



## Chemoenzymatic Synthesis of Fluorinated Carbohydrates: 2-Deoxy-2-fluoro-D-glucose and 5-Deoxy-5-fluoro-manno- $\gamma$ -lactol

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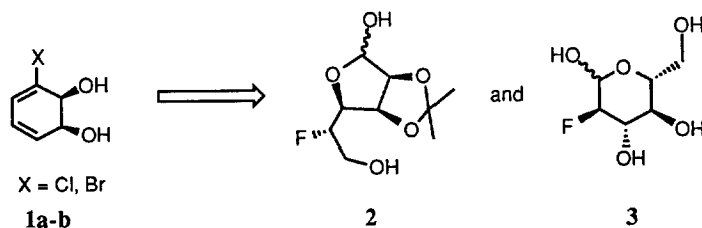
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**Abstract:** Two fluorinated hexoses were prepared from optically active *cis*-diols **1**, which were obtained by microbial oxidation of the corresponding halobenzenes with *E. coli* JM109 (pDTG 601). The stereochemistry of the products was controlled by careful introduction of fluorine onto the periphery of the *cis*-diols *via* opening of epoxides with tetrabutylphosphoniumfluoride dihydrofluoride (TBPF-DF). Oxidative cleavage of the cyclohexene skeleton followed by reductive cyclization led to the fluorinated hexoses. © 1997 Elsevier Science Ltd.

### INTRODUCTION

Fluorinated sugars are of interest because of their applications as molecular probes in the elucidation of biochemical processes such as carbohydrate metabolism and enzymology,<sup>1</sup> the use as noninvasive diagnostic agents,<sup>2</sup> and their potential as antiviral and antitumor drugs.<sup>3</sup> Because of these properties, the search for efficient and versatile methods of synthesis of fluorinated sugars continues to challenge synthetic chemists.

The synthesis of fluorinated sugars by modifying known carbohydrates is tedious and time consuming because (i) numerous protection and deprotection steps of parent sugars are required for the introduction of fluorine; (ii) some sugars are not available in unnatural configurations; and (iii) fluoride ion is a poor nucleophile for S<sub>N</sub>2 substitution reactions and may catalyze eliminations.<sup>4,5</sup> The synthesis of fluorinated sugars currently depends on chemical procedures<sup>6</sup> which often present difficulty in controlling stereochemistry at the multiple adjacent asymmetric centers. Limited enzymatic approaches to the synthesis of 6-deoxy-6-fluoro hexoses by means of FDP-aldolase and glucose isomerase have recently been reported,<sup>7</sup> but the discipline would benefit from a general and versatile method for the synthesis of fluorinated carbohydrate analogs.



Cyclohexadiene *cis*-diols (**1**), produced by controlled microbial oxidation of arenes with the mutant or recombinant strains of *Pseudomonas putida* (Pp 39D) and *E. coli* JM109,<sup>8</sup> respectively, have been used

extensively in the syntheses of diverse natural products.<sup>9</sup> Notable work from our group includes the concise syntheses of cyclitols,<sup>10</sup> aminocyclitols,<sup>11</sup> sugars,<sup>12</sup> aza-sugars,<sup>13</sup> amino-sugars,<sup>14</sup> several conduritols,<sup>15</sup> and alkaloids.<sup>16</sup> This paper further demonstrates the versatility of optically active cyclohexadiene *cis*-diols in the design of a general method for the synthesis of fluorinated sugars. This strategy is illustrated by the synthesis of two deoxyfluorosugars, protected 5-deoxy-5-fluoro-manno- $\gamma$ -lactol (**2**) and 2-deoxy-2-fluoro-D-glucose (**3**).

## RESULTS AND DISCUSSION

This systematic approach to the synthesis of a fluorinated sugar is based on the controlled introduction of functionalities in positions C<sub>4</sub> and C<sub>5</sub> in synthons of type **4** in Figure 1. The key feature of our approach is the ozonolysis of the C<sub>1</sub>-C<sub>6</sub> double bond after the substitution pattern at C<sub>4</sub> and C<sub>5</sub> is established. The C<sub>1</sub> and C<sub>6</sub> of compound **4** represent a latent acid halide (or carboxylate) and an aldehyde, respectively. These latent functionalities are expressed after oxidative cleavage and subsequent reductive work-up. Annulation by a C<sub>4</sub>-C<sub>1</sub> closure (path a), a C<sub>2</sub>-C<sub>6</sub> cyclization (path b), or a C<sub>5</sub>-C<sub>1</sub> (path c) ring closure selectively generates 5-fluoro, 2-fluoro, 3-fluoro, or 4-fluoro-deoxysugar derivatives (**2**, **3**, **6**, and **7**), respectively, as shown in Figure 1. In addition, cyclization of C<sub>4</sub>-C<sub>1</sub> (path a) could lead to any of the four isomers of 5-deoxy-5-fluoro-lactol (**2**) (depending on the stereochemistry at C<sub>4</sub> and C<sub>5</sub>).

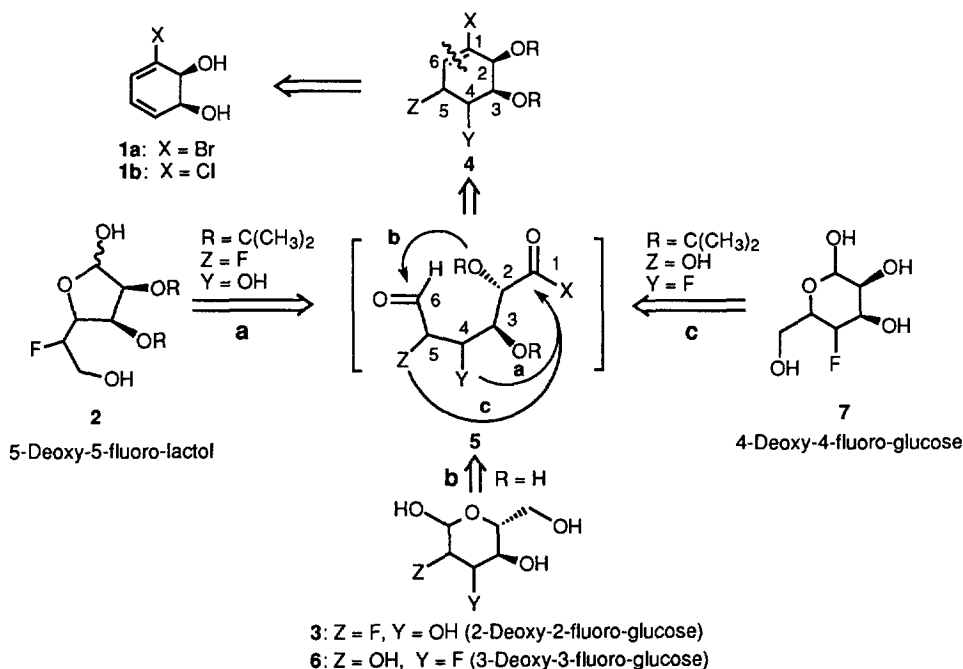
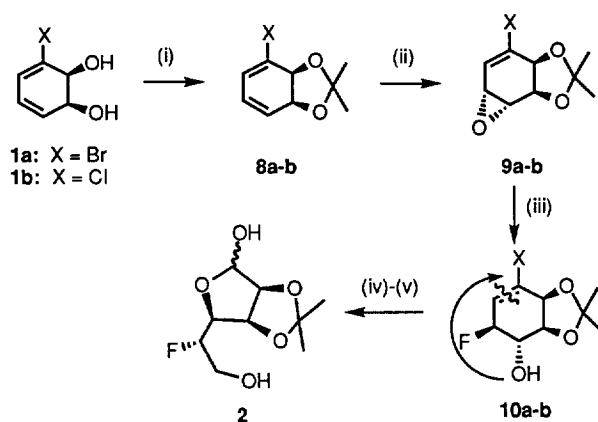


Figure 1: General Design of Fluorodeoxy Sugars

This methodology is designed to be general for the preparation of any deoxymonosaccharide containing fluorine in a specifically desired position. In this aspect, traditional synthetic routes are limited and cannot compete. A preliminary demonstration of this flexible method is demonstrated in the synthesis of **2** and **3**.

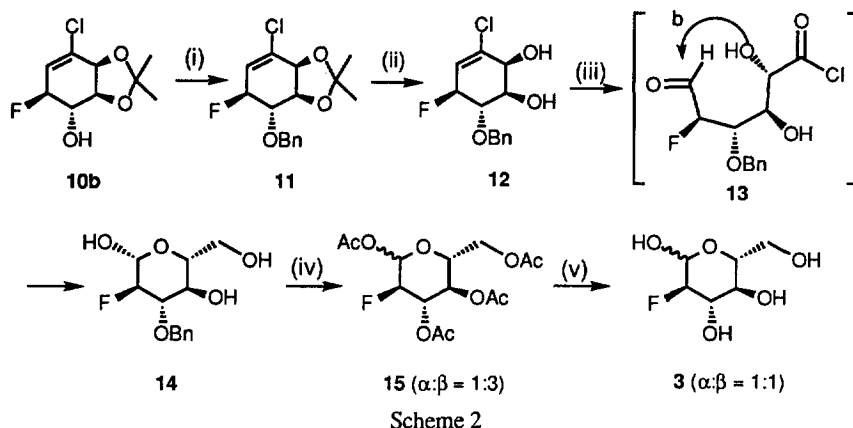
Regio- and stereoselective epoxidation of dienediol **8** with *m*-CPBA afforded the  $\alpha$ -epoxide **9** as a single diastereomer (Scheme 1).<sup>17</sup> This stereoselectivity arises from the efficient shielding of the  $\beta$ -face by the *endo* methyl group of the acetonide and deactivation by the inductive effect of the olefin by the halogen. Opening of the epoxide by fluoride anion (TBPf-DF) resulted in alcohol **10**.<sup>15b</sup> This compound served as an important intermediate in the synthesis of 3-deoxy-3-fluoro-*L*-chiro-inositol.<sup>18</sup> Based on the rationale in Figure 1, ozonolysis of olefin **10a** followed by cyclization led to fluorinated lactol **2** protected as the acetonide to avoid equilibration of five- and six-membered forms (Scheme 1).



Scheme 1

Reagents and Conditions: (i) 2,2-DMP, acetone, cat. TsOH; (ii) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h; (iii) TBPf-DF, 100 °C, 24 h; (iv) O<sub>3</sub>, MeOH, -78 °C, 15 min; (v) NaBH<sub>4</sub>.

Benzyl ether **11**, prepared from **10b** by protection of hydroxyl group, was converted to diol **12** by hydrolysis of the acetonide group. Ozonolysis of **12** and *in situ* cyclization of **13** was followed by hydrolysis and diborane reduction of the carboxylic acid to provide **14**, the precursor to  $\beta$ -D-glucose. The benzyl group in **14** was removed by treatment with FeCl<sub>3</sub>-Ac<sub>2</sub>O to give  $\beta$ -tetraacetates **15** as the major product ( $\alpha$ : $\beta$  = 1:3). The desired 2-deoxy-2-fluoro-D-glucose (**3**) was obtained by removal of the acetyl groups as shown in Scheme 2, and was found by NMR to consist of an anomeric mixture ( $\alpha$ : $\beta$  = 1:1). <sup>1</sup>H and <sup>19</sup>F NMR data of a standard sample (Aldrich Chemical Co.) was identical to that for the  $\alpha$ -anomer. The commercial sample upon standing in CD<sub>3</sub>OD for 48 hours equilibrated to a mixture of anomers ( $\alpha$ : $\beta$  = 1:1) that was identical to the anomeric mixture of **3**.



Reagents and Conditions: (i) NaH, BnBr, THF; (ii) HCl, THF; (iii) a. O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; b. DMS, -78 °C - rt; c. H<sub>2</sub>O; d. BH<sub>3</sub>·THF; (iv) FeCl<sub>3</sub>-Ac<sub>2</sub>O; (v) CH<sub>3</sub>OH, CH<sub>3</sub>ONa.

## CONCLUSION

A combination of enzymatic and chemical methods resulted in the efficient synthesis of two deoxyfluorosugars from cyclohexadiene *cis*-diols. In principle, the design disclosed in this paper will be applicable to the synthesis of a variety of deoxyfluorosugars. Further applications of this methodology are in progress and will be reported in due course.

## EXPERIMENTAL SECTION

**General Procedure:** Melting points were measured on a Thomas-Hoover capillary melting point apparatus and were not corrected. Infrared Spectra (IR) were recorded on a Perkin-Elmer FT-IR. <sup>1</sup>H (300 MHz), <sup>19</sup>F (282 MHz), and <sup>13</sup>C (75 MHz) NMR Spectra were obtained on Varian 300 MHz spectrometer using CDCl<sub>3</sub> unless otherwise indicated, and the chemical shifts are reported in δ (ppm) values downfield from TMS (<sup>1</sup>H NMR), CFC<sub>3</sub> (<sup>19</sup>F NMR), and CDCl<sub>3</sub> (<sup>13</sup>C NMR, 77.05 ppm), respectively, as internal standards. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter. High resolution mass spectra and elemental analyses were performed at the University of Florida. All reactions in aprotic solvents were carried out in an atmosphere of argon or nitrogen. Glassware used for moisture-sensitive reactions was dried under vacuum. Analytical TLC was performed on Whatman K6F silica gel 60-Å plates. Flash chromatography was performed on chromatographic silica gel, 230-400 mesh (Fisher Chemical). Compounds **8a-b**, **9a-b**, and **10a-b** were prepared according to literature methods.<sup>18</sup>

**5-Deoxy-5-fluoro-manno-γ-lactol acetonide (2).** A solution of bromide **10a** (0.4 g, 1.5 mmol) in 10 mL of MeOH was cooled to -78 °C. A stream of O<sub>3</sub>/O<sub>2</sub> was passed through the reaction mixture. After the

reaction finished, the unreacted O<sub>3</sub> was removed at - 78 °C with a stream of nitrogen, and the reaction mixture was warmed to 0 °C. NaBH<sub>4</sub> (0.14 g, 3.75 mmol) was added to the reaction mixture. The reaction was quenched with water, and the mixture adjusted to pH 6 with 0.5 M HCl. The product was extracted with diethyl ether (3 × 10 mL) and then ethyl acetate (3 × 10 mL). The organic layers were combined and dried over MgSO<sub>4</sub>. After filtration, the solvent was removed and the crude product was introduced onto a silica-gel column and eluted with hexane/ethyl acetate (1/2) to give 0.25 g (75%) of **2** as a white solid. Mp: 68-69 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 11.5 (*c* 0.52, MeOH); IR (KBr): 3410, 2939, 1381, 1215 (cm<sup>-1</sup>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 6.38 (dd, *J* = 10.5, 2.7 Hz, 1H), 5.77 (d, *J* = 5.4 Hz, 1H), 4.85 (ddd, *J* = 49.1, 6.8, 2.7 Hz, 1H), 4.67 (d, *J* = 6.1 Hz, 1H), 4.18 (t, *J* = 6.8 Hz, 1H), 3.66 (m, 1H), 3.52 (m, 3H), 1.40 (s, 3H), 1.32 (s, 3H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): 112.9 (s), 101.3 (s), 93.5 (d, *J* = 170.1 Hz), 85.6 (s), 79.4 (d, *J* = 9.2 Hz), 78.8 (d, *J* = 18.3 Hz), 62.1 (d, *J* = 20.6 Hz), 26.0 (s), 24.6 (s); <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>): - 198.39 (m); HRMS: C<sub>9</sub>H<sub>15</sub>FO<sub>5</sub> (M+H) cal. 223.0977, found 223.1010; Anal. calcd for C<sub>9</sub>H<sub>15</sub>FO<sub>5</sub>: C, 48.63; H, 6.81. Found: C, 48.93; H, 6.99.

**(3a*S*,4*S*,5*S*,7a*S*)-4-Benzoyloxy-7-chloro-5-fluoro-2,2-dimethyl-4,5-dihydrobenzo[*d*][1,3]dioxole (11)**. To a solution of **10b** (2.81 g, 12.6 mmol) in DMF (15 mL) was added NaH (0.91 g, 37.9 mmol) at room temperature. After 10 min, the reaction mixture was cooled to 0 °C, and benzyl bromide (4.28 g, 25.2 mmol) was added. The mixture was warmed to room temperature for 1h. The reaction was quenched with NH<sub>4</sub>Cl at 0 °C. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The organic layers were combined and dried over MgSO<sub>4</sub>. After filtration, the solvent was removed and the residue was introduced onto a silica-gel column and eluted with hexane/ethyl acetate (10/1) to give 3.77 g (96%) of **11** as a white solid. Mp: 59.5-60 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 19.0 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr): 3020, 2997, 2938, 1652, 1455, 1382, 1217, 1088, 988 (cm<sup>-1</sup>); <sup>1</sup>H NMR: 7.28-7.42 (m, 5H), 6.05 (dd, *J* = 11.7, 2.7 Hz, 1H), 5.03 (dddd, *J* = 49.2, 6.6, 2.7, 0.9 Hz, 1H), 4.82 (s, 2H), 4.60 (d, *J* = 6.3 Hz, 1H), 4.32 (dd, *J* = 6.3, 7.6 Hz, 1H), 3.73-3.84 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H); <sup>13</sup>C NMR: 137.6 (s), 132.1 (d, *J* = 12.5 Hz), 128.3 (s), 128.0 (s), 127.8 (s), 126.1 (dd, *J* = 24.7, 6.0 Hz), 111.4 (s), 89.5 (dd, *J* = 174.2, 8.0 Hz), 77.4 (d, *J* = 18.1 Hz), 76.4 (d, *J* = 7.5 Hz), 75.5 (d, *J* = 5.0 Hz), 73.7 (m), 27.7 (d, *J* = 4.5 Hz), 26.0 (d, *J* = 4.5 Hz); <sup>19</sup>F NMR: - 184.03 (dt, *J* = 48.8, 12.1 Hz); HRMS: C<sub>16</sub>H<sub>18</sub>ClFO<sub>3</sub> (M+H) cal. 313.7757, found 313.7281; Anal. calcd for C<sub>16</sub>H<sub>18</sub>ClFO<sub>3</sub>: C, 61.44; H, 5.80. Found: C, 61.75; H, 6.04.

**(1*S*,2*S*,5*S*,6*S*)-6-Benzoyloxy-3-chloro-5-fluoro-3-cyclohexene-1,2-diol (12)**. To **11** (2.0 g, 6.39 mmol) was added THF (20 mL), AcOH (7 mL), and HCl (7 mL, 10%). The reaction mixture was stirred at room temperature and monitored by TLC. After 4 h, the reaction mixture was poured into brine (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with aq. NaHCO<sub>3</sub> and aq. NaCl then dried over MgSO<sub>4</sub>. After the solvent was removed, the residue was introduced onto a silica-gel column and eluted with hexane/ethyl acetate (3/1) to give 1.6 g (92 %) of **12** as a white solid. Mp: 92.5-93.5 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 92.0 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr): 3355, 3065, 3061, 2915, 1655, 1450, 1411, 1293, 1125 (cm<sup>-1</sup>); <sup>1</sup>H NMR: 7.34-7.40 (m, 5H), 5.99 (dd, *J* = 11.4, 2.7 Hz, 1H), 5.07 (ddd, *J* = 49.8, 6.9, 2.7 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.34 (dd, *J* = 3.6, 3.0 Hz, 1H), 3.93 (ddd, *J* = 10.3, 15.3, 6.9 Hz, 1H), 3.65-3.74 (m, 1H), 2.94 (d, *J* = 2.7 Hz, 1H, OH), 2.91 (d, *J* = 3.0 Hz, 1H, OH); <sup>13</sup>C NMR: 137.4 (s), 134.8 (d, *J* = 13.7 Hz), 128.4 (s), 128.0 (s), 125.4 (dd, *J* = 23.7, 6.5 Hz), 91.8 (dd, *J* = 173.7, 9.6 Hz),

77.2 (d,  $J = 17.7$  Hz), 73.9-74.4 (m), 70.9 (d,  $J = 4.5$  Hz), 69.0 (d,  $J = 10.0$  Hz);  $^{19}\text{F}$  NMR: - 178.27 (dt,  $J = 51.4, 13.4$  Hz); HRMS:  $\text{C}_{13}\text{H}_{14}\text{ClFO}_3$  (M+H) cal. 273.7111, found 273.7186; Anal. calcd for  $\text{C}_{13}\text{H}_{14}\text{ClFO}_3$ : C, 57.26; H, 5.17. Found: C, 57.48; H, 5.45.

**(2R,3R,4S,5R,6S)-4-Benzoyloxy-3-fluoro-6-hydroxymethyl-perhydro-2,5-pyrandiol (14).** A solution of chloro diol **12** (0.5 g, 1.83 mmol) in 20 mL of  $\text{CH}_2\text{Cl}_2$  was cooled to  $-78$  °C. A stream of  $\text{O}_3/\text{O}_2$  was passed through until a blue color persisted for 5 min. After the excess ozone was removed by a stream of nitrogen, dimethyl sulfide (1.2 mL, 10 eq) was added, and the reaction mixture was warmed to room temperature and stirred for two additional hours. The reaction was quenched with water (0.01 mL) and the solvent removed to give an oily product. The oil, briefly dried in vacuum, was diluted with THF (15 mL) and slowly added to  $\text{BH}_3\cdot\text{THF}$  (20 mL, 20 mmol) at room temperature over 20 min. After stirring for 4 h, the reaction was quenched with water at 0 °C. The product was extracted with ethyl acetate ( $3 \times 50$  mL). The organic layers were combined and dried over  $\text{MgSO}_4$ . The solvent was removed and the residue was introduced onto a silica-gel column and eluted with hexane/ethyl acetate (1/1) to give 0.3 g (60%) of protected  $\beta$ -D-glucose **14**. Mp: 118-119 °C;  $[\alpha]_{\text{D}}^{20} + 17.4$  ( $c$  0.54, MeOH); IR (KBr): 3231, 1492, 1456, 1359, 1085, 739 ( $\text{cm}^{-1}$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ): 7.26-7.36 (m, 5H), 4.84 (d,  $J = 11.7$  Hz, 1H), 4.69 (d,  $J = 11.1$  Hz, 1H), 4.67 (dd,  $J = 8.1, 2.7$  Hz, 1H), 4.11 (dt,  $J = 52.0, 7.8$  Hz, 1H), 3.70 (ABd,  $J = 12.0, 5.4, 3.0$  Hz, 2H), 3.41-3.58 (m, 2H), 3.32 (s, 3H, OH), 3.29-3.31 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ): 139.6 (s), 129.1 (s), 128.9 (s), 128.5 (s), 95.4 (dd,  $J = 23.2, 7.6$  Hz), 95.1 (d,  $J = 185.6$  Hz), 83.9 (d,  $J = 16.6$  Hz), 77.7 (s), 75.4-75.8 (m), 70.9 (d,  $J = 7.8$  Hz), 62.3 (s);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{OD}$ ): - 196.98 (dd,  $J = 51.4, 14.7$  Hz); Anal. calcd for  $\text{C}_{13}\text{H}_{17}\text{FO}_5$ : C, 57.35; H, 6.29. Found: C, 57.34; H, 6.04.

**Tetra-O-acetyl-2-deoxy-2-fluoro-D-glucose (15).** A round-bottom flask was charged with **14** (0.10 g, 0.37 mmol),  $\text{FeCl}_3$  (0.06 g, 0.37 mmol), and acetic anhydride (4 mL). The reaction mixture was stirred at 45 °C. After 2 h, the reaction mixture was poured into 5 mL water and extracted with ethyl acetate ( $3 \times 5$  mL). The combined organic layer was washed with aq.  $\text{NaHCO}_3$  and dried over  $\text{MgSO}_4$ . The residue was introduced onto a silica-gel column and eluted with hexane/ethyl acetate (5/1) to give 0.11 g (86%) of tetraacetate anomers **15** as a colorless oil.  $[\alpha]_{\text{D}}^{20} + 88.6$  ( $c$  0.99,  $\text{CH}_2\text{Cl}_2$ );  $\alpha$ -tetraacetate:  $^1\text{H}$  NMR: 5.74 (dd,  $J = 8.1, 3.3$  Hz, 1H), 5.33 (dt,  $J = 14.4, 9.6$  Hz, 1H), 5.01 (t,  $J = 9.6$  Hz, 1H), 4.39 (dt,  $J = 50.7, 8.5$  Hz, 1H), 4.19-4.28 (m,  $\alpha+\beta$ -1H), 3.97-4.08 (m,  $\alpha+\beta$ -1H), 3.82 (dm,  $J = 9.9, 2.4$  Hz, 1H), 2.12 (s, 3H), 2.03 (s,  $\alpha+\beta$ -3H), 2.02 (s,  $\alpha+\beta$ -3H), 1.98 (s, 3H);  $^{19}\text{F}$  NMR: - 201.40 (dd,  $J = 51.3, 12.1$  Hz);  $\beta$ -tetraacetate: 6.36 (d,  $J = 3.9$  Hz, 1H), 5.50 (dt,  $J = 12.1, 9.3$  Hz, 1H), 5.04 (t,  $J = 9.9$  Hz, 1H), 4.60 (ddd,  $J = 48.6, 9.6, 3.9$  Hz, 1H), 4.19-4.28 (m,  $\alpha+\beta$ -1H), 3.97-4.08 (m,  $\alpha+\beta$ -2H), 2.15 (s, 3H), 2.03 (s,  $\alpha+\beta$ -3H), 2.02 (s,  $\alpha+\beta$ -3H), 1.99 (s, 3H);  $^{19}\text{F}$  NMR: - 202.73 (dd,  $J = 48.8, 12.1$  Hz).

**2-Deoxy-2-fluoro-D-glucose (3).** The tetraacetate anomers **15** (0.08 g, 0.23 mmol) were dissolved in methanol (10 mL), and a 0.5 M solution of sodium methoxide in methanol (20 mL) was added. After 15 h, the reaction mixture was demineralized by shaking it with Amberlite MBS (10 g), filtered, and concentrated to dryness to give 0.037 g (89%) of a mixture of  $\alpha, \beta$  isomers **3** ( $\alpha:\beta = 1:1$ ) as a white solid, which had the same NMR spectrum as authentic sample<sup>19</sup> of **3**. Mp: 167-169 °C;  $[\alpha]_{\text{D}}^{20} + 40.1$  ( $c$  0.58,  $\text{CH}_3\text{OH}$ );  $\alpha$ -glucose:  $^1\text{H}$

NMR (CD<sub>3</sub>OD): 4.69 (dd,  $J = 7.8, 2.4$  Hz, 1H), 3.91 (ddd,  $J = 51.3, 9.0, 7.8$  Hz, 1H), 3.51-3.95 (m,  $\alpha+\beta$ -3H), 3.34-3.41 (m,  $\alpha+\beta$ -2H); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 198.51 (dd,  $J = 51.4, 14.7$  Hz);  $\beta$ -glucose: <sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.26 (d,  $J = 3.6$  Hz, 1H), 4.18 (ddd,  $J = 50.1, 9.6, 3.9$  Hz, 1H), 3.51-3.95 (m,  $\alpha+\beta$ -3H), 3.34-3.41 (m,  $\alpha+\beta$ -2H); <sup>19</sup>F NMR (CD<sub>3</sub>OD): - 199.56 (dd,  $J = 49.9, 12.1$  Hz).

### ACKNOWLEDGMENTS

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