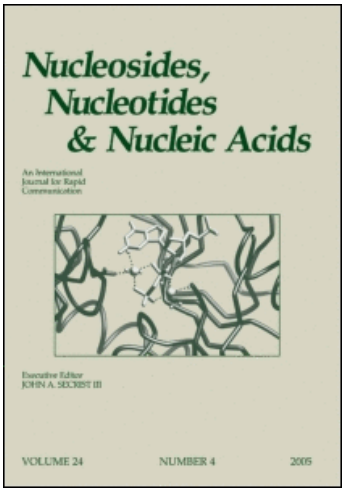

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Synthesis of New Dideoxynucleosides Bearing Ring-Extended Nucleobases

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SYNTHESIS OF NEW DIDEOXYNUCLEOSIDES BEARING RING-EXTENDED NUCLEOBASES

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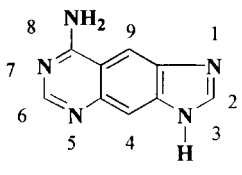
ABSTRACT: New dideoxynucleosides where the nucleobase is *lin*-benzoadenine is reported. The key target compound, (*S,S*)-isodideoxybenzoadenosine, is stable with respect to hydrolytic cleavage of the glycosyl bond and it is a poor substrate for adenosine deaminase. Its monophosphate is not a substrate for AMP deaminase.

While many dideoxynucleosides of antiviral interest with modifications of both the carbohydrate and base moieties are known,[1-5] there are few examples within this family of compounds with hypermodification in the base moiety such as ring extension. Among the known ring-extended bases, one of the more interesting is *lin*-benzoadenine (**1**) synthesized by Leonard and coworkers.[6-8] This molecule possesses all characteristic features of adenine except that it is larger in lateral dimension by 2.4 Å than adenine. Several years ago, we reported the synthesis and antiviral studies of 4(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol, [(S,S)-IsoddA] (**2**), an isomeric dideoxy-nucleoside which has potent activity against HIV-1 and HIV-2.[9-11] In the search for new dideoxynucleosides with antiviral activity, we have synthesized and studied both normal and isomeric dideoxynucleosides with *lin*-benzoadenine as the nucleobase and this is the focus of our report.



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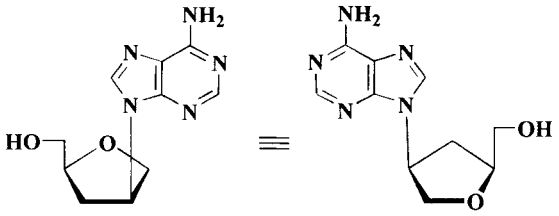

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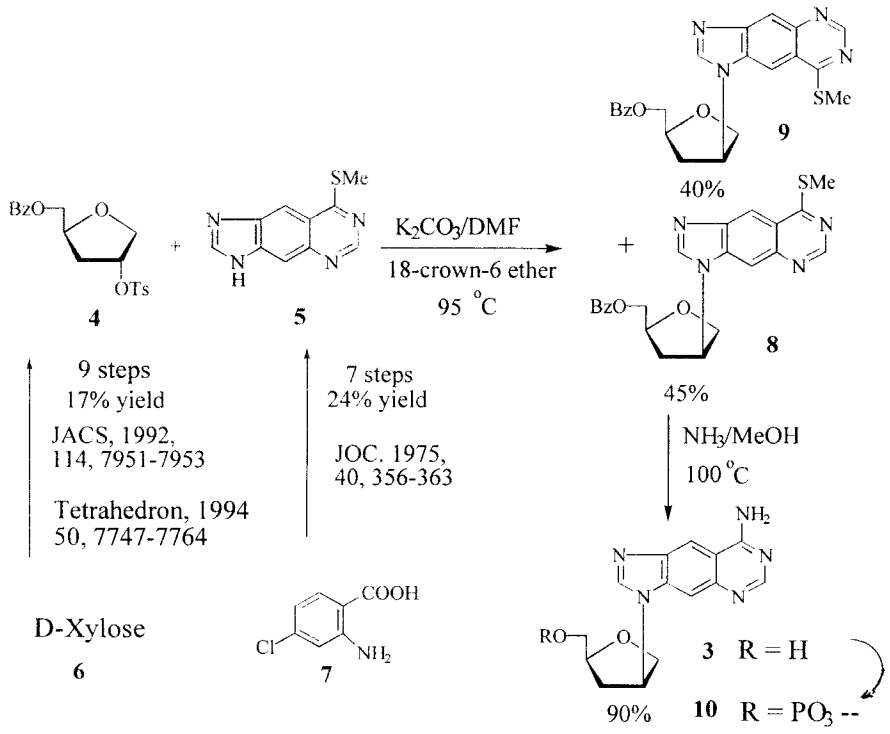
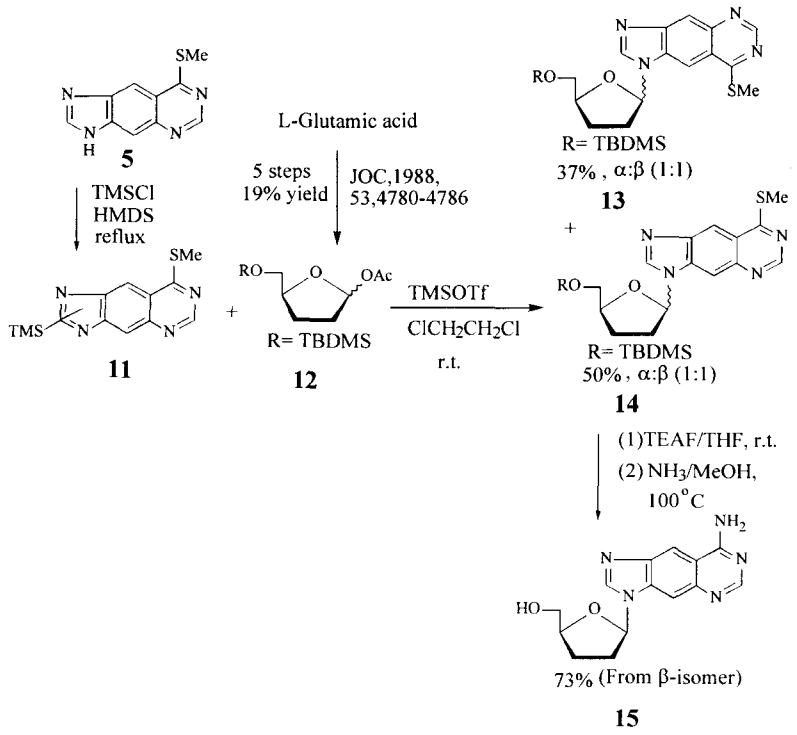


Scheme 1

The approach to the synthesis of isodideoxybenzoadenosine **3** involves coupling of benzopurine thiomethyl ether with an appropriately tailored sugar moiety (Scheme 1). The coupling sugar **4** can be synthesized in nine steps from xylose as previously described by us.[9] The base used for the direct coupling was 8-methylthioimidazo[4,5-g]quinazoline **5** which is more soluble in organic solvents than benzoadenine. Compound **5** can be synthesized in seven steps from **7**.[6] Nucleophilic displacement of the tosyl group of **4** with **7** in the presence of potassium carbonate and 18-crown-6 gave **8** and its N-1 isomer **9** which could be easily separated by preparative TLC. The two regioisomers could be easily distinguished by their UV spectra. Treatment of the desired isomer **8** with methanolic NH_3 at 100 °C (sealed bomb) gave the target compound **3**. Compound **3** was purified by preparative TLC and crystallized from methanol as white needles, mp 278-279 °C. Its structure was confirmed by quantitative UV data, 1-D and 2-D multinuclear



Scheme 2

NMR spectra, and elemental analysis. It was converted to its monophosphate by standard phosphorylation methods.

We have also synthesized dideoxybenzoadenosine (**15**) as summarized in Scheme 2. Compound **15** was characterized by spectral data as described for **3**.

The glycosidic bond stabilities of **3** and **15** were studied. Like other normal purine dideoxynucleosides, compound **15** was unstable under acidic conditions ($t_{1/2}$ = 1 h at pH 2, 25 °C). However, the isomeric nucleoside **3** was extremely stable under the same conditions and did not show any decomposition even after 15 days.

The behavior of **3** and **15** towards the ubiquitous enzyme, adenosine deaminase, was also studied. The relative substrate efficiency based on V_{max}/K_m were as follows: adenosine (100), dideoxyadenosine (12), isodideoxyadenosine (0.0008), dideoxybenzo-adenosine (30), and isodideoxybenzoadenosine (2). Thus, while compound **15** was a

moderately good substrate for adenosine deaminase, its isomeric counterpart, **3**, was a poor substrate for this enzyme, consistent with the resistance of the parent molecule, (*S,S*)-IsoddA toward this enzyme.[11] Interestingly, the monophosphate of compound **3** (i.e. **10**) is not a substrate for AMP deaminase. IsoddAMP also is not a substrate for this enzyme.[12] 2'-Isodideoxybenzoadenosine exhibits low anti-HIV activity.

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