 481.2034 [$(M-H)^{+\bullet}$ requires 481.2026].

Methyl 2,3,4-Tri-O-*benzyl-5-fluoro-α-L-idopyranoside* ***43*** *and Methyl 2,3,4-Tri*-O-*benzyl-5-fluoro-β-D-glucopyranoside*

(*a*) 3-Chloroperbenzoic acid (190 mg, 1.1 mmol) was added to the alkene **37** (500 mg, 1.1 mmol) in a mixture of CH_2Cl_2 (10 mL) and 0.5 M $NaHCO_3$ solution (10 mL), and the mixture stirred at room temperature (5 min). Separation of the organic phase followed by evaporation of the solvent gave the epoxides **39** as an inseparable mixture (ratio of D-*gluco* to L-*ido* 2 : 1; 517 mg).

(*b*) Hydrogen fluoride/pyridine (0.5 mL) was added to the epoxides **39** (500 mg) in CH_2Cl_2 (5 mL) at −78°C and the solution stirred (10 min). Water was added and the usual workup (CH_2Cl_2) followed by flash chromatography (EtOAc/toluene, 1 : 9) furnished the α-L-*idoside* **43** as colourless plates (140 mg, 27%), mp 132–135°C (Pr^i_2O), $[\alpha]_D$ +16.6° (Found: C 69.8, H 6.5. $C_{28}H_{31}FO_6$ requires C 69.7, H 6.5%). m/z 481.2038 [$(M-H)^{+\bullet}$ requires 481.2026].

Next to elute was *methyl 2,3,4-tri*-O-*benzyl-5-fluoro-β-D-glucopyranoside* as a colourless oil (200 mg, 38%), $[\alpha]_D$ +3.9°. δ_H (600 MHz) 7.38–7.28 (15H, m, Ph), 4.95–4.75 (7H, m, H1, CH_2Ph), 4.00 (dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.8, H3), 3.78 (dd, $J_{4,F}$ 23.6, H4), 3.74–3.68 (2H, m, H6), 3.59 (s, OMe), 3.51 (dd, $J_{1,2}$ 8.2, H2), 2.38 (br s, OH). δ_C (150.8 MHz) 138.26–127.68 (Ph), 111.35 (d, $J_{5,F}$ 227, C5), 101.72 (d, $J_{1,F}$ 4.0, C1), 81.62, 80.61 (C2, C3), 76.97 (d, $J_{4,F}$ 24.0, C4), 75.91, 75.39, 74.84 (3C, CH$_2$Ph), 62.65 (d, $J_{6,F}$ 35.0, C6), 57.68 (OMe). m/z 481.2029 [$(M-H)^{+\bullet}$ requires 481.2026].

Structure Determination of Compounds ***16*** *and* ***40***

Both determinations were of less than optimal standard, by virtue of crystal quality and bulk, presenting difficulties involving compromises in procedure as noted; in neither case did the determination lead to assignment of absolute configuration (in both cases, assumed from the chemistry) and Friedel data were combined in the merging process. In both cases monochromatic $Mo_{K\alpha}$ radiation sources (λ 0.7107_3 Å) were employed.

For **16**, a full sphere of data was measured at approximately 295 K using a single counter instrument ($2\theta/\theta$ scan mode), $N_{t(otal)}$ reflections merging to N unique (R_{int} cited), N_o with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least-squares refinement without absorption correction, refining anisotropic displacement parameter forms for C, F, O, $(x, y, z, U_{iso})_H$ being constrained at estimates. For **40**, data were measured at approximately 153 K using a Bruker AXS CCD area-detector instrument and processed similarly (observed criteria: $F > 4\sigma(F)$; $(x, y, z, U_{iso})_H$ refined). Conventional residuals R, R_w are quoted at convergence [weights: $(\sigma^2(F) + 0.0004F^2)^{-1}$]; neutral

atom scattering factors were employed within the *Xtal 3.7* program system.[16] Pertinent results are given below and in the Figures (which show 50% for **16**, and 20% for **40**, probability amplitude displacement ellipsoids for C, O, (F), hydrogen atoms having arbitrary radii of 0.1 Å). CIFs are deposited with the Cambridge Crystallographic Data Centre.

Crystal/Refinement Data

16, $C_{41}H_{31}FO_{11}$, *M* 718.7. Triclinic, space group *P*1 (C_1^1, no. 1), *a* 12.658(6), *b* 10.520(3), *c* 7.469(5) Å, α 105.20(4), β 90.70(5), γ 110.85(3)°, *V* 890.7(9) Å^3. D_c (*Z* 1) 1.34$_0$ g cm^{-3}. μ_{Mo} 1.0 cm^{-1}; specimen: 0.70 × 0.42 × 0.10 mm^3. $2\theta_{max}$ 50°; N_t 4058, *N* 2573 (R_{int} 0.031), N_o 1786; *R* 0.055, R_w 0.061. $|\Delta\rho_{max}|$ 0.32(3) e Å^{-3}. CCDC no. 220141.

40, $C_{27}H_{28}O_6$, *M* 448.5. Monoclinic, space group *C*2 (C_2^3, no. 5), *a* 20.665(7), *b* 5.911(2), *c* 19.155(7) Å, β 102.511(6)°, *V* 2284 Å^3. D_c (*Z* 4) 1.30$_4$ g cm^{-3}. μ_{Mo} 0.92 cm^{-1}; specimen: 0.40 × 0.05 × 0.05 mm^3. $2\theta_{max}$ 58°; N_t 12547, *N* 3051 (R_{int} 0.056), N_t 2200; *R* 0.060, R_w 0.059. $|\Delta\rho_{max}|$ 0.4(1) e Å^{-3}. CCDC no. 220142.

Acknowledgments

We thank the Australian Research Council for financial support, and Professor Steve Withers for suggestions and discussion. K.A.S. thanks the University of Western Australia for the assistance of a Hackett Postgraduate Scholarship.

References

[1] S. J. Williams, S. G. Withers, *Carbohydr. Res.* **2000**, *327*, 27. doi:10.1016/S0008-6215(00)00041-0
[2] S. G. Withers, I. P. Street, P. Bird, D. H. Dolphin, *J. Am. Chem. Soc.* **1987**, *109*, 7530.
[3] S. G. Withers, K. Rupitz, I. P. Street, *J. Biol. Chem.* **1988**, *263*, 7929.
[4] R. J. Ferrier, R. H. Furneaux, *J. Chem. Soc., Perkin Trans. 1* **1977**, 1996.
[5] L. Somsák, R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 37.
[6] R. Blattner, R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1523.
[7] R. J. Ferrier, P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1528.
[8] J. D. McCarter, S. G. Withers, *J. Am. Chem. Soc.* **1996**, *118*, 241. doi:10.1021/JA952732A
[9] J. P. Praly, G. Descotes, *Tetrahedron Lett.* **1987**, *28*, 1405. doi:10.1016/S0040-4039(00)95938-0
[10] R. J. Ferrier, S. R. Haines, *J. Chem. Soc., Perkin Trans. 1* **1984**, 1675.
[11] R. J. Ferrier, P. C. Tyler, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2762.
[12] R. J. Ferrier, S. R. Haines, *J. Chem. Soc., Perkin Trans. 1* **1984**, 1689.
[13] J. C. McAuliffe, R. V. Stick, *Aust. J. Chem.* **1997**, *50*, 193. doi:10.1071/CH96151
[14] A. M. Sanseverino, M. C. S. de Mattos, *Synthesis* **1998**, 1584. doi:10.1055/S-1998-2187
[15] M. C. T. Hartman, J. K. Coward, *J. Am. Chem. Soc.* **2002**, *124*, 10036. doi:10.1021/JA0127234
[16] *The Xtal 3.7 System* (Eds S. R. Hall, D. J. du Boulay, R. Olthof-Hazekamp) **2001** (University of Western Australia: Perth).
[17] A. J. Eagle, T. M. Herrington, N. S. Isaacs, *J. Chem. Res. (M)* **1993**, 2663.
[18] G. H. Posner, S. R. Haines, *Tetrahedron Lett.* **1985**, *26*, 5. doi:10.1016/S0040-4039(00)98451-X
[19] J. D. McCarter, *Ph.D. Thesis* **1995** (University of British Columbia: Vancouver, BC).
[20] E. W. Baxter, A. B. Reitz, *J. Org. Chem.* **1994**, *59*, 3175.
[21] F. Cramer, G. Mackensen, K. Sensse, *Chem. Ber.* **1969**, *102*, 494.
[22] B. Helferich, E. Himmen, *Chem. Ber.* **1928**, *61*, 1825.