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Total Syntheses of *N*-Boc-Protected 3'-Deoxy-4'-azathymidine and 4'-Azauridine

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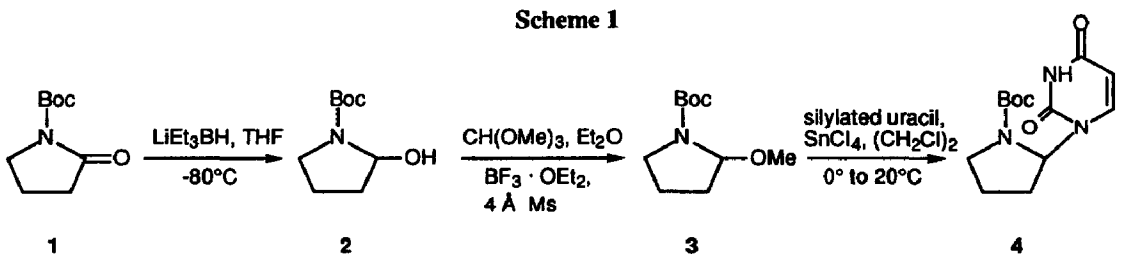
Abstract: Novel modified nucleosides **4**, **11**, *ent*-**11**, and **17**, wherein the furanose ring oxygen is replaced by nitrogen, have been synthesized by reacting azasugars **3**, **10**, *ent*-**10**, and **15** with silylated uracil or thymine bases.

The wide ranging biological activity of structurally modified nucleosides makes them prime synthetic targets and promising candidates to develop improved drug therapies to treat human deseases.[1] In particular, sugar-modified derivatives, as 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxynucleosides [2,3] as well as sulfur- and selenosugar compounds[4] have proved to be of interest and use in cancer and viral chemotherapy,[5] as enzyme inhibitors,[6] and in the synthesis of modified nucleotides.[7]

Our interest was in synthesizing potentially bioactive nucleoside analogs, wherein the furanose ring oxygen is replaced by nitrogen. We now describe brief syntheses of certain azafuranose nucleosides, by a route based on stereospecific formation of the azasugar substrates and their subsequent coupling with a suitable nucleobase. We have applied the method to synthesize *N-tert*-butoxycarbonyl-protected 3'-deoxy-4'-azathymidine **11**, its enantiomer *ent*-**11**, and 4'-azauridine **17**, representatives of a novel class of nitrogen modified nucleosides.[8,9]

The key question centered around the feasibility of establishing the delicate aminal system of the pyrrolidine nucleosides by a Vorbrüggen-type protocol,[10] joining a pyrrolidinose with a silylated nucleobase under Lewis acid catalysis. To simplify the synthesis program, the preparation of unsubstituted uridine model **4** was first planned, as outlined in Scheme 1.

Scheme 1

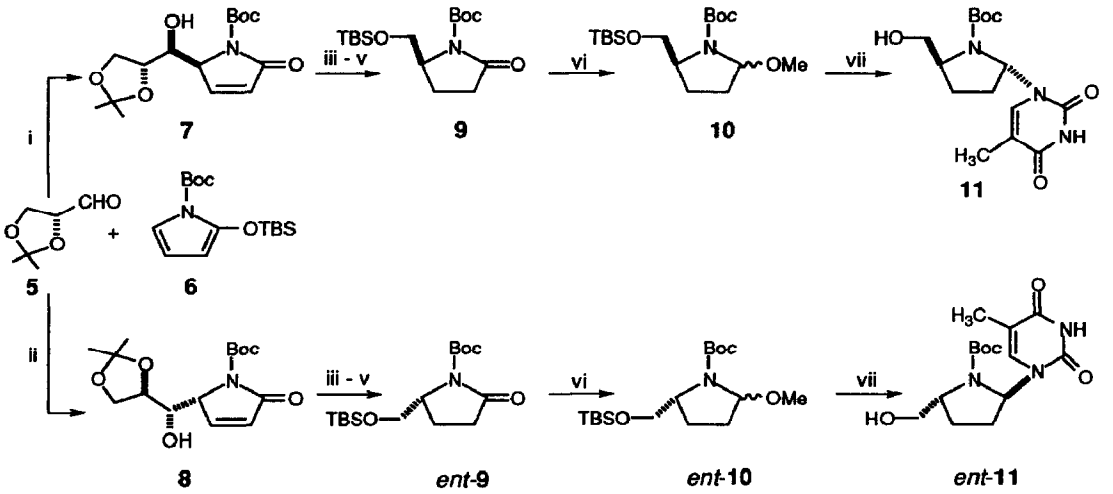


Thus, reduction of pyrrolidinone **1** with lithium triethylborohydride (Super Hydride®) in THF at -80°C cleanly afforded pyrrolidinol **2** (98%),[11] which was converted to its *O*-methyl derivative **3** (90%) by treatment

with methyl orthoformate in the presence of catalytic amount of BF_3-etherate and powdered molecular sieves. We were pleased to observe that **3** underwent facile $SnCl_4$-promoted coupling with 2,4-bis[(trimethylsilyl)oxy]uracil in 1,2-dichloroethane, as planned. Upon chromatographic purification, racemic pyrrolidinyl uracil **4** emerged in 93% isolated yield.[12]

The next goals included the preparations of 3'-deoxy-4'-azathymidine **11** and its enantiomer *ent*-**11**. The synthetic sequences are given in Scheme 2.

Scheme 2



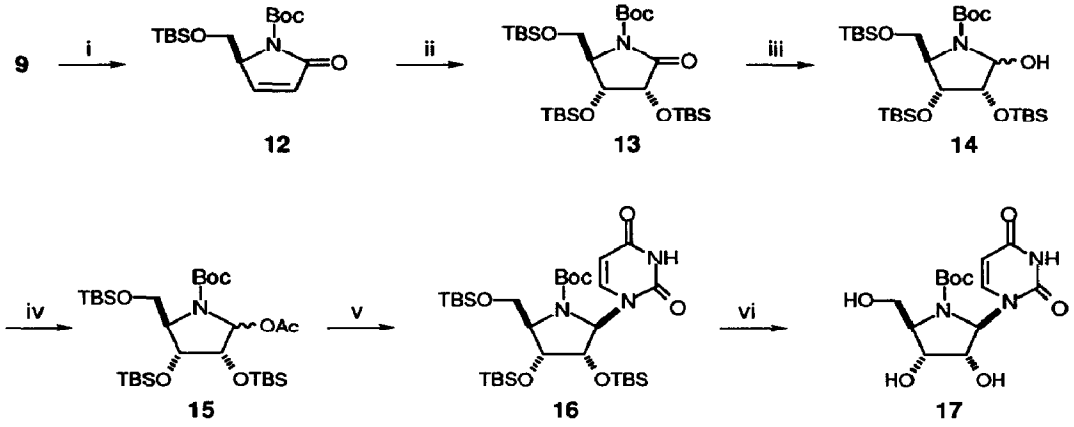
Reagents: i, BF_3-OEt_2,CH_2Cl_2, -80°C; ii, $SnCl_4$, Et_2O, -80°C; iii, H_2, Pd/C, THF, AcONa; iv, 70% aq. AcOH, 50°C; then aq. $NaIO_4$, CH_2Cl_2, SiO_2; v, $NaBH_4$, MeOH; then TBSCl, imidazole, DMF, DMAP; vi, $LiEt_3BH$, THF, -80°C; then $CH(OMe)_3$, BF_3-Et_2O, 4Å molecular sieves; vii, silylated thymine, $SnCl_4$, $(CH_2Cl)_2$, 0° to 20°C; then TBAF, THF, 0°C.

The requisite pyrrolidinone precursors **9** and *ent*-**9** were prepared in enantiomerically pure forms (overall yield ca 50%) by conventional chemistry utilizing the diastereomeric lactam intermediates **7** and **8**, obtainable in multigram quantities by reacting 2,3-*O*-isopropylidene-D-glyceraldehyde **5** with *N*-*tert*-butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole **6**, as previously described.[13] The synthesis of **11** and *ent*-**11** was based on the synthesis of **4** described in Scheme 1. Super Hydride® reduction of **9** and subsequent *O*-methylation was performed as described for **3** and produced D-pyrrolidinose **10** (1:1 anomeric mixture) in 80% isolated yield. In the same manner *ent*-**9** was converted to *ent*-**10** (77%). Treatment of **10** with 2,4-bis[(trimethylsilyl)oxy]thymine, as described for **4**, followed by TBAF-promoted desilylation in THF gave 80% yield of *N*-Boc-protected 3'-deoxy-4'-azathymidine **11** as the predominant stereoisomer (9:1 α/β isomeric ratio).[14] Enantiomeric azathymidine *ent*-**11** was prepared by a route analogous to that used for **11**, by using L-pyrrolidinose *ent*-**10**.[15]

As a further extension, the preparation of 4'-azauridine **17** was finally pursued by a slightly modified route (Scheme 3). α,β-Unsaturated lactam **12** was prepared from **9** (80% yield) according to a known procedure[16] and subjected to dihydroxylation ($KMnO_4$) under solid-liquid phase-transfer conditions.[17] The crude diol formed was then protected as bis-*tert*-butyldimethylsilyl ether to **13** (66%), which was quantitatively

converted to azaribose **14** by Super Hydride® treatment. Exposure of **14** to Ac_2O/pyridine/DMAP provided **15** (96%) which was coupled with silylated uracil as described for **4**. This treatment provided protected 4'-azauridine **16** as planned in a gratifying 73% yield (92:8 β/α isomeric ratio). TBAF-promoted desilylation and final silica gel chromatographic purification (90:10 EtOAc/MeOH) provided pure β-*N*-Boc-4'-azauridine **17** in 80% isolated yield.[18]

Scheme 3



Reagents: i, LDA, THF, -80°C; then PhSeCl, -80°C; then 30% H_2O_2, CH_2Cl_2; ii, $KMnO_4$, DCH-18-crown-6, CH_2Cl_2; then TBSCl, imidazole, DMAP, DMF, 60°C; iii, $LiEt_3BH$, THF, -50°C; iv, Ac_2O, pyridine, DMAP; v, silylated uracil, $SnCl_4$, $(CH_2Cl)_2$, 0° to 20°C; vi, TBAF, THF, 20°C; then silica gel chromatography.

The anomeric stereochemistries of the major epimers α-**11** and β-**17** was determined using 2-D correlation techniques. The spectrum of α-**11** showed that the signal of H-1', which is β-located, correlated with H_2-5', but not with H-4', which is α-located. For β-**17**, instead, a correlation cross-peak was solely observed between H-1' and H-4' in cisoid orientation.

N-Boc-protected azanucleosides **4**, **11**, *ent*-**11**, and **17** proved stable in solution at room temperature; however, preliminary attempts to remove the *N*-Boc protections by using conventional acidic treatments resulted in extensive decomposition.

In summary, we have developed a synthesis of nitrogen thymidine and uridine analogs which is concise (only three steps from readily available γ-lactams), high yielding and versatile. This route should be well suited to the preparation of several analogs by variation of either the azasugar or nucleobase ring systems.

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References and Notes

1. Mizuno, Y. *The Organic Chemistry of Nucleic Acids*; Elsevier: Amsterdam, 1986. Moffatt, J. G. In *Nucleoside Analogues; Chemistry, Biology, and Medical Applications*; Walker, R. T., De Clercq, E., Eckstein, F., Eds.; Plenum: New York, 1979. Perigaud, C.; Gosselin, G.; Imbach, J. L. *Nucleosides Nucleotides* **1992**, *11*, 903-945.
2. Mitsuya, H.; Broder, S.; *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911-1915. Balzarini, J.; Masanori, B.;

Pauwels, R.; Herdewijn, P.; Wood, S. G.; Robins, M. J.; De Clercq, E. *Mol. Pharmacol.* **1988**, *33*, 243-249. De Clercq, E.; van Aerschot, A.; Herdewijn, P.; Baba, M.; Panwels, R.; Balzarini, J. *Nucleosides Nucleotides* **1989**, *8*, 659-664.

3. Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol* . **1987**, *32* 162-167. Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E.; Desmyter, J.; Vandeputte, M. *Biochem. Biophys. Res. Commun.*. **1987**, *142*, 128-134. Hitchcock, H. J. M. *Antiviral Chem. Chemother.* **1991**, *2*, 125-132.
4. Secrist III, J. A.; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med; Chem.* **1992**, *35*, 533-538. Wnuk, S. F. *Tetrahedron* **1993**, *49*, 9877-9936.
5. MacCoss, M.; Robins, M. J. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie & Son Ltd: Glasgow, 1990; pp 261-298. Robins, R. K.; Kini, G. D. *ibid* pp 299-321. Revankar, G. R.; Robins, R. K. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Howe-Grant, M., Ed.; John Wiley & Sons: New York, 1992, pp 576-607. Hahn, E. F.; Buddo, M.; Mian, A. M.; Resnik, L. In *Nucleoside Analogues as Antiviral Agents (ACS Symp. Ser. 401);* Martin, J. C., Ed.; Am. Chem. Soc.: Washington DC, 1989, pp 156-169.
6. Liu, S.; Wnuk, S. F.; Yuan, C.; Robins, M. J.; Borchardt, R. T. *J. Med. Chem.* **1993**, *36*, 883-887. Stoeckler, J. D.; Ryden, J. B.; Parks, R. E., Jr.; Chu, M. Y.; Lim, M. I.; Ren, W. Y.; Klein, R. S. *Cancer Res.* **1986**, *46*, 1774-1778.
7. Cook, P.D. In *Antisense Research and Applications*; Crooke, S. T., Lebleu, B., Eds.; CRC Press, Inc.: Boca Raton, FL, 1993. Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543-584.
8. Just prior to submission of this manuscript, we became aware of an approach to pyrrolidine-based analogs of 3'-deoxythymidine which utilizes (*S*)-pyroglutamic acid, in a fashion which is complementary to our procedure. See: Altmann, K.-H. *Tetrahedron Lett.* **1993**, *34*, 7721-7724.
9. *C*-Nucleoside analogues: Horenstein, B. A.; Zabinski, R. F.; Schramm, V. T. *Tetrahedron Lett.* **1993**, *34*, 7213-7216.
10. Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256-1268. Vorbrüggen, H.; Bennua, B. *ibid* **1981**, *114*, 1279-1286.
11. While DIBAL-H was uneffective, use of NaBH4/MeOH resulted in extensive opening of the lactam ring.
12. Compound **4**: a glass; ^{1}H NMR (300 MHz, $CDCl_3$, 50°C) δ 9.65 (bs, 1H, NH), 7.17 (d, *J* = 8.1 Hz, 1H, H-6), 6.04 (m, 1H, H-1'), 5.70 (d, *J* = 8.1 Hz, 1H, H-5), 3.62 (m, 1H, H_2-4'), 2.36 (m, 1H, H-2'a), 1.99 (m, 3H, H-2'b and H_2-3), 1.41 (s, 9H, Bu^t); ^{13}C NMR (75.2 MHz, $CDCl_3$, 50°C) δ 163.2, 153.2, 139.5, 101.8, 81.5, 70.3, 46.4, 33.3, 28.2, 22.9. Anal. Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.44; H, 6.89; N, 15.00.
13. Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760-3763; Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L.; Gasparri Fava, G.; Belicchi Ferrari, M.; Pelosi, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1035-1048.
14. Compound α–**11**: a waxy solid, $[\alpha]_D$ -36.00° (*c* 2.78, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 8.11 (d, *J* = 1.2 Hz, 1H, H-6), 6.09 (dd, *J* = 7.4, 5.1 Hz, 1H, H-1'), 4.11 (dd, *J* = 11.1, 4.6, 1H, H-5'a), 3.92 (m, 1H, H-4'), 3.69 (dd, *J* = 11.1, 2.7 Hz, 1H, H-5'b), 2.29 (m, 1H, H-2'a), 2.07 (m, 3H, H-2'b and H_2-3'), 1.87 (s, 3H, CH_3), 1.39 (s, 9H, Bu^t); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 163.9, 154.9, 150.6, 136.4, 110.2, 81.8, 71.5, 64.5, 60.7, 31.2, 28.1, 25.5, 12.3. Anal. Calcd for: $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.91. Found: C, 55.48; H, 7.20; N, 12.98.
15. Compound α-*ent*-**11**: a waxy solid, $[\alpha]_D$ +35.91° (*c* 2.10, $CHCl_3$); ^{1}H and ^{13}C NMR, see compound α–**11**. Anal. Calcd for: $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.91. Found: C, 55.43; H, 7.25; N, 13.00.
16. Woo, K.-C.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949-6952. Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, III, H.-S. *J. Org. Chem.* **1981**, *46*, 2920-2923.
17. Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tatrahedron* **1990**, *46*, 265-276.
18. Compound β-**17**: a waxy solid, $[\alpha]_D$ -8.0° (*c* 0.5, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.88 (d, *J* = 8.1 Hz, 1H, H-6), 6.22 (d, *J* = 7.5 Hz, 1H, H-1'), 5.66 (d, *J* = 8.1 Hz, 1H, H-5), 4.61 (dd, *J* = 7.2, 4.8 Hz, 1H, H-2'), 4.18 (bd, *J* = 4.8 Hz, 1H, H-3'), 3.94 (m, 1H, H-4'), 3.81 (dd, *J* = 11.4, 4.5 Hz, 1H, H-5'a), 3.61 (dd, *J* = 11.4, 2.1 Hz, 1H, H-5'b), 1.36 (s, 9H, Bu^t); ^{13}C NMR (75.2 MHz, CD_3OD) δ 166.5, 154.6, 153.2, 144.6, 101.3, 82.5, 73.8, 71.5, 70.4, 67.9, 60.8, 28.5. Anal. Calcd. for $C_{14}H_{21}N_3O_7$: C, 48.98; H, 6.17; N, 12.24. Found: C, 49.11; H, 6.31; N, 12.06.

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