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Chemical Synthesis of 1′-Deoxy-1′-fluorosucrose

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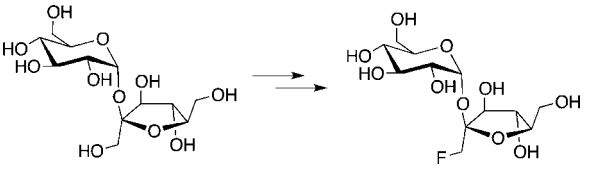
ABSTRACT



The first chemical synthesis of 1′-deoxy-1′-fluorosucrose has been accomplished in eight steps from sucrose by an unlikely, but ultimately successful, S_N2 displacement reaction.

As part of a program focusing on carbon partitioning in higher plants,[1] we have begun a study of the synthesis of fluorosucroses. These syntheses are designed to be amenable to the incorporation of ^{18}F so that the target compounds can be used for the purpose of real-time PET imaging of sucrose transport.

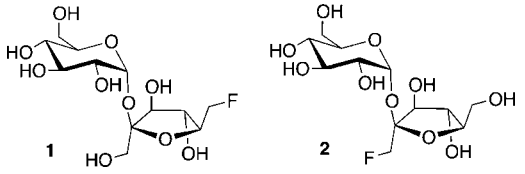


Figure 1. 6′-Deoxy-6′-fluorosucrose (**1**) and 1′-deoxy-1′-fluorosucrose (**2**).

For example, we recently reported the synthesis of 6′-deoxy-6′-fluorosucrose (**1**) in which the key fluorination step was both simple and rapid (Figure 1).[2] This methodology has been successfully transferred to the corresponding hot synthesis, and imaging studies are currently in progress.

In order to provide a fluorosucrose for such studies that would likely be more resistant to the action of invertase, we decided to pursue a synthesis of 1′-deoxy-1′-fluorosucrose (**2**). This compound has been prepared enzymatically via coupling of 1-deoxy-1-fluorofructose and uridine diphosphate glucose.[3] However, the process required 24 h, too long for application to the synthesis of hot material, with ^{18}F having a half-life of only 110 min.[4]

The possibility of doing a direct nucleophilic substitution at the 1′ position of sucrose was considered. This position is hindered, flanked by two electron-withdrawing oxygen atoms, and is formally neopentyl. These features do not bode well for such a plan.[5] Further, it had been reported by Guthrie and co-workers that treatment of **3** or **4** with a variety of nucleophilic fluoride sources did not result in the formation of **5** (Scheme 1).[6] Nevertheless, we felt that the progress that had been made since that report, particularly with respect to cation-binding agents, and the use of a triflate leaving group, might enable us to accomplish this difficult substitution reaction. This report details our success in this effort.

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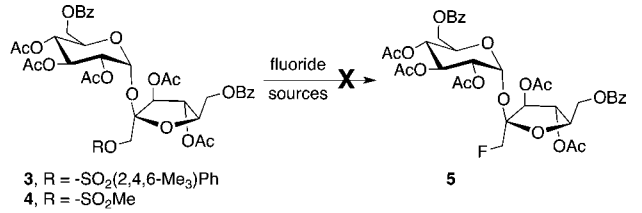
Scheme 1. Reported Attempted Synthesis of a 1′-Deoxy-1′-flourosucrose Derivative



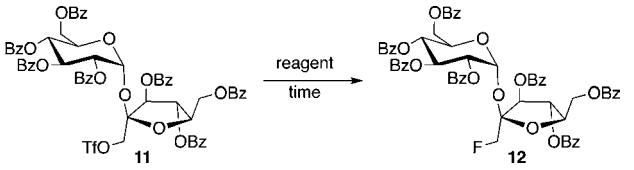
We began our work with a selective desilylation[7] at the 6- and 6′- positions of the 6,1′,6′-tri-*O*-*tert*-butyldiphenylsilyl-2,3,4,3′,4′-penta-*O*-benzoylsucrose (**7**), which was prepared from commercially available sucrose (**6**) in 70% yield over two steps (Scheme 2). We found that selective desilylation could yield 1′-*O*-*tert*-butyldiphenylsilyl-2,3,4,3′,4′-penta-*O*-benzoylsucrose (**8**) in 60% yield in acetonitrile. Other solvents such as ethyl acetate, dichloromethane, THF, and acetone required longer reaction times and often suffered from low yields. After benzoylation of **8** (99% yield), 1′-*O*-*tert*-butyldiphenylsilyl-2,3,4,6,3′,4′,6′-hepta-*O*-benzoylsucrose (**9**) was desilylated with TBAF/AcOH in refluxing THF to afford 2,3,4,6,3′,4′,6′-hepta-*O*-benzoylsucrose (**10**) in 98% yield. Triflation of **10** with triflic anhydride and 2,6-lutidine gave 1′-*O*-trifluoromethanesulfonyl-2,3,4,6,3′,4′,6′-hepta-*O*-benzoylsucrose (**11**) in 95% yield.

Due to the poor solubility of typical inorganic fluoride sources such as KF and CsF and their low nucleophilicity, fluorination of aliphatic halides or triflates by the fluoride ion typically requires the use of crown ethers such as 18-crown-6 or cryptands such as Kryptofix 222[8] to complex the metal (e.g., K^+) ions, increasing not only the solubility of the salt but also the nucleophilicity of the attendant anion.[9]

The optimization studies of the nucleophilic fluorination of (**11**) are summarized in the Table 1. Our goal was not only to demonstrate that we could synthesize the target but also to develop a process that was simple and amenable to application in the synthesis of a hot version of the target. We knew at the outset that the reaction would be difficult, but decided to investigate the possibility that rather mild reaction conditions could effect it. In refluxing acetonitrile, our solvent of choice for other fluorination reactions that we have studied,[2] none of the product **12** could be detected (Table 1, entries 1, 3, and 5) regardless of the fluoride source. Better results were obtained at higher temperatures in a sealed tube. However, at these higher temperatures, fluorides with metal counterions resulted in a side reaction to form 2,3,4,6,1′,3′,4′,6′-octa-*O*-benzoylsucrose (**13**) (Scheme 3) in approximately 5% yield (Table 1, entries 2, 4, 6, and 8).

Interestingly, tetrabutylammonium fluoride (TBAF) provided a 50% isolated yield of desired product

Table 1. Optimization Studies for the Synthesis of **12**



entry	reagent/equiv	time (min)	yield (%)
1[a]	CsF/1.0	20	0
2[b]	CsF/1.0	20	0
3[a]	AgF/1.0	20	trace
4[b]	AgF/1.0	20	5
5[a]	KF/1.0	20	0
6[b]	KF/1.0	20	0
7[b]	TBAF/1.2	20	50[c]
8[b]	KF/1.0 18-crown-6/1.0	20	trace
9[a]	KF/1.0 Kryptofix 222/1.0	10	49
10[b]	KF/1.0 Kryptofix 222/1.0	10	60

[a] Compound **11** in refluxing acetonitrile at 0.05 M. [b] Compound **11** in acetonitrile in a sealed tube at 135 °C. [c] Compound **13** formed in 29% yield.

1′-deoxy-1′-fluoro-2,3,4,6,3′,4′,6′-hepta-*O*-benzoylsucrose (**12**) (Table 1, entry 7). In this case, the side product **13** was isolated in 29% yield. The complex of KF/18-crown-6 gave only a trace amount of **12** (entry 8), while the complex of KF/Kryptofix 222 gave the best result, a 60% isolated yield of **12** (entry 10).

The structure of the side product **13** was based on NMR analysis and confirmed by the conversion of sucrose to **13** by exhaustive benzoylation (Scheme 3). How this side product arises is not clear, but it is quite conceivable that adventitious water is converted to hydroxide via reaction with fluoride[10] and results in some hydrolysis of the starting material. The resulting benzoate could displace the triflate in **11** to readily form **13**. This is consistent with the formation of **13** with TBAF, since it likely contains hydroxide ions.

The ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of product **12** displayed a peak centered at 103.6 ppm (d, J = 21.4 Hz, C-2′), due to the coupling of C-2′ with the fluorine atom at C-1′, as well as another peak centered at 82.5 ppm (d, J = 179.8 Hz, C-1′), due to the coupling of C-1′ with the fluorine atom at C-1′. The ^{19}F NMR spectrum (235 MHz, $CDCl_3$) showed a triplet centered at −228.3 ppm (J = 46.5 Hz), arising from the coupling of the fluorine atom on C-1′ with the two hydrogen atoms on the same carbon. The ^{1}H NMR spectrum of **12** was not exceptionally revealing as the protons attached to C1′ were obscured by other signals.

To prepare the target compound **2**, compound **12** was hydrolyzed with potassium carbonate in refluxing methanol for 5 min. This afforded 1′-deoxy-1′-fluorosucrose in

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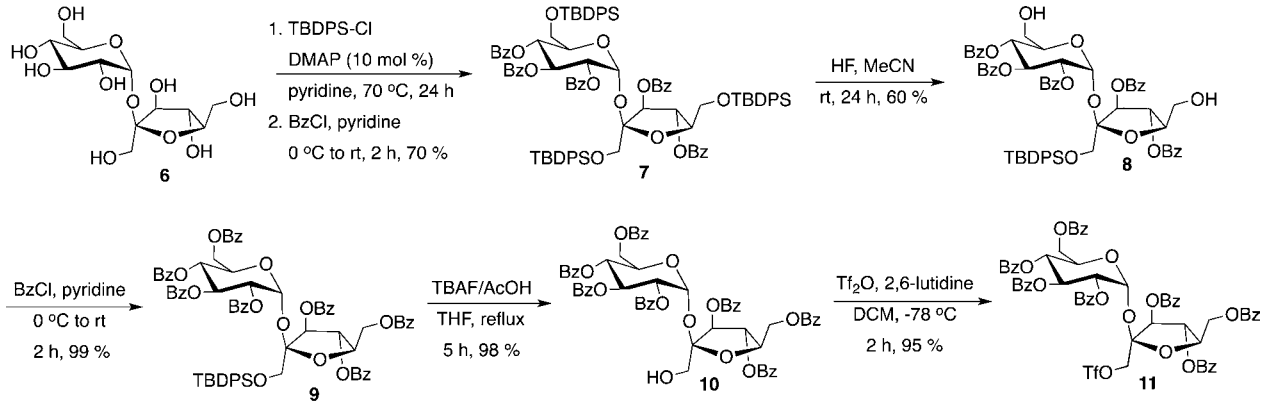
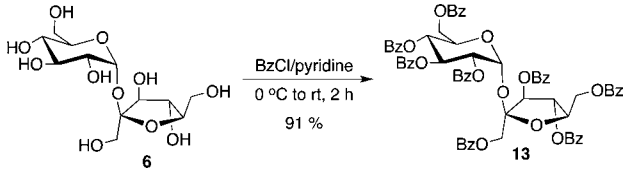
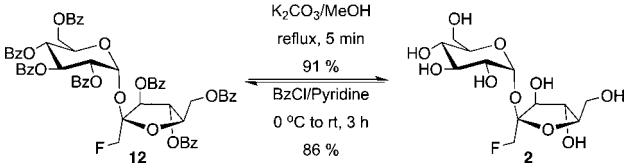
Scheme 2. Preparation of Key Triflate **11** from Sucrose



Scheme 3. Preparation of 2,3,4,6,1′,3′,4′,6′-Octa-*O*-benzoylsucrose **13**



Scheme 4. Synthesis of 1′-Deoxy-1′-fluorosucrose **2**



91% yield. To affirm that no change in the molecular skeleton occurred, the product was benzoylated and the precursor **12** was obtained in 86% yield (Scheme 4).

The ^{1}H NMR spectrum (500 MHz, D_2O) of **2** showed two second-order doublet of doublets at 4.40 ppm (J = 10.5, 46.5 Hz) and 4.33 ppm, due to the coupling between two hydrogen atoms at C-1′ and the coupling of them with the fluorine atom. We modeled the spin system using SpinWorks spectrum simulation software and obtained excellent agreement with the experimental results. The ^{13}C NMR sprectrum (125 MHz, D_2O) of **2** displayed a peak centered at 101.7 (d, J = 20.1 Hz, C-2′), due to the coupling of C-2′ with the fluorine atom on C-1′, as well as another peak centered on 80.6 (d, J = 173.5 Hz, C-1′), due to the coupling of C-1′ with the fluorine atom on C-1′. The ^{19}F NMR spectrum (235 MHz, D_2O) of **2** displayed a triplet centered at −229.1 (J = 46.5 Hz), arising from the coupling of the fluorine atom on C-1′ with the two hydrogen atoms on the same carbon.

In conclusion, we have developed the first purely chemical synthesis of 1′-deoxy-1′-fluorosucrose, with the advantages of good yields and short reaction times for the last two steps, which open the door for application of ^{18}F labeling for PET studies. This radioactive labeling and related plant studies are under investigation. Results will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data (^{1}H, ^{13}C, and ^{19}F NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.