Synthesis of Convolutamydine A from Isatin†

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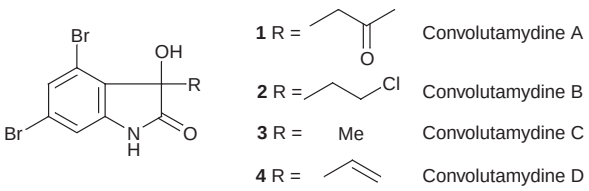
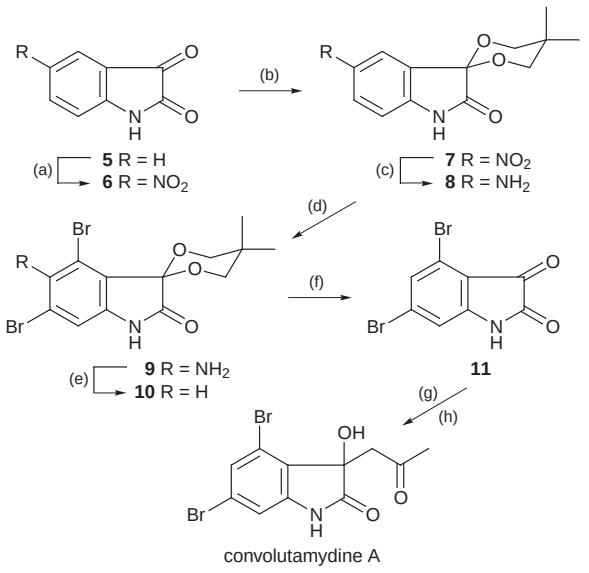
Synthesis of the marine alkaloid convolutamydine A is described starting from commercially available isatin.

The sea is a rich source for marine natural products. Many of these natural products carry a unique structure making them distinct from other natural products; for example, halogenated compounds.[1] Recently Pettit and coworkers isolated a new series of alkaloids from the marine bryozoan *Amathia convoluta* containing a dibromohydroxyindole moiety and named them as convolutamydines A–D[2] (**1**–**4**). The alkaloids convolutamydine A[3] and B were found to exhibit a potent activity in the differentiation of HL-60 human promyelocytic leukemia cells.



For the synthesis of convolutamydine A an obvious precursor is 4,6-dibromoisatin. In the literature 4,6-dibromoisatin has been prepared using modified Sandmeyer conditions starting from 3,5-dibromoaniline.[4] Recently, we have developed a microwave-assisted Sandmeyer method for the preparation of 4,6-dibromoisatin[5] in good yield.



Scheme 1 *Reagents and conditions*: (a) KNO_3, H_2SO_4, 0 °C (70%); (b) 2,2-dimethylpropane-1,3-diol, *p*-TSA, cycloyhexane (82%); (c) Pd/C (10%), H_2, MeOH (69%); (d) Br_2, EtOH (78%); (e) ^{t}BuONO, DMF, 65 °C; (f) aqueous oxalic acid, 60 °C (24%); (g) acetone, 15% ethanolic KOH solution, 1 drop (88%) or (h) acetone, benzyltrimethylammonium hydroxide (aqueous; 40%), 1 drop (96%).

In the present finding commercially available isatin (**5**) was used as a starting material to prepare 4,6-dibromoisatin[5] (**11**). Isatin was nitrated using potassium nitrate in sulfuric acid at 0°C to give 5-nitroisatin (**6**) in 70% yield.[6] The keto group of **6** was protected to **7** by azeotropic reflux of a suspension of 5-nitroisatin, 2,2-dimethylpropane-1,3-diol and *p*-TSA in cyclohexane. The Pd/C catalysed hydrogenation of nitroketal **7** gave aminoketal **8**. Its further bromination in rectified spirit gave 4,6-dibromo-5-aminoketal **9**[7] (Scheme 1). The deamination using *tert*-butyl nitrite[8] in DMF at 65 °C gave 4,6-dibromoketal **10** which was subjected to deprotection with aqueous oxalic acid at 60 °C to give 4,6-dibromoisatin (**11**). The 4,6-dibromoisatin (**11**) obtained by the present method was found to be identical with the reported data.[4,5]

Garden *et al.*[4] have reported the condensation of 4,6-dibromoisatin (**11**) with acetone using a catalytic amount of Et_2NH to give (±)-convolutamydine A (**1**) in 77% yield. In the present work similar condensation of 4,6-dibromoisatin and acetone in the presence of either a catalytic amount of 15% ethanolic KOH or triethylbenzylammonium hydroxide afforded (±)-**1** in 88 and 96% yield respectively.

Experimental

IR spectra were recorded in chloroform on a Perkin Elmer 137-E spectrometer. The ^{1}H NMR spectra were recorded on a Bruker 200 MHz instrument and the chemical shifts were reported with Me_4Si as an internal standard. The mass spectra were recorded on an automatic Finnigan-MAT 1020 C mass spectrometer using an ionisation energy of 70 eV.

5-*Nitroisatin* **6**.—Isatin (6.00 g, 40.8 mmol) was added in portion wise to precooled (−5 °C) concentrated sulfuric acid (12 ml) with stirring in 15 min. The mixture was then stirred for 30 min more and then KNO_3 (4.10 g, 41 mmol) was added in portions. During this period, the mixture turned to brown and was stirred at 0 °C for 1 hr. To this mixture pieces of ice were added at 0 °C and the resultant yellow solid was filtered, washed several times with cold water and then air dried to give 5-nitroisatin **6**. Yield 5.5 g, 70%, mp 253 °C (lit.[6] mp 252 °C).

5-*Nitroisatin Ketal* **7**.—A mixture of 5-nitroisatin **6** (3.00 g, 15.6 mmol), 2,2′-dimethylpropane-1,3-diol (1.62 g, 15.6 mmol) and a catalytic amount of *p*-TSA was suspended in cyclohexane (20 ml) and refluxed with azeotropic removal of water using Dean–Stark apparatus. The reaction mixture was cooled to room temperature and the light greenish solid that separated was filtered, washed with dilute aqueous sodium bicarbonate, water and then air dried to yield 5-nitroisatin ketal (**7**). Yield 4.72 g, 82%, mp 198 °C. IR (Nujol) 3600, 1720, 1600 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.90 (s, 3H), 1.45 (s, 3H), 3.28 (d, J = 12.9 Hz, 2H), 4.55 (d, J = 12.9 Hz, 2H), 7.05–7.70 (m, 1H), 8.10–8.15 (m, 1H), 8.30–8.35 (m, 1H), 9.5 (bs, 1H). MS *m/z* (relative intensity) 278 M^+ (5), 250 (100), 164 (90), 90 (40).

5-*Aminoisatin Ketal* **8**.—The 5-nitroisatin ketal **7** (2.76 g, 9.9 mmol) in 20 ml of methanol was stirred with 10% Pd/C (100 mg) under a H_2 atmosphere overnight. The mixture was then filtered to remove the catalyst and the methanol was concentrated to give a solid residue which was purified by column chromatography over silica gel to give aminoisatin ketal (**8**). Yield 1.69 g, 69%, mp 135 °C. IR (Nujol) 3560, 1720, 1600 cm^{-1}. ^{1}H NMR (200 MHz, acetone-d_6) δ 0.90 (s, 3H), 1.44 (s, 3H), 3.29 (d, J = 12.9 Hz, 2H), 4.70 (d, J = 12.9 Hz, 2H), 6.50–6.55 (m, 2H); 6.80–6.85 (m, 1H), 8.5 (bs, 1H). MS *m/z* (relative intensity) 248 M^+ (45), 220 (100), 134 (60), 106 (43). Analysis: calc. C 62.9; H 6.4; N 11.29. Found. C 62.85; H 6.4; N 11.24%.

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4,6-*Dibromo*-5-*aminoisatin Ketal* **9**.—Aminoisatinketal **8** (0.580 g, 2.33 mmol) in rectified spirit (5 ml) was cooled to 0 °C, a solution of bromine in chloroform (1 ml Br_2 dissolved in 50 ml $CHCl_3$) (1 ml, 5.6 mmol) was added slowly and the reaction mixture was stirred for 3 h. The solvent was removed, the residue was washed with water, dried and the product was recrystallised from ethanol to give **9**. Yield 0.74 g, 78%, mp 240 °C. IR (Nujol) 3600, 1720, 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.45 (s, 3H), 3.45 (d, $J = 12.9$ Hz, 2H), 4.55 (d, $J = 12.9$ Hz, 2H), 6.95 (s, 1H), 8.25 (bs, 1H). MS: *m/z* (relative intensity) 406 (M + 2), 404 (M^+), 202 (20), 141 (15), 97 (10). Analysis: calc. C 38.42; H 3.448; N 6.89, Br 39.16; Found C 38.38; H 3.42; N 6.85; Br 39.10%.

4,6-*Dibromoisatin* **11**.—A mixture of ketal **9** (0.220 g, 0.54 mmol), and *tert*-butyl nitrite (1 ml) in DMF (5 ml) was stirred for 10 h at 60 °C. After the reaction was over (TLC) the mixture was diluted with ethyl acetate and the organic layer was washed several times with water then brine solution and concentrated to give the ketal **10** which was directly stirred with saturated oxalic acid solution at 60 °C overnight and cooled. The mixture was diluted with water and the solid separated was recrystallised from ethanol. Yield 0.040 g, 24%, mp 256 °C (lit.[4] mp 254 °C). ^1H NMR (200 MHz, $CDCl_3$) δ 7.05 (s, 1H), 7.30 (s, 1H), 10.05 (bs, 1H).

Convolutamydine A **1**.—*Method A:* 4,6-Dibromoisatin **11** (0.2 g, 0.65 mmol) in acetone (5 ml) was stirred with 1 drop (0.002 g) of 15% ethanolic KOH solution for 15 min. The acetone was evaporated from the reaction and a white solid after washing with water was recrystallised from hexane–ethyl acetate to afford pure **1** (0.20 g, 88%) which showed identical spectral and analytical properties to the literature values.[4] *Method B:* A solution of 3,5-dibromoisatin **11** (0.2 g, 0.65 mmol) in acetone (5 ml) was treated with a drop of benzyltrimethylammonium hydroxide (aqueous; 40%) at ambient temperature and stirred for 3 h. After the reaction was over, solvent was evaporated at reduced pressure, the residue was taken up in ethyl acetate, washed with water and concentrated to afford pure **1** (0.23 g, 96%) which showed identical spectral and analytical properties to the literature values.[4]

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