RING CONTRACTION IN THE FLUORINATION OF METHYL 2-O-BENZYL-3,6-DIDEOXY- AND METHYL 2,3-DI-O-BENZYL-6-DEOXY-α-D-HEXOPYRANOSIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE (DAST)

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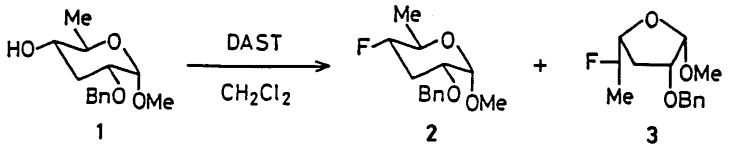
Fluorination of methyl 2-O-benzyl-3,6-dideoxy-α-D-*ribo*- and α-D-*arabino*-hexopyranosides (**1** and **4**) with diethylaminosulfur trifluoride (DAST) yielded methyl 2-O-benzyl-3,5,6-trideoxy-5-fluoro-β-L-*arabino*- and β-L-*ribo*-hexofuranosides (**3** and **6**), respectively, along with the corresponding 4-deoxy-4-fluoro-α-D-hexopyranosides with retained configuration at C-4. The reaction of methyl 2,3-di-O-benzyl-6-deoxy-α-D-glucopyranoside (**7**) with DAST predominantly afforded methyl 2,3-di-O-benzyl-5,6-dideoxy-5-fluoro-β-L-altrofuranoside (**9**).

KEYWORDS ring contraction; fluorination; DAST; fluorinated carbohydrate; 5,6-dideoxy-5-fluoro-hexofuranose; 3,5,6-trideoxy-5-fluoro-hexofuranose

Among a large number of strategies for the introduction of fluorine into carbohydrates, diethylaminosulfur trifluoride (DAST) is known as a useful reagent for the direct replacement of hydroxyl group by fluorine.[1-4] However, unusual reactions caused by the action of DAST have also been reported.[4]

In our attempts at direct fluorination using DAST at 4-position of 3,6-dideoxyhexopyranosides, it was found that the substitution of the equatorial 4-hydroxyl group by fluorine proceeded with exclusive retention of configuration.[5] Investigation of the by-products in those reactions revealed the formation of the fluorides having furanoid structure such as **3** and **6**. There have been reports of similar results on the iodination of methyl 2,3-O-isopropyridene-α-L-rhamnopyranoside,[6] the deamination of the 4-amino derivatives of methyl α-L-manno-[7] and α-D-glucopyranosides,[8] and the hydrolysis of methyl 4-O-(4-nitrobenzenesulfonyl)-α-D-glucopyranoside.[9] The ring-contracted 5-fluorides were obtained in the fluorination of racemic methyl N-acetylacosaminides with sulfur tetrafluoride-hydrogen fluoride.[10] This communication provides an example of ring contraction of hexopyranoside induced by DAST.

When methyl 2-O-benzyl-3,6-dideoxy-α-D-*ribo*-hexopyranoside (**1**) was treated with 1.2 molar equivalents of DAST in dichloromethane at -13℃ for 0.5 h and then at room temperature for 1.5 h, methyl 2-O-benzyl-3,4,6-trideoxy-4-fluoro-α-D-*ribo*-hexopyranoside (**2**) and methyl 2-O-benzyl-3,5,6-trideoxy-5-fluoro-β-L-*arabino*-hexofuranoside (**3**) were isolated through silica gel column chromatography in yields of 66% and 17%, respectively. The reaction of the α-D-*arabino* isomer **4** with DAST under the same reaction conditions as those for **1** gave the 4-fluoride **5** in 28% yield and methyl 2-O-benzyl-3,5,6-trideoxy-5-fluoro-β-L-*ribo*-hexofuranoside (**6**) in 21% yield along with 34% recovery of **4**. No 5-epi-fluoride was isolated from both reactions.



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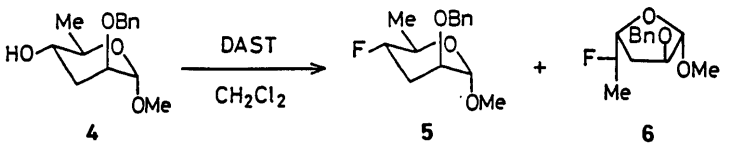
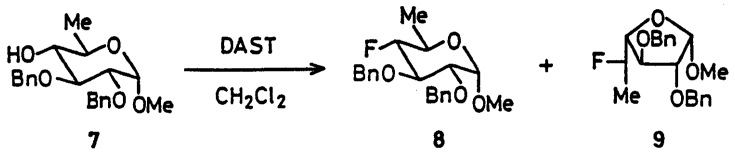


4 5 6

In a similar reaction of the 2,3-di-O-benzyl derivative **7**,[11] methyl 2,3-di-O-benzyl-5,6-dideoxy-5-fluoro-β-L-altrofuranoside (**9**) was obtained in 38% yield as the major product along with



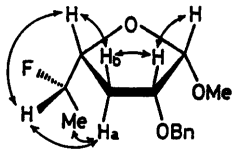
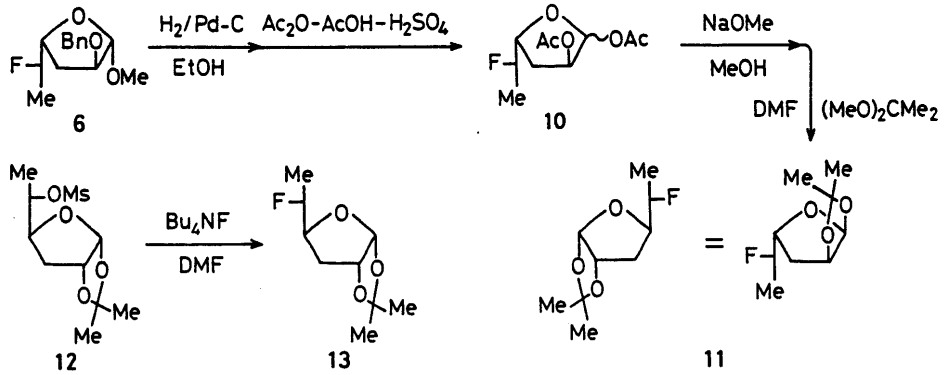


Fig. 1. NOEs observed for 3

only 2% yield of the 4-fluoride **8**, and **7** recovered (39%); no α-D-galacto isomer of **9** was produced.

The ^{1}H- and ^{13}C-NMR spectral data of the ring-contracted compounds (**3**, **6**, and **9**) are summarized in Tables I and II, respectively. The NOEs observed for the protons of **3** are shown in Fig. 1. The stereochemistry at C-4 of **3** was determined by the presence of the NOEs between H-2 and H-3b, H-3b and H-4, H-3a and H-5, and H-3a and H-6's. Similarly, the NOEs observed between H-2 and H-3a, and H-3b and H-4 of **6**, and that observed between H-3 and H-5 of **9** were reasonable for their proposed configuration at C-4.

The absolute configuration at C-5 was verified in the following synthetical manner. The compound **6** was readily converted through hydrogenolysis and subsequent acetolysis into the 1,2-diacetate **10**, which was deacetylated and then isopropylidenated to form **11**. The ^{1}H-NMR spectrum of **11** was identical with that of **13** independently prepared by the reaction of 3,6-dideoxy-1,2-O-isopropylidene-4-O-methanesulfonyl-β-L-*lyxo*-hexofuranose (**12**, $[\alpha]_D^{20}$ -31.8° (c 0.9, chloroform)) with tetrabutylammonium fluoride in N,N-dimethylformamide. The specific rotations for **11** and **13**, measured in chloroform at 20°C, are +25.4° and -25.7° , respectively. Thus, it is ascertained that **11** is the enantiomer of **13**, and this indicates that the proposed structure of **6** is correct. Details of the syntheses of **1**, **4**, **11**, **12**, and **13** are to be published elsewhere.



Stereospecific formation of single isomers of both the 4- and the 5-fluorides suggests that the bicyclic oxonium ion I (Chart 1) formed by the participation of ring oxygen is a plausible intermediate for the production of the 4-fluoride (route a) and the 5-fluoride (route b). However, the ring contraction concerted with the intramolecular attack of fluorine at C-5 (depicted as II), being analogous to the formation of a furanoid structure through migration of a sulfonyloxyl group from C-4 to C-5,[12] seems to be more presumable to the predominant formation of **9**. Further experiments for elucidating the mechanisms are in progress.

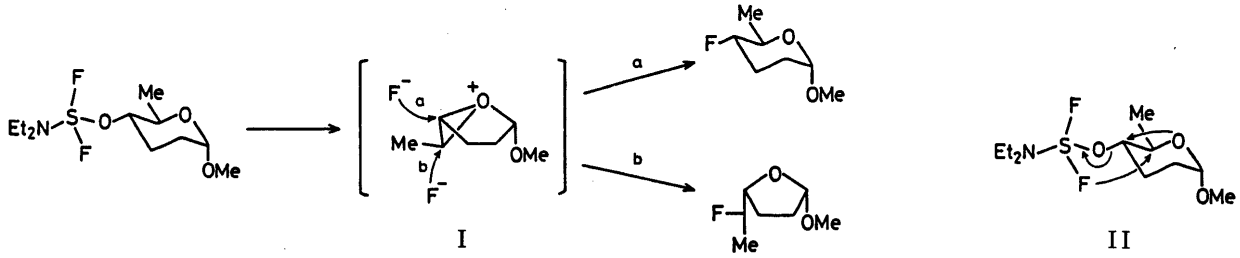


Chart 1

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Table I. ^{1}H-NMR Data for **3**, **6**, **9**, and **11(13)** (Measured at 300 MHz in $CDCl_3$)

Compound	δ (ppm) $J_{H,H}$ (Hz) ($J_{F,H}$ (Hz))						
	H-1	H-2	H-3a[A]	H-3b	H-4	H-5	H-6's
3	4.73 4.0 10.8 7.1 11.6 6.5 9.0 (11.0)	3.97 6.2 (47.3)	1.99 6.2 (24.4)	2.28	3.92	4.53	1.37
6	4.95 ~0 4.9 1.3 13.4 6.6 8.7 (13.0)	4.01 6.2 (48.2)	2.04 6.2 (24.5)	2.14	4.28	4.57	1.38
9	4.70 4.2 6.7 (0.8)	4.06	4.27	5.2	3.85 7.0 (12.5)	4.60 6.2 (47.3)	1.39 (24.5)
11(13)	5.83 3.7 4.9 ~0 13.2 4.7 10.4 (19.1)	5.76 3.5 (49.0)	1.84 6.4 (24.1)	2.12	4.18	4.78	1.34

[A] H-3a represents a H-3 oriented to the same side as C-5.

Table II. ^{13}C-NMR Data for **3**, **6**, **9**, and **11** (Measured at 75.4 MHz in $CDCl_3$)

Compound	δ (ppm) ($J_{C,F}$ (Hz))					
	C-1	C-2	C-3	C-4	C-5	C-6
3	101.7	78.3	30.5 (2.8)	78.7 (26.5)	91.9 (169.3)	17.3 (22.1)
6	107.0	82.9	31.4 (3.2)	81.5 (25.1)	91.5 (170.2)	17.7 (22.0)
9	101.8	84.3	82.9	83.1 (27.5)	90.3 (169.6)	17.5 (22.0)
11	105.5	80.3	32.8 (4.6)	80.1 (22.6)	89.5 (171.5)	17.5 (22.1)

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