Discovery of a Novel Route to β-Thymidine: a Precursor for anti-AIDS Compoundst

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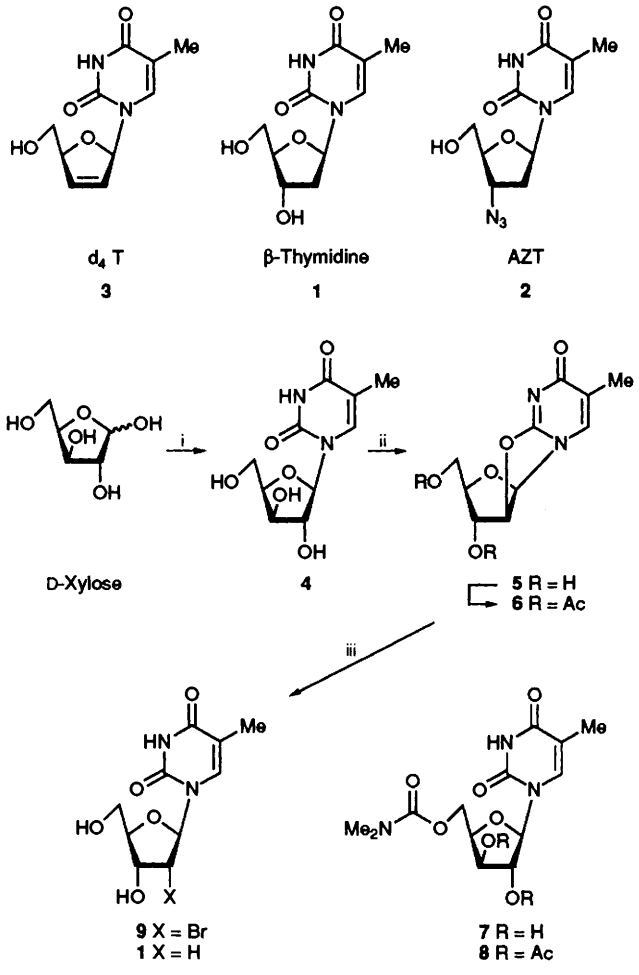
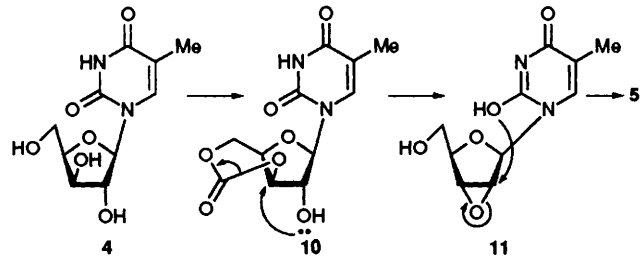
A new approach to the synthesis of β-thymidine from D-xylose is described.

Being a key intermediate for the preparation[1] of the anti-AIDS drug AZT **2**, β-thymidine **1** synthesis shall play a decisive role in determining the price of this drug.[2] β-Thymidine is also a starting material for d_4T **3**, which is presently undergoing clinical trials for anti-HIV activity.[3] Many processes are reported for β-thymidine. However, these processes are fraught with difficulties such as the formation of α- and β-anomers with 2-deoxy-D-ribose as a starting material. Although, with D-ribose, the problem of α- and β-anomers was circumvented, the high cost of D-ribose poses limitations.[2] During our studies on 2′,3′-dideoxynucleosides,[4] we discovered[5] a novel rearrangement by serendipity leading to the formation of β-thymidine starting from an inexpensive D-xylose.



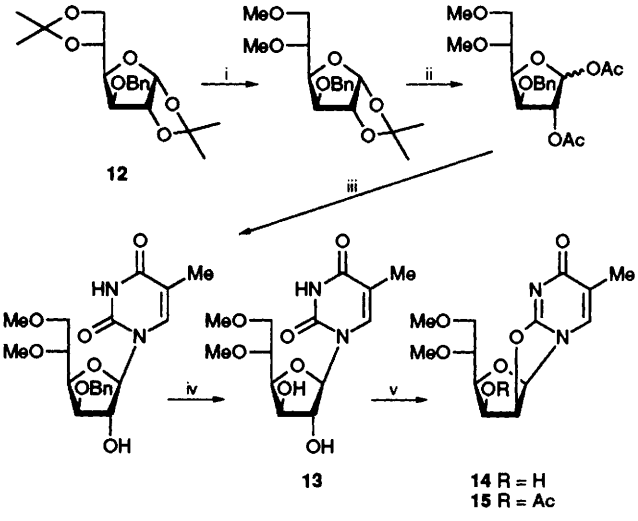
Scheme 1 *Reagents and conditions*: i, (*a*) MeCOMe, $CuSO_4$, H_2SO_4, room temp., 18 h; 77%; (*b*) 0.2% HCl, room temp., 6 h; 86%; (*c*) Py, Ac_2O, room temp., 5 h; 91%; (*d*) AcOH, Ac_2O, H_2SO_4, room temp., 10 h; 88%; (*e*) *O,O*-bis(trimethylsilyl)thymine, $SnCl_4$, CH_2Cl_2, room temp., 18 h; 82.5%; (*f*) NaOMe, MeOH, room temp., 6 h, 94%; (ii). (*a*) $PhOCO_2Ph$, $NaHCO_3$ (cat), DMF, 140–150 °C, 4 h, 55%; (*b*) Py, Ac_2O, room temp., 1 h; (iii). (*a*) Py-HBr salt, Py, reflux, 3 h, 85%; (*b*), H_2/Raney Ni, MeOH, 45 psi 90%



Scheme 2

β-D-Xylofuranosyl-thymine **4** was prepared[6] by a modified route starting from D-xylose. Subsequent treatment of **4** with diphenylcarbonate (1.2 equiv.) in the presence of catalytic amount of sodium hydrogencarbonate in DMF at 140–150 °C for 4 h gave two products after silica gel chromatography. The polar fraction was identified as the 2,2′-anhydro derivative **5** (55%) and found identical with the sample prepared by the known procedure starting from D-ribose.[2] In addition, **5** was conventionally converted into the diacetate derivative **6** whose ^1H NMR, IR and MS analyses and optical rotation values were identical with the diacetate prepared from the authentic sample.‡ On the basis of ^1H NMR and MS data the non-polar component was assigned the structure **7** (20%). This structure was further substantiated by converting **7**, with pyridine and acetic anhydride, into the corresponding diacetate derivative **8**. The above reaction was also conveniently carried out by using diethyl carbonate (6 equiv.) at 150 °C in an autoclave for 7 h to provide **5** in 50% yield. In one experiment the crude mixture from the above reaction was acetylated with pyridine and acetic anhydride and then crystallised from benzene to provide the pure diacetate **6** in 40% yield, without recourse to chromatography.

The 2,2′-anhydro ring in **5** was opened efficiently with pyridiniumhydrobromide salt in pyridine to give the 2′-



Scheme 3 *Reagents and conditions*: i. (*a*) 0.8% H_2SO_4, room temp., 12 h, 88%; (*b*) NaH, MeI, THF, room temp., 8 h, 74.5%; ii. (*a*) 6 mol dm^{-3} H_2SO_4, dioxan, 100 °C, 2 h, 90%; (*b*) AcOH, Ac_2O, H_2SO_4, room temp., 10 h, 88%; iii. (*a*) *O,O*-bis(trimethylsilyl)thymine, $SnCl_4$, CH_2Cl_2, room temp., 18 h, 85%; (*b*) NaOMe, MeOH, room temp., 6 h, 94%; iv. H_2, Pd/C, MeOH, 94%; v. (*a*) $PhOCO_2Ph$, $NaHCO_3$ (cat), DMF, 150 °C, 20 h, 20%; (*b*) Py, Ac_2O, room temp., 1 h, 89%

bromo-2′-deoxy derivative **9** which on hydrogenation over Raney nickel gave β-thymidine **1** mp 182–184 °C (lit.[2] 186–187 °C) (Scheme 1).

The unusual formation of 2,2′-anhydro derivative **5** with concomitant epimerisation at C-3′ was indeed surprising. Mechanistically we suggest that **5** was probably formed from the 3′,5′-carbonate intermediate **10** which underwent rearrangement *via* the 2′,3′-oxirane intermediate **11**, as presented in Scheme 2. We substantiated this mechanistic consideration by blocking the 5′-position in the precursor 5′,6′-di-*O*-methyl-β-D-glucofuranosyl thymine **13** prepared from the diacetonide derivative **12**[7] (Scheme 3). The reaction of **13** with diphenylcarbonate, sodium hydrogencarbonate in DMF at 150 °C was found to be sluggish. However, after 20 h **14** was isolated in 20% yield in which no epimerisation had occurred at C-3′. On the basis of spectral analysis,§ the structures of **14** and its monoacetate **15** were unambiguously assigned.

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Footnotes

† IICT Communication No. 3340.

‡ **6**: mp 178 °C; $[\alpha]_D$ −75 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H), 1.92 (s, 3H), 2.13 (s, 3H), 3.96 (dd, 1H, *J* 4.2, 12.7 Hz), 4.25 (dd, 1H, *J* 3.8, 12.7 Hz), 4.44 (br s, 1H), 5.34 (br s, 1H), 5.40 (d, 1H, *J* 6.3 Hz), 6.29 (d, 1H, *J* 6.3 Hz), 7.20 (s, 1H); mass: 324 (M^+).

§ **15**: mp 219 °C; $[\alpha]_D$ −120.5 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.0 (s, 3H), 2.12 (s, 3H), 3.34, 3.4 (2s, 6H), 3.45 (m, 2H), 3.66 (m, 1H), 4.28 (dd, 1H, *J* 4.2, 6.3 Hz), 5.42 (t, 1H, *J* 6.3 Hz), 5.64 (t, 1H, *J* 6.3 Hz), 6.02 (d, 1H, *J* 6.3 Hz), 7.22 (s, 1H).

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