J. Serb. Chem. Soc. 67(1)1–6(2002)
JSCS – 2917

UDC 546.56+546.47:66.061+620.168.3
Original scientific paper

An efficient *de novo* synthesis of 3'-deoxythymidine from D-xylose

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(Received 24 April 2001)

An efficient stereospecific synthesis of 3'-deoxythymidine has been achieved, starting from D-xylose. The key step of the synthesis involved the NBS promoted conversion of 5-*O*-benzoyl-2,3-di-*S*-ethyl-2,3-dithio-D-ribose diethyl dithioacetal (**4**) into the 1-*O*-acetyl-5-*O*-benzoyl-2,3-di-*S*-ethyl-2,3-dithio-β-D-ribofuranose (**5**), followed by the stereospecific coupling of the intermediate **5** with silylated thymine, in the presence of ethylaluminium dichloride as the catalyst.

Keywords: 3'-deoxythymidine, dethioacetalization, *N*-glycosylation, modified nucleosides, D-xylose.

INTRODUCTION

Since the discovery of the Human Immunodeficiency Virus (HIV) as the etiologic agent of AIDS,[1] intense efforts have been devoted to the synthesis and biological evaluation of compounds with potential anti-HIV activity. Several 2',3'-dideoxy nucleosides have proved to be selective inhibitors of HIV replication. Among them 3'-azido-3'deoxythymidine (AZT),[2] 2',3'-dideoxycytidine (ddC)[3] and 2',3'-dideoxyinosine (ddI)[3,4] have been used clinically for the treatment of AIDS patients. Significant progress has been made in the synthesis of new dideoxynucleosides and their analogues[5] due to the urgent demand for better, as well as for a wider variety of therapeutic agents for the treatment of AIDS. Generally, the best method for synthesizing pyrimidine nucleosides seems to be a convergent strategy in which a protected furanose derivative is coupled with a silylated base in the presence of a Lewis acid as catalyst. However, this type of condensation gives poor stereoselectivity with 2',3'-dideoxy sugar derivatives.[6,7] This disadvantage has recently been overcome by introducing a phenylselenyl group at the C-2 of the sugar moiety, which directs the *N*-glycosylation to-

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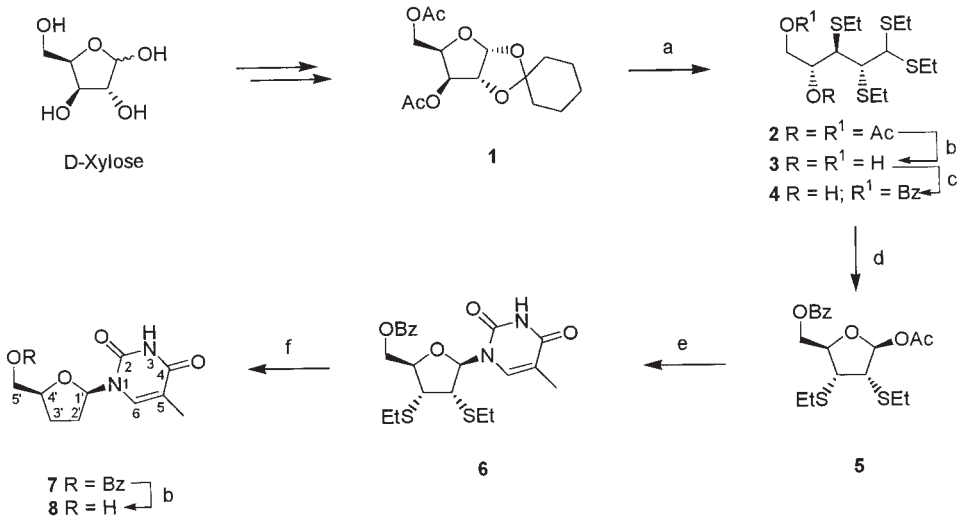


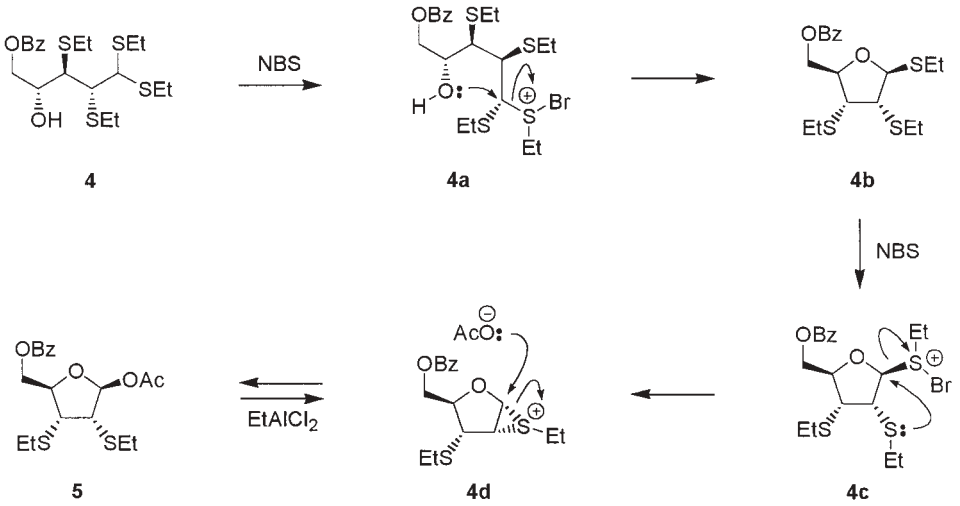
Scheme 1. (a) EtSH, HCl, 0 ºC; (b) NaOMe, MeOH, RT; (c) BzCl, Py, –10 ºC; (d) NBS, AcONa, AcOH, MeCN, 0 ºC; (e) Silylated thymine, $EtAlCl_2$, CH_2Cl_2, RT; (f) RaNi, EtOH, reflux.

wards the formation of a nucleoside with the *trans* relationship of the phenylselenyl group and the pyrimidine base.[8,9] These findings prompted us to prepare a protected 2,3-di-*S*-ethyl-2,3-dithio-D-ribofuranose derivative **5** (Scheme 1), assuming that presence of a C-2 ethylthio group would also enable a favorable selectivity for the formation of β-nucleosides. This paper illustrates the value of D-xylose as a starting material for the *de novo* synthesis of 3'-deoxythymidine[10] (**8**) *via* the intermediate **5**.

RESULTS AND DISCUSSION

D-Xylose was converted to the 3,5-di-*O*-acetyl derivative **1** by using slightly modified literature procedures[11,12] which enabled the preparation of **1** in multi-gram quantities, and in 62 % overall yield.[13] Compound **1** was further transformed to the diethyl dithioacetal derivative **4** by using a known,[14] but rather efficient, three-step sequence. This sequence consists of first the ethanethiolysis of **1** to give the acyclic diethyl dithioacetal **2** (82 %), followed by *O*-deacetylation of **2** into the corresponding diol **3** (90 %) and finally the selective benzoylation of **3** to give the 5-*O*-benzoyl derivative **4** (98 %). The key intermediate **4** was thus obtained in an overall yield of 72 % from the last 3 synthetic steps (43 % from D-xylose).

Treatment of compound **4** with *N*-bromosuccinimide in the presence of sodium acetate and glacial acetic acid afforded the 1-*O*-acetyl derivative **5**. The reaction was carried out in dry acetonitrile at 0 ºC for 10 min, whereupon the desired product **5** was obtained as a single stereoisomer in 86 % yield. The absence of vicinal couplings between H-1 and H-2 ($J_{1,2} \approx 0$ Hz), which would indicate a *trans* relationship of these protons confirmed the β-configuration at the anomeric position of product **5**. A possible mechanism of this reaction (Scheme 2) presumably involves the bromination of the thioacetal function in **4** followed by nucleophilic ring closure to the thioglycoside **4b**.



Scheme 2. Possible mechanism of the formation of **5**.

Further bromination of the anomeric thioethyl group of intermediate **4b**, followed by intramolecular nucleophilic attack of the C-2 thioether function, leads to a bicyclic sulfonium ion **4d**, which, after being subjected to nucleophilic opening with acetate ions (or acetic acid), gives the intermediate **5**. The last step of the process was fully regio- and stereospecific, allowing the isolation of β-anomer as the only stereoisomer. To the best of our knowledge, the transformation of **4** to **5** represents the first example of a direct conversion of an acyclic sugar dithioacetal derivative into the corresponding furanosyl acetate. If this reaction is general it would be a convenient method for the preparation of protected 1-*O*-acyl sugar derivatives.

The condensation of **5** and silylated thymine in the presence of trimethylsilyl triflate gave an unseparable mixture of the corresponding α and β anomers in 60 % combined yield, containing the β- anomer **6** as the predominant component in the mixture*. However, when derivative **5** was allowed to react with silylated thymine in the presence of ethylaluminium dichloride as the catalyst, the β-anomer **6** was obtained as a single stereosomer in 72 % yield. No α-anomer was detected in the reaction mixture by either TLC or ^{1}H-NMR. The high stereoselectivity observed in this reaction is presumably due to an initial Lewis acid promoted conversion of **5** to the episulfonium ion **4d** (Scheme 2), followed by a regio- and stereospecific nucleophilic ring opening in **4d** with silylated thymine, analogously to the well known Vorbrüggen method.[15]

Raney nickel desulfurization of **6** gave the corresponding dideoxy derivative **7** (62 %), which was further deprotected by treatment with sodium methoxide in methanol to afford the final product **8** in 82 % yield. The overall yield of 3'-deoxythymidine (**8**) from D-xylose was 13.6 %.

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* According to ^{1}H-NMR spectral data, it appeared to be an 1:12 mixture of the α and β anomer, as established by integration of the corresponding proton signals [δ 6.23 (*d*, $J_{1',2'}$ 4.2 Hz, H-1' α) and 5.98 (*d*, $J_{1',2'}$ 2.4 Hz, H-1' β)].

In summary, this paper reports a practical ten-step synthesis of 3'-deoxythymidine (**8**) from D-xylose through key steps which involved the NBS dethioacetalization of the diethyl dithioacetal derivative **4**, followed by the stereospecific coupling of the 1-*O*-acetyl derivative **5** with silylated thymine. Considering that the synthetic precursor of **1** is readily available by direct derivatization of the crude xylose syrup isolated from corncobs,[12] the 3'-deoxythymidine (**8**) might be prepared in an overall yield of 3.4 % with respect to corncobs as the starting material.

EXPERIMENTAL

General methods

Melting points were determined on a Kofler apparatus and are not corrected. Optical rotations were measured on a Polamat A (Carl Zeiss, Jena) automatic polarimeter at room temperature. NMR spectra were recorded on a Bruker AC 250 E instrument and the chemical shifts are expressed in ppm downfield from Me_4Si. Thin-layer chromatography was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Column chromatography was carried out on Kieselgel 60 (0.040 – 0.063 mm; E. Merck). All organic extracts were dried with anhyd Na_2SO_4. Organic solutions were concentrated using a rotary evaporator under reduced pressure with the bath temperature below 30 ºC.

1-O-*Acetyl-5*-O-*benzoyl-2,3-di*-S-*ethyl-2,3-dithio*-β-*D-ribofuranose* (***5***)

To a stirred and cooled suspension (–10 ºC) of **4** (2 g, 4.47 mmol) and sodium acetate (6.1 g, 73 mmol) in a mixture of glacial acetic acid (40 mL) and acetonitrile (40 mL) *N*-bromosuccinimide (2g, 11.16 mmol) was added. The reaction mixture was stirred for 10 min at 0 ºC, then poured into cooled aq 10 % $Na_2S_2O_3 \times 5\ H_2O$ (100 mL) and extracted with EtOAc (3×50 mL). The extracts were washed with satd. aq. $NaHCO_3$ and brine, dried and concentrated. The residue was purified by column chromatography (5:1 light petroleum–Me_2CO) to give pure **5** (1.5 g, 86 %) as a colourless syrup: $[\alpha]_D$ – 25.2º (*c* 1.08 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 7.39–8.13 (*m*, 5 H, Ph), 6.28 (*s*, 1 H, H-1), 4.74 (*dd*, 1 H, $J_{5a,5b}$ 12.1, $J_{4,5b}$ 2.5 Hz, H-5*b*), 4.41 (*dd*, 1 H, $J_{4,5a}$ 4.3 Hz, H-5*a*), 4.34 (*m*, 1 H, $J_{3,4}$ 10.8 Hz, H-4), 3.74 (*dd*, 1 H, $J_{2,3}$ 6.3 Hz, H-3), 3.55 (*d*, 1 H, H-2), 2.81–2.60 (*m*, 4 H, 2 × S$CH_2$$CH_3$), 1.90 (*s*, 3 H, CH_3CO), 1.35–1.24 (*m*, 6 H, 2 × S$CH_2C$$H_3$); ^{13}C-NMR ($CDCl_3$): δ 169.70 ($CH_3$*C*O), 165.90 (Ph*C*O), 129.80, 133.10, 129.60 and 128.30 (aromatic), 101.90 (C-1), 83.30 (C-4), 63.60 (C-5), 54.30 (C-2), 45.90 (C-3), 26.90 and 26.00 (2 × SCH_2*C*H_3), 21.10 (*C*H_3CO), 14.60 and 14.40 (2 × SCH_2*C*H_3).

1-(5-O-*Benzoyl-2,3-di*-S-*ethyl-2,3-dithio*-β-*D-ribofuranosyl)thymine* (***6***)

A mixture of thymine (0.0393 g, 0.312 mmol), 1,1,1,3,3,3-hexamethyldisilazane (0.3 mL, 1.42 mmol), and ammonium sulfate was refluxed for 2 h and then cooled to room temperature. The mixture was concentrated *in vacuo* to give a residue, to which a solution of compound **5** (0.1 g, 0.26 mmol) in dry dichloromethane (5 mL) was added, followed by the addition of a 1.8 M solution of $EtAlCl_2$ in toluene (0.2 mL, 0.36 mmol) over a period of 1 h at room temperature. The reaction mixture was stirred further for 1 h at room temperature and then poured into satd. aq. $NaHCO_3$ with stirring. The mixture was stirred for 10 min and then extracted with dichloromethane (3 × 5 mL). The extracts were washed with brine, dried and concentrated. The syrupy residue was purified by column chromatography (3:2 light petroleum–Me_2CO) to give pure **6** (0.085 g, 72 %): m.p. 112 ºC, $[\alpha]_D$ +82.33º (*c* 0.95 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.24 (*bs*, 1 H, D_2O exchangeable, NH), 8.08–7.43 (*m*, 5 H, Ph), 7.41 (*q*, 1 H, $J_{6,Me}$ 1.2 Hz, H-6), 5.98 (*d*, 1 H, $J_{1',2'}$ 2.4 Hz, H-1'), 4.86 (*dd*, 1 H, $J_{5a',5b'}$ 12.8, $J_{4',5b'}$ 2.1 Hz, H-5*b*'), 4.59 (*dd*, 1 H, $J_{4',5a'}$ 3.8 Hz, H-5*a*'), 4.42 (*m*, 1 H, $J_{3',4'}$ 10.2 Hz, H-4'), 3.80 (*dd*, 1 H, $J_{2',3'}$ 7.0 Hz, H-2'), 3.61 (*dd*, 1 H, H-3'), 2.86 and 2.67 (2 × *q*, 4 H, 2 × S$CH_2$$CH_3$), 1.59 (*d*, 3 H, 5-$CH_3$ from Thy), 1.35–1.21 (2 × *t*, 6 H, 2 × S$CH_2C$$H_3$); ^{13}C-NMR ($CDCl_3$): δ 165.93 (Ph*C*O), 163.78 (C_4=O), 150.15 (C_2=O), 135.03 (C-6), 133.66, 129.47 and 128.74 (aromatic), 110.67 (C-5), 91.83 (C-1'), 83.29 (C-4'), 62.97 (C-5'), 54.11 (C-2'), 46.05 (C-3'), 26.87 and 26.09 (2 × SCH_2CH_3), 14.57 and 14.46 (2 × SCH_2*C*H_3), 12.30 (5-CH_3 from Thy).

*1-(5'-*O*-Benzoyl-2',3'-dideoxy-*β*-D-glycero-pentofuranosyl)thymine* (***7***)

To a solution of **6** (75 mg, 0.155 mmol) in ethanol (1 mL) was added a suspension of Raney nickel (1.5 mL) in ethanol and the reaction mixture was stirred at reflux temperature for 2 h. The suspension was filtered through a Celite pad and the catalyst was washed with ethanol. The combined filtrate and washings were concentrated and the remaining oily residue was treated with dry dichloromethane (3 × 5 mL). The organic solutions were washed with brine, dried and concentrated. Column chromatography (3:2 light petroleum–Me_2CO) of the residue afforded pure 7 (32 mg, 62 %) as a colourless syrup: $[\alpha]_D$ +31.7º (*c* 0.86 CH_3OH); ^{1}H-NMR ($CDCl_3$): δ 8.44 (*bs*, 1 H, D_2O exchangeable, NH), 8.1–7.4 (*m*, 5 H, Ph), 7.37 (*q*, 1 H, $J_{6,Me}$ 1.2 Hz, H-6), 6.10 (*dd*, 1 H, $J_{1',2a'}$ 6.4, $J_{1',2b'}$ 4.3 Hz, H-1'), 4.66 (*dd*, 1 H, $J_{5a',5b'}$ 11.9, $J_{4',5b'}$ 2.7 Hz, H-5*b*'), 4.53 (*dd*, 1 H, $J_{4',5a'}$ 4.6 Hz, H-5*a*'), 4.34 (*m*, 1 H, H-4'), 2.40–2.00 (*m*, 4 H, C-2' and C-3'), 1.71 (*d*, 3 H, 5-CH_3 from Thy); ^{13}C-NMR ($CDCl_3$): δ 166.10 (Ph*C*O), 163.40 (C_4=O), 145.80 (C_2=O), 136.52 (C-6), 133.72, 129.50 and 128.60 (aromatic), 110.55 (C-5), 86.28 (C-1'), 81.21 (C-4'), 63.46 (C-5'), 32.12 (C-2'), 25.08 (C-3'), 12.35 (5-CH_3 from Thy).

3'-Deoxythymidine (***8***)

To a solution of compound **7** (25 mg, 0.076 mmol) in dry MeOH (1 mL) was added a 1 M solution of sodium methoxide 0.2 mL). The mixture was stirred for 16 h at room temperature and then neutralized (glac. AcOH), filtered and concentrated. The residue was extracted with dichloromethane (3 × 5 mL), the combined extracts were washed with brine, dried and evaporated to give chromatographically homogeneous **8** (14 mg, 83 %) as bright yellow crystals: m.p. 147 ºC, lit[8]. 150–151 ºC, lit[6]. (for L-isomer) 148–149 ºC; $[\alpha]_D$ +26.4º (*c* 0.79, MeOH), lit[8]. +18.3º (*c* 0.99, MeOH), lit[6]. (for L-isomer) –31.2º (*c* 0.1, MeOH); ^{1}H-NMR ($CDCl_3$): δ 9.24 (*bs*, 1 H, D_2O exchangeable, NH), 7.56 (*q*, 1 H, $J_{6,Me}$ 1.2 Hz, H-6), 5.98 (*d*, 1 H, $J_{1',2a'}$ 6.7, $J_{1',2b'}$ 3.5 Hz, H-1'), 4.20 (*m*, 1 H, $J_{4',5a'}$ 4.0, $J_{4',5b'}$ 2.7 Hz, H-4'), 4.00 (*dd*, 1 H, $J_{5a',5b'}$ 12.0 Hz, H-5*b*'), 3.74 (*dd*, 1 H, H-5*a*'), 2.13 (*m*, 2 H, C-2'), 2.00 (*m*, 2 H, C-3'), 1.92 (*d*, 3 H, 5-CH_3 from Thy); ^{13}C-NMR ($CDCl_3$): δ 164.29 (C_4=O), 150.53 (C_2=O), 136.44 (C-6), 110.55 (C-5), 86.28 (C-1'), 81.21 (C-4'), 63.46 (C-5'), 32.12 (C-2'), 25.08 (C-3'), 12.51 (CH_3 from Thy).

Acknowledgement: This work was supported by a research grant from the Ministry of Science and Technology of the Republic of Serbia.

И З В О Д

ЕФИКАСНА *DE NOVO* СИНТЕЗА 3´-ДЕОКСИТИМИДИНА ИЗ D-КСИЛОЗЕ

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У раду је остварена ефикасна стереоспецифична синтеза 3´-деокситимидина полазећи из D-ксилозе. Кључну етапу синтезе представља двофазна секвенца која обухвата хемоселективну трансформацију 5´-*O*-бензоил-2,3-ди-*S*-етил-2,3-дитио-D-рибозе (**4**) у 1-*O*-ацетил-5-*O*-бензоил-2,3-ди-*S*-етил-2,3-дитио-β-D-рибофуранозу (**5**), уз накнадно стереоспецифично куповање интермедијера **5** са силилованим тимином у присуству етилалуминијум-дихлорида као катализатора.

(Примљено 24. априла 2001)

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