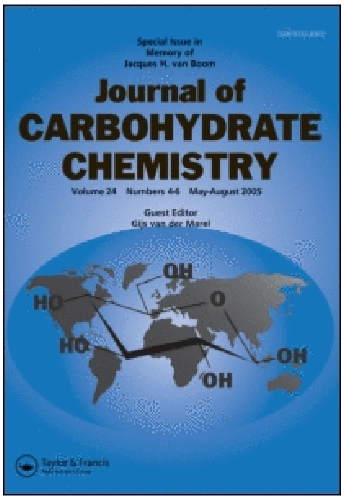

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REACTION OF 1,2-O-ALKYLIDENEHEXOFURANURONO-6,3-LACTONES WITH DIETHYLAMINOSULFUR TRIFLUORIDE (DAST)

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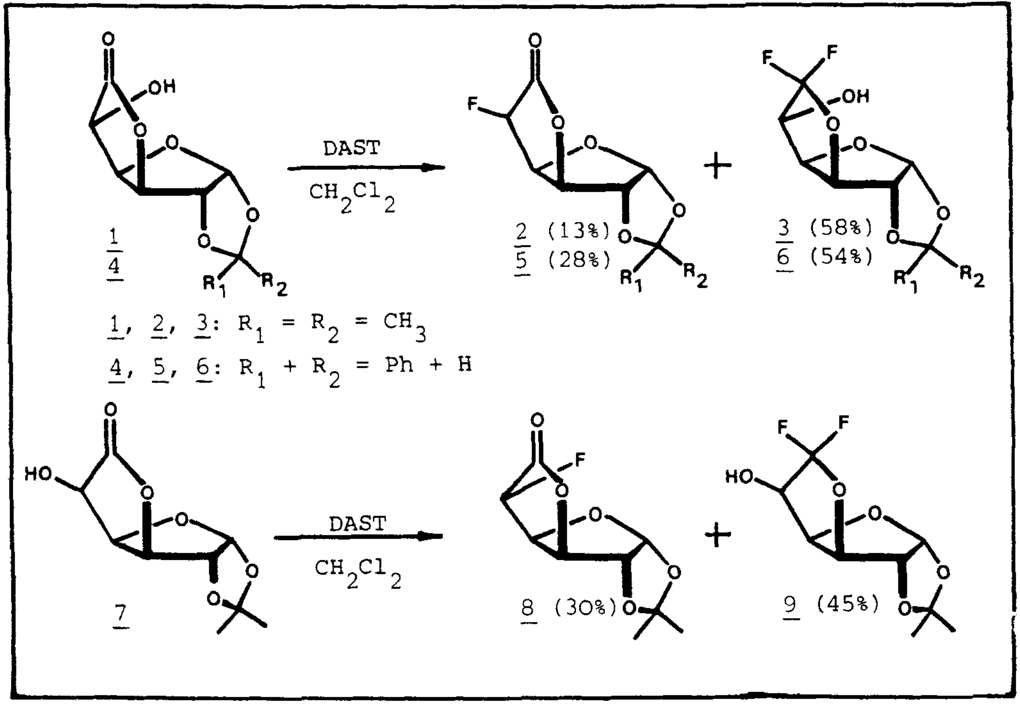
ABSTRACT

Reaction of 1,2-O-alkylidenehexofuranurono-6,3-lactones with diethylaminosulfur trifluoride (DAST) led to 1,2-O-alkylidene-5-deoxy-5-fluorohexofuranurono-6,3-lactones (13-30%) together with 1,2-O-alkylidene-3,6-anhydro-6,6-difluorohexofuranoses (45-58%). Evidence was found for participation of the hydroxyl group at C-5 in the formation of the difluorides. Trifluoro compounds could not be prepared by reaction with DAST but were formed from the difluorides by triflate formation and displacement using tetra-n-butylammonium fluoride.

Treatment of the triflates of 1,2-O-isopropylidenehexofuranurono-6,3-lactones with tetra-n-butylammonium fluoride gave 5-deoxy-5-fluoro-derivatives (with inversion of configuration).[1] When we, intending to bring about the same transformation, applied diethylaminosulfur trifluoride[2,3] (DAST) to the lactones 1, 4, and 7 (Scheme 1), the products of a direct substitution of hydroxyl group at C-5 by fluoride (2, 5, and 8) were obtained in minor proportions only. In each case, transformation of the lactone into an α,α-difluoroether (3, 6, and 9, respectively) was the principal reaction.

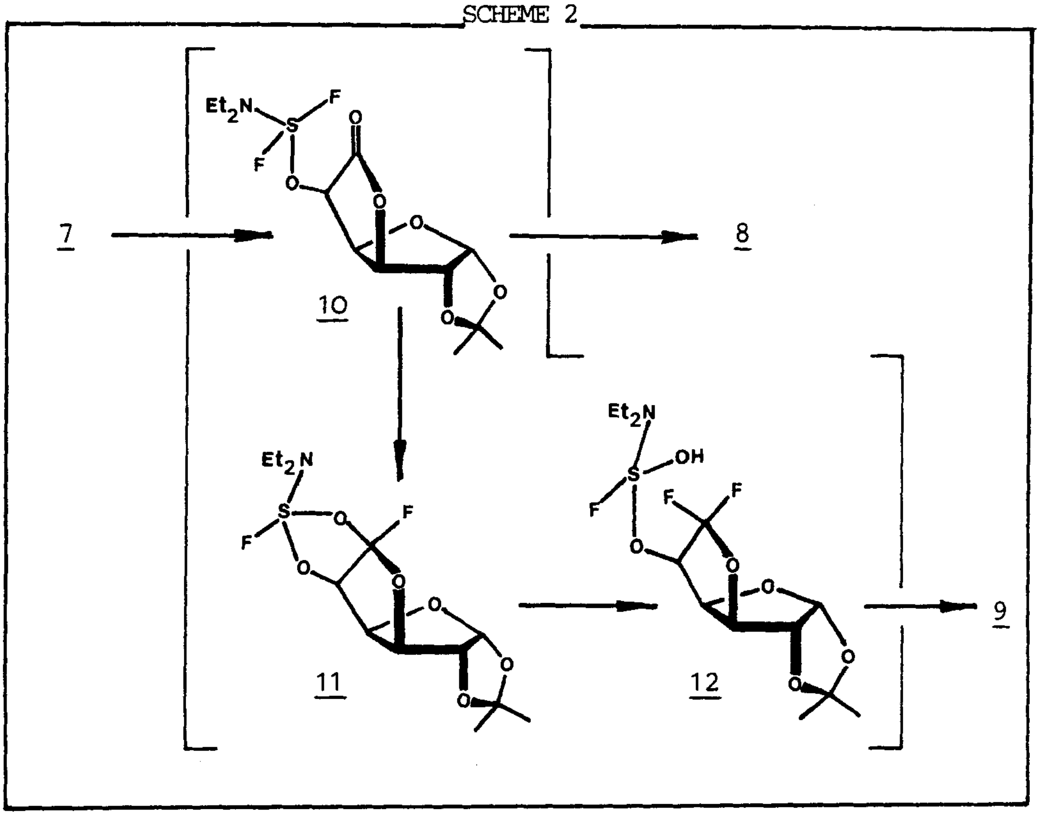
0732-8303/85/0404-0521$3.50/0

SCHEME 1



Although this particular course of fluorination is known from the reaction of carboxylic esters and anhydrides with sulfur tetrafluoride,[4] and the conversion of aldehydic as well as ketonic carbonyl groups into *geminal* difluorides was the very first domain of DAST,[2,5] the ease of the transformation in our case (warming up the mixture from -80 °C to room temperature) was surprising. Under identical conditions, no reaction of DAST occurred with 5-O-protected or 5-deoxygenated derivatives of 1.[6] From this, it was concluded that participation of the hydroxyl group at C-5 in the reaction mechanism leads to the α,α-difluoroethers, although the C-5 hydroxyl group is preserved in the final product, unaffected even in its stereochemistry. Considering the mechanisms discussed for the fluorination of alcohols[3,10,11] and carbonyl groups[3] by DAST and the molar ratios applied in our case (20% excess of DAST only), the involvement of a cyclic intermediate such as 11 in the reaction of 7 (Scheme 2) is suggested.

SCHEME 2



Interestingly, as observed with 2, 5, and 8, the difluorides 3, 6, and 9 (after isolation) did not react further with DAST, even under forced conditions.[12] The synthesis of the trifluorides 13 and 14 finally was accomplished by the triflate - tetra-n-butylammonium fluoride route starting from 3 and 9, respectively (Scheme 3).

SCHEME 3

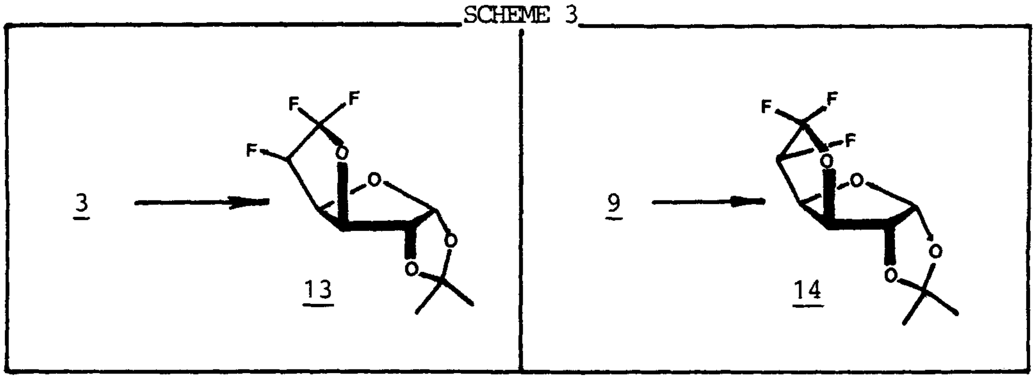


TABLE 1: PROTON CHEMICAL SHIFT [δ, ppm], PROTON - FLUORINE AND PROTON - PROTON COUPLINGS [*J*, Hz]

	5	3	6	9	13	14
1	6.17 *3.6(H-2)*	5.92 *3.6(H-2)*	6.11 *3.6(H-2)*	5.92 *3.6(H-2)* *0.6(H-4)* *0.4(F)*	5.91 *3.6(H-2)* *0.6(H-3)*	6.00 *3.5(H-2)* *0.6(H-3)* *0.4(H-5)*
2	5.09 *3.6(H-1)*	4.70 *3.6(H-1)*	4.85 *3.6(H-1)*	4.76 *3.6(H-1)* *0.7(H-3)* *0.6(H-4)* *0.6(H-5)*	4.78 *3.6(H-1)* *0.6(H-3)* *0.6(H-4)* *0.6(H-5)*	4.78 *3.5(H-1)* *3.5(F)* *0.6(H-3)* *0.6(H-4)*
3	5.40 *4.0(H-4)*	4.78-4.86	4.92-5.01	4.69 *3.5(F)* *3.5(H-4)* *0.7(H-2)* *0.6(H-5)*	5.07 *5.6(F)* *3.7(H-4)* *0.6(F)* *0.6(F)* *0.6(H-1)* *0.6(H-2)*	4.94 *6.3(F)* *3.4(H-4)* *1.3(F)* *0.6(F)* *0.6(H-1)* *0.6(H-2)*
4	5.22 *10 (F)* *4.0(H-3)*			4.95 *5.8(F)* *3.5(H-3)* *0.6(F)* *0.6(H-1)* *0.6(H-2)* *0.6(H-5)*	4.95 *9.4(F)* *3.6(F)* *3.7(H-3)* *0.6(H-2)* *0.6(H-5)*	5.07 *4.5(H-5)* *3.4(H-3)* *2.0(F)* *1.5(F)* *0.6(H-4)*
5	5.09 *47.5(F)*	4.39 *11 (F)* *7 (F)* *4 (H-4)*	4.44 *11 (F)* *7 (F)* *4 (H-4)*	4.24 *3.2(F)* *1.2(F)* *0.6(H-2)* *0.6(H-3)* *0.6(H-4)*	5.10 *47.4(F)* *2.8(F)* *1.4(F)* *0.6(H-2)* *0.6(H-4)*	5.35 *48.0(F)* *9.0(F)* *5.6(F)* *4.5(H-4)* *0.4(H-1)*
	6.12 7.37-7.48	1.26 1.39	5.97 7.32-7.44	1.29 1.42	1.24 1.37	1.28 1.40

TABLE 2: CARBON-13 CHEMICAL SHIFT [δ, ppm] AND FLUORINE - CARBON COUPLINGS[a] [*J*, Hz]

	5	3	6	9	13	14
1	105.1	106.1	105.1	106.1	105.4	106.0
2	82.3	83.2 *1.8*	84.9	85.5	86.0	83.8
3	84.5	83.4 *2.0*	84.1	86.7 *2*	81.7 *3*	83.0
4	81.0 *28.2*	79.6 *6.2* *1.6*	82.1 *6*	82.9 *3*	80.9 *30*	77.6 *14* *4*
5	87.5 *179.8*	72.9 *30* *25*	74.2 *31* *26*	74.9 *37* *22*	89.7 *188* *42* *22*	88.1 *204* *33* *24*
6	169.0 *20*	127.3 *264* *248*	128.7 *265* *260*	130.2 *259* *259*	126.7 *258* *258* *22*	126.5 *266* *250* *22*
others	104.2 126.0 127.4 128.9 135.0	112.1 26.9 26.4	106.9 127.6 129.0 130.5 136.8	112.1 26.9 26.6	111.3 26.0 25.4	112.2 26.8 26.3

[a] Those smaller than 1 Hz are omitted.

TABLE 3: FLUORINE-19 CHEMICAL SHIFT [δ,[a] ppm] AND FLUORINE - FLUORINE COUPLINGS [*J*, Hz]

	2	3	5	6	8	9	13	14
5	-199.7		-199.0		-216.3		-201.1 *12.2*	-216.8 *12.2* *12.2*
6		-82.8 *144.3* -76.4 *144.3*		-82.9 *144.0* -76.5 *144.0*		-87.0 *150.4* -68.7 *150.4*	-86.6 *152.6* *12.2* -68.5 *152.6*	-79.3 *140.4* *12.2* -75.7 *140.4* *12.2*

[a] relative to $CFCl_3$

Proof of the structures of the compounds described comes from the respective ^{1}H, ^{13}C, and ^{19}F NMR spectra (Table 1, 2, and 3).

EXPERIMENTAL

General Methods. The general methods, including those for column chromatography, were the same as given in the preceding paper except for TLC, where toluene - ethyl acetate 5:1 (*A*) or 9:1 (*B*) was used as eluant. NMR spectra were recorded from $CDCl_3$ solutions. DAST is a commercial product of the Aldrich Chemical Co.

General Procedure for the Reaction with DAST. To a 10% solution of the respective starting material in anhydrous dichloromethane at -80 °C a 20% molar excess of DAST was added and the mixture set aside. After warming to room temperature (1-2 h), the solution was slowly poured into a stirred, 10% solution of sodium hydrogen carbonate (~2 mL/mmol starting material). After separation, the organic layer was dried over sodium sulfate and the solvent evaporated. From the residue, the products were isolated by chromatography.

3,6-Anhydro-6,6-difluoro-1,2-O-isopropylidene-α-D-glucofuranose (3). From the reaction of 1 [3.0 g, 13.9 mmol; R_f (*A*) 0.06] with DAST (2 mL, 2.64 g, 16.4 mmol) compounds 2[1] [0.4 g, 13%; R_f (*A*) 0.61] and 3 [1.92 g, 58%; R_f (*A*) 0.31] were obtained. Compound 3 had the following properties: mp 86-87 °C, $[\alpha]_D^{20}$ +63.9° (c 3.1, $CHCl_3$).

Anal. Calcd for $C_9H_{12}F_2O_5$ (238.2): C, 45.38; H, 5.08. Found: C, 45.57; H, 5.29.

1,2-O-Benzylidene-5-deoxy-5-fluoro-β-L-idofuranurono-6,3-lactone (5) and 3,6-Anhydro-1,2-O-benzylidene-6,6-difluoro-α-D-glucofuranose (6). The treatment of 4[13] [3.7 g, 14 mmol; R_f (*A*) 0.06] with DAST (2 mL, 2.64 g, 16.4 mmol) led to compounds 5 [1.04 g, 28%; R_f (*A*) 0.63] and 6 [2.16 g, 54%; R_f (*A*) 0.36].

Data for compound 5: mp 153-155 °C, $[\alpha]_D^{20}$ +79.5° (c 0.66, $CHCl_3$).

Anal. Calcd for $C_{13}H_{11}FO_5$ (266.2): C, 58.65; H, 4.16. Found: C, 59.01; H, 4.30.

Properties of compound **6**: mp 120-122 °C, $[\alpha]_D^{20}$ +170.2° (c 1.18, $CHCl_3$).

Anal. Calcd for $C_{13}H_{12}F_2O_5$ (286.2): C, 54.55; H, 4.23. Found: C, 54.76; H, 4.28.

3,6-Anyhdro-6,6-difluoro-1,2-O-isopropylidene-β-L-idofuranose (**9**). Reaction of **7** [3.0 g, 13.9 mmol; R_f (*A*) 0.19] with DAST (2 mL, 2.64 g, 16.4 mmol) gave **8**[1] [0.9 g, 30%; R_f (*A*) 0.38] and **9** [1.35 g, 45%; R_f (*A*) 0.34] and two unidentified, minor products (R_f 0.50 and 0.43). Compound **9** had the following properties: mp 74-76 °C, $[\alpha]_D^{20}$ +81.4° (c 1.77, $CHCl_3$).

Anal. Calcd for $C_9H_{12}F_2O_5$ (238.2): C, 45.38; H, 5.08. Found: C, 45.44; H, 5.25.

3,6-Anhydro-5-deoxy-5,6,6-trifluoro-1,2-O-isopropylidene-β-L-idofuranose (**13**). Reaction of compound **3** [1.0 g, 4.2 mmol; R_f (*B*) 0.24] with triflic anhydride gave the corresponding triflate [R_f (*B*) 0.59] which was reacted immediately with tetra-n-butylammonium fluoride, according to the procedure described in reference 1, to give, after chromatography, compound **13** (0.3 g, 30%), R_f (*B*) 0.67, mp 51-53 °C, $[\alpha]_D^{20}$ +21.3° (c 0.87, $CHCl_3$).

Anal. Calcd for $C_9H_{11}F_3O_4$ (240.2): C, 45.00; H, 4.62. Found: C, 45.53; H, 4.69.

3,6-Anhydro-5-deoxy-5,6,6-trifluoro-1,2-O-isopropylidene-α-D-glucofuranose (**14**). Compound **14** was obtained from **9** [R_f (*B*) 0.30] via the triflate [R_f (*B*) 0.60] in a very low yield after application of the same procedure used to convert **3** into **13**. Compound **14** [R_f (*B*) 0.47] had the following physical properties: mp 81-83 °C, $[\alpha]_D^{20}$ +41.6° (c 1.32, $CHCl_3$).

Anal. Calcd for $C_9H_{11}F_3O_4$ (240.2): C, 45.00; H, 4.62. Found: C, 45.24; H, 4.58.

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