contact and pseudocontact shifts at these relative concentrations and experimental conditions must be first determined.[11,12]

Experimental Section

All NMR spectra were recorded on either a Varian Associates A-60A or XL-100 spectrometer and are referenced to internal tetramethylsilane. *N*-Methylnicotinium iodide was prepared by iodomethylation of nicotine in acetic acid as previously described.[4] Dimethyldodecylamine and trimethyldodecylammonium chloride were obtained from Lachat Chemicals, Inc., MeQuon, Wis., and dried under vacuum and stored over P_2O_5 until used. Eu(fod)$_3$ was freshly sublimed immediately before use. All transfers of LSR were made under dry nitrogen.

3-Dimethylaminotrimethylpropylammonium Iodide (5). To a solution of 10.0 g (77 mmol) of *N,N,N′,N′*-tetramethyl-1,3-propanediamine in 150 mL of benzene was added all at once 5.5 g (38 mmol) of iodomethane (caution: cancer suspect agent). A precipitate immediately formed. After 25 h, the precipitate was filtered, washed with additional benzene, and dried under high vacuum giving 10.1 g (98% based on iodomethane) of **5**, mp 173.5–174 °C.

Anal. Calcd for $C_8H_{21}N_2I$: C, 35.30; H, 7.78; N, 10.30; I, 46.63. Found: C, 35.13; H, 7.68; N, 10.36; I, 46.42.

Representative Procedure of LIS Study. A solution of known concentration of quaternary salt was prepared in an oven-dried NMR tube. To this solution were added known volumes of a Eu(fod)$_3$ solution prepared to known molarity. NMR spectra were recorded after each addition. The relative concentration of Eu(fod)$_3$:substrate was kept below 0.2:1. Replicate experiments were performed.

Acknowledgment. Discussions with Drs. T. Phil Pitner, A. Kassman, and J. F. Whidby are acknowledged with pleasure.

Registry No.—**1**, 21446-46-8; **4**, 62126-65-2; **5**, 110-95-2; **6**, 112-18-5; **7**, 112-00-5; iodomethane, 74-88-4.

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(6) Walker and co-workers[7] have recently reported LIS studies on penta- and hexanitratolanthanate complexes of a number of pyridinium cations, e.g., $[R_4N]_2Ln(NO_3)_5$ and $[R_4N]_3Ln(NO_3)_6$. In these studies, the lanthanide shift "reagent" is in fact the anion of the quaternary ammonium salt.

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(11) Following the completion of this portion of our work, K. B. Lipkowitz reported (Ph.D. Thesis, Montana State University, 1975, pp 171–178, Xerox University Microfilms No. 76-13,307) a LIS study of a sulfonium iodide. Two modes of lanthanide complexation are suggested, either with the remaining lone pair on sulfur or the halide counterion.

(12) **Note Added in Proof.** A competitive shift study between *N*-methyldodecylamine and **7** led to results nearly identical with those shown in Figure 3, i.e., significantly greater LIS were observed for the *N*-methyl and *N*-methylene protons of the quaternary salt than for the corresponding protons of the free base. A similar competitive study between dodecylamine and **7** resulted in nonlinear LIS, indicating the probable need for association constant determinations in these systems.

Thermolysis of *N*-Acyl Substituted 2-Allylthioimidazolines. Evidence for a [3,3] Sigmatropic Rearrangement

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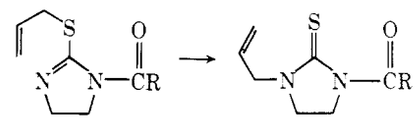
Thermal allylic rearrangements have been a subject of continuing synthetic[1] and mechanistic[2] interest. In relation to a current project dealing with the mechanism of biotin catalysis,[3] *N*-acetyl-2-allylthioimidazoline (**1a**) and *N*-carbomethoxy-2-allylthioimidazoline (**1b**) were prepared as potential model substrates. In light of the molecular framework of **1a** and **1b** it also became of interest to investigate the thermal properties of each of these compounds.

Pyrolysis of **1a** (145 °C, 72 h) gave the rearranged imidazolidinethione (**2a**) as the only product in 75% yield. Conversion of **1a** → **2a** could be monitored by the characteristic

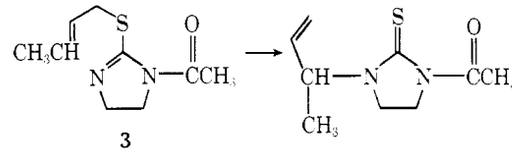


1a, R = CH_3 2a, R = CH_3
b, R = OCH_3 b, R = OCH_3

downfield NMR shift of the acetyl methyl protons from δ 2.20 to δ 2.80.[4]

Mechanistically, the thermal allylic rearrangement of **1a** can be formulated in terms of a number of different dissociative-recombination and concerted reaction pathways. Additional insight into the mechanism operative in this system comes from the thermolysis of compound **3**. *N*-Acetyl-2-crotylthioimidazoline (**3**) was readily prepared by the treatment of *N*-acetylimidazolidinethione[5] with a commercial mixture of 1-bromo-2-butene (80%) and 3-bromo-1-butene (20%) and triethylamine. Despite the possibility of forming a number of different positional isomers, a 91% yield of **3** (a mixture of *E* and *Z* isomers) was obtained.

Thermolysis of **3** under comparable reaction conditions (145 °C, 30 h) gave a 90% yield of *N*-acetyl-*N′*-(3′-butenyl)imidazolidinethione (**4**) as the only isolated product. Support for



3 4

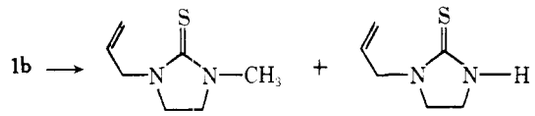
the indicated substitution pattern in the butenyl side chain comes from three complementary NMR observations. First, the lone methine proton resonance was identified as part of the complex multiplet at δ 5.10–6.04 by two successive proton decoupling experiments. Double irradiation of the protons at δ 1.23–1.30 in compound **4** simplified the multiplet at δ 5.10–6.04. Correspondingly, when the multiplet at δ 5.10–6.04 was doubly irradiated, the doublet at δ 1.23–1.30 collapsed into a singlet. Second, a comparison of the NMR spectrum of **2a** with that of **4** showed that the resonance associated with the allylic methylene protons (δ 4.22–4.40) in the former compound was absent in the spectrum of compound **4**. Third, an upfield shift of the high-field methyl proton resonance from δ 1.60–1.82 in **3** to δ 1.23–1.30 in **4** was noted. The resonance at ca. δ 1.60 is a diagnostic peak for vinylic methyl protons,[6] and the absence of this resonance in the spectrum of **4** is a further evidence of structure. The thermal rearrangement can

be conveniently monitored by NMR by observing the characteristic downfield shift of the acetyl methyl protons[4] as well as the upfield shift of the methyl doublet associated with the butenyl side chain. In a preliminary kinetic study, this rearrangement showed first-order behavior in benzene over 2 half-lives ($k_1 = 8.3 \pm 0.1 \times 10^{-6}$ s^{-1} at 141 ± 0.5 °C).

The high yield noted for the conversion of **3** → **4**, the absence of any other positional isomers, and the first-order kinetic behavior of the reaction argue that the thermolysis of **3** as well as **1a** proceeds by a [3,3] sigmatropic pathway. The reaction, therefore, can be considered as an additional example of a thio-Claisen rearrangement.[2,7] It is of interest to note that the [3,3] sigmatropic route is more favorable than either a dissociative-recombination pathway or a thermal Chapman-type four-center rearrangement for these compounds. These results parallel those previously observed for the thermal rearrangements of *O*-allyl imidates.[8]

When, however, compound **1b** was subjected to similar thermolysis conditions (170 °C, 72 h) the isomeric product (**2b**) was not formed, but instead *N*-methyl-*N'*-allylimidazolidinethione (**5**) and *N*-allylimidazolidinethione[9] (**6**) were isolated in 65 and 25% yields, respectively.

There are several intermolecular as well as intramolecular mechanisms that can account for the formation of both **5** and **6**. Precedent does exist for the loss of carbon dioxide in carbamates. Recently, Loozen, Drouen, and Piepers have shown that thermolysis of *N*-alkoxycarbonylimidazoles yielded the corresponding N-alkylated imidazoles,[10] and have suggested a four-center Chapman-type rearrangement for these reactions.[11] We are currently investigating the mechanism of this reaction.[14]



5 6

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus. Infrared spectra (IR) were run on Perkin-Elmer Model 700 and 237B spectrometers and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance spectra were recorded on Varian Associates Model T-60 and EM-390 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on a Varian Associates Model XL-100-15 spectrometer. The XL-100 was equipped with a Nicolet Technology Corp. TT-100 data system. Chemical shifts are expressed in parts per million relative to Me_4Si. Mass spectra (MS) data were obtained at an ionizing voltage of 70 eV on a Hitachi Perkin-Elmer Model RMU-6H mass spectrometer. High-resolution mass spectra were performed by Dr. R. Grigsby at the Department of Biochemistry and Biophysics, Texas A & M University, on a CEC21-110B double focusing magnetic sector spectrometer at 70 eV. Exact masses were determined by peak matching. Elemental analyses were obtained at Spang Microanalytical Laboratories, Ann Arbor, Mich.

The solvents and reactants were of the best commercial grade available and were used without further purification. All reactions were run under nitrogen, and all glassware oven dried before use.

Thermolysis of *N*-Acetyl-2-allylthioimidazoline (1a). Preparation of *N*-Acetyl-*N'*-allylimidazolidinethione (2a). Compound **1a**[4] (0.40 g, 0.002 mol) was sealed in a glass tube and heated at 145 ± 2 °C for 72 h. The reaction product was then triturated overnight with hexane (25 mL), the hexane layer filtered, and the filtrate allowed to stand at 0 °C for 24 h. The hexane layer was refiltered and evaporated in vacuo, and the resultant oil vacuum distilled to give 0.30 g (75%) of **2a**: bp 160 °C (0.4 mm); IR (neat, NaCl) 1680, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (s, 3 H), 3.40–4.14 (m, 4 H), 4.22–4.40 (d, J = 4 Hz, 2 H), 5.10–5.40 (m, 2 H), 5.50–6.10 (m, 1 H); MS *m/e* (rel intensity) 184 (60), 169 (100), 141 (51), 127 (88), 70 (77), 43 (81); mol wt 184.0672 (calcd for $C_8H_{12}N_2OS$, 184.0670).

Thermolysis of *N*-Carbomethoxy-2-allylthioimidazoline (1b). The preceding reaction and workup was repeated using 0.40 g (0.002 mol) of **1b**.[4] The bath temperature was maintained at 170 ± 2 °C for 72 h. Distillation of the resultant oil gave 0.26 g (65%) of **5**: bp 160 °C (0.25 mm); IR (neat) 1700, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.11 (s, 3 H), 3.40–3.55 (m, 4 H), 4.15–4.33 (d, J = 4 Hz, 2 H), 5.00–5.40 (m, 2 H), 5.41–6.20 (m, 1 H); MS *m/e* (rel intensity) 156 (94), 141 (100), 113 (72), 69 (39); mol wt 156.0726 (calcd for $C_7H_{12}N_2S$, 156.0721).

Anal. Calcd for $C_7H_{12}N_2S$: C, 53.81; H, 7.74; N, 17.93. Found: C, 53.88; H, 7.80; N, 17.84.

The white solid recovered from the second filtration was recrystallized from hexane to give 0.07 g (25%) of **6**:[9] mp 81–82.5 °C; IR (KBr) 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.45–3.65 (m, 4 H), 4.12–4.25 (d, J = 4 Hz, 2 H), 5.00–5.35 (m, 2 H), 5.61–6.08 (m, 2 H); MS *m/e* (rel intensity) 142 (100), 127 (87), 100 (9), 70 (48).

Preparation of *N*-Acetyl-2-crotylthioimidazoline (3). To a stirred CH_2Cl_2 solution (125 mL) containing *N*-acetylimidazolidinethione[5] (2.88 g, 0.02 mol) and triethylamine (4.04 g, 0.04 mol), 4.1 mL (0.04 mol) of a 80:20 mixture of 1-bromo-2-butene and 3-bromo-1-butene was slowly added. The solution was refluxed (16 days), then consecutively washed with aqueous 5% $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), and dried (Na_2SO_4). The CH_2Cl_2 layer was evaporated in vacuo, the residue triturated with hexane (250 mL), and the hexane layer concentrated to give 3.60 g (91%) of **3**: mp 81–82.5 °C; IR (KBr) 1680, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.60–1.82 (d, J = 4 Hz, 3 H), 2.20 (s, 3 H), 3.50–3.76 (m, 2 H), 3.95 (s, 4 H), 5.50–5.75 (m, 2 H); MS *m/e* (rel intensity) 198 (52), 183 (100), 155 (81), 141 (61), 123 (55), 102 (26), 70 (12); mol wt 198.0820 (calcd for $C_9H_{14}N_2OS$, 198.0827).

Thermolysis of *N*-Acetyl-2-crotylthioimidazoline (3). Preparation of *N*-Acetyl-*N'*-(3'-butenyl)imidazolidinethione (4). Thermolysis and workup of **3** (0.04 g, 0.002 mol) under similar reaction conditions (145 ± 2 °C, 30 h) used for the preparation of **2a** gave 0.36 g (90%) of **4** after vacuum distillation, bp 130 °C (0.4 mm). The product was further purified by chromatography (silica gel, 70–230 mesh, 1.5 × 76 cm column) using a 5:95% mixture of Et_2O–CH_2Cl_2 as the eluent. Fractions 9–12 (10-mL fractions) after concentration gave 0.32 g of **4** (80%): IR (neat, NaCl) 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.23–1.30 (d, J = 8 Hz, 3 H), 2.83 (s, 3 H), 3.25–4.13 (m, 4 H), 5.10–6.04 (m, 4 H). Double irradiation of the protons at δ 1.23–1.30 simplified the multiplet at δ 5.10–6.04. Correspondingly, when the multiplet at δ 5.10–6.04 was doubly irradiated, the doublet at δ 1.23–1.30 collapsed to a singlet. ^{13}C NMR ($CDCl_3$) 15.0, 26.6, 40.5, 43.6, 52.6, 117.2, 135.5, 171.9 ppm; MS *m/e* (rel intensity) 198 (100), 183 (84), 155 (87), 141 (82); mol wt 198.0833 (calcd for $C_9H_{14}N_2OS$, 198.0827).

Themolysis of *N*-Acetyl-2-crotylthioimidazoline (3). General Kinetic Method. The kinetics were performed by immersing a sealed NMR tube (Wilmad No. 501-PS) containing an 0.56 M solution of **3** in benzene-d_6 in a vapor bath of refluxing xylene (141 ± 0.5 °C) for specific time intervals. The reactions were quenched by removing the tube from the bath. Runs were carried out in duplicate and followed through over 2 half-lives.

Acknowledgment. We would like to thank the National Institutes of Health for their support of our work and the National Science Foundation for a matching instrumental grant for the purchase of the Varian XL-100-15 NMR spectrometer and Nicolet TT-100 data system.

Registry No.—**1a**, 61076-81-1; **1b**, 61076-84-4; **2a**, 62139-89-3; *E*-**3**, 62182-95-0; *Z*-**3**, 62182-96-1; **4**, 62139-90-6; **5**, 62139-91-7; **6**, 24521-43-5; *N*-acetylimidazolidinethione, 5391-52-6; 1-bromo-2-butene, 4784-77-4; 3-bromo-1-butene, 22037-73-6.

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(5) J. G. Roberts, *J. Chem. Soc.*, 176 (1964).

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(7) At the suggestion of a referee we have examined whether this reaction

(3 → 4) is subject to nucleophilic catalysis. In a recent study on the mechanism of the thio-Claisen rearrangement of allylic phenyl sulfides, Kwart and Schwartz[2a] have carefully demonstrated that these rearrangements were susceptible to catalysis by tertiary amines and a number of anionic bases. Addition of 1.1 equiv of pyridine to a 0.56 M benzene solution of **3**, however, did not affect the rate of conversion to imidazolidinethione **4** ($k_1 = 8.2 \pm 0.3 \times 10^{-6}$ s^{-1} at 141 ± 0.5 °C).

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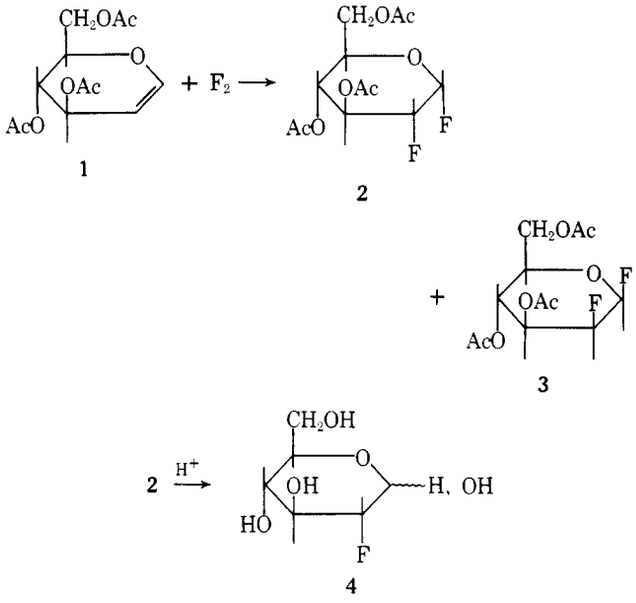
(11) The Chapman rearrangement was originally restricted to the thermal conversion of aryl *N*-arylbenzimidates to *N*-aroyldiphenylamines.[12] The molecular constraints of this definition and the mechanistic deviations noted for the corresponding alkyl analogues of benzimidates suggests that alternative processes (i.e., intermolecular, radical) should also be considered for these reactions.[12,13]
(12) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965).
(13) For a discussion on the mechanism of the decarboxylation of *N*-carbalkoxypyrazoles see J. J. Wilczynski and H. W. Johnson, *J. Org. Chem.*, **39**, 1909 (1974), and references cited therein.
(14) Analogously, pyrolysis of *N*-carbomethoxy-*N*-methylimidazolidinethione[4] under similar reaction conditions (170 °C, 72 h) gave *N,N'*-dimethylimidazolidinethione (55%) and *N*-methylimidazolidinethione (45%) by NMR.

Scheme I



Fluorination with F_2. A Convenient Synthesis of 2-Deoxy-2-fluoro-D-glucose[1a]

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Received December 30, 1976

For many years molecular fluorine (F_2) was considered to be of limited value in organic synthetic applications owing to its extreme chemical reactivity as well as difficulty in handling.[2] More recently, however, the use of fluorine diluted with an inert gas has led to some remarkably selective and controllable transformations such as electrophilic additions to double bonds[3,4] and regioselective fluorine substitution at saturated carbon.[5]

In our work on the development of a labeled tracer to serve as a probe for local glucose metabolism in man,[6] we required a convenient synthesis of 2-deoxy-2-fluoro-D-glucose (2-FDG) that was adaptable to labeling with readily available chemical forms of fluorine-18 (^{18}F)[7] such as ^{18}F-labeled F_2.

Previous synthetic routes to 2-FDG involve fluoride displacement on an anhydro sugar[8,9] and electrophilic fluorination with trifluoromethyl hypofluorite (CF_3OF).[10] Since both of these routes required starting materials that were not readily available and neither could be readily adapted to labeling with ^{18}F, we investigated direct fluorination with F_2.

We report here the direct conversion of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) to 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride (**2**) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (**3**) by reaction with F_2 (Scheme I). Hydrolysis of **2** and **3** to 2-FDG and 2-deoxy-2-fluoro-D-mannose has previously been described.[10]

Since this method can be used to prepare **2** and **3** in yields of 35 and 26%, respectively, direct fluorination followed by hydrolysis is a convenient synthetic alternative route to deoxyfluoro sugars.

Experimental Section

Melting points are not corrected. NMR spectra were taken with a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard.

Handling Fluorine. F_2 is extremely reactive and highly toxic. Those who work with it should be familiar with the potential hazards associated with the storage and use of compressed fluorine and the proper techniques for the safe manipulation of small quantities of F_2 in the laboratory. A detailed description of the reactivity of F_2 as it applies to its safe use in the laboratory has appeared in the literature.[11] Systems for the remote handling of cylinders of compressed F_2 along with technical bulletins are commercially available.[12]

In this synthesis F_2 was passed through a sodium fluoride trap to remove HF, then diluted with argon in a nickel cylinder. Reaction vessels and related equipment exposed to F_2 were dried prior to use and were constructed of glass, Teflon, Kel-F, or passivated nickel or Monel. Although F_2 is a strong oxidant and we have experienced no difficulty when it is diluted with an inert gas prior to use in organic synthesis, we recommend adherence to these safety precautions to protect the chemist from explosion and exposure to F_2.

Reaction of 3,4,6-Tri-*O*-acetyl-D-glucal (1) with Fluorine. A solution of **1** (272.4 mg, 1.0 mmol) in $CFCl_3$ (10 mL, dried over 4 Å molecular sieves) was cooled to −78 °C. F_2 (3 mmol) diluted with argon (1:40) was passed into the solution (4–5 mL/min) for 2 h. The reaction mixture was allowed to warm to room temperature and the excess F_2 and $CFCl_3$ were removed using a stream of He. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The $NaHCO_3$ layer was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and concentrated to give 288 mg of a viscous oil. GLC analysis of the oil [XE60 nitrile (20%), 6 ft × 0.25 in. column, 250 °C, 86 mL/min] showed peaks at 1.1, 2.9, 3.8, 4.6, 5.3, 6.4, and 9.1 min in an area ratio of 1.4:0.5:0.8:0.5:22.6:0.5:1.0. The three peaks at 1.1, 5.3, and 9.1 min correspond to 1, 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride (**2**),[13] and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (**3**).[13] Compounds **2** and **3** were separated by column chromatography on 2 × 20 cm silicic acid (100 mesh) column and eluted with *n*-hexane, ether, methylene chloride, and methanol, yielding 123 mg (39.7%) of **2** and 80 mg (25.8%) of **3**.[14] Further purification of **2** on a second column gave 108 mg (34.8%) of colorless crystals which were recrystallized from hexane–ether (1:1): mp 69–70 °C (lit.[10] mp 91–92 °C); NMR spectrum ($CDCl_3$) was identical with that of an authentic sample of **2**[13] and showed three singlets at δ 2.1 (9 H, $CH_3C{=}O$), a multiplet at 4.1–4.4 (3 H, H_5 and H_6) which is overlapping with another multiplet centered at 4.6 (1 H, H_2, multiplet, $J_{H_1H_2} = 2.9$, $J_{H_2H_3} = 9.5$, $J_{H_2F_1} = 23.8$, $J_{H_2F_2} = 46$ Hz), a quasi-triplet at 5.16 (1 H, H_4, $J = 9.5$ Hz), a multiplet at 5.25–5.8 (1 H, H_3) which is overlapping with a doublet of doublets centered at 5.9 (1 H, H_1, $J_{H_1H_2} = 2.9$, $J_{H_1F_1} = 51$ Hz). Compound **3** had mp 114–115 °C (lit.[10] mp 113–114 °C); NMR spectrum ($CDCl_3$) was identical with that of an authentic sample of **3**[13] and showed three singlets at δ 2.1 (9 H, $CH_3C{=}O$), a doublet at 4.3 (2 H, H_6, $J = 7.5$ Hz), multiplets at 3.8–4.0 (1 H, H_5), 4.3–4.8 (1 H, H_2, $J_{H_2F_1} = 7.6$, $J_{H_2F_2} = 34$ Hz), 5.1–5.5 (1 H, H_3) which is overlapping with a doublet of doublets (1 H, H_1, $J_{H_1F_2} = 12.8$, $J_{H_1F_1} = 48$ Hz). Coupling constants for **2** and **3** are in agreement with previously reported values.[10]

2-Deoxy-2-fluoro-D-glucose (4). The glucosyl fluoride **2** (108 mg, 0.35 mmol) was hydrolyzed according to the method of Adamson and