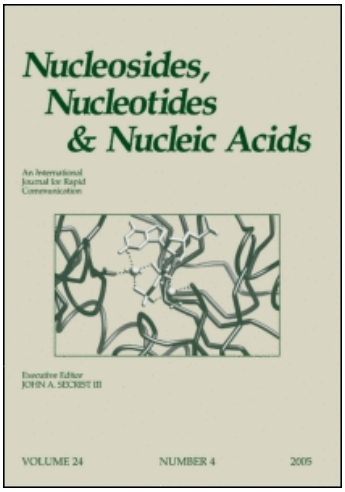

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Progress in the Synthesis of A Potential PNP Transition State Inhibitor

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PROGRESS IN THE SYNTHESIS OF A POTENTIAL PNP TRANSITION STATE INHIBITOR

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Abstract:

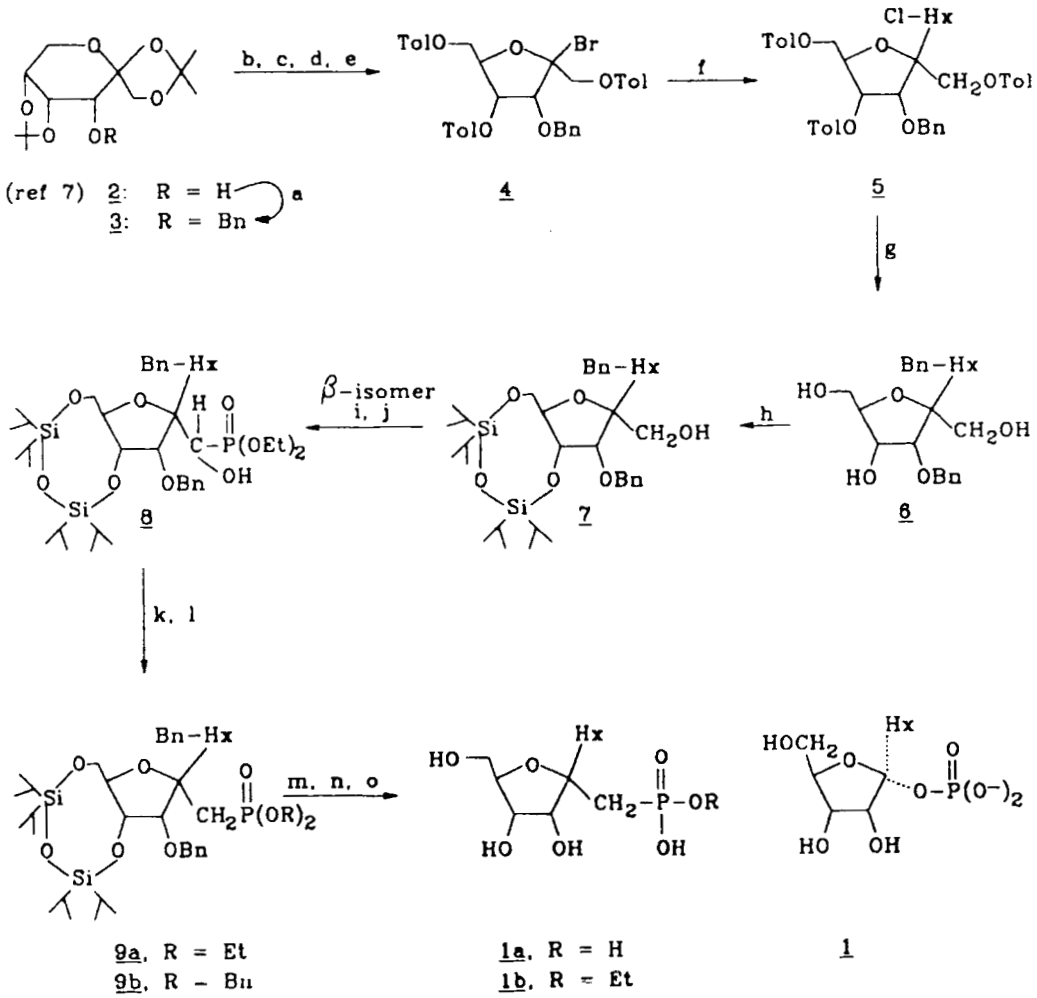
Phosphonic acid **1a** has been proposed as a multisubstrate analog of the suggested transition state **1** for the PNP catalyzed reversible conversion of inosine and phosphate to hypoxanthine and ribose-1-phosphate. A 20 step synthesis of the monoethyl ester **1b** from D-fructose is described.

Purine nucleoside phosphorylase (PNP) is a purine metabolizing enzyme that catalyzes the phosphorolysis of nucleosides such as inosine, guanosine and their 2'-deoxy forms. The products of this reversible reaction are purine bases and their corresponding 1-ribose and deoxyribose phosphates. PNP deficiency has been identified as a genetic defect associated with severe T-cell immune deficiency.[1] Since proliferating T-cells have been associated with rheumatoid arthritis, transplant rejection, and T-cell leukemia, the syntheses of PNP inhibitors which can regulate T-cell populations could lead to useful new drugs.

PNP inhibitors can also potentiate the cytotoxicity of nucleosides used as antitumor or antiviral agents by inhibiting their breakdown by phosphorolysis. This has been demonstrated by 8-aminoguanine and 8-aminoguanosine,[2] competitive inhibitors of human PNP that markedly potentiate the toxicity of 2'-deoxyguanosine for, and the accumulation of dGTP in, T lympoblasts.[3-5] Accumulation of dGTP in T-cells causes cell death and blocks lymphocytes clonal expansion.

The transition state **1** has been suggested for the PNP catalyzed reversible conversion of inosine and phosphate to hypoxanthine and ribose-1-phosphate. We have proposed **1a** as a stable multisubstrate analog which could mimic the transition state **1** and bind to PNP at the position normally occupied by **1**. This binding, if sufficiently tight, could lead to inhibition or inactivation of PNP.

The following scheme was utilized for the synthesis of the phosphonate monoethyl ester **1b**. Attempts to remove the remaining ethyl group from **1b** using TMSI or snake venom phosphodiesterase were unsuccessful. Assays of **1b** for inhibition of calf splene PNP[6] showed definite inhibitory activity (IC_{50} = ~ 110 μm); however the inhibition is much less than that of the known inhibitor 8-aminoguanosine (~4 μm). Full experimental details with biological data will be presented when a synthesis of **1a** *via* the dibenzyl phosphonate **9b** is complete.



Cl-Hx=6-chloropurine; Bn-Hx= 6-O-benzylhypoxanthine; a: NaH, BnOH; b: oxalic acid, H_2O; c: MeOH, HCl; d: toluoyl chloride; e: HBr-AcOH; f: 6-chloropurine, $Hg(CN)_2$; g: BnOH, NaH; h: TIPSCl, imidazole; i: DMSO, pyridine, TFA, DCC; j: diethylphosphite, Et_3N; k: thiocarbonyldiimidazole; l: $(Bu)_3SnH$, toluene; m: $(Bu)_4\overset{+}{N}\overset{-}{F}$, THF; n: H_2, Pd-C; o: TEAB buffer, snake venom phosphodiesterase.

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