

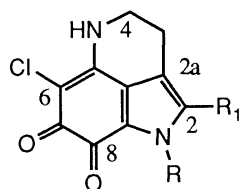
Total Syntheses of Batzelline C and Isobatzelline C, the Novel Pyrroloquinoline Alkaloids
Isolated from the Marine Sponge *Batzella* Sp.

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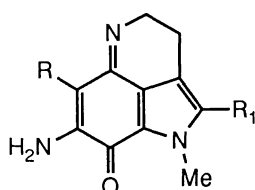
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Total syntheses of batzelline C and isobatzelline C, two chlorine-containing alkaloids have been successfully accomplished employing the tricyclic indole derivative as a key intermediate.

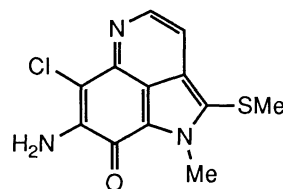
The family of batzellines A - C and isobatzellines A - D were isolated from the marine sponge *Batzella* sp. during the course of screening herbicidal agents from marine organisms.¹⁾ Interestingly, isobatzellines possess *in vitro* cytotoxic activities against P388 leukemia cell as well as antifungal activities against *Candida albicans*. The structures of these alkaloids have been deduced from spectroscopic and chemical correlations with batzelline A whose structure was determined by an X-ray crystallographic analysis. We have included synthetic studies of alkaloids bearing chlorine and sulfur atoms as a part of our extensive investigations of biologically active marine natural products. We describe herein the first total syntheses of batzelline C and isobatzelline C which share some common functionalities as other members of the batzellines and isobatzellines families.



BATZELLINE A
R = Me, R₁ = SMe
BATZELLINE B
R = H, R₁ = SMe
BATZELLINE C (1)
R = Me, R₁ = H

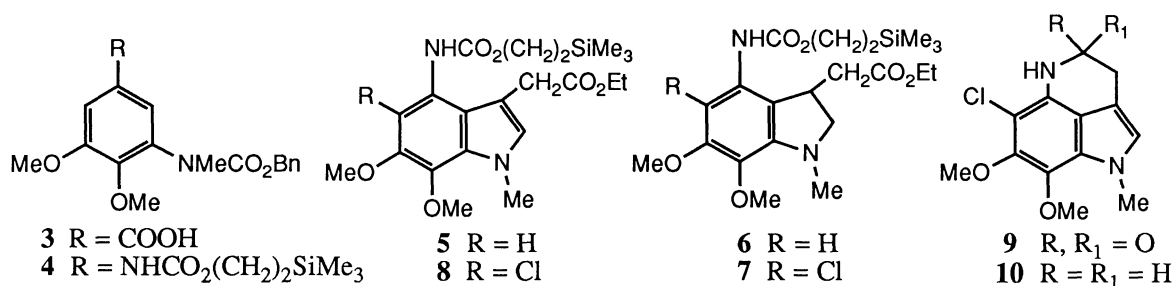


ISOBATZELLINE A
R = Cl, R₁ = SMe
ISOBATZELLINE B
R = H, R₁ = SMe
ISOBATZELLINE C (2)
R = Cl, R₁ = H



ISOBATZELLINE D

Our synthetic approach was initiated with 3,4-dimethoxy-5-nitrobenzaldehyde,²⁾ which was transformed into the carboxylic acid (**3**)³⁾ in four steps [1. Fe, HCl; 2. CbzCl, NaHCO₃; 3. MeI, NaH / DMF (79% in 3 steps); 4. Jones oxid. (89%)]. Conversion of the carboxyl group of **3** to the corresponding trimethylsilyl-ethoxycarbonylamido group was effected by transformation involving the Curtius reaction [1. CO(Imd)₂ / THF, room temp; 2. NaN₃; 3. toluene, refluxing temp, then trimethylsilylethanol, 60 °C (86% yield in 3 steps)]. Compound **4**³⁾ obtained was subsequently submitted to hydrogenolysis in the presence of catalytic 10% Pd on carbon, followed by reaction with ClCH₂COCH₂CO₂Et in refluxing EtOH to give the indole (**5**)³⁾ in 87% overall yield. Compound **5** was reduced with NaBH₃CN in AcOH to yield the dihydro derivative (**6**), which



was subsequently treated with NCS in CH₂Cl₂ to give the monochloro product (**7**) along with **8**³⁾ in 69 and 6% yields, respectively. Oxidation of **7** with DDQ in CH₂Cl₂ resulted in olefination of the C₂ - C_{2a} position to yield **8**. In the next stage, compound **8** was transformed into the lactam (**9**)³⁾ in three steps [1. AcOH - HClO₄ (20 : 1), room temp (60%); 2. KOH / aq. MeOH, room temp; 3. DCC / THF, 0 °C → room temp (58% in 2 steps)]. Reduction of **9** with BH₃·SMe₂ in THF afforded the expected intermediate (**10**)³⁾ in 80% yield. Compound **10** was deprotected with BBr₃ in CH₂Cl₂, followed by autoxidation in aq. HCl to yield batzelline C (**1**) in 78% overall yield. Additionally, the key intermediate (**10**) was converted to isobatzelline C (**2**) in two steps [1. CAN / aq. CH₃CN (64%); 2. NH₄Cl / EtOH (64%)]. The synthetic batzelline C and isobatzelline C were identical to authentic samples in all respects of the spectroscopic data. Further synthetic studies on other congeners possessing the thioether functions are in progress.

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References

- 1) Batzelline: S. Sakemi, H. H. Sun, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, **30**, 2517 (1989); Isobatzelline: H. H. Sun, S. Sakemi, N. Burres, and P. McCarthy, *J. Org. Chem.*, **55**, 4964 (1990).
- 2) O. L. Brady and L. B. Monjunath, *J. Chem. Soc.*, **125**, 1067 (1924).
- 3) **3**: IR (film): 1700 and 1585 cm⁻¹; δ (CDCl₃) 3.24 (3H, s), 3.84 (3H, s), 3.91 (3H, s), 5.16 (2H, s), 7.29 (1H, d, J = 2 Hz, overlapped with 5H signal), 7.61 (1H, d, J = 2 Hz), and 8.65 (1H, broad s). **4**: C₂₃H₃₂N₂O₆Si [m/z 460.2038 (M⁺)]; IR (film): 3350, 1710, 1605, 1550, and 1505 cm⁻¹; δ (CDCl₃) 0.09 (9H, s), 0.87 - 1.06 (2H, complex), 3.14 (3H, s), 3.63 (3H, s), 3.79 (3H, s), 4.07 - 4.27 (2H, complex), 5.07 (2H, s), 6.43 (1H, broad s), 6.55 (1H, d, J = 3 Hz), 7.12 (1H, d, J = 3 Hz), and 7.22 (5H, complex). **5**: C₂₁H₃₂N₂O₆Si [m/z 436.1997 (M⁺)]; IR (film): 3300, 1720, 1620, 1580 and 1530 cm⁻¹; δ (CDCl₃) 0.06 (9H, s), 1.00 - 1.20 (2H, complex), 1.28 (3H, t, J = 7 Hz), 3.71 (2H, s), 3.88 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 4.10 - 4.30 (2H, complex), 4.35 (2H, q, J = 7 Hz), 6.71 (1H, s), 7.29 (1H, s), and 8.73 (1H, broad s). **8**: C₂₁H₃₁³⁵ClN₂O₆Si [m/z 470.1624 (M⁺)]; IR (film): 3300, 1725, 1600, and 1500 cm⁻¹; δ (CDCl₃) 0.02 (9H, s), 0.90 - 1.20 (2H, complex), 1.27 (3H, t, J = 7 Hz), 3.69 (2H, s), 3.90 (3H, s), 3.91 (3H, s), 3.97 (3H, s), 4.10 - 4.35 (2H, complex), 4.16 (2H, q, J = 7 Hz), 6.83 (1H, s), and 7.10 (1H, broad s). **9**: C₁₃H₁₃³⁵ClN₂O₃ [m/z 280.0591 (M⁺)]; IR (film): 3250, 1665, 1615, and 1515 cm⁻¹; δ (CDCl₃) 3.90 - 3.96 (2H, complex), 3.90 (3H, s), 3.93 (3H, s), 3.96 (3H, s), 6.62 (1H, s), and 7.70 (1H, broad s). **10**: C₁₃H₁₅³⁵ClN₂O₂ [m/z 266.0810 (M⁺)]; IR (film): 3400, 1620, and 1510 cm⁻¹; δ (CDCl₃) 2.95 (2H, t, J = 6 Hz), 3.49 (2H, t, J = 6 Hz), 3.90 (9H, s), and 6.51 (1H, s).

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