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Synthesis of All Configurational Isomers of 1,6-Anhydro-2,3,4-trideoxy-2,3-epimino-4-fluoro-β-D-hexopyranoses

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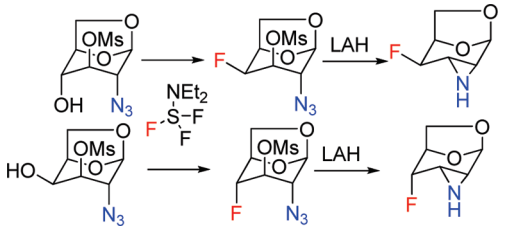

We have prepared a full series of 1,6-anhydro-2,3,4-trideoxy-4-fluoro-2,3-epimino-β-D-hexopyranoses. The key step was the reaction of azido sulfonates possessing a free C-4 hydroxyl with DAST and subsequent $LiAlH_4$ reduction. Nucleophilic displacement of the hydroxyl activated by DAST proceeded without rearrangement and with moderate to good yields. A convenient synthesis of D-manno-epimine from a readily available 3-benzylamino derivative was also developed.

Fluorinated carbohydrates and nucleosides have continuously received considerable attention from organic chemists.[1] The introduction of fluorine into a carbohydrate molecule can lead to significant changes in biochemical action, lipophilicity, acidity, and dipole interactions in comparison with the parent sugar.[2] For example, fluorosugars are indispensable as probes for studies of carbohydrate−protein interaction[3] and for medical imaging using positron emission tomography, and some fluorinated nucleosides are also important therapeuticals.[4] Their troublesome synthesis[5] does not cease to stimulate the efforts of synthetic chemists. In connection with our ongoing program focused on hexopyranose-based aziridines,[6] the need arose to prepare 1,6-anhydro-2,3-epiminohexopyranoses with a strong electron-withdrawing substituent at the pyranose carbon vicinal to the aziridine ring. As fluorine is widely used to alter electronic properties of carbohydrates,[7] we supposed that 4-fluoro-2,3-epiminopyranoses may well suit this purpose and exhibit reactivity different from their nonfluorinated counterparts. In addition, fluorinated epimines represent important examples of fluorinated amino sugars with potentially interesting biochemical implications, such as precursors of enzyme inhibitors or as fluorinated analogues of some glycoconjugate components. Here we wish to report the synthesis of all configurational isomers of 1,6-anhydro-2,3,4-trideoxy-4-fluoro-2,3-epimino-β-D-hexopyranoses.

We envisioned two routes to the target fluoro compounds: (i) preparation of suitable azido sulfonates with a free C-4 hydroxyl group, subsequent displacement of the hydroxyl with fluorine on reaction with diethylaminosulfur trifluoride (DAST), followed by reductive aziridine ring closure, and (ii) direct conversion of 1,6-anhydro-2,3-epiminopyranoses into the corresponding 4-fluoro compounds on reaction with DAST.

Of these two routes, the first proved to be of general utility. Starting 4-O-benzylated azido derivatives **1**, **6**, **8**, **9**, and **10** (Scheme 1) were prepared according to the literature procedures.[8] Conventional mesylation of **1** afforded **2**. Azido tosylate **14** was prepared from dianhydrotalopyranose **13** by azidolysis[9] with NaN_3 and subsequent tosylation. Azido tosylate **16** was prepared using a modified literature procedure.[10] Synthesis of suitable azido sulfonates with a free C-4 hydroxyl group was accomplished using oxidative debenzylation of the corresponding 4-*O*-benzyl pyranoses with the

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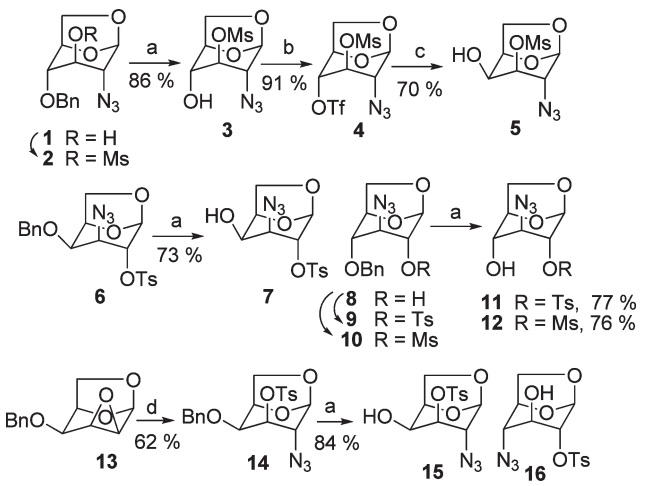
SCHEME 1. Synthesis of Azido Sulfonates[a]



[a]Reagents and conditions: (a) $KBrO_3$, $Na_2S_2O_4$, AcOEt, rt, 2−5 h; (b) Tf_2O, py, CH_2Cl_2 −15 to 0 °C, 1 h; (c) TBAN, DMF, rt, 5 h; (d) (i) NaN_3, NH_4Cl, $CH_3OC_2H_4OH$, H_2O, reflux, (ii) TsCl, py, 80 °C.

$KBrO_3/Na_2S_2O_4$ system.[11] Attempted inversion of configuration at C-4 of compound **3** by Mitsunobu reaction with DEAD/Ph_3P/4-$NO_2C_6H_4COOH$ to obtain compound **5** returned only the unreacted starting compound **3**, probably due to steric crowding caused by the axial OMs and CH_2 groups at C-3 and C-5. On the other hand, reaction of triflate **4** with tetrabutylammonium nitrite[12] proceeded smoothly at room temperature and yielded the desired D-galacto compound **5**.

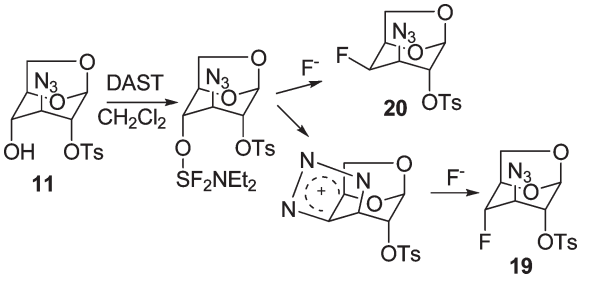
Reactions of DAST with azido sulfonates having a free 4-hydroxyl group are summarized in Table 1. It is known[1c] that nucleophilic fluorination of pyranoses is complicated by undesirable reactions, mostly rearrangements or eliminations. For instance, among 31 nucleophilic fluorination reactions at C-4 of hexopyranoses listed in the review article[1c] by Dax et al., nine give an undesirable major product. We found that all azido sulfonates gave only products of fluorination at C-4. Moreover, in most cases, the stereochemistry of the major product at C-4 corresponded to inversion of configuration with respect to the configuration of the hydroxyl group in the educt. Only *trans*-diaxial 3-azido-2-sulfonates **11** and **12** afforded significant proportion of both epimers. We assume that formation of noninverted products **19** and **21** is caused by competing anchimeric assistance of the neighboring *trans*-diaxially disposed azido group as depicted in Scheme 2 for reaction of **11**. Because the tetrahydropyran ring is locked in $^1C_4$ conformation, the attack of fluoride anion at position 3 of the intermediate cation (Scheme 2) is unlikely by analogy to the Fürst−Plattner rule.[13] The stereochemical outcome of the reaction of 4-azido derivative **16** with DAST seems to further support this postulated mechanism because only the noninverted product **25** was isolated. A similar participation of a neighboring azido group was

TABLE 1. Reaction of Azido Sulfonates with DAST[a]

entry	educt	axial product	yield (%)	equatorial product	yield (%)
1	**3**	-		**17**	71
2	**5**	**18**	60	**17**	3
3	**7**	**19**	55	**20**	6
4	**11**	**19**	33	**20**	25
5	**12**[b]	**21**	29	**22**	24
6	**15**	**23**	44	**24**	3
7	**16**	**25**	72	-	

[a]Conditions (based on ref 5): DAST, CH_2Cl_2, −20 °C to rt. [b]**21** and **22**: yield and structure determined only by NMR. Analytical samples obtained by a semipreparative HPLC on reverse phase C18.

SCHEME 2. Suggested Mechanism for Formation of 19



also postulated[14] for reaction of methyl 4,6-di-*O*-benzylidene-3-azido-3-deoxy-α-D-altropyranoside. Fluorinated azido mesylates **21** and **22** could not be properly separated by column chromatography on silica gel, and we obtained only enriched fractions. Fluoro derivative **22** crystallized from the respective enriched chromatographic fraction and was obtained in 80% purity. The corresponding tosylates **19** and

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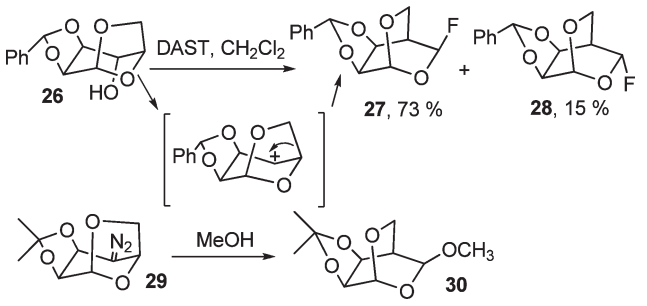
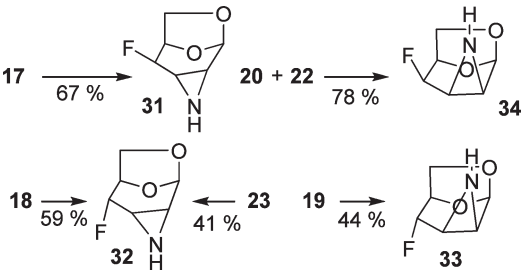
SCHEME 3. Skeletal Rearrangements of 26 and 29



SCHEME 4. Reductive Cyclization[a]



[a]Reagents and conditions: $LiAlH_4$, THF, −15 °C to rt, 24 h.

20 of the same configuration could be separated by careful column chromatography.

The structures of the 4-hydroxy and 4-fluoro derivatives were determined from ^1H and ^{13}C NMR spectra. The gCOSY and gHSQC spectra were measured for structural assignment of ^1H and ^{13}C signals (see Supporting Information). The position of the hydroxyl group was determined from the observation of the *J*-coupling of 6−10 Hz to H-4. The *trans*-diaxial disposition of substituents at C-2 and C-3 was manifested by small values of *J*-couplings of the equatorial H-2 and H-3 protons ($J(2,1)$ = 1.1−1.7, $J(2,3)$ = 1.3−2.8, $J(3,4ax)$ = 4.7−6.1, and $J(3,4eq)$ = 1.3−1.7 Hz); the position of the tosyl/mesyl group is manifested by the significant downfield ^1H NMR chemical shift compared to the chemical shift of the azide group. The increase of coupling constants $J(2,3)$ and $J(3,4)$ of **19** and **21** indicates a certain population of the boat form $B_{O,3}$.[15] The equatorial position of H-2 and H-3 is further supported by the observation of long-range couplings $J(1,3)$, $J(2,4)$, $J(3,5) \sim 0-1.7$. Coupling constants $J(5,6en)$ = 0.6−1.2 Hz and $J(5,6ex)$ = 4.9−5.9 Hz are in agreement with ^{O1}E conformation of the five-membered dioxolane ring.

Introduction of the fluorine atom causes additional splitting of the ^1H and ^{13}C NMR signals in the pyranose moiety. This splitting is also reflected in the ^{19}F NMR spectra of **17**−**24** in which the characteristic doublet of triplet or plain doublet can be usually found for axial and equatorial F-4, respectively. In most cases, both epimers were prepared, and thus we can generalize that the axial fluorine atom in position 4 shows not only geminal coupling to H-4 but also strong vicinal coupling to H-3 and H-5 while the equatorial F-4 possesses, in addition to the geminal coupling, only weak vicinal couplings.

During preliminary experiments, we tried to introduce fluorine at C-4 by the reaction of 2,3-di-*O*-benzylidene-D-mannosane **26** with DAST. Here a skeletal rearrangement took place to provide branched-chain pyranosyl fluorides **27** and **28** (Scheme 3). Both products are crystalline compounds, but **28** contained impurities and decomposed on standing at 4 °C within several weeks whereas anomer **27** is stable. The structures of products **27** and **28** were determined by X-ray analysis. A similar rearrangement also took place[16] on methanolysis of diazo compound **29** and yielded methyl pyranoside **30**. The formation of these rearrangement products is consistent with initial formation of C-4 carbocationic species followed by 1,2-alkyl shift, as depicted in Scheme 3. It is noteworthy that the major product **27** of reaction with DAST has the same configuration at C-9 (C-5 in numbering of **26**) as the product of methanolysis **30**. The stereochemical outcome of this reaction was attributed to a concerted process with synchronous formation of C-4 carbocation, a shift from C-6 to C-4, and an equatorial attack of the nucleophile at C-5.[16] The 1,2-alkyl shift involved in formation of products **27** and **28** seems to indicate that with some substrates the fluorination with DAST should follow a S_N1 cationic mechanism rather than the otherwise more usual S_N2 mechanism.[17] The S_N2-type displacement reactions at C-4 of mannose derivative **26** are probably suppressed because of the steric hindrance exerted by the substituents at the β-face of the substrate.[18]

Treatment of azido sulfonates **17**, **18**, **19**, and **23** with lithium aluminum hydride afforded the respective aziridine derivatives **31**−**33** (Scheme 4). The D-taloepimine **34** was prepared by treatment of a mixture of mesylate **20** and tosylate **22**. The epimines **31**−**34** represent all possible configurations within 1,6-anhydro-β-D-hexopyranose series. Epimines **31**−**34** are stable crystalline compounds which sublimate around 90 °C. They show the characteristic ^1H NMR chemical shift of H-2 and H-3 under 3 ppm, which is accompanied by the rise of the $J(2,3)$ up to 4.9−5.8 Hz, indicating the E_O conformation of the tetrahydropyran ring. The NMR assignment and structures were confirmed by X-ray crystallography of all epimines **31**−**34** (see Supporting Information).

Finally, we turned our attention to direct conversion of 4-hydroxy-2,3-epimines into 4-fluoro analogues. During preliminary experiments, we discovered that treatment of galactoepimine **35** with DAST in dichloromethane at −50 °C resulted in formation of 4-fluoro-2,3-mannoepimine **37** as a major product instead of the expected 2-fluoro-3,4-taloepimine (Scheme 5). Epimine **37** was probably formed by nucleophilic aziridine ring opening of the intermediate **36** with fluoride anion and subsequent aziridine ring closure at C-2. 2-Fluoro-galactoepimine **39** was detected by NMR as a minor product but could not be isolated by column chromatography as a pure compound. A very convenient preparation of epimine **37** consists of treatment of readily available[19] 3-benzylamino derivative **38** with DAST. Mannoepimine **37** was isolated in one step in 49% yield. Possible formation of **37** from **38** involves activation of the 4-OH group by DAST

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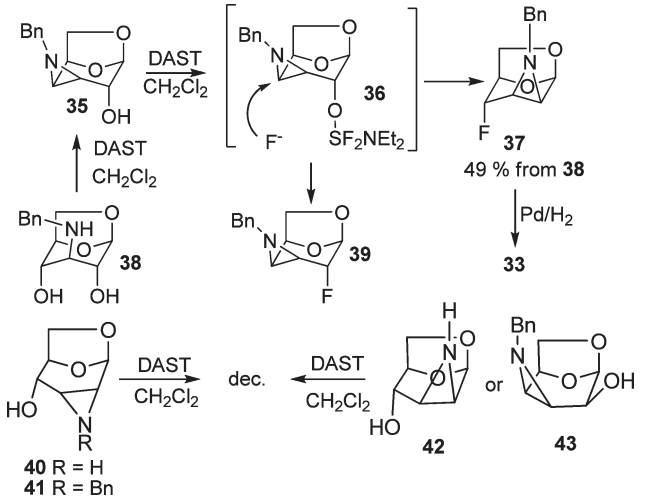
SCHEME 5. Reaction of 35, 38, and 40−43 with DAST



followed by aziridine ring closure at C-4 to give galactoepimine **35**. Aziridine ring closure at C-2 directly from **38** is unlikely because C-4 hydroxyl consistently exhibits higher reactivity than C-2 hydroxyl.[19] Hydrogenolytic de-N-benzylation of **37** gave free epimine **33**.

Encouraged by these results, we subjected 2,3-epimino derivatives **40** and **42** to treatment with DAST in dichloromethane at −50 °C. However, these experiments only resulted in formation of complex syrupy mixtures which contained no fluoro compounds according to ^{19}F NMR. N-Protection by the benzyl group brought no improvement because *N*-benzylepimines **41** and **43** gave again only complex mixtures with no fluorine-containing products according to ^{19}F NMR. Epimines **40**−**43** were prepared by published[8b,19] procedures.

In conclusion, we have developed a methodology for the introduction of fluorine at C-4 of 1,6-anhydro-β-D-hexopyranoses substituted at C-2 and C-3 by *trans*-diaxially disposed azide and alkene/arenesulfonyloxy groups. Subsequent reductive cyclization provided the corresponding 4-fluoro-2,3-epimino derivatives in all possible configurations. The reactivity of these fluoro epimines is currently being studied, and the results will be reported in due course.

Experimental Section

Example procedures are given below. Full experimental details are available in Supporting Information.

1,6-Anhydro-2-azido-2,4-dideoxy-4-fluoro-3-*O*-methanesulfonyl-β-D-galactopyranose (17). A solution of hydroxy mesylate **3** (444 mg, 1.67 mmol) in dichloromethane (3 mL) was added to a stirred, cooled (−15 °C) solution of DAST (0.7 mL, 5.30 mmol) in dichloromethane. The cooling bath was removed after 20 min, and the reaction mixture was allowed to stand at rt for 48 h. TLC in ethyl acetate indicated one product (R_f 0.6). The reaction mixture was diluted with dichloromethane, MeOH (2 mL) was added dropwise under cooling to quench the reaction, and the reaction mixture was successively washed with 5% HCl and aqueous $NaHCO_3$, dried, and concentrated. Chromatography in 1:1 ethyl acetate−hexane afforded **17** (316 mg, 71%): mp 81−83 °C (ethanol), $[\alpha]^{25}_D$ +55 (*c* 0.21, $CHCl_3$). Anal. Calcd for $C_7H_{10}FN_3O_5S$: C, 31.46; H, 3.77; N, 15.72. Found: C, 31.53; H, 3.82; N, 15.39.

1,6-Anhydro-2,3,4-trideoxy-4-fluoro-2,3-epimino-β-D-gulopyranose (31). A suspension of $LiAlH_4$ (75 mg, 1.98 mmol) in THF (2.5 mL) was added dropwise to a stirred, cooled (−15 °C) solution of fluoro derivative **17** (208 mg, 0.78 mmol) in THF (5 mL). The cooling bath was removed after 30 min, and stirring continued overnight. TLC in acetone and 10:1 dichloromethane−methanol revealed one product (R_f 0.41). The remaining $LiAlH_4$ was decomposed by addition of wet diethyl ether. The white precipitate was filtered off and washed with THF, and the combined filtrates were concentrated. Chromatography in 20:1 dichlorormethane−methanol afforded epimine **31** (76 mg, 67%): mp 95−97 °C (ethanol−ether), $[\alpha]^{25}_D$ +48 (*c* 0.17, $CHCl_3$). Anal. Calcd for $C_6H_8FNO_2$: C, 49.65; H, 5.56; N, 9.65. Found: C, 49.67; H, 5.47; N, 9.51.

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Supporting Information Available: Full experimental details, tables of NMR chemical shifts and coupling constants, crystallographic data, ORTEP projections, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.