Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 15, pp. 1815-1818, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00322-8

SYNTHESIS OF FURO[2,3-*c*]PYRAN-β-D-THYMIDINE

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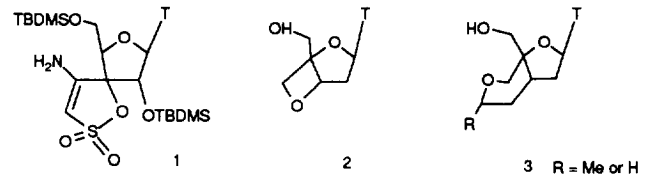
Abstract: A furo[2,3-*c*]pyran-β-D-thymidine nucleoside analog was synthesized from 5'-O-TBDMS-3'-C-allyl-thymidine by 4'-C-hydroxymethylation followed by an electrophilic 6-membered ring annellation. The new bicyclonucleoside was devoid of activity against HIV. Copyright © 1996 Elsevier Science Ltd

Although nucleoside and nucleotide analogs such as 3'-azido-3'-deoxy thymidine (AZT), dideoxycytidine (ddC) and dideoxyinosine (ddI) have shown remarkable activity as inhibitors of the human immunodeficiency virus (HIV),[1] the quest of new antiviral agents has fostered a flurry of research in the area of 2',3'-dideoxynucleoside.[2] The reason is that their long usefulness is somewhat limited by their toxicity and by the appearance of resistant strains on prolonged clinical use.[3]

In this way, and owing to their biological activies, there is a great interest in the synthesis of C-branched-chain nucleosides with alkyl substituent on C-3'[4] and/ or C-4'[5] on the furanose ring. Some of these nucleoside analogs have been found to be endowed with noteworthy antiviral activities and it has been demonstrated that both the nature and the exact location of the substituent could have a major impact on the conformational properties of the furanose ring.[6] However, direct relation-activity towards furanose conformation should only be carefully considered because of the flexibility of the sugar ring.[7]

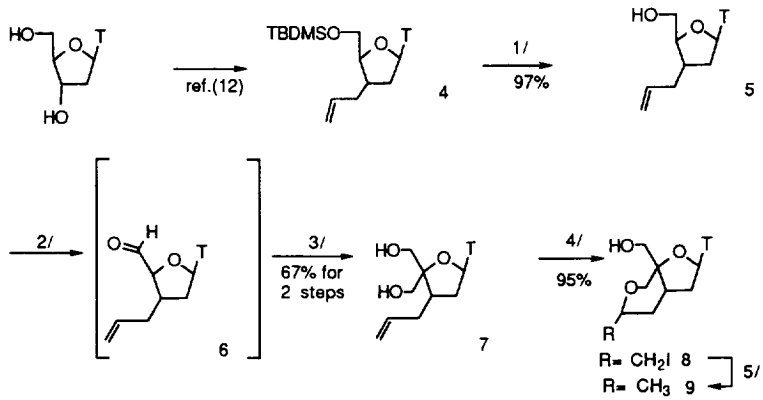
A new class of conformationally restricted modified nucleosides recently appeared in the literature, in particular the spironucleoside TSAO **1**, a potent inhibitor of HIV-l reverse transcriptase,[8] the oxetane nucleoside **2**[9] but also some other fused bicyclic nucleoside analogs.[10]

Some time ago, we initiated a program towards the synthesis of 3',4' fused nucleoside analogs. We report here, as a preliminary result, the synthesis of a new [2,3-*c*]-pyran-β-D-thymidine derivative **3**.[11]



Scheme 1

For this purpose, we adopted a strategy based on the successive introduction of two carbon-carbon bonds at C-3' and C-4' in *anti* orientation to the heterocyclic base. By this way, it was expected that electrophilic, nucleophilic or radical ring closure would give access to various fused-rings having different sizes and/or heteroatom substitutions.



Scheme 2

Reagents : 1/ Dowex 50 x 2 (H^+) in MeOH; 2/ Cl_2COOH, DMSO, DCC, 2 h ; 3/ 2.5 eq. of 37% aq. CH_2O, 1.5 eq. NaOH (1N) in dioxane, 12 h, r.t.; 4/ I_2, $NaHCO_3$, THF-Et_2O at O°C; 5/ H_2, C/Pd in MeOH with 1 eq. Et_3N or Bu_3SnH, AIBN reflux 12 h.

Our synthetic route to **3** started from the already known 3'-C-allyl derivative **4** easily accessible from thymidine.[12] After removal of the silyl substituent at C-5' [Dowex resin (H^+)], the first attempts to oxidize the 5'-OH compound **5** into the corresponding aldehydo-derivative **6** were carried out by using Swern[13]or Moffat[14] procedures. As both methodologies gave the aldehydo-compound **6** in rather poor yields (< 20%), we next turned our attention towards the use of the Dess-Martin reagent.[15] Under these conditions, compound **7** was formed in better yield (57%). Finally, a modified Moffat procedure [17] (Cl_2COOH, DMSO, DCC, 2 h, r.t.) furnished **6**

in very good yield (84%). The crude oxidized product was treated under tandem aldol-cannizaro reaction[17] (0.1 N NaOH-HCHO), giving the gem diol **7** in 67% overall yield. Iodocyclization of **7** (molecular I_2, Et_2O, $NaHCO_3$, 0 °C, 24 h) led to the bicyclo-nucleoside **8** as a mixture of diastereoisomers in 95% overall yield and 1/1 ratio. This was converted into the corresponding dehalogeno analog **9** either by catalytic reduction (H_2, Pd/C, in MeOH, Et_3N) or by radical way (Bu_3SnH, AIBN, Ph-Me, reflux 10 h, 97%).[18]

The conformationally restricted nucleoside analogs **8** and **9** exhibited low *in vitro* inhibitory activity ($IC_{50} > 10^{-4}$ on CEM-SS cells) as well as low cytotoxicity ($CC_{50} > 10^{-4}$ on CEM-SS cells).[19] Therefore, and although structurally closely related, dramatic differences concerning the anti-HIV activity were observed between the oxetane-fused **2** and the pyrano-fused nucleosides **9**. It became interesting to ascertain whether it was due to the ring size of the fused ring or to the presence of a methyl group on the fused pyranose ring. Syntheses of the corresponding demethyl analogs, but also of the furano-fused analogs with or without a methyl group, are in progress.

Acknowledgement. We wish to thank the Fondation pour la Recherche Médicale for the support of this investigation by a SIDACTION grant awarded to I. Bousquié.

References and Notes

1) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2505 and references cited therein.

2) a) Mitsuya, H.; Yarchoan, R.; Broder S. *Science* **1990**, *249*, 1553. b) De Clercq, E.; Van Aerschot, A.; Herdewijn, P.; Baba, M.; Pauwels, R.; Balzarini, J. *Nucleosides & Nucleotides* **1989**, *8*, 659. c) De Clercq, E. *in* "Design of Anti-Aids Drugs", De Clercq Editor, Pharmacochemistry Library, vol. 14, pp. 1-24, Elsevier (Amsterdam) **1990**.

3) Sommadossi, J.-P.; Carlisle, R. *Antimicrob. Agents Chemother.* **1987**, *31*, 452.

4) a) Mann, J.; Tench, A.; Weymouth-Wilson, A.; Shaw-Ponter, S.; Young, R. *J. Chem. Soc., Perkin Trans. I.* **1995**, 677. b) Bamford, M.J.; Coe, P.L.; Walker, R.T. *J. Med. Chem.* **1990**, *33*, 2488. c) Tseng, C.K.-H.; Marquez, V.E.; Milne, G.W.A.; Wysocki, R.J.; Mitsuya, H.; Shirasaki, T.; Driscoll, J.S. *J. Med. Chem.* **1991**, *34*, 343. d) Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson B. *Nucleosides & Nucleotides* **1992**, *11*, 1353. e) Czernecki, S.;

Ezzitouni, A. *J. Org. Chem.* **1992**, *57*, 7325. f) Xi, Z.; Agback, P.; Plavec, J.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1992**, *48*, 349.

5) Surzhykofand S.A.; Krayevsky A. *Nucleosides & Nucleotides* **1994**,*13* (10), 2283-2305.

6) a) Koole, L.H.; Neidle, S.; Crawford, M.D.; Krayevshi, A.A.; Gurskaya, G.V.; Sandström, A.; Wu, J.C.; Tong, W.; Chattopadhyaya, J. *J. Org. Chem.* **1991**, *56*, 6884.; b) Thibaudeau, C.; Plâcec, J.; Garg, N.; Papchikhin, A.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 4038.

7) Maag, H.; Nelson, J.T.; Rios Steiner, J.L.; Prisbé, E.J. *J. Med. Chem.* **1994**, *37*, 431.

8) Alvarez, R.; Velasquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.; Karlsson, A.; Balzarini, J.; Camarasa, M.J. *J. Med. Chem.* **1994**, *37*, 4185.

9) Yang, C.O.; Kurz, W.; Eugui, E.M.; McRoberts, M.J.; Verheyden, J.P.H.; Kurz, L.J.; Walker, K.A.M. *Tetrahedron Lett.* **1992**, *33*, 41.

10) a) Krayevsky, M.A.; Watanabe, K.A. *Nucleosides & Nucleotides* **1993**, *12* (6), 649. b) Pratap, R.; Gulati, D.; Bhakuni, D.S.; George, C.X. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1661. c) Altmann, K.H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *15*, 2331. g) Altmann, K.H., Imwinkelried, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett.* **1995**, *36*, 7375.

11) For other [2,3-*c*]-pyran derivatives of β-D-thymidine, see: Xi, Z.; Agback, P., Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1991**, *47*, 9675.

12) a) Chu, C.K.; Doboszewki, B.; Schmidt, W.; Ullas, G.V. *J. Org. Chem.* **1989**, *54*, 2767. b) Fiandor, J.; Tam, S.Y. *Tetrahedron Lett.* **1992**, *31*, 597.

13) Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165.

14) Jones, G.H.; Tanigushi, M.; Tegg, D.; Moffatt, J.G. *J. Org. Chem.* **1979**, *44*, 1309.

15) Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

16) Montgomery, J.A.; Thomas, H.J. *J. Org. Chem.* **1981**, *46*, 594.

17) Youssefyeh, R.; Tegg, D.; Verheiden, J.P.H.; Jones, G.H.; Moffatt, J.G. *Tetrahedron Lett.* **1977**, *18*, 435 .

18) ^{1}H NMR for **9** ($CDCl_3$, 300 MHz) : 8.81 (bs, NH), 7.61 (dd, J = 2 Hz, J'= 1 Hz, CH_3-6), 7.55 (s, CH_3-6), 6.20 (dd, J = 8.5 Hz, J'= 5.5 Hz, H-1'), 4.10 (AB syst., d, 1H, J = 13 Hz, CH_2-O), 3.80 (m, 2H), 3.66 (m, 2H), 3.41 (AB syst., d, 1H, J = 13 Hz, CH_2-O), (2.45 (m, 1H), 2.15 (d, 1H, J = 6 Hz, $C\underline{H}_3$-CH), 2.05 (d, J = 6 Hz, $C\underline{H}_3$-CH). MS (DIC): *m/z* 324 $[M + NH_4]^+$; 297 $[M + H]^+$; 188; 171; 127.

19) Maag, C.; Wick, A.; Le Ber, P.; Kirn, A.; Aubertin, A.-M. *Antiviral Res.* **1994**, 24, 275.

(*Received in Belgium* 9 *May* 1996; *accepted* 4 *July* 1996)