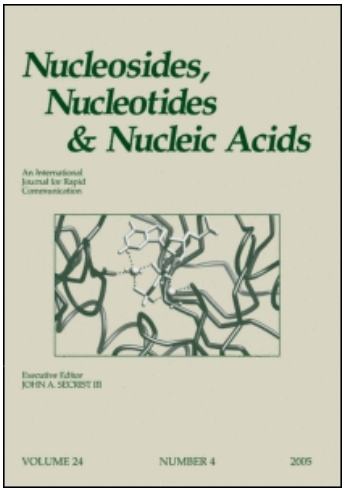

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ABSTRACT

Based on the fact that the ring expanded 3′-*C*-hydroxymethyl analogue of oxetanocin A exhibited potent antiviral activity, two types of conformationally rigid 3′-*C*-hydroxymethyl derivatives in which 2′-hydroxyl group is linked to the 4′-position or to the 6′-position were synthesized starting from 1,2;5,6-di-*O*-isopropylidene-D-glucose, respectively.

INTRODUCTION

Oxetanocin A is a naturally occurring nucleoside which shows potent anti-HIV activity (1). The ring expanded 3′-*C*-hydroxymethyl analogue of oxetanocin A also exhibited similar antiviral activity (2), but its carbocyclic analogue was totally devoid of antiviral activity (3). This difference in antiviral activity might be due to differences in the sugar conformation. Since antiviral activity of the ring expanded

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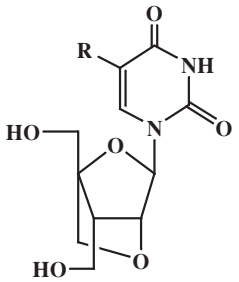
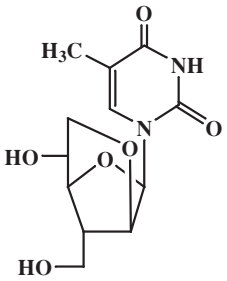


1 (R = H)
2 (R = CH_3)



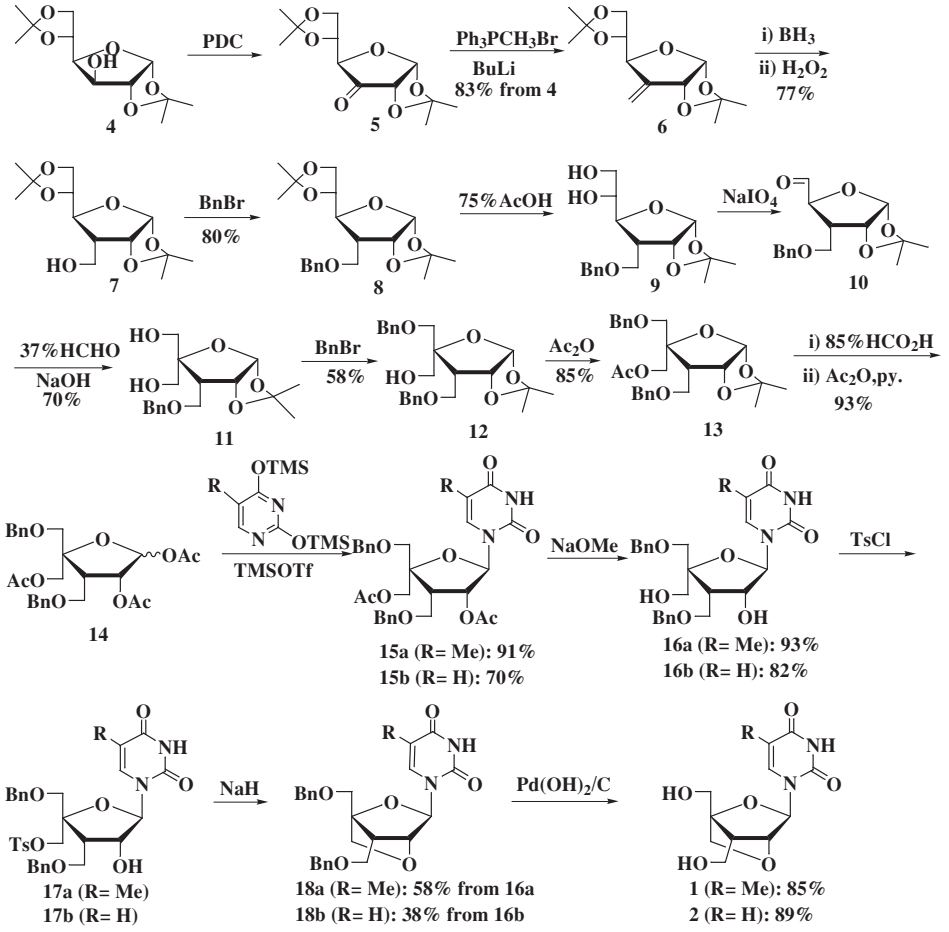
3

analogue was reported to be due to the superposition of its 3′-*C*-hydroxymethyl group and hydroxymethyl substituent of oxetanocin A (2), we synthesized conformationally rigid 3′-*C*-hydroxymethyl derivative in which 2′-hydroxyl group is linked to the 4′-position. We also synthesized another conformationally rigid 3′-*C*-hydroxymethyl derivative in which the 2′-hydroxyl group is connected to the 6′-position. These types of nucleosides will fix the orientations of 3′- or 5′-hydroxymethyl group which will affect the affinity to kinases and finally antiviral activity.

Here, we report the synthesis of conformationally rigid nucleosides starting from 1,2;5,6-di-*O*-isopropylidene-D-glucose as potential antiviral agents.

RESULTS AND DISCUSSION

For the synthesis of the 2′,4′-linked nucleosides (**1** and **2**), 1,2;5,6-di-*O*-isopropylidene-D-glucose (**4**) was oxidized with PDC to give ketone **5** as shown in Scheme 1. Wittig reaction of **5** followed by hydroboration-oxidation of the resulting methylene **6** yielded hydroxymethyl derivative **7**. Treatment of **7** with benzyl bromide gave the benzylate **8**, in which 5,6-*O*-isopropylidene was selectively removed using 75% acetic acid to give diol **9**. Oxidative cleavage of **9** with $NaIO_4$ afforded aldehyde **10**. Conversion of aldehyde **10** to the diol **11** was achieved using NaOH and 37% HCHO in dioxane. Selective benzylation of one hydroxymethyl group in **11** followed by acetylation of the resulting monobenzylate **12** produced **13**. Treatment of **13** with 85% formic acid gave 1,2-diol which was reacted with acetic anhydride to afford the glycosyl donor **14**. Condensation of the acetate **14** with silylated thymine and uracil gave the protected nucleosides **15a** and **15b**, respectively. Deacetylation of **15a** and **15b** followed by selective tosylation of the primary hydroxyl group in the resulting diol **16a** and **16b** yielded **17a** and **17b**, respectively. Cyclization of **17a** and **17b** to give the locked nucleosides **18a** and **18b** was successful with NaH Finally, debenzylation of **18a** and **18b** with catalytic hydrogenation to afford the final nucleosides **1** and **2**, respectively.

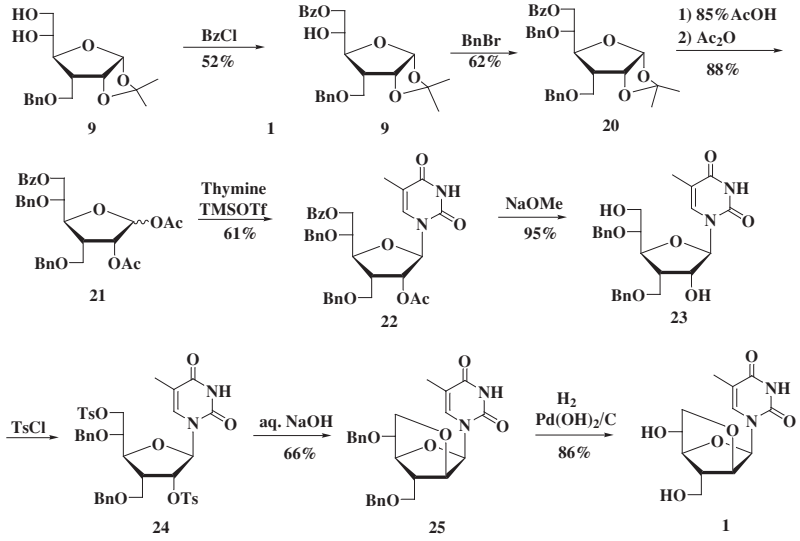


Scheme 1.

The 2′,6′-linked nucleoside **3** was synthesized from **9** (Scheme 2). The primary hydroxyl group of **9** was protected as benzoate **19** whose remaining secondary hydroxyl was benzyalted to give **20**. Hydrolysis of the 1,2-acetonide in **20** with 85% aqueous acetic acid followed by acetylation yielded diacetate **21** as a key intermediate. Condensation of diacetate **21** with silylated thymine gave the protected nucleoside **22**.

Deacetylation and debenzoylation of **22** followed by tosylation afforded ditosylate **24** which was treated with aqueous sodium hydroxide to give the cyclized derivative **25**. Debenzylation of **25** using catalytic hydrogenation yielded the final locked nucleoside **3**.

In summary, we synthesized two types of conformationally locked nucleosides whose hydroxymethyl side chain might be superimposed well with those of



Scheme 2.

oxetanocin A. Antiviral assay and molecular modeling study are in progress in our laboratory and will be reported in due course.

ACKNOWLEDGMENTS

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