SYNTHESIS OF 3,4-DISUBSTITUTED-1-β-D-RIBOFURANOSYLPYRAZOLO[3,4-d]PYRIMIDINES

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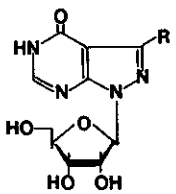
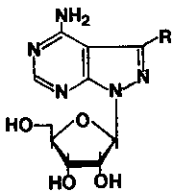
Renewed interest has been generated recently in the chemistry and biochemistry of pyrazolo-[3,4-d]pyrimidine nucleosides. Allopurinol ribonucleoside (1, R = H) exhibits antileishmanial activity.[1-3] In addition to L. braziliensis, 4-aminopyrazolo[3,4-d]pyrimidine nucleoside (4-APP riboside, 2, R = H) was found to be active against T. cruzi and T. rangeli in vitro. Recently, we reported a convenient synthesis of 6-aminoallopurinol riboside and related 4,6-disubstituted pyrazolo[3,4-d]pyrimidine nucleosides.[4] We now wish to report on the synthesis of selected 3-substituted allopurinol/4-APP nucleosides of the general formulas 1 and 2.



1

R = Br, CN, OH, NH_2, SCH_3



2

Glycosylation of the TMS 3-bromoallopurinol with acylated β-D-ribofuranose in presence of a Lewis-acid catalyst gave the protected 1-ribosyl-3-bromoallopurinol as the major product, which on reaction with a number of nucleophiles produced a variety of 3-substituted allopurinol ribosides. A similar glycosylation of 3-methylthioallopurinol and subsequent deprotection provided 1 (R = SCH_3). However, direct ribosylation and deprotection of 3-bromo-4-APP gave 2 (R = Br). Chlorination of blocked 3-bromoallopurinol riboside with phosphoryl chloride followed by amination provided the hitherto inaccessible 3-amino-4-APP riboside 2 (R = NH_2). Reaction of the TMS 3-cyanoallopurinol with blocked glycone gave the blocked 3-cyanoallopurinol riboside in which the nitrile function was available for further transformations. The detailed synthetic studies leading to these analogs and their structural elucidation will be presented.

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