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A synthesis of 6-deoxy-6-fluorosucrose suitable for PET applications

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ABSTRACT

A new route to 6-deoxy-6-fluorosucrose has been developed. The process proceeds in 8 linear steps in 25% overall yield from sucrose. The steps incorporating fluorine and subsequent deprotection are quite rapid, making the procedure useful in the context of ^{18}F-labeling for PET applications.

1. Introduction

In the context of our interest in examining sucrose transport in plants, we recently reported syntheses of both 6′-deoxy-6′-fluorosucrose[1] and 1′-deoxy-1′-fluorosucrose.[2] These compounds are currently being used in their 'hot' (^{18}F) form in imaging studies concerning sucrose transport in maize.[3] In order to get more complete information on the nature of sucrose transport, we require a sucrose derivative that is functionalized in the glucose half of the molecule. For this purpose, we chose 6-deoxy-6-fluorosucrose (6-F-sucrose).

A synthesis of 6-F-sucrose was reported by Eklund and Robyt a number of years ago.[4] The key step of the process involved treatment of the sucrose derivative **1** with diethylaminosulfur trifluoride (DAST) in dichloromethane at 30 °C for 22 h (Scheme 1). While the overall yield from sucrose was 11%, the length of time needed for fluorination was much too long for our needs. We thus set out to develop an improved synthesis.

2. Results and discussion

Our synthesis began with the selective protection of the 6 and 6′ hydroxy groups of sucrose (**3**) with *tert*-butyldiphenylsilyl (TBDPS) chloride[5] followed by perbenzoylation of the remaining hydroxyls to afford 6,6′-(bis)-*O*-*tert*-butyldiphenylsilyl-2,3,4,1′,3′,4′-hexa-*O*-benzoylsucrose (**4**) in an overall yield of 61% (Scheme 2). Selective cleavage of the 6′ silyl protecting group was accomplished with NCS (*N*-chlorosuccinimide) in DMSO[6] to afford **5** in 64% yield based on recovered starting material. This means of deprotecting the TBDPS group is apparently new, but we have not attempted to develop it in any way beyond this synthesis. The selectivity is likely due to steric effects, but a more definitive conclusion would require a detailed mechanistic investigation.

Compound **5** could be protected with benzoyl chloride to afford **6** essentially quantitatively. Deprotection of the TBDPS ether at position 6 was accomplished with bromine in methanol[7] and the resulting alcohol was converted to its corresponding triflate under standard conditions, giving **7** in 74% yield for the two steps.

The last two steps were key with respect to our ultimate goals for the project. Treatment of **7** with potassium fluoride in the presence of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (K222) gave the corresponding fluoride after 10 min in refluxing acetonitrile. Global hydrolysis with potassium carbonate in refluxing methanol afforded 6-deoxy-6-fluorosucrose (**8**) in only 5 min in a two-step yield of 89%. The product possessed spectral, chemical, and optical properties that matched those in the literature. The overall yield was 25% from sucrose over eight steps.

3. Conclusion

We have developed a synthetic protocol to 6-deoxy-6-fluorosucrose that is quite suitable for application to an ^{18}F-labeled species. We will apply the hot compound to studies of sucrose transport in maize. Results will be reported in due course.

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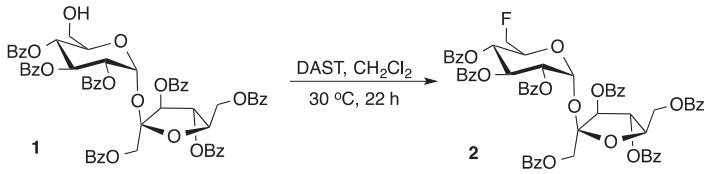
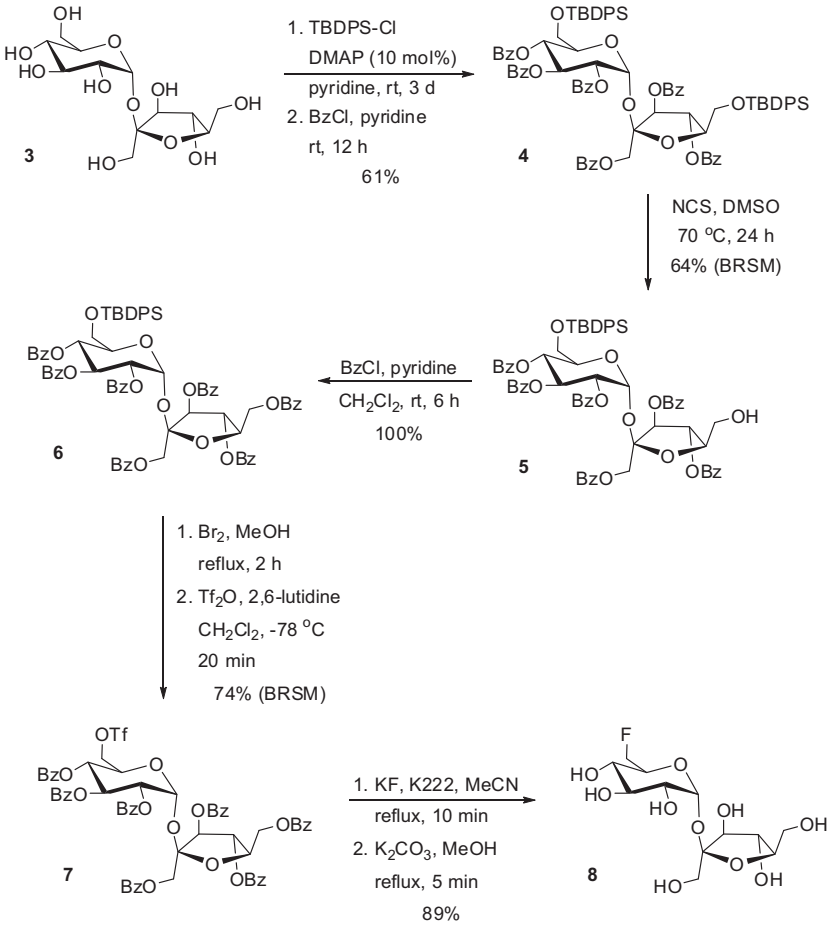


Scheme 1. Fluorination step in the Eklund–Robyt approach to 6-F-sucrose.



Scheme 2. Synthesis of 6-deoxy-6-fluorosucrose.

4. Experimental section

4.1. General methods

All reactions were carried out in oven-dried or flame-dried flasks under an atmosphere of argon. Acetonitrile, dichloromethane, and methanol were freshly distilled over calcium hydride. Analytical thin layer chromatography was performed on normal and reverse phase silica gel plates impregnated with a UV indicator. Flash chromatography was carried out using 230–400 mesh silica gel with HPLC grade solvents. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) spectrometer in $CDCl_3$ (TMS as internal standard) or D_2O. ^{19}F NMR was recorded on a Bruker ARX-250 (235.3 MHz for ^{19}F) spectrometer in D_2O ($CFCl_3$ as external standard). Melting points were determined with a Fisher–Johns melting point apparatus. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra were performed by the College of Science Major Instrumentation Center, Old Dominion University, with a Bruker 12 Tesla APEX–Qe FTICR-MS. Optical rotations were measured with a JASCD DIP-370 digital polarimeter.

4.2. 6,6′-(Bis)-*O*-*tert*-butyldiphenylsilylsucrose

To a solution of 20 g (58.4 mmol) of sucrose in 200 mL pyridine was added 200 mg of DMAP (10 mol %), followed by 36.3 mL (140.2 mmol, 2.2 equiv) of TBDPSCl. The solution was stirred at rt for 3 days, then concentrated under reduced pressure. One hundred mL of EtOAc was added, and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 1–2.5% MeOH in EtOAc, which resulted in 29 g (35.6 mmol, 61% yield) of product as a white solid. This was further purified by recrystallization from EtOAc, affording 14.85 g (18.1 mmol, 31% yield) of pure product as a white solid, mp 208–209 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.56 (m, 8H), 7.40–7.20 (m, 12H), 5.41 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 4.09 (t, $J_{3',4'}$ = 7.5 Hz, 1H, H-3′), 4.02 (t, $J_{3'4'} = J_{4',5'}$ = 7.5 Hz, 1H, H-4′), 3.91–3.73 (m, 5H, H-6′, H-5′, H-5, H-6α), 3.71–3.53 (m, 5H, H-3, H-1′, H-4, H-6β), 3.34

(dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 0.96 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 136.80, 136.77, 136.74, 136.71, 134.83, 134.51, 134.49, 134.48, 130.78, 130.76, 130.71, 130.69, 128.81, 128.78, 128.73, 128.68, 105.95 (C-2′), 93.42 (C-1), 83.95 (C-5′), 79.49 (C-3′), 77.06 (C-4′), 74.95 (C-3), 74.20 (C-5), 73.33 (C-2), 71.33 (C-4), 66.46 (C-6′), 64.44 (C-6), 64.36 (C-1′), 27.34, 20.09, 20.00; IR (cm^{-1}) 3395, 3305, 3187, 3070, 2976, 2928, 2884, 2855, 1588, 1472, 1461, 1426, 1389, 1363, 1339, 1322, 1300, 1266, 1188,1152, 1102, 1046, 1013, 989, 960, 937, 910, 880, 824, 800, 741, 701, 689; HRMS *m*/*z* calcd for $(C_{44}H_{58}O_{11}Si_2)Na^+$ 841.3410, found 841.3404; $[\alpha]_D^{20}$ = 25.0 (*c* 1.00, MeOH).

4.3. 6,6′-(Bis)-*O*-*tert*-butyldiphenylsilyl-2,3,4,1′,3′,4′-hexa-*O*-benzoylsucrose (4)

To a solution of 14.85 g (18.1 mmol) of 6,6′-(bis)-*O*-*tert*-butyldiphenylsilylsucrose in 90.7 mL of CH_2Cl_2 was added 17.6 mL of pyridine (218 mmol, 12 equiv). The solution was stirred vigorously at rt for 10 min, then 25.3 mL (218 mmol 12 equiv) of benzoyl chloride was added and the mixture was stirred at rt for 12 h. The solution was then washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. One hundred mL of hexanes was added, and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (5–20% EtOAc in hexanes), affording 26.1 g (18.1 mmol, 100% yield) of a white solid, mp 159–160 °C (recrystallized from MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 9 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 7.0 Hz, 2H), 7.60–7.12 (m, 34H), 7.06 (t, *J* = 7.7 Hz, 2H), 6.10 (t, $J_{2,3} = J_{3,4}$ = 10.0 Hz, 1H, H-3), 6.02 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1), 5.96 (t, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 1H, H-4), 5.95 (t, $J_{3',4'} = J_{4',5'}$ = 6.5 Hz, 1H, H-4′), 5.86 (d, $J_{3',4'}$ = 6.0 Hz, 1H, H-3′), 5.40 (dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.5 Hz, 1H, H-2), 4.63 (d, $J_{1'\alpha,1'\beta}$ = 12.0 Hz, 1H, H-1′α), 4.58 (d, $J_{1'\alpha,1'\beta}$ = 12.0 Hz, 1H, H-1′β), 4.31 (m, 2H, H-5, H-5′), 3.92 (dd, $J_{5',6'\alpha}$ = 5.5 Hz, $J_{6'\alpha,6'\beta}$ = 11.0 Hz, 1H, H-6′α), 3.88 (dd, $J_{5',6'\beta}$ = 5.5, $J_{6'\alpha,6'\beta}$ = 11.0 Hz, 1H, H-6′β), 3.52 (d, $J_{6\alpha,6\beta}$ = 12.0 Hz, 1H, H-6α), 3.43 (d, $J_{6\alpha,6\beta}$ = 12.0 Hz, 1H, H-6β),. 1.01 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.72, 165.65, 165.55, 165.44, 164.96, 164.69, 135.71, 135.54, 135.50, 135.47, 133.34, 133.21, 133.08, 133.02, 132.96, 132.93, 132.81, 132.77, 132.70, 130.07, 129.88, 129.81, 129.78, 129.72, 129.65, 129.55, 129.49, 129.43, 129.36, 129.18, 129.04, 128.87, 128.52, 128.37, 128.27, 128.22, 128.17, 127.67, 127.64, 127.60, 127.41, 103.93 (C-2′), 90.71 (C-1), 81.17 (C-5′), 77.75 (C-3′), 75.26 (C-4′), 71.40 (C-2, C-5), 70.96 (C-3), 68.10 (C-4), 65.31 (C-1′), 63.74 (C-6′), 61.00 (C-6), 26.68, 26.64, 19.11, 19.02; IR (cm^{-1}) 3071, 2959, 2931, 2858, 1966, 1733, 1602, 1585, 1492, 1472, 1451, 1428, 1390, 1362, 1315, 1265, 1177, 1106, 1070, 1026, 824, 802, 739, 708; HRMS *m*/*z* calcd for $(C_{86}H_{82}O_{17}Si_2)Na^+$ 1465.4983, found 1465.4968; $[\alpha]_D^{20}$ = 8.2 (*c* 1.00, $CHCl_3$).

4.4. 6-*O*-*tert*-Butyldiphenylsilyl-2,3,4,1′,3′,4′-hexa-*O*-benzoylsucrose (5)

To a solution of 26.1 g of **4** (18.1 mmol) in 181 mL of DMSO (0.1 M), 7.25 g (54.3 mmol, 3 equiv) of *N*-chlorosuccinimide (NCS) was added. The reaction was stirred at 70 °C for 24 h and monitored by TLC (small amount of solution was transferred to a test tube, diluted with EtOAc, and washed with water; analyzed by TLC with 30% EtOAc in hexanes, for **4** R_f = 0.5, for **5** R_f = 0.43.) To the reaction was added 200 mL of EtOAc at rt and the mixture was stirred for 1 min. The EtOAc layer was washed with water, brine, and dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) affording 12 g of a white solid (55%, 64% yield based on recovered starting material), along with 3.46 g of recovered starting material. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.5 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 3.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.54–7.32 (m, 13H), 7.32–7.22 (m, 7H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.14 (d, *J* = 6.5 Hz, 2H), 6.26–6.20 (m, 2H, H-1, H-3), 6.08 (t, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 1H, H-4), 6.05–5.99 (m, 2H, H-3′, H-4′), 5.41 (dd, $J_{2,1}$ = 3.0 Hz, $J_{2,3}$ = 10.5 Hz, 1H, H-2), 4.59 (s, 2H, H-1′), 4.38 (d, $J_{5,4}$ = 10.0 Hz, 1H, H-5), 4.25 (s, 1H, H-5′), 3.86–3.80 (m, 1H, H-6′α), 3.80–3.72 (m, 1H, H-6′β), 3.66 (s, 2H, H-6), 3.05 (t, $J_{6',OH}$ = 7.5 Hz, 1H, H-OH), 1.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.53, 165.62, 165.47, 165.43, 165.18, 164.59, 135.74, 135.47, 133.46, 133.34, 133.02, 133.00, 132.84, 132.76, 132.73, 129.99, 129.71, 129.67, 129.58, 129.42, 129.28, 129.27, 129.19, 128.81, 128.72, 128.49, 128.43, 128.40, 128.28, 128.19, 128.13, 127.58, 127.41, 103.77 (C-2′), 90.70 (C-1), 81.71 (C-5′), 77.80 (C-3′), 74.41 (C-4′), 71.97 (C-2), 71.84 (C-5), 70.33 (C-3), 67.75 (C-4), 65.60 (C-1′), 61.03 (C-6), 60.83 (C-6′), 26.64, 19.09; IR (cm^{-1}) 3512, 3071, 2931, 2858, 1733, 1602, 1585, 1492, 1472, 1451, 1428, 1390, 1315, 1267, 1178, 1160, 1095, 1070, 1026, 850, 824, 802, 739, 708, 686; HRMS *m*/*z* calcd for $(C_{70}H_{64}O_{17}Si)Na^+$ 1227.3805, found 1227.3797; $[\alpha]_D^{20}$ = 21.8 (*c* 1.00, $CHCl_3$).

4.5. 6-*O*-*tert*-Butyldiphenylsilyl-2,3,4,1′,3′,4′,6′-hepta-*O*-benzoylsucrose (6)

To a solution of 12.36 g (10.25 mmol) of **5** in 51.3 mL CH_2Cl_2 (0.2 M) was added 2.49 mL of pyridine (30.76 mmol, 3.0 equiv) followed by 3.57 mL of benzoyl chloride (30.76 mmol, 3.0 equiv) at room temperature. The reaction was stirred at rt for 6 h, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 20% EtOAc/hexane), which resulted in 13.4 g (10.25 mmol) of **6**, solid foam mp 87–90 °C; R_f = 0.48, 30% EtOAc/hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 2H), 8.01–7.94 (m, 6H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 7.0 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.54–7.44 (m, 4H), 7.43–7.22 (m, 19H), 7.17–7.10 (m, 4H), 6.26 (t, $J_{3,2} = J_{3,4}$ = 10.0 Hz, 1H, H-3), 6.22 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 6.09 (t, $J_{4,3} = J_{4,5}$ = 10.0 Hz, 1H, H-4), 6.01 (d, $J_{3',4'}$ = 6.5 Hz, 1H, H-3′), 5.95 (t, $J_{4',3'} = J_{4',5'}$ = 6.5 Hz, 1H, H-4′), 5.47 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.70–4.58 (m, 5H, H-1′(2H), H-5′, H-6′(2H)), 4.53 (d, $J_{5,4}$ = 10.0 Hz, 1H, H-5), 3.85 (d, $J_{6\alpha,6\beta}$ = 12.0 Hz, 1H, H-6α), 3.76 (d, $J_{6\beta,6\alpha}$ = 12.0 Hz, 1H, H-6β), 1.08 (s, 9H, H-*t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.79, 165.73, 165.66, 165.30, 165.27, 165.19, 164.67, 135.67, 135.45, 133.46, 133.35, 133.14, 133.00, 132.96, 132.89, 132.81, 130.03, 129.75, 129.74, 129.69, 129.60, 129.57, 129.52, 129.39, 129.36, 129.31, 129.18, 128.74, 128.64, 128.55, 128.36, 128.21, 128.13, 127.56, 127.43, 104.14 (C-2′), 90.77 (C-1), 78.72 (C-5′), 77.15 (C-3′), 75.85 (C-4′), 71.59 (C-5), 71.54 (C-2), 70.66 (C-3), 68.02 (C-4), 64.84 (C-1′), 64.12 (C-6′), 61.22 (C-6), 26.66, 19.11; IR (cm^{-1}) 3070, 2959, 2857, 1732, 1602, 1585, 1492, 1472, 1451, 1428, 1315, 1269, 1177, 1160, 1107, 1070, 1026, 823, 802, 739, 708, 686; HRMS *m*/*z* calcd for $(C_{77}H_{68}O_{18}Si)Na^+$ 1331. 4067, found 1331.4705; $[\alpha]_D^{20}$ = 16.2 (*c* 1.00, $CHCl_3$).

4.6. 2,3,4,1′,3′,4′,6′-hepta-*O*-benzoylsucrose (1)

To a 1 L flask charged with 400 mL MeOH was added 10.56 g (8.06 mmol) of **6**. The mixture was refluxed with vigorous stirring for 10 min. Then to the solution was added 2.08 mL (40.3 mmol, 5 equiv) of Br_2 and the mixture was refluxed for another 2 h, after which the reaction was quenched with a saturated sodium hydrosulfite solution. The solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc in hexanes, R_f = 0.27), which

resulted in 4.78 g of product (4.46 mmol, 55%, 86% yield based on recovered SM) as a viscous oil (3.79 g **6** was recovered), which foamed upon evacuation (mp 82–88 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 7.5 Hz, 2H), 8.03–7.96 (m, 6H), 7.86 (d, J = 7.5 Hz, 2H), 7.84 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.61–7.47 (m, 7H), 7.42–7.28 (m, 10H), 7.25 (t, J = 7.5 Hz, 2H), 7.11 (t, J = 7.5 Hz, 2H), 6.24 (t, $J_{3,2} = J_{3,4}$ = 10.0 Hz, 1H, H-3), 6.16 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 6.03 (d, $J_{3',4'}$ = 6.0 Hz, 1H, H-3′), 6.00 (t, $J_{4',3'} = J_{4',5'}$ = 6.0 Hz, 1H, H-4′), 5.53 (t, $J_{4,3} = J_{4,5}$ = 10.0 Hz, 1H, H-4), 5.41 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.83 (dd, $J_{6'\alpha,\ 5'}$ = 6.5 Hz, $J_{6'\alpha,6'\beta}$ = 12.0 Hz, 1H, H-6′α), 4.73 (dd, $J_{6'\beta,5'}$ = 5.0 Hz, $J_{6'\beta,6'\alpha}$ = 12.0 Hz, 1H, H-6′β), 4.65 (t, $J_{5',4'} = J_{5'6'}$ = 6.0 Hz, 1H, H-5′), 4.62 (d, $J_{1'\alpha,1'\beta}$ = 12.0 Hz, 1H, H-1′α), 4.56 (d, $J_{1'\alpha,1'\beta}$ = 12.0 Hz, 1H, H-1′β), 4.44 (d, $J_{5,4}$ = 10.0 Hz, 1H, H-5), 3.74 (dd, $J_{6\alpha,6\beta}$ = 12.0 Hz, $J_{6\alpha,5}$ = 8.0 Hz, 1H, H-6α), 3.67–3.61 (m, 1H, H-6β), 2.82 (t, $J_{OH,6}$ = 7.0 Hz, 1H, H-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.20, 165.95, 165.67, 165.48, 165.44, 165.39, 165.25, 133.59, 133.51, 133.21, 133.14, 133.07, 132.99, 130.17, 129.95, 129.85, 129.82, 129.72, 129.68, 129.51, 129.34, 129.18, 129.10, 128.82, 128.69, 128.61, 128.54, 128.45, 128.42, 128.31, 128.29, 128.27, 128.22, 128.18, 104.25 (C-2′), 90.57 (C-1), 78.96 (C-5′), 77.29 (C-4′), 76.20 (C-3′), 71.66 (C-5), 71.20 (C-2), 69.83 (C-3), 69.11 (C-4), 64.85 (C-1′), 64.35 (C-6′), 60.92 (C-6); IR (cm^{-1}) 3530, 3063, 2961, 1729, 1602, 1584, 1492, 1451, 1379, 1316, 1270, 1178, 1095, 1070, 1026, 854, 803, 708, 686; HRMS m/z calcd for $(C_{61}H_{50}O_{18})Na^+$ 1093.2889, found 1093.2878; $[\alpha]_D^{20}$ = 20.6 (c 1.00, $CHCl_3$).

4.7. 6-*O*-Trifluoromethanesulfonyl-2,3,4,1′,3′,4′,6′-hepta-*O*-benzoylsucrose (7)

To a solution of 3.93 g of **1** (3.67 mmol, 0.05 M) in 73 mL of dichloromethane (0.05 M) at −78 °C was added 765 μL of 2,6-lutidine (6.60 mmol, 1.8 equiv) and followed by 925 μL trifluoromethanesulfonic anhydride (5.50 mmol, 1.5 equiv). The reaction was stirred for 20 min, and then the solution was filtered through a short plug of silica gel, and washed with CH_2Cl_2. The resulting solution was concentrated under reduced pressure, and then purified by flash chromatography (SiO_2, 30% EtOAc/hexanes, R_f = 0.40), to afford 3.8 g of **7** as a white solid foam (86% yield); mp 87–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 7.5 Hz, 2H), 8.05–7.96 (m, 6H), 7.88–7.82 (m, 4H), 7.79 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.57–7.46 (m, 6H), 7.42–7.27 (m, 10H), 7.24 (t, J = 7.5 Hz, 2H), 7.11 (t, J = 7.5 Hz, 2H), 6.26–6.20 (m, 2H, H-1, H-3), 6.00–5.95 (m, 2H, H-3′, H-4′), 5.66 (t, $J_{4,3} = J_{4,5}$ = 10.0 Hz, 1H, H-4), 5.39 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.79–4.62 (m, 6H, H-5, H-1′, H-5′, H-6′), 4.53 (d, $J_{6\alpha,6\beta}$ = 11.0 Hz, 1H, H-6α), 4.46 (d, $J_{6\alpha,6\beta}$ = 11.0 Hz, 1H, H-6β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.98, 165.50, 165.41, 165.35, 165.31, 165.17, 164.90, 133.69, 133.61, 133.54, 133.23, 133.14, 133.09, 129.99, 129.84, 129.81, 129.79, 129.68, 129.60, 129.52, 129.30, 129.05, 128.81, 128.78, 128.70, 128.56, 128.50, 128.44, 128.32, 128.29, 128.20, 128.18, 118.43 (q, J = 317.92 Hz, 1C), 104.92 (C-2′), 90.82 (C-1), 79.21 (C-5′), 77.63 (C-3′), 76.25 (C-4′), 72.83 (C-6), 70.86 (C-2), 69.57 (C-3), 68.63 (C-5), 67.94 (C-4), 64.52 (C-1′), 63.83 (C-6′); IR (cm^{-1}) 3064, 2958, 1729, 1602, 1585, 1492, 1452, 1419, 1316, 1267, 1214, 1178, 1144, 1094, 1070, 1026, 983, 935, 845, 803, 707, 686; HRMS m/z calcd for $(C_{62}H_{49}F_3O_{20}S)Na^+$ 1225.2382, found 1225.2368; $[\alpha]_D^{20}$ = 19.6 (c 1.00, $CHCl_3$).

4.8. 6-Deoxy-6-fluoro-2,3,4,1′,3′,4′,6′-hepta-*O*-benzoylsucrose (2)

To a solution of 98.3 mg of **7** (0.0817 mmol) in 8.2 mL of CH_3CN at room temperature was added 7.1 mg (0.1226 mmol, 1.5 equiv) of KF, followed by 46 mg K222 (0.1226 mmol, 1.5 equiv). The solution was then refluxed for 10 min. Once the reaction was complete, the solvent was removed by reduced pressure, and the product was purified by flash chromatography (SiO_2, 30% EtOAc in hexanes, R_f = 0.38), to afford 78 mg of a semisolid (0.0727 mmol, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 7.5 Hz, 2H), 8.04–7.96 (m, 6H), 7.85 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.57–7.47 (m, 6H), 7.43–7.29 (m, 10H), 7.26 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.5 Hz, 2H), 6.24–6.17 (m, 2H, H-1, H-3), 6.05–5.96 (m, 2H, H-3′, H-4′), 5.64 (t, $J_{4,3} = J_{4,5}$ = 10.0 Hz, 1H, H-4), 5.40 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.76–4.70 (m, 2H, H-6′), 4.66–4.38 (m, 6H, H-5, H-6, H-1′, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.05, 165.63, 165.46, 165.42, 165.40, 165.29, 165.04, 133.60, 133.59, 133.44, 133.25, 133.10, 133.09, 133.03, 130.16, 129.87, 129.84, 129.73, 129.72, 129.58, 129.43, 129.20, 129.07, 128.88, 128.73, 128.66, 128.55, 128.47, 128.44, 128.33, 128.31, 128.29, 128.26, 128.21, 104.20 (C-2′), 90.39 (C-1), 80.89 (d, J = 173.75 Hz, 1C, C-6), 78.78 (C-5′), 77.39 (C-3′), 75.90 (C-4′), 71.07 (C-2), 70.02 (d, J = 18.75 Hz, 1C, C-5), 70.01 (C-3), 68.08 (d, J = 6.25 Hz, 1C, C-4), 65.03 (C-1′), 64.14 (C-6′); ^{19}F NMR (235 MHz, $CDCl_3$) δ −232.81 (dt, J = 23.5, 47.0 Hz, 1F); IR (cm^{-1}) 3063, 2961, 1728, 1602, 1584, 1492, 1451, 1377, 1315, 1265, 1177, 1095, 1070, 1026, 802, 707, 686; HRMS m/z calcd for $(C_{61}H_{49}FO_{17})Na^+$ 1095.2846, found 1095.2836; $[\alpha]_D^{20}$ = 22.6 (c 1.00, $CHCl_3$).

4.9. 6-Deoxy-6-fluorosucrose (8)

To a solution of 1.07 g (1.00 mmol) of **2** in 20 mL MeOH (0.05 M) was added 138 mg of K_2CO_3 (1.00 mmol, 1.0 equiv) at rt. The solution was then refluxed for 5 min. The reaction was monitored with TLC. The solvent was then removed under reduced pressure. The product was purified by flash chromatography (SiO_2, 10% H_2O in CH_3CN, R_f = 0.28), to afford 346 mg of **8** (1.00 mmol, 100% yield). The product was recrystallized from water, mp 181–182 °C; ^{1}H NMR (500 MHz, D_2O) δ 5.43 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 4.78 (s, 7H, OH), 4.69 (dd, $J_{6\alpha,6\beta}$ = 11.0 Hz, $J_{6\alpha,5}$ = 3.5 Hz, 1H, H-6α), 4.63 (d, $J_{6\alpha,6\beta}$ = 11.0 Hz, 1H, H-6β), 4.22 (d, $J_{3',4'}$ = 9.0 Hz, 1H, H-3′), 4.08–3.97 (m, 2H, H-5, H-4′), 3.92–3.86 (m, 1H, H-5′), 3.84–3.73 (m, 3H, H-3, H-6′), 3.67 (s, 2H, H-1′), 3.58 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 3.50 (t, $J_{4,3} = J_{4,5}$ = 10.0 Hz, 1H, H-4); ^{13}C NMR (125 MHz, D_2O) δ 106.43 (C-2′), 94.81 (C-1), 85.01 (d, J = 167.5 Hz, 1C, C-6), 84.07 (C-5′), 78.95 (C-3′), 76.73 (C-4′), 75.06 (C-3), 74.02 (d, J = 17.5 Hz, 1C, C-5), 73.63 (C-2), 71.12 (d, J = 7.5 Hz, 1C, C-4), 65.11 (C-6′), 63.95 (C-1′); ^{19}F NMR (235 MHz, D_2O) δ −234.83 (dt, J = 28.2, 47.0 Hz, 1F); IR (cm^{-1}) 3576, 3338, 3008, 2975, 2935, 1650, 1454, 1435, 1411, 1388, 1365, 1346, 1332, 1277, 1235, 1207, 1159, 1126, 1112, 1068, 1049, 1014, 988, 939, 921, 862, 735, 680; HRMS m/z calcd for $(C_{12}H_{21}FO_{10})Na^+$ 367.1011, found 367.1010; $[\alpha]_D^{20}$ = 60.0 (c 1.00, H_2O), $[\alpha]_D^{20}$ = 63.4 (c 1.00, MeOH).

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Supplementary data

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References

1. Gaddam, V.; Harmata, M. *Carbohydr. Res.* **2013**, *369*, 38–41.

2. Ying, W.; Gaddam, V.; Harmata, M. *Org. Lett.* **2013**, *15*, 2723–2725.
3. Rotsch, D.; Brossard, T.; Ying, W.; Gaddam, V.; Harmata, M.; Robertson, J. D.; Swyers, X.; Braun, D. M.; Jurisson, S. S., manuscript in preparation.
4. Eklund, S. H.; Robyt, J. F. *Carbohydr. Res.* **1988**, *177*, 253–258.
5. (a) Andrade, M. M.; Barros, M. T. *Tetrahedron* **2004**, *60*, 9235–9243; (b) Karl, H.; Lee, C. K.; Khan, R. *Carbohydr. Res.* **1982**, *101*, 31–38.
6. Batten, R. J.; Dixon, A. J.; Taylor, R. J. K.; Newton, R. F. *Synthesis* **1980**, 234–236.
7. Barros, M. T.; Maycock, C. D.; Thomassigny, C. *Synlett* **2001**, 1146–1148.