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Influence of substitution at the 5α-Position on the side chain conformation of glucopyranosides

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ABSTRACT

We describe the preparation of methyl 5α-methyl-α-D-glucopyranoside and of 5α-fluoro-β-D-glucopyranose per acetate and the NMR-based conformational analysis of their side chains. Both the 5α-methyl and 5α-fluoro substituents increase the population of the *gauche*,*gauche* side chain conformer to the extent that it becomes the predominant conformation. In the 5α-methyl series this is attributed to steric effects, whereas in the 5α-fluoro series the optimization of attractive gauche effects is the more likely reason.

1. Introduction

We and others are interested in the control of side conformation in glycosyl donors and glycosides as a means modulation of anomeric reactivity [1–9] and of influencing affinity for receptors, whether protein or nucleotide-based [10–17]. To this end, adding to the literature precedent [18], we have conducted NMR-based conformational analyses of variously substituted pyranosides with emphasis on substitutions at the 2-, 4-, and 6-positions [16,19,20]. Continuing this theme we now report on the influence of methylation and fluorination at the 5α-position of glucopyranosides, and show both stabilize the *gg*-side chain conformation [21].

2. Results

Synthesis. Adapting the method of Werz and coworkers [22], Dess-Martin oxidation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **1** followed by potassium carbonate promoted reaction with isobutyric anhydride gave the enol ether **2** as a 1:22 *E*:*Z* mixture in 62% yield. Simmons-Smith cyclopropanation with methylene iodide and diethylzinc then afforded the spirocyclic derivative **3** as an unassigned mixture of diastereomers in 71% yield. Treatment with aqueous methanolic potassium carbonate led to saponification with concomitant ring opening and isolation of the 5β-methyl derivative **4** and its 5α-diastereomer **5** in 15 and 77% yield, respectively, and was followed by reduction with sodium borohydride leading to **6** and **7** in 80 and 91% yield, respectively. Finally, hydrogenolysis of **7** afforded the target methyl 5α-methyl-α-D-glucopyranoside **8** in 92% yield (Scheme 1).

Photolysis of β-D-glucopyranosyl pentaacetate **9** with *N*-bromosuccinimide in tetrachloromethane according to Blattner and Ferrier afforded 5α-bromo-β-D-glucopyranosyl pentaacetate **10** in 89% yield [23]. Subsequent treatment with silver tetrafluoroborate in toluene following the method of Stick and coworkers then gave the desired 5α-fluoro-β-D-glucopyranosyl pentaacetate **11** in 24% yield (Scheme 2) [24].

Conformational analysis of methyl 5α-methyl-α-D-glucopyranoside 8. To gauge the side chain conformation of **8** we first measured the $^{3}J_{C,H}$ heteronuclear coupling constants from the 5α-methyl group to H_{6R} and H_{6S} (Table 1) [25], a technique widely applied in establishing anomeric configuration in the sialic and ulosonic acids [3,8,26,27]. These measurements were complemented by nOe measurements, with double irradiation of H4 and of the 5α-methyl group and inspection of the relative enhancements of the diastereotopic pro-*R* and pro-*S* H_{6R} and H_{6S} protons (Table 1).

Both diastereotopic side chain protons displayed a $^{3}J_{C,H}$ coupling constant of <1 Hz to the 5α-methyl group ruling out a predominant antiperiplanar relationship of either hydrogen to the methyl group but suggestive of approximate gauche relationships [3,8,25–27]. Irradiation of H_4 caused approximately twice the enhancement of the intensity of the side chain proton resonance at δ 3.45 than that at δ 3.40, while irradiation of the 5α-methyl group lead to comparable enhancements of the two side chain protons. Excluding eclipsed conformations from

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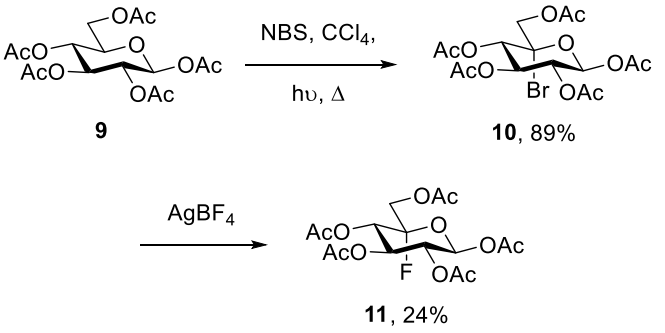
consideration, this pattern is only consistent with the assignment of the resonance at δ 3.45 as the pro-*R* side chain proton, that at δ 3.40 as the pro-*S* hydrogen, and a predominant gg conformation of the side chain (Fig. 1).

Conformational analysis of 5α-fluoro-β-D-glucopyranosyl pentaacetate 11. While it would have been preferable to study the influence of the 5α-fluoro substituent in aqueous solution in the absence of protecting groups, the known instability of **11** toward deprotection precluded this [24]. Previous work from our laboratory has shown that protecting groups at the 4- and 6-positions of glucopyranosides have only minor influence on the side chain conformation [7]. Likewise, we have demonstrated that solvents have no significant impact on the magnitude of coupling constants in conformationally locked systems [28], leading us to continue with the conformation analysis of **11** in deuteriomethanol with the acetates in place. To determine the side chain conformation of **11** we measured $^{3}J_{H,F}$ heteronuclear coupling constants from the axial fluorine atom to both side chain protons, relative nOe enhancements of the side chain protons on irradiation of H_4, and relative HOESY enhancements of the side chain protons on irradiation of the fluorine atom (Table 2).

In order to draw conclusions from the data presented in Table 2 it is first necessary to appreciate the magnitude of $^{3}J_{H,F}$ heteronuclear coupling constants. In decalinoid systems lacking electron-withdrawing C–O bonds likely to reduce their magnitude, coupling constants between a proton and a vicinal anti-periplanar fluorine are typically >40 Hz, whereas those between corresponding gauche pairs are 9–10 Hz [29]. A measure of the influence of an electron-withdrawing C–O bond on such coupling constants can be derived from the $^{3}J_{H4,F}$ heteronuclear coupling constant in **11**, which is 22 Hz. The $^{3}J_{H6,F}$ heteronuclear coupling constants found in **11** are most consistent with a gauche relationship and indeed approximate those found between gauche hydrogen and fluorine atoms in multivicinal fluoroalkanes [30,31]. On this basis, we conclude that the major conformer of **11** approximates the *gg* conformation in which both diastereotopic protons at the 6-position have a gauche relationship to the fluorine atom (Fig. 2); significant population of either the *gt* or *tg* conformers is excluded on the grounds that this would require considerably larger $^{3}J_{H,F}$ couplings to H_{6R} or H_{6S}, respectively. This assignment allows attribution of the resonance at δ 4.40 ppm in the ^{1}H NMR spectra to the H_{6R} proton, on the basis of the relatively large nOe to H_4, and consequently of the signal at δ 4.03, with the smaller nOe to H_4, to the H_{6S} proton.

3. Discussion

The side chain of simple glucopyranosides is typically considered to be an approximately 50:50 mixture of the *gg* and *gt* conformers (Fig. 3a) depending on the analysis method [18,28,32–37]. The predominant *gg* conformation of the side chain in **8** (Fig. 3b) is readily understood in terms of the additional steric gauche interaction between the methyl group and the side chain hydroxyl group that destabilize the *gt*



Scheme 2. Synthesis of 5α-fluoro-β-D-glucopyranosyl pentaacetate.

Table 1
Diagnostic NMR parameters for the side chain conformation of **8** in D_2O.

Resonance	δ_H (ppm)	$^{2}J_{H6R,H6S}$ (Hz)	$^{3}J_{C,H}$ (Hz)	nOe Enhancement Ratio	
				H4 Irradiation	Me Irradiation
H_{6R}	3.45	12.0	<1	2.20	1.00
H_{6S}	3.40	12.0	<1	1.00	1.14

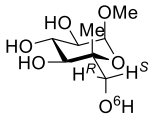


Fig. 1. Predominant side chain conformation of **8**.

Table 2
Diagnostic NMR parameters for the side chain conformation of **11** in CD_3OD.

Resonance	δ_H (ppm)	$^{2}J_{H6R,H6S}$ (Hz)	$^{3}J_{H,F}$ (Hz)	nOe/HOESY Enhancement Ratio	
				H4 Irradiation	F Irradiation
H_{6R}	4.38	12.0	8.4	2.0	1.00
H_{6S}	4.03	12.0	5.4	1.0	0.89

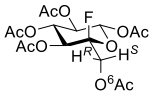
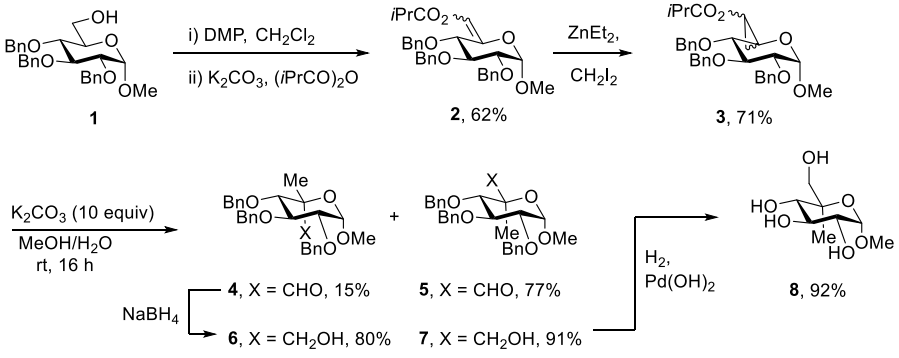


Fig. 2. Predominant side chain conformation of **11**.



Scheme 1. Synthesis of methyl 5α-methyl-α-D-glucopyranoside **8**.

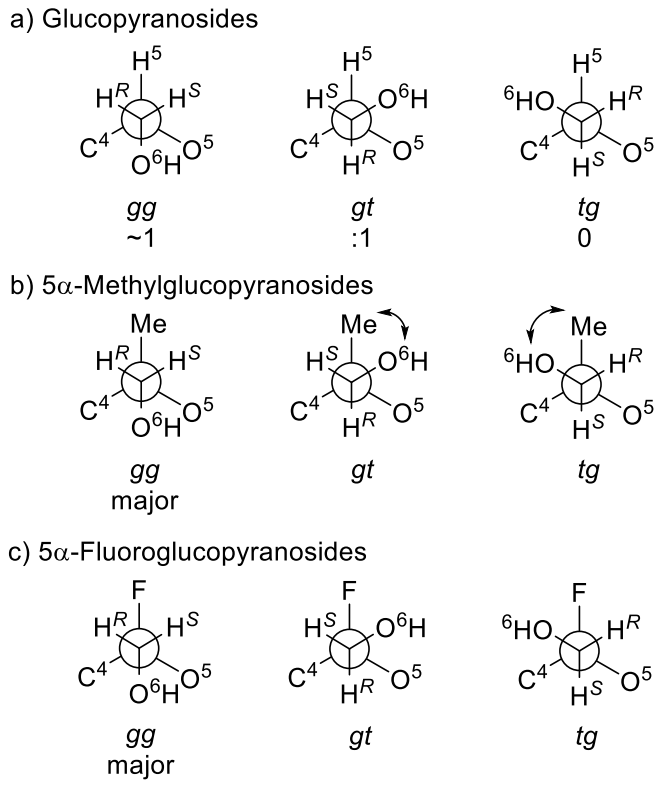


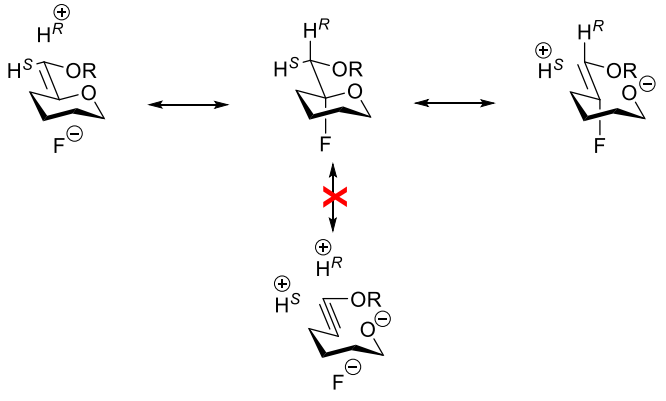
Fig. 3. Staggered Side Chain Conformations of a) Glucopyranosides; b) 5α-Methylglucopyranosides; and c) 5α-Fluoroglucopyranosides.

conformation. A comparable gauche interaction also further destabilizes the higher energy *tg* conformer in **8**.

In the case of **11**, the preference for the *gg* conformation with its single stabilizing gauche interaction over the *gt* conformation with the potential for two stabilizing gauche interactions (Fig. 3c) can be understood in terms of the competing nature of the two interactions and the obviously high energy consequences of involving two geminal C–H bonds in hyperconjugative interactions at the same time (Scheme 3).

4. Conclusion

Through the influence of steric interactions the installation of a methyl group at the 5α-position of methyl α-D-glucopyranoside has the effect of changing the population of the side chain from an approximately 50:50 *gg*:*gt* mixture to one in which the *gg* conformation predominates. The 5α-methyl modification is therefore functionally equivalent to the replacement of the pro-*S* hydrogen at the D-glucopyranose 6-position by a methyl group, as demonstrated recently with the aminoglycoside paromomycin [16]. The installation of a 5α-fluorine atom in a D-glucopyranosyl model also has the effect of strongly favoring the *gg* conformation of the side chain, but for reasons due to the optimization of the attractive gauche effect. 5-Fluoropyranose derivatives have been widely studied as inhibitors of glycoside hydrolases and are considered to be effective as such because of the strongly electron-withdrawing effect of the fluorine atom on positive charge in the locus of the anomeric center [38]: it is now apparent that this electron-withdrawing effect is complemented by preorganization of the side chain into the *gg* conformation enforced by most GH's acting on substrates with the glucose configuration. Indeed, inspection of X-ray crystal structures of the GH from *Bacteroides thetaiomicrometer* in complex with the 5-fluoro-glucooxazolidine **12**, and of the covalent enzyme bound 5-fluoro-*N*-acetylglucosamine **13** (PDB 2WZI), with the *Salmonella typhimurium* NagZ (PDB 4GVH) reveal the side chain to be bound in the typical *gg* conformation enforced by these GHs from families 84 and 3, respectively (Fig. 4) [15,39,40].



Scheme 3. Competing Hyperconjugative Interactions and a High Energy Double Hyperconjugative Interaction in the *gt* Conformer of 5α-Fluoropyranose Derivatives.

5. Experimental

5.1. General experimental

All experiments were carried out under a dry argon atmosphere unless otherwise specified. Chromatographic purifications were carried over silica gel (230–400 mesh). Thin layer chromatography was performed with precoated glass backed plates (w/UV 254). TLC plates were visualized by UV irradiation (254 nm) and by charring with sulfuric acid in ethanol (20:80, v/v) or with ceric ammonium molybdate solution [Ce $(SO4)_2$: 4 g, $(NH_4)_6Mo7O24$: 10 g, H_2SO_4: 40 mL, H_2O: 360 mL]. Optical rotations were measured at 589 nm and 21 °C on a digital polarimeter with a path length of 10 cm. NMR spectra were recorded in $CDCl_3$, C_6D_6, D_2O, or CD_3OD as indicated using a 500, 600, or 900 MHz instrument and assignments made with the help of COSY, HMBC, and HSQC spectra. Chemical shifts (δ) are given in ppm, with multiplicities abbreviated as follows: s (singlet), m (multiplet), br (broad), d (doublet), t (triplet), q (quartet) and sept (septet). High-resolution (HRMS) mass spectra were recorded in the electrospray mode with an Orbitrap analyzer. Heating of reaction mixtures was carried out on an aluminum heating block of appropriate size.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-isobutyroyl-α-D-glucohex-5-enopyranoside (2). To a stirred solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (1.1 g, 2.34 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added Dess Martin periodinane (1.21 g, 2.84 mmol). The resulting mixture was brought to room temperature and stirred for 2 h then quenched with 20% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to dryness, and the crude compound was used for the next step without further purification. The crude aldehyde was dissolved in acetonitrile (20 mL) and potassium carbonate (1.96 g, 14.2 mmol) and isobutyric anhydride (2.36 mL, 14.2 mmol) were added. The reaction mixture was refluxed for 1 h and after completion reaction, cooled to room temp., diluted with ethyl acetate (40 mL) and water (40 mL). The aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. Purification by column

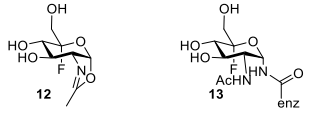


Fig. 4. 5α-Fluoro-*N*-acetylglucosamine Derivatives Crystallographically Established to Bind to GHs with the *gg* Side Chain Conformation.

chromatography (hexane:ethyl acetate, 10:1) afforded the enol ester as an *E/Z* mixture (1:22) (780 mg, 62% yield) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.27 (m, 15H), 7.19 (d, J = 1.8 Hz, 1H, H-6), 4.91–4.82 (m, 3H, $PhCH_2$), 4.80–4.73 (m, 2H, $PhCH_2$), 4.70 (d, J = 3.4 Hz, 1H, H-1), 4.66 (d, J = 12.2 Hz, 1H, $PhCH_2$), 4.03–3.93 (m, 2H, H-4, H-3), 3.59 (dd, J = 8.5, 3.4 Hz, 1H, H-2), 3.48 (s, 3H, OCH_3), 2.66 (sept, J = 7.0 Hz, 1H, H-7), 1.21 (dd, J = 7.0, 1.8 Hz, 6H, $CH(CH_3)_2$)·^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5 (CO), 138.5 (ArC), 138.0 (ArC), 137.6 (ArC), 134.8 (ArC), 128.50 (ArC), 128.48 (ArC), 128.4 (ArC), 128.01 (ArC), 128.0 (ArC), 127.97 (ArC), 127.9 (ArC), 127.7 (ArC), 123.1 (C-6), 99.7 (C-1), 81.3 (C-3), 79.0 (C-2), 77.9 (C-4), 75.7 ($PhCH_2$), 74.6 ($PhCH_2$), 73.7 ($PhCH_2$), 56.1 (OCH_3), 33.8 (C-7), 18.9 ($CH(CH_3)_2$), 18.7 ($CH(CH_3)_2$). HRMS (ESI): *m/z* calcd for $C_{32}H_{36}O_7Na$ [M + Na] 555.2353, found 555.2339.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-isobutyroyl-5,6-methanediyl-α-D-glucopyranoside (3). A solution of compound **2** (750 mg, 1.41 mmol) in 1,2-dichloroethane (12 mL) was treated with 4 Å molecular sieves and diiodomethane (1.14 mL, 14.1 mmol), followed by stirring at room temperature for 0.5 h, before dropwise addition of a solution of diethylzinc (1 M in hexane, 7.05 mL, 7.05 mmol). The reaction mixture was heated to 50 °C for 24 h then was diluted with dichloromethane (30 mL), filtered and quenched with saturated Na_2CO_3 solution. The aqueous layer was extracted with dichloromethane (3 x 15 mL), and the combined organic phases dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (hexane:ethyl acetate, 10:1) afforded the target compound as an inseparable mixture of diastereomers (550 mg, 71% yield) as a yellow oil. Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48–7.13 (m, 15H), 4.97 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.90 (d, J = 11.0 Hz, 1H, $PhCH_2$), 4.85–4.80 (m, 2H, $PhCH_2$), 4.70–4.64 (m, 2H, $PhCH_2$), 4.63 (d, J = 3.9 Hz, 1H, H-1), 3.97 (t, J = 9.3 Hz, 1H, H-3), 3.90 (dd, J = 7.9, 4.4 Hz, 1H, H-6), 3.86 (d, J = 9.1 Hz, 1H, H-4), 3.66 (dd, J = 9.5, 3.9 Hz, 1H, H-2), 3.41 (s, 3H, OCH_3), 2.60 (sept, J = 7.0 Hz, 1H, H-8), 1.52–1.45 (m, 1H, H-7a), 1.19 (dd, J = 7.0, 0.8 Hz, 6H,-$CH(CH_3)_2$, 0.97 (dd, J = 7.7, 4.5 Hz, 1H, H-7b).^{13}C NMR (151 MHz, $CDCl_3$) δ 177.9 (CO), 138.8 (ArC), 138.2 (ArC), 138.1 (ArC), 128.5 (ArC), 128.47 (ArC), 128.41 (ArC), 128.38 (ArC), 128.36 (ArC), 128.35 (ArC), 128.1 (ArC), 128.09 (ArC), 127.97 (ArC), 127.95 (ArC), 127.9 (ArC), 127.7 (ArC), 127.64 (ArC), 127.60 (ArC), 127.57 (ArC), 127.5 (ArC), 100.3 (C-1), 81.1 (C-3), 80.0 (C-2), 77.6 (C-4), 75.7 ($PhCH_2$), 75.3 ($PhCH_2$), 73.6 ($PhCH_2$), 56.5 (C-5), 55.5 (OCH_3), 49.7 (C-6), 33.7 (C-8), 19.0 ($CH(CH_3)_2$), 18.8 ($CH(CH_3)_2$), 13.7 (CH_2-7). HRMS (ESI): *m/z* calcd for $C_{33}H_{38}O_7Na$ [M + Na] 569.2510, found 569.2499.

Methyl 2,3,4-Tri-*O*-benzyl-5-C-methyl-β-L-ido-hexodialdo-1,5-pyranoside 4 and Methyl 2,3,4-Tri-*O*-benzyl-5-C-methyl-α-D-gluco-hexodialdo-1,5-pyranoside 5. Potassium carbonate (556 mg, 4.03 mmol) was added to a solution of **3** (220 mg, 0.40 mmol) in a 15:1 mixture of methanol/water (5 mL). The reaction mixture was stirred for 12 h at room temperature, then was diluted with ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (3x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. Purification by column chromatography (hexane:ethyl acetate, 10:2) afforded both aldehydes **4** (30 mg, 15% yield) and **5** (148 mg, 77% yield) as colorless oils.

4: $[\alpha]_D^{22} = +20.0$ (*c* 0.10, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.39–7.26 (m, 15H), 5.04 (d, J = 10.7 Hz, 1H, $PhCH_2$), 4.98 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.89–4.80 (m, 2H, $PhCH_2$), 4.68 (dd, J = 13.2, 11.6 Hz, 2H, $PhCH_2$), 4.48 (d, J = 3.6 Hz, 1H, H-1), 4.31 (t, J = 9.6 Hz, 1H, H-3), 3.53 (dd, J = 9.7, 3.6 Hz, 1H, H-2), 3.51 (d, J = 9.5 Hz, 1H, H-4), 3.24 (s, 3H, OCH_3), 1.28 (s, 3H, CH_3)·^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5 (CHO), 151.1, 138.5, 137.9, 137.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.8, 127.7, 99.3, 83.4, 80.1, 79.1, 77.3, 76.2, 75.9, 73.6, 56.3, 21.4. HRMS (ESI): *m/z* calcd for $C_{29}H_{32}O_6Na$ [M + Na] 499.2097, found 499.2083.

5: $[\alpha]_D^{22} = +104.0$ (*c* 0.75, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.42–7.26 (m, 15H), 5.01–4.80 (m, 4H, $PhCH_2$), 4.75 (d, J = 3.9 Hz, 1H, H-1), 4.65 (dd, J = 67.3, 11.5 Hz, 2H, $PhCH_2$), 4.14 (t, J = 9.4 Hz, 1H, H-3), 3.62 (d, J = 9.1 Hz, 1H, H-4), 3.58 (dd, J = 9.6, 3.9 Hz, 1H, H-2), 3.48 (s, 3H, OMe), 1.58 (s, 3H, CH_3)·^{13}C NMR (150 MHz, $CDCl_3$) δ 198.9 (CHO), 138.5 (ArC), 138.0 (ArC), 137.9 (ArC), 128.55 (ArC), 128.46 (ArC), 128.44 (ArC), 128.43 (ArC), 128.41 (ArC), 128.39 (ArC), 128.38, 128.15 (ArC), 128.13 (ArC), 128.09 (ArC), 128.05 (ArC), 128.04 (ArC), 128.95 (ArC), 127.85 (ArC), 127.77 (ArC), 99.9 (C-1), 81.3 (C-5), 79.6 (C-4), 78.4 (C-2), 78.3 (C-3), 75.9 ($PhCH_2$), 75.3 ($PhCH_2$), 73.6 ($PhCH_2$), 56.4 (OCH_3), 16.4 (CH_3). HRMS (ESI): *m/z* calcd for $C_{29}H_{32}O_6Na$ [M + Na] 499.2091, found 499.2077.

Methyl 2,3,4-Tri-*O*-benzyl-5-C-methyl-β-L-idopyranoside 6. A solution of aldehyde **4** (20 mg, 0.1 mmol) in methanol (1 mL) was treated with sodium borohydride (5 mg, 0.34 mmol) at 0 °C and stirred for 1 h before the solvent was removed under vacuum and the residue purified by column chromatography (hexane:ethyl acetate, 3:1) to afford the alcohol **6** (16 mg, 80%) as colorless oil. $[\alpha]_D^{22} = -12.9$ (*c* 0.35, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.29 (m, 15H, ArH), 5.00 (dd, J = 13.3, 10.9 Hz, 2H, $PhCH_2$), 4.85 (dd, J = 12.5, 11.2 Hz, 2H, $PhCH_2$), 4.67 (dd, J = 11.6, 7.1 Hz, 2H, $PhCH_2$), 4.58 (d, J = 4.2 Hz, 1H, H-1), 4.27 (t, J = 9.7 Hz, 1H, H-3), 3.92 (dd, J = 12.0, 3.1 Hz, 1H, H-6a), 3.65 (dd, J = 12.0, 10.4 Hz, 1H, H-6b), 3.55 (dd, J = 9.9, 4.2 Hz, 1H, H-2), 3.50 (s, 3H, OCH_3), 3.45 (d, J = 9.5 Hz, 1H, H-4), 3.18 (dd, J = 10.4, 3.2 Hz, 1H, OH), 1.25 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.7 (ArC), 138.07 (ArC), 138.04 (ArC), 128.55 (ArC), 128.48 (ArC), 128.44 (ArC), 128.1 (ArC), 128.04 (ArC), 128.02 (ArC), 127.91 (ArC), 127.88 (ArC), 127.7 (ArC), 99.4 (C-1), 86.0 (C-4), 80.2 (C-5), 79.2 (C-2), 78.9 (C-3), 76.4 ($PhCH_2$), 75.8 ($PhCH_2$), 73.6 ($PhCH_2$), 66.9 (C-6), 57.1 (OCH_3), 24.3 (CH_3). HRMS (ESI): *m/z* calcd for $C_{29}H_{34}O_6Na$ [M + Na] 501.2248, found 501.2232.

Methyl 2,3,4-Tri-*O*-benzyl-5-C-methyl-α-D-glucopyranoside 7. A solution of aldehyde **5** (46 mg, 0.1 mmol) in methanol (2 mL) was treated with sodium borohydride (11 mg, 0.29 mmol) at 0 °C and stirred for 1 h before the solvent was removed under vacuum and the residue purified by column chromatography (hexane:ethyl acetate, 3:1) to afford the alcohol **7** (42 mg, 91%) as colorless oil. $[\alpha]_D^{22} = +8.4$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6) δ 7.33–7.01 (m, 15H, ArH), 5.01–4.96 (m, 2H, $PhCH_2$), 4.78 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.64 (d, J = 11.3 Hz, 1H, $PhCH_2$), 4.57 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.54 (d, J = 4.0 Hz, 1H, H-1), 4.45 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.26 (t, J = 9.8 Hz, 1H, H-3), 3.89 (d, J = 9.7 Hz, 1H, H-4), 3.44–3.40 (m, 2H, H-2, H-6a), 3.35–3.26 (m, 1H, H-6a), 3.11 (s, 3H, OCH_3), 1.82–1.49 (m, 1H, OH), 1.32 (s, 3H, CH_3); ^{13}C NMR (151 MHz, C_6D_6) δ 139.4 (ArC), 139.1 (ArC), 139.0 (ArC), 128.2 (ArC), 128.13 (ArC), 128.09 (ArC), 127.9 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 127.2 (ArC), 100.0 (C-1), 81.0 (C-2), 79.0 (C-5), 78.8 (C-3), 78.7 (C-4), 75.5 ($PhCH_2$), 75.2 ($PhCH_2$), 72.6 ($PhCH_2$), 67.4 (C-6), 55.4 (OCH_3), 18.4 (CH_3). HRMS (ESI): *m/z* calcd for $C_{29}H_{34}O_6Na$ [M + Na] 501.2248, found 501.2237.

Methyl 5-C-methyl-α-D-glucopyranoside 8. $Pd(OH)_2$/C (30% w/w, 5 mg) was added to a solution of **7** (15 mg, 0.03 mmol) in methanol (1 mL), and the suspension degassed and stirred vigorously under 1 atm of H_2 (balloon) for 24 h, after which it was filtered through a Celite pad, which was washed with MeOH. Evaporation of the solvent which on repeated washing with hexane:ethyl acetate (3:1) gave the title compound (8 mg, 92%). $[\alpha]_D^{22} = +60.0$ (*c* 0.1, CH_2Cl_2); ^{1}H NMR (900 MHz, D_2O) δ 4.75 (d, J = 4.2 Hz, 1H, H-1), 3.78 (t, J = 9.9 Hz, 1H, H-3), 3.52 (d, J = 9.8 Hz, 1H, H-4), 3.47 (dd, J = 10.0, 4.2 Hz, 1H, H-2), 3.46–3.38 (m, 2H, H-6a, H-6b), 3.36 (s, 3H, OCH_3), 1.17 (s, 3H, CH_3). ^{13}C NMR (225 MHz, D_2O) δ 100.7 (C-1), 79.3 (C-5), 71.5 (C-2), 70.7 (C-4), 69.3 (C-3), 66.2 (C-6), 55.7 (OCH_3), 16.9 (CH_3)). HRMS (ESI): *m/z* calcd for $C_8H_{16}O_6Na$ [M + Na] 231.0839, found 231.0833.

Penta-*O*-acetyl-5-bromo-β-D-glucopyanose (10). This compound was prepared according to the literature method [23] from glucose pentaacetate in 89% yield as colorless syrup. $[\alpha]_D^{22} = -28.8$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.25 (d, J = 8.6 Hz, 1H), 5.59 (t, J = 9.7 Hz, 1H), 5.28 (dd, J = 9.7, 8.6 Hz, 1H), 5.26 (d, J = 9.7 Hz, 1H), 4.59 (d, J = 12.3 Hz, 1H), 4.33 (d, J = 12.3 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$)

δ 169.7, 169.6, 169.3, 169.0, 168.3, 95.9, 91.4, 71.1, 69.4, 68.2, 65.7, 20.7, 20.6, 20.5, 20.5. HRMS (ESI): *m/z* calcd for $C_{16}H_{21}O_{11}BrNa$ [M + Na] 491.0159, found 491.0151.

Penta-*O*-acetyl-5-fluoro-β-D-glucopyanose (11). This compound was prepared according to the literature method [24] from **10** in 24% yield as colorless syrup. $[\alpha]_D^{22} = +10.0$ (*c* 0.2, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.21 (dd, $J = 8.3$, 1.5 Hz, 1H, H-1), 5.53 (td, $J = 9.7$, 1.5 Hz, 1H, H-3), 5.36 (ddd, $J = 22.8$, 9.9, 1.5 Hz, 1H, H-4), 5.31–5.24 (m, 1H, H-2), 4.40 (ddd, $J = 12.0$, 7.0, 1.5 Hz, 1H, H-6a), 4.08–3.92 (m, 1H, H-6b), 2.16 (d, $J = 1.5$ Hz, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H). ^{1}H NMR (600 MHz, CD_3OD) δ 6.14 (d, $J = 8.2$ Hz, 1H), 5.44 (t, $J = 9.6$ Hz, 1H), 5.37 (dd, $J = 22.6$, 9.9 Hz, 1H), 5.23 (dd, $J = 9.3$, 8.3 Hz, 1H), 4.38 (dd, $J = 12.0$, 8.4 Hz, 1H), 4.04 (dd, $J = 12.1$, 5.4 Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$) δ −131.34 (ddd, $J = 22.7$, 7.1, 4.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 169.7, 169.4, 169.2, 168.4, 110.3, 108.8, 88.7, 88.6, 69.8, 69.4, 67.8, 67.7, 61.7, 61.4, 20.7, 20.5, 20.5, 20.5, 20.4. HRMS (ESI): *m/z* calcd for $C_{16}H_{21}O_{11}FNa$ [M + Na] 431.0960, found 431.0948.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2021.108254.

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