Syntheses of Polybrominated Indoles from the Red Alga *Laurencia brongniartii* and the Brittle Star *Ophiocoma erinaceus*

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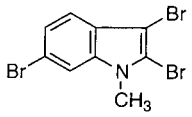
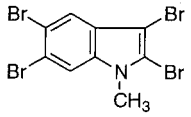
The red alga *Laurencia brongniartii* and brittle star *Ophiocoma erinaceus* metabolites 2,3,6-tribromo-1-methylindole (**1**) and 2,3,5,6-tetrabromo-1-methylindole (**2**) are easily synthesized selectively from 2,3-dibromo-1-methylindole (**5**), which in turn is prepared from indole (**3**) in one continuous sequence in 92% yield. Moreover, **2** can be made from both **1** and **5** in 67% and 65% yields, respectively.

Polybrominated indoles comprise a significant fraction of the 1850 known naturally occurring organobromine compounds,[1] most of which have been isolated from marine organisms. For example, the red alga *Laurencia brongniartii* has yielded both 2,3,6-tribromo-1-methylindole (**1**) and 2,3,5,6-tetrabromo-1-methylindole (**2**).[2] The latter metabolite has also recently been isolated from the brittle star *Ophiocoma erinaceus*.[3] One synthesis of **2** from *N*-methylindole in 53% yield has been described.[4]



1

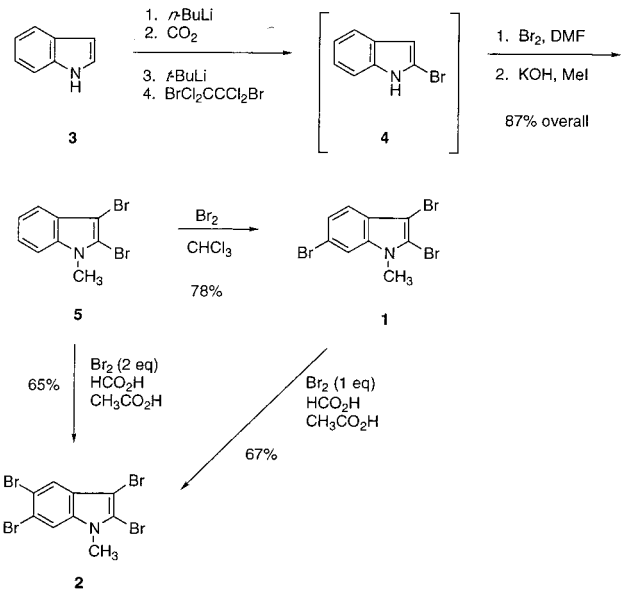


2

We now report simple syntheses of **1** and **2** from indole (**3**) that make available sufficient quantities of these compounds in pure form for biological testing, since polybrominated indoles seem to possess antibacterial and antifungal activity.[2,5] Our syntheses, which are summarized in Scheme 1, make use of chemistry we developed recently for the synthesis of 2,3-diiodo-1-methylindole.[6] Thus, using a combination of Bergman's excellent procedure[7] for the synthesis of 2-bromoindole (**4**) with a one-pot bromination−methylation sequence[8] afforded 2,3-dibromo-1-methylindole (**5**) in 92% overall yield. Subsequent bromination of **5** in chloroform gave 2,3,6-tribromo-1-methylindole (**1**) (78% yield), and bromination of **5** with bromine (2 equiv) in a mixture of acetic and formic acid afforded 2,3,5,6-tetrabromo-1-methylindole (**2**) (65%). Compound **2** was also prepared by bromination of **1** with bromine (1 equiv) under these conditions (67%). The overall yields of **1** and **2** from indole are 72% and 60%, respectively. Although we were unable to obtain authentic samples or spectra of the natural materials,[2] our spectral data agreed with the published information.[2−4]

In conclusion, the synthesis of the red alga polybrominated indole metabolites **1** and **2** is readily achieved by selective bromination of 2,3-dibromo-1-methylindole (**5**). The latter compound is prepared from indole in one continuous operation in 92% yield. Given the utility of 2,3-dihaloindoles in organic synthesis,[6,9] our simple preparation of **5** should find applications in this area.

Scheme 1



Experimental Section

General Experimental Procedures. Melting points are uncorrected. NMR spectra were obtained on a Varian XL-300 or a Varian Unit plus 500 MHz spectrometer operating at 300 or 500 MHz for ^{1}H and 125 MHz for ^{13}C channels, respectively. Chemical shifts are reported in parts per million (δ) using the residual protonated solvents ($CHCl_3$: δ_H 7.27; DMSO: δ_H 2.50, δ_C 39.5). High-resolution mass spectra (HRMS) were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana−Champaign. Tetrahydrofuran (THF) was distilled from sodium/benzophenone.

2,3-Dibromo-1-methylindole (5). To a solution of indole (**3**) (1.17 g, 10.0 mmol) in THF (20 mL) at −78 °C was added dropwise *n*-butyllithium (4.2 mL, 2.5 M in hexane, 10.5 mmol) under N_2. The resulting white suspension was stirred for 10 min at −78 °C, and then CO_2 was bubbled through the mixture for 10 min. The resulting clear solution was stirred for 10 min and then subjected to a vacuum (1 Torr) until bubbling was no longer observed. To this solution was added THF (10 mL) and *tert*-butyllithium (7.0 mL, 1.5 M in pentane, 10.5 mol) dropwise at −78 °C to afford a bright yellow solution. This solution was maintained at −78 °C for 30 min and then treated with a solution of 1,2-dibromotetrachloroethane (3.26 g, 10.0 mmol) in THF (10 mL) via cannula. The mixture was allowed to warm to room temperature, then poured into water, and extracted with ether (50 mL). The organic layer was washed with water (2 × 50 mL), dried ($MgSO_4$), and removed in vacuo (1 Torr) at 0 °C. The residue was treated with DMF (20 mL)

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and with stirring at 0 °C and was treated with a solution of bromine (0.54 mL, 10.5 mmol) in DMF (10 mL). The resulting solution was warmed to room temperature, treated with KOH (2.24 g, 40.0 mmol) and methyl iodide (2.49 mL, 40.0 mmol), and stirred at room temperature for 3 h. The mixture was poured into water and extracted with ether (3 × 50 mL). The organic layer was washed with water (5 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo to give 2.66 g (92%) of **5** as an off-white solid: mp 38.5−40 °C (lit.[10] mp 39−40 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.57 (1H, m, H-4), 7.41 (1H, m, H-7), 7.27 (1H, m, H-6), 7.18 (1H, m, H-5), 3.82 (3H, s, NCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 136.1 (C-7a), 126.0 (C-3a), 122.9 (C-4), 120.9 (C-5), 117.9 (C-6), 115.3 (C-2), 110.8 (C-7), 91.3 (C-3), 32.4 (CH_3). This material was used directly in the next steps.

2,3,6-Tribromo-1-methylindole (1). To a stirred solution of **5** (0.200 g, 0.692 mmol) in chloroform (15 mL) at room temperature was added dropwise with stirring under N_2 a solution of bromine (0.111 g, 0.694 mmol) in chloroform (5 mL). The resulting solution was heated at reflux for 2 h, allowed to cool to room temperature, and poured into saturated aqueous sodium sulfite solution. The organic layer was washed with water (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was purified by flash chromatography over silica gel (hexane/ether, 4:1) to give 0.198 g (78%) of **1** as white crystals: mp 89−90 °C (lit.[2] mp 90.5−91 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (1H, d, J = 1.5 Hz, H-7), 7.38 (1H, d, J = 8.4 Hz, H-4), 7.29 (1H, dd, J = 8.4, 1.5 Hz, H-5), 3.78 (3H, s, NCH_3); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.90 (1H, d, J = 1.5 Hz, H-7), 7.35 (1H, d, J = 8.5 Hz, H-4), 7.30 (1H, dd, J = 8.5, 1.5 Hz, H-5), 3.80 (3H, s, NCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 136.8 (C-7a), 125.1 (C-3a), 123.9 (C-4), 119.7 (C-5), 116.6 (C-6), 115.8 (C-2), 113.7 (C-7), 91.6 (C-3), 32.7 (CH_3); HREIMS m/z 364.8046 (calcd for $C_9H_6NBr_3$, 364.8050). Unfortunately, samples and spectra of this compound[2] were unavailable for direct comparison.

2,3,5,6-Tetrabromo-1-methylindole (2) from 5. To a stirred solution of **5** (0.100 g, 0.346 mmol) in a mixture of formic acid and acetic acid (1:1, 10 mL) cooled in an ice bath was added dropwise a solution of bromine (0.111 g, 0.694 mmol) in formic acid and acetic acid (1:1, 1 mL). The mixture was stirred in the ice bath for an additional 2 h. The resulting mixture was poured into water (50 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (2 × 50 mL), saturated aqueous sodium bicarbonate solution (20 mL), and water (50 mL) and dried ($MgSO_4$). The crude solid after removal of solvent was recrystallized from hexane to give 0.100 g (65%) of **2** as white needles: mp 170−171 °C (lit.[2] mp 171.5−172 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, s, H-4), 7.60 (1H, s, H-7), 3.77 (3H, s, NCH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 135.7 (C-7a), 126.7 (C-3a), 121.9 (C-4), 118.5 (C-6), 117.4 (C-2), 116.1 (C-7), 115.4 (C-5), 90.6 (C-3), 32.9 (CH_3); HREIMS m/z 442.7148 (calcd for $C_9H_5NBr_4$, 442.7155). Unfortunately, samples and spectra of this compound[2] were unavailable for direct comparison.

2,3,5,6-Tetrabromo-1-methylindole (2) from 1. To a stirred solution of **1** (0.100 g, 0.271 mmol) in a mixture of formic acid and acetic acid (1:1, 10 mL) cooled in an ice bath was added a solution of bromine (0.0430 g, 0.271 mmol) in formic acid and acetic acid (1:1, 1 mL). The mixture was stirred in the ice bath for an additional 2 h. The resulting mixture was poured into water (50 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (2 × 50 mL), saturated aqueous sodium bicarbonate solution (20 mL), and water (50 mL) and dried ($MgSO_4$). The crude solid after removal of solvent was recrystallized from hexane to give 0.081 g (67%) of **2** as white needles, identical with that obtained above.

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References and Notes

(1) (a) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335−346. (b) Gribble. G. W. *Environ. Sci., Pollut. Res.* **2000**, *7*, 37−49. (c) Gribble, G. W. Unpublished compilation.
(2) Carter, G. T.; Rinehart Jr., K. L.; Li, L. H.; Kuentzel, S. L.; Connor, J. L. *Tetrahedron Lett.* **1978**, 4479−4482.
(3) Ooi, T.; Utsumi, K.; Kusumi, T. *Heterocycles* **2001**, *54*, 577−579.
(4) Settimo, A. D.; Nannipieri, E. *J. Org. Chem.* **1970**, *35*, 2546−2551.
(5) For example, the crude polyhaloindole extract from the red alga *Rhodophyllis membranacea* exhibits strong antifungal activity: Brennan, M. R.; Erickson, K. L. *Tetrahedron Lett.* **1978**, 1637−1640. 3,6-Dibromoindole from the Palauan ascidian *Distaplia regina* shows antibacterial activity: Qureshi, A.; Faulkner, D. J. *Nat. Prod. Lett.* **1999**, *13*, 59−62.
(6) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2001**, *42*, 2949−2951.
(7) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495−2497.
(8) Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096−1097.
(9) (a) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, *41*, 8717−8721. (b) Gribble, G. W.; Liu, Y. *Org. Prep. Proc. Int.* **2001**, *33*, 615−619.
(10) Zajc, B.; Zupan, M. *Tetrahedron* **1989**, *45*, 7869−7878.

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