A facile and efficient route to 3′,5′-diamino-3′,5′-dideoxynucleosides

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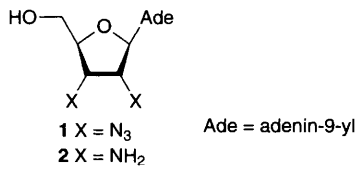
An efficient synthesis of 9-(3′,5′-diamino-3′-5′-dideoxy-β-D-ribofuranosyl)adenine is described (40% overall yield); the synthetic route is applicable to all the nucleoside bases and can serve as a general procedure for the synthesis of 3′,5′-diaminonucleosides.

Recently there has been a marked resurgence of interest in the field of nucleoside chemistry.[1] Keen interest in the chemistry of 2′,3′-dideoxynucleosides and their azido-sugar derivatives has been spurred by the potency of 3′-azido-3′-deoxythymidine (AZT) as an inhibitor of human immunodeficiency virus (HIV).[2] Examples of 2′-amino-2′-deoxy- and 3′-amino-3′-deoxy-ribonucleosides are known to possess antibacterial, anticancer and biosynthetic inhibitory effects.[3] More recently, we have reported the synthesis[4] of the doubly secondary-substituted 2′,3′-diazido-2′,3′-dideoxy- (**1**) and 2′,3′-diamino-2′,3′-dideoxy-adenosine (**2**) and shown that both technetium(v) and rhenium(v) complexes of **2** are potent inhibitors of ribonucleases.[5]

In an ongoing study to elucidate the effects of amino-derivatized nucleosides on critical biosynthetic pathways and for the synthesis of 3′,5′-cyclic monophosphate phosphodiesterase enzyme inhibitors, we first sought an efficient synthesis of 3′,5′-diamino-3′,5′-dideoxynucleosides. There is very little literature precedence for the synthesis of such nucleosides. The first reports are unneccesarily long and low yielding, being based on a primary synthesis and protection of 3′-amino-3′-deoxynucleosides.[6] A more recent route involved coupling of the preformed, derivatised sugar with the appropriate purine or pyrimidine base.[7] However, the problem of possible formation of a mixture of regioisomers meant that the critical glycosylation step led to a yield of only 50–52% for all the bases synthesised. With these considerations in mind, we here report a high yielding synthetic route to 3′,5′-diamino-3′,5′-dideoxyadenosine **3** which utilises chemistry known to have general applicability to all the nucleoside bases (Scheme 1).[8]

This route does not require extensive protection/deprotection strategies and is designed to allow orthogonal deprotection of the 3′- and 5′-amino groups, which is essential for subsequent incorporation into a polyribonucleotide.

Treatment of 9-(β-D-arabinofuranosyl)adenine **4** with triphenylphosphine (PPh_3) and diethylazodicarboxylate (DEAD) in 1,4-dioxane–DMF at 70 °C gave 9-(2′,3′-anhydro-β-D-lyxofuranosyl)adenine[4,9] **5** in 95% yield after recrystallisation from methanol (MeOH). This method generates the strained epoxide under essentially neutral conditions. Treatment of **5** with phthalimide, PPh_3 and DEAD in THF at room temperature gave 9-[2′,3′-anhydro-5′-deoxy-5′-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-β-D-lyxofuranosyl] adenine **6** in 79% yield after silica gel chromatography.[10] The use of Mitsunobu-type chemistry in the first two steps of the synthesis to give **5** and **6** offered the tantalising prospect that **6** might be generated in a one-pot reaction. However, when such a procedure was adopted, variable yields of **6** were obtained (20–70%). It is much more efficient therefore to perform the synthesis of the phthalimide derivative **6** in two distinct steps.

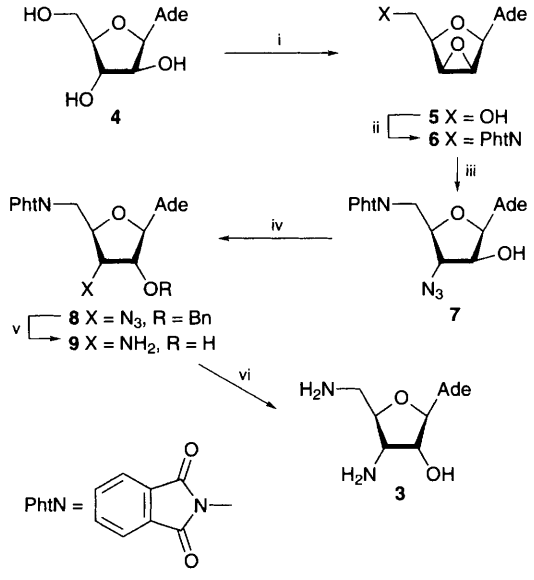


1 X = N_3
2 X = NH_2

Ade = adenin-9-yl

Ring opening of the epoxide **6** was achieved with LiN_3 in DMF at room temperature† to give 9-[3′-azido-3′,5′-dideoxy-5′-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-β-D-arabino-furanosyl]adenine **7** and its 2′-azido-2′-deoxy-*xylo* isomer in a ratio of 10 : 1. Previous reports of azide opening of the 2′,3′-anhydro derivative without substitution at the 5′-hydroxy group resulted in a similar regioselectivity.[4,11] It is interesting to note that the presence of the bulky 5′-phthalimido group does not significantly reduce this regioselectivity. Following recrystallisation from water, isomer **7** was obtained in 87% yield without any observed contamination by the 2′-azido compound.

Epimerization at the 2′-position of **7** was a challenging point in the synthesis. Most reports document the epimerization of the *ribo*- to the *arabino*-isomer, not the obverse.[12] We also required that the 2′-protection be orthogonal to only one of either the azide or phthalimido groups so that there was no need for an extra deprotection step. Initially we attempted this inversion by formation of the 2′-trifluoromethanesulfonate ester followed by displacement with acyloxy nucleophiles such as caesium acetate,[13] but this gave only low yields of the required 2′-acetoxy-*ribo* derivative. However, when the azido alcohol **7** was treated under Mitsunobu[14] conditions with PPh_3, benzyl alcohol and DEAD in warm 1,4-dioxane–DMF (1 : 1), 9-[3′-azido-2′-*O*-benzyl-3′,5′-dideoxy-5′-(1,3-dihydro-1,3-dioxo-

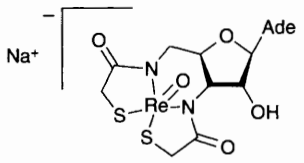


Scheme 1 *Reagents and conditions*: i, PPh_3, DEAD, DMF, 1,4-dioxane, 70 °C (95%); ii, phthalimide, PPh_3, DEAD, THF (79%); iii, LiN_3, DMF (87%); iv, PPh_3, DEAD, benzyl alcohol (75%); v, Pd/C (10%), H_2 (30 psi), MeOH; vi, hydrazine (aq.), anion (OH^-) exchange chromatography (84% from **8**)

2*H*-isoindol-2-yl)-β-D-ribofuranosyl]adenine **8** was obtained in 75% yield after silica gel chromatography.‡ Catalytic hydrogenation of **8** in neutral MeOH, followed by treatment of crude 9-[3′-amino-3′,5′-dideoxy-5′-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-β-D-ribofuranosyl]adenine **9** with aqueous hydrazine and purification by anion exchange chromatography followed by lyophilisation gave 3′,5′-diamino-3′,5′-dideoxyadenosine **3** in an excellent yield (84%).

This mild, six step procedure from readily available starting materials gave **3** in an overall yield of *ca.* 40%. Each of the steps is compatible with any of the nucleoside bases and therefore this route is the most efficient yet developed for the production of 3′,5′-diamino-3′,5′-dideoxynucleosides.

Aminonucleoside **3** is under investigation as a monomer for antisense oligonucleotides. In addition, as part of our ongoing attempts to develop new penta-coordinate transition state analogues for phosphoryl transfer reactions, **3** has been converted to a diamidodithiol (DADT) ligand for complexation with rhenium(V) donors. We have shown such complexes to be excellent inhibitors of ribonucleases and are now examining these new derivatives **I**, as inhibitors of cyclic 3′,5′-phosphodiesterase enzymes.



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Footnotes

† If the reaction was warmed to >60 °C, significant hydrolysis of the phthalimide protecting group accompanied epoxide opening. However at room temperature, only epoxide ring opening was observed.

‡ Although the reaction could not be driven to completion, by recycling the *arabino* isomer **7** excellent conversion to **8** can be achieved.

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