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FIRST TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF KERAMAMINE C

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Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday

Abstract – Asymmetric first total synthesis of keramamine C, a tetrahydro-β-carboline alkaloid from an Okinawan marine sponge *Amphimedon* sp., has been accomplished with the Bischler–Napieralski reaction and the Noyori catalytic asymmetric hydrogen-transfer reaction. The absolute configuration of keramamine C was elucidated to be 1*R* from comparison of the ^{1}H and ^{13}C NMR, CD spectral data and $[\alpha]_D$ values of synthetic and natural keramamine C, respectively.

Keramamine C was a new tetrahydro-β-carboline alkaloid with an azacycloundecene moiety, which was considered to be generated from coupling of keramaphidin C with tryptamine and a C_3 unit, isolated from the Okinawan marine sponge *Amphimedon* sp.[1] (Figure 1). Keramaphidin C, (*Z*)-azacycloundec-6-ene moiety in keramamine C, could be biogenetically[2] derived from a C_{10} unit and ammonia. Though the

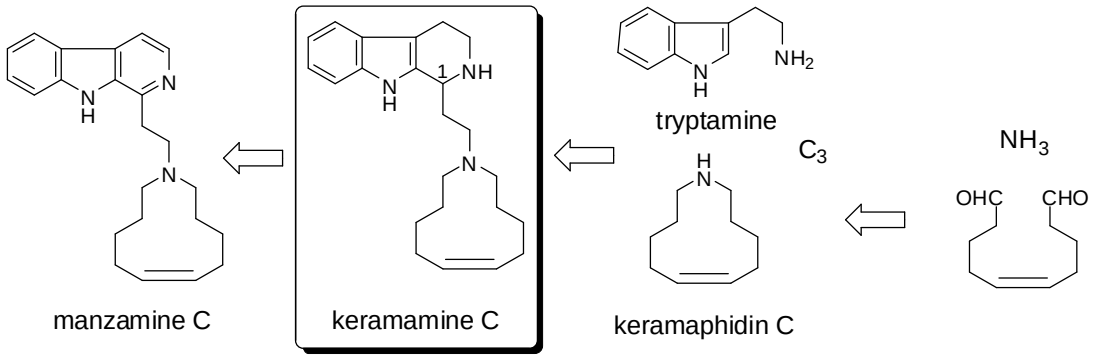
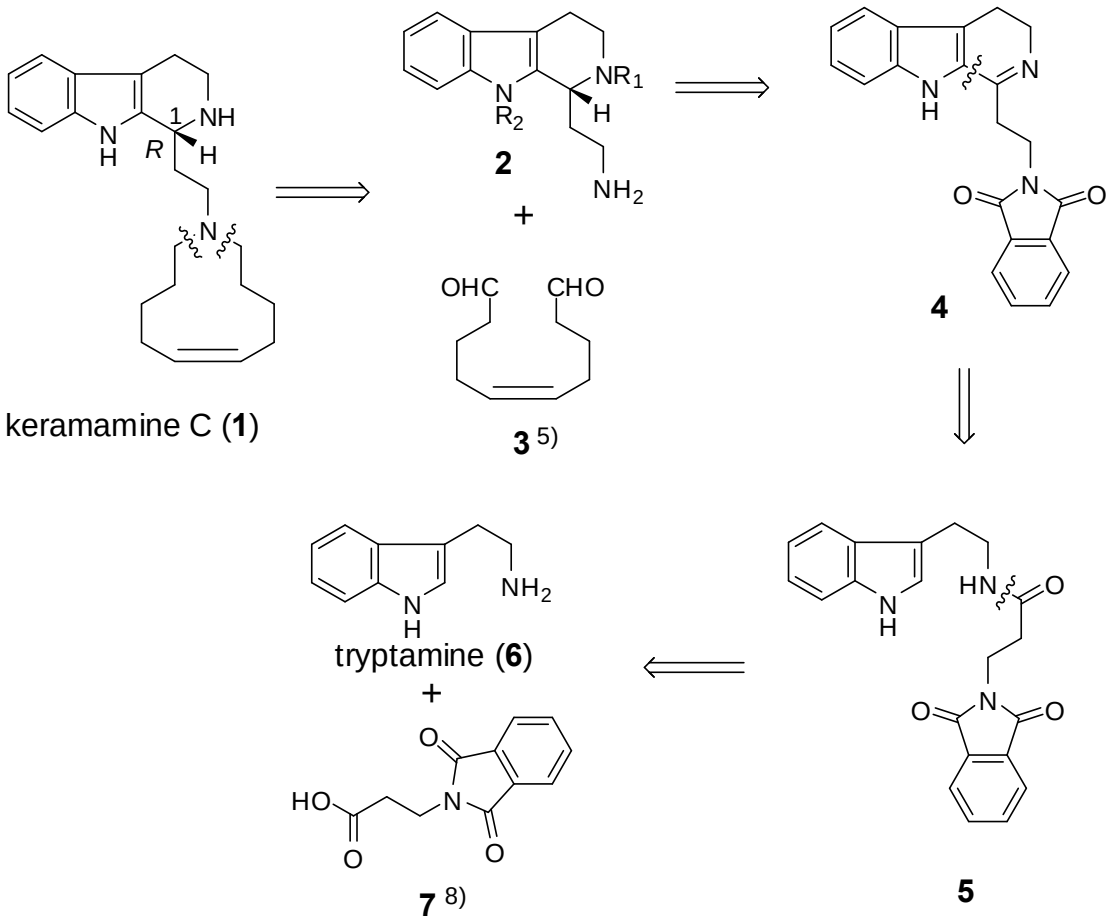


Figure 1. Possible biogenetic pathway to keramamine C and manzamine C

unique structure and biological activity of manzamine C,[3] dehydro analogue of keramamine C, has prompted studies of its total syntheses,[4] the enantioselective synthesis of keramamine C has not been achieved so far since necessity for introduction of required stereochemistry at C-1. In this paper, we describe the first total synthesis of (1*R*)-keramamine C (**1**) and establishment of the absolute configuration of keramamine C.

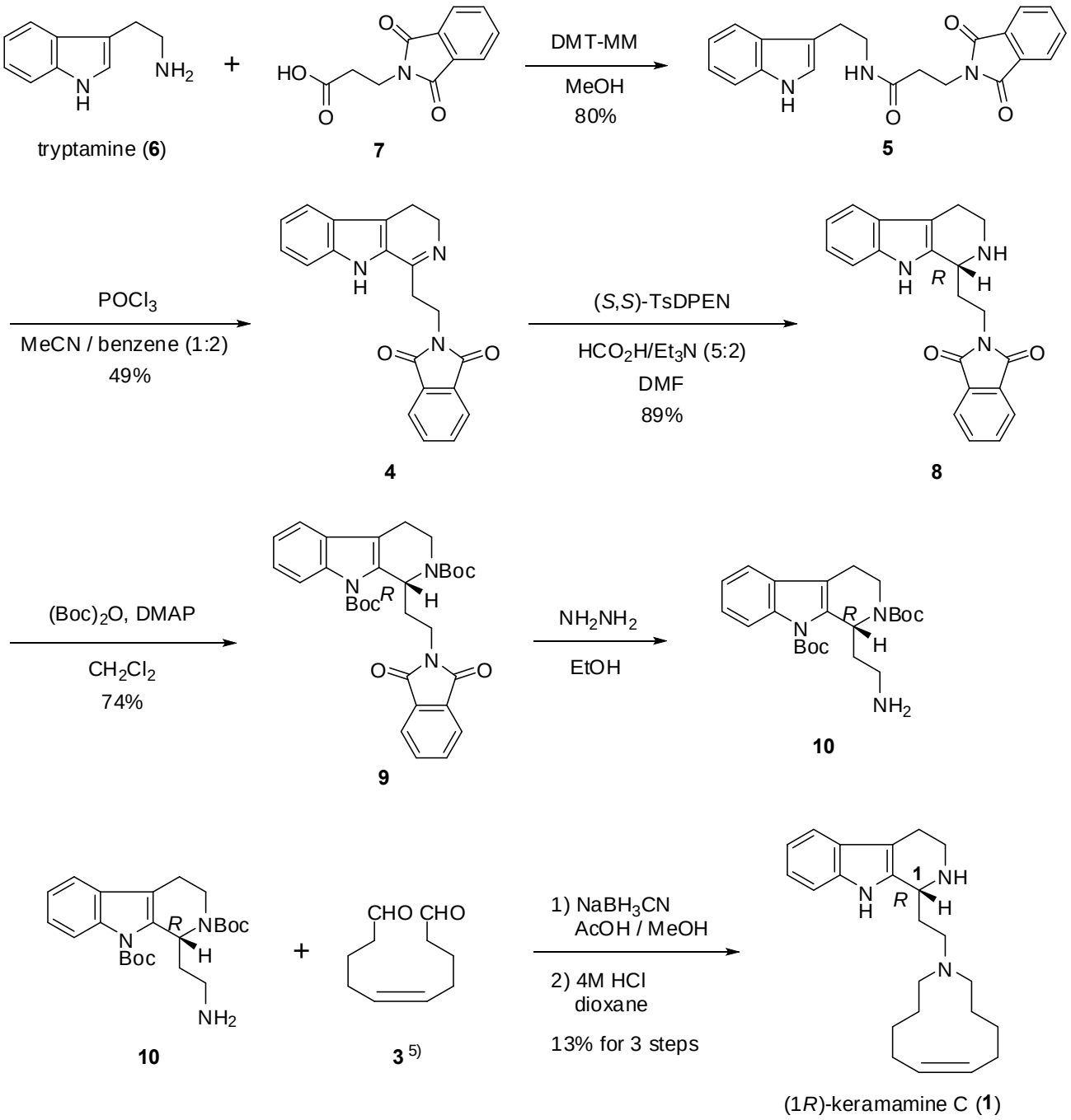
As shown in Scheme 1, (1*R*)-keramamine C (**1**) could be obtained by cyclocondensation of known aldehyde **3**[5] with amine **2**, which could be provided by the Noyori catalytic asymmetric hydrogen-transfer reaction[6] of **4** in contrast to the previous syntheses[4] of manzamine C. Dihydro-β-carboline **4** could be derived from amide **5** via Bischler–Napieralski reaction,[7] which could be available by condensation between tryptamine (**6**) and known carboxylic acid **7**.[8]



Scheme 1. Retrosynthetic analysis of (1*R*)-keramamine C (**1**)

Amide formation of tryptamine (**6**) with known carboxylic acid **7**[8] was successful by using DMT-MM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride)[9] as a condensing agent to give amide **5** (Scheme 2). The Bischler-Napieralski reaction[7] of **5** with $POCl_3$ in benzene and acetonitrile yielded dihydro-β-carboline **4**. To introduce the required stereochemistry at C-1 in **4**, Noyori

asymmetric hydrogen-transfer reaction[6] was applied. The asymmetric transfer hydrogenation of dihydro-β-carboline **4** was accomplished with (*S*,*S*)-TsDPEN-Ru(II) complex in DMF and a HCO_2H-Et_3N mixture to afford **8**. Protection of two NH groups in **8** with Boc groups followed by removal of a phthaloyl group using H_2NNH_2 afforded amine **10** via **9**. The absolute configuration of compound **9** was determined using single-crystal X-ray analysis (Figure 2).[10] Cyclocondensation of **10** with known aldehyde **3**[5] in the presence of $NaBH_3CN$ followed by removal of Boc groups in 4M HCl dioxane solution furnished (1*R*)-keramamine C (**1**).



Scheme 2. Synthesis of (1*R*)-keramamine C (**1**)

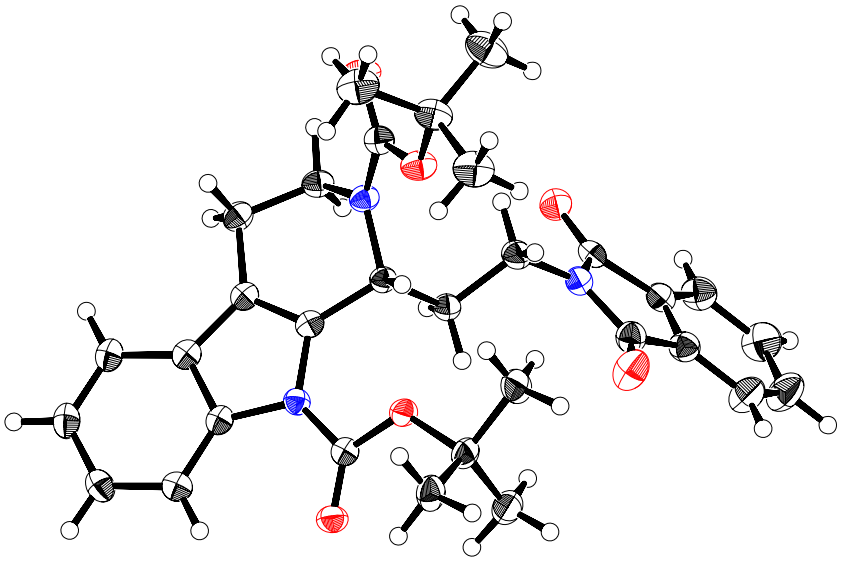


Figure 2. X-Ray structure of compound **9**

^{1}H and ^{13}C NMR data of the synthetic **1**[11] were identical with those of natural keramamine C,[12] respectively. While CD spectral data of the synthetic **1**[11] showed the same Cotton curve pattern of natural keramamine C,[12] $[\alpha]_D$ value of synthetic **1** {$[\alpha]_D^{20}$ +16.9 (*c* 0.3, MeOH)} was coincident with that of natural keramamine C {$[\alpha]_D^{25}$ +20 (*c* 0.92, MeOH)}.[1] Thus, the absolute configuration at C-1 in keramamine C was elucidated to be 1*R*.

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REFERENCES AND NOTES

1. M. Tsuda, N. Kawasaki, and J. Kobayashi, *Tetrahedron Lett.*, 1994, **35**, 4387.
2. J. E. Baldwin and R. C. Whitehead, *Tetrahedron Lett.*, 1992, **33**, 2059.
3. R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, 1987, **28**, 5493.
4. Y. Torisawa, A. Hashimoto, M. Nakagawa, and T. Hino, *Tetrahedron Lett.*, 1989, **30**, 6549; Y. Torisawa, A. Hashimoto, M. Nakagawa, H. Seki, R. Hara, and T. Hino, *Tetrahedron*, 1991, **47**, 8067; W. Nowak and H. Grelach, *Liebigs Ann. Chem.*, 1993, 153; D. I. MaGee and E. J. Beck, *Can. J. Chem.*, 2000, **78**, 1060.

5. U. Hennecke, C. H. Müller, and R. Fröhlich, *Org. Lett.*, 2011, **13**, 860.
6. N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916.
7. A. Bischler and B. Napieralski, *Chem. Ber.*, 1893, **26**, 1891.
8. C. O. Usifoh, D. M. Lambert, J. Wouters, and G. K. E. Scriba, *Arch. Pharm. Pharm. Med. Chem.*, 2001, **334**, 323.
9. M. Kunishima, C. Kawachi, K. Hioki, K. Terao, and S. Tani, *Tetrahedron*, 2001, **57**, 1551.
10. Compound **9**: Colorless block crystal; Mp 187~188 °C (recrystallized from EtOH). The crystal having approximate dimensions of 0.16 x 0.09 x 0.08 mm was mounted in a roop. All measurements were made on a Rigaku R-AXIS RAPID II diffractometer using multi-layer mirror monochromated Cu-Kα radiation (1.54187 Å) at -180 °C. Crystal data: Formula $C_{31}H_{35}N_3O_6$, Formula weight 545.63, Space group P-1 (#1), a = 11.4055(2) Å, b = 11.8842(2) Å, c = 12.3995(2) Å, α = 70.806(5)°, β = 66.530(5)°, γ = 77.039(5)°, V = 1447.46(8) Å^3, Z = 2, D_{calcd} = 1.252 g/cm^3, 27777 reflections measured, 9747 reflections unique, $2\theta_{max}$ = 136.5°, R_{int} = 0.0188, $R_1 = \Sigma||F_O|-|F_C|| / \Sigma|F_O|$ = 0.0277 for 9747 reflections with $I>2\sigma(I)$, $wR_2 = [\Sigma(w(F_O^2-F_C^2)^2) / \Sigma w(F_O^2)^2]^{1/2}$ = 0.0758 for all reflections, goodness of fit 1.081. The structure was solved by direct methods (SIR2008) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The absolute configuration was determined based on Flack parameter, 0.04(8), calculated using 4520 Friedel pairs. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97. Crystallographic data for compound **9** have been deposited at the Cambridge Crystallographic Data Center (deposition number CCDC 906710).
11. Synthetic **1**: UV (MeOH) λ_{max} 290 (ε 5,100), 282 (5,800), 274 (sh 5,800), and 224 nm (24,000); CD (MeOH) λ_{ext} 262 (Δε -0.8), 234 (-1.8), and 219 nm (+5.7); ^{1}H NMR (600 MHz, CD_3OD) δ: 7.55 (d, 1H, J = 7.7 Hz, H-5), 7.42 (d, 1H, J = 7.7 Hz, H-8), 7.22 (t, 1H, J = 7.7 Hz, H-7), 7.12 (t, 1H, J = 7.7 Hz, H-6), 5.53 (m, 2H, H-17, H-18), 3.78 (m, 1H, H-3), 3.57 (m, 1H, H-3), 3.40 (m, 2H, H_2-11), 3.32 (m, 3H, H-1, H-13, H-22), 3.13 (m, 2H, H-13, H-22), 2.67 (m, 1H, H-4), 2.46 (m, 1H, H-4), 2.38 (m, 4H, H_2-16, H_2-19), 1.87 (m, 4H, H_2-14, H_2-21), 1.65 (m, 4H, H_2-15, H_2-20); ^{13}C NMR (150 MHz, CD_3OD) δ: 139.2 (C-8a), 133.0 (C-17,18), 129.2 (C-9a), 128.2 (C-4b), 124.8 (C-7), 121.7 (C-6), 120.1 (C-5), 113.3 (C-8), 108.9 (C-4a), 53.0 (C-1), 51.2 (C-11), 50.5 (C-13,22), 43.2 (C-3), 29.4 (C-10), 27.4 (C-16,19), 25.4 (C-15,20), 23.2 (C-14,21), 20.2 (C-4); MS (ESI) *m/z* 352 $(M+H)^+$; HRMS (ESI) calcd for $C_{23}H_{34}N_3$ $(M+H)^+$ 352.2746, found 352.2747.
12. Natural keramamine C: UV (MeOH) λ_{max} 290 (ε 5,000), 281 (6,100), 274 (sh 6,100), and 223 nm (27,000); CD (MeOH) λ_{ext} 262 (Δε -1.2), 234 (-2.2), and 219 nm (+8.5); ^{1}H NMR (600 MHz, CD_3OD) δ: 7.55 (d, 1H, J = 7.7 Hz, H-5), 7.43 (d, 1H, J = 7.7 Hz, H-8), 7.23 (t, 1H, J = 7.7 Hz, H-7),

7.12 (t, 1H, *J* = 7.7 Hz, H-6), 5.54 (m, 2H, H-17, H-18), 3.79 (m, 1H, H-3), 3.58 (m, 1H, H-3), 3.39 (m, 2H, H_2-11), 3.33 (m, 3H, H-1, H-13, H-22), 3.14 (m, 2H, H-13, H-22), 2.68 (m, 1H, H-4), 2.47 (m, 1H, H-4), 2.38 (m, 4H, H_2-16, H_2-19), 1.87 (m, 4H, H_2-14, H_2-21), 1.65 (m, 4H, H_2-15, H_2-20); ^{13}C NMR (CD_3OD 150 MHz) δ: 139.2 (C-8a), 133.0 (C-17,18), 129.2 (C-9a), 128.2 (C-4b), 124.8 (C-7), 121.7 (C-6), 120.1 (C-5), 113.3 (C-8), 108.7 (C-4a), 53.0 (C-1), 51.2 (C-11), 50.5 (C-13,22), 43.1 (C-3), 29.4 (C-10), 27.4 (C-16,19), 25.4 (C-15,20), 23.2 (C-14,21), 20.2 (C-4); MS (EI) *m/z* 198, 351 (M^+); HRMS (EI) calcd for $C_{23}H_{33}N_3$ (M^+) 351.2674, found 351.2687.