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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 ¹H and ¹³C 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 C₃ unit, isolated from the Okinawan marine sponge *Amphimedon* sp.¹ (Figure 1). Keramaphidin C, (*Z*)-azacycloundec-6-ene moiety in keramamine C, could be biogenetically² derived from a C₁₀ unit and ammonia. Though the

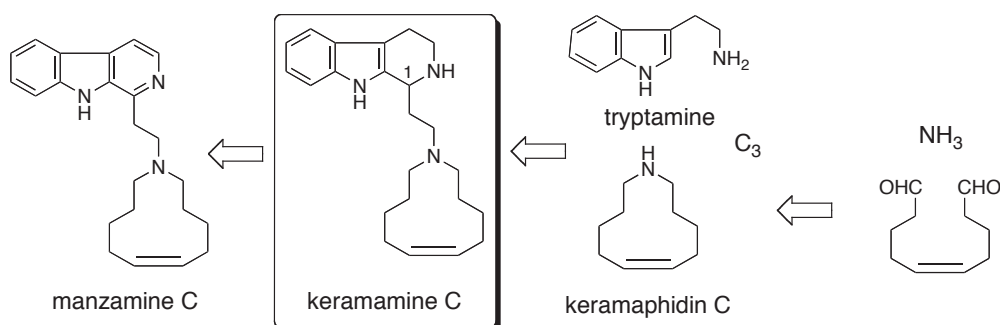
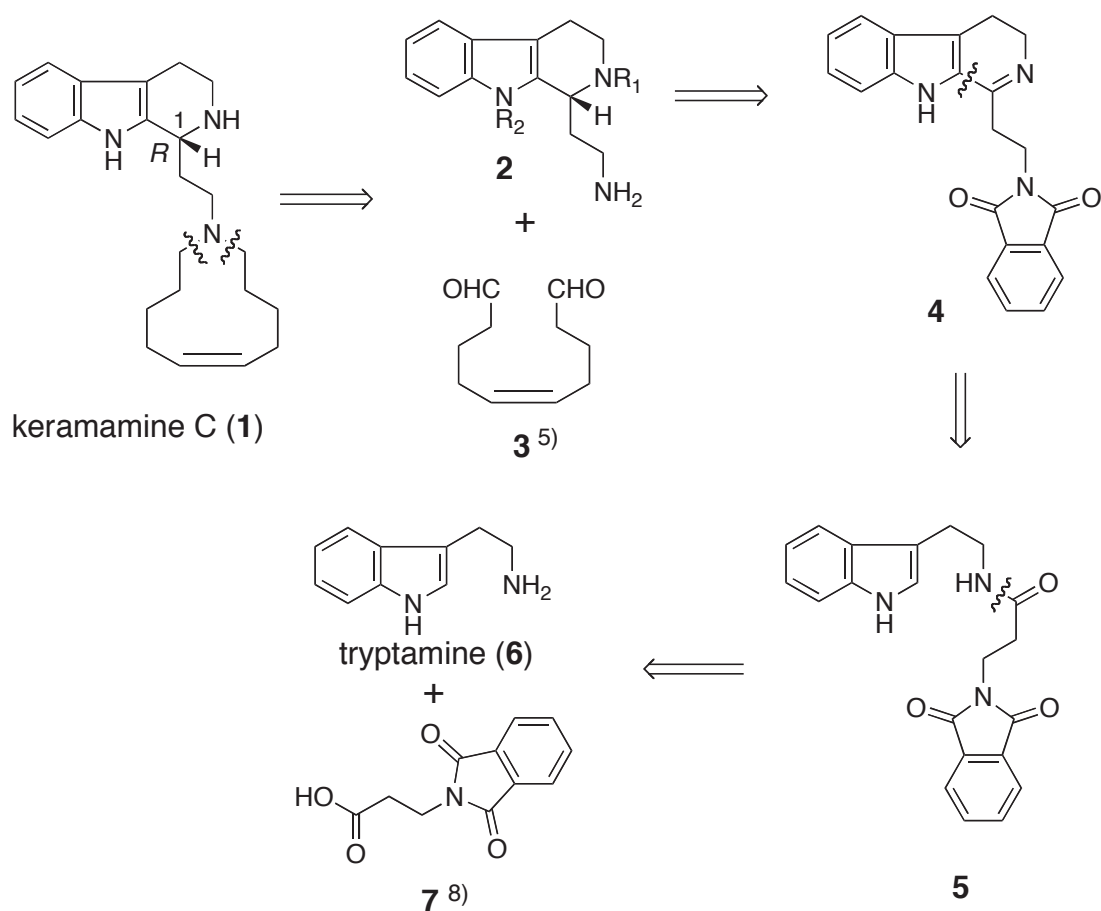


Figure 1. Possible biogenetic pathway to keramamine C and manzamine C

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.

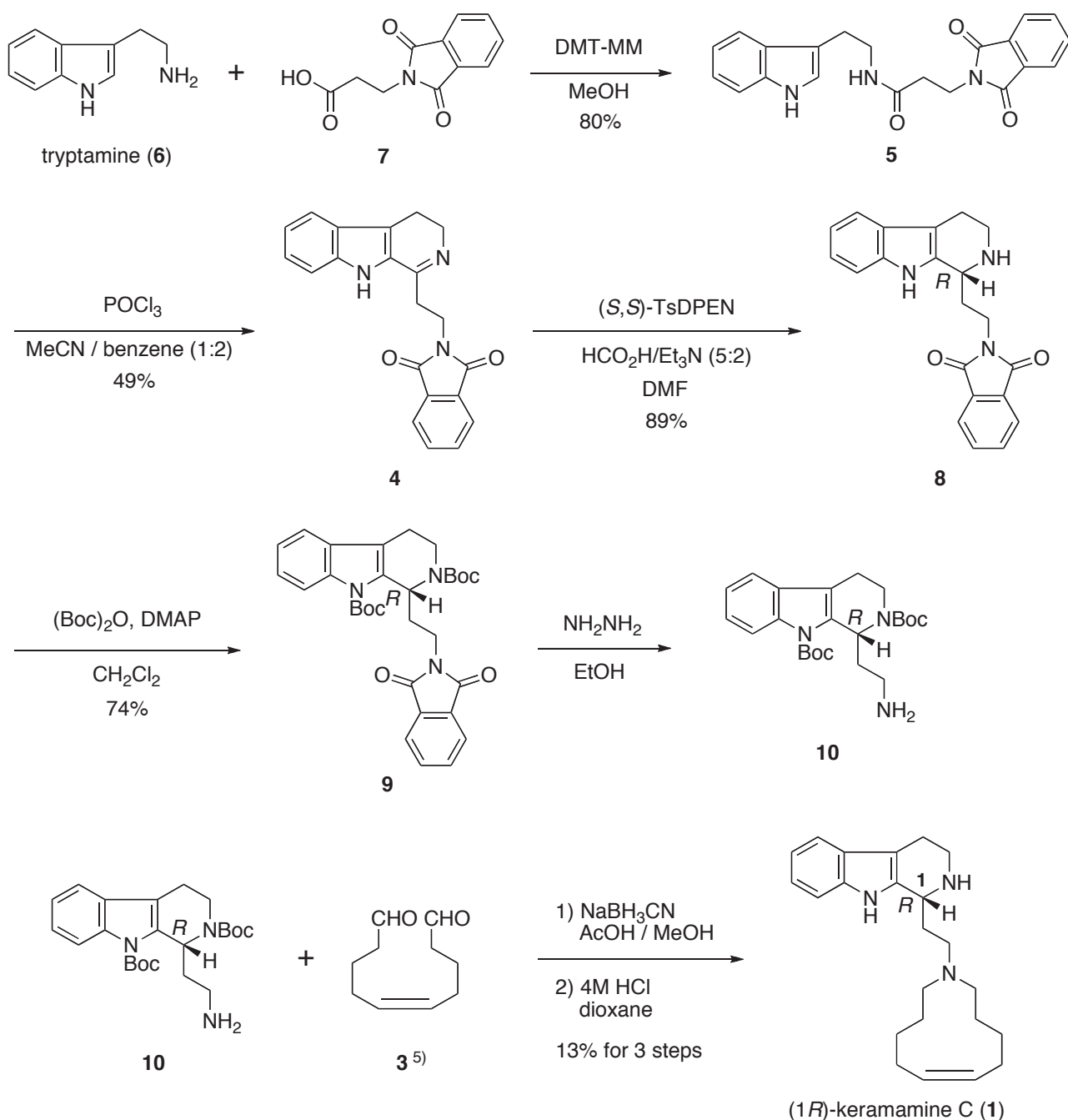
As shown in Scheme 1, (1*R*)-keramamine C (**1**) could be obtained by cyclocondensation of known aldehyde **3**⁵ with amine **2**, which could be provided by the Noyori catalytic asymmetric hydrogen-transfer reaction⁶ of **4** in contrast to the previous syntheses⁴ of manzamine C. Dihydro- β -carboline **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 reaction⁷ of **5** with POCl₃ in benzene and acetonitrile yielded dihydro- β -carboline **4**. To introduce the required stereochemistry at C-1 in **4**, Noyori

asymmetric hydrogen-transfer reaction⁶ was applied. The asymmetric transfer hydrogenation of dihydro- β -carboline **4** was accomplished with (*S,S*)-TsDPEN-Ru(II) complex in DMF and a HCO₂H-Et₃N mixture to afford **8**. Protection of two NH groups in **8** with Boc groups followed by removal of a phthaloyl group using H₂NNH₂ 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 NaBH₃CN followed by removal of Boc groups in 4M HCl dioxane solution furnished (*1R*)-keramamine C (**1**).



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

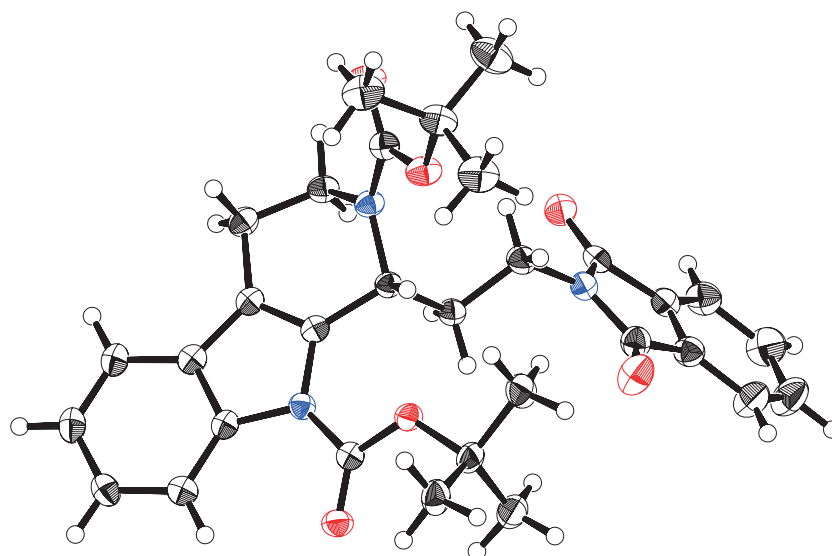


Figure 2. X-Ray structure of compound **9**

^1H 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 $[\alpha]_{\text{D}}$ value of synthetic **1** $\{[\alpha]_{\text{D}}^{20} +16.9 (c 0.3, \text{MeOH})\}$ was coincident with that of natural keramamine C $\{[\alpha]_{\text{D}}^{25} +20 (c 0.92, \text{MeOH})\}$ ¹. Thus, the absolute configuration at C-1 in keramamine C was elucidated to be 1*R*.

ACKNOWLEDGEMENTS

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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 loop. All measurements were made on a Rigaku R-Axis RAPID II diffractometer using multi-layer mirror monochromated Cu-K α radiation (1.54187 Å) at -180 °C. Crystal data: Formula C₃₁H₃₅N₃O₆, Formula weight 545.63, Space group P-1 (#1), $a = 11.4055(2)$ Å, $b = 11.8842(2)$ Å, $c = 12.3995(2)$ Å, $\alpha = 70.806(5)^\circ$, $\beta = 66.530(5)^\circ$, $\gamma = 77.039(5)^\circ$, $V = 1447.46(8)$ Å³, $Z = 2$, $D_{\text{calcd}} = 1.252$ g/cm³, 27777 reflections measured, 9747 reflections unique, $2\theta_{\text{max}} = 136.5^\circ$, $R_{\text{int}} = 0.0188$, $R_1 = \sum \|F_o\| - |F_c| / \sum \|F_o\| = 0.0277$ for 9747 reflections with $I > 2\sigma(I)$, $wR_2 = [\sum (w(F_o^2 - F_c^2)^2) / \sum w(F_o^2)^2]^{1/2} = 0.0758$ 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 ($\Delta\epsilon$ -0.8), 234 (-1.8), and 219 nm (+5.7); ¹H NMR (600 MHz, CD₃OD) 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, H₂-11), 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, H₂-16, H₂-19), 1.87 (m, 4H, H₂-14, H₂-21), 1.65 (m, 4H, H₂-15, H₂-20); ¹³C NMR (150 MHz, CD₃OD) 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 C₂₃H₃₄N₃ (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 ($\Delta\epsilon$ -1.2), 234 (-2.2), and 219 nm (+8.5); ¹H NMR (600 MHz, CD₃OD) 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, H₂-11), 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, H₂-16, H₂-19), 1.87 (m, 4H, H₂-14, H₂-21), 1.65 (m, 4H, H₂-15, H₂-20); ¹³C NMR (CD₃OD 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 C₂₃H₃₃N₃ (M⁺) 351.2674, found 351.2687.