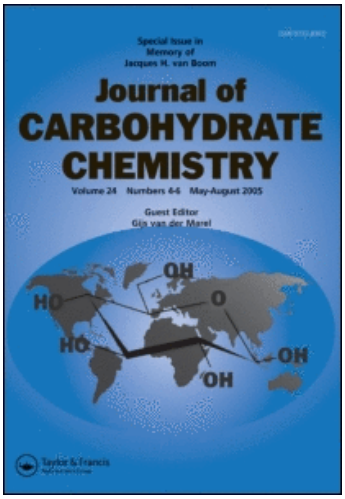


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# Synthesis of Fluorinated Carbohydrates

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REVIEW ARTICLE

# SYNTHESIS OF FLUORINATED CARBOHYDRATES

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## I. INTRODUCTION

The similarities in bond length and polarization between C-F and C-OH, as well as the altered hydrogen-bonding properties present in carbohydrates bearing a fluorine atom in place of an hydroxyl group can be exploited in biochemical investigations (enzyme-carbohydrate interactions, lectin-carbohydrate affinities, antibody-carbohydrate binding, etc.).[1-5] In addition, the different chemistries exhibited by the fluorinated carbohydrates have made them important reagents in both





0732-8303/85/0404-0451$3.50/0

metabolic studies and disease diagnosis such as the use of 2-deoxy-2-[$^{18}$F]-D-fluoroglucose in positron emission tomography.[6,7] Because of their widespread utility, the synthesis of fluorinated carbohydrates is of importance. However, the introduction of fluorine into a carbohydrate moiety can be an arduous task because of (1) the protection and deprotection steps required to set up the desired hydroxyl group for the introduction of fluoride, (2) the low nucleophilicity of fluoride ion, and (3) fluoride ion catalyzed elimination reactions.[8,9] The search for milder and more selective methods for the introduction of fluorine into carbohydrates has continued at a rapid pace and it is appropriate to review some of the recent results.

This article is concerned with the syntheses of fluorinated carbohydrates that were reported from 1979 to 1984. Because of the large number of contributions to the literature since the Penglis review,[9] we have limited this discussion to various methodologies which have been employed to introduce fluorine onto the carbohydrate nucleus. Even in this context, the references are not all inclusive as we have concentrated our efforts to present those articles which describe significantly new information.

## II. DISPLACEMENT OF SULFONATES BY FLUORIDE ION

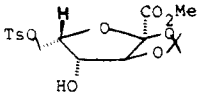
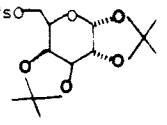
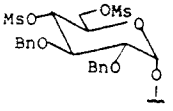
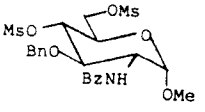
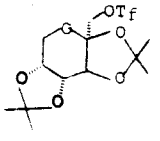
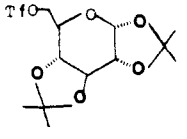
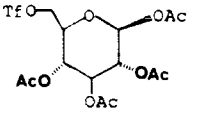
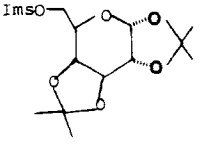
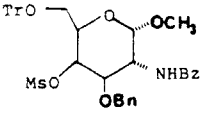
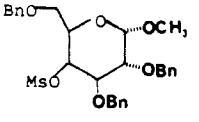
The preparation of fluorinated carbohydrates via nucleophilic displacement of the corresponding sulfonate by fluoride ion is a well known reaction.[9] In general, the displacement of primary sulfonates by any number of anhydrous fluoride ion sources is a facile process and tosylates or mesylates have usually been employed as the leaving groups (Table I, entries 1-4). However, the introduction of a fluorine atom at a sterically hindered primary carbon, or at a secondary carbon, can be quite difficult because of the low nucleophilicity of fluoride ion and its ability to catalyze elimination reactions.

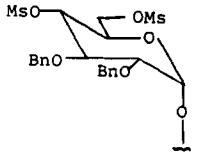
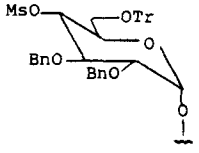
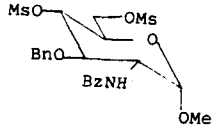
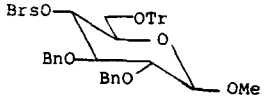
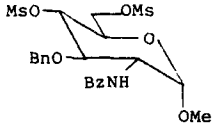
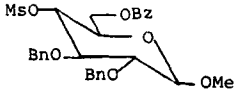
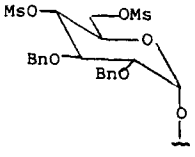
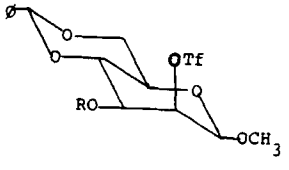
One method to overcome these difficulties is to use a more reactive leaving group and, in recent years, the trifluoromethanesulfonate (triflate) group has been widely used. Triflates are easy to prepare, are approximately $5.6 \times 10^4$ times better leaving groups than the corresponding mesylates, and have frequently yielded displacement products where other sulfonate esters have failed.[14] An illustration of this point comes from our own work[15] (entry 5) in which attempts to displace the mesylate analog of 1 with fluoride ion gave none or only low yields of the desired 1-deoxy-1-fluorofructose derivative. In contrast, use of the triflate leaving group and TASF [tris(dimethylamino)sulfonium difluorotrimethylsilicate][16] afforded the primary fluoride in excellent yield. TASF is an excellent source of anhydrous fluoride ion and it is soluble in certain organic solvents (THF, $CH_3CN$), but it is also very hygroscopic and must be handled accordingly. We have found that it is a very useful reagent for the introduction of fluorine into carbohydrates which have previously proven difficult to fluorinate.

In addition to triflate, the imidazylate group has also been employed as a highly reactive leaving group.[19] Hanessian has reported the preparation of 6-deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (75%; entry 8) via fluoride displacement of the imidazylate group under remarkably mild conditions (3 h at 25°C). The ease of this substitution stands in contrast to the long reaction time required in the case of the corresponding tosylate.[20]

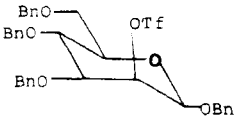
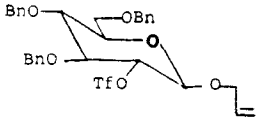
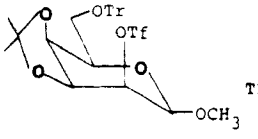
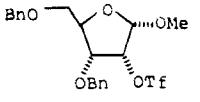
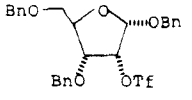
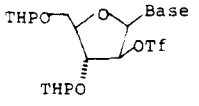
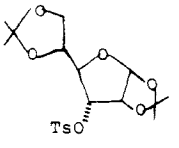
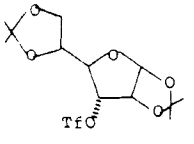
The formation of fluorides via displacment (inversion) of secondary sulfonates is considerbly more complex than in the primary case. While factors influencing nucleophilic displacement of secondary sulfonate esters have been the subject of earlier reviews,[9,21,22,23] it should be noted that the use of anhydrous salts where $TBA^{\oplus}$, $TAS^{\oplus}$, or $Cs^{\oplus}$ is the

TABLE I

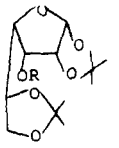
| Entry | Substrate | Nucleophile | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 1. |  | KF | | DMF | 150 | | 10 |
| 2. |  | Amberylst A26(F⁻) | 96 | Benzene | 80 | 75 | 11 |
| 3. |  | TBAF | 16 | $CH_3CN$ | 80 | 80 | 12 |
| 4. |  | TBAF | 1 | $CH_3CN$ | 80 | 87 | 13 |
| 5. |  | TASF | 18 | THF | 67 | 85 | 15 |
| 6. |  | TASF | 18 | THF | 67 | 70 | 17 |
| 7. |  | TBAF | 15 | Benzene | 80 | 27 | 18 |
| 8. |  | TBAF | 3 | Toluene | 25 | 75 | 19 |
| 9. |  | TBAF | 24 | $CH_3CN$ | 80 | 67 | 13 |
| 10. |  | TBAF | 72 | $CH_3CN$ | 80 | 73 | 24 |

| Entry | Substrate | Nucleophile | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 11. |  | TBAF | 96 | $CH_3CN$ | 80 | 71 | 25 |
| 12. |  | TBAF | 48 | $CH_3CN$ | 80 | 59 | 25 |
| 13. |  | TBAF | days | $CH_3CN$ | 80 | 77 | 13 |
| 14. |  | A-26-F | 84 | Benzene | 80 | 77 | 55 |
| 15. |  | KF | 20 min | HOOH | 197 | 62 | 13 |
| 16. |  | A-26-F | | Benzene | 80 | 44 | 5 |
| 17. |  | TBAF | 72 | $CH_3CN$ | 80 | 65 | 26 |
| |  | | | | | | |
| 18. | R=Me | CsF | 0.5 | DMF | 130 | 42 | 27 |
| 19. | R=Me | CsH[$^{18}$F]$F_2$ | 0.5 | DMF | 130 | 30 | 28, |
| 20. | R=Bn | TBAF | | DMF | 25 | 35-60 | 30 |
| 21. | R=Bz | TBAF | | DMF | 25 | 35-60 | 30 |

(continued)

| Entry | Substrate | Nucleophile | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 22. |  | TBAF | 30 min | DMF | 60 | 45-50 | 47 |
| 23. |  | TBAF | | THF | 50 | 77 | 31 |
| 24. |  | TEAF | 50 min | $CH_3CN$ | 50 | 50 | 32 |
| 25. |  | TBAF | 3.5 | THF | -10 | 62 | 33 |
| 26. |  | TBAF | 3 | THF | 0 | 50 | 34 |
| 27. |  | TBAF | 2-15 | THF | 4-50 | 20-60 | 35-3 |
| 28. |  | A-26-F | 96 | Benzene | 80 | 72 | 11 |
| 29. |  | TEAF | 10 min | HMPA | 150 | 70-90 | 38 |

(continued)

| Entry | Substrate | Nucleophile | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 30. |  R=Brs | A-26-F | 18 | Benzene | 80 | 51 | 46 |

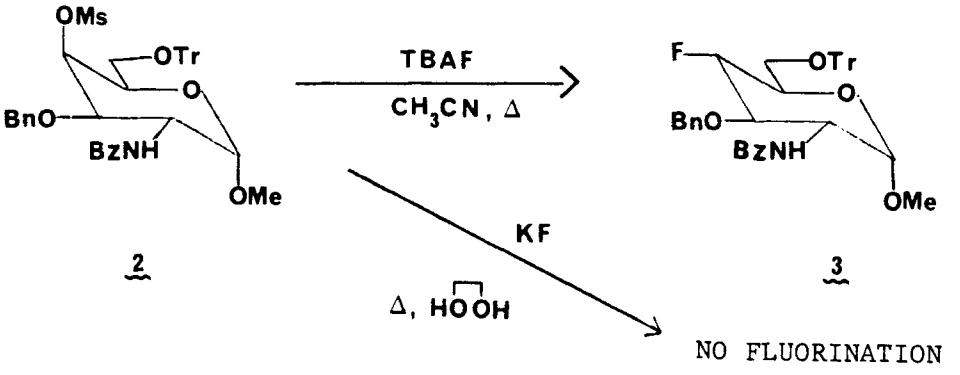


counterion and fluoride ion is "naked" and solvents (THF, $CH_3CN$) which do not strongly solvate the fluoride ion, are recommended to maximize fluoride nucleophilicity, to minimize elimination reactions, and to effect substitution under the mildest posible conditions.

There are many reported syntheses of derivatives of 4-deoxy-4-fluoro-D-glucopyranose for among other reasons, these molecules are useful in assaying monosaccharide binding to proteins.[5,24] As described above, proper choice of reaction partners can be crucial to the successful introduction of fluorine. As an example, when the galacto-mesylate 2 was treated with potassium fluoride in refluxing ethylene glycol, no fluorination product was obtained;[13] however, use of TBAF in acetonitrile afforded 3 in 67% yield (entries 9 and 10). Along these lines, treatment of a methyl 4,6-dimesyloxy-α-D-galacto-pyranoside derivative with potassium fluoride in refluxing ethylene glycol gave a 3:2 mixture of displacement and elimination products.[13] The six reported syntheses of 4-deoxy-4-fluoro-D-galactopyranosides all proceed via mesylate displacement (entries 11-16). It is of interest to note that since in the gluco-configuration, the 4-(methylsulfonyl)oxy group is not trans-diaxial to H-5 and H-3, elimination is no

(continued)

longer a major concern and even potassium fluoride affords good yields.



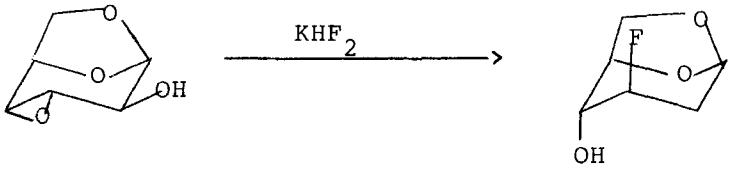

Without question most of the contributions concerning fluorinated carboyhydrate synthesis have centered around 2-deoxy-2-fluoro-D-glucopyranose because of the use of 2-deoxy-2-[$^{18}$F]fluoro-D-glucopyranose in positron emission tomographic studies probing glucose metabolism in the brain.[6,7] While the majority of work deals with additions to glucals, two groups have reported stereocontrolled syntheses of 2-deoxy-2-fluoro-D-glucose based upon triflate displacement. The C-2 hydroxy group of glycosides has been notoriously resistant to nucleophilic displacement; however, treatment of 2-trifluoromethylsulfonyloxy-β-D-mannopyranosides with fluoride ion (entries (18-22) gave modest yields of 2-deoxy-2-fluoro-D-glucose. The excellent use of $BBr_3$ for a one-step removal of all the blocking groups should also be noted. The disadvantage of this methodology, however, is the need for the relatively unavailable methyl β-D-mannopyranoside. Entries 23 and 24 demonstrate the use of this methodology for the preparation of 2-deoxy-2-fluoro-mannopyranose[31] and 2-deoxy-2-fluoro-D-galactopyranose[32] derivatives, respectively.

The synthesis of 2- or 3-fluorinated nucleosides is of intense interest because of their demonstrated antiherpetic and antileukemic activities. While the introduction of fluorine into such molecules, and

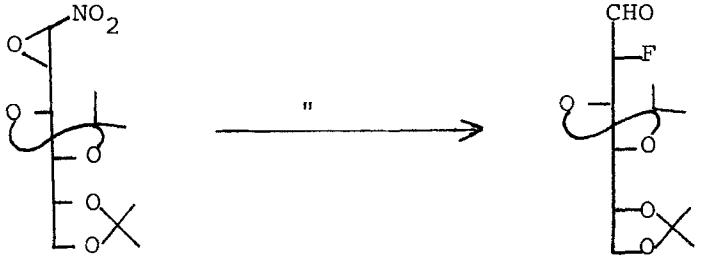
furanosides in general, previously required vigorous conditions, the use of the triflate leaving group allows for preparations in good yield under very mild conditions (entries 25-30).

## III. FLUORIDE OPENING OF EPOXIDES AND CYCLIC SULFATES

Cerny[39] has reported a synthesis of 3-deoxy-3-fluoro-D-mannose based upon fluoride ion opening of an epoxide ring. Thus, when 1,6:3,4-dianhydro-β-D-altropyranose (4) was treated with potassium hydrogen fluoride in ethylene glycol at 200°C, 1,6-anhydro-3-deoxy-3-fluoro-β-D-manno-pyranose (5), the expected product of trans-diaxial ring-opening was obtained in 59% yield. An epoxide cleavage route to 2-deoxy-2-fluoro-D-glucose has also been




4 5

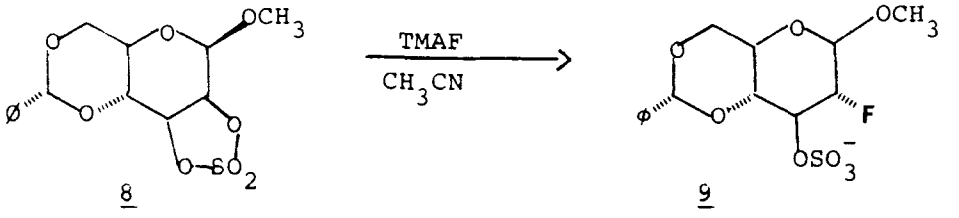



6 7

reported.[40] Since $S_N2$ routes to 2-deoxy-2-fluoro-D-glucose proceed in low (<20%) radiochemical yield, Szarek has developed a reportedly superior pathway. Ring opening of the indicated stereoisomer 6 at C-2 with potassium hydrogen fluoride in ethylene glycol at 110°C afforded

2-deoxy-2-fluorogluco analog 7 in 79% yield. Removal of the acetonide group with $BCl_3$ gave an 85% yield of 2-deoxy-2-fluoro-D-glucose.

Along similar lines, Tewson has reported[41,42] a synthesis of 2-deoxy-2-fluoro-D-glucose via sulfate ring opening of 8 with fluoride ion. The reaction proceeds as expected, via displacement of the axial oxygen at C-2 with formation of the 3-sulfate 9. Workup consisting of acid hydrolysis of the sulfate and benzylidene moieties, and isolation of the product as the triacetate afforded an 84% overall yield.




8 9

## IV. FLUORINATION WITH THE DAST REAGENT

Diethylaminosulfur trifluoride (DAST)[43] is an effective reagent for converting alcohols into the corresponding fluorides. The application of DAST to the synthesis of fluorinated carbohydrates has been well studied. The obvious advantage of DAST is that it allows for the direct replacement of an hydroxyl group by fluorine. In addition, DAST is relatively mild, can be used on acid-sensitive substrates, and in the absence of neighboring group participation, always affords products resulting from Walden inversion.

The fluorination of primary hydroxyl groups in carbohydrates where the remaining hydroxyls are protected is a facile process and many examples have been recorded.[9] Korytnyk and Robyt have recently reported syntheses of 2-amino-2,6-dideoxy-6-fluoro-mannopyranose (Table II; entry 31) and 6,6'-dideoxy-6,6'-difluorosucrose (entry

**Table II**

**Reaction of Carbohydrates with DAST**

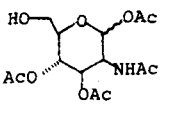
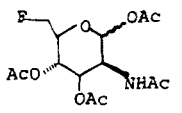
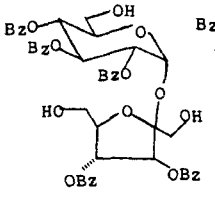
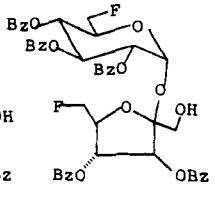
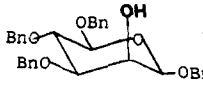
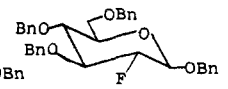
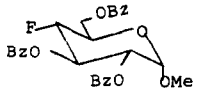
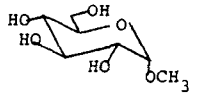
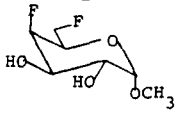
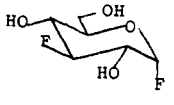
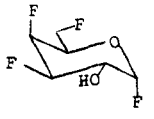
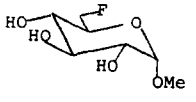
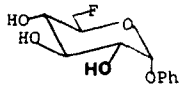
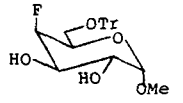
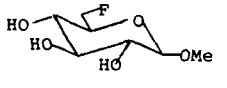
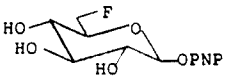
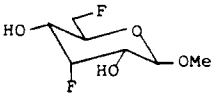
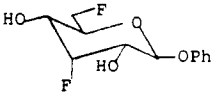
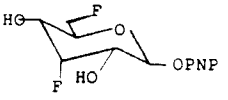
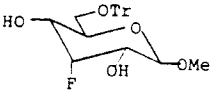
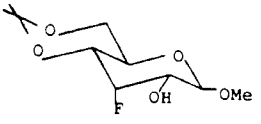
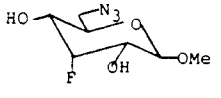
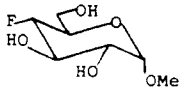
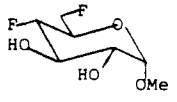
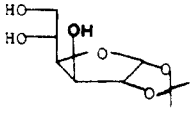
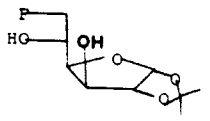
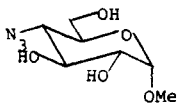
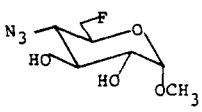
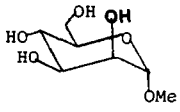
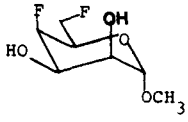
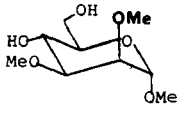
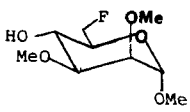
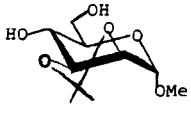
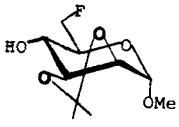
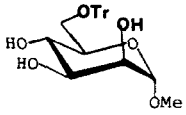
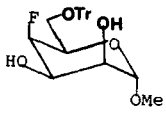
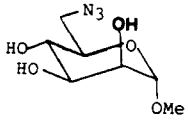
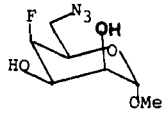
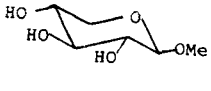
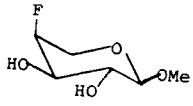
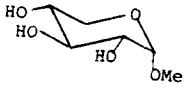
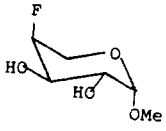
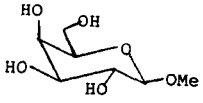
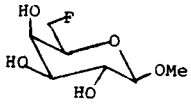
| Entry | Substrate | Product | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 31. |  |  | 3 | Diglyme | 40 | 62 | 44 |
| 32. |  |  | 1 | Diglyme | 90 | 28 | 45 |
| 33. |  |  | 5 min. | $CH_2Cl_2$ | 40 | 80 | 47 |
| 34. | 14 |  | 18 | $CH_2Cl_2$ | 25 | 41 | 48 |
| 35. |  | 15  | 18 | neat | 25 | 60 | 49 |
| 36. |  |  | 120 | neat | 25 | 48 | 50 |
| 37. | 16 |  | 1 | $CH_2Cl_2$ | -30→25 | 88 | 48 |
| 38. | a |  | 2 | $CH_2Cl_2$ | -40→25 | 58 | 51 |
| 39. | 19 |  | 72<br>18 | $CH_2Cl_2$<br>DAST | 25<br>25 | 23<br>42 | 51<br>52 |
| 40. | 21 |  | 15 min | $CH_2Cl_2$ | 25 | 60 | 51 |

Table 2 cont.

Table 2 cont.

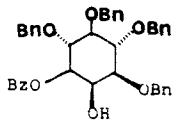
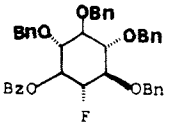
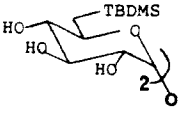
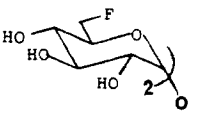
| Entry | Substrate | Product | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 41. | a |  | 35 min | $CH_2Cl_2$ | 25 | 55 | 51 |
| 42. | 21 |  | 18<br>18 | $CH_2Cl_2$<br>DAST | 25<br>25 | 51<br>32 | 51<br>52 |
| 43. | a |  | 18 | $CH_2Cl_2$ | 25 | 70 | 51 |
| 44. | a |  | 18 | $CH_2Cl_2$ | 25 | 78 | 51 |
| 45. | a |  | 18 | $CH_2Cl_2$ | 25 | 50 | 51 |
| 46. | a |  | 18 | $CH_2Cl_2$ | 25 | 45 | 51 |
| 47. | a |  | 3 | $CH_2Cl_2$ | 25 | 28 | 51 |
| 48. |  |  | 18 | $CH_2Cl_2$ | 25 | 71 | 51 |
| 49. |  |  | 1.5 | $CH_2Cl_2$ | 25 | 70 | 51 |

[a]Corresponding alcohol prior to $S_N2$ displacement.

| Entry | Substrate | Product | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 50. |  |  | 18 | $CH_2Cl_2$ | 25 | 68 | 51 |
| 51. |  |  | 20 min<br>18 | $CH_2Cl_2$<br>DAST | 25<br>25 | 80<br>72 | 48,<br>52 |
| 52. |  |  | 1 | $CH_2Cl_2$ | 25 | 60 | 51 |
| 53. |  |  | 15 min | $CH_2Cl_2$ | 25 | 14 | 51 |
| 54. |  |  | 2 | $CH_2Cl_2$ | 25 | 40 | 51 |
| 55. |  |  | 1 | $CH_2Cl_2$ | 25 | 56 | 51 |
| 56. |  |  | 18 | $CH_2Cl_2$ | -40→25 | 19 | 51 |
| 57. |  |  | 18 | $CH_2Cl_2$ | -40→25 | 52 | 51 |
| 58. |  |  | 45 min | $CH_2Cl_2$ | -40→25 | 15 | 55 |

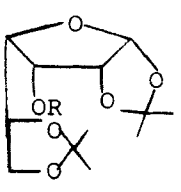
(continued)

Table 2 cont.

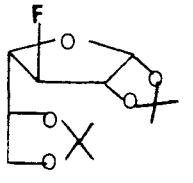
| Entry | Substrate | Product | Reaction Time, h | Solvent | Temp °C | Yield | Ref. |
|---|---|---|---|---|---|---|---|
| 59. |  |  | | Toluene | 75 | 86 | 58 |
| 60. |  |  | 2 | $CH_2Cl_2$ | 25 | 36 | 56 |



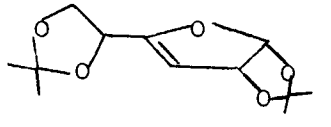
32) derivatives, respectively, using this methodolgy. The conversion of secondary hydroxyl groups to fluorides via DAST is usually preferable to sulfonate displacement because of the reduced number of steps, generally higher yields, and minimization of elimination products. Thus, treatment of brosylate 10 with fluoride ion (A-26-F) afforded a mixture of 11 and 12 from which 11 was isolated in 51% yield after hydrogenation and chromatography. In contrast, when 13 was allowed to react with DAST in $CH_2Cl_2$ containing DMAP as base, 11 was obtained in 90% yield.[46]



10 R=Brs



11



12

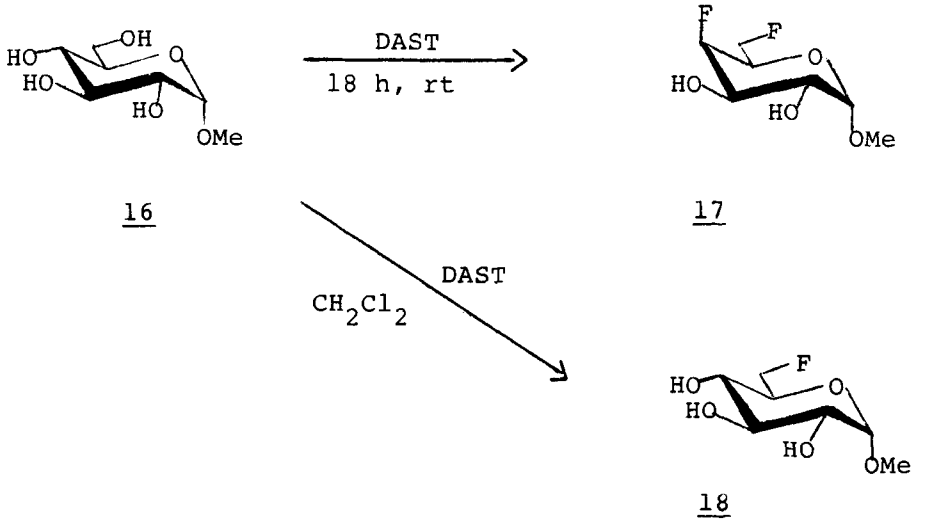
13 R-H

Along similar lines, DAST fluorination of 1,3,4,6-tetra-O-benzyl-β-D-mannopyranose gave the 2-deoxy-2-fluoro-D-glucose analog in 80% yield (entry 33), whereas, fluoride ion displacement of the corresponding triflate proceeded

in only 45%. Facile access to 4-fluoroglucosides is provided by treatment of methyl 2,3,6-tri-O-benzoyl-α-D-galacto-pyranoside (14) with DAST in $CH_2Cl_2$ which affords 15 in 41% yield (entry 34).

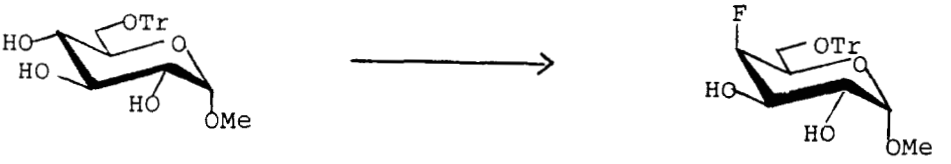
In contrast to the previous applications of DAST for the synthesis of fluorinated carbohydrates, the real advantage of DAST is that protection of all the hydroxyl groups is not required. Therefore, the number of steps involved in the synthesis of deoxyfluoro sugars may be reduced. As the remainder of this section will demonstrate, the regiospecificity of fluorination is dictated by the stereochemical configuration, the conformation, and the anomeric configuration of the substrate sugar. Thus, proper choice of substrate sugar allows for the synthesis of a specific fluorinated derivative with little or no protection steps.

When methyl α-D-glucopyranoside (16) was allowed to react with neat DAST, the hydroxyl groups at both C-4 and C-6 were selectively replaced by fluorine to afford 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside 17 in 60% yield.[49] Note that the reaction at C-4 proceeded with inversion as expected from an $S_N2$ mechanism. Sidhu has also reported a similar observation employing a difluorinated substrate (entry 36). This reaction can be moderated by use of dichloromethane as reaction solvent.



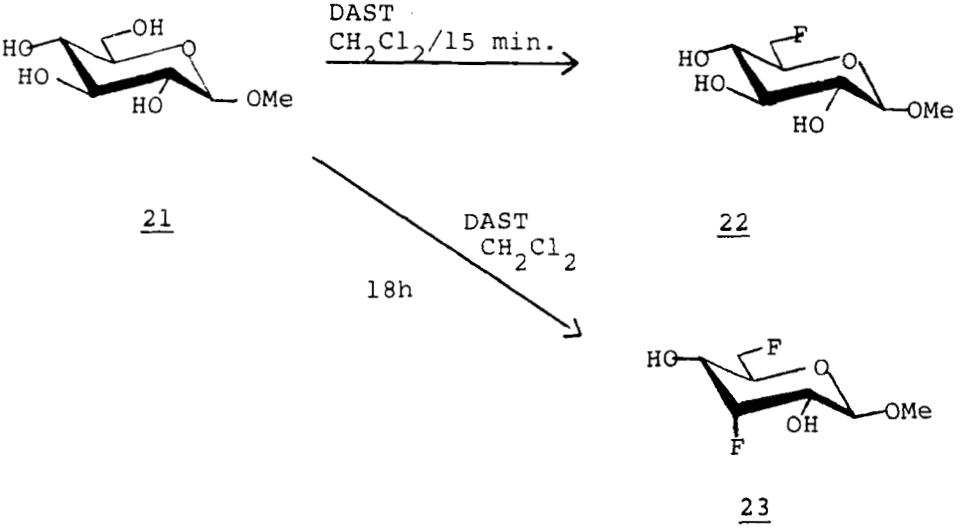

16 17 18

Thus, treatment of a suspension of 16 in $CH_2Cl_2$ with excess DAST gave the monofluorinated product 18 in up to 88% yield[48] (entry 37). Prolonged (48-72h) treatment of 18 with DAST in $CH_2Cl_2$, also results in replacement of the 4-OH group to produce 17.[51] These methodologies have been used to obtain easy access to 4-deoxy-4-fluoro-galacto-D-pyranosides. Reaction of the readily available trityl derivative 19 with DAST (neat or $CH_2Cl_2$) gave 20 in 23-41% yield (entry 39).




19 20

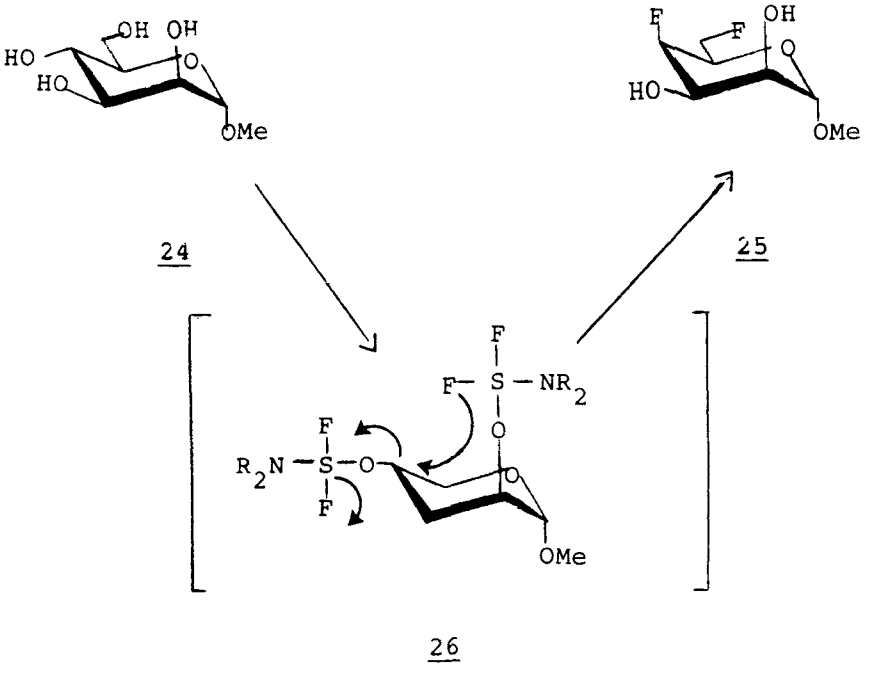
Similar to the case of α-D-glucopyranosides, the reaction of DAST with β-D-glucosides (such as 21) can be moderated via use of a solvent. Limiting the reaction of 21 with DAST in $CH_2Cl_2$ to a period of 15 min, gives a 60% yield of the monofluorinated product 22 (entry 40). In




21 22 23

contrast to the α-glucosides, treatment of β-glucosides with DAST for longer periods results in replacement of both the 3- and 6-OH groups and the production of the 3,6-difluoroalloside 23 in 51% yield (entries 42-44). Use of the 6-O-trityl derivative of 21 thus affords rapid entry into the 3-deoxy-3-fluoro-β-allopyranoside system (entries 45-46). As the above examples concerning ring fluorination illustrate, β-glucosides react rapidly with DAST at C-3 to give 3-fluoro-β-allo products, while α-glucosides react only sluggishly and at C-4 to afford 4-fluoro-α-galacto products. We ascribe the lack of reactivity at C-3 in the α-glucosides toward the DAST reagent to a steric interaction between the incoming nucleophile and the glycosidic oxygen and aglycon moiety.[53,54]

Since the regioselectivity of ring-fluorination is determined by the stereochemical configuration of the substrate, each sugar exhibits a unique reactivity pattern and affords correspondingly unique fluorodeoxy products. As an example, contrast the reactivity of methyl α-D-glucopyranoside (16) with methyl α-D-mannopyranoside (24). Treatment of 16 with DAST/$CH_2Cl_2$ at 25°C for 1 h afforded the monofluorinated 18 in up to 88% yield (entry 37). Ring-fluorination of 19 occurred at C-4 but only after prolonged treatment (entry 39). In contrast, we were totally unable to limit the reaction of 24 with DAST to monofluorination, methyl, 4,6-dideoxy-4,6-difluro-α-D-talopyranoside (25) was obtained in up to 80% yield after only 10 min (entry 51).[48,51,52] From this striking difference in reactivity at C-4 and the fact that $S_N2$-type displacement reactions at C-4 of mannose derivatives are frequently unsuccessful because of the steric hinderance exerted by the axial substituent at C-2, we assumed that an intramolecular fluoride-ion delivery via an intermediate such as 26 was occurring. The fact that methyl 2,3-di-O-methyl-α-D-mannopyranoside, after 1h reaction with DAST, affords only the monofluorinated product (entry 52) corroborates this assumption. Selective fluorination



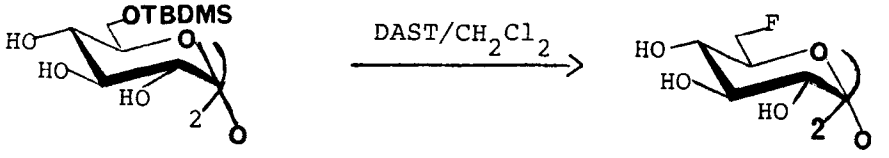

26

at C-6 or C-4 of α-mannopyranosides is now thus easily achieved. Treatment of the readily available methyl 2,3-O-isopropylidene-α-D-mannopyranoside with DAST affords the 6-deoxy-6-fluoro derivative (entry 53), whereas methyl 6-O-trityl-α-D-mannopyranoside gives the 4-deoxy-4-fluoro-α-talopyranoside analog (entries 54-55).

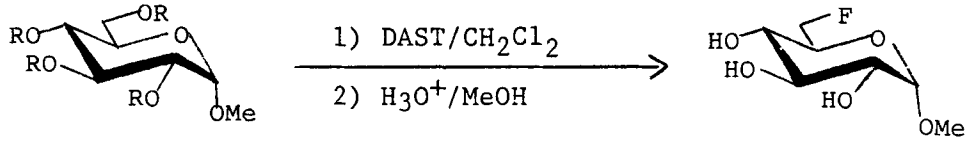
Examples of the reaction of DAST with xylo-, and galactopyranosides and a cyclitol have also been studied and may be found in Table II, entries 56-59.

In addition to mono-, disaccharides may also be fluorinated using this technique. A problem here is that some disaccharides do not dissolve in the DAST or DAST/$CH_2Cl_2$ mixtures. To overcome this, we have found (1) that the silyl ether protecting group may be used to solubilize the sugar in $CH_2Cl_2$, and (2) that DAST will cleave the silyl ether moiety and then convert the alkoxy group into the desired fluoride. This can be illustrated with two examples. 6,6'-Dideoxy-6,6'-difluoro-α,α-trehalose (27) has been synthesized and studied as a

competitive inhibitor of insect trehalase.[57] While 27 is a trivial molecule, its synthesis nonetheless required seven steps. We found that trehalose is not soluble in DAST/$CH_2Cl_2$, but that treatment of the readily prepared 28 with DAST afforded 27 in 36% yield (entry 60).[56] Along similar lines, per-trimethylsilylation can also be used. Thus 29, after reaction with DAST and subsequent hydrolysis of the remaining silyl ether moieties with aqueous acid, afforded 18 in 35% overall yield.[56]




28 27



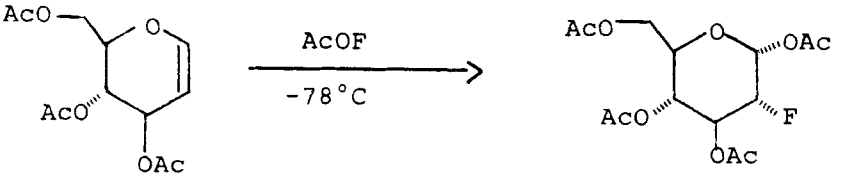

29 R=TMS 18

## V. ADDITION TO GLYCALS AND OTHER VINYL ETHERS

The reactions of glycals with various fluorinating reagents has been intensely investigated.[9] The extensive activity in this area stems from the use of 2-deoxy-2-[$^{18}$F]fluoro-glucose as a tracer for the in vivo measurement of regional glucose metabolism by means of positron emission tomography[6,7] (PET). The multiple productions of 2-$^{18}$FDG required for clinical studies has

led to the development of remote semiautomated production facilities.[59,60] These processes are based upon the cis-addition of $[^{18}F]F_2$ to 3,4,6-tri-O-acetyl-D-glucal (TAG) in $CFCl_3$ at -78°C which affords a mixture of 2-FDG and 2-FDM derivatives in a 95:5 ratio.[61] Hydrolysis and chromatography subsequently affords 2-FDG of 95% radiochemical purity which is sufficient for most purposes. Several reports concerning refinement of this methodology have appeared in the recent literature[59,62-64] including application to galactal and the altro-analog.[65]

Rosen has demonstrated the syn and regiospecific addition of acetyl hypofluorite across double bonds.[66] This methodology has been investigated as a route to 2-FDG. Adam[67] first reported the addition of AcOF to TAG in $CFCl_3$-HOAc at -78°C to give 30 in 78% yield.

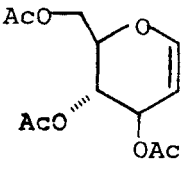
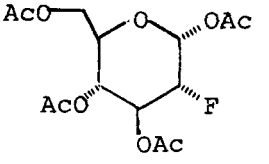
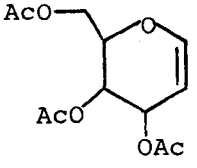
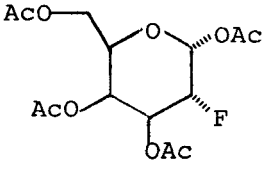
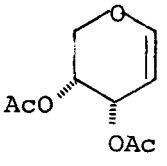
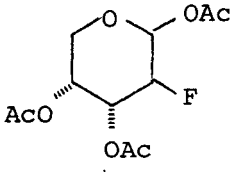
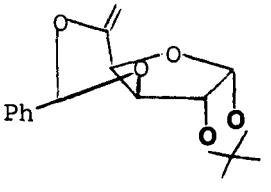
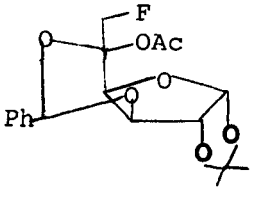
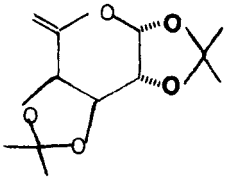
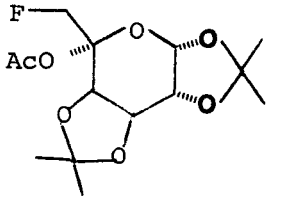
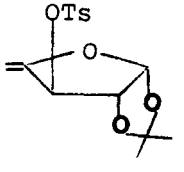
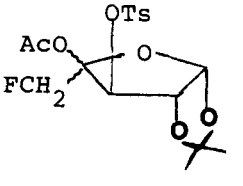



30

Subsequently, additions of AcOF to glucals in acetic acid, water, and $CFCl_3$ have also been reported.[68,69,70] Barrio has recently published studies concerning 2-FDG synthesis in which the effect of solvent, the nature of the fluorinating agent, and the structure of the glycal substrate were examined.[68] The results of this investigation revealed that the reaction of AcOF with TAG in a nonpolar medium such as $CFCl_3$ represents the most appropriate choice of fluorinating agent, glycal substrate, and solvent for the production of 2-FDG.

## TABLE III

### Additions of AcOF to Carbohydrate Vinyl Ethers

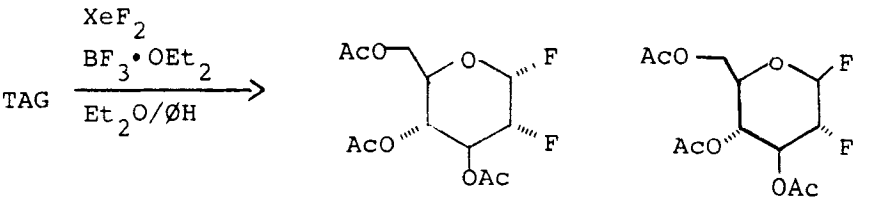
| Substrate | Product | Yield |
|---|---|---|
|  |  | 76% |
|  |  | 84% |
|  |  | 96 |
|  |  | 53 |
|  |  | 83[a] |
|  |  | 71[a] |

a. Contaminated with a minor by-product.

Adam has also reported on the addition of acetyl hypofluorite to other vinyl ether derivatives of sugars.[71] These additions (Table III) were shown to be rapid (<5 min. at -78°C), to yield exclusively cis-addition products, and to be highly regioselective.

Additions of trifluoromethyl hypofluoride to 3,4,5-tri-O-acetyl-1,5-anhydro-2-C-cyano-2-deoxy-D-lyxo-hex-1-eitol and 4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-3-ethoxycarbonylamino-D-arabino-hex-1-enitol have also been reported.[72]

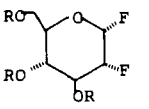
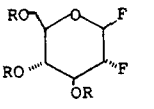
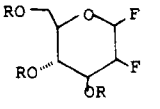
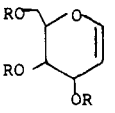
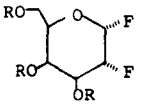
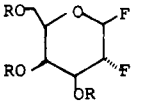
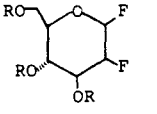
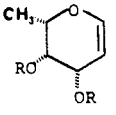
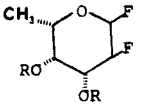
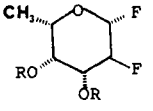
Xenon difluoride is a mild and versatile fluorinating agent. Korytnk[73,74] has recently reported the $XeF_2$ fluorination of TAG as a route to 2-FDG. Thus, treatment of TAG with a stoichiometric amount of $XeF_2$ in ether-benzene using $BF_3 \cdot OEt_2$ as catalyst afforded 31 (61%), 32 (12%), and 5% of the 2-fluoro-β-D-mannopyranosyl fluoride (33) after 24 hr at 25°C. Use of tri-O-acetyl-D-galactal and di-O-acetyl-L-fucal gave similar products (Table IV).




31 32

Shiue[75] has reported the synthesis of 2-$^{18}$FDG from TAG and $Xe^{18}F_2$ in an overall chemical yield of 50% in a 60 minute time period. In this latter synthesis, no manno (33) analog was detected and therefore the tedious chromatographic separation step is not required. A study concerning the effects of the concentration and reactant ratios on the yield of 2-FDG has also appeared.[76] In the improved procedure, the overall chemical yield has been raised to 75%.

TABLE IV

| Substrate | Reagent(s) | Products | | | Ref. |
|---|---|---|---|---|---|
| TAG | $XeF_2/BF_3 \cdot OEt_2$ 24h/25°C $Et_2O$/Benzene R=Ac |  61% |  12% |  5% | 73,74 |
|  | $XeF_2/BF_3 \cdot OEt_2$ 24h/25°C $Et_2O$/Benzene R=Ac |  69% |  11% |  5% | 73, 74 |
|  | $XeF_2/BF_3 \cdot OEt_2$ 24h/25°C $Et_2O$/Benzene R-Ac |  53% |  1.5% | | 74 |



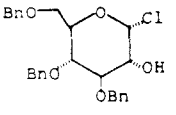
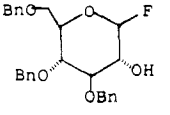
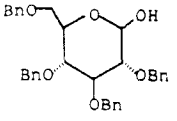
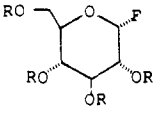
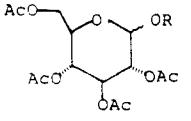
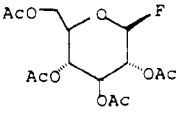
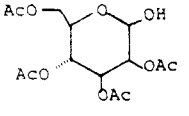
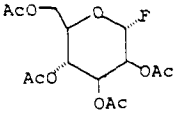
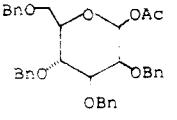
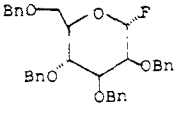
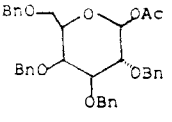
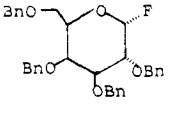
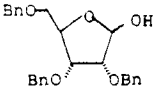
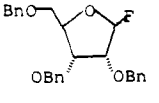
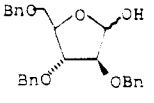
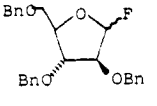
## VI. GLYCOSYL FLUORIDES - SYNTHESIS AND REACTIONS

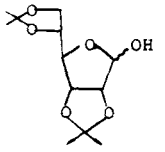
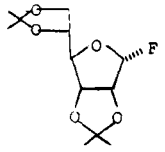
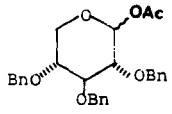
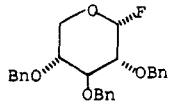
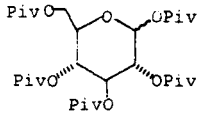
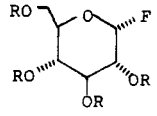
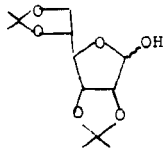
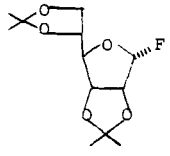
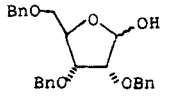
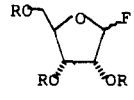
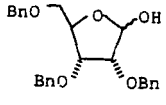
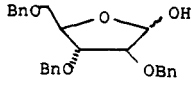
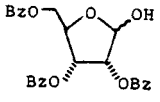
Glycosyl fluorides are much more stable and easier to handle than the corresponding chlorides or bromides that are typically employed in glycoside synthesis. In the past, glycosyl fluorides were thought to be too inert to be useful in glycosylation reactions; however, developments in recent years have proven glycosyl fluorides to be extremely useful reagents for glycoside synthesis.

The classical methods for synthesizing glycosyl fluorides are (1) treatment of acylated glycosyl chlorides or bromides with AgF, and (2) reaction of peracylated aldoses with hydrogen fluoride.[9] Since the Penglis review,[9] a report concerning use of AgF (Table V, entry 60) and reports of improvements in the hydrogen fluoride methodology (entries 61-70) have appeared. Indeed, the use of pyridinium poly(hydrogen fluoride) is a vast improvement over HF because of its apparent mildness. While mixtures of $\alpha/\beta$-anomers are obtained, this method

## TABLE V

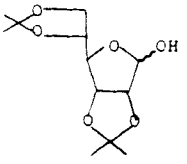
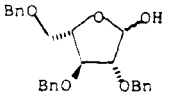
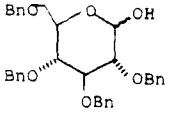
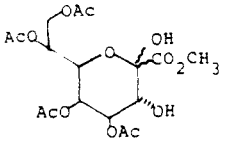
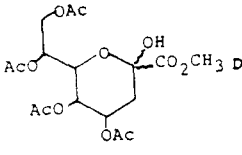
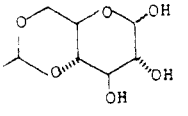
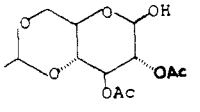
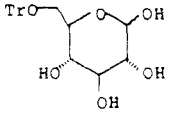
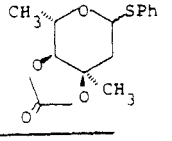
## Glycosyl Fluoride Synthesis

| Entry | Substrate | Reagent(s) & Conditions | Product | α/β | Yield | Re |
|---|---|---|---|---|---|---|
| 60. |  | AgF, rt Benzene/ $CH_3CN$ |  | 100%β | - | 77 |
| 61. |  | PPHF, -20→25° $CH_2Cl_2$ or toluene, 10h |  | 97:3 | 82-89 | 78,7 |
| 62. |  | " |  | R=H 100%β<br>R=Ac 95:5 | 53<br>72 | 79<br>78 |
| 63. |  | " |  | 100%α | 69 | 79 |
| 64. |  | 0°C, 6h |  | >95:5 | 84 | 78 |
| 65. |  | " |  | >95:5 | 80 | 78 |
| 66. |  | " |  | 65:35<br>50:50 | 68<br>79 | 78<br>79 |
| 67. |  | " |  | 3:1 | 58 | 79 |

| Entry | Substrate | Reagent(s) & Conditions | Product | α/β | Yield | Re |
|---|---|---|---|---|---|---|
| 68. |  | " |  | 100%α | 31 | 79 |
| 69. |  | $HF/CH_2Cl_2$ 30min/-70° |  | 100%α | 100 | 80 |
| 70. |  | $HF/CH_2Cl_2$ -30→-10°2 |  | 100%α | 74 | 80 |
| 71. |  | $\Phi_3P$/DEAD $Et_3O\cdot BF_4$ $CH_2Cl_2$ -78°/4h |  | 100%α | 54 | 80 |
| 72. |  | FMPT/$Et_3N$ $CH_2Cl_2$/25° |  | 58:42 | 84 | 82 |
| 73. |  34 | hexafluoro-propylamine 96h/rt | a | 1:2.9 | 75 | 83 |
| 74. | 34 | DAST/THF -30°→25° 20 min. | a | 1:9.9 | 90 | 84 |
| 75. |  | DAST(neat)/0° DAST/$CH_2Cl_2$ | a | 3:1 9:1 | 78 75 | 85 56 |
| 76. |  | DAST/THF -30→25° | a | 1:1.4 | 99 | 84 |

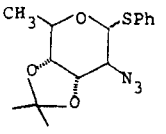
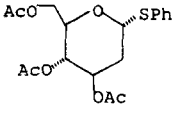
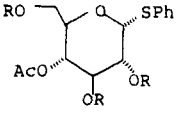
(continued)

Table 5 cont.

| Entry | Substrate | Reagent(s) & Conditions | Product | α/β | Yield | Re |
|---|---|---|---|---|---|---|
| 77. |  | DAST/THF -30→25°<br>DAST/$CH_2Cl_2$ -20→25° | a | 6.6:1<br>>10:1 | 87/13<br>59 | 84<br>56 |
| 78. |  | DAST/THF -30→25° | a | 10.5:1 | 95 | 84 |
| 79. |  | DAST(neat) 0°<br>DAST/THF -30→25°<br>DAST/$CH_2Cl_2$ -20→25° | a | 1:4<br>1:7.7<br>1:4 | 91<br>99<br>88 | 85<br>84<br>56 |
| 80. |  | DAST(neat) 0° | a | 100%β | 60 | 85 |
| 81. |  | DAST(neat) 0° | a | 2:1 | 73 | 85 |
| 82. |  | DAST/$CH_2Cl_2$<br>-78° | a | ≥2:98 | 80 | 86 |
| 83. |  | DAST/$CH_2Cl_2$<br>-30→25° | a | ≥4:96 | 97 | 86 |
| 84. |  | DAST/$CH_2Cl_2$<br>-78°C | a | 1:2 | 65 | 56 |
| 85. |  | HF.pyr/NBS | a | 1:2 | 75 | 87 |

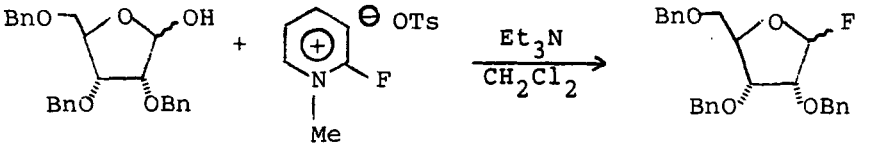
[a]Corresponding glycosyl fluorides formed.

Table 5 cont.

| Entry | Substrate | Reagent(s) & Conditions | Product | α/β | Yield | Re |
|---|---|---|---|---|---|---|
| 86. |  | DAST/NBS, $CH_2Cl_2$ 0°→25°<br>HF.pyr/NBS | a | 2:1<br>2:1 | 80<br>73 | 87<br>87 |
| 87. |  | DAST/NBS<br>$CH_2Cl_2$, 0→25° | a | 100%α | 70 | 87 |
| 88. |  <br>R=$^{t}BuPh_2$ | DAST/NBS<br>HF.pyr | a | 5:1<br>5:1 | 82<br>74 | 87<br>87 |

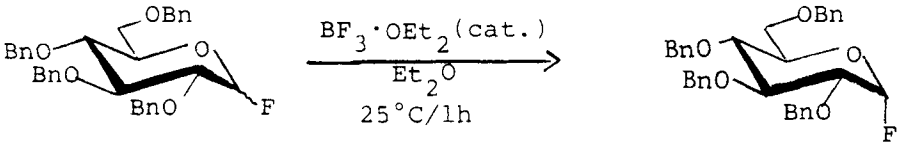


generally gives the thermodynamically more stable anomer in predominate amounts. Entries 61-68 are only representative of the many examples reported.[78,79] A modified Mitsunobu reaction has also been employed to prepare a glycosyl fluoride (entry 71).[80] Mukaiyama has extended his 2-halo-1-methylpyridinium tosylate chemistry[81] to glycosyl fluoride synthesis. Thus 2-fluoro-1-methylpyridinium tosylate (FMPT) was used to activate the anomeric hydroxyl group in 34 and afforded 35 in 84% yield (entry 72).



34 35

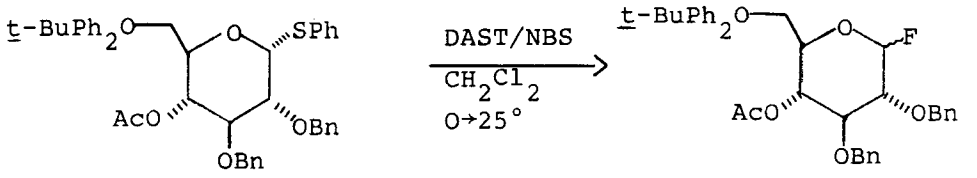
Direct replacement of anomeric hydroxyl groups have also been effected using either DAST or diethyl 1,1,2,3,3,3-hexafluoropropylamine. Treatment of 34 with the latter reagent produced a 75% yield of 35 after 96h (entry 73)[83], whereas use of DAST gave 35 (90%) after only 20 min. (entry 74).[84] Entries 75-84 illustrate further the use of DAST for glycosyl fluoride synthesis. Posner has found that there is an important solvent effect on the α/β ratio that is obtained, THF affording the highest selectivity.[84] It is also important to note that column chromatography is usually sufficient to separate the anomers into pure form. In addition, anomerization may be effected with Lewis acids to afford desired anomers such as that illustrated for the preparation of 36.[86,82] Entries 82 and 84 demonstrate the selectivity of the DAST reagent in that all hydroxyls need not be protected especially at -78°C. Likewise, the utility of glycosyl fluorides is expanded because of the reduced number of protection and deprotection steps required when they are employed in glycoside synthesis.




α / β-14/86 74% 100% α

36

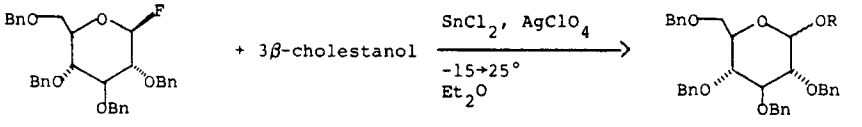
Thioglycosides have been employed as substrates for glycosyl fluoride formation using a combination of either DAST or HF pyridine with N-bromosuccinimide.[87] Thus, treatment of a thioglycoside such as 37 with DAST/NBS affords glycosyl fluoride 38 (a/b=1:1) in 90% yield. Entries 85-88 further demonstrate this methodology. In addition, the above reaction and entry 88 illustrate the mildness of these reagents as t-butyldiphenylsilyl ethers are not cleaved during glycosyl fluoride formation.




37 38

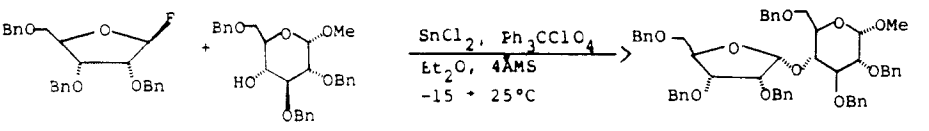
## Reactions

The formation of glycosides from glycosyl fluorides and alcohols under Konigs-Knorr type conditions has been reported by Mukaiyama and others.[80,83,87] For example, reaction of fluoride 39 with 3β-cholestanol in the presence of $SnCl_2$ and $AgClO_4$ for 24h gave a 96% yield of the corresponding glycoside (40) with α/β=92:8 Glycoside




39 40

formation was achieved using a range of alcohols [MeOH (82%, 86/14), t-BuOH (87%, 81/19)] and monosaccharides with yields ranging from 76-96% and typical α/β ratios of about 4/1. The thermodynamically more stable α-glycoside is predominately formed. After screening various mixtures of Lewis acids and solvents, Mukaiyama[82] found the combination of $SnCl_2$ and trityl perchlorate in ether to give the highest α/β selectivity. Thus treatment of fluoride 41 with methyl 2,3,6-tri-O-benzyl-α-D-gluco-pyranoside in the presence of the above reagents gave disaccharide 42 in 96% yield with α/β=85:15. A similar result was obtained with 2,3,5-tri-O-benzyl-α-L-arabinofuranosyl fluoride.



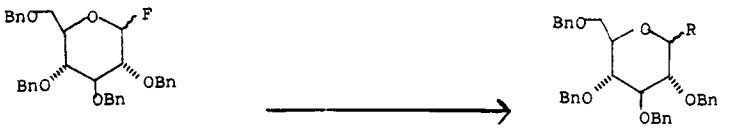

41 42

Along similar lines, Nicolau[89] has reported $BF_3 \cdot OEt_2$ to be an effective catalyst for the preparation of glycosyl esters (Table VI, entry 89), glycosyl phosphates (entry 90), glycosides (entry 91), thiogycosides (entry 92), and glycosyl azides (entry 93). Glycosyl amines can also be prepared using aliphatic amines with $MgBr_2 \cdot OEt_2$ (entry 94) and $AlMe_3$ (entry 95) as catalysts, or heterocyclic bases using $SnCl_4$. Kunz[80] has reported similar results using both alcohols and trimethylsilyl ethers.

Using glycopyranosyl fluoride 39 and trimethylsilyl ether derivatives of various aglycones, Noyori[90] has demonstrated the catalytic effectiveness of $SiF_4$ and trimethylsilyl triflate (entries 96-99). A marked solvent effect on the stereochemical outcome of reactions with substrates having a nonparticipating group at C-2 was noted; contrast entries 96 vs. 97, and 98 vs. 99. This general trend was not affected by the stereochemistry of the starting fluorides, nor do the products undergo anomerization under the reaction conditions, thus indicating kinetic control of product formation.

Two groups have reported the synthesis of C-glycosides from glycosyl fluorides. Ishido[83] found trimethylsilyl enol ether 43 coupled with glycosyl fluoride 41 using $BF_3 \cdot OEt_2$ as catalyst to afford C-glycoside 44 in 95% yield. Nicolaou[91] has extensively studied the C-glycosylation of fluoride 39. Thus, treatment of 39 with allytrimethylsilane and $BF_3 \cdot OEt_2$ gave the allyl

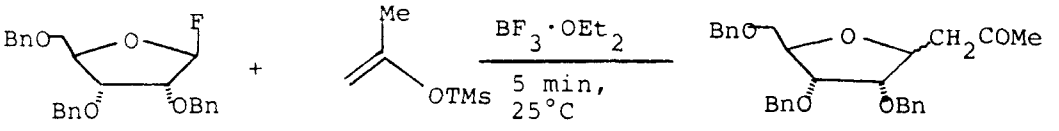
TABLE VI



39

39

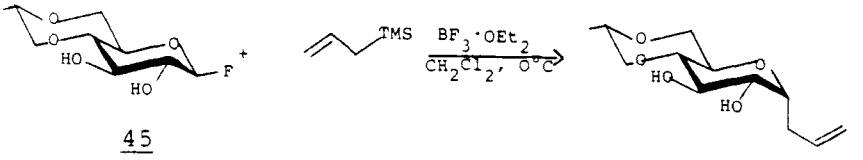
| Entry | Reagents and Conditions | R | α/β | Yield | Ref. |
|---|---|---|---|---|---|
| 89. | $MeCO_2H/BF_3\cdot OEt_2/CH_2Cl_2$ 4A MS 0→25°C | OCOMe | 3:2 | 83 | 89 |
| 90. | $(BnO)_2P(O)OSnBu_3/BF_3\cdot OEt_2$ $Et_2O$/0→25°C | $O(O)P(OBn)_2$ | 10:1 | 50 | 89 |
| 91. | ROH/$BF_3\cdot OEt_2$/4A MS −15→0°C | OR | 2:1 | 51 | 89 |
| 92. | $RSH/BF_3\cdot OEt_2/CH_2Cl_2$ 25°C | SR | 1:20 | 80 | 89 |
| 93. | $Me_3SiN_3/BF_3\cdot OEt_2/CH_2Cl_2$ 0→25° | $N_3$ | 10:1 | 90 | 89 |
| 94. | morpholine/$MgBr_2\cdot OEt_2/CH_2Cl_2$ 25°C |  | 1:10 | 90 | 89 |
| 95. | $H_2NCH_2CH=CH_2/AlMe_3/CH_2Cl_2$ 25°C | $-NHCH_2CH=CH_2$ | 2:1 | 95 | 89 |
| 96. | $CH_3OTMS/TMSOT_f/CH_3CN$ 0°C,5h | $OCH_3$ | 16:84 | 87 | 90 |
| 97. | $CH_3OTMS/TMSOT_f/Et_2O$ 5°C, 20h | $OCH_3$ | 90:10 | 86 | 90 |
| 98. | $c\text{-}C_6H_{11}OTMS/SiF_4/CH_3CN$ 0°C, 3h | $OC_6H_{11}$ | 15:85 | 88 | 90 |
| 99. | $c\text{-}C_6H_{11}OTMS/SiF_4/Et_2O$ 5°C, 24h | $OC_6H_{11}$ | 74:26 | 62 | 90 |
| 100. | $CH_2=CHCH_2TMS/BF_3\cdot OEt_2$ | $-CH_2CH=CH_2$ | >20:1 | 95 | 86,9 |
| 101. | $AlMe_3$/toluene/0°C | -Me | >20:1 | 95 | 91 |
| 102. | $AlMe_2CN$/toluene/0°C | -CN | ~10:1 | 96 | 9 |
| 103. | $CH_2=CHCN/MgBr_2\cdot OEt_2/Bu_3SnH$ | $-CH_2CH_2CN$ | >10:1 | 61 | 91 |




41 43 44 α/β = >20:1

glycoside in 95% yield (α/β >20:1). In addition, aluminum reagents and free radical reactions were also employed to transform glycosyl fluoride 39 into C-glycosides (entries 100-103).

Of special note is the ability to prepare C-glycosides from glycosyl fluorides containing unprotectd hydroxyl groups. We have found[86] that glycosyl fluoride 45 can be C-allylated using allyltrimethylsilane/$BF_3 \cdot OEt_2$ to give the C-glycoside in modest (33%) yield.

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