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Novel Asymmetric Synthesis of Penaresidin B as a Potent Actomyosin ATPase Activator

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Abstract: An efficient and novel synthetic process is described for the preparation of an azetidine ring with the contiguous stereogenic centers and the total synthesis of penaresidin B by featuring the elaboration of the functionalized homochiral lactam derived from D-glutamic acid.
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Penaresidin A (**1**) and B (**2**), first isolated in 1991 from an Okinawan marine sponge *Penares* sp. by Kobayashi et al.[1], exhibit potent actomyosin ATPase-activating activity. After structural characterization as a mixture of the corresponding tetraacetyl derivatives, these were revealed to be the first sphingosine-derived alkaloids[2] possessing an azetidine ring. During our synthetic studies of these substances, the syntheses of both a straight-chain analog by Kamikawa et al.[3] and three stereoisomers of **1** with **2*S*,3*R*,4*S***-configurations of the azetidine ring and syn configuration between C-15 and C-16 of the side chain by Mori et al.[4] have been established. In addition, recently the initially proposed structure of penaresidin B was revised to be **2**[5] as shown in Fig.1 and the absolute configuration at C-15 in **1** and **2** has been determined to be ***S***.[6]

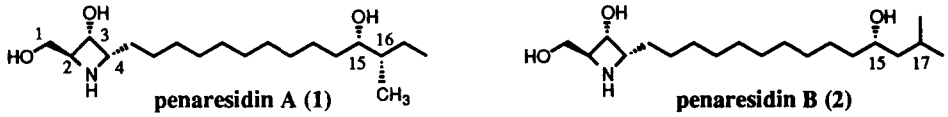
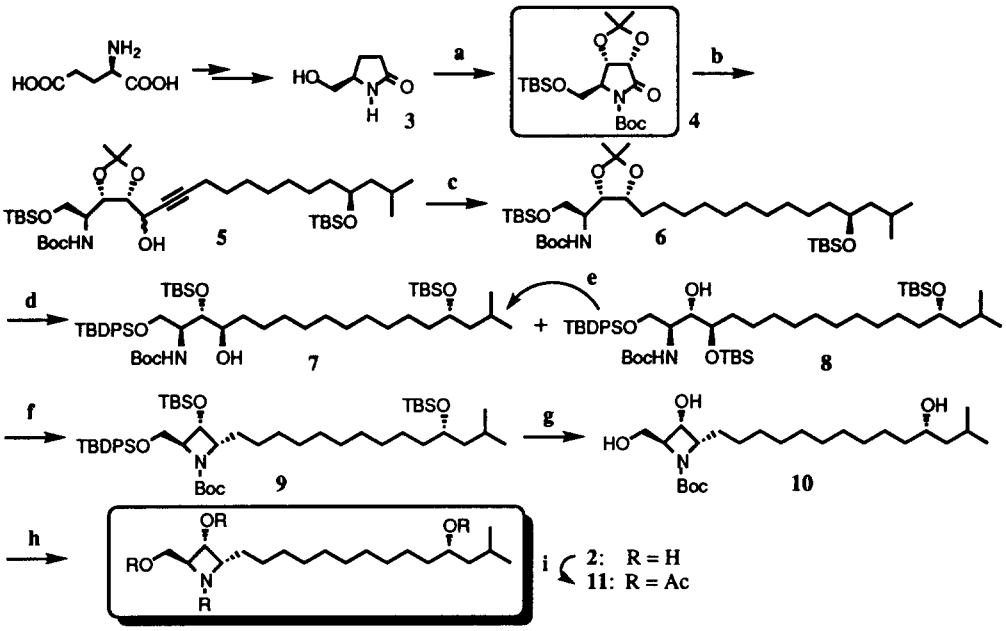


Fig. 1

With the above stereochemical outcome in mind, the central feature of this report is to communicate the details of the novel and expeditious route from D-glutamic acid for the construction of the azetidine ring with the desired contiguous stereogenic centers and the total synthesis of penaresidin B (**2**).

N-Boc lactam **4** obtained from D-glutamic acid through lactam **3** (99% ee) was treated with the acetylide elaborated from D-leucine in 9 steps[7] via the acetylene zipper reaction,[8] followed by the reduction with $NaBH_4$ of the corresponding tautomer of ketoamide and hydroxy pyrrolidine form[9] to give the alcohol **5** as a diastereomer mixture. Formation of thioimidazolide and successive radical deoxygenation with Bu_3SnH[10] resulted in the clean preparation of **6**, $[\alpha]_D^{18}$+27.3° (c 1.47, $CHCl_3$). After deprotection of the four hydroxyl groups of **6**, reprotection of the primary alcohol with TBDPSCl and the secondary ones with TBSCl brought about undesirable regioselectivity, leading to the mixture of alcohols **7** and **8** (2:98 determined by HPLC) in high yield. Fortunately, it has become apparent that the major product **8** was smoothly trasnformed into the desired **7** with 1,4-silyl rearrangement under basic conditions.[11] After chromatographic isolation of **7**, $[\alpha]_D^{20}$+10.4° (c 1.69, $CHCl_3$), mesylation and cyclization with NaH were subsequently submitted to produce **9**, $[\alpha]_D^{24.5}$+40.0° (c 0.36, $CHCl_3$) with the azetidine ring containing the same contiguous configurations as those of natural one. Finaly, **9** was treated with Bu_4NF to give the *N*-Boc derivative **10**, $[\alpha]_D^{20}$+42.6° (c 0.23,



Scheme 1. Reagents and conditions:
(a) 6 steps; see ref. 2; (b) 1, (*S*)-HC≡C$(CH_2)_7$CH(OTBS)CH_2CH$(CH_3)_2$, BuLi, THF, -78 °C; 2, $NaBH_4$, EtOH; 58% (2 steps); (c) 1, (thiocarbonyl)diimidazole, THF, 40 °C; 98%; 2, Bu_3SnH, AIBN, toluene, 95 °C; 70%; (d) 1, *p*-TsOH, MeOH; 63%; 2, TBDPSCl, Et_3N, CH_2Cl_2; 75%; 3, TBSCl, imidazole, DMF; 98% (**8** : **9** = 2 : 98); (e) NaH, THF, 35% (conv. 80%); (f) 1, MsCl, pyridine; 2, NaH, THF, 58% (2 steps); (g) Bu_4NF, THF, 79%; (h) 1, $BF_3 \cdot OEt_2$, CH_2Cl_2, -40∼-30 °C; (i) Ac_2O, pyridine, CH_2Cl_2; quant. (2 steps).

MeOH) of penaresidin B (**2**) and the *N*-Boc group was removed with $BF_3 \cdot OEt_2$ to complete the synthesis of **2**. The structure was confirmed by conversion to the known tetraacetate **11**, $[\alpha]_D^{22}$+49.1° (c 0.695, $CHCl_3$) [lit. $[\alpha]_D^{25}$ +47° (c 0.42, $CHCl_3$)],[5] whose physical data were completely identical with the reported values in all respects.[5]

This process starting from D-glutamic acid provides a new synthetic strategy and represents a short and easily accessible pathway to penaresidins.

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