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Synthesis of the 2,3,4-trisubstituted indole fragments of nosiheptide and glycothiohexide

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Two routes to the protected 4-hydroxymethyl-3-methylindole-2-carboxylate fragment **17** of the thiopeptide antibiotic nosiheptide are described starting from methyl 4-methylindole-2-carboxylate **11**, itself prepared in two steps, or from 3-amino-4-chlorobenzoic acid **26**. The first route can be adapted to the synthesis of a fragment of the related antibiotic glycothiohexide-α, the 3,4-bis(hydroxymethyl)indole-2-carboxylate in which the two hydroxymethyl groups are differentiated as in indole **19** or the lactone **20**.

Introduction

The antibiotic nosiheptide **1** (RP9671) was originally isolated from *Streptomyces actuous* 40037 in the early 1960s by French workers,[1,2] and its structure, determined by chemical degradation[3] and X-ray crystallography,[4,5] is characterised by the presence of seven heterocyclic rings (five 2,4-disubstituted thiazoles, one 2,3,4-trisubstituted indole, one 2,3,5,6-tetrasubstituted pyridine) in a double macrocyclic array. Nosiheptide, which is identical to multhiomycin isolated from *Streptomyces antibioticus* 8446CC,[6] is a member of the thiopeptide antibiotics, a growing class of sulfur rich modified cyclic peptides, and has been subject of detailed biosynthetic studies which establish the origin of the heterocyclic rings from modification of the amino acid side chains with cyclisation.[7–9] Some thiopeptides have pronounced biological activity against Gram-positive bacteria and anaerobes, including pathogens resistant to antibiotics in current use, and also against the malaria parasite,[10,11] being powerful inhibitors of protein synthesis in the organism acting directly on the ribosome and inhibiting the action of GTP-dependent elongation factors.[12–14] Although none of the thiopeptides are used clinically as yet, nosiheptide is in commercial use as a feed additive to increase weight gain in poultry and pigs.[15,16]

The syntheses of various fragments of nosiheptide have been reported,[17–22] including two syntheses of the unusual 2,3,4-trisubstituted indole,[23,24] a structural unit shared by the closely related thiopeptide antibiotic glycothiohexide-α **2**,[25,26] and the recently isolated nocathiacins,[27–29] for example nocathiacin III **3**, although in these natural products, the methyl group at the 3-position of the indole has been oxidised to hydroxymethyl. In continuation of our interest in the synthesis of the thiopeptide antibiotics,[30] we now report details of flexible routes to the 2,3,4-trisubstituted indole fragment **4** (X = H) of nosiheptide and the more functionalised fragments **4** (X = OH) and **5** of glycothiohexide-α.[31]

Results and discussion

Our first approach to the synthesis of a suitably substituted indole involved the thermal decomposition of an α-azidocinnamate derivative, a reaction originally developed by Hemetsberger *et al.*,[32] and subsequently used by us[33–36] and others[37] as an efficient route to a range of indole-2-carboxylate derivatives. Thus the known 2-tetrahydropyranyloxymethyl benzaldehyde **6**[38] was condensed with methyl azidoacetate under basic conditions to give the azidocinnamate **7**, heating of which in boiling xylene gave the desired indole **8**. The modest yields of these two steps (44 and 55%), coupled with the fact that introduction of the 3-substituent by formylation (see below) proceeded poorly, led us to investigate a simpler indole. Repeating the sequence starting from 2-tolualdehyde **9** gave the 4-methylindole-2-carboxylate **11** in excellent 84% yield over the two steps. The indole **11** was also prepared in an alternative manner from 2-bromo-3-nitrotoluene by Heck reaction with methyl acrylate to give the 2-nitrocinnamate **12** followed by a phosphite mediated deoxygenative cyclisation to give the indole **11** (Scheme 1).[39]

The bromination of the methyl group in *N*-protected methylindoles is reported in the literature, with the unprotected derivatives undergoing electrophilic substitution in the indole ring.[40] However, it was thought that with the presence of the electron withdrawing ester in the 2-position of **11** might be sufficient to prevent bromination in the ring, and thus avoid the additional protection step. In the event, this was found not to be the case since treatment of the unprotected indole **11** with NBS and AIBN, resulted in electrophilic substitution of bromine into the 3-position of the indole. Therefore, protection of the indole nitrogen with di-*tert*-butyl dicarbonate to give **13** was followed by radical bromination of the 4-methyl substituent with NBS, using AIBN as the radical initiator, gave the required 4-bromomethyl compound **14** in good yield. At this stage it was decided to introduce the required substituent at C-3 by formylation, since reduction of the formyl group under appropriate conditions could rise to both the required methyl or hydroxymethyl substituents. Treatment of the 4-bromomethyl indole **14** with phosphorus oxychloride and *N*-methylformanilide (NMF) in 1,2-dichloroethane yielded the 3-formyl derivative **15** in good yield, but with complete halide exchange from bromine to chlorine and concomitant deprotection of the indole nitrogen. Subsequent Finkelstein reaction of the chloride **15** with sodium iodide in acetone followed by treatment with aqueous potassium carbonate and protection of the free hydroxyl with *tert*-butyldimethylsilyl triflate in pyridine gave the desired protected alcohol **16**, a key intermediate, in a moderate yield for the two steps (Scheme 1).

Our first synthesis of the nosiheptide indole fragment simply involved reduction of the formyl group; the optimum conditions employed sodium cyanoborohydride in the presence of zinc iodide,[41] and gave the indole **17** which contains suitably protected functionality for nosiheptide in 63% yield (Scheme 2). The formyl group in indole **16** also served as a precursor to the 3-hydroxymethyl group found in the glycothiohexide-α indole fragment although prior protection of the indole nitrogen was

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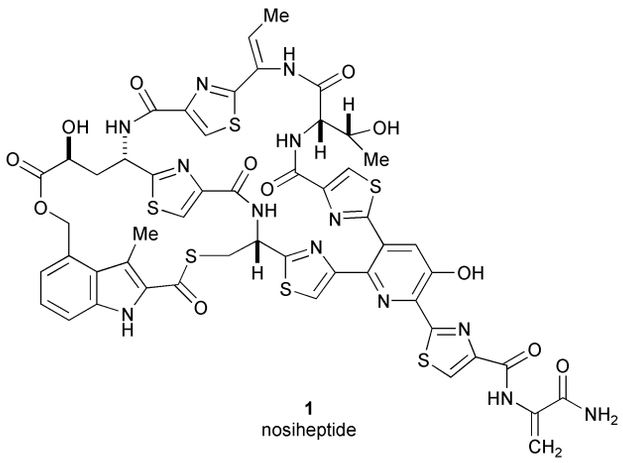
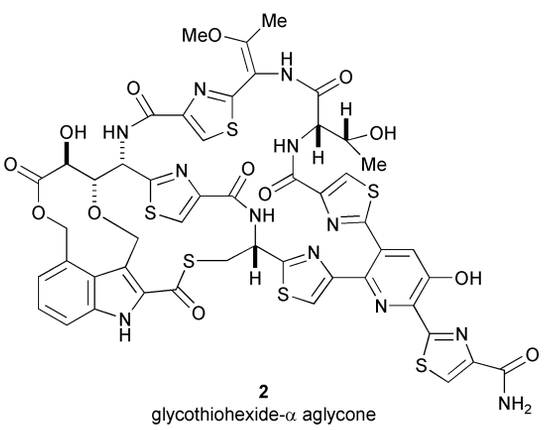


1
nosiheptide



2
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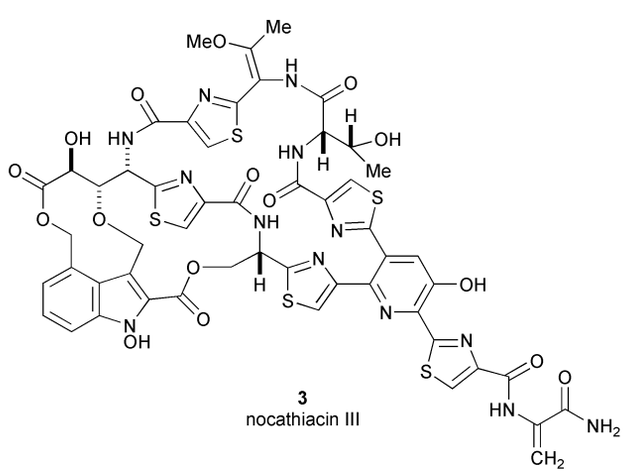
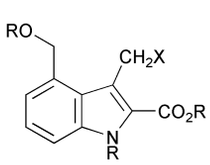
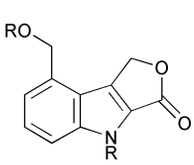


3
nocathiacin III

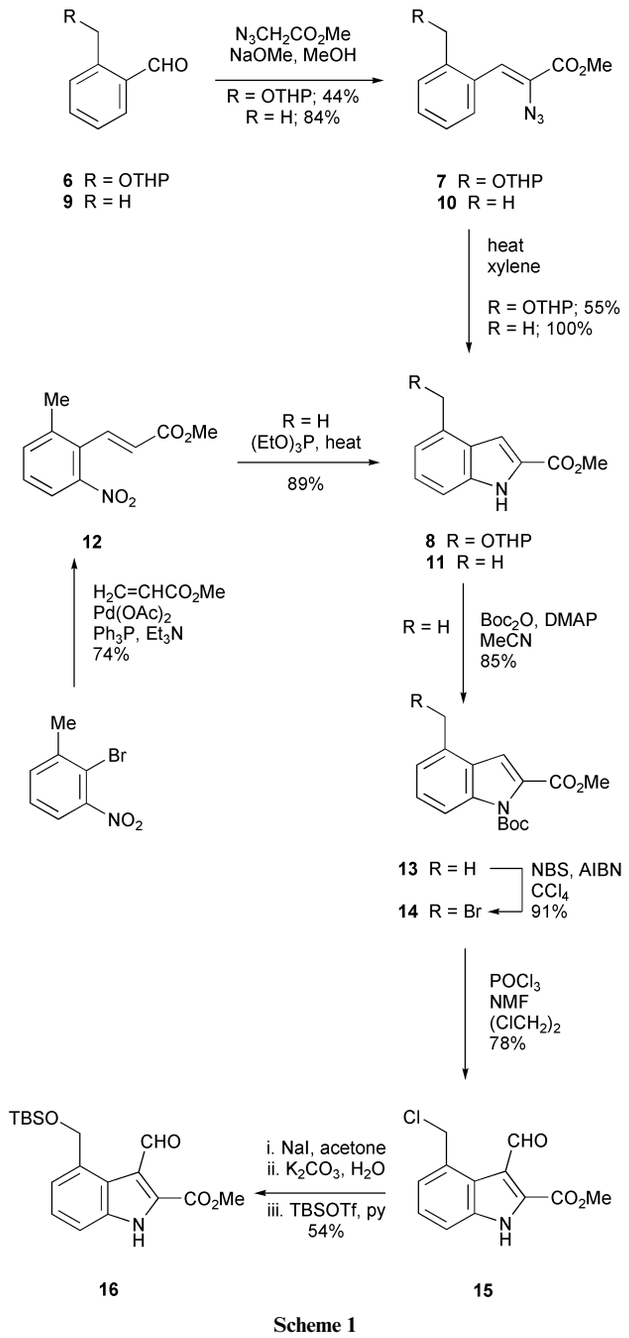


4



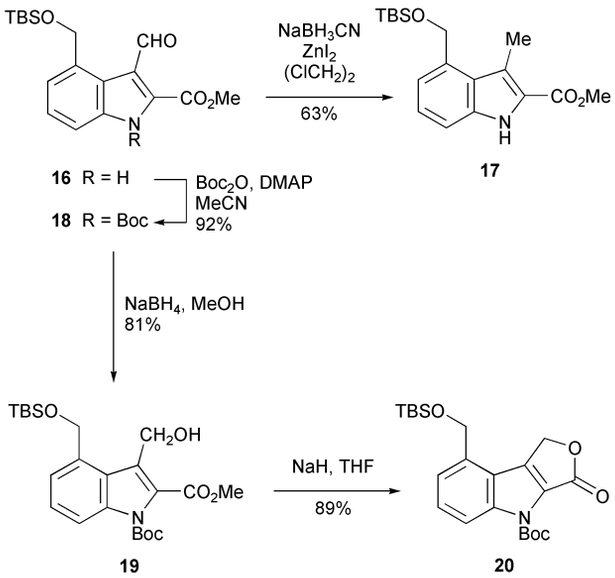
5

necessary because of the high reactivity of 3-hydroxymethylindoles.[42] Thus reintroduction of the Boc group (92%) was followed by reduction of the aldehyde with sodium borohydride to give the required indole **19** in good yield. At this stage, rather than protect the new hydroxymethyl with a group which would allow orthogonal deprotection from the existing protected 4-hydroxymethyl group, it was decided to use the C-2 carboxyl as an internal protecting group. Hence treatment of the hydroxyester **19** with base gave the lactone **20** in good yield (Scheme 2).

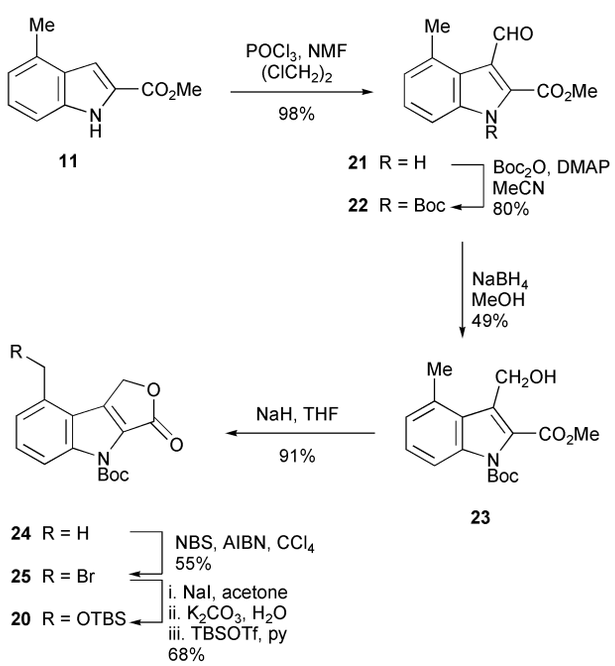


Scheme 1

Although the above route successfully gave the lactone **20**, a suitable intermediate for our projected synthesis of glycothiohexide-α, it did involve unwanted deprotection and reprotection steps. Therefore an alternative was investigated, again starting from the simple 4-methylindole-2-carboxylate **11**, but altering the order of steps. Thus formylation using phosphorus oxychloride and NMF as above gave the aldehyde **21**, *N*-protection of which gave the aldehyde ester **22**, both steps proceeding in good yield (Scheme 3). Reduction of the aldehyde with sodium borohydride and lactonisation of the resulting 3-hydroxymethylindole **23** with base gave the lactone **24**, although this last step had to be carried out by careful addition of the base to prevent deprotection of the indole nitrogen, presumably by the liberated methoxide.[43] Reaction of the protected lactone **24** with NBS and AIBN in carbon tetrachloride gave the bromomethyl compound **25** with no products resulting from bromination of the lactone methylene group being observed. Finally, Finkelstein reaction of the bromide **25** with sodium iodide in acetone followed by treatment with aqueous potassium carbonate and protection of the free hydroxyl with *tert*-butyldimethylsilyl triflate in



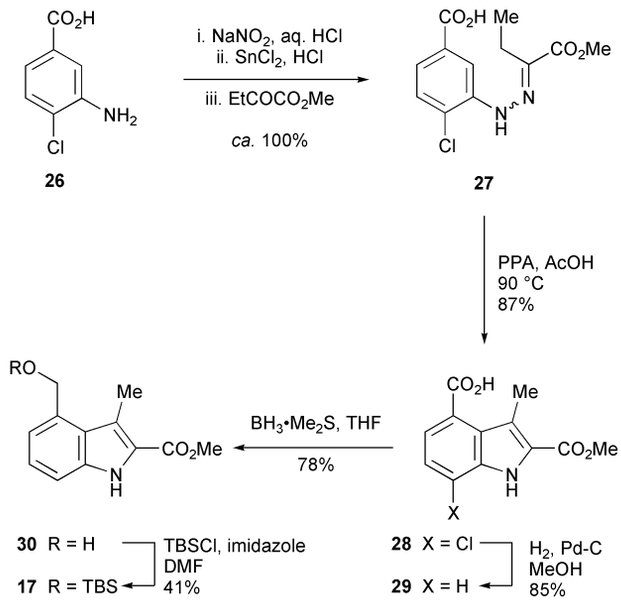
Scheme 2



Scheme 3

pyridine provided a second route to the protected alcohol **20** (Scheme 3).

Finally, a shorter alternative route to the nosiheptide indole fragment **17** was developed using a Fischer indole synthesis as a key step. The starting hydrazine was prepared from the commercially available 3-amino-4-chlorobenzoic acid **26** by diazotisation and reduction with tin(II) chloride, and was immediately condensed with methyl 2-oxobutanoate to give the hydrazone **27**. Fischer cyclisation of hydrazone **27** using polyphosphoric acid (PPA) in acetic acid gave the indole **28** in good yield. The chlorine substituent having served its purpose in preventing the formation of an alternative indole that could have resulted from Fischer cyclisation of a simple *meta*-substituted phenyl hydrazone was then simply removed by hydrogenolysis over palladium-on-carbon to give the indole **29**. Reduction of the free carboxylic acid by careful addition of borane dimethyl sulfide complex was followed by protection of the resulting alcohol **30** with *tert*-butyldimethylsilyl chloride to give the indole **17** (Scheme 4).



Scheme 4

Conclusions

In conclusion, we have developed two routes to the protected 4-hydroxymethyl-3-methylindole-2-carboxylate fragment **17** of the thiopeptide antibiotic nosiheptide, the second of which is amenable to large-scale working. One route can also be adapted to the synthesis of a fragment of the related antibiotic glycothiohexide-α, the 3,4-bis(hydroxymethyl)indole-2-carboxylate in which the two hydroxymethyl groups are differentiated as in indole **19** or the lactone **20**.

Experimental

For general experimental details, see ref. 44.

2-Tetrahydropyranyloxymethylbenzaldehyde 6

(a) 3,4-Dihydropyran (4.0 g, 0.047 mol) was added to a solution of 2-bromobenzyl alcohol (8.0 g, 0.043 mol) in dichloromethane (50 ml) and stirred at room temperature overnight. The mixture was partitioned between dichloromethane (50 ml) and water (50 ml). The aqueous layer was further extracted with dichloromethane (50 ml) and the organic extracts combined, washed sequentially with water (50 ml) and brine (50 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with dichloromethane to give 2-bromobenzyltetrahydropyranyl ether as a colourless oil (10.4 g, 90%); ν_{max} (film)/cm^{-1} 2954, 2863, 1527, 1445, 1342, 1193, 1127; δ_H (300 MHz; $CDCl_3$) 7.51 (2H, m, ArH), 7.34 (1H, t, *J* 6.5, ArH), 7.16 (1H, m, ArH), 4.85 (1H, d, *J* 13.3, C*H*H), 4.77 (1H, m, OCHO), 4.60 (1H, d, *J* 13.3, CH*H*), 3.90 (1H, m, C*H*H), 3.59 (1H, m, CH*H*), 2.16–1.50 (6H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 137.8 (C), 132.4 (C), 129.0 (CH), 128.7 (CH), 127.3 (CH), 122.7 (CH), 98.4 (CH), 68.6 (CH_2), 62.1 (CH_2), 30.5 (CH_2), 25.5 (CH_2), 19.3 (CH_2). Spectroscopic data agrees with those previously reported.[45]

(b) *n*-Butyllithium (14.7 ml, 0.023 mol) was added dropwise to a stirred solution of 2-bromobenzyl tetrahydropyranyl ether (3.00 g, 0.011 mol) in THF (40 ml) at −78 °C under nitrogen. The reaction mixture was allowed to warm to 0 °C and re-cooled to −78 °C and DMF (3.0 ml, 0.039 mol) added. The resulting solution was stirred for 2 h and then allowed slowly to warm to room temperature. Saturated ammonium chloride solution (50 ml) was added and the solution extracted with ether (3 × 60 ml). The combined ethereal extracts were washed sequentially with water (50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound **6**

as a pale yellow oil (2.24 g, 92%); ν_{max} (film)/cm^{-1} 2934, 2860, 1691, 1598, 1437, 1205, 1122, 1087; δ_H (300 MHz; $CDCl_3$) 10.48 (1H, s, CHO), 7.87 (1H, d, *J* 6.5, ArH), 7.64 (1H, d, *J* 7.4, ArH), 7.58 (1H, t, *J* 6.2, ArH), 7.47 (1H, t, *J* 6.4, ArH), 5.20 (1H, d, *J* 14.2, C*H*$_2$), 4.95 (1H, d, *J* 11.1, C*H*$_2$), 3.88 (1H, m, CH_2), 3.56 (1H, m, CH_2), 1.84–1.52 (6H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 192.7 (C), 140.9 (C), 133.9 (C), 132.0 (C), 128.4 (CH), 127.5 (CH), 98.4 (CH), 66.4 (CH_2), 62.3 (CH_2), 30.6 (CH_2), 25.4 (CH_2), 19.4 (CH_2). Spectroscopic data agrees with those previously reported.[38]

Methyl 2-azido-3-[(2-tetrahydropyranyloxymethyl)phenyl]-propenoate 7

Sodium metal (1.13 g, 0.049 mol) was added portionwise to methanol (60 ml) at room temperature. The resulting solution was cooled to −20 °C and a solution of 2-tetrahydropyranyloxymethylbenzaldehyde **6** (3.00 g, 0.014 mol) and methyl azidoacetate (6.27 g, 0.054 mol) in methanol (15 ml) was added dropwise over 45 min. The reaction mixture was stirred at −30 °C for 5 h and then 4 °C overnight. The solvent was evaporated *in vacuo* and the residue partitioned between water (30 ml) and ether (70 ml). The aqueous layer was further extracted with ether (2 × 70 ml) and the organic extracts were combined and washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica eluting with ethyl acetate–light petroleum (1 : 3), to give the *title compound* **7** as a yellow oil (1.89 g, 44%) (Found: M$^+$, 317.1382. $C_{16}H_{19}N_3O_4$ requires 317.1375); ν_{max} (film)/cm^{-1} 2949, 2124, 1719, 1618, 1598; δ_H (400 MHz; $CDCl_3$) 7.42 (1H, d, *J* 2.0, ArH), 7.32 (2H, m, ArH), 7.26 (1H, d, *J* 10.7, ArH), 4.84 (1H, d, *J* 12.2, PhC*H*H), 4.72 (1H, m, OCHO), 4.50 (1H, d, *J* 12.2, PhCH*H*), 3.80 (3H, s, OMe), 3.60 (1H, m, PhC*H*=), 1.90–1.55 (8H, m, 4 × CH_2); δ_C (100 MHz; $CDCl_3$) 163.9 (C), 137.2 (C), 131.9 (C), 129.9 (CH), 129.14 (CH), 129.10 (CH), 127.8 (CH), 126.5 (C), 122.9 (CH), 98.1 (CH), 67.3 (CH_2), 62.0 (CH_2), 52.9 (Me), 30.5 (CH_2), 25.5 (CH_2), 19.2 (CH_2); *m*/*z* (EI) 317 (M$^+$, 10%), 289 (100), 273 (30), 188(32), 129 (65), 107 (53), 104 (44).

Methyl 4-(2-tetrahydropyranoxymethyl)indole-2-carboxylate 8

A solution of methyl2-azido-3-[(2-tetrahydropyranyloxymethyl)-phenyl]propenoate **7** (0.90 g, 3.3 mmol) in dry xylene (30 ml) was added dropwise, by means of a pressure equalising dropping funnel to a stirred solution of boiling xylenes (100 ml). After the addition was complete (*ca*. 45 min), the solution was heated under reflux for a further 1 h, cooled and concentrated *in vacuo* and the residue purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 5) to give the *title compound* as a pale yellow solid (0.45 g, 55%); mp 106–108 °C (from ether) (Found: C, 66.3; H, 6.6; N, 4.8. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.8%); ν_{max} (KBr)/cm^{-1} 3339, 2945, 2827, 1675, 1521, 1434, 1347, 1265, 1163, 1065; δ_H (400 MHz; $CDCl_3$) 8.95 (1H, s, NH), 7.35 (2H, m, 6-H, 7-H), 7.30 (1H, s, 3-H), 7.17 (1H, dd, *J* 6.9, 0.9, 5-H), 5.10 (1H, d, *J* 11.9, PhC*H*H), 4.83 (1H, d, *J* 11.9, PhCH*H*), 4.77 (1H, m, OCHO), 3.95 (3H, s, OMe), 1.95–1.50 (8H, m, 4 × CH_2); δ_C (100 MHz; $CDCl_3$) 162.4 (C), 137.0 (C), 136.5 (C), 132.3 (C), 127.0 (C), 125.4 (CH), 120.2 (CH), 111.4 (CH), 107.5 (CH), 97.8 (CH), 67.1 (CH_2), 62.2 (CH_2), 52.0 (Me), 30.6 (CH_2), 25.5 (CH_2), 19.4 (CH_2); *m*/*z* (EI) 290 (M$^+$, 7%), 189 (52), 156 (38), 130 (46), 119 (24), 85 (100), 77 (23).

Methyl 2-azido-(2-methylphenyl)propenoate 10

Sodium metal (3.17 g, 0.14 mol) was added portionwise to methanol (100 ml) at room temperature. The resulting solution was cooled to −20 °C and a solution of *o*-tolualdehyde **9** (4.50 g, 0.04 mol) and methyl azidoacetate (17.24 g, 0.15 mol) in methanol (30 ml) was added dropwise over 1 h. The reaction mixture was then stirred at −30 °C for 5 h and then at 4 °C overnight. The solvent was evaporated *in vacuo* and the residue partitioned between water (30 ml) and ether (40 ml). The aqueous layer was further extracted with ether (30 ml) and the organic extracts were combined, washed sequentially with water (30 ml) and brine (30 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a pale yellow solid (6.87 g, 84%); mp 44–45 °C (from ether) (Found: M$^+$, 217.0846. $C_{11}H_{11}N_3O_2$ requires 217.0851); ν_{max}(Nujol)/cm^{-1} 2954, 2860, 2123, 1724, 1376, 1241, 1077; δ_H (400 MHz; $CDCl_3$) 7.95 (1H, m, ArH), 7.22 (3H, m, ArH), 7.15 (1H, s, CH), 3.93 (3H, s, OMe), 2.37 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 137.6 (C), 131.9 (C), 130.3 (CH), 129.6 (CH), 129.2 (CH), 126.1 (C), 125.8 (CH), 123.5 (CH), 52.9 (Me), 20.1 (Me); *m*/*z* (EI) 217 (M$^+$, 3%), 189 (20), 157 (30), 144 (10), 130 (55), 103 (100), 77 (48), 59 (63).

Methyl 4-methylindole-2-carboxylate 11

A solution of the methyl 2-azido-(2-methylphenyl)propenoate **10** (2.00 g, 9.0 mmol) in dry xylene (80 ml) was added dropwise by means of a pressure equalising dropping funnel to a stirred solution of dry xylene (270 ml) heated under reflux over 1 h. After the addition was complete, the solution was heated under reflux for a further 1 h, cooled and the solvent removed *in vacuo* to yield the *title compound* as a yellow solid (1.74 g, 100%) used without further purification. A sample was recrystallised from ethyl acetate; mp 135–137 °C; (Found: C, 69.6; H, 5.8; N, 7.3. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%) (Found: M$^+$, 189.0795. $C_{11}H_{11}NO_2$ requires 189.0790); ν_{max} (KBr)/cm^{-1} 3314, 2965, 2934, 1685, 1531, 1434, 1337, 1255, 1214, 1147; δ_H (400 MHz; $CDCl_3$) 9.05 (1H, s, NH), 7.21–7.28 (3H, m, ArH), 6.96 (1H, m, 5-H), 3.96 (3H, s, OMe), 2.57 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 162.5 (C), 136.8 (C), 132.3 (C), 127.7 (C), 126.5 (C), 125.6 (CH), 120.8 (CH), 109.4 (CH), 107.5 (CH), 52.0 (Me), 18.6 (Me); *m*/*z* (CI) 190 (MH$^+$, 100%), 189 (M$^+$, 25), 174 (7), 157 (9), 129 (54), 103 (47), 77 (32).

Methyl 3-(2-methyl-6-nitrophenyl)propenoate 12

2-Bromo-3-nitrotoluene (5.00 g, 23.2 mmol), methyl acrylate (4.17 ml, 46.3 mmol), palladium acetate (292 mg, 1.16 mmol), triphenylphosphine (608 mg, 2.32 mmol) and triethylamine (4.03 ml, 28.9 mmol) were combined in a sealed Young's tube and heated to 95 °C for 24 h. The residue was dissolved in methanol, the solvent removed and the crude product purified by column chromatography (15% ethyl acetate–light petroleum) to give the *title compound* **12** (3.77 g, 74%) as a yellow oil (Found: MH$^+$, 222.0769. $C_{11}H_{11}NO_4$ + H requires 222.0766); ν_{max} (neat)/cm^{-1} 2952, 1724, 1527, 1350, 1313, 1279, 1200, 1173; δ_H (300 MHz; $CDCl_3$) 7.88 (1H, d, *J* 16.5, C*H*=CHCO$_2$Me), 7.77 (1H, d, *J* 8.1, H-5), 7.48 (1H, d, *J* 7.7, H-3), 7.36 (1H, apparent t, apparent *J* 7.9, H-4), 5.97 (1H, d, *J* 16.5, CH=C*H*CO$_2$Me), 3.81 (3H, s, OMe), 2.39 (3H, s, ArMe); δ_C (75 MHz; $CDCl_3$) 166.4 (C), 149.5 (C), 140.5 (CH), 139.0 (C), 135.2 (CH), 130.2 (C), 129.0 (CH), 124.8 (CH), 122.3 (CH), 52.3 (Me), 21.4 (Me); *m*/*z* (CI) 222 (MH$^+$, 11%), 190 (100), 141 (44).

Methyl 4-methylindole-2-carboxylate 11

Methyl 3-(2-methyl-6-nitrophenyl)propenoate **12** (1.00 g, 4.52 mmol) was dissolved in triethyl phosphite (4 ml, 22.60 mmol) and heated under reflux for 20 h. The solvent was removed *in vacuo* and the crude product purified by SiO_2 chromatography (15% ethyl acetate: light petroleum) to give the *title compound* **11** (0.76 g, 89%) as a pale yellow solid; data as above.

Methyl 1-*tert*-butoxycarbonyl-4-methylindole-2-carboxylate 13

Di-*tert*-butyl dicarbonate (2.31 g, 10.6 mmol) and DMAP (0.10 g, 0.82 mmol) were added to a stirred solution of methyl 4-methylindole-2-carboxylate **11** (1.00 g, 5.3 mmol) in

acetonitrile (50 ml). The resulting mixture was stirred at room temperature overnight and the solvent evaporated *in vacuo*. The residue was partitioned between ethyl acetate (50 ml) and water (50 ml). The aqueous layer was further extracted with ethyl acetate (2 × 50 ml) and the organic extracts combined, washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 9), to leave the *title compound* as a pale yellow oil that crystallised on standing (1.30 g, 85%); mp 66–68 °C (from dichloromethane) (Found: C, 66.6; H, 6.7; N, 4.8. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.8) (Found: M^+, 289.1318. $C_{16}H_{19}NO_4$ requires 289.1314); ν_{max} (KBr)/cm^{-1} 3000, 2980, 2953, 1733, 1599, 1275, 1209, 1147; δ_H (300 MHz; $CDCl_3$) 7.93 (1H, dd, *J* 8.3, 0.6, 7-H), 7.34 (1H, dd, *J* 8.3, 1.0, 6-H), 7.18 (1H, s, 3-H), 7.07 (1H, dd, *J* 7.1, 0.6, 5-H), 3.93 (3H, s, OMe), 2.55 (3H, s, Me), 1.62 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 162.4 (C), 149.4 (C), 137.8 (C), 131.9 (C), 129.8 (C), 127.3 (C), 127.0 (CH), 123.6 (CH), 113.6 (CH), 112.3 (CH), 84.5 (C), 52.3 (Me), 27.8 (Me), 18.4 (Me); *m*/*z* (EI) 289 (M^+, 2%), 216 (8), 202 (3), 189 (56), 157 (87), 129 (20), 103 (16), 77 (8), 57 (100).

Methyl 4-bromomethyl-1-*tert*-butoxycarbonylindole-2-carboxylate 14

A solution of methyl *N*-*tert*-butoxycarbonyl-4-methylindole-**2**-carboxylate**13** (2.70 g, 9.3 mol), NBS (1.74 g, 9.8 mmol), and AIBN (77 mg, 0.5 mmol) in carbon tetrachloride (40 ml) was heated to reflux for 3 h. The reaction mixture was cooled and filtered and the filtered solid washed with carbon tetrachloride (2 × 30 ml) The filtrate was evaporated *in vacuo* to leave a yellow oil that was purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 20), to give the *title compound* as a pale yellow solid (3.12 g, 91%); mp 96–98 °C (from ether) (Found: C, 52.0; H, 4.8; N, 3.6. $C_{16}H_{18}BrNO_4$ requires C, 52.2; H, 4.9; N, 3.8%) (Found: M^+, 367.0418. $C_{16}H_{18}{}^{79}BrNO_4$ requires 367.0420); ν_{max} (KBr)/cm^{-1} 2979, 2951, 1739, 1652, 1460, 1436, 1256, 1173, 1035; δ_H (400 MHz; $CDCl_3$) 8.08 (1H, d, *J* 8.4, 7-H), 7.36 (1H, t, *J* 7.4, 6-H), 7.29 (2H, m, 3-H and 5-H), 4.73 (2H, s, CH_2Br), 3.95 (3H, s, OMe), 1.63 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 162.1 (C), 149.0 (C), 138.1 (C), 130.9 (C), 130.6 (C), 126.9 (CH), 126.5 (C), 123.9 (CH), 115.6 (CH), 112.4 (CH), 85.0 (C), 52.4 (Me), 30.4 (CH_2), 27.8 (Me); *m*/*z* (EI) 369/367 (M^+, 3%), 269 (6), 257 (6), 189 (15), 188 (100), 156 (32), 129 (12), 128 (12), 57 (40).

Methyl 4-chloromethyl-3-formylindole-2-carboxylate 15

Phosphorus oxychloride (0.21 g, 1.35 mmol) and *N*-methylformanilide (0.18 g, 1.35 mmol) were stirred at room temperature for 15 min. A solution of methyl 1-*tert*-butoxycarbonyl-4-bromomethylindole-2-carboxylate **14** (0.34 g, 0.87 mmol) in 1,2-dichloroethane (15 ml) was added and the resulting mixture heated to reflux for 40 h. The reaction mixture was poured onto a solution of sodium acetate (1 g) and ice–water (30 ml) and stirred for 15 min. Dichloromethane (20 ml) was added and the aqueous layer further extracted with dichloromethane (2 × 20 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 5), to give the *title compound* as a pale yellow solid (0.17 g, 78%); mp 186–188 °C (from chloroform) (Found: C, 57.0; H, 3.7; N, 5.4. $C_{12}H_{10}ClNO_3$ requires C, 57.3; H, 4.0; N, 5.6) (Found: M^+, 251.0354. $C_{12}H_{10}{}^{35}ClNO_3$ requires 251.0349); ν_{max} (KBr)/cm^{-1} 3315, 2914, 1716, 1649, 1398, 1239, 1198, 1168, 1034; δ_H (300 MHz; $CDCl_3$) 10.82 (1H, s, CHO), 9.69 (1H, br s, NH), 7.45 (3H, m, 5-H, 6-H and 7-H), 5.43 (2H, s, CH_2), 4.12 (3H, s, OMe); δ_C (100 MHz; $CDCl_3$) 187.5 (CHO), 160.7 (C), 136.3 (C), 133.6 (C), 133.2 (C), 126.8 (CH), 125.9 (CH), 122.8 (C), 121.4 (C), 112.6 (CH), 53.1 (Me), 47.0 (CH_2); *m*/*z* (CI) 253/251 (M^+, 18/54%), 238/236 (25/80), 218 (28), 216 (27), 215 (32), 201 (13), 200 (83), 163 (24), 162 (15), 157 (25), 156 (69), 129 (50), 128 (100), 102 (54), 101 (41), 77 (31), 76 (28).

Methyl 4-*tert*-butyldimethylsiloxymethyl-3-formylindole-2-carboxylate 16

Methyl 4-chloromethyl-3-formylindole-2-carboxylate **15** (100 mg, 0.40 mmol) and sodium iodide (50 mg, 0.33 mmol) were heated to reflux in acetone (5 ml) for 20 min, and a precipitate observed. A solution of potassium carbonate (80 mg, 0.58 mmol) in water (3 ml) was added and the solution heated for a further 30 min. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was further extracted with ethyl acetate (10 ml), dried ($MgSO_4$), evaporated *in vacuo* to give a yellow solid. The material was then used without further purification. TBDMSOTf (110 mg, 0.42 mmol) was added to a solution of the crude hydroxmethylindole in pyridine (5 ml) at −35 °C and the resulting mixture stirred at −35 °C for 5 h and then allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was further extracted with ethyl acetate (2 × 10 ml), combined extracts washed with water (3 × 10 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 3), to give the *title compound* as a colourless solid (75 mg, 54%); mp 166–168 °C (from dichloromethane) (Found: C, 61.9; H, 7.2; N, 4.0. $C_{18}H_{25}NO_4Si$ requires C, 62.2; H, 7.3; N, 4.0%) (Found: M^+, 347.1554. $C_{18}H_{25}NO_4Si$ requires 347.1553); ν_{max} (KBr)/cm^{-1} 3304, 2960, 2919, 2843, 1716, 1700, 1260, 1241; δ_H (400 MHz; $CDCl_3$) 10.74 (1H, s, CHO), 9.43 (1H, br s, NH), 7.63 (1H, dd, *J* 6.2, 1.6, 7-H), 7.45 (1H, t, *J* 8.2, 6-H), 7.34 (1H, dd, *J* 7.3, 0.9, 5-H), 5.37 (2H, s, CH_2), 4.05 (3H, s, OMe), 1.50 (9H, s, CMe_3), 0.16 (6H, s, 2 × Me); δ_C (100 MHz; $CDCl_3$) 187.4 (CH), 160.8 (C), 138.2 (C), 135.8 (C), 132.0 (C), 126.9 (CH), 122.0 (C), 121.1 (C), 120.6 (CH), 110.3 (CH), 64.6 (CH_2), 52.9 (Me), 26.1 (Me), 18.5 (C), −5.3 (Me); *m*/*z* (EI) 347 (M^+, 4%), 332 (12), 304 (14), 292 (30), 291 (100), 260 (24), 258 (71), 230 (35), 216 (30), 184 (41), 128 (40).

Methyl 4-*tert*-butyldimethylsiloxymethyl-3-methylindole-2-carboxylate 17

Sodium cyanoborohydride (0.140 g, 2.2 mmol) and zinc iodide (0.140 g, 0.43 mmol) were added to a solution of methyl 4-*tert*-butyldimethylsiloxymethyl-3-formylindole-2-carboxylate **16** (0.100 g, 0.29 mmol) in 1,2-dichloroethane (10 ml) and the resulting mixture heated under reflux for 1 h. The reaction mixture was cooled and poured into an ice cold sodium hydrogen carbonate solution (20 ml). The mixture was extracted with ethyl acetate (3 × 20 ml), dried ($MgSO_4$) and purified by column chromatography on silica eluting with ethyl acetate–light petroleum (1 : 4) to give the *title compound* as a colourless oil (0.063 g, 63%); mp 136–137 °C (from ether) (Found: C, 64.6; H, 8.3; N, 4.0. $C_{18}H_{27}NO_3Si$ requires C, 64.8; H, 8.2; N, 4.2%); ν_{max} (KBr)/cm^{-1} 3338, 2954, 2927, 2889, 1675, 1265, 1111; δ_H (400 MHz; $CDCl_3$) 8.72 (1H, br s, NH), 7.27 (2H, m, 6-H, 7-H), 7.15 (1H, m, 5-H), 5.17 (2H, s, CH_2), 3.95 (3H, s, OMe), 2.83 (3H, s, Me), 0.94 (9H, s, CMe_3), 0.10 (6H, s, 2 × SiMe); δ_C (75 MHz, $CDCl_3$) 163.4 (C), 136.8 (C), 136.7 (C), 126.1 (C), 125.8 (CH), 123.4 (C), 121.5 (C), 119.3 (CH), 111.5 (CH), 64.1 (CH_2), 52.1 (Me), 26.4 (Me), 18.8 (C), 12.5 (Me), −4.7 (Me); *m*/*z* (EI) 333 (M^+, 7%), 276 (11), 203 (82), 171 (100), 170 (47), 142 (69), 115 (50), 84 (14).

Methyl 1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsiloxymethyl-3-formylindole-2-carboxylate 18

Di-*tert*-butyl dicarbonate (87 mg, 0.40 mmol) and DMAP (10 mg, 0.08 mmol) were added to a stirred solution of methyl

4-*tert*-butyldimethylsiloxymethyl-3-formylindole-2-carboxylate **16** (92 mg, 27.0 mmol) in acetonitrile (5 ml). The resulting mixture was stirred at room temperature for 30 min and the solvent evaporated *in vacuo*. The residue was partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was further extracted with ethyl acetate (2 × 10 ml) and the organic extracts washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 4), to give the *title compound* (109 mg, 92%) as a yellow oil (Found: MH^+, 448.2151. $C_{23}H_{33}NO_6Si$ requires 448.2155); ν_{max} (film)/cm^{-1} 2950, 2930, 2848, 1752, 1675, 1536, 1260, 1115; δ_H (300 MHz; $CDCl_3$) 10.28 (1H, s, CHO), 8.14 (1H, dd, *J* 7.8, 1.6, 7-H), 7.44 (2H, m, 5-H, 6-H), 5.12 (2H, s, CH_2), 4.03 (3H, s, OMe), 1.68 (9H, s, CMe_3), 0.90 (9H, s, $SiCMe_3$), 0.07 (6H, s, 2 × Me); δ_C (75 MHz; $CDCl_3$) 186.8 (CH), 162.8 (C), 148.2 (C), 136.2 (C), 135.8 (C), 135.2 (C), 126.5 (CH), 123.4 (C), 122.6 (C), 121.0 (CH), 114.7 (CH), 86.9 (C), 64.8 (CH_2), 53.4 (Me), 27.9 (Me), 25.9 (Me), 18.3 (C), −5.2 (Me); *m*/*z* (CI) 448 (MH^+, 100%), 348 (85), 316 (30), 216 (22).

Methyl 1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsiloxymethyl-3-hydroxymethylindole-2-carboxylate 19

Sodium borohydride (4.7 mg, 0.12 mmol) was added to a stirred solution of methyl 1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsiloxymethyl-3-formylindole-2-carboxylate **18** (110 mg, 0.25 mmol) in degassed methanol (10 ml) and the resulting mixture stirred at room temperature for 10 min. Acetone (1 ml) was added and the solvent removed *in vacuo*. The residue was taken up in dichloromethane (10 ml) and water (10 ml). The aqueous layer was further extracted with dichloromethane (2 × 10 ml). The combined extracts were dried ($MgSO_4$), and the solvent evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 5), to give the *title compound* as a pale yellow oil (90 mg, 81%) that crystallised on standing; mp 157–159 °C (from ether) (Found M^+, 449.2235. $C_{23}H_{35}NO_6Si$ requires 449.2234); ν_{max} (KBr)/cm^{-1} 3431, 2950, 2925, 2883, 1731, 1323, 1117, 1004; δ_H (400 MHz; $CDCl_3$) 8.11 (1H, d, *J* 7.8, 7-H), 7.36 (1H, apparent t, apparent *J* 7.5, 6-H), 7.21 (1H, d, *J* 7.3, 5-H), 5.13 (2H, s, CH_2OTBS), 4.92 (2H, d, *J* 6.0, C*H*$_2$OH), 3.96 (3H, s, OMe), 3.92 (1H, t, *J* 6.0, CH_2OH), 1.62 (9H, s, CMe_3), 0.90 (9H, s, $SiCMe_3$), 0.09 (6H, s, 2 × Me); δ_C (100 MHz; $CDCl_3$) 163.1 (C), 149.0 (C), 137.4 (C), 133.9 (C), 128.8 (C), 126.3 (CH), 125.0 (C), 125.4 (C), 124.2 (CH), 115.1 (CH), 84.9 (C), 64.9 (CH_2), 55.9 (CH_2), 52.5 (Me), 27.9 (Me), 25.9 (Me), 18.3 (C), −5.1 (Me); *m*/*z* (EI) 449 (M^+, 2%), 446 (17), 394 (33), 319 (47), 303 (28), 274 (30), 262 (100), 218 (70), 189 (53), 180 (47).

4-*tert*-Butoxycarbonyl-8-*tert*-butylsiloxymethyl-1,3-dihydro-4*H*-furo[3,4-*b*]indol-3-one 20

Sodium hydride (4 mg, 0.15 mmol) was added portionwise to a stirred solution of methyl 1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsiloxymethyl-3-hydroxymethylindole-2-carboxylate **19** (65 mg, 0.15 mmol) in THF over 1 h. The resulting solution was stirred at room temperature for a further 3 h. Water (10 ml) and dichloromethane (10 ml) were added and the aqueous layer further extracted with dichloromethane (2 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and purified by column chromatography on silica eluting with ethyl acetate–light petroleum (1 : 9) to give the *title compound* as a colourless oil (54 mg, 89%) (Found: MH^+, 418.2040. $C_{22}H_{31}NO_5Si$ + H requires 418.2050); ν_{max} (film)/cm^{-1} 2950, 2929, 2858, 1772, 1736, 1255, 1137; δ_H (400 MHz; $CDCl_3$) 8.30 (1H, d, *J* 8.6, 5-H), 7.47 (1H, dd, *J* 8.6, 7.3, 6-H), 7.20 (1H, d, *J* 7.3, 7-H), 5.36 (2H, s, CH_2), 4.88 (2H, s, CH_2OTBS), 1.71 (9H, s, $OCMe_3$), 0.89 (9H, s, $SiCMe_3$), 0.07 (6H, s, 2 × Me); δ_C (100 MHz; $CDCl_3$) 160.9 (C), 148.8 (C), 143.4 (C), 142.7 (C), 134.6 (C), 128.5 (CH), 127.9 (C), 122.0 (CH), 120.7 (C), 116.3 (CH), 85.4 (C), 66.6 (CH_2), 64.8 (CH_2), 28.1 (Me), 25.9 (Me), 18.4 (C), −5.1 (Me); *m*/*z* (CI) 418 (MH^+, 60%), 379 (78), 362 (81), 335 (14), 244 (24), 194 (39), 146 (100), 2132 (55), 91 (86).

Methyl 3-formyl-4-methylindole-2-carboxylate 21

A mixture of phosphorus oxychloride (8.50 g, 55 mmol) and *N*-methylformanilide (7.50 g, 55 mmol) were stirred at room temperature for 15 min. A solution of methyl 4-methylindole-2-carboxylate **11** (7.00 g, 36 mmol) in 1,2-dichloroethane (120 ml) was added and the resulting mixture heated under reflux for 2.5 h. The reaction mixture was then poured onto a solution of sodium acetate (5.0 g) and ice–water (100 ml) and the mixture stirred for 15 min. The mixture was extracted with dichloromethane (3 × 150 ml) and the combined organic layers dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 3), to give the *title compound* as a yellow solid (7.87 g, 98%); mp 188–189 °C (from ether) (Found: C, 66.1; H, 4.9; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%) (Found: M^+, 217.0742. $C_{12}H_{11}NO_3$ requires 217.0739); ν_{max} (KBr)/cm^{-1} 3426, 2914, 2852, 1708, 1649, 1511, 1449, 1383, 1193, 1065; δ_H (400 MHz; $CDCl_3$) 10.80 (1H, s, CHO), 9.46 (1H, s, NH), 7.30 (2H, m, 6-H, 7-H), 7.15 (1H, m, 5-H), 4.05 (3H, s, OMe), 2.83 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 187.0 (CHO), 161.0 (C), 136.1 (C), 135.1 (C), 126.8 (CH), 125.4 (CH), 124.5 (C), 122.3 (C), 109.4 (CH), 52.9 (Me), 23.2 (Me), one ArC not observed; *m*/*z* (CI) 217 (M^+, 59%), 202 (100), 184 (99), 157 (32), 128 (56), 102 (47), 77 (30).

Methyl 1-*tert*-butoxycarbonyl-3-formyl-4-methylindole-2-carboxylate 22

Di-*tert*-butyl dicarbonate (8.04 g, 36.0 mmol) and DMAP (0.34 g, 2.8 mmol) were added to a stirred solution of 3-formyl-4-methylindole-2-carboxylate **21** (4.0 g, 18.0 mmol) in acetonitrile (140 ml). The resulting mixture was stirred at room temperature overnight and the solvent evaporated *in vacuo*. The residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The aqueous layer was further extracted with ethyl acetate (2 × 100 ml) and the organic extracts combined, washed with saturated aqueous sodium hydrogen carbonate solution (50 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 5), to give the *title compound* (4.60 g, 80%) as a yellow solid; mp 196–108 °C (from ether) (Found: C, 64.3; H, 6.0; N, 4.3. $C_{17}H_{19}NO_5$ requires C, 64.3; H, 6.0; N, 4.4%) (Found: M^+, 317.1264. $C_{17}H_{19}NO_5$ requires 317.1263); ν_{max} (KBr)/cm^{-1} 3001, 2960, 2883, 1698, 1685, 1531, 1106; δ_H (400 MHz; $CDCl_3$) 10.36 (1H, s, CHO), 8.05 (1H, dd, *J* 8.5, 0.8, 7-H), 7.32 (1H, dd, *J* 8.5, 7.4, 6-H), 7.17 (1H, dd, *J* 7.4, 0.8, 5-H), 4.03 (3H, s, OMe), 2.75 (3H, s, Me), 1.66 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 185.6 (CH), 162.7 (C), 148.2 (C), 136.5 (C), 135.9 (C), 132.3 (C), 126.7 (CH), 126.6 (CH), 124.3 (C), 121.7 (C), 113.1 (CH), 86.8 (C), 53.3 (Me), 27.9 (Me), 22.6 (Me); *m*/*z* (EI) 317 (M^+, 1%), 217 (81), 202 (93), 184 (100), 157 (65), 129 (93), 102 (70), 90 (12), 77 (29).

Methyl 1-*tert*-butoxycarbonyl-3-hydroxymethyl-4-methylindole-2-carboxylate 23

Sodium borohydride (18 mg, 0.47 mmol) was added to a stirred solution of methyl 1-*tert*-butoxycarbonyl-3-formyl-4-methylindole-2-carboxylate **22** (300 mg, 0.95 mmol) in DME (10 ml), and the mixture heated under reflux for 1 h. Water (20 ml), citric acid to pH~3 and ether (20 ml) were added and the aqueous layer was further extracted with ether (2 × 20 ml), dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 3), to give the *title compound* as a yellow oil (150 mg, 49%) (Found: M^+, 319.1418. $C_{17}H_{21}NO_5$ requires 319.1420); ν_{max} (film)/cm^{-1} 3436, 2986, 2955, 1736, 1577, 1460, 1321, 1255;

δ_H (400 MHz; $CDCl_3$) 7.94 (1H, d, *J* 7.5, 7-H), 7.24 (1H, ~t, *J* 7.5, 6-H), 6.99 (1H, d, *J* 7.3, 5-H), 4.83 (2H, s, C*H*$_2$OH), 3.91 (3H, s, OMe), 2.80 (1H, s, CH$_2$O*H*), 2.70 (3H, s, Me), 1.59 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 187.8 (C), 163.4 (C), 149.2 (C), 137.0 (C), 132.6 (C), 128.4 (C), 126.2 (CH), 125.1 (C), 124.8 (CH), 112.5 (CH), 84.7 (C), 55.4 (CH_2), 52.5 (Me), 27.8 (Me), 19.6 (Me); *m*/*z* (EI) 319 (M^+, 6%), 219 (18), 186 (21), 170 (9), 158 (15), 143 (21), 130 (13), 115 (10), 57 (100).

4-*tert*-Butoxycarbonyl-8-methyl-1,3-dihydro-4*H*-furo[3,4-*b*]-indol-3-one 24

Sodium hydride (1.0 g, 2.36 mmol) was added portionwise to a stirred solution of methyl *N*-*tert*-butoxycarbonyl-3-formyl-4-methylindole-2-carboxylate **23** (1.50 g, 4.70 mmol) in THF (50 ml) over 30 min. The resulting solution was stirred at room temperature for 3 h. Water (30 ml) and ether (30 ml) were added. The aqueous layer was extracted with ether (2 × 50 ml) and the ethereal extracts dried ($MgSO_4$), evaporated *in vacuo* and the material recrystallised from ether to give the *title compound* (1.23 g, 91%) as colourless needles; mp 159–160 °C (from ether) (Found: C, 66.8; H, 5.9; N, 4.8. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 6.0; N, 4.9%) (Found M^+, 287.1153. $C_{16}H_{17}NO_4$ requires 287.1158); ν_{max} (KBr)/cm^{-1} 2976, 1768, 1732, 1140; δ_H (400 MHz; $CDCl_3$) 8.18 (1H, d, *J* 8.5, 5-H), 7.42 (1H, dd, *J* 8.5, 7.3, 6-H), 7.14 (1H, dt, *J* 7.3, 0.8, 7-H), 5.39 (2H, s, CH_2), 2.52 (3H, s, Me), 1.71 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 160.7 (C), 148.8 (C), 143.0 (C), 142.8 (C), 131.4 (C), 129.0 (CH), 127.4 (C), 124.2 (CH), 122.0 (C), 114.5 (CH), 85.3 (C), 65.6 (CH_2), 28.1 (Me), 19.2 (Me); *m*/*z* (EI) 287 (M^+, 5%), 187 (100), 158 (94), 143 (71), 130 (54), 115 (48), 103 (55), 89 (51), 57 (84).

4-*tert*-Butoxycarbonyl-4-bromomethyl-1,3-dihydro-4*H*-furo-[3,4-*b*]indol-3-one 25

A solution of 4-*tert*-butoxycarbonyl-4-methyl-1,3-dihydro-4*H*-furo[3,4-*b*]indol-3-one **24** (0.30 g, 1.0 mmol), NBS (0.20 g, 1.1 mmol), and AIBN (9 mg, 0.05 mmol) in carbon tetrachloride (20 ml) was heated under reflux for 4.5 h. The reaction mixture was cooled and filtered and the precipitate washed with carbon tetrachloride (2 × 20 ml). The filtrate was evaporated *in vacuo* to leave a pale yellow oil that was purified by column chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 4) to give the *title compound* (0.21 g, 55%) as a colourless solid; mp 100–102 °C (from dichloromethane) (Found: MH^+, 366.0339. $C_{16}H_{16}{}^{79}BrNO_4$ requires 366.0341); ν_{max} (KBr)/cm^{-1} 2996, 2954, 2925, 1767, 1734, 1460, 1363, 1168, 1040; δ_H (300 MHz; $CDCl_3$) 8.35 (1H, dd, *J* 8.8, 0.8, 5-H), 7.48 (1H, dd, *J* 8.8, 7.1, 6-H), 7.32 (1H, d, *J* 7.0, 7-H), 5.52 (2H, s, CH_2), 4.62 (2H, s, CH_2Br), 1.72 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 162.7 (C), 143.3 (C), 141.1 (C), 130.9 (C), 128.8 (C), 127.6 (C), 124.5 (CH), 122.9 (CH), 119.1 (C), 117.9 (CH), 68.3 (C), 60.4 (CH_2) 28.1 (CH_2), 25.2 (Me); *m*/*z* (CI) 385/383 (M + NH_4, 19%), 366/364 (13), 329/327 (100), 305 (96), 288 (97), 283 (28), 279 (45), 266 (10), 263 (37).

4-*tert*-Butoxycarbonyl-4-tert-butylsiloxymethyl-1,3-dihydro-4*H*-furo[3,4-*b*]indol-3-one 20

Sodium iodide (45 mg, 0.30 mmol) was added to a solution of 4-*tert*-butoxycarbonyl-4-bromomethyl-1,3-dihydro-4*H*-furo[3,4-*b*]indol-3-one **25** (100 mg, 0.27 mmol) in acetone (5 ml) and the resulting mixture heated under reflux for 20 min, during which time the reaction mixture turned cloudy. Potassium carbonate (80 mg, 0.60 mmol) in water (2 ml) was added and the mixture heated for a further 20 min. The reaction mixture was cooled and solvent removed *in vacuo* and the residue taken up in dichloromethane (10 ml) and water (10 ml). The aqueous layer was further extracted with dichloromethane (2 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow solid which was used directly without any further purification. TBDMSOTf (0.12 g, 0.6 mmol) was added to a stirred of solution of the crude 4-*tert*-butoxycarbonyl-4-hydroxymethyl-1,3-dihydro-4*H*-furo[3,4-*b*]indol-3-one in pyridine (5 ml) at −35 °C and the resulting solution stirred at −35 °C for 5 h and then allowed to warm to room temperature overnight. The pyridine was removed *in vacuo* and the residue taken up in ethyl acetate (15 ml) and water (15 ml). The aqueous layer was further extracted with ethyl acetate (2 × 10 ml), and the combined organic extracts washed with water (2 × 20 ml), dried ($MgSO_4$) and purified by column chromatography on silica eluting with ethyl acetate–light petroleum (1 : 9) to give the *title compound* (78 mg, 68%) as a colourless oil; data as above.

Methyl 2-oxobutanoate (5-carboxy-2-chlorophenyl) hydrazone 27

Sodium nitrite (2.41 g, 34.99 mmol) in water (12 ml) was added dropwise to a solution of 3-amino-4-chlorobenzoic acid **26** (5.00 g, 29.15 mmol) in conc.. HCl (23 ml) and water (23 ml) at 0 °C not allowing the temperature to rise above 4 °C. The resulting yellow solution was allowed to stir at 0 °C for 10 min. Tin(II) chloride dihydrate (19.76 g, 87.46 mmol) in conc. HCl (20 ml) was then added and the mixture stirred for a further 10 min at 0 °C. Methyl 2-oxobutanoate (12.8 g, 58.31 mmol) was then added to the resulting white suspension and the mixture heated to 90 °C for 1 h. The reaction mixture was allowed to cool and the product extracted into ethyl acetate (5 × 100 ml). The organic extracts were washed repeatedly with hydrochloric acid (3 M, 6 × 300 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* **27** (8.29 g, 100%) as a cream solid; mp 228–230 °C (Found: MH^+, 285.0641. $C_{12}H_{13}{}^{35}ClN_2O_4$ + H requires 285.0642); ν_{max} (KBr)/cm^{-1} 3498, 1685, 1579, 1294, 1238, 1151, 1138, 1127; δ_H (300 MHz; DMSO) 13.16 (1H, v br s, COOH), 12.36 (1H, br s, NH), 8.10 (1H, d, *J* 1.8, ArH), 7.56 (1H, d, *J* 8.3, ArH), 7.48 (1H, dd, *J* 1.8, 8.3, ArH), 3.83 (3H, s, OMe), 2.55 (2H, q, *J* 7.3, C*H*$_2$Me), 1.14 (3H, t, *J* 7.3, CH_2*Me*); δ_C (75 MHz; DMSO) 167.0 (C), 163.8 (C), 140.0 (C), 134.2 (C), 131.3 (C), 130.1 (CH), 122.7 (CH), 121.9 (C), 114.5 (CH), 52.6 (Me), 26.3 (CH_2), 11.9 (Me).

7-Chloro-2-methoxycarbonyl-3-methylindole-4-carboxylic acid 28

A solution of **27** (8.29 g, 29.14 mmol) in acetic acid (146 ml) was heated to 90 °C and polyphosphoric acid (15 ml) was added and the reaction mixture stirred for 2 h at 90 °C. The reaction mixture was then allowed to cool and the solvent removed *in vacuo*. The residue was suspended in water, filtered and dried *in vacuo* to give the *title compound* **28** (6.81 g, 87%) as a cream solid; mp 243–245 °C (Found: MH^+, 268.0374. $C_{12}H_9{}^{35}ClNO_4$ + H requires 268.0376); ν_{max} (neat)/cm^{-1} 3602, 3255, 1715, 1687, 1231, 1179; δ_H (300 MHz; DMSO) 13.12 (1H, br s, COOH), 11.86 (1H, s, NH), 7.42 (2H, s, ArH), 3.90 (3H, s, OMe), 2.60 (3H, s, ArMe); δ_C (75 MHz; DMSO) 168.8 (C), 161.8 (C), 134.0 (C), 126.7 (C), 126.3 (C), 125.7 (C), 123.6 (CH), 122.2 (CH), 119.9 (C), 119..8 (C), 51.8 (Me), 11.8 (Me); *m*/*z* (CI) 270/268 (MH^+, 29/100%), 238/236 (20/63).

2-Methoxycarbonyl 3-methylindole-4-carboxylic acid 29

Palladium on carbon (10%; 3.44 g) was added to a solution of **28** (9.2 g, 34.39 mmol) in methanol (172 ml) which was purged with hydrogen and stirred under a balloon of hydrogen for 48 h. The reaction mixture was then filtered through a pad of Celite which was rinsed with methanol, and the solvent removed *in vacuo* to give the *title compound* **29** (6.8 g, 85%) as a pale cream solid; mp 191–194 °C (Found: MH^+, 234.0777. $C_{12}H_{11}NO_4$ + H requires 234.0766); ν_{max} (KBr)/cm^{-1} 3242, 2960, 2617, 1700, 1667, 1388, 1260, 1230, 1199; δ_H (400 MHz; DMSO) 12.92 (1H, v br s, CO_2H), 11.85 (1H, br s, NH), 7.61 (1H, dd, *J* 8.2, 1.1,

ArH), 7.37 (1H, dd, *J* 7,2, 1.1, ArH), 7.27 (1H, dd, 8.2, 7.2, ArH), 3.91 (3H, s, OMe), 2.63 (3H, s, Me); δ_C (100 MHz; DMSO) 169.4 (C), 162.2 (C), 137.0 (C), 127.5 (C), 124.4 (C), 123.8 (CH), 121.4 (CH), 118.5 (C), 115..8 (CH), 51.6 (Me), 11.7 (Me); *m/z* (CI) 234 (MH^+, 63%), 202 (100), 190 (54), 176 (47), 158 (46).

Methyl 4-hydroxymethyl-3-methylindole-2-carboxylate 30

Borane dimethylsulfide complex (7.75 ml, 15.52 mmol) was added dropwise to a solution of **29** (3.00 g, 12.93 mmol) in THF (13 ml) at 0 °C. The reaction mixture was then heated to 60 °C for 18 h, cooled and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate (50 ml) and saturated sodium hydrogen carbonate (50 ml) and the layers separated. The aqueous phase was further extracted with ethyl acetate (1 × 50 ml), the organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* **30** (2.19 g, 78%) as a yellow solid; mp 192–195 °C (Found: MH^+, 220.0972. $C_{12}H_{13}NO_3$ + H requires 220.0973); ν_{max} (neat)/cm^{-1} 3257, 2945, 2909, 2254, 1700, 1450, 1255, 1045, 1020, 999; δ_H (300 MHz; DMSO) 7.31 (1H, d, *J* 8.1, H-7), 7.18 (1H, dd, *J* 8.1, 7.0, H-6), 7.02 (1H, d, *J* 7.0, H-5), 5.16 (1H, t, *J* 5.4, CH_2OH), 4.89 (2H, d, *J* 5.4, CH_2OH), 3.87 (3H, s, OMe), 2.76 (3H, s, Me); δ_H (300 MHz; DMSO) 162.4 (C), 136.9 (C), 136.8 (C), 125.3 (C), 124.6 (CH), 122.7 (C), 119.5 (C), 118.7 (CH), 111.7 (CH), 61.6 (CH_2), 51.4 (Me), 11.7 (Me); *m/z* (CI) 220 (MH^+, 26%), 219 (M^+, 46), 202 (100), 188 (50).

Methyl 4-(*tert*-butyldimethylsiloxymethyl)-3-methylindole-2-carboxylate 17

tert-Butyldimethylchlorosilane (1.81 g, 12.0 mmol) was added to a solution of imidazole (1.02 g, 15.0 mmol) in DMF (10 ml) and the mixture stirred for 15 min. A solution of **30** (2.19 g, 10.0 mmol) in DMF (10 ml) was then added and the reaction mixture stirred for 18 h. The reaction mixture was diluted with water (50 ml) and the product extracted with ethyl acetate (2 × 50 ml). The combined extracts were washed with brine (100 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by column chromatography (20% ethyl acetate–light petroleum) to give the *title compound* **17** (1.36 g, 41%) as a pale yellow solid; data as above.

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References

1 Rhone-Poulenc S.A. Belg. Pat. 614211/1962 (*Chem. Abstr.*, 1963, **58**, 9601).
2 F. Benazet, M. Cartier, J. Florent, C. Godard, G. Jung, J. Lunel, D. Mancy, C. Pascal, J. Renaut, P. Tarridec, J. Theilleux, R. Tissier, M. Dubost and L. Ninet, *Experientia*, 1980, **36**, 414.
3 H. Depaire, J.-P. Thomas, A. Brun and G. Lukacs, *Tetrahedron Lett.*, 1977, 1365.
4 T. Prange, A. Ducruix, C. Pascard and J. Lunel, *Nature*, 1977, **265**, 189.
5 C. Pascard, A. Ducroix, J. Lunel and T. Prange, *J. Am. Chem. Soc.*, 1977, **99**, 6418.
6 T. Endo and H. Yonehara, *J. Antibiot.*, 1978, **31**, 623.
7 D. R. Houck, L. C. Chen, P. J. Keller, J. M. Beale and H. G. Floss, *J. Am. Chem. Soc.*, 1987, **109**, 1250.
8 D. R. Houck, L. C. Chen, P. J. Keller, J. M. Beale and H. G. Floss, *J. Am. Chem. Soc.*, 1988, **110**, 5800.
9 U. Mocek, A. R. Knaggs, R. Tsuchiya, T. Nguyen, J. M. Beale and H. G. Floss, *J. Am. Chem. Soc.*, 1993, **115**, 7557.
10 P. Tavecchia, M. Kurz, L. Colombo, R. Bonfichi, E. Selva, S. Lociuro, E. Marzorati and R. Ciabatti, *Tetrahedron*, 1996, **52**, 8763.
11 M. J. Rogers, E. Cundliffe and T. F. McCutchan, *Antimicrob. Agents Chemother.*, 1998, **42**, 715.
12 E. Cundliffe and J. Thompson, *J. Gen. Microbiol.*, 1981, **126**, 185.
13 Y. Y. Xing and D. E. Draper, *Biochemistry*, 1996, **35**, 1581.
14 D. E. Draper, in *The Many Faces of RNA*, ed. D. S. Eggleston, C. D. Prescott and N. D. Pearson, San Diego, 1998, 113.
15 C. H. McGinnis, C. A. Johnson and J. E. Fox, *Poultry Sci.*, 1978, **57**, 1641; M. Casteels, H. Bekaert and F. X. Buysse, *Rev. Agric. (Brussels)*, 1980, **33**, 1069.
16 S. Horii and N. Oku, *J. AOAC Int.*, 2000, **83**, 17.
17 M. Iwakawa, Y. Kobayashi, S. Ikuta and J. Yoshimura, *Chem. Lett.*, 1982, 1975.
18 C. Shin, Y. Nakamura, Y. Yamada, Y. Yonezawa, K. Umemura and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3151.
19 K. Umemura, T. Tate, M. Yamaura, J. Yoshimura, Y. Yonezawa and C. Shin, *Synthesis*, 1995, 1423.
20 K. Koerber-Plé and G. Massiot, *J. Heterocycl. Chem.*, 1995, **32**, 1309.
21 K. Umemura, H. Noda, J. Yoshimura, A. Konn, Y. Yonezawa and C. G. Shin, *Tetrahedron Lett.*, 1997, **38**, 3539.
22 K. Umemura, H. Noda, J. Yoshimura, A. Konn, Y. Yonezawa and C. G. Shin, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1391.
23 K. Koerber-Plé and G. Massiot, *Synlett*, 1994, 759.
24 C. Shin, Y. Yamada, K. Hayashi, Y. Yonezawa, K. Umemura, T. Tanji and J. Yoshimura, *Heterocycles*, 1996, **43**, 891.
25 P. T. Northcote, D. Williams, J. K. Manning, D. B. Borders, W. M. Maiese and M. D. Lee, *J. Antibiotics*, 1994, **47**, 894.
26 P. T. Northcote, M. Siegel, D. B. Borders and M. D. Lee, *J. Antibiotics*, 1994, **47**, 901.
27 K. L. Constantine, L. Mueller, S. Huang, S. Abid, K. S. Lam, W. Y. Li and J. E. Leet, *J. Am. Chem. Soc.*, 2002, **124**, 7284.
28 J. E. Leet, W. Y. Li, H. A. Ax, J. A. Matson, S. Huang, R. Huang, J. L. Cantone, D. Drexler, R. A. Dalterio and K. S. Lam, *J. Antibiot.*, 2003, **56**, 232.
29 W. Y. Li, J. E. Leet, H. A. Ax, D. R. Gustavson, D. M. Brown, L. Turner, K. Brown, J. Clark, H. Yang, J. Fung-Tomc and K. S. Lam, *J. Antibiot.*, 2003, **56**, 226.
30 M. C. Bagley, K. E. Bashford, C. L. Hesketh and C. J. Moody, *J. Am. Chem. Soc.*, 2000, **122**, 3301; C. J. Moody, R. A. Hughes, S. P. Thompson and L. Alcaraz, *J. Chem. Soc., Chem. Commun.*, 2002, 1760.
31 A similar indole substitution pattern can be obtained by photochemical ring contraction of 5-substituted quinoline-*N*-oxides; C. Kaneko, A. Yamamoto and H. Atsushi, *Chem. Pharm. Bull.*, 1979, **27**, 946.
32 H. Hemetsberger, D. Knittel and H. Weidman, *Monatsh. Chem.*, 1970, **101**, 161.
33 C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1333.
34 A. R. MacKenzie, C. J. Moody and C. W. Rees, *Tetrahedron*, 1986, **42**, 3259.
35 T. Martin and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1988, 241.
36 G. B. Jones and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2455.
37 For example, see: D. L. Boger, T. Ishizaki, H. Zarrinmayeh, P. A. Kitos and O. Suntornwat, *J. Org. Chem.*, 1990, **55**, 4499; M. S. Reddy and J. M. Cook, *Tetrahedron Lett.*, 1994, **35**, 5413.
38 V. P. Baillargeon and J. K. Stille, *J. Am. Chem. Soc.*, 1986, **108**, 452.
39 For early work, see: R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604; J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie and R. J. G. Seaarle, *J. Chem. Soc.*, 1965, 4831. For a more recent example, see: A. S. Cotterill, C. J. Moody and J. R. A. Roffey, *Tetrahedron*, 1995, **51**, 7223.
40 R. Y. Liu, P. W. Zhang, T. Gan and J. M. Cook, *J. Org. Chem.*, 1997, **62**, 7447.
41 C. K. Lau, C. Dufresne, P. C. Bélanger, S. Piétré and J. Scheigetz, *J. Org. Chem.*, 1986, **51**, 3038.
42 R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970.
43 Methoxide readily removes Boc groups from indole, for examples, see: K. J. Doyle and C. J. Moody, *Synthesis*, 1994, 1021.
44 J. C. A. Hunt, P. Laurent and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2378.
45 W. Y. Lee, W. Sim and K. D. Choi, *J. Chem. Soc., Perkin Trans. 1*, 1992, 881.