A New Method for the Synthesis of Fluoro-Carbohydrates and Glycosides Using Selectfluor

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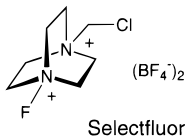
Abstract: This paper describes a high-yield, one-step synthesis of 2-deoxy-2-fluoro sugars and their glycosides from glycals using the available electrophilic fluorination reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in the presence of a nucleophile. The method was further expanded to the synthesis of glycosyl fluorides and glycosides from anomeric hydroxy or thioglycoside derivatives.

Electrophilic N−F fluorinating reagents have been commercially available for several years and have utility in many important transformations;[1] however, none has yet found any application in carbohydrate chemistry. Carbohydrates tend to react unpredictably with these molecules, which are well-known to be limited in scope of application,[2] yielding multiple, mostly undesirable products. We have found 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor), a relatively new electrophilic fluorinating reagent,[3] to be an extremely selective and potent reagent for the one-pot synthesis of 2-deoxy-2-fluoro glycosides and glycosyl fluorides and serves as a new activating reagent for use in glycosylation reactions.

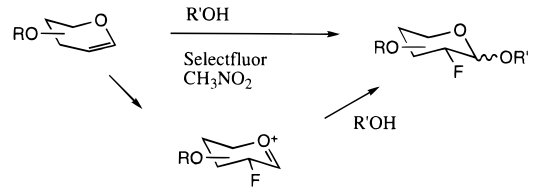


Selectfluor

Selectfluor has been demonstrated in recent years to be a very mild reagent for efficient fluorination.[4,5] The reagent is relatively inexpensive, safe,[6] and easy to handle.[7] It has been shown that this reagent reacts with silyl enol ethers and alkenyl boronic acids to give stereoselectively pure products,[8,9] but the reagent has never been shown to react with glycals or carbohydrate derivatives.

We have found that Selectfluor reacts with glycals in the presence of a nucleophile to give 2-deoxy-2-fluoro derivatives with a concurrent introduction of the nucleophile to the anomeric position, providing a new route to various 2-deoxy-2-fluoro monosaccharides, glycosides, and disaccharides in high yields (Scheme 1). This synthesis is the first example of a one-pot

Scheme 1. Synthesis of 2-Deoxy-2-fluoro Glycosides



fluorination and anomeric functionalization of a carbohydrate which circumvents multiple steps of previous synthetic methodology.[10] Previous methods of preparing 2-deoxy-2-fluoro monosaccharides have been plagued by difficult or dangerous procedures and poor yields. The most desirable of these methods involves the use of molecular fluorine[11,12] or solid xenon difluoride in reaction with glycals.[13−15] Unfortunately these methods require stringent conditions to hydrolyze the resulting 1,2-difluoro saccharides that often give low yields. Other methods give low yields or are very toxic.[16−19] The use of DAST involves inversion of stereochemistry, which is not feasible to many synthetic applications.[20] We believe that Selectfluor is a better reagent for the preparation of 2-deoxy-2-fluoro monosaccharides and their derivatives. Entries 1−9 of Table 1 demonstrate the synthetic flexibility of this reaction. We have found that the stereochemistry of fluorine addition is directed by steric constraints of the glycal. When the nucleophile is in great excess, acetonitrile may be used as solvent to

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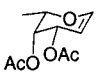
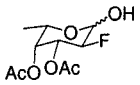
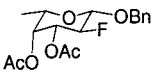
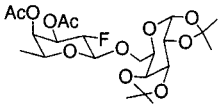
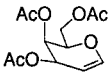
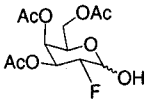
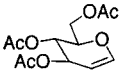
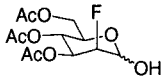
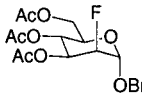
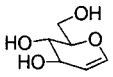
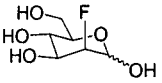
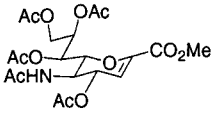
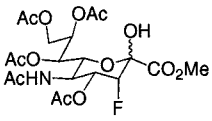
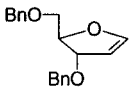
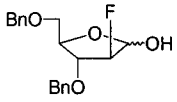
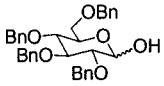
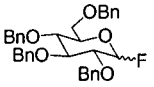
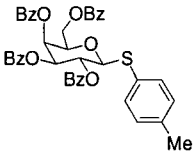
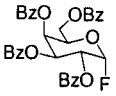
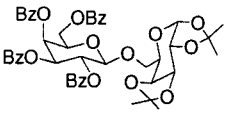
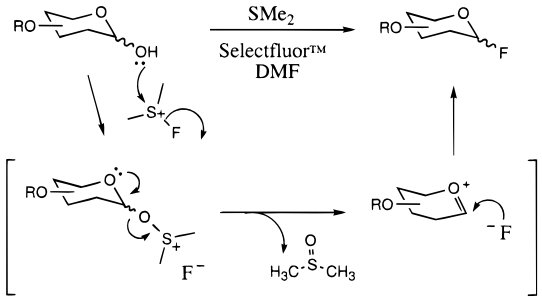
Table 1. Synthesis of 2-Deoxy-2-Fluoro Sugars, Glycosyl Fluorides, and Glycosides Using Selectfluor[a]

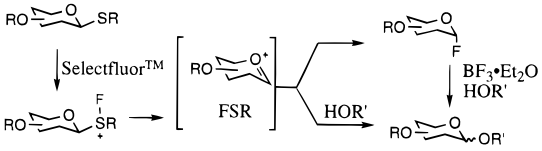
Entry	Substrate	Condition	Product	Yield (%)	Selectivity (C-F bond)	α/β ratio
1		A		97	100	1:1
2		B		71	100	0:1
3		C		40	100	1:2
4		A		79	75	1:1
5		A		90	67	1:1
6		D		60	67	1:2.5
7		E		85	67	1:1.5
8		F		80	75	ND
9		A		73	88	ND
10		G		70	-	1:1
11		H		82	-	1:0
12		I		95	-	0:1

[a] A: Selectfluor (1.5 equiv), DMF/H_2O (3/1), room temperature. B: Selectfluor (1.5 equiv), MeCN/BnOH (3/1), room temperature. C: Selectfluor (1.5 equiv), donor (2 equiv), CH_3NO_2, room temperature. D: Selectfluor (1.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), MeCN/BnOH (3/1), room temperature. E: Selectfluor (1.5 equiv), H_2O, room temperature. F: Selectfluor (4 equiv), DMF/H_2O (3/1), 50 °C. G: Selectfluor (3 equiv), SMe_2/DMF (1/1), room temperature. H: Selectfluor (3 equiv), 4 Å M.S., MeCN, 0 °C. I: Selectfluor (1.5 equiv), $BF_3{\cdot}Et_2O$ (1.5 equiv), donor (1.5 equiv), 4 Å M.S., MeCN, 0 °C.

Scheme 2. Conversion of 1-Hydroxy Sugars to Glycosyl Fluorides



Scheme 3. Plausible Thioglycoside Activation and Glycosylation by Selectfluor



favor β configuration at the anomeric position as with other glycosylation reactions.[21]

The transformation of 1-hydroxy sugars to glycosyl fluorides is usually accomplished by use of the DAST reagent.[22] Although a versatile reagent, DAST decomposes readily during storage and is expensive. We have found that Selectfluor in conjunction with methyl sulfide transforms 1-OH monosaccharides to 1-F derivatives presumably in a similar manner as does DAST (Table 1, entry 10). The reaction likely proceeds through a fluorosulfonium ion which then reacts with the anomeric hydroxy group of the sugar followed by displacement of the sulfoxide by fluoride (Scheme 2). Similarly, we also found that Selectfluor can replace the DAST reagent in the conversion of thioglycosides to glycosyl fluorides (Table 1, entry 11). Normally, DAST is used in conjunction with an activator to achieve this transformation.[23] Here Selectfluor acts alone in both activation and fluorination of the saccharide (Scheme 3).

Finally, we have found that Selectfluor can be used in glycosylations as an activator of thioglycosides (Scheme 3). Standard methods of glycosylation from thioglycosides use NBS, NIS, or DMTST to activate the anomeric thio followed by attack by a hydroxy acceptor.[24] Here we report very good yields in glycosylation from thioglycoside activation by Selectfluor and resulting glycosylation (Table 1, entry 12). This method provides the flexibility and convenience of thioglycoside activation and more options in synthesis. Both NIS and NBS are not suitable for hindered alcohol acceptors as succinimide competes with the acceptor for the donor.

In summary, we have developed a safe and efficient technique for synthesizing 2-deoxy-2-fluoro sugars and glycosides in one step with the use of Selectfluor, providing a useful extension of the glycal chemistry.[25] Given the importance of 2-deoxy-2-fluoroglycosides as inhibitors and mechanistic probes for glycosidases[10a] and glycosyltransferases,[10b] this method should find use in various applications of glycobiology research. Additionally, we found this reagent useful for the synthesis of glycosyl fluorides and for the activation of thioglycosides in oligosaccharide synthesis, an alternative to traditional methods.[24] Work is in progress to investigate whether the reactions proceed through a homolytic or heterolytic cleavage of the N−F bond.

Experimental Section

Condition A. 3,4-Di-*O*-acetyl-2-deoxy-2-fluoro-L-fucopyranose. To a solution of 3,4-di-*O*-acetyl-L-fucal (15 mg, 70.1 μmol) in DMF (0.5 mL) was added H_2O (0.5 mL) and F-TEDA-BF_4 (Selectfluor) (390 mg, 0.11 mmol). The solution was stirred at room temperature for 12 h, diluted with EtOAc (50 mL), and washed with water. The organic layer is dried over $MgSO_4$ and evaporated to dryness to yield a light-yellow syrup (17 mg, 97%), both α and β forms (1:1). β-Anomer: ^{1}H NMR (CD_3OD, 400 MHz) δ 5.28 (br. ddd, J = 3.6, 10.6, 10.6, 1H), 5.17 (br. ddd, J = 3.5, 4.7, 4.7, 1H), 4.69 (dd, J = 3.8, 7.6, 1H), 4.29 (br. dd, J = 1.9, 6.5, 1H), 4.22 (ddd, J = 7.6, 9.8, 51.8, 1H), 2.02 (s, 3H), 1.89 (s, 3H), 0.98 (d, J = 6.5 Hz, 1H); α-anomer: ^{1}H NMR (CD_3OD, 400 MHz) δ 5.23 (d, J = 3.8, 1H), 5.12 (br. ddd, J = 1.8, 3.6, 3.6, 1H), 5.05 (ddd, J = 3.6, 9.9, 13.2, 1H), 4.59 (ddd, J = 3.8, 10.2, 50.3, 1H), 3.86 (ddd, J = 1.0, 6.4, 1H), 1.91 (s, 3H), 2.03 (s, 3H), 1.04 (d, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 170.0, 94.6 (d, J = 22.5 Hz), 89.2 (d, J = 185.0 Hz), 71.2 (d, J = 17.5 Hz), 70.3 (d, J = 8.8 Hz), 69.4, 20.5, 20.4, 15.8; HRMS (M + Na) calcd for $C_{10}H_{15}FNaO_6$ 273.0750, found 273.0757.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose, **3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose**, **3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranose, and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-talopyranose** were synthesized by following the condition A above. Products acetylated with Ac_2O/pyridine (1:2) in order to separate anomers. The NMR data (^{1}H and ^{13}C) are the same as previously described.[11,18, 27]

3,5-Di-*O*-benzyl-2-deoxy-2-fluoro-arabifuranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 10 H), 5.48 (dd, J = 10.1, 6.9 Hz, 1 H), 4.95 (dd, J = 50.3, 1.2 Hz, 1 H), 4.65, 4.59 (ABq, J = 11.9 Hz, 2 H), 4.55 (s, 2 H), 4.47 (dd, J = 9.8, 5.7 Hz, 1 H), 4.02 (dd, J = 19.5, 4.0 Hz, 1 H), 3.59 (dd, J = 10.2, 5.7 Hz, 1 H), 3.51 (dd, J = 10.2, 5.7 Hz, 1 H), 3.07−3.05 (m, 1 H).

Condition B. Benzyl 3,4-Di-*O*-acetyl-2-deoxy-2-fluoro-β-L-fucopyranoside. To solid 3,4-di-*O*-acetyl-L-fucal (50 mg, 0.23 mmol) in dry acetonitrile (0.75 mL) was added F-TEDA-BF_4 (124 mg, 0.35 mmol) and benzyl alcohol (0.25 mL). The solution was stirred for 12 h, evaporated to near-dryness, and coevaporated three times with water to remove excess benzyl alcohol. The residue was then diluted with EtOAc (30 mL), washed with water, and dried with Mg_2SO_4. Silica gel chromatography (2:1 hexanes-EtOAc) yielded product (55 mg, 71%). ^{1}H NMR (C_6D_6, 400 MHz): δ 5.23 (ddd, J = 1.0, 3.5, 3.6, 1 H), 5.17 (ddd, J = 3.6, 9.8,13.4 Hz, 1 H), 4.84 (ddd, J = 7.69.8, 52.0, 1 H), 4.65 (ABq, J = 124.3, 12.2 Hz, 1 H), 4.34 (q, J = 7.6, 3.5 Hz, 1 H), 4.19 (dq, J = 6.4, 1.0, 1 H), 1.67 (s, 6 H, 2 C(O)CH_3), 1.60 (s, 3 H, C(O)CH_3), 0.92 (d, J = 6.4, 3 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 170.0, 169.7, 137.6, 128.6, 128.3, 128.2, 128.0, 99.6 (d, J = 22.5 Hz), 88.7 (d, J = 185.0 Hz), 71.9 (d, J = 18.8 Hz), 71.1 (d, J = 8.75 Hz), 70.6, 68.9, 20.2, 19.9, 15.9; HRMS (M + Na) calcd for $C_{17}H_{21}NaFO_6$ 363.1220, found 363.1231.

Condition C. 3,4-Di-*O*-acetyl-2-deoxy-2-fluoro-β-L-fucopyranosyl-(1−6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. To a mixture of 3,4-di-*O*-acetyl-L-fucal (15 mg, 70.1 μmol) and 1,2:3,4-di-*O*-isopropylidine-α-D-galactose (36.5 mg, 140.2 μmol) in dry CH_3NO_2 (0.5 mL) was added F-TEDA-BF_4 (50 mg, 104.0 μmol). The solution was stirred for 2 h, diluted with 50 mL EtOAc, and filtered. The solution was evaporated to a clear oil and purified with silica gel chromatography (4:1 hexane/EtOAc) to yield products (13.8 mg, 40%)

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with a α/β ratio of 2:1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.54 (d, J = 5.0 Hz, 1 H), 5.25 (t, J = 2.6 Hz, 1 H), 5.09 (ddd, J = 3.6, 9.3, 13.0 Hz, 1 H), 4.63 (m, 2 H), 4.51 (ddd, J = 7.7, 9.8, 58.8 Hz, 1 H), 4.34 (dd, J = 1.7, 8.0 Hz, 1 H), 4.32 (dd, J = 2.3, 5.0 Hz, 1 H), 4.01 (m, 2 H), 3.83 (m, 2 H), 2.16 (s, 3H), 2.05 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 170.5, 170.1, 108.8 (d, J = 75.5), 101.3 (d, J = 27.5), 96.2, 87.8 (d, J = 232.5), 71.5 (d, J = 22.5), 70.8 (d, J = 11.3), 70.6, 70.5, 70.5, 69.1, 68.7, 66.2, 29.7, 26.1, 26.0, 24.9, 24.4, 20.7, 20.6, 15.9; HRMS (M + Cs^+) calcd for $C_{22}H_{33}FO_{11}$ 625.1061, found 625.1084. **3,4-Di-*O*-acetyl-2-deoxy-2-fluoro-α-L-fucopyranosyl-(1−6)-1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.18 (d, J = 5.0 Hz, 1 H), 5.39 (ddd, J = 3.5, 10.6, 14.0 Hz, 1 H), 5.32 (ddd, J = 1.1, 3.4, 5.5 Hz, 1 H), 5.16 (d, J = 3.8 Hz, 1 H), 4.75 (ddd, J = 3.9, 10.2, 50.0 Hz, 1 H), 4.64 (dd, J = 2.4, 7.9 Hz, 1 H), 4.31 (m, 3 H), 4.12 (dd, J = 7.2, 11.4 Hz, 1 H), 4.05 (ddd, J = 2.0, 6.1, 7.7 Hz, 1 H), 3.92 (dd, J = 7.6, 9.7 Hz, 1 H), 3.66 (dd, J = 6.0, 9.7 Hz, 1 H), 2.16 (s, 3H), 2.04 (s, 3H), 1.55 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 170.5, 170.1, 109.0 (d, J = 58.8), 96.2, 96.1 (d, J = 25.0), 85.3 (d, J = 237.5), 71.8 (d, J = 9.4), 70.8, 70.5, 68.7 (d, J = 2.3), 66.3, 65.7, 64.5, 29.7, 26.0, 26.0, 24.9, 24.6, 20.7, 20.6, 15.6; HRMS (M + Cs^+) calcd for $C_{22}H_{33}FO_{11}$ 625.1061, found 625.1085.

Condition D. Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-mannopyranoside. To 3,4,5-tri-*O*-acetyl glucal (200 mg, 0.73 mmol) in dry acetonitrile (3 mL) with 4 Å powdered M.S. (100 mg) was added anhydrous benzyl alcohol (1 mL), 2,6-di-*tert*-butyl-4-methylpyridine (226 mg, 1.1 mmol), F-TEDA-BF_4 (390 mg, 1.1 mmol), and the solution was stirred for 12 h. The reaction was then diluted with EtOAc/Et_2O (9:1, 100 mL) to precipitate salts. The solution was filtered and evaporated to a clear oil. Repeated coevaporation with water removes excess benzyl alcohol. Silica gel chromatography (4:1 hexane/EtOAc) yielded products (171 mg, 60%), 67% mannose form. Proton NMR shows α/β ratio 2.5:1: (R_f 0.49, hexane/EtOAc 3:1) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (m, 5H), 5.33 (dd, J = 1.5, 2.9 Hz, 1H), 5.06 (dd, J = 1.9, 7.4 Hz, 1H), 4.75 (dt, J = 2.1, 2.1, 49.9Hz, 1H), 4.58 (ABq, J = 11.8, 62.8 Hz, 2H), 4.28 (m, 2H), 4.06 (dd, J = 2.3, 12.3 Hz, 1H), 3.99 (ddd, J = 2.2, 4.6, 9.3 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 170.1, 169.5, 136.1, 128.6,128.4, 128.3, 127.9, 96.2 (d, J = 36.3 Hz), 87.0 (d, J = 223.2 Hz), 69.9 (d, J = 21.8 Hz), 69.8, 68.7, 65.8, 62.0; HRMS (M + Na) calcd for $C_{19}H_{23}FNaO_8$ 421.1275, found 421.1288. **Benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (m, 5H), 5.29 (dt, J = 9.4, 14.5 Hz, 1H), 5.04 (t, J = 9.4 Hz, 1H), 4.82 (ABq, J = 12.0, 95.9 Hz), 4.62 (dd, J = 2.6, 7.7 Hz, 1H), 4.36 (dd, J = 7.7, 9.4, 50.6 Hz, 1H), 4.28 (dd, J = 4.8, 12.3 Hz, 1H), 4.14 (dd, J = 2.4, 12.3 Hz, 1H), 3.67 (ddd, J = 2.4, 4.8, 10.0 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 170.1, 169.7, 169.1, 137.4, 128.7, 128.3, 127.8, 96.7 (d, J = 36.3 Hz), 87.5 (d, J = 223.0 Hz), 70.4 (d, J = 20.9 Hz), 69.7, 69.4, 66.1, 61.9.

Condition E. 2-Deoxy-2-fluoro-D-mannopyranose. To a 4 mL aqueous solution of glucal (200 mg, 1.4 mmol) cooled in an ice bath was added F-TEDA-BF_4 (744 mg, 2.1 mmol). The solution was allowed to reach room temperature, stirred for 1 h, and evaporated to dryness. Quantitative acetylation with pyridine and acetic anhydride (2:1, 50 mL) followed by evaporation and coevaporation twice with toluene gives a yellow oil. Silica gel chromatography (4:1 CH_2Cl_2/MeOH) yielded products (174 mg, 85%) **2-deoxy-2-fluoro-D-glucopyranose** and **2-deoxy-2-fluoro-D-mannopyranose** (1:2). The spectral data are consistent with published results.[27]

Condition F. Methyl 5-Acetetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-*S*-fluoro-D-erythro-L-gluco-2-nonulopyranosonate and Methyl 5-Acetetamido-4,7,8,9-tetra-*O*-acetyl-3,5-di-deoxy-3-*R*-fluoro-D-erythro-L-gluco-2-nonulopyranosonate. To methyl 5-acetetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-galactonon-2-enonate (50 mg, 0.11 mmol) in DMF (0.75 mL) is added H_2O (0.25 mL) and F-TEDA-BF_4 (150 mg, 0.42 mmol). The solution is stirred at 50 °C for 12 h, diluted with EtOAc (50 mL), and washed with water. The organic layer is dried over $MgSO_4$, filtered, evaporated, and purified by column chromatography (MeOH/$CHCL_3$ = 1/18) to yield **3S** (32.2 mg, 60%) and **3R** (10.8 mg, 20%). **3S:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05−6.03 (m, 1 H), 5.41−5.32 (m, 2 H), 5.28 (dt, J = 8.5, 2.7 Hz, 1 H), 4.94 (dd, J = 49.6, 2.3 Hz, 1 H), 4.91 (dt, J = 12.2, 2.4 Hz, 1 H), 4.45−4.32 (m, 2 H), 4.09 (dd, J = 12.4, 8.5 Hz, 1 H), 3.85 (s, 3 H), 2.17 (s, 3 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 1.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.07, 171.43, 170.69, 170.50, 170.36, 167.37, 94.34 (d, J = 25.6 Hz), 86.76 (d, J = 185.4 Hz), 72.65, 71.22, 69.28 (d, J = 17.2 Hz), 68.39, 62.76, 58.65, 53.32, 45.00, 23.09, 21.10, 20.97, 20.87, 20.78, 20.69; HRMS (M + Cs) calcd for $C_{20}H_{28}FNO_{13}Cs$, 642.0599; found 642.0578. **3R:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90−5.72 (m, 1 H), 5.37−5.18 (m, 3 H), 4.89 (dd, J = 49.5, 9.4 Hz, 1 H), 4.46−4.15 (m, 3 H), 3.97 (dd, J = 12.5, 7.1 Hz, 1 H), 3.93 (s, 3 H), 2.13 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.01 (s, 3 H), 1.88 (s, 3 H).

Condition G. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl Fluoride. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranoside (37 mg, 0.07 mmol) was dissolved in anhydrous DMF/SMe_2 (1:1, 3 mL), and to this solution was added F-TEDA-BF_4 (72.6 mg, 0.21 mmol). After 5 min, the solution was diluted with 50 mL EtOAc, washed with water and brine, and dried over $MgSO_4$. Silica gel chromatography yielded product (26 mg, 70%) and unreacted starting material. The spectral data are consistent with published results.[22]

Condition H. 2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl Fluoride. To a mixture of thiocresyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (100 mg, 0.142 mmol) and 4 Å powdered M.S. (300 mg) in dry CH_3CN (3 mL), stirred at 0 °C for 15 min under argon, was added F-TEDA-BF_4 (78 mg, 0.220 mmol). The mixture was stirred at 0 °C for 20 min, then solid $NaHCO_3$ (200 mg) was added, and the mixture was stirred for 5 min, diluted with CH_2Cl_2 (20 mL), further diluted with Et_2O (20 mL), and then filtered through Celite. The solid cake was washed with CH_2Cl_2/Et_2O (1:1, 40 mL). The residue was concentrated and chromatographyed (SiO_2, hexanes−AcOEt 4:1→ 2:1) to give title compound (69.5 mg, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.82, 5.68 (dd, 1H, J = 2.6 and 53.2 Hz), 5.48 (d, 1H, J = 2.0 Hz), 5.30 (dd, 1H, J = 3.2 and 10.9 Hz), 5.16, 5.10 (ddd, 1H, J = 2.7, 10.9 and 23.8 Hz), 4.36 (t, 1H, J = 6.3 Hz), 4.09 (m, 2H), 2.11, 2.07, 2.01, 1.96 (s, 3H each).

Condition I. 2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl-(1−6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. A mixture of a thio-cresyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (67 mg, 0.096 mmol), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (30 mg, 0.115 mmol), and M.S. 4 Å (powder, 300 mg) in dry CH_3CN (4 mL), under Ar protection, was stirred at 0 °C for 15 min. BF_3−Et_2O (12 μL, 0.096 mmol) and F-TEDA-BF_4 (38.8 mg, 0.110 mmol) were added successively. The reaction was stirred at 0 °C for 15 min, solid $NaHCO_3$ (200 mg) was added and stirred for 5 min, diluted with CH_2Cl_2 (20 mL), and further diluted with Et_2O (20 mL). The mixture was stirred for 5 min then filtered through Celite. The solid cake was washed with CH_2Cl_2/Et_2O (1:1, 40 mL). The residue was concentrated and chromatographyed (SiO_2, hexanes−AcOEt 4:1→ 2:1) to give the title compound (68.4 mg, 85%): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.99 (d, 1H, J = 3.0 Hz), 5.81 (dd, 1H, J = 8.0 and 10.5 Hz), 5.61 (dd, 1H, J = 3.0 and 10.5 Hz), 5.42 (d, 1H, J = 5.0 Hz), 5.02 (d, 1H, J = 8.0 Hz), 4.67 (dd, 1H, J = 6.5 and 11.0 Hz), 4.35 (t, 11H, J = 6.5 Hz), 4.21 (dd, 1H, J = 2.5 and 5.0 Hz), 1.40, 1.24, 1.22, and 1.20 (S, 3H each); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.0, 165.5, 165.5, 165.3, 109.2, 108.4, 101.7, 96.1, 71.8, 71.2, 70.9, 70.5, 70.3, 69.6, 68.4, 68.1, 67.4, 62.0, 26.0, 25.9, 25.0, 24.2; HRMS (M + Cs) calcd for $C_{46}H_{46}O_{15}Cs$ 971.1891, found 971.1920.

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