An Efficient Route to Pyrimidine Nucleosides with the 2,3-Anhydro-β-D-lyxofuranosyl Stereochemistry

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Dedicated to the memory of Raymond U. Lemieux.

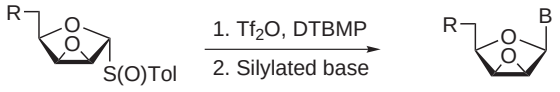
Abstract: Described is the efficient preparation of 2,3-anhydro-β-D-lyxofuranosyl pyrimidine nucleosides via the coupling of a 2,3-anhydrosugar-containing glycosyl donor (**5** or **6**) with a silylated nucleoside base. The products are obtained with a high degree of stereoselectivity and in 65–77% yield.

Key words: epoxides, glycosylations, carbohydrates, nucleosides, anhydrosugars

2,3-Anhydro-β-D-lyxofuranosyl nucleosides (e.g., **1**–**4**, Figure 1) are important intermediates in the synthesis of nucleoside derivatives, through further modification of the epoxide ring.[1] These compounds are particularly useful for the preparation of β-arabinofuranosyl nucleotides as nucleophilic opening of the epoxide generally proceeds by regioselective attack of the nucleophile at C–3 of the furanose ring.[1,2] In addition, some of these compounds have been shown to be weak antiviral agents.[3]

To date, the methods described in the literature for the preparation of 2,3-anhydronucleosides all involve the installation of the epoxide ring on a preformed nucleoside.[1,2,4] Thus, the synthesis of derivatives possessing non-natural bases requires first the synthesis of the parent nucleoside followed by further reactions to form the oxirane ring. More convergent routes to this class of compounds are desirable.

We describe here an efficient route for the synthesis of pyrimidine nucleosides possessing the 2,3-anhydro-β-D-lyxofuranosyl stereochemistry. As outlined in Scheme 1, the products are formed with a high degree of stereoselectivity in a single step upon glycosylation of a silylated pyrimidine base with a glycosyl sulfoxide[5] in which the epoxide moiety is already in place (**5** or **6**, Figure 1).



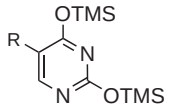
5, R = OBz
6, R = N_3

12–**15**,**19**, R = OBz
16–**18**, R = N_3

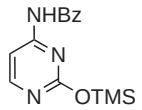
Scheme 1 Approach to 2,3-anhydro-β-D-lyxofuranosyl pyrimidine nucleosides.

1, R = H
2, R = CH_3
3, R = F
4, R = I

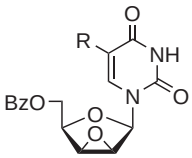
5, R = OBz
6, R = N_3



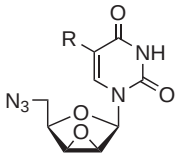
7, R = H
8, R = CH_3
9, R = F
10, R = I



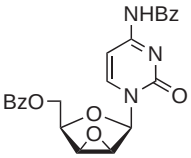
11



12, R = H
13, R = CH_3
14, R = F
15, R = I



16, R = H
17, R = CH_3
18, R = F



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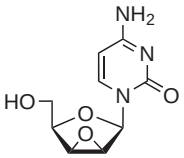

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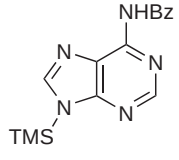

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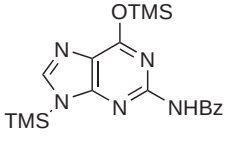

22

Figure 1 Structures of nucleosides, persilylated nucleoside bases and glycosyl donors.

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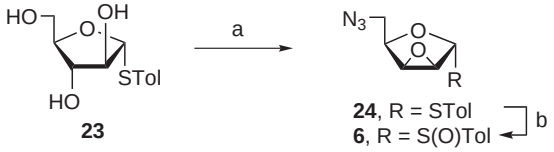
Art Id.1437-2096,E;2003,0,09,1271,1274,ftx,en;S03403ST.pdf.

The targets chosen for synthesis were nucleosides **12**–**19** (Figure 1). The donor used for the synthesis of **12**–**15** and **19**, glycosyl sulfoxide **5**, was prepared as previously described.[6] The 5′-azido nucleosides **16**–**18** were obtained starting with sulfoxide **6**, which was easily synthesized as outlined in Scheme 2 from the known thioglycoside **23**.[7] Thus, treatment[6] of **23** with diphenylphosporyl azide, triphenylphosphine, and diisopropylazodicarboxylate afforded an 82% yield of azido epoxy thioglycoside **24**.[8] Subsequent oxidation of **24** with MCPBA[6] provided **6**[9] in 83% yield as a single sulfoxide stereoisomer; however, the stereochemistry at sulfur was not established.



Scheme 2 Synthesis of **6**. (a) $(PhO)_2P(O)N_3$ (1.2 equiv), Ph_3P (2.5 equiv), diisopropylazodicarboxylate (2.5 equiv), THF, 0 ºC → r.t., 82%. (b) MCPBA (1.1 equiv), CH_2Cl_2, –78 ºC → r.t., 83%.

With donors **5** and **6** in hand, their use in the synthesis of nucleosides was explored. The activation protocol used for these glycosylations involved[10] first treating the sulfoxide donor with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine at –78 °C, followed a few minutes later by the addition of the persilylated nucleoside base (**7**–**11**).[11] As detailed in Table 1, for a variety of pyrimidine bases the yields of these glycosylations were uniformly good, ranging between 65% and 77% and a single nucleoside product was isolated following chromatography.

Data obtained for these products was consistent with their proposed structures as 2,3-anhydro-β-D-lyxofuranosyl nucleosides.[12] Confirmation of the structures of benzoates **12**–**15**, and **19** was obtained by removal of the benzoate ester with sodium methoxide to provide known nucleosides **1**–**4**, and **20**.[13] In addition, we were successful in obtaining an X-ray crystal structure of **14** (Figure 2),[14] which clearly demonstrates the *cis* relationship between the nucleoside and the epoxide ring. For the 5′-azido derivative **16**, the NMR spectra obtained were identical to those previously reported.[15] For compounds **17** and **18** we propose the anomeric stereochemistry is also β, given not only the high fidelity of the glycosylation method,[6,16] but also the close similarities in the NMR spectra of **17** and **18**, with those measured on **16**.

In a previous investigation,[17] we demonstrated that the unambiguous determination of anomeric stereochemistry in 2,3-anhydrosugar glycosides can be most straightforwardly and reliably done through measurement of the $^1J_{C1\text{-}H1}$. In glycosides in which the anomeric hydrogen is *trans* to the epoxide moiety, $^1J_{C1-H1}$ = 163−168 Hz, and when this hydrogen is *cis* to the oxirane ring, $^1J_{C1-H1}$ = 171−174 Hz. Other parameters generally used for assigning anomeric configuration in furanosides[18] ($^3J_{H1\text{-}H2}$ or the chemical shift of C-1) are not diagnostic in 2,3-anhydrofuranose rings. In an effort to assign the stereochemistry in the nucleosides produced by this method, we therefore measured the $^1J_{C1\text{-}H1}$ magnitudes in these compounds. Unfortunately, as could be expected[19] given the substantial differences in electronegativity between the nucleoside bases and the oxygen-containing aglycones studied in our previous investigation, the magnitudes of these $^1J_{C1\text{-}H1}$ values did not fall within the ranges previously established by us. We could not, therefore, use this coupling constant to unequivocally assign the anomeric stereochemistry in **12**–**19**. However, we note that the measured $^1J_{C1\text{-}H1}$ values are all very similar (see Table 1) and therefore these data support our earlier proposed assignment of the anomeric stereochemistry in **17** and **18** as β.

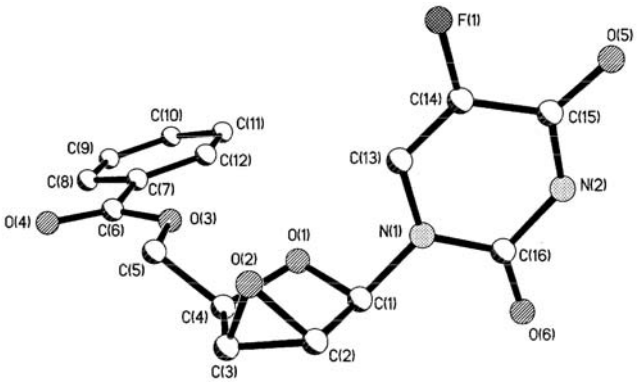


Figure 2 X-ray crystal structure of **14**.

Table 1 Synthesis of 2,3-Anhydro-β-D-lyxofuranosyl Pyrimidine Nucleosides from **5** and **6**[a]

Donor	Nucleotide Base	Product	Yield (%)[b]	$^1J_{C1\text{-}H1}$ (Hz)
5	**7**	**12**	68	178.9
5	**8**	**13**	73	179.5
5	**9**	**14**	70	178.7
5	**10**	**15**	77	179.0
6	**7**	**16**	74	179.3
6	**8**	**17**	69	179.9
6	**9**	**18**	71	178.7
5	**11**	**19**	65	180.2

[a] See ref.[10] for glycosylation procedure.
[b] Isolated yield following chromatography.

In summary, we have described the efficient synthesis of 2,3-anhydro-β-D-lyxofuranoyl pyrimidine nucleosides via a highly convergent route. The method should enable the synthesis of a range of other nucleoside analogs either directly from these compounds (e.g., via opening of the epoxide ring or the use of iodouridine derivative **15** in palladium catalyzed cross coupling reactions[20]) or though the reaction of **5** and **6** with other persilylated pyrimidine

derivatives. In this regard, we note that in order to further expand the utility of this method we have also attempted the reaction of **5** and **6** with the adenine and guanine derivatives **21** and **22**. However, only very low yields of the products were formed and it appears that the method is, at this time, limited to the synthesis of pyrimidine nucleosides.

Acknowledgment

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(8) **24**: White solid, mp 68–69 °C; R_f 0.61 (hexanes/EtOAc, 5:1); $[\alpha]_D$ +129.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ) 7.31 (d, 2 H, *J* = 8.0 Hz), 7.18 (d, 2 H, *J* = 8.0 Hz), 5.51 (s, 1 H), 4.09 (dd, 1 H, *J* = 6.2 Hz, 6.2 Hz), 3.97 (d, 1 H, *J* = 2.8 Hz), 3.77 (d, 1 H, *J* = 2.8 Hz), 3.55 (dd, 1 H, *J* = 6.2 Hz, 12.5 Hz), 3.46 (dd, 1 H, *J* = 6.2 Hz, 12.5 Hz) 2.38 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 134.4, 129.9, 129.8, 128.3, 86.9, 75.1, 57.7, 55.6, 49.8, 21.0. Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H 4.98. Found: C, 54.70; H, 4.95.

(9) **6**: White solid, mp 77–78 °C; R_f 0.66 (3:1, hexanes/EtOAc,); $[\alpha]_D$ –161.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.31 (d, 2 H, *J* = 8.0 Hz), 7.18 (d, 2 H, *J* = 8.0 Hz), 5.58 (s, 1 H), 4.12 (dd, 1 H, *J* = 6.2 Hz, 6.2 Hz), 3.99 (d, 1 H, *J* = 2.8 Hz), 3.83 (d, 1 H, *J* = 2.8 Hz), 3.59 (dd, 1 H, *J* = 6.2 Hz, 12.5 Hz), 3.49 (dd, 1 H, *J* = 6.2 Hz, 12.5 Hz) 2.36 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ_C) 134.0, 129.9, 129.8, 128.3, 96.0, 74.3, 57.7, 55.8, 48.9, 21.0. Anal. Calcd for $C_{12}H_{13}N_3O_3S$: C, 51.60, 4.69. Found: C, 51.66; H, 4.73.

(10) **General Procedure for Glycosylations.** Donor **5** or **6** (0.5 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (513 mg, 2.5 mmol), 4 Å molecular sieves (0.1 g) were dried for 3 h under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (10 mL) and the reaction mixture was cooled to –78 °C. Triflic anhydride (0.17 mL, 0.6 mmol) was added and the mixture was allowed to stir for 10 min before a solution of the persilylated nucleoside (**7**–**11**, 0.6 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise via syringe over 2 min. After 15 min, the reaction mixture turned dark brown/green and a saturated solution of $NaHCO_3$ was added before the solution was allowed to warm to room temperature. The resulting solution was filtered through Celite, dried, filtered, and concentrated to yield a crude oil that was purified by chromatography.

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(12) **12**: Oil; R_f 0.09 (2:1, hexanes/EtOAc); $[\alpha]_D$ +37.2 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 8.04 (dd, 2 H, *J* = 1.2 Hz, 8.0 Hz), 7.65–7.61 (m, 2 H), 7.50 (dd, 2 H, *J* = 8.0 Hz, 8.0 Hz), 6.36 (s, 1 H), 5.72 (d, 1 H, *J* = 8.2 Hz), 4.73 (dd, 1 H, *J* = 3.8 Hz, 3.8 Hz), 4.59 (dd, 1 H, *J* = 3.7 Hz, 12.2 Hz), 4.50 (dd, 1 H, *J* = 3.9 Hz, 12.2 Hz), 4.12 (d, 1 H, *J* = 2.8 Hz), 4.01 (d, 1 H, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, δ_C) 166.5, 164.4, 151.0, 141.5, 133.9, 129.8, 129.7, 129.2, 128.9, 102.3, 82.5, 77.4, 64.4, 57.0, 56.6; HRMS (ESI) calcd for (M + Na) $C_{16}H_{14}N_2O_6$: 353.0750, found 353.0761. **13**: Oil; R_f 0.15 (2:1, hexanes/EtOAc); $[\alpha]_D$ +89.1 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 8.01 (dd, 2 H, *J* = 1.2 Hz, 8.1 Hz), 7.50 (dddd, 1 H, *J* = 1.2 Hz, 1.2 Hz, 7.4 Hz, 7.4 Hz), 7.39 (dd, 2 H, *J* = 8.0 Hz, 8.0 Hz), 6.23 (s, 1 H), 4.71–4.60 (m, 2 H), 4.35 (dd, 1 H, *J* = 3.8 Hz, 3.8 Hz), 4.00 (s, 2 H), 1.81 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ_C) 166.6, 164.0, 151.1, 136.9, 133.8, 130.1, 129.8, 128.9, 111.7, 81.7, 75.5, 62.7, 56.1, 55.9, 12.9; HRMS (ESI) calcd for (M + Na) $C_{17}H_{16}N_2O_6$: 367.0906, found 367.0921. **14**: Oil; R_f 0.10 (2:1, hexanes/EtOAc); $[\alpha]_D$ +73.8 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 7.92 (dd, 2 H, *J* = 1.2 Hz, 8.2 Hz), 7.59 (d, 1 H, *J* = 6.2 Hz), 7.52 (dddd, 1 H, *J* = 1.2 Hz, 1.2 Hz, 7.4 Hz, 7.4 Hz), 7.39 (dd, 2 H, *J* = 8.0 Hz, 8.0 Hz), 6.24 (s, 1 H), 4.63 (dd, 1 H, *J* = 3.8 Hz, 3.8 Hz), 4.49 (dd, 1 H, *J* = 3.7 Hz, 12.2 Hz), 4.38 (dd, 1 H, *J* = 3.5 Hz, 12.2 Hz), 4.00 (d, 1 H, *J* = 2.8 Hz), 3.89 (d, 1 H, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, δ_C) 166.6, 157.9 (d, *J* = 26.3 Hz), 149.7, 140.9 (d, *J* = 236.4 Hz), 134.1, 129.9, 129.3, 129.0, 125.7 (d, *J* = 34.9 Hz). 82.7, 64.4, 57.1, 56.7; HRMS (ESI) calcd for (M + Na) $C_{16}H_{13}FN_2O_6$: 371.0655, found 371.0667. A small amount of this material was recrystallized from a 10:1 mixture of dichloromethane and hexanes to provide a sample for X-ray crystallography. **15**: Oil; R_f 0.29 (2:1, hexanes/EtOAc); $[\alpha]_D$ +93.3 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 8.17 (d, 2 H, *J* = 1.2 Hz, 8.1 Hz), 8.05 (s, 1 H), 7.59 (dddd, 1 H, *J* = 1.2 Hz, 1.2 Hz, 7.4 Hz, 7.4 Hz), 7.49 (dd, 2 H, *J* = 7.9 Hz, 7.9 Hz), 6.17 (s, 1 H), 4.75 (dd, 1 H, *J* = 5.0 Hz, 12.0 Hz), 4.63 (dd, 1 H, *J* = 5.0 Hz, 12.0 Hz), 4.41 (dd, 1 H, *J* = 4.7 Hz, 4.7 Hz), 4.02–4.01 (m, 2 H); ^{13}C NMR ($CDCl_3$, δ_C) 166.9, 160.9, 150.8, 145.8, 133.8, 130.1, 129.7, 129.0, 82.1, 75.9, 69.3, 62.7, 56.2, 56.0; HRMS (ESI) calcd for (M + Na) $C_{16}H_{13}IN_2O_6$: 478.9716, found 478.9722. **17**: Oil; R_f 0.16 (2:1, hexanes/EtOAc); $[\alpha]_D$ +41.3 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 7.44 (d, 1 H, *J* = 1.2 Hz), 6.36 (s, 1 H), 4.14 (dd, 1 H, *J* = 5.9 Hz, 5.9 Hz), 3.95 (d, 1 H, *J* = 2.8 Hz), 3.86 (d, 1 H, *J* = 2.8 Hz), 3.60 (d, 2 H, *J* = 5.9 Hz), 1.90 (d, 3 H, *J* = 1.2 Hz); ^{13}C NMR ($CDCl_3$, δ_C) 164.5, 151.2, 136.9, 111.7, 81.6,

76.1, 56.2, 55.5, 50.6, 12.9; HRMS (ESI) calcd for (M + Na) $C_{10}H_{11}N_5O_4$: 288.0709, found 288.0720. **18**: Oil; R_f 0.11 (2:1, hexanes/EtOAc); $[\alpha]_D$ +33.6 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 7.76 (d, 1 H, *J* = 6.1 Hz), 6.17 (d, 1 H, *J* = 1 Hz), 4.21 (dd, 1 H, *J* = 6.0 Hz, 6.0 Hz), 4.01 (d, 1 H, *J* = 2.8 Hz), 3.94 (d, 1 H, *J* = 2.8 Hz), 3.68–3.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, δ_C) 162.1 (d, *J* = 26.4 Hz), 149.6, 140.9 (d, *J* = 236.8 Hz) 125.4 (d, *J* = 38.5 Hz), 82.9, 76.2, 56.0, 55.7, 50.4; HRMS (ESI) calcd for (M + Na) $C_9H_8FN_5O_4$: 292.0458, found 292.0467. **19**; Oil; R_f 0.21 (2:1, hexanes/EtOAc); $[\alpha]_D$ +65.4 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, δ_H) 8.06–8.03 (m, 3 H), 7.95 (d, 2 H, *J* = 7.4 Hz), 7.62–7.57 (m, 3 H), 7.51–7.45 (m, 4 H), 6.24 (s, 1 H), 4.75 (dd, 1 H, *J* = 5.4 Hz, 11.9 Hz), 4.61 (dd, 1 H, *J* = 4.6 Hz, 11.9 Hz), 4.49 (dd, 1 H, *J* = 4.9 Hz, 5.4 Hz), 4.16 (d, 1 H, *J* = 2.8 Hz), 4.00 (d, 1 H, *J* = 2.8 Hz), ^{13}C NMR ($CDCl_3$, δ_C) 169.0, 166.9, 160.9, 159.0, 133.9, 133.5, 130.0, 129.6, 129.1, 128.9, 128.3, 97.9, 84.2, 76.5, 62.7, 56.9, 56.3; HRMS (ESI) calcd for (M + Na) $C_{23}H_{19}N_3O_6$: 456.1172, found 456.1168.

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