L-2- DEOXYTHREOSE NUCLEOSIDES: SYNTHESIS AND SCREENING AGAINST VIRAL STRAINS

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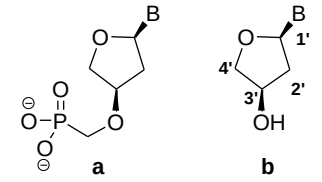
Several nucleoside analogs are well-known to inhibit the reverse transcription (RT) process in HIV by terminating the synthesis of a proviral DNA strand. Recently, Herdewijn and coworkers showed that some L-2-deoxythreose nucleoside phosphonates (**a**; Figure 1) selectively inhibit HIV without affecting human DNA synthesis.[1] These nucleoside analogues require two additional phosphorylation steps by cellular kinases before they are incorporated in the viral genome and lead to chain termination. It is believed that a *cis* orientation of the base and the 3'-substituent is a structural requirement for optimal conversion to the diphosphate. Inspired by these findings, we decided to explore the antiviral properties of the threose-based nucleoside analogues (**b**; Figure 1), which are anticipated to have superior bioavailability compared to the parent phosphonates. Remarkably, such α-L-2'-deoxythreofuranosyl analogues (exhibiting a 1'R,3'R configuration) have not been reported before.

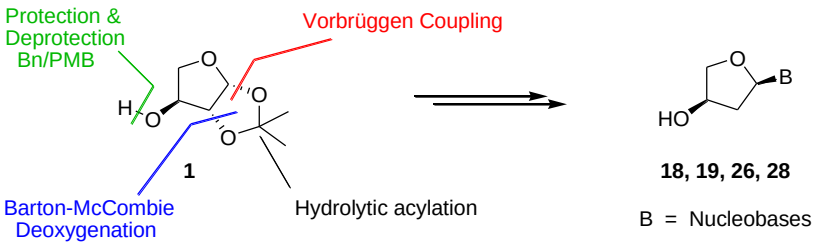
Fig. 1



B = Natural/ Modified Bases

The synthesis of the desired T, U, C and A analogs (Scheme-**1**), were completed involving a Vorbrüggen coupling [2] and a Barton-McCombie deoxygenation [3] as key steps. The synthetic course also revealed the importance of proper protecting groups.

Scheme-1



All the α-L-2'-deoxythreofuranosyl analogues synthesized were evaluated in vitro for cytotoxicity and for their activity against a variety of viruses, while their capacity to inhibit a panel of deoxyribonucleoside kinases was also assessed.

References:

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2) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, 114, 1234 - 1255.
3) Barton, D. H. R. and McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574 – 1585.