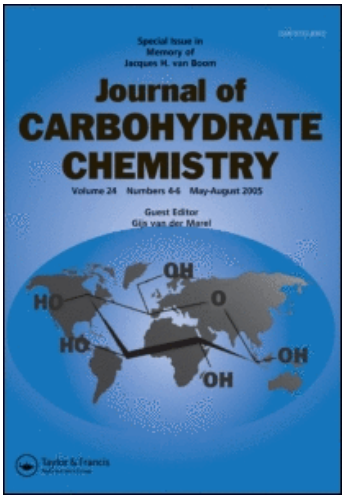

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Synthesis of Sucrose Analogues Modified at Position 4

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SYNTHESIS OF SUCROSE ANALOGUES MODIFIED AT POSITION 4

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ABSTRACT

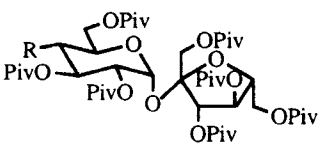
Upon reaction with sodium nitrite, the corresponding triflate **2** of known 1,3,4,6-tetra-*O*-pivaloyl-β-D-fructofuranosyl 2,3,6-tri-*O*-pivaloyl-α-D-glucopyranoside (**1**), afforded the *galacto*-sucrose **3** in high yield. This compound was converted into 4-deoxy-4-fluorosucrose derivative **4** by treatment with DAST. The reaction of triflate **6**, derived from **3**, with lithium azide afforded 4-azido-4-deoxysucrose derivative **7** which was transformed into 4-amino-4-deoxysucrose **9**. S_N2 Displacement of the triflate of compound **6** with thioacetate ion provided the expected 4-*S*-acetyl-4-thiosucrose derivative **10** in excellent yield. Deacetylation of **10** afforded a mixture of 4-thiosucrose **11** and 4-thiosucrose disulfide **12**.

INTRODUCTION

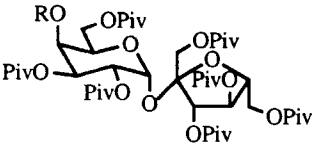
We have already described in a recent paper the preparation of sucrose analogues in which the 3-OH group was replaced by an amino or mercapto group.[1] This paper deals with chemical modifications of sucrose which lead to sucrose analogues in which heteroatoms are introduced at C-4. These new compounds are of particular interest for mapping the active site of enzymes such as dextransucrases and sucrosephosphorylase involved in the biotransformation or biodegradation of sucrose. These enzymes have high glucosyl specificity and only close analogues of sucrose can act as potential substrates or inhibitors.[2]

RESULTS AND DISCUSSION

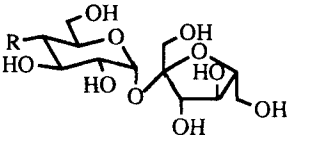
Selective pivaloylation of sucrose has been reported more than 10 years ago,[3] but has not been widely exploited for the synthesis of sucrose analogues modified at C-4. Using the above described procedure, 1',2,3,3',4',6,6'-heptapivalate **1** was obtained in lower yield than expected (44% *versus* 52%). Inversion at the 4-position of **1** was achieved in good yield (77%) by displacement of the triflate group of compound **2** by nitrite ion, followed by *in situ* hydrolysis of the intermediate.[4]



1 R = OH
2 R = OTf
4 R = F
7 R = N_3
10 R = SAc



3 R = H
6 R = Tf



5 R = F
8 R = N_3
9 R = NH_2
11 R = SH
12 R = S-S-Sucrose

Since the product **2** possesses a free 4-OH available for further transformations, this approach is much more versatile than the displacement reaction of tosyl or mesyl groups at the 4 position by benzoate ion, as used in the synthesis of *galacto*-sucrose.[3,5]

Evidence for the epimerisation was provided by examination of the ^1H NMR spectrum of compound **3**. The 3-H appeared as a doublet of doublets at δ 5.56 ($J_{3,2}$ = 10.4 Hz, $J_{3,4}$ = 3.1 Hz) and the 4-H as a doublet at δ 4.26 ($J_{4,5}$ = 3.1 Hz), spectral characteristics indicative of the *galacto*-configuration.

The replacement of a hydroxyl group by a fluoro group in sucrose would provide a sucrose analogue whose steric features and electronic structure are little altered from the parent compound. Several fluorosucrose derivatives have been already synthesized,[6] but 4-fluorosucrose has never been reported. We therefore considered this synthesis starting from **3** since access to 4-fluoroglucosides was provided by treatment of 4-OH-galactosides with diethylaminosulfur trifluoride (DAST).[7] When **3** was reacted with DAST in diglyme, the expected fluorosucrose **4** was obtained in 68% yield. Conventional deacylation afforded 4-deoxy-4-fluorosucrose (**5**) in 69% yield after preparative HPLC on a μ-Bondapak NH_2-column. The ^1H NMR spectrum of **4** was complicated by hydrogen-fluorine couplings, but a TOCSY experiment allowed the assignment of the H-4 signal, a doublet of triplets at δ 4.50 ($J_{4,F}$ = 43 Hz, $J_{4,3} \sim J_{4,5} \sim$ 9.0 Hz), which confirmed the *gluco*-configuration. The ^{13}C NMR spectrum of **4** shows

fluorine splitting of signals attributed to C-4 ($J_{4,F}$ = 180 Hz), C-5($J_{5,F}$ = 18.7 Hz), C-3 ($J_{3,F}$ = 24 Hz) and C-2 ($J_{2,F}$ = 7.5 Hz).

Triflate **6** constituted another ideal precursor for the preparation of analogues of sucrose modified at C-4. Compound **6** reacted with lithium azide in DMF to give the C-4 inverted 4-azido-4-deoxysucrose derivative **7**. Deacylation of **7**, followed by hydrogenation of the resulting compound **8** afforded 4-amino-4-deoxysucrose **9** in high yield over the three steps.

S_N2 displacement of the triflyl group of **6** by thioacetate ion lead to the expected 4-thiosucrose derivative **10** in good yield (75%). This result can be compared with the displacement of the triflate at C-3 of *allo*-sucrose by thioacetate and thiobenzoate ions, which occured with a concurrent elimination reaction, leading to an inseparable mixture of compounds.[1]

EXPERIMENTAL

General methods. NMR spectra were recorded using a Bruker AC300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C. Mass spectra were recorded using a Nermag R-1010C spectrometer. For spectra acquired in the FAB mode, a 0.1M HCl-glycerol matrix (1:4 v/v) was used. Optical rotations were measured at 25 °C using a Perkin Elmer 241 polarimeter. All solvents were evaporated under reduced pressure (40 °C). When CH_2Cl_2 solutions were extracted with water, the aqueous phases were re-extracted with CH_2Cl_2 and the collected phases were combined and dried on Na_2SO_4. For flash chromatography, Merck Silica gel 60, 230-400 mesh was used.

1,3,4,6-Tetra-*O*-pivaloyl-β-D-fructofuranosyl 2,3,6-Tri-*O*-pivaloyl-α-D-galactopyranoside (3). To an ice-cold solution of **1** (430 mg, 0.46 mmol) in CH_2Cl_2-pyridine (15:1, 9 mL) was added trifluoromethanesulfonic anhydride (0.15 mL). The mixture was stirred for 30 min at 0 °C, then for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 (100 mL) and the organic solution was washed successively with ice-cold aq KHSO4 (10%), ice-cold saturated aq $NaHCO_3$ and water. After drying and concentration, the crude **2** was used in the next step without further characterization and was dissolved in DMF (6.5 mL). $NaNO_2$ (150 mg) was added to this solution and after 12 h at room temperature the mixture was concentrated, the residue was diluted with CH_2Cl_2, the mixture filtered, and the filtrate again concentrated. Compound **3** was isolated by flash chromatography (ethyl acetate/light petroleum 1:10 v/v) as a yellow

syrup (334 mg, 77%): $[\alpha]_D^{25}$ +63° (*c* 0.55, chloroform); ^{1}H NMR (C_6D_6) δ 5.96 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.93 (d, 1H, $J_{3',4'}$ = 7.8 Hz, H-3'), 5.82 (dd 1H, $J_{4',5'}$ = 7.8 Hz, H-4'), 5.70 (dd, 1H, $J_{2,3}$ = 10.4 Hz, H-2), 5.56 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 4.75-4.30 (m, 8H), 4.26 (d, 1H, $J_{4,5}$ ~ 1.5 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 177.9-177.0 (CO), 102.5 (C-2'), 89.9 (C-1), 78.1, 74.6, 73.3, 69.7, 68.1, 67.0; 66.9 (C-2,3,3',4,4',5,5'), 64.4, 63.3, 61.2 (C-1', 6, 6'), 38.8-38.6 (C), 27.2-26.9 (CH_3); MS (DCI, NH_3 + isobutane): *m/z* 948 $[M+NH_4]^+$.

Anal. Calcd for $C_{47}H_{78}O_{18}$: C, 60.63; H, 8.44. Found: C, 60.41; H, 8.45.

1,3,4,6-Tetra-*O*-pivaloyl-β-D-fructofuranosyl 4-Deoxy-4-fluoro-2,3,6-tri-*O*-pivaloyl-α-D-glucopyranoside (4). To an ice-cold solution of **3** (556 mg, 0.59 mmol) in diglyme (5 mL) was slowly added DAST (0.2 mL). The mixture was stirred for 12 h at room temperature, then poured into saturated aq $NaHCO_3$ and extracted with chloroform. Flash chromatography (ethyl acetate/light petroleum 1:20 v/v) gave **4** as a syrup (370 mg, 68%). $[\alpha]_D^{25}$ +44° (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.5-5.6 (m, 3H, H-1, 3, 3'), 5.35 (dd, $J_{4',3'} = J_{4',5'}$ = 7.9 Hz, H-4'), 4.82 (dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 4.6-4.4 (m, 3H, $J_{4,F}$ = 43 Hz, H-4,5,6a), 4.35-4.25 (m, 3H, H-1'a, 1'b, 6b), 4.11 (m, 1H, H-5'), 4.03 (d, 1H, J_{ab} = 11.8 Hz, H-6'a), 3.85 (d, 1H, H-6'b) ; ^{13}C NMR ($CDCl_3$) δ 177.8-176.8 (CO) 102.7 (C-2'), 89.2 (C-1), 87.4 (C-4, $J_{F,4}$ = 186 Hz), 78.2, 74.5, 73.3 (C-3',4',5'), 69.6, 69.5, 69.3, 67.9, 67.6 (C-2,3,5), 64.2, 63.1, 61.0 (C-1',6,6'), 38.8-38.6 (C), 27.1-26.8 (CH_3); MS $(FAB)^+$: *m/z* 932 $[M+K]^+$.

Anal. Calcd for $C_{47}H_{77}FO_{17}$: C, 60.50; H, 8.32; F, 2.04. Found: C, 60.37; H, 8.50; F, 1.89.

β-D-Fructofuranosyl 4-Deoxy-4-fluoro-α-D-glucopyranoside (5). To a solution of **4** (368 mg, 0.39 mmol) in MeOH (50 mL) was added M methanolic MeONa (1.5 mL). The mixture was stirred for 12 h at room temperature, then neutralized with Amberlite IRN 77 (H^+) resin and, after filtration of the mixture, the solvent was evaporated. HPLC on a μ-Bondapak NH_2 column (10 μm, 19 x 50 mm, Waters Assoc.) using MeCN/water (80:20 v/v as eluent) afforded pure **5** (93 mg, 69%); $[\alpha]_D^{25}$ +51° (*c* 0.54, water); ^{13}C NMR (D_2O) δ 105.2 (C-2'), 93.4 (C-1), 90.3 (C-4, $J_{4,F}$ = 180 Hz), 82.9, 77.9, 75.6 (C-3', 4', 5'), 72.4 (C-5, $J_{5,F}$ = 19 Hz), 72.1 (C-2, $J_{2,F}$ = 7.5 Hz), 71.3 (C-3, $J_{3,F}$ = 24 Hz), 63.9, 62.9, 61.1 (C-1', 6, 6'); MS (DCI, NH_3 + isobutane): *m/z* 362 $[M+NH_4]^+$.

Anal. Calcd for $C_{12}H_{21}FO_{10}\cdot H_2O$: C, 39.78; H, 6.40; F, 5.24. Found: C, 39.28; H, 6.42; F, 4.68.

1,3,4,6-Tetra-*O*-pivaloyl-β-D-fructofuranosyl 4-Azido-4-deoxy-2,3, 6-tri-*O*-pivaloyl-α-D-glucopyranoside (7). To an ice-cold solution of **3**

(177 mg; 0.19 mmol) in CH_2Cl_2-pyridine (15:1, 4 mL) was added trifluoromethanesulfonic anhydride (95 µL). The mixture was stirred 30 min at 0 °C and then for 1 h at room temperature. The mixture was diluted with CH_2Cl_2, the organic solution was washed successively with ice-cold aq $KHSO_4$ (10%), ice-cold saturated $NaHCO_3$ and water and then concentrated. The crude triflate **6** (222 mg) was diluted with DMF (3 mL) and lithium azide (57 mg) was added. The mixture was stirred at room temperature for 12 h. The mixture was diluted with Et_2O and washed with water. Flash chromatography with EtOAc/light petroleum (1:15 v/v) gave **7** isolated as a colorless syrup (138 mg, 76%). $[\alpha]_D^{25}$ +71° (*c* 0.52, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 177.5-176.1 (CO), 102.6 (C-2'), 89.4 (C-1), 78.1, 74.4, 73.1, 70.1, 69.8, 68.9 (C-2, 3, 3', 4', 5, 5'), 64.1, 63.1, 62.1, 61.7 (C-1', 4, 6, 6'), 38.9-38.6 (C), 27.1-26.8 (CH_3); IR: 2115 cm^{-1} (N_3); MS (FAB)$^+$: *m/z* 994 $[M+K]^+$.

Anal. Calcd for $C_{47}H_{77}N_3O_{17}$: C, 59.04; H, 8.12; N, 4.39. Found: C, 58.72; H, 8.26; N, 4.28.

β-D-Fructofuranosyl 4-Azido-4-deoxy-α-D-glucopyranoside (8). To a solution of azide **7** (367 mg, 0.38 mmol) in MeOH (10 mL) was added methanolic M NaOMe (700 µL). The mixture was stirred for 3 h, then neutralized with Amberlite IRN 77 (H^+) resin and concentrated. HPLC on a µ-Bondapak NH_2-column as already described, afforded pure **8** (100 mg, 71%): $[\alpha]_D^{25}$ +115° (*c* 0.72, H_2O); ^{13}C NMR (D_2O) δ 105.1 (C-2'), 93.6 (C-1), 82.9, 77.9, 75.5, 73.2, 72.5, 72.4 (C-2, 3, 3', 4', 5, 5'), 63.8, 62.9, 61.9 (C-1', 6, 6'), 63.1 (C-4); MS (FAB)$^+$: *m/z* 390 $[M+Na]^+$, 368 $[M+H]^+$.

Anal. Calcd for $C_{12}H_{21}N_3O_{10}.H_2O$: C, 37.40; H, 6.02, N, 10.90. Found: C, 37.31; H, 5.72; N, 10.74.

β-D-Fructofuranosyl 4-Amino-4-deoxy-α-D-glucopyranoside (9). A solution of **8** (200 mg, 0.54 mmol) in EtOH (60 mL) was hydrogenated (H_2, 7 atm) in the presence of neutralized Raney nickel (2 mL in H_2O) for 20 h at room temperature. Removal of the catalyst by filtration and evaporation of the solvent gave homogeneous **9** (140 mg, 76%): $[\alpha]_D^{25}$ +57° (*c* 0.61, H_2O); ^1H NMR (D_2O) δ 5.31 (d, 1H, $J_{1,2}$ = 4.3 Hz, H-1), 4.10 (d, 1H, $J_{3',4'}$ = 8.7 Hz, H-3'), 3.90 (dd, 1H, $J_{4',5'}$ = 8.9 Hz, H-4'), 3.8-3.5 (m), 3.44 (dd, 1H, $J_{2,3}$ = 10.1 Hz, H-2), 2.65 (dd, $J_{4,3} = J_{4,5}$ = 9.4 Hz, H-4). ^{13}C NMR (D_2O) δ 105.1 (C-2'), 93.8 (C-1), 82.8, 78.1, 75.6, 7; 5, 5'), 63.8, 63.0, 62.1 (C-1', 6, 6') 53.7 (C-4); MS (DCI, NH_3 + isobutane): *m/z* 342 $[M+H]^+$.

Anal. Calcd for $C_{12}H_{23}NO_{10}·H_2O$: C, 40.11; H, 7.01; N, 3.90. Found: C, 39.50; H, 6.90; N, 3.45.

1,3,4,6-Tetra-*O*-pivaloyl-β-D-fructofuranosyl 4-*S*-acetyl-4-deoxy-4-thio-2,3,6-tri-*O*-pivaloyl-α-D-glucopyranoside (10). Starting from **3** (338

mg, 0.36 mmol), crude **6** (397 mg) was obtained as already described for the synthesis of **7**. This syrup diluted with DMF (5 mL) and then potassium thioacetate (150 mg) was added. The mixture was stirred at room temperature for 12 h. The mixture was diluted with Et_2O and washed with water. Flash chromatography (ethyl acetate/light petroleum 1:14 v/v) gave **10** as a colorless syrup (273 mg, 75%). Crystallization from hexane gave the analytical sample: mp 128-129 °C; $[\alpha]_D^{25}$ +61° (*c* 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.65 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.53 (d, 1H, $J_{3',4'}$ = 8.2 Hz, H-3'), 5.40 (dd, 1H, $J_{3,2}$ = 10.5 Hz, $J_{3,4}$ = 11.2 Hz, H-3), 5.32 (dd, 1H, $J_{4',5'}$ = 8.2 Hz, H-4'), 4.92 (dd, 1H, H-2), 4.45-4.25 (m, 5H), 4.11 (m, 1H, H-5 or 5'), 4.03 (d, 1H, $J_{a,b}$ = 12.0 Hz, H-6'a), 3.96 (dd, 1H, $J_{4,5}$ = 11.2 Hz, H-4), 3.88 (d, 1H, H-6'b); ^{13}C NMR ($CDCl_3$) δ 191.6 (SCO), 177.9-176.8 (CO), 102.7 (C-2'), 89.7 (C-1), 78.2, 74.5, 73.4, 71.3, 69.6, 68.0 (C-2, 3, 3', 4', 5, 5'), 64.2, 63.1, 62.2 (C-1', 6, 6'), 43.6 (C-4), 38.9-38.6 (C), 30.4 ($SCOCH_3$), 27.2, 26.9 (CH_3CO). MS(DCI): *m/z* 1006 $[M+ NH_4]^+$.

Anal. Calcd for $C_{49}H_{80}O_{18}S$: C, 59.50; H, 8.15; S, 3.24. Found: C, 59.29; H, 8.07; S, 3.13.

β-D-Fructofuranosyl 4-Deoxy-4-thio-α-D-glucopyranoside (11) and 4,4'-Dithiobis(β-D-fructofuranosyl-α-D-glucopyranoside) (12). To a solution of **10** (490 mg, 0.49 mmol) in MeOH (20 mL) was added M methanolic NaOMe (1.5 mL). The mixture was stirred for 12 h at room temperature, then neutralized with Amberlite IRN 77 (H^+) resin and concentrated. HPLC on a μ-Bondapak NH_2 column as described for compound **5** afforded pure **11** (39 mg, 22%) and pure **12** (73 mg, 41%). Treatment of disulfide **12** (10 mg, 0.014 mmol) in solution in water (100 μL) with dithioerythritol (4.2 mg, 0.026 mmol) afforded **11** quantitatively.

Compound **11**: ^1H NMR (D_2O) δ 5.35 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.10 (d, 1H, $J_{3,4}$ = 8.8 Hz, H-3'), 4.0-3.55 (m), 3.44 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 2.67 (dd, 1H, $J_{4,5}$ = 10.5 Hz, H-4); ^{13}C NMR (D_2O) δ 105.1 (C-2'), 93.8 (C-1), 82.8, 75.8, 75.6, 74.6, 73.6 (C-2,3,3',4',5,5'), 63.9, 62.9, 62.6 (C-1',6,6'), 43.2 (C-4); MS (FAB^+): *m/z* 359 $[M+ H]^+$, 381 $[M+ Na]^+$.

Compound **12**: $[\alpha]_D^{25}$ +24° (*c* 0.58, H_2O); ^1H NMR (D_2O) δ 5.35 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.09 (d, 1H, $J_{3',4'}$ = 8.3 Hz, H-3'), 4.05-3.60 (m), 3.51 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 2.70 (dd, 1H, $J_{4,3} = J_{4,5}$ = 10.6 Hz, H-4); ^{13}C NMR (D_2O) δ 105.2 (C-2'), 93.7 (C-1), 82.8, 78.1, 75.6, 74.0, 73.6, 70.3 (C-2,3,3',4',5,5'), 63.8, 62.9, 62.4 (C-1',6,6'), 54.5 (C-4). MS $(FAB)^+$: *m/z* 753 $[M+ K]^+$.

Anal. Calcd for $C_{24}H_{42}O_{20}S_2 \cdot 4H_2O$: C, 36.64; H, 6.40; S, 8.15. Found: C, 37.22; H, 6.14; S, 7.56.

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