

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

Mikyung Yun, Keun Ho Chun, Jeong E. Nam Shin,* and Jonghoon Oh[†]

Department of Chemistry, Soongsil University, Seoul 156-743, Korea

[†]Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea

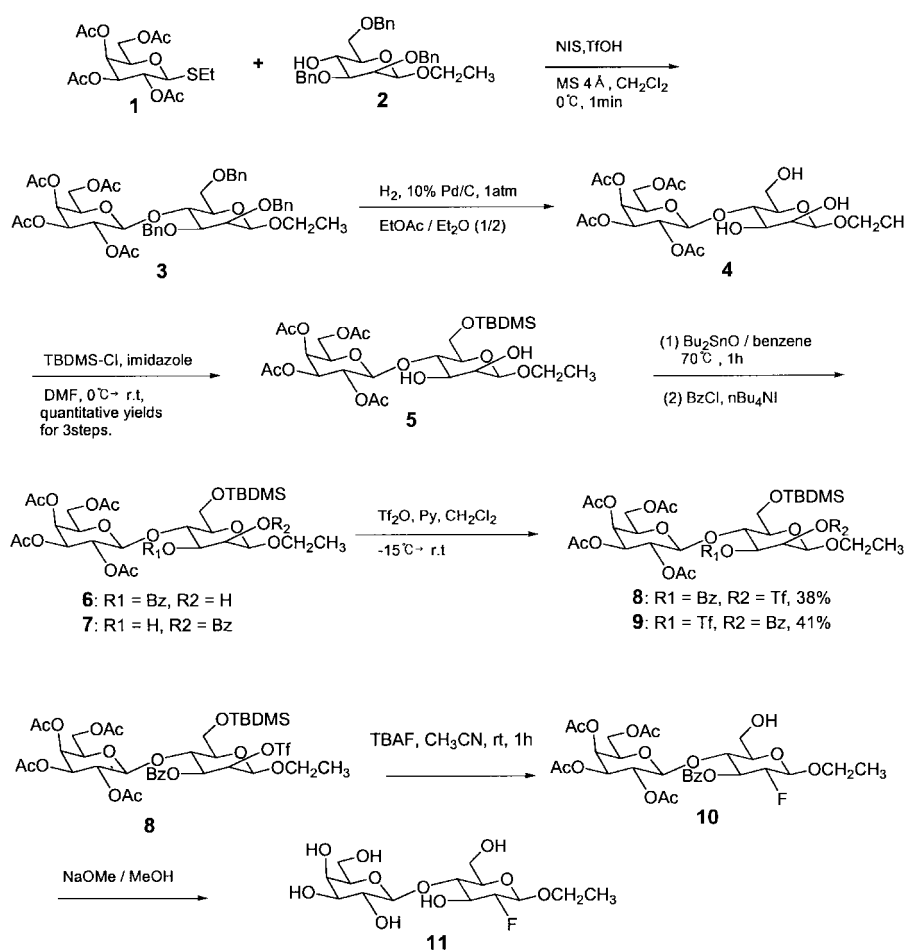
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Various positron emitter labeled sugars have been applied for Positron Emission Tomography (PET) measurements. For example, ^{18}F -labeled 2-deoxy glucose (FDG) is most widely used in PET experiments for medical diagnosis.¹ In our researches, ^{18}F -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 available² **1** with **2** under NIS/TfOH conditions³ 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 iodide⁶ gave a mixture of two inseparable regioisomers (almost 1 : 1 ratio) in excellent 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 ¹H-NMR and ¹³C-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 TBA¹⁸F was the only available reagent for ¹⁸F 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 ¹³C-NMR data of **11**, coupling constants between ¹⁹F-C (D₂O, 100 MHz): C-1 (δ 107.1, ²J_{CF} = 22.9 Hz), C-2 (δ 98.9, ¹J_{CF} = 194.4 Hz), C-4 (δ 86.1, ³J_{CF} = 6.9 Hz), C-3 (δ 84.9, ²J_{CF} = 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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7. selective nmr data: **8** ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 100 MHz) δ 170.4, 170.0 (2C), 169.0, 165.2, 149.7 (CF₃), 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** ¹H-NMR (CDCl₃, 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* = 8 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); **Ethyl β -D-galactopyranosyl-(1 \rightarrow 4)-2-deoxy-2-fluoro- β -D-glucopyranoside (**11**)** ¹H-NMR (D₂O, 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); ¹³C-NMR (D₂O, 100 MHz) δ 107.4 (C-1'), 107.1 (²J_{CF} = 22.9 Hz, C-1), 98.9 (¹J_{CF} = 194.4 Hz, C-2), 86.1 (³J_{CF} = 6.9 Hz, C-4), 84.9 (²J_{CF} = 21.0 Hz, C-3), 78.5, 76.6, 76.3, 72.2, 68.5, 68.45, 67.6, 62.8, 21.4.
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