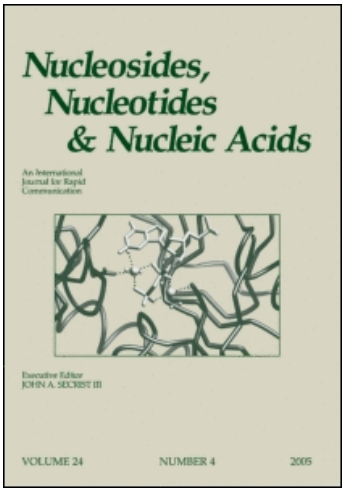

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Synthesis of 2,2'-Anhydro Nucleosides with a Modified Sugar Side-Chain

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SYNTHESIS OF 2,2′-ANHYDRO NUCLEOSIDES WITH A MODIFIED SUGAR SIDE-CHAIN

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Abstract: 2,2′-Anhydro-1-(5,6-di-*O*-benzoyl-β-D-altrofuranosyl)thymine **6** and uracil derivative **7** are prepared by transformation of the corresponding 5′,6′-di-*O*-benzoyl-3′-*O*-mesyl-β-D-glucofuranosyl nucleosides **4** and **5** into the 2,2′-anhydro derivatives **6** and **7** using DBU.

Anhydro pyrimidine nucleoside derivatives are the key intermediates for the synthesis of certain biologically active nucleosides (i. e. AZT). Their synthetic potential has been successfully used for the stereo-controlled introduction of nucleophiles (N_3, F, Cl, Br, SR, SeC_6H_6)[1-4] into the ribo configuration in the sugar moiety of nucleosides and for the selective inversion[5-7] of the *ribo* configuration of the carbohydrate unit yielding the corresponding 2′-epimeric *arabino*- or 3′-epimeric *xylo*-derivatives. 2,2′-Anhydro pyrimidine nucleoside derivatives are intermediates in economical processes amenable for large-scale production of 2′-deoxynucleosides[8,9] (i. e. thymidine precursor for AZT) and for the synthesis of 2′,3′-didehydro-3′-deoxythymidine (d4T)[10].

As part of our program directed to investigate the antiviral activities of side chain derivatives[11,12] of biologically active nucleosides in which the 4′-C-hydroxymethyl group of the sugar moiety is replaced by a hydroxyethyl group (homonucleosides) or one of the diastereotopic protons at 5′-C is substituted by a hydroxymethyl group (5′-C-

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hydroxymethyl nucleosides) or by a methyl group (5′-C-methyl nucleosides) we were interested in an effective and general synthesis of their corresponding 2,2′-anhydro pyrimidine nucleoside derivatives.

The methods for the preparation of 2,2′-anhydro pyrimidine nucleosides described in the literature[13-20] were developed for nucleosides having a ribofuranose as sugar component. They are based on the presence of a *cis* orientated diol system in which the two secondary alcohols display a different reactivity. When 5′-*O*-trityl protected ribonucleosides are treated with diphenylcarbonate[1, 13] or bis-(imidazol-1-yl)thione[14, 15] the corresponding 2,2′-anhydronucleosides can be isolated. The treatment of 5′-O-acetyl uridine with two equivalents of tetraacetoxysilane in the presence of two equivalents of zinc chloride in acetic acid afforded 2,2′-anhydro-1-(3,5-di-O-acetyl-β-D-arabinofuranosyl)uracil[16]. The use of 2-acetoxybenzoyl chloride[17] and α-acetoxyisobutyryl chloride[18] results in the formation of 2′-chloropyrimidine nucleosides as side products. Treatment of 1-[3,5-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]uracil with triflic anhydride[19] or triphenylphosphine/diethyl azodicarboxylate[20] yielded the desired 2,2′-anhydrouridine derivative exclusively. Reaction of 5′-*O*-tritylated uridine with tosyl chloride takes place predominantly at the 2′-OH group resulting in an ideal starting material for the formation of the 2,2′-*O*-anhydro nucleoside[3].

In general these strategies are not suitable for the large scale synthesis of 2,2′-anhydro pyrimidine nucleosides with the aforementioned modified 4′-C- side chains bearing an additional secondary OH group (5′-C-methyl- and 5′-C-hydroxymethyl analogues) without excessive use of protecting groups.

In this paper we report an efficient and general strategy for the synthesis of 2,2′-anhydro nucleoside derivatives with a modified 4′-C side chain. Crystalline diacetate **1**[21] (mp 109-111°C) was selected as the starting material of choice for the preparation of the desired 2,2′-anhydro nucleoside derivatives (FIG. 1). **1** is available in high yield from 1,2;5,6-di-*O*-isopropylidene-α-D-glucose in an overall yield of 50% and has already the necessary 6 carbons and in addition the furanose ring system. **1** was coupled with thymine (T), and uracil (U) to give the β-D-glucofuranosyl nucleosides[22] **2** and **3** (yield: 58 and 66%). Treatment of these highly functionalised nucleosides **2-3** with hydrazine hydrate[23]

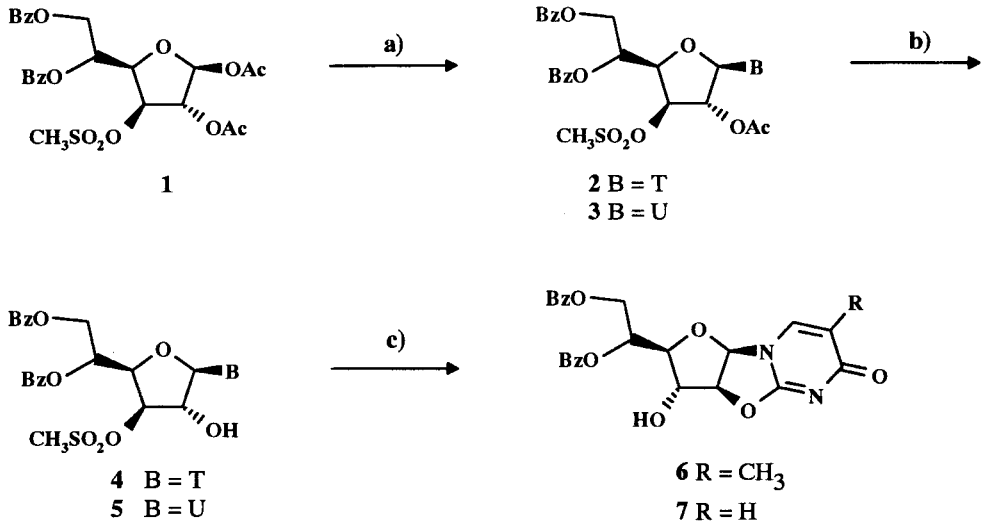

FIGURE 1: a) nucleobase, $[(CH_3)_3Si]_2NH$, $(CH_3)_3SiCl$, CF_3SO_3H, CH_3CN, 80°C, 12h; b) 3 equiv. $NH_2NH_2 \cdot H_2O$, pyridine/AcOH = 4/1, 25°C, 16h; c) DBU, toluene, 1h at 25°C, 15min at 90°C.

gave nucleosides **4-5** with a free OH group at 2´- position (yield: 95 and 90%). The 3´-*O*-mesyl group which is *trans* to the OH group was not effected.

When the glucofuranosyl nucleoside derivative **4** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, FIG. 1) we isolated compound **6** in 75% yield whose $J_{1,2}$ = 6.0 Hz, $J_{2,3}$ = 1.5 Hz are typical for a *cis-trans*-relationship of the protons at C-1´, C-2´, and C-3´.

In addition the NMR spectrum of the isolated compound **6** is different from the isomeric 2,3´-anhydro-1-(5,6-di-*O*-benzoyl-β-D-glucofuranosyl)thymine[11] ($J_{1,2}$ = < 0.5 Hz, $J_{2,3}$ = < 0.5 Hz). These NMR data confirm that **6** is a 2,2´-anhydro nucleoside generated by opening of the intermediary formed oxirane by the C-2 carbonyl oxygen to give the kinetically favored 2,2´-anhydro derivative **6**. Starting with **5** the corresponding 2,2´-anhydro uracil derivative **7** was obtained (yield: 78%).

In summary the treatment of nucleosides with *xylo*-configuration in the carbohydrate unit having a 3´-*O*-mesyl and a free 2´- OH group with a base (e. g. DBU) results in the

simultaneous inversion of the configuration at C-2´- and C-3´ forming the *arabino* configurated anhydro nucleoside derivative with a free 3´-OH group. Compounds **6** and **7** are versatile starting materials and will be used for the continuation of our studies focused on the 4´- C- side chain analogues of biologically active pyrimidine nucleosides.

EXPERIMENTAL SECTION

General: Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker WM 250 or Bruker WM 400 spectrometer. The deuterated solvent will be given for each compound. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Precoated Merck silica gel F 254 plates were used for TLC, and the spots were examined with UV light and by spraying with a solution of 2% $Ce(NO_3)_4$ in 2N H_2SO_4 followed by heating at 200°C. Flash chromatography was performed with 230-400 mesh silica from E. Merck.

General procedure for the synthesis of the nucleosides: The nucleosides were prepared according to the literature[22] by coupling **1**[21] with thymine and uracil. The appropriate reaction time (t_R) and the solvent system for the flash chromatography (FC) will be given for the corresponding compounds.

1-(2-*O*-Acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-β-D-glucofuranosyl)thymine (2):

t_R: 12h, FC: petroleum ether / ethyl acetate = 1 / 1; yield: 58%; foam; Rf = 0.22 (petroleum ether / ethyl acetate = 1 / 1).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.95(d, 3, J(5-CH_3,6) = 1.0Hz, 5-CH_3), 2.17(s, 3, OAc), 3.11(s, 3, mesyl-CH_3), 4.95(dd, 1, J(6´a, 6´b) = 12.5Hz, J(6´a, 5´) = 5.5Hz, 6´-Ha), 4.60(dd, 1, J(3´, 4´) = 3.0Hz, J(4´, 5´) = 9.0Hz, 4´-H), 4.97(dd, 1, J(6´b, 5´) = 3.0Hz, 6´-Hb), 5.17(d, 1, 3´-H), 5.37(d, 1, J(1´, 2´) = 2.5Hz, 2´-H), 5.86(ddd, 1, 5´-H), 6.18(d, 1, 1´-H), 7.28(d, 1, 6-H), 7.41-7.62(m, 6, aromatic-H), 7.97-8.04(m, 4, aromatic-H), 9.24(br s, 1, 3-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ 12.57, 20.44, 38.74, 63.14, 67.76, 78.08, 79.40, 79.91, 88.70, 112.52, 128.43, 129.44, 129.66, 129.74, 133.27, 133.65, 134.68, 150.17, 163.29, 165.28, 165.97, 169.05.

Anal. ($C_{28}H_{28}N_2O_{12}S$, MW: 616.60): Calculated: C 54.54; H 4.58; N 4.54; Found: C 54.84; H 4.60; N 4.60.

1-(2-*O*-Acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-β-D-glucofuranosyl)uracil (3):

t_R: 12h, FC: petroleum ether / ethyl acetate = 1 / 1; yield: 66%; oil; Rf = 0.24 (petroleum ether / ethyl acetate = 1 / 1).

^{1}H-NMR (400MHz, $CDCl_3$) δ 2.17(s, 3, OAc), 3.12(s, 3, mesyl-CH_3), 4.57(dd, 1, J(6´a, 6´b) = 12.5Hz, J(6´a, 5´) = 5.5Hz, 6´-Ha), 4.65(dd, 1, J(3´, 4´) = 3.5Hz, J(4´, 5´) = 9.0Hz, 4´-H), 4.96(dd, 1, J(6´b, 5´) = 2.5Hz, 6´-Hb), 5.18(d, 1, 3´-H), 5.37(d, 1, J(1´, 2´) = 2.5Hz, 2´-H), 5.82(d, 1, J(5,6) = 8.5Hz, 5-H), 5.85(ddd, 1, 5´-H), 6.16(d, 1, 1´-H), 7.44(d, 1, 6-H), 7.40-7.60(m, 6, aromatic-H), 7.98-8.03(m, 4, aromatic-H), 9.64(br s, 1, 3-H).

^{13}C-NMR (100MHz, $CDCl_3$) δ 20.43, 38.63, 63.10, 67.67, 78.54, 78.94, 79.88, 88.94, 103.59, 128.40, 128.46, 129.03, 129.39, 129.63, 129.71, 133.24, 133.55, 138.88, 150.05, 162.83, 165.20, 165.94, 169.05.

Anal. ($C_{27}H_{26}N_2O_{12}S$, MW: 602.57): Calculated: C 53.82; H 4.35; N 4.65; Found: C 53.92; H 4.45; N 4.66.

General procedure for selective deacetylation at 2´- position: The nucleoside (1mmol) was dissolved in pyridine/AcOH = 4/1 (10mL). $NH_2NH_2.H_20$ (3mmol, 0.15mL) was added and stirred at 25°C over night (TLC-control: ethyl acetate). The reaction solution was transferred into a funnel and ethyl acetate (100mL) and 3% HCl solution were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 50mL), the combined organic phases were washed with brine (100mL), dried with Na_2SO_4, filtered and the filtrate was concentrated. The residue was filtered over silica gel to give the deacetylated product. The appropriate solvent system for the filtration (FC) will be given for the corresponding compounds.

1-(5,6-Di-*O*-benzoyl-3-*O*-mesyl-β-D-glucofuranosyl)thymine (4):

FC: ethyl acetate; yield: 95%, oil. Rf = 0.25 (ethyl acetate).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.94(d, 3, J(5-CH_3,6) = 1.0Hz, 5-CH_3), 2.91(s, 3, mesyl-CH_3), 4.57(dd, 1, J(6´a, 6´b) = 12.5Hz, J(6´a, 5´) = 6.0Hz, 6´-Ha), 4.71(s, 1, 2´-H), 4.93(dd, 1, J(3´, 4´) = 3.0Hz, J(4´, 5´) = 9.0Hz, 4´-H), 5.03(dd, 1, J(6´b, 5´) = 2.5Hz, 6´-Hb), 5.13(d, 1, 3´-H), 5.80(br s, 1, D_2O-exchangeable, 2´-OH), 5.89(ddd, 1, 5´-H), 5.96(d, 1, 1´-H), 7.40-7.47(m, 5, 6-H, 4 aromatic-H), 7.54-7.61(m, 2, aromatic-H), 7.99-8.04(m, 4, aromatic-H), 10.30(br s, 1, 3-H).

Anal. ($C_{26}H_{26}N_2O_{11}S$, MW: 574.56): Calculated: C 54.35; H 4.56; N 4.88; Found: C 54.53; H 4.68; N 4.98.

1-(5,6-Di-*O*-benzoyl-3-*O*-mesyl-β-D-glucofuranosyl)uracil (5):

FC: ethyl acetate; yield: 90%, oil. Rf = 0.27 (ethyl acetate).

^{1}H-NMR (400MHz, CDCl3) δ 2.92(s, 3, mesyl-CH3), 4.58(dd, 1, J(6´a, 6´b) = 12.0Hz, J(6´a, 5´) = 5.5Hz, 6´-Ha), 4.74(s, 1, 2´-H), 4.95(dd, 1, J(3´, 4´) = 3.0Hz, J(4´, 5´) = 9.0Hz, 4´-H), 4.98(dd, 1, J(6´b, 5´) = 2.5Hz, 6´-Hb), 5.12(d, 1, 3´-H), 5.50(br s, 1, D2O-exchangeable, 2´-OH), 5.80(d, 1, J(5,6) = 8.0Hz, 5-H), 5.85(ddd, 1, 5´-H), 5.90(s, 1, 1´-H), 7.40-7.47(m, 4, aromatic-H), 7.54-7.62(m, 3, 6-H, 2 aromatic-H), 7.98-8.03(m, 4, aromatic-H), 10.15(br s, 1, 3-H).

Anal. ($C_{25}H_{24}N_2O_{11}S$, MW: 560.54): Calculated: C 53.57; H 4.32; N 5.00; Found: C 53.67; H 4.45; N 5.10.

General procedure for the synthesis of 2,2´-anhydro nucleosides: The nucleoside (1mmol) was dissolved in dry toluene (10mL). DBU (1mmol) was added and the solution was stirrred for 1h at 25°C. Then the reaction mixture was kept for 15 min at 90°C to complete the reaction. Then the reaction mixture was cooled to 25°C and 1mL of AcOH was added. The solvents were evaporated and the residue was dissolved in $CHCl_3$ and filtered over silica gel with $CHCl_3$ / MeOH = 19 / 1.

2,2´-Anhydro-1-(5,6-di-*O*-benzoyl-β-D-altrofuranosyl)thymine (6):

Yield: 75%, oil, Rf = 0.56 ($CHCl_3$ / MeOH = 5 / 1).

^{1}H-NMR (400MHz, d_6-DMSO) δ 1.67(d, 3, J(5-CH_3,6) = 1.0Hz, 5-CH_3), 4.39(dd, 1, J(6´a, 6´b) = 12.0Hz, J(6´a, 5´) = 6.0Hz, 6´-Ha), 4.43(dd, 1, J(3´, 4´) = 3.0Hz, J(4´, 5´) = 7.5Hz, 4´-H), 4.53(br s, 1, 3´-H), 4.63(dd, 1, J(6´b, 5´) = 3.0Hz, 6´-Hb), 5.25(dt, 1, 5´-H), 5.28(dd, 1, J(1´, 2´) = 6.0Hz, J(2´, 3´) = 1.5Hz, 2´-H), 6.23(br s, 1, D_2O-exchangeable, 3´-OH), 6.34(d, 1, 1´-H), 7.70(d, 1, 6-H), 7,44-7.50(m, 4, aromatic-H), 7.60-7.65(m, 2, aromatic-H), 7.83-7.88(m, 4, aromatic-H).

Anal. ($C_{25}H_{22}N_2O_8$, MW: 558.54): Calculated: C 62.76; H 4.63; N 5.85; Found: C 63.00; H 4.76; N 5.95.

2,2´-Anhydro-1-(5,6-di-*O*-benzoyl-β-D-altrofuranosyl)uracil (7):

Yield: 78%, foam. Rf = 0.59 ($CHCl_3$ / MeOH = 5 / 1).

^{1}H-NMR (400MHz, d_6-DMSO) δ 4.39(dd, 1, J(6´a, 6´b) = 12.5Hz, J(6´a, 5´) =

6.5Hz, 6´-Ha), 4.44(dd, 1, J(3´, 4´) = 3.0Hz, J(4´, 5´) = 6.5Hz, 4´-H), 4.54(br s, after D_2O-exchange dd, 1, 3´-H), 4.62(dd, 1, J(6´b, 5´) = 3.0Hz, 6´-Hb), 5.23(dt, 1, 5´-H), 5.30(d, 1, J(1´, 2´) = 6.0Hz, 2´-H), 5.79(d, 1, J(5,6) = 7.5Hz, 5-H), 6.23(br s, 1, D_2O-exchangeable, 3´-OH), 6.37(d, 1, 1´-H), 7.45-7.66(m, 6, aromatic-H), 7.83-7.87(m, 4, aromatic-H), 7.88(d, 1, 6-H).

Anal. ($C_{24}H_{20}N_2O_8$, MW: 464.43): Calculated: C 62.07; H 4.34; N 6.03; Found: C 62.17; H 4.43; N 6.17.

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REFERENCES

1. Verheyden, J. P. H.; Wagner, D.; Moffatt, J. G. *J. Org. Chem.* **1971**, *36*, 250- 254.
2. Kowollik, G.; Etzold, G.; von Janta-Lipinski, M.; Gaertner, K.; Langen, P. *J. Prakt. Chem.* **1973**, *315*, 895-900.
3. Codington, J. F.; Doerr, I. L.; Fox, J. J. *J. Org. Chem.* **1964**, *29*, 558-564.
4. Wnuk, S. F. *Tetrahedron* **1993**, *49*, 9877-9936.
5. Fox, J. J.; Miller, N. C. *J. Org. Chem.* **1963**, *28*, 936-941.
6. Katalenic, D.; Škaric, V. *J. Chem. Soc., Perkin Trans. I*, **1992**, 1065-1072.
7. Lin, T.-S.; Yang, J.-H.; Liu, M.-C.; Shen, Z.-Y.; Cheng, Y.-C.; Prusoff, W. H.; Birnbaum, G. I.; Giziewicz, J.; Ghazzouli, I.; Brankovan, V.; Feng, J.-S.; Hsiung, G.-D. *J. Med. Chem.* **1991**, *34*, 693-701.
8. Marumoto, R.; Honjo, M. *Chem. Pharm. Bull.* **1974**, *22*, 128-134.
9. Chen, B.-C.; Stark, D. R.; Baker, S. R.; Quinlan, S. L. European Patent EP-A-0653436, filed 3. 11.1994 to Bristol-Myers Sqibb Company.
10. Chen,B.-C.; Quinlan, S. C. US-Patent 5466787, 14. 11. 1995.
11. Hiebl, J.; Zbiral, E.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3016-3023.
12. Hiebl, J.; Zbiral, E.; von Janta-Lipinski, M.; Balzarini, J.; De Clercq, E. *Antivir. Chem. Chemother.* **1996**, *7*, 173-177.

13. Hampton, A.; Nichol, A. W. *Biochemistry*, **1966**, *5*, 2076-2082.
14. Fox, J. J.; Wempen, I. *Tetrahedron Lett.* **1965**, 643-646.
15. Ruyle, W. V.; Shen, T. Y.; Patchett, A. A. *J. Org. Chem.*, **1965**, *30*, 4353-4355.
16. Kondo, K.; Adachi, T.; Inoue, I. *J. Org. Chem.*, **1976**, *41*, 2995-2999.
17. Reichman, U.; Chu, C. K.; Hollenberg, D. H.; Watanabe, K. A.; Fox, J. J. *Synthesis* **1976**, 533-534.
18. Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016-4025.
19. Matsuda, A.; Yasuoka, J.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 999-1002.
20. Hiebl, J. unpublished results.
21. Avasthi, K.; Deo, K.; Garg, N.; Bhakuni, D. S. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 249-252.
22. Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279-1286.
23. Ishido; Y.; Nakazaki, N.; Sakairi, N. *J. Chem. Soc. Perkin I*, **1979**, 2088-2098.

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