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

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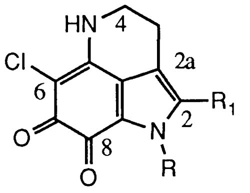
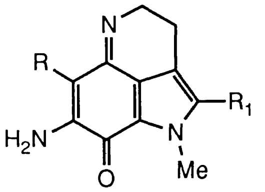
Total syntheses of batzelline C and isobatzelline C, two chlorine-containing alkaloids have been successfully accomplished employing the tricyclic indole derivative as a key intermediate.

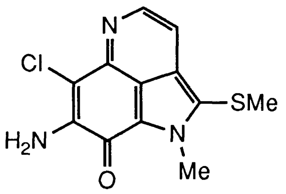
The family of batzellines A - C and isobatzellines A - D were isolated from the marine sponge *Batzella* sp. during the course of screening herbicidal agents from marine organisms.[1] Interestingly, isobatzellines possess *in vitro* cytotoxic activities against P388 leukemia cell as well as antifungal 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, R_1 = SMe
BATZELLINE B
R = H, R_1 = SMe
BATZELLINE C (**1**)
R = Me, R_1 = H

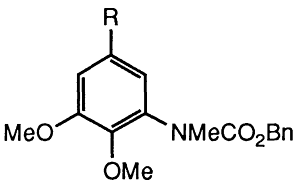


ISOBATZELLINE A
R = Cl, R_1 = SMe
ISOBATZELLINE B
R = H, R_1 = SMe
ISOBATZELLINE C (**2**)
R = Cl, R_1 = H

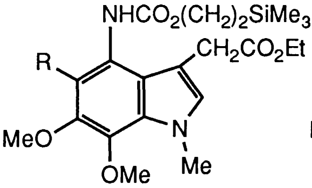


ISOBATZELLINE D

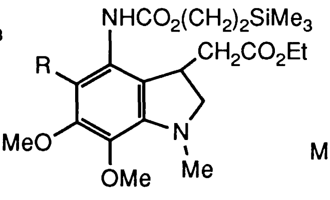
Our synthetic approach was initiated with 3,4-dimethoxy-5-nitrobenzaldehyde,[2] which was transformed into the carboxylic acid (**3**)[3] in four steps [1. Fe, HCl ; 2. CbzCl, $NaHCO_3$: 3. MeI, NaH / DMF (79% in 3 steps); 4. Jones oxid. (89%)]. Conversion of the carboxyl group of **3** to the corresponding trimethylsilylethoxycarbonylamido group was effected by transformation involving the Curtius reaction [1. $CO(Imd)_2$ / THF, room temp; 2. NaN_3; 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 $ClCH_2COCH_2CO_2Et$ in refluxing EtOH to give the indole (**5**)[3] in 87% overall yield. Compound **5** was reduced with $NaBH_3CN$ in AcOH to yield the dihydro derivative (**6**), which



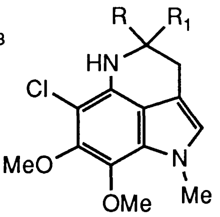
3 R = COOH
4 R = $NHCO_2(CH_2)_2SiMe_3$



5 R = H
8 R = Cl



6 R = H
7 R = Cl



9 R, R_1 = O
10 R = R_1 = H

was subsequently treated with NCS in CH_2Cl_2 to give the monochloro product (**7**) along with **8**³⁾ in 69 and 6% yields, respectively. Oxidation of **7** with DDQ in CH_2Cl_2 resulted in olefination of the C_2 - C_{2a} position to yield **8**. In the next stage, compound **8** was transformed into the lactam (**9**)³⁾ in three steps [1. AcOH - $HClO_4$ (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 $BH_3•SMe_2$ in THF afforded the expected intermediate (**10**)³⁾ in 80% yield. Compound **10** was deprotected with BBr_3 in CH_2Cl_2, 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. CH_3CN (64%); 2. NH_4Cl / 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 ($CDCl_3$) 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**: $C_{23}H_{32}N_2O_6Si$ [m/z 460.2038 (M^+)]; IR (film): 3350, 1710, 1605, 1550, and 1505 cm^{-1}; δ ($CDCl_3$) 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**: $C_{21}H_{32}N_2O_6Si$ [m/z 436.1997 (M^+)]; IR (film): 3300, 1720, 1620, 1580 and 1530 cm^{-1}; δ ($CDCl_3$) 0.06 (9H, s), 1.00 - 1.20 (2H, complex), 1.28 (3H, t, J= 7Hz), 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**: $C_{21}H_{31}{}^{35}ClN_2O_6Si$ [m/z 470.1624 (M^+)]; IR (film): 3300, 1725, 1600, and 1500 cm^{-1}; δ ($CDCl_3$) 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**: $C_{13}H_{13}{}^{35}ClN_2O_3$ [m/z 280.0591 (M^+)]; IR (film): 3250, 1665, 1615, and 1515 cm^{-1}; δ ($CDCl_3$) 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**: $C_{13}H_{15}{}^{35}ClN_2O_2$ [m/z 266.0810 (M^+)]; IR (film): 3400, 1620, and 1510 cm^{-1}; δ ($CDCl_3$) 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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