Synthesis of Ethyl β-D-Galactopyranosyl-(1→4)-2-deoxy-2-fluoro-β-D-glucopyranoside

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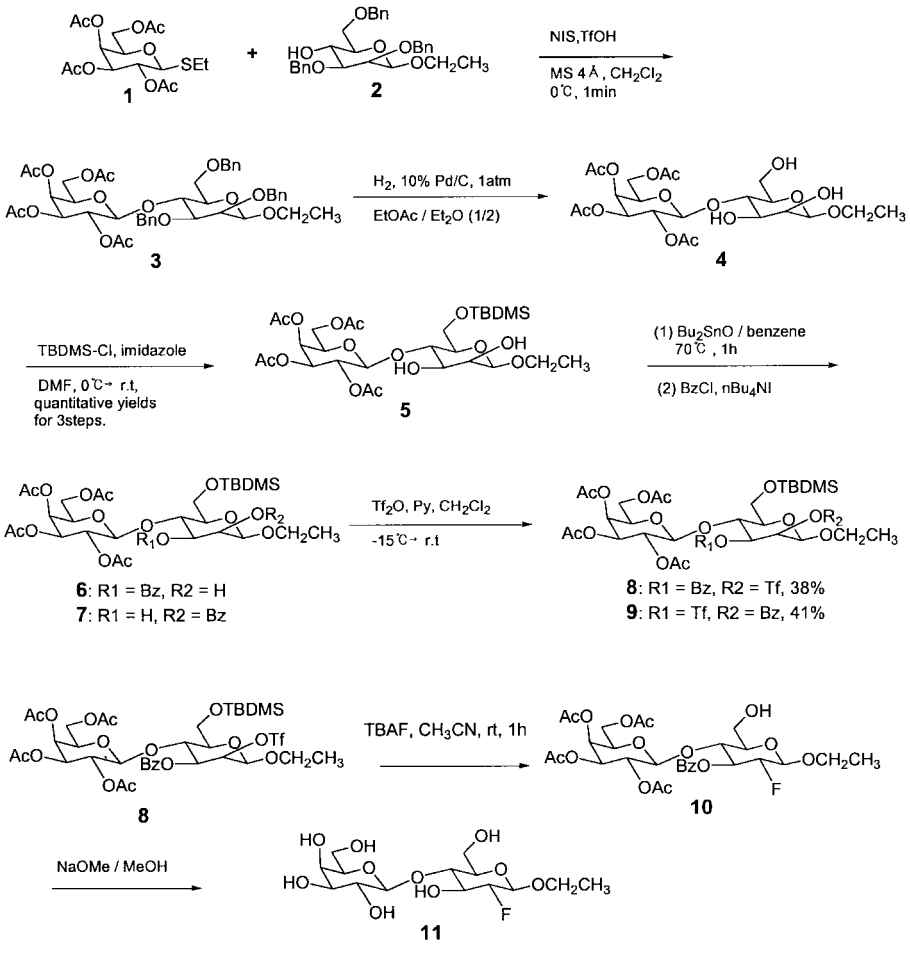
Various positron emitter labeled sugars have been applied for Positron Emission Tomography (PET) measurements. For example, ^{18}F-labeled 2-deoxy glucose (FDG) is most widely used in PET experiments for medical diagnosis.[1] In our researches, ^{18}F-labeled lactose derivatives are designed as the new positron emitter probes for the nuclear medical imaging technology targeting β-galactosidase as a reporter system. β-Galactosidase is one of the most important reporter systems that have been studied in molecular biology. However, little development has been achieved. Hence, our attention was drawn to find an effective synthetic method for the fluorine-incorporated disaccharide which can be useful for a PET imaging material.

Herein, we report our preliminary result of the synthesis of C-2 fluorinated lactose derivative. Our synthesis started with glycosylation of readily available[2] **1** with **2** under NIS/TfOH conditions[3] to give disaccharide **3** in highly quantitative yield (Scheme 1). The latter was then subjected to hydrogenolysis condition to remove three benzyl protecting groups to afford **4** in quantitative yield. The primary alcohol of **4** was protected with *tert*-butyldimethylsilyl group leaving two secondary alcohol groups intact.[4]

In our previous work, we reported on the regioselectivity between 2- and 3-OH groups of mannose derivatives in *p*-methoxybenzylation condition.[5] When methyl 6-O-trityl-α-D-mannopyranoside was treated with dibutyltin oxide, *p*-methoxybenzyl chloride, and tetra-*n*-butylammonium iodide, only mono *p*-methoxybenzylated product at 3-OH group was produced. Therefore, for compound **5,** we envisioned that the differentiation of two hydroxyl groups would be



Scheme 1

possible through partial acylation of stannylene acetal. However, treatment of **5** with dibutyltin oxide followed by benzoyl chloride and tetrabutylammonium iodide[6] gave a mixture of two inseparable regioisomers (almost 1 : 1 ratio) in execllent yield. At this point we decided to proceed further reactions using this mixture to make the intermediate for fluorinated disaccharide.

Triflation of **6** along with **7** using triflic anhydride and pyridine provided **8** and **9**, respectively, without incident in high yields. Fortunately the two isomers were separated by silica gel chromatography. The structural identification of **8** and **9** were based on ^{1}H-NMR and ^{13}C-NMR data.[7] Once we had compound **8** in hand, we were all set to incorporate fluorine on C-2 of disaccharide. TBAF was found to be the only choice of reagents since TBA^{18}F was the only available reagent for ^{18}F labeling.[8] To investigate the feasibility of our approach to radiofluorinated disaccharides, synthetic effort was focused on the reaction of **8** and TBAF for the stereospecific fluorination on C-2 of lactose. Treatment of **8** with TBAF provided compound **10**, albeit in a low yield (15%). Fluoride nucleophile from TBAF substituted trifluoromethane sulfonyl group and deprotected TBDMS group at the same time. The synthesis was completed by deacylation using sodium methoxide to afford **11** in quantitative yield. The incorporation of F on C-2 was confirmed by ^{13}C-NMR data of **11**, coupling constants between ^{19}F-C (D_2O, 100 MHz); C-1 (δ 107.1, $^{2}J_{C,F}$ = 22.9 Hz), C-2 (δ 98.9, $^{1}J_{C,F}$ = 194.4 Hz), C-4 (δ 86.1, $^{3}J_{C,F}$ = 6.9 Hz), C-3 (δ 84.9, $^{2}J_{C,F}$ = 21.0 Hz).

In conclusion we demonstrated the stereospecific incorporation of F on C-2 of disaccharide in a simple and efficient way. This method would be suitable for the preparation of radiofluorinated lactose derivatives for PET imaging.

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References

1. Coleman, R. E. *Nucl. Med. Biol*. **2000**, *27*, 689.
2. Park, J.; Yoon, S.; Yun, M.; Chun, K. H.; Nam Shin, J. E. *J. Korean Chem. Soc*. **1998**, *42*(5), 549.
3. (a) Ehara, T.; Kameyama, A.; Yamada, Y.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem*. **1996**, *281*, 237. (b) Veeneman, G. H.; Van Leeuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett*. **1990**, *31*, 1331. (c) Hotta, W.; Itoh, K.; Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem*. **1995**, *14*, 115.
4. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.
5. Shin, Y.; Chun, K. H.; Nam Shin, J. E; Aspinal, G. *Bull. Korean Chem. Soc*. **1995**, *16*(7), 625.
6. (a) Alais, J.; Maranduba, A.; Veyrieres, A. *Chem. Pharm. Bull*. **1985**, *33*(1), 165. (b) Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363-2369. (c) Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc. Comm*. **1994**, 1373.
7. selective nmr data: **8** ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.05 (m, 2H), 7.48 (m, 1H), 7.34 (m, 2H), 5.23 (m, 1H), 5.05 (m, 2H), 4.95 (m, 1H), 4.80 (m, 1H), 4.6 (m, 2H), 4.30 (t, *J* = 9.80 Hz, 1H), 3.86-3.77 (m, 4H), 3.57-3.45 (m, 3H), 3.28 (m, 1H), 1.93 (s, 3H), 1.92 (s, 3H), 1.82 (s, 3H), 1.79 (s, 3H), 1.15 (t, *J* = 8 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.4, 170.0 (2C), 169.0, 165.2, 149.7 ($\underline{C}F_3$), 133.5, 130.0, 129.1, 128.3, 100.1, 96.4 , 83.1, 75.7, 70.9, 70.79, 70.76, 70.2, 69.2, 66.8, 65.0, 61.4, 60.7, 25.7, 20.7, 20.5, 20.4, 20.3, 18.1, 14.7, -5.3; for **9** ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.95-7.11 (m, 5H, aromatic H), 5.69 (d, *J* = 3.2 Hz, 1H), 5.17 (d, *J* = 2.8 Hz, 1H), 5.03 (m, 1H), 4.78 (m, 2H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.49 (m, 1H), 4.31 (m, 1H), 3.89-3.63 (m, 6H), 3.42 (m, 1H), 3.16 (m, 1H), 1.96 (s, 3H), 1.90 (s, 3H), 1.83 (s, 3H), 1.54 (s, 3H), 0.98 (t, *J* = 8Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); **Ethyl β-D-galactopyranosy-(1→4)-2-deoxy-2-fluoro-β-D-glucopyran-oside (11)** ^{1}H-NMR (D_2O, 400 MHz) δ 4.72 (m, 1H), 4.25 (m, 1H), 3.90-3.19 (m, 16H), 1.08 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (D_2O, 100 MHz) δ 107.4 (C-1'), 107.1 ($^{2}J_{C,F}$ = 22.9 Hz, C-1), 98.9 ($^{1}J_{C,F}$ = 194.4 Hz, C-2), 86.1 ($^{3}J_{C,F}$ = 6.9 Hz, C-4), 84.9 ($^{2}J_{C,F}$ = 21.0 Hz, C-3), 78.5, 76.6, 76.3, 72.2, 68.5, 68.45, 67.6, 62.8, 21.4.
8. Alauddin, M. M.; Conti, P. S.; Mathew, T.; Fissekis, J. D.; Prakash, G. K. S.; Watanabe, K. A. *J. Fluorine Chem*. **2000**, *106*, 87.