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Note

# A facile synthesis of 1-(5′-*O*-acetyl-3′-*O*-benzyl-β-D-xylofuranosyl)thymidine: a potentially viable intermediate for the preparation of the anti-AIDS drugs, AZT and D4T

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**Abstract**

The title compound has been synthesized by smooth condensation of 1,2-anhydro-5-*O*-acetyl-3-*O*-benzyl-α-D-xylofuranose, obtained from D-xylose through a series of mild and effective reactions, with activated thymine in the absence of catalyst. 

*Keywords:* Nucleoside; 1,2-Anhydro sugar; Xylose

## 1. Introduction

3′-Azido-3′-deoxythymidine (AZT) and 2′,3′-didehydro-3′-deoxythymidine (D4T) are known to be useful for the treatment of viral infections, most notably for the treatment of AIDS [1]. AZT and D4T are prepared from the 2′-deoxyribonucleoside, thymidine [2,3]. Recently effective syntheses of AZT and D4T with the ribonucleoside, 5-methyluridine, as the starting material, have been reported [4]. However, thymidine and 5-methyluridine are relatively expensive materials, and their commercial availability is relatively limited. Thus, extensive research has been focused on developing more efficient procedures for AZT and D4T using D-xylose [5] or D-glucofuranose [6] as the starting material by taking advantage of the 2′,α-hydroxy group (in the carboxylic ester form) to direct the required β-coupling. This method seems most hopeful because of the use of inexpensive and readily available materials and the highly anomeric selectivity in the thymine-base coupling, but the lengthy selective 5-protection and 2-deprotection of the sugar moieties and tedious separation and purification of the regioisomers and the glycose-base coupling product remain problems. Here we would like to report a facile procedure for preparation of 1-(5′-*O*-acetyl-3′-*O*-benzyl-β-D-xylofuranosyl)thymidine: a potentially viable intermediate for the synthesis of anti-AIDS drugs, AZT and D4T.

Intermediate **4** was prepared in four steps in 75% overall yield starting from D-xylose [7,8]. Treatment of **4** in methanol containing NaOH

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smoothly gave methyl 3,5-di-*O*-benzyl-α-D-lyxofuranoside (**5**) in nearly quantitative yield. This is a highly effective two-step, one-pot reaction via an intermediate of 1,2-anhydro-3,5-di-*O*-benzyl-β-D-lyxofuranose. Tosylation of **5** quantitatively afforded the corresponding xylofuranoside 2-sulfonate **6**. Selective acetolysis of **6** using $AcOH–Ac_2O–H_2SO_4$ gave the corresponding 1,5-diacetate **7**. It was found that selective removal of the 1-*O*-acetyl group of **7** by known methods such as using $SnCl_4$ [9] or $N_2H_4$·AcOH [10] suffered from low yields and tedious separation. However the 1-*O*-acetyl group was very successfully removed under the conditions designated for selective removal of the 2-*O*-trichloroacetyl group [11] of 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucopyranosyl chloride. Thus the key intermediate **8** was quantitatively obtained from treatment of **7** in anhydrous ether saturated with dry ammonia. Since most of the above-applied reactions gave very high yields, the intermediates **2**, **3**, **5**, **6**, and **7** involved in the procedure could be subjected directly to the next reaction without chromatographic separation. We were also gratified to note that ring closure of **8** with KO′Bu in THF gave the 5-*O*-acetyl-1,2-anhydro-3-*O*-benzyl-α-D-xylofuranose (**9**) in almost quantitative yield. The anhydro sugar **9** was identified from its $^1$H NMR spectrum showing upfield peaks from H-2 at 3.50 ppm, a salient feature of the epoxide ring. Reaction of **9** with trimethylsilylated thymine in the absence of Lewis acid provided a mixture of **10** (60%) and **11** (26%) in a total yield of 86%. Compound **10** is unstable and easily converted to **11** under weakly acidic conditions.

In summary, we have successfully developed a facile procedure for preparation of 1-(5′-*O*-acetyl-3′-*O*-benzyl-β-D-xylofuranosyl)-thymidine. Most of the reactions involved in the procedure were carried out readily in high yields under mild conditions (see Scheme 1), and coupling of the base with the xylofuranosyl donor was neat, giving the target nucleoside in high yield. Compound **11**, as well as its precursors such as **9**, may be useful for other applications in organic synthesis, e.g., it may be a potentially viable intermediate for the synthesis of anti-AIDS drugs, AZT and D4T.

## 2. Experimental

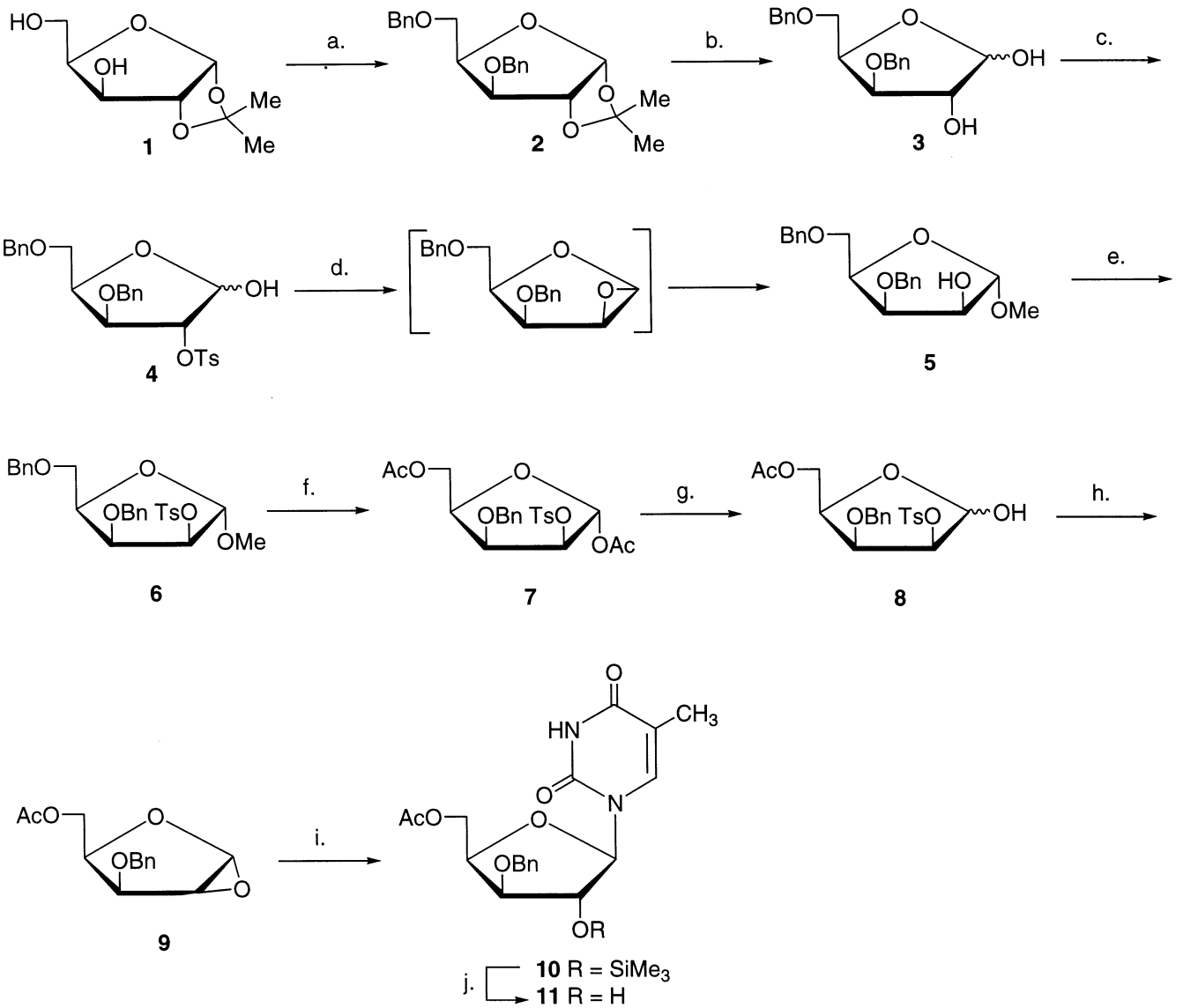
*General methods.*—Optical rotations were determined at 25 °C with a Perkin–Elmer model 241-Mc automatic polarimeter. Melting points were determined with a 'Mel-Temp' apparatus. $^1$H NMR spectra were recorded with Bruker ARX 400 spectrometers for solutions in $CDCl_3$. Chemical shifts are given in parts per million (ppm) downfield from internal $SiMe_4$. Mass spectra were recorded with a JMS-D300S mass spectrometer using a direct sample introduction technique. Thin-layer chromatography (TLC) was performed on Silica Gel $HF_{254}$ with detection by charring with 30% (v/v) $H_2SO_4$ in MeOH or in some cases by UV detection. Column chromatography was conducted by elution of a column ($16 \times 240$, $18 \times 300$, $35 \times 400$ mm) of silica gel (100–200 mesh) with EtOAc–petroleum ether (60–90 °C) as the eluent. Solutions were concentrated at $< 60$ °C under diminished pressure.

*Methyl 3,5-di*-O-*benzyl*-α-D-*lyxofuranoside* (**5**).—3,5-Di-*O*-benzyl-2-*O*-tosyl-D-xylofuranose (**4**) [8] (3.5 g, 7.23 mmol) was dissolved in anhyd MeOH (50 mL) containing NaOH (0.35 g, 8.75 mmol), and the mixture was stirred at room temperature (rt) for 30 min. TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated to dryness, the residue was repeatedly extracted with 3:1 petroleum ether–EtOAc, and the combined extracts were concentrated to afford **5** quantitatively as a syrup. The $^1$H NMR data of compound **5** thus obtained were identical to those of the same compound prepared from methanolysis of 1,2-anhydro-3,5-di-*O*-benzyl-β-D-lyxofuranose [8].

*Methyl 3,5-di*-O-*benzyl-2*-O-*tosyl*-α-D-*lyxofuranoside* (**6**).—To a soln of **5** (5.2 g, 15.1 mmol) in pyridine (50 mL) was added TsCl (4.3 g, 22.8 mmol). The mixture was stirred at 50 °C for about 24 h. Then the reaction mixture was poured into ice-cold water and extracted with $CH_2Cl_2$ ($3 \times 25$ mL). The organic layer was washed with 1 N HCl ($3 \times 50$ mL) dried over $Na_2SO_4$, concentrated to a syrup,

which was subjected to column chromatography with 3:1 petroleum ether–EtOAc as the eluent. Compound **6** was obtained as a syrup (7.2 g, 96%,); $[\alpha]_D$ +46° (*c* 5.5, $CHCl_3$); $^1H$ NMR: $\delta$ 7.79 (d, 2 H, Ph-*H* of Ts), 7.39–7.19 (m, 12 H, 2 Ph-*H*), 4.90 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.78 (dd, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 6.3 Hz, H-2), 4.58, 4.46 (2 d, 2 H, *J* 11.8 Hz, PhC$H_2$), 4.51, 4.34 (2 d, 2 H, *J* 12.1 Hz, PhC$H_2$), 4.37–4.26 (m, 2 H, H-3, 4), 3.74–3.58 (m, 2 H, H-5, 5′), 3.23 (s, 3 H, OC$H_3$), 2.40 (s, 3 H, PhC$H_3$). Anal. Calcd for $C_{27}H_{30}O_7S$: C, 65.04; H, 6.07. Found: C, 65.14; H, 6.05.

*1,5-Di-*O*-acetyl-3-*O*-benzyl-2-*O*-tosyl-α-*D*-lyxofuranose* (**7**).—A soln of compound **6** (3.4 g, 6.83 mmol) in AcOH (34 mL) and $Ac_2O$ (5 mL) was cooled to 10 °C in an ice bath, and $H_2SO_4$ (3 mL) was added dropwise over 20 min. After the addition was complete, the ice-bath was removed, and the reaction was continued for 16 h at ambient temperature. The reaction soln was poured into a soln of ice-water (120 mL). Stirring was continued for an additional 30 min, and the aq soln was extracted with $CHCl_3$ (3 × 25 mL). The com-




Scheme 1. Reagents and reaction conditions: (a) BnBr (2.2 equivalents)/THF/NaH (3.3 equivalents), reflux, 4 h, 94%. (b) 30% AcOH, reflux, 3 h, 95%. (c) TsCl (1.5 equivalents)/$K_2CO_3$ (1.5 equivalents)/pyridine, rt, 75%. (d) $CH_3OH$/NaOH (1.2 equivalents), rt, 1 h, 98%. (e) TsCl (1.5 equivalents), pyridine, 50 °C, 10 h, 96%. (f) 7:1:0.6 (v/v) AcOH–$Ac_2O$–$H_2SO_4$, rt, 24 h, 97%. (g) anhydrous ether saturated with dry ammonia, rt, 24 h, 96%. (h) potassium *tert*-butoxide (1.1 equivalents), THF, rt, 20 min, 97%. (i) silylated thymine (1.3 equivalents), $CH_2Cl_2$, rt, 12 h, 86%. (j) $CH_3CN$ containing 4% HCOOH, rt, 15 min, 100%.

bined $CHCl_3$ extracts were carefully washed with 10% aq $NaHCO_3$ ($3 \times 70$ mL), and the solvent was removed in vacuo to a constant weight affording 3.17 g (97%) of compound **7** as a syrup; $[\alpha]_D$ +18° (*c* 6.3, $CHCl_3$); $^1$H NMR: (Mainly α anomer), $\delta$ 7.80 (d, 2 H, Ph-*H* of Ts), 7.41–7.22 (m, 7 H, Ph-*H*), 6.15 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.0 (dd, 1 H, $J_{1,2}$ 3.4, $J_{2,3}$ 8.8 Hz, H-2), 4.68, 4.47 (2 d, 2 H, *J* 12.1 Hz, PhC$H_2$), 4.50–4.30 (m, 2 H, H-3, 4), 4.18–4.04 (m, 2 H, H-5, 5′), 2.41 (s, 3 H, PhC$H_3$), 2.02, 1.98 (2 s, 6 H, 2 COC$H_3$). Anal. Calcd for $C_{23}H_{26}O_9S$: C, 57.73; H, 5.48. Found: C, 57.83; H, 5.48.

*5*-O-*Acetyl*-*3*-O-*benzyl*-*2*-O-*tosyl*-D-*lyxofuranose* (**8**).—A soln of compound **7** (3.5 g, 7.32 mmol) in anhyd ether (100 mL) satd with dry $NH_3$ was stirred for 24 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The soln was concentrated to afford 3.06 g (96%) of compound **8** as an approx equal mixture of α and β anomers. An analytical sample was obtained as an anomeric mixture by column chromatographic purification using 3:1 petroleum ether–EtOAc as the eluent; $[\alpha]_D$ +19° (*c* 4.3, $CHCl_3$); $^1$H NMR: $\delta$ 7.85 (d, $2 \times 0.5$ H, Ph*H* of Ts of β anomer), 7.80 (d, $2 \times 0.5$ H, Ph-*H* of Ts of α anomer), 7.41–7.18 (m, 7 H, Ph*H*), 5.45 (d, 0.5 H, $J_{1,2}$ 3.0 Hz, H-1 of α anomer), 4.98 (d, 0.5 H, $J_{1,2}$ 6.8 Hz, H-1 of β anomer), 4.84 (dd, 0.5 H, H-2 of α anomer), 4.71 (t, $J_{1,2} = J_{2,3} = 6.8$ Hz, H-2 of β anomer), 4.66–4.24 (m, 4 H, PhC$H_2$, H-3, 4), 4.19–4.04 (m, 2 H, H-5, 5′), 2.44 (s, $3 \times 0.5$ H, PhC$H_3$ of α anomer), 2.41 (s, $3 \times 0.5$ H, PhC$H_3$ of β anomer), 2.02 (s, $3 \times 0.5$ H, COC$H_3$ of α anomer), 2.00 (s, $3 \times 0.5$ H, COC$H_3$ of β anomer). Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.78; H, 5.54. Found: C, 57.88; H, 5.46.

*1,2*-*Anhydro*-*5*-O-*acetyl*-*3*-O-*benzyl*-α-D-*xylofuranose* (**9**).—To a soln of **8** (560 mg, 1.28 mmol) in dry oxolane (6 mL) was added potassium *tert*-butoxide (158 mg, 1.41 mmol), and the mixture was stirred at rt for 10 min, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the starting material had disappeared. The mixture was concentrated to dryness, and the residue was repeatedly extracted with 3:1 petroleum ether–EtOAc. Concentration of the combined extracts yielded **9** as a syrup (314 mg, 96%); $[\alpha]_D$ −20.3° (*c* 2.9, $CHCl_3$); $^1$H NMR: $\delta$ 7.44–7.24 (m, 5 H, Ph-*H*), 5.28 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 4.63, 4.58 (2 d, 2 H, *J* 11.8 Hz, PhC$H_2$), 4.39–4.10 (m, 4 H, H-3,4,5a,5b), 3.60 (t, 1 H, $J_{1,2} = J_{2,3} = 1.4$ Hz, H-2), 2.02 (s, 3 H, COC$H_3$); *m*/*z*: $[M]^+$ 264, $[M - Bn]^+$ 173.

*1-(5′*-O-*Acetyl*-*3′*-O-*benzyl*-β-D-*xylofuranosyl)thymidine* (**11**).—To a stirred soln of *O*,*O*-bis-(trimethylsilyl)thymidine (235 mg, 0.87 mmol) in dry $CH_2Cl_2$ (4 mL) with molecular sieves (4 Å, 0.5 g) was added compound **9** (204.8 mg, 0.80 mmol) in dry $CH_2Cl_2$ (4 mL). The mixture was stirred for 10 h at rt, at the end of which time TLC (1:1 petroleum ether–EtOAc) indicated that the starting material **9** had disappeared. The mixture was diluted with $CH_2Cl_2$ (30 mL) and filtered, and the filtrate was concentrated to a syrup, which was subjected to column chromatography with 1:2 petroleum ether–EtOAc as the eluent. Compound **10** (225.4 mg, 61%) and **11** (78 mg, 25%) were obtained. $^1$H NMR For **10**: $\delta$ 9.16 (s, 1 H, N-*H*), 7.61 (s, 1 H, H-6), 7.41–7.20 (m, 5 H, Ph*H*), 5.74 (s, 1 H, H-1′), 4.71–4.05 (7 H, H-2′,3′,4′,5′a,5′b, PhC$H_2$), 2.03 (s, 3 H, COC$H_3$), 1.53 (s, 3 H, C$H_3$), 0.09 (s, 9 H, Si(C$H_3$)$_3$). Compound **10** was quantitatively converted to **11** in a solution of $CH_3CN$ (10 mL) containing HCOOH (0.4 mL) within 5 min. Compound **11** crystallized from its dilute soln of 1:2 petroleum ether–EtOAc; mp 81–83 °C; $[\alpha]_D$ −33.1° (*c* 2.9, $CHCl_3$);. $^1$H NMR: $\delta$ 9.44 (s, 1 H, N-*H*), 7.54 (s, 1 H, H-6), 7.40–7.21 (m, 5 H, Ph*H*), 5.82 (s, 1 H, H-1′), 4.70–4.00 (7 H, H-2′,3′,4′,5′a,5′b, PhC$H_2$), 3.10 (bs, 1 H, O*H*), 2.04 (s, 3 H, COC$H_3$), 1.52 (s, 3 H, C$H_3$). Anal. Calcd for $C_{19}H_{22}N_2O_7$: C, 58.45; H, 5.68. Found: C, 58.38; H, 5.71.

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