



## An efficient synthesis of base-substituted analogues of *S*-adenosyl-DL-homocysteine

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### ABSTRACT

An efficient method for the preparation of base-substituted *S*-adenosyl-DL-homocysteine analogues as well as of 2-chloro-*N*<sup>6</sup>-alkylated *S*-adenosyl-DL-homocysteine analogues is described. The method uses a convergent strategy that employs a common intermediate late in the overall synthesis and allows small libraries of SAH analogues to be prepared in a relatively short period of time.

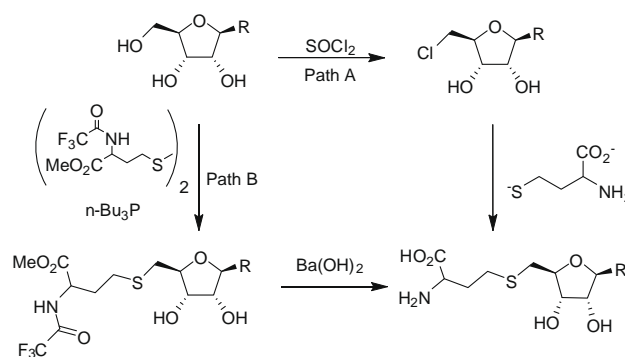
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*S*-Adenosyl-L-homocysteine (L-SAHA) and its analogues are a potent class of inhibitors for a number of biologically important enzymes including *S*-adenosyl-L-homocysteine hydrolase<sup>1</sup> and *S*-adenosylmethionine-dependant methyltransferases.<sup>2</sup> However, in spite of their biological importance there are relatively few distinct synthetic pathways to SAH analogues which are both convenient and reliable.<sup>3,4</sup>

Currently, SAH analogues are synthesized using one of two general methods. In the most common approach, the 5' position of a nucleoside is activated as the corresponding 5'-chloro derivative and then displaced with homocysteine, or a homocysteine analogue<sup>1c,3</sup> (Scheme 1, path A). Alternatively, the 5' position of a nucleoside can be activated in situ and coupled to a protected homocysteine unit which is then deprotected (Scheme 1, path B).<sup>4</sup> Both of these approaches are convenient and provide the desired SAH analogue in two steps so long as the parent nucleoside is commercially available. If, however, the nucleoside is not commercially available, these two approaches become inefficient. This is because the entire reaction sequence, starting from the synthesis of the nucleoside, must be performed from beginning to end for each different SAH analogue that is desired.<sup>5</sup> In fact, prior to the study presented here there were no reported synthetic pathways to SAH analogues which allowed the addition of the base substituent at the end of the reaction sequence rather than at the beginning. This is surprising since such an approach would enable base-modified SAH analogues to be synthesized from a common intermediate, significantly reducing the amount of time required to prepare large numbers of these compounds.

In order to develop a convenient synthesis for SAH analogues which would allow the base substituent to be added at the end of the reaction sequence rather than at the beginning, we envi-

sioned synthesizing an intermediate similar to  $\beta$ -D-ribofuranose 1,2,3,5-tetraacetate (TAR). TAR is a common starting material for the syntheses of ribose-based nucleosides and can be glycosidated under mild conditions with a high degree of stereocontrol.<sup>6</sup> The intermediate developed in this study, **1**, possesses the same 1', 2' and 3' acetate groups as TAR as well as a protected homocysteine unit (Fig. 1). As a result, SAH analogues can be prepared from **1** in only two synthetic steps; glycosidation, using standard procedures developed for the glycosidation of TAR, followed by a single deprotection under basic conditions.



Scheme 1. Current methods used for synthesis of SAH analogues.

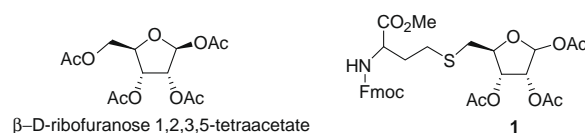
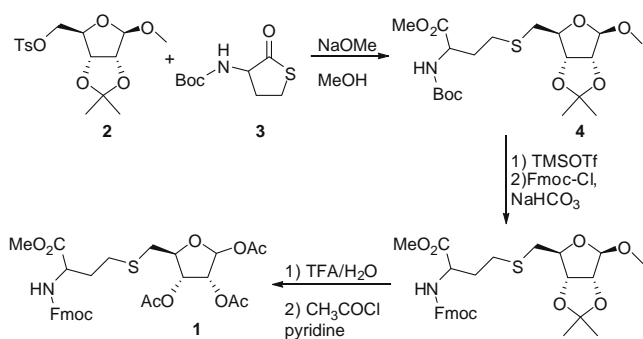


Figure 1. Comparison of TAR and intermediate **1**.

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Scheme 2. Synthesis of intermediate **1**.

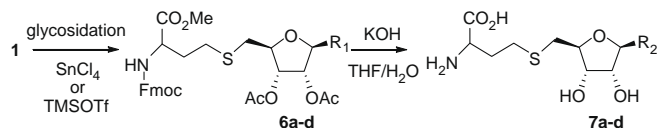
The synthesis of **1** was accomplished in three steps from commercially available methyl 2,3-isopropylidene-5-*o*-*p*-tolylsulfonyl- $\beta$ -D-ribofuranoside (**2**) and racemic *N*-Boc-DL-homocysteine thiolactone (**3**) in 55% overall yield (Scheme 2). In the first step, the tosylate group of **2** was displaced with the sodium salt of *N*-Boc-DL-homocysteine methyl ester, generated in situ by the addition of sodium methoxide to **3**, affording **4** in 83% yield. The BOC protecting group of **4** was then selectively cleaved using TMSOTf and the resulting free nitrogen was reprotected with the acid-stable Fmoc protecting group (**5**, 94% yield). The introduction of the Fmoc group allows all of the protecting groups in the final products to be removed under basic conditions. In addition, the replacement of the acid-labile Boc group in **4** with the acid-stable Fmoc group prevents decomposition of the intermediate triol that is generated

when **4** is treated with TFA/H<sub>2</sub>O.<sup>7</sup> Treatment of **5** with a 50/50 mixture of TFA/H<sub>2</sub>O, followed by precipitation with water and acetylation with acetyl chloride provided **1** in 77% yield as a mixture of anomers (1.7:1 of  $\beta/\alpha$ ).

As representative examples of how **1** can be used to synthesize a range of SAH analogues, **1** was coupled to a variety of adenine substituents using TMSOTf and SnCl<sub>4</sub> as catalysts in CH<sub>3</sub>CN (Scheme 3). As shown in Table 1, the addition of benzimidazole, 8-azaadenine and phenol to **1** (entries 1, 2 and 4, respectively) occurred with similar regio- and stereochemistry as the addition of these bases to TAR under the same reaction conditions.<sup>8</sup> However, in our hands the addition of 7-nitroimidazo[4,5-*b*]pyridine to **1**, in the presence of SnCl<sub>4</sub>, did not result in any of the desired product. This is despite a report that 7-nitroimidazo[4,5-*b*]pyridine can couple with TAR using similar conditions.<sup>9</sup> Nevertheless, the reaction between 7-nitroimidazo[4,5-*b*]pyridine and **1** proceeded smoothly using TMSOTf as a catalyst and gave **6c** in 53% yield (Table 1, entry 3). Reduction of the nitro group in **6c** with Fe/HCl, followed by deprotection with KOH, provided *S*-(1-deazaadenosyl)-DL-homocysteine (**7c**) in 34% overall yield from **1**. Compared to the synthesis of *S*-(1-deazaadenosyl)-L-homocysteine from TAR, which required five steps with a reported overall yield of 20%,<sup>9,10</sup> the synthesis of *S*-(1-deazaadenosyl)-DL-homocysteine (**7c**) from **1** occurs in less synthetic steps and also gives higher yields.

To further demonstrate the utility of **1** as an intermediate for the syntheses of SAH analogues, a number of N<sup>6</sup>-alkylated analogues were also prepared (Scheme 4). The coupling of 2,6-dichloropurine to **1**, using TMSOTf as a catalyst, provided **8** in good overall yield (81%).<sup>11c</sup> Treatment of **8** with a variety of primary or secondary amines in 1,2-dichloroethane resulted in the in situ displacement of the chloride at the 6-position of the purine base.<sup>11a-c</sup> Evaporation of the solvent and deprotection of the aminated intermediate provided the N<sup>6</sup>-alkylated SAH analogues **9a-e** in 54–72% yield (Table 2).

The ability to synthesize N<sup>6</sup>-alkylated SAH analogues from **8** in only two steps, one of which is performed in situ, is a significant improvement over published procedures that have been used to prepare similar analogues<sup>11d</sup> and substantially reduces the amount of time required to prepare libraries of these compounds. For

Scheme 3. Synthesis of **6a-d** and **7a-d**.Table 1  
Yields and conditions for the synthesis of **6a-d** and **7a-d**

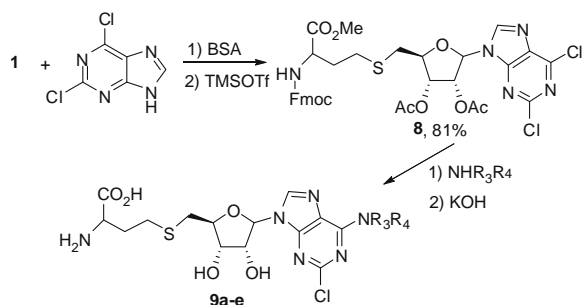
Entry	R <sub>1</sub>	R <sub>2</sub>	Catalyst	Yield <b>6a-d</b> (%)	Yield <b>7a-d</b> (%)
1			TMSOTf	76	73
2			SnCl <sub>4</sub>	62 <sup>a</sup>	79
3			TMSOTf	53	65 <sup>b</sup>
4			SnCl <sub>4</sub>	38 <sup>c</sup>	97

Only isolated yields are reported.

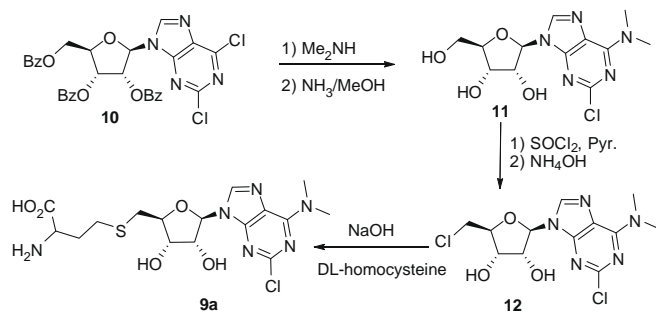
<sup>a</sup> Yield of N<sup>7</sup>-isomer only.

<sup>b</sup> The nitro group in **6c** was reduced before deprotection.

<sup>c</sup> Yield for the  $\beta$  isomer only.

Scheme 4. Synthesis of **9a–e**.Table 2  
Yields for the synthesis of **9a–e**<sup>a</sup>

Entry	Product	HNR <sub>3</sub> R <sub>4</sub>	Yield (%)
1	<b>9a</b>		58
2	<b>9b</b>		54
3	<b>9c</b>		63
4	<b>9d</b>		69
5	<b>9e</b>		71

<sup>a</sup> Only isolated yields are reported.Scheme 5. Alternative synthesis of **9a** from its parent nucleoside.

example, the preparation of **9a** from **10**,<sup>12</sup> via intermediates **11** and **12** (Scheme 5) required four steps and occurred with an overall yield of 11%, which is a significantly longer and lower yielding route than that used for the synthesis of **9a** from intermediate **1** (Table 2, entry 1).

In conclusion, a new method to synthesize base-substituted analogues of SAH is described. By using **1** as a starting point, SAH analogues can be prepared in as few as two synthetic steps rather than the usual four steps that would be required to prepare the same analogues from TAR. In addition, the synthesis of SAH analogues from **1** offers milder reaction conditions and generally gives higher overall yields than previously developed procedures.

Considering the divergent nature of the synthesis and the ease with which libraries of SAH analogues can be generated, the concepts presented here should find wide spread use in both academic research and drug development.

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## Supplementary data

Supplementary data (experimental procedures and spectroscopic characterizations of compounds **1–5**, **6a–d**, **7a–d** and **9a–e**) associated with this paper can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.076.

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