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Synthesis of the calothrixins, pentacyclic indolo[3,2-*j*]-phenanthridine alkaloids, using a biomimetic approach

Christopher S. P. McErlean,[a] Jonathan Sperry,[b] Alexander J. Blake[a] and Christopher J. Moody[a,*]

[a]*School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK*
[b]*Department of Chemistry, University of Exeter, Exeter EX4 4QD, UK*

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Abstract—Oxidation of the indolo[2,3-*a*]carbazole **16**, readily obtained in six steps from indigo, followed by deprotection results in formation of the indolo[3,2-*j*]phenanthridine quinone alkaloid calothrixin B **2**, demonstrating the viability of the proposed biosynthetic route to this unique ring system.

1. Introduction

Calothrixin A **1** and its *N*-deoxy derivative calothrixin B **2** (Fig. 1) are pentacyclic heterocyclic quinones isolated by Rickards et al. in 1999 from a *Calothrix* cyanobacterium.[1] These alkaloids exhibit remarkable biological activity, most notably their growth inhibitory effects at nanomolar concentrations on a chloroquine-resistant strain of the malarial parasite *Plasmodium falciparum*, as well as activity against human cancer cells, and inhibition of RNA polymerase activity.[1–5] In addition, calothrixin A appears to induce intracellular formation of reactive oxygen species.[6]

The pentacyclic indolo[3,2-*j*]phenanthridine ring system of the calothrixins is unique amongst natural products and was proposed to arise in nature from the more common tryptophan-derived indolo[2,3-*a*]carbazole framework.[7] The fascinating proposal by Rickards et al. for the biogenesis of the calothrixins is outlined in Scheme 1,[1] and involves oxidation of the putative indolocarbazole intermediate **3**.

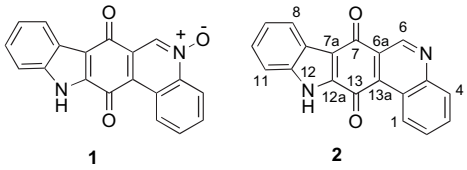
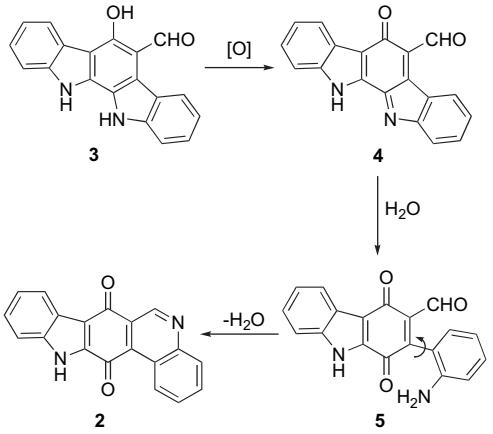


Figure 1. Structures of the alkaloid calothrixins A and B, showing numbering system for the indolo[3,2-*j*]phenanthridine ring system.



Scheme 1. Proposed biogenesis of the indolo[3,2-*j*]phenanthridine ring by oxidation of an indolo[2,3-*a*]carbazole.[1]

The resulting quinoneimine **4** could undergo hydrolysis to the anilinoquinone **5**, which after rotation around the biaryl bond and condensation of the amino group with the aldehyde would give calothrixin B (Scheme 1).

Due to their potent biological activity and unique ring system, these alkaloids have attracted much attention from synthetic chemists. The first total synthesis was reported by Kelly and co-workers, and involved coupling of indole and isoquinoline fragments by addition of a 3-lithioisoquinline-4-carboxamide to an indole-3-carbaldehyde (formation of C6a–C7 bond), followed by lithiation at indole C-2 and addition to the C-4 isoquinoline carbonyl (formation of C12a–C13 bond).[8] Subsequently Chai and co-workers reported a route involving Friedel–Crafts acylation of indole

* Corresponding author. Fax: +44 115 951 3564; e-mail: c.j.moody@nottingham.ac.uk

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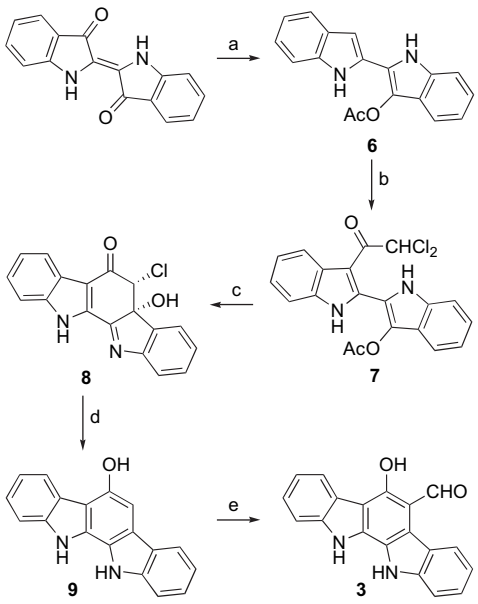
at C-3 with a 4-alkoxycarbonylisoquinoline-3-carboxylic acid derivative (formation of C7–C7a bond), again followed by formation of the C12a–C13 bond by lithiation at indole C-2 and addition to the C-4 isoquinoline ester group.[4,9,10] A hetero-Diels–Alder reaction of a 2-azadiene with a carbazolequinone was employed by Guingant and co-workers (simultaneous formation of C6–C6a and C13a–C13b bonds),[11] whilst the Hibino group used a 6π-electrocyclic reaction of a 3-allenylindole (formation of C6a–C13a bond),[12] and Bennasar et al. effected ring closure of an acyl radical at the indole 2-position onto isoquinoline C-4 to form the C13–C13a bond.[13]

In view of our interest in quinone natural products[14–19] and other heterocyclic quinones with anticancer properties,[20–25] we were intrigued by the Rickards proposal for the biosynthesis of the calothrixin skeleton, and initiated a programme designed to test that hypothesis.[1] Our results are described in detail herein and follow a preliminary report by Hibino and co-workers on a similar biogenetically patterned synthesis of calothrixin B[26] and our own communication.[27]



Scheme 2. Reagents and conditions: (a) Sn, Ac_2O, AcOH, 64–66 °C (85%); (b) $Cl_2CHCOCl$, EtOAc, reflux (79%); (c) aq NH_3, DMF, MeOH (75%); (d) Zn, NH_4Cl, THF, MeOH (55%); (e) $POCl_3$, DMF (82%).

2. Results and discussion

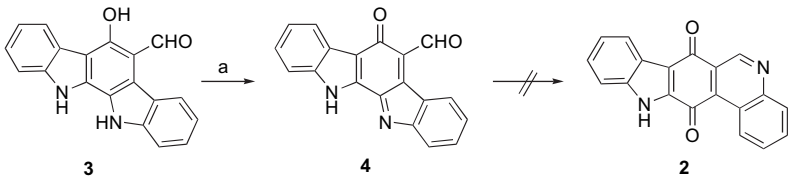
The wide occurrence and biological activity of indolo[2,3-*a*]carbazoles[7] have ensured that there are a number of methods available for the synthesis of this ring system.[28–33] Our route to the key indolo[2,3-*a*]carbazole carboxaldehyde **3** is based on the synthesis of 5-cyano-6-methoxy-12-methylindolo[2,3-*a*]carbazole, a cytotoxic natural product isolated from the blue-green alga *Nostoc sphaericum*,[34] developed by Somei and co-workers.[35–37] Thus a mixture of indigo and tin powder was heated under carefully controlled conditions (64–66 °C) in a solution of acetic anhydride in acetic acid to give the mono-acetoxylated bis-indole **6** that was then acylated with dichloroacetyl chloride. Treatment of the resulting bis-indole **7** with aqueous ammonia effected ring closure and gave the *cis*-chlorohydrin **8** whose structure and stereochemistry were confirmed by X-ray crystallographic analysis.[27] Reduction of the chlorohydrin **8** gave the known 5-hydroxyindolo[2,3-*a*]carbazole **9** and subsequent Vilsmeier formylation delivered the desired indolocarbazole-5-carboxaldehyde **3** (Scheme 2). The ^{1}H NMR spectrum of the phenolic aldehyde **3** showed four low field singlets—a sharp signal at δ 13.86, indicative of an intramolecularly hydrogen-bonded OH group, two NH signals at δ 12.23 and δ 11.63 and the aldehyde proton at δ 10.92.

In an attempt to effect the proposed biomimetic transformation, the indolocarbazole **3** was subjected to a plethora of oxidative conditions, including reagents such as chloranil, DDQ, $NaIO_4$, CAN, $Pb(OAc)_4$, MnO_2, AgO, H_2O_2, Fremy's salt and hypervalent iodine reagents. In some cases, an unstable intermediate was formed, but it could never be characterized. However, treatment of the indolocarbazole **3** with *tert*-butyl hypochlorite gave a bright yellow compound that was characterized as the quinoneimine **4** (Scheme 3), as evidenced by loss of two of the low field singlets in the ^{1}H NMR spectrum, and its reconversion into **3** upon reduction with sodium dithionite. Disappointingly, the quinoneimine **4** resisted all attempts to hydrolyze it to the anilinoquinone **5** and hence calothrixin B **2**. Under mild conditions, the quinoneimine **4** remained unchanged, but was degraded under more forcing conditions.

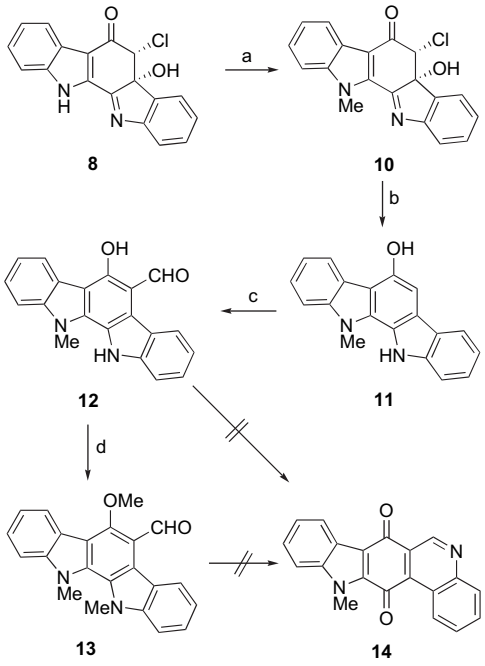
The universal failure of these conditions to produce the calothrixin framework led us to consider whether the second *NH* on the indolo[2,3-*a*]carbazole skeleton may be adversely affecting the oxidation. To test whether a mono-*N*-protected indolocarbazole would undergo the desired biomimetic oxidation-rearrangement, compound **12** was synthesized. Thus, the chlorohydrin **8** was methylated by the action of dimethyl sulfate to give **10**. Reduction and subsequent Vilsmeier formylation delivered the mono-protected indolocarbazole **12** (Scheme 4) whose structure was supported by ^{1}H NMR spectroscopy—three low field resonances at δ 13.83 (intramolecularly H-bonded OH), 11.67 (NH), 10.93 (CHO)—and confirmed by X-ray crystallography.[27] Disappointingly, subjecting this compound to a similar battery of oxidative reagents did not result in the isolation of the desired *N*-methylcalothrixin B **14**.

The failure to convert the hydroxyindolocarbazoles **3** and **12** into the indolo[3,2-*j*]phenanthridine system prompted the speculation that the strongly hydrogen-bonded OH group was interfering with the transformation. We therefore investigated the oxidation of further derivatives of the 6-hydroxyindolocarbazole-5-carboxaldehyde. Initially, the trimethyl compound **13**, prepared in modest yield by alkylation of indolocarbazole **12** (Scheme 4), was investigated. The compound, whose structure was unambiguously confirmed by X-ray crystallography (Fig. 2),[38] was subjected to oxidation with cerium(IV) ammonium nitrate (CAN), a reagent well known for its ability to effect oxidative demethylation of electron rich aromatic rings,[39] but with no effect.

Although the trimethyl compound **13** did not undergo oxidation when treated with CAN, the use of an alternative



Scheme 3. Reagents and conditions: (a) *t*-BuOCl, THF (63%).



Scheme 4. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone (100%); (b) Zn, NH_4Cl, THF, MeOH (61%); (c) $POCl_3$, DMF (82%); (d) LDA, THF, 0 °C, MeI (52%).

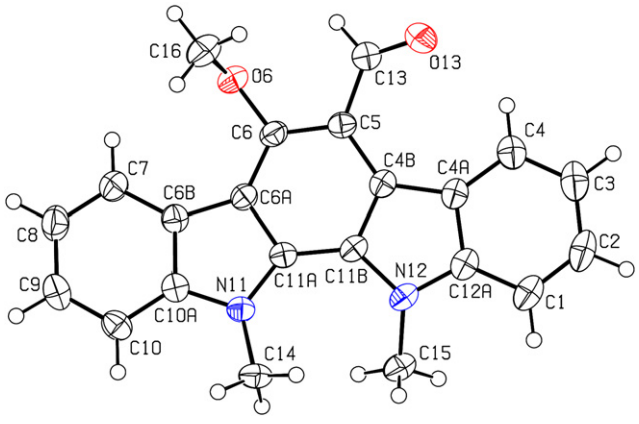
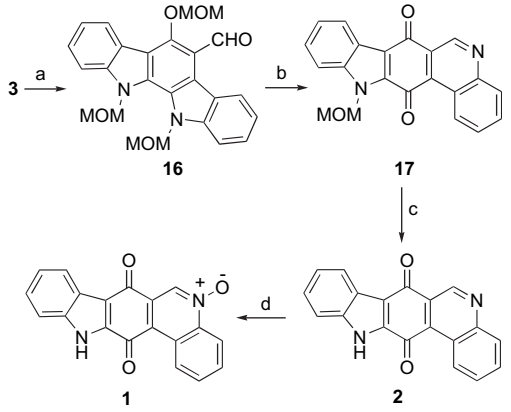


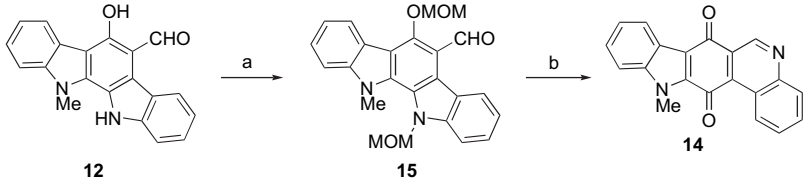
Figure 2. X-ray structure of indolecarbazole-5-carboxaldehyde **13**.

alkyl group, the methoxymethyl (MOM) group, proved successful. Thus, the bis-MOM compound **15** gratifyingly underwent oxidation and in situ rearrangement to give *N*-methyl-calothrixin B **14** in 52% yield (Scheme 5), thereby demonstrating that the biosynthetic transformation proposed by Rickards could be reproduced under laboratory conditions.

With this new found knowledge about the need to alkylate the phenolic *OH* and indolic *NH* groups in the putative biosynthetic precursor indolocarbazole-5-carboxaldehyde **3** for a successful oxidative transformation of the ring system into the indolo[3,2-*j*]phenanthridine-quinone, the synthesis of calothrixin B **2** could be accomplished. As in the first synthesis of calothrixin B by Kelly et al.,[8] we elected to use the readily removable methoxymethyl group as the indole NH protecting group. Thus, indolocarbazole **3** was treated with excess chloromethyl methyl ether to give the tris-MOM-protected compound **16**, an intermediate also employed in Hibino's biomimetic approach.[26] Oxidation was effected by the action of cerium(IV) ammonium nitrate, and subsequent in situ hydrolysis, bond rotation and condensation delivered *N*-MOM-calothrixin B **17** in moderate yield. Deprotection under acidic conditions gave calothrixin B **2** (Scheme 6), whose NMR spectroscopic properties were identical to those



Scheme 6. Reagents and conditions: (a) $MeOCH_2Cl$, NaH, DMF (44%); (b) CAN, aq MeCN (31%); (c) concd HCl, THF, 55 °C (100%); (d) $MeCO_3H$, CH_2Cl_2 (52%).



Scheme 5. Reagents and conditions: (a) LHMDS, THF, 0 °C, $MeOCH_2Cl$ (60%); (b) CAN, aq MeCN (52%).

of an authentic sample of the natural product. Finally, oxidation of calothrixin B with peroxyacetic acid gave the corresponding *N*-oxide, calothrixin A **1** (Scheme 6).

In conclusion, we have investigated the proposed biomimetic oxidative transformation of the indolo[2,3-*a*]carbazole framework into the indolo[3,2-*j*]phenanthridine quinone ring system. Whilst the unprotected compounds failed to undergo the desired reaction cascade, a judicious use of protecting groups facilitated oxidation and subsequent rearrangement. This methodology was then utilized to complete a biomimetic synthesis of calothrixin B, and hence calothrixin A.

3. Experimental section

3.1. General

Commercially available reagents and solvents were used throughout without further purification. Indium powder ~100 mesh was purchased from Aldrich. 'Light petroleum' refers to the fraction that boils between 40 °C and 60 °C. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Developed plates were visualized under ultraviolet light (254 nm) and/or potassium permanganate, ethanolic anisaldehyde, or ninhydrin dip. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Fully characterized compounds were chromatographically homogeneous.

IR spectra were recorded on Nicolet Magna 550 or Perkin Elmer 1600 FTIR spectrometer with internal calibration. Spectra were recorded as potassium bromide discs, as solutions in $CHCl_3$, or as films between sodium chloride plates. NMR spectra were recorded on Bruker AM 300, AV400, DRX 400 or DRX500 spectrometer at the frequencies stated. Chemical shifts are recorded in parts per million and *J* values in hertz. Chemical shift values are referenced against deuterated chloroform at 7.27 ppm, and are accurate to ±0.01 ppm (δ_H) and ±0.10 ppm (δ_C). In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT; all others are C. Mass spectra (CI and EI) were obtained from EPSRC National Mass Spectrometry Service Centre, Swansea or on Agilent 6890 series GC, Micromass GCT or Bruker MicroTof spectrometer.

3.1.1. 3-Acetoxy-2-2′-bis-indole 6. Tin powder (4.77 g, 40.2 mmol) was added to a solution of indigo (1.05 g, 4.02 mmol) in acetic acid (20 ml) and acetic anhydride (20 ml), and the reaction mixture was stirred vigorously at 64–66 °C for 3 h. After being left to reach room temperature for 12 h, the reaction mixture was filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to give the *title compound* as a pale yellow solid (0.99 g, 85%), mp 183–184 °C (from ethanol) (lit.,[40] mp 180–183 °C); ν_{max} (KBr)/cm^{-1} 3411, 3380, 1731, 1337, 1224, 742, 732; δ_H (400 MHz; MeOD) 7.55 (1H, d, *J* 8.0, ArH), 7.44 (1H, d, *J* 8.2, ArH), 7.37 (1H, d, *J* 8.2, ArH), 7.32 (1H, d, *J* 8.0, ArH), 7.14 (2H, m, ArH), 7.01 (2H, m, ArH), 6.78 (1H, s, ArH), 2.49 (3H, s, Me), 2×NH not observed; δ_C (75 MHz; $CDCl_3$) 169.8, 136.8, 134.1, 129.0, 128.9, 127.2, 123.5 (CH), 122.9 (CH), 122.0 (CH), 121.0 (CH), 120.8 (CH), 120.7, 120.3, 118.1 (CH), 111.8 (CH), 111.3 (CH), 100.9 (CH), 21.4 (Me).

3.1.2. 3-Acetoxy-3′-dichloroacetyl-2-2′-bis-indole 7. Dichloroacetyl chloride (1.64 ml, 2.51 g, 17 mmol) was added dropwise to a solution of **6** (500 mg, 1.7 mmol) in ethyl acetate (60 ml) and the mixture was heated under reflux for 3 h with stirring. After cooling to room temperature, water (60 ml) was cautiously added, and the organic layer removed. The aqueous layer was extracted with ethyl acetate (2×60 ml) and the combined organic layers were combined, washed with brine (60 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting residue was suspended in ether (150 ml), filtered, washed with cold ether (150 ml) and dried to give the *title compound* as yellow needles (550 mg, 79%), mp 233–236 °C (from ether) (lit.,[36] mp 227–229 °C (decomp.); δ_H (400 MHz; DMSO-d_6) 12.65 (1H, br s, NH), 11.90 (1H, br s, NH), 8.10 (1H, d, *J* 7.5, ArH), 7.53–7.47 (3H, m, ArH), 7.35–7.27 (3H, m, ArH), 7.14 (1H, t, *J* 7.5, ArH), 6.69 (1H, s, $CHCl_2$), 2.22 (3H, s, Me).

3.1.3. (4a*R,5*R**)-5-Chloro-4a-hydroxy-6-oxo-4a,5,6,11-tetrahydroindolo[2,3-*a*]carbazole 8.** Ammonia (28% w/w aqueous solution; 2 ml) was added dropwise to a solution of **7** (2.435 g, 6.07 mmol) in methanol (20 ml) and DMF (20 ml). The solution was stirred at room temperature for 1 h. Water (40 ml) was added and the whole extracted with ethyl acetate (3×40 ml). The combined organic extracts were washed with water (120 ml) and brine (120 ml) then dried ($MgSO_4$), filtered and the solvent removed in vacuo. Purification by flash chromatography on silica gel (ethyl acetate/hexanes) gave the *title compound* as a yellow solid (1.18 g, 75%), mp 229–231 °C (from ethyl acetate/hexanes, 1:1) (lit.,[36] mp 236–238 °C (decomp.); δ_H (400 MHz; DMSO-d_6) 13.11 (1H, br s, NH), 8.14 (1H, d, *J* 8.1, ArH), 7.80 (1H, d, *J* 7.2, ArH), 7.71 (1H, d, *J* 7.2, ArH), 7.59 (1H, d, *J* 8.1, ArH), 7.52 (1H, t, *J* 7.6, ArH), 7.42 (1H, t, *J* 7.2, ArH), 7.36 (1H, t, *J* 7.4, ArH), 7.33 (1H, t, *J* 7.4, ArH), 6.78 (1H, s, OH), 5.38 (1H, s, CH).

3.1.4. 5-Hydroxyindolo[2,3-*a*]carbazole 9. Zinc powder (558 mg, 7.75 mmol) was added to a solution of **8** (500 mg, 1.55 mmol) and saturated ammonium chloride solution (15 ml) in methanol (35 ml) and the reaction mixture was stirred at room temperature for 1 h. The solvent was concentrated in vacuo and the residue partitioned between ethyl acetate (50 ml) and water (50 ml). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (50 ml). The combined organic extracts were washed with brine (50 ml) and the solvent removed in vacuo. Immediate purification by flash chromatography on silica gel (ethyl acetate/hexanes, 1:1) gave the *title compound* as a colourless solid (232 mg, 55%), for use directly in the next step, mp >275 °C (lit.,[35] mp >300 °C); ν_{max} (KBr)/cm^{-1} 3528 (NH), 3508 (NH), 3416, 3406, 3048, 2914, 2843, 1659, 1440, 1329, 1209, 1081, 738; δ_H (400 MHz; DMSO-d_6) 11.02 (1H, br s, NH), 10.67 (1H, br s, NH), 9.63 (1H, br s, OH), 8.30 (1H, d, *J* 7.8, ArH), 7.99 (1H, d, *J* 7.8, ArH), 7.62 (2H, m, ArH), 7.36–7.30 (2H, m, ArH), 7.21–7.13 (3H, m, ArH); δ_C (100 MHz; DMSO-d_6) 147.9, 139.8, 138.8, 126.8, 124.5 (CH), 124.0 (CH), 123.9, 123.8, 122.3

(CH), 120.7, 120.2, 119.9 (CH), 119.2 (CH), 118.6 (CH), 111.9 (CH), 111.3 (CH), 111.1, 94.9 (CH).

3.1.5. 6-Hydroxyindolo[2,3-*a*]carbazole-5-carbaldehyde 3. Phosphorus oxychloride (90 μl, 0.9 mmol) was added dropwise to DMF (400 μl) at 0 °C with stirring. The reaction mixture was warmed to room temperature, stirred for 30 min and cooled back to 0 °C. A cooled solution of **9** (100 mg, 0.38 mmol) in DMF (4 ml) was added dropwise over 5 min with stirring. The reaction mixture was stirred at 0 °C for 30 min and poured onto a stirred solution of brine and crushed ice (~20 ml). After 30 min, the whole was extracted with ethyl acetate (4×10 ml) and the combined organic extracts were washed with brine (25 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:1) gave the *title compound* as an orange solid (93 mg, 82%), mp >275 °C (from THF/light petroleum); found: C, 76.0; H, 4.0; N, 9.3. $C_{19}H_{12}N_2O_2$ requires C, 75.5; H, 4.2; N, 9.2%; found: MH^+, 301.0990. $C_{19}H_{12}N_2O_2$+H requires 301.0970; λ_{max} (MeCN)/nm 400 (log ε 3.92), 398 (3.98), 366 (4.05); ν_{max} (KBr)/cm^{-1} 3421, 2914, 2847, 1649, 1608, 1552, 1455, 1373, 1255, 1122, 1091, 1014, 789, 737, 687; δ_H (400 MHz; DMSO-d_6) 13.86 (1H, s, OH), 12.23 (1H, s, NH), 11.63 (1H, s, NH), 10.92 (1H, s, CHO), 8.30 (1H, d, *J* 8.1, ArH), 8.24 (1H, d, *J* 8.1, ArH), 7.71–7.68 (2H, m, ArH), 7.45–7.38 (2H, m, ArH), 7.30 (1H, t, *J* 7.3, ArH), 7.18 (1H, t, *J* 7.3, ArH); δ_C (100 MHz; DMSO-d_6) 192.9 (CH), 158.7, 140.0, 139.3, 133.4, 125.53 (CH), 125.51 (CH), 123.6, 123.5 (CH), 122.32, 122.27 (CH), 121.5 (CH), 120.6, 120.2 (CH), 118.3, 113.0 (CH), 112.6 (CH), 108.7, 108.4; *m/z* (CI) 301 (MH^+, 100), 300 (M^+, 26), 273 (56), 272 (21).

3.1.6. 5-Oxo-12-iminoindolo[2,3-*a*]carbazole-6-carbaldehyde 4. To a solution of **3** (30 mg, 0.1 mmol) in THF (0.5 ml) was added a solution of *tert*-butyl hypochlorite in dichloromethane (0.5 ml) and the reaction mixture was stirred with exclusion of light at room temperature for 3 h. The reaction mixture was concentrated in vacuo and the crude product purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:1) to give the *title compound* as a yellow solid (19 mg, 63%), mp 215 °C (decomp.) (from ether); found: M^+, 298.0739. $C_{19}H_{10}N_2O_2$ requires 298.0742; ν_{max} (KBr)/cm^{-1} 3436, 3324, 3240, 3067, 2924, 2854, 1742, 1723, 1669, 1649, 1625, 1587, 1503, 1477, 1450, 1418, 1393, 1334, 1322, 1288, 1251, 1148, 1134, 1109, 762, 748; δ_H (300 MHz; $CDCl_3$) 10.75 (1H, br s, NH), 10.44 (1H, s, CHO), 8.33 (1H, d, *J* 7.0, ArH), 7.83–7.76 (2H, m, ArH), 7.68–7.43 (5H, m, ArH); δ_C (75 MHz; $CDCl_3$) 190.2 (CH), 184.9, 164.9, 154.4, 139.2, 135.4, 134.3, 132.6, 132.4 (CH), 129.2 (CH), 128.1 (CH), 126.9 (CH), 125.8, 125.6, 125.0 (CH), 123.2 (CH), 122.7 (CH), 114.8, 113.2 (CH); *m/z* (EI) 298 (M^+, 24%), 276 (19), 270 (100), 242 (39), 241 (70), 214 (20).

3.1.7. (4a*R,5*R**)-5-Chloro-4a-hydroxy-11-methyl-6-oxo-4a,5,6,11-tetrahydroindolo[2,3-*a*]carbazole 10.** Dimethyl sulfate (18 μl, 0.28 mmol) was added to a stirred solution of **8** (50 mg, 0.16 mmol) and potassium carbonate (45 mg, 0.33 mmol) in acetone (2 ml). The reaction mixture was stirred at room temperature for 2 h. The resulting solid was filtered and taken up in ethyl acetate (10 ml), washed with water (2×10 ml), dried ($MgSO_4$) and concentrated in vacuo to give the *title compound* as a yellow solid (54 mg, 100%), mp 221–223 °C (from ethyl acetate/light petroleum) (lit.,[36] mp 223–225 °C (decomp.); δ_H (300 MHz; DMSO-d_6) 8.16 (1H, d, *J* 7.8, ArH), 7.91–7.87 (3H, m, ArH), 7.68–7.66 (2H, m, ArH), 7.51–7.38 (2H, m, ArH), 6.84 (1H, br s, OH), 5.33 (1H, s, CH), 4.24 (3H, s, Me).

3.1.8. 6-Hydroxy-11-methylindolo[2,3-*a*]carbazole 11. Zinc powder (70 mg, 0.98 mmol) was added to a stirred solution of **10** (65 mg, 0.2 mmol) and saturated ammonium chloride solution (2 ml) in THF (8 ml). The reaction mixture was stirred at room temperature for 30 min, filtered and partitioned between ethyl acetate (50 ml) and water (50 ml). The organic layer was removed, and the aqueous layer extracted with ethyl acetate (50 ml). The combined organic extracts were washed with brine (50 ml), concentrated in vacuo and immediately purified by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:1) to give the *title compound* as a colourless solid (35 mg, 61%), for use directly in the next step, mp >275 °C (from ethyl acetate/light petroleum); found: C, 80.0; H, 5.1; N, 9.7. $C_{19}H_{14}N_2O$ requires C, 79.7; H, 4.9; N, 9.8%; found M^+, 286.1117. $C_{19}H_{14}N_2O$ requires 286.1106; ν_{max} (KBr)/cm^{-1} 3382, 1694, 1641, 1476, 1423, 1384, 1362, 1327, 1259, 1224, 1182, 816, 740; δ_H (400 MHz; DMSO-d_6) 11.22 (1H, s, NH), 9.73 (1H, s, OH), 8.30 (1H, d, *J* 7.7, ArH), 8.00 (1H, t, *J* 7.7, ArH), 7.98–7.57 (2H, m, ArH), 7.40–7.31 (2H, m, ArH), 7.20–7.17 (2H, m, ArH), 7.13 (1H, t, *J* 7.2, ArH), 4.29 (3H, s, Me); δ_C (100 MHz; DMSO-d_6) 148.0, 140.5, 139.9, 128.5, 124.7 (CH), 124.0 (CH), 123.3, 123.2, 122.4 (CH), 121.9, 119.8, 119.2 (CH), 118.6 (CH), 111.8 (CH), 110.6, 109.0 (CH), 95.1 (CH), 32.0 (Me), 1×CH not observed; *m/z* (FI) 287 (MH^+, 31%), 286 (M^+, 100), 272 (11).

3.1.9. 6-Hydroxy-11-methylindolo[2,3-*a*]carbazole-5-carbaldehyde 12. Phosphorus oxychloride (45 μl, 0.45 mmol) was added dropwise to DMF (0.3 ml) at 0 °C with stirring. The reaction mixture was warmed to room temperature, stirred for 30 min, and cooled back to 0 °C. A cooled solution of **11** (30 mg, 0.11 mmol) in DMF (1 ml) was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 2 h, and poured onto a stirred solution of brine (30 ml) and crushed ice (~20 ml). The whole was extracted with ethyl acetate (3×10 ml) and the combined organic extracts washed with brine (25 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (ethyl acetate/light petroleum, 1:1) gave the *title compound* as an orange solid (27 mg, 82%), mp >275 °C (from THF/light petroleum); found: C, 76.2; H, 4.4; N, 8.9. $C_{20}H_{14}N_2O_2$ requires C, 76.4; H, 4.5; N, 8.9%; found: MH^+, 315.1147. $C_{20}H_{14}N_2O_2$+H requires 315.1133; λ_{max} (MeCN)/nm 412 (log ε 3.95), 396 (4.04), 368 (4.09); ν_{max} (KBr)/cm^{-1} 3436, 3305, 2929, 1609, 1509, 1490, 1471, 1419, 1397, 1322, 1288, 1261, 1236, 1196, 1161, 1128, 1055, 1016, 918, 851, 846, 770, 746, 736, 691, 646, 583, 558, 534, 426; δ_H (400 MHz; DMSO-d_6) 13.83 (1H, s, OH), 11.67 (1H, s, NH), 10.93 (1H, s, CHO), 8.31–8.27 (2H, m, ArH), 7.75–7.69 (2H, m, ArH), 7.51–7.47 (1H, m, ArH), 7.44–7.40 (1H, t, *J* 7.2, ArH), 7.31 (1H, t *J* 7.6, ArH), 7.17 (1H, t, *J* 8.0, ArH), 4.34 (3H, s, Me); δ_C (75 MHz; DMSO-d_6) 192.6 (CHO), 158.5, 140.8, 140.5, 140.5, 134.4, 125.5 (CH), 125.4 (CH), 123.4 (CH), 123.0,

122.3 (CH), 121.7 (CH), 121.6 (CH), 120.2, 120.1, 119.3 (CH), 112.9 (CH), 110.4, 108.3, 34.8 (Me); *m/z* (CI) 315 (MH^+, 100%), 314 (M^+, 65).

3.1.10. 6-Methoxy-11,12-dimethylindolo[2,3-*a*]carbazole-5-carbaldehyde 13. To a solution of diisopropylamine (58 μl, 0.41 mmol) in THF (1 ml) at 0 °C was added *n*-butyllithium (1.68 M in hexanes; 0.25 ml, 0.41 mmol) and the mixture was stirred at room temperature for 15 min. A solution of **12** (25 mg, 0.083 mmol) in THF (2 ml) was added and the mixture was stirred for 30 min before iodomethane (25 μl, 0.41 mmol) was added. The reaction mixture was allowed to stir for a further 1 h and then quenched by the careful addition of water (10 ml). The mixture was extracted with ethyl acetate (3×10 ml), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography (ethyl acetate/light petroleum, 1:4) to give the *title compound* (15 mg, 52%) as a yellow solid, mp 156–160 °C; found: MH^+, 343.1437. $C_{22}H_{18}N_2O_2$+H requires 343.1446; ν_{max} ($CHCl_3$)/cm^{-1} 2926, 1668, 1385, 1320, 1084; δ_H (500 MHz; $CDCl_3$) 10.9 (1H, s, CHO), 9.29 (1H, d, *J* 8.2 Hz, ArH), 8.35 (1H, d, *J* 7.8, ArH), 7.59–7.50 (4H, m, ArH), 7.44 (1H, dd, *J* 7.8, 7.8, ArH), 7.39 (1H, dd, *J* 8.0, 8.0, ArH), 4.22 (3H, s, NMe), 4.20 (3H, s, NMe), 4.1 (3H, s, OMe); δ_C (125 MHz; $CDCl_3$) 189.9 (CH), 158.2, 145.5, 143.6, 134.8, 127.5, 126.6 (CH), 126.3 (CH), 126.0 (CH), 124.7, 122.9, 122.6 (CH), 121.7 (CH), 121.6, 120.4 (CH), 117.7, 115.7, 110.3 (CH), 110.1 (CH), 64.2 (Me), 37.0 (Me), 36.4 (Me).

3.1.11. 6-(Methoxy)methoxy-12-methoxymethyl-11-methylindolo[2,3-*a*]carbazole-5-carbaldehyde 15. To a solution of **12** (110 mg, 0.35 mmol) in THF (10 ml) was added lithium bis(trimethylsilyl)amide (1 M in THF; 870 μl, 0.87 mmol) and the mixture was stirred for 30 min before chloromethyl methyl ether (66 μl, 0.87 mmol) was added. The reaction mixture was allowed to stir for a further 4 h and then quenched by the careful addition of saturated aqueous ammonium chloride (40 ml). The mixture was extracted with ethyl acetate (4×10 ml), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography (acetone/light petroleum, 3:17) to give the *title compound* (85 mg, 60%) as an orange solid, mp 108–110 °C; found: MH^+, 403.1670. $C_{24}H_{22}N_2O_4$+H requires 403.1658; ν_{max} ($CHCl_3$)/cm^{-1} 2928, 1672, 1382, 1345, 1323, 1085; δ_H (500 MHz; $CDCl_3$) 10.9 (1H, s, CHO), 9.20 (1H, d, *J* 8.2 Hz, ArH), 8.38 (1H, d, *J* 7.8, ArH), 7.63 (1H, d, *J* 8.1, ArH), 7.59–7.54 (3H, m, ArH), 7.42 (1H, dd, *J* 9.2, 7.9, ArH), 7.39 (1H, dd, *J* 7.2, 7.2, ArH), 5.62 (2H, s, NC*H*$_2$OMe), 5.43 (2H, s, NC*H*$_2$OMe), 4.24 (3H, s, NMe), 3.68 (3H, s, OCH$_2$O*Me*), 3.42 (3H, s, NCH$_2$O*Me*); δ_C (125 MHz; $CDCl_3$) 190.5 (CH), 154.7, 144.7, 143.6, 134.4, 127.0 (CH), 126.3 (CH), 126.2 (CH), 125.7, 125.2, 122.9, 122.2, 122.1 (CH), 121.7 (CH), 121.5 (CH), 118.7, 115.9, 110.9 (CH), 110.3 (CH), 101.6 (CH_2), 79.9 (CH_2), 58.6 (Me), 55.6 (Me), 34.4 (Me).

3.1.12. 12-Methylindolo[3,2-*j*]phenanthridine-7,13-dione (*N*-methyl-calothrixin B) 14. To a solution of compound **15** (7.0 mg, 0.017 mmol) in acetonitrile (1 ml) were added water (100 μl) and cerium(IV) ammonium nitrate (100 mg, 0.017 mmol). The mixture was stirred at room temperature for 20 h before being diluted with water (10 ml) and extracted with ethyl acetate (3×10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography (ethyl acetate/light petroleum, 3:7) to give the *title compound* (2.8 mg, 52%) as an orange solid, mp >230 °C; found: M+Na^+, 335.0771. $C_{20}H_{12}N_2O_2$+Na requires 335.0796; ν_{max} ($CHCl_3$)/cm^{-1} 2927, 1650, 1456, 1348, 1108, 1069; δ_H (500 MHz; $CDCl_3$) 9.81 (1H, s, CHN), 9.61 (1H, d, *J* 9.6 Hz, ArH), 8.45 (1H, d, *J* 7.9, ArH), 8.21 (1H, d, *J* 7.1, ArH), 7.86 (1H, td, *J* 6.8, 1.3, ArH), 7.79 (1H, td, *J* 7.9, 1.3, ArH), 7.55–7.41 (3H, m, ArH), 4.31 (3H, s, NMe); δ_C (125 MHz; $CDCl_3$) 182.3, 180.8, 152.8, 147.9, 138.6, 138.3, 131.3 (CH), 130.3 (CH), 130.1 (CH), 127.76, 127.70 (CH), 127.5 (CH), 125.3, 125.0 (CH), 124.3, 123.83 (CH), 123.80 (CH), 110.9 (CH), 109.9, 32.3 (Me).

3.1.13. 5-(Methoxy)methoxy-11,12-bis(methoxymethyl)-indolo[2,3-*a*]carbazole-5-carbaldehyde 16. To a solution of **3** (130 mg, 0.43 mmol) in DMF (4 ml) was added sodium hydride (60% w/w in mineral oils; 87.0 mg, 2.16 mmol). The resulting mixture was stirred for 30 min after which time the evolution of gas had ceased. Chloromethyl methyl ether (165 μl, 2.16 mmol) was then added in a dropwise manner and the reaction mixture was heated to 55 °C and stirred at that temperature for 48 h. After cooling to room temperature, the mixture was diluted with water (20 ml) and extracted with ethyl acetate (3×10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography (ethyl acetate/light petroleum, 1:3) to give the *title compound* (77 mg, 44%) as a yellow solid, mp 165–167 °C; R_f: 0.31 (25% ethyl acetate in light petroleum); found: MH^+, 433.1743. $C_{25}H_{24}N_2O_5$+H requires 433.1758; ν_{max} ($CHCl_3$)/cm^{-1} 2929, 1677, 1383, 1341, 1083; δ_H (400 MHz; $CDCl_3$) 10.90 (1H, s, CHO), 9.16 (1H, d, *J* 8.2 Hz, ArH), 8.38 (1H, d, *J* 7.8, ArH), 7.65 (2H, dd, *J* 8.1, 7.2, ArH), 7.58 (2H, ddd, *J* 8.1, 7.1, 1.3, ArH), 7.44 (1H, dd, *J* 8.1, 7.8, ArH), 7.39 (1H, ddd, *J* 8.2, 7.1, 1.2, ArH), 5.85 (2H, s, NC*H*$_2$OMe), 5.73 (2H, s, NC*H*$_2$OMe), 5.43 (2H, s, OC*H*$_2$OMe), 3.68 (3H, s, OCH$_2$O*Me*), 3.49 (6H, s, NCH$_2$O*Me*); δ_C (125 MHz; $CDCl_3$) 190.7 (CH), 154.2, 145.0, 143.0, 132.9, 127.2 (CH), 126.6 (CH), 126.2 (CH), 125.9, 124.9, 123.5, 122.6, 122.5 (CH), 122.2 (CH), 121.5 (CH), 119.6, 116.6, 111.3 (CH), 110.9 (CH), 101.7 (CH_2), 78.6 (CH_2), 77.9 (CH_2), 58.5 (Me), 56.0 (Me), 55.9 (Me).

3.1.14. 12-Methoxymethylindolo[3,2-*j*]phenanthridine-7,13-dione (*N*-methoxymethyl-calothrixin B) 17. A solution of **16** (9.9 mg, 0.024 mmol) in a mixture of acetonitrile (2 ml) and water (200 μl) was cooled to 0 °C. Cerium(IV) ammonium nitrate (90 mg, 0.16 mmol) was added and the mixture was stirred at room temperature for 6.5 h. Water (20 ml) was added and the mixture was extracted with ethyl acetate (2×10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography (ethyl acetate/light petroleum, 1:4) to give the *title compound* (2.6 mg, 31%) as an orange solid, mp >230 °C (lit.,[8] mp 234–235 °C); found: MH^+, 343.1091. $C_{21}H_{14}N_2O_3$+H requires 343.1077; ν_{max} ($CHCl_3$)/cm^{-1} 2929, 1658, 1348, 1053; δ_H (500 MHz; $CDCl_3$) 9.80 (1H, s, CHN), 9.61 (1H, d, *J* 8.5 Hz, ArH), 8.46 (1H, d, *J* 8.0, ArH), 8.22 (1H, d, *J* 8.0,

ArH), 7.86 (1H, td, *J* 8.0, 1.3, ArH), 7.78 (1H, td, *J* 8.5, 1.3, ArH), 7.67 (1H, d, *J* 8.0, ArH), 7.56 (1H, t, *J* 8.0, ArH), 7.53 (1H, t, *J* 8.0, ArH), 6.18 (2H, s, NCH_2OMe), 3.39 (3H, s, NCH_2OMe); δ_C (100 MHz; $CDCl_3$) 182.1, 181.4, 152.3, 147.8 (CH), 140.2, 135.4, 133.3, 131.5 (CH), 130.4 (CH), 130.2 (CH), 128.3 (CH), 127.6 (CH), 125.3 (CH), 124.3, 123.9 (CH), 123.3, 123.2, 118.6, 111.9 (CH), 75.4 (CH_2), 56.6 (Me).

3.1.15. Calothrixin B 2. To a solution of MOM-calothrixin B **17** (3.2 mg, 9.4 μmol) in THF (5 ml) was added concd hydrochloric acid (2 ml) and the mixture was heated to 55 °C and stirred at that temperature for 24 h. After cooling to room temperature, the mixture was carefully neutralized by the addition of saturated aqueous sodium hydrogen carbonate (20 ml) followed by the addition of solid sodium hydrogen carbonate until the evolution of gas had ceased. The mixture was extracted with ethyl acetate (3×10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography (ethyl acetate/light petroleum, 1:3) to give the *title compound* (2.8 mg, 100%) as an orange solid, mp >230 °C (lit.,[8] mp ≥280 °C); R_f: 0.28 (25% ethyl acetate in light petroleum); found: MH^+, 299.0803. $C_{19}H_{10}N_2O_2$+H requires 299.0820; ν_{max} ($CHCl_3$)/cm^{-1} 2926, 2854, 1654, 1456, 1323, 1076; δ_H (400 MHz; DMSO-d_6) 9.63 (1H, s, CHN), 9.58 (1H, d, *J* 8.5 Hz, ArH), 8.19 (1H, d, *J* 7.5, ArH), 8.17 (1H, d, *J* 7.0, ArH), 7.96 (1H, td, *J* 6.5, 1.0, ArH), 7.89 (1H, td, *J* 6.5, 1.0, ArH), 7.62 (1H, d, *J* 8.0, ArH), 7.47 (1H, t, *J* 7.0, ArH), 7.40 (1H, d, *J* 7.0, ArH); δ_C (125 MHz; DMSO-d_6) 180.7, 180.2, 151.7, 147.4 (CH), 138.2, 137.9, 132.5, 131.5 (CH), 130.1 (CH), 129.7 (CH), 127.06 (CH), 127.04 (CH), 124.7, 124.2, 123.2, 122.4 (CH), 122.1 (CH), 115.3, 113.8 (CH).

3.1.16. Calothrixin A 1. Calothrixin B **2** (6.0 mg, 20 μmol) was dissolved in dichloromethane (2 ml) and cooled to 0 °C. Peracetic acid (40% in acetic acid/water; 17 μl, 100 μmol) was added dropwise, the reaction mixture was stirred at room temperature for 72 h and then poured into saturated aqueous sodium hydrogen carbonate (30 ml). The mixture was extracted with dichloromethane (3×15 ml), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude material was subjected to flash chromatography, eluting with dichloromethane containing triethylamine (1% v/v), to give the *title compound* (3.3 mg, 52%) as a dark orange solid, mp >230 °C (lit.,[1] mp 280 °C (decomp.)); δ_H (500 MHz; DMSO-d_6) 9.68 (1H, dd, *J* 9.0, 1.5 Hz, ArH), 8.88 (1H, s, CHN), 8.60 (1H, dd, *J* 10.0, 1.5 Hz, ArH), 8.12 (1H, d, *J* 8.0, ArH), 7.99–7.93 (2H, m, ArH), 7.60 (1H, d, *J* 8.0, ArH), 7.45 (1H, dd, *J* 8.5, 8.0, ArH), 7.38 (1H, dd, *J* 8.0, 8.0, ArH).

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