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Nucleosides and Nucleotides. 132. Synthesis and Biological Evaluations of Ring-Expanded Oxetanocin Analogues: Purine and Pyrimidine Analogues of 1,4-Anhydro-2-deoxy-D-arabitol and 1,4-Anhydro-2-deoxy-3-hydroxymethyl-D-arabitol[1]

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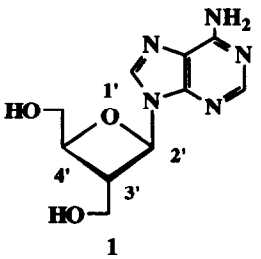
Abstract: (2*R*)-2-*C*-(Adenin-9-yl)-1,4-anhydro-2-deoxy-D-arabitol (**2**) and (2*R*, 3*R*)-2-*C*-(adenin-9-yl)-1,4-anhydro-2,3-dideoxy-3-*C*-hydroxymethyl-D-arabitol (**3**), and their 2,6-diaminopurine analogues **4** and **5** were synthesized from corresponding 1,4-anhydro-D-ribitol derivatives, which were readily obtained from D-glucose. The corresponding guanine isonucleosides **6** and **7** were obtained from **4** and **5** by enzymatic deamination with adenosine deaminase. Pyrimidine counterparts **8** and **9** were synthesized via construction of the pyrimidine moiety from amino derivatives of the 1,4-anhydro-D-arabitol derivatives. Antiviral activity of these ring-expanded derivatives of oxetanocins towards HSV-1, HSV-2, HCMV, and HBV *in vitro* was examined along with their cytotoxicity against L1210 and KB cells *in vitro*.

INTRODUCTION

Oxetanocin A (OXT-A, **1**), which was isolated from *Bacillus megaterium NK84-0218*, has a unique structure bearing an oxetanose instead of a furanose in the sugar moiety of the nucleoside.[2] Due to its unique structure and biological activity, including anti-HIV activity, various analogues of OXT-A both at the sugar and the base moieties have been synthesized to improve its chemotherapeutic index.[3] A guanine congener of OXT-A (OXT-G) and a carbocyclic OXT-G also had potent antiviral activities against HSV and HBV,[3] and their 5'-triphosphates[4] were found to be incorporated into DNA molecules and to terminate the elongation. The 2-fluoroadenine analogue was much more potent against HIV-1 than OXT-A, due in part to not being a substrate of adenosine deaminase.[3b] Therefore, these OXT analogues would be phosphorylated by virus and/or cellular kinases similarly to other antiviral nucleosides. Although the sugar moiety of OXT analogues



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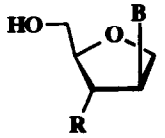
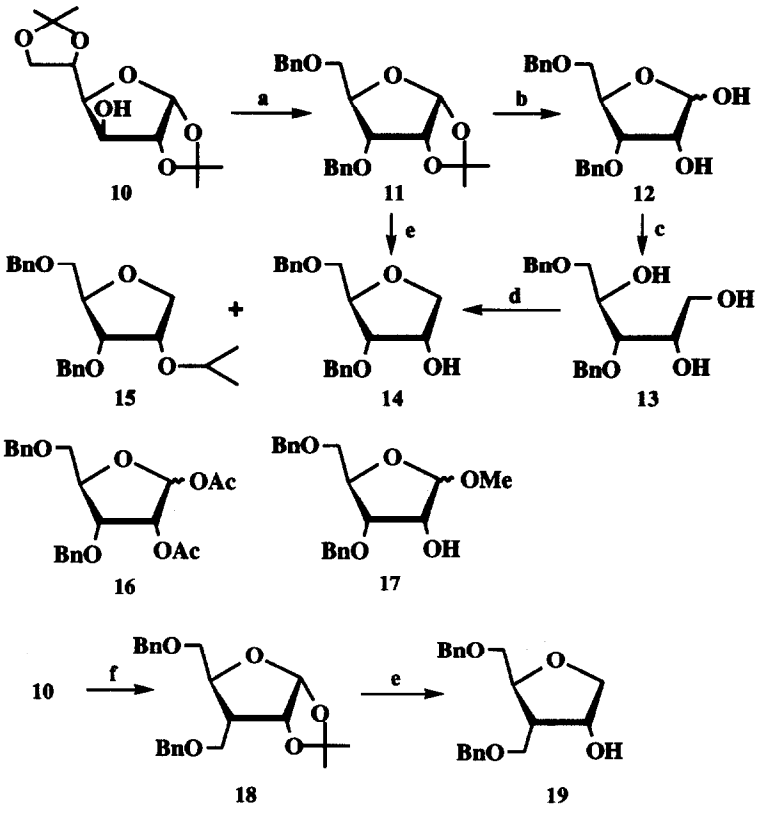


2 ; B = adenine, R = OH
3 ; B = adenine, R = CH_2OH
4 ; B = 2,6-diaminopurine, R = OH
5 ; B = 2,6-diaminopurine, R = CH_2OH
6 ; B = guanine, R = OH
7 ; B = guanine, R = CH_2OH
8 ; B = cytosine, R = OH
9 ; B = cytosine, R = CH_2OH

are constituted by the oxetanose and the cyclobutane ring with two primary hydroxyl groups at 3' and 4' positions, it is surprising that such nucleosides were recognized as substrates of kinases. Therefore, further modified-sugar nucleosides could be selectively recognized by the less substrate-specific viral kinases without affecting cellular enzymes. In our efforts to find out new antiviral sugar-modified nucleosides we design ring-expanded oxetanocin analogues, purine and pyrimidine derivatives of 1,4-anhydro-D-arabitol analogues **2-9**, which are isonucleosides without having glycosyl linkages. From these nucleosides, we would expect to avoid enzymatic deactivations such as glycosyl bond cleavage reactions by phosphorylases and also chemical stability due to having no glycosyl linkage in the molecules. In this report, we describe the synthesis of these nucleosides and their antiviral activity.[5]

Chemistry. To synthesize the target nucleosides, we required tetrahydrofuran derivatives **14** and **19** in large quantities. First, we examined the synthesis of 1,4-anhydro-3,5-di-*O*-benzyl-D-ribitol (**14**) from 1,2:5,6-di-*O*-isopropylidene-α-D-glucose (**10**). Conversion of **10** to 3,5-di-*O*-benzyl-1,2-isopropylidene-α-D-ribofuranose (**11**) was done using modifications of the literature methods.[6] After hydrolysis of the isopropylidene group by aqueous 80% AcOH, **12** was obtained, which was treated with $NaBH_4$ in MeOH to

Scheme 1[a]



[a]Reagents and conditions: a) ref. 6; b) 80% AcOH, 100 °C; c) $NaBH_4$, MeOH; d) Ph_3P, DEAD, THF, 60 °C; e) Et_3SiH, TMSOTf, CH_2Cl_2, -18 °C to room temperature; f) ref. 8, 9.