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# Regioselective 2′-*O*-debenzoylation of 2',3'-di-*O*-benzoyl threose nucleosides

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ABSTRACT

A simple and convenient procedure for the regioselective 2′-*O*-debenzoylation of 2',3'-di-*O*-benzoyl threose nucleosides has been achieved successfully affording 3′-*O*-benzoyl threose nucleosides, which are useful starting material synthons for the synthesis of modified threose nucleosides for different purposes.


(3′–2′) α-L-Threose nucleic acid (TNA) is an artificial genetic polymer in which the five-carbon ribose sugar of RNA and DNA is replaced by the four-carbon threose sugar and linked together through their 3′- and 2′-hydroxyls in a diaxial orientation.[1–4] A systematic study of alternative carbohydrate-based nucleic acids has revealed that TNA can form stable Watson–Crick base-pairing duplexes with DNA, RNA, and TNA. As a possible RNA progenitor, TNA has received considerable attention and numerous α-L-threose nucleoside analogues have been synthesized and assembled chemically to TNA analogues.[5,6] It was also demonstrated that threose nucleoside triphosphates (tNTPs, substrates) are incorporated well into DNA or RNA primers by selected DNA polymerases.[7–10] Recently, we have demonstrated that L-2′-deoxythreose nucleoside phosphonates PMDTA and PMDTT selectively inhibit HIV without affecting normal cell proliferation.[11]

As part of a research program to discover new threose-nucleoside analogues as anti-viral agents, we were interested in developing efficient synthetic routes for the introduction of various functionalities at the 2′- and/or 3′- position of threose nucleosides.

One of the current strategies for the synthesis of sugar protected threose nucleosides, developed by Eschenmoser and coworkers, includes a full-deprotection of the dibenzoyl threose moiety followed by mono-protection of the 2′- and 3′-hydroxyl groups[2] (Fig. 1). However, this reaction typically resulted in a mixture of regioisomers and required tedious chromatographic separations.

In the case of ribonucleosides, several procedures for the regioselective deacylation have been developed. For example, the reaction of fully acylated ribonucleosides (**1**) with small alkoxide such as sodium methoxide resulted in 2′ and 3′-*O*-deacylated compound (**2**)[12] while bulkier alkoxide such as potassium *tert*-butoxide afforded 2′-*O*-deacylated compound (**3a**)[13] as a major product. The hydroxylaminolysis (treatment with hydroxylaminium acetate) also resulted in 2′-*O*-deacylated compound (**4a**) as a major product[14] (Fig. 2(a)). It seems that the 2'-*O*-acyl group of nucleosides is the most active ester function toward an appropriate nucleophile, due to the electronic effect of the aglycone moiety. Moreover, in the case of xylonucleoside (**5**), hydroxylaminolysis gave **6** as a sole product[14] (Fig. 2(b)). The high selectivity of xylonucleoside may reflect steric hindrance as 3′-ester function is sterically less accessible by the adenyl moiety. As 2',3'-di-*O*-acyl threose nucleosides have N-type conformation,[2] they may also have different accessibility toward nucleophilic attack on 2′ and 3′-ester functions. The central C atom in the ester function in the top (3′) is sterically less accessible by the presence of the nucleobase (*t*-BuO$^-$ needs to attack from the front, next to the plane of the nucleobase) (Fig. 3(a)). The central carbon of the ester in the bottom (2′) is completely accessible (Fig. 3(b)). Therefore, we envisioned to explore a procedure for the regioselective mono-deprotection of 2',3'-di-*O*-acyl threose nucleosides with potassium *tert*-butoxide.

Herein, we describe a simple and convenient procedure for the regioselective 2′-*O*-debenzoylation of 2',3'-di-*O*-benzoyl threose

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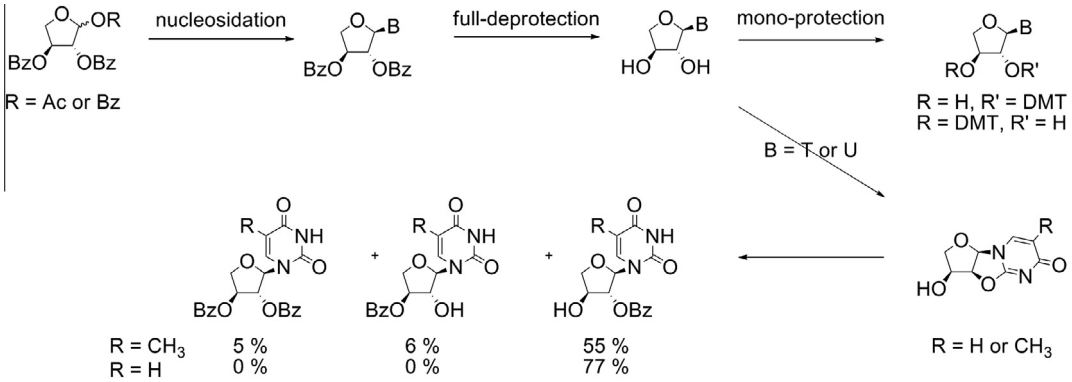



**Figure 1.** Current strategy for the synthesis of threose nucleosides.

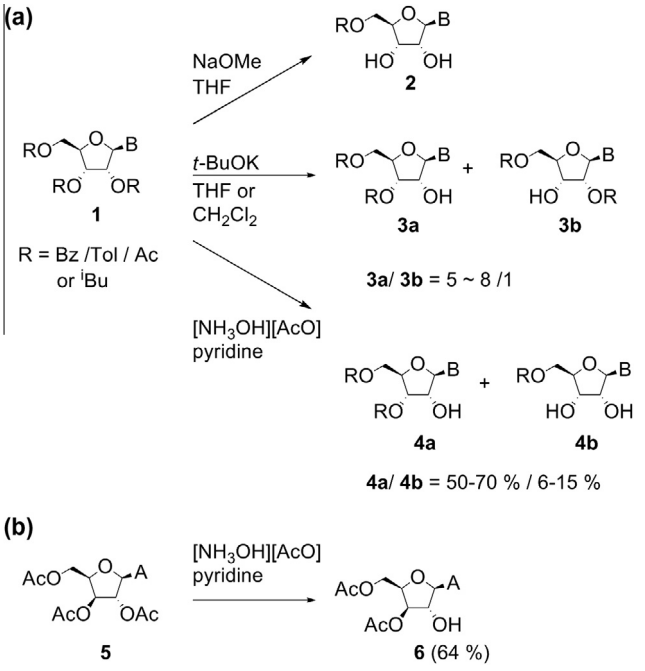



**Figure 2.** Regioselective *O*-deacylation of fully acylated ribonucleosides (a) and xylonucleoside (b).

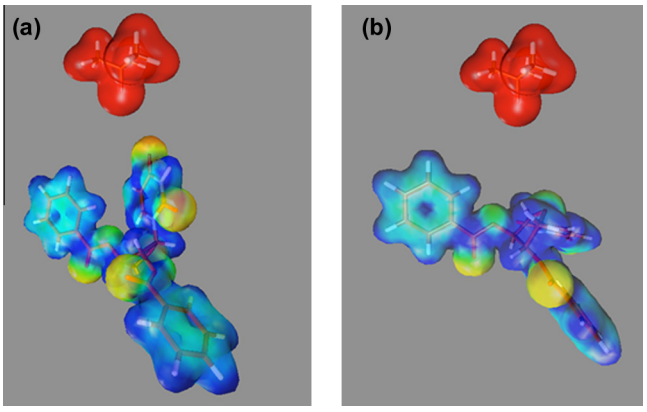
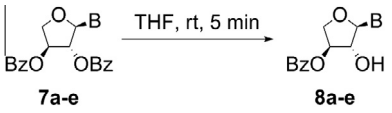
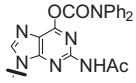



**Figure 3.** Isodensity surfaces of 1′α-(uridin-1-yl)-2',3'-di-*O*-benzoyl-L-threose[15] and *t*-BuO$^-$ at contour value 0.02 color coded by the electrostatic potential from negative to positive colored red, yellow, green, light blue, dark blue.[16,17] The C-atoms of the ester groups susceptible for reaction are in a dark blue area (more positive potential). The *t*-BuO$^-$ oxygen potential is colored red (negative electrostatic potential). (a) the approach of *t*-BuO$^-$ to the 3′ ester carbon; (b) the approach of *t*-BuO$^-$ to the 2′ ester carbon.

**Table 1**
Regioselective 2′-*O*-debenzoylation of 2',3'-di-*O*-benzoyl threose nucleosides with potassium *tert*-butoxide




**7a-e** **8a-e**

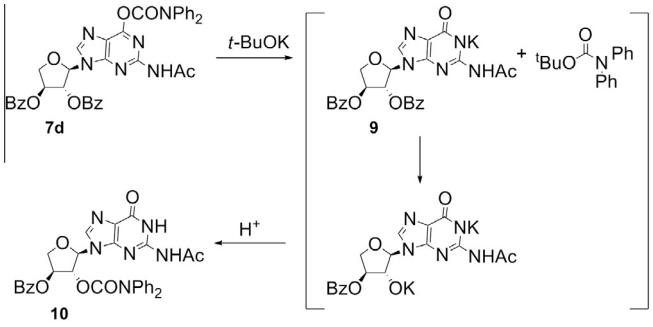
| Entry | Reactant | B | *t*-BuOK (equiv) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | **7a** |  | 2.5 | **8a** | 70[a] |
| 2 | **7b** |  | 2.5 | **8b** | 91 |
| 3 | **7c** |  | 2.5 | **8c** | 90 |
| 4 | **7d** |  | 2.5 | **8d** | —[b] |
| 5 | **7e** |  | 4.5 | **8e** | 67[a] |

[a] Starting material was recovered in 10% yield.
[b] Products: 50% yield (3:1 mixture of **7e** and **10**), starting material was recovered in 15% yield.

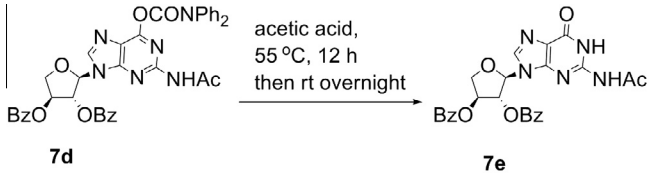
nucleosides affording 3′-*O*-benzoyl threose nucleosides, which are useful starting material synthons for the synthesis of modified threose nucleosides for different purposes.

2',3'-di-*O*-benzoyl threose nucleosides (**7a–d**, Table 1) were prepared by the procedure described by Eschenmoser and co-workers.[2] Treatment of nucleosides **7a**, **7b,** and **7c** with 2.5 equivalents of freshly prepared 0.1 M solution of potassium *tert*-butoxide in THF at room temperature gave mono-2′-*O*-debenzoylated products in good to moderate yields (Table 1). Their structure was confirmed by HMBC analysis. A clear HMBC cross-peak between H3′ and carbonyl carbon of the *O*-benzoyl group was observed.

However, reaction of compound **7d**, under the same conditions, resulted in the formation of 2 products. The $O^6$-diphenylcarbamoyl group of guanine-base proved to be labile under the reaction conditions and it was deprotected releasing **9** and *tert*-butyl diphenylcarbamate as a by-product (Scheme 1). The remaining potassium *tert*-butoxide deprotected 2′-*O*-benzoyl group and the resulting alkoxide reacted with *tert*-butyl diphenylcarbamate affording compound **10**. The structure of compound **10** was




**Scheme 1.** Proposed mechanism of synthesis of compound **10**.




**Scheme 2.** Selective deprotection of $O^6$-diphenylcarbamoyl group of compound **7d**.

confirmed by HMBC and mass analysis. An attempt to obtain only one product (compound **10**) in the reaction mixture by adding more potassium *tert*-butoxide was not successful. Even with 10 equiv of potassium *tert*-butoxide, a considerable amount of starting material remained and a complex mixture of products was obtained. To avoid this side reaction, the diphenylcarbamoyl group of **7d** was selectively removed by a treatment with glacial acetic acid[18] (Scheme 2). Compound **7e** could be successfully mono 2′-*O*-debenzoylated with 4.5 equivalents of potassium *tert*-butoxide (Table 1).

Purine threose nucleosides showed lower yield compared to pyrimidine threose nucleosides as a certain amount of starting material (~10%) remained. Adding more base or longer reaction time did not improve the yield because it caused 3′-*O*-debenzoylation.

In summary, we have developed a simple and efficient regioselective 2′-*O*-debenzoylation method of 2',3'-di-*O*-benzoyl threose nucleosides.[19] The resulting products are valuable intermediates for the synthesis of new 2′-modified threose nucleosides.

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19. *General procedure of mono-2'-O-debenzoylation of 2',3'-dibenzoyl threose nucleosides:* to a solution of 1′α-(thymin-1-yl)-2',3'-di-*O*-benzoyl-L-threose **7b** (1.0 g, 2.35 mmol) in dry THF (100 ml) was added fresh prepared 0.1 M KO$^t$Bu in THF (58.6 ml, 5.86 mmol). After stirring for 5 min, the mixture was quenched by addition of 1 N HCl (5.86 ml, 5.86 mmol). After removing volatiles, the residue was dissolved with DCM and washed with water, brine, dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography ($CH_2Cl_2$/MeOH 30/1) to afford 1′α-(thymin-1-yl)-3′-*O*-benzoyl-L-threose (0.71 g, 91%) as white foam.
*1′α-(N$^6$-Benzoyladenin-9-yl)-3′-O-benzoyl-L-threose* (**8a**): $^1$H NMR (300 MHz, $CDCl_3$): δ 9.44 (br s, 1H, NH), 8.65 (s, 1H, H8), 8.34 (s, 1H, H2), 7.99 (d, *J* = 7.2 Hz, 2H, Bz), 7.70 (d, *J* = 7.1 Hz, 2H, Bz), 7.55 (t, *J* = 7.4 Hz, 1H, Bz), 7.45 (t, *J* = 7.6 Hz, 3H, Bz), 7.32 (t, *J* = 7.8 Hz, 2H, Bz), 6.23 (d, *J* = 1.7 Hz, 1H, H1′), 5.48–5.49 (m, 1H, H3'), 5.03 (s, 1H, H2′), 4.59 (dd, *J* = 4.5, 10.8 Hz, 1H, H4'), 4.47(dd, *J* = 1.4, 10.6 Hz, 1H, H4′) ppm. $^{13}$C NMR (75 MHz, DMSO): δ 165.56, 164.93, 151.76, 151.57, 150.31, 142.41, 133.53, 133.39, 132.38, 129.17, 128.89, 128.69, 128.47, 128.42, 125.88, 90.47, 78.25, 77.21, 72.59 ppm. HRMS (ESI+) calcd for $C_{23}H_{20}N_5O_5$ $[M+H]^+$ 446.1459, found 446.1460.
*1′α-(Thymin-1-yl)-3′-O-benzoyl-L-threose* (**8b**): $^1$H NMR (300 MHz, $CDCl_3$): δ 10.30 (br s, 1H, NH), 7.83 (d, *J* = 7.1 Hz, 2H, Bz), 7.58 (t, *J* = 7.4 Hz, 1H, Bz), 7.44 (s, 1H, H6), 7.41 (t, *J* = 7.5 Hz, 2H, Bz), 5.87 (s, 1H, H1′), 5.45 (d, *J* = 3.4 Hz, 1H, H3'), 4.60 (dd, *J* = 3.6, 11.1 Hz, 1H, H4′), 4.58 (s, 1H, H2′), 4.46 (d, *J* = 10.8 Hz, 1H, H4′), 1.84 (d, *J* = 0.9 Hz, 3H, CH3) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 165.21, 164.77, 151.01, 135.89, 133.94, 129.61, 128.98, 128.78, 110.27, 93.98, 79.38, 77.63, 75.10 ppm. HRMS (ESI+) calcd for $C_{16}H_{17}N_2O_6$ $[M+H]^+$ 333.1081, found 333.1077.
*1′α-(N$^4$-Benzoylcytosin-1-yl)-3′-O-benzoyl-L-threose* (***8c***): $^1$H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.5 Hz, 1H, H6), 7.95 (d, *J* = 7.2 Hz, 2H, Bz), 7.72 (d, *J* = 7.2 Hz, 2H, Bz), 7.61 (d, *J* = 7.5 Hz, 1H, H5), 7.57 (t, *J* = 7.3 Hz, 1H, Bz), 7.43–7.50 (m, 3H, Bz), 7.30 (t, *J* = 7.8 Hz, 2H, Bz), 6.00 (s, 1H, H1′), 5.55 (d, *J* = 3.3 Hz, 1H, H3′), 4.72 (s, 1H, H2′), 4.66 (dd, *J* = 3.7, 10.9 Hz, 1H, H4′), 4.46 (d, *J* = 10.8 Hz, 1H, H4′) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 166.85, 165.31, 162.89, 155.94, 144.40, 133.63, 133.13, 133.10, 129.65, 128.93, 128.89, 128.49, 127.94, 94.60, 94.88, 79.18, 78.09, 74.95 ppm. HRMS (ESI+) calcd for $C_{22}H_{20}N_3O_6$ $[M+H]^+$ 422.1347, found 422.1351.
*1′α-(N$^2$-Acetylguanin-9-yl)-3′-O-benzoyl-L-threose* (***8e***): $^1$H NMR (300 MHz, MeOD): δ 8.11 (s, 1H, H8), 7.66 (d, *J* = 8.5 Hz, 2H, Bz), 7.55 (t, *J* = 7.44 Hz, 1H, Bz), 7.38 (t, *J* = 7.8 Hz, 2H, Bz), 5.99 (d, *J* = 0.72 Hz, 1H, H1′), 5.39–5.54 (m, 1H, H3′), 4.93 (s, 1H, H2′), 4.57 (dd, *J* = 4.5, 10.8 Hz, 1H, H4′), 4.48 (dd, *J* = 1.1, 10.7 Hz, 1H, H4′), 2.18 (s, 3H, CH3) ppm. $^{13}$C NMR (75 MHz, MeOD): δ 174.85, 166.70, 157.29, 149.70, 149.32, 139.09, 134.63, 130.36, 130.27, 129.62, 92.77, 79.70, 79.34, 74.52, 23.84 ppm. HRMS (ESI+) calcd for $C_{18}H_{18}N_5O_6$ $[M+H]^+$ 400.1251, found 400.1248.
*1′α-(N$^2$-Acetylguanin-9-yl)-3′-O-benzoyl-2′-O-diphenylcarbamoyl-L-threose* (***10***): $^1$H NMR (300 MHz, $CDCl_3$): δ 11.93 (s, 1H, NH), 9.89 (s, 1H, NH), 7.95 (s, 1H, H8), 7.66 (d, *J* = 7.2 Hz, 2H, Bz), 7.52 (t, *J* = 7.4 Hz, 1H, Bz), 7.21–7.36 (m, 12H, Bz, Ph), 6.15 (s, 1H, H2′), 5.99 (s, 1H, H1′), 5.43 (br s, 1H, H3′), 4.30 (dd, *J* = 1.8, 10.8 Hz, 1H, H4′), 4.21 (dd, *J* = 4.8, 10.8 Hz, 1H, H4′) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.38, 165.43, 155.63, 152.99, 147.91, 147.65, 141.74, 137.29, 134.09, 129.47, 128.76, 128.37, 126.99, 121.72, 89.01, 79.89, 75.79, 73.50, 24.26 ppm. HRMS (ESI+) calcd for $C_{31}H_{27}N_6O_7$ $[M+H]^+$ 595.1936, found 595.1938.