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# Study of the synthesis of poecillanosine

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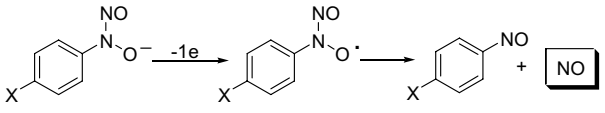
**Abstract**—The synthesis of poecillanosine, a natural *N*-hydroxy-*N*-nitroso-alkylamine compound, was studied. Poecillanosine was shown to be unstable under acidic nitrosation conditions. Only degradation compounds of poecillanosine were obtained under such conditions, however, the *O*-methyl derivative of poecillanosine was synthesised and confirmed.


The chemistry of *N*-hydroxy-*N*-nitrosoamines had not received much attention prior to the discoveries that (1) nitric oxide (NO) can be released from these compounds[1,2] and (2) NO has diverse and dramatic physiological effects.[3–5] Recently, the chemical and biological properties of a series of aromatic *N*-hydroxy-*N*-nitrosoamines have been studied.[6–8] The results revealed that these compounds yield NO by undergoing a one-electron oxidation. The oxidation can be achieved through chemical, electrochemical and enzymatic methods (Scheme 1). The amount of NO generation is dependent on both the oxidation potential applied and the substituents on the phenyl ring. Therefore, these compounds are considered as new types of redox-sensitive, and redox-adjustable NO donors.

*N*-Hydroxy-*N*-nitrosoamine derivatives were also reported to be inhibitors of some metal containing enzymes such as tyrosinase[9] and superoxide dismutase.[10] The inhibition activity is likely to be derived from the *N*-hydroxy-*N*-nitrosoamine group, which could potentially interact with the metal ion at the enzyme active sites.

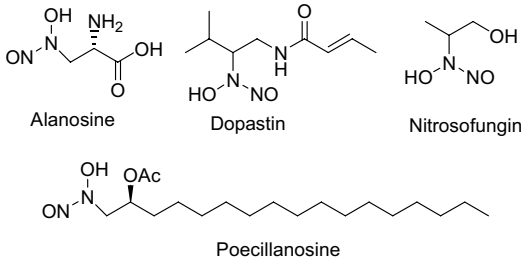



**Scheme 1.**

In general, *N*-hydroxy-*N*-nitroso-alkylamines are rare natural products. So far, only four have been reported (Scheme 2): alanosine,[11] dopastin,[12] nitrosofungin[13] and poecillanosine.[14] Poecillanosine was the most recent one, isolated from a marine sponge in 1997 and acts as a free radical scavenger.[14] Since mass spectral and NMR peaks of poecillanosine itself provided no useful information (it is likely that poecillanosine decomposes under analytic conditions),[14] it was converted into a more stable methyl ether derivative which led to the structure elucidation. Poecillanosine structurally differs from other *N*-hydroxy-*N*-nitroso-alkylamine natural products with the inclusion of a long lipophilic carbon chain.

In order to investigate NO-related biological properties of poecillanosine, we carried out the synthesis of this natural product. Here we report the synthetic study results.

From the retrosynthetic perspective, (*S*)-1,2-heptadecanediol **1** serves as the key intermediate (Scheme 3). Obviously, sharpless asymmetric dihydroxylation (AD)




**Scheme 2.**

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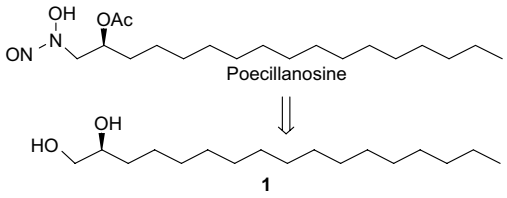
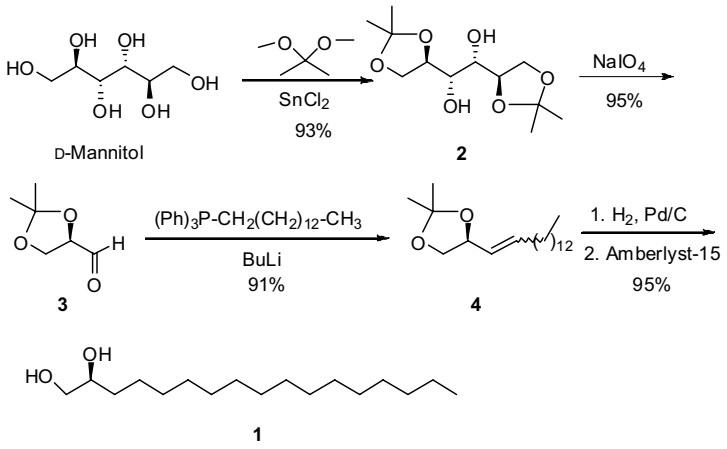


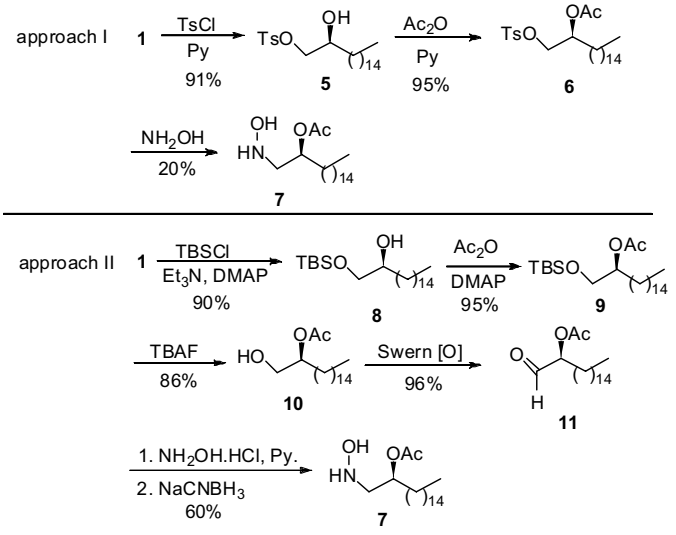

**Scheme 3.**

of corresponding olefin is the most efficient pathway to prepare **1**. However, similar to previous reports,[15,16] AD reactions on 1-heptadecene provided desired diol **1** in 90–93% yields with 72% ee as the highest enantiomeric excess. Therefore, another route was adopted as described in Scheme 4. *R*-Glyceraldehyde (**3**) was prepared from D-mannitol by acetonide formation and oxidative cleavage of diol **2**.[17] Then, the alkyl chain was enlarged under Wittig olefination.[18,19] Olefin **4** was obtained as the mixture of $Z/E$ isomers ($Z/E = 92/8$). In this case, the $E/Z$ ratio of the products presented no problem because hydrogenation of the double bond followed. Catalytic hydrogenation of **4** followed by the removal of the acetonide furnished chiral diol **1** in an excellent yield. This five-step sequence allowed us to prepare **1** in a large quantity with a high enantiomeric excess (98% ee).

With diol **1** in hand, we turned to explore the synthesis of the precursor of poecillanosine (compound **7**). As shown in Scheme 5, the first approach was to convert the primary hydroxyl of **1** into a tosylate **5**. Then, acetylation of **5** followed by displacement of the tosylate with hydroxylamine provided *N*-alkyl-*N*-hydroxyamine **7**. This approach involved three steps, but the overall yield (17%) was low. In the second approach, the primary hydroxyl group was selectively protected as TBS silyl ether **8** and the secondary hydroxyl group was protected as acetate. The resulting compound **9** was then treated with tetrabutylammonium fluoride to provide alcohol **10**. Swern oxidation[20] of **10** followed by oxime formation with hydroxylamine and $NaCNBH_3$ reduc-




**Scheme 4.**



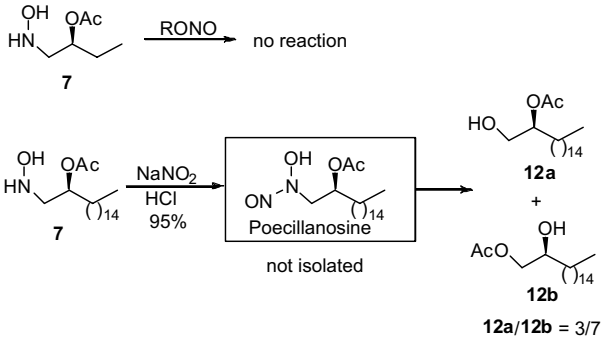

**Scheme 5.**

tion furnished **7**, the precursor of poecillanosine. The second approach was three steps longer than the first approach, but the overall yield (42%) was more acceptable.

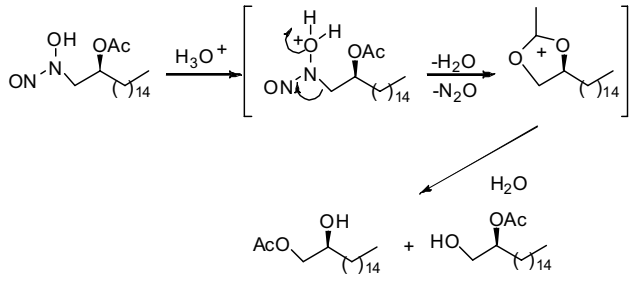
Next, two nitrosation methods were applied to **7** to complete the synthesis of poecillanosine. However, both methods failed. The nitrosation employing alkyl nitrites (ethyl nitrite, butyl nitrite, *iso*-butyl nitrite) under different temperatures and solvents did not lead to any product even after 24 h. Only starting materials were recovered. In contrast, upon the treatment with $NaNO_2$/HCl, the starting material was consumed completely, however, two isolated products were **12a** and **12b** (Scheme 6), instead of the desired poecillanosine.

In this nitrosation step, we propose that the treatment with $NaNO_2$/HCl of **7** did lead to the formation of poecillanosine temporarily. However, as an unstable species (especially under acidic conditions), poecillanosine underwent hydronium ion catalysed solvolysis to generate $N_2O$ and alcohol derivatives (Scheme 7). A similar mechanism has been proposed for the hydrolysis of other *N*-hydroxy-*N*-nitroso-alkylamines.[21] In the case of poecillanosine, because of the presence of α-acetate group, two regio-isomers (**12a** and **12b**) were formed.

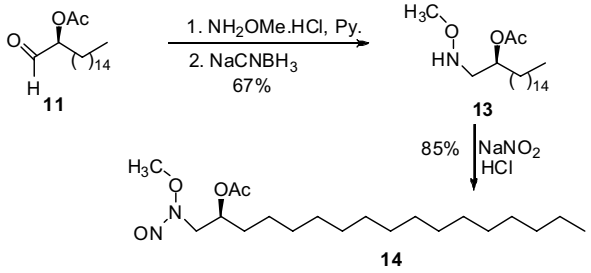
Unable to obtain stable poecillanosine, we then adopted a similar route towards the synthesis of the *O*-methyl ether of poecillanosine **14** (Scheme 8). The treatment of aldehyde **11** with *O*-methyl hydroxylamine followed by sodium cyanoborohydride reduction provided alkyl hydroxylamine derivative **13**. Nitrosation of **13** with $NaNO_2$/HCl went smoothly to furnish the *O*-methyl ether of poecillanosine **14** in a good yield.




**Scheme 6.**




**Scheme 7.**




**Scheme 8.**

In conclusion, the synthesis of poecillanosine, a natural *N*-hydroxy-*N*-nitroso-alkylamine compound, was studied. Poecillanosine was shown to be unstable under acidic nitrosation conditions. Only degradation compounds of poecillanosine were obtained under such conditions. However, the *O*-methyl derivative of poecillanosine was synthesised and confirmed. Currently we are carrying out experiments to synthesise other stable derivatives of poecillanosine using the procedure reported here. Their biological activities will also be studied.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.059.

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