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Synthesis of 6′-deoxy-6′-fluorosucrose

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ABSTRACT

A facile synthesis of 6′-deoxy-6′-fluorosucrose has been developed. The title compound is available in six linear steps in 44% overall yield from commercially available sucrose. The synthesis involves rapid and convenient fluorination and deprotection conditions. This procedure would be very useful for the incorporation of radioactive [^{18}F].

1. Introduction

Fluorine-containing organic compounds have received much attention because of their pharmaceutical properties.[1] The synthesis of targets containing fluorine and the development of methods for the incorporation of fluorine into organic molecules have been and remain of intense interest.[2]

Sucrose is one of the main dietary sugars and is consequently the starting point for many biochemical processes. This disaccharide is also the primary vehicle by which carbon transport occurs in higher plants and serves as a signaling molecule, regulating gene expression and consequently plant development.[3]

Sucrose derivatives labeled in some fashion have been of interest for monitoring sucrose metabolism, especially transport in higher plants.[4] These derivatives can be isotopically or radiochemically labeled for easy detection.

Fluorinated sucrose derivatives and fluorinated carbohydrates in general have been of interest for some time. Fluorinated carbohydrates are important in understanding the role of carbohydrate metabolism in both plants and animals. Generally, a fluorinated carbohydrate is prepared by replacement of one of the hydroxyl groups on the carbohydrate with a fluorine atom. Such a substitution removes the possibility of that position serving as a hydrogen-bond donor, but not as a hydrogen bond acceptor. Hence, biochemical differences may exist in the behavior of the fluorinated vis-à-vis a native carbohydrate.

Perhaps the best known example of the utility of a fluorosugar is ^{18}F-2-deoxy-2-fluoroglucose, which finds important applications in positron emission tomography (PET) imaging in a clinical setting.[5]

Fluorinated sucrose derivatives offer opportunities for applications in potentially many areas of biology. The fluorinated derivatives that have been prepared include 3-deoxy-3-fluorosucrose,[6] 4-deoxy-4-fluorosucrose,[7] 6-deoxy-6-fluorosucrose,[8] 1′-deoxy-1′-fluorosucrose,[9] 4′-deoxy-4′-fluorosucrose,[10] 6′-deoxy-6′-fluorosucrose,[10] and 6,6′-dideoxy-6,6′-difluorosucrose.[9,11]

6′-Deoxy-6′-fluorosucrose[10] was prepared from the corresponding 6-deoxy-6-fluorofructose and UDP-glucose by using chemoenzymatic methods involving glucose isomerase and sucrose synthetase. To the best of our knowledge, there has been no purely synthetic approach reported for the synthesis of 6′-deoxy-6′-fluorosucrose. We set out to accomplish a synthesis of 6′-deoxy-6′-fluorosucrose that would be efficient, rapid, and amenable to application in the area of positron emission tomography (PET).[12] Our successful approach is detailed below.

2. Results and discussion

Our synthetic approach began with commercially available sucrose (**1**). The selective protection of the hydroxyl function of the 6′ position of **1** with *tert*-butyldiphenylsilyl (TBDPS),[13] was followed by the benzoylation of remaining hydroxyl groups with benzoyl chloride in pyridine, affording 6′-O-*tert*-butyldiphenylsilyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**2**) in 65% overall yield (Scheme 1). Selective deprotection of the silyl ether to yield the alcohol, 2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**3**), was achieved by using 1% bromine in methanol in good yield (86%) without migration of any of the benzoyl groups.[14] For the conversion of the alcohol to its corresponding triflate, we examined different bases including NEt_3, DIPEA, pyridine, and 2,6-lutidine along with

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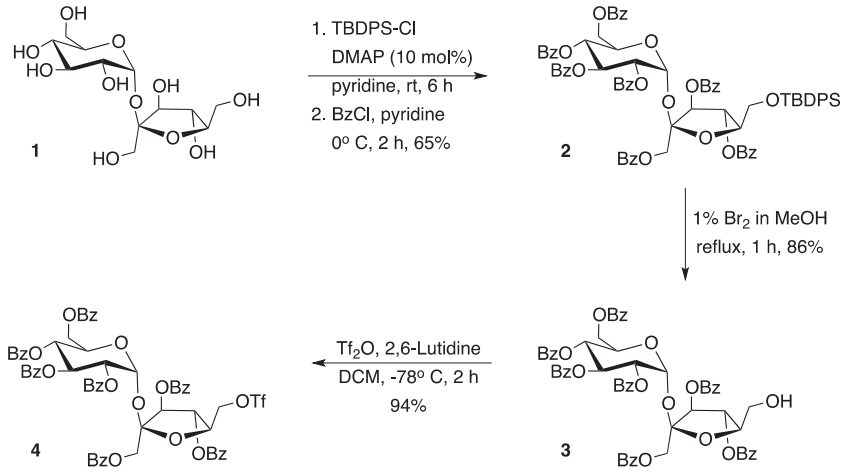


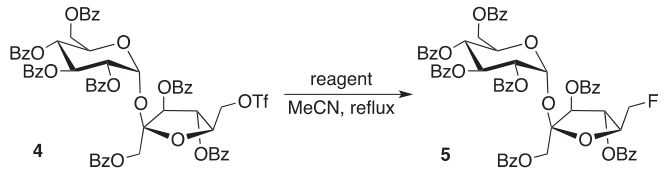
Scheme 1. Synthesis of sucrose-6′-triflate.

triflic anhydride under different reaction conditions. The latter base proved to be the most effective in terms of yield. Ultimately, we obtained the triflate, 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**4**), in excellent yield (94%) by treating the alcohol (**3**) with 1.5 equiv of Tf_2O and 2,6-lutidine at −78 °C in dichloromethane (DCM).

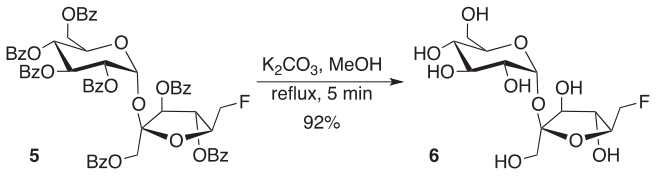
The typical procedure for the fluorination of aliphatic halides and triflates is by nucleophilic displacement with fluoride ion.[15] Alkali metal fluorides like KF and CsF are common reagents for this reaction. However, the poor solubility in organic solvents of KF in particular and low nucleophilicity of fluoride generally require harsh reaction conditions for successful substitution. To increase the nucleophilicity and solubility of metal fluorides, the use of crown ether derivatives such as 18-crown-6 and Kryptofix [2.2.2] has been reported.[16]

Table 1 demonstrates the nucleophilic fluorination of 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**4**) with various metal fluorides and tetrabutylammonium fluoride (TBAF) as fluoride sources in acetonitrile at reflux temperature. Fluorination of triflate (**4**) with KF in the presence of 18-crown-6 occurred after 12 h reflux in acetonitrile, affording 6′-deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**5**) (Table 1, entry 1) in 39% yield. The product (**5**) clearly showed the absence of OTf peak at 120 ppm in the ^{13}C NMR spectrum. In (**5**), C-6′ is shifted to downfield to 81.9 ppm, where it appears as a doublet due to splitting by the α-fluorine atom (J_{C-F} = 173.6 Hz). In addition, both C-4′ and C-5′ are coupled with F-6′, δ 75.2 (J_{C-F} = 6.3 Hz) and δ 80.3 (J_{C-F} = 20.0 Hz), respectively. The ^{19}F NMR spectrum shows a doublet of triplets that are centered at −229.1 ppm, due to signals arising from the fluorine atom on C-6′ coupled to the two hydrogen atoms on C-6′. The same reaction with the KF/Kryptofix [2.2.2] complex was finished within 10 min at reflux temperature giving (**5**) in excellent yield (92%, entry 3). We also carried out the fluorination with TBAF and obtained 70% yield of (**5**) after 30 min reflux (entry 2). Entry 4 of Table 1 shows that the use of silver fluoride (AgF) afforded the desired product in 92% yield in 10 min without any byproducts. We also examined the fluorination with CsF (entry 5), which proceeded smoothly and provided the corresponding fluoride product in 96% yield. The many options for successful fluorination are encouraging with respect to planned future applications of this procedure.

Table 1
Fluorination of triflate (**4**) with various fluoride sources in acetonitrile



Entry	Reagent	Time	Yield (%)
1	KF/18-crown-6	12 h	39
2	TBAF	30 min	70
3	KF/Kryptofix 222	10 min	92
4	AgF	10 min	92
5	CsF	10 min	96



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

In the final step of the process, deprotection of benzoyl groups on 6′-deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**5**) by using K_2CO_3 in methanol at reflux temperature for 5 min provided the 6′-deoxy-6′-fluorosucrose (**6**) in 92% yield (Scheme 2). The complete deprotection occurred within 5 min as evidenced by crude ^{19}F NMR, which showed a single peak at −227.1 ppm. The product was purified by reverse phase silica gel column chromatography with 1% H_2O/CH_3CN. The deprotection reaction was also successful using NaOMe/MeOH at reflux temperature for 5 min (80% yield). We have also developed a one-pot fluorination and deprotection reaction and obtained **6** in 84% overall yield.

3. Conclusion

In summary, we have described a novel and practical method for the synthesis of 6′-deoxy-6′-fluorosucrose (**6**). This procedure has the advantages of high yield and short reaction times for the final two steps. Applications of this fluorination method to [^{18}F] labeling for diagnostic agents are also under investigation.

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 ARX-250 (250 MHz), DRX-300 (300 MHz), and DRX-500 (500 MHz) spectrometer in $CDCl_3$ (TMS as internal standard) and D_2O. ^{19}F NMR was recorded on a Bruker ARX-250 (250 MHz) 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 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′-*O*-Trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (4)

To a stirred solution of 2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose **3** (1.5 g, 1.40 mmol) in dry CH_2Cl_2 (28 mL, 0.05 M) under argon was added 2,6-lutidine (0.244 mL, 2.1 mmol) dropwise at −78 °C. After 10 min, trifluoromethanesulfonic anhydride (0.354 mL, 2.1 mmol) was added dropwise and stirring was continued for another 2 h. The reaction mixture was quenched with water (1 mL) at −78 °C and slowly warmed to room temperature. Then the CH_2Cl_2 layer was washed with water (3 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash silica column chromatography with 20% EtOAc/hexanes to afford 1.58 g (94% yield) of the product, 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**4**) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.12 (2H, t, J = 7.0 Hz), 7.96–8.01 (6H, m), 7.88 (2H, t, J = 7.5 Hz), 7.83 (2H, t, J = 7.0 Hz), 7.79 (2H, t, J = 7.0 Hz), 7.55–7.60 (2H, m), 7.45–7.52 (7H, m), 7.25–7.44 (10H, m), 7.14 (2H, t, J = 8.0 Hz), 6.25 (1H, t, J = 10.5 Hz), 6.10 (1H, d, J = 3.5 Hz), 6.05 (1H, d, J = 5.5 Hz), 5.76 (1H, t, J = 10.0 Hz), 5.70 (1H, t, J = 6.5 Hz), 5.47 (1H, dd, J = 10.5, 3.5 Hz), 5.11 (1H, dd, J = 11.0, 7.0 Hz), 4.90 (1H, dd, J = 11.0, 2.5 Hz), 4.77–4.79 (1H, m), 4.66 (1H, d, J = 12.0 Hz), 4.54–4.59 (2H, m), 4.51–4.78 (1H, m), 4.43 (1H, dd, J = 12.5, 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.0, 165.7 (2C), 165.5, 165.4, 165.2, 165.1, 133.9, 133.7, 133.4, 133.3, 133.3, 133.1, 133.0, 130.1 (2C), 130.0 (2C), 129.9 (2C), 129.9 (2C), 129.8 (4C), 129.6 (2C), 129.5, 129.1, 129.0, 128.8, 128.7 (2C), 128.6 (2C), 128.5, 128.4, 128.3 (2C), 128.3 (2C), 128.3 (4C), 128.2 (2C), 128.1, 118.6 (q, J = 319.9 Hz) (CF_3), 104.7, 91.1, 79.1, 76.6, 75.8, 75.4, 71.1, 69.9, 69.2, 69.1, 64.0, 62.5; HRMS m/z Calcd for ($C_{62}H_{49}F_3O_{20}S$) Na^+ is 1225.2382, found 1225.2390.

4.3. 6′-Deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (5)

A solution of 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose **4** (50 mg, 0.0415 mmol), Kryptofix 222 (15.6 mg, 0.0415 mmol), and KF (2.4 mg, 0.0415 mmol) in MeCN (0.83 mL, 0.05 M) was vigorously refluxed under argon for 10 min. The reaction was cooled and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (5 mL), washed with water (3 × 5 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash silica column chromatography with 20% EtOAc/hexanes to give 41 mg (92% yield) of the product, 6′-deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15 (2H, d, J = 7.5 Hz)), 7.97–8.04 (6H, m), 7.79–7.85 (6H, m), 7.58 (1H, t, J = 10.0 Hz), 7.32–7.57 (14H, m), 7.25–7.30 (4H, m), 7.12 (2H, t, J = 8.0 Hz), 6.21 (1H, t, J = 10.5 Hz), 6.12 (1H, d, J = 3.5 Hz), 6.02 (1H, d, J = 6.0 Hz), 5.90 (1H, t, J = 6.0 Hz), 5.76 (1H, t, J = 10.0 Hz), 5.42 (1H, dd, J = 10.5, 3.5 Hz), 4.58–4.86 (5H, m), 4.33–4.44 (3H, m); ^{13}C NMR (125 M Hz, $CDCl_3$) δ: 166.1, 165.8, 165.5, 165.5, 165.4, 165.3, 165.1, 133.7, 133.6, 133.3, 133.2, 133.1, 133.0, 133.0, 130.2 (2C), 129.9 (4C), 129.9 (2C), 129.8 (2C), 129.7 (2C), 129.7, 129.6 (2C), 129.2 (2C), 128.9, 128.8, 128.8 (2C), 128.6, 128.6 (3C), 128.3 (4C), 128.3 (2C), 128.3 (2C), 128.2 (2C), 104.6, 91.1, 81.9 (d, J = 173.6 Hz, C-6′), 80.3 (d, J = 20.0 Hz, C-5′), 75.2 (d, J = 6.3 Hz, C-4′), 71.5, 70.1, 69.1, 69.0 (2C), 64.7, 62.4; ^{19}F NMR (235 MHz, $CDCl_3$) δ: −229.1 (dt, J = 23.5, 47.0 Hz); HRMS m/z Calcd for ($C_{61}H_{49}FO_{17}$) Na^+ is 1095.2845, found 1095.2819.

4.4. Fluorination procedure with KF/18-crown-6

A solution of 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose **4** (50 mg, 0.0415 mmol), 18-crown-6 (219 mg, 0.083 mmol), and KF (4.8 mg, 0.083 mmol) in MeCN (0.83 mL, 0.05 M) was vigorously refluxed under argon for 12 h. The reaction was cooled and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (5 mL), washed with water (3 × 5 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash silica column chromatography with 20% EtOAc/hexanes to afford 17 mg (39% yield) of the product, 6′-deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**5**) as a white solid.

4.5. Fluorination procedure with TBAF, AgF, and CsF

A solution of 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose **4** (1.0 equiv) and fluorinating agent (1.0 equiv) in MeCN (0.05 M) was vigorously refluxed, under argon for the appropriate time. The reaction was cooled and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (5 mL), washed with water (3 × 5 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash silica column chromatography with 20% EtOAc/hexanes to afford the product, 6′-deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose (**5**) as a white solid.

4.6. 6′-Deoxy-6′-fluorosucrose (6)

A solution of 6′-deoxy-6′-fluoro-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose **5** (100 mg, 0.0931 mmol) and K_2CO_3 (13.0 mg, 0.0931 mmol) in methanol (1.8 mL, 0.05 M) was refluxed for 5 min. The solvent was removed and the crude product was purified by reverse phase silica column chromatography with 1% H_2O/CH_3CN to give 29 mg (92% yield) of the product, 6′-deoxy-6′-fluorosucrose (**6**). ^{1}H NMR (500 MHz, D_2O) δ: 5.39 (1H, d, J = 4.0 Hz)), 4.71–4.77 (1H, m), 4.62–4.69 (1H, m), 4.25 (1H, d, J = 8.5 Hz), 4.16 (1H, t, J = 8.5 Hz), 4.03–4.10 (1H, m), 3.83–3.87 (1H, m) 3.78 (1H, dd, J = 4.5, 10.0 Hz), 3.75 (1H, d, J = 9.5 Hz), 3.72 (2H, s), 3.55 (1H, dd, J = 4.0, 10.0 Hz), 3.45 (1H, t, J = 9.5 Hz); ^{13}C NMR (125 MHz, D_2O) δ: 103.8, 92.2, 83.2 (d, J = 166.3 Hz, C-6′), 79.3 (d, J = 18.8 Hz, C-5′), 76.1 (d, J = 2.5 Hz, C-3′), 72.5 (d, J = 8.7 Hz, C-4′), 72.4, 72.3, 71.0, 69.2, 60.9, 60.8; ^{19}F NMR (235 MHz, D_2O) δ: −227.1 (dt, J = 21.1, 47.0 Hz). HRMS m/z Calcd for ($C_{12}H_{21}FO_{10}$) Na^+ is 367.1011, found 367.1008.

4.7. One pot synthesis of 6′-deoxy-6′-fluorosucrose (6)

A solution of 6′-*O*-trifluoromethanesulfonyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzoylsucrose **4** (50 mg, 0.0415 mmol), Kryptofix 222

(15.6 mg, 0.0415 mmol), and KF (2.4 mg, 0.0415 mmol) in MeCN (0.83 mL, 0.05 M) was vigorously refluxed, under argon for 10 min. After cooling, K_2CO_3 (5.7 mg, 0.0415 mmol) and methanol (0.2 mL) were added and reflux was continued for another 5 min. The solvent was removed and the crude product was purified by reverse phase silica column chromatography with 1% H_2O/CH_3CN affording 13 mg (84% yield) of the product, 6′-deoxy-6′-fluorosucrose **6**.

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Supplementary data

Supplementary data (copies of proton, carbon and fluorine spectra for selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.12.001.

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