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Note

2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl azide and 2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosyl azide

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In extending our work[1] on cytostatic, alkylating derivatives of 1,2,3-triazole nucleosides obtained by 1,3-dipolar cycloaddition of glycosyl azides to acetylenes, 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl azide (**1**) and 2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosyl azide (**8**) were required. We now report the synthesis and characterisation of these compounds.

Treatment[2] of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose with trimethylsilyl azide and stannic chloride gave 93% of 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl azide (**1**). This method is reported to give products with N_3-1 and AcO-2 *trans*; hence **1** should be the β anomer.

That **1** was the β anomer was established as follows. 1,3-Dipolar cycloaddition of **1** to 2-propynyl alcohol gave a mixture of 4- (**2**) and 5-hydroxymethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,3-triazole (**3**), from which only **3** could be obtained pure. The position of the hydroxymethyl group in **2** and **3** was determined by p.m.r. spectroscopy, on the basis of the differences ($\Delta\delta$) in chemical shifts of H-4 or H-5 for solutions of the triazoles in chloroform and methyl sulphoxide. For 1-methyl-1,2,3-triazole[3], the chemical shift of the proton (H-5) adjacent to the substituted nitrogen is more sensitive to solvent and substituent changes than is H-4. Thus, the isomer having the larger $\Delta\delta$ value was assigned the structure **2**. The anomeric configurations of **2** and **3** could not be assigned on the basis of the $J_{1',2'}$ values (3.5 and 2.5 Hz, respectively) (*cf.* ref. 4).

Deacetylation of the mixture of **2** and **3** with methanolic ammonia, and acetonation of the products (**4** and **5**) gave 4- (**6**) and 5-hydroxymethyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole (**7**), which were separated by p.l.c. The β configuration of **6** and **7** was deduced from the differences ($\Delta\delta$) in the chemical shifts for the protons of the isopropylidene methyl groups[5]. These $\Delta\delta$ values were 0.17 [$(CD_3)_2SO$] and 0.20 p.p.m. ($CDCl_3$) for **6**, and 0.18 [$(CD_3)_2SO$] and 0.21 p.p.m.

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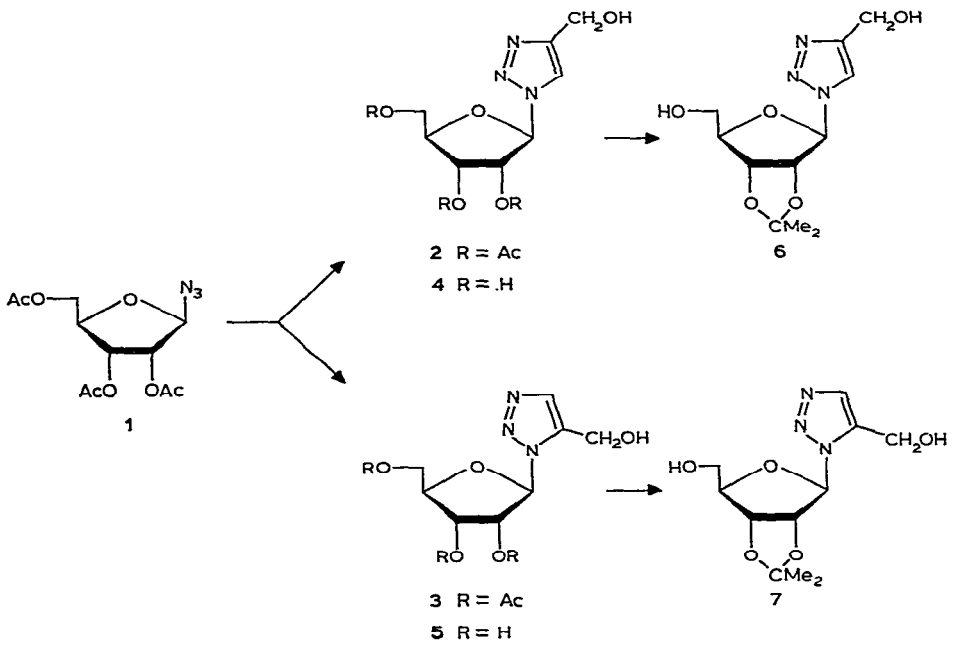
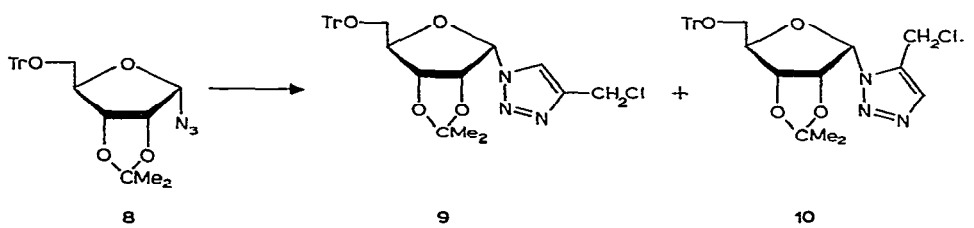


($CDCl_3$) for **7**. Since no anomerisation is expected in the initial cycloaddition reaction[1,6-9], **1** is also assigned the β configuration.

The reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride[10] with sodium azide[11] gave the α-azide **8**, since the absence of acyl protecting-groups eliminated the possibility[12] of a neighbouring-group reaction and allowed an S_N2 displacement of Cl-1.



The structure of **8** was determined in a manner similar to that used for **1**. Thus, 1,3-dipolar cycloaddition of **8** to 2-propynyl chloride gave a mixture of 4- (**9**) and 5-chloromethyl-1,2,3-triazole (**10**). The location of the chloromethyl group in **9** and **10** was determined on the basis of the differences in sensitivity of the chemical shifts of H-4 or H-5 to change in solvent[3], and the α configuration on the basis of the $\Delta\delta$ values for the isopropylidene methyl groups[5], namely, 0.09 [$(CD_3)_2SO$] and 0.11 p.p.m. ($CDCl_3$) for **9**, and 0.04 [$(CD_3)_2SO$] and 0.06 p.p.m. ($CDCl_3$) for **10**.

EXPERIMENTAL

General. — Melting points are uncorrected. N.m.r. spectra (100 MHz, internal Me_4Si) were recorded with a Varian XL-100 spectrometer. Optical rotations were measured at 23 ±2° with a Perkin–Elmer 141 polarimeter. T.l.c. was performed on Silica Gel $60F_{254}$ (Merck), and p.l.c. on Silica Gel PF_{254} (Merck). Compounds were detected, as appropriate, by using a u.v. light (254 nm) or by charring with sulphuric acid. Column chromatography was performed on Silica Gel 60 (Merck, 70–230 mesh).

*2,3,5-Tri-*O*-acetyl-β-*D*-ribofuranosyl azide* (**1**). — To a mixture of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.18 g, 0.01 mol) and trimethylsilyl azide (1.5 ml) was added a solution of stannic chloride (1 ml) in anhydrous dichloromethane (90 ml). The mixture was stirred at room temperature for 3.5 h, washed with water (2 × 50 ml), saturated aqueous $NaHCO_3$ (40 ml), and water (40 ml), dried ($CaCl_2$), and concentrated. The resulting, yellow syrup was purified by p.l.c. with ethyl acetate–light petroleum (1:3), to yield **1** (2.8 g, 93%) as a pale-yellow syrup, $[\alpha]_D$ −116° (*c* 1, chloroform); ν_{max} 2140 cm^{-1} (N_3). P.m.r. data ($CDCl_3$): δ 2.05 (s, 3 H, AcO), 2.09 (s, 6 H, 2 AcO), 4.01–4.47 (m, 3 H, H-4,5,5), 5.26 (d, 1 H, H-3), 5.10 (dd, 1 H, $J_{2,3}$ 5 Hz, H-2), and 5.33 (d, 1 H, $J_{1,2}$ 2 Hz, H-1).

Anal. Calc. for $C_{11}H_{15}N_3O_7$: C, 43.85; H, 5.01; N, 13.94. Found: C, 43.73; H, 5.08; N, 13.74.

*2,3-*O*-Isopropylidene-5-*O*-trityl-α-*D*-ribofuranosyl azide* (**8**). — A mixture of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose[10] (4.32 g, 0.01 mol), triphenylphosphine (3.26 g, 0.012 mol), carbon tetrachloride (5 ml), and acetonitrile (25 ml) was stirred at room temperature for 24 h, and then concentrated to dryness. The residue was extracted with ether–light petroleum (1:1, 5 × 30 ml). The combined extracts were filtered rapidly through Silica Gel 60 (20 g), to remove traces of triphenylphosphine oxide. The silica gel was then washed with ether–light petroleum (1:2), and the combined filtrate and washings were concentrated under diminished pressure. To a solution of the resulting syrup in acetonitrile (40 ml) was added sodium azide (1.3 g, 0.02 mol), and the mixture was boiled under reflux, with exclusion of moisture, for 3 days, and then filtered and concentrated *in vacuo*. The resulting syrup was purified by p.l.c. with ethyl acetate–hexane (1:2), to give amorphous **8** (2.28 g, 50%), $[\alpha]_D$ +8° (*c* 1, chloroform); ν_{max} 2135 cm^{-1} (N_3). P.m.r. data ($CDCl_3$): δ 1.33 and 1.58 (2 s, 6 H, CMe_2), 3.10 (dd, 1 H, $J_{4,5a}$ 3, $J_{5a,5b}$ 10.5 Hz, H-5a), 3.47 (dd, 1 H, $J_{4,5b}$ 3.5 Hz, H-5b), 4.31 (t, 1 H, H-4), 4.63 (d, 1 H, $J_{2,3}$ 6, $J_{3,4}$ <0.5 Hz, H-3), 4.82 (dd, 1 H, H-2), 5.25 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), and 7.3 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{27}H_{27}N_3O_4$: C, 70.87; H, 5.94; N, 9.18. Found: C, 71.11; H, 5.75; N, 9.09.

*4- (**2**) and 5-Hydroxymethyl-1-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)-1,2,3-triazole* (**3**). — A mixture of **1** (3 g, 0.01 mol), 2-propynyl alcohol (2.4 ml, 0.04 mol), and anhydrous toluene (20 ml) was boiled under reflux for 17 h, with the exclusion of moisture, and then concentrated to dryness. The residue was subjected to p.l.c. with ethyl acetate–hexane (2:1). The slower and faster halves of the resulting, broad

band were separately extracted with ethyl acetate. The latter half gave a yellow syrup (1.2 g) that crystallised on storage at 0°, and recrystallisation from ethyl acetate–light petroleum yielded **3** (0.9 g, 25%), m.p. 65–66°, $[\alpha]_D$ −6.5° (*c* 1, chloroform). P.m.r. data: [$(CD_3)_2SO$]: δ 1.89, 2.07, and 2.09 (3 s, 9 H, 3 AcO), 3.89–4.48 (m, 3 H, H-4′,5′,5′), 4.59 (s, 2 H, CH_2OH), 5.59 (dd, 1 H, $J_{3',4'}$ 6 Hz, H-3′), 5.90 (dd, 1 H, $J_{2',3'}$ 5 Hz, H-2′), 6.26 (d, 1 H, $J_{1',2'}$ 2.5 Hz, H-1′), and 7.65 (s, 1 H, H-4); ($CDCl_3$): δ 4.74 (s, 2 H, CH_2OH), 6.21 (d, 1 H, H-1′), and 7.48 (s, 1 H, H-4).

Anal. Calc. for $C_{14}H_{19}N_3O_8$: C, 47.05; H, 5.35; N, 11.76. Found: C, 47.04; H, 5.31; N, 11.71.

The product from the slower half of the band was re-chromatographed, to give a 55:45 mixture (1.98 g, 55%) of **2** and **3**, as determined by p.m.r. spectroscopy. P.m.r. data for **2** [$(CD_3)_2SO$]: δ 1.97 (s, 3 H, AcO), 2.08 (s, 6 H, 2 AcO), 4.08–4.62 (m, 3 H, H-4′,5′,5′), 4.51 (d, 2 H, $J_{H,OH}$ 5.5 Hz, CH_2OH), 5.52 (dd, 1 H, $J_{3',4'}$ 6 Hz, H-3′), 5.77 (dd, 1 H, $J_{2',3'}$ 5.5 Hz, H-2′), 6.30 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1′), and 8.14 (s, 1 H, H-5); ($CDCl_3$): δ 4.73 (s, 2 H, CH_2OH), 6.10 (d, 1 H, H-1′), and 7.71 (s, 1 H, H-5).

4- (**6**) *and 5-Hydroxymethyl-1-(2,3-*O*-isopropylidene-β-*D*-ribofuranosyl)-1,2,3-triazole* (**7**). — A solution of a 4:6 mixture (0.5 g, 1.4 mmol) of **2** and **3** in methanolic ammonia (20 ml) was left overnight at room temperature and then concentrated *in vacuo*. To a solution of the resulting syrupy mixture of **4** and **5** in anhydrous acetone (7 ml) were added ethyl orthoformate (0.33 ml, 0.002 mol) and M HCl in dry ether (0.18 ml). The mixture was protected from moisture and stirred at room temperature for 21 h, and then neutralised with conc. ammonia, and concentrated under diminished pressure. The residue was dissolved in the minimum amount of water and extracted thrice with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated, and the syrupy residue (0.33 g) was subjected to p.l.c. with ethyl acetate. Two major bands were separately extracted with ethyl acetate–methanol (2:1). The faster-moving band yielded a yellow syrup that was re-chromatographed, to give **7** (0.115 g, 31%), $[\alpha]_D$ −61° (*c* 1, chloroform). P.m.r. data [$(CD_3)_2SO$]: 1.39 and 1.56 (2 s, 6 H, CMe_2), 4.30 (m, 2 H, H-5′), 4.25 (m, 1 H, H-4′), 4.75 (d, 2 H, CH_2OH), 5.02 (dd, 1 H, H-3′), 5.70 (dd, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 6.40 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), and 7.80 (s, 1 H, H-4); ($CDCl_3$): δ 1.42 and 1.62 (2 s, 6 H, CMe_2), 6.35 (d, 1 H, H-1′), and 7.68 (s, 1 H, H-4).

Anal. Calc. for $C_{11}H_{17}N_3O_5$: C, 48.70; H, 6.31; N, 15.49. Found: C, 48.37; H, 6.32; N, 15.21.

The slower-moving band yielded a syrup that was re-chromatographed, to afford **6** (0.094 g, 25%), $[\alpha]_D$ −73° (*c* 1, chloroform). P.m.r. data [$(CD_3)_2SO$]: δ 1.36 and 1.54 (2 s, 6 H, CMe_2), 4.5–4.8 (m, 5 H, H-4′,5′,5′ and CH_2OH), 5.00 (t, 1 H, $J_{3',4'}$ 6 Hz, H-3′), 5.37 (dd, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 6.31 (d, 1 H, $J_{1',2'}$ 2.5 Hz, H-1′), and 8.27 (s, 1 H, H-5); ($CDCl_3$): δ 1.40 and 1.61 (2 s, 6 H, CMe_2), 6.19 (d, 1 H, $J_{1',2'}$ 2 Hz, H-1′), and 7.93 (s, 1 H, H-5).

Anal. Found: C, 48.35; H, 6.01; N, 15.70.

4- (**9**) *and 5-Chloromethyl-1-(2,3-*O*-isopropylidene-5-*O*-trityl-β-*D*-ribofuranosyl)-*

1,2,3-triazole (**10**). — A mixture of **8** (4.57 g, 0.01 mol), 2-propynyl chloride (4.91 g, 0.066 mol), and toluene (7 ml) was protected from moisture and boiled under reflux for 2 days, and then concentrated *in vacuo*. The residue was subjected to p.l.c. (ethyl acetate–hexane, 1:1). Under u.v. light, three major bands were observed, which were separately extracted with ethyl acetate.The faster-moving band yielded triphenylmethyl alcohol (0.59 g). The second band gave a solid (3.5 g) that crystallised from ethyl acetate–hexane, with a molecule of ethyl acetate, to yield **9** (2.115 g, 34%) as an amorphous solid, $[\alpha]_D$ −20° (*c* 1, chloroform). P.m.r. data [$(CD_3)_2SO$]: δ 1.16 (t, 3 H, $CH_3CH_2OCOCH_3$), 1.28 and 1.37 (2 s, 6 H, CMe_2), 1.98 (s, 3 H, $CH_3CH_2OCOCH_3$), 3.28 (bs, 2 H, H-6′), 4.01 (q, 2 H, $CH_3CH_2OCOCH_3$), 4.47 (t, 1 H, H-4′), 4.82 (d, 1 H, H-3′), 4.87 (s, 2 H, CH_2Cl), 5.09 (dd, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 6.60 (d, 1 H, $J_{1',2'}$ 4.5 Hz, H-1′), 7.37 (m, 15 H, 3 Ph), and 8.20 (s, 1 H, H-5); ($CDCl_3$): δ 1.20 and 1.31 (2 s, 6 H, CMe_2), 4.73 (s, 2 H, CH_2Cl), 6.79 (d, 1 H, H-1′), and 7.90 (s, 1 H, H-5).

Anal. Calc. for $C_{30}H_{30}N_3O_4Cl \cdot C_4H_8O_2$: C, 65.85; H, 6.17; N, 6.77; Cl, 5.72. Found: C, 66.20; H, 6.20; N, 7.03; Cl, 6.13.

The product from the slower-moving band was recrystallised from ethyl acetate–hexane, to give **10** (0.253 g, 5%), which melted at 77–80°, crystallised at 100–110°, and melted again at 139–141°; $[\alpha]_D$ −18° (*c* 1, chloroform). P.m.r. data [$(CD_3)_2SO$]: δ 1.20 and 1.24 (2 s, 6 H, CMe_2), 3.27 (bs, 2 H, H-5′), 4.63–4.87 (m, 2 H, H-3′,4′), 4.98 (s, 2 H, CH_2Cl), 6.65 (d, 1 H, $J_{1',2'}$ 5 Hz, H-1′), 7.40 (m, 15 H, 3 Ph), and 7.80 (s, 1 H, H-4); ($CDCl_3$): δ 1.28 and 1.36 (2 s, 6 H, CMe_2), 4.82 (s, 2 H, CH_2Cl), 6.89 (d, 1 H, H-1′), and 7.78 (s, 1 H, H-4).

Anal. Calc. for $C_{30}H_{30}N_3O_4Cl$: C, 67.73; H, 5.68; N, 7.90; Cl, 6.66. Found: C, 67.48; H, 5.27; N, 7.70; Cl, 6.94.

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