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The metathesis reaction for side chain construction in carbocyclic sinefungin analogue synthesis

Qi Chen, Chong Liu, Tetyana S. Shulyak, Stewart W. Schneller *

Molette Laboratory for Drug Discovery, Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849-5312, USA

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ABSTRACT

The naturally occurring nucleoside sinefungin has found considerable use in biological investigations. More extensive sinefungin studies have been limited because few analogues have been reported due to the synthetic challenges associated with such studies. Reported herein are preparative ways to two carbocyclic sinefungin analogues: 6′-deaminocarbocyclic sinefungin and (*S*)-6′-hydroxy-6′-deamino-carbocyclic sinefungin. The synthetic routes were made efficient and practical by the application of two metathesis reactions employing second generation Grubbs catalyst.

1. Introduction

Biological methylations play a major role in cellular metabolism and replication.[1] A ubiquitous cofactor for the methyltransferases (MTases) that conduct these reactions is *S*-adenosylmethionine (**1**, AdoMet).[2] Numerous studies have been undertaken to enlighten the unique steps associated with these processes. Sinefungin (**2**), a naturally occurring nucleoside isolated from *Streptomyces griseolus*[3] and *Streptomyces incarnates*,[4] has found a prominent place for this purpose.

Recent examples of **2** serving in this capacity include analysis of (1) the active site of human histone MTases (lysine MTase, PKMT; and, arginine MTase, PRMT);[5–12] (2) the viral mRNA MTase capping process;[13–17] (3) methylation of TrmN/Trm14 tRNA in archaea, bacteria, and eukaryotes;[18,19] (4) DNA methylation associated with gene expression, particularly related to cancer development;[20,21] (5) the phosphoethanolamine MTase in *Plasmodium falciparum*;[22] and, (6) the long range conformational effects of binding in the AdoMet binding domain of histone MTase G9a.[23]

Sinefungin has also found application beyond MTase investigations. Recent representatives in this category are (1) the mapping of the putative binding site of 7,8-diaminopelargonic acid synthase (DAPAS), an aminotransferase involved in mycobacterium tuberculosis biotin synthesis;[24,25] (2) the AdoMet transporter mechanism in Pneumocystis, an organism that requires host AdoMet for replication;[26] (3) the structure and mechanism of the chalcogen-detoxifying bacterial protein TheB;[27] and, (4) an aid in understanding base recognition by endonucleases (e.g., TspGWI)[28].

Carbocyclic nucleoside analogues of the natural products aristeromycin (**3**) and neplanocin (**4**) have been extensively studied in our group,[29] including carbocyclic sinefungin (**5**, Fig. 1).[30] To

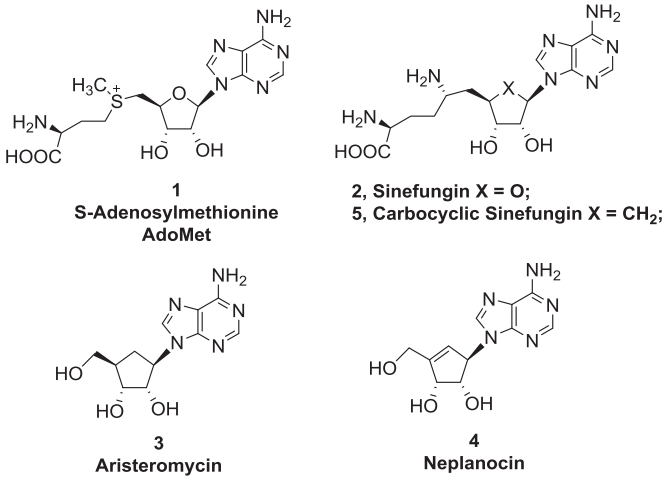

Fig. 1. Structures of AdoMet, Sinefungin, and carbocyclic nucleosides.

* Corresponding author. Tel.: +1 334 844 6947; fax: +1 334 844 0239; e-mail address: schnest@auburn.edu (S.W. Schneller).

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further develop the carbocyclic sinefungin series, the synthesis of 6′-deaminocarbocyclic sinefungin (**6**) and (*S*)-6′-hydroxy-6′-deaminocarbocyclic sinefungin (**7**) was sought. The preparation of the structurally simplified **6** was envisioned to provide a synthetic pathway strategy adaptable to obtaining **7**. It is noteworthy that **7** represents the first sinefungin analogue where the C-6′ amino is replaced by the less basic, yet similarly polar hydroxyl group, while retaining the sinefungin (*S*)-6′ stereochemistry (Fig. 2).

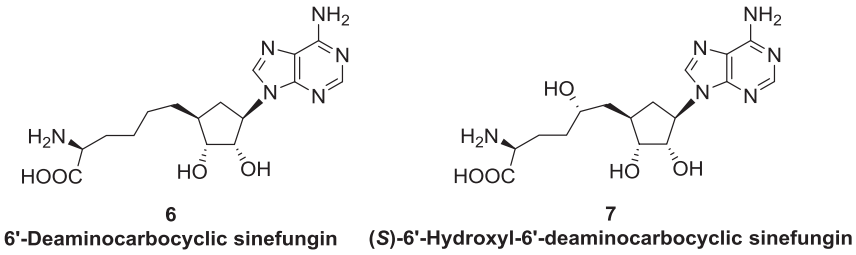

Fig. 2. Structures for target compounds **6** and **7**.

2. Results and discussion

A retrosynthetic analysis revealed that discovering an efficient and practical bond formation between C-7′ and C-8′ would be a cornerstone feature of our synthesis of both **6** and **7** (Fig. 3). In this plan, the requisite amino acid side-chain with the necessary chirality was planned to be introduced prior to joining the purine with an appropriately functionalized carbocyclic unit.

Mitsunobu coupling of **14** with the N-6 protected adenine **15** gave **16**, the sole coupled product.[34] Oxidative cleavage of the butenyl double bond with osmium tetroxide/sodium periodate transformed **16** to aldehyde **17**, which was unstable and, hence, was used promptly in a Wittig reaction with the synthon **8**. This gave only a 25% yield of **18**, which readily lost one Boc protecting group (by ^{1}H NMR) if care was not taken to control the reaction and/or purification time. The product instability of **17** coupled with the low yield of the Wittig option rendered this route unsatisfactory.

Attention then turned to plan 2 (Scheme 1). First, a 1:1 ratio of **16** and **19** in a standard metathesis reaction using a second generation Grubbs catalyst was carried out. The reaction proceeded smoothly to **20** in 61% yield along with the self-coupled by-product **21** (37% yield). The work of Grubbs suggests[35,36] that **21** is the consequence of **16** being of a type 1 class olefin, and it competes with an equivalent amount of type 2 olefin **19** resulting in self-coupled product. Support for **16** being of type 1 and **19** being of

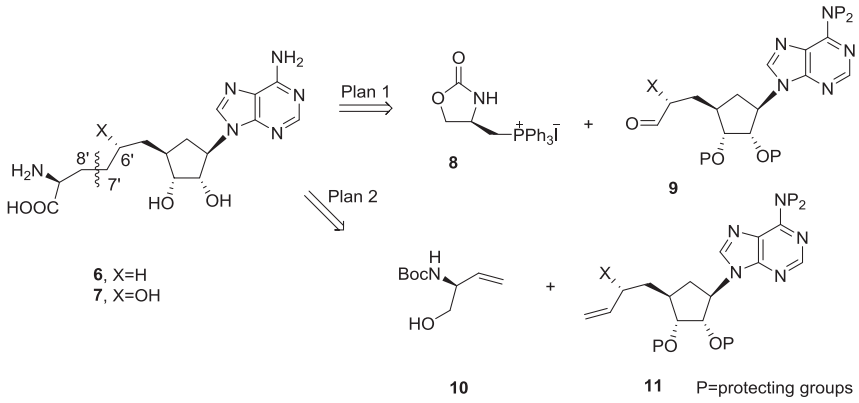

Fig. 3. Retrosynthetic analysis for target compounds.

A search of the synthetic literature for sinefungin analogues indicated that no coupling approaches between C-7′ and C-8′ had been studied. Our analysis suggested assembling the structurally relatively simple **6** by including either (plan 1) a Wittig reaction of an alaninol synthon (i.e., **8**) with nucleoside **9** (X=H) or (plan 2) a cross-metathesis coupling of **10** and suitably equipped nucleoside precursor (**11**) offered synthetic promise. The desired **8** and **10** are readily accessible from naturally occurring D-serine bearing the desired amino acid chiral center.[31,32]

With this blueprint in mind, our synthesis began with plan 1 and the copper salt promoted 1,4-conjugate addition of 3-butenylmagnesium bromide to cyclopentenone **12** (available from D-ribose in five steps)[33] to yield **13** (Scheme 1). The butenyl group was chosen as a source of the 7′-aldehyde. Stereoselective reduction of **13** with lithium aluminum hydride yielded alcohol **14**. A type 2 follows from the exclusive formation of **20** in the *E*-configuration ($J_{H\text{-}7'/H\text{-}8'}$=15 Hz).[35,36]

Catalytic hydrogenation of the double bond in **20** yielded **22** (quantitative). Treatment of **22** with a low concentration of *p*-toluenesulfonic acid with the intention to selectively remove the aza-acetonide proceeded to **23** and **24**, whose formation significantly lowered the yield of **23** (23%). Despite this unacceptable yield of **23**, the process validated the idea of moving forward with an olefin metathesis procedure (plan 2). Also, compared to plan 1, this methodology was mild and efficient.

To circumvent the deprotection outcome (i.e., **23**+**24**), attention turned to the partially deblocked **10** as the metathesis partner (Scheme 2). Also the formation of the aforementioned **21** (using **19**) suggested that the ratio of **10** to **16** be increased at a ratio of 1.5:1. As a sequence, **25** was obtained free of **21**. As with **20**, the ^{1}H NMR