Synthesis of Congeners of Adenosine Resistant to Deamination by Adenosine Deaminase

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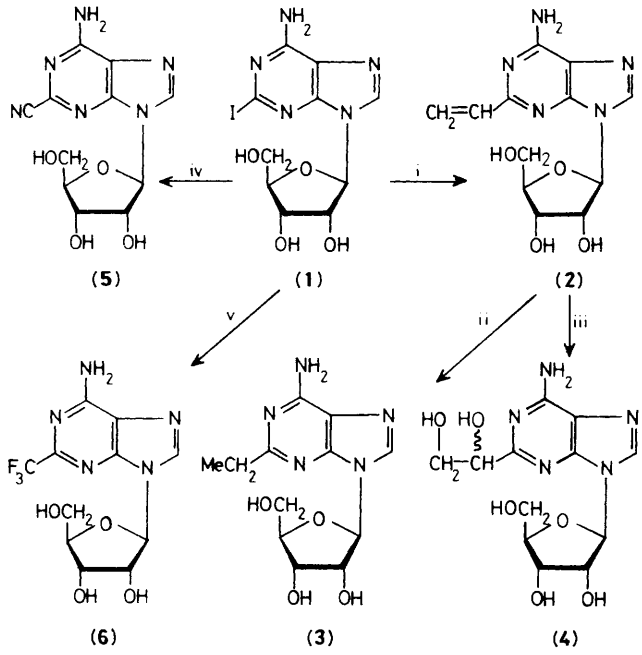
The novel metal-mediated syntheses of adenosine deaminase resistant congeners of adenosine are described.

Development of methodologies for the efficient and regiospecific functionalization of the adenine ring is of fundamental importance in the design and synthesis of therapeutically useful nucleosides of this family. Of particular interest are strategic functionalizations that result in congeners that are totally resistant to hydrolytic deamination by the ubiquitous mammalian enzyme, adenosine deaminase (ADA). This enzyme limits the therapeutic efficacy of adenosine analogues, including those such as 2',3'-dideoxyadenosine (ddA), which exhibit significant inhibition of the cytopathic effect of the human immunodeficiency virus (HIV-1).[1,2] We report on the novel, metal-mediated syntheses of some analogues of adenosine specifically functionalized at the 2-position and the behaviour of these nucleosides towards mammalian adenosine deaminase.

2-Iodoadenosine (**1**)[3] served as the precursor for the



Scheme 1. *Reagents and conditions:* i, $PdCl_2(MeCN)_2$, $Bu_3SnCH{=}CH_2$, DMF, heat; ii, Pd/C, H_2, EtOH; iii, OsO_4, pyridine; iv, $Pd^0(Ph_3P)_4$, Bu_3SnCN, DMF, heat; v, CF_3ZnBr, CuBr, hexamethylphosphoric triamide, DMF, heat.

synthesis of the target compounds. One approach for the regiospecific functionalization at the 2-position using this compound was a palladium-catalysed cross-coupling reaction with organostannanes.[4] Thus, when *unprotected* 2-iodoadenosine (**1**) was treated with $PdCl_2(MeCN)_2$ in the presence of $Bu^n_3SnCH{=}CH_2$ in dimethylformamide (DMF) with heating, the novel compound 2-vinyladenosine (**2**) was isolated in 84% yield. Reduction of (**2**) with H_2–5% Pd/C gave (**3**) (76%). Hydroxylation of (**2**) with osmium tetroxide in pyridine gave the novel diastereoisomeric diols (**4**) in 67% yield. Other regiospecific modifications involving 2-iodoadenosine and the palladium-catalysed cross-coupling approach are also possible. Thus, treatment of (**1**) with $Pd^0(Ph_3P)_4$ and Bu^n_3SnCN in DMF gave, on heating, 2-cyanoadenosine (**5**) in 86% yield.

Other metal-mediated reactions also allow direct functionalization of halogenated purine nucleosides. For example, compound (**1**) is easily converted to the trifluoromethyl compound (**6**) (70%) by treatment with 'CF_3Cu', generated *in situ* from CF_3ZnBr and CuBr.[5] This reaction presumably involves insertion of copper into the C–I bond of the iodopurine moiety followed by transfer of the trifluoromethyl group. These direct organometallic approaches to compounds (**5**) and (**6**) are superior to the previously reported syntheses of these compounds.[6,7]

Substrate activity studies of compounds (**1**)—(**6**) with mammalian adenosine deaminase were followed spectrophotometrically.[8] All these compounds were found to be totally resistant to deamination by this enzyme.[9] It is likely that substitution at the 2-position interferes with the normal substrate binding of this enzyme at N-1 of adenine nucleosides. Studies on the extension of these metal-mediated methodologies utilizing unprotected nucleosides are in progress.

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