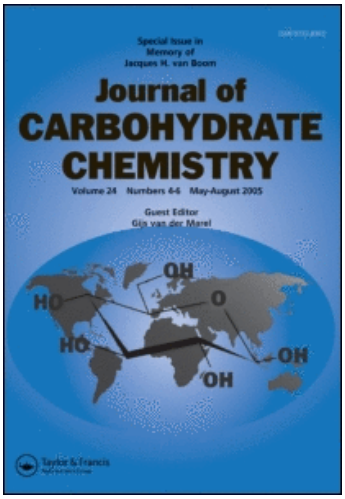

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Two Methyl Tri-*O*-benzoyl-hex-enopyranosides Are Amongst the Products of the Reaction of Methyl 2,3,6-Tri-*O*-benzoyl-β-D-galactopyranoside with Dimethylaminosulfur Trifluoride (DAST)

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COMMUNICATION

TWO METHYL TRI-*O*-BENZOYL-HEX-ENOPYRANOSIDES ARE AMONGST THE PRODUCTS OF THE REACTION OF METHYL 2, 3, 6-TRI-*O*-BENZOYL-β-D-GALACTOPYRANOSIDE WITH DIMETHYLAMINOSULFUR TRIFLUORIDE (DAST)

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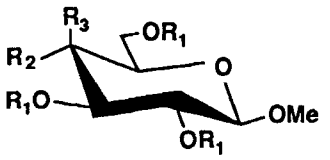
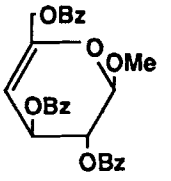
INTRODUCTION

In the past, we have used deoxyfluoro sugars as probes for studies of ligand-antibody interactions.[1-3] Investigations of the putative role of hydrogen bonding in the binding process involving antibodies that show specificity for epitopes containing β-D-glucopyranose required hitherto unknown methyl 4-deoxy-4-fluoro-β-D-glucopyranoside (**5**). For the synthesis of **5**, we have chosen the readily available[4] methyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside (**1**) as the starting material, and diethylaminosulfur trifluoride (DAST) as the fluorinating reagent. Although DAST has been frequently used to produce fluorinated carbohydrates in high yields, the outcome of the reaction is somewhat unpredictable. Treatment of carbohydrates with the reagent has occasionally resulted in the formation of unexpected side products,[5-9] and no specific rules exist regarding the application of DAST for the preparation of fluorosugars. In fact, high yields of the desired products of the substitution with fluoride ion have been sometimes obtained when DAST was applied under conditions generally known to favor elimination over substitution, *e.g.* in the presence of a

base.[10-13] Olefinic products resulting from treatments of carbohydrates with DAST have been sporadically isolated and characterized. Here we describe the title reaction which we believe is unique in that two products of elimination have been formed, as a consequence of attacks of the proton-abstracting species at different sites in the molecule.





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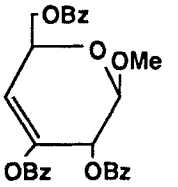

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	R_1	R_2	R_3
1	Bz	H	OH
2	Bz	F	H
5	H	F	H

RESULTS AND DISCUSSION

Initially, compound **1** was treated with DAST (100% molar excess) in 1,2-dimethoxyethane at room and elevated temperatures in the absence of a base. In these reactions (not described in the Experimental) the conversion of **1** was either largely incomplete, or the reaction mixtures contained a large proportion of by-products (60 °C). An appreciable amount of undesired products was still formed when the reaction was carried out in the presence of pyridine at 60 °C but, in this solvent, the number and the overall amount of by-products formed was smaller than when the reaction was conducted in the absence of the base (TLC). The three major products of such a reaction were isolated by chromatography, identified and fully characterized. The expected methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-β-D-glucopyranoside (**2**, showing the slowest chromatographic mobility) was isolated in 47.7% yield. The amounts of the isolated olefinic by-products **3** (showing fastest chromatographic mobility) and **4** were 23.4 and 12.8%, respectively. These yields are of purified compounds, two of the three having been recrystallized. Thus the remainder of the reaction products accounting for less than some 10%, consisted of several trace impurities, and were not further investigated. Conventional debenzoylation of **2** readily yielded the crystalline target compound **5**. When the reaction was conducted in dichloromethane as the solvent, in the absence of a base, the formation of the olefinic by-products was somewhat

less pronounced (TLC), similar to what has been found by others.[14] The reaction of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside has been reported with DAST in dichloromethane to yield the 4-deoxy-4-fluoro derivative in 41% yield.[15] This is in agreement with Richardson's observation[16] that anomeric configuration appears to play no significant role in influencing nucleophilic substitution at C-4.

The structures **2** and **5** followed clearly from the first-order analysis of the one-dimensional ^{1}H- and ^{13}C-NMR spectra, and the structures **3** and **4** were deduced, *inter alia*, from the analysis of 2D NMR spectral data. When analyzed by TLC, both compounds immediately reduced the potassium permanganate spray reagent, indicative of unsaturation.[17] Elemental analysis obtained for each of the unsaturated compounds agreed with their being methyl tri-*O*-benzoyl-hex-enopyranosides. That is consistent with their chemical ionization mass spectra, showing peaks at *m/z* 506 ($[M + NH_4]^+$). The discussion of the structurally relevant features in the NMR spectra of **3** and **4** follows. The olefinic nature of these compounds was supported by the ^{13}C-NMR spectra showing signals in the region characteristic of unsaturated carbons. The comparable chemical shifts observed for the methylene protons H-6a and H-6b in **1**- **4** suggest that the olefinic by-products do not contain an exocyclic double bond. Rather, the observed chemical shifts, δ 150.69 in the spectrum of **3** and δ 142.61 in the spectrum of **4**, assigned to C-5 and C-3, respectively, are consistent with these carbons being part of an enolic arrangement.[18]

The unambiguous assignment of lines in the NMR spectra of **3** followed from results of 2D NMR experiments. The differentiation between C-1 and C-4 (and H-1 and H-4) could not be readily made, due to their similar chemical shifts. The unambiguous assignment was achieved by a selective proton-decoupling ^{13}C-NMR experiment. Selective irradiation at δ 3.57, the proton chemical shift of OCH_3, resulted in a sharpening of the doublet at δ 99.25, but not of the one at δ 98.85, thus permitting the assignment of the former resonance to C-1. Such assignment is consistent with the results of a HMQC spectrum,[19] in which a one-bond ^{13}C-^{1}H shift correlation is observed between C-1 and H-1 (and C-4 and H-4).

Unsaturated products **3** and **4** are formed by common elimination that frequently accompanies S_N2 substitution reactions during fluorinations with DAST or with other nucleophiles.[20, 21] Their formation in an approximate ratio of 2 : 1 (see Experimental) quite likely reflects the more acidic nature of H-5 in **1**, as compared with H-3, due to the proximity of the ring oxygen atom.

EXPERIMENTAL

General Methods. Melting points were determined on a Kofler hot stage. Optical rotations were measured at 25 °C with a Perkin Elmer automatic polarimeter,

Model 241 MC. All reactions were monitored by thin-layer chromatography (TLC) on precoated slides of Silica Gel G F254 (Analtech). Detection was effected by charring with 5% sulfuric acid in ethanol and, when applicable, with UV light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, No. 9385). Chemical ionization mass spectra (CIMS) using ammonia as the reactive gas were obtained with a Finnigan 1015 D spectrometer. ^{1}H- and ^{13}C-NMR spectra were routinely measured at ambient temperature using a Varian FX 300 spectrometer. Solvents for compounds used in measurements are reported as required. Chemical shifts found in the spectra recorded for solutions in $CDCl_3$ and D_2O are reported, respectively, using TMS and methanol as internal standards (δ_{MeOH} vs. δ_{TMS} 49.0). The ^{1}H, COSY, HMQC, and ^{13}C selective proton decoupled spectra were obtained with a Varian VXR-500S spectrometer. Spectra of compound **3** were measured in acetone-d_6 and those of **4** in $CDCl_3$. Chemical shifts are reported relative to the solvent peak, i.e., 7.20 (δ_H) and 77.0 (δ_C) in $CDCl_3$, and 2.04 (δ_H) and 39.5 (δ_C) in acetone-d_6.

Methyl 2,3,6-Tri-*O*-benzoyl-4-deoxy-4-fluoro-β-D-glucopyranoside (2). To a stirred solution of the starting derivative **1** (1 g, 2 mmol) in a mixture of anhydrous dimethoxyethane (3 mL) and pyridine (0.5 mL, 6.1 mmol) was added diethylaminosulfur trifluoride (0.66 mL, 4.96 mmol). The reaction mixture was stirred at 60 °C for 15 min when TLC (toluene : ethyl acetate, 15 : 1) showed that all starting material had been consumed. After conventional processing, chromatography (carbon tetrachloride : ethyl acetate, 20 : 1 - 12 : 1) gave amorphous methyl 4-deoxy-2,3,6-tri-*O*-benzoyl-α-L-*threo*-hex-4-enopyranoside (**3**) (0.235 g), 23.4 %, $[\alpha]_D$ + 104° (chloroform, *c* 0.9). CIMS: *m/z* 506 ($[M+NH_4]^+$). ^{1}H-NMR (500 MHz, acetone-d_6) 5.60 (1 H, ddd, $J_{3,4}$=4.4 Hz, H-3), 5.51 (1 H, m, $J_{2,3}$=3.3 Hz, $J_{2,4}$=1.1 Hz, H-2), 5.50 (1 H, m, $J_{4,6a}$=0.7 Hz, $J_{4,6b}$=1.0 Hz, H-4), 5.36 (1 H, dd, $J_{1,2}$=3.8 Hz, $J_{1,3}$=0.8 Hz, H-1), 4.97 (1 H, dd, H-6_b), 4.87 (1 H, dd, $J_{6a,6b}$=13.2Hz, H-6_a). ^{13}C-NMR (125 MHz, $CDCl_3$) 150.69 (C-5), 99.25 (C-1), 98.85 (C-4), 69.99 (C-2), 67.06 (C-3), 63.97 (C-6), 56.91 (OMe).

Anal. Calcd for $C_{28}H_{24}O_8$: C, 68.85; H, 4.95. Found: C, 68.76; H, 5.01.

Continued elution gave methyl 2,3,6-tri-*O*-benzoyl-β-D-*erythro*-hex-3-enopyranoside (**4**) (0.128 g, 12.75 %), mp 96-96.5 °C (from methanol), $[\alpha]_D$ - 86° (chloroform, *c* 0.64. CIMS: *m/z* 506 ($[M+NH_4]^+$). ^{1}H-NMR (300 MHz, $CDCl_3$) 6.15 (1 H, d, $J_{4,5}$=2.6 Hz, H-4), 5.75 (1 H, d, $J_{1,2}$ =3.3 Hz, $J_{2,5}$=1.6 Hz, H-2), 5.05 (1 H, d, H-1), 4.96 (1 H, m, $J_{5,6b}$=7.0 Hz, $J_{5,6a}$=5.6 Hz, H-5), 4.58 (1 H, dd, $J_{6a,6b}$=11.1 Hz, H-6_a), 4.48 (1 H, dd, H-6_b). ^{13}C-NMR (75 MHz, $CDCl_3$) 142.61 (C-3), 116.65 (C-4), 100.97 (C-1), 70.27 (C-5), 67.49 (C-2), 66.70 (C-6), 56.31 (OMe).

Anal. Calcd for $C_{28}H_{24}O_8$: C, 68.85; H, 4.95. Found: C, 68.73; H, 4.90.

Eluted next was **2** (0.479 g, 47.7 %), mp 123-124 °C, from methanol, ether, $[\alpha]_D$ + 57° (chloroform, *c* 0.7). ^{1}H-NMR (300 MHz, $CDCl_3$) 8.11-7.26 (15 H, m, 3 Ph), 5.86

(1 H, $J_{3,F}$=14.2 Hz, $J_{2,3}$=$J_{3,4}$ 9.3 Hz, H-3), 5.44 (1 H, dd, $J_{1,2}$=7.9 Hz, $J_{2,3}$=9.6 Hz, H-2), 4.93-4.76 (2 H, m, H-4, 6_a), 4.72 (1 H, d, $J_{1,2}$=7.8 Hz, H-1), 4.61 (1 H, m, H-6_b), 4.05 (1 H, m, H-5), 3.52 (3 H, s, OMe). ^{13}C-NMR (75 MHz, $CDCl_3$) 166.11, 165.60, 165.16 (3x C=O), 101.97 (C-1), 87.47 (d, $J_{4,F}$=188.8 Hz, C-4), 72.98 (d, $J_{5,F}$=19.7 Hz, C-5), 71.67 (d, $J_{3,F}$=23.2 Hz, C-3), 71.40 (d, $J_{2,F}$=8.5 Hz, C-2), 62.63 (C-6), 57.16 (OMe).

Anal. Calcd for $C_{28}H_{25}FO_8$: C, 66.13; H, 4.95; F, 3.73. Found: C, 65.97; H, 4.98; F, 3.87.

Methyl 4-deoxy-4-fluoro-β-D-glucopyranoside (5). To a solution of the tri-*O*-benzoyl derivative **2** (0.769 g, 1.5 mmol) in toluene (30 mL) was added methanol (30 ml), followed by 1 M methanolic sodium methoxide (0.1 mL). The reaction mixture was heated at 50 °C for 4 h, and then kept overnight at room temperature. TLC (dichloromethane : methanol, 10 : 1) showed that no starting material remained. The reaction mixture was neutralized (Amberlite IR 120, H^+ resin), filtered, concentrated and chromatographed (dichloromethane : methanol, 15 : 1 - 12 : 1), to give **5** (0.257 g, 86.5 %), mp 145.5 - 146.5 °C, from methanol/ethyl acetate, $[\alpha]_D$ - 47° (water, *c* 0.9). ^{1}H-NMR (500 MHz, D_2O) 4.44 (1 H, d, $J_{1,2}$=8.1 Hz, H-1), 4.32 (1 H, ddd, $J_{4,F}$=50.8 Hz, $J_{3,4}$=8.8 Hz, $J_{4,5}$=9.8 Hz, H-4), 3.92 (1 H, ddd, $J_{6a,F}$=2.2 Hz, $J_{5,6a}$=2.4 Hz, $J_{6a,6b}$=12.5 Hz, H-6_a), 3.82 (1 H, ddd, $J_{3,F}$=15.9 Hz, $J_{2,3}$=9.5 Hz, H-3), 3.78 (1 H, ddd, $J_{6b,F}$=1.7 Hz, $J_{5,6b}$=5.1 Hz, H-6_b), 3.70 (1 H, dddd, $J_{5,F}$=2.7 Hz, H-5), 3.32 (1 H, ddd, $J_{2,F}$=1.0 Hz, H-2). ^{13}C-NMR (125 MHz, D_2O) 103.87 (C-1), 89.62 (d, $J_{4,F}$=180.6 Hz, C-4), 74.29 (d, $J_{3,F}$=18.1 Hz, C-3), 73.77 (d, $J_{5,F}$=24.4 Hz, C-5), 73.18 (d, $J_{2,F}$=8.5 Hz, C-2), 60.48 (C-6), 57.74 (OMe).

Anal. Calcd for $C_7H_{13}O_5F$: C, 42.86; H, 6.68; F, 9.68. Found: C, 43.23; H, 6.73; F, 9.42.

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