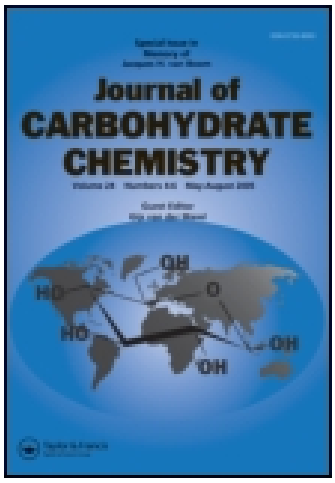

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SYNTHESIS AND TASTE PROPERTIES OF 4,1′, 6′-TRIHALODEOXY SUCROSE ANALOGUES

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SYNTHESIS AND TASTE PROPERTIES OF 4,1′, 6′-TRIHALODEOXY SUCROSE ANALOGUES[1,2]

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ABSTRACT

Treatment of 3,4-di-*O*-acetyl-1,6-di-*O*-trityl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-*O*-triflyl-α-D-galactopyranoside **(3)** with a halide source gave, via S_N2 displacement, the corresponding C-4 halogenated compounds which were subsequently transformed into the monohalogenated 4-deoxy-4-halogenosucrose derivatives, **10–12**. Trihalogenated sucrose derivatives, 4-bromo-1′,6′-dichloro **17**, 1′,6′-dibromo **18**, and 1′,6′-diiodosucrose **19**, were synthesized from **5**. Exploiting the distinct reactivity at C-1′ and C-6′ trifluoromethanesulfonates enabled the introduction of different halogens at these positions. This pathway led to the preparation of the 4-bromo-1′,6′-dihalodeoxysucrose derivatives, **24–27**. Preliminary taste properties of these mono- and tri-halogenated sucrose analogues were also investigated.

INTRODUCTION

The intense sweetness of halodeoxy analogues of sucrose, many of which are several thousand times sweeter than sucrose, had puzzled researchers since the discovery of the first of these in 1976.[3] Currently, the Shallenberger-Kier AH, B, γ model[4,5] is the most widely accepted model used to explain the initial mechanism of sweet-taste response. However, the location of the AH,B,γ glucophore for this group of sucrose compounds is still uncertain and intensely debated. [6–12]

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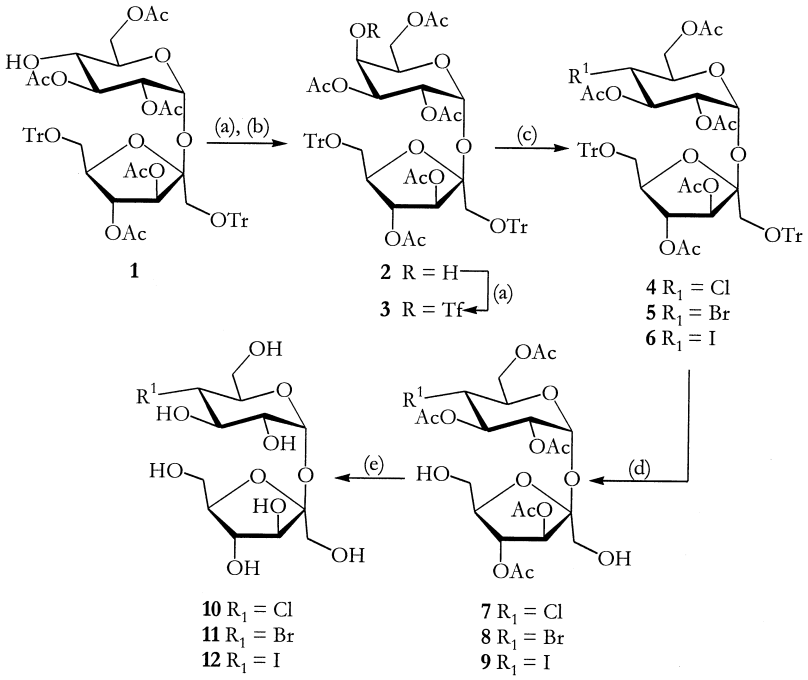
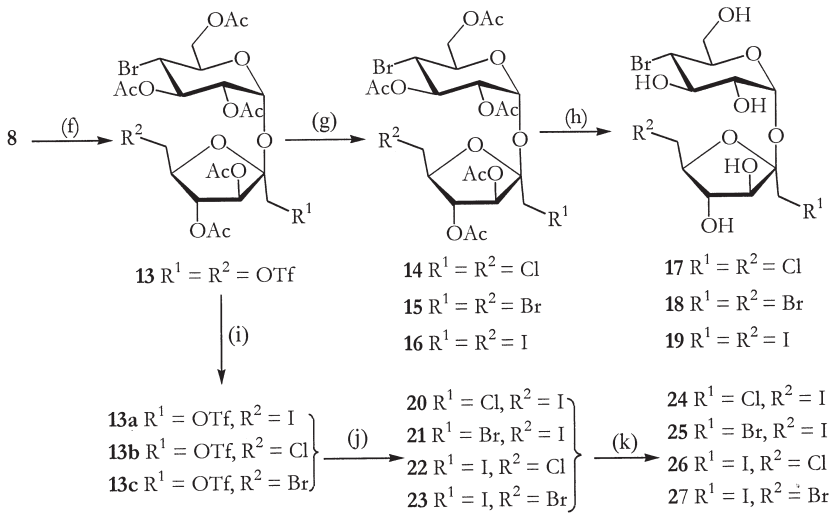
The high sweetness of these sucrose derivatives is clearly inexplicable in terms of either the glucopyranosyl or fructofuranosyl residues alone since the chlorodeoxy hexopyranoses or fructofuranoses are either very bitter or only moderately sweet. The most likely location of the AH, B entity is located at hydroxyl group of C-3′ and the oxygen of the C-2 hydroxyl.[12] The intense sweetness of the halodeoxy sucrose derivatives clearly shows the importance of a halogen substituent(s) in enhancing sweetness, and it has been widely assumed that one or more of these could be acting as the third γ-site in these halodeoxy analogues. In addition, the stereochemical disposition of the halogen substituent(s) is/are critical.[13] 1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside (sucralose)[14] and related 4-chloro-4-deoxy-galactosucrose derivatives have been reported but, apart from 4,6,1′,6′-tetrachloro-4,6,1′,6′-tetradeoxysucrose,[14] we are not aware of any reports of the synthesis and taste of the 4-chlorodeoxy sucrose derivatives. These derivatives are critical for determining the importance of a halogen substituent at C-4. We now report the synthesis as well as the taste properties of these compounds.

RESULTS AND DISCUSSION

A convenient starting intermediate for the synthesis of the mono- and tri-halogenated derivatives of sucrose is 3,4-di-*O*-acetyl-1,6-di-*O*-trityl-β-D-



Scheme 1. (a) Tf_2O, pyridine/CH_2Cl_2; (b) $NaNA_2$, DMF, rt, (c) **4:** LiCl, acetone, rt, **5:** LiBr, acetone, rt; **6:** KI, acetone, rt; (d) AcOH-CH_2Cl_2 (1:1), concd HCl, 0 °C; (e) NaOMe, MeOH, rt.



Scheme 2. (f) Tf_2O, pyridine/CH_2Cl_2; (g) **14:** LiCl, acetone, rt, **I5:** LiBr, acetone, rt; **16:** KI, acetone, rt; (h) NaOMe, MeOH, rt; (i) **13a:** KI, acetone, 0 °C; **13b:** LiCl, acetone, 0 °C; **13c:** LiBr, acetone, rt; (j) **20:** LiCl, acetone, rt, **21:** LiBr, acetone, rt; **22** and **23:** KI, acetone, rt; (k) NaOMe, MeOH, rt.

fructofuranosyl 2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (**1**)[15] (Scheme 1). This was conveniently converted into the *galacto* isomer **2** *via* the C-4 triflate followed by displacement with nitrite ion and *in situ* hydrolysis of the nitrite intermediate.[16] The *galacto* configuration was evident from the small $J_{3,4}$ coupling (2.7 Hz) in its ^{1}H NMR spectrum.

The C-4 halodeoxy sucrose derivatives were synthesized by displacement of the triflyl substituent of **3** using lithium chloride (→**4**), lithium bromide (→**5**) or potassium iodide (→**6**). The ^{1}H NMR spectra of compounds **4–6** all showed H-3 and H-4 as triplets with $J_{2,3} = J_{3,4} = \sim 10$ Hz, characteristic of the *gluco*-configuration. Further evidence was obtained from their ^{13}C NMR spectra. The resonances for C-4 in these compounds showed upfield shifts of between 13 to 43 ppm compared to that of **1**.

Detritylation of **4–6** in dichloromethane-acetic acid (1:1) in the presence of concd HCl at 0°C (→**7–9**, respectively), followed by conventional deacetylation gave the 4-halodeoxy derivatives **10–12**, respectively, in good yields (Scheme 1).

Compounds **7 –9** served as key intermediates in the synthesis of a variety of trihalogenated sucrose analogues. Thus, triflation of **8** gave the corresponding 1′,6′-disulfonate, which was easily converted to the 4-bromo-1′,6′-dichloro (**14**), 4,1′,6′-tribromo (**15**) and 4-bromo-1′,6′-diiodo (**16**) derivatives, respectively, on treatment with lithium chloride, lithium bromide and potassium iodide. Zemplén deacetylation of these compounds then gave the free trihalogenated derivatives **17 –19** (Scheme 2).

The triflate groups at C-1′ and C-6′ have been reported[17] to show considerable difference in reactivity. This enables the introduction of different halogen substituents at these two positions. The reaction of **13** with potassium iodide at 0°C gave the 4-bromo-6′-iodo-4,6′-dideoxy-1′-*O*-triflate (**13a**), which was then converted to the corresponding chloro derivative **20** by reaction with lithium chloride in acetone at room temperature. Compounds **21–23** were synthesized in a similar manner. These were then deacetylated to give **24–27** (Scheme 2).

Preliminary taste properties of the above C-4 monohalodeoxy derivatives showed all to possess little or no sweetness. The presence of only one halogen substituent in the sucrose is clearly not sufficient to produce an optimum hydrophilic-lipophilic[18,19] balance for interaction with the receptor. The trihalodeoxy derivatives, on the other hand, were very much sweeter but all were lower than that of sucralose. Thus, if the halo substituent at C-4 functions as a γ-site,[6,10] then it appears that the stereochemistry of the halogen substituent at this carbon is extremely important for optimum binding to the receptor. The results of these taste tests will be reported in detail elsewhere.

EXPERIMENTAL

General Methods. Melting points were measured with a Thermo Galen Hot Stage Microscope. Optical rotations were taken with a Perkin Elmer 241 polarimeter at 26°C. NMR spectra were recorded at 298 K in $CDCl_3$ (unless otherwise specified) on a Bruker DPX 300 spectrometer (300.13 MHz for ^1H and 75.47 MHz for ^{13}C). Mass spectra were recorded on either on a Finnigan MAT95XL-T instrument using electronic ionisation (EI) (70 eV) mode with an accelerating voltage of 5 KV and a resolution of 1000 (10% valley definition), or on a Finnigan TSQ 7000 (ion trap) spectrometer using electron spray ionisation (ESI) with a spray voltage of 4.5 KV. The elemental composition of ions was determined with a resolution of 7,000 (10% valley definition). Microanalyses were carried out using a Perkin Elmer 2400 Elemental Analyser. Flash chromatography was performed on Silica Gel 60 (0.63–0.200 nm, Merck) at 5–10 p.s.i. Thin-layer chromatography was run on glass plates precoated with silica gel $60F_{254}$ (Merck, Darmstadt, Germany); detection was effected by observation under short wavelength UV light (254 nm), then spraying with 10% sulphuric acid in ethanol and charring them on a hot plate.

3,4-Di-*O*-acetyl-1,6-di-*O*-trityl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-α-D-galactopyranoside (2). To a solution of **1** (15.3 g, 14.8 mmol) in dry CH_2Cl_2-pyridine (15:1, 64 mL) at −78°C, was added trifluoromethanesulfonic anhydride (4.9 mL, 29.9 mmol). The mixture was stirred for 15 min at −78°C, then for about 2 h at 0°C. The mixture was diluted with dichloromethane and the organic solution was washed successively with aq $KHSO_4$ (10%), satd $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated to give a syrupy product. This was dissolved in DMF (60 mL) and sodium nitrite (5.6 g) was added. The solution was then stirred at room temperature overnight, concentrated, and the residue diluted with

dichloromethane. The filtered solution was again concentrated. Flash chromatography (ethyl acetate/hexane, 1:2) gave **2**, (10.6 g, 69%), mp 103–105°C; $[\alpha]_D$ +70.5° (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.83–2.06 (s, 15H, 5 × CH_3), 3.20 (s, 2H, H-1′a, b), 3.33–3.52 (m, 2H, H-6′a, b), 4.02 (d, 1H, $J_{3,4}$ 2.7 Hz, H-4), 4.10–4.36 (m, 4H, H-5, 5′, 6′a, b), 5.05 (dd, 1H, $J_{2,3}$ 10.8 $J_{3,4}$ 2.7 Hz, H-3), 5.14 (dd, 1H, $J_{1,2}$ 3.7 $J_{2,3}$ 10.8 Hz, H-2), 5.37 (t, 1H, $J_{3',4'} = J_{4',5'}$ 7.3 Hz, H-4′), 5.56 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.84 (d, 1H, $J_{3',4'}$ 7.3 Hz, H-3′) and 7.21–7.51 (m, 30H, Ar-H). ^{13}C NMR δ 170.9, 170.0, 169.9, 169.8, 169.6 (*C*OCH_3), 143.6, 143.4 (*C*Ph_3), 129.0–127.0 (Ar-C), 104.1 (C-2′), 89.5 (C-1), 78.8 (C-5′), 75.7, 74.7 (C-3′, 4′), 69.9, 67.8, 67.2, 66.9 (C-2, 3, 4, 5), 63.8, 62.1 (C-1′,6, 6′) and 20.8, 20.7, 20.5, 20.4 (CO*C*H_3). EI-MS *m/z* (%): 1036 [M^+] (<0.5), 731 [M - $C_{12}H_{17}O_9$]$^+$ (<0.5), 289 [M - $C_{48}H_{43}O_8$]$^+$ (6), 244 (32), 243 (100), 242 (26), 228 (9), 215 (6), 43 (100).

Anal. Calcd for $C_{60}H_{60}O_{16}$: C, 69.49; H, 5.83. Found: C, 69.87; H, 5.46.

3,4-Di-*O*-acetyl-1,6-di-*O*-trityl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-glucopyranoside (4). A solution of **2** (1.66 g, 1.60 mmol) in CH_2Cl_2- pyridine (15:1, 32 mL) at −78°C was triflated as described above to give crude **3**.

Without purification and characterization, the crude triflate **3** (1.70 g, 1.45 mmol) in dry acetone (20 mL), was stirred with lithium chloride (0.2 g) at room temperature under argon for 4 h. When TLC (ether/hexane, 3:1) showed that all starting material had reacted, the solution was concentrated and dichloromethane added and filtered. The organic layer was washed with satd $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Flash chromatography (ether/hexane, 1:1) gave **4** as colourless crystals (1.25 g, 81%), mp 97–99°C; $[\alpha]_D$ +44.0° (*c* 1.17, $CHCl_3$); ^1H NMR δ 1.83–2.06 (s, 15H, 5 × CH_3), 3.20 (s, 2H, H-1′a, b), 3.31–3.45 (2 × dd, 2H, $J_{5',6'a}$ 5.6 $J_{5',6'b}$ 4.8 $J_{6'a,6'b}$ 10.0 Hz, H-6′a, b), 3.81 (t, 1H, $J_{3,4} = J_{4,5}$ 10.0 Hz, H-4), 4.15 (m, 1H, H-5′), 4.23 (m, 3H, H-5, 6a,b), 4.66 (dd, 1H, $J_{1,2}$ 4.0 $J_{2,3}$ 10.0 Hz, H-2), 5.33 (t, 1H, $J_{2,3} = J_{3,4}$ 10.0 Hz, H-3), 5.42 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.47 (d, 1H, $J_{3',4'} = J_{4',5'}$ 6.0 Hz, H-4′), 5.80 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′) and 7.20–7.47 (m, 30H, Ar-H). ^{13}C NMR δ 170.3, 169.8, 169.7, 169.5, 169.4 (*C*OCH_3), 143.6, 143.3 (*C*Ph_3), 128.7–127.1 (Ar-C), 104.7 (C-2′), 89.5 (C-1), 79.7 (C-5′), 76.0, 75.2 (C-3′, 4′), 71.4, 70.5, 70.2 (C-2, 3, 5), 63.7, 63.6, 62.4 (C-1′, 6, 6′), 55.1 (C-4) and 21.0, 20.8, 20.6, 20.5, 20.3 (CO*C*H_3). EI-MS *m/z* (%): 1054 [M^+] (<0.5), 731 [M - $C_{12}H_{16}ClO_8$]$^+$ (1.5), 307, 309 [M - $C_{48}H_{43}O_8$]$^+$ (3:1, 47), 244 (56), 243 (52), 242 (70), 241 (72), 215 (43), 43 (100).

Anal. Calcd for $C_{60}H_{59}ClO_{15}$: C, 68.22; H, 5.63; Cl, 3.31. Found: C, 67.98; H, 5.92; Cl, 3.67.

3,4-Di-*O*-acetyl-1,6-di-*O*-trityl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (5). A solution of crude **3** (11.3 g, 9.67 mmol) in dry acetone (60 mL) was treated with lithium bromide (2.5 g) as for **4** to give after flash chromatography (ether/hexane, 1:1), **5** as colourless crystals (9.0 g, 85%), mp 97–99°C; $[\alpha]_D$ +40.9° (*c* 1.12, $CHCl_3$); ^1H NMR δ 1.79–2.05 (s, 15H, 5 × CH_3), 3.21–3.43 (m, 4H, H-1′a, b and H-6′a, b), 3.85 (t, 1H, $J_{3,4} = J_{4,5}$ 10.8

Hz, H-4), 4.08–4.35 (m, 4H, H-5, 5′, 6a, b), 4.63 (dd, 1H, $J_{1,2}$ 4.0 $J_{2,3}$ 10.0 Hz, H-2), 5.38–5.49 (m, 3H, H-1, 3, 4′), 5.79 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′) and 7.19–7.46 (m, 30H, Ar-H). ^{13}C NMR δ 170.2, 169.8, 169.7, 169.5, 169.3 (*C*OCH$_3$), 143.6, 143.3 (*C*Ph$_3$), 129.5–126.5 (Ar-C), 104.6 (C-2′), 89.5 (C-1), 79.7 (C-5′), 76.0, 75.2 (C-3′, 4′), 71.3, 70.4, 70.2 (C-2, 3, 5), 63.7, 63.5, 63.1 (C-1′, 6, 6′), 46.1 (C-4) and 20.8, 20.6, 20.3 (CO*C*H$_3$). EI-MS *m/z* (%): 351, 353 [M - $C_{48}H_{43}O_8$]$^+$ (1:1, 8), 291, 293 (1:1, 12), 244 (83), 243 (88), 242 (79), 241 (80), 229 (26), 215 (19), 183 (54), 169 (21), 165, 167 (1:1, 79), 43 (100).

Anal. Calcd for $C_{60}H_{59}BrO_{15}$: C, 65.50; H, 5.41; Br, 7.62. Found: C, 67.89; H, 5.41; Br, 6.99.

3,4-Di-*O*-acetyl-1,6-di-*O*-trityl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-iodo-α-D-glucopyranoside (6). Treatment of crude **3** (1.51 g, 1.29 mmol) with potassium iodide (0.65 g) as described for **4** gave after flash chromatography (ether/hexane, 1:1), crystalline **6** (1.20g, 81%), mp 95–97°C; $[\alpha]_D$ +38.6° (*c* 1.01, $CHCl_3$); ^{1}H NMR δ 1.79–2.07 (s, 15H, 5 × CH_3), 3.21–3.44 (m, 4H, H-1′a, b and H-6′a, b), 3.92 (t, 1H, $J_{3,4} = J_{4,5}$ 11.0 Hz, H-4), 4.09–4.42 (m, 4H, H-5, 5′, 6a, b), 4.63 (dd, 1H, $J_{1,2}$ 4.0 $J_{2,3}$ 10.0 Hz, H-2), 5.41–5.50 (m, 3H, H-1, 3, 4′), 5.79 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′) and 7.19–7.46 (m, 30H, Ar-H). ^{13}C NMR δ 170.1, 169.7, 169.6, 169.4, 169.0 (*C*OCH$_3$), 143.6, 143.3 (*C*Ph$_3$), 129.0–126.9 (Ar-C), 104.6 (C-2′), 89.6 (C-1), 79.6 (C-5′), 76.0, 75.2 (C-3′, 4′), 72.2, 71.0, 70.5 (C-2, 3, 5), 64.6, 63.8, 63.4 (C-1′, 6, 6′), 24.8 (C-4) and 20.7, 20.6, 20.5, 20.3 (CO*C*H$_3$). EI-MS *m/z* (%): 399 [M - $C_{48}H_{43}O_8$]$^+$ (9), 279 (13), 244 (92), 243 (94), 242 (62), 241 (60), 165 (90), 43 (100); exact mass calcd for [$C_{12}H_{16}IO_7$]$^+$ 398.9941, found 398.99285.

Anal. Calcd for $C_{60}H_{59}IO_{15}$: C, 62.83; H, 5.18; I, 11.06. Found: C, 62.68; H, 5.61; I, 10.70.

3,4-Di-*O*-acetyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-chloro-4-deoxy-α-D-glucopyranoside (7). To a solution of **4** (1.20 g, 1.14 mmol) in ice-cold CH_2Cl_2-AcOH (1:1, 20 mL) was added dropwise, concentrated hydrochloric acid (0.15 mL). After all starting material had reacted (~2 h), the solution was neutralized with $NaHCO_3$, filtered and concentrated under reduced pressure. The crude product was subject to column chromatography (ethyl acetate/hexane, 1:1) to afford **7** as colourless crystals (0.52 g, 80%), mp 99–101°C; $[\alpha]_D$ +25.0° (*c* 1.12, $CHCl_3$); ^{1}H NMR δ 2.07–2.20 (s, 15H, 5 × CH_3), 3.55–3.84 (m, 4H, H-1′a, b and H-6′a, b), 3.91 (t, 1H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 4.06 (m, 1H, H-5′), 4.33–4.55 (m, 3H, H-5, 6a, b), 4.84 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.4 Hz, H-2), 5.43–5.55 (m, 3H, H-3, 3′, 4′)and 5.68 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1). ^{13}C NMR δ 170.6, 170.5, 170.2, 169.6 (*C*OCH$_3$), 104.8 (C-2′), 90.0 (C-1), 81.8 (C-5′), 76.7, 74.2 (C-3′, 4′), 71.0, 70.9, 70.7 (C-2, 3, 5), 64.1, 62.3, 61.5 (C-1′, 6, 6′), 54.9 (C-4) and 20.7, 20.6, 20.5 (CO*C*H$_3$). EI-MS *m/z* (%): 307, 309 [M - $C_{10}H_{15}O_8$]$^+$ (3:1, 24), 247 [M - $C_{12}H_{16}ClO_8$]$^+$ (51), 225, 207 (3:1, 24), 187 (41), 43 (100).

Anal. Calcd for $C_{22}H_{31}ClO_{15}$: C, 46.28; H, 5.47; Cl, 6.21. Found: C, 46.57; H, 5.63; Cl, 6.33. HRMS-ESI (positive mode): calcd for [M + Na]$^+$ 593.1294, 595.1219. Found: 593.1263, 595.1247 (3:1).

3,4-Di-*O*-acetyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (8). Treatment of **5** (5.97 g, 5.44 mmol) as for **7** gave **8** as colourless crystals (2.8 g, 84%), mp 77–80°C; $[\alpha]_D$ +26.9° (*c* 1.01, $CHCl_3$); ^{1}H NMR δ 2.06–2.21 (s, 15H, 5 × CH_3), 3.56–3.86 (m, 4H, H-1′a, b and H-6′a, b), 3.95 (t, 1H, $J_{3,4} = J_{4,5}$ 10.3 Hz, H-4), 4.05–4.57 (m, 4H, H-5, 5′, 6a, b), 4.82 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.3 Hz, H-2), 5.31–5.48 (m, 2H, H- 3′, 4′), 5.56 (t, 1H, $J_{2,3} = J_{3,4}$ 10.3 Hz, H-3) and 5.70 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1). ^{13}C NMR δ 170.6, 170.4, 170.2, 170.1, 169.4 (*C*OCH$_3$), 104.8 (C-2′), 90.1 (C-1), 81.8 (C-5′), 76.7, 74.3 (C-3′, 4′), 71.1, 70.7 (C-2, 3, 5), 64.1, 63.0, 61.5 (C-1′, 6, 6′), 45.8 (C-4) and 20.7, 20.6, 20.5, 19.6 (CO*C*H$_3$). EI-MS *m/z* (%): 351, 353 [M - $C_{10}H_{15}O_8$]$^+$ (1:1, 7), 291, 293 (1:1, 12), 247 [M - $C_{12}H_{16}BrO_8$]$^+$ (21), 231, 233 (1:1, 9), 189, 191 (1:1, 10), 187 (13), 169 (29), 43 (100); exact mass calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0059, found 351.0059, 353.0038 (1:1); calcd for [$C_{10}H_{15}O_7$]$^+$ 247.0817, found 247.0813.

Anal. Calcd for $C_{22}H_{31}BrO_{15}$: C, 42.94; H, 5.08; Br, 12.98. Found: C, 42.67; H, 5.19; Br, 13.32.

3,4-Di-*O*-acetyl-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-iodo-α-D-glucopyranoside (9). Treatment of **6** (1.29 g, 1.12 mmol) as for **7** gave **9** as colourless crystals (0.56 g, 75%), mp 93–95°C; $[\alpha]_D$ +15.5° (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 2.06–2.21 (s, 15H, 5 × CH_3), 3.56–3.86 (m, 4H, H-1′a, b and H-6′a, b), 3.95 (t, 1H, $J_{3,4} = J_{4,5}$ 10.3 Hz, H-4), 4.05–4.57 (m, 4H, H-5, 5′, 6a, b), 4.82 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.3 Hz, H-2), 5.31–5.48 (m, 2H, H- 3′, 4′), 5.56 (t, 1H, $J_{2,3} = J_{3,4}$ 10.3 Hz, H-3) and 5.70 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1). ^{13}C NMR δ 170.6, 170.4, 170.2, 170.1, 169.4 (*C*OCH$_3$), 104.8 (C-2′), 90.3 (C-1), 81.9 (C-5′), 76.8, 74.4 (C-3′, 4′), 72.0, 71.6, 71.0 (C-2, 3, 5), 64.5, 64.2, 61.5 (C-1′, 6, 6′), 24.3 (C-4) and 20.8, 20.7, 20.6 (CO*C*H$_3$). EI-MS *m/z* (%): 399 [M - $C_{12}H_{16}IO_8$]$^+$ (21), 289 (16), 279 (27), 247 [M -$C_{10}H_{15}O_8$]$^+$ (15), 211 (25), 187 (19), 169 (41), 45 (100); exact mass calcd for [$C_{12}H_{16}IO_7$]$^+$ 398.9941, found 398.9957; calcd for [$C_{10}H_{15}O_7$]$^+$ 247.0817, found 247.0812.

Anal. Calcd for $C_{22}H_{31}IO_{15}$: C, 39.89; H, 4.72; I, 19.16. Found: C, 40.14; H, 5.11; I, 19.22.

β-D-Fructofuranosyl 4-chloro-4-deoxy-α-D-glucopyranoside (10). A solution of **7** (0.23 g, 0.40 mmol) in dry methanol (10 mL) was adjusted to pH ~10 with methanolic sodium methoxide (0.5 M). It was stirred at room temperature for 4 h. It was then neutralized with Amberlite IR120 (H^+) ion exchange resin and concentrated. Flash chromatography (chloroform/methanol, 4:1) gave **10** as a colourless syrup (0.12 g, 82%), $[\alpha]_D$ +53.5° (*c* 0.52, H_2O); ^{1}H NMR (D_2O) δ 4.05 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.8 Hz, H-2), 4.66 (d, 1H, $J_{3',4'}$ 8.7 Hz, H-3′) and 5.91 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 106.4 (C-2′), 94.8 (C-1), 84.0 (C-5′), 79.1, 76.7 (C-3′, 4′), 75.3, 75.2, 74.2 (C-2, 3, 5), 65.0, 64.0, 63.0 (C-1′, 6, 6′) and 60.5 (C-4).

Anal. Calcd for $C_{12}H_{21}ClO_{10}$: C, 39.93; H, 5.87; Cl, 9.83. Found: C, 40.27; H, 5.69; Cl, 10.02. HRMS-ESI (positive mode): calcd for [M + Na]$^+$ 383.0721, 385.0691. Found: 383.0733, 385.0720 (3:1).

β-D-Fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (11). Treatment of **8** (0.24 g, 0.39 mmol) as for **10** gave **11** as a colourless syrup (0.14 g, 89%), $[\alpha]_D$ +34.7° (*c* 0.49, H_2O); ^{1}H NMR (D_2O) δ 4.11 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.7 Hz, H-2), 4.73 (d, 1H, $J_{3',4'}$ 8.7 Hz, H-3′) and 6.01 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 106.4 (C-2′), 94.8 (C-1), 84.0 (C-5′), 79.0, 76.6 (C-3′, 4′), 75.3, 75.2, 74.4 (C-2, 3, 5), 64.9, 63.9, 63.7 (C-1′, 6, 6′) and 52.9 (C-4).

Anal. Calcd for $C_{12}H_{21}BrO_{10}$: C, 35.57; H, 5.22; Br, 19.72. Found: C, 35.42; H, 5.69; Br, 19.52. HRMS-ESI (positive mode): calcd for $[M + Na]^+$ 427.0215, 429.0195. Found: 427.0232, 429.0219 (1:1).

β-D-Fructofuranoside 4-deoxy-4-iodo-α-D-glucopyranosyl (12). Deacetylation of **9** (0.23 g, 0.35 mmol) as for **10** gave **12** as a colourless syrup (0.13 g, 83%): $[\alpha]_D$ +39.1° (*c* 1.62, H_2O); ^{1}H NMR (D_2O) δ 4.06 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.1 Hz, H-2), 4.71 (d, 1H, $J_{3',4'}$ 8.7 Hz, H-3′) and 5.98 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 106.4 (C-2′), 95.0 (C-1), 84.0 (C-5′), 79.1, 76.6 (C-3′, 4′), 76.2, 75.9, 74.3 (C-2, 3, 5), 65.4, 65.0, 63.9 (C-1′, 6, 6′) and 33.5 (C-4).

Anal. Calcd for $C_{12}H_{21}IO_{10}$: C, 31.87; H, 4.68; I, 28.06. Found: C, 31.49; H, 4.69; I, 27.92. HRMS-ESI (positive mode): calcd for $[M + Na]^+$ 475.0077. Found: 475.0077.

3,4-Di-*O*-acetyl-1,6-dideoxy-1,6-dichloro-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (14). To a solution of **8** (0.79 g, 1.29 mmol) in dry CH_2Cl_2-pyridine (15:1, 32 mL) at −78°C, was added trifluoromethanesulfonic anhydride (0.86 mL, 5.24 mmol). The mixture was stirred at −78°C for 15 min and then at 0°C for 2 h. It was diluted with dichloromethane and the organic solution was washed successively with aq $KHSO_4$ (10%), satd $NaHCO_3$, and water. After drying (Na_2SO_4) and concentration, the crude product **13** (0.47 g, 0.53 mmol) was dissolved in dry acetone (20 mL) and lithium chloride (0.10 g) was added to the solution. The mixture was then allowed to stir overnight at room temperature, and concentrated. The residue was taken up in dichloromethane, filtered, and the organic layer was washed with satd $NaHCO_3$, water, dried and concentrated. Flash chromatography (ether/hexane, 3:1) gave **14** as colourless crystals (0.30 g, 86%): 50–52°C; $[\alpha]_D$ +22.9° (*c* 1.11, $CHCl_3$); ^{1}H NMR δ 2.07–2.19 (s, 15H, 5 × CH_3), 3.56–3.79 (m, 4H, H-1′a, b and H-6′a, b), 3.92 (t, 1H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 4.22–4.60 (m, 4H, H-5, 5′, 6a, b), 4.83 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.1 Hz, H-2), 5.38 (t, 1H, $J_{3',4'} = J_{4',5'}$ 5.9 Hz, H-4′), 5.54 (t, 1H, $J_{2,3} = J_{3,4}$ 10.1 Hz, H-3), 5.65 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1) and 5.67 (d, 1H, $J_{3',4'}$ 5.9 Hz, H-3′). ^{13}C NMR δ 170.4, 170.0, 169.7, 169.5, 169.4 (*C*OCH_3), 104.4 (C-2′), 90.3 (C-1), 81.4 (C-5′), 77.0, 75.9 (C-3′, 4′), 70.9, 70.8 (C-2, 3, 5), 63.3 (C-6), 45.8 (C-4), 44.8 (C-1′), 43.8 (C-6′) and 20.7, 20.6, 20.5, 20.4 (CO*C*H_3). EI-MS *m/z* (%): 351, 353 $[M - C_{10}H_{13}Cl_2O_6]^+$ (1:1, 39), 347 (43), 292, 294 (1:1, 52), 285 (46), 284, 286, 288 $[M - C_{12}H_{16}BrO_8]^+$ (9:6:1, 14), 283 (61), 249, 251 (15), 231, 233 (1:1, 59), 225 (55), 224, 226, 228 (16), 223 (69), 189, 191 (1:1, 50), 43 (100), exact mass calcd for ($C_{12}H_{16}BrO_7$) 351.0079, 353.0058, found 351.0076, 353.0054 (1:1); calcd for ($C_{10}H_{13}Cl_2O_5$) 283.0141, 285.0114, 287.0081, found 283.0136, 285.0114, 287.0077 (8:5:1)

Anal. Calcd for $C_{22}H_{29}BrCl_2O_{13}$: C, 40.51; H, 4.48; Br, 12.25; Cl, 10.87. Found: C, 40.32; H, 4.58; Br, 11.19.

3,4-Di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (15). Treatment of a solution of **13** (6.54 g, 7.45 mmol) in acetone (60 mL) with lithium bromide (3.0 g) as for **14** gave, after column chromatography, crystalline **15** (4.5 g, 82%), mp 72–73°C; $[\alpha]_D$ +24.6° (*c* 2.79, $CHCl_3$); ^{1}H NMR δ 2.07–2.21 (s, 15H, 5 × CH_3), 3.47–3.64 (m, 4H, H-1′a, b and H-6′a, b), 3.92 (t, 1H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 4.26–4.60 (m, 4H, H-5, 5′, 6a, b), 4.84 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.4 Hz, H-2), 5.35 (t, 1H, $J_{3',4'} = J_{4',5'}$ 6.0 Hz, H-4′), 5.56 (t, 1H, $J_{2,3} = J_{3,4}$ 10.4 Hz, H-3), 5.66 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1) and 5.71 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′). ^{13}C NMR δ 170.3, 170.0, 169.7, 169.4, 169.3 (*C*OCH_3), 103.9 (C-2′), 90.4 (C-1), 81.2 (C-5′), 77.2 (C-3′, 4′), 71.0, 70.8, 70.7, (C-2, 3, 5), 63.3 (C-6), 45.8 (C-4), 32.6 (C-1′), 31.2 (C-6′) and 20.7, 20.6, 20.4 (CO*C*H_3). EI-MS *m/z* (%): 371, 373, 375 [M - $C_{12}H_{16}O_8$]$^+$ (1:2:1, 39), 351, 353 [M - $C_{10}H_{13}Br_2O_6$]$^+$ (1:1, 44), 291, 293 (1:1, 50), 269, 271, 273 (1:2:1, 15), 249, 252 (1:1, 10), 231, 233 (1:1, 55), 189, 191 (1:1, 56), 169 (46), 43 (100); exact mass calcd for [$C_{10}H_{13}Br_2O_5$]$^+$ 370.9129, 372.9109, 374.9089, found 370.9128, 372.9111, 374.9090 (1:2:1); calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0058, found 351.0076, 353.0061 (1:1).

Anal. Calcd for $C_{22}H_{29}Br_3O_{13}$: C, 35.65; H, 3.94; Br, 32.34. Found: C, 35.42; H, 3.51; Br, 32.32.

3,4-Di-*O*-acetyl-1,6-dideoxy-1,6-diiodo-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (16). A solution of **13** (0.49 g, 0.56 mmol) in acetone (20 mL) was stirred with potassium iodide (0.40 g) for ~15 h at room temperature. The solvent was removed and the residue taken up in dichloromethane. The suspension was filtered and the organic solution was washed with aq $Na_2S_2O_3$ (10%), satd $NaHCO_3$, water, dried (Na_2SO_4) and concentrated. Flash chromatography (ether/hexane, 3:1) gave **16** as colourless crystals (0.38 g, 82%), mp 75–77°C; $[\alpha]_D$ +21.9° (*c* 1.81, $CHCl_3$); ^{1}H NMR δ 2.10–2.20 (s, 15H, 5 × CH_3), 3.41–3.43 (m, 4H, H-1′a, b and H-6′a, b), 3.93 (t, 1H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 4.21–4.59 (m, 4H, H-5, 5′, 6a, b), 4.84 (dd, 1H, $J_{1,2}$ 3.6 $J_{2,3}$ 10.4 Hz, H-2), 5.30 (t, 1H, $J_{3',4'} = J_{4',5'}$ 6.0 Hz, H-4′), 5.58 (t, 1H, $J_{2,3} = J_{3,4}$ 10.4 Hz, H-3), 5.64 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1) and 5.70 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′). ^{13}C NMR δ 170.4, 169.6, 169.4 (*C*OCH_3), 103.3 (C-2′), 90.7 (C-1), 80.9 (C-5′), 77.8, 77.6 (C-3′, 4′), 70.8, 70.6 (C-2, 3, 5), 63.3 (C-6), 45.8 (C-4), 20.9, 20.8, 20.6, 20.5 (CO*C*H_3), 6.3 (C-1′), and 3.4 (C-6′). EI-MS *m/z*(%): 467 [M - $C_{12}H_{16}BrO_8$]$^+$ (43), 351, 353 [M - $C_{10}H_{13}I_2O_6$]$^+$ (1:1, 44), 291, 293 (1:1, 65), 249, 251 (1:1, 14), 237 (51%), 231, 233 (1:1, 65), 189, 191 (1:1, 48), 169 (72), 43 (100); exact mass calcd for [$C_{10}H_{13}I_2O_5$]$^+$ 466.8853, found 466.8858; exact mass calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0058, found 351.0073, 353.0055 (1:1).

Anal. Calcd for $C_{22}H_{29}BrI_2O_{13}$: C, 31.64; H, 3.50; Br, 9.57, I, 30.39. Found: C, 31.54; H, 3.57; Br, 9.32, I, 29.99.

1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (17). Compound **14** (0.33 g, 0.51 mmol) was treated with sodium methoxide (0.566 M) as described for **10** to afford **17** as a colourless syrup (0.18 g, 80%): $[\alpha]_D$ +54.5° (*c* 1.44, H_2O); ^{1}H NMR (D_2O) δ 4.12 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.4 Hz, H-2), 4.91 (d, 1H, $J_{3',4'}$ 8.7 Hz, H-3′) and 6.01 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 106.1 (C-2′), 95.5 (C-1), 83.7 (C-5′), 79.0, 77.9 (C-3′, 4′), 75.6, 75.2, 74.4 (C-2, 3, 5), 63.9 (C-6), 53.0 (C-4), 47.5 (C-6′) and 46.0 (C-1′).

Anal. Calcd for $C_{12}H_{19}BrCl_2O_8$: C, 32.60; H, 4.32; Br, 18.07, Cl, 16.04. Found: C, 32.45; H, 4.73; Br, 18.29, Cl, 16.09. HRMS-ESI (positive mode): calcd for $[M + Na]^+$ 462.9539, 464.9519, 466.9489, 468.9459. Found: 462.9540, 464.9514, 466.9491, 468.9433 (10:16:7:1).

1,6-Dibromo-1,6-dideoxy-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (18). Compound **15** (0.16 g, 0.22 mmol) was deacetylated as for **10** to afford **18** as a colourless syrup (0.10 g, 87%), $[\alpha]_D$ +47.4° (c 1.90, H_2O); ^{1}H NMR (D_2O) δ 4.12 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.8 Hz, H-2), 4.17–4.31 (m, 4H), 4.35–4.77 (m, 7H), 4.97 (d, 1H, $J_{3',4'}$ 8.0 Hz, H-3′) and 6.01 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 103.6 (C-2′), 93.5 (C-1), 81.5 (C-5′), 77.8, 77.0 (C-3′,4′), 73.6, 73.2, 72.4 (C-2, 3, 5), 61.9 (C-6), 51.0 (C-4), 33.5, 32.4 (C-1′, 6′).

Anal. Calcd for $C_{12}H_{19}Br_3O_8$: C, 27.14; H, 3.61; Br, 45.14. Found: C, 26.84; H, 3.77; Br, 44.89. HRMS-ESI (positive mode): calcd for $[M + Na]^+$ 550.8519, 552.8507, 554.8487, 556.8467. Found: 550.8519, 552.8526, 554.8486, 556.8468 (1:3:3:1).

1,6-Dideoxy-1,6-diiodo-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (19). Compound **16** (0.43 g, 0.51 mmol) was deacetylated as for **10** to afford **19** as a colourless syrup (0.26 g, 81%), $[\alpha]_D$ +43.5° (*c* 0.83, H_2O); ^{1}H NMR (D_2O) δ 3.86–4.74 (m, 11H), 4.97 (d, 1H, $J_{3',4'}$ 8.4 Hz, H-3′) and 5.99 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1) ^{13}C NMR (D_2O) δ 102.9 (C-2′), 93.4 (C-1), 81.4 (C-5′), 79.1, 78.3 (C-3′,4′), 73.4, 73.0, 72.2 (C-2, 3, 5), 61.8 (C-6), 50.8 (C-4), 6.2, 5.6 (C-1′, 6′).

Anal. Calcd for $C_{12}H_{19}BrI_2O_8$: C, 23.06; H, 3.06; Br, 12.79, I, 40.61. Found: C, 23.34; H, 3.27; Br, 12.92, I, 40.99. HRMS-ESI (positive mode): calcd for $[M + Na]^+$ 646.8251, 648.8231. Found 646.8250, 648.8229 (1:1).

3,4-Di-*O*-acetyl-1-chloro-1,6-dideoxy-6-iodo-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (20). A solution of **13** (0.93 g, 1.06 mmol) in acetone (25 mL) was stirred with potassium iodide (0.35 g) for 30 min at 0°C. The mixture was concentrated and the residue was taken up in dichloromethane. Work-up in the usual manner gave a syrupy residue, which was dissolved (0.49 g, 0.57 mmol) in acetone (15 mL) and treated with lithium chloride (0.10 g) at room temperature overnight and worked up in the usual way. Flash chromatography (ethyl acetate/hexane, 1:2) gave **20** as colourless crystals (0.35 g, 63%), mp 49–51°C; $[\alpha]_D$ +24.8° (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 2.08–2.18 (s, 15H, 5 × CH_3), 3.39–3.77 (m, 4H, H-1′a, b and H-6′a, b), 3.93 (t, 1H, $J_{3,4} = J_{4,5}$ 10.3

Hz, H-4), 4.22–4.59 (m, 4H, H-5, 5′, 6a, b), 4.84 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.3 Hz, H-2), 5.31 (t, 1H, $J_{3',4'} = J_{4',5'}$ 6.0 Hz, H-4′), 5.56 (t, 1H, $J_{2,3} = J_{3,4}$ 10.3 Hz, H-3) and 5.65–5.69 (m, 2H, H-1, 3′) ^{13}C NMR δ 170.4, 170.0, 169.4 (*C*OCH$_3$), 104.3 (C-2′), 90.4 (C-1), 81.5 (C-5′), 77.3, 76.3 (C-3′, 4′), 71.0, 70.9, 70.8 (C-2, 3, 5), 63.3 (C-6), 45.8 (C-4), 44.7 (C-1′), 20.8, 20.7, 20.6, 20.5 (CO*C*H$_3$) and 3.3 (C-6′). EI-MS *m/z*(%): 375, 377 [M - $C_{12}H_{16}BrO_8$]$^+$ (3:1, 63), 351, 353 [($C_{10}H_{13}ClIO_6$]$^+$ (1:1, 64), 317 (75), 315 (63), 291, 293 (1:1, 71), 275 (45), 249, 251 (1:1, 24), 231, 233 (1:1, 74), 189, 191 (1:1, 78), 169 (74), 43 (100), exact mass calcd for [$C_{10}H_{13}ClIO_6$]$^+$ 374.9497, 376.9467, found 374.9489, 376.9471; calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0058, found 351.0078, 353.0061 (1:1).

Anal. Calcd for $C_{22}H_{29}BrClIO_{13}$: C, 35.53; H, 3.93; Br, 10.74, Cl, 4.77; I, 17.02. Found: C, 35.41; H, 3.73; Br, 11.12; Cl, 4.78; I, 16.87.

3,4-Di-*O*-acetyl-1-bromo-1,6-dideoxy-6-iodo-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (21). Treatment of **13** (0.46 g, 0.52 mmol) with potassium iodide (0.18 g) and then lithium bromide (0.12 g) as for **20** gave crystalline **21** (0.30 g, 67%), mp 58–61°C; [α]$_D$ +22.3° (*c* 1.27, $CHCl_3$); ^{1}H NMR δ 2.08–2.20 (s, 15H, 5 × CH_3), 3.37–3.63 (m, 4H, H-1′a, b and H-6′a, b), 3.93 (t, 1H, $J_{3,4} = J_{4,5}$ 10.3 Hz, H-4), 4.23–4.59 (m, 4H, H-5, 5′, 6a, b), 4.85 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.3 Hz, H-2), 5.30 (t, 1H, $J_{3',4'} = J_{4',5'}$ 6.0 Hz, H-4′), 5.56 (t, 1H, $J_{2,3} = J_{3,4}$ 10.3 Hz, H-3), 5.65 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1) and 5.72 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′). ^{13}C NMR δ 170.4, 170.1, 169.8, 169.5, 169.4 (*C*OCH$_3$), 103.8 (C-2′), 90.5 (C-1), 81.4 (C-5′), 77.6, 77.1 (C-3′, 4′), 71.0, 70.9, 70.8 (C-2, 3, 5), 63.3 (C-6), 45.8 (C-4), 32.6 (C-1′), 20.8, 20.7, 20.6, 20.5 (CO*C*H$_3$) and 3.3 (C-6′). EI-MS *m/z*(%): 419, 421 [M -$C_{10}H_{13}BrIO_6$]$^+$ (1:1, 68), 359, 361 (1:1, 75), 351, 353 [M - $C_{12}H_{16}BrO_8$]$^+$ (1:1, 55), 317, 319 (1:1, 40), 291, 293 (1:1, 63), 249, 251 (1:1, 21), 231, 233 (1:1, 71), 189, 191 (1:1, 58), 169 (60), 43 (100); exact mass calcd for [$C_{10}H_{13}BrIO_5$]$^+$ 418.8991, 420.8971, found 418.8987, 420.8968 (1:1); exact mass calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0058, found 351.0079, 353.0056 (1:1).

Anal. Calcd for $C_{22}H_{29}Br_2IO_{13}$: C, 33.53; H, 3.71; Br, 20.28; I, 16.10. Found: C, 33.44; H, 3.37; Br, 20.12, I, 16.37.

3,4-di-*O*-acetyl-6-chloro-1,6-dideoxy-1-iodo-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (22). Compound **13** (0.33 g, 0.37 mmol) in acetone (10 mL) was stirred with lithium chloride (0.05 g) at 0°C for 30 minutes. The mixture was concentrated, then taken up in dichloromethane, filtered, and the organic solution was washed with satd $NaHCO_3$, water, dried (Na_2SO_4) and concentrated. The residue (0.24 g, 0.31 mmol) was dissolved in acetone (10 mL) and stirred with potassium iodide (0.15 g) at room temperature overnight, and then worked-up in the usual method. Flash chromatography (ethyl acetate/hexane, 1:2) on the crude product gave **22** as colourless crystals (0.19 g, 60%), 50–52°C; [α]$_D$ +36.3° (*c* 0.52, $CHCl_3$); ^{1}H NMR δ 2.03–2.11 (s, 15H, 5 × CH_3), 3.40 (s, 2H, H-1′a, b), 3.70 (d, 2H, $J_{5',6'a,b}$ 6.3 Hz, H-6′a, b), 3.86 (t, 1H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 4.17 (q, 1H, $J_{4',5'}$ 5.9 $J_{5',6'a,b}$ 6.3 Hz, H-5′),

4.29 (dd, 1H, $J_{5,6a}$ 4.5 $J_{6a,6b}$ 12.2 Hz, H-6a), 4.40 (m, 1H, H-5), 4.49 (dd, 1H, $J_{5,6b}$ 1.7 $J_{6a,6b}$ 12.2 Hz, H-6b), 4.77 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.4 Hz, H-2), 5.29 (t, 1H, $J_{3',4'} = J_{4',5'}$ 5.9 Hz, H-4′), 5.50 (t, 1H, $J_{2,3} = J_{3,4}$ 10.4 Hz, H-3), 5.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1) and 5.63 (d, 1H, $J_{3',4'}$ 5.9 Hz, H-3′). ^{13}C NMR δ 170.3, 170.0, 169.6, 169.5, 169.2 (*C*OCH$_3$), 103.3 (C-2′), 90.4 (C-1), 80.9 (C-5′), 77.3, 76.1 (C-3′, 4′), 70.7, 70.6, 70.5 (C-2, 3, 5), 63.2 (C-6), 45.7 (C-4), 43.8 (C-6′), 20.6, 20.5, 20.4 (CO*C*H$_3$) and 6.4 (C-1′). EI-MS *m/z* (%): 375, 377 [M - $C_{12}H_{16}BrO_8$]$^+$ (3:1, 64), 351, 353 [M - $C_{10}H_{13}ClIO_6$]$^+$ (1:1, 65), 291, 293 (1:1, 66), 249, 251 (1:1, 24) 231, 233 (1:1, 74), 189, 191 (1:1, 78), 169 (100), 43 (90); exact mass calcd for [$C_{10}H_{13}ClIO_5$]$^+$ 374.9497, 376.9470, found 374.9489, 376.9471 (3:1); exact mass calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0058, found 351.0078, 353.0061 (1:1).

Anal. Calcd for $C_{22}H_{29}BrClIO_{13}$: C, 35.53; H, 3.93; Br, 10.74, Cl, 4.77; I, 17.02. Found: C, 34.41; H, 3.73; Br, 11.12, I, 16.87.

3,4-Di-*O*-acetyl-6-bromo-1,6-dideoxy-1-iodo-β-D-fructofuranosyl 2,3,6-tri-*O*-acetyl-4-bromo-4-deoxy-α-D-glucopyranoside (23). Treatment of **13** (0.45 g, 0.51 mmol) in acetone (15 mL) with lithium bromide (0.08 g) and then potassium iodide (0.22 g) gave **23** as colourless crystals (0.29 g, 67%), mp 50–52°C; $[\alpha]_D$ +30.9° (*c* 1.07, $CHCl_3$); ^{1}H NMR δ 2.03–2.10 (s, 15H, 5 × CH_3), 3.40 (s, 2H, H-1′a, b), 3.55 (d, 2H, $J_{5',6'a,b}$ 6.4 Hz, H-6′a, b), 3.87 (t, 1H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 4.21 (q, 1H, $J_{4',5'}$ 6.0 $J_{5',6'a,b}$ 6.4 Hz, H-5′), 4.29 (dd, 1H, $J_{5,6a}$ 4.5 $J_{6a,6b}$ 12.2 Hz, H-6a), 4.42 (m, 1H, H-5), 4.49 (dd, 1H, $J_{5,6b}$ 1.7 $J_{6a,6b}$ 12.2 Hz, H-6b), 4.77 (dd, 1H, $J_{1,2}$ 3.5 $J_{2,3}$ 10.4 Hz, H-2), 5.28 (t, 1H, $J_{3',4'} = J_{4',5'}$ 5.9 Hz, H-4′), 5.50 (t, 1H, $J_{2,3} = J_{3,4}$ 10.4 Hz, H-3), 5.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1) and 5.63 (d, 1H, $J_{3',4'}$ 6.0 Hz, H-3′). ^{13}C NMR δ 170.3, 170.1, 169.7, 169.5, 169.3 (*C*OCH$_3$), 103.4 (C-2′), 90.5 (C-1), 80.7 (C-5′), 77.7, 77.0 (C-3′, 4′), 70.9, 70.8, 70.7 (C-2, 3, 5), 63.3 (C-6), 45.8 (C-4), 31.3 (C-6′), 20.7, 20.6, 20.5 (CO*C*H$_3$) and 6.5 (C-1′). EI-MS *m/z* (%): 419, 421 [M - $C_{12}H_{16}BrO_8$]$^+$ (1:1, 55), 359, 361 (1:1, 67), 351, 353 [M - $C_{10}H_{13}BrIO_6$]$^+$ (1:1, 56), 317, 319 (1:1, 28), 291, 293 (1:1, 53), 249, 251 (1:1, 12), 231, 233 (1:1, 56), 189, 191 (1:1, 78), 169 (66), 43 (100); exact mass calcd for [$C_{10}H_{13}BrIO_6$]$^+$ 418.8991, 420.8971, found 418.9000, 420.8980 (1:1); exact mass calcd for [$C_{12}H_{16}BrO_7$]$^+$ 351.0079, 353.0058, found 351.0080, 353.0060 (1:1).

Anal. Calcd for $C_{22}H_{29}Br_2IO_{13}$: C, 33.53; H, 3.71; Br, 20.28; I, 16.10. Found: C, 33.86; H, 3.97; Br, 20.54; I, 15.92.

1-Chloro-1,6-dideoxy-6-iodo-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (24). Deacetylation of **20** (0.20 g, 0.27 mmol) as described for **10** afforded **24** as a colourless syrup (0.12 g, 84%), $[\alpha]_D$ +55.6° (*c* 1.34, H_2O); ^{1}H NMR (D_2O) δ 4.12 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.4 Hz, H-2), 4.91 (d, 1H, $J_{3',4'}$ 8.7 Hz, H-3′) and 6.02 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 106.0 (C-2′), 95.5 (C-1), 83.8 (C-5′), 80.3, 79.5 (C-3′, 4′), 75.6, 75.2, 74.4 (C-2, 3, 5), 64.0 (C-6), 53.0 (C-4), 45.9 (C-1′) and 8.1 (C-6′).

Anal. Calcd for $C_{12}H_{19}BrClIO_8$: C, 27.01; H, 3.59; Br, 14.98; Cl, 6.64; I, 23.79. Found: C, 36.97; H, 3.72; Br, 14.61; Cl, 6.33; I, 24.09. HRMS-ESI (positive

mode): calcd for [M + Na]$^+$ 554.8895, 556.8875, 558.8845. Found: 554.8906, 556.8868, 556.8856 (3.7:4.7:1).

1-Bromo-1,6-dideoxy-6-iodo-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (25). Deacetylation of **22** (0.29 g, 0.37 mmol) as above gave **25** as a colourless syrup (0.18 g, 85%), $[\alpha]_D$ +49.7° (*c* 1.53, H_2O); ^{1}H NMR (D_2O) δ 4.10 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.7 Hz, H-2), 4.96 (d, 1H, $J_{3',4'}$ 8.4 Hz, H-3′) and 6.00 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 103.3 (C-2′), 93.3 (C-1), 81.5 (C-5′), 78.1, 77.9 (C-3′, 4′), 73.4, 73.0, 72.2 (C-2, 3, 5), 61.8 (C-6), 50.7 (C-4), 32.1 (C-1′) and 5.6 (C-6′).

Anal. Calcd for $C_{12}H_{19}Br_2IO_8$: C, 24.94; H, 3.62; Br, 27.65; I, 21.96. Found: C, 27.39; H, 3.72; Br, 14.61; I, 24.09. HRMS-ESI (positive mode): calcd for [M + Na]$^+$ 598.8389, 600.8369, 602.8349. Found: 598.8391, 600.8372, 602.8354 (1:2:1).

6-Chloro-1,6-dideoxy-1-iodo-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (26). Deacetylation of **21** (0.21 g, 0.28 mmol) as above gave **26** as a colourless syrup (0.12 g, 80%), $[\alpha]_D$ +45.1° (*c* 0.92, H_2O); ^{1}H NMR (D_2O) δ 4.12 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.8 Hz, H-2), 4.99 (d, 1H, $J_{3',4'}$ 8.4 Hz, H-3′) and 6.00 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 105.3 (C-2′), 95.6 (C-1), 83.6 (C-5′), 80.9, 78.0 (C-3′, 4′), 75.6, 75.2, 74.5 (C-2, 3, 5), 63.9 (C-6), 53.0 (C-4), 47.4 (C-6′) and 8.5 (C-1′).

Anal. Calcd for $C_{12}H_{19}BrClIO_8$: C, 27.01; H, 3.59; Br, 14.98; Cl, 6.64; I, 23.79. Found: C, 26.87; H, 3.27; Br, 14.57; Cl, 7.01; I, 23.60. HRMS-ESI (positive mode): calcd for [M + Na]$^+$ 554.8895, 556.8875, 558.8845. Found: 554.8901, 556.8879, 558.8841 (3.8:4.9:1)

6-Bromo-1,6-dideoxy-1-iodo-β-D-fructofuranosyl 4-bromo-4-deoxy-α-D-glucopyranoside (27). Deacetylation of **23** (0.29 g, 0.37 mmol) as above gave **27** as a colourless syrup (0.17 g, 80%), $[\alpha]_D$ +41.7° (*c* 1.53, H_2O); ^{1}H NMR (D_2O) δ 4.13 (dd, 1H, $J_{1,2}$ 3.8 $J_{2,3}$ 9.6 Hz, H-2), 5.01 (d, 1H, $J_{3',4'}$ 8.4 Hz, H-3′) and 6.02 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1). ^{13}C NMR (D_2O) δ 105.4 (C-2′), 95.7 (C-1), 83.5 (C-5′), 81.2, 79.2 (C-3′, 4′), 75.6, 75.2, 74.4 (C-2, 3, 5), 64.0 (C-6), 53.1 (C-4), 35.6 (C-6′) and 8.6 (C-1′).

Anal. Calcd for $C_{12}H_{19}Br_2IO_8$: C, 24.94; H, 3.31; Br, 27.65; I, 21.96. Found: C, 25.35; H, 3.23; Br, 26.61; I, 21.70. HRMS-ESI (positive mode): calcd for [M + Na]$^+$ 598.8389, 600.8369, 602.8349. Found: 598.8386, 600.8389, 602.8352 (1:2:1).

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