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Tetrahedron Letters 45 (2004) 2255–2258
Tetrahedron Letters

Synthesis and synthetic applications of 1-(3-*O*-tosyl-β-D-glucopyranosyl) thymines: toward new classes of hexopyranosyl pyrimidines

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Received 15 August 2003; revised 9 December 2003; accepted 18 December 2003

Abstract—1-(2,4,6-Tri-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranosyl) thymine has been synthesized by combining thymine with the appropriate carbohydrate. The availability of this key nucleoside made possible the synthesis of 2,2′-*O*-anhydro-(4,6-*O*-phenylmethylene-β-D-altropyranosyl) thymine and 1-(2,3-*O*-anhydro-4,6-*O*-phenylmethylene-β-D-mannopyranosyl) thymine. A wide range of modified hexopyranosyl nucleosides can be easily prepared from these functionalized starting materials.

Although a significant level of interest has been generated in the synthesis and biological properties of pentofuranosyl nucleosides over the years,[1] the very first nucleoside ever synthesized, namely 9-β-D-glucopyranosyladenine was a hexopyranosyl derivative.[2] 1-(2-Deoxy-β-D-arabinohexopyranosyl) thymine was recognized to be an inhibitor of a pyrimidine nucleoside phosphorylase.[3] Hexopyranosyl nucleosides derived from allose, altrose, gulose, talose, and mannose have been synthesized and tested against various microorganisms.[4] 1-(2-Deoxy-6-*O*-phosphono-β-D-ribohexopyranosyl)-2,4-pyrimidinedione demonstrated antiviral and antileukemic activities.[5] Synthetic studies on the pyranosyl nucleoside-based naturally occurring antibiotics have also been documented.[6] Furthermore, the synthesis and biological properties of a large number of pyranosyl azidonucleosides have been reviewed.[1] More recently, the synthesis and biological properties of a new class of sugar-modified nucleosides derived from 1,5-anhydrohexitols have been reported.[7]

Although the functionalization of hexopyranosyl nucleosides at the 2′, 3′, or 4′ positions poses major synthetic challenges, reported methodologies are narrowly focused to prepare only special classes of compounds.[2–8] Surprisingly, no serious effort has been made so far to develop general methodologies for the synthesis of modified hexopyranosyl nucleosides from common intermediates as was the case for the pentofuranosyl nucleosides.[1,9] It is, therefore, necessary to develop general strategies for the synthesis of a wide range of hexopyranosyl nucleosides.

The starting materials for the modification of 2′- and/or 3′-sites of pentofuranosyl pyrimidine nucleosides were mainly the sulfonylated pyrimidines **1**–**4**, 2,2′-*O*-anhydrouridine **5**, 2,3′-*O*-anhydrothymidine **6**, or the 2′,3′-*O*-anhydronucleosides **7** (Fig. 1).[1,9] We envisaged that the synthesis of selectively tosylated-, epoxy-, or 2,2′-*O*-anhydronucleosides of the hexopyranosyl type would pave the way for generating a wide range of unnatural nucleosides. In the present report, we focus on the synthesis of three functionalized starting materials, namely 1-(2,4,6-tri-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranosyl) thymine **8**, 2,2′-*O*-anhydro-(4,6-*O*-phenylmethylene-β-D-altropyranosyl) thymine **9**, and 1-(2,3-*O*-anhydro-4,6-*O*-phenylmethylene-β-D-mannopyranosyl) thymine **10** (Fig. 2). Intermediates **8**, **9**, and **10**, when reacted with nonoxygenated nucleophiles, are expected to generate 3′-deoxy-3′-modified allo-nucleosides, 2′-

Keywords: Hexopyranosyl; Nucleosides; Modified; Allopyranosyl; Altropyranosyl; Azidonucleosides; Thionucleosides; Aminonucleosides.
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0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.153

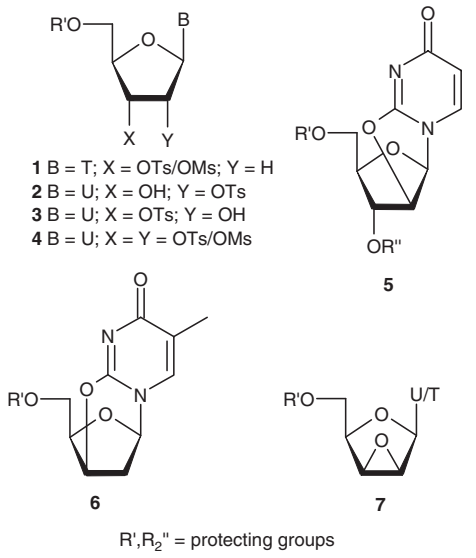


Figure 1.

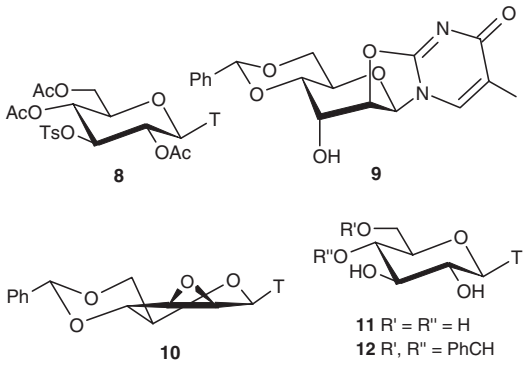
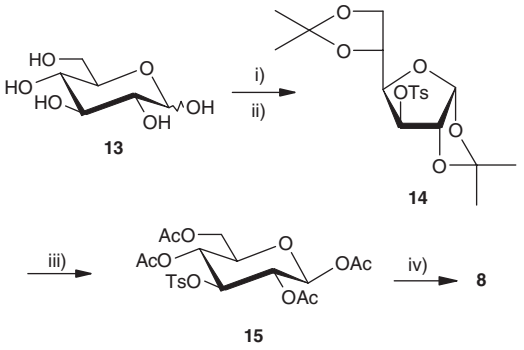


Figure 2.

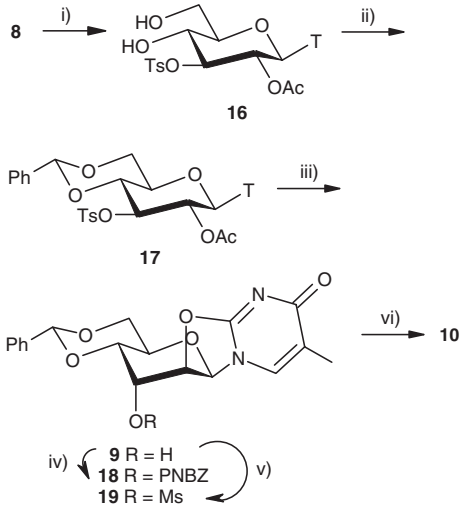
deoxy-2′-modified allo-nucleosides, and 3′-deoxy-3′-modified altro-nucleosides, respectively.

The accessibility to all three compounds **8**, **9**, and **10** is crucially dependent on the selective tosylation of the 3′-hydroxyl group of the tetrol **11** or the partially protected diol **12** had these latter compounds been used as starting materials.[10] Furthermore, for the synthesis of hexopyranosyl thymine, the selection of a glucose derivative was vital because a 'down' 2-*O*-acetyl group would control the configuration of the glycosidic bond by blocking the bottom of the pyranosyl ring through neighboring group participation. However, it was reported that the attempted selective tosylation of methyl β-D-glucopyranoside derivatives did not produce the required 3-*O*-tosylated compounds.[11] We expected that the same trend of tosylation would be followed in the case of compounds **11** or **12** (Fig. 2). Therefore, in the absence of any suitable methodology for the selective tosylation of the 3-hydroxyl group of β-D-glucopyranosides we decided to incorporate the tosyl group in the sugar moiety prior to the synthesis of the nucleoside.

For this purpose, 1,2,4,6-tetra-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranose **15**[12] was prepared in large scale from glucose **13** via 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose **14**[13] following a literature procedure used for the synthesis of pentaacetyl glucose.[14] Compound **15** was coupled with bistrimethylsilylated thymine in the presence of $SnCl_4$ to produce a single nucleoside **8** in 75% yield (Scheme 1). A large coupling constant for H1′–H2′ ($J_{1,2} = 9.3$ Hz) indicated the β-configuration of **8**.[8c] Treatment of **8** with isopropylamine in MeOH afforded a clean monoacetyl derivative **16**, which was isolated as the fully protected benzylidene nucleoside **17**. Reaction of **17** with NaOMe/MeOH produced the highly hygroscopic material **9**, which was identified as its *p*-nitrobenzoyl derivative **18**. Mesylation of **9** with mesyl chloride in pyridine at 0 °C afforded **19**. The crude mesylated product **19** was converted directly to 2′,3′-*O*-anhydro-mannopyranosyl nucleoside **10** by aq NaOH treatment in 30% overall yield over the three steps (**17** → **9** → **19** → **10**; Scheme 2).



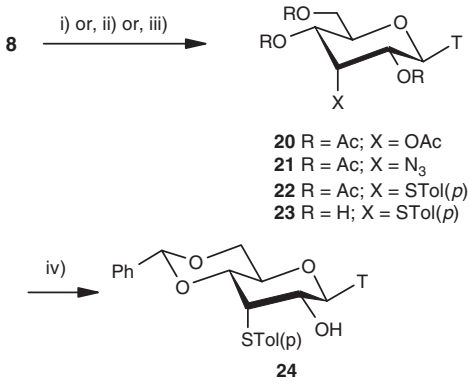
Scheme 1. Reagents and conditions: (i) $FeCl_3$, acetone, reflux, 5 h, 70%; (ii) TsCl, py, rt, 2.5 d, 90%; (iii) a. 0.5 N H_2SO_4, dioxane, reflux, 5 h; b. NaOAc, Ac_2O (crude 70%, crystal 40%); (iv) 2,4-di-*O*-trimethylsilylthymine, $SnCl_4$, dichloroethane, 50 °C, 75%.



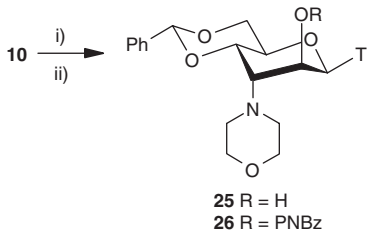
Scheme 2. Reagents and conditions: (i) isopropylamine, MeOH, rt, 5 h; (ii) $PhCH(OCH_3)_2$, TsOH, DMF, 100 °C, 1.5 h, 70% (in two steps); (iii) NaOMe, MeOH, rt, 30 h; (iv) *p*-$NO_2C_6H_4COCl$, py, 0 °C to rt, overnight, 65%; (v) MsCl, py, +4 °C, overnight; (vi) 2.5 M NaOH, dioxane, rt, 0.5 h, 30% (in three steps; **17** → **9** → **19** → **10**).

In order to establish the usefulness of these new hexopyranosyl nucleosides, **8** was subjected to nucleophilic displacement. Problems associated with any loss of acetyl groups were circumvented by reacetylating the product mixture. Thus, a DMF solution of **8** was treated with NaOAc at 150 °C for 20 h and the resulting mixture of products was acetylated. A typical work-up and purification yielded 1-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyl) thymine **20** in 70% yield. Although the synthesis of allopyranosyl thymine had been reported earlier,[8a] the present work is the first report on the conversion of a versatile intermediate such as **8** into an allopyranosyl nucleoside. Since this route to allopyranosyl thymine derivatives is expected to be general in nature, treatment of compound **8** with LiN_3 in DMF at 120 °C for 20 h followed by reacetylation gave 1-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-allopyranosyl) thymine **21** in 61% yield. Compound **21** is the first of its kind to be reported. Similarly, treatment of **8** with Na(*p*)STol in DMF at 90 °C, followed by acetylation afforded 1-(2,4,6-tri-*O*-acetyl-3-deoxy-3-*S*-tolyl-β-D-allopyranosyl) thymine **22** in 70% yield. In a different set of experiments the mixture of products obtained from the reaction of **8** with the sodium salt of *p*-tolylthiol, was deacetylated using NaOMe in methanol to give **23**. A DMF solution of **23** was benzylidenated using a standard procedure to afford **24** in 65% overall yield in three steps (Scheme 3). The 2′,3′-*O*-anhydro hexopyranosyl thymine **10** was also subjected to nucleophilic ring opening reactions. Thus, a DMSO solution of **10** was treated with morpholine at 90 °C for 25 h. A single compound, the 3′-deoxy-3′-*N*-morpholino-altropyranosyl nucleoside **25** was obtained in 80% yield, which was identified as its *p*-nitrobenzoyl derivative **26** (Scheme 4).

In conclusion, we have devised a methodology for the synthesis of a strategically tosylated hexopyranosyl nucleoside **8**, which can be easily transformed into several allopyranosyl nucleosides. Moreover, **8** can be transformed into two other extremely important key synthons **9** and **10**. It should be noted that the synthesis



Scheme 3. Reagents and conditions: (i) a. NaOAc, DMF, 150 °C, 20 h; b. Ac_2O, py, rt, overnight, 70%; (ii) a. LiN_3, DMF, 120 °C, 20 h; b. Ac_2O, py, rt, overnight, 61%; (iii) a. *p*-TolSH, NaOMe, DMF, 90 °C, 10 h; b. Ac_2O, py, rt, overnight, 70%; (iv) a. *p*-TolSH, NaOMe, DMF, 90 °C, 10 h; b. NaOMe, MeOH, rt, 6 h; c. $PhCH(OCH_3)_2$, TsOH, DMF, 100 °C, 1.5 h, 65% (in three steps).



Scheme 4. Reagents and conditions: (i) morpholine, DMSO, 90 °C, 25 h, 80%; (ii) *p*-$NO_2C_6H_4COCl$, py, rt, 5 h, 80%.

of the mannoepoxide **10** would not have been possible without the formation of **9**. The usefulness of the epoxy nucleoside **10** has been exemplified by synthesizing a new deoxyaminonucleoside **25**. Moreover, the easy availability of **24** and **25** would enable us to broaden the scope of our studies on aminonucleosides[1] and vinyl sulfone-modified nucleosides.[15] Research is currently in progress to study the widest possible application of these intermediates for the synthesis of an array of new hexopyranosyl nucleosides.[16]

Acknowledgements

T.P. thanks the DST, New Delhi, India for financial support. S.G.D. thanks CSIR, New Delhi, India for a fellowship. Both the authors thank Dr. M. S. Shashidhar for his support and interest in this work.

References and notes

1. Pathak, T. *Chem. Rev.* **2002**, *102*, 1623–1667, and references cited therein.
2. Fischer, E.; Helferich, B. *Ber.* **1914**, *47*, 210–235.
3. (a) Zorbach, W.; Durr, G. J., Jr. *J. Org. Chem.* **1962**, *27*, 1474–1477; (b) Langen, P.; Etzold, G. *Biochem. Z.* **1963**, *339*, 190–197.
4. Lerner, L. M.; Kohn, P. *J. Med. Chem.* **1964**, *7*, 655–658.
5. Nord, L. D.; Dalley, N. K.; McKernan, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044–1054.
6. Knapp, S. *Chem. Rev.* **1995**, *95*, 1859–1876.
7. (a) Ostrowski, T.; Wroblowski, B.; Busson, R.; Rozenski, J.; De Clercq, E.; Bennett, M. S.; Champness, J. N.; Summers, W. C.; Sanderson, M. R.; Herdewijn, P. *J. Med. Chem.* **1998**, *41*, 4343–4353; (b) Wouters, J.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1563–1566.
8. (a) Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Janssen, G.; Herdewijn, P. *J. Org. Chem.* **1993**, *58*, 2977–2982; (b) Bjoersne, M.; Classon, B.; Kvarnstroem, I.; Samuelsson, B. *Tetrahedron* **1993**, *49*, 8637–8644; (c) Hanessian, S.; Conde, J. J.; Khai, H. H.; Lou, B. *Tetrahedron* **1996**, *52*, 10827–10834; (d) Sugimura, H.; Sujino, K. *Nucleos. Nucleot.* **1998**, *17*, 53–63.
9. Moffatt, J. G. *Nucleoside Analogs: Chem., Biol., Med. Appl.*; NATO Adv. Study Inst. Ser., Ser. A **1979**, *A26*, 71–165.
10. A 'monotosyl monoacetate' hexopyranosyl nucleoside is known, see: Stevens, C. L.; Nielsen, N. A.; Blumbergs, P. *J. Am. Chem. Soc.* **1964**, *86*, 1894–1895.

11. (a) Munavu, R. M.; Szmant, H. H. *J. Org. Chem.* **1976**, *41*, 1832–1836; (b) Takeo, K.; Shibata, K. *Carbohydr. Res.* **1984**, *133*, 147–151.
12. Yamada, M.; Horio, Y.; Tachibana, K.; Kuroda, T.; Sakakibara, T. *Carbohydr. Res.* **1981**, *96*, 121–125.
13. Whistler, R. L.; Doner, L. W. *Methods Carbohydr. Chem.* **1972**, *6*, 215–217.
14. Wolfrom, M. L.; Thompson, A. *Methods Carbohydr. Chem.* **1963**, *2*, 211–220.
15. (a) Bera, S.; Sakthivel, K.; Langley, G. J.; Pathak, T. *Tetrahedron* **1995**, *51*, 7857–7866; (b) Bera, S.; Langley, G. J.; Pathak, T. *J. Org. Chem.* **1998**, *63*, 1754–1760.
16. Satisfactory spectral and analytical data were obtained for all new compounds.