Tetrahedron Letters, Vol. 33, No. 5, pp. 679-682, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

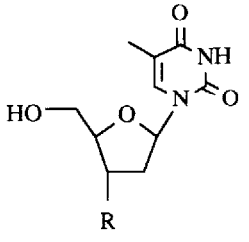
SYNTHESIS OF 3'-ETHYNYLTHYMIDINE, 3'-VINYLTHYMIDINE AND 3'-BROMOVINYLTHYMIDINE AS POTENTIAL ANTIVIRAL AGENTS

Christer Sahlberg

Medivir AB, Lunastigen 7, S-141 44 Huddinge, Sweden

***Abstract**: The synthesis of three novel 3'-unsaturated carbon analogues of AZT and FLT is described. The key step in the synthesis is a Cu(I)- catalyzed addition of vinylmagnesium bromide to a 2,3-unsaturated lactone, followed by, in the case of compounds 2 and 3, elimination reactions of a dibromo-compound.*

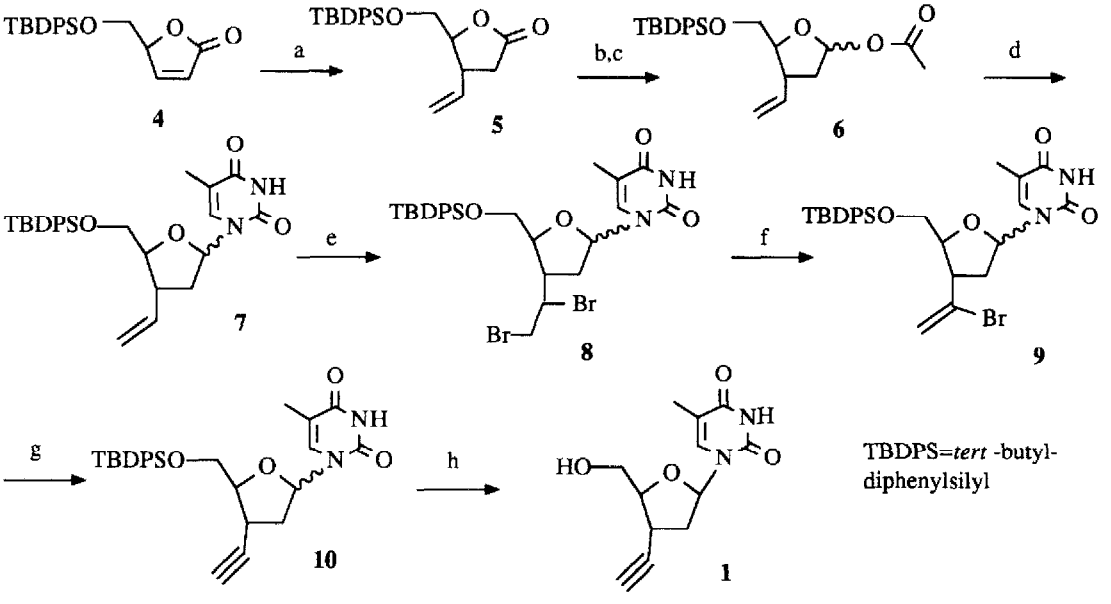
The discovery of the HIV-virus as the causative agent of AIDS, have led to enormous efforts to make and find compounds that can prevent the growth of the HIV-virus. This have led to a resurgent interest for nucleoside analogues, since it was in this class of compounds the first anti-HIV compounds were found. The two most active nucleoside analogues reported are 3'-azido-3'-deoxythymidine (AZT)[1] and 3'-fluoro-3'-deoxythymidine (FLT)[2]. They are about equipotent *in vitro* , however FLT is about 10 times more effective than AZT *in vivo* using a model with monkeys infected by the SIV virus[3]. AZT is the only anti-AIDS drug on the market today and FLT is undergoing clinical trials. In view of this, we have focused our interest on the 3'-unsaturated carbon substituted nucleoside analogues **1, 2** and **3**. These compounds are not reported in the literature and this letter describes their synthesis in a preliminary form.



R = N_3 ; AZT
R = F ; FLT
R = C≡CH ; **1**
R = CH=CH_2 ; **2**
R = CBr=CH_2; **3**

We were first interested in the synthesis of compound **1**, the 3'-ethynyl analogue of AZT. We ruled out the direct route, i.e. reaction of a "up-derivative" with an ethynyl anion, due to preliminary failures upon reactions of the triflate of methyl 5-O-TBDPS-2-deoxy-D-*threo*-pentafuranoside with TMS-ethynyllithium or the ethylendiamine complex of lithium acetylide. Those reactions gave, not unexpectedly, only elimination products. We decided then to change our strategy to the Hanessian's lactone strategy[4], i.e. conjugate addition of a nucleophile, in an anti-fashion, to a chiral lactone. This approach has been used in the synthesis of AZT and analogues[5] and 3'-alkylsubstituted nucleosides[6]. Since it is not possible to add an

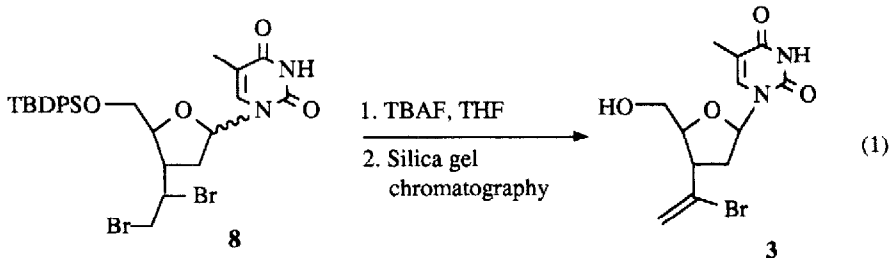
ethynylcuprate to an appropriate lactone[7], an indirect route had to be chosen for the synthesis of the ethynyl compound **1**. This route involves the addition of a vinylcuprate and subsequently transform the vinyl group to the ethynyl group. This approach should also give, besides the target ethynyl nucleoside, also other novel 3'-unsaturated nucleoside analogues. The starting lactone derivative, (S)-(-)-5-(hydroxymethyl)-2(5H)-furanone[8], was transformed to the 5-O-protected analogue **4**. According to preliminary experiments, a catalytic vinylcuprate at about -30°C seemed to be reactive enough to give the 1,4-addition product, a diorganocuprate gave no reaction and a catalytic reagent operating at -70°C gave a very sluggish reaction. Subsequently, compound **4** was reacted with a vinylcuprate, derived from vinylmagnesium bromide and 10% Cu(I)Br•Me_2S complex in THF:ether 3:1, and the desired product **5**[9] was formed in a yield of about 70%. Carbon 13 NMR of **5** showed one single diastereomer and since there are many reported examples in the literature[4,5,6,10] that similair types of reactions give *trans*-products, one can assume with a high degree of certainity that compound **5** is a *trans* product. Furthermoore, the coupling constant of 6.3 Hz between the protons at carbon 3 and 4 is close to the one reported for the analogous methyl compound which is 5.6 Hz[10].



Reagents: [a]CH_2=CH-MgBr, CuBr•Me_2S; [b]DIBAL-H, [c]Ac_2O, DMAP; [d]silylated thymine, *tert*-butylmethylsilyl triflate; [e]Br_2; [f]CH_3ONa; [g]KOH; [h]TBAF.

The vinyllactone was then reduced with DIBAL-H and acetylated with acetic anhydride in the presence of 4-DMAP to give a α,β-mixture of compound **6** in a yield of 71%. The acetate was then condensed with silylated thymine in dichloroethane using *tert*-butyldimethylsilyl triflate as catalyst. This procedure gave a α,β-mixture of **7** in a yield of 79%. The α,β- ratio was about 2:1 as determined by proton

NMR. Now, the desired vinyl nucleoside analogue, i.e. compound **2**[11], could easily be prepared by deprotection of **7**. This was achieved by tetrabutylammonium fluoride in THF and separation of the formed α,β- isomers on silica gel afforded 3'-vinyl-3'-deoxythymidine in a yield of 20%. Bromination of compound **7** using bromine in carbon tetrachloride gave compound **8** in a yield of about 50%. The next step in the synthetic strategy for making the ethynyl compound was to eliminate bromine from **8**. This was achieved by using a 2-step procedure. In the first step, sodium methoxide was used as a base and the vinylbromide compound **9** was formed in a yield of 80%.



(1)

Interestingly, this elimination could also be done by tetrabutylammonium fluoride in THF which gave directly the desired 3'-bromovinylnucleoside **3**[12] in a yield of about 40% (Eq 1). Also, notable is, when reacting **8** with LDA in THF at room temperature the dehalogenated product **7** was formed in a high yield (84%), this type of reaction has been reported using other bases but not[13], to our knowledge, with LDA. The second elimination step was done by KOH in refluxing n-propanol and compound **10** was formed in a yield of about 50%. The final deprotection using TBAF in THF gave after silica gel chromatography compound **1**[14] in a yield of 40%.

The determination of the antiviral activities of these novel 3'-unsaturated nucleoside analogues are in progress in our laboratories.

References and notes

1. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St.Clair, M.H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096-7100.
2. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S,; Vanderhaeghe, H. *J. Med. Chem.*, **1987**, *30*, 1270-1278.
3. Lundgren, B.; Bottiger, D.; Ljungdahl-Stahle, E.; Norrby, E.; Stahle, L.; Wahren, B.; Oberg, B. *J. Acq. Immune Defic. Synd.*, **1991**, *4*, 489-498.
4. Hanessian, S. *Aldrichimica Acta*, **1989**, *22*, 3-14 and references cited therein.
5. Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett.*, **1988**, *29*, 5349-5352.
6. Agyei-Aye, K.; Baker, D. C. *Carbohydrate Research*, **1988**, *183*, 261-275.
7. Alkyne groups are used as "dummy" non transferable ligands in organocuprate chemistry cf. Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.*, **1972**, *94*, 7210-7211.

8. Commercially available from Oxford Chirality, Oxford, U.K.
9. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.44 (dd, j=8.5, 17.6 Hz, 1H), 2.82 (dd, j=8.5, 17.6 Hz, 1H), 3.20 (m, 1H), 3.70 (dd, j=3.5 Hz, 11.7 Hz, 1H), 3.93 (dd, j=2.8, 11.7 Hz, 1H), 4.25 (m, irradiation at 3.82 ppm gave a doublet with j=6.3 Hz, 1H), 5.06-5.14 (m, 2H), 5.68-5.82 (m, 1H), 7.35-7.73(m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.16, 26.69, 34.99, 40.68, 42.37, 63.30, 84.48, 117.34, 127.77, 129.84,132.49, 132.85, 135.48, 135.57, 136.37, 175.80. Anal. Calcd for $C_{23}H_{28}O_3Si$: C, 72.6; H, 7.4. Found: C, 72.6, H,7.5.
10. Mattes, H.; Hamada, K.; Benezra, C. *J. Med. Chem.* **1987,** *30,* 1948-1951, and references cited therein.
11. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.95 (d, j=1.2 Hz, 3H), 2.24-2.42 (m, 2H), 2.52 (t, j=5.2 Hz, 1H), 3.02 (q, j=9.2 Hz, 1H),3.48-3.84 (m, 2H), 3.99-4.06 (m, 1H), 5.14-5.27 (m, 2H), 5.59-5.74 (m, 1H), 6.14-6.18 (m, 1H), 7.65 (d, j=1.2 Hz, 1H), 8.93 (broad s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.72, 39.30, 41.80, 61.03, 85.26, 85.56, 110.65, 118.42, 135.90, 136.42, 150.45, 164.00. HRMS (EI) calculated for $C_{12}H_{16}N_2O_4$: 252.1110, found: 252.1093.
12. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90 (d, j=1.0 Hz, 3H), 2.22-2.35 (m, 1H), 2.63-2.75 (m, 1H), 3.35-4.13 (m, 4H), 5.59 (d, j=1.9 Hz, 1H), 5.89 (d, j=1.9 Hz, 1H), 6.13 (dd, j=3.5, 7.6 Hz), 7.55 (d, j=1.2 Hz, 1H), 9.25 (broad s,). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.72, 37.96, 46.90, 60.83, 83.95, 85.96, 110.96, 120.56, 132.28, 136.87, 150.53, 164.21. HRMS (EI) calculated for $C_{12}H_{15}N_2O_4Br$: 330.0215, found: 330.0236..
13. March, J. *Advanced Organic Chemistry*, Wiley-Interscience: New York 1985; p. 924 and references cited therein.
14. ^{1}H NMR (250 MHz,$CDCl_3$) δ 1.91 (d, j=1.1 Hz, 3H), 2.19 (d, j=2.4 Hz, 1H), 2.40-2.60 (m, 2H), 3.20-3.30 (m4, 1H), 3.84-4.14 (m, 3H), 6.14 (dd, j= 3.5, 3.8 Hz, 1H), 7.49 (d, j=1.3 Hz, 1H), 8.65 (broad s, 21H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.57, 28.57, 39.07, 60.88, 71.39, 81.31, 85.53, 85.71, 110.06, 136.20, 150.01, 163.39. HRMS (EI) calculated for $C_{12}H_{16}N_2O_4$: 250.0954, found: 250.0954.

(Received in UK 22 November 1991)