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Synthesis of a 4′,4′-spirothietane-2′, N^3-cycloadenosine as a highly constrained analogue of 5′-deoxy-5′-methylthioadenosine (MTA)

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ABSTRACT

The synthesis of the highly constrained adenosine derivative **7** featuring at spirothietane at C-4′, which may be considered as a rigid analogue of MTA, is described.

S-Adenosylmethionine (AdoMet) is a key partner in many biochemical processes. In particular, it is known to be the common precursor for the synthesis of polyamines and the transfer of methyl groups to macromolecules. In these reactions, methylthioadenosine (MTA) and adenosylhomocysteine (AdoHcy) are formed as by-products in polyamine syntheses (via decarboxylated *S*-adenosylmethionine) and methyl transfer reactions, respectively (Fig. 1).[1]

In mammalian cells, AdoHcy is catabolized by AdoHcy hydrolase to give adenosine and homocysteine, the latter serves to

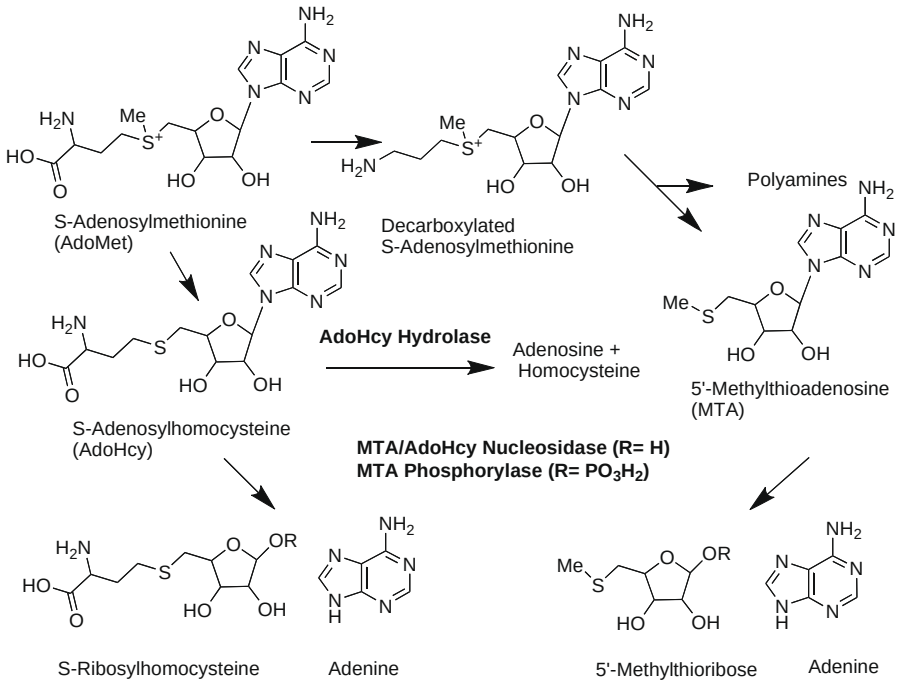

Figure 1. Metabolism pathways of the by-products derived from *S*-adenosylmethionine (SAM) reactions.

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regenerate AdoMet. The microbial MTA/AdoHcy nucleosidase is responsible for the degradation of AdoHcy into adenine and *S*-ribosylhomocysteine.[2] On the other hand, MTA is metabolized by the eukaryote MTA phosphorylase and the prokaryote MTA/AdoHcy nucleosidase that irreversibly depurinates MTA to give adenine and 5-methylthioribose-1-phosphate (MTR-1-P) in one case and 5-methylthioribose (MTR) in the other.[3]

AdoHcy has been observed to be a toxic intermediate in AdoMet-dependent methylation reactions. Accordingly, considerable efforts have been undertaken to develop inhibitors of AdoHcy hydrolase to serve as agents for antiviral and antitumor therapies.[4] In addition, since MTA is known to be a natural inhibitor of AdoHcy hydrolase,[5] inhibition of MTA metabolizing enzymes (eukaryote MTA phosphorylase or microbial MTA/AdoHcy nucleosidase), can lead to an MTA build-up within the cell which may have detrimental biological consequences.[6]

Taking advantage of the recent information gained from the structural studies of the AdoHcy and MTA metabolizing enzymes,[7] the design of novel potential inhibitors of these enzymes can be proposed.

As a preliminary step along this line, we envisioned the construction of a series of analogues of MTA exhibiting a constrained conformation. Such rigid analogues of MTA might help to confirm the mechanistic importance of the interactions delineated by the enzyme/substrate structural investigations. Furthermore, these new compounds might hopefully be: (1) potent inhibitors of the different MTA metabolizing enzymes and (2) less rapidly metabolized and excreted than their flexible counterparts.

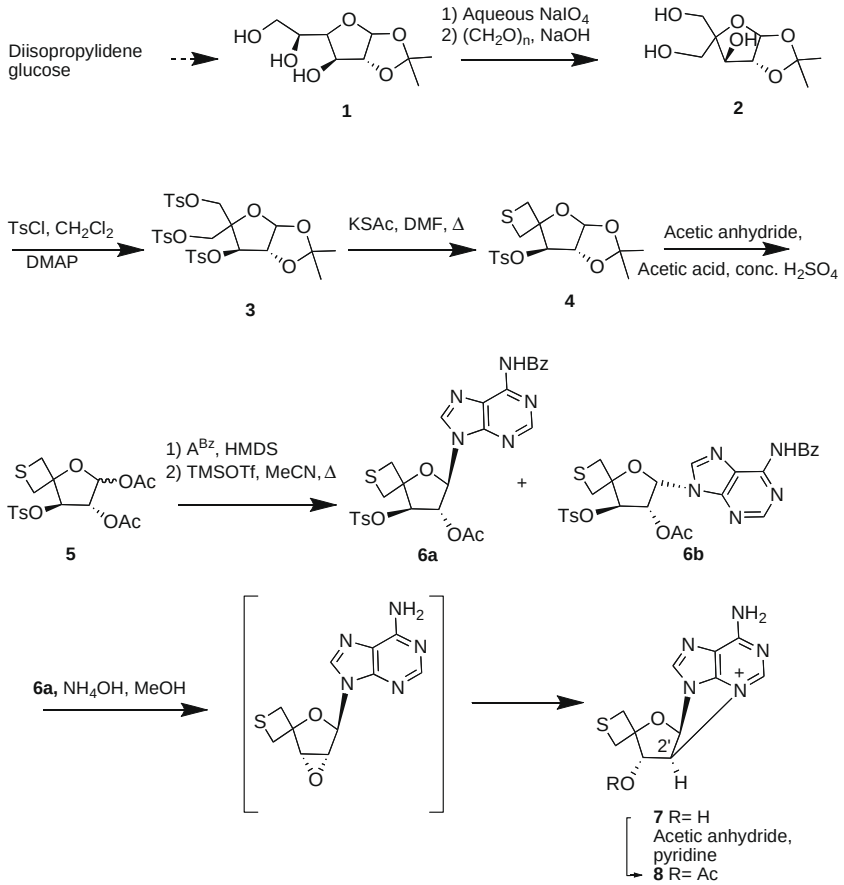
In the present work, we describe the synthesis of the new tetracyclic adenine nucleoside **7** as shown in Scheme 1. For this purpose, the starting material, diisopropylidene glucose, was selectively hydrolyzed to give the known triol **1**.[8] After a periodic acid degradation step, the resulting aldehyde intermediate was treated in situ with formaldehyde using a classical literature procedure to furnish triol **2**.[9]

A solution of this compound in methylene chloride was treated with a large excess of *p*-toluenesulfonyl chloride, in the presence of DMAP, to give the tri-*O*-tosyl derivative **3** in 90% yield. The spectral data (MS, NMR) confirmed that compound **3** was a tritosylate consistent with the presence of three methyl singlet signals observed at 2.45, 2.46, and 2.50 ppm in its ^{1}H NMR spectrum. Subsequently, treatment of **3** with potassium thioacetate in refluxing DMF directly furnished the spirothietane derivative **4**.[10]

Conversion of **4** into the di-*O*-acetate **5** was then readily accomplished in one step using a mixture of acetic anhydride/acetic acid containing concentrated sulfuric acid. Synthesis of the adenosine analogue was performed by introduction of N^6-benzoyl adenine onto the spirothietane carbohydrate **5** by means of reaction of the latter with the corresponding silylated purine in the presence of TMS-triflate in acetonitrile under refluxing conditions.[11]

This reaction yielded the protected nucleosides **6a** and **6b** in a 65% combined yield as a 7/3 mixture of a pair of β- and α-anomers, respectively. In view of the reaction conditions, which favor anchimeric assistance by the neighboring acetyl group, formation of the β-anomer as the major product was anticipated.

However, the stereoselectivity was found to be only moderate in this case. This result might be ascribed to a conformational effect due to the presence of the bulky β-oriented *O*-tosyl substituent at the 3′-position together with the rigid spirothietane at C-4′. Finally,



Scheme 1. Synthesis of the constrained derivative of MTA **7**.

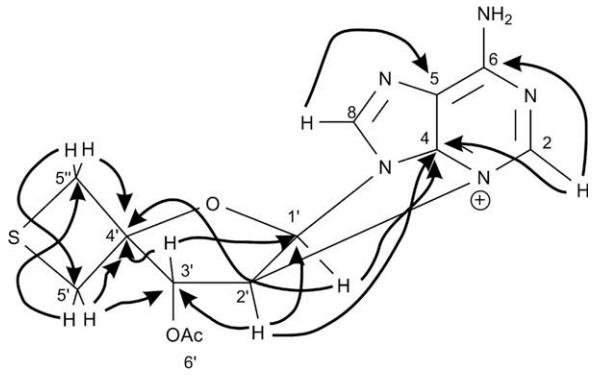


Figure 2. Key HMBC ^{1}H–^{13}C correlations for compound **8**.

complete separation of the two protected nucleoside isomers was achieved by means of HPLC.

The ultimate step in the sequence was the full deprotection of the β-anomer **6a**. For this purpose, the compound was treated with a solution of ammonium hydroxide in methanol. Under these conditions, the *N*-benzoyl group of adenine was eliminated with, probably, the concomitant formation of a 2′,3′-epoxide which undergoes a nucleophilic attack by the nitrogen at the N^3-position of the adenine moiety to provide the pentacyclic derivative **7**.

The structure of the new compound **7** was firmly established on the basis of an interpretation of its spectral data as well as those of its acetylated derivative **8**. In the latter case, detailed NMR analyses included COSY, NOESY, HMQC, and HMBC spectra.

It is highly significant that the HMBC spectrum of **8** showed a correlation between the H-2′ proton with the C-4 carbon of adenine establishing a bonding relation between atoms N^3 and C-2′ (Fig. 2 and Table 1).

In view of the previous literature observations concerning the behavior of 2′,3′-cycloadenosine, we considered that the mechanistic interpretation for the formation of **7** deserved to be examined further. Indeed, according to a preceding report, appreciable formation of a cyclonucleoside was observed after treatment of a 2′,3′-cycloadenosine derivative with sodium azide. The isolated compound was not fully characterized; however, reasonable arguments were given to suggest that its formation was the result of a cyclization reaction between atoms N^3 and C-3′.[12]

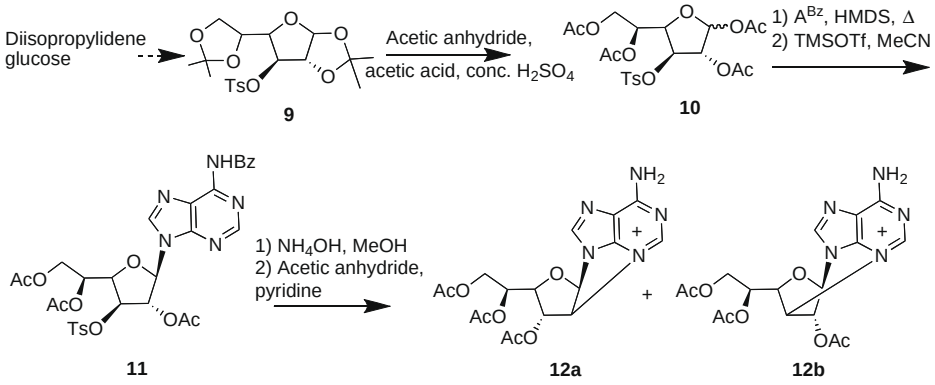
To reappraise the reactivity of an adenosine 2′,3′-epoxide, but devoid of the spirothietane ring system, we proposed to synthesize nucleoside **11** and to examine its behavior in basic medium (Scheme 2). To prepare nucleoside **11,** the diisopropylidene glucose tosylate **9** was first treated with a mixture of acetic anhydride/acetic acid in the presence of concentrated sulfuric acid. This reaction provided tetraacetate **10** that was used to glycosylate N^6-benzoyl adenine under the classical Vorbrüggen conditions.[11] As expected, the major product of this reaction (isolated in 60% yield) was the nucleoside derivative **11** whose proposed structure was found to be fully consistent with its spectral data.

Finally, as above, compound **11** was treated with a solution of ammonium hydroxide in methanol. To facilitate the purification step, the crude reaction product was acetylated and after column chromatography two triacetates **12a** and **12b** (ratio 3/1) were isolated in a 67% combined yield.

Table 1
^{1}H, ^{13}C and HMBC data for compound **8** and ^{1}H, NOESY data for compound **7**[a]

Position	^{13}C δ (**8**)	^{1}H δ (**8**) (mult, *J* in Hz)	^{1}H δ (**7**) (mult, *J* in Hz)	NOESY ^{1}H–H (**7**)	HMBC ^{1}H–^{3}C (**8**)
2	141.8	8.01 (s; 1H)	7.97 (s; 1H)	—	4 and 6
4	151.5	—	—	—	—
5	110.2	—	—	—	—
6	159.9	—	—	—	—
8	149.0	8.68 (s; 1H)	8.25 (s; 1H)	1′	5
1′	91.5	6.12 (d; 1H; 5.6)	6.39 (d; 1H; 6.0)	2′ and 8	4′ and 4
2′	74.9	4.61 (d; 1H; 5.6)	4.69 (d;1H; 6.0)	1′	1′, 3′ and 4
3′	79.3	5.58 (s; 1H)	4.77 (s; 1H)	—	1′ and 4′
4′	87.3	—	—	—	—
5′	39.1	3.00 (dd; 2H; 2.1; 9.6)	3.00 (dd; 2H; 2.5; 9.2)	5′	3′; 4′ and 5‴
5″	33.5	3.40 (dd; 2H; 2.1; 9.6)	3.50 (dd; 2H; 2.5; 9.8)	5″	3′, 4′ and 5′
6′	170.7	2.28 (s; 3H)	—	—	—

[a] The experiments were performed at 500 MHz for ^{1}H and 100 MHz for ^{13}C in CD_3OD (compound **7**), $CDCl_3$ (compound **8**) and TMS as internal reference (δ 0.00 ppm).



Scheme 2. Synthesis of the N^3,C-2′ and N^3,C-3′ nucleosides.

Elucidation of their respective structures was made by inspection of their COSY NMR spectra that allowed the unambiguous attribution of the signals due to the glycosyl protons of **12a** and **12b**. Thus, in the case of **12a,** the signals ascribed to H-2′ and H-3′ appeared at 4.36 and 5.36 ppm, respectively. Conversely, in the case of **12b,** the corresponding signals were found at 5.71 and 4.63 ppm in full support of the proposed structures.

From this experiment, it is clear that in basic medium 2′,3′-cycloadenosine (adenosine 2′,3′-epoxide) undergoes a cyclization and that this reaction manifests a preference for the formation of the linkage between atoms N^3 and C-2′ over the linkage between atoms N^3 and C-3′.

In conclusion, in this work, we have reconsidered the behavior of adenosine 2′,3′-epoxide in basic medium and devised a synthetic route to yield constrained analogues of 5′-methylthioadenosine (MTA) such as nucleoside **7** that derives from N^3, C-2′-cycloadenosine featuring a spirothietane in position 4′.

Acknowledgments

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Supplementary data

Supplementary data (Procedures for the preparation of derivatives **2**–**8** and **10**–**12** and ^{1}H NMR spectra for compounds **6a** and **8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.039.

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