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SYNTHESIS OF 3'-DEOXY-3'-(2-PROPYNYL)THYMIDINE AND 3'-CYANOMETHYL-3'-DEOXYTHYMIDINE, ANALOGS OF AZT[1]

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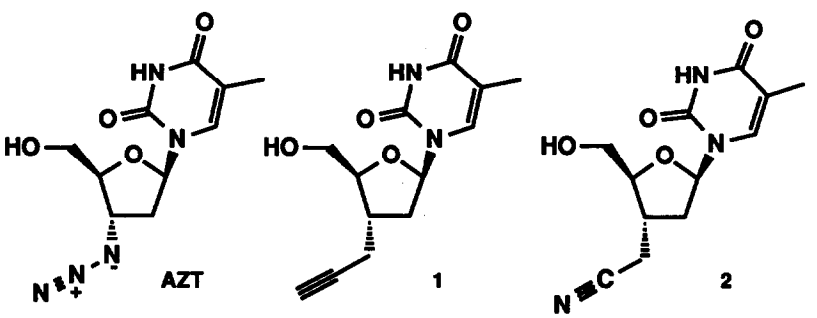
Abstract: An efficient procedure using free radical chemistry for introducing a carbon substituent to the 3'-position of 3'-deoxythymidine is described. An application of this procedure to the synthesis of 3'-deoxy-3'-(2-propynyl)thymidine and 3'-cyanomethyl-3'-deoxythymidine, two close analogs of AZT, is presented.

The introduction of 3'-azido-3'-deoxythymidine (AZT)[2] as the first drug for the treatment of acquired immunodeficiency syndrome (AIDS) has elicited much new interest in the synthesis of 2',3'-dideoxynucleosides. A few additional close analogs of AZT, such as 2',3'-dideoxycytidine (ddC),[3] 2',3'-dideoxyinosine (ddI),[4] are now undergoing active clinical development. Despite the intense synthetic effort in this area,[5] the class of 3'-carbon-substituted-2',3'-dideoxynucleosides remains relatively unexplored. In this paper we report an efficient procedure for introducing a carbon substituent to the 3'-position of the 2',3'-dideoxynucleoside molecule and the application of this procedure to the synthesis of 3'-deoxy-3'-(2-propynyl)thymidine and 3'-cyanomethyl-3'-deoxythymidine, **1** and **2** respectively, two close analogs of AZT.



The strategy we chose to pursue utilizes free radical chemistry to form a new carbon-carbon bond at the 3'-position of nucleosides. The starting material used in our approach was 5'-O-[(1,1-dimethylethyl)-dimethylsilyl]-3'-O-[phenoxythioxomethyl]thymidine (**4**) which was readily obtained from thymidine (**3**) in two steps. Reaction of **4** with three equivalents of allyltributyltin under the conditions developed by Keck[6] (with photochemical initiation) afforded a 76% yield of the 3'-allyl substituted compound **5**[7] together with 10-20% of the 3'-deoxy derivative as a minor product. It is notable that this reaction is stereospecific, resulting in the exclusive formation of the 3'-α-isomer. The stereochemistry at C-3' was inferred from nOe

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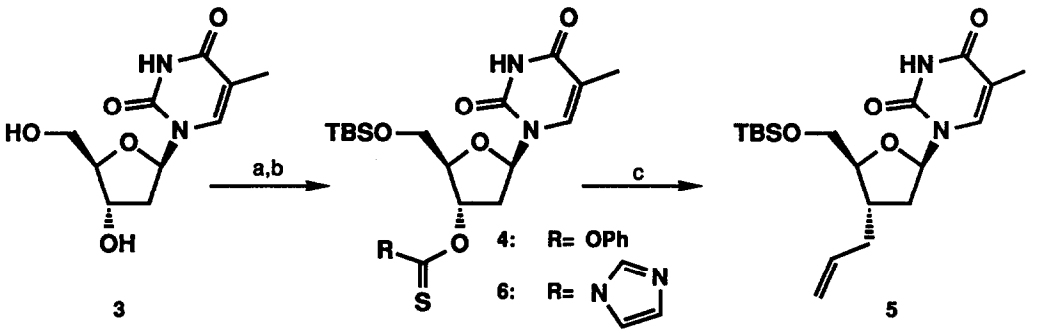
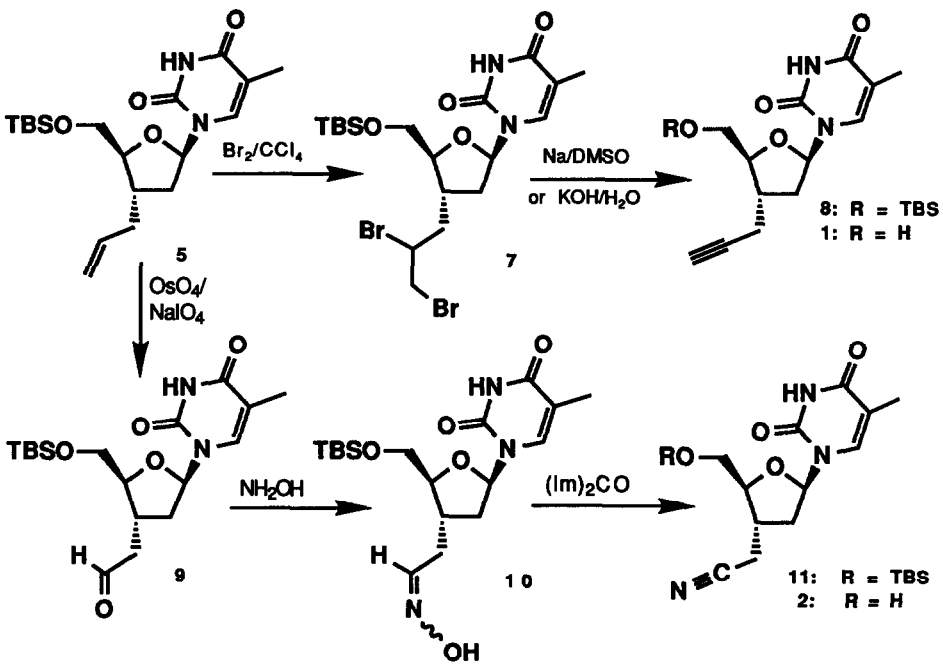
measurements. This assignment was subsequently confirmed by a single crystal X-ray analysis of a related compound which will be discussed below. The same transformation could be carried out utilizing radical initiation by chemical means and thioacylimidazole **6** as the starting material. However, the yield was slightly lower.



Reagents: [a] *t*-BuSi$(CH_3)_2$Cl, imidazole, DMF, 25° C; [b](for **4**): PhOCSCl, dimethylaminopyridine, CH_2Cl_2, 25° C; (for **6**): thiocarbonyldiimidazole, toluene, 80° C; [c](from **4**): CH_2=$CHCH_2Sn(n\text{-}Bu)_3$, toluene, *hv;* (from **6**): CH_2=$CHCH_2Sn(n\text{-}Bu)_3$, AIBN,toluene, 80° C.

Since the allyl group is suitable for diverse structural manipulation, the efficient synthesis of the nucleoside **5** allows easy access to many other structures in this series. As an example, we have converted **5** into two novel 2',3'-dideoxynucleosides, **1** and **2**. These compounds are of interest to us because the side chain at the C-3' position of these molecules are conformationally similar to that of the azido group in AZT.

The synthesis of **1** started with the reaction of the allyl compound **5** with bromine in carbon tetrachloride. The dibromide **7**, obtained in 59% yield, was a mixture of two partially separable isomers. The mixture of these isomers on treatment with Na/DMSO gave a 49% yield of the propargyl compound **8**. Deblocking of **8** with Bu_4NF/THF afforded target compound **1** (85%).[8] Interestingly, this compound was obtained directly from **7** in 77% yield by treatment with aqueous potassium hydroxide. A single crystal X-ray analysis of **1** confirmed our stereochemical assignment at C-3' position as illustrated by the computer drawn structure in Figure 1. Its conformation is very similar to the conformation of one of the two different AZT molecules found in its unit crystal cell.[9] In both cases, the thymine adopts the anti-conformation and the furanose ring pucker is C2' endo/C3' exo. However, the orientation of the side chains at C3' (i.e. N_3 and $CH_2C{\equiv}CH$) relative to the deoxyribose ring is different.



For the synthesis of **2**, the allyl compound **5** was first oxidized with $OsO_4/NaIO_4$ to give a 57% yield of the aldehyde **9**. Attempts to carry out this transformation by ozonolysis led to extensive decomposition. Compound **9** on treatment with hydroxylamine afforded the oxime **10**, which on a subsequent reaction with carbonyldiimidazole followed by deblocking of the 5'-silyl protecting group gave the target compound **2**.[9] The overall yield from **5** was 42%.

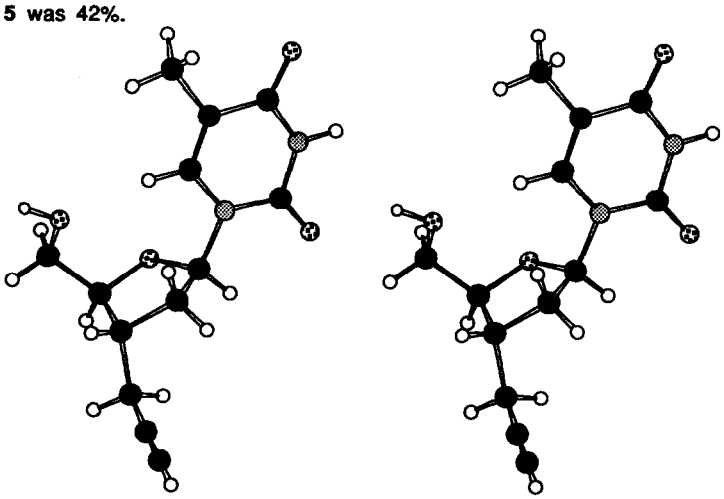


Fig. 1. Stereoview of X-ray structure of compound **1**

In conclusion, free radical chemistry has been utilized successfully to provide an easy entry into the 3'-C-substituted-2',3'-dideoxynucleosides and has made possible the synthesis of two close analogs of AZT, **1** and **2**. Extension of this methodology to the synthesis of other novel nucleosides and the results of biological testing will be reported in due course.

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References and Notes

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8. **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H, CH_3 at C-5), 2.06 (t, 1H, J=2.6 Hz, H-8'), 2.15 (t, 1H, J=5.2 Hz, OH), 2.24-2.39 (m, 4H, H-2', H-6'), 2.62 (m, 1H, H-3'), 3.82 (m, 1H, H-5'), 3.93 (m, 1H, H-4'), 4.07 (m, 1H, H-5'), 6.12 (dd, $J_{1',2'a}$=3.8 Hz, $J_{1',2'b}$=7.3 Hz, H-1'), 7.55 (s, 1H, H-6), 8.29 (br s, 1H, NH-3).

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10. **2**: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 1.86 (s, 3H, CH_3 at C-5), 2.29 (m, 2H, H-2'), 2.61 (m, 2H, H-6'), 2.72 (m, 1H, H-3'), 3.71-3.93 (m, 3H, H-4', H-5'), 5.08 (t, 1H, J=5.2 Hz, OH), 6.11 (dd, 1H, $J_{1',2'a}$=4 Hz, $J_{1',2'b}$=6.3 Hz, H-1'), 7.84 (s, 1H, H-6), 11.10 (br s, 1H, NH-3).

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