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Novel Rearrangement Reactions in the Fluorination of Methyl 3-*C*-Methyl-3-nitro-α-L-hexopyranosides by the DAST Reagent

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Abstract: A simple method for the preparation of 1-fluoro- and/or 5-fluoro-3-branched-chain sugar derivatives by reaction of DAST with methyl 3-*C*-methyl-3-nitro-α-L-hexopyranosides is described. The reaction involves rearrangement with or without ring contraction, depending on the 1,2 relative configuration and the presence of a free OH group at C-4 in the substrate. A new, useful *aldehydo*-sugar ramified at C-3 is easily accessible in good yield by the route reported here.

Diethylaminosulphur trifluoride (DAST) has been widely used in the fluorination of sugars.[1,2] The fluorination at a position with a free hydroxyl group occurs with inversion of configuration (S_N2 mechanism). When the reaction is somewhat hindered, and an electron-rich group is at a *vicinal* position, the product with retained configuration and products showing migration of the neighbouring group may be obtained.[3,4] These facts have been explained[5,6] in terms of a classical neighbouring group effect involving a cyclic onium ion intermediate, thus requiring the 1,2-*trans* relationship of the substituents in the starting material.

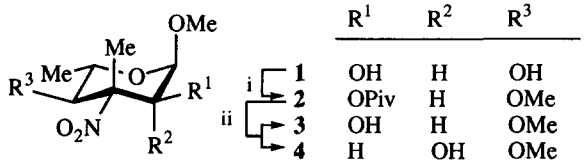
In an attempt to prepare 2-fluoro analogues of evernitrose with enhanced therapeutic activity by treatment of 3-branched-3-nitrosugars derived from methyl α-L-rhamnopyranoside with DAST, we have instead obtained rearranged 1-fluoro and/or 5-fluoro derivatives, depending on the substrate. The interest of these findings is in the following considerations: i) the low number of fluoronitro sugars described in the literature; ii) the novelty of some of the rearrangements observed; iii) the latent functionality as *aldehydo*-sugars of some of the rearrangement products obtained.

Methyl 3,6-dideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-2-*O*-pivaloyl-α-L-*gluco*-hexopyranoside (**2**), readily available[7] from methyl α-L-rhamnopyranoside through the 2,4-*O*-unprotected compound **1**, was selectively deprotected at *O*-2 by treatment with an excess of tetrabutylammonium hydroxide in 1:1 dioxane-water at room temperature for 1 h,[8] to give, after column chromatography, the 2-*O*-deprotected crystalline epimers **3** (60%) and **4** (30%).

When compound **4** was treated with 5 mol.-eq. of DAST in CH_2Cl_2 at reflux for 1.5 h, 58% of the 1.3:1 mixture of the anomeric glycosyl fluorides **5** and **6** was obtained after column chromatography, as expected for a 1,2-*trans* disubstituted substrate. Under the same conditions, the 1,2-*cis* disubstituted isomer **3** gave 70% of a 3:1 mixture of the epimeric 2,5-anhydro-1-fluoro-1-*O*-methylhexitols **7** and **8**. Similar treatment of the 2,4-*O*-unprotected glycoside **1**[7] afforded, after separation by column chromatography, the methyl 5-deoxy-5-fluoro-hexofuranoside **9** (46%) and the 4,5-anhydro-1-fluoro-1-*O*-methylhexitol **10** (40%), both of which retained the HO-2 free (Scheme 1).

The new structures were elucidated on the basis of analytical and spectral (ms, ir, ^{1}H- and ^{13}C-nmr) data.[9] Thus, the ^{1}H-nmr spectra of **3** and **4** showed $J_{1,2}$ values of 4.5 and 1.5 Hz respectively. Separate signals

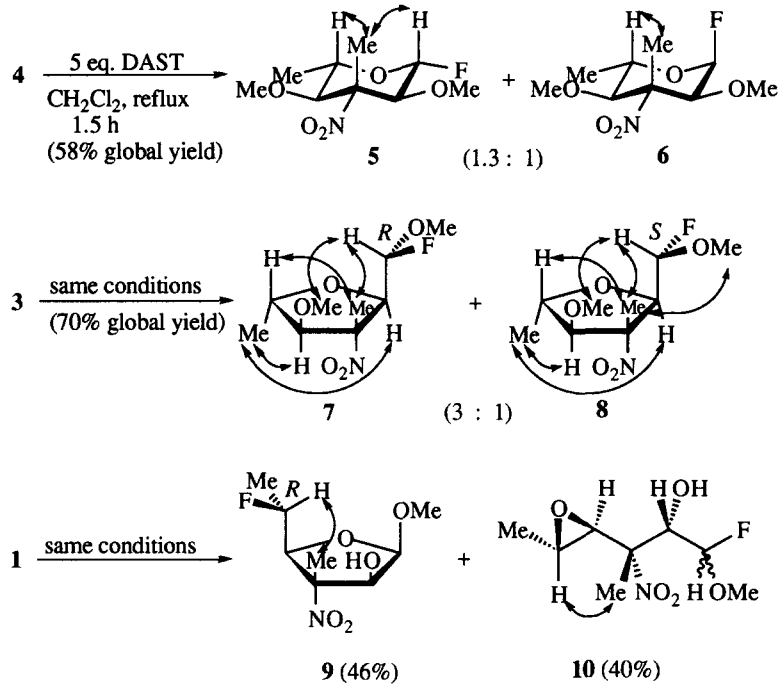
were assigned to **5** and **6** in the ^{1}H-nmr spectrum of the mixture; the observed $J_{1,2}$ values were 7.2 and 3.2 Hz respectively. Fluorine couplings[10] were also observed: $^2J_{1,F}$ (53.1 and 54.0 Hz respectively); $^3J_{2,F}$ (12.7 and 25.6 Hz), $^4J_{5,F}$ (0.5 Hz, only for **5**), $^5J_{2\text{-OMe},F}$ (1.3 Hz for **5**), and $^5J_{\text{Me-3},F}$ (1.3 Hz for **6**). The ^{13}C-nmr spectrum of the same mixture showed doublets for the carbon atoms coupled with F: $^1J_{1,F}$ (213.0 and



	R^1	R^2	R^3
1	OH	H	OH
2	OPiv	H	OMe
3	OH	H	OMe
4	H	OH	OMe

i: ref. 7. ii: Bu_4N^+ HO^- (1:1 dioxane-H_2O), room. temp., 1h

232.4 Hz, respectively), $^2J_{2,F}$ (24.0 and 23.2 Hz), $^3J_{3,F}$ (11.4 and 3.3 Hz), $^3J_{5,F}$ (5.2 and 1.4 Hz), $^4J_{\text{MeO-2},F}$ (2.1 Hz for **5**), and $^4J_{\text{Me-3},F}$ (6.5 Hz for **6**). Differential NOE's, marked with curved arrows in Scheme 1,

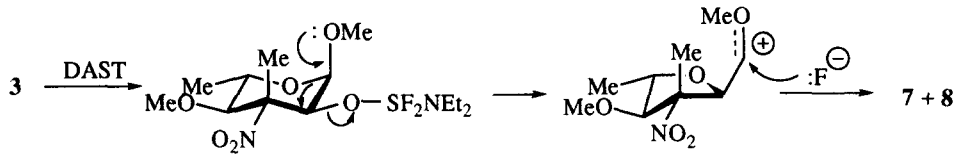


Scheme 1

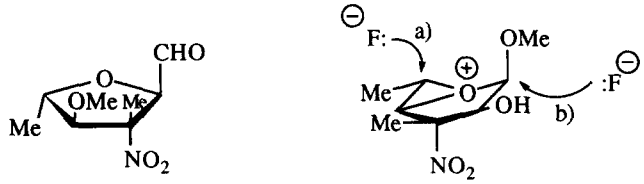
were studied to elucidate configurations in compounds **5-10**. The 1*R* configuration is tentatively proposed for **7** having in mind also the values of H/F and C/F coupling constants: $^3J_{\text{H-2},F}$ = 6.8 Hz, indicative of a *gauche* relationship between H-2 and F at C-1 (Baer observed[11] values of 8 and 25 Hz for the *gauche* and *anti* orientations, respectively, in related compounds), and $^2J_{\text{C-2},F}$ = 30.6 Hz, also in agreement with observations of Baer[11] for compounds having the ring oxygen *anti* with regard to a F atom. For **8**, the respective values are

10.4 Hz (H-2 *gauche* to F at C-1) and 24.9 Hz (F *gauche* to the ring O), and beside NOE's similar to those mentioned for **7**, an additional NOE between Me-3 and MeO-1 was observed, indicating that both compounds should be epimers at C-1. This was confirmed by the quantitative formation of a unique *aldehydo*-sugar (**11**) (δ_{CHO} 9.65; $J_{1,2}$ 1.2 Hz) after treating the **7**-**8** mixture in $CDCl_3$ with aqueous HCl. Compound **9** is tentatively formulated as having the 5*R* configuration and the preferential conformation indicated, on the basis of the NOE observed (Scheme 1) and the following data: i) $J_{4,5}$ has the value 9.3 Hz, showing the *anti* arrangement for these protons; ii) $^3J_{H\text{-}4,F}$ = 5.9 Hz suggests[11] a *gauche* orientation between H-4 and F; iii) the ring oxygen and F are *anti* each other ($^2J_{C\text{-}4,F}$ = 30.1 Hz). The structure assigned to **10** is in agreement with the value of 2.1 Hz observed for $J_{4,5}$ and the intense NOE between Me-3 and H-5; other couplings observed ($J_{1,2}$ = 4.1 Hz; $^3J_{H\text{-}2,F}$ = 9.0 Hz) might suggest that H-2 is *gauche* to both H-1 and F in the preferential conformation around the 1-2 bond.

The formation of **5** and **6** from **4** is to be considered as a new case of the 1,2-rearrangement cited above,[3,4] and therefore may be explained in terms of a mechanism similar to that proposed for related compounds.[5,6] For the ring contraction observed in the fluorination by DAST of compound **3**, the explanation would be of the same type as that argued for other hexopyranoside—to—2,5-anhydro-*aldehydo*-hexose contractions[11,12] (Scheme 2); the predominance of **7**, with retained configuration at C-1, over **8** in the mixture is probably due to the effect of the bulky neighbouring leaving group at C-2, forcing the fluoride anion to attack the C-1 from the opposite side. The rearrangements observed in the fluorination of **1** belong to a novel kind that may be rationalised by assuming the oxonium ion **12** as intermediate; the subsequent attack by the fluoride anion at (a) C-5, or (b) C-1, might account for the formation of **9** and **10**, respectively, with the configurations indicated, the position 4 of **12** being hindered by the leaving group.



Scheme 2



11 **12**

General procedure for fluorination: An ice-cold water solution of the methyl 3-*C*-methyl-3-*C*-nitro-hexopyranoside (**1**, **3**, **4**) (1 mmol) in dry CH_2Cl_2 (10 mL) was treated with DAST (0.66 mL, 5 mmol) under argon atmosphere. After 15 min, the mixture was left to rise to room temperature, then heated at reflux under stirring until almost complete transformation of the starting substrate (2 h) (controlled by TLC, 2:1 or 1:1 ether-petroleum ether). The mixture was poured onto an iced aqueous saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (25 mL), dried

($MgSO_4$), and concentrated. Separation and purification of the new products were achieved by column chromatography.

In conclusion, the course of the reaction depends on the 1,2 relative configuration in the substrate, as well as on the presence of a free HO group at C-4, so that a 4-*O*-protected-1,2-*trans* glycoside such as **4** leads to the hexopyranosyl fluorides mixture of **5** and **6**, synthetically interesting due to their nature of glycosyl donors.[13] The same reaction on the 1,2-*cis* glycoside **3** involves ring contraction, to give a C-1 epimeric mixture of 2,5-anhydro-1-fluoro-1-*O*-methylalditols (**7**, **8**). On the other hand, the 2,4-*O*-unprotected substrate **1** affords a 5-fluoro-hexofuranoside (**9**) and the 4,5-anhydro-1-fluoro-1-*O*-methylalditol **10**. The *aldehydo*-sugar latent functionality of **7**, **8**, and **10** gives synthetic interest to these reactions; in fact, quantitative transformation of the **7**-**8** mixture into a sole *aldehydo*-sugar (**11**) has been achieved. This kind of *aldehydo*-sugar can be considered a valuable intermediate for the synthesis, among others, of branched-chain *C*-nucleosides.

Currently, we are studying the scope and synthetic utility of the last two kinds of rearrangement, as well as further transformations of their resulting products.

Acknowledgements

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8. This procedure was first applied to another compound by van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1979**, 37, 3561-3564.
9. Correct elemental analyses for **3** and **4** and satisfactory HRMS for the rest of the new compounds were obtained. Physical data **3**: mp 99-101°C; $[\alpha]_D^{26}$ -17°(*c* 1, CH_2Cl_2). **4**: mp 101-103°C; $[\alpha]_D^{22}$ -22° (*c* 1, CH_2Cl_2). **9**: $[\alpha]_D^{22}$ -104° (*c* 1.2, CH_2Cl_2). **10**: $[\alpha]_D^{22}$ -28°(*c* 0.9, CH_2Cl_2).
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13. See, for example, Koide, K.; Ohno, M.; Kobayashi, S. *Synthesis* **1996**, 1175-1176 and references therein.

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