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Novel and practical asymmetric synthesis of an azetidine alkaloid, penaresidin B

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Abstract—A novel and efficient asymmetric synthesis of the potent actomyosin ATPase activator, penaresidin B, is described in a short and complete stereoselective manner by featuring the elaboration of the fully functionalized homochiral lactam, which can also be regarded as an advanced intermediate for the synthesis of other azetidine alkaloids.

Marine sponges have frequently afforded a wide variety of sphingosine-related compounds,[1] in which penaresidins A (**1**) and B (**2**) isolated in 1991 from an Okinawan marine sponge *Penares* sp. by Kobayashi et al. are the first sphingosine-derived alkaloids possessing an interesting azetidine ring structure.[2] Tested as an inseparable mixture, these two compounds exhibit potent actomyosin ATPase-activating activity. As shown in Figure 1, the exact absolute configurations of five stereogenic centers in **1** were established to be 2*S*,3*R*,4*S*,15*S* and 16*S*, and the initially proposed structure of penaresidin B was revised to be **2**[3] after structural characterization based on spectroscopic methods[2,4] supplemented by synthetic studies.[3,5,6] On the other hand, a new azetidine alkaloid, penazetidine A (**3**), possessing potent protein kinase C inhibitory activity was isolated in 1994 from the Indo-Pacific marine sponge *Penares* sollasi by Crews and co-workers.[7] The structure of the substituted azetidine closely related to penaresidins was confirmed to be **3** by the synthesis of Mori et al.[8] except for the side-chain stereochemistry. Due to their significant activities and unique structural characteristics, they have been the subject of extensive synthetic efforts which have culminated in several syntheses.[8,9] Synthetic strategies described to date including our recent method,[12b] however, in general require multistep reactions or crucial techniques and were not necessarily satisfactory. The purpose of the present communication is to report a novel and convenient process for the asymmetric synthesis of **2**, which in turn would make it possible to provide a new opportunity for the synthesis of other azetidine alkaloids.

As shown in Scheme 1, we investigated the utilization of amino sugar for the synthesis of the functionalized

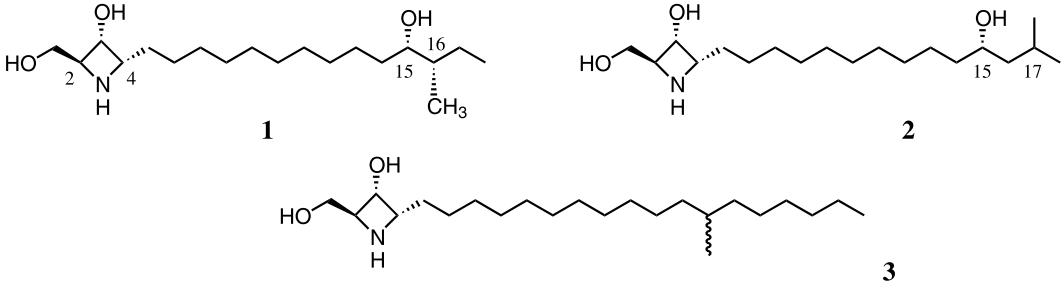

Figure 1. Penaresidin A (**1**), penaresidin B (**2**) and penazetidine A (**3**).

Keywords: penaresidin; azetidine alkaloid; lactam; nucleophilic addition; arabinofuranose.

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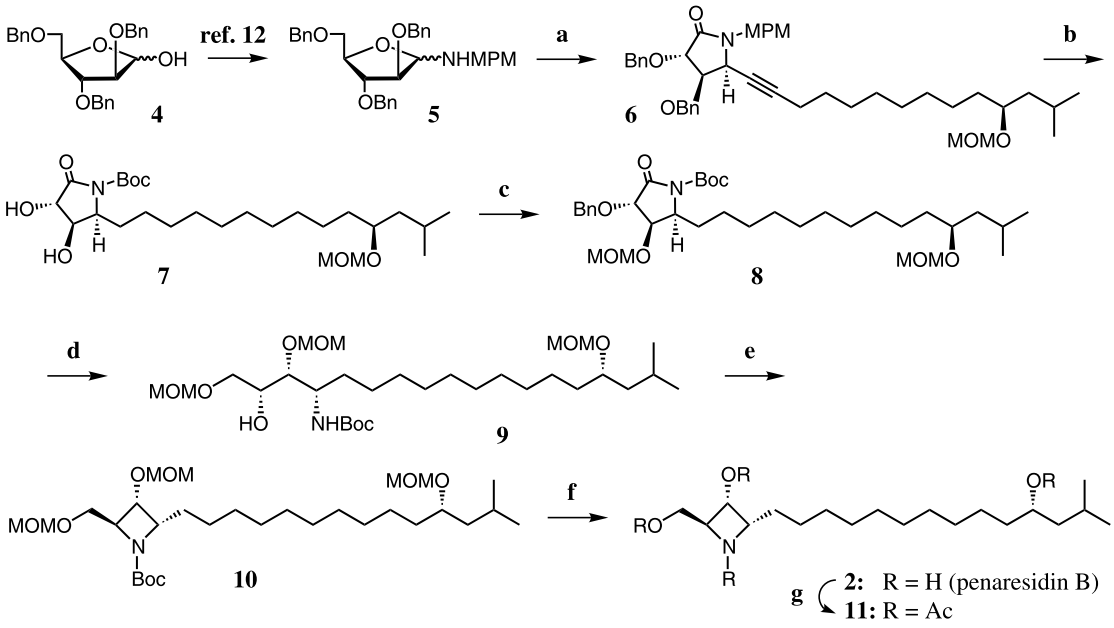

Scheme 1. *Reagents and conditions*: (**a**) **1**, (S)-HC≡C$(CH_2)_7$CH(OMOM)CH_2CH$(CH_3)_2$, BuLi, THF, −78–0°C; 82%; **2**, PCC, 4 Å MS, CH_2Cl_2; 62%; (**b**) **1**, CAN, CH_3CN–H_2O (9:1); 66%; **2**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; quant.; **3**, Pd (black), 4.4% HCOOH–MeOH; 95%; (**c**) **1**, BnBr, Ag_2O, CH_3COOEt; 74%; **2**, MOMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2; quant.; (**d**) **1**, $NaBH_4$, MeOH; quant.; **2**, MOMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2; quant.; **3**, Pd (black), 4.4% HCOOH–MeOH; quant.; (**e**) **1**, MsCl, Et_3N, CH_2Cl_2; **2**, NaH, THF; 50% (two steps); (**f**) conc. HCl, MeOH; (**g**) Ac_2O, pyridine, DMAP; quant.

homochiral lactam intermediate with desired stereogenic centers. When the acetylide elaborated from D-leucine[10] via the acetylene zipper reaction[11] was treated with the furanosylamine **5** prepared from D-arabinose derivative **4** at low temperature followed by oxidative degradation with PCC,[12] it afforded the non-terminal alkyne-lactam **6** with three substituents exclusively (>99% d.e., determined by ^{13}C NMR and HPLC) in good yield. After exchange of the MPM(*p*-methoxybenzyl)-protecting group to the *N*-Boc function in **6** to enhance the nucleophilicity, deprotection of the benzyl groups accompanying simultaneous hydrogenation of the triple bond was effected by using Pd (black) in 4.4% HCOOH–MeOH to furnish the dihydroxylactam **7**. Then, **7** was regioselectively transformed through successive Bn- and MOM-protections into the synthetically useful homochiral lactam **8** in 74% and quantitative yields, respectively. No base-induced racemization of the γ-position in **8** was observed in these reactions (determined by ^{13}C NMR). Reduction of **8** with $NaBH_4$ cleanly opened the lactam ring and afforded the corresponding acyclic alcohol quantitatively again, which was in turn submitted to MOM-protection followed by debenzylation with Pd (black) to afford the desired *N*-Boc alcohol **9** in extremely high yield. In contrast to Lin's results[9d] construction of the azetidine ring was accomplished under mild basic conditions after introduction of the methanesulfonyl group to provide the *N*-Boc and tri-*O*-methoxymethylated penaresidin B **10** in 50% yield (two steps).[13] Finally, removal of the protecting groups in **10** was conducted under acidic conditions to complete the total synthesis of **1** in 12% overall yield from the commercially available D-arabinose derivative **4**, whose structure was characterized after derivatization to the known tetraacetate **11**, $[\alpha]_D^{25}$ +47.3° (*c* 0.75, $CHCl_3$) {lit. $[\alpha]_D^{25}$ +47° (*c* 0.42, $CHCl_3$)[3]}. The spectral data of synthetic **11** were completely identical to those of the reported values in all respects.[3]

This process involves no separation of stereoisomers through the entire sequence until penaresidin B was synthesized from the starting D-arabinose derivative **4**, which constitutes a new synthetic strategy and represents a short and easily accessible pathway to penaresidins. We anticipate that the non-terminal alkyne lactam such as **6** will serve as an advanced template for the synthesis of other nitrogen-containing natural alkaloids.

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13. Recently Lin et al. reported that the same type of nitrogen-directed cyclization to azetidine ring did not proceed under any conditions,[9d] however, in our case the desired cyclized product **10** was obtained in good yield (50%, two steps) with no difficulty. These different results would be ascribed to the steric bulkiness of both hydroxyl- and amino-protecting groups.