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Novel Enantioselective Synthesis of Penaresidin A and *Allo*-penaresidin A *via* the Construction of a Highly Functionalized Azetidine

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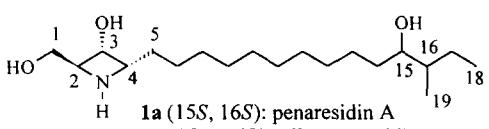
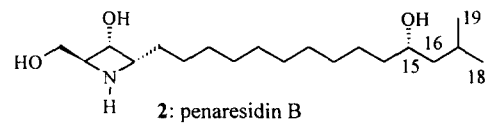
Abstract : A new and highly enantioselective synthesis of penaresidin A has been achieved *via* the construction of a highly functionalized azetidine with the requisite stereogenic centers, which can also be regarded as an advanced intermediate for the synthesis of penaresidin B and penazetidine A.

Keywords : Alkaloids; Azetidine; Cyclization; Wittig reactions; Reduction

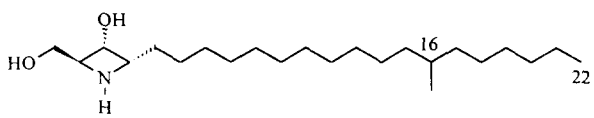
In 1991, penaresidin A (**1**) and B (**2**), the first two sphingosine-derived alkaloids possessing an azetidine ring, were isolated from the Okinawan marine sponge *Penares* sp.[1]. Tested as an inseparable mixture, these two compounds exhibit potent actomyosin ATPase-activating activity. After structural characterization through spectroscopic methods [1,2] supplemented by synthetic studies [3,4], the absolute configurations of five stereogenic centers in **1a** were established to be 2*S*,3*R*,4*S*,15*S* and 16*S*. In 1994, from the Indo-Pacific marine sponge *Penares*



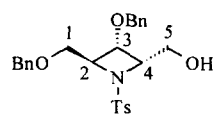
1a (15*S*, 16*S*): penaresidin A
1b (15*R*, 16*R*): *allo*-penaresidin A



2: penaresidin B



3: penazetidine A



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Scheme 1

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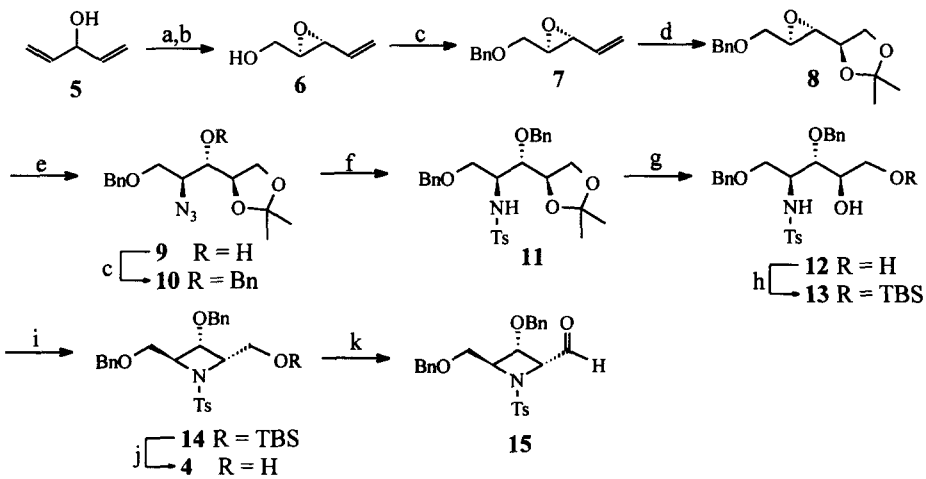
sollasi, Crews *et al* [5] isolated a structurally related alkaloid, penazetidine A (**3**), which possesses potent protein kinase C inhibitory activity. Additionally, the structure of the substituted azetidine in **3** was confirmed to be the same as that in penaresidins by synthesis [6] in 1996. During our enantioselective synthetic studies of penaresidins, two groups [4,7] have reported their strategies to penaresidin A from the same material of Garner aldehyde since 1995. In addition, there were also two reports [4b,8] about the synthesis of penaresidin B. In early this year, we reported the synthesis [9] of two penaresidin A analogues from divinylcarbinol (**5**). However, we had to change our strategy due to some unconquerable difficulty [10] in the cyclization to form an azetidine moiety with the desired stereogenic centers. In this paper, we wish to communicate our new strategy for the total synthesis of penaresidin A (**1a**) and its stereoisomer **1b** from the same material **5** based on the construction of a highly functionalized azetidine **4** with the requisite stereogenic centers.

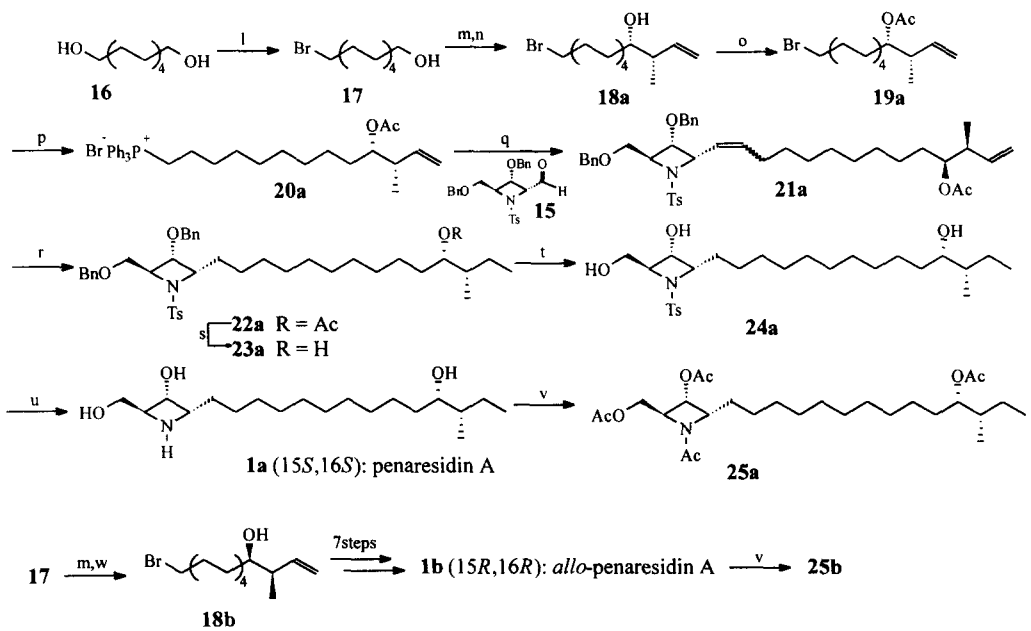


Scheme 2

Reagents and Conditions: a) TBHP, D-(-)-DIPT, Ti(O-*iso*-Pr)$_4$, 4Å MS, CH_2Cl_2, -20°C, 10 days, 65%; b) 0.5 N NaOH, -10°C, 89%; c) NaH, BnBr, Bu_4NI, THF, 87%; d) i) DHQ-PYR, $K_2[OsO_2(OH)_4]$, K_2CO_3, $K_3[Fe(CN)_6]$, *t*-BuOH/H_2O(1:1) ii) 2,2-dimethoxypropane, PTS, CH_2Cl_2, 73% (2 steps); e) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH/H_2O$ (8:1), reflux, 87%; f) i) $LiAlH_4$, THF; ii) TsCl, NEt_3, CH_2Cl_2, 92% (2 steps); g) 2N HCl/CH_3OH(1:1), 40°C, 95%; h) TBSCl, DMAP, NEt_3, CH_2Cl_2, 100%; i) PPh_3, DEAD, CH_2Cl_2, 60%; j) *n*-Bu_4NF, THF, 100%; k) $(COCl)_2$, DMSO, -78°C, then NEt_3, 95%.

As shown in Scheme 2, compound **6** was readily prepared from **5** in two steps as described in ref [11] and the resulting hydroxyl group was protected as benzyl ether to furnish **7**. Sharpless asymmetric dihydroxylation [12] of **7** with DHQ-PYR as ligand was followed by isopropylidenation of the resultant diol to yield **8** with high stereoselectivity (d.e, 11:1). Regioselective cleavage [13] of the epoxide **8** afforded **9** in 87% yield, whose hydroxyl group was benzylated to give **10**. The next conversion of **10** to **12** was accomplished by the efficient three step sequence. Reduction of **10** with $LiAlH_4$ and subsequent tosylation of the resulting amino group followed by ring cleavage of the acetonide with 2N HCl in CH_3OH (1:1) at 40°C

afforded **12** in 87% overall yield. Attempt to regioselectively protect the primary hydroxyl group in **12** with TBSCl and imidazole in DMF at 0°C resulted in modest conversion of the material. Finally, compound **12** was converted quantitatively to **13** while treated with TBSCl and NEt_3 in CH_2Cl_2 at room temperature in the presence of a catalytic amount of DMAP [14]. The next crucial cyclization of **13** was carried out smoothly under Mitsunobu [15] conditions to furnish **14** in 60% yield. Finally, deprotection of the TBS group was accomplished effectively by reaction of **14** with *n*-Bu_4NF in THF. To this stage, we completed the construction of a highly functionalized azetidine **4** [16], which can be regarded as a key intermediate for penaresidins and penazetidine A. In our attempt to complete the synthesis of penaresidin A, it was necessary to obtain an aldehyde **15**, which was accessible by Swern oxidation of alcohol **4**. The crude **15** was directly used without further purification in the next step.



Scheme 3

Reagents and Conditions: l) HBr, benzene, reflux, 80%; m) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then NEt_3; n) *Z*-(*S*,*S*)-crotylboronate, 4Å MS, toluene, -78°C, 88% (2 steps); o) Ac_2O, pyridine, DMAP, CH_2Cl_2, 96%; p) PPh_3, 130°C, 95%; q) NaDMSO, THF, -10°C, then -78°C, **15**, 60%; r) NH_2OH, EtOAc, DMF, 90-100°C, 92%; s) $LiAlH_4$, Et_2O, 85%; t) 10% Pd/C, H_2, 95% EtOH, 79%; u) Na, naphthalene, DME, -60°C; v) Ac_2O, pyridine, DMAP, CH_2Cl_2, 86% (2 steps); w) *Z*-(*R*,*R*)-crotylboronate, 4Å MS, toluene, -78°C, 86% (2 steps).

The synthesis of penaresidin A and that of *allo*-penaresidin A are summarized in Scheme 3. Compounds **18a** and **18b** were prepared according to the known protocol [7] from 1,10-decanediol. The bromo alcohol **18a** was protected as *O*-acetyl derivative and then converted to Wittig salt **20a**. With the two requisite fragments in hand, the Wittig coupling reaction was explored at -78°C and then warmed to room temperature with NaHMDS as the base. However,

the yield was rather poor (20%). When NaHMDS was replaced by NaDMSO, fortunately, the yield was improved to give a mixture of *Z* and *E* -**21a** in 60% yield. Treatment of **21a** with catalytic hydrogenation on 10% Pd/C failed to afford the desired product because of the high tendency to hydrogenolysis of the vinyl azetidine. Diimide reduction [17] of the double bonds led to produce **22a** and partial deacylation product **23a**. Conversion of **22a** to **23a** was smoothly completed by reduction with $LiAlH_4$. Finally, removal of the both benzyl and Ts groups of **22a** completed the synthesis of penaresidin A (**1a**), which was converted to the known tetraacetate **25a** $[\alpha]_D$ = + 34.6° (c 0.68, $CHCl_3$) (lit.[4] : $[\alpha]_D$ = + 38° (c 0.378, $CHCl_3$)). For the synthesis of (15*R*,16*R*)-*allo*-penaresidin A, the intermediate **18b** was subjected to the same procedure as mentioned before, and the product **1b** was acetylated to afford the tetraacetyl derivative **25b** $[\alpha]_D$ = + 42.6° (c 1.30, $CHCl_3$) (lit.[4] : $[\alpha]_D$ = + 42° (c 0.41, $CHCl_3$)). Their physical data were completely identical with the reported values in all respects.

In summary, our process starting from divinylcarbinol provides a new synthetic strategy and represents a short and general approach to penaresidins and penazetidine A.

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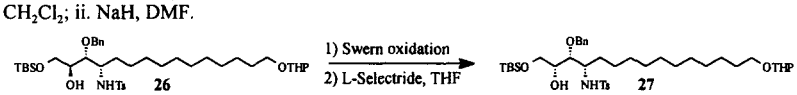
[10] Compound **26** was converted to **27** in two steps, and the diastereoselectivity in the reduction was 9:1. However, when compound **27** was subjected to the following two procedures, no desired product of cyclization was afforded: 1) PPh_3, DEAD, THF; 2) i. MsCl, NEt_3, CH_2Cl_2; ii. NaH, DMF.



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[16] Properties of compound **4**: $[\alpha]_D$ = + 47.1° (c 1.16, $CHCl_3$); IR (film): 3524, 2927, 2868, 1599, 1497, 1455, 1335, 1207, 1154, 1093, 1043, 914, 815, 738, 699, 680 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz) δ ppm: 2.35 (3H, s, Ar-CH_3), 2.92 (1H, b, OH), 3.46 (1H, dd, J = 3.1, 10.6 Hz, 1-H), 3.58 (1H, dd, J = 4.8, 10.6 Hz, 1-H'), 3.91-4.11 (2H, m, 5-H), 4.30-4.43 (5H, m), 4.45, 4.50 (2H, AB, J_{AB} = 12.0 Hz, Bn-H), 7.10-7.40 (12H, m, Ar-H), 7.71 (2H, d, J = 8.3 Hz, Ar-H); MS (m/z, %): 468 (M^++1, 1.47), 312 (5.86), 181 (6.73), 92 (10.00), 91 (100), 65 (13.01). (Found: C, 66.71; H, 5.92; N, 2.71. $C_{26}H_{29}NO_5S$: requires: C, 66.79; H, 6.25; N, 3.00%).
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