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Synthesis of Branched Nucleosides Closely Related to AZT, Involving SN_2' Opening of Anhydronucleosides.#

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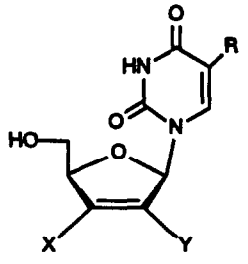
Abstract: Three 2',3'-unsaturated pyrimidine nucleosides, bearing an azido-methyl group at 2' or 3' were synthesized as potential anti-HIV agents. The key step involves an SN_2' opening of 2,2' or 2,3'-anhydronucleosides by azide ion.

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'-dideoxynucleosides 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 including 3'-azido-2',3'-dideoxyuridine (CS87) 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 *in vitro* activity.[4,5] Although the exact mechanism of action of these nucleosides analogues is not fully understood, it has been shown[6] that AZT is converted to its corresponding triphosphate by cellular enzymes and this triphosphate may inhibit the HIV reverse transcriptase (RT), or be incorporated into the growing viral DNA chain, resulting in chain termination because of the lack of 3'-hydroxyl group.[7]

In an attempt to understand the structural requirements for anti-HIV activity we decided to prepare slightly modified analogues of active nucleosides. Since they are the more active ones, pyrimidine nucleosides bearing an azido function in the sugar moiety were chosen as model compounds and a small structural modification was introduced in the structure. It is already known that 2'-azido-2'-deoxyuridine and thymidine are devoid of activity against HIV.[3] Recently 4'-azido-nucleosides were reported to show an appreciable anti-HIV activity.[8] We report herein the synthesis of congeners of AZT and CS87 in which the azido group is slightly moved around the 3' position by means of a methylene group branched at C-2' or C-3' of a 2',3'-unsaturated pyrimidine nucleosides.



1 R = H, X = H Y = CH_2N_3

2 R = CH_3, X = CH_2N_3 Y = H

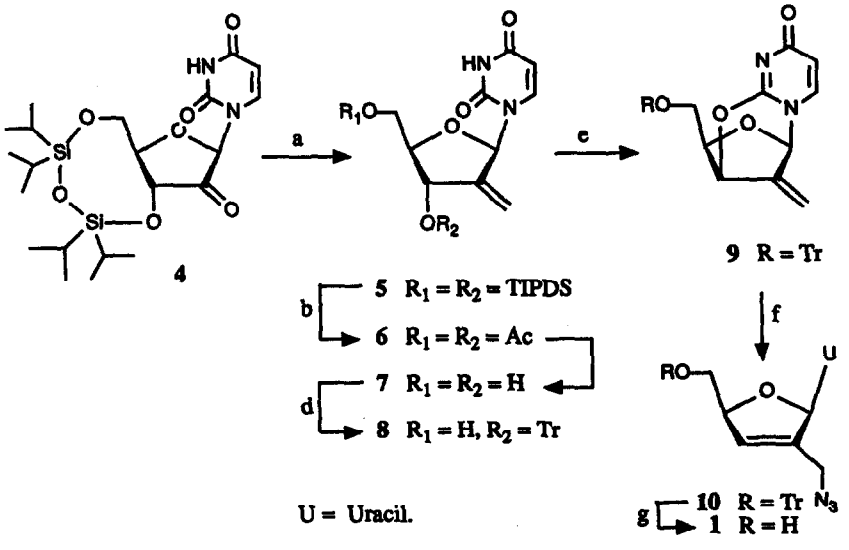
3 R = H, X = CH_2N_3 Y = H

\#*Communicated in part as a poster, at the EUROCARB VI, Edinburgh, Scotland, September 1991.*

Since we recently deviced a very efficient synthesis of 2,3'-anhydrothymidine[14] which nucleophilic opening by azide ion afforded AZT in high yield,[15] we anticipated that, under the same conditions, branched anhydronucleosides **9** and **14** would afford the target molecules **1**, **2** and **3**.

The C-2' branched nucleoside **1** was prepared via a Wittig reaction on a 2'-keto nucleoside (Scheme I).

Scheme I



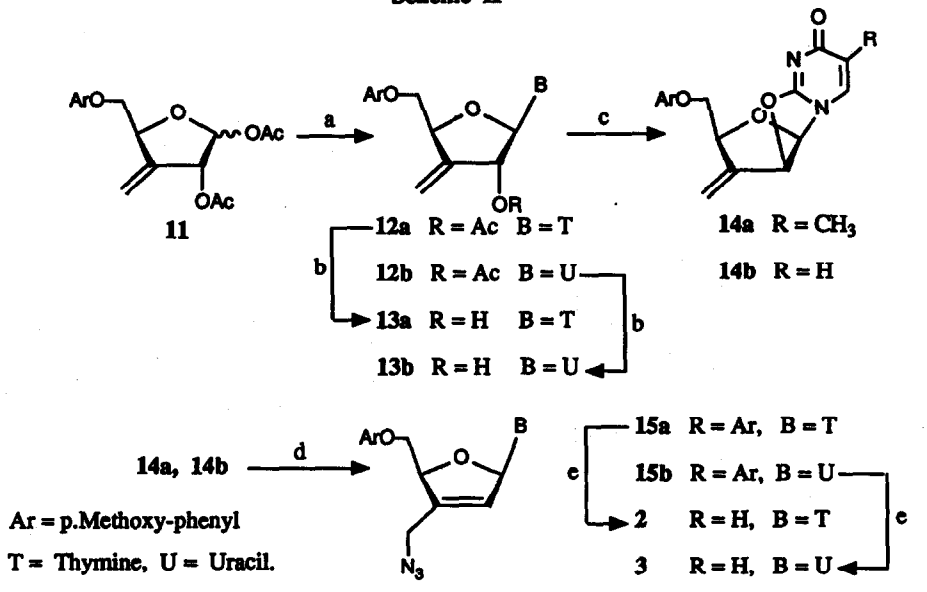
a) $Ph_3P{=}CH_2$ 2.1 eq. , THF, r.t. (83%). b) Et_3N,3HF 5 eq. , CH_3CN, r.t. , then pyridine, Ac_2O, 2.2 eq. , r.t. (92%). c) MeOH, H_2O, Et_3N, r.t. (100%). d) Ph_3CCl 1.5 eq. , pyridine, DMAP 0.2 eq. , (70%). e) Ph_3P 1.5 eq. , DEAD, 1.5 eq. , DMF, r.t. (70%). f) LiN_3 3 eq. , DMF, 100°C, 2h, (12%). g) BF_3OEt_2 2 eq. , Et_3SiH, 2 eq. , CH_3CN, -40°C, (68%).

Selective protection of 3' and 5' hydroxyl groups of uridine with dichloro-1,3-tetraisopropyl-1,1,3,3-disiloxane[9] followed by pyridinium dichromate oxidation[10] of the remaining hydroxyl afforded the required 2'-keto-nucleoside **4**.[11] Only 1.5 molar equivalent of PDC was employed, and the chromium salts were efficiently removed by precipitation with diethyl ether followed by slow filtration (silicagel-Florisil, 1-1). This system was found to be superior to other reagents widely used for the oxidation of nucleosides.[12] A Wittig reaction on **4** was conducted with methylene triphenyl phosphorane generated from methyl triphenylphosphonium iodide and *sec*-butyl lithium in THF at -78 °C. This procedure avoids the use of DMSO[13] and compares favorably with the "salt-free" conditions employed by Samano and Robins.[12] Deprotection of **5** was achieved with $Et_3N.3HF$ in acetonitrile but, since the deprotected nucleoside was soluble in water, it was directly acetylated for convenience of work-up. The crystalline diacetate **6** was quantitatively deacetylated to **7** which was tritylated to **8**.[13] Intramolecular Mitsunobu reaction[14] carried out with **8** afforded 2,3'-anhydronucleoside **9**.[16] Heating (100°C) **9** in the presence of an excess of lithium azide in DMF resulted in the formation of **10** [17] by SN_2' opening of the anhydronucleoside and other unidentified nucleoside derivatives. Detritylation of **10** under classical acidic conditions was not possible because the allylic nucleosidic bond was also cleaved. When BF_3,OEt_2 was employed at

low temperature in the presence of Et_3SiH as reducing agent, the target molecule **1** was obtained in acceptable yield.

For C-3' branched nucleosides **2** and **3**, rather than following a linear route by modifying a nucleoside, we decided to start from a common intermediate **11** [18] that could be coupled with different heterocyclic bases (Scheme II).

Scheme II



a) Base (thymine or uracil), TMSCl, HMDS, TMSTf, $C_2H_4Cl_2$, 60 °C, 2h, (64-70 %) ; b) NaOMe/MeOH, r.t., 12h, (78-63 %) ; c) DEAD, Ph_3P, DMF, r.t. 2h, (70-94 %) ; d) LiN_3, DMF, 100 °C, 1h, (94-85 %) ; e) $(NH_4)_2Ce(NO_3)_6$, $MeCN/H_2O$, 0 °C, 5 min., (46-19 %).

Coupling of **11** with thymine and uracil under conditions previously described,[18] afforded respectively **12a** and **12b**. Deacetylation by transesterification led to **13a** and **13b** which were submitted to intramolecular Mitsunobu reaction.[14] The 2,2'-anhydronucleosides **14a** and **14b** were obtained in good yield . This procedure proved to be more efficient that the classical one.[19] The presence of the 2,2'-anhydro linkage was shown by high polarity of **14a** and **14b**, the chemical shift of H-1' (6.21 and 6.36 ppm), the value of the coupling between H-1' and H-2' (5.90 and 6.05 Hz)[20] and the presence of an absorption band at 248.7 nm.[21] As for **9**, reaction with lithium azide occurred with transposition but, in this case, the reaction was clean and only one product was formed and isolated. This difference of reactivity could be attributed to the higher strain of the 2,2'-anhydro than in the 2,3'-anhydronucleoside. The ^{1}H-NMR spectra of **15a** and **15b** showed no signals for geminal vinylic protons which were present in the spectra of **14a** and **14b** but two allylic protons (4.08 and 4.02 respectively) and a vinylic proton coupled with H-1'. The synthesis of **2** and **3** was completed by removing the 5'-protective group under oxidative conditions with cerium ammonium nitrate.[15] Some cleavage of the allylic nucleosidic bond occurred at this stage due to acidic conditions, resulting in loss of material.

The antiviral activity of these novel nucleoside analogs will be published in due course.

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References and Notes.

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. *Recent Progress Chem. Syn. Antib.* , ed. Lukacs, C. and Ohno, M., Springer-Verlag, Berlin, Heidelberg, **1990**, *320*. (c) De Clercq, E. "Design of Anti-AIDS Drugs", ed. Timmerman, H. , Elsevier, Pharmacochemistry Library, Amsterdam, Oxford, Nex-York, Tokyo, **1990**, 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. Waggar, M. A. ; Evans, M. J. ; Manlg, K. F. ; Hughes, R. G. ; Huberman, J. A. *J. Cell. Physiol.* **1984**, *121*, 402.
8. Maag, H. ; Chu, N. ; Crawford-Ruth, D. ; Eugui, E. ; McRoberts, M. J. ; Mickowitch, A. ; Pettitou, M. ; Prisbe, E. J. ; Rydzewski, R. M. ; Verheyden, J. P. H. *Antiviral Res.* , **1991** ; *Suppl.1*, 43.
9. Markiewicz, W. T. *J. Chem. Research (S)*, **1979**, 24.
10. Czernecki, S. ; Georgoulis, C. ; Stevens, C. L. ; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.
11. Hansske, F. ; Madej, D. ; Robins, M. J. *Tetrahedron*, **1984**, *40*, 125.
12. Samano, V. ; Robins, M. J. *Synthesis*, **1991**, 283.
13. Somo, T. ; Shuto, S. ; Inoue, H. ; Ueda, T. *Chem. Pharm. Bull.* **1985**, *33*, 3617.
14. Czernecki, S. ; Valéry, J. M. *J. Chem. Soc. Chem. Comm.* **1990**, 801.
15. Czernecki, S. ; Valéry, J. M. *Synthesis*, **1991**, 239.
16. All new compounds gave analytical and spectral data in agreement with their structure.
17. While this paper was in preparation, a synthesis of compound **10** by SN_2' displacement of a 3'-mesylate was published: Hassan, A. A. A.; Matsuda, A. *Heterocycles*, **1992**, *34*, 657. ^{1}H-NMR ($CDCl_3$/TMS) of **10** was identical to that reported.
18. Czernecki, S.; Ezzitouni, A. ; Krausz, P. *Synthesis*, **1990**, 651.
19. Hampton, A. ; Nickol, A. W. *Biochemistry*, **1966**, *5*, 2076.
20. Greenberg, S. ; Moffatt, J. G. *J. Am. Chem. Soc.*, **1973**, *95*, 4016.
21. Brown, D. M. ; Todd, A. R. ; Varadarajan, S. *J. Chem. Soc.* **1956**, 2388.

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