Synthesis of Various 3′-Branched 2′,3′-Unsaturated Pyrimidine Nucleosides as Potential Anti-HIV Agents

S. Czernecki* and A. Ezzitouni

Laboratoire de Chimie des Glucides, Université Pierre et Marie Curie, 4 Place Jussieu, T74, E6, 75005 Paris, France

Received June 30, 1992

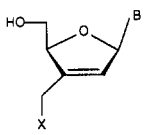
A series of four new 2′,3′-dideoxypyrimidine nucleosides was synthesized and their activity against HIV was evaluated. Coupling of a suitably protected 3-methylidene xylofuranose derivative **5** with thymine and uracil afforded branched nucleosides **7a** and **7b**. The latter was transformed into 2′,3′-dideoxy-2′,3′-didehydro 3′-branched nucleoside **1** by Barton deoxygenation during which an allylic rearrangement occurred. Compounds **7a** and **7b** were converted into the corresponding 2,2′-anhydro derivatives by an intramolecular Mitsunobu reaction. Treatment of these compounds with LiN_3 in DMF afforded the branched azidonucleosides by S_N2' reaction. Palladium-catalyzed azidation of the allylic ester **6a** allowed the introduction of an azido group in a highly regio- and stereoselective manner at C-2′, affording **12**. The *p*-anisyl group employed for the protection of the primary hydroxyl of **5** was stable in acidic and basic conditions, allowing its removal only at the end of the synthesis.

Acquired immunodeficiency syndrome (AIDS) is a consequence of infection by human immunodeficiency virus (HIV),[1] and much research is currently aimed at controlling the responsible virus by chemotherapeutic agents. Several 2′,3′-dideoxynucleoside derivatives have so far proved to be selective inhibitors of HIV replication.[2,3] Among them, 3′-azido-3′-deoxythymidine (AZT) is employed in the treatment of patients with AIDS. Other 3′-azido-2′,3′-dideoxynucleosides have shown comparable in vitro activity to AZT against HIV.[3] Several unsaturated nucleosides such as 2′,3′-didehydro-2′,3′-dideoxycytidine (d4C) and its thymidine analogue (d4T) have also exhibited promising results in vitro activity.[4,5] Although the exact mechanism of action of these nucleoside analogues is not fully understood, it has been shown[6] that AZT is converted to its corresponding triphosphate by cellular enzymes which inhibits the HIV reverse transcriptase (RT).

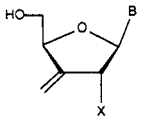
In addition, selective inhibition of RT was demonstrated due to the higher affinity of AZT triphosphate for the reverse transcriptase than for cellular DNA polymerase α.[6-8] Furthermore, if incorporated into a growing viral DNA chain, these 2′,3′-dideoxynucleoside analogues would halt further DNA synthesis since they lack a 3′-hydroxyl group.[9,10]

Our interest in the branched-chain sugar nucleosides was stimulated by anti-HIV activity of oxetanocin, a naturally occurring nucleoside, and its derivatives.[11,12] In an attempt to understand the structural requirements for anti-HIV activity, we decided to prepare slightly modified analogues of the most active pyrimidine nucleosides bearing azido, fluoro, or double-bond functional groups in the sugar moiety.

In this study we report the synthesis of 3′-branched nucleosides **1–4** closely related to AZT and d4T. Of special interest are compounds **2**, **3**, and **4** in which the azido group is slightly moved around the 3′-position.



1 X = H, B = U
2 X = N_3, B = U
3 X = N_3, B = T



4 X = N_3, B = T

Results and Discussion

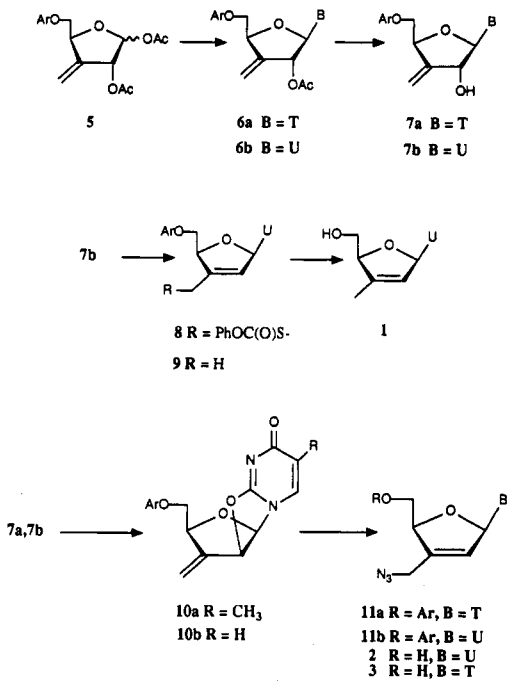
Modified nucleosides **1–3** were prepared according to the reactions in Scheme I. Rather than modifying an existing nucleoside, we decided to start from a common intermediate that could be coupled with different heterocyclic bases. For that purpose the versatile synthon **5** was readily prepared from commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose.[13] The protection of the primary hydroxyl group as a *p*-anisyl ether allowed us to use the same protecting group during the synthesis. The presence of an acetate on the α face at C-2 would insure complete stereocontrol during the condensation with the heterocyclic bases by neighboring-group participation. Coupling of **5** with uracil in the presence of trimethylsilyl trifluoromethanesulfonate according to Vorbrüggen[14] afforded **6b**.

An analytical sample was obtained by column chromatography (70% yield) and characterized as the β-anomer by ^{1}H-NMR spectroscopy ($J_{1',2'}$ = 5.34 Hz). The β configuration was confirmed by transformation into the 2,2′-anhydro derivative (vide infra). For synthetic pur-

(1) Barré-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868.
(2) Mitsuya, H.; Broder, S. *Nature* **1987**, *325*, 773.
(3) (a) Nasr, M.; Litterts, C.; McGrowan, J. *Antiviral Res.* **1990**, *14*, 125. (b) De Las Heras, F. G.; Camarasa, M. J.; Fiandor, J. R. P. *Chem. Syn. Antib.*, Luckac, C., Ed.; Springer-Verlag: Berlin, Heidelberg, 1990; Vol. 320. (c) De Clercq, E. *Design of Anti-AIDS Drugs*; Timmerman, H., Ed.; Elsevier: Pharmacochemistry Library, Amsterdam, Oxford, New York, Tokyo, 1990; p 14.
(4) Lin, T. S.; Prusoff, W. H.; Schinazi, R. F. *Biochem. Pharm* **1987**, *36*, 2713.
(5) De Clercq, E. *Adv. Drug. Res.* **1988**, *17*, 1.
(6) (a) Furman, P. A.; Fyfe, J. A.; St. Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Nusinoff-Lehrman, S.; Bolognesi, D. P.; Broder, S.; Mitsuya, H.; Barry, D. W. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 8333. (b) De Clercq, E. *J. Med. Chem.* **1986**, *29*, 1561. (c) St. Clair, M. H.; Richards, C. A.; Spector, T.; Weinhold, K.; Miller, W. H.; Langlois, A. J.; Furman, P. A. *Antimicrob. Agents Chemother.* **1987**, *31*, 1972.
(7) Wang, A. H.-J.; Quigley, G. J.; Kolpak, F. J.; Crawford, J. L.; van Boom, J. H.; van der Marel, G.; Rich, A. *Nature* **1979**, *282*, 680.
(8) Waggar, M. A.; Evans, M. J.; Manlg, K. F.; Hughes, R. G.; Huberman, J. A. *J. Cell. Physiol.* **1984**, *121*, 402.
(9) Atkinson, M. R.; Deutcher, M. P.; Koruberg, A.; Russel, A. F.; Moffatt, J. G. *Biochemistry* **1969**, *8*, 4897.
(10) Mitsuya, H.; Jarrett, R. F.; Matsukura, M.; Jeroucse, F. D. M.; Devico, A. L.; Sarugadharan, M. G.; Johns, D. G.; Reitz, M. S.; Broder, S. *Proc. Nat. Acad. Sci. U.S.A.* **1987**, *84*, 2033.
(11) Hoshimo, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077.
(12) Hayashi, S.; Phadtare, S.; Zemlicka, J.; Matsukura, M.; Mitsuya, H.; Broder, S. *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 6127.
(13) Czernecki, S.; Ezzitouni, A.; Krausz, P. *Synthesis* **1990**, 651.
(14) Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279.

0022-3263/92/1957-7325$03.00/0

Scheme I[a]



[a] Ar = *p*-anisyl.

poses, crude **6b** was directly deacetylated with a catalytic amount of potassium cyanide in methanol. After evaporation, the crude product was dissolved in water and nonpolar impurities were extracted with toluene. The aqueous phase containing the nucleoside was neutralized (ion exchange resin) and evaporated to afford **7b** in 63% yield from **5**.

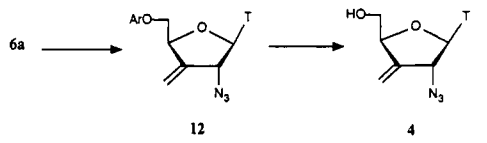
As observed before for **7a**,[13] an allylic rearrangement occurred during the transformation of **7b** into its (phenoxycarbonyl)thio derivative and the 2′,3′-unsaturated nucleoside **8** was obtained. Its structure was unambiguously determined by examination of the ^{1}H-NMR spectrum which indicated the disappearance of the AB system of the two vinylic protons (δ = 5.29 and 5.51 ppm) and the presence of only one vinylic proton (δ = 7.02 ppm) coupled with H-1′.

Reaction of **8** with 3 equiv of tributyltin hydride in the presence of a catalytic amount of α,α-azobis(isobutyronitrile)[15] (AIBN) for 2 h yielded the 3′-branched unsaturated nucleoside **9** in 67% yield. Evidence for the maintenance of the double bond in the sugar ring is shown by the coupling between H-1′ and H-2′ protons and the presence of a singlet (δ = 1.61 ppm) attributable to the C′-CH_3 group.

Final deprotection to **1** by oxidative cleavage of the *p*-anisyl group with cerium ammonium nitrate (CAN)[13,16] occurred in only 22% yield due to partial hydrolysis of the allylic nucleosidic bond.

Introduction of the azido group in the sugar moiety was achieved by opening of an anhydro derivative as previously described for the synthesis of AZT.[17] Treatment of **7a** and **7b** with triphenylphosphine in the presence of diethyl azodicarboxylate (DEAD) afforded 2,2′-anhydro nucleosides **10a** and **10b** (70 and 94%, respectively). In our hands, this procedure proved to be more efficient than the classical one.[18] Evidence for the presence of the 2,2′-anhydro linkage is shown by the high polarity of **10a** and **10b**, the chemical shift of H-1′ (6.21 and 6.36 ppm), and the large coupling between H-1′ and H-2′ protons (5.90 and 6.05 Hz).[19] In addition the presence of λ_{max} at 248.7 nm in the UV spectrum is characteristic of the 2,2′-anhydro structure.[20] Compounds **10a** and **10b** were reacted with lithium azide in DMF,[17] from which **11a** and **11b** were obtained in 94 and 85% yield, respectively. The ^{1}H-NMR spectra of **11a** and **11b** showed no signals for two geminal vinylic protons which were present in the spectra of **10a** and **10b** instead of two allylic protons (4.08 and 4.02, respectively) and a vinylic proton coupled with H-1′ appeared. These data indicate that an allylic rearrangement occurred during the opening of the 2,2′-anhydro derivatives by LiN_3.

Scheme II



The synthesis of **2** and **3** was completed by removing the 5′-protective group by oxidation with cerium ammonium nitrate.[13,16]

Palladium-catalyzed substitution of the allylic acetate of **6a** was employed for the introduction of the azido group at C-2′ (Scheme II).[21] It is well established that this reaction occurs at the acetoxy-bearing carbon with retention of configuration[21c,22] via a (π-allyl)palladium complex, so the azido group was expected to be introduced on the α face. Treatment of **6a** with several combinations of palladium complex in the presence of various azide donors, including trimethylsilyl azide,[21a] afforded **12**. The best yield was obtained under Murahashi's conditions.[21c] The presence of two vinylic protons in the ^{1}H-NMR spectrum of **12** (δ = 5.23 and 5.44 ppm) confirmed the position of the azido group at C-2′. The stereochemistry was established by ^{1}H NMR of **4** after deprotection of the primary hydroxyl of **12** ($J_{1',2'}$ = 5.4 Hz).

For anti-HIV studies, MT_2 cells infected by HIV-1-bru were used. None of these unsaturated nucleosides showed substantial anti-HIV activity.[23]

Experimental Section

Melting points were measured with a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded with a Unicam spectrometer. ^{1}H-NMR spectra were recorded on a Brucker AM250 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in a 10-cm cell at 22 °C. Analytical TLC was performed on Merck aluminum precoated plates of silica gel 60 F-254 with detection by UV and by spraying with 6 N H_2SO_4 and hearing about 2 min at 300 °C. The following systems were used: eluent A (19:1 chloroform–methanol), eluent B (9:1 chloroform–methanol), eluent C (20:1 chloroform–methanol), eluent D (1:1 ether–petroleum ether), eluent E (4:1 ethyl acetate–methanol), eluent F (20:1 ethyl acetate–methanol). Merck

(15) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.
(16) (a) Skarzewski, J. *J. Chem. Res., Synop.* **1980**, 410. (b) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765. (c) Petitou, M.; Duchaussoy, P.; Choay, J. *Tetrahedron Lett.* **1988**, *29*, 1389.
(17) Czernecki, S.; Valery, J. M. *Synthesis* **1991**, 239.
(18) Hampton, A.; Nickol, A. W. *Biochemistry* **1966**, *5*, 2076.
(19) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016.
(20) Brown, D. M.; Todd, A. R.; Varadarajan, S. *J. Chem. Soc.* **1956**, 2388.
(21) For recent examples of palladium-catalyzed azidation of allylic esters, see: (a) Safi, R.; Fahrang, R.; Sinou, D. *Tetrahedron Lett.* **1990**, *31*, 527. (b) Deardorff, D. R.; Schulman, M. J.; Sheppeck, J. E., II. *Tetrahedron Lett.* **1989**, *30*, 6625. (c) Murahashi, S. I.; Tanigushi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.
(22) Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Schulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759.
(23) Chams, V.; Klatzmann, D. To be published.

silica gel 60 (300–400) and anhydrous solvents were employed for column chromatography, and silica gel 60 GF-254 for preparative TLC.

Elemental analyses were performed at the Service de microanalyse of the Pierre et Marie Curie University.

2′-*O*-Acetyl-3′-deoxy-5′-*O*-(4-methoxyphenyl)-3′-methylidene-β-D-uridine (6b). Under a positive pressure of argon, dry 1,2-dichloroethane (2.4 mL), **5** (180 mg, 0.535 mmol), and uracil (60 mg, 0.535 mmol) were placed in a 5-mL flask equipped with a rubber septum. To the resulting solution were introduced Me_3SiCl (56 μL, 0.428 mmol), hexamethyldisilazane (92 μL, 0.428 mmol), and trimethylsilyl trifluoromethanesulfonate (119 μL, 0.642 mmol) successively through a syringe. The mixture was stirred at 60 °C for 2 h and then quenched with H_2O (3 mL) and satd aqueous $NaHCO_3$ (2 mL). After decantation, the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated. The crude mixture was directly deacetylated (vide infra). An analytical sample was obtained by preparative TLC. Elution with $CHCl_3$/MeOH (19:1) afforded pure **6b** (68 mg): yield 70%; mp 94–96 °C (ethyl acetate/ether); $[\alpha]_D$ +13° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 2.15 (3 H, s, CH_3CO), 3.78 (3 H, s, CH_3O), 4.09 (1 H, dd, H-5′a, $J_{5'a,4'}$ = 3.1 Hz, $J_{5'a,5'b}$ = 10.61 Hz), 4.30 (1 H, dd, H-5′b, $J_{5'b,4'}$ = 2.59 Hz), 4.98 (1 H, dd, H-4′), 5.34 (1 H, t, H-3″a, $J_{3''a,3''b}$ = 3.56 Hz, $J_{3''a,4'}$ = 1.78 Hz), 5.45 (1 H, t, H-3″b, $J_{3''b,4'}$ = 1.78 Hz), 5.72 (1 H, d, H-5, $J_{5,6}$ = 8.33 Hz), 5.77 (1 H, dd, H-2′, $J_{2',1'}$ = 5.34 Hz, $J_{2',3'}$ = 1.83 Hz), 6.09 (1 H, d, H-1′), 6.80–6.84 (4 H_{Arom}, m), 7.69 (1 H, d, H-6), 8.91 (1 H, br s, 3-NH). Anal. Calcd for $C_{19}H_{20}N_2O_7$: C, 58.75; H, 5.19; N, 7.21. Found: C, 58.53; H, 5.20; N, 6.98.

3′-Deoxy-5′-*O*-(4-methoxyphenyl)-3′-methylidene-β-D-uridine (7b). The crude mixture (790 mg) obtained from the coupling of **5** (897 mg, 2.667 mmol) with activated uracil as described above was dissolved in dry MeOH (15 mL) at rt, KCN (91 mg) was then added, and the mixture was stirred for 12 h at rt. After evaporation, the obtained syrup (702 mg) was partitioned between H_2O (15 mL) and toluene (5 mL) and the toluene was extracted with H_2O (2 × 10 mL). The aqueous layer was neutralized with Amberlite resin IRN 77 (H^+ form, 0.28 g), filtered, evaporated, and coevaporated with toluene (2 × 4 mL) to afford **7b**; 445 mg (63%) from **5**: mp 109–113 °C (ethyl acetate/ether); $[\alpha]_D$ 0° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 3.77 (3 H, s, CH_3O), 4.02 (1 H, dd, H-5′a, $J_{5'a,5'b}$ = 10.59 Hz), 4.28 (1 H, dd, H-5′b), 4.73 (1 H, br s, 2′-OH), 5.03 (1 H, br s, H-4′), 5.29 (1 H, br s, H-3″a), 5.51 (1 H, br s, H-3″b), 5.69 (1 H, d, H-5, $J_{5,6}$ = 8.10 Hz), 5.87 (1 H, d, H-1′, $J_{1'2'}$ = 5.57 Hz), 6.78–6.87 (4 H, m, H_{Arom}), 7.73 (1 H, d, H-6), 9.36 (1 H, br s, 3-NH). Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.02. Found: C, 58.73; H, 5.20; N, 7.95.

2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-(4-methoxyphenyl)-3′-*C*-(((phenoxycarbonyl)thio)methyl)-β-D-uridine (8). To a stirred solution of **7b** (70 mg, 0.2 mmol) and 4-(dimethylamino)pyridine (DMAP, 50 mg, 0.41 mmol) in pyridine (2 mL) at rt was added *O*-phenyl carbonochloridothioate (101 μL, 0.6 mmol). Stirring was continued for 12 h at rt and the solvent evaporated under reduced pressure. Removal of traces of pyridine by coevaporation with toluene (2 × 6 mL) led to the isolation of crude **8** (190 mg). An analytical sample was obtained by recrystallization from ethyl acetate/ether: mp 102–110 °C; $[\alpha]_D$ −43.5° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 3.73–3.76 (2 H, m, 3′-CH_2S), 3.77 (3 H, s, CH_3O), 4.23–4.26 (2 H, m, H-5′a,b), 5.12 (1 H, br s, H-2′, $J_{2',1'}$ = 1 Hz), 5.64 (1 H, d, H-5, $J_{5,6}$ = 8.06 Hz), 5.90 (1 H, br s, H-1′), 6.82–6.85 (4 H_{Arom}, m), 7.02 (1 H, br s, H-2′), 7.09–7.14 (5 H, m, Ph), 7.83 (1 H, d, H-6), 8.37 (1 H, br s, 3-NH). Anal. Calcd for $C_{24}H_{22}N_2O_7S$: C, 59.74; H, 4.59; N, 5.81. Found: C, 59.51; H, 4.47; N, 5.92.

2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-(4-methoxyphenyl)-3′-*C*-methyl-β-D-uridine (9). Under a positive pressure of argon, **8** (125 mg, 0.26 mmol) and azobis(isobutyronitrile) (AIBN; 10 mg, 0.052 mmol) were dissolved in toluene (6 mL). The solution was heated to reflux and tributyltin hydride (346 μL, 0.78 mmol) was added. Heating was continued for 2 h. The solvent was evaporated under reduced pressure and the crude compound purified by preparative TLC. Elution with Et_2O/EtOAc (1:1) afforded **9** (64 mg, 67%): mp 117–119 °C (ether); $[\alpha]_D$ −16° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.61 (3 H, s, 3′-CH_3), 3.77 (3 H, s, CH_3O), 4.10 (1 H, dd, H-5′a, $J_{5'a,4'}$ = 2.0 Hz, $J_{5'a,5'b}$ = 10.93 Hz), 4.20 (1 H, dd, H-5′b, $J_{5'b,4'}$ = 2.01 Hz), 4.89 (1 H, d, H-4′), 5.54 (1 H, br s, H-1′, $J_{1',2'}$ < 1 Hz), 5.64 (1 H, d, H-5, $J_{5,6}$ = 8.21 Hz), 6.78–6.86 (4 H_{Arom}, m), 6.95 (1 H, br s, H-2′), 7.89 (1 H, d, H-6), 8.24 (1 H, br s, 3-NH). Anal. Calcd for $C_{17}H_{18}N_2O_5 \cdot 0.5H_2O$: C, 60.16; H, 5.64; N, 8.25. Found: C, 59.98; H, 5.51; N, 8.16.

2′,3′-Didehydro-2′,3′-dideoxy-3′-*C*-methyl-β-D-uridine (1). To a cooled (0 °C) solution of **9** (60 mg, 0.18 mmol) in CH_3CN/H_2O (1.5 mL, 4:1) was added CAN (200 mg, 0.36 mmol). The reaction was complete after 3 min. The mixture was partioned between $CHCl_3$ (3 × 2 mL) and satd brine (1 × 4 mL), dried ($MgSO_4$), filtered, and evaporated. The resulting product was purified by preparative TLC. Elution with $CHCl_3$/MeOH (9:1) afforded **1**: yield 8 mg (20%); mp 210–213 °C (ethyl acetate/methanol); $[\alpha]_D$ −37° (*c* 0.1, $CHCl_3$); ^1H NMR (DMSO-d_6) 1.85 (3 H, s, 3′-CH_3), 4.11 (2 H, m, H-5′a,b), 4.90 (1 H, br s, H-4′), 5.62–5.70 (2 H, d+s, H-1′, H-5), 6.76 (1 H, s, H-2′), 7.75 (1 H, d, H-6, $J_{5,6}$ = 8.10 Hz), 11.30 (1 H, br s, 3-NH). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.39; N, 12.49. Found: C, 53.51; H, 5.20; N, 12.30.

2,2′-Anhydro-3′-deoxy-5′-*O*-(4-methoxyphenyl)-3′-methylidene-5-methyl-*threo*-pentofuranosyl-β-D-uracil (10a). At room temperature, under a positive pressure of argon, **7a** (328 mg, 0.91 mmol) and PPh_3 (355 mg, 1.36 mmol) were dissolved in 5 mL of dry DMF. Then 218 μL (1.36 mmol) of DEAD was slowly added (30 min). The reaction was complete after 2 h of stirring. The mixture was poured in dry ether (10 mL) at 0 °C to precipitate **10a**. Filtration and recrystallization from ether furnished **10a** as a white solid (217 mg, 70%): mp 222–223 °C; $[\alpha]_D$ −182.2° (*c* 1.08, MeOH); ^1H NMR ($CDCl_3$) 1.88 (3 H, d, 5-CH_3, $J_{5\text{-}CH_3,6}$ = 1.17 Hz), 3.72 (3 H, s, CH_3O), 3.81 (1 H, dd, H-5′a, $J_{5'a,4'}$ = 4.11 Hz, $J_{5'a,5'b}$ = 10.52 Hz), 4.08 (1 H, dd, H-5′b, $J_{5'b,4'}$ = 3.31 Hz), 5.03–5.11 (1 H, m, H-4′), 5.61 (1 H, br s, H-3″a), 6.65 (1 H, d, H-2′), 5.87 (1 H, br s, H-3″b), 6.21 (1 H, d, H-1′, $J_{1'2'}$ = 5.90 Hz), 6.68–6.79 (4 H_{Arom}, m), 7.15 (1 H, d, H-6); UV (EtOH) λ_{max} 256, 223, 198.8 nm. Anal. Calcd for $C_{18}H_{18}N_2O_5 \cdot 0.5H_2O$: C, 61.53; H, 5.45; N, 7.97. Found: C, 61.20; H, 5.73; N, 7.71.

2,2′-Anhydro-3′-deoxy-5′-*O*-(4-methoxyphenyl)-3′-methylidene-*threo*-pentofuranosyl-β-D-uracil (10b). Compound **10b** was prepared by the method described for **10a** using **7b** (400 mg, 1.15 mmol), PPh_3 (454 mg, 1.72 mmol), and DEAD (115 μL, 1.72 mmol) in DMF (11 mL) to give after recrystallization from methanol–ether 356 mg (94%) of pure **10b**: mp 211–216 °C; $[\alpha]_D$ −67° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 3.66 (3 H, s, CH_3O), 3.89 (1 H, dd, H-5′a, $J_{5'a,4'}$ = 3.37 Hz, $J_{5'a,5'b}$ = 10.74 Hz), 4.03 (1 H, dd, H-5′b, $J_{5'b,4'}$ = 2.62 Hz), 5.07 (1 H, br s, H-3″a), 5.69 (1 H, br s, H-3″b), 5.80 (1 H, d, H-5, $J_{5,6}$ = 7.34 Hz), 5.84–5.87 (2 H, m, H-2′,4′), 6.36 (1 H, d, H-1′, $J_{1'2'}$ = 6.05 Hz), 6.68–6.78 (4 H_{Arom}, m), 7.83 (1 H, d, H-6); UV (EtOH) λ_{max} 287.2, 248.7, 223.6 nm. Anal. Calcd for $C_{17}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 60.52; H, 5.08; N, 8.30. Found: C, 60.73; H, 4.81; N, 8.28.

3′-(Azidomethyl)-3′-deoxy-2′,3′-didehydro-5′-*O*-(4-methoxyphenyl)-β-D-thymidine (11a). Compound **10a** (30 mg, 0.087 mmol) and LiN_3 (13 mg, 0.263 mmol) were heated at reflux for 2 h in DMF (0.3 mL). After cooling, 10 mL of chloroform–water 1:1 was added and stirring was continued for 10 min. The mixture was extraced with $CHCl_3$ (3 × 4 mL) and washed with water (3 × 4 mL). The organic layer was dried ($MgSO_4$), evaporated, and coevaporated with toluene (2 × 3 mL) to give a white solid (31 mg, 94%). An analytical sample was obtained by recrystallization from ethyl acetate–ether: mp 164–166 °C; $[\alpha]_D$ −68° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.80 (3 H, d, 5-CH_3, $J_{5\text{-}CH_3,6}$ < 1 Hz), 3.75 (3 H, s, CH_3O), 4.08 (1 H, s, 3′-CH_2), 4.10 (1 H, s, 3′-CH_2), 4.15–4.35 (2 H, m, H-5′a,b), 5.04–5.11 (1 H, m, H-4′), 5.88 (1 H, s, H-1′, $J_{1'2'}$ < 1 Hz), 6.83–6.85 (4 H_{Arom}, m), 7.06 (1 H, br s, H-2′), 7.58 (1 H, d, H-6, $J_{6,5\text{-}CH_3}$ < 1 Hz), 8.55 (1 H, br s, 3-NH). Anal. Calcd for $C_{18}H_{19}N_5O_5 \cdot 0.5H_2O$: C, 54.81; H, 5.11; N, 17.75. Found: C, 54.73; H, 5.24; N, 17.68.

3′-(Azidomethyl)-2′,3′-didehydro-2′,3′-dideoxy-5′-*O*-(4-methoxyphenyl)-β-D-uridine (11b). Compound **10b** (100 mg, 0.3 mmol) and LiN_3 (45 mg, 0.9 mmol) were heated at reflux for 1.5 h in DMF (1 mL). After completion, the reaction mixture was partitioned in 20 mL of chloroform–water 1:1. The mixture was extracted with chloroform (3 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a white foam (96 mg, 85%). An analytical sample was obtained by recrystallization from ethyl acetate–ether: mp 118–119 °C; $[\alpha]_D$ −17° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 3.70 (3 H, s, CH_3O), 4.01–4.03 (2 H, m, N_3CH_2-3′),

4.12-4.13 (2 H, m, H-5'a,b), 4.99 (1 H, s, H-4'), 5.59 (1 H, d, H-5, $J_{5,6}$ = 8.12 Hz), 5.83 (1 H, s H-1'), 6.70-6.80 (4 H_{Arom}, m), 6.99 (1 H, br s, H-2'), 7.77 (1 H, d, H-6), 9.20 (1 H, br s, 3-NH). Anal. Calcd for $C_{17}H_{17}N_5O_5 \cdot 0.5H_2O$: C, 53.64; H, 4.76; N, 18.40. Found: C, 53.35; H, 4.63; N, 18.37.

3'-(Azidomethyl)-2',3'-didehydro-3'-deoxy-β-D-thymidine (3). To a cooled (0 °C) solution of **11a** (18 mg, 0.046 mmol) in CH_3CN/H_2O (4:1) (1.2 mL) was added CAN (51 mg, 0.092 mmol). After a procedure simular to the one used for **1**, **3** (6 mg, 46%) was isolated: mp 201-205 °C (ethyl acetate/methanol); $[\alpha]_D$ -12° (c 0.15, MeOH); ^1H NMR ($CDCl_3$) 1.84 (3 H, s, 5-CH_3), 3.10 (1 H, br s, 5'-OH), 3.80-4.20 (4 H, m, 3'-CH_2, H-5'a,b), 4.81 (1 H, br s, H-4'), 5.80 (1 H, s, H-1'), 7.01 (1 H, s, H-2'), 7.50 (1 H, s, H-6), 8.75 (1 H, br s, 3-NH). Anal. Calcd for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found: C, 47.28; H, 4.53; N, 25.10.

3'-(Azidomethyl)-2',3'-didehydro-2',3'-dideoxy-β-D-uridine (2). Reaction of **10b** (60 mg, 0.16 mmol) with CAN (181 mg, 0.33 mmol) as described above for **11a** led after purification to **2** (18 mg, 19%): mp 114-117 °C (ethyl acetate/methanol); $[\alpha]_D$ -22° (c 1, MeOH); ^1H NMR ($CDCl_3$) 3.65 (2 H, s, N_3CH_2-3'), 4.15-4.25 (2 H, m, H-5'a,b), 4.71 (1 H, s, 5'-OH), 5.07 (1 H, t, H-4', $J_{4',5'}$ = 4.7 Hz), 5.57 (1 H, d, H-5, $J_{5,6}$ = 8.10 Hz), 5.90 (1 H, s, H-1'), 6.80 (1 H, s, H-2'), 7.53 (1 H, d, H-6), 11.3 (1 H, br s, 3-NH). Anal. Calcd for $C_{10}H_{11}N_5O_4$: C, 45.28; H, 4.18; N, 26.41. Found: C, 45.25; H, 4.20; N, 26.73.

2'-Azido-2',3'-didehydro-2',3'-dideoxy-5'-O-(4-methoxyphenyl)-3'-methylidene-β-D-5-methyluridine (12). At room temperature, under argon, $Pd(OAc)_2$ (13 mg, 0.058 mmol) and PPh_3 (15 mg, 0.057 mmol) were dissolved in THF (3 mL). After 10 min, nucleoside **6a** (23 mg, 0.058 mmol) in solution in THF (3 mL) and NaN_3 (11 mg, 0.17 mmol) in THF/H_2O (9:1, 1 mL) were successively added, and the mixture was stirred for an additional 10 h. The solution was evaporated and the resulting residue poured into water (6 mL) with stirring. This solution was then extracted with chloroform (3 × 5 mL). The chloroform extract was dried ($MgSO_4$) and evaporated to give **12** containing traces of triphenylphosphine. An analytical sample was obtained by recrystallization from ethyl acetate-ether (14 mg, 65%); mp 80-83 °C; $[\alpha]_D$ -25.8° (c 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) 2.03 (3 H, s, 5-CH_3), 3.74 (3 H, s, CH_3O), 3.98 (1 H, dd, H-5'a, $J_{5'a,4'}$ = 4.26 Hz, $J_{5'a,5'b}$ = 10.31 Hz), 4.13 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 3.56 Hz), 4.80 (1 H, d, H-2', $J_{2',1'}$ = 1.77 Hz), 5.23 (1 H, br s, H-3'a), 5.44 (1 H, br s, H-3'b), 5.83 (1 H, d, H-4', $J_{4',5'}$ = 3.3 Hz), 6.29 (1 H, d, H-1'), 7.24-7.26 (4 H_{Arom}, m), 7.72-7.78 (1 H, m, H-6). Anal. Calcd for $C_{18}H_{19}N_5O_5$: C, 56.09; H, 4.97; N, 18.17. Found: C, 56.28; H, 5.14; N, 18.31.

2'-Azido-2',3'-didehydro-2',3'-dideoxy-3'-methylidene-β-D-methyluridine (4). Reaction of **12** (71 mg, 0.073 mmol) with CAN (71 mg, 0.13 mmol) in $MeCN/H_2O$ 4:1 (2 mL) according to the procedure used for **1** led after purification to **4** as an oil (5 mg, 28%): $[\alpha]_D$ -18° (c 0.5, MeOH); ^1H NMR ($CDCl_3$) 1.91 (3 H, d, 5-CH_3, J = 1.01 Hz), 3.81 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.27 Hz, $J_{5'a,5'b}$ = 12.20 Hz), 3.99 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.43 Hz), 4.77 (1 H, br s, 5'-OH), 5.29 (1 H, t, H-3''a, $J_{3''a,2'}$ = 1.97 Hz, $J_{3''a,4'}$ = 2.00 Hz), 5.42 (1 H, t, H-3''b, $J_{3''b,4'}$ = 2.03 Hz), 5.67-5.69 (1 H, m, H-4'), 5.77-5.80 (1 H, m, H-2'), 5.88 (1 H, d, H-1', $J_{1',2'}$ = 5.41 Hz), 7.65 (1 H, d, H-6, $J_{6,5}$ = 1.01 Hz), 8.13 (1 H, br s, 3-NH); MS 280 (M + 1), 297 (M + 18).

Acknowledgment. Dr. Jean-Marc Valery is gratefully acknowledged for recording the ^1H-NMR spectra and Dr. D. Klatzmann for the biological evaluation.

Reactions of Some Pyranoside Diol Monotriflates with Nucleophiles and Bases

Spencer Knapp,* Andrew B. J. Naughton, Carlos Jaramillo, and Brenda Pipik

Department of Chemistry, Rutgers The State University of New Jersey, New Brunswick, New Jersey 08903

Received August 25, 1992

Reaction of pyranoside diol (equatorial) monotriflates with soft, nonbasic nucleophiles is a useful way to make axial heteroatom-substituted and "epimerized" pyranosides, particularly where a fused acetal ring inhibits ring contraction. Among the substrates examined (**1**, **2**, **3**, **4**, **35**), only **4** shows a strong tendency to give ring-contracted products. The reaction of **1-3** with more basic nucleophiles (F^-, t-BuO^-) leads to the anhydrosugars **8**, **25**, and **26**, respectively. The S_N2 reaction of **35** with tetra-n-butylammonium iodide forms the basis for a new synthesis of the Cerny epoxide **32**.

Introduction

Two factors contribute to the difficulty of carrying out bimolecular nucleophilic substitution reactions on carbohydrate substrates. First, the hindered nature of the heavily oxygenated carbohydrate carbon chain or ring greatly increases the activation energy for the S_N2 process relative to a hydrocarbon chain or ring.[1] Second, nearby hydroxyls, protecting groups, and ether oxygens can participate at the carbon undergoing substitution, resulting in rearranged or doubly-inverted products.[2] We have recently described the preparation of carbohydrate diol and triol monotriflates[3] by selective monotriflation.[4,5] Pyranoside diols can give particularly good selectivity, and the derived diol monotriflates are frequently (but not always[5,6]) stable enough to be isolated and characterized. Inasmuch as the carbohydrate triflate group is reactive toward displacement by nucleophiles,[7] and the neighboring (unprotected) hydroxyl is relatively small, this class of compounds promises to be useful for carrying out substitution reactions with inversion at the triflate-bearing

(1) Hough, L.; Richardson, A. C. In *Rodd's Chemistry of Carbon Compounds*; Coffey, G., Ed.; Elsevier: Amsterdam, 1967; Vol. 1F, pp 403-406.

(2) See, for example: (a) Mantell, S. J.; Ford, P. S.; Watkin, D. J.; Fleet, G. W. J.; Browne, D. *Tetrahedron Lett.* **1992**, *33*, 4503. (b) Binkley, R. W. *J. Carbohydr. Chem.* **1992**, *11*, 189. (c) Sato, K.; Hoshi, T.; Kajihara, Y. *Chem. Lett.* **1992**, 1469.

(3) "Triflate" = trifluoromethanesulfonate. We use the term "diol monotriflate" rather than "hydroxy triflate", to emphasize that the compound was made by monotriflation of a diol.

(4) Knapp, S.; Kukkola, P. J.; Sharma, S.; Dhar, T. G. M.; Naughton, A. B. J. *J. Org. Chem.* **1990**, *55*, 5700.

(5) Knapp, S.; Naughton, A. B. J.; Kukkola, P. J.; Shieh, W.-C. *J. Carbohydr. Chem.* **1991**, *10*, 981.

(6) Binkley, R. W. *J. Org. Chem.* **1992**, *57*, 2353 and references cited therein.

(7) Binkley, R. W.; Ambrose, M. G. *J. Carbohydr. Chem.* **1984**, *3*, 1.

0022-3263/92/1957-7328$03.00/0