Tetrahedron Letters, Vol.31, No.41, pp 5839-5842, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

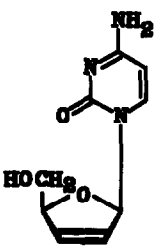
SYNTHESIS OF 2',3'-DIDEOXY-3'-METHYLENE PYRIMIDINE NUCLEOSIDES AS POTENTIAL ANTI-AIDS AGENTS

M. Sharma and M. Bobek*

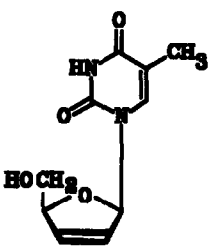
Grace Cancer Drug Center, Roswell Park Cancer Institute
Buffalo, New York 14263

Summary: Efficient synthesis of 2',3'-dideoxy-3'-methylene nucleoside analogs starting from 2'-deoxy-3'-keto-nucleosides is described.

Reverse transcriptase inhibitors such as triphosphates of AZT and other 2'3'-dideoxy nucleosides[1] are currently the most effective chemotherapeutic agents in treatment of human immunodeficiency virus (HIV) infections. 2',3'-Didehydro-2',3'-dideoxycytidine 1 and the corresponding thymidine derivative 2 have been identified as both potent and selective inhibitors[2-5] of the HIV replication. However, they are less stable than the corresponding 2',3'-dideoxy nucleoside due to spontaneous degradation[6,7]. Analogs of 2',3'-dideoxy nucleosides with an exocyclic methylene group at C-3' can be expected to be more stable while retaining the conformational characteristics of 1 and 2.



1

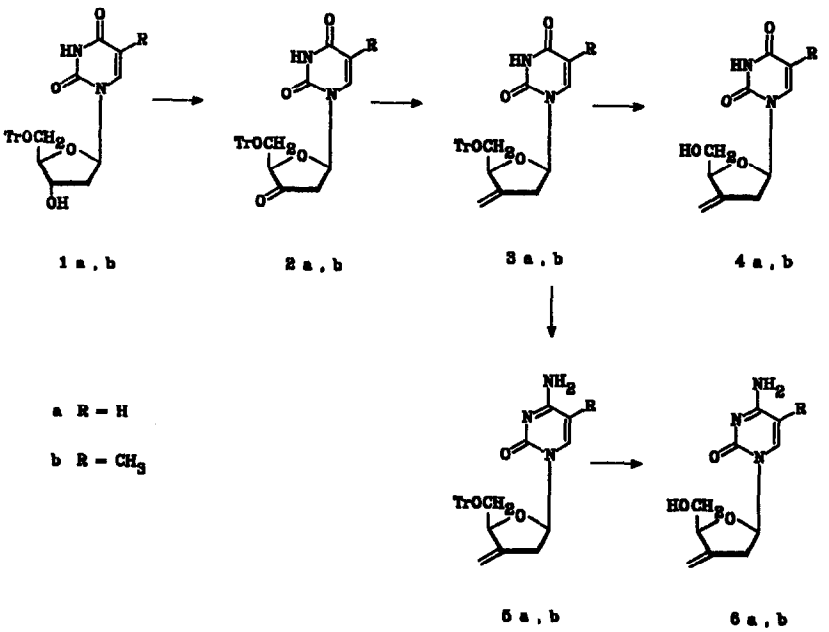


2

Synthesis of these analogs is illustrated in Scheme 1. The 2'-deoxy-3'-ketonucleosides are known to be unstable, especially in the presence of silica gel and base[8]. Efficient preparation of the 2'-deoxy-3'-keto nucleosides depends, therefore, to a large extent on rapid isolation of the products. The 5'-O-trityl nucleosides 1a and 1b were oxidized with pyridine-chromium trioxide complex in methylene chloride and in the presence of acetic anhydride with reaction times of 10 and 40 min., respectively. Reaction mixtures were rapidly filtered through thick beds of silica gel (sufficient to entrap the chromium compounds) and eluted with ethyl acetate. Evaporation of the solvent and co-evaporation of the residue with toluene followed by crystallization from chloroform-ether gave 65% of 2a and 92% of 2b. Compound 2a, which is unstable in the

presence of a base, also decomposes if the reaction time is prolonged, giving 1,2-didehydro-1,2-dideoxy-3-keto-5-O-trityl-pentofuranose and uracil.

Scheme 1



Treatment of the 3'-keto-nuclosides 2a and 2b with the Wittig reagent[9], *methy*lenetriphenyl phosphorane, failed to give 3'-methylene derivatives, presumably due to the basic properties of the reagent; however, the highly electrophilic reagent $Zn/CH_2Br_2/TiCl_4$,[10,11] was effective. In a typical reaction, the slurry reagent[11] (15 ml), prepared from Zn (2.9 g), CH_2Br_2 (1.01 mL) and $TiCl_4$ (1.2 mL) in tetrahydrofuran (25 mL), was added to a stirred solution of 2a (1 g) in methylene chloride (20 ml) at 0°, in three portions at 10 min. intervals. After 10-15 min. at 0°, the mixture was stirred at 20° for 3 hr. The mixture was poured into ice-water saturated with sodium bicarbonate, stirred with chloroform and filtered. The separated water phase and the residue were washed with chloroform, and the combined chloroform solution was dried and evaporated. Chromatographic purification on a silica gel column, eluted with acetone: ether (1:9), gave the product 3a as a heavy amorphous solid in 60% yield (620 mg), ir (KBr): 1750 cm^{-1} (amide), 900 cm^{-1} (CH_2=), 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$): 2.98 (m, 2H, H-2'), 3.20 (d, 2H; H5'), 4.55 (br.s, 1H, H-4'), 4.95 (d, 1H, 3'-CH_2=, J 1.7 Hz), 5.25 (d, 1H, CH_2=, J 1.7Hz), 5.35 (d, 1H, H-5), 6.25 (t, 1H, H-1'), 7.30 (m, 15H, aromatic), 7.75 (d, 1H, H-6), 9.40 (br.s, 1H, NH).

In a similar experiment 3b was obtained as a dry foam (95%); ir (KBr): 1725 cm^{-1} (amide), 900 cm^{-1} (CH_2=), 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$): 1.55 (s, 3H,

CH_3), 2.88 (m, 2H, H-2'), 3.40 (d, 2H, H-5'), 4.50 (br.s, 1H, H-4'), 4.85 (d, 1H, CH_2=, J 1.2 Hz), 5.65 (d, 1H, CH_2=, J 1.2 Hz), 6.20 (t, 1H, H-1'), 7.35 (m, 15H, aromatic), 7.60 (s, 1H, H-6), 9.75 (s, 1H, NH).

After removal of the trityl groups with CH_3COOH/H_2O (8:2), at 25° for 24 hr. 4a and 4b were obtained in high yield (71% and 78%), ^1H NMR ($CDCl_3$): (4a) - 2.98 (m, 2H, H-2'), 3.75 (br.s, 2H, H-5'), 4.45 (br.s, 1H, H-4'), 4.95 (d, 1H, CH_2=, J 1.7 Hz), 5.15 (d, 1H, CH_2= J 1.7Hz), 5.65 (d, 1H, H-5), 6.15 (t, 1H, H-1'), 7.65 (d, H, H-6), 9.8 (br.s, 1H, NH). (4b) - 1.85 (s, 3H, CH_3), 2.90 (m, 2H, H-2'), 3.85 (br.s, 2H, H-5'), 4.50 (br.s, 1H, H-4'), 4.98 (d, 1H, CH_2= J 1.7-Hz), 5.65 (d, 1H, CH_2=, J 1.7Hz), 6.15 (t, 1H, H-1'), 7.45 (s, 1H H-6), 9.15 (br. s, 1H NH).

Compound 3a (770 mg) was converted to 5a by sequential treatment with triflic anhydride (2 ml) in 1,2-dichloroethane (40 ml) containing pyridine (6 ml) for 3 h and with saturated methanolic ammonia[12], in 65% yield (500 mg); ^1H NMR ($CDCl_3$): 2.98 (m, 2H, H-2'), 3.35 (d, 2H, H-5'), 4.65 (br.s, 1H, H-4'), 4.95 (d, 1H, CH_2=, J 1.6Hz), 5.10 (d, 1H, CH_2=, J 1.65Hz), 5.55 (d, 1H, H-5), 6.15 (t, 1H, H-1'), 7.30 (m, 17H, aromatic and NH_2), 7.65 (d, 1H, H-5). However, similar reaction of 3b with triflic anhydride and methanolic ammonia did not afford compound 5b. In this case the amination reaction was achieved in 70% yield by reacting 3b with 1,2,4-triazole-phosphoryl chloride-triethylamine[13] and then with liquid ammonia. ^1H NMR ($CDCl_3$): 1.55 (s, 3H, CH_3), 2.85 (m, 2H, H-2'), 3.50 (d, 2H, H-5'), 4.65 (br.s., 1H, H-4'), 4.95 (d, H, CH_2=, J 1.5 Hz); 5.25 (d, 1H, CH_2=, J 1.5 Hz), 6.35 (t, 1H, H-1'), 7.35 (m, 15H, aromatic), 7.75 (s, 1H, H-6), 8.20 (s, 2H, NH_2).

Compound 5a and 5b were detritylated with CH_3COOH/H_2O (8:2) to give 6a and 6b; ^1H NMR (D_2O): 6a - 3.40 (m, 2H, H-2') 4.25 (m, 2H, H-5'), 5.49 (d, 1H, CH_2=, J 1.6Hz) 5.65 (d, 1H, CH_2=, J 1.6 Hz). 6.35 (d, 1H, H-6), 6.65 (t, 1H, H-1') 8.15 (d, 1H, H-5). 6b: 2.25 (s, 3H, CH_3), 3.25 (m, 2H, H-2'), 4.25 (m, 2H, H-5'), 4.95 (br.s, 1H, H-4'), 5.45 (d, 1H, CH_2=, J 1.7Hz), 5.55 (d, 1H, CH_2=, J 1.7 Hz) 6.55 (t, 1H, H-1'), 7.95 (s, 1H, H-6), 8.75 (s, 2H, NH_2).

The new analogs were found to have no cytotoxic or antitumor properties in vitro at 10^{-4}M concentration and their evaluation as inhibitors of the HIV (AIDS) virus is underway.

Acknowledgement: This investigation was supported in part by Grant CA13038 awarded by the National Cancer Institute.

References and Notes:

1. H. Mitsuya, R.F. Jarrett, M. Matsukura, F.D. Veronese, A.L. DeVico, M.G. Sarngadharan, D.G. Johns and M.S. Reitz, Proc. Natl. Acad. Sci. (USA) 84, 2033, (1987); H. Mitsuya and S. Broder, Proc., Natl. Acad. Sci. (USA) 83, 1911 (1986).
2. J. Balzarini, R. Pauwels, P. Herdewijn, E. DeClercq, D.A. Cooney, G.J., Kang, M. Dalal, D.G. Johns and S. Broder, Biochem. Biophys. Res. Commun. 140, 735 (1986).

3. T.S. Lin, R.F. Schinazi, M.S. Chen, E. Kinney-Thomas and W.H. Prusoff, Biochem. Pharmacol. 36, 311 (1987).
4. M. Baba, R. Pouwels, P. Herdewijn, E. DeClercq, J. Desmyter and M. Vandeputte, Biochem. Biophys. Res. Commun. 142, 128 (1987).
5. T.S. Lin, R.F. Schinazi and W.H. Prusoff, Biochem. Pharmacol. 36, 2713 (1987).
6. J. Balzarini, G.J. Kang, M. Dalal, P. Herdewijn, E. DeClerq, S. Broder and D.G. Johns, Mol. Pharmacol. 32, 162 (1987).
7. T. Kawaguchi, K. Ishikawa, T. Seki, K. Juni, S. Fukushima and M. Nakano, Chem. Pharm. Bull 37, 2547 (1989).
8. F. Hansske, D. Madej and M.J. Robbins, Tetrahedron 40, 125 (1984); P.J. Garegg and B. Samuelsson Carbohydr. Res. 67, 267 (1978).
9. K. Takenuki, A. Matsuda, T. Ueda, T. Sasaki, A. Fujii and K. Yamagami, J. Med. Chem. 31, 1064 (1988).
10. K. Oshima, K. Takai, Y. Hotta and H. Nozaki, Tetrahedon Lett. 18 2417 (1978).
11. L. Lombardo, Tetrahedron Lett. 23, 4293 (1982).
12. A. VanAerschot, P. Herdewijn, J. Balzarini, R. Ponwels and E. DeClercq, J. Med. Chem. 32, 1743 (1989).
13. K.J. Divakar and C.B. Reese, J. Chem. Soc. Perkin Trans. I, 1171 (1982).

(Received in USA 3 July 1990)