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SYNTHESIS OF (+/-)-1'-AZA-CARBOCYCLIC-PYRIMIDINE-2',3'-DIDEOXYNUCLEOSIDE ANALOGUES AS POTENTIAL ANTI-HIV AGENTS

Tarek S. Mansour* and Haolun Jin
Medicinal Chemistry Division, IAF BioChem International Inc.
531 des Prairies Blvd., Laval, Qc, Canada, H7V 1B7.

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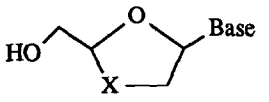
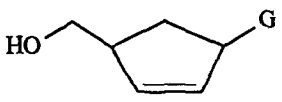
Dedicated to the memory of Professor Bernard R. Belleau

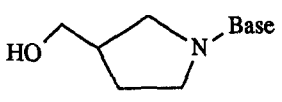
ABSTRACT

1'-Aza-carbocyclic-2',3'-dideoxyuridine, 3'-deoxythymidine and 2',3'-dideoxycytidine were synthesized from 1-aminopyrrolidine intermediate **13** and evaluated as anti-HIV agents in MT-4 cells.

Inhibitors of the HIV reverse transcriptase continue to be the most promising chemotherapeutic agents for the treatment of acquired immunodeficiency syndrome (AIDS). Foremost amongst the class of compounds which selectively inhibit the reverse transcriptase are 2',3'-dideoxynucleoside analogues such as AZT **(1)** ddC **(2)** and ddI **(3)**[1]. Recent efforts to synthesize new analogues that lack the side effects associated with **1, 2** and **3** have focused on modification of the tetrahydrofuran moiety. BCH-189 **(4)**[2,3], Carbovir **(5)**[4] and to some extent iso-ddA[5], (+/-)dioxolane-T[2,6] and BCH-203[2] emerged as active compounds whereas other ring isomers[7], including tetrahydrothiophenes[8] were inactive. Substitution of the oxygen atom of the THF ring with carbon renders the analogues refractory to the action of nucleoside phosphorylases and hydrolyases. Since the conformation of nucleoside analogues have been correlated with anti-HIV activity[9], we have examined pyrimidine analogues possessing flexible N-N glycosyl link.







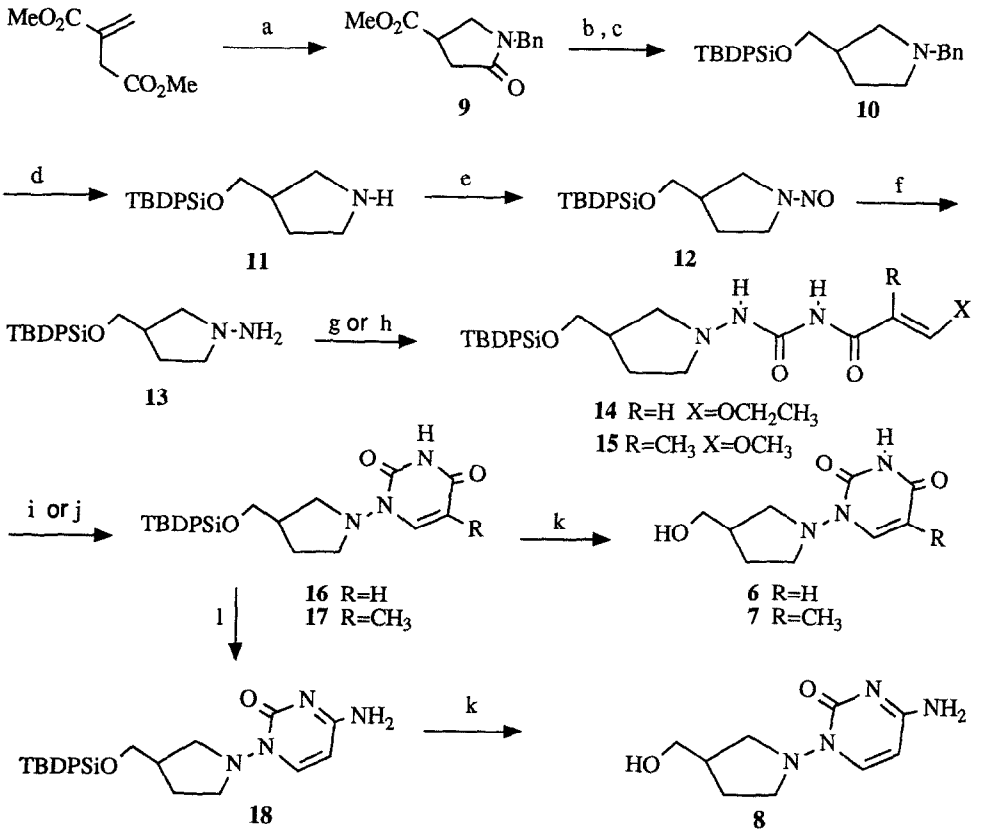
1 X=(α)CHN_3 Base = Thymine
2. X=CH_2 Base = Cytosine
3. X=CH_2 Base = Hypoxanthine
4. X=S Base = cytosine

5.

6. Base = Uracil
7. Base = Thymine
8. Base = Cytosine

Recent report describing the synthesis but not the HIV activity of such analogues[10] prompts us to disclose our synthetic work on compounds **6-8** and their anti-HIV activity. The corresponding 3'-substituted thymine analogues have also been reported[11].

Scheme 1



Reagents and conditions: a. $BnNH_2$, neat, RT, quantitative; b. LAH/THF, RT; c. TBDPSiCl, Imidazole, THF-DMF, 65% from **9**; d. 10% Pd/C, $NH4HCO_2$, MeOH, reflux 2h, 94%; e. $NaNO_2$/HOAc, RT, 1h, quantitative; f. LAH/THF, 0°C --> RT, 1h, 84%; g. 3-Ethoxy-acryloyl isocyanate/Benzene, RT, 70%; h. 3-Methoxy-2-methylacryloyl isocyanate/Benzene, RT, 47%; i. NaH (60% suspension in mineral oil)/DME, 70°C, 50%; j. NaH/DME, 70°C, 23% for **17**; k. TBAF/THF, RT, 72%; l. Tf_2O/Pyridine, -20°C; NH_3/EtOH.

Our synthetic strategy for the preparation of the pyrrolidine nucleosides **6-8** parallels that of Jarvest[10] and Youn[11] in that the pyrimidine nucleus was formed from an appropriate 1-aminopyrrolidine precursor.

Michael addition of benzylamine to the readily accessible dimethyl itaconate afforded the pyrrolidinone **9** in quantitative yield[12]. Lithium aluminium hydride reduction of **9** at room temperature gave 3-hydroxymethyl pyrrolidine which was subsequently converted to t-butyldiphenylsilyl ether **10** in the presence of imidazole in 65% overall yield. Attempted N-debenzylation employing hydrogenolysis techniques in acetic acid at 1 or 11 atm resulted in 15% yield of **11** (65% based on recovery of starting material) whereas Birch reduction or catalytic transfer hydrogenation with cyclohexene employing Pearlman's catalyst in refluxing ethanol, failed to improve the yield. Subsequently, it was found that with ammonium formate[13] as the H-donor N-debenzylation proceeded smoothly giving **11** in 94% yield.

The silyloxymethyl pyrrolidine **11** was nitrosated with sodium nitrite in acetic acid to give a 1:1 mixture of E and Z isomers of **12**. This mixture proved to be inert to reduction by zinc in acetic acid or titanium trichloride[14] but readily reduced by LAH in THF to 1-aminopyrrolidine **13** in 84% yield[15].

In order to obtain the uracil nucleoside **6** compound **13** was treated with 3-ethoxy-acryloyl isocyanate generated *in situ* from 3-ethoxyacrylic acid[16] to afford **14** in 50-70% yield. Crude **14** underwent smooth ring closure with sodium hydride in DME at 70°C to give **16** in 50% yield. Standard deprotection with tetrabutylammonium fluoride (TBAF) in THF afforded **6** in 72% yield.

The thymine derivative **7** was produced by treatment of crude **13** with 3-methoxy-2-methylacryloyl isocyanate[16] in benzene to afford **15** in 47% yield. Subsequent ring closure with NaH in DME at 70°C gave **17** in 23% yield. Formation of the pyrrolidine **11**, resulted from cleavage of the N-N bond was responsible for the low efficiency at this step. Standard deprotection with TBAF afforded **7** in 53% yield.

The cytosine nucleoside **8** was generated by the treatment of **16** with triflic anhydride at -20°C followed by the addition of ethanolic ammonia to provide **18** (62%). Desilylation with TBAF led to compound **8** which was contaminated with an impurity from TBAF. The nucleoside **8** was best purified by chromatography of the corresponding acetylated derivative followed by deacetylation with methanolic ammonia.

The nucleoside analogues **6,7** and **8** were tested for inhibitory activity against HIV in whole cell assay (MT-4, RF strain of HIV-1) at concentrations up to 100 μg/ml and were found to be inactive and not toxic.

In summary, we have described a general route for the preparation of the title compounds based on the aminopyrrolidine **13** which was efficiently prepared from readily accessible and cheap reagents.

Acknowledgements

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References and Notes

1. Mitsuya, H.; Yarchoan, R. and Broder, S. *Science*, **1990**, 249, 1533.
2. Belleau, B.; Dixit, D.; Nguyen-Ba, N.; Kraus, J.L. Fifth International Conf. on Aids, Montreal, Canada, June 4-9, 1989, paper no. T.C.O.I.
3. Soudeyns, H.; Yao, X-J; Gao, Q.; Belleau, B.; Kraus, J.L.; Nguyen-Ba, N.; Spira, B. and Wainberg, M.A. *Antimicrob. Agents Chemther.*, **1991**, 35, 1386.
4. Vince, R. and Hua, M. *J. Med. Chem.*, **1990**, 33, 17.
5. Huryn, D.M.; Sluboski, B.C.; Tam, S.Y.; Todaro, L.J. and Weigele, M. *Tetrahedron Lett.*, **1989**, 30, 6259.
6. Norbeck, D.W.; Sparton, S.; Broder, S. and Mitsuya, H.; *Tetrahedron, Lett.*, **1989**, 30, 6263. Chu, C.K.; Ahn, S.K.; Kim, H.O.; Beach, J.W.; Alves, A.J.; Jeong, L.S.; Islam, Q.; Van Roey, P.; Schinazi, R.F. *Tetrahedron Lett.*, **1991**, 32, 3791.
7. Bamford, M.J.; Humber, D.C. and Storer, R. *Tetrahedron Lett.*, **1991**, 32, 271.
8. Jones, M.F.; Noble, S.A.; Robertson, C.A. and Storer, R. *Tetrahedron Lett.* **1991**, 32, 247.
9. Van Roey, P.; Salerno, J.M.; Chu, C.K. and Schinazi, R. *Proc. Natl. Acad. Sci. USA,* **1989**, 86, 3929. Tseng, C.K.H.; Marquez, V.E.; Milne, G.W.A.; Wysocki, R.J.; Mitsuya, T. and Driscoll, J.S. *J. Med. Chem.*, **1991**, 34, 343.
10. Harnden, M.R. and Jarvest, R.L. *Tetrahedron Lett.*, **1991**, 32, 3863.
11. Lee, Y.H.; Kim, H.K.; Youn, I.K. and Chae, Y.B. *BioMed. Chem. Lett.*, **1991**, 1, 287.
12. Wu, Y.H. and Feldkamp, R.F. *J. Org. Chem.*, **1961**, 26, 1519.
13. Adger, B.M.; O'Farrell, C.O.; Lewis, M.B. *Synthesis* **1987**, 53.
14. Lunn, G.; Sansone, E.B. and Keefer, L.K.; *J. Org. Chem.* **1984**, 49, 3470.
15. Neat **13** was unstable at room temperature but can be stored for a long time as a frozen benzene solution at -20°C. ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.53 (m, 1H), 1.91 (m, 1H), 2.45 (m, 1H), 2.54-2.96 (m, 4H), 3.10 (bs, NH_2, 2H), 3.59 (d, J=7 Hz, 2H), 7.38 (m, 6H), 7.65 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.85, 26.53, 27.42, 39.37, 60.23, 63.30, 67.34, 128.21, 130.18, 134.34, 136.13.
16. G. Shaw and R.N. Warrener; *J. Chem. Soc.*, **1958**, 157.
17. Physical and ^{1}H NMR data for **6, 7** and **8** are already presented in reference 10. ^{13}C NMR **6** ($CDCl_3$-DMSO-d_6) δ 27.09, 39.83, 51.37, 54.22, 65.61, 101.35, 148.60, 150.10, 164.31. **7** (DMSO-d_6) δ 26.87, 39.61, 50.25, 53.54, 64.27, 93.36, 149.07, 154.27, 165.61. **8** ($CDCl_3$) δ 12.67, 27.10, 39.68, 51.44, 54.17, 66.15, 100.04, 144.92, 150.11, 164.50.