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Note

The action of diethylaminosulfur trifluoride (DAST) on 1-(4,6-*O*-isopropylidene-β-D-glucopyranosyl)pyrimidines, a one-pot synthesis of 2,2′-anhydro-1-(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-altropyranosyl)pyrimidines

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In recent years, considerable interest has been focused on the introduction of fluorine into nucleosides[1] in order to find new antitumor, antiviral, or anti-HIV drugs. Until now, in contrast to deoxyfluoropentopyranosyl analogs of AZT, which have been studied extensively[1], few deoxyfluorohexopyranose nucleosides have been reported[2]. We have described[3] the fluorination at positions 3′, 4′, and 6′ of 7-(β-D-glucopyranosyl)-theophylline and we now report the action of diethylaminosulfur trifluoride (DAST) on derivatives of 1-(β-D-glucopyranosyl)pyrimidines.

Reaction of DAST (3 equiv.) severally with the 1-(4,6-*O*-isopropylidene-β-D-glucopyranosyl)pyrimidines **1a–d** in dichloromethane under nitrogen gave ~10% of the 2,2′-anhydro-(β-D-mannopyranosyl)pyrimidines **2a-d** and 25% of 2,2′-anhydro-(3-deoxy-3-fluoro-β-D-altropyranosyl)pyrimidines **3a–d.**

The reaction involves inversion at C-2′ and C-3′. Although no 3-deoxy-3-fluoro-β-D-allopyranosyl derivative was isolated, attack of DAST must occur first at C-2′ and the mechanism **1**→**4**→**5**→**3** accords with that described[4]. The yields could not be increased by extending the time of reaction up to 16 h. However, if **2a–d** were each treated with 2 equiv. of DAST under the same conditions, **3a–d** were obtained in yields of ~70%.

All of the new compounds were characterised by their ^{1}H-n.m.r. data. For **2a–d**, the $J_{1,2}$ and $J_{2,3}$ values showed that H-2 was equatorial and H-3 was still axial as in **1a–d.** For **3a–d**, the $J_{1,2}$ and $J_{2,3}$ values indicated H-2 and H-3 to be equatorial and that a double Walden inversion had occurred at C-2 and C-3. The $^2J_{F,H}$ values of 53.4–46.3 Hz were in agreement with other data on deoxyfluoro sugars[4,5] and deoxyfluoronucleosides[3]. The $J_{F-3,4}$ values of 29.9–30.5 Hz confirmed the vicinal *trans*-diaxial H/F relationships[3–5] and the $J_{F-3,2}$ values of 10–11.2 Hz indicated a *gauche* H/F relationship.

DAST, which is a well-known fluorinating agent[6,7], has been employed by Baker *et al.*[8] to prepare 2,3′-anhydro-(2-deoxyribofuranosyl)pyrimidines but no fluorination was reported. Anhydro-(hexopyranosyl)-nucleosides have been reported and, as far as

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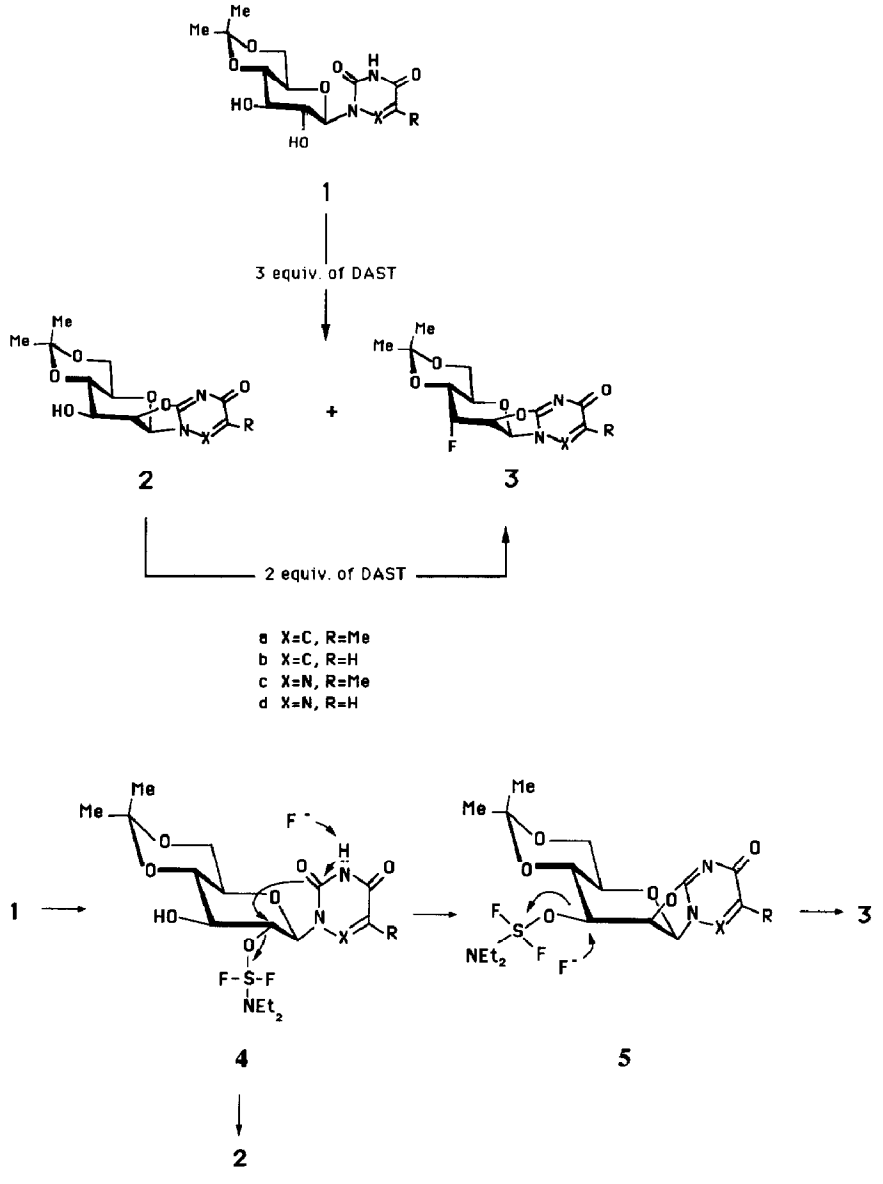
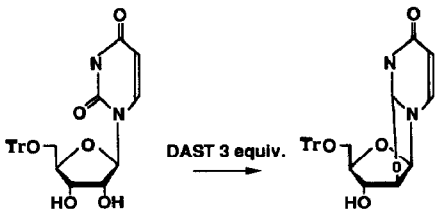


we know, they have always been prepared from sulfonates[9,10] in a two-step process. Therefore, the synthesis of anhydro-(deoxyfluorohexopyranosyl)-nucleosides in a single step as described above is a valuable alternative method.

The reaction of 5'-*O*-trityluridine (**6**) with DAST gave only the 2,2'-anhydro derivative (**7**) and fluorination did not occur. Reaction of (5-*O*-trityl-β-D-xylofuranosyl)-uracil with DAST gave only degraded products.



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EXPERIMENTAL

General methods.—Melting points are uncorrected. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) and flash-column chromatography on Silica Gel 60 (240–400 mesh, Merck). $[\alpha]_D^{20}$ values were determined on solutions in methanol (*c* 0.1). N.m.r. spectra were recorded at room temperature with a Bruker 300 MSL spectrometer with internal Me_4Si for ^1H, internal C_6H_6 for ^{19}F, and solutions in $CDCl_3$ for **1a–d** and in $(CD_3)_2SO$ for **2a–d, 3a–d**, and **4**. The positions in the carbohydrate moieties are designated by primes.

1-(4,6-O-Isopropylidene-β-D-glucopyranosyl)pyrimidines.—According to the Vobruggen procedure[11], a solution of the silylated pyrimidine[12] (2.6 mmol) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (2 mmol) in dry actonitrile (25 mL) was boiled under reflux for 3 h, using $SnCl_4$ (58.5 mL, 0.5 equiv.) as catalyst, to give the expected 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)pyrimidine (~70%). *O*-Deacetylation with methanolic M sodium methoxide at room temperature for 2 h gave the corresponding 1-β-D-glucopyranosylpyrimidine which was crystallized from methanol (yield 90%).

A mixture of 1-β-D-glucopyranosylpyrimidine (14 mmol), 2,2-dimethoxypropane (15 mL), and dry *p*-toluenesulfonic acid (30 mg) in dry *N,N*-dimethylformamide (45 mL) was stirred at room temperature for 2 h. M $NaHCO_3$ (2 mL) was added and the mixture concentrated under vacuum. A solution of the residue in dichloromethane was filtered and concentrated, and the residue was crystallized from ethyl acetate. The following compounds were prepared in this manner.

1-(4,6-*O*-Isopropylidene-β-D-glucopyranosyl)thymine (**1a**, 80%) had m.p. 105–107°, $[\alpha]_D^{20}$ +7.5°. ^1H-N.m.r. data: δ 7.26 (s, 1 H, H-6), 5.69 (d, 1 H, $J_{1,2}$ 8.9 Hz, H-1'), 3.90 (m, 2 H, $J_{1,2}$ 8.9, $J_{2,3}$ 6.0, and $J_{3,4}$ 4.6 Hz, H-2',3'), 3.74 (q, 1 H, $J_{3,4}$ 4.6, $J_{4,5}$ 10.8 Hz, H-4'), 3.70–3.50 (m, 3 H, H-5',6'a,6'b).

Anal. Calc. for $C_{14}H_{19}N_2O_7 \cdot 0.5H_2O$: C, 50.00; H, 5.95; N, 8.33. Found: C, 49.55; H, 5.98; N, 8.21.

1-(4,6-*O*-Isopropylidene-β-D-glucopyranosyl)uracil (**1b**, 82%) had m.p. 220–223°, $[\alpha]_D^{20}$ −2.5°. ^1H-N.m.r. data: δ 7.8 (s, 1 H, H-6), 5.8 (s, 1 H, H-5), 5.64 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1'), 5.46 (q, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 8.9 Hz, H-2'), 3.79 (q, 1 H, $J_{2,3}$ 8.9, $J_{3,4}$ 3.8 Hz, H-3'), 3.62 (q, 1 H, $J_{3,4}$ 3.8, $J_{4,5}$ 10.0 Hz, H-4'), 3.53–3.34 (m, 3 H, H-5',6'a,6'b).

Anal. Calc. for $C_{13}H_{17}N_2O_7$: C, 49.84; H, 5.43; N, 8.95. Found: C, 49.83; H, 5.39; N, 8.40.

1-(4,6-*O*-Isopropylidene-β-D-glucopyranosyl)azathymine (**1c**, 78%) had m.p. 156–157°, $[\alpha]_D^{20}$ −55°. ^{1}H-N.m.r. data: δ 5.63 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1'), 4.20 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 8.0 Hz, H-2'), 3.95–3.60 (m, 5 H, H-3', 4',5',6'a,6'b).

Anal. Calc. for $C_{13}H_{18}N_3O_7$: C, 47.56; H, 5.49; N, 12.80. Found: C, 47.61; H, 5.67; N, 12.77.

1-(4,6-*O*-Isopropylidene-β-D-glucopyranosyl)azauracil (**1d**, 80%) had m.p. 220–221°, $[\alpha]_D^{20}$ −35°. ^{1}H-N.m.r. data: δ 7.48 (s, 1 H, H-5), 5.72 (d, 1 H, $J_{1,2}$ = 9.0 Hz, H-1'), 4.28 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 9.0 Hz, H-2'), 3.97 (q, 1 H, $J_{2,3}$ 9.0, $J_{3,4}$ 6.9 Hz, H-3'), 3.90–3.50 (m, 4 H, H-4',5',6'a,6'b).

Anal. Calc. for $C_{12}H_{16}N_3O_7$: C, 45.86; H, 5.09; N, 13.38. Found: C, 45.97; H, 5.21; N, 13.43.

Reaction of DAST with 1-(4,6-O-isopropylidene-β-D-glucopyranosyl)pyrimidines.— A mixture of 1-(4,6-*O*-isopropylidene-β-D-glucopyranosyl)pyrimidine (**1a–d**, 1 mmol) and 4-dimethylaminopyridine (3 mmol) in dry CH_2Cl_2 (20 mL) was stirred at −30° under nitrogen. DAST (3 mmol) was then added slowly, the resulting solution was allowed to attain room temperature, and stirring was continued for 16 h. The mixture was cooled to 0°, triethylamine (1 mL) was added, the solvent was evaporated, and the resulting oil was subjected to flash-column chromatography (ethyl acetate–hexane, 3:1). The major product (**3a–d**) was eluted first and pure **2a–d** were obtained from the last fractions. The following compounds were obtained on this manner.

2,2'-Anhydro-1-(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-altropyranosyl)-thymine (**3a**, 28%) had m.p. 288–290° (from EtOH), $[\alpha]_D^{20}$ −20°. ^{1}H-N.m.r. data: δ 7.20 (s, 1 H, H-6), 6.09 (d, 1 H, $J_{1,2}$ 2.20 Hz, H-1'), 5.37 (dt, 1 H, $J_{2,3}$ = $J_{3,4}$ = 2.45, $J_{F,3}$ 46.7 Hz, H-3'), 5.15 (dq, 1 H, $J_{1,2}$ 2.20, $J_{2,3}$ 2.45, $J_{F,2}$ 10 Hz, H-2'), 3.98 (dq, 1 H, $J_{3,4}$ 2.45, $J_{4,5}$ 9.26, $J_{F,4}$ 29.9 Hz, H-4'), 3.85–3.70 (m, 3 H, H-5',6'a,6'b); ^{19}F, δ −39.2.

Anal. Calc. for $C_{14}H_{17}FN_2O_5$: C, 53.85; H, 5,45; N. 8.97; F, 6.09. Found: C, 53.66; H, 5.53; N, 8.80; F, 5.95.

2,2'-Anhydro-1-(4,6-*O*-isopropylidene-β-D-mannopyranosyl)thymine (**2a**, 10%) had m.p. 284–286° (from MeOH), $[\alpha]_D^{20}$ −72.5°. ^{1}H-N.m.r. data: δ 7.25 (s, 1 H, H-6), 5.88 (s, 1 H, H-1'), 5.80 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-2'), 4.91 (q, 1 H, $J_{1,2}$ 3.9, $J_{2,3}$ 7.8 Hz, H-3'), 4.03 (q, 1 H, $J_{3,4}$ 7.8, $J_{4,5}$ 9.5 Hz, H-4'), 3.69–3.41 (m, 3 H, H-5',6'a,6'b).

Anal. Calc. for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.81; N, 9.03. Found: C, 54.11; H, 5.84; N, 8.92.

2,2'-Anhydro-1-(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-altropyranosyl)-uracil (**3b**, 30%) had m.p. 240° (from MeOH), $[\alpha]_D^{20}$ −10° ^{1}H-N.m.r. data: δ 7.92 (s, 1 H, H-6), 6.10 (d, 1 H, $J_{1,2}$ 3.43 Hz, H-1'), 5.91 (s, 1 H, H-5), 5.38 (d, $J_{F,3}$ 53.4 Hz, H-3'), 5.18 (q, 1 H, $J_{1,2}$ 3.43, $J_{F,2}$ 10.5 Hz, H-2'), 3.94 (q, 1 H, $J_{4,5}$ 8.78, $J_{F,4}$ 30.4 Hz, H-4'), 3.85–3.70 (m, 3 H, H-5',6'a,6'b); ^{19}F, δ −30.6.

Anal. Calc. for $C_{13}H_{15}FN_2 \cdot 0.5CH_3OH$: C, 51.59; H, 5.41; N, 8.91; F, 6.05. Found: C, 51.47; H, 5.18; N, 9.15; F, 6.12.

2,2'-Anhydro-1-(4,6-*O*-isopropylidene-β-D-mannopyranosyl)uracil (**2b**, 12%) had m.p. 288° (dec.) (from MeOH), $[\alpha]_D^{20}$ −110°. ^{1}H-N.m.r. data: δ 7.85 (s, 1 H, H-6), 5.93 (d, 1 H, $J_{1,2}$ 2.3 Hz, H-1'), 5.85 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 2.3 Hz, H-2'), 4.98 (q, 1 H, $J_{2,3}$ 2.3,

$J_{3,4}$ 7.5 Hz, H-3'), 4.06 (q, 1 H, $J_{3,4}$ 7.5, $J_{4,5}$ 9.6 Hz, H-4'), 3.85–3.40 (m. 3 H, H-5',6'a,6'b).

Anal. Calc. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.46; N, 9.46. Found: C, 52.23; H, 5.10; N, 9.10.

2,2'-Anhydro-1-(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-altropyranosyl)-azathymine (**3c**, 22%) had m.p. 238–240° (from MeOH), $[\alpha]_D^{20}$ −27.5°. ^{1}H-N.m.r. data: δ 6.23 (d, 1 H, $J_{1,2}$ 2.90 Hz, H-1'), 5.40 (q, 1 H, $J_{2,3}$ 2.90, $J_{F,3}$ 48.6 Hz, H-3'), 5.28 (dt, 1 H, $J_{1,2} = J_{2,3}$ = 2.90, $J_{F,2}$ 10.8 Hz, H-2'), 3.97 (q, 1 H, $J_{4,5}$ 9.69, $J_{F,4}$ 30.5 Hz, H-4'), 3.89–3.69 (m, 3 H, H-5',6'a,6'b); ^{19}F, δ −30.4.

Anal. Calc. for $C_{13}H_{16}FN_3O_5 \cdot 0.5CH_3OH$: C, 49.24; H, 5.47; N, 12.76; F, 5.77. Found: C, 49.63; H, 5.48; N, 12.76; F, 5.72.

2,2'-Anhydro-1-(4,6-*O*-isopropylidene-β-D-mannopyranosyl)azathymine (**2c**, 8%) had m.p. 287–288° (dec.) (from MeOH), $[\alpha]_D^{20}$ −110°. ^{1}H-N.m.r. data: δ 5.77 (s, 1 H, H-1'), 5.04 (d, 1 H, $J_{2,3}$ 2.37 Hz, H-2'), 4.15 (q, 1 H, $J_{2,3}$ 2.37, $J_{3,4}$ 7.58 Hz, H-3'), 3.94 (q, 1 H, $J_{3,4}$ 7.58, $J_{4,5}$ 9.30 Hz, H-4'), 3.90–3.37 (m, 3 H, H-5',6'a,6'b).

Anal. Calc. for $C_{13}H_{17}N_3O_6$: C, 50.16; H, 5.46; N, 13.50. Found: C, 50.27; H, 5.70; N, 13.50.

2,2'-Anhydro-1-(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-altropyranosyl)-azauracil (**3d**, 25%) had m.p. 215–217° (from MeOH), $[\alpha]_D^{20}$ −15°. ^{1}H-N.m.r. data: δ 7.77 (s, 1 H, H-5), 6.28 (d, 1 H, $J_{1,2}$ 3.26 Hz, H-1'), 5.46 (d, 1 H, $J_{F,3}$ 46.3 Hz, H-3'), 5.30 (q, 1 H, $J_{1,2}$ 3.26, $J_{F,2}$ 11.2 Hz, H-2'), 4.02 (q, 1 H, $J_{4,5}$ 9.50, $J_{F,4}$ 30.50 Hz, H-4'), 3.94–3.70 (m, 3 H, H-5',6'a,6'b); ^{19}F, δ −30.7.

Anal. Calc. for $C_{12}H_{14}FN_3O_5$: C, 48.16; H, 4.68; N, 14.05; F, 6.35. Found: C, 47.96; H, 4.81; N, 14.35; F, 5.95.

2,2'-Anhydro-1-(4,6-*O*-isopropylidene-β-D-mannopyranosyl)azauracil (**2d**, 10%) had m.p. 250° (from MeOH), $[\alpha]_D^{20}$ −57.5°. ^{1}H-N.m.r. data: δ 7.67 (s, 1 H, H-5), 5.55 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1'), 5.32 (q, 1 H, $J_{1,2}$ 3.3, $J_{2,3}$ 4.3 Hz, H-2'), 3.78 (q, 1 H, $J_{2,3}$ 4.3, $J_{3,4}$ 6.2 Hz, H-3'), 3.64–3.40 (m, 4 H, H-4',5',6'a,6'b).

Anal. Calc. for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.79; H, 5.05; N, 14.15.

*Reaction of DAST with the 2,2'-anhydro-1-(4,6-*O*-isopropylidene-β-D-mannopyranosyl)pyrimidines* **2a–d**.—To a stirred solution of **2a–d** (1 mmol) and 4-dimethylaminopyridine (244 mg, 2 mmol) in dry dichloromethane (20 mL) at −30° was added DAST (0.195 mL, 2 mmol) during 15 min under nitrogen. The mixture was then allowed to attain room temperature and, after 24 h, cooled to 0°. Methanol was added, solvents were evaporated under vacuum, and the resulting oil was subjected to flash-column chromatography (ethyl acetate–hexane, 3:1) to give pure **3a–d** in yields of 70, 75, 68, and 65%, respectively.

*Reaction of DAST with 5'-*O*-trityluridine.*—5'-*O*-Trityluridine (**6**) (449 mg, 1 mmol), prepared[13] from uridine and trityl chloride, was reacted with 4-dimethylaminopyridine (3 mmol) and DAST (3 mmol) as described for **1a–d**. After column chromatography of the product, no traces of fluorinated compound were detected and 2,2'-anhydro-1-(5-*O*-trityl-β-D-arabinofuranosyl)uracil (**7**, 50%) was obtained with m.p. 203–205° (from MeOH), $[\alpha]_D^{20}$ −50°. ^{1}H-N.m.r. data: δ 7.94 (d, 1 H, $J_{5,6}$ 7.5 Hz, H-6),

6.32 (d, 1 H, $J_{1,2}$ 5.6 Hz, H-1'), 5.98 (d, 1 H, $J_{OH,3}$ 4.3 Hz, 3'-OH), 5.86 (d, $J_{5,6}$ 7.5 Hz, H-5), 5.21 (d, 1 H, $J_{1,2}$ 5.6 Hz, H-2'), 4.40–4.21 (m, 2 H, H-3', 4'), 2.96 (dd, 1 H, $J_{5a,4}$ 5.97, $J_{5a,5b}$ 10.1 Hz, H-5'a), 2.82 (dd. 1 H, $J_{5b,4}$ 7.34, $J_{5a,5b}$ 10.1 Hz, H-5'b).

Anal. Calc. for $C_{25}H_{24}N_2O_5$: C, 69.44; H, 5.55; N, 6.48. Found: C, 68.98; H, 5.47; N, 5.97.

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