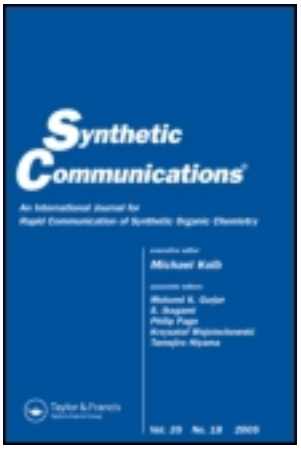

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SYNTHESIS OF A DUAL-PURPOSE 2-DEOXY-2-FLUORO-GLUCOPYRANOSYL BUILDING BLOCK

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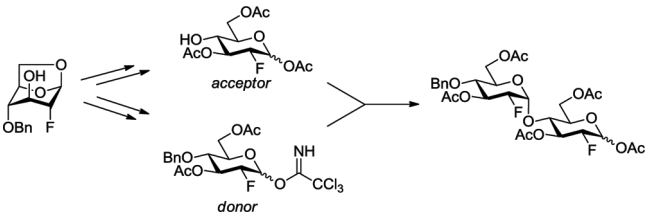
GRAPHICAL ABSTRACT



Abstract *We demonstrate a straightforward route to 1,3,6-tri-O-acetyl-4-O-benzyl-2-deoxy-2-fluoro-D-glucopyranose through potassium hydrogen fluoride opening of a Černý epoxide under microwave irradiation followed by acetolysis. The fluoroglucose building block was used as a key intermediate in the synthesis of 2,2′-dideoxy-2,2′-difluoromaltose.*

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Keywords Epoxide opening; glycosylation; maltose; microwave

INTRODUCTION

The introduction of fluorine into bioactive compounds can be a demanding synthetic task but is a widely used and often valuable maneuver to obtain compounds with increased bioactivity and/or stability.[1] In practice, both a nucleophilic (fluoride or diethylaminosulfurtrifluoride, DAST) and an electrophilic (SelectFluor)[2] approach can be used for placing a fluorine atom at a sp^3 center in an organic molecule.

Conducting nucleophilic substitution reactions at C-2 of aldohexoses is known to be notoriously difficult. For the synthesis of the 2-deoxy-2-fluoroglucose building block, a good leaving group (triflate or $Et_2NS(O)F$ from DAST)[3] and a favorable dipole orientation[4] (β-mannose) is required to obtain a successful reaction. This nucleophilic approach is used for the preparation of ^{18}F labelled 2-deoxy-2-fluoroglucose (FDG) for

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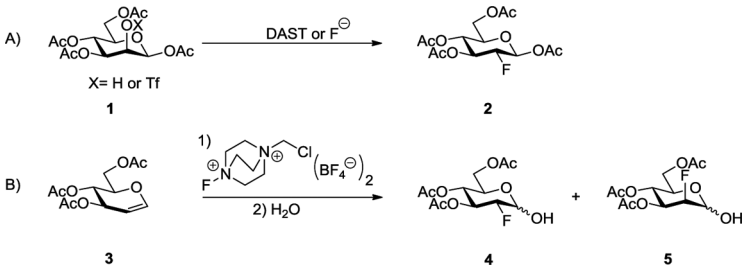


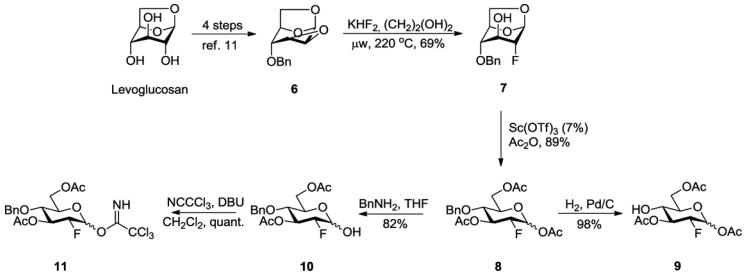
Scheme 1. Often used approaches for preparing 2-deoxy-2-fluoroglucopyranoses.

use in tumor localization by positron emission tomography[5] but is additionally widely used for the synthesis of the unlabelled FDG (Scheme 1A).[6] Another often employed preparation of this building block (FDG) is electrophilic fluorination of D-glucal with SelectFluor.[7] A significant drawback with this protocol, however, is that the reaction outcome is often an inseparable mixture of D-manno/D-gluco isomers (Scheme 1B).[8]

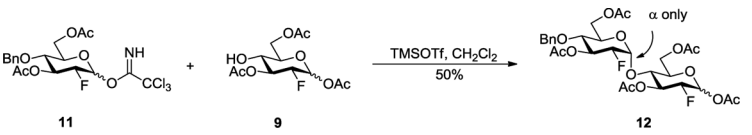
The presence of fluorine in place of O-2 in synthetic glycosides leads to dramatically increased hydrolytic stability of the glycosidic linkage[9] and in some cases interesting biological results have been obtained.[10] Both approaches for attaining 2-deoxy-2-fluoro-D-glucose building blocks for disaccharide synthesis, for example, are not ideal because still a number of steps will be required for installation of the appropriate protecting groups and donor function. As a supplement to the existing methods we here present a straightforward strategy for the synthesis of a dual-purpose 2-deoxy-2-fluoroglucose building block, which can be converted to both a glucosyl donor and 4-OH glucosyl acceptor.

RESULTS AND DISCUSSION

Our synthesis started from commercially available levoglucosan, which in four steps was converted into Černý epoxide **6** without the need for chromatographic purification (Scheme 2).[11] *trans*-Diaxial opening of this epoxide with KHF_2 has previously been demonstrated, albeit with moderate success, giving a yield of 40% of the 1,6-anhydro-4-*O*-benzyl-2-deoxy-2-fluoro-glucopyranose sugar (**7**) along with



Scheme 2. Synthesis of fluorinated acceptor (**9**) and donor (**11**) from levoglucosan.



Scheme 3. Synthesis of 2,2′-dideoxy-2,2′-difluoro maltose.

its anti-Fürst–Plattner opened 1,6-anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-altropyranose (3%, structure not shown).[12] We decided to investigate whether carrying out the reaction in a sealed tube under microwave irradiation had a beneficial effect on the reaction outcome. To our delight, full conversion of the epoxide starting material (**6**) was observed after only 20 min at 220 °C, affording the desired *gluco*-configured fluorosugar **7** in an isolated yield of 69% without any traces of the *trans*-diequatorial product.

Next, the 2-fluoro-1,6-anhydrosugar (**7**) was smoothly opened by an acetolysis reaction under scandium triflate catalysis[13] to give an anomeric mixture of triacetate **8**. To obtain a 4-OH acceptor (**9**), the benzyl ether was uneventfully cleaved by hydrogenolysis without any sign of acetyl migration.

To translate the key tri-acetate (**8**) into a useful glucosyl donor, the anomeric acetate was successfully removed by benzylamine in tetrahydrofuran (THF) to give reducing sugar **10** before this was treated with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give trichloroacetimidate glucosyl donor **11**.

To demonstrate the usefulness of the acceptor (**9**) and donor (**11**), the synthesis of a disaccharide from the two prepared building blocks was attempted. The reaction was carried out in the nonparticipating solvent dichloromethane and a majority of maltose rather than cellubiose was expected.[14] Because of the strongly electron-withdrawing nature of fluorine, no activation was found to take place below 0 °C by using TMSOTf as the promoter.

Only the α-linked product could be isolated from the reaction mixture in the moderate yield of 50%. Yields in this range are not uncommon for glycosylations with 2-fluoro-donors.[10]

CONCLUSION

We have shown that Černý epoxide **6** can be efficiently opened by KHF_2 under microwave irradiation and produce a 2-deoxy-2-fluoro sugar, which in a straightforward manner can be converted into both a glucosyl donor and a 4-OH glucosyl acceptor. The present approach is well suited for the synthesis of larger oligosaccharide fragments containing 1,4-linkages to and from a 2-deoxy-2-fluoro-glucosyl building block. This was demonstrated by the synthesis of 2,2′-deoxy-2,2′-fluoro-maltose.

EXPERIMENTAL

General experimental details about the synthesis of compounds **8–11** can be found in the Supporting Information, available online.

1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (7)

The 2,3-epoxy-1,6-anhydrosugar (489 mg, 2.1 mmol) and potassium hydrogen fluoride (1.19 g, 15.2 mmol, 7 eq) was added to ethylene glycol (6 mL) in a 10 to 20-mL microwave vial. The mixture was subjected to microwave irradiation for 20 min at 220 °C. The reaction was then cooled to rt and diluted with water (50 mL) before the aqueous layer was extracted with ethyl acetate (7 × 30 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc 1:2) to give the product (**7**) as a colorless oil (351 mg, 69%). R_f (pentane/EtOAc 2:3) 0.44. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.27 (m, 5H, Ar*H*), 5.52 (d, 1H, $J_{1,F}$ 5.2 Hz, H1), 4.70 (d, 1H, J_{gem} 12.2 Hz, PhC*H*H), 4.65 (d, 1H, PhCH*H*), 4.59 (d, 1H, $J_{5,6a}$ 5.4 Hz, H5), 4.24 (dd, 1H, $J_{2,3}$ 2.8 Hz, $J_{2,F}$ 47.2 Hz, H2), 3.97 (dt, 1H, $J_{2,3;3,4}$ 2.8 Hz, $J_{3,F}$ 20.0 Hz, H3), 3.87 (d, 1H, $J_{6a,6b}$ 7.6 Hz, H6a), 3.66 (dd, 1H, $J_{5,6b}$ 5.4 Hz, H6b), 3.32 (d, 1H, H4), 2.60 (b s, 1H, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 137.5, 128.6, 128.1, 127.9 (Ar), 99.5 (d, ^2J 30 Hz, C1), 89.7 (d, ^1J 181.5 Hz, C2), 78.2 (d, ^3J 6.2 Hz, C4), 74.9 (C5), 71.7 (*C*H_2Ph), 69.8 (d, ^2J 26.2, C3), 66.1 (C6). LRMS (ES): calcd. for $C_{13}H_{15}FO_4Na$: 277.1, found 277.0.

4-(3,6-Di-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)-1,3,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α/β-D-glucopyranose (12)

Donor **11** (220 mg, 0.44 mmol, 2.1 eq) and acceptor **9** (64 mg, 0.21 mmol) were mixed in CH_2Cl_2 and concentrated under reduced pressure. The mixture was then redissolved in dry CH_2Cl_2 (4 mL) and cooled to 0 °C before TMSOTf (0.09 mL, 0.50 mmol, 2.4 eq) was added under an N_2 atmosphere. The reaction was left to react overnight at 5 °C, after which additional TMSOTf (0.03 mL) was added. After stirring for additional 3 h at 0 °C, the reaction was quenched with Et_3N, concentrated under reduced pressure, and purified by flash column chromatography (pentane/EtOAc 20:1→5:1→CH_2Cl_2/EtOAc 20:1) to give disaccharide (67 mg, 50%). R_f (pentane/EtOAc 2:1) 0.14. $[\alpha]^{295K}_D$ 10.6 (*c* 1, $CHCl_3$). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33–7.17 (m, 5H, Ar*H*), 6.31 (d, 1H, $J_{1,2}$ 3.8 Hz, H1), 5.59 (q, 1H, *J* 9.6 Hz, H3/H3′), 5.50 (q, 1H, *J* 9.8 Hz, H3′/H3), 5.15 (d, 1H, $J_{1',2'}$ 3.9 Hz, H1′), 4.55 (d, 1H, J_{gem}11.1 Hz, PhC*H*H), 4.49 (d, 1H, PhCH*H*), 4.44 (dd, 1H, $J_{2,F}$ 48.6 Hz, $J_{2,3}$ 9.7 Hz, H2), 4.30 (dd, 1H, $J_{2',3'}$ 9.8 Hz, $J_{2',F}$ 48.6 Hz, H2′), 4.35 (dd, 1H, *J* 1.9 Hz, *J* 12.3 Hz, H6a/H6′a), 4.28–4.12 (m, 3H, H6′a/H6a, H6b, H6′b), 3.97 (ddd, 1H, *J* 1.8 Hz, *J* 4.2 Hz, *J* 10.1 Hz, H5/H5′), 3.92 (ddd, 1H, *J* 2.2 Hz, *J* 4.2 Hz, *J* 10.0 Hz, H5′/H5), 3.77 (t, 1H, *J* 9.6 Hz, H4/H4′), 3.48 (t, 1H, *J* 9.6, H4′/H4), 2.19 (s, 3H, C*H*$_3$), 2.05 (s, 3H, C*H*$_3$), 2.03 (s, 3H, C*H*$_3$), 2.01 (s, 3H, C*H*$_3$), 1.99 (s, 3H, C*H*$_3$). Major isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.5, 170.5, 169.5, 169.3, 169.0 (*C*O), 137.1, 128.7, 128.3, 128.1 (Ar*C*), 98.8 (d, $J_{2',F}$ 21.1, C2′), 88.4 (d, $J_{1,F}$ 22.2, C1), 87.6 (d, $J_{2',F}$ 195.4, C2′), 86.8 (d, $J_{2,F}$ 195.8, C2), 75.4 (C4′/C4), 75.4 (C4/C4′), 74.8 (Ph*C*H$_2$), 71.8 (d, *J* 17.6 Hz, C3/C3′), 71.3 (d, *J* 18.9 Hz, C3′/C3), 70.5 (C5/C5′), 70.1 (C5′/C5), 62.5 (C6/C6′), 62.3 (C6′/C6), 21.1, 21.0, 20.9, 20.8, 20.7 (*C*H$_3$). Major isomer: ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −200.8 (dd, *J* 12.4 Hz, *J* 52.4 Hz), −202.5, (dd, *J* 12.0 Hz, *J* 52.0 Hz). Minor isomer ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −201.4 (dd, *J* 12.4 Hz, *J* 52.4 Hz), −202.35 (dd,

J 12.8 Hz, *J* 51.2 Hz). HRMS (ES): calcd. for $C_{36}H_{38}O_6Na$ 669.1971; found 669.1974.

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REFERENCES

1. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
2. Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. Selectfluor: Mechanistric insight and applications. *Angew. Chem. Int. Ed.* **2005**, *44*, 192–212.
3. Kováč, P. A short synthesis of 2-deoxy-2-fluoro-D-glucose. *Carbohydr. Res.* **1986**, *153*, 168–170.
4. Richardson, A. C. Nucleophilic reactions of sulphonates, part VI. *Carbohydr. Res.* **1969**, *10*, 395–402.
5. Beuthien-Baumann, B.; Hamacher, K.; Oberdorfer, F.; Steinbach, J. Preparation of fluorine-18 labelled sugars and derivatives and their application as tracer for positron-emission-tomography. *Carbohydr. Res.* **2000**, *327*, 107–118.
6. Sugiyama, S.; Haque, W.; Diakur, J. Synthesis of (1→4)-linked 2-deoxy-2-fluoroglucose oligomers. *Org. Lett.* **2000**, *2*, 3489–3491.
7. Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. A new method for the synthesis of fluoro-carbohydrates and glycosides using Selectfluor. *J. Am. Chem. Soc.* **1997**, *119*, 11743–11746.
8. (a) Dax, K.; Albert, M.; Ortner, A.; Paul, B. J. Synthesis of deoxyfluoro sugars from carbohydrate precursors. *Carbohydr. Res.* **2000**, *327*, 47–86; (b) Ortner, A.; Albert, M.; Weber, H.; Dax, K. Studies on the reaction of D-glucal and its derivatives with 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane salts. *J. Carbohydr. Chem.* **1999**, *18*, 297–316; (c) Benito, D.; Matheu, M. I.; Morère, A.; Díaz, Y.; Castillón, S. Towards the preparation of 2″-deoxy-2″-fluoro-adenophostin A: Study of the glycosylation reaction. *Tetrahedron* **2008**, *64*, 10906–10911.
9. (a) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. The role of sugar substituents in glycoside hydrolysis. *J. Am. Chem. Soc.* **2000**, *122*, 1270–1277; (b) Bols, M.; Liang, X.; Jensen, H. H. Equatorial contra-axial polar substituents: The relation of a chemical reaction to stereochemical substituent constants. *J. Org. Chem.* **2002**, *67*, 8970–8974.
10. (a) Allman, S. A.; Jensen, H. H.; Vijayakrishnan, B.; Garnett, J. A.; Leon, E.; Liu, Y.; Anthony, D. C.; Sibson, N. R.; Feizi, T.; Matthews, S.; Davis, B. G. Potent fluoro-oligosaccharide probes of adhesion in toxoplasmosis. *ChemBioChem* **2009**, *10*, 2522–2529; (b) Wagner, S.; Mersch, C.; Hoffmann-Röder, A. Fluorinated glycosyl amino acids for mucin-like glycopeptide antigen analogues. *Chem. Eur. J.* **2010**, *16*, 7319–7330; (c) Boutureira, O.; D'Hooge, F.; Fernández-González, M.; Bernades, G. J. L.; Sánchez-Navarro, M.; Koeppe, J. R.; Davis, B. G. Fluoroglycoproteins: ready chemical site-selective incorporation of fluorosugars in proteins. *Chem. Commun.* **2010**, *46*, 8142–8144.
11. Rasmussen, T. S.; Jensen, H. H. Synthesis and glycosidase inhibitory activity of noeurostegine—a new and potent inhibitor of β-glucoside hydrolases. *Org. Biomol. Chem.* **2010**, *8*, 433–441.

12. Pacák, J.; Podešva, J.; Točík, Z.; Černý, M. Synthesis with anhydro sugars, XI: Preparation of 2-deoxy-2-fluoro-D-glucose and 2,4-dideoxy-2,4-difluoro-D-glucose. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2589–2599.
13. Lee, J.-C.; Tai, C.-A.; Hung, S. C. $Sc(OTf)_3$-catalyzed acetolysis of 1,6-anhydro-β-hexopyranoses and solvent-free per-acetylation of hexoses. *Tetrahedron Lett.* **2002**, *43*, 851–855.
14. Bucher, C.; Gilmore, R. Steering glycosylation with the carbon-fluorine bond. *Synlett* **2011**, 1043–1046.