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M. K. Gurjar^a; S. M. Pawar^a; A. V. Rama Rao^a

^a Regional Research Laboratory, Hyderabad, India

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COMMUNICATION

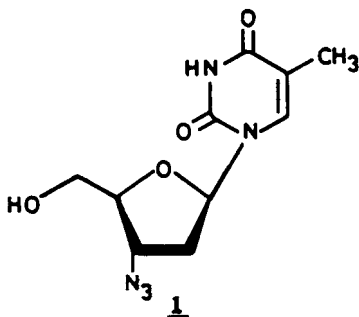
A SYNTHESIS OF 1,5-DI-O-ACETYL-3-AZIDO-2,3-DIDEOXY-D-RIBOFURANOSE

M.K. Gurjar*, S.M. Pawar and A.V. Rama Rao

Regional Research Laboratory
Hyderabad 500 007, India

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The renewed interest in azido-nucleosides, particularly when the azido group is present at position 3, has been intensified¹ since the approval of 3'-azido-thymidine (**1**) for the treatment of AIDS.² Moreover, 3'-amino-2,3-dideoxy-nucleosides are also important due to various biological activities associated³⁻⁵ with them. In dealing with the synthesis of such molecules, 3-azido-2,3-dideoxy-pentoses have been realised as valuable synthons.⁴

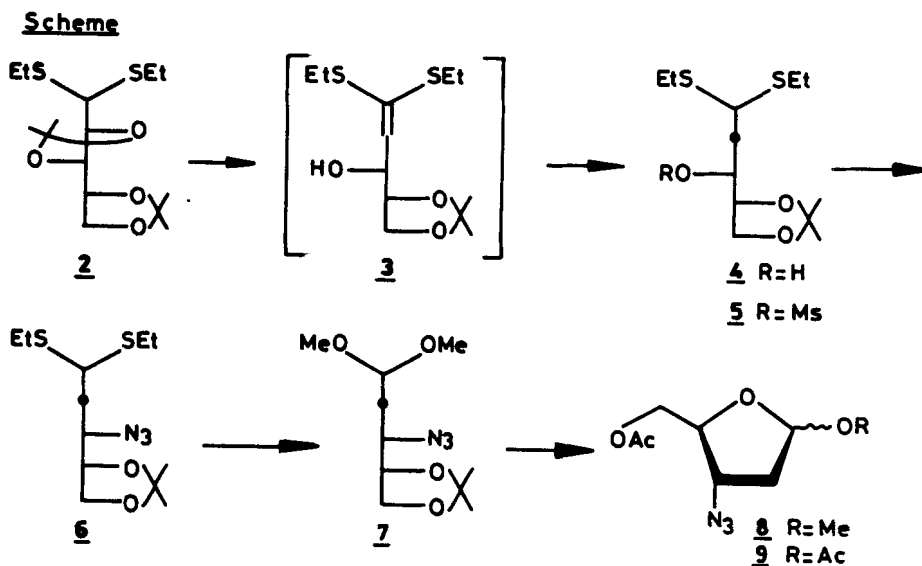


Recently, Dyatkina et al⁵ have synthesised methyl 3-azido-2,3-dideoxy-5-O-p-methylbenzoyl-D-ribofuranoside from 1,2:3,5-di-O-isopropylidene-D-xylose. However, the synthesis involves a large number of steps in part due to protecting-deprotecting steps. The present synthesis was planned to circumvent these steps. As the crucial step the deoxygenation at C-2 of D-xylose

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was effected in one step by a stereoselective reduction of the ketene dithioacetal intermediate (3) by a modified procedure.⁶

Thus, treatment of 2,3:4,5-di-O-isopropylidene-D-xylose diethyl-dithioacetal (2)⁶ in tetrahydrofuran with *n*-butyllithium at -78 °C for 2 h followed by *in situ* reduction the resulting ketene dithioacetal derivative (3) with lithium aluminium hydride gave the 2-deoxy product (4) in 70% yield. The product 4 was identical in all respects with the sample prepared earlier.⁶ Subsequent mesylation of 4 with methanesulfonyl chloride-pyridine for 2 h gave the 3-mesylate (5). In the ¹H NMR spectrum of 5, a singlet observed at 3.06 ppm was assigned to the mesyloxy methyl group whereas a double triplet in the downfield region (4.90 ppm) corresponded with H-3.



The mesylate 5 was heated with excess sodium azide in dimethylformamide at 100 °C for 12 h to yield the 3-azido derivative (6) in 80% yield. The IR spectrum of 6 revealed the characteristic absorption for an azido group at 2100 cm^{-1} . The ¹H NMR spectrum was compatible with the assigned structure (6).

Treatment of 6 with yellow mercuric oxide-mercuric chloride in dry methanol for 2 h afforded⁶ the dimethylacetal derivative (7). Compound 7 was treated with 0.8 % aqueous sulfuric acid in methanol and then the resulting product was conventionally acetylated to give both the anomers methyl 5-O-acetyl-3-azido-2,3-dideoxy- α - and β -D-ribofuranoside (8). The

-structure of the β -anomer of **8** was confirmed by ^1H NMR, IR and mass spectral analysis. Successive hydrolysis with 50 % aqueous acetic acid and reacetylation afforded the title product (**9**).

In an alternate but direct procedure, compound **7** was treated with trifluoroacetic acid at 0 °C for 24 h followed by acetylation to give **9** in 75 % yield.

EXPERIMENTAL

General Procedures. Solvents were removed under diminished pressure below 45 °C by using a Buchi rotary evaporator. All the solvents were distilled before use and light petroleum refers to fraction, bp 60-80 °C. ^1H NMR spectrum were scanned on either a Jeol FX90Q or Varian 80FTA instruments in CDCl_3 with TMS as the internal standard. IR spectra were run on Perkin Elmer Model 1310 spectrometer. Silica gel (60-120 mesh) for column chromatography was purchased from Acme Synthetic Chemicals. Optical rotations were determined on JASCO 361 Polarimeter.

2-Deoxy-4,5-O-isopropylidene-D-threo-pentose diethyl-dithioacetal(4).

Compound **2** (20g, 59.5 mmol) in dry tetrahydrofuran (150 mL) was stirred at -78 °C and then 2.8 M *n*-butyllithium (25 mL) was gradually added. After 2 h at -78 °C solid lithium aluminium hydride (2.0 g, 52.7 mmol) was introduced and then stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous sodium sulfate and filtered. The filtrate was extracted with chloroform, dried and concentrated. The residue was subjected to column chromatography on silica gel using light petroleum-ethyl acetate (5:1) to afford compound **4** (11.6 g, 70 %): $[\alpha]_{\text{D}} + 22.8^\circ$ (c 0.9, chloroform), lit.⁶ $[\alpha]_{\text{D}} + 25.6^\circ$ (chloroform).

3-Azido-2,3-dideoxy-4,5-O-isopropylidene-D-erythro-pentose diethyl-dithioacetal (6). To a solution of the 2-deoxyproduct **4** (11.0 g, 39.3 mmol) in pyridine (25 mL) at 0 °C was added methanesulfonyl chloride (5.0 g, 43.6 mmol) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was diluted with ice-water and extracted with chloroform. The chloroform layer was washed with dilute hydrochloric acid, sodium bicarbonate solution, water, dried and concentrated. The residue was chromatographed on a column of silica gel with light petroleum-ethyl acetate (8:1) to give the mesylate **5** (11.2 g, 80 %): $[\alpha]_{\text{D}} + 20.6^\circ$ (c 1.3, chloroform); ^1H NMR (CDCl_3) δ 1.09 (t, 6H, $\text{CH}_3\text{CH}_2\text{S}$), 1.10, 1.15 (2s, 6H,

(CH₃)₂), 1.5-2.2 (m, 2H, H-2,2'), 2.4-2.7 (m, 4H, SCH₂CH₃), 3.06 (s, 3H, CH₃SO₂), 3.5-4.45 (m, 4H, H-1,4,5,5'), 4.90 (dt, 1H, H-3).

A solution of the 3-mesylate (5) (5.0 g, 13.96 mmol) and sodium azide (6.0 g, 92.3 mmol) in dimethylformamide (50 mL) was stirred at 100 °C for 12 h. It was then diluted with water and extracted with chloroform. The chloroform layer was washed with water, dried, concentrated and the residue subjected to column chromatography on silica gel with light petroleum-ethyl acetate (9:1) as eluent to give the azide 6 (3.3 g, 80 %): [α]_D -18.4° (c, 1.1, chloroform); ¹H NMR (CDCl₃) δ 1.15 (t, 6H, CH₃CH₂S), 1.22, 1.30 (2s, 6H, (CH₃)₂), 1.5-2.0 (m, 2H, H-2,2'), 2.3-2.8 (q, 4H, SCH₂CH₃), 3.4-4.65 (m, 5H, H-1,3,4,5,5').

Anal. Calcd for C₁₂H₂₃N₃O₂S₂ : C, 47.2; H, 7.5 Found : C, 47.6; H, 7.5.

Methyl 5-O-acetyl-3-azido-2,3-dideoxy-α/β-D-ribofuranoside (8). The azide 6 (3.0 g, 9.83 mmol), yellow mercuric oxide (12.0 g, 55.4 mmol) and mercuric chloride (12.0 g, 25.42 mmol) in methanol (50 mL) were stirred vigorously at room temperature for 2 h, filtered through Celite, and the solid residue was washed with methanol. The combined filtrates were concentrated and dissolved in chloroform. The chloroform layer was successively washed with 1N potassium iodide solution, water, dried and concentrated to give compound 7 (1.4 g, 60 %), IR: 2100 cm⁻¹ (N₃); MS:m/z 214 (M⁺-OMe).

To the crude product 7 (1.4 g, 5.7 mmol) in methanol (10 mL) was added 0.8 % sulfuric acid (8 mL) and the reaction mixture heated under reflux for 4 h. It was neutralised with barium carbonate, filtered through Celite and concentrated. The resulting product was treated with pyridine (3 mL) and acetic anhydride (1.5 mL) for 3 h. The reaction mixture was diluted with water and extracted with chloroform. The chloroform layer was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate solution, and water, dried and concentrated. The residue was chromatographed on a column of silica gel using light petroleum-ethyl acetate (6:1) as eluent to afford compound 8 (430 mg, 70 %), (α:β=12:88): [α]_D + 83.3° (c 2.0, chloroform); ¹H NMR (β-isomer) (CDCl₃) δ 2.1 (s, 3H, Ac), 2.3-2.7 (m, 2H, H-2,2'), 3.38 (s, 3H, OMe), 3.5-4.3 (m, 4H, H-3,4,5,5'), 5.1 (dd, 1H, J_{1,2a} = 1.5 & J_{1,2b} = 5.5 Hz, H-1), IR (neat): 1740(C=O) 2110(N₃) cm⁻¹, MS:m/z 184 (M⁺).

Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.6; H, 6.0. Found : C, 44.3; H, 6.0.

1,5-Di-O-acetyl-3-azido-2,3-dideoxy-D-ribofuranose (9). A solution of **8** (430 mg, 2 mmol) in 50 % aqueous acetic acid (5 mL) was heated on a water bath for 5 h, concentrated to dryness and then codistilled with toluene. The crude residue was treated with pyridine (2 mL) and acetic anhydride (1 mL) for 3 h. After the usual work up, the product was chromatographed on silica gel using light petroleum-ethyl acetate (6:1) to give **9** (340 mg, 70 %): $[\alpha]_D - 58.9^\circ$ (c 0.9, chloroform); 1H NMR ($CDCl_3$) δ 2.0 (4s, 6H, 2xAc), 6.2 (bs, 1H, H-1).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.4; H, 5.3. Found : C, 44.1; H, 5.2.

In an another procedure, compound **7** (200 mg) was stirred with 0.01 N trifluoroacetic acid (15 mL) at 0 °C for 24 h. The reaction mixture was concentrated under vacuum and then codistilled with toluene. The residue was acetylated with pyridine (2 mL) and acetic anhydride (1 mL). The diacetate (**9**) was purified by column chromatography on silica gel to give pure **9** (225 mg, 75 %).

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