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A Modified Sandmeyer Methodology and the Synthesis of (±)-Convolutamydine A.

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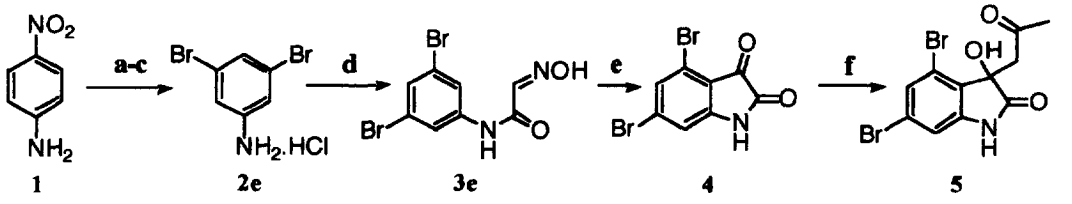
Abstract: (±)-Convolutamydine A (**5**) has been prepared by a concise synthesis from 3,5-dibromoaniline using a modified Sandmeyer methodology. The modified Sandmeyer methodology has also been found to be beneficial for the synthesis of other α-isonitrosoacetanilides. The 4,6-dibromohydroxyoxindole nucleus was further confirmed by comparison with the isomeric 5,7-dibromohydroxyoxindole.

Convolutamydine A (**5**), a metabolite isolated from the marine Bryozoan *Amathia convoluta*, presents an interesting 4,6-dibromohydroxyoxindole nucleus. This compound has been described to exhibit a potent activity in the differentiation of HL-60 human promyelocytic leukemia cells.[1,2] An obvious precursor to the synthesis of this compound, the 4,6-dibromoisatin (**4**), has been previously described although the global yield from 3,5-dibromoaniline was a disappointing 10%.[3] The low yield can be ascribed to inefficient formation of the intermediate α-isonitrosoacetanilide (**3e**, 11% yield) while the following cyclisation proceeded in excellent yield (88%).

3,5-Dibromoaniline was prepared as its hydrochloride salt (**2e**, Scheme 1) by initial bromination of *p*-nitroaniline (**1**) in glacial acetic acid[4] followed by reductive deamination using sodium nitrite in acidifed ethanol to form the 3,5-dibromonitrobenzene.[5] Raney nickel hydrogenation of 3,5-dibromonitrobenzene was found to proceed with difficulty using some published methods of preparation of the catalyst,[6] but when the nickel catalyst was prepared under more extreme conditions[7] 3,5-dibromoaniline was smoothly produced in excellent overall yield. The aniline was subsequently precipitated, and recrystallised, as its hydrochloride salt (**2e**).



1 **2e** **3e** **4** **5**

Scheme 1. **a** Acetic acid, Br_2, 98%; **b** ethanol, $NaNO_2$, H_2SO_4, 97%; **c** (i) ethanol, Raney Ni, H_2, (ii) aqueous ethanolic HCl, 86-96%; **d** Chloral, $(H_2NOH)_2H_2SO_4$, Na_2SO_4, H_2O/ethanol (3:1 v/v), 82-88%; **e** 86% H_2SO_4, 80-86%; **f** acetone, Et_2NH, 77%.

Initial investigations into the synthesis of isonitrosoacetanilides (**3a-e**) readily revealed that the conditions commonly employed in the Sandmeyer methodology, high reaction temperatures and short reaction times, were not the best conditions particularly when the appropriate aniline is insoluble in the hot reaction matrix and contains electron withdrawing groups. Typical reaction conditions[3,8] utilising a variety of anilines (**2a-e**) lead to the formation of black resinous materials from which the appropriate isonitrosoacetanilides (**3a-e**) could only be purified in low yields. It was found that reducing the reaction temperature (60-80°C) and prolonging the reaction time (2-6 hours) had a very beneficial effect upon the yields and purity of the intermediate isonitrosoacetanilides **3a** and **3b** (Table 1). However, these minor modifications were not sufficient in themselves to allow successful synthesis of the 3,5-dibromoisonitrosoacetanilide (**3e**). On attempted synthesis of **3e** it was observed that the heating of the hydrochloride salt, **2e,** in the reaction matrix resulted in the formation of a dark viscous material (around 60°C) that could not be mixed with the other soluble reagents. In order to overcome this problem ethanol[9] was added resulting in the partial precipitation of the dissolved Na_2SO_4 but also in the formation of two liquid phases that with vigorous agitation dispersed the minor darkly coloured ethanolic amine solution. Continued heating of the reaction mixture (≈ 80°C) whilst allowing the ethanol to evaporate resulted in the formation of an off white crystalline product, **3e** (mp. 196-200°C, lit.[3] 197-200°C). The addition of smaller volumes of ethanol during the reaction was neccessary in order to avoid formation of an insoluble viscous material.[10] The isonitrosoacetanilide **3e**, so formed, was removed by filtration, washed with water and dried in a dessicator over silica gel (82-88% yield).

The ethanolic modification resulted in more controllable conditions for the formation of the intermediate isonitrosoacetanilides **3c-e**, whilst the formation of **3a** and **3b** merely required the use of lower reaction temperatures and longer reaction times. The reaction times are considerably longer in comparison to standard conditions but this is offset by the improvement in yield, the reduction of waste and the simplicity of isolation.

Table 1. Conditions for the Synthesis of α-Isonitrosoacetanilides (**3a-e**).

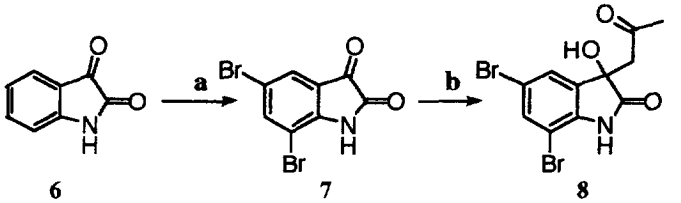
	Aniline[a] **2**	Time (hours)	Temperature (°C)	yield (%) **3**	lit. yield (%) (reference)
a	*p*-CH_3	2	60-80	96-99	83-86[(8b)]
b	*p*-Cl	3	70-80	96-99	92[e(8c)]
c	*o*-Cl[b]	6	60-80	85-89	47[(8d)]
d	*o*-CF_3[b]	6	60-80	93-97[d]	64[(8e)]
e	3,5-dibromo[b,c]	3.5	70-80	82-88	11[(3)]

a Reagent stoichiometry: aniline (50 mmoles); chloral (60 mmoles); $(H_2NOH)H_2SO_4$ (75 mmoles); Na_2SO_4 (425 mmoles); H_2O (150 ml); conc. HCl (1.5 ml); **b** Use of an additional 1/3 volume of ethanol; **c** The hydrochloride salt was used; **d** Obtained as an oil after extraction from the reaction medium which slowly crystallised on storage over silica gel; **e** The yield quoted is for *p*-fluoro-isonitrosoacetanilide. Although *p*-chloro-isonitrosoacetanilide has been reported in chemical abstracts on a number of occasions no yield data was available.

Subsequent cyclisation of **3e** in 86% sulphuric acid (60-110°C) readily yielded 4,6-dibromoisatin (**4**) on quenching on ice. The filtered product was recrystallised from aqueous ethanol (mp. 259-260°C, lit.[3] 254-6°C). Dissolution of **4** in acetone with a catalytic quantity of diethylamine resulted in the formation of (±)-**5** (mp. 198-202°C with decomposition, lit.[1] 190-5°C).[11,12] The NMR spectra of synthetic **5**, allowing for the

differences in solvent medium, are in 98-99% agreement with the chemical shift data for the natural product.[1,2,13]

In addition, 5,7-dibromoisatin (**7**), prepared by the bromination of isatin (**6**) in ethanol,[14] readily undergoes an aldol type reaction with acetone under analogus conditions to yield the 5,7-dibromo-3-hydroxy-3-(2-oxopropyl)-2-oxindole (**8**, Scheme 2).[11,15] Comparison of the NMR data for the 4,6- and 5,7-dibromoisomers (**5** and **8** respectively) further substantiates the 4,6 disubstitution pattern of convolutamydine A.[13,15]



6 7 8

Scheme 2. a (i) ethanol, Br_2, (ii) H_2O, 94%; **b** acetone, Et_2NH, 83%.

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7. Preparation of Raney Ni for reduction of 3,5-dibromonitrobenzene (50g). $NiAl_2$ (6.0g) was added in small portions to aqueous NaOH (40 ml H_2O, 10g NaOH, 100°C) over a period of 15 minutes. Digestion was continued for a further 2.5 hours (110°C). The catalyst was filtered by suction, washed with water (80 ml in small portions) then ethanol (40 ml) and transfered as an ethanolic suspension to the hydrogenation bottle. At no time was the catalyst allowed to become dry.
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9. Trichloroisonitrosoacetanilides have been prepared by dissolving the appropriate trichloroanilines in a minimum quantity of hot ethanol before addition to the hot reaction mixture and boiling of the resultant reaction mixture for 15 minutes.[8d]
10. At the same time, however, it is necessary that the ethanol be allowed to evaporate from the reaction mixture in order that the isonitrosoacetanilide may precipitate. A procedure has been developed where the ethanol is not allowed to evaporate from the reaction mixture (by use of a condensor) until TLC indicates that isonitrosoacetanilide formation is complete, the reaction temperature is maintained at 80°C through all processes.
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12. In a model study of the reaction of isatin with acetone, at fixed concentration, using varying quantities of S(-)-proline, no asymmetric induction was observed in the final product as determined by measurement of optical rotation at various concentrations after isolation of the product.
13. (±) 4,6-dibromo-3-(2-oxopropyl)-3-hydroxy-2-oxindole, **5**. The title compound undergoes a retro-aldol reaction on GC-MS analysis revealing only 4,6-dibromoisatin as characterised by comparison of retention time and mass spectra. ^{1}H NMR ($CDCl_3$/DMSO-d_6): 2.07[s, CH_3], 3.21 and 3.82[d, geminal CH's, J 17.5], 6.96[d, CH, J 1.6], 7.17[d, CH, J 1.6], 10.51[s, NH]; ^{13}C NMR (PENDANT): 29.7[C-10], 48.1[C-8], 73.6[C-3], 111.9[C-7], 118.6[C-6], 122.4[C-4], 126.8[C-5], 128.0[C-3a], 146.0[C-7a], 177.3[C-2], 204.4[C-9]; Chem. Anal. Calc. for $C_{11}H_9Br_2NO_3$: C, 36.40; H, 2.50; N, 3.86; Found: C, 36.27; H, 2.43; N, 3.96.
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15. (±) 5,7-dibromo-3-(2-oxopropyl)-3-hydroxy-2-oxindole, **8** (mp. 173-5°C). ^{1}H NMR ($CDCl_3$/DMSO-d_6): 2.17[s, CH_3], 3.19 and 3.29[d, geminal CH's, J 17.3], 7.34[d, CH, J 1.7], 7.48[d, CH, J 1.7], 10.10[s, NH]; ^{13}C NMR (PENDANT): 30.2[C-10], 50.1[C-8], 73.7[C-3], 102.9[C-7], 114.0[C-5], 125.4[C-6], 133.6[C-4], 134.0[C-3a], 140.8[C-7a], 177.3[C-2], 204.6[C-9]; ^{1}H NMR (acetone-d_6): 2.93[s, CH_3], 3.40 and 3.64[d, geminal CH's, J 17.5], 5.44[s, OH], 7.63[d, CH, J 1.8], 7.72[d, CH, J 1.8], 9.7[sbr, NH]; ^{13}C NMR: 51.0[C-8], 75.2[C-3], 103.7[C-7], 115.0[C-5], 127.2[C-6], 135.0[C-4], 136.1[C-3a], 141.2[C-7a], 177.8[C-2], C-10 and C-9 are obscured by the solvent; Mass (70eV): 361[M+, 6%, $C_{11}H_9{}^{79}Br_2NO_3$], 343[13%, $C_{11}H_7{}^{79}Br_2NO_2$], 328[13%, $C_{10}H_4{}^{79}Br_2NO_2$], 277[100%, $C_7H_3{}^{79,81}Br_2NO$], 275[50%, $C_7H_3{}^{79}Br_2NO$], 247[12%, $C_6H_3{}^{79}Br_2N$], 168[21%, $C_6H_3{}^{79}BrN$], 141[12%, $C_4{}^{79}BrN$].

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