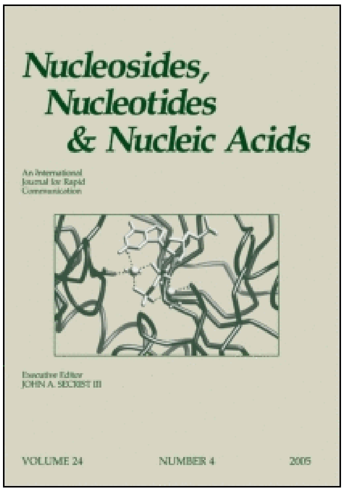

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Synthetic Approaches to Rare 2-Substituted Purine Nucleosides

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SYNTHETIC APPROACHES TO RARE 2-SUBSTITUTED PURINE NUCLEOSIDES

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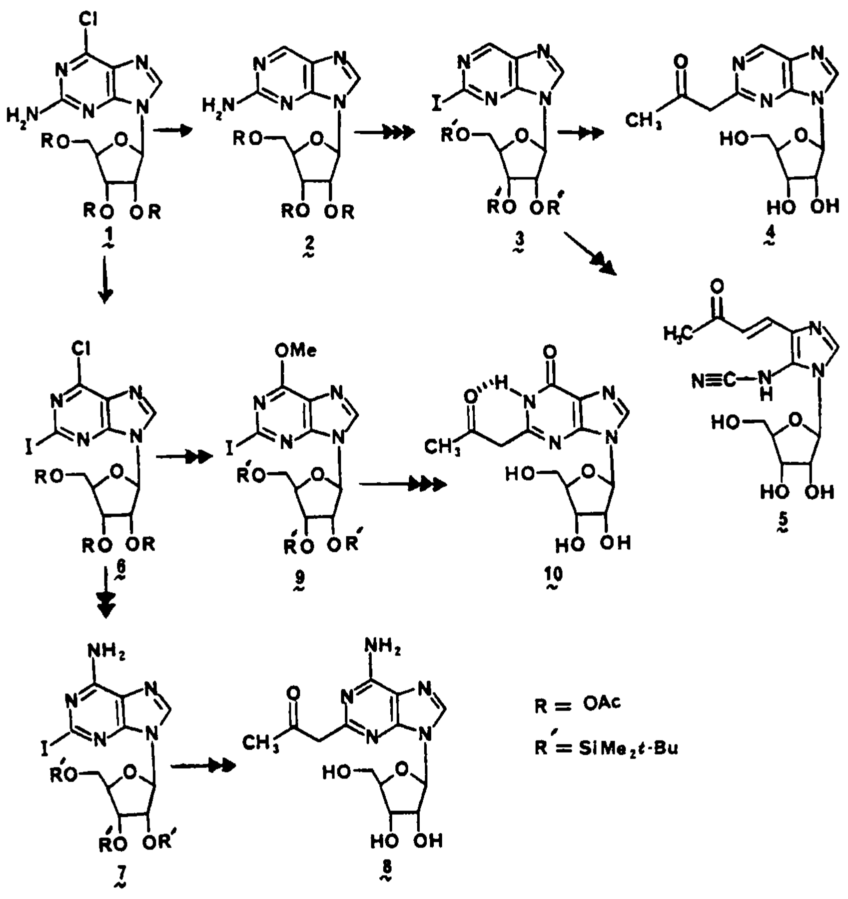
Summary: The syntheses of several novel functionalized 2-substituted purine nucleosides are described. Key reactions in these transformations include photoinduced reductive dehalogenation, radical deamination-halogenation, and functionalized carbon-carbon bond formation involving palladium catalysis. An interesting ring opening reaction of 2-iodopurine nucleoside to an imidazole derivative under $S_{RN}1$ conditions is mentioned. High-field ^{13}C NMR data suggest that the 2-substituted purine nucleosides prefer the *anti* conformation in solution. Biological evaluation of these compounds is currently being carried out.

The discovery of the antiviral and anticancer chemotherapeutic value of a number of structurally modified purine nucleosides has stimulated considerable interest both in the synthesis of novel nucleosides and in the development of efficient methodologies for their preparation. Synthetic access to some biologically interesting classes of 2-substituted purine nucleosides has been restricted because of limitations in synthetic methodology available to obtain them. This paper reports on the development and application of new approaches to some rare 2-substituted purine nucleosides.

A common precursor to these compounds was the 6-chloro-2-aminopurine **1**. In the synthesis of **4** this compound was first converted very efficiently to **2** by a photoinduced reductive dehalogenation reaction (hv, THF-Et_3N). This is a new reaction in purine nucleoside chemistry and represents an excellent synthesis of 2-aminopurine nucleoside, a potent inhibitor of a number of purine metabolizing enzymes. Compound **2** (as its silylated derivative) can be converted to the new 2-iodopurine **3** by a modification of a radical deamination-halogenation reaction previously reported by us.[1,2] The 2-halogenated



Scheme 1

compound 3 is potentially a precursor to a variety of novel 2-substituted purine nucleosides through functionalized carbon-carbon bond forming reactions. Alkylation of purine nucleosides at carbon-6[3-7] and especially at carbon-2[7-9] has received little synthetic attention. We have recently reported on a new approach to the synthesis of functionalized alkylated purine nucleosides through a photoinduced $S_{RN}1$ reaction.[10,11] However, the reaction of 3 with the potassium enolate of acetone under photolytic conditions did not result in the formation of 4 but gave rise to a ring opened imidazole nucleoside 5 (Scheme 1).[12] The behavior of the 2-halogenated purine 3 is in sharp contrast to the corresponding 6-halogenated compound which is readily alkylated under these conditions.

Functionalized alkylation of 3 was successfully carried out with tributylstannylacetone[13] under palladium catalysis. Deprotection of this product gave 2-acetonylpurine nucleoside 4.

Using related methodologies for carbon-carbon bond formation, 2-acetonyladenosine 8 and 2-acetonylinosine 10 were prepared from the appropriate 2-iodinated precursors (Scheme 1). 2-Acetonyladenosine is resistant to reductive deamination and hydrolytic deamination under a variety of conditions. It is a poor substrate for adenosine deaminase. High-field carbon-13 NMR data suggests that all of the target compounds prefer the *anti* conformation in solution. Biological evaluation of these compounds is currently being carried out.

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