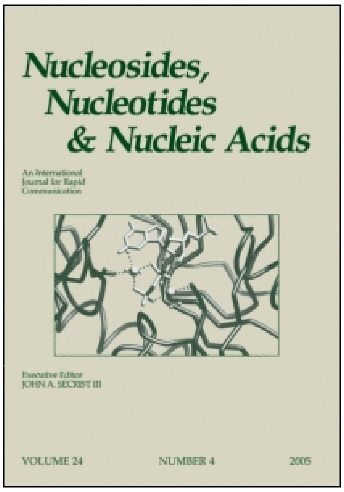

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STRUCTURE-ACTIVITY RELATIONSHIPS OF APIO NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

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STRUCTURE-ACTIVITY RELATIONSHIPS OF APIO NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

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ABSTRACT

Several types of novel apio nucleosides were synthesized starting from 1,3-dihydroxyacetone and evaluated for antiviral activity. Among compounds tested, amino substituted apio dideoxynucleosides exhibited anti-HBV activity, while thioapio dideoxynucleosides were found to be active against HIV-1. Apio dideoxydidehydro nucleosides showed moderate to potent anti-HCMV activity, but their bioisosteric thioapio dideoxydidehydro nucleosides did not exhibit any significant antiviral activity.

INTRODUCTION

One of the nonclassical nucleosides, apio dideoxynucleoside (1–5) in which 4′-hydroxymethyl group of the classical 2′,3′-dideoxynucleosides moves to the 3′-position has been shown anti-HIV activity (1) in MT-4 cells. In addition to antiviral activity, these nucleosides also showed metabolic advantages such as

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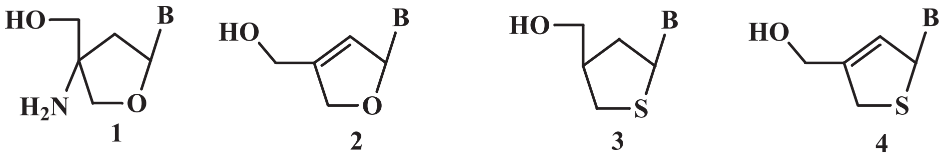


Figure 1.

resistance to adenosine deaminase and glycosyl bond hydrolysis (3). In order to study structure-activity relationships of apio nucleosides, we synthesized several types of apio nucleosides such as azido or amino substituted apio dideoxynucleosides (**1**), apio dideoxydidehydro nucleosides (**2**), thioapio dideoxynucleosides (**3**), and thioapio dideoxydidehydro nucleosides (**4**) and evaluated them for antiviral activities (Fig. 1).

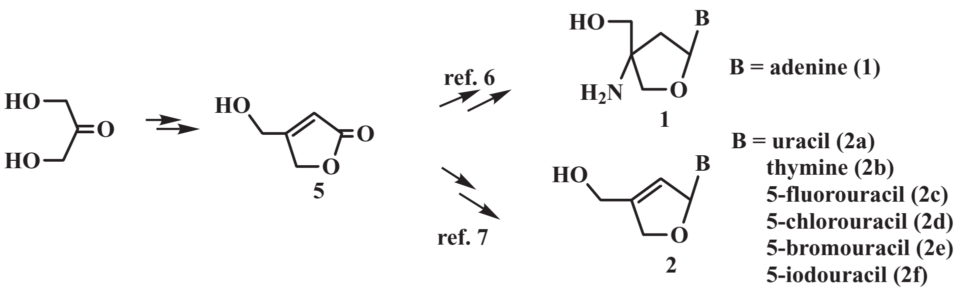
Here, we report the synthesis and structure-activity relationship study of novel apio nucleosides as antiviral agents.

RESULTS AND DISCUSSION

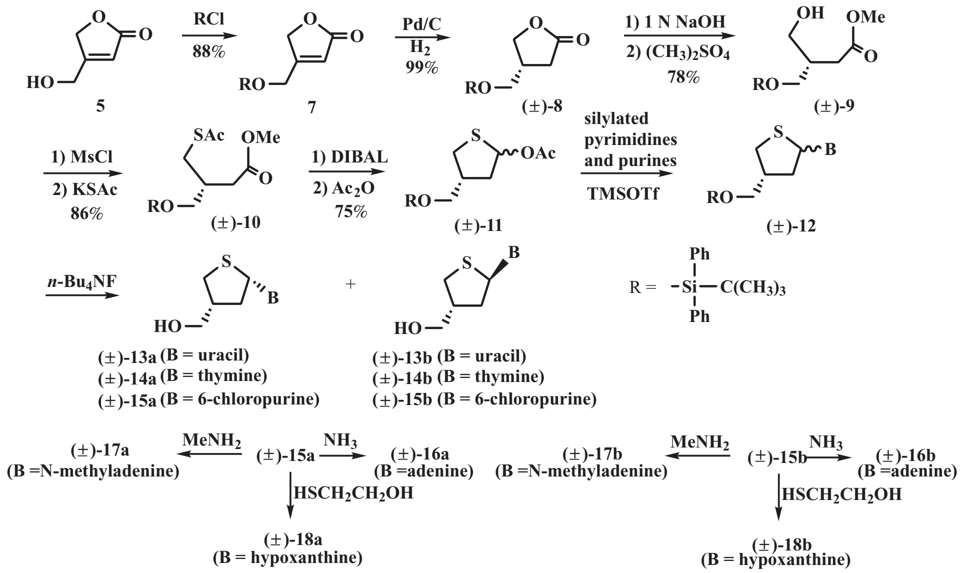
The amino substituted apio nucleosides (**1**) and apio dideoxydidehydro nucleosides (**2a**–**2f**) were synthesized using 1,3-dihydroxyacetone as a common starting material via lactone **5** as the common intermediate (Scheme 1). These two classes of nucleosides were synthesized according to the known procedure reported by our laboratory (6,7).

Thioapio dideoxynucleosides which may act as bioisosteres of apio dideoxynucleosides were synthesized starting from the lactone **5** (Scheme 2).

The lactone **5** was protected as *tert*-butyldiphenylsilyl ether to give **7** which was hydrogenated under palladium on carbon to afford saturated lactone (±)-**8** in quantitative yield. Treatment of (±)-**8** with 1 N NaOH followed by methylation of the resulting acid gave the hydroxyester (±)-**9** which was converted to the thioacetate (±)-**10** in two steps. Cyclization of (±)-**10** was achieved using DIBAL at −78°C to give lactol, which was acetylated to give the thioapio acetate (±)-**11**.



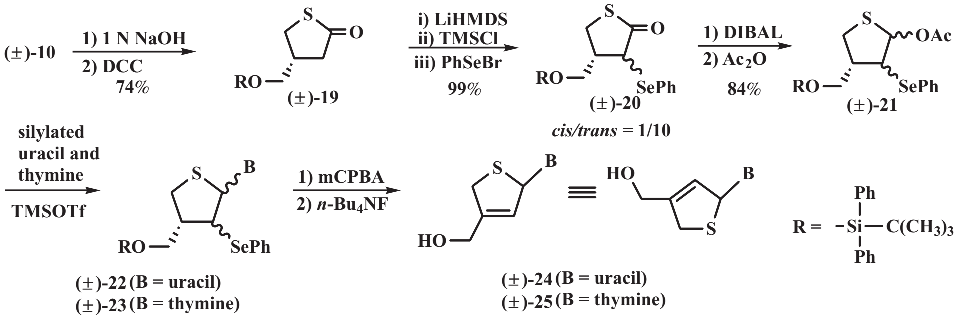
Scheme 1.



Scheme 2.

The glycosyl donor (±)-**11** was condensed with silylated uracil, thymine, and 6-chloropurine in the presence of TMSOTf to give the inseparable anomeric mixture of protected nucleosides to give the inseparable anomeric mixtures of protected nucleosides (±)-**12**, respectively. The protected nucleosides (±)-**12** was treated with tetra-*n*-butylammonium fluoride to give β anomers ((±)-**13a**, **14a**, and **15a**) and α-anomers ((±)-**13b**, **14b**, and **15b**), respectively. The 6-chloropurine derivatives, (±)-**15a** and (±)-**15b** were converted to the adenine ((±)-**16a** and (±)-**16b**), N-methyladenine ((±)-**17a** and (±)-**17b**), and hypoxanthine ((±)-**18a** and (±)-**18b**) derivatives, respectively according to the conventional methods.

Synthesis of the thioapio dideoxydidehydro nucleosides is shown in Scheme 3. Treatment of (±)-**10** with 1 N NaOH gave the mercapto acid which without purification, was cyclized using DCC to the thiolactone (±)-**19**. Treatment of (±)-**19**



Scheme 3.

with LiHMDS at −78°C followed by the trapping of the enolate with TMSCl gave silylenol ether, which was reacted with phenyl selenenyl bromide at −78°C to afford (±)-**20** (cis/trans = 10/1 as determined by ^{1}H NMR). Reduction of (±)-**20** with DIBAL followed by acetylation gave the key intermediate (±)-**21**. Condensation of (±)-**21** with silylated uracil and thymine gave the inseparable mixture of protected nucleosides (±)-**22** and (±)-**23**, respectively. Syn-elimination using *m*CPBA and catalytic amounts of pyridine followed by desilylation yielded the final nucleosides (±)-**24** and (±)-**25**, respectively.

All synthesized compounds were assayed against several viruses such as against HIV-1, HSV-1, HSV-2, HCMV, and HBV. Among compounds tested, amino substituted apio dideoxynucleoside (**1**) exhibited anti-HBV activity, while their bioisosteric thioapio dideoxynucleosides were found to be only active against HIV-1. Most apio dideoxydidehydro nucleosides showed moderate to potent anti-HCMV activity without cytotoxicity, among which 5-fluorouracil derivative **2c** was found to be the most potent. However, thioapio analogues, (±)-**24** and (±)-**25** did not exhibit any significant antiviral activities.

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