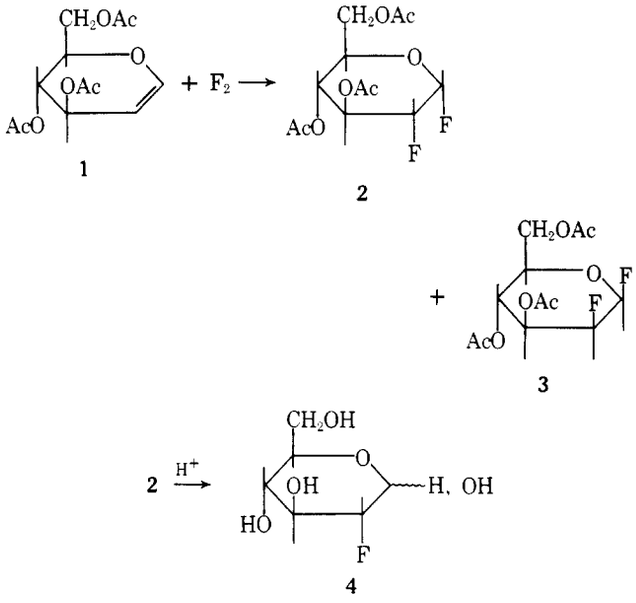
(3 → 4) is subject to nucleophilic catalysis. In a recent study on the mechanism of the thio-Claisen rearrangement of allylic phenyl sulfides, Kwart and Schwartz[2a] have carefully demonstrated that these rearrangements were susceptible to catalysis by tertiary amines and a number of anionic bases. Addition 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).

(8) (a) O. Mumm and F. Möller, *Chem. Ber.*, **70**, 2214 (1937); (b) O. H. Wheeler, F. Roman, and O. Rosado, *J. Org. Chem.*, **34**, 966 (1969).
(9) L. M. De Haes, J. J. Vanheertum, and H. K. Gevers, Belgian Patent 720 695 (March 12, 1969); *Chem. Abstr.*, **72**, 7939h (1970).
(10) H. J. J. Loozen, J. J. M. Drouen, and O. Piepers, *J. Org. Chem.*, **40**, 3279 (1975).
(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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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

co-workers,[10] to give 37 mg (58.4%) of **4** which had the same R_f (0.67) on TLC [cellulose, isobutyric acid–ammonia–water (66:1:33)], on high-pressure liquid chromatography [Waters μBondapak carbohydrate column, 30 cm × 4 mm, CH_3CN–H_2O (85:15), 1.5 mL/min, retention time 6 min, refractive index detector] as an authentic sample of **4**.[13] The NMR spectrum was also identical with that of an authentic sample of **4**.

Registry No.—**1**, 2873-29-2; **2**, 24679-90-1; **3**, 24679-92-3; **4**, 23094-77-1; fluorine, 7782-41-4.

References and Notes

(1) (a) Research carried out at Brookhaven National Laboratory under contract with the U.S. Energy Research and Development Administration and supported by its Division of Physical Research and Division of Biomedical and Environmental Research and also by the National Institutes of Health (USPHS Grant 2 R01 GM-16, 248-16 S1, and USPHS Grant 1-P07—RR00657-01A1). (b) National Institute of Radiological Sciences, Anagawa, Chiba-City, Japan.

(2) (a) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, p 30 ff; (b) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, N.Y., 1969, p 52 ff.

(3) R. F. Merritt and T. E. Stevens, *J. Am. Chem. Soc.*, **88**, 1822 (1966); R. F. Merritt, *ibid.*, **89**, 609 (1967); R. F. Merritt and F. A. Johnson, *J. Org. Chem.*, **31**, 1859 (1966); R. F. Merritt, *ibid.*, **31**, 3871 (1966).

(4) D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, **37**, 329 (1972); P. D. Schuman, G. Westmoreland, R. Anderson, and D. Warner, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 12–17, 1971; D. Cech and A. Holý, *Collect. Czech. Chem. Commun.*, **41**, 3335 (1976).

(5) D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and H. T. Toh, *J. Am. Chem. Soc.*, **98**, 3034 (1976); D. H. R. Barton, R. H. Messe, R. E. Markwell, M. M. Pechet, and S. Rozen, *ibid.*, **98**, 3036 (1976).

(6) M. Reivich et al., manuscript in preparation.

(7) Fluorine-18 is a short-lived radioactive isotope of fluorine ($t_{1/2}$ = 110 min). It decays by positron annihilation resulting in the production of two 511-keV photons which can be detected outside the body barrier. Therefore it is a useful label of biologically important molecules since it can be used to probe their metabolic fate in living systems including man.

(8) J. Pacák, Z. Točik, and M. Černý, *Chem. Commun.*, 77 (1969).

(9) J. Pacák, J. Podešva, Z. Točik, and M. Černý, *Collect. Czech. Chem. Commun.*, **37**, 2589 (1972).

(10) J. Adamson, A. B. Foster, L. D. Hall, R. N. Johnson, and R. H. Hesse, *Carbohydr. Res.*, **15**, 351 (1970).

(11) R. Landau and R. Rosen, *Ind. Eng. Chem.*, **39**, 281 (1947).

(12) Matheson Gas Products, Report No. G-115B and Technical Bulletin, "Fluorine".

(13) Authentic samples of **2**, **3**, and **4** were prepared according to the method of Adamson et al.[10] The authors are grateful to Dr. R. H. Hesse for an authentic sample of **4** which served as a spectral and chromatographic standard.

(14) The relative areas of **2** and **3** on GLC do not reflect their isolated yields because **3** undergoes decomposition on GLC.

1,4-Transannular Nitrogen to Carbon Rearrangement Following Intramolecular Carbenoid Insertion. Formation of 6-*trans*-Styryl-3-azabicyclo[3.1.0]hexane

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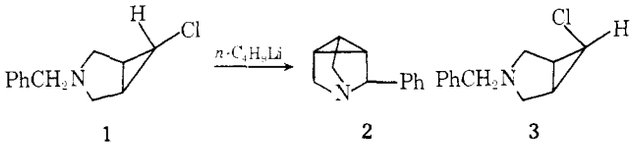
We are reporting a novel nitrogen to carbon transannular rearrangement following a carbenoid insertion reaction. Previously, we reported the formation of 3-phenyl-4-azatricyclo[2.2.1.0^{2,6}]heptane (**2**) from 3-benzyl-6-*exo*-chloro-3-

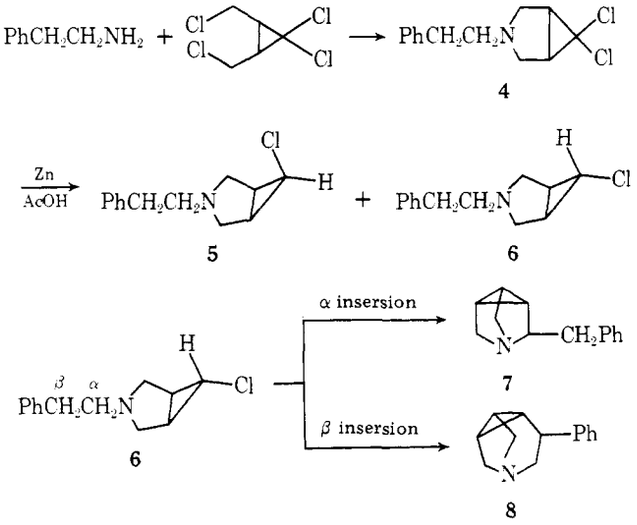


1 2 3

azabicyclo[3.1.0]hexane (**1**) by a proposed intramolecular carbenoid carbon–hydrogen insertion.[2] In addition, it was shown that the epimeric *endo*-chlorocyclopropane (**3**) did not undergo the intramolecular insertion reaction.

To further explore the scope of this reaction, 6-*exo*-chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**6**) was prepared[3] utilizing the procedure previously reported (Scheme I). It was anticipated that reaction of **6** with butyllithium

Scheme I



would yield 3-benzyl-4-azatricyclo[2.2.1.0^{2,6}]heptane (**7**) or 3-phenyl-5-azatricyclo[3.2.1.0^{2,7}]octane (**8**) by intramolecular carbenoid insertions into either the α or β C–H bonds, respectively. Addition of phenethylamine to 1,1-dichloro-*cis*-2,3-bis(chloromethyl)cyclopropane yielded 6,6-dichloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**4**). Reduction of **4** with zinc dust in glacial acetic acid[4] yielded the epimeric *endo*- and *exo*-monochloro isomers **5** and **6**. The exo isomer **6** was the major product (63% yield), whereas **5** was isolated in 5% yield.

When the reaction was carried out by addition of butyllithium solution to an ethereal solution of the exo isomer **6** at room temperature, a solid product having a molecular weight of 185 was isolated in low yield after extensive column chromatography. Spectral data were not consistent with structures **7** or **8**. On the basis of its ^{1}H NMR, IR, and UV spectral characteristics, the substance was determined to be 6-*trans*-styryl-3-azabicyclo[3.1.0]hexane (**9**). The ^{1}H NMR spectrum

9

of **9** was characterized by a singlet at δ 1.72 (N–H) which disappeared on addition of D_2O and by olefinic proton absorptions at δ 5.87 (1 H, d of d, $^3J_{vic}$ = 8 Hz, $^3J_{olefinic}$ = 16 Hz) and δ 6.45 (1 H, d, $^3J_{olefinic}$ = 16 Hz). The large value of the olefinic proton coupling constant suggests trans couplings.[5] A multiplet at δ 1.45 (3 H) in the spectrum of **9** indicated that the cyclopropyl ring remained intact. Irradiation at δ 1.45 caused the doublet of doublets at δ 5.78 to collapse to a simple doublet. A singlet at δ 3.03 (4 H) was attributed to the four protons on the carbons adjacent to the nitrogen, in contrast to the ^{1}H NMR spectrum of **2** which was characterized by two sets of unequally coupled doublets of δ 2.28 and δ 2.70 for the protons adjacent to the nitrogen due to the shielding effect of the benzene ring.

The UV maximum of **9** occurred at 248 nm (ε 22 900). This comparatively large value for the extinction coefficient indicated the presence of a strong chromophore which was not seen in previous products and strongly supports the presence of the styryl group. *trans*-β-Methylstyrene, for example, has an absorption maximum of 251 nm (ε 17 000).[6] In the infrared