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Preparation of 2,2′-anhydronucleosides: regio- and stereoselective modifications of the base and sugar moieties

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Abstract

2′-Deoxy-2′-iodonucleosides **4**–**9**, obtained from suitably protected furanoid glycals **1** and **2** with different silylated pyrimidine bases, were transformed into the corresponding 2,2′-anhydronucleosides **10**–**15** with inversion of the configuration at C-2′, by heating in DMF with *n*-dibutyltin oxide. Regio- and stereospecific opening at C-2′ of the 2,2′-ring in compounds **10**, **11**, and **12** with sodium azide afforded the related 2′-azido-2′-deoxynucleosides **16**, **17** and **18**, respectively. Action of sodium hydroxide on **12** caused the regioselective opening of the above-mentioned ring at C-2 with retention of the configuration at C-2′ giving **19**. Compound **19** could be transformed straightforwardly into **18** by well-established methodology. On the other hand, compound **15** could be transformed into the related 2′,3′-anhydronucleoside **23** by a regio- and stereoselective addition at N-3–C-2′ of allyl bromide concomitant with 2,2′-ring opening and inversion of the configuration at C-2′ to afford the intermediate 2′-bromo-2′-deoxynucleoside **21**, which was subsequently treated with sodium methoxide giving **23**.

1. Introduction

Much attention has recently been paid to 2,2′- and 2,3′-anhydronucleosides due to the possibility shown by these compounds of being transformed by attack from a great variety of nucleophiles at the C-2′ or C-3′ positions to afford compounds with anti-AIDS activity.[1]

Methods for the transformation of nucleosides into tricyclic 2,2′-anhydro analogues have been reported since 1958, when Fox[2] treated 1-(3′,5′-*O*-isopropylidene-2′-*O*-methanesulfonyl-β-D-xylofuranosyl)thymine with sodium hydroxide in refluxing aqueous ethanol to afford the related 2,2′-anhydro nucleoside. Lately, Watanabe,[1d] Rama Rao,[1f] Chen,[1g] Tolstikov,[3] Mustafin,[4] and Hrebabecky[5] used the action of a base (sodium hydrogen carbonate/DMF, sodium benzoate or DBU) on the appropriated 2′-*O*-phenyloxycarbonyl or 2′-*O*-methanesulfonyl derivative of a nucleoside, respectively, in order to promote anhydrization, whereas Chattopadhyaya[1h] treated a

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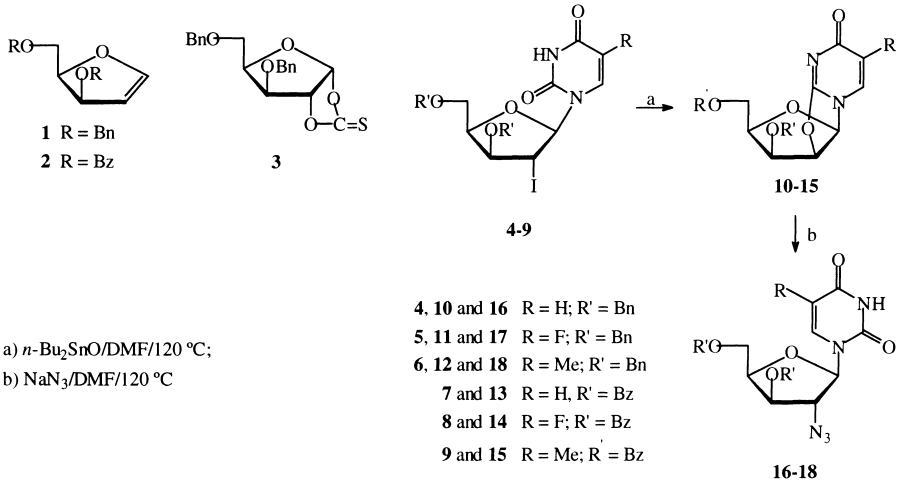
partially protected nucleoside with bis-(imidazol-1-yl)thiocarbonyl in refluxing toluene. We report herein a new and mild method for the preparation, in high yield, of 2,2′-anhydronucleosides based on the easy access, from furanoid glycals,[6] of 2′-deoxy-2′-iodonucleoside with a *trans* disposition of substituents at C-1′,2′ and the subsequent elimination of hydrogen iodide by *n*-dibutyltin oxide.

2. Results and discussion

As has been already stated, the starting nucleosides **6–9** for the present work were readily synthesized[7] from furanoid glycals **1** and **2** (see Scheme 1). Thus, compound **1** was prepared from **3** after heating with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, whereas **2** was synthesized from 3,5-di-*O*-benzoyl-D-xylose by reaction with I_2/Ph_3P/imidazole in dichloromethane. Both glycals **1** and **2** had to be used at once, since they decomposed on standing. For the purposes of this work nucleosides **4** and **5** are described for the first time.

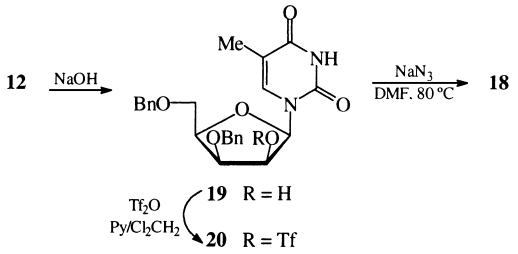


Scheme 1.

In a previous experiment of reductive dehalogenation of nucleoside **9** with *n*-tributyltin hydride partial formation of 2,2′-anhydronucleoside **15** was observed. Similar results were achieved by Chen[8] when 5′-*O*-benzoyl-2′-bromo-2′-deoxy-3′-*O*-methanesulfonylthymidine reacted with the mentioned hydride giving a mixture of the normal dehalogenation product, together with the 2,3′-anhydro-2′-deoxy nucleoside as a minor component. These results could be explained as a consequence of the presence of some oxidation product from the *n*-tributyltin hydride. Thus, we treated nucleoside **9** with *n*-dibutyltin oxide and the corresponding **15** was isolated in high yield by a clean reaction. In order to see the scope of this procedure, compounds **4–8** were prepared and treated in the same way giving the expected 2,2′-anhydronucleosides **10–14**, indicating its efficiency.

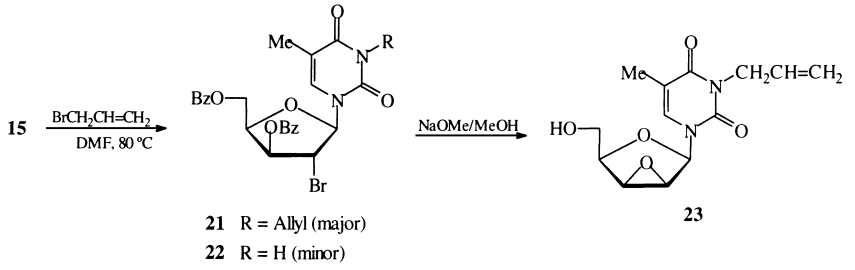
Attempts at opening the 2,2′-anhydro ring of the above compounds with sodium azide[9] as the nucleophile, clearly indicated the important role played by the protecting groups on the sugar moiety on the course and result of the reaction. Thus, when benzoyloxyl groups were present on the sugar moiety **13**–**15**, complex reaction mixtures resulted and the expected products were formed in low yield; however, in the case of the *O*-benzyl derivatives **10**–**12**, the 2′-azido-2′-deoxy derivatives **16**–**18** were isolated in moderate yield (33–55%).

In order to improve the yields of the $I^- \rightarrow N_3^-$ interchange and using **12** as a model, a new strategy was envisaged (see Scheme 2), consisting of the regioselective opening at C-2 by sodium hydroxide[1e] to afford the D-*lyxo* nucleoside **19** which was transformed into the intermediate 2′-*O*-triflate derivative **20** which, on subsequent treatment with sodium azide in DMF, gave **18** in a 73% yield.



Scheme 2.

On the other hand, compound **15** was chosen as a model to be subjected to a series of transformations leading to the related 2′,3′-anhydro analogues, due to the interest shown for this kind of structure in nucleoside chemistry. With this aim, compound **15** was allowed to react with an excess of allyl bromide (see Scheme 3) and two new products were isolated and identified as 3-allyl- (**21**, major) and 1-(3′,5′-di-*O*-benzoyl-2′-bromo-2′-deoxy-β-D-xylofuranosyl)thymine (**22**, minor), the former as the result of the addition, in a highly regioselective manner, of bromide and the allyl group at the C-2′ and N-3 positions, respectively.



Scheme 3.

Similar ring opening reactions, although on 2,3′-anhydronucleosides, have been previously reported by other authors.[10] Finally, treatment of **21** with sodium methoxide in methanol unequivocally led to 3-allyl-1-(2′,3′-anhydro-β-D-lyxofuranosyl)thymine **23**, since the presence of the allyl group at N-3 avoided the formation of the 2,2′-anhydro nucleoside.

3. Experimental

3.1. General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with 5% conc. H_2SO_4 in ethanol. Column chromatography was performed on silica gel (Merck, 7734).

3.2. 1-(3′,5′-Di-O-benzyl-2′-deoxy-2′-iodo-β-D-xylofuranosyl)uracil **4** or its 5-fluoro derivative **5**

To a stirred solution of glycal **1**[6] (2 mmol) in dry dichloromethane (15 mL) was added *N*-iodosuccinimide (2 mmol) and the appropriate silylated base (2.5 mmol) in the same solvent, and the mixture was kept at room temperature for 2 h, when TLC (ether) revealed the absence of **2** and the presence of a compound of lower mobility. The solvent was removed and the residue supported on silica gel and chromatographed (ether:hexane = 3:→ ether) to afford the corresponding 2′-deoxy-2′-iodonucleoside derivatives **4** and **5**.

Compound **4**: (1.05 g, quantitative), m.p. 113–114°C, $[\alpha]_D^{22}$: +21.5 (*c* 1); ν_{max}^{KBr} 1705, 1679, 1663, and 1267 cm^{-1}. NMR data: ^1H, 9.67 (bs, 1H, H-3), 7.51 (d, 1H, $J_{5,6}$ = 7.2 Hz, H-6), 7.34–7.30 and 7.18–7.12 (2 m, 10H, aromatic), 6.31 (d, 1H, $J_{1',2'}$ = 1.9 Hz, H-1′), 5.52 (d, 1H, H-5), 4.77 (dt, 1H, $J_{4',5'}$ = 5.5, $J_{3',4'}$ = 3.6 Hz, H-4′), 4.61 and 4.55 (2d, 2H, J = 11.9 Hz, PhCH_2), 4.53 and 4.44 (2d, 2H, J = 11.6 Hz, PhCH_2), 4.28–4.25 (m, 2H, H-2′,3′), and 3.82 (d, 2H, H-5′,5′); ^{13}C, 163.7 (C-4), 150.4 (C-2), 139.7 (C-6), 137.5, 136.4, 128.8, 128.6, 128.1, and 127.9 (*Ph*CH_2), 101.5 (C-5), 93.9 (C-1′), 84.6 and 81.4 (C-3′,4′), 73.7 and 72.6 (Ph*C*H_2), 67.7 (C-5′), and 24.9 (C-2′). Anal. calcd for $C_{23}H_{23}IN_2O_5$: C, 51.69; H, 4.34; N, 5.24. Found: C, 51.73; H, 4.53; N, 5.37.

Compound **5**: (995 mg, 90%), m.p. 154–155°C, $[\alpha]_D^{22}$: +21.8 (*c* 1); ν_{max}^{KBr} 1718, 1706, and 1646 cm^{-1}. NMR data: ^1H, 9.51 (bs, 1H, H-3), 7.66 (d, 1H, $J_{6,F}$ = 6.4 Hz, H-6), 7.35–7.28 and 7.16–7.12 (2 m, 10H, aromatic), 6.32 (t, 1H, $J_{1',2'} = J_{1',F}$ = 1.7, H-1′), 4.75 (dt, 1H, $J_{4',5'}$ = 5.4, $J_{3',4'}$ = 3.5 Hz, H-4′), 4.63 and 4.57 (2d, 2H, J = 11.9 Hz, PhCH_2), 4.55 and 4.49 (2d, 2H, J = 11.6 Hz, PhCH_2), 4.27 (t, 1H, $J_{2',3'}$ = 1.6 Hz, H-2′), 4.26 (bd, 1H, H-3′), and 3.83 (d, 2H, H-5′,5′); ^{13}C, 157.0 (d, $J_{4,F}$ = 28.5 Hz, C-4), 148.8 (C-2), 140.0 (d, $J_{5,F}$ = 235 Hz, C-5), 137.4, 136.3, 128.9, 128.6, 128.1, and 128.0 (*Ph*CH_2), 124.2 (d, $J_{6,F}$ = 37.1 Hz, C-6), 93.9 (C-1′), 84.5 and 81.5 (C-3′,4′), 73.6 and 72.8 (Ph*C*H_2), 67.7 (C-5′), and 29.5 (C-2′). Anal. calcd for $C_{23}H_{22}FIN_2O_5$: C, 50.01; H, 4.01; N, 5.07. Found: C, 49.69; H, 4.17; N, 5.20.

3.3. Reaction of **4–9** with n-dibutyltin oxide. Preparation of 2,2′-anhydronucleosides **10–15**

To a well stirred solution of **4–9** (1 mmol) in DMF (5 mL), *n*-dibutyltin oxide (249 mg, 1 mmol) was added and the mixture was heated at 120°C for 3 h. TLC (ether:acetone = 3:2) then revealed the presence of a product of much lower mobility. The reaction mixture was concentrated and the residue dissolved in dichloromethane (20 mL) and the solution was washed with a slightly

alkaline water solution (10 mL), and water (10 mL). Concentration of the solvent gave a residue that was supported on silica gel and chromatographed (ether:acetone = 3.1) to yield the corresponding 2,2′-anhydro derivative **10**–**15**.

Compound **10**: (317 mg, 78%), m.p. 163–164°C, $[\alpha]_D^{27}$: –84.3 (*c* 1); ν_{max}^{KBr} 1666, 1646, 1549, and 1478 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{23}H_{22}N_2O_5$: C, 67.96; H, 5.45; N, 6.89. Found: C, 67.68; H, 5.48; N, 6.90.

Table 1
^{1}H NMR data for compounds **10**–**18**

Compound	*^{1}H-Chemical shifts (δ), with multiplicities and coupling constants (Hz)*								
	H-3	H-5	H-6	H-1'	H-2'	H-3'	H-4'	H-5'a	H-5'b
10	--	6.00d	7.36d	6.08d	5.33t	4.36dd	4.31q	3.53dd	3.34dd
11[a]	--	--	8.33d	6.18d	5.58t	4.49m	4.49m	3.48dd	3.17dd
12[b]	--	--	7.78s	6.17d	5.50t	4.43m	4.43m	3.50dd	3.15dd
13	--	6.06d	7.42d	6.31d	5.69t	5.78t	4.85dt	4.48dd	4.37dd
14	--	--	7.49d	6.39d	5.75t	5.81t	4.87q	4.47bs	4.46bs
15[b]	--	--	7.28s	6.25d	5.66t	5.80t	4.87q	4.53dd	4.38dd
16	9.22bs	5.55dd	7.55d	5.88d	4.13t	3.93dd	4.38q	3.82dd	3.78dd
17	8.96d	--	7.71d	5.86t	4.13t	3.97dd	4.36q	3.82dd	3.78dd
18[b]	9.15bs	--	7.37s	5.94d	4.17t	3.97dd	4.37q	3.84dd	3.79dd

	$J_{5,6}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{6,F}$
10	7.5	6.0	6.0	6.3	3.6	6.1	10.9	--
11	--	5.8	5.4	--	2.5	5.8	11.1	4.7
12	--	5.8	5.3	--	2.9	6.4	11.1	--
13	7.5	5.6	5.8	6.0	5.1	8.6	12.2	--
14	--	5.6	5.8	5.9	6.0	6.1	--	3.3
15	--	5.7	5.9	6.2	5.3	7.5	12.1	--
16	8.2	2.0	2.0	3.9	5.1	5.8	12.0	--
17[c]	--	1.6	2.1	4.0	5.1	5.5	10.3	6.3
18	--	2.3	2.1	4.0	5.1	5.6	10.7	--

[a]Recorded in DMSO-d_6; [b]Tymine methyl group for **12**, **15**, and **18** at δ 1.79, 1.95, and 1.69, repectively; [c]$J_{1',F}$ and $J_{3,F}$ 1.6 and 4.0 Hz, respectively.

Table 2
^{13}C NMR data for compounds **10**–**18**

Compound	C-2	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	Me
10	160.5	172.0	110.5	134.6	89.1	80.9*	76.8	80.3*	67.5	--
11	157.8	163.3d	145.2d	121.3d	89.5	81.1*	76.8	79.5*	67.5	--
12	160.1	172.5	119.0	130.3	89.3	80.8*	76.8	80.2*	67.8	14.1
13	160.1	171.8	110.4	135.2	89.3	80.4	71.4	80.4	62.2	--
14	157.6	164.3d	146.3d	119.7d	90.0	81.5*	71.4	78.4*	62.0	--
15	159.7	172.2	119.3	130.4	89.4	80.0*	71.4	78.1*	62.0	14.0
16	150.3	163.3	101.7	139.9	89.1	68.5	80.4*	81.8*	67.2	--
17	148.7	156.7d	140.1d	124.4d	89.0	68.5	80.3*	81.8*	67.2	--
18	150.4	163.9	110.4	135.6	88.5	68.5	80.7*	81.4*	67.3	12.4

*Interchangeable assignments.

Compound **11**: (301 mg, 71%), m.p. 155–156°C, $[\alpha]_D^{27}$: –76.5 (*c* 1); ν_{max}^{KBr} 1661, 1577, and 1495 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{23}H_{21}FN_2O_5$: C, 65.08; H, 4.98; N, 6.60. Found: C, 64.74; H, 5.05; N, 6.72.

Compound **12**: (315 mg, 75%), m.p. 160–161°C, $[\alpha]_D^{27}$: –97.3 (*c* 1); ν_{max}^{KBr} 1671, 1638, 1635, 1565, and 1491 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{24}H_{24}N_2O_5$: C, 68.55; H, 5.75; N, 6.66. Found: C, 68.28; H, 5.86; N, 6.81.

Compound **13**: (348 mg, 80%), m.p. 85–86°C, $[\alpha]_D^{22}$: –6 (*c* 1); ν_{max}^{KBr} 1728, 1660, 1647, and 1542 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{23}H_{18}N_2O_7$: C, 63.58; H, 4.17; N, 6.45. Found: C, 63.35; H, 4.23; N, 6.38.

Compound **14**: (407 mg, 90%), m.p. 104–105°C, $[\alpha]_{405}^{27}$: +46.8 (*c* 1); ν_{max}^{KBr} 1733, 1725, 1662, 1650, and 1576 cm^{-1}. NMR data: see Tables 1 and 2, which were in accordance with those found in the literature.[3] Anal. calcd for $C_{23}H_{17}FN_2O_7$: C, 61.06; H, 3.78; N, 6.12. Found: C, 60.78; H, 3.87; N, 6.16.

Compound **15**: (372 mg, 83%), m.p. 90–91°C, $[\alpha]_D^{27}$: –33 (*c* 1); ν_{max}^{KBr} 1729, 1646, 1565, and 1482 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{24}H_{20}N_2O_7$: C, 64.27; H, 4.49; N, 6.24. Found: C, 64.05; H, 4.45; N, 6.35.

*3.4. Preparation of 1-(2′-azido-3′,5′-di-*O*-benzyl-2′-deoxy-β-D-xylofuranosyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidines **16**–**18***

To a stirred solution of nucleosides **10**–**12** (1 mmol) in dry DMF (5 mL) was added sodium azide (65 mg, 1 mmol) and the mixture was heated at 120°C for 48 h. TLC (ether:acetone = 3:2) then showed the presence of a faster-running product. The mixture was concentrated and the

reaction crude partitioned into toluene–water, the organic phase was separated, concentrated and the residue supported on silica gel and chromatographed (ether) to give the corresponding 2′-azido-2′-deoxy derivatives **16**–**18**.

Compound **16**: (128 mg, 55%), m.p. 86–87°C, $[\alpha]_D^{22}$: –8.3 (*c* 1.3); ν_{max}^{KBr} 2113 (N_3), 1696, and 1455 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{23}H_{23}N_5O_5$: C, 61.46; H, 5.16; N, 15.58. Found: C, 61.22; H, 5.35; N, 15.29.

Compound **17**: (77 mg, 33%), m.p. 51–52°C, $[\alpha]_D^{24}$: +7.5 (*c* 1); ν_{max}^{KBr} 2113 (N_3), 1714, and 1456 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{23}H_{22}FN_5O_5$: C, 59.09; H, 4.74; N, 14.98. Found: C, 59.31; H, 5.05; N, 15.06.

Compound **18**: (110 mg, 47%), m.p. 94–95°C, $[\alpha]_D^{22}$: –22 (*c* 1); ν_{max}^{KBr} 2110 (N_3), 1700, and 1684 cm^{-1}. NMR data: see Tables 1 and 2. Anal. calcd for $C_{24}H_{25}N_5O_5$: C, 62.19; H, 5.44; N, 15.11. Found: C, 62.43; H, 5.25; N, 15.20.

3.5. *Preparation of 1-(3′,5′-di-*O*-benzyl-β-D-lyxofuranosyl)thymine* **19**

To a warmed solution of **12** (460 mg, 1.1 mmol) in acetonitrile (20 mL) was added 1N aqueous sodium hydroxide solution (1 mL) and the mixture kept at room temperature for 2 h. TLC (ether:acetone = 3:1) then showed the presence of a faster-running product. The reaction mixture was neutralized with Amberlite-IR 120 (H^+, form), the solvent removed and the crude percolated (ether:acetone = 3:1) through a short silica gel column to yield **19** (460 mg, 95%) as a colourless thick syrup, $[\alpha]_D^{27}$: +25 (*c* 0.8); ν_{max}^{film} 1720, 1711, 1455, and 1280 cm^{-1}. NMR data: ^1H, 9.31 (bs, 1H, H-3), 7.49 (s, 1H, H-6), 7.30 (m, 10H, aromatic), 6.04 (d, 1H, $J_{1',2'} = 3.5$ Hz, H-1′), 4.64 (2 d, 2H, J = 11.2 Hz, PhCH_2), 4.60 (s, 2H, PhCH_2), 4.39 (t, 1H, $J_{2',3'} = J_{3',4'} = 3.9$ Hz, H-3′), 4.35–4.28 (m, 2H, H-2′,4′), 3.83 (dd, 1H, $J_{4',5'a} = 3.4$, $J_{5'a,5'b} = 10.5$ Hz, H-5′a), and 3.71 (dd, 1H, $J_{4',5'b} = 2.7$ Hz, H-5′b); ^{13}C, 164.2 (C-4), 150.8 (C-2), 137.8 (C-6), 137.2, 136.7, 128.7, 128.6, 128.3, 128.2, 128.0, and 127.9 (*Ph*CH_2), 109.0 (C-5), 85.2 (C-1′), 78.0 and 77.2 (C-3′,4′), 73.9 and 72.9 (Ph*C*H_2), 69.2 (C-2′), 68.0 (C-5′), and 12.5 (Me). Mass spectrum (LSIMS): *m*/*z* 461.16895 (M^++Na). For $C_{24}H_{26}N_2O_6Na$ 461.16886 (deviation –0.2 ppm).

3.6. *Preparation of 1-(2′-azido-3′,5′-di-*O*-benzyl-2′-deoxy-β-D-xylofuranosyl)thymine* **18**

To an ice–water cooled and stirred solution of **19** (246 mg, 0.56 mmol) in dry dichloromethane:pyridine = 1:1 (10 mL) was added dropwise a solution of trifluoromethanesulfonyl anhydride (130 μmol) in dry dichloromethane (2 mL). The mixture was then allowed to reach room temperature and kept for 30 min when TLC (ether) revealed the presence of a faster-running product. The reaction mixture was diluted with dichloromethane (20 mL) and washed with 3N aqueous hydrochloric acid, water, aqueous 10% sodium hydrogencarbonate, and water. Concentration of the solvent gave a residue, presumably the 2′-*O*-trifluromethanesulfonyl derivative **20**, that was used in the next step without further purification.

Compound **20** was taken-up in dry DMF (5 mL) and treated with sodium azide (56 mg, 0.86 mmol) at 120°C with stirring overnight. The solvent was removed and the residue partitioned in dichloromethane–water, the organic phase was separated, concentrated and the residue supported on silica gel and chromatographed (ether:hexane = 1:1) to afford the title compound (**18**, 190 mg, 73%).

3.7. Reaction of **15** with allyl bromide. Preparation of 3-allyl- (**21**) and 1-(3′,5′-di-O-benzoyl-2′-bromo-2′-deoxy-β-D-xylofuranosyl)thymine **22**

A solution of **15** (400 mg, 0.9 mmol) in dry DMF (5 mL) was treated with allyl bromide (500 μL, 5.8 mmol) and heated in a sealed tube at 80°C overnight. TLC (ether) then revealed two new faster-running products. Concentration of the solvent, followed by column chromatography (ether:hexane = 1:1) of the residue afforded first crystalline **21** (380 mg, 74%), m.p. 58–59°C (from ether–hexane), $[\alpha]_D^{27}$: +90 (*c* 1); ν_{max}^{KBr} 1730, 1700, 1656, and 1259 cm^{-1}. NMR data: ^1H, (inter alia) 6.29 (d, 1H, $J_{1',2'} = 1.5$ Hz, H-1′), 5.82 (m, 1H, =CH), 5.77 (dd, 1H, $J_{2',3'} = 1.3$, $J_{3',4'} = 3.3$ Hz, H-3′), 5.18–5.09 (m, 3H, H-4′ and C=CH_2), 4.88 (dd, 1H, $J_{4',5'a} = 6.9$, $J_{5'a,5'b} = 12.1$ Hz, H-5′a), 4.67 (dd, 1H, $J_{4',5'b} = 4.3$ Hz, H-5′b), 4.49 (m, 2H, N-CH_2), 4.41 (t, 1H, H-2′), and 1.86 (d, 3H, $J_{6,Me} = 1.1$ Hz, Me); ^{13}C, 166.2 and 164.6 (2 Ph*C*O), 162.8 (C-4), 150.6 (C-2), 134.4, 133.6, 129.8, 129.7, 129.2, 128.9, 128.6, and 128.1 (*Ph*CO), 132.5 (C-6), 131.4 (=CH), 118.1 (=CH_2), 110.0 (C-5), 93.1 (C-1′), 79.7 (C-4′), 77.7 (C-3′), 61.5 (C-5′), 50.7 (C-2′), 43.3 (N-CH_2), and 13.3 (Me). Anal. calcd for $C_{27}H_{25}BrN_2O_7$: C, 56.94; H, 4.42; N, 4.92. Found: C, 56.78; H, 4.61; N, 4.66.

Eluted second was crystalline **22** (21 mg, 25%), m.p. 176–177°C (from ether–hexane), $[\alpha]_D^{27}$: +76.2 (*c* 1); ν_{max}^{KBr} 1717, 1684, and 1279 cm^{-1}. NMR data: ^1H, (inter alia) 8.83 (s, 1H, H-3), 6.31 (d, 1H, $J_{1',2'} = 1.9$ Hz, H-1′), 5.78 (dd, 1H, $J_{2',3'} = 2.4$, $J_{3',4'} = 3.5$ Hz, H-3′), 5.10 (dt, 1H, H-4′), 4.87 (dd, 1H, $J_{4',5'a} = 6.9$, $J_{5'a,5'b} = 12.1$ Hz, H-5′a), 4.69 (dd, 1H, $J_{4',5'b} = 4.3$ Hz, H-5′b), 4.42 (t, 1H, H-2′), and 1.83 (d, 3H, $J_{6,Me} = 1.2$ Hz, Me); ^{13}C, 166.2 and 164.7 (2 Ph*C*O), 163.5 (C-4), 150.1 (C-2), 134.5 (C-6), 134.4, 133.6, 129.8, 129.7, 129.2, 128.9, 128.6, and 128.1 (*Ph*CO), 110.9 (C-5), 92.4 (C-1′), 79.6 (C-4′), 77.8 (C-3′), 61.5 (C-5′), 50.4 (C-2′), and 12.5 (Me). Anal. calcd for $C_{24}H_{21}BrN_2O_7$: C, 54.45; H, 4.00; N, 5.29. Found: C, 54.23; H, 3.85; N, 5.10.

3.8. Treatment of **21** with sodium methoxide

To a solution of **21** (210 mg, 0.37 mmol) in dry methanol (5 mL) was added 0.5N sodium methoxide solution (1 mL) and the mixture was kept at room temperature for 5 h. TLC (ether) showed the presence of a slower-running product. The reaction mixture was neutralized with acetic acid, concentrated and the residue subjected to column chromatography (ether) to give **23** (91 mg, 88%) as a colourless syrup, $[\alpha]_D^{27}$: +23 (*c* 0.7); ν_{max}^{film} 3451, 1701, 1477, and 1114 cm^{-1}. NMR data: ^1H, 7.42 (s, 1H, H-6), 6.21 (s, 1H, H-1′), 5.86 (m, 1H, =CH), 5.28–5.15 (4m, 2H, =CH_2), 4.55 and 4.53 (2s, 2H, H-2′,3′), 4.14 (t, 1H, $J_{4',5'} = 5.6$ Hz, H-4′), 3.98–3.87 (m, 4H, N-CH_2,H-5′,5′), 2.05 (bs, 1H, OH), and 1.93 (s, 3H, Me); ^{13}C, 163.1 (C-4), 151.0 (C-2), 134.8 (C-5), 131.6 (=CH), 118.1 (=CH_2), 110.5 (C-6), 82.0 (C-1′), 77.5 (C-4′), 61.4 (C-5′), 55.8 and 55.4 (C-2′,3′), 43.5 (N-CH_2), and 13.4 (Me). Mass spectrum (LSIMS): *m*/*z* 303.09541 (M^++Na). For $C_{13}H_{16}N_2O_5Na$ 303.09569 (deviation 0.9 ppm).

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