Bioorganic & Medicinal Chemistry Letters, Vol.1, No.6, pp. 287-290, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

SYNTHESIS OF NOVEL 1'-NITROGEN REPLACED CARBOCYCLIC THYMIDINE ANALOGS AS POTENTIAL ANTI AIDS AGENTS

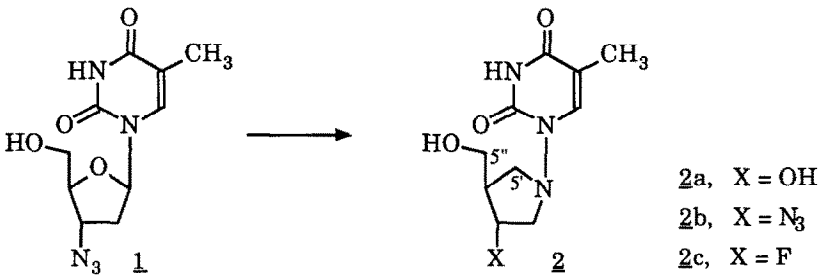
Young Hee Lee, Hee Kap Kim, In Kwon Youn* and Yung Bog Chae
Division of Medicinal Chemistry, Korea Research Institute of
Chemical Technology, Dae-Deog Danji P.O.Box 9, Dae-Jeon, Korea

(*Received* 10 *April* 1991)

Summary : The racemic, 1'-nitrogen substituted 3'-hydroxy, 3'-azido and 3'-fluoro -2',3'-dideoxy carbocyclic pyrimidine nucleosides were synthesized.

The introduction of 3'-azido-2',3'-dideoxythymidine (AZT) 1 as the first drug for the treatment of acquired immunodeficiency syndrome (AIDS)[1] has elicited interest in the synthesis of numerous 2', 3'-dideoxy nucleosides including carbocyclic analogs[2]. While AZT is the only chemotherapeutic agent approved to date for AIDS patients, the side effects caused by the drug are quite severe and part of the problem is that AZT is metabolically unstable in the human body thus requiring administration of a high dosage[3]. These results emphasize the urgent need for a new class of compounds that might have potent anti-HIV activity. Although many nucleoside analogues have been synthesized, no information is available concerning modification at the anomeric position[1d]

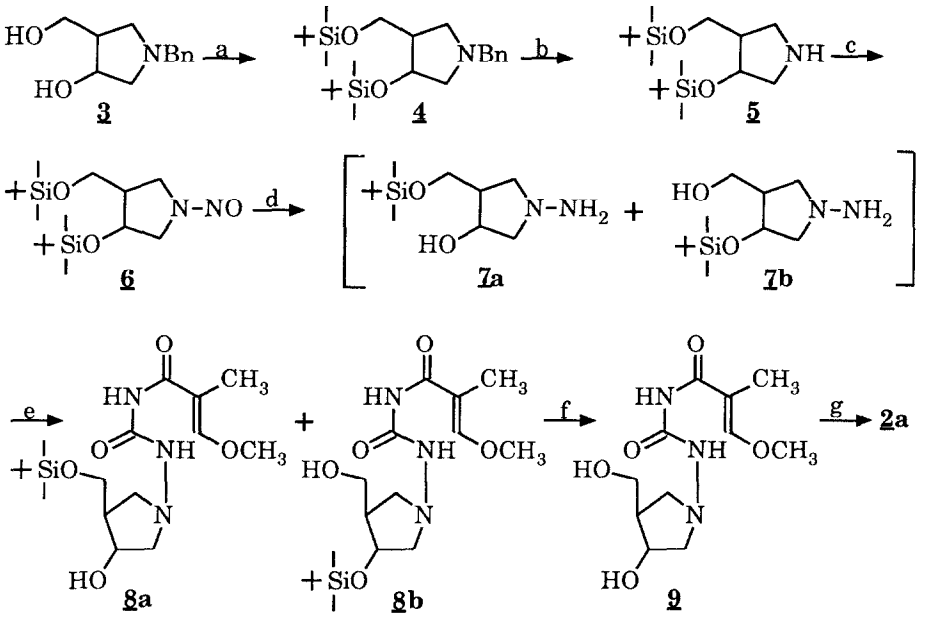
Now we report the synthesis of the first examples of carbocyclic nucleosides to be modified at the anomeric position by nitrogen substitution that complement the recent report on the synthesis of acyclic nucleosides which have hetero atom at the 1'-position[4].



As shown in Scheme 1 and 2, the synthesis was started from the known N-benzyl pyrrolidine diol(3) (trans: cis=7:1).[5] Protection of 3 with 2.2 equivalent of t - butyldimethylsilyl chloride (TBDMSCl) in the presence of 1,8-diazabicyclo[5,4,0] undec-7-ene(DBU) gave the trans disilyl pyrrolidine 4 in 76% yield after column chromatographic separation [hexane:ethylacetate 9:1(V/V)]. After debenzylation [cyclohexene, 10% Pd/C, 94% yield], the disilyl pyrrolidine 5 was nitrosated with excess

isoamylnitrite to give the crystalline 6 in 83% yield. Lithium aluminium hydride reduction of the corresponding 1-nitroso pyrrolidine 6 gave the 1-amino pyrrolidine 7 as a mixture of (ca, 1:1) mono desilylated product in 67% combined yield. Several attempts to prevent desilylation failed, but we could use the mixture for the next step without any difficulty.

(Scheme 1)



Reagent ; a. TBDMSCl, DBU, CH_2Cl_2, b. cyclohexene, 10% Pd/C, EtOH c. isoamylnitrite, THF d. $LiAlH_4$, THF e. $CH_3OCH=C(CH_3)CONCO$, CH_3CN, ether, benzene, f. trifluoroaceticacid g. 15N aq. NH_4OH

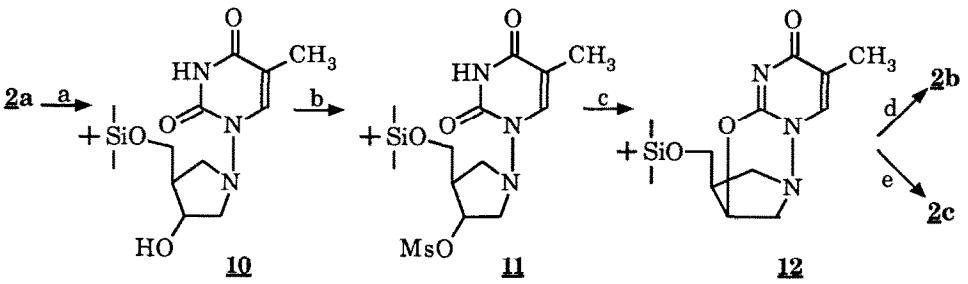
The crude 1-aminopyrrolidine 7 was treated with 3-methoxy-2-methylacryloyl isocyanate[6] generated in situ to give 8 as a mixture (ca, 1:1) of two isomer in 37% combined yield. Even though the mixture 8 was cyclized to pyrimidine by 15N aqueous ammonia solution, a better yield was accomplished by the following two step operation. Crude 8 was treated with trifluoroacetic acid to remove the silyl group (87%) followed by heating under 15N aqueous ammonia in a pressure bottle (90°C, 24h) to give 2a in 94% yield.

In order to get the target azido (2b) and fluoro (2c) compounds, the key intermediate 12 was prepared by the following sequence (Scheme 2). Selective protection of the 5'-hydroxy group with TBDMSCl in the presence of DBU gave 10 in 93% yield. Then compound 10 was converted to

3'-mesylate 11 in 85% yield. The desired anhydro nucleoside 12 was obtained in 89% yield after refluxing 11 for 1.5hr in the presence of 2.0 equivalent of DBU in THF. The target 3'-azido nucleoside (2b)[7] was obtained in 65% yield by treatment of excess LiN_3 (110°C, 16hr, DMF) followed by standard deprotection with tetrabutylammonium fluoride (TBAF). Another target 3' fluoro nucleoside (2c)[7] was prepared in one step (41% yield) by the reaction of the anhydro nucleoside 12 with excess HF.pyridine.

The nucleosides 2a, 2b, and 2c were tested for activity against HIV in cell culture. No significant activity was noted against HIV-1 at concentrations up to 100ug/ml. This approach to 1'-nitrogen replaced carbocyclic nucleosides has been proved to be efficient and applicable to the synthesis of a number of potential antiviral agents. Further examples of the synthesis of other nucleoside analogs and biological data will be given in future publications.

(Scheme 2)



Reagent; a. TBDMSCl, DBU, CH_2Cl_2, b. CH_3SO_2Cl, N,N-diisopropylethylamine CH_2Cl_2 c. DBU, THF d. i) LiN_3, DMF ii) TBAF, THF e. HF. pyridine, dioxane

ACKNOWLEDGMENT. We thank Dr. C.K.Lee, Pharmacological Screening Center, KRICT and Prof. T.J.Kim, Dept. of Microbiology, Tokyo Medical School, Japan for their biological evaluation.

REFERENCES AND NOTES

1) a) Mitsuya, H.; Weinhold, K. J.; Fuhrman, P. A; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. L.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci., U.S.A.* **1985**, 82, 7096.

b) Furman, A.; Fyfe, J. A.; St. Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Lehrman, S. N.; Bolognesi, D. P.; Broder, S.; Mitsuya, H. and Barry, D. W.; *Prod. Natl. Acad. Sci., U.S.A.* **1986**, 83, 8333.

c) Richmann, D. D.; Fischl, M. A.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Hirsh, M. S.; Jackson, G. G.; Durack D. T. and Lehrman, S. N. *N. Engl. J. Med.* **1987**, 317, 185. d) Nasr, M.; Litterst, C. and McGown, J. Antiviral Research, **1990**, 14, 125.

d) Nasr, M.; Litterst, C. and McGown, J. *Antiviral Research*, **1990**, 14, 125.

2) a) Chu, C. K.; Schinazi, R. F.; Ahn, M. K.; Ullas, G. V. *J. Med. Chem.* **1989**, 32, 612. b) Bodenteich, M. and Griengl, H. *Tet. Lett.* **1987**, 28, 5311. c) Beres, J.; Tomoskozi, G. S.; Gruber, L.; Baitz-Gacs, E.; Otvos, L. and Clercq, E. D. *J. Med. Chem.* **1990**, 33, 1353. d) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Todaro, L. J. and Weigele, M. *Tet. Lett.* **1989**, 30, 6259. e) Maruyama, T.; Sato, Y.; Hori, T.; Shiota, H.; Nitta, K.; Shirasaka, T.; Mitsuya, H. and Honji, M. *Chem. Pharm. Bull.* **1990**, 38, 2719. f) Bamford, M. J.; Humber, D. C. and Storer, R. *Tet. Lett.* **1991**, 32, 271.

3) a) Klecker, R. W.; Collins, J. M.; Yarchoan, R.; Thomas, R.; Jenkins, J. F.; Broder, S. and Myers, C. E. *Clin. Pharmacol. Ther.* **1987**, 47, 407.

4) a) Harnden, M. R.; Jennings, L. J. and Parkin, A. *Tet. Lett.* **1988**, 29, 4013. b) Harnden, M. R. and Jarvest, R. L. *Tet. Lett.* **1988**, 29, 5995. c) Harnden, M. R.; Wyatt, P. G.; Boyd, M. R. and Sutton, D. *J. Med. Chem.* **1990**, 33, 187.

5) Jaeger, E. and Biel, J. H. *J. Org. Chem.* **1965**, 30, 740.

6) Fletcher, C. A.; Hilpert, H.; Myers, P. L.; Roberts, S. M. and Storer, R. *J. Chem. Soc. Chem. Comm.* **1989**, 1707.

7) All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means including mass spectrum analysis, significant ^{1}H NMR(300MHz) and mass spectral data of selected compounds are the following. 2a; δ(DMSO-d_6) 1.73(s, CH_3-5, 3H); 2.11(m, H-4', 1H); 3.12(m, 2H); 3.37(m, 2H); 3.45(m, 1H); 3.55(m, 1H); 3.96(m, H-3', 1H); 4.64(t,J=5Hz, HO-5", 1H); 5.00(d,J=5Hz, HO-3', 1H); 7.52(s, H-6, 1H); 11.30(s, H-3, ^{1}H);m/e 241(M). 2b;δ($CDCl_3$) 1.89(s, CH_3-5, 3H); 2.48(m, H-4', 1H); 3.22(s, HO-5", 1H); 3.29(dd, J=9.0 and J=3.5Hz, H-2', 1H); 3.42(dd, J=9Hz, 7Hz, H-5', 1H); H-2', 1H);3.54(t, J=9.0Hz, H-5'); 3.78(bs, H-5", 2H); 3.85(dd, J=10.0 and J=7.0Hz, H-2', 1H); 4.02(m, H-4', 1H); 7.25(s, H-6, 1H); 10.01(bs, H-3, 1H); m/e 266(M). 2c; δ($CDCl_3$) 1.89 (s, CH_3-5, 3H): 2.64(m. JF-3', H-4'=27Hz, H-4', 1H); 3.41(t, J=9.5Hz, H-5', 1H); 3.46(dd, J=9.5Hz, 7.5Hz, H-2', 1H); 3.62(t, J=8.5Hz, H-5', 1H); 3.78(d, J=6.0Hz, H-5", 2H): 3.88(ddd, JF-3', H-2'=33.0, J=12.0 and J=5.0Hz, H-2', 1H); 5.12(dd, JF-3'. H-3'=53.0 and J=5.0Hz, H-3', 1H); 7.30(S, H-6, 1H); 9.90(s, H-3, 1H); m/e 243 (M).