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Note

Synthesis of 4-*O*- and 6-*O*-(2′-iodoethyl)-D-glucose

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Abstract

O-Allylation of 1,2,3,6-tetra-*O*-acetyl-D-glucopyranose followed by an ozonation/reduction sequence gave the 4-hydroxyethyl derivative. This hydroxyethyl substituent was also introduced at C-6, starting from 1,2:3,5-bis(*O*-methylidene)-α-D-glucofuranose using an alkylation/reduction sequence. These 4- and 6-*O*-hydroxyethyl derivatives were then converted to the title compounds by iodination followed by deprotection. Noteworthy is the particular stability of the carbon–iodine bond in these ethers, a prerequisite for their potential use in Single Photon Emitted Computed Tomography medical imaging (SPECT). © 1998 Elsevier Science Ltd. All rights reserved

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The quest for glucose analogues suitable for Single Photon Emitted Computed Tomography (SPECT) medical imaging [1] has resulted in the evaluation of 6-deoxy-6-iodo-D-glucose (6-DIG) [2] as a possible tracer of glucose transport [3,4]. Still to be designed however are glucose derivatives which would interact with the transport protein GluT while not being transported since such radiopharmaceuticals [5] could provide the basis for SPECT imaging of the glucose carrier GluT [6–9]. Towards this goal iodinated acetals of D-glucose, and in particular 4,6-*O*-iodoethylidene-D-glucose [10], have been prepared. The synthesis of 4- and 6-iodoethoxy glucose derivatives, **1** and **2**, is now presented as more conformational flexibility is expected from these analogues. In these derivatives the stable β-iodoethoxyl group, of interest in radiolabelling [11], has been grafted to sites not required for recognition by the GluT transport system for entry into the cell [12,13], i.e. OH-4 or OH-6.

To synthesize **1**, the triacetate **3**, the preparation of which was recently improved [10], was selectively acetylated at the primary hydroxyl group, in 50% yield, using acetyl chloride at −78 °C [14], to give the tetraacetate **4** [15–18]. These acetylation conditions substantially improve the previously reported [19] selective acetylation with acetic anhydride at room temperature (9% yield) at the primary alcohol group of **4**. Introduction of the 2-iodoethyl moiety at OH-4 in **4** was then carried out by successive introduction and ozonolysis of an allyl unit. Formation of the allyl ether **5** by allyl transfer using allyl trichloroacetimidate [20] was ineffective but allyl ethyl carbonate proved remarkably efficient (90%) under Pd(O)-catalysis [21]. Ozonolysis of the allyl group of **5** was

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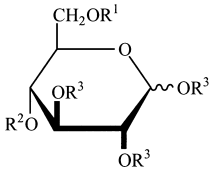
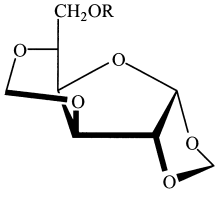
followed by an in situ reduction with sodium borohydride to afford the 4-(2-*O*-hydroxyethyl) derivative **6**. Formation of the mesylate **7** followed by a displacement on the sulfonate using sodium iodide in acetone gave the 2-iodoethyl derivative **8** which was de-*O*-acylated to afford the desired target compound, 4-*O*-(2-iodoethyl)-D-glucose, **1**.



	R^1	R^2	R^3
1	H	CH_2CH_2I	H
2	CH_2CH_2I	H	H
3	H	H	$COCH_3$
4	$COCH_3$	H	$COCH_3$
5	$COCH_3$	$CH_2CH{=}CH_2$	$COCH_3$
6	$COCH_3$	CH_2CH_2OH	$COCH_3$
7	$COCH_3$	$CH_2CH_2OSO_2CH_3$	$COCH_3$
8	$COCH_3$	CH_2CH_2I	$COCH_3$



9 : R = $COCH_3$

10 : R = H

11 : R = $CH_2COOCH_2CH_3$

12 : R = CH_2CH_2OH

13 : R = CH_2CH_2I

The preparation of its positional isomer, **2**, was more straightforward as it could be obtained in six steps from D-glucose. Thus, the bis(methylene) acetal **10** is readily available [22–24] from the corresponding 6-acetate **9**, which is itself obtained in a single step from D-glucose [22]. The base-stable hydroxyl protecting groups in **10** allow alkylation to be performed at O-6 and, upon reaction of its alcoholate with ethyl bromoacetate, the ester **11** was obtained. Reduction of **11** gave the hydroxyethyl derivative **12**, previously prepared [24,25] but in unspecified yields and without characterization. Direct iodination of **12** was then effected, using triiodoimidazole–triphenylphosphine as developed by Garegg and Samuelsson [26]. The moderate yield (ca. 50%) of this one-step conversion of the alcohol to the iodide was not improved by an alternative procedure involving iodide displacement on a sulfonate derived from **12**. This reflects the enhanced stabilization towards displacement by a neighbouring β-alkoxy substituent [27]. For the same reason, a similar stability is conferred to the carbon–iodine bond of **13**, and also to the final product, 6-*O*-(2′-iodoethyl)-D-glucose **2**, obtained by hydrolysis of the acetal groups. That no significant de-iodination can take place in such glucose derivatives is of primary importance for their potential in vivo applications.

The obtention of **1** and **2**, stable analogues of glucose where iodine has been introduced in a region of the molecule of glucose not judged essential [12,13] for recognition by GluT, will enable their biological evaluation [28] after suitable radiolabelling (i.e. ^{123}I: $t_{1/2} = 13$-14 h; $\gamma = 159$ KeV) towards SPECT imaging.

1. Experimental

General methods.—Dry solvents were obtained as follows: methanol was distilled from magnesium methoxide, tetrahydrofuran over sodium and diethyl ether over calcium hydride; dichloromethane was dried on 4 Å molecular sieves before use. After work-up, the volatiles were evaporated under reduced pressure without heating and the iodo derivatives were protected from light. Column chromatography was performed on Silica Gel SI 60 (70–230 mesh) Geduran. Standard abreviations are used for NMR description of spectra which were recorded on Bruker AC 200, WM 250 and AM 300 apparatus, using built-in software, at the field and in the solvent indicated for each compound. The residual absorption of the NMR solvent was taken as the internal reference, except for ^{13}C NMR spectra in water. A Perkin–Elmer 241 polarimeter was used for the determination of optical rotations. Elemental analyses were performed by the Service Central d'Analyses du CNRS, Vernaison (France).

1,2,3,6-Tetra-O-*acetyl*-α,β-D-*glucopyranose* (**4**).—To a soln of 1,2,3-tri-*O*-acetyl-α,β-D-glucopyranose [10] (1.1 g, 3.59 mmol) in CH_2Cl_2 (10 mL) stirred under argon at −70 °C, were added dropwise pyridine (570 μl, 7.1 mmol, 2 equiv) then acetyl chloride (300 μL, 4.2 mmol, 1.2 equiv). After stirring the heterogeneous mixture for 30 min at −70 °C, ice was added before removing the cooling bath. The layers were separated and extraction of the aq phase performed with CH_2Cl_2. The organic layers were pooled, washed with brine and dried (Na_2SO_4) before evaporation of the volatiles. The crude product was purified by column chromatography on

silica gel. Elution with 49:1 CH_2Cl_2–MeOH gave **4** (641 mg, 52%, α/β 3:1). Some NMR data can be found in the literature [29,30] and full assignments are as follows; ^{1}H NMR (250 MHz, $CDCl_3$), α anomer: δ 6.25 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.3 (app. t, 1H, $J_{2,3}$ 9.5 Hz, H-3), 5.0 (dd, 1H, $J_{1,2}$ 3.9, $J_{2,3}$ 9.5 Hz, H-2), 4.5–4.4 (M, 1H, H-6), 4.3–4.2 (M, 1H, H-6′), 3.95–3.9 (M, 1H, H-4), 3.7–3.5 (M, 1H, H-5), 3.2–3.1 (large s, 1H, OH), 2.10 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 1.90 (s, 3H, CH_3CO). β anomer: δ 5.7 (d, 1H, $J_{1,2}$ 7.9 Hz, H-1), 5.15–5.0 (M, 2H, H-2, 3), 4.6–4.45 (M, 1H, H-6), 4.3–4.2 (M, 1H, H-6′), 3.7–3.5 (M, 2H, H-4, 5), 3.05 (d, 1H, J 3.5 Hz, OH), 2.10 (s, 3H, CH_3CO), 2.05 (2s, 6H, 2*CH_3CO), 2.00 (s, 3H, CH_3CO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 171.8, 171.3, 168.9 (CO), 91.8 (C-1β), 89.3 (C-1α), 72.3, 72.0, 69.1, 68.4 (C-2 to 5α), 74.9 (2*), 70.4, 68.2 (C-2 to -5β), 62.4 (C-6α, 6β), 20.8, 20.5 (*C*H_3CO).

4-O-*Allyl-1,2,3,6-tetra*-O-*acetyl*-α,β-D-*glucopyranose* (**5**).—To a stirred soln of **4** (1.2 g, 3.45 mmol) in dry THF (30 mL) under argon was added a soln of tris(dibenzylideneacetone)dipalladium(0) (55 mg, 60 mmol) and 1,4-bis(diphenylphosphino)butane (160 mg, 375 mmol) in dry THF (15 mL). Allyl ethyl carbonate [31] (2 g, 15.4 mmol) was added and the mixture stirred at 60 °C for 2 h. After cooling and evaporation of the volatiles, the mixture was purified by column chromatography on silica gel, 49:1 CH_2Cl_2−MeOH, to afford **5** (1.2 g, 90%, α/β 3:1) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$), α anomer: δ 6.2 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.85–5.7 (m, 1H,−CH = CH_2), 5.45 (app. t, 1H, $J_{2,3}$ 10 Hz, H-3), 5.3–5.1 (M, 2H,−CH = CH_2), 5.0 (dd, 1H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10 Hz, H-2), 4.35–4.2 (M, 2H, H-6, -6′), 4.05 (d, 2H, $J_{1'\text{-}2'}$ 5.5 Hz, OCH_2−CH = CH_2), 4.0–3.9 (M, 1H, H-5), 3.55 (app. t, 1H, J 10 Hz, H-4), 2.12 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 1.97 (s, 3H, CH_3CO). β anomer: δ 5.8–5.7 (m, 1H, −CH = CH_2), 5.65 (d, 1H, $J_{1,2}$ 8 Hz, H-1), 5.2–5.1 (M, 3H, H-3,−CH = CH_2), 5.0 (dd, 1H, $J_{1,2}$ 8, $J_{2,3}$ 10.4 Hz, H-2), 4.35–4.2 (M, 2H, H-6, 6′), 4.05 (d, 2H, $J_{1',2'}$ 5.1 Hz, OCH_2−CH = CH_2), 3.7–3.65 (M, 1H, H-5), 3.65 (dd, 1H, J 9.1, 10 Hz, H-4), 2.06 (s, 6H, 2*CH_3CO), 2.03 (s, 3H, CH_3CO), 1.98 (s, 3H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 169.9, 169.7, 169.6, 168.9 (CO $\alpha+\beta$), 133.7 (−CH = CH_2), 117.8 (−CH = CH_2), 91.7 (C-1β), 89.2 (C-1α), 75.3, 71,8; 71.1, 69.6 (C-2α to 5α), 75.2, 74.8, 73.6, 70.8 (C-2β to -5β), 73.8 (O*C*H_2−CH = CH_2), 62.2 (C-6$\alpha+\beta$), 20.9, 20.8, 20.4 (CO*C*H_3). Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.58; H, 6.20.

4-O-*(2′-Hydroxyethyl)-1,2,3,6-tetra*-O-*acetyl*-α,β-D-*glucopyranose* (**6**).—A soln of **5** (700 mg, 1.8 mmol) in 1:1 CH_2Cl_2–MeOH (20 mL) was stirred at −78 °C and ozone was bubbled till a blue colour persisted. After 30 min, the soln was flushed with argon and $NaBH_4$ (350 mg, 5.1 equiv) was added portionwise while keeping the temperature at −78 °C. The cooling bath was removed and acetone (5 mL) added at room temperature. The reaction mixture was neutralized with 1N HCl, and evaporated to dryness. The residue was taken up in CH_2Cl_2 and this soln washed with water, then dried (Na_2SO_4) before evaporation of the volatiles. The crude product was purified by column chromatography on silica gel and elution with 19:1 CH_2Cl_2–MeOH, gave **6** (430 mg, 61%, α/β 6:1) as a colourless thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.15 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1α), 5.6 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1β), 5.4 (t, 1H, $J_{2,3}$ 10 Hz, H-3α), 5.1 (t, 1H, $J_{2,3}$ 9.5 Hz, H-3β), 4.9 (m, H-2$\alpha+\beta$), 4.3–4.1 (M, H-6$\alpha+\beta$), 6′$\alpha+\beta$), 3.95–3.8 (M, H-5$\alpha+\beta$), 3.7–3.45 (M, OCH_2CH_2OH, H-4$\alpha+\beta$), 2.1 (s, 3H, CH_3COα), 2.0 (2s, 6H, 2*CH_3COα), 1.9 (s, 3H, CH_3COα), 1.95, 1.9 (2s, CH_3COβ); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.2, 170.1, 169.7, 169.4, 168.7 (CO$\alpha+\beta$), 91.5 (C-1β), 89.0 (C-1α), 76.2, 71.5, 71.0 and 69.3 (C-2 to −5α), 76.1, 74.4, 73.8, 70.5 (C-2 to −5β), 74.2 (C-2′ $\alpha+\beta$), 62.1, 61.6 (C-1′, 6 $\alpha+\beta$), 20.9, 20.6, 20.3, 20.2 (CH_3CO $\alpha+\beta$). Anal. Calcd for $C_{16}H_{24}O_{11}$: C, 48.98; H, 6.17. Found: C, 49.12; H, 6.18.

4-O-*(2′-Iodoethyl)-1,2,3,6-tetra*-O-*acetyl*-α,β-D-*glucopyranose* (**8**).—A soln of **6** (110 mg, 0.28 mmol) in dry CH_2Cl_2 (5 mL) was stirred under Ar at −10 °C before the addition of pyridine (140 μL, 6 equiv) and methanesulfonyl chloride (100 μL, 4.6 equiv). The cooling bath was removed and the reaction was stirred for 6 h before hydrolysis with ice. Extraction with CH_2Cl_2 was performed and the residue obtained after drying was purified by column chromatography on silica gel. Elution with 49:1 CH_2Cl_2–MeOH, gave 4-*O*-(2′-methanesulfonyloxyethyl)-1,2,3,6-tetra-*O*-acetyl-α,β-D-glucopyranose **7** (100 mg, 76%, α/β 6:1) as a thick oil which was used as such in the following step; ^{1}H NMR (300 MHz, $CDCl_3$), α-anomer δ: 6.1 (d, 1H, $J_{1\text{-}2}$ 3.7 Hz, H-1), 5.3 (dd, 1H, $J_{2\text{-}3}$ 10.3, $J_{3\text{-}4}$ 10 Hz, H-3), 5.1 (m, H-3), 4.8 (dd, 1H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.3 Hz, H-2), 4.2–4.05 (M, 4H, H-6, -6′, OCH_2), 3.8 (M, 1H, H-5), 3.7 (M, 2H, OCH_2), 3.4 (app. t,

1H, $J_{3\text{-}4}$ 10 Hz, H-4), 2.95 (s, 3H, CH_3SO_2), 2.0 (s, 3H, CH_3CO), 1.95 (s, 6H, 2*CH_3CO), 1.8 (s, 3H, CH_3CO). β-anomer: δ 5.55 (d, $J_{1\text{-}2}$ 8.1 Hz, H-1), 2.9 (s, 3H, CH_3SO_2), 1.95 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO) other resonances are obscured by those of the α-anomer; ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 169.8, 169.7, 168.7 (CO), 91.3 (C-1β), 88.9 (C-1α), 76.1, 71.2, 70.6, 69.3 (C-2α to 5α), 74.3, 73.1 (2 C amongst C-2β to 5β), 70.4, 67.9 (OCH_2–CH_2OH), 61.8 (C-6), 37.2 (CH_3SO_2), 20.7, 20.6, 20.3 (CH_3CO). To a soln of **7** (85 mg, 0.18 mmol) in acetone (2 mL) was added sodium iodide (540 mg, 3.6 mmol, 20 equiv) and the mixture heated at 60 °C overnight under protection from light. After cooling, it was evaporated to dryness and the residue was partitioned between water and CH_2Cl_2. The aq layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude oil was purified by column chromatography on silica gel. Elution with 49:1 CH_2Cl_2–MeOH gave **8** (85 mg, 94%, α/β: 6:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.2 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1α), 5.65 (d, $J_{1,2}$ 8,5 Hz, H-1β), 5.45 (app. t, 1H, $J_{2,3} = J_{3,4}$ 10 Hz, H-3α), 5.25 (dd., J 12.4, 9.1 Hz, H-3β), 5.00 (dd, 1H, $J_{1,2}$ 3.7, $J_{2,3}$ 10 Hz, H-2α), 4.35 (m, 2H, H-6aα, -6bα), 4.00 (M, 1H, H-5α), 3.9–3.7 (M, 2H, OCH_2CH_2I), 3.55 (t, 1H, $J_{3,4} = J_{4,5}$ 10 Hz, H-4α), 3.15 (t, 2H, $J_{1',2'}$ 6.4 Hz, CH_2I), 2.15 (s, 3H, CH_3COα), 2.12 (s, 3H, CH_3COα), 2.10 (s, 3H, CH_3COα), 2.09 (s, CH_3COβ), 2.04 (s, CH_3COβ), 2.03 (s, 3H, CH_3COα); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.8, 169.6, 168.8 (CO$\alpha + \beta$), 91.5 (C-1β), 89.1 (C-1α), 75.8, 71.6, 70.8, 69.6 (C-2α to 5α), 75.7, 74.6, 73.5, 73.0 (C-2β to 5β), 73.1 (OCH_2CH_2I $\alpha + \beta$), 62.2 (C-6β), 62.1 (C-6α), 21.0, 20.9, 20.7, 20.5, 20.4 (CH_3CO $\alpha + \beta$), 1.8 (CH_2I $\alpha + \beta$). Anal. Calcd for $C_{16}H_{23}IO_{10}$: C, 38.26; H, 4.62. I, 25.27. Found: C, 38.51; H, 4.71 I, 24.93.

4-O-*(2′-Iodoethyl)*-α,β-D *glucopyranose* (**1**).—Compound **8** (70 mg, 0.139 mmol) was dissolved in dry 1:1 CH_2Cl_2–MeOH (1 mL) and put at −20 °C before the addition of a few drops of a soln of 1 M NaOMe in MeOH. After 2 days at −10 °C, water was added (1 mL) and the solution concd to half volume. Neutralisation was performed with Amberlite IR 120 (H^+) and after filtration, the soln was evaporated to dryness. The residue was purified by column chromatography on silica gel (prewashed with methanol and dried); elution with 85:15 CH_2Cl_2–MeOH gave **1** (40 mg, 86%, $\alpha/\beta = 1$) as a colourless oil: $[\alpha]_D^{21} + 36°$ (at 5 min→ + 39.5° (24 h), (c 0.73, THF). ^{1}H NMR (200 MHz, D_2O): δ 5.8 (d, $J_{1,2}$ 3.9 Hz, H-1α), 5.2 (d, $J_{1,2}$ 8.5 Hz, H-1β), 4.8–4.6, 4.6–3,8 (2M, other H's), 2.8 (m, CH_2I $\alpha + \beta$); ^{13}C NMR (50 MHz, D_2O): δ 96.6 (C-1β), 92.4 (C-1α), 78.5, 78.3, 76.6, 75.5, 75.0, 73.6, 72.5, 70.8 (C-2 to 5 $\alpha + \beta$), 73.0 (C-1′$\alpha + \beta$170), 61.1 (C-6$\alpha + \beta$), 4.6 (C-2′ $\alpha + \beta$). Anal. Calcd for $C_8H_{15}IO_6$: C, 28.76; H, 4.53; I, 37.98. Found: C, 29.02; H, 4.65; I, 37.63.

6-O-*Acetyl-1,2:3,5-bis(*O-*methylidene)*-α-D-*glucofuranose* (**9**).—Prepared according to ref [22]. mp 102 °C (lit.: 104 °C [22]); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.0 (d, 1H, J 4.1 Hz, H-1), 5.05 and 4.95 (2s, 2H, OCH_2O), 4.90 and 4.75 (AB system, 2H, J 6.8 Hz, OCH_2O), 4.45 (d, 1H, J 4.1 Hz, H-2), 4.50–4.35 (M, 1H, H-3 or 4); 4.25–4.10 (M, 3H, H-3 or 4, H-6a, 6b), 3.87 (M, 1H, H-5), 2.05 (s, 3H, CH_3O); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 170.3 (CO), 104.4 (C-1), 96.5, 87.1 (2×OCH_2O), 83.5, 76.2, 75.0, 70.5 (C-2 to -5), 62.5 (C-6), 20.7 (CH_3).

*1,2:3,5-Bis(*O-*methylidene)*-α-D-*glucofuranose* (**10**).—To a stirred soln of **9** (5 g, 20.3 mmol) in dry MeOH (100 mL), under argon was added sodium (pre-washed with *n*-pentane, 0.58 g, 25.23 mmol). After 30 min, the soln was neutralized with 1 M hydrochloric acid and the volatiles were removed. The crude product was purified by column chromatography on silica gel 49:1 CH_2Cl_2–MeOH, to afford, **10** [22] (3.92 g, 95%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.0 (d, 1H, $J_{1,2}$ 4.1 Hz, H-1), 5.0 and 4.95 (2 s, 2 H, OCH_2O), 4.95 and 4.75 (AB system, 2 H, J 6.8 Hz, OCH_2O); 4.45 (d, 1H, $J_{1,2}$ 4.1 Hz, H-2); 4.25 (m, H-3 or H-4); 4.1–3.65 (M, 4H, H-3 or H-4, and other H's). ^{13}C NMR (50 MHz, $CDCl_3$): δ 104.5 (C-1), 97.1, 87.8 (OCH_2O), 84.3, 76.9, 76.2, 73.9 (C-2 to 5), 62.1 (C-6).

*1,2:3,5-Bis(*O-*methylidene)-6*-O-*(ethoxycarbonylmethyl)*-α-D-*glucofuranose* (**11**).—To a suspension of sodium hydride (257 mg, 6.42 mmol) in dry THF (5 mL), stirred at 0 °C under Ar, was slowly added a soln of **10** (1.17 g, 5.7 mmol) in dry THF (3 mL). After the gas evolution had ceased, ethyl bromoacetate (3.2 mL, 5 equiv, 28.6 mmol) was added dropwise and stirring was continued for 3 h at 0 °C, then 16 h at room temperature. Methanol was then slowly added before evaporation of the volatiles and the residue was taken up in CH_2Cl_2, washed with water and dried. After evaporation, the crude product was purified by column chromatography on silica gel. Elution with 99:1 CH_2Cl_2–MeOH, afforded **11** (1.1 g, 67%) as a colourless oil: $[\alpha]_D^{21}$ + 29° (*c* 0.84, $CHCl_3$). ^{1}H NMR (200 MHz,

$CDCl_3$): δ 5.95 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.1 and 4.75 (AB system, 2 H, J 6.9 Hz, OCH_2O), 5.0 and 4.95 (2 s, 2H,OCH_2O), 4.4 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-2), 4.35 (m, 1H) and 4.20–4.0 (M, 8 H, H-3, -4, -5, OCH_2CH_3, OCH_2COO), 3.90–3.70 (m, 2 H, H-6a, 6b), 1.2 (t, 3 H, J 10.0 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.4 (CO), 103.8 (C-1), 96.1, 87.5 (OCH_2O), 83.4, 76.3, 75.3, 70.9 (C-2 to 5), 72.0, 68.0, 60.5 (C-6, $OCH_2COOCH_2CH_3$), 13.8 (CH_3). Anal. Calcd for $C_{12}H_{18}O_8$: C,49.65; H, 6.25. Found: C, 49.54; H, 6.10.

*1,2:3,5-Bis(*O*-methylidene)-6-*O*-(2′-hydroxyethyl)-*α*-*D*-glucofuranose* (**12**).—A suspension of $LiAlH_4$ (340 mg, 8.97 mmol) in dry diethyl ether (10 mL) was stirred at 4 °C under Ar a soln of **11** (1.06 g, 3.65 mmol) in diethyl ether (5 mL) was added dropwise followed after 30 min by EtOAc then water. After filtration on Celite, the volatiles were removed and the residue was purified by column chromatography on silica gel, 49:1 CH_2Cl_2–MeOH, to afford **12** (540 mg, 60%) as a colourless oil: $[\alpha]_D^{21}$ +41° (*c* 2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 6.0 (d, 1H, J 4.2 Hz, H-1), 5.05 and 5.0 (2 s + A part of an AB system, 3 H) and 4.75 (B part of an AB system, 1 H, J 7.3 Hz, OCH_2O), 4.45 (d, 1 H, J 4.2 Hz, H-2); 4.3 (s, 1 H), 4.15 (t, 1 H, J 2.8 Hz), 4.0 (s, 1 H), 3.8–3.5 (M, 7 H, other H's); ^{13}C NMR (50 MHz, $CDCl_3$): δ 104.0 (C-1), 96.1, 87.4 (OCH_2O), 83.3, 76.2, 75.5, 71.3 (C-2 to 5), 72.7, 70.9, 61.2 (C-6, OCH_2CH_2OH). Anal. Calcd for $C_{10}H_{16}O_7$: C,48.38; H, 6.50. Found: C, 48.25; H, 6.44.

*1,2:3,5-Bis(*O*-methylidene)-6-*O*-(2′-iodoethyl)-*α*-*D*-glucofuranose* (**13**).—To a stirred soln of **12** (346 mg, 1.39 mmol) in toluene (20 mL) Under Ar, were added triphenylphosphine (544 mg, 2.076 mmol), then triiodoimidazole [26] (272 mg, 1.044 mmol). After 3 h stirring at 120 °C under protection from light, additional triphenylphosphine (360 mg, 1.37 mmol) and triiodoimidazole (180 mg, 0.690 mmol) were added. After 90 min, the mixture was cooled and a saturated aq soln of $NaHCO_3$ (20 mL) was added which was followed after 5 min stirring by introduction of I_2 till persistent colouration. After 10 min, aq sodium thiosulfate was added till discolouration and the organic layer was separated and dried. The crude residue obtained after removal of the volatiles was purified by column chromatography on silica gel. Elution with 99:1 CH_2Cl_2–MeOH, yielded **13** (230 mg, 46%) as a yellow oil: $[\alpha]_D^{21}$ +26° (*c* = 0.22, MeOH); ^1H NMR (200 MHz, $CDCl_3$): δ 5.9 (d, 1H, J 4.0 Hz, H-1), 5.1 and 4.7 (AB system, 2H, J 6.5 Hz, OCH_2O), 5.0 and 4.95 (2s, 2H, OCH_2O), 4.4 (m, 2H), 4.05 (m, 1H), 4.0 (l s, 1H), 3.8–3.5 (M, H-2 to 6, 1′a,-1′b), 3.20 (t, J 7.0 Hz, 2H, H-2′a, 2′b); ^{13}C NMR (50 MHz, $CDCl_3$): δ 104.1 (C-1), 96.5 (OCH_2O), 83.2 (OCH_2O), 83.7, 76.5, 75.8, 71.2 (C-2 to 5), 72.5, 71.7 (C-6, 1′), 2.8 (C-2′). Anal. Calcd for $C_{10}H_{15}IO_6$: C, 33.54; H, 4.22. Found: C, 33.73; H, 4.31.

*6-*O*-(2′-Iodoethyl)-*α*-*D*-glucopyranose* (**2**).—To a soln of **13** (70 mg, 195 μmol) in 1:1 dioxane–water (2 mL) was added Amberlite IR 120 (340 mg, 1.5 equiv) and the mixture was stirred at 60 °C for 1 day. After cooling, the soln was filtered off and the resin washed with water and the combined layers were poured into a KH_2PO_4–Na_2HPO_4 buffer (pH 5.5) solution (5 mL). After evaporation of the volatiles, the crude residue was purified by column chromatography on silica gel. Elution with 9:1 CH_2Cl_2–MeOH, yielded **2** (32 mg, 49%) as a white solid: mp 125 °C. $[\alpha]_D^{22}$ +14.7° (5 min), → +18.3° (12 h)(*c* 0.3; H_2O); ^1H NMR (200 MHz, D_20): δ 5.2 (d, $J_{1,2}$ 4 Hz, H-1α), 4.75 (d, $J_{1,2}$ 8.1 Hz, H-1β), 3.85–3.2 (M, other H's). ^{13}C NMR (50 MHz, D_2O) δ: 95.9 (C-1β), 92.0 (C-1α), 75.7, 74.7, 74.0, 69.7 (C-2 to −5β), 72.7, 71.4, 70.2, 69.7 (C-2 to 5α); 71.6 (C-1′), 69.1, 68.9 (C-6α, 6β), 3.4 (C-2′). Anal. Calcd for $C_8H_{15}IO_6$: C, 28.76; H, 4.53; I, 37.98. Found: C, 29.12; H, 4.62; I, 37.45. compound 2 was acetylated conventionally to yield 6-*O*-(2′-iodoethyl)-1,2,3,4-tetra-*O*-acetyl-α,β-D-glucopyranose, ^1H NMR (250 MHz, D_2O, α/β 1.5:1): δ 6.3 (d, $J_{1,2}$ 4 Hz, H-1α), 5.65 (d, $J_{1,2}$ 8.7 Hz, H-1β), 5.45 (m, H-3α), 5.15–5.0 (M, H-3β, H-2, 4α, 4β), 4.25–4.15 (M, H-5β), 4.05–3.95 (M, H-5α), 3.8–3.5 (M, H-6α, 6β, 1′α, 1′β), 3.2 (t, $J_{1',2}$ 7.1 Hz, H-2′α, 2′β), 3.15 (t, $J_{1',2'}$ 7 Hz, H-2′α, 2′β), 2.15 (s, CH_3COα or β), 2.08 (s, CH_3COβ), 2.06 (s, CH_3COβ), 2.02 (s, CH_3COα), 2.01 (s, CH_3COβ), 1.99 (s, CH_3COα), 1.98 (s, CH_3COα); ^{13}C NMR (62.5 MHz, D_2O): δ 170.2, 170.1, 169.6, 169.4, 169.2, 168.9, 168.8 (CO), 91.6 (C-1β), 88.9 (C-1α), 74.1, 72.9, 71.2, 70.2, 69.8, 69.6, 69.2, 68.5 (C-2 to 5), 72.5, 68.9 (C-6, 1′), 20.9, 20.7, 20.6, 20.5 (CH_3), 2.2 (C-2′). Anal. Calcd for $C_{16}H_{23}IO_{10}$: C, 38.26; H, 4.62; I, 25.27. Found: C, 38.32; H, 4.64; I, 25.03.

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