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Keramaphidin C and Keramamine C, Plausible Biogenetic Precursors of Manzamine C from an Okinawan Marine Sponge

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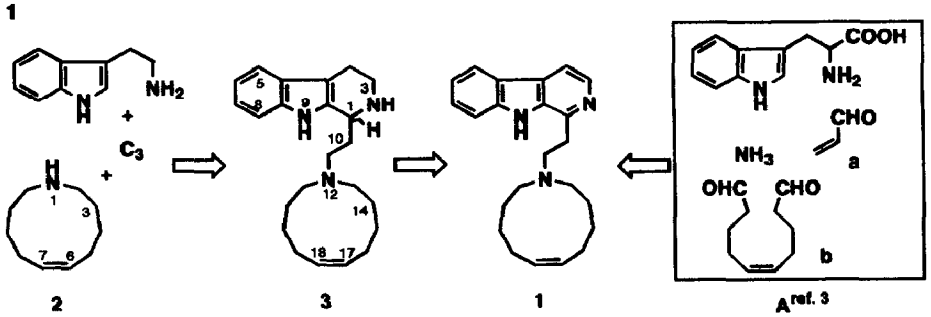
Abstract: Two new alkaloids, keramaphidin C (**2**) and keramamine C (**3**), have been isolated from the Okinawan marine sponge *Amphimedon* sp. These compounds may be plausible biogenetic precursors of manzamine C (**1**), which is considered to generate from coupling of keramaphidin C (**2**) with tryptamine and a C_3 unit through keramamine C (**3**).

Manzamines[1,2] are a series of β-carboline alkaloids with unique heterocyclic systems from marine sponges. The unusual ring systems arise a strong interest in the biogenetic process. Baldwin *et al.* proposed without any evidence that all manzamines may generate from coupling of tryptophan, a C_3 unit (**a**), and a C_{10} unit (**b**) with ammonia[3] [Scheme 1 (A) for manzamine C (**1**)][3]. On the other hand, we proposed that manzamines A and B may be biosynthetically derived from condensation of tryptamine with ircinals A and B[4], respectively, which were isolated from an Okinawan marine sponge *Ircinia* sp. Although manzamine C[2] (**1**) with a 6*Z*-azacycloundecene moiety possesses the simplest structure among the manzamine alkaloids, the biogenetic process of **1** has remained unknown. Further search for biogenetic precursors of manzamine alkaloids led to the isolation of two new alkaloids, named keramaphidin C (**2**) and keramamine C (**3**), which might be plausible biogenetic precursors of manzamine C (**1**), from the Okinawan marine sponge *Amphimedon* sp. Especially keramaphidin C (**2**) is considered to be an important key intermediate in the biogenetic path of manzamine C (**1**).

The sponge *Amphimedon* sp., collected off the Kerama Islands, Okinawa, was extracted with MeOH. The *n*-butanol soluble material of the MeOH extract was subjected to silica gel chromatography using $CHCl_3$/MeOH (95:5) and then organic layer of $CHCl_3$/MeOH/H_2O (6:1:1) to afford keramaphidin C (**2**, 0.0020%, wet weight) and keramamine C (**3**, 0.0026%) together with known manzamine C (**1**) and tryptamine.

Scheme 1



The ^1H and ^{13}C NMR data[5] of keramaphidin C (**2**) having the molecular formula, $C_{10}H_{19}N$, were reminiscent of the 6*Z*-azacycloundecene moiety for manzamine C (**1**). The chemical shift of C-2 (δ_C 42.8) for **2** was observed in higher field than that (δ_C 48.9) for manzamine C (**1**), indicating that **2** possessed a secondary amine group. Thus the structure of keramaphidin C (**2**) was assigned to be 6*Z*-azacycloundecene. This is the first isolation of **2** from natural sources, although compound **2** has been synthesized as an intermediate in total synthesis of manzamine C (**1**)[6,7].

The molecular weight of keramamine C (**3**)[8] having the molecular formula, $C_{23}H_{33}N_3$, was larger than that of manzamine C (**1**) by four mass unit, and the ^1H and ^{13}C NMR data of **3** were similar to those of **1**[9] except for aromatic region. Three aromatic carbon signals at C-1 (δ_C 145.7), C-3 (δ_C 137.5), and C-4 (δ_C 113.1) for **1** were not observed in the ^{13}C NMR spectrum of **3**, while carbon signals due to two sp^3 methylenes (δ_C 42.1 and 21.7) and an sp^3 methine (δ_C 53.9) were newly appeared for **3**. Thus the structure of keramamine C was concluded to be **3**.

Isolation of keramaphidin C (**2**) and keramamine C (**3**) together with manzamine C (**1**) and tryptamine seems to substantiate partly the biogenetic path of manzamine C (**1**), which may be derived from coupling of keramaphidin C (**2**), probably generated from a C_{10} unit and ammonia, with tryptamine and a C_3 unit through keramamine C (**3**) (Scheme 1).

References and Notes

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5. **2**: Colorless amorphous solid; mp 106 ~ 109 °C; IR (KBr) ν_{max} 3400 and 2940 cm^{-1}; ^1H NMR (CD_3OH) δ 1.58 (4H, m, H_2-4, and H_2-9), 1.76 (4H, m, H_2-3, and H_2-10), 2.30 (4H, m, H_2-5, and H_2-8), 3.08 (4H, t, J = 7.6 Hz, H_2-2 and H_2-11), 4.55 (2H, brs, NH_2-1), and 5.46 (2H, m, H-6 and H-7); ^{13}C NMR (CD_3OD) δ 23.8 (t, 2C, C-3 and C-10), 25.1 (t, 2C, C-4 and C-9), 26.5 (t, 2C, C-5 and C-8), 42.8 (t, 2C, C-2 and C-11), and 132.2 (d, 2C, C-6 and C-7); FABMS (Pos., glycerol) *m/z* 154 (M^++H); HRFABMS (Pos., glycerol) *m/z* 153.1493 (M^+, calcd for $C_{10}H_{19}N$, 153.1517).
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7. The presence of an NH_2 signal (δ_H 4.55, 2H) for natural **2** suggested that keramaphidin C (**2**) might exist as a salt form.
8. **3**: Colorless oil; $[\alpha]_D^{25}$ +20 ° (*c* 0.92, MeOH); IR (KBr) ν_{max} 3400 and 2940 cm^{-1}; UV (MeOH) λ_{max} 225 (sh.), 271 (ε 5600), 285 (sh.), and 290 (sh.) nm; ^1H NMR (CD_3OH) δ 1.52 (4H, m, H_2-15 and H_2-20), 1.68 (4H, m, H_2-14 and H_2-21), 2.22 (1H, m, H-10), 2.27 (4H, m, H_2-16 and H_2-19), 2.31 (1H, m, H-10), 2.83 (1H, m, H-4), 2.88 (1H, m, H-4), 2.92 (1H, m, H-11), 2.95 (2H, m, H-13 and H-22), 2.99 (2H, m, H-13 and H-22), 3.04 (1H, m, H-11), 3.13 (1H, m, H-3), 3.36 (1H, m, H-3), 5.43 (2H, m, H-17 and H-18), 7.02 (1H, t, J = 7.8 Hz, H-6), 7.11 (1H, t, J = 7.8 Hz, H-7), 7.32 (1H, d, J = 7.8 Hz, H-8), 7.43 (1H, d, J = 7.8 Hz, H-5), and 11.20 (1H, brs, NH-9); ^{13}C NMR (CD_3OD) δ 21.7 (t, C-4), 23.0 (2C, t, C-14 and C-21), 25.0 (2C, t, C-15 and C-20), 26.8 (2C, t, C-16 and C-19), 27.7 (t, C-10), 42.1 (t, C-3), 48.9 (t, C-13), 52.9 (t, C-11), 53.9 (d, C-1), 109.5 (s, C-4a), 112.2 (d, C-8), 115.9 (s, C-9a), 119.0 (d, C-5), 120.3 (d, C-6), 123.1 (d, C-7), 128.0 (s, C-4b), 132.1 (2C, d, C-17 and C-18), and 138.1 (s, C-8a); EIMS *m/z* 351 (M^+) and 198; HREIMS *m/z* 351.2687 (M^+, calcd for $C_{23}H_{33}N_3$, 351.2674).
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