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# Improved Synthesis of 2-Deoxy-2-fluoro-D-glucose Using Fluoride Ion

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Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside (**7**) was examined as a substrate for the preparation of 2-deoxy-2-fluoro-D-glucose (**1**) by fluoride ion treatment. The triflate (**7**) reacted rapidly with tetraalkylammonium fluorides in acetonitrile or tetrahydrofuran to give methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside (**10**) in 52—57% yield. Removal of the protecting groups from **10** by the use of 50% methanesulfonic acid afforded the required **1** in good yield. This synthetic sequence may provide an effective alternative to known methods for preparing $^{18}$F-labeled **1**.

**Keywords**——fluorination; nucleophilic displacement; tetraalkylammonium fluoride; methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside; 2-deoxy-2-fluoro-D-glucose

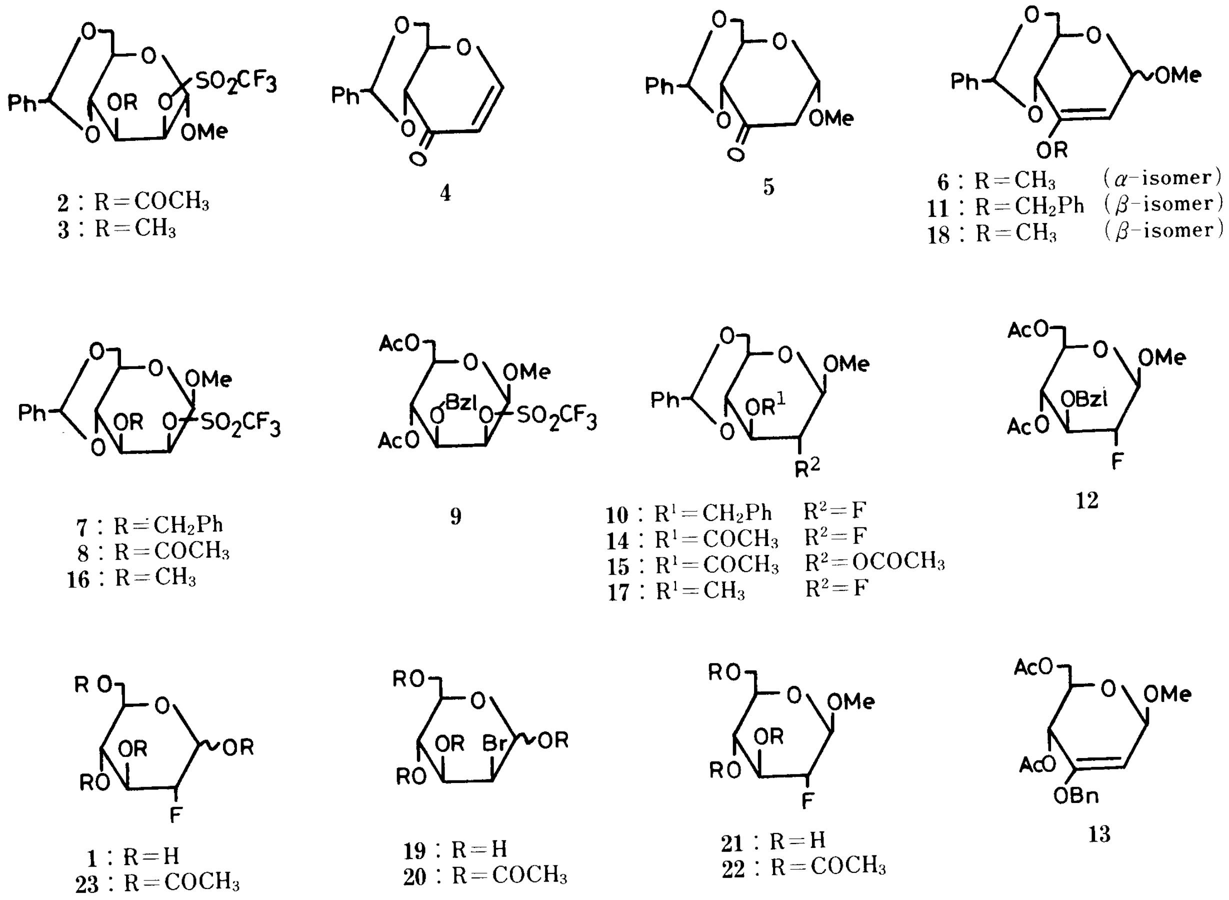
## Introduction

In recent years there has been intense interest in developing improved methods for the synthesis of $^{18}$F-labeled 2-deoxy-2-fluoro-D-glucose (**1**) because of its increasing importance in the field of nuclear medicine for studies of regional cerebral glucose metabolism in man.[1] A recent method for the radiopharmaceutical preparation of **1**, like the original one,[2] which includes in the initial step electrophilic addition of either acetyl hypofluorite[3] (prepared from molecular fluorine) or xenon difluoride[4] to 3,4,6-tri-*O*-acetyl-D-glucal, entails the inherent loss of 50% of the fluorine activity, because only one of the two fluorine atoms in the reagent is utilized in the product. On the other hand, new approaches based on nucleophilic displacement by fluoride ion involve the reaction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside with cesium fluoride in *N*,*N*-dimethylformamide (DMF)[5] and the reaction of methyl 4,6-*O*-benzylidene-β-D-mannopyranoside 2,3-cyclic sulfate with tetramethylammonium fluoride (TMAF) in acetonitrile,[6] with subsequent deblocking. We reinvestigated in detail these two approaches based on the published procedures. In the former case, the fluorination proceeded in reasonable yield, but considerable difficulty was encountered in removing the 3-*O*-methyl group from the fluorinated intermediate. The latter method required a tedious purification stage for isolating **1**, although this sequence has been reported to give a high yield of **1**. A unique synthesis of **1** by epoxide ring cleavage with potassium hydrogen fluoride has also been reported.[7] A synthetic route based on fluoride ion is very attractive for the radiosynthesis of **1** because $^{18}$F-fluoride ion is easily obtained at very high specific activity and, moreover, such a reaction has the potential ability to utilize all the available fluorine.

The present investigation originated from our recent report[8] on the synthesis of 2-deoxy-2-fluoro-D-mannose (FDM) which involves the efficient fluorination of the 3-*O*-benzyl and 3-*O*-acetyl derivatives of methyl 4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-β-D-glucopyranoside by fluoride ion and subsequent easy conversion into FDM. In concurrent work, we have examined the possible use of a similar synthetic route in the mannopyranoside series in developing an alternative approach to **1** for the purpose of labeling with $^{18}F$, although sulfonyloxy groups situated at $C_2$ of mannopyranose derivatives were expected to be very sensitive to elimination because of the favorable *trans*-diaxial arrangement. We have found that a synthetic approach to **1** starting from methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside (**7**), which was chosen as a triflate having a readily removable protecting group for $C_3$–OH, provides an effective alternative to a method described by Levy *et al.*[5] After this work had been completed, a similar synthesis of **1** using benzyl 3,4,6-tri-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside was reported.[9]

## Results and Discussion

Although the literature precedents[10] suggested that nucleophilic displacement reactions of sulfonate ester groups at $C_2$ of α-D-mannopyranosides do not normally proceed satisfactorily compared with those of the β-anomers, the reactivities of the 3-*O*-acetyl and 3-*O*-methyl derivatives (**2** and **3**) of methyl 4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-α-D-mannopyranoside were initially examined in displacement reactions because of their greater accessibility. As was predicted, attempted fluorination of these triflates with various fluorinating agents failed to give only the elimination products such as the hex-1-enopyran-3-ulose (**4**) and/or the hexopyranosid-3-ulose (**5**) or the hex-2-enopyranoside (**6**), as shown in Table I.



2 : R=COCH₃
3 : R=CH₃

4

5

6 : R=CH₃ (α-isomer)
11 : R=CH₂Ph (β-isomer)
18 : R=CH₃ (β-isomer)

7 : R=CH₂Ph
8 : R=COCH₃
16 : R=CH₃

9

10 : R¹=CH₂Ph R²=F
14 : R¹=COCH₃ R²=F
15 : R¹=COCH₃ R²=OCOCH₃
17 : R¹=CH₃ R²=F

12

1 : R=H
23 : R=COCH₃

19 : R=H
20 : R=COCH₃

21 : R=H
22 : R=COCH₃

13

Chart 1

TABLE I. Fluorination of Protected Methyl 2-*O*-(Trifluoromethanesulfonyl)-α- and β-D-Mannopyranosides

| Compd. | Fluorinating agent | Solvent | Temp. (°C) | Time (min) | Product (yield %)[a] |
|---|---|---|---|---|---|
| **2** | KF | $CH_3CONH_2$ | 120 | 30 | **4** (61) |
| | CsF | $CH_3CN$ | Reflux | 180 | **5** (40) |
| | $Bu_4NF$ | $CH_3CN$ | 50 | 60 | **4**[b] (13) **5**[b] (18) |
| **3** | $Bu_4NF$ | $CH_3CN$ | 50 | 10 | **6** (82) |
| **7** | CsF | DMF | 145 | 30 | **10** (42) |
| | $Et_4NF$ | $CH_3CN$ | 50 | 20 | **10** (57) **11** (21) |
| | $Et_4NF$ | THF | Reflux | 20 | **10** (54) **11** (16) |
| | $Me_4NF$ | $CH_3CN$ | 50 | 30 | **10** (52) **11** (33) |
| | $Bu_4NF$ | $CH_3CN$ | r.t. | 30 | **10** (54) **11** (30) |
| | $Bu_4NF$ | THF | r.t. | 30 | **10** (55) **11** (28) |
| **8** | $Me_4NF$ | $CH_3CN$ | 70 | 50 | **14** (21) **15** (14) |
| **9** | $Et_4NF$ | $CH_3CN$ | 50 | 20 | **12** (36) **13** (63) |
| | $Me_4NF$ | $CH_3CN$ | Reflux | 40 | **12** (17) **13** (53) |
| **16** | $Et_4NF$ | $CH_3CN$ | 50 | 20 | **17** (63) **18** (27) |
| | $Bu_4NF$ | $CH_3CN$ | r.t. | 30 | **17** (64) **18** (30) |

*a*) Isolated yield unless otherwise specified.
*b*) Yield as determined by $^1$H-NMR.
r.t. = room temperature.

The use of a β-anomer derivative led to the desired fluorination, although some elimination of the sulfonyloxy group also occurred, which served to confirm a previous observation. The methyl 2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranosides in which the hydroxy functions were protected by a benzyl (**7**) or acetyl group (**8**) with a 4,6-*O*-benzylidene moiety, or by a benzyl group (**9**) with 4,6-di-*O*-acetyl groups, were studied in this work. These blocking groups at $C_3$ were chosen as being more removable under acidic conditions than the methyl ether group previously used by Levy *et al.*[5] The results in the fluorination step with these triflates under various conditions and with various sources of fluoride ion are also summarized in Table I. When **7** was allowed to react with tetraalkylammonium fluorides for short reaction times (20—30 min) in acetonitrile or tetrahydrofuran (THF) at room temperature or under more vigorous conditions in order to obtain reasonable rates of reaction, the expected methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside (**10**) was obtained in satisfactory yields (52—57%) together with the undesired 2-ene compound (**11**); these products were easily separable by column chromatography. The three quaternary ammonium fluorides used as fluorinating agents showed little difference in the efficiency or rate of the reaction, but the use of the combination of cesium fluoride in DMF required a higher temperature to achieve a similar yield of **10**. However, fluorination of **9** with tetraethylammonium fluoride (TEAF) or TMAF proceeded unsatisfactorily to give predominantly the elimination product (**13**), although methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-β-D-glucopyranoside (**12**) was obtained in an appreciable yield. Similar treatment of **8** was again disappointing, giving only a 21% yield of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside (**14**) in addition to **15** (14%). The reason for the formation of **15** is not clear and this was not further investigated.

Our attention was next focused on the reaction of the 3-*O*-methyl triflate (**16**) already described by Levy *et al.*,[5] who obtained a 42.9% yield of methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-3-*O*-methyl-β-D-glucopyranoside (**17**) on treatment of **16** with cesium fluoride in DMF and reported no other products. We reinvestigated this reaction with different fluorinating agents, and it was found that the yield of **17** was greatly improved by conducting the reaction with tetra-*n*-butylammonium fluoride (TBAF) or TEAF in acetonitrile. The elimination product (**18**) was obtained as a by-product.

The structures of all the products were determined on the basis of elemental analyses, and mass and proton nuclear magnetic resonance ($^1$H-NMR) spectra. In particular, the $^1$H-NMR spectral analyses of the fluorinated compounds (**10**, **12**, **14** and **17**) allowed definitive configurational assignments (see Experimental).

The next stage in the synthesis was removal of the protecting groups in a single reaction step to give the required **1**, because it was necessary to shorten the time required for the completion of the synthesis. Considerable difficulty was experienced in the direct conversion of **17** into **1** with various acidic reagents, even by the method described by Levy *et al.*[5] which involves treatment with boron tribromide in methylene chloride at room temperature. Attempted removal of the protecting groups from **17** with boron tribromide caused concomitant defluorination of the product to give 2-bromo-2-deoxy-D-mannose (**19**) in 53% yield, as determined by elemental analysis, mass and $^1$H-NMR spectral analyses of the tetraacetate (**20**). Conditions could not be found that would favor the isolation of **1** from the reaction mixture. Therefore the 3-*O*-methyl triflate (**16**), although it gave an improved fluorination in the present study, does not appear to be a suitable substrate for the preparation of **1**. The reason for the discrepancy between our result on the boron tribromide treatment of **17** and that previously reported is not clear at present. A similar defluorination has also been observed in the treatment of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-D-mannopyranoside or methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-3-*O*-methyl-β-D-mannopyranoside with the same reagent.[8]

Refluxing of **10** in 30% methanesulfonic acid for 30 min gave the required **1** in 54% yield along with methyl 2-deoxy-2-fluoro-β-D-glucopyranoside (**21**) (18%). However, a better-yielding conversion (70%) to **1** was accomplished by the use of 50% methanesulfonic acid under the same conditions. The mp, optical rotation, $^1$H- and $^{13}$C-nuclear magnetic resonance ($^{13}$C-NMR) spectral properties of **1** thus obtained were in agreement with the reported values[11-13] and the product was further characterized by conversion into an anomeric mixture of the tetraacetate (**23**).[11]

In the present research, the trifluoromethanesulfonyloxy group in **7** underwent ready fluoride displacement and the use of benzyl ether at $C_3$ as a protecting group in the synthesis of **1** offered the great advantages of extremely facile deblocking and a simple isolation procedure. Thus, this synthetic route provides an alternative method for the preparation of **1** and may also be suitable for the radiopharmaceutical synthesis of **1** labeled with $^{18}$F.

## Experimental

All melting points are uncorrected. $^1$H-NMR spectra were recorded on a JNM PS-100 or a JEOL FX-100 spectrometer, with tetramethylsilane (in $CDCl_3$) or sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) (in $D_2O$) as an internal standard. $^{13}$C-NMR spectra were recorded on a JEOL FX-100 spectrometer in $D_2O$ with DSS as an internal reference. IR spectra were recorded on a JASCO IRA-1 spectrometer. Optical rotations were determined with a JASCO DIP-SL automatic polarimeter at ambient temperature. Elemental analyses were performed by the staff of the microanalytical section of Kyushu University. Column chromatography was carried out on silica gel (Kiesel gel-60, 70—230 mesh, Merck). Thin layer chromatography (TLC) on Kiesel gel 60-F (Merck) was used to monitor the reactions and to ascertain the purity of reaction products. The spots were visualized by spraying with aqueous sulfuric acid and then heating. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed under reduced pressure on a rotary evaporator. Commercial tetraalkylammonium fluorides were used for the fluorinations immediately after a drying procedure as reported previously.[8]

**Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-α-D-mannopyranoside (2)**——Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-mannopyranoside[14] (1.0 g, 3.1 mmol) was dissolved in dry pyridine (10 ml). Trifluoromethanesulfonic anhydride (1 ml, 6.2 mmol) was slowly added at −10 °C. The mixture was stirred for 1 h at 0 °C, then poured into ice water. The precipitate formed was filtered off, washed with water, and dissolved in chloroform. The solution was dried and evaporated at 40 °C. The resulting solid was chromatographed on silica gel using *n*-hexane–ethyl acetate (10 : 1) as the eluent to give **2** (0.94 g, 67%) as colorless needles, after recrystallization from *n*-hexane–ether, mp 91—92 °C. $[\alpha]_D$ −9° ($c$=0.73, chloroform). IR (chloroform): 1140 ($SO_2$), 1750 (C=O) $cm^{-1}$. MS *m/e*: 456 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.12 (3H, s, $OCOCH_3$), 3.42 (3H, s, $OCH_3$), 3.80—4.34 (4H, m, H-4, 5, 6), 4.83 (1H, d, $J_{1,2}$=2 Hz, H-1), 5.10 (1H, dd, $J_{2,3}$=4 Hz, H-2), 5.43 (1H, dd, $J_{3,4}$=10 Hz, H-3), 5.58 (1H, s, PhCH), 7.26—7.60 (5H, m, aromatic). *Anal.* Calcd for $C_{17}H_{19}F_3O_9S$: C, 44.74; H, 4.20. Found: C, 44.81; H, 4.23.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-(trifluoromethanesulfonyl)-α-D-mannopyranoside (3)**——Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside[10b] (1.75 g, 5.9 mmol) was dissolved in dry pyridine (25 ml). Trifluoromethanesulfonic anhydride (2 ml, 11.9 mmol) was slowly added at −10 °C. The mixture was stirred for 1.5 h at 0 °C. The gummy product that separated when the mixture was poured into ice–water was taken up in chloroform. The combined extracts were dried and evaporated at 40 °C. The syrupy residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (10 : 1) to give **3** (1.4 g, 55%) as a syrup. IR (chloroform): 1140 ($SO_2$) $cm^{-1}$. MS *m/e*: 428 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.44, 3.55 (3H, s, $OCH_3$), 3.74—4.31 (5H, m, H-3, 4, 5, 6), 4.86 (1H, d, $J_{1,2}$=1.7 Hz, H-1), 5.08 (1H, t, $J_{2,3}$=1.7 Hz, H-2), 5.61 (1H, s, PhCH), 7.32—7.55 (5H, m, aromatic). *Anal.* Calcd for $C_{16}H_{19}F_3O_8S$: C, 44.86; H, 4.47. Found: C, 44.64; H, 4.42.

**Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside (7)**——Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside[14] (0.9 g, 2.4 mmol) was dissolved in dry pyridine (14 ml). Trifluoromethanesulfonic anhydride (0.82 ml, 4.9 mmol) was slowly added at −10 °C. The mixture was stirred for 80 min at 0 °C, then worked up as described for the preparation of **2**. Column chromatography on silica gel with benzene gave **7** (0.96 g, 79%) as colorless needles, after recrystallization from *n*-hexane–ether, mp 99 °C. $[\alpha]_D$ −36.2° ($c$=0.74, chloroform). IR (Nujol): 1150 ($SO_2$) $cm^{-1}$. MS *m/e*: 504 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.25—4.11 (3H, m, H-5, 6), 3.56 (3H, s, $OCH_3$), 3.75 (1H, dd, $J_{2,3}$=3 Hz, $J_{3,4}$=10 Hz, H-3), 4.34 (1H, dd, $J_{4,5}$=4.9 Hz, H-4), 4.52 (1H, s, H-1), 4.80 (2H, s, $PhCH_2O$), 5.12 (1H, d, H-2), 5.62 (1H, s, PhCH), 7.29—7.55 (10H, m, aromatic). *Anal.* Calcd for $C_{22}H_{23}F_3O_8S$: C, 52.38; H, 4.60. Found: C, 52.49; H, 4.49.

**Methyl 4,6-Di-*O*-acetyl-3-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside (9)**——A mixture of **7** (500 mg, 0.99 mmol) and trifluoroacetic acid (0.72 ml) containing water (0.8 ml) was allowed to stand for 25 min at room temperature, according to a method described by Christensen *et al.*[15] After removal of the solvent, the residue was dissolved in chloroform. This solution was washed three times with water, dried, and evaporated. The residue was chromatographed on silica gel with chloroform–acetone (8 : 1) to give methyl 3-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside (346 mg, 82%) as a solid. Acetylation of this solid with acetic anhydride (1.2 ml) in pyridine (0.6 ml) for 3 h at room temperature and subsequent chromatography on silica gel with chloroform–acetone (10 : 1) gave **9** (396 mg, 98%) as a syrup. $[\alpha]_D$ −77.4° ($c$=0.56, chloroform). IR (chloroform): 1150 ($SO_2$), 1760 (C=O) $cm^{-1}$. MS *m/e*: 500 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.99, 2.07 (3H, s, $OCOCH_3$), 3.46—3.70 (2H, m, H-3, 5), 3.56 (3H, s, $OCH_3$), 4.18 (2H, d, $J_{5,6}$=4.4 Hz, H-6), 4.45 and 4.79 (2H, 2d, $J_{gem}$ = 12.5 Hz, $PhCH_2O$), 4.48 (1H, s, H-1), 5.14 (1H, d, $J_{2,3}$=3.4 Hz, H-2), 5.16 (1H, t, $J_{3,4}$=$J_{4,5}$=9.8 Hz, H-4), 7.14—7.44 (5H, m, aromatic). *Anal.* Calcd for $C_{19}H_{23}F_3O_{10}S$: C, 45.60; H, 4.63. Found: C, 45.84; H, 4.86.

**Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranoside (8)**——A mixture of the 2- and 3-*O*-acetyl derivatives of methyl 4,6-*O*-benzylidene-β-D-mannopyranoside, prepared as described in the literature,[14] was dissolved in dry pyridine (10 ml). Trifluoromethanesulfonic anhydride (0.5 ml, 3 mmol) was slowly added at −10 °C, and the mixture was stirred for 90 min at 0 °C. After work-up as described for the preparation of **3**, the syrupy residue (TLC showed two major spots) was chromatographed on silica gel with *n*-hexane–ethyl acetate (5 : 1) to give **8** (240 mg) as colorless needles, after recrystallization from *n*-hexane–ether, mp 155 °C. $[\alpha]_D$ −91.8° ($c$=0.86, chloroform). IR (chloroform): 1140 ($SO_2$), 1760 (C=O) $cm^{-1}$. MS *m/e*: 456 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.14 (3H, s, $OCOCH_3$), 3.4—4.11 (3H, m, H-5, 6), 3.56 (3H, s, $OCH_3$), 4.37 (1H, dd, $J_{3,4}$=11.6 Hz, $J_{4,5}$=5 Hz, H-4), 4.66 (1H, s, H-1), 5.16 (1H, d, $J_{2,3}$=4 Hz, H-2), 5.18 (1H, dd, H-3), 5.57 (1H, s, PhCH), 7.27—7.44 (5H, m, aromatic). *Anal.* Calcd for $C_{17}H_{19}F_3O_9S$: C, 44.74; H, 4.20. Found: C, 44.77; H, 4.10.

**Reaction of 2 with Potassium Fluoride**——A mixture of **2** (100 mg, 0.22 mmol) and acetamide (3 g) containing anhydrous potassium fluoride (52 mg) was heated at 120 °C for 30 min. After cooling, the resulting solid was dissolved in chloroform. The solution was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with chloroform to give 4,6-*O*-benzylidene-1,2-dideoxy-D-*erythro*-hex-1-enopyran-3-ulose (**4**) (31 mg, 61%) as needles, after recrystallization from *n*-hexane–acetone, mp 123—125 °C (lit.[16] 128—129 °C). IR (chloroform): 1600 (C=C), 1760 (C=O) $cm^{-1}$. MS *m/e*: 232 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.93—4.60 (4H, m, H-4, 5, 6), 5.47 (1H, d, $J_{1,2}$=6 Hz, H-2), 5.60 (1H, s, PhCH), 7.29 (1H, d, H-1), 7.26—7.58 (5H, m, aromatic). *Anal.* Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.14; H, 5.35.

**Reaction of 2 with Cesium Fluoride**——A mixture of **2** (100 mg, 0.22 mmol) and anhydrous cesium fluoride (159 mg) in freshly distilled acetonitrile (3 ml) was heated under reflux for 3 h until the starting material disappeared (TLC, chloroform). After removal of the solvent, the residue was treated as described for the reaction with potassium fluoride to give methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**5**) (23 mg, 40%) as needles, after recrystallization from *n*-hexane–acetone, mp 167—168 °C (lit.[17] 170—171 °C). IR (Nujol): 1740 (C=O) $cm^{-1}$. MS *m/e*: 264 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.64 (1H, dd, $J_{1,2e}$=2 Hz, $J_{2a,2e}$= 14 Hz, H-2e), 2.85 (1H, dd, $J_{1,2a}$=4 Hz, H-2a), 3.36 (3H, s, $OCH_3$), 3.80—4.50 (4H, m, H-4, 5, 6), 5.12 (1H, dd, H-1), 5.58 (1H, s, PhCH), 7.24—7.58 (5H, m, aromatic). *Anal.* Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.67; H, 6.37.

**Reaction of 2 with Tetra-*n*-butylammonium Fluoride**——A solution of **2** (200 mg, 0.44 mmol) and tetra-*n*-butylammonium fluoride (354 mg) in freshly distilled acetonitrile (3 ml) was stirred for 1 h at 50 °C. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (4 : 1) to give a mixture of **4** and **5** (34 mg) as a solid, which could not be further separated by column chromatography. The ratio of **4** and **5** (5 : 7) was estimated from the $^1$H-NMR spectrum.

**Reaction of 3 with Tetra-*n*-butylammonium Fluoride**——A solution of **3** (164 mg, 0.44 mmol) and tetra-*n*-butylammonium fluoride (369 mg) in freshly distilled acetonitrile (3 ml) was stirred for 10 min at 50 °C. After removal of the solvent, the resulting solid was chromatographed on silica gel with *n*-hexane–ethyl acetate (4 : 1) to give methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*erythro*-hex-2-enopyranoside (**6**) (87 mg, 82%) as colorless needles, after recrystallization from ether, mp 168.5—170 °C. $[\alpha]_D$ +77.8° ($c$=0.46, chloroform). IR (chloroform): 1680 (C=C) cm$^{-1}$. MS *m/e*: 278 ($M^+$). $^1$H-NMR ($CDCl_3$)[18] $\delta$: 3.44, 3.62 (3H, s, $OCH_3$), 3.72—4.38 (4H, m, H-4, 5, 6), 4.68 (1H, dd, $J_{1,2}$=2.9 Hz, $J_{1,4}$=1.4 Hz, H-1), 5.06 (1H, d, H-2), 5.57 (1H, s, PhCH), 7.39—7.58 (5H, m, aromatic). *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.76; H, 6.58.

**Reaction of 7 with Cesium Fluoride**——Anhydrous cesium fluoride (1.0 g) was added to a solution of **7** (0.51 g, 1.0 mmol) in freshly distilled DMF (4 ml). The mixture was heated at 145 °C until the starting material disappeared (TLC; *n*-hexane–ethyl acetate, 6 : 1). After 30 min, the solvent was evaporated off and the residue was dissolved in chloroform. The solution was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (10 : 1) to give methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside (**10**) (160 mg, 42%) as colorless needles, after recrystallization from ether, mp 156—158 °C. $[\alpha]_D$ −42° ($c$=0.85, chloroform). IR (Nujol): 1100 (C–O–C) cm$^{-1}$. MS *m/e*: 374 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.59 (3H, s, $OCH_3$), 3.40—3.94 (4H, m, H-3, 5, 6), 4.34 (1H, dt, $J_{1,2}$=$J_{2,3}$=7.8 Hz, $J_{2,F}$=51 Hz, H-2), 4.38 (1H, dd, $J_{3,4}$=10 Hz, $J_{4,5}$=4.6 Hz, H-4), 4.49 (1H, dd, $J_{1,F}$=2.0 Hz, H-1), 4.86 (2H, s, $PhCH_2O$), 5.56 (1H, s, PhCH), 7.28—7.55 (10H, m, aromatic). *Anal.* Calcd for $C_{21}H_{23}FO_5$: C, 67.37; H, 6.19. Found: C, 67.30; H, 6.21.

**Reaction of 7 with Tetraalkylammonium Fluorides**——A) Tetraethylammonium fluoride (75 mg) was added to a solution of **7** (104 mg, 0.21 mmol) in freshly distilled acetonitrile (2 ml), and the mixture was stirred at 50 °C until the starting material disappeared. After 20 min, the solvent was evaporated off and the residue was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (20 : 1) gave crystalline **10** (44 mg, 57%), which was identical with that obtained by the reaction of **7** with cesium fluoride.

Further elution with the same solvent system gave methyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-deoxy-β-D-*erythro*-hex-2-enopyranoside (**11**) (15 mg, 21%) as a solid, after recrystallization from *n*-hexane–ether, mp 83 °C. $[\alpha]_D$ −110° ($c$=0.34, chloroform). IR (Nujol): 1660 (C=C) cm$^{-1}$. MS *m/e*: 354 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.42 (3H, s, $OCH_3$), 3.67—4.50 (4H, m, H-4, 5, 6), 4.70 (1H, t, $J_{1,2}$=$J_{1,4}$=1.5 Hz, H-1), 4.88 (2H, s, $PhCH_2O$), 5.39 (1H, dd, $J_{2,4}$=−2.2 Hz, H-2), 5.63 (1H, s, PhCH), 7.30—7.58 (10H, m, aromatic). *Anal.* Calcd for $C_{21}H_{22}O_5$: C, 71.13; H, 6.26. Found: C, 71.13; H, 6.27. The use of THF (2 ml) as the solvent in the reaction of **7** (99 mg) with tetraethylammonium fluoride (77 mg) under reflux for 20 min afforded **10** and **11**, after the same procedure as described above, in the yields shown in Table I.

B) The reaction of **7** (80 mg) in acetonitrile (2 ml) with tetramethylammonium fluoride (66 mg) was carried out for 30 min at 50 °C by the same procedure as described in part A; the yields of the products are shown in Table I.

C) The reaction of **7** (100 mg) with tetra-*n*-butylammonium fluoride (2.5 eq) in acetonitrile or tetrahydrofuran was carried out for 30 min at room temperature. The same work-up and purification as described in part A gave **10** and **11** in the yields shown in Table I.

**Reaction of 8 with Tetramethylammonium Fluoride**——Compound **8** (95 mg, 0.21 mmol) was added to a solution of tetramethylammonium fluoride (91 mg) in freshly distilled acetonitrile (2 ml), and the mixture was stirred at 70 °C until the starting material disappeared (TLC; *n*-hexane–ethyl acetate, 5 : 1). After 50 min, the solvent was evaporated off and the residue was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (5 : 1) gave methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside (**14**) (14.5 mg, 21%) as colorless prisms, after recrystallization from ether, mp 177—179 °C. $[\alpha]_D$ −155.2° ($c$=0.18, chloroform). IR (chloroform): 1750 (C=O) cm$^{-1}$. MS *m/e*: 326 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.13 (3H, s, $OCOCH_3$), 3.49—3.89 (3H, m, H-5, 6), 3.60 (3H, s, $OCH_3$), 4.28 (1H, ddd, $J_{1,2}$=7.6 Hz, $J_{2,3}$=8.8 Hz, $J_{2,F}$=49.0 Hz, H-2), 4.39 (1H, dd, $J_{3,4}$=9.9 Hz, $J_{4,5}$=4.1 Hz, H-4), 4.55 (1H, dd, $J_{1,F}$=1.5 Hz, H-1), 5.29—5.60 (1H, m, H-3), 5.49 (1H, s, PhCH), 7.30—7.50 (5H, m, aromatic). *Anal.* Calcd for $C_{16}H_{19}FO_6$: C, 58.89; H, 5.87. Found: C, 58.87; H, 5.87.

Further elution with the same solvent system gave methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**15**) (10.3 mg, 14%) as a solid, after recrystallization from ether, mp 170—172 °C (lit.[19] 171—172 °C). IR (chloroform): 1760 (C=O) cm$^{-1}$. MS *m/e*: 366 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.04, 2.07 (3H, s, $OCOCH_3$), 3.49—3.91 (3H, m, H-5, 6), 3.52 (3H, s, $OCH_3$), 4.39 (1H, dd, $J_{3,4}$=9.3 Hz, $J_{4,5}$=4.2 Hz, H-4), 4.51 (1H, d, $J_{1,2}$=7.8 Hz, H-1), 4.99 (1H, dd, $J_{2,3}$=9.3 Hz, H-2), 5.23 (1H, t, H-3), 5.51 (1H, s, PhCH), 7.30—7.52 (5H, m, aromatic). *Anal.* Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.01; H, 6.05.

**Reaction of 9 with Tetraalkylammonium Fluorides**——A) Tetraethylammonium fluoride (238 mg) was added to a solution of **9** (391 mg, 0.78 mmol) in freshly distilled acetonitrile (4 ml), and the mixture was stirred at 50 °C until the starting material disappeared (TLC; *n*-hexane–ethyl acetate, 4 : 1). After 20 min, the solvent was evaporated off and the residue was chromatographed on silica gel. Elution with *n*-hexane–ether (4 : 1) gave methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-*β*-D-*erythro*-hex-2-enopyranoside (**13**) (172 mg, 63%) as colorless needles, after recrystallization from *n*-hexane–ether, mp 81—83 °C. $[\alpha]_D$ −86 ($c$=0.58, chloroform). IR (chloroform): 1680 (C=C), 1760 (C=O) cm$^{-1}$. MS *m*/*e*: 319 ($M^+ - OCH_3$). $^1$H-NMR ($CDCl_3$)18) $\delta$: 2.09, 2.10 (3H, s, $OCOCH_3$), 3.45 (3H, s, $OCH_3$), 4.05—4.18 (3H, m, H-5, 6), 4.83 (2H, s, $PhCH_2O$), 4.98 (1H, d, $J_{1,2}$=2.7 Hz, H-1), 5.19 (1H, dd, $J_{2,4}$= −0.5 Hz, $J_{4,5}$=2.6 Hz, H-4), 5.35 (1H, dd, H-2). *Anal.* Calcd for $C_{18}H_{22}O_7$: C, 61.71; 6.33. Found: C, 61.73; H, 6.32.

Further elution with the same solvent system gave methyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-*β*-D-glucopyranoside (**12**) (104 mg, 36%) as colorless needles, after recrystallization from *n*-hexane–ether, mp 74—75 °C. $[\alpha]_D$ −9.9° ($c$=0.61, chloroform). IR (chloroform): 1760 (C=O) cm$^{-1}$. MS *m*/*e*: 370 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.97, 2.07 (3H, s, $OCOCH_3$), 3.49—4.34 (4H, m, H-3, 5, 6), 3.58 (3H, s, $OCH_3$), 4.39 (1H, dt, $J_{1,2}=J_{2,3}$=7.7 Hz, $J_{2,F}$=52 Hz, H-2), 4.42 (1H, dd, $J_{1,F}$=1.7 Hz, H-1), 4.60 and 4.87 (2H, 2d, $J_{gem}$=11.9 Hz, $PhCH_2O$), 5.05 (1H, t, $J_{3,4}=J_{4,5}$=9.7 Hz, H-4), 7.22—7.38 (5H, m, aromatic). *Anal.* Calcd for $C_{18}H_{23}FO_7$: C, 58.37; H, 6.26. Found: C, 58.59; H, 6.27.

B) The reaction of **9** (165 mg) in acetonitrile (3 ml) with tetramethylammonium fluoride (141 mg) was carried out under reflux for 40 min by the same procedure as described in part A, and the yields of the products are shown in Table I.

**Reaction of 16 with Tetraalkylammonium Fluorides**——A) Tetraethylammonium fluoride (172 mg) was added to a solution of **16**5a) (200 mg, 0.47 mmol) in freshly distilled acetonitrile (3 ml), and the mixture was stirred at 50 °C until the starting material disappeared (TLC; *n*-hexane–ethyl acetate, 5 : 1). After 20 min, the solvent was evaporated off and the residue was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (10 : 1) gave methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-3-*O*-methyl-*β*-D-glucopyranoside (**17**) (88 mg, 63%) as colorless needles, after recrystallization from *n*-hexane–ether, mp 113 °C (lit.5a) 108 °C). IR (Nujol): 1100 (C–O–C) cm$^{-1}$. MS *m*/*e*: 298 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.59, 3.65 (3H, s, $OCH_3$), 3.40—3.88 (4H, m, H-3, 5, 6), 4.25 (1H, dt, $J_{1,2}=J_{2,3}$=7.9 Hz, $J_{2,F}$=51.2 Hz, H-2), 4.38 (1H, dd, $J_{3,4}$=10.2 Hz, $J_{4,5}$=4.5 Hz, H-4), 4.49 (1H, dd, $J_{1,F}$=2.7 Hz, H-1), 5.55 (1H, s, PhCH), 7.33—7.55 (5H, m, aromatic). *Anal.* Calcd for $C_{15}H_{19}FO_5$: C, 60.40; H, 6.42. Found: C, 60.21; H, 6.43.

Further elution with the same solvent system gave methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-*β*-D-*erythro*-hex-2-enopyranoside (**18**) (35 mg, 27%) as colorless needles, after recrystallization from *n*-hexane–ether, mp 131—132 °C. $[\alpha]_D$ −153° ($c$=0.15, chloroform). IR (Nujol): 1680 (C=C) cm$^{-1}$. MS *m*/*e*: 278 ($M^+$). $^1$H-NMR ($CDCl_3$)18) $\delta$: 3.48, 3.68 (3H, $OCH_3$), 3.77—4.47 (4H, m, H-4, 5, 6), 4.64 (1H, t, $J_{1,2}=J_{1,4}$=1.5 Hz, H-1), 5.40 (1H, dd, $J_{2,4}$= −2.3 Hz, H-2), 5.60 (1H, s, PhCH), 7.30—7.56 (5H, m, aromatic). *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.68; H, 6.51.

B) The reaction of **16** (202 mg) in acetonitrile (3 ml) with tetra-*n*-butylammonium fluoride (300 mg) was carried out for 30 min at room temperature by the same procedure as described in part A; the yields of the products are shown in Table I.

**Hydrolysis of 10 with Methanesulfonic Acid**——A) A mixture of **10** (148 mg, 0.4 mmol) and water (1.4 ml) containing methanesulfonic acid (0.6 ml) was heated under reflux for 30 min. The cooled solution was neutralized with ion exchange resin (AG 11A8, Bio Rad Lab.) and then the resin was removed by filtration. The filtrate was evaporated to dryness and the residue was chromatographed on dry silica gel. Elution with ethyl acetate gave methyl 2-deoxy-2-fluoro-*β*-D-glucopyranoside (**21**) (13.7 mg, 18%) as a solid. Acetylation of **21** (10 mg) with acetic anhydride in pyridine in the usual manner and subsequent chromatography on silica gel with chloroform–ethyl acetate (10 : 1) gave methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-*β*-D-glucopyranoside (**22**) (14.4 mg) as colorless needles, after recrystallization from *n*-hexane–ether, mp 131.5—132.5 °C (lit.6a) 128—129 °C). IR (chloroform): 1760 (C=O) cm$^{-1}$. MS *m*/*e*: 291 ($M^+ - OCH_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.04, 2.09, 2.10 (3H, s, $OCOCH_3$), 3.58 (3H, s, $OCH_3$), 3.65—4.38 (3H, m, H-5, 6), 4.29 (1H, dt, $J_{1,2}=J_{2,3}$=9 Hz, $J_{2,F}$=51 Hz, H-2), 4.50 (1H, dd, $J_{1,F}$=4 Hz, H-1), 5.03 (1H, t, $J_{3,4}=J_{4,5}$=10 Hz, H-4), 5.17—5.50 (1H, m, H-3). *Anal.* Calcd for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.94. Found: C, 48.68; H, 5.91.

Further elution with the same solvent gave pure 2-deoxy-2-fluoro-D-glucose (**1**) (39 mg, 54%) as a solid, after recrystallization from methanol–ethyl acetate, mp 173—176 °C (lit.11) 160—165 °C). $[\alpha]_D$ +54.8° ($c$=6.5, water) (lit.11) $[\alpha]_D$ +56°). $^1$H-NMR ($D_2O$)12) $\delta$: 3.32—4.08 (m, H-3, 4, 5, 6), 4.05 (ddd, $J_{1,2}$=7.8 Hz, $J_{2,3}$=8.8 Hz, $J_{2,F}$=50 Hz, H-2, *β*-anomer), 4.36 (ddd, $J_{1,2}$=3.7 Hz, $J_{2,3}$=9.5 Hz, $J_{2,F}$=48.9 Hz, H-2, *α*-anomer), 4.85 (dd, $J_{1,F}$=2.5 Hz, H-1, *β*-anomer), 5.39 (d, $J_{1,F}<0.5$ Hz, H-1, *α*-anomer). $^{13}$C-NMR ($D_2O$)13) *α*-anomer $\delta$: 62.97 (s, $C_6$), 71.76 (d, $J_{4,F}$=8.54 Hz, $C_4$), 73.73 (d, $J_{3,F}$=17.1 Hz, $C_3$), 73.83 (s, $C_5$), 92.23 (d, $J_{1,F}$=20.8 Hz, $C_1$), 92.82 (d, $J_{2,F}$=186.8 Hz, $C_2$). *β*-anomer $\delta$: 63.16 (s, $C_6$), 71.86 (d, $J_{4,F}$=8.54 Hz, $C_4$), 76.61 (d, $J_{3,F}$=17.1 Hz, $C_3$), 78.61 (s, $C_5$), 95.47 (d, $J_{2,F}$=183.1 Hz, $C_2$), 96.11 (d, $J_{1,F}$=22.0 Hz, $C_1$). *Anal.* Calcd for $C_6H_{11}FO_5$: C, 39.57; H, 6.09. Found: C, 39.63; H, 6.19.

B) A mixture of **10** (120 mg) and water (0.9 ml) containing methanesulfonic acid (0.9 ml) was refluxed for 30 min. The hydrolyzate was worked up as described in part A, and the resulting residue was purified by dry-column chromatography with ethyl acetate to give pure **1** (40.8 mg, 70%) as a solid, which was identical with that obtained in part A.

**Acetylation of 1**——Compound **1** (100 mg) thus obtained was acetylated with a large excess of acetic anhydride in pyridine for 12 h at room temperature. The usual work-up and subsequent chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) afforded 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose (**23**) (168 mg) as a syrup, which was shown by $^1$H-NMR to consist of a mixture of the $\alpha$ and $\beta$-anomers (1 : 1.5). IR (chloroform): 1760 (C=O) cm$^{-1}$. MS *m*/*e*: 291 ($M^+ - OCOCH_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.04—2.21 (m, $OCOCH_3$), 3.77—4.40 (m, H-5, 6), 4.45 (ddd, $J_{1,2}=8.1$ Hz, $J_{2,3}=8.9$ Hz, $J_{2,F}=49.3$ Hz, H-2, $\beta$-anomer), 4.66 (ddd, $J_{1,2}=3.9$ Hz, $J_{2,3}=9.5$ Hz, $J_{2,F}=48.5$ Hz, H-2, $\alpha$-anomer), 5.06 (t, $J_{3,4}=J_{4,5}=9.5$ Hz, H-4, $\beta$-anomer), 5.09 (t, $J_{3,4}=J_{4,5}=9.5$ Hz, H-4, $\alpha$-anomer), 5.22—5.62 (m, H-3), 5.78 (dd, $J_{1,F}=3.2$ Hz, H-1, $\beta$-anomer), 6.42 (d, $J_{1,F}<0.5$ Hz, H-1, $\alpha$-anomer). *Anal.* Calcd for $C_{14}H_{19}FO_9$: C, 48.0; H, 5.47. Found: C, 47.97; H, 5.66.

**Reaction of 17 with Boron Tribromide**——A mixture of **17** (232 mg, 0.78 mmol) and boron tribromide in methylene chloride solution (3.7 ml of 2 M solution) was allowed to stand at room temperature. After 50 min, the mixture was quenched by addition of crushed ice and the solution was neutralized with powdered silver carbonate. The resulting suspension was filtered through Celite and evaporated. The syrupy residue was chromatographed on dry silica gel with chloroform–methanol (8 : 1) to give 2-bromo-2-deoxy-D-mannose (**19**) (99.7 mg, 53%) as a syrup. Acetylation of **19** (80 mg) with acetic anhydride in pyridine for 3 h at room temperature followed by chromatography on silica gel with benzene–ethyl acetate (8 : 1) gave 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-D-mannopyranose (**20**) (136 mg) as a syrup. The $^1$H-NMR spectrum showed that it was an anomeric mixture with a ratio of $\alpha : \beta = 3.5 : 1$. IR (chloroform): 1750 (C=O) cm$^{-1}$. MS *m*/*e*: 353 ($M^+ + 2 - OCOCH_3$), 351 ($M^+ - OCOCH_3$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.04—2.18 (m, $OCOCH_3$), 3.73—4.36 (m, H-5, 6), 4.44 (dd, $J_{1,2}=1.9$ Hz, $J_{2,3}=4.2$ Hz, H-2, $\alpha$-anomer), 4.60 (dd, $J_{1,2}=1.5$ Hz, $J_{2,3}=3.7$ Hz, H-2, $\beta$-anomer), 4.99 (dd, $J_{3,4}=9.6$ Hz, H-3, $\beta$-anomer), 5.20 (dd, $J_{3,4}=9.8$ Hz, H-3, $\alpha$-anomer), 5.43 (t, $J_{4,5}=9.6$ Hz, H-4, $\beta$-anomer), 5.50 (t, $J_{4,5}=9.8$ Hz, H-4, $\alpha$-anomer), 5.74 (d, H-1, $\beta$-anomer), 6.32 (d, H-1, $\alpha$-anomer). *Anal.* Calcd for $C_{14}H_{19}BrO_9$: C, 40.89; H, 4.66. Found: C, 40.72; H, 4.60.

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