Aminonucleosides and their Derivatives; VI[1]. A New Synthesis of 1,2,5-Tri-*O*-acyl-3-azido-3-deoxy-β-D-ribofuranose

Ainars M. OZOLS, Alexey V. AZHAYEV*, Natalia B. DYATKINA, Alexander A. KRAYEVSKY

Institute of Molecular Biology, Academy of Sciences of the USSR, Vavilov str. 32, 117984 Moscow V-334, USSR

We have previously reported the synthesis of 3′-amino-3′-deoxynucleosides which included the preparation of 1,2,5-tri-*O*-acyl-3-azido-3-deoxy-D-ribofuranose[2,3], glycosidation of nucleic bases with this ribofuranose according to Ref.[4,5], and reduction of the resultant azidonucleosides. The principle of the synthesis of the 1,2,5-tri-*O*-acyl-3′-azido-3′-deoxy-D-ribofuranose consisted of the selective protection of the 5-hydroxy group in 1,2-*O*-isopropylidene-α-D-xylofuranose by a benzoyl group (or an analog thereof) with subsequent activation of the 3-hydroxy group by *O*-tosylation or *O*-mesylation. This latter ester group (*p*-toluenesulfonic or methanesulfonic ester) was then replaced by the azido group with inversion of configuration at C-3. As a drawback of this method, the relatively low reactivity of the tosyloxy or mesyloxy group at C-3 in the reaction with lithium azide led to the necessity of harsh conditions (150 °C for 3 h in HMPT) and thereby to a side reaction at C-5. In order to avoid this side reaction, the benzoyl group at the 5-O atom had to be removed and replaced by the 2-tetrahydropyranyl group which had in turn to be removed after the reaction with lithium azide; after these reactions, the 5-hydroxy group had to be 4-nitrobenzoylated. Thus, too many reaction steps were required and the yield of end product was relatively low.

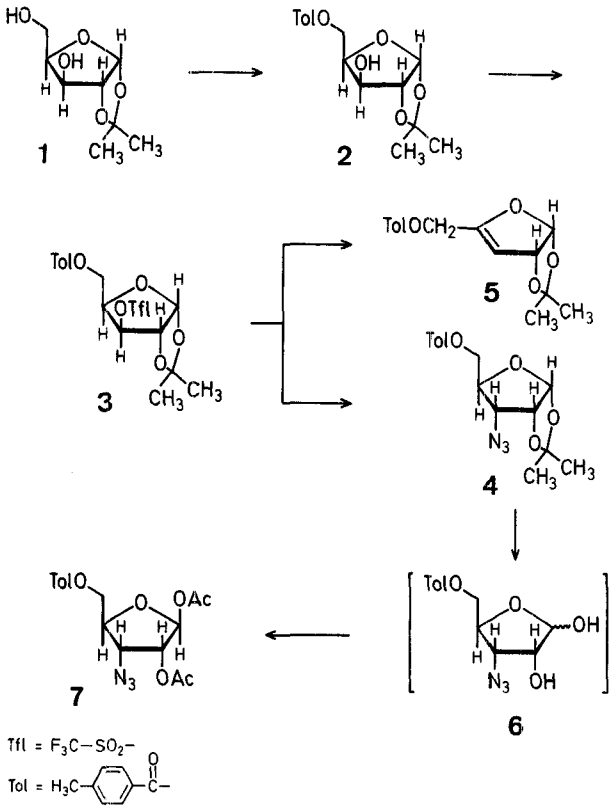
In sugar[6] and nucleoside chemistry[7], hydroxy groups have frequently been activated by conversion into the triflic ester (*O*-trifluoromethanesulfonylation). This activation makes possible nucleophilic substitution under relatively mild conditions in cases in which *O*-tosylation or *O*-mesylation are of little use.

We prepared the 3-*O*-trifluoromethanesulfonyl derivative **3** of 1,2-*O*-isopropylidene-5-*O*-(4-methylbenzoyl)-α-D-xylofuranose. Reaction of compound **3** with lithium azide in boiling ethanol (5 h) afforded a mixture of azide **4** (51%) and alkene **5**. Performance of the reaction with lithium azide or tetrabutylammonium azide in hexamethylphosphoric triamide (HMPT) at 0 °C or dimethylformamide at 20 °C led to an increase in reaction rate whereas the yield of **4** remained practically unaffected. Removal of the isopropylidene group in **4** followed by *O*-acetylation of the resultant **6** afforded 1,2-di-*O*-acetyl-3-azido-5-*O*-(4-methylbenzoyl)-3-deoxy-β-D-ribofuranose (**7**) the structure of which was confirmed by a number of methods including ^{1}H-N.M.R. spectrometry. Thus, modification of the known method allowed the scheme to be curtailed by 4 stages and the overall yield of end product per the initial sugar **1** to be increased to 36% (two-fold as compared to the unmodified procedure). It should be mentioned that compounds **2**, **3**, **4**, and **7** crystallize readily.

Glycosidation of trimethylsilylated N^6-benzoyladenine with the azidosugar **7** using the method of Ref.[3] and subsequent removal of the protective groups gave 3′-azido-3′-

0039-7881/80/0732-0557 $ 03.00 © 1980 Georg Thieme Verlag · Stuttgart · New York

Downloaded by: University of Illinois. Copyrighted material.



deoxyadenosine in 63% yield (based on 7). The activated xylofuranose **3** is being used in this laboratory to prepare various 3′-substituted ribonucleosides.

T.L.C. separations were carried out on Silufol UV 254 plates (Kavalier, Czechoslovakia) using hexane/ether (2/1, System A) or ethyl acetate/benzene (3/17, System B). The I.R. spectra were recorded with a UR-10 spectrometer. The ^{1}H-N.M.R. spectra were recorded with a Varian XL-100 instrument using TMS as internal standard. All melting points are corrected.

1,2-*O*-Isopropylidene-5-*O*-(4-methylbenzoyl)-α-D-xylofuranose (2):
A solution of 4-methylbenzoyl chloride (39 g, 240 mmol) in dry pyridine (40 ml) is added dropwise to a stirred solution of 1,2-*O*-isopropylidene-α-D-xylofuranose (**1**; 46 g, 240 mmol) in dry pyridine (150 ml) at 0 °C. Stirring is continued for 1 h at 0 °C and the mixture then poured onto crushed ice (1.5 kg). The precipitated product is isolated by filtration, washed with water, and dried in vacuo. The product is recrystallized twice from hexane/chloroform; yield: 46 g. The mother liquors of both recrystallizations are combined, evaporated, and the residue chromatographed on a silica gel column (4 × 40 cm). A small amount of 4,6-*O*,*O*-bis[4-methylbenzoyl] derivative is eluted with benzene. Product **2** is then eluted with benzene/ethyl acetate (3/1). The fractions containing **2** are evaporated to dryness and the residue is recrystallized from chloroform/hexane; total yield: 67 g (97%); m.p. 73–74 °C; R_f: 0.14 in System A and 0.38 in System B; $[\alpha]_D$: 5.2° (*c* 0.568, chloroform).

$C_{16}H_{20}O_6$	calc.	C 62.32	H 6.54
(308.2)	found	62.29	6.57

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 8.00, 7.26 (2 d, *J* = 8 Hz, 4 H_{arom}); 5.96 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1); 4.94–4.24 (m, 4 H, H-2 + H-4 + H-$5_{a,b}$); 4.59 (d, $J_{2,3}$ = 0 Hz, H-2); 4.18 (dd, 1 H, $J_{3,4}$ = 2.5 Hz, H-3); 2.78 (d, 1 H, $J_{3,3\text{-OH}}$ = 4.1 Hz, 3-OH); 2.42 (s, 3 H, H_3C–Ar); 1.51, 1.32 ppm [2 s, 6 H, $C(CH_3)_2$].

1,2-*O*-Isopropylidene-5-*O*-(4-methylbenzoyl)-3-*O*-trifluoromethanesulfonyl-α-D-xylofuranose (3):
A solution of trifluoromethanesulfonic anhydride (10.2 g, 36 mmol) in 1,2-dichloroethane (60 ml) is added to a stirred, precooled (−10 °C) solution of pyridine (3.3 ml) in 1,2-dichloroethane (240 ml). To this mixture, a solution of derivative **2** (9.15 g, 30 mmol) in 1,2-dichloroethane (40 ml) is added with stirring and the mixture is held at −10 °C for 30 min. Then, 5% aqueous sodium hydrogen carbonate (600 ml) is added and stirring is continued for 20 min at room temperature. The organic layer is separated, dried with sodium sulfate, and evaporated to dryness. The residue is re-evaporated with toluene (3 × 50 ml) and crystallized from methanol; yield 12 g (93%); m.p. 92–93 °C; R_f: 0.92 in System A and 0.94 in System B; $[\alpha]_D$: −32.93° (*c* 0.502, chloroform).

$C_{17}H_{19}F_3O_8S$	calc.	C 49.14	H 4.12
(464.4)	found	49.27	4.01

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.86, 7.18 (2 d, *J* = 8.0 Hz, 4 H_{arom}); 6.00 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1); 5.29 (d, 1 H, $J_{3,4}$ = 2.2 Hz, H-3); 4.76 (d, 1 H, $J_{2,3}$ = 0 Hz, H-2); 4.71–4.27 (m, 3 H, H-4 + H-$5_{a,b}$); 2.41 (s, 3 H, H_3C–Ar); 1.53, 1.35 ppm [2 s, 6 H, $C(CH_3)_2$].

3-Azido-1,2-*O*-isopropylidene-5-*O*-(4-methylbenzoyl)-3-deoxy-α-D-ribofuranose (4):
Lithium azide (12 g, 295 mmol) is added to a solution of derivative **3** (10 g, 30 mmol) in ethanol (250 ml) and the mixture is refluxed for 5 h. Ethanol is then evaporated and the residue is distributed between chloroform (150 ml) and water (150 ml). The aqueous layer is separated and washed with chloroform (100 ml). The chloroform extracts are combined, dried with sodium sulfate, and evaporated to dryness. The residue is chromatographed on a silica gel column (3 × 20 ml) and eluted with ether/hexane (1/5). The first U.V.-absorbing fraction is evaporated and dried in vacuo to give the olefinic compound **5** as a colorless oil; yield 2.69 g (41%); R_f: 0.88 in System A.

I.R. (KBr): ν = 1670 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.99, 7.18 (2 d, *J* = 8 Hz, 4 H_{arom}); 6.05 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1); 5.26 (d, 1 H, $J_{2,1}$ = 5.0 Hz, H-2); 5.23 (s, 1 H, H-3); 4.79 (s, 2 H, O–CH_2–); 2.35 (s, 3 H, H_3C–Ar); 1.42, 1.37 ppm [2 s, 6 H, $C(CH_3)_2$].

The second U.V.-absorbing fraction is evaporated to dryness and the residue recrystallized from methanol; yield of **4**: 3.8 g (51%); m.p. 56–57 °C (methanol); R_f: 0.61 in system A and 0.86 in System B; $[\alpha]_D$: 116.00° (*c* 0.670, chloroform).

$C_{16}H_{19}N_3O_5$	calc.	C 57.65	H 5.75	N 12.61
(333.3)	found	57.61	5.78	12.52

I.R. (KBr): ν = 2095 cm^{-1} (N_3).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.86, 7.16 (2 d, *J* = 8 Hz, 4 H_{arom}); 5.79 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1); 4.73 (dd, 1 H, $J_{2,3}$ = 4.5 Hz, H-2); 4.61–4.21 (m, 3 H, H-4 + H-$5_{a,b}$); 3.38 (dd, 1 H, $J_{3,4}$ = 8.6 Hz, H-3); 2.38 (s, 3 H, H_3C–Ar); 1.58, 1.36 ppm [2 s, 6 H, $C(CH_3)_2$].

3-Azido-1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-3-deoxy-β-D-ribofuranose (7):
The azido derivative **4** (2 g, 6 mmol) is added to 75% formic acid (70 ml), the mixture is heated at 50 °C for 1 h, and then evaporated to dryness. The residue is dissolved and reevaporated successively with butanol (2 × 50 ml) and toluene (2 × 50 ml). The residue is dissolved in pyridine (30 ml) + acetic anhydride (20 ml), the mixture is allowed to stand at room temperature for 2 h, and is then poured onto crushed ice (250 g). The resultant mixture is extracted with chloroform (3 × 100 ml); the chloroform layers are combined, washed with saturated sodium hydrogen carbonate (100 ml) and with water (100 ml), dried with sodium sulfate, and evaporated to dryness. The residue is recrystallized from methanol to give **7** as colorless needles; yield: 1.96 g (84%); m.p. 66–67 °C, R_f: 0.27 in System A and 0.77 in System B; $[\alpha]_D$: 7.29° (*c* 0.503, chloroform).

$C_{17}H_{19}N_3O_7$	calc.	C 54.11	H 5.08	N 11.14
(377.4)	found	54.08	5.11	11.09

I.R. (KBr): ν = 2116 cm^{-1} (N_3).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.88, 7.16 (2 d, *J* = 8 Hz, 4 H_{arom}); 6.09 (s, 1 H, $J_{1,2}$ = 0 Hz, H-1); 5.31 (d, 1 H, $J_{2,3}$ = 4.6 Hz, H-2); 4.70–4.04 (m, 4 H, H-3 + H-4 + H-$5_{a,b}$); 2.48 (s, 3 H, H_3C–Ar); 2.15, 1.90 ppm (2 s, 6 H, 2 H_3C–CO–).

Received: September 17, 1979
(Revised form: October 30, 1979)

Downloaded by: University of Illinois. Copyrighted material.

* Address for correspondence.

[1] Part V. A. V. Azhayev, A. A. Krayevsky, J. Smrt, *Collect. Czech. Chem. Commun.* **44**, 792 (1979).
[2] A. V. Azhayev, J. Smrt, *Collect. Czech. Chem. Commun.* **43**, 1520 (1978).
[3] A. V. Azhayev et al., *Nucleic Acids Res.* **6**, 625 (1979).
[4] H. F. Vorbrüggen, U. Niedballa, K. Krolikiewicz, B. Bennua, *Chemistry and Biology of Nucleosides and Nucleotides*, p. 251, Academic Press Inc., New York, 1978.
[5] F. W. Lichtenthaler, P. Voss, A. Heerd, *Tetrahedron Lett.* **74**, 2141 (1974).
[6] R. W. Binkley, D. G. Hehemann, *J. Org. Chem.* **43**, 3244 (1978).
[7] R. Ranganathan, *Tetrahedron Lett.* **15**, 1291 (1977).
M. Ikehara, M. Miki, *Chem. Pharm. Bull.* **26**, 2449 (1978).
[8] B. R. Baker, R. E. Shaub, *J. Am. Chem. Soc.* **72**, 5900 (1955).

0039-7881/80/0732-0559 $ 03.00
© 1980 Georg Thieme Verlag · Stuttgart · New York

Downloaded by: University of Illinois. Copyrighted material.