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TETRAHEDRON: *ASYMMETRY*

Higher iodinated analogues of D-glucose: syntheses of 3-*C*-iodomethyl, 6-*C*-iodomethyl and 6-*C*-iodophenyl derivatives

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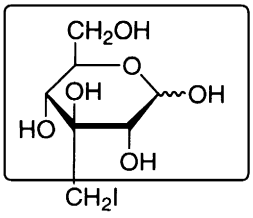
Abstract

C-Substituted iodinated analogues of D-glucose have been prepared from diacetone-D-glucose or D-glucuronic acid derivatives; in these compounds, each hydroxyl group of glucose is present.

1. Introduction

The quest for iodinated analogues of carbohydrates which could be used in SPECT (single photon emitted computed tomography) medical imaging[1] has resulted in the preparation of derivatives in which one of the oxygen atoms is substituted by an iodinated moiety (to get, for example, β-iodoethers)[2] or in compounds in which iodine has replaced a hydroxyl group. However, no higher homologues of the general formula $C_7H_{15}XO_6$ (X being any halogen), whether linear or branched, have been described to date. In such compounds, the basic skeleton of the parent D-glucose together with each of its hydroxyl group would be preserved; this work reports on the synthesis of two such analogues, namely **1** and **2**, as well as on the preparation of a *C*-iodophenyl derivative, **3**.



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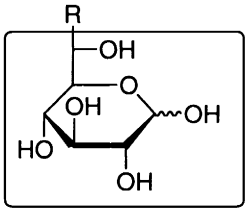

2 : R = CH_2I
3 : R = C_6H_4-I

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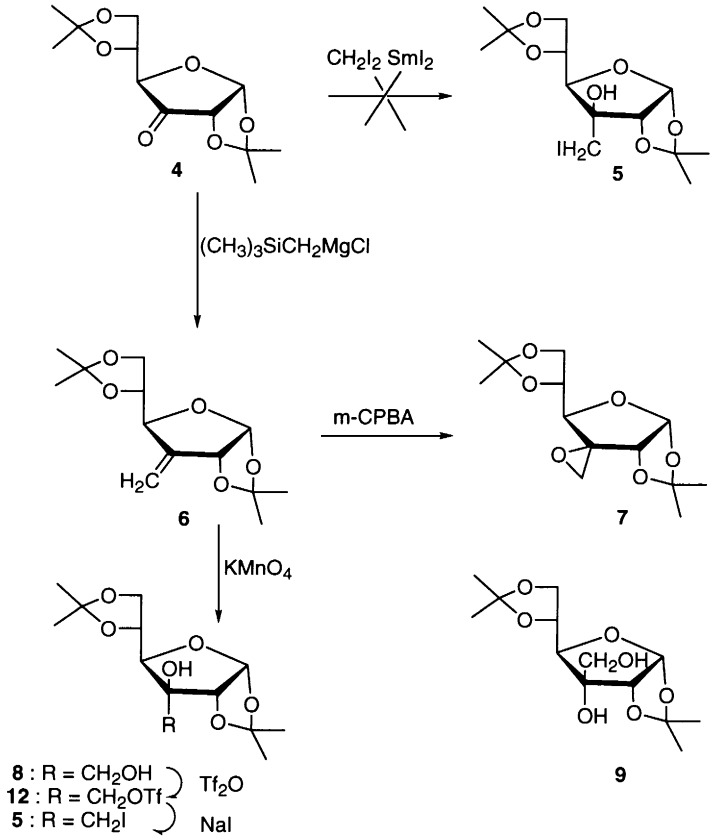
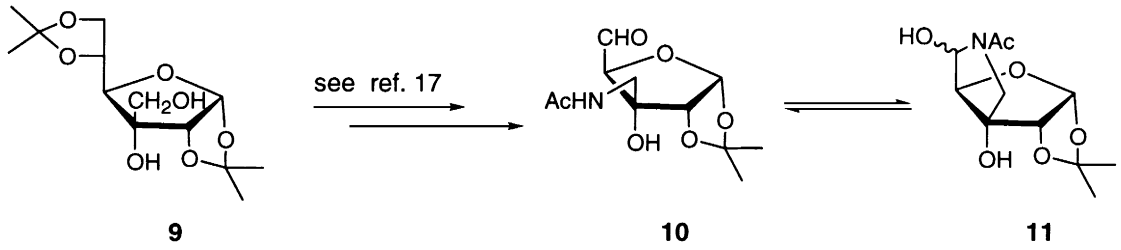
2. Preparation of a C-3 branched derivative

The rationale for linking an iodinated group to C-3 of glucose stems from the fact that although substitution of O-3 by a methyl group is well tolerated,[3] this is not the case when bulkier substituents are introduced;[4] the replacement of the OH-3 by iodine, as in 3-deoxy-3-iodoglucose,[5] is also detrimental. In **1**, the 3-OH group is retained and the iodinated group has been introduced on carbon to give a C-3-branched iodomethyl derivative of *gluco* configuration (Scheme 1).



Scheme 1.

Readily available ketone **4** [6,7] appeared as a convenient starting material for the preparation of **1**, by direct iodomethylation to get **5** using SmI_2/CH_2I_2.[8,9] No such reaction occurred under these conditions, however, presumably because of the difficulties in completely freeing **4** from its hydrate.[7] Compound **4** was, therefore, converted by Peterson olefination[10] to the known *exo*-methylene derivative **6**[11] but no electrophilic iodination (to get **5**) using *N*-iodosuccinimide,[12] hypoiodous acid[13] or iodine[14] could be achieved. Epoxidation of **6** gave a 50:50 mixture of epimeric epoxides (83%) from which a small amount of pure **7** could be obtained by crystallisation. Its configuration was identified as *gluco* by comparison of its properties with those of the epoxide obtained[15] by addition of diazomethane on ketone **4**. However, none of these methods is of preparative value to get pure epoxide **7**.[16] Compound **6** was then reacted[17] with aqueous potassium permanganate to yield glycol **8** (70%) where configuration was assigned as *gluco* because its C-3 *allo* epimer, **9**, had been correlated with aldehyde **10**. Aldehyde **10** was indeed shown to exist in equilibrium with aminal **11**, thus establishing the *cis*-relationship of their C-3 and C-4 substituents (Scheme 2).[17]



Scheme 2.

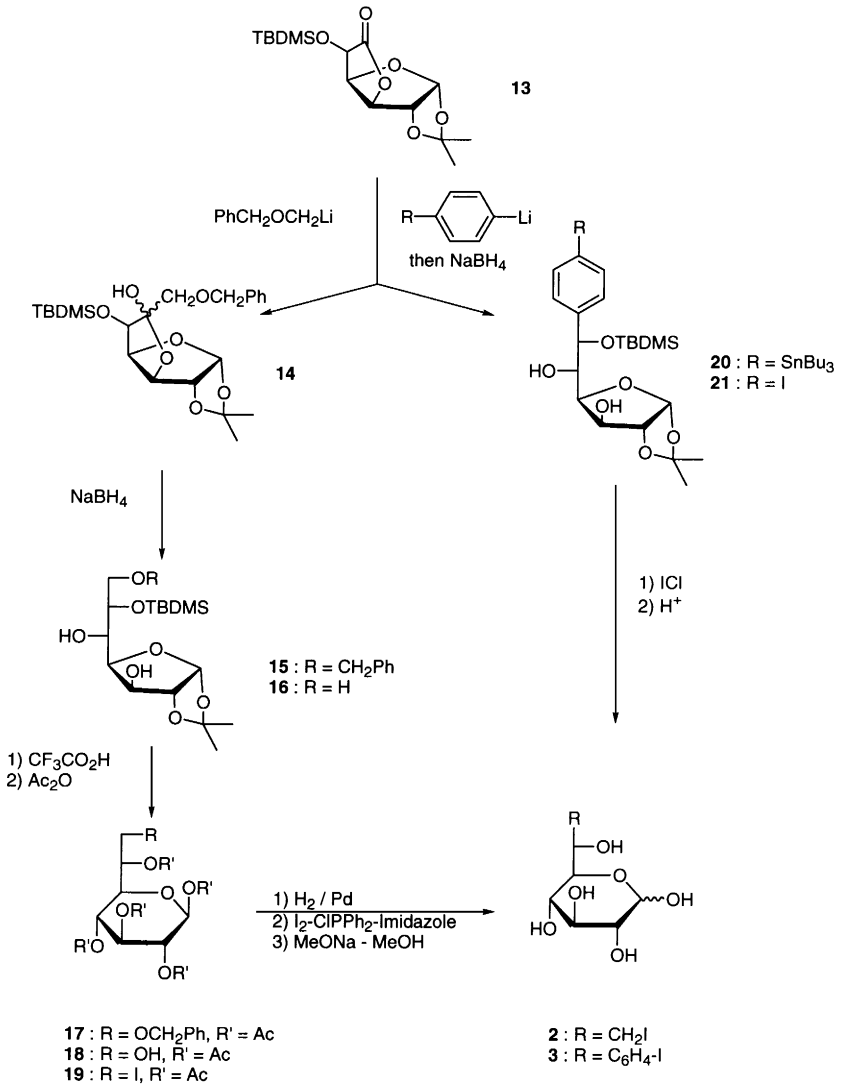
To achieve the introduction of iodine on **8**, displacement of its primary alcohol-derived sulfonate proved to be the method of choice. As both tosylate and mesylate remained unreactive,[18] it became necessary to use triflate **12** (Tf_2O, 2,4,6-collidine, −10°C, 15 min) which was reacted with sodium iodide under protection from light to afford iodohydrin **5** (78% from **8**). Trifluoracetic acid deprotection of both of its acetals (62%) then gave the desired *C*-iodomethyl analogue **1** (δ CH_2I=12.9 ppm).

3. Derivatives substituted at C-6

Position-6 was also selected for introduction of an iodinated moiety as structure/affinity relationships of glucose derivatives have shown the possibility of modifications at C-6,[19] which has been used in particular for the development of 6-deoxy-6-iodo-D-glucose[20,21] as a tracer of glucose transport.[22] Glucuronamide derivatives, as probes for the study of glucose transport proteins,[23] have also been prepared by derivatisation of glucose at position-6. In all these analogues, however, the 6-OH of glucose is 'lost' and since this hydroxyl can interact with hexokinases[24–27] or phosphatases,[25] the preparation of C-6 substituted analogues **2** and **3** was undertaken; their synthesis is based on the methodology developed by Fleet and co-workers[24,25] starting with conformationally-locked glucuronolactone derivative **13**.

Reaction of **13**[24,25] with benzyloxymethyllithium, prepared in situ from (benzyloxymethyl)tributylstannane and *n*-butyllithium at −100°C,[28,29] gave lactol **14**, the best yields (45%) being obtained with a 1:2:1.8 (**13**:Sn:Li) ratio. As observed previously in related cases,[24,25] sodium borohydride reduction (98%) of lactol **14** was accompanied by migration of the silyl group (O-5 to O-6) and the stereochemistry at C-6 of the single 7-deoxy-heptose derivative thus obtained was assigned as *S* in accordance with previous work.[25] Since selective replacement by iodine of the 7-OH of **16** obtained after debenzylation of **15** could not be effected satisfactorily, **15** was converted (CF_3COOH then Ac_2O) to a mixture of acetylated anomers from which pure α-pyranose **17** could be crystallised. Completion of the synthesis involved debenzylation (to get **18**, 95%), iodination with the iodine/chlorodiphenylphosphine/imidazole system[30] (**19**, 56%) and Zemplén deacylation to give **2** (95%) (Scheme 3).

Preparation of **3** was straightforward: reaction of lactone **13** with tributylstannylphenyl lithium (prepared in situ by monolithiation of 1,4-bis(tributylstannyl)benzene at −100°C)[31] gave a lactol which was not isolated but which could be reduced ($NaBH_4$, 77% from **13**) to give a single epimer at C-6;[32] its stereochemistry at C-6 was assigned as *R*[33] after comparison of its ^1H NMR data with those of a similar compound (**20**, R=H) whose structure could be established unambiguously.[24] Electrophilic iodination[34] (iodine chloride, 95%) gave **21** whose acetal was cleaved (CF_3COOH, 65%) to afford **3**.



Scheme 3.

In all three derivatives **1**, **2** and **3**, the iodinated moiety has been found to be stable, which should enable radiolabelling (^{123}I or ^{131}I) of these glucose analogues for their biological evaluation towards SPECT medical imaging.

4. Experimental

4.1. General methods

Anhydrous solvents were obtained as follows: methanol was distilled over magnesium methoxide, tetrahydrofuran and toluene over sodium, 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 abbreviations 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).

4.2. 1,2:5,6-Di-O-isopropylidene-3-C-trifluoromethanesulfonyloxymethyl-α-D-glucofuranose ***12***

To a stirred solution of **8**[17] (100 mg, 0.34 mmol) in dichloromethane (3 mL) at −10°C were added successively 2,4,6-collidine (72 μL, 1.6 equiv.) and a solution of trifluoromethanesulfonic anhydride (72 μL, 1.3 equiv.) in dichloromethane (3 mL). After 15 min stirring at −10°C, ice was added followed by dichloromethane (20 mL). The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give **12** (115 mg, 79%) as a colourless oil which was used without delay in the next step. ^1H NMR (200 MHz, $CDCl_3$) δ 5.85 (d, J_{1-2}=4 Hz, 1H, H-1), 4.75 (AB system, J=12 Hz, 2H, SO_2CH_2), 4.4 (d, J_{1-2}=4 Hz, 1H, H-2), 4.4–3.9 (m, 3H, H-5, H-6, H-6′), 3.7 (d, J_{4-5}=11 Hz, 1H, H-4), 1.5 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.3 (s, 6H, 2*CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 113.2, 109.9 (2*C(Me)$_2$), 104.8 (C-1), 84.6, 80.6, 72.0 (C-2, C-4 and C-5), 81.1 (C-3), 76.1 (SO_2CH_2), 67.6 (C-6), 26.9, 26.6, 26.3, 24.8 (4*C(Me)$_2$).

4.3. 1,2:5,6-Di-O-isopropylidene-3-C-iodomethyl-α-D-glucofuranose ***7***

To a solution of **12** (115 mg, 0.72 mmol) in acetone (3 mL) was added sodium iodide (410 mg, 2.735 mmol, 10 equiv.) and the solution was stirred overnight at 60°C under protection from light. After cooling and evaporation of the solvent, the residue was partitioned between dichloromethane and water, the latter being extracted with dichloromethane. The combined organic layers were washed with brine, dried and concentrated to dryness. Silica gel column chromatography (dichloromethane:methanol, 98:2) afforded **7** as a yellowish oil (108 mg, 0.27 mmol, 99%). $[\alpha]_D^{20}$=+48 (c 0.44, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (d, J_{1-2}=3.8 Hz, 1H, H-1), 4.2 (d, J_{1-2}=3.8 Hz, 1H, H-2), 4.35–3.9 (m, 3H, H-5, H-6, H-6′), 3.85 (d, J_{4-5}=8.2 Hz, 1H, H-4), 3.6 (AB system, J=10 Hz, 2H, CH_2I), 1.5 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.3 (s, 6H, 2*CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 112.8, 109.6 (2*C(CH_3)$_2$), 103.8 (C-1), 87.5, 79.7, 72.7 (C-2, C-4, C-5), 80.7 (C-3), 67.8 (C-6), 27.1, 26.8, 26.4, 25.1 (4*C(CH_3)$_2$), 11.5 (CH_2I). Anal. calcd for $C_{13}H_{21}IO_6$: C, 39.02; H, 5.29. Found: C, 39.11; H, 5.32.

4.4. 3-C-Iodomethyl-α,β-D-glucopyranose ***1***

To a stirred solution of **7** (160 mg, 0.4 mmol) in 9:1 dichloromethane:water (5 mL) at 4°C was added dropwise trifluoracetic acid (1.6 mL, 20 mmol, 50 equiv.). The mixture was stirred at rt for 2 h and the volatiles were evaporated. The residue obtained after co-evaporation with toluene was taken up in water and extracted with dichloromethane. After drying and evaporation, the residue was recrystallised from ethanol to afford **1** as white crystals (80 mg, 62%). M.p.=132.5°C. $[\alpha]_D^{21}$=+33 (c 0.23, H_2O) 5 min→+42°C (24 h). ^1H NMR (200 MHz, D_2O) δ 5.4 (d, J_{1-2}=3.2 Hz, H-1α), 4.85 (detected in DOH, H-1β), 3.95–3.4 (m, other Hs). ^{13}C NMR (62.5 MHz, D_2O+$(CD_3)_2C$=O) δ 102.2 (C-1β), 96.3 (C-1α), 82.1, 80.6, 78.7, 78.4, 70.9, 70.1 (C-2, C-4, C-5α+β), 82.0, 81.1 (C-3α+β), 64.1 (C-6α+β), 12.9 (CH_2Iα+β). Anal. calcd for $C_7H_{13}IO_6$: C, 26.27; H, 4.09; I, 39.65. Found: C, 26.32; H, 4.11; I, 39.44.

4.5. 7-O-*Benzyl*-5-O-tert-*butyldimethylsilyl*-1,2-O-*isopropylidene*-D,L-glycero-α-D-gluco-*hepto*-keto-6,3-*aldo*-1,5-*difuranose* **14**

To a stirred solution of benzyloxymethyltributylstannane[29] (13.9 g, 33.8 mmol, 2 equiv.) in dry THF (50 mL) under argon at −100°C was added *n*-butyllithium (21 mL of a 1.45 M soln in hexane, 30.4 mmol, 1.8 equiv). Then **13**[24,25] (5.6 g, 16.95 mmol, 1 equiv.), dissolved in the minimum amount of dry THF, was added at once and the mixture was warmed to −50°C before quenching with water (50 mL). The mixture was then brought to room temperature, diluted with diethyl ether (100 mL) and washed with brine. After drying and evaporation of the volatiles, column chromatography on silica gel (99:1, dichloromethane:methanol) afforded **14** (3.56 g,45%) as a colourless oil. $[\alpha]_D^{22}$=+31 (*c* 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H, *Ar*-CH_2O), 5.95 (d, J_{1-2}=4 Hz, 1H, H-1), 4.7–4.45 (m, 5H, H-2, H-3, H-4, H-6a, H-6b), 4.25 (d, J_{4-5}=4.8 Hz, 1H, H-5), 4.0 (s, 1H, OH), 3.45–3.3 (AB system, *J*=11 Hz, 2H, Ar-CH_2O), 1.4 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 0.85 (s, 9H, Si-C(CH_3)$_3$), 0.1, 0.0 (2*s, 2*3H, Si-(CH_3)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.9 (Ph$_{ipso}$), 128.3, 127.8, 127.7 (Ph$_{ortho,\ meta}$ and *para*), 112.4 (*C*(CH_3)$_2$), 107.1 (C-1), 104.6 (C-6), 85.5, 83.8, 82.2, 72.5 (C-2 to C-5), 73.6, 70.5 (*C*H_2O*C*H_2Ar), 27.3, 26.8 (C(*C*H_3)$_2$), 25.7 (Si-C(*C*H_3)$_3$), 18.1 (Si-*C*(CH_3)$_3$), −4.7, −5.1 (Si-(*C*H_3)$_2$). Anal. calcd for $C_{23}H_{36}O_7Si$: C, 61.04; H, 8.02. Found: C: 61.24; H, 7.89.

4.6. 7-O-*Benzyl*-6-O-tert-*butyldimethylsilyl*-1,2-O-*isopropylidene*-L-glycero-α-D-gluco-*heptofuranose* **15**

To a solution of **14** (2.76 g, 6 mmol) in ethanol (30 mL) at 4°C was added sodium borohydride (346 mg, 9.15 mmol, 1.5 equiv.). The cooling bath was removed and when the room temperature was reached aqueous saturated ammonium chloride solution was added. Extraction was performed with ethyl acetate (100 mL) and the organic layer was washed with brine. After drying and evaporation of the volatiles, the residue was purified by column chromatography on silica gel. Elution with dichloromethane:methanol (95:5) gave **15** as a colourless oil (2.72 g, 98%). $[\alpha]_D^{22}$=+1.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H, Ar), 5.85 (d, J_{1-2}=4 Hz, 1H, H-1), 4.55–4.45 (m, 3H, Ar-CH_2O, H-2), 4.5–4.3 (m, 1H, H-3), 4.1–4.05 (m, 2H, H-4, H-6), 3.95 (t, *J*=8 Hz, 1H, H-5), 3.6–3.4 (m, 2H, BnO-CH_2), 3.0 (d, *J*=4 Hz, 1H, OH), 2.8 (d, *J*=9 Hz, 1H, OH), 1.4 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 0.85 (s, 9H, Si-C(CH_3)$_3$), 0.1, 0.05 (2*s, 2*3H, Si-(CH_3)$_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.9 (Ph$_{ipso}$), 128.3, 127.8 (Ph$_{ortho,\ meta}$ and *para*), 111.0 (*C*(CH_3)$_2$), 105.1 (C-1), 85.1, 79.6, 75.4, 70.1, 69.7 (C-2 to C-6), 71.6, 70.1 (Ar-*C*H_2-O-*C*H_2), 26.6, 25.9 (C(*C*H_3)$_2$), (Si-C(*C*H_3)$_3$), 18.1 (Si-*C*(CH_3)$_3$), −4.4, −5.0 (Si-(*C*H_3)$_2$). Anal. calcd for $C_{23}H_{38}O_7Si$: C, 60.76; H, 8.42. Found: C, 60.84; H, 8.39.

4.7. 7-O-*Benzyl*-1,2,3,4,6-*penta*-O-*acetyl*-L-glycero-β-D-gluco-*heptopyranose* **17**

Dichloromethane (4.5 mL) and water (0.5 mL) were added to **15** (200 mg, 0.44 mmol) and the biphasic mixture was stirred efficiently. Trifluoracetic acid was added and when deprotection was complete (tlc), the volatiles were removed. Co-evaporation with toluene was performed twice and the residue was then taken up in pyridine (2 mL) before the addition of acetic anhydride (1 mL, 10.6 mmol, 24 equiv.). After stirring overnight, ice was added and the mixture extracted with dichloromethane (3×10 mL). After washing the organic layer with brine and water, crystallisation of the residue — which consisted mainly of a 1:1 mixture of anomers — from ethanol gave **17** (52 mg, 23%). M.p.=160–162°C. $[\alpha]_D^{22}$=−15 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H, Ar), 5.7 (d, J_{1-2}=8 Hz, 1H, H-1), 5.3–5.0 (m, 4H, H-2, H-3, H-4, H-6), 4.6–4.4 (AB system, *J*=12 Hz, 2H, Ar-CH_2O), 3.95 (dd, *J*=1.5 Hz, *J*=8.5

Hz, 1H, H-5), 3.55 (m, 2H, BnO-CH_2), 2.1 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.0 (s, 3H, CH_3CO), 1.95 (s, 6H, 2*CH_3CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170. 1, 170.0, 169.4, 169.1, 168.7 (CH$_3$*C*O), 137.8 (Ph$_{ipso}$), 128.3, 127.8, 127.7 (Ph$_{ortho,\ meta}$ and $_{para}$), 92.2 (C-1), 73.5 (Ar-*C*H$_2$O), 73.1, 72.3, 70.4, 67.1, 66.9 (C-2 to C-6), 66.8 (BnO-*C*H$_2$), 20.7 (*C*H$_3$CO), 20.6 (*C*H$_3$CO), 20.5 (*C*H$_3$CO). Anal. calcd for $C_{23}H_{38}O_{12}$: C, 56.47; H, 5.92. Found: C, 56.16; H, 5.84.

4.8. 1,2,3,4,6-Penta-O-*acetyl*-L-glycero-β-D-gluco-*heptopyranose* ***18***

Methanol (3 mL) was added to **17** (100 mg, 0.196 mmol) followed by the minimum amount of dichloromethane to ensure dissolution. Palladium (10% on carbon, 40 mg) was then added and the mixture was stirred overnight under an atmosphere of hydrogen. After filtration on Celite, evaporation of the volatiles afforded pure **18** (78 mg, 95%) as a colourless solid. M.p.=149–150°C. $[\alpha]_D^{21}=-12$ (*c* 0.1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.5 (d, J_{1-2}=8 Hz, 1H, H-1), 5.3–5.0 (m, 4H, H-2, H-3, H-4, H-6), 3.9 (dd, *J*=2.4 Hz, *J*=9.5 Hz, 1H, H-5), 3.7 (m, 2H, CH_2OH), 3.4 (s, 1H, OH), 2.15 (s, 3H, CH_3CO), 2.1 (s, 3H, CH_3CO), 2.0 (s, 3H, CH_3CO), 1.95 (s, 6H, 2*CH_3CO). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.4, 169.9, 169.4, 169.3, 169.1 (CH$_3$*C*O), 92.2 (C-1), 72.7, 72.3, 69.9, 68.7, 66.7 (C-2 to C-6), 59.9 (*C*H$_2$OH), 20.5, 20. 3 (*C*H$_3$CO). Anal. calcd for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.75. Found: C, 48.61; H, 5.73.

4.9. 7-Deoxy-7-iodo-1,2,3,4,6-penta-O-*acetyl*-L-glycero-β-D-gluco-*heptopyranose* ***19***

To a stirred solution of **18** (510 mg, 1.21 mmol) protected from light in dry toluene (40 mL) were added successively imidazole (186 mg, 2.73 mmol, 2.25 equiv.), freshly distilled chlorodiphenylphosphine (287 μL, 1.6 mmol, 1.32 equiv.) and, after having stirred the turbid mixture for 10 min at 40°C, iodine (399 mg, 1.57 mmol, 1. 3 equiv.). After 30 min stirring, the same quantities of imidazole, chlorodiphenylphosphine and iodine were added in that order and the mixture was stirred overnight at room temperature. After addition of a saturated aqueous sodium hydrogenocarbonate, iodine was added portionwise under stirring until a persistent brown colouration of the organic layer was observed. Ethyl acetate (100 mL) was added and the organic layer was washed with a saturated aqueous solution of sodium thiosulfate, then brine. After drying and evaporation of the volatiles, the orange oil was purified by column chromatography on silica gel. Elution with dichloromethane:methanol (99:1) gave **19** after crystallisation from diethyl ether (361 mg, 56%). M.p.=187–190°C. $[\alpha]_D^{22}=-21$ (*c* 0.31, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.7 (d, J_{1-2}=8 Hz, 1H, H-1), 5.25–5.0 (m, 4H, H-2, H-3, H-4, H-6), 4.1 (dd, *J*=2 Hz, *J*=10 Hz, 1H, H-5), 3.3–3.1 (AB of ABMX, *J*=9 Hz, 2H, CH_2I), 2.1 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.0 (s, 3H, CH_3CO), 1.95 (s, 3H, CH_3CO), 1.9 (s, 3H, CH_3CO). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169. 9, 169.8, 169.3, 169.1, 168.6 (CH$_3$*C*O), 92.2 (C-1), 72.9, 72.8, 70.2, 68.9, 67.5 (C-2 to C-6), 20.6, 20.5, 20.4 (*C*H$_3$CO), −0.7 (*C*H$_2$I). Anal. calcd for $C_{17}H_{23}IO_{11}$: C, 38.50; H, 4.37; I, 29.93. Found: C, 38.75; H, 4.42; I, 23.73.

4.10. 7-Deoxy-7-iodo-L-glycero-α,β-D-gluco-*heptopyranose* ***2***

To a solution of **19** (300 mg, 0.57 mmol) in dry 1:1 dichloromethane:methanol (20 mL) was added sodium methoxide (10 drops of a 1 M solution in dry methanol). The solution was set at 4°C overnight and water (20 mL) was added. Concentration to half-volume was performed under reduced pressure and the pH was adjusted to 7.0 (Dowex 50 (H^+)). After filtration, evaporation of the volatiles afforded **2** (172 mg, 95%) as an amorphous solid. $[\alpha]_D^{22}$=+40 (*c* 0.1, CH_3OH) 5 min→+47°C (24 h). ^{1}H NMR (250 MHz, D_2O+CD_3OD) (α/β=1) δ 5.25 (d, J_{1-2}=3 Hz, 1H, H-1α), 4.7 (d, J_{1-2}=8 Hz, 1H, H-1β), 4.3–3.25 (m, other Hs). ^{13}C NMR (62.5 MHz, D_2O+CD_3OD) δ 96.6 (C-1β), 92.1 (C-1α), 75.9, 75.2, 74.2, 73.1, 71.5,

70.6, 69.9, 68.9 (C-2α+β to C-6α+β), 7.2 (*C*H$_2$Iα+β). Anal. calcd for $C_7H_{13}IO_6$: C, 26.27; H, 4.09; I, 39.65. Found: C, 26.38; H, 4.18; I, 39.41.

4.11. 6-O-tert-*Butyldimethylsilyl-1,2*-O-*isopropylidene-6*-C-*(4-(tri*-n-*butylstannyl)phenyl)*-L-glycero-α-D-gluco-*hexofuranose* ***20***

To a stirred solution of 1,4-bis-(tri-*n*-butylstannyl)benzene[31] (3 g, 4.74 mmol, 1.28 equiv.) in dry THF (15 mL) under argon at −100°C, was added *n*-butyllithium (2.31 mL of 1.6 M soln in hexane, 3.7 mmol, 0.8 equiv.). The cooling bath was removed and when the temperature had reached −20°C the solution was cooled again at −100°C and **13**[24,25] (1.51 g, 4.4 mmol, 1.1 equiv.) in dry THF (2 mL) was rapidly added. The mixture was then stirred at −78°C for 1 h and the cooling bath was removed. A saturated aqueous ammonium chloride solution was added, followed by diethyl ether (100 mL). The organic layer was washed with brine, dried and the volatiles were evaporated under reduced pressure. The residue was purified by column chromatography. Elution with dichloromethane:methanol (99:1) gave crude 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-6-*C*-(4′-(tri-*n*-butylstannyl)phenyl)-D,L-*glycero*-α-D-*gluco*-hepto-keto-6,3-aldo-1,5-difuranose (2.8 g) which was used without further purification. ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 140.7 (Ph$_{ipso\ \text{and}\ para}$), 136.2, 125.3 (Ph$_{ortho,\ meta}$), 112.4 (*C*(CH$_3$)$_2$), 107.3 (C-1), 103.7 (C-6), 85.9, 84.3, 82.4, 80.0 (C-2 to C-5), 29.1 (SnCH$_2$CH$_2$*C*H$_2$CH$_3$), 27.3, 26.8 (C(*C*H$_3$)$_2$), 27.2 (SnCH$_2$*C*H$_2$CH$_2$CH$_3$), 25.5 (Si-C(*C*H$_3$)$_3$), 18.0 (Si-*C*(CH$_3$)$_3$), 13.5 (SnCH$_2$CH$_2$CH$_2$*C*H$_3$), 9.5 (Sn*C*H$_2$CH$_2$CH$_2$CH$_3$), −5.0, −5.4 (Si-(*C*H$_3$)$_2$).

To a solution of this lactol (2.6 g) in ethanol (20 mL) at 4°C was added sodium borohydride (210 mg, 5.55 mmol). The cooling bath was removed and, after stirring for 2 h, aqueous ammonium chloride solution was added followed by ethyl acetate (100 mL). The organic layer was washed with water, brine and dried. After evaporation of the volatiles the residue was purified by column chromatography on silica gel. Elution with 95:5 dichloromethane:methanol gave **20** (2.0 g, 77%) as a colourless oil. $[\alpha]_D^{21}$=+9 (*c* 2.8, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 and 7.25 (AA′XX′, $J_{app.}$=8 Hz, 4H, Ar), 5.9 (d, J_{1-2}=3 Hz, 1H, H-1), 4.85 (d, J_{5-6}=2.4 Hz, 1H, H-6), 4.5 (d, J_{1-2}=3 Hz, 1H, H-2), 4.3 (m, 1H, H-3), 4.05 (dd, *J*=8, 2.4 Hz, 1H, H-4), 3.85 (m, 1H, H-5), 3.3 (d, *J*=3 Hz, 1H, OH), 2.95 (d, *J*=7 Hz, 1H, OH), 1.5 (m, *J*=8 Hz, 2H, SnCH$_2$CH$_2$C*H*$_2$CH$_3$), 1.4 (s, 3H, C(C*H*$_3$)$_2$), 1.35 (m, *J*=8 Hz, 2H, SnCH$_2$C*H*$_2$), 1.3 (s, 3H, C(C*H*$_3$)$_2$), 1.05 (m, 2H, SnC*H*$_2$), 0.95 (s, 9H, Si-C*(C*H$_3$*)*$_3$), 0.9 (t, *J*=7.1 Hz, 3H, SnCH$_2$CH$_2$CH$_2$C*H*$_3$), 0.1, −0.15 (2*s, 2*3H, Si-(C*H*$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 141.1 (Ph$_{ipso\ \text{and}\ para}$), 136.2 (Ph$_{meta}$), 125.9 (Ph$_{ortho}$), 111.2 (*C*(CH$_3$)$_2$), 104.9 (C-1), 85.2, 79.3, 75.4, 74.6, 74.1 (C-2 to C-6), 29.1 (SnCH$_2$CH$_2$*C*H$_2$CH$_3$), 27.2 (SnCH$_2$*C*H$_2$), 26.5, 26.1 (C(*C*H$_3$)$_2$), 25.8 (Si-C(*C*H$_3$)$_3$), 18.1 (Si-*C*(CH$_3$)$_3$), 13.6 (SnCH$_2$CH$_2$CH$_2$*C*H$_3$), 9.5 (Sn*C*H$_2$), −4.6, −5.1 (Si-(*C*H$_3$)$_2$). Anal. calcd for $C_{33}H_{60}O_6SiSn$: C, 56.65; H, 8.64. Found: C, 56.72; H, 8.66.

4.12. 6-O-tert-*Butyldimethylsilyl-6*-C-*(4-iodophenyl)-1,2*-O-*isopropylidene*-L-glycero-α-D-gluco-*hexofuranose* ***21***

To a solution of **20** (500 mg, 0.15 mmol) in dichloromethane (10 mL) was added dropwise a 0.2 M solution of iodine chloride in dichloromethane until a persistent orange–brown colouration was observed. After evaporation of dichloromethane, the residue was purified by column chromatography on silica gel. Elution with 98:2 dichloromethane:methanol afforded **21** as a colourless syrup (365 mg, 95%). $[\alpha]_D^{21}$=+8.5 (*c* 0.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.6–7.05 (AA′XX′ syst., $J_{app.}$=8 Hz, 4H, Ar), 5.85 (d, J_{1-2}=4 Hz, 1H, H-1), 4.85 (d, J_{5-6}=1.5 Hz, 1H, H-6), 4.45 (d, J_{1-2}=4 Hz, 1H, H-2), 4.25 (m, 1H, H-3), 4.00 (dd, *J*=8, 3 Hz, 1H, H-4), 3.7 (m, 1H, H-5), 3.1 (M, 1H, OH), 2.75 (d, *J*=9 Hz, 1H, OH),

1.4 (s, 3H, C(CH_3)$_2$), 1.25 (s, 3H, C(CH_3)$_2$), 0.9 (s, 9H, Si-C(CH_3)$_3$), 0.1, −0.15 (2*s, 2*3H, Si-(CH_3)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.6 (Ph$_{ipso}$), 137.2 (Ph$_{meta}$), 128.2 (Ph$_{ortho}$), 111.3 (*C*(CH$_3$)$_2$), 105.0 (C-1), 93.0 (C-I), 85.0, 79.5, 75.0, 73.9, 73.0 (C-2 to C-6), 26.6, 26.0 (C(*C*H$_3$)$_2$), 25.8 (Si-C(*C*H$_3$)$_3$), 18.1 (Si-*C*(CH$_3$)$_3$), −4.6, −5.1 (Si-(*C*H$_3$)$_2$). Anal. calcd for $C_{21}H_{33}IO_6Si$: C, 47.02; H, 6.20; I, 23.65. Found: C, 46.83; H, 6.08.; I, 23.83.

*4.13. 6-*C*-(4-Iodophenyl)-*L*-glycero-α,β-*D*-gluco-hexopyranose **3***

Dichloromethane (4.5 mL) and water (0.5 mL) were added to **21** (210 mg, 0.39 mmol) and the biphasic mixture was stirred efficiently. Trifluoroacetic acid was added and when deprotection was complete (tlc), the volatiles were removed. Co-evaporation with toluene was performed and the residue dissolved in water (20 mL). The aqueous layer was washed with dichloromethane and evaporated. The residue was recrystallised from ethanol to afford **3** (97 mg, 65%) as white crystals. M.p.=158–159°C. $[\alpha]_D^{21}$=+29.5 (*c* 0.38, CH_3OH) 5 min→+32°C (24 h). ^{1}H NMR (250 MHz, D_2O) δ 7.55–7.05 (AA′XX′ system, $J_{app.}$=8 Hz, 4 H, Ar), 5.0 (d, J_{1-2}=3.2 Hz, H-1α), 4.9–4.75 (M, H-6α, H-6β), 4.25 (d, J_{1-2}=8 Hz, 1H, H-1β), 3.85–3.1 (m, other Hs). ^{13}C NMR (62.5 MHz, D_2O+(CD$_3$)$_2$C=O) δ 140.7, 140.4 (Ph$_{ipso}$ α+β), 136.8 (Ph$_{meta}$ α+β), 128.0, 127.7 (Ph$_{ortho}$ α+β), 95.7 (C-1β), 92.8, 92.4 (Ph$_{para}$ α+β), 91.6 (C-1α), 77.5, 75.3, 73.7, 73.2, 72.5, 71.0, 69.4, 69.2, 69.1, 68.9 (C-2α+β to C-6α+β). Anal. calcd for $C_{12}H_{15}IO_6$: C, 37.72; H, 3.96; I, 33.21. Found: C, 37.89; H, 3.93; I, 33.12.

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