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Absolute Stereochemistry of Keramaphidin B

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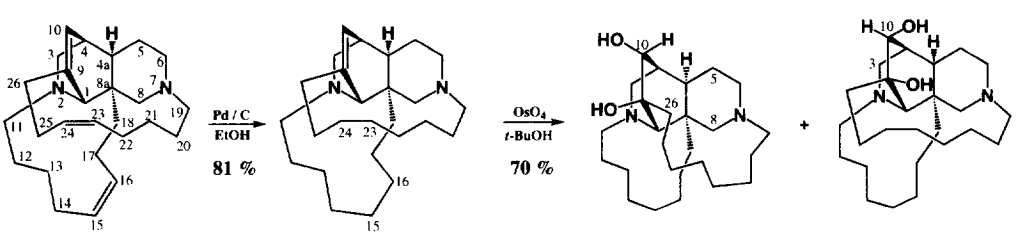
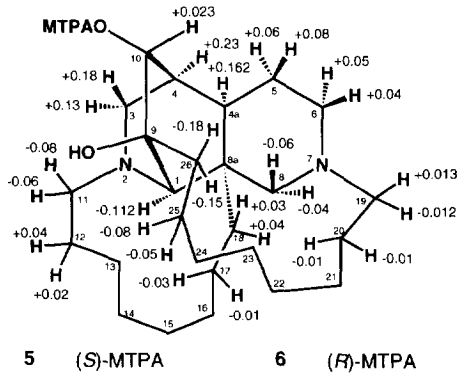
Abstract: Absolute stereochemistry of the (+)-enantiomer of keramaphidin B (**1**) was established to be 1*R*, 4*S*, 4a*R*, and 8a*S* on the basis of ^{1}H NMR data of the MTPA esters of 9,10-dihydroxy-15,16,23,24-tetrahydrokeramaphidin B (**3**).

Keramaphidin B (**1**), which is a manzamine-related alkaloid isolated from the sponge *Amphimedon* sp. by our group,[1] corresponds to a biogenetic precursor of manzamines A[2] or B[3] proposed by Baldwin and Whitehead.[4] Recently we have successfully separated both enantiomers of **1** by using chiral HPLC, and found the ratio of (+)- and (-)-**1** to be ca. 20:1.[5] Although the relative configuration of keramaphidin B (**1**) was established by X-ray analysis of a crystal of the racemic mixture, absolute stereochemistry of keramaphidin B (**1**) has remained undefined. This paper describes elucidation of absolute stereochemistry of the major (+)-enantiomer of keramaphidin B (**1**).

(+)-Keramaphidin B {(+)-**1**} was subjected to reduction with Pd/C to afford the tetrahydro derivative (**2**) as a single product. The ^{1}H NMR spectrum of **2** revealed the presence of an olefinic proton (δ 5.62 br.d) at C-10, suggesting that **2** was 15,16,23,24-tetrahydro form of (+)-**1**. Oxidation of **2** with OsO_4 gave two dihydroxy products (**3** and **4**) in the ratio of ca. 9:1. Relative stereochemistry at C-9 and C-10 of the major product **3** was elucidated from NOE's for H-10/H-5β and H-26a/H-8β. On the other hand, relative stereochemistry at C-9 and C-10 of the minor product **4** was deduced from NOE for H-10/H-3β. Treatment of **3** with (*R*)-(-)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) gave the (*S*)- and (*R*)-MTPA esters (**5** and **6**), respectively. The ^{1}H NMR chemical shifts[6,7] of **5** and **6** were assigned by detailed analyses of ^{1}H-^{1}H COSY and HOHAHA spectra. The ^{1}H chemical shift differences ($\Delta\delta$; $\delta_S - \delta_R$) were shown in Fig. 1. Positive $\Delta\delta$ values were observed for H_2-3, H-4, H-4a,





5 (*S*)-MTPA 6 (*R*)-MTPA

Fig. 1. Δδ Values [Δδ (in ppm) = δ_S -δ_R] Obtained for (*S*)- and (*R*)-MTPA Esters (5 and 6) of 9,10-dihydroxy-15,16,23,24-tetrahydrokeramaphidin B (3).

H_2-5, H_2-6, H_2-12, H_2-18, and H-19, whereas negative values were observed for H-1, H_2-8, H_2-11, H_2-17, H-19a, H_2-20, H_2-25, and H_2-26, indicating that the absolute configuration at C-10 of **3** was *R*.[8] Although H_2-12, H_2-18, and H-19b seem to be located on the left side of the plane consisting of H-10, and trifluoromethyl and ester carbonyl groups of the MTPA moiety (called MTPA plane), model consideration of the MTPA esters (**5** and **6**) and the most stable conformation calculated using MacroModel ver. 5.0 suggested that these protons actually existed on the right side of the MTPA plane. Thus the absolute configurations at C-1, C-4, C-4a, and C-8a of (+)-keramaphidin B {(+)-**1**} were concluded to be *R*, *S*, *R*, and *S*, respectively.

Biogenetically it is interesting that the minor enantiomer {(-)-**1**} of keramaphidin B possesses the same absolute configuration as those of the major manzamine alkaloids with dextrorotation represented by manzamines A and B and ircinals A and B[9] in this sponge, while the absolute stereochemistry of the major enantiomer {(+)-**1**} of keramaphidin B corresponds to those of the minor manzamine alkaloids with raevorotation such as ircinols A and B.[10] Furthermore, ingenamine, ingamine A, and ingenamine E, manzamine-related alkaloids isolated from the sponge *Xestospongia ingens*,[11] have the same absolute stereochemistry as that of keramaphidin B {(+)-**1**}.

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6. ^{1}H NMR Data of **5** in $CDCl_3$: δ 0.95 (1H, dd, *J* = 6.3 and 10.4 Hz, H-4a), 1.04 (1H, m, H-5), 1.35 (1H, m, H-17), 1.37 (1H, m, H-12), 1.38 (1H, m, H-20), 1.42 (1H, m, H-5), 1.43 (1H, m, H-12), 1.44 (1H, m, H-17), 1.48 (1H, m, H-25), 1.54 (1H, m, H-20), 1.59 (1H, m, H-18), 1.67 (1H, m, H-25), 1.72 (1H, m, H-3), 1.91 (1H, m, H-26), 1.92 (1H, m, H-4), 1.94 (1H, m, H-18), 1.97 (1H, m, H-8), 2.18 (1H, m, H-19), 2.24 (1H, d, *J* = 16.7 Hz, H-8), 2.24 (1H, m, H-11), 2.25 (1H, m, H-26), 2.34 (1H, m, H-3), 2.54 (1H, m, H-6), 2.82 (1H, m, H-6), 3.08 (1H, s, H-1), 3.11 (1H, m, H-19), 3.18 (1H, m, H-11), 3.50 (3H, s, OMe), 4.32 (1H, d, *J* = 4.8 Hz, H-10), and 7.35 ~ 7.55 (5H, m, Ph).
7. ^{1}H NMR Data of **6** in $CDCl_3$: δ 0.79 (1H, dd, *J* = 5.8 and 9.8 Hz, H-4a), 0.96 (1H, m, H-5), 1.35 (1H, m, H-12), 1.36 (1H, m, H-5), 1.38 (1H, m, H-17), 1.39 (1H, m, H-12), 1.39 (1H, m, H-20), 1.45 (1H, m, H-17), 1.53 (1H, m, H-25), 1.55 (1H, m, H-18), 1.55 (1H, m, H-20), 1.59 (1H, m, H-3), 1.69 (1H, m, H-4), 1.75 (1H, m, H-25), 1.91 (1H, m, H-18), 2.03 (1H, m, H-8), 2.06 (1H, m, H-26), 2.16 (1H, m, H-3), 2.19 (1H, m, H-19), 2.28 (1H, d, *J* = 13.5 Hz, H-8), 2.30 (1H, m, H-11), 2.43 (1H, m, H-26), 2.50 (1H, m, H-6), 2.77 (1H, m, H-6), 3.10 (1H, m, H-19), 3.19 (1H, s, H-1), 3.26 (1H, m, H-11), 3.53 (3H, m, s, OMe), 4.30 (1H, d, *J* = 5.2 Hz, H-10), and 7.35 ~ 7.55 (5H, m, Ph).
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