New Approaches to the Synthesis of 3-Deoxy-3-fluoro-D-glucose[1]

Timothy J. Tewson* and Michael J. Welch

Division of Radiation Sciences, The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri 63110

Received August 5, 1977

The diisopropylidene hexose derivatives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) and 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) react with diethylaminosulfur trifluoride (DAST) to give stable but labile intermediates which can undergo further nucleophilic attack at sulfur rather than fluorination. Distillation of the reaction mixtures of **1** and DAST gives 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hex-3-enofuranose (**3**), while **5** and DAST gave 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**). The formation of **6** is shown to be an S_N2 displacement by labeling experiments with the radioisotope ^{18}F. In a rapid and simple reaction, **6** can also be prepared from the trifluoromethanesulfonate of **5** and cesium fluoride.

There is considerable interest in the fluorinated sugars as probes for the normal and abnormal metabolism of glucose and other carbohydrates.[2,3] 3-Deoxy-3-fluoro-D-glucose (**7**) appears an attractive compound, as in experimental animals it is phosphorylated, transported across cell membranes, and enters the metabolic cycle in a similar fashion to glucose[3] but does not complete the cycle.[4] However, present synthetic reactions[5] are somewhat lengthy, and our interest in ^{18}F ($t_{1/2}$ = 110 min)[6] labeled compounds made a faster procedure necessary.

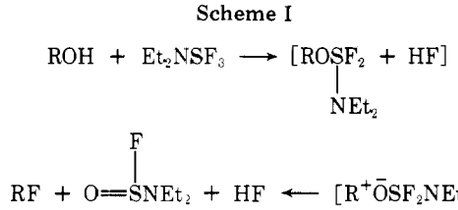
Diethylaminosulfur trifluoride (DAST) has recently been introduced as a mild and rapid reagent for effecting the F for –OH conversion with retention of configuration at the reaction center[7] (Scheme I) and has been used for the synthesis of 6-deoxy-6-fluorohexoses.[8] The reaction between DAST and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[9] (**1**) appeared a simple, rapid route for the synthesis of **7**.

Results and Discussion

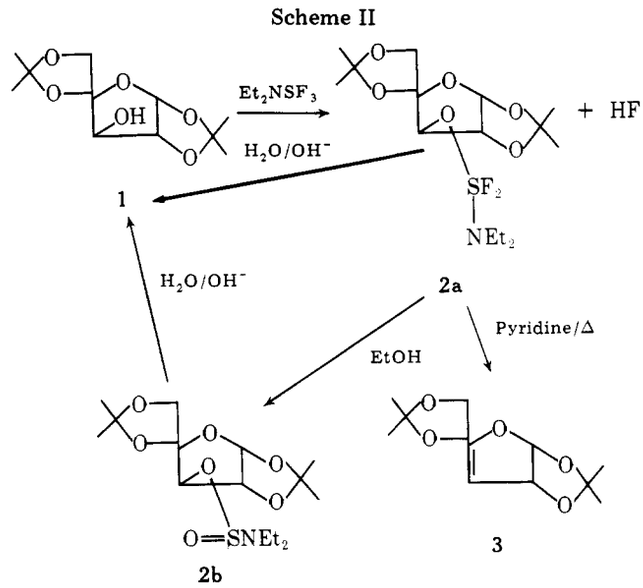
When **1** was reacted with DAST under conventional conditions (CH_2Cl_2 solution, 0 °C, aqueous workup)[7] the starting material was isolated in excellent yield, but with the introduction of 2 equiv of pyridine followed by direct distillation of the reaction mixture (80 °C, 0.05 mmHg) the olefin[10] **3** was isolated in 75% yield. Control experiments with **1** in the absence of DAST established that it did not eliminate under these conditions, so establishing that an intermediate was being formed but not undergoing spontaneous decomposition to give the fluorinated product. Attempts to isolate this intermediate failed, either the starting material **1** or the olefin **3** being the only isolated products, but the ^{19}F NMR spectrum of an equimolar mixture of DAST and **1** in methylene chloride showed no signal at −40 ppm for DAST[11] but a poorly resolved five-line signal at −59 ppm (J = 2 Hz), suggesting long-range coupling in an intermediate such as **2a**.

Treatment of this intermediate with ethanol gave a major product and a minor product on GC, but once again attempts at isolation led only to starting material **1**. The GC/MS of the major product gave a highest mass ion at 306, with M^+ +2 5% of M^+, characteristic of sulfur-containing compounds and is probably due to the loss of Et_2NH from **2b**. Therefore, the most likely course of reaction is as shown in Scheme II, and in the intermediate a second nucleophilic displacement is more favored at sulfur than at carbon.[12]

Scheme I



Scheme II



This is compatible with the observations that **1** does not give the 3-chloro compound on treatment with phosphorus pentachloride but rearrangement products[13] and that the tosylate of **1** only gives simple nucleophilic displacement reactions with "soft" nucleophiles in dipolar aprotic solvents[14-16] and does give elimination products.[10]

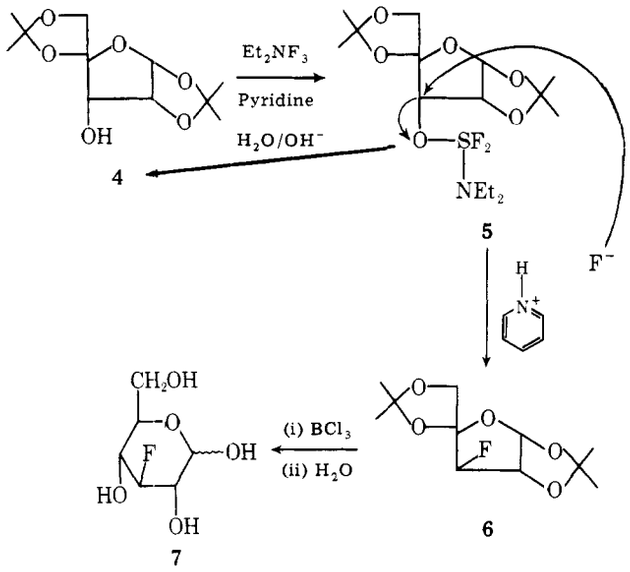
Nucleophilic displacement on 1,2:5,6-di-*O*-isopropylidene-3-tosyl-α-D-allofuranose is a reasonably facile process, giving the product with inversion of configuration at the 3 position.[5] Therefore, the reaction between 1,2:5,6-*O*-isopropylidene-α-D-allofuranose[9] (**4**) and DAST was performed to determine whether the intermediate, if formed, could undergo nucleophilic displacement to give the 3-fluorogluco derivative **6**. With an aqueous workup the only product was the starting material, but on direct distillation of the reaction mixture (0.05 mmHg, 60 °C) 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**)[5] was isolated in 90% yield.

The intermediates in the allose series were more labile than with the glucose compounds, but the ^{19}F NMR spectrum showed a poorly resolved multiplet at −58 ppm with more complex coupling than was shown in the glucose compound, suggesting an intermediate **5**.[10] The products from the addition of ethanol were not observed in this case. If the intermediate **5** is added to a solution of $H^{18}F$[17] in pyridine and heated to 150 °C, the product **6** is isolated, incorporating the ^{18}F activity. This provides additional evidence that there is a discrete S_N2 displacement rather than an ion pair or cyclic transition state (Scheme III).

As the DAST is apparently reacting to give a very good leaving group which is then rapidly displaced by fluoride ion,

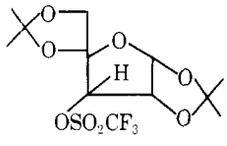
0022-3263/78/1943-1090$01.00/0

Scheme III



the alternative of a very good leaving group and an external source of fluoride ion appeared attractive.

The trifluoromethane sulfonate of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**8**)[18] was refluxed with a 10% excess of cesium fluoride in DMF for 25 min and after workup and evaporation of the solvent gave **6** as a chromatographically pure liquid in 95% yield. Distillation (0.05 mmHg, 50 °C) reduced the yield somewhat, depending on the scale of the reaction. No precautions were taken to exclude air and water, with the exception of using freshly distilled DMF. In order to remove the protecting groups and convert **6** to **7**, **6** was dissolved in methylene chloride and treated with an excess of boron trichloride[17] for 2 min, followed by an aqueous workup. This gave a syrup that was chromatographically identical both quantitatively and qualitatively with **7** obtained from the sulfuric acid hydrolysis, but neither sample has yet been induced to crystallize.[5] However, on forming the tetraacetate,[5] the sample from the boron trichloride hydrolysis was considerably harder to crystallize than that from the sulfuric acid procedure, and finally had to be seeded to obtain clean, sharp, melting crystals. Thus, it could represent a different anomeric mixture.



8

These experiments establish that in these compounds DAST reacts with the alcohols to give intermediates rather than transition states, which can have reaction pathways other than simple fluorination. The isolation of both the allo and gluco isomers, unchanged from the aqueous hydrolysis of their reactions with DAST, establishes that solvolysis is occurring at sulfur rather than at carbon. The experiments with $H^{18}F$ make it very probable that a S_N2 displacement is involved, as the alternative reaction of fluoride exchange at sulfur followed by a cyclic transition state or tight ion pair carbenium ion[7] would give a maximum incorporation of 50% of the ^{18}F activity rather than the 90% observed. The difference in reaction between the two isomeric furanose derivatives could be ascribed either to the difference in stability of the two olefins that would be formed by transdiaxial elimination (i.e., the $\Delta^{2,3}$ isomer is a more strained structure than the $\Delta^{3,4}$ isomer **3**) or to the steric effects of the 1,2-isopropylidene ring blocking the approach of the nucleophile to the α face of the ring. Of the two reactions to give **6** the second is less hazardous and more convenient than the first, especially if **6** is hydrolyzed directly without distillation, which is a necessary step in the first reaction. However, the reagents in the second reaction are much more expensive and so may be less suitable for a large-scale synthesis.

Experimental Section

NMR spectra were recorded on a T-60 NMR spectrometer at 60 and 56.4 MHz with Me_4Si and $CFCl_3$ as internal standards. IR spectra were recorded on a Perkin-Elmer 297 spectrometer as liquid films or in $CHCl_3$ solutions. Melting points are uncorrected.

Reactions of DAST with 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (1). (a) DAST (0.9 g, 5.5 mmol) in methylene chloride (20 mL) was cooled to 0 °C under nitrogen, and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) (1.3 g, 5 mmol) in methylene chloride (20 mL) and pyridine (2 mL) was slowly added. The solution was stirred for 30 min, warmed to room temperature, and after removal of the volatile components distilled at 80 °C (0.05 mmHg) to give 1 g of brown oil homogeneous on TLC. Chromatography on silica gel and elution with methylene chloride, followed by crystallization from petroleum ether (40–60 °C), gave 0.75 g of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-*gluco*-hex-3-enefuranose (**3**): [mp 50–52 °C (lit. mp 50 °C);[10] IR 1670 cm^{-1} (m, unsaturated ether); NMR δ 6.35 (1 proton doublet J = 5 Hz, H-1), 5.5 (1 proton singlet overlapping 1 proton doublet, H-3, H-2), 4.9 (2 proton triplet, J = 6 Hz, H-5), 4.30 (1 proton multiplet H-6), 1.7 (12 proton singlet methyl groups).

(b) DAST (0.9 g) and **1** (1.3 g) were reacted together as above and then treated with ethanol (2 mL). GC analysis showed a major (~90%) and a minor (~10%) peak, and the GC/MS showed a high mass for the major peak of 306 (with 308 being 5% of 306) assigned to **4b**, while the minor peak showed a high mass of 323 (325 is 5% of 323) and is as yet unidentified. On attempted aqueous workup of these solutions, starting material was isolated (1.2 g, 90% recovery).

Preparation of 3-Deoxy-3-fluoro-1,2:5,6-di-*O*-propylidene-α-D-glucofuranose (6). (a) DAST (3.5 g, 22 mmol) was dissolved in methylene chloride (50 mL) and pyridine (5 mL), and the solution was cooled to 0 °C under nitrogen. **4** (5.2 g, 20 mmol) was added slowly and the solution warmed to room temperature. The solvent was removed under vacuum and the residue distilled at 60 °C (0.05 mmHg) to give 5.1 g of **6** as a light yellow oil that was ~90% pure by GC. A second distillation gave 3.2 g of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) as a pure colorless liquid: ^1H NMR[18] δ 6.0 (1 proton doublet, J = 3 Hz, H-1), 5.1 (1 proton double doublet, J = 48, 1 Hz, H-3), 4.6 (1 proton double doublet, J = 20, 3 Hz, H-4), 4.6–4.0 (unresolved 5 proton multiplet, H-2, H-5, and H-6), 1.5 (four 3 proton singlets, methyl groups); ^{19}F NMR +208 ppm (double double doublet, above $CFCl_3$, J = 48, 28, and 10 Hz).

(b) The reaction was repeated as above except that before distillation a solution containing 1.1 mCi of $H^{18}F$ in 0.5 mL of pyridine was added. GC analysis of the product showed that >90% of the ^{18}F activity was incorporated into **6**.

Preparation of 1,2:5,6-di-*O*-Isopropylidene-3-*O*-trifluoromethanesulfonyl-α-D-allofuranose (8).[18] **4** (5.2 g, 20 mmol) was dissolved in methylene chloride (300 mL) and pyridine (10 mL) and cooled to −15 °C under nitrogen. Trifluoromethanesulfonic anhydride (3.8 mL, 23 mmol) in methylene chloride (20 mL) was slowly added and allowed to react for 90 min. The solution was washed with saturated bicarbonate and the solvents were removed under vacuum. Crystallization from petroleum ether (40–60 °C) gave 6.9 g (88%) of 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-α-D-allofuranose (**8**) as colorless needles, mp 46–47 °C (lit. mp 40 °C).[18]

Preparation of 3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6). **8** (0.79 g, 2 mmol) was dissolved in DMF (25 mL) (distilled from CaH_2), and cesium fluoride (0.34 g, 2.2 mmol) was added. The solution was refluxed for 25 min, poured into water (200 mL), and extracted (3 × 100 mL) with methylene chloride. Evaporation of the solvent gave 0.51 g of a pale yellow, chromatographically pure oil **6**. Distillation (60 °C, 0.05 mmHg) gave 0.37 g (71%) of pure 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **6**.

Preparation of 3-Deoxy-3-fluoro-D-glucose (7) and Its Tetraacetate (5). **6** (1.4 g, 4 mmol) was dissolved in methylene chloride (20 mL), and boron trichloride (10 mL of a 1 M solution in methylene chloride) was added. The solution was stirred for 2 min at room temperature, water was added, and the methylene chloride was removed under vacuum. The solution was neutralized with AG501-X8

ion-exchange resin and the water removed under vacuum to give 0.8 g of a syrup identical on a Waters carbohydrate column to that obtained from the sulfuric acid catalyzed hydrolysis of **6**.

This syrup (0.36 g) was dissolved in acetic anhydride (7 mL) with sodium acetate (0.6 g) and boiled for 10 min. Workup and crystallization (petroleum ether 60–80 °C) gave 0.2 g of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-α-D-glucose: mp 116–120 °C (lit. mp 119–120 °C).[5]

Acknowledgments. We thank Maria Straatmann for doing the preliminary experiments with DAST, Steve Wittmer for preparing starting materials, Bill Margenau for preparing ^{18}F, Dr. William R. Sherman of the Department of Psychiatry for the GC/MS, and Dr. Michel Ter-Pogossian for his continuing interest in this work.

Registry No.—**1**, 582-52-5; **3**, 2774-28-9; **4**, 2595-05-3; **5**, 64872-56-6; **6**, 14049-05-9; **7**, 14049-03-7; **8**, 55951-90-1; DAST, 38078-09-0; trifluoromethanesulfonic anhydride, 358-23-6; acetic anhydride, 108-24-7.

References and Notes

(1) This work was supported by U.S. Public Health Service Grants 5 P01 HL13851 and P50 NSO 6833.
(2) P. W. Kent, pp 169–214, and N. F. Taylor, pp 215–238, in "Carbon–Fluorine Compounds", A CIBA Symposium, Associated Scientific Publishers, Amsterdam, 1972.
(3) N. F. Taylor, A. Romaschin, and D. Smith, *ACS Symp. Ser.* **28**, 99–116 (1976).
(4) A. Romaschin, N. F. Taylor, D. A. Smith, and D. Lopes, *Can. J. Biochem.*, **55**, 369 (1977).
(5) A. B. Foster, R. Hems, and J. M. Webber, *Carbohydr. Res.*, **5**, 292 (1967).
(6) ^{18}F decays by positron emission and is of interest for positron emission tomography. M. G. Straatmann and M. J. Welch, *J. Nucl. Med.* **18**, 151 (1977).
(7) W. Middleton, *J. Org. Chem.*, **40**, 574 (1975).
(8) M. Sharma and W. Korytnyk, *Tetrahedron Lett.*, 573 (1977).
(9) J. D. Stevens, *Methods Carbohydr. Chem.*, **6**, 123–128 (1972).
(10) H. Zinner, G. Wulf, and R. Heinatz, *Chem. Ber.*, **97**, 3536 (1964).
(11) D. G. Ibbott and A. F. Janzen, *Can. J. Chem.*, **50**, 2428 (1972).
(12) R. N. Haszeldine, A. E. Tipping, and T. J. Tewson, *J. Chem. Soc., Perkin Trans. 1*, in press.
(13) D. C. C. Smith, *J. Chem. Soc.*, 1244 (1956).
(14) M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, **27**, 4505 (1962).
(15) V. G. Nayak and R. L. Whistler, *J. Org. Chem.*, **34**, 3819 (1969).
(16) R. L. Whistler and L. W. Doner, *J. Org. Chem.*, **35**, 3562 (1970).
(17) Produced on the Washington University Medical School cyclotron by bombardment of neon/15% H_2 with 7 MeV deuterons. Procedure is similar to that in ref 5. Exact details to be published elsewhere.
(18) L. D. Hall and D. C. Miller, *Carbohydr. Res.*, **47**, 299 (1976).
(19) T. G. Bonner and N. M. Saville, *J. Chem. Soc.*, 2851 (1960).
(20) A. B. Forster, R. Hems, and L. D. Hall, *Can. J. Chem.*, **48**, 3937 (1970).

Antineoplastic Agents. 55. Isolation and Structure of Multigilin and Multistatin[1]

George R. Pettit,* Cherry L. Herald, Devens Gust, Delbert L. Herald, and Lawrence D. Vanell

Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received August 26,1977

Two new cytotoxic and antineoplastic pseudoguaianolides designated multigilin (**2b**) and multistatin (**2d**) have been isolated from *Baileya multiradiata* Harv. and Gray. The related sesquiterpene lactone fastigilin A (**1c**) was also found to be a constituent of this plant. With the x-ray crystal structure of radiatin (**1a**) serving as a valuable reference, complete structural and stereochemical assignments were made for fastigilin A (**1c**), multigilin (**2b**), and multistatin (**2d**). Interpretation of the ^{13}C nuclear magnetic resonance spectra provided a firm basis for these assignments and allowed further confirmation of structures previously proposed for fastigilin B (**1b**), fastigilin C (**2a**), and multiradiatin (**2c**).

A detailed investigation of *Baileya multiradiata* Harv. and Gray (Compositae) cytotoxic and antineoplastic constituents begun in 1966 led to the isolation of six sesquiterpene lactones displaying such physiological activity.[2] Of these growth inhibitory substances radiatin (**1a**), fastigilin B (**1b**), fastigilin C (**2a**), and multiradiatin (**2c**) appeared most promising. Until 1973, requirements for these compounds were met through re-collections of the plant made in June within a 40-mile radius in Mohave County, Arizona. In April 1975 when it became necessary to increase supplies of radiatin and fastigilin C for further biological evaluation, re-collection of the plant was made at lower elevations some 100–150 miles south of previous collections. Sesquiterpene fractions from these specimens of *Baileya multiradiata* expected to contain primarily radiatin were found instead to be largely fastigilin B (**1b**) and fastigilin A[3,4] (**1c**), and those fractions presumed to contain fastigilin C and multiradiatin were found to also contain two new pseudoguaianolides that we have designated multigilin (**2b**) and multistatin (**2d**). The terpene assumed to be fastigilin A (**1c**) was confirmed by comparison with authentic fastigilin A provided by Professor W. Herz. A summary of the compelling spectral evidence supporting structural assignments for sesquiterpene lactones **1c**, **2b**, and **2d** and further confirmation for the structures previously assigned to fastigilin B[2,4] (**1b**), fastigilin C[3,4] (**2a**), and multiradiatin[2] (**2c**) now follow.

On casual inspection fastigilin A, multigilin, and multistatin could readily be mistaken for the isomeric and known constituents of *Baileya multiradiata* lactones **1b**, **2a**, and **2c**. The mass spectra by electron impact and thin-layer chromatographic behavior were indistinguishable from the known constituents. However, inspection of the ^1H NMR spectra revealed that the ester side chain methyl group resonances were shifted from the expected δ 1.80 and 2.12 (typical of a senecioate ester[4]) to δ 1.72 and 1.82, respectively (typical of an angelate). Eventually this observation served as a useful qualitative method for distinguishing between mixtures of multigilin with fastigilin C and fastigilin A with fastigilin B and the pure substances. Indeed certain compositions of multigilin with fastigilin C behaved in other respects as a pure substance and resisted all attempts at complete separation. A further challenge was presented by the quantities available, with fastigilin A and multigilin obtainable in approximately 0.002% yield while multistatin was isolated in only trace amounts. Both the ^1H NMR and infrared spectra of multigilin and multistatin suggested that they bore the same relationship

0022-3263/78/1943-1092$01.00/0