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Absolute Stereochemistry of Penaresidins A and B

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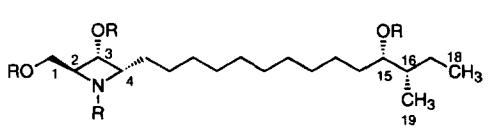
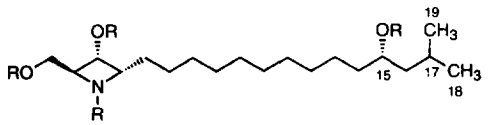
Abstract: Absolute stereochemistry at C-15 in penaresidins A (**1**) and B (**2**) was established to be *S* on the basis of ^{1}H NMR data of the tri-*O*-MTPA esters, indicating that the absolute configurations of **1** and **2** are 2*S*, 3*R*, 4*S*, 15*S* (**1** and **2**), and 16*S* (**1**).

Marine sponges have frequently afforded a wide variety of sphingosine-related compounds,[1] in which penaresidins A (**1**) and B (**2**) isolated from an Okinawan marine sponge *Penares* sp. are the first sphingosine-derived alkaloids possessing an azetidine ring with potent actomyosin ATPase-activating activity.[2] The structures including relative stereochemistry of the azetidine ring have been elucidated from analyses of 2D NMR data of a 1.5:1 mixture of the tetraacetates (**3** and **4**) of **1** and **2**, since the mixture of **1** and **2** as well as **3** and **4** were inseparable. Recently 2*S*,3*R*,4*S*-configurations of the azetidine ring of **1** and **2** and *syn* configuration between C-15 and C-16 of **1** have been established from synthetic studies of penaresidins, where the initially proposed structure of penaresidin B was revised to be **2**.[3] However, the absolute configuration at C-15 in **1** and **2** has remained undefined. In this paper we describe the determination of the absolute stereochemistry at C-15 in penaresidins A (**1**) and B (**2**) on the basis of ^{1}H NMR data of the tri-*O*-MTPA esters of natural specimens.

The mixture of the tetraacetates (**3** and **4**) of penaresidins A (**1**) and B (**2**) was subjected to alkaline hydrolysis followed by treatment with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)-(-)-MTPACl] to give a mixture of tri-*O*-(*S*)-MTPA esters (**5** and **6**) of *N*-acetyl penaresidins A and B. The mixture was completely separated by C_{18} HPLC (MeOH/H_2O) to afford **5**[4] and **6**.[5] On the other hand, tri-*O*-(*R*)-MTPA esters (**7**[6] and **8**[7]) of *N*-acetyl penaresidins A and B were prepared by treatment of the mixture of *N*-acetyl penaresidins A and B with (*S*)-(+)-MTPACl followed by C_{18} HPLC separation. The ^{1}H NMR[8] chemical shifts of each MTPA ester (**5** ~ **8**) were assigned by detailed analyses of ^{1}H-^{1}H COSY and HOHAHA spectra. The ^{1}H



1 R = H **3** R = Ac



2 R = H **4** R = Ac

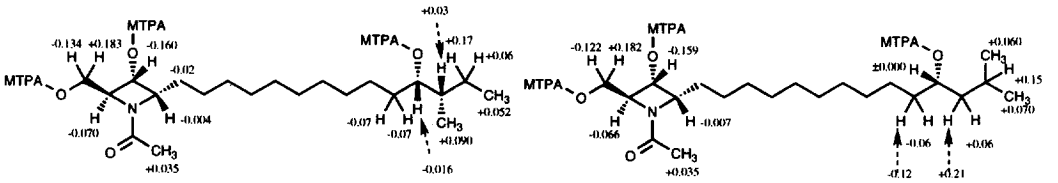


Fig. 1. Δδ Values [Δδ (in ppm) = δ_S -δ_R] Obtained for (*S*)- and (*R*)-MTPA Esters (5 and 7) of *N*-Acetyl Penaresidin A and Those for (*S*)- and (*R*)-MTPA Esters (6 and 8) of *N*-Acetyl Penaresidin B

chemical shift differences (Δδ; δ_S - δ_R) for the (*S*)- and (*R*)-MTPA esters (**5** and **7**, respectively) of *N*-acetyl penaresidin A and those (**6** and **8**, respectively) of *N*-acetyl penaresidin B revealed that the absolute configuration at C-15 of in **1** and **2** was *S*.[9] Furthermore, spectral data of **7** and **8** were identical with those of the corresponding (*R*)-MTPA esters derived from synthetic (2*S*,3*R*,4*S*,15*S*,16*S*)-penaresidin A and (2*S*,3*R*,4*S*,15*S*)-penaresidin B.[3]

Thus, the absolute configurations of penaresidins A (**1**) and B (**2**) were concluded to be 2*S*, 3*R*, 4*S*, 15*S* (**1** and **2**), and 16*S* (**1**).

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Reference and Notes

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4. ^{1}H NMR Data of **5** in $CDCl_3$: δ 0.89 (3H, t, *J* = 6.8 Hz, H_3-18), 0.93 (3H, t, *J* = 6.5 Hz, H_3-19), 1.13 (1H, m, H-17), 1.1 ~ 1.3 (16 H, m, H_2-6, H_2-7, H_2-8, H_2-9, H_2-10, H_2-11, H_2-12, H_2-13), 1.41 (1H, m, H-17), 1.49 (1H, m, H-14), 1.57 (1H, m, H-14), 1.62 (1H, m, H-16), 1.73 (2H, m, H_2-5), 1.77 (3H, s, N-Ac), 3.49 (3H, s, OMe), 3.53 (3H, s, OMe), 3.54 (3H, s, OMe), 4.18 (1H, m, H-4), 4.32 (1H, br.s, H-2), 4.67 (1H, dd, *J*, = 1.1 and 11.8 Hz, H-1), 5.07 (1H, dd, *J*, = 3.9 and 7.1 Hz, H-3), 5.07 (1H, m, H-15), 5.15 (1H, dd, *J*, = 2.5 and 11.8 Hz, H-1), and 7.35 ~ 7.55 (15H, m, Ph)
5. ^{1}H NMR Data of **6** in $CDCl_3$: δ 0.90 (3H, d, *J* = 6.8 Hz, H_3-18), 0.92 (3H, t, *J* = 6.8 Hz, H_3-19), 1.27 (1H, m, H-14), 1.35 (1H, m, H-16), 1.1 ~ 1.3 (16 H, m, H_2-6, H_2-7, H_2-8, H_2-9, H_2-10, H_2-11, H_2-12, H_2-13), 1.53 (1H, m, H-14), 1.58 (1H, m, H-16), 1.60 (1H, m, H-17), 1.61 (1H, m, H-5), 1.77 (1H, m, H-5), 1.77 (3H, s, N-Ac), 3.49 (3H, s, OMe), 3.54 (3H, s, OMe), 3.55 (3H, s, OMe), 4.18 (1H, m, H-4), 4.32 (1H, br.s, H-2), 4.67 (1H, dd, *J*, = 1.1 and 11.8 Hz, H-1), 5.07 (1H, dd, *J* = 3.9 and 7.1 Hz, H-3), 5.17 (1H, m, H-15), 5.15 (1H, dd, *J* = 2.5 and 11.8 Hz, H-1), and 7.35 ~ 7.55 (15H, m, Ph)
6. ^{1}H NMR Data of **7** in $CDCl_3$: δ 0.84 (3H, t, *J* = 6.8 Hz, H_3-18), 0.84 (3H, t, *J* = 6.5 Hz, H_3-19), 1.07 (1H, m, H-17), 1.24 (1H, m, H-17), 1.1 ~ 1.3 (16 H, m, H_2-6, H_2-7, H_2-8, H_2-9, H_2-10, H_2-11, H_2-12, H_2-13), 1.56 (1H, m, H-14), 1.59 (1H, m, H-16), 1.64 (1H, m, H-14), 1.74 (3H, s, N-Ac), 1.75 (2H, m, H_2-5), 3.49 (3H, s, OMe), 3.53 (3H, s, OMe), 3.54 (3H, s, OMe), 4.19 (1H, m, H-4), 4.39 (1H, br.s, H-2), 4.49 (1H, dd, *J* = 1.1 and 11.8 Hz, H-1), 5.23 (1H, dd, *J* = 3.9 and 7.1 Hz, H-3), 5.09 (1H, m, H-15), 5.28 (1H, dd, *J* = 2.5 and 11.8 Hz, H-1), and 7.35 ~ 7.55 (15H, m, Ph)
7. ^{1}H NMR Data of **8** in $CDCl_3$: δ 0.83 (3H, d, *J* = 6.8 Hz, H_3-18), 0.86 (3H, t, *J* = 6.8 Hz, H_3-19), 1.04 (1H, m, H-6), 1.14 (1H, m, H-16), 1.1 ~ 1.3 (15 H, m, H-6, H_2-7, H_2-8, H_2-9, H_2-10, H_2-11, H_2-12, H_2-13), 1.39 (1H, m, H-16), 1.45 (1H, m, H-17), 1.52 (1H, m, H-16), 1.53 (1H, m, H-5), 1.59 (1H, m, H-14), 1.61 (1H, m, H-5), 1.74 (3H, s, N-Ac), 3.53 (3H, s, OMe), 3.54 (3H, s, OMe), 3.55 (3H, s, OMe), 4.19 (1H, m, H-4), 4.39 (1H, br.s, H-2), 4.49 (1H, dd, *J* = 1.1 and 11.8 Hz, H-1), 5.23 (1H, dd, *J* = 3.9 and 7.1 Hz, H-3), 5.17 (1H, m, H-15), 5.28 (1H, dd, *J* = 2.5 and 11.8 Hz, H-1), and 7.35 ~ 7.55 (15H, m, Ph)
8. The ^{1}H NMR spectrum of each MTPA ester (**5** ~ **8**) suggested that there were no rotational isomers around the amide bond of the *N*-acetyl group.
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