DIDEOXYAPIOSE NUCLEOSIDES REVISITED: SYNTHESES AND PROTIDE DERIVATIVES

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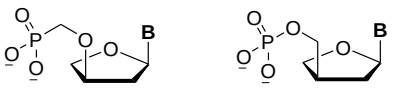
Almost two decades after the first synthesis of the dideoxy apiose nucleosides, we sought to revisit their synthesis and convert them to the corresponding phosphoramidate (ProTides).

INTRODUCTION

Dideoxyapiose nucleosides (ddAN) were synthesized in the early 90's as potential antivirals. However, the interest in this class of nucleosides faded away after they were reported to be inactive.[1] It might be expected that the inadequate cellular conversion to the corresponding triphosphate is responsible for their non-activity. Recently, Herdewijn and coworkers showed that the related L-2-deoxythreose nucleoside phosphonates (**I**; Figure **1**) selectively inhibit HIV without affecting human DNA synthesis.[2] A serious problem associated with phosphonates, however, is their low bioavailability. Inspired by the cellular activity of **I**, we decided to reinvestigate the synthesis of the ddANs. Note that the monophosphate forms of the envisaged L-ddANs (**II**), can be considered as the parent nucleotides from which the bioisosteric phosphonates **I** have been derived. Since cellular conversion to this monophosphate might form the bottleneck in the activation of the ddANs, we decided to convert them in to their masked monophosphates (ProTides).[3]



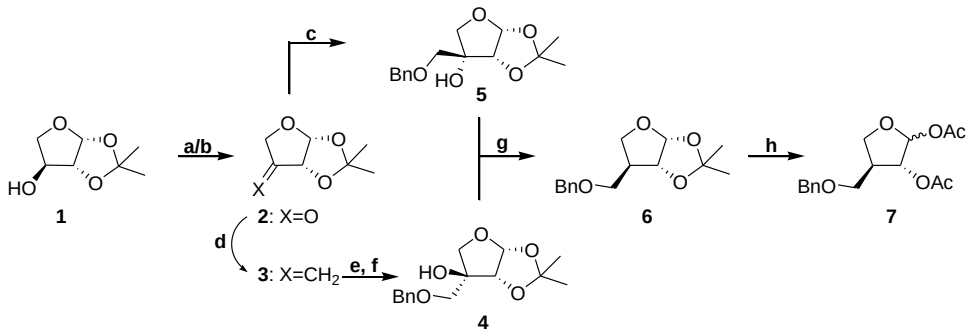
Ia B = thymin-1-yl (PMDTT)
Ib B = adenin-9-yl (PMDTA)

IIa B = thymin-1-yl
IIb B = adenin-9-yl

FIGURE 1

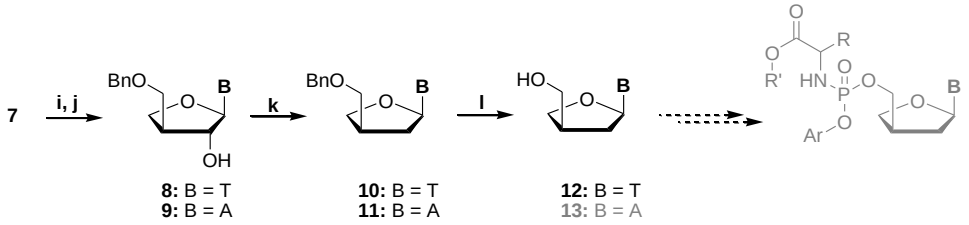
RESULTS AND DISCUSSION

The threose compound **1** (Scheme **1**) was synthesized following the reported procedure.[4] The oxidation of secondary hydroxyl group was performed using pyridinium chlorochromate (PCC). To avoid the toxicity issues pertaining to PCC, we explored alternative oxidation conditions. Surprisingly, TMPO-BAIB oxidation, text book conditions to convert primary alcohol groups to the corresponding acid without affecting other hydroxyl groups, proved a valuable alternative for oxidation of **1** to **2**. Initially, the key intermediate **7** was produced via compound **5**,[5] obtained by hydroxylation of exomethylene group of **3**, but afterword we followed a shorter and more consistent route through the apiose derivative **5**.



SCHEME 1

The nucleobases were installed by modified Vorbrüggen coupling of **7** with the appropriate silylated bases, followed by removal of the acetyl and benzoyl groups (Scheme **2**). The compounds **10** and **11** were obtained by Barton-McCombie deoxygenation. The *dd*AN **12** was obtained after palladium catalysed debzylation.



SCHEME 2

The synthesis of the nucleoside analogue **13** and the final ProTides is in progress. The ability of these phosphoramidates to inhibit various viral strains will be discussed.

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