Cyclopenta[*b*]indoles. Part 2.[1] Model studies towards the tremorgenic mycotoxins

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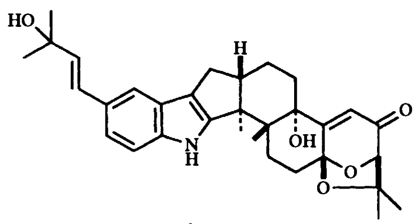
The 7-bromocyclopenta[*b*]indole **3** has been converted into the hydroxybutenyl derivatives **5** and **6**, and the tetrahydrofuranylidene derivative **8** in model studies towards the elaboration of paspalitrem and lolitrem type side chains. In a parallel approach, the cyclopentapyrrole **13** was converted into the fused α-pyrone **16** which acted as a pyrrole-2,3-quinodimethane, and underwent Diels–Alder reaction to give, after loss of carbon dioxide, the cyclopentaindoles **17–21**.

The indole alkaloids constitute one of the most structurally diverse class of natural products,[2] with the indole ring itself appearing in a vast array of different substitution patterns. The cyclopenta[*b*]indole ring system, in which the indole is fused across its 2,3-positions to a cyclopentane ring, appears in a number of alkaloids, notably the indole monoterpenoid yuehchukene[3] and the tremorgenic mycotoxins.[4] These structurally complex indole terpenoids, such as paspalitrem B **1**[5] and lolitrem B **2**,[6] represent a considerable challenge to the



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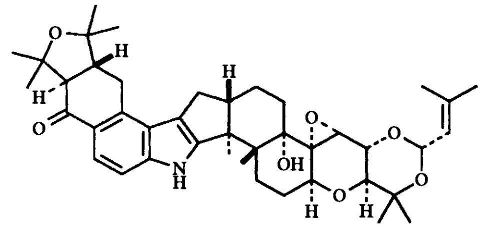

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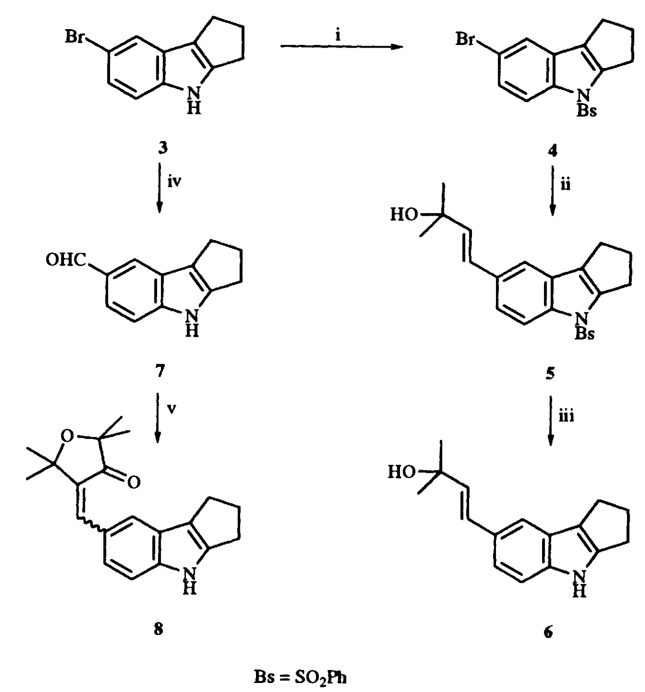
synthetic chemist, but have already been the subject of a number of studies.[7] In the previous paper, we described a new approach to the cyclopenta[*b*]indoles substituted in the cyclopentane ring,[1] and we now report the results of preliminary studies on the synthesis of compounds substituted in the benzene ring as models for the tremorgenic indoles.

Results and discussion

Our initial work was aimed at establishing simple methods for the introduction of appropriate side chains for the paspalitrems and lolitrem onto the indole nucleus, and therefore a simple model study was undertaken. Thus, 7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indole **3** was prepared in 60% yield by a Fischer indole synthesis starting from 4-bromophenylhydrazine hydrochloride and cyclopentanone. *N*-Protection as the benzenesulfonyl derivative **4**, was followed by a Heck reaction with 2-methylbut-3-en-2-ol to give the cyclopenta[*b*]indole **5**, containing the paspalitrem B side chain, in moderate yield. Deprotection gave the cyclopentaindole **6** (Scheme 1).

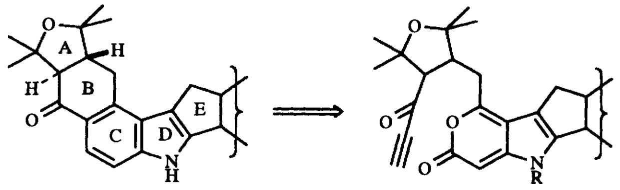


Scheme 1 *Reagents and conditions:* i, NaH, DMF, $PhSO_2Cl$; ii, 2-methylbut-3-en-2-ol, Ph_3P, $Pd(OAc)_2$, Et_3N, 120 °C; iii, aq. NaOH, MeOH, heat; iv, KH, ether, 0 °C, then Bu^tLi, −30 °C then DMF; v, 2,2,5,5-tetramethyltetrahydrofuran-3-one, aq. NaOH, MeOH, heat

The bromocyclopentaindole **3** was also converted into the corresponding aldehyde **7**. Thus, using the method of Rapoport and co-workers,[8] whereby the indole NH is initially deprotonated with potassium hydride before lithium–halogen exchange of the bromo group with *tert*-butyllithium, and quenching with *N*,*N*-dimethylformamide (DMF) the 7-aldehyde **7** was formed in 57% yield. Subsequent aldol reaction with 2,2,5,5-tetramethyltetrahydrofuran-3-one, readily available from 2,5-dimethylhex-3-yne-2,5-diol,[9] gave the cyclopentaindole **8** (as a mixture of alkene geometric isomers), containing an appropriate substituent for further elaboration into the A-ring of lolitrem B (Scheme 1).

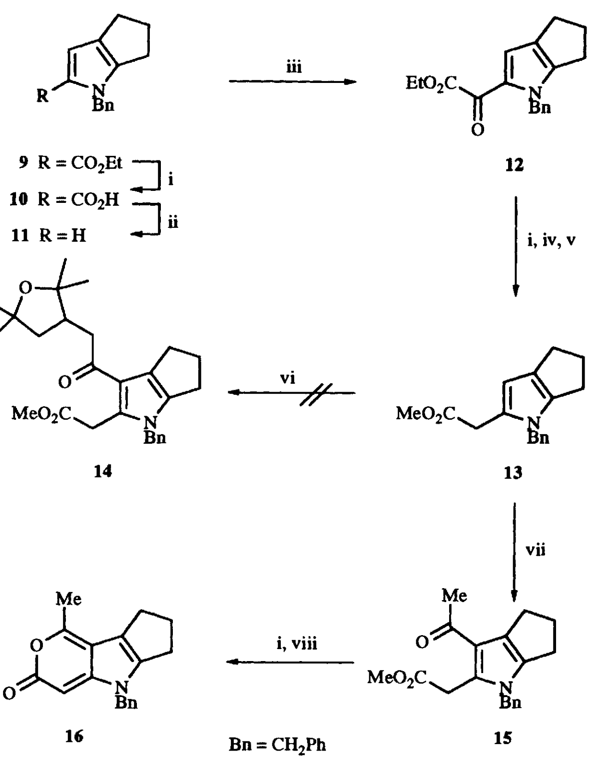
In an alternative approach to lolitrem B, we also investigated the possibility of constructing the ABCD-ring system of the natural product using an intramolecular Diels–Alder reaction of a stable pyrrole-2,3-quinodimethane, a pyranopyrrolone, as indicated in Scheme 2.[10]

The model system that we chose to study was based on the tetrahydrocyclopenta[*b*]pyrrole system as shown in Scheme 3,



Scheme 2

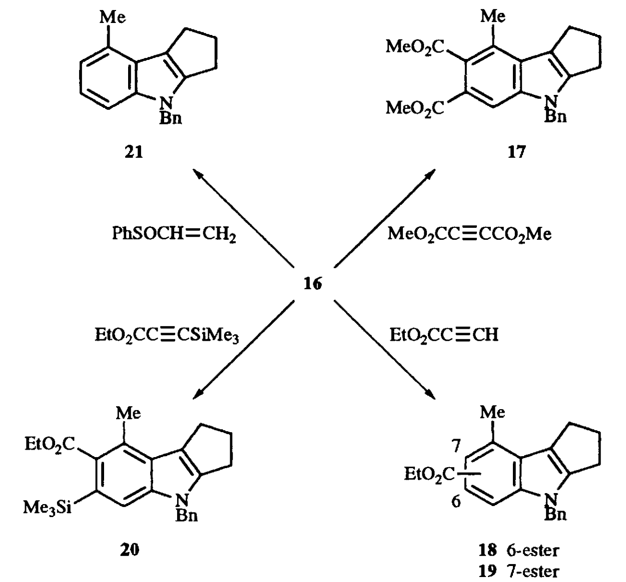
with the fused α-pyrone being built up in the usual way.[10] The known *N*-benzylcyclopentapyrrole ester **9**[11] was hydrolysed and decarboxylated to the parent ring system **11**. Reaction with ethyl oxalyl chloride introduced the required acetic acid type side chain, the keto group of which was removed using a Wolff–Kishner reduction. Finally, re-esterification gave the desired cyclopentapyrrole-2-acetic ester **13** (Scheme 3).



Scheme 3 *Reagents and conditions:* i, aq. KOH, THF, MeOH, heat; ii, heat; iii, EtO_2CCOCl, py, CH_2Cl_2; iv, $N_2H_4{\cdot}H_2O$, KOH, EtOH, heat; v, CH_2N_2, ether; vi, (2,2,5,5-tetramethyltetrahydrofuran-3-yl)acetyl chloride, $TiCl_4$, CH_2Cl_2; vii, AcCl, $TiCl_4$, CH_2Cl_2; viii, Bu^iO_2CCl, Et_3N, THF

Attempts to introduce the lolitrem ring A by acylation of the pyrrole **13** with (2,2,5,5-tetramethyltetrahydro-3-furyl)acetyl chloride, prepared from the corresponding acid,[12] were unsuccessful, with no evidence for the formation of the desired pyrrole **14**. Therefore, in order to test out the formation, and subsequent Diels–Alder reactions, of the required α-pyrone, a simpler acylation was effected. Thus, acetylation of the pyrrole **13** with acetyl chloride in the presence of titanium(IV) chloride gave the 3-acetylpyrrole **15**. Hydrolysis of the ester, followed by cyclodehydration of the resulting keto acid using isobutyl chloromethanoate gave the pyranopyrrolone **16** (Scheme 3).

As expected, the pyranopyrrolone **16** acted as a pyrrole-2,3-quinodimethane diene, and underwent Diels–Alder reaction with a range of alkynes (or an alkyne equivalent, phenyl vinyl sulfoxide) to give, after loss of carbon dioxide, the corresponding cyclopenta[*b*]indoles **17**–**21** (Scheme 4) in varying yield. Thus, reaction with dimethyl acetylenedicarboxylate gave the diester **17** (89%), and phenyl vinyl sulfoxide gave the cyclopentaindole **21** (47%). Ethyl propiolate, as expected on the basis of earlier results,[10] was not regioselective in its Diels–Alder reaction with the pyranopyrrolone and gave a mixture of the cyclopentaindole 6- and 7-esters **18** and **19** in a combined yield of 89%. The structure of the 6-ester **18** was assigned on the basis that its ^{1}H NMR spectrum showed two (approximate) singlets at δ 7.54 and 7.83 for 5-H and 7-H. In the 7-ester **19**, the aromatic protons 5-H and 6-H should appear as two doublets; one of these is clearly seen at δ 7.67 (*J* 8.7 Hz), the other is presumably hidden under the other aromatic signals. From the ^{1}H NMR spectrum of the mixture it was possible to determine that the 6-ester predominated in the ratio of *ca.* 1.8:1. Since the ester functionality was required at the cyclopentaindole 7-position if it were to be used for further elaboration towards lolitrem model structures, the use of ethyl trimethylsilylpropynoate as an alternative dienophile was investigated because it was expected to give greater regioselectivity in the desired sense.[10] This indeed proved to be the case, and the Diels–Alder reaction gave, after loss of carbon dioxide, the cyclopentaindole 7-ester **20** in 53% yield (Scheme 4). The regiochemistry of the Diels–Alder reacion was proved by the subsequent desilylation of **20** to the 7-ester **19**.



Scheme 4

Experimental

For general points, see ref. 13.

7-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indole 3

A mixture of 4-bromophenylhydrazine hydrochloride (3 g, 13 mmol) and cyclopentanone (1.2 cm^3, 13 mmol) was refluxed in dry ethanol for 4 h. After removal of ethanol under reduced pressure the residue was taken up in dichloromethane and washed with water. The organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* **3** (2.3 g, 60%) as a brown powder, mp 136–137 °C (from methanol–water) (Found: C, 56.0; H, 4.2; N, 5.9%; M$^+$, 234.9997; $C_{11}H_{10}BrN$ requires C, 56.0; H, 4.3; N, 5.9%; *M*, 234.9996; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3464, 3054 and 2977; δ_H(250 MHz; $CDCl_3$) 2.54 (2 H, m), 2.77 (4 H, m), 7.10 (2 H, s), 7.25 (1 H, s) and 7.87 (1 H, s, NH); δ_C(62.5 MHz; $CDCl_3$) 24.18 (CH_2), 25.76 (CH_2), 28.50 (CH_2), 112.52 (CH), 112.63 (C), 119.38 (C), 121.03 (CH), 123.04 (CH), 126.30 (C), 139.47 (C) and 145.13 (C); *m*/*z* 235 (M$^+$, 100%) and 154 (50).

4-Phenylsulfonyl-7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]-indole 4

To a suspension of freshly washed and dried sodium hydride (130 mg, 3.4 mmol) in dry *N,N*-dimethylformamide (DMF) (6 cm^3) was added a solution of the indole **3** (600 mg, 2.8 mmol) in dry DMF (4 cm^3). When hydrogen evolution had ceased, benzenesulfonyl chloride (0.4 cm^3, 3.4 mmol) was added dropwise to it and the mixture was stirred at room temperature for 3 h. After dilution with brine the mixture was extracted with dichloromethane and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* **4** (870 mg, 86%) as a brown powder, mp 170 °C (decomp.) (from methanol–water) (Found: C, 54.2; H, 3.8; N, 3.8. $C_{17}H_{14}BrNO_2S$ requires C, 54.3; H, 3.8; N, 3.7%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3054 and 2987; δ_H(250 MHz; $CDCl_3$) 2.51 (2 H, m), 2.68 (2 H, m), 3.13 (2 H, m), 7.33 (2 H, m), 7.46 (4 H, m) and 7.82 (2 H, m); δ_C(62.5 MHz; $CDCl_3$) 23.94 (CH_2), 27.42 (CH_2), 28.01 (CH_2), 115.73 (CH), 116.96 (C), 121.94 (CH), 126.06 (CH), 126.53 (CH), 128.26 (C), 128.90 (CH), 129.36 (CH), 133.83 (CH), 138.55 (C), 138.97 (C) and 145.17 (C); *m/z* 375 (M^+, 35%), 234 (65), 154 (60), 127 (40) and 77 (100).

4-Phenylsulfonyl-7-[(*E*)-3-hydroxy-3-methylbut-1-enyl]-1,2,3,4-tetrahydrocyclopenta[*b*]indole 5

A mixture of the indole **4** (200 mg, 0.5 mmol), palladium(II) acetate (12 mg, 0.05 mmol), triphenylphosphine (28 mg, 0.1 mmol), 2-methylbut-3-en-2-ol (0.08 cm^3, 0.8 mmol) and dry triethylamine (0.14 cm^3, 1.0 mmol) was placed in a strong glass bottle with a Teflon screw cap, the system flushed with nitrogen and the bottle tightly sealed. The system was heated at 120 °C for 60 h. After cooling, the residue was extracted with dichloromethane and the extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to chromatography (silica, diethyl ether–light petroleum, 1:1) to give the *title compound* **5** (91 mg, 45%) as a colourless powder, mp 121–123 °C (from methanol–water) (Found: M^+, 381.1426. $C_{22}H_{23}NO_3S$ requires *M*, 381.1398); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3163, 3050, 2969, 2952 and 2857; δ_H(250 MHz; $CDCl_3$) 1.41 (6 H, s, 2 × CH_3), 1.77 (1 H, s, OH), 2.50 (2 H, m), 2.67 (2 H, m), 3.10 (2 H, m), 6.29 (1 H, d, *J* 16, C=CH), 6.58 (1 H, d, *J* 16, C=CH), 7.24 (2 H, m), 7.42 (3 H, m), 7.81 (2 H, dd, *J* 1.5 and 7.4) and 7.96 (1 H, d, *J* 8.6); δ_C(62.5 MHz; $CDCl_3$) 23.94 (CH_2), 27.35 (CH_2), 27.93 (CH_2), 29.86 (CH_3), 70.98 (C), 114.33 (CH), 116.90 (CH), 121.84 (CH), 126.35 (CH), 126.37 (CH), 126.40 (C), 126.87 (C), 129.16 (CH), 132.47 (C), 133.54 (CH), 136.76 (CH), 138.59 (C), 139.64 (C) and 144.15 (C); *m/z* 381 (M^+, 20%), 363 (30), 222 (100), 77 (65) and 64 (20).

7-[(*E*)-3-Hydroxy-3-methylbut-1-enyl]-1,2,3,4-tetrahydrocyclopenta[*b*]indole 6

The indole **5** (25 mg) was heated under reflux in 10% sodium hydroxide–methanol for 2 h after which the solution was diluted with water and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* **6** (14 mg, 91%) as a colourless solid, mp 142–144 °C (from methanol–water) (Found: M^+, 241.1470. $C_{16}H_{19}NO$ requires *M*, 241.1466); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3431, 3222, 3052, 2960 and 2848; δ_H(250 MHz; $CDCl_3$) 1.43 (6 H, s, 2 × CH_3), 1.56 (1 H, s, OH), 2.50 (2 H, m), 2.79 (4 H, m), 6.28 (1 H, d, *J* 16, C=CH), 6.64 (1 H, d, *J* 16, C=CH), 7.15 (1 H, dd, *J* 1.6 and 6.8), 7.20 (1 H, d, *J* 8.4), 7.43 (1 H, s) and 7.81 (1 H, s, NH); δ_C(62.5 MHz; $CDCl_3$) 24.24 (CH_2), 25.74 (CH_2), 28.49 (CH_2), 29.84 (CH_3), 71.02 (C), 111.19 (CH), 116.76 (CH), 119.04 (CH), 119.92 (C), 124.88 (C), 127.59 (CH), 128.47 (C), 134.27 (CH), 140.55 (C) and 144.17 (C); *m/z* 241 (M^+, 25%), 223 (100), 208 (90), 194 (75) and 180 (80).

1,2,3,4-Tetrahydrocyclopenta[*b*]indole-7-carbaldehyde 7

To a suspension of freshly washed and dried potassium hydride (180 mg, 1.6 mmol) in dry diethyl ether (ether) (10 cm^3) at 0 °C was added dropwise, a solution of the indole **3** (370 mg, 1.6 mmol) in dry ether (15 cm^3). After being stirred at 0 °C for 15 min the mixture was cooled to −30 °C and precooled Bu^tLi (1.85 cm^3, 1.6 mmol) was added to it so that the temperature did not rise above −30 °C. After being stirred at −30 °C for a further 10 min, the mixture was treated with dry DMF (0.3 cm^3, 1.6 mmol), added dropwise. The mixture was stirred at −30 °C for 30 min and then allowed to warm to room temperature after which it was diluted with water and extracted with ether. The combined extracts were washed with dilute hydrochloric acid, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to chromatography (silica, light petroleum–ether, 1:1) to give the *title compound* **7** (166 mg, 57%) as an orange powder, mp 144–146 °C (from methanol–water) (Found: C, 77.3; H, 6.0; N, 7.4%; M^+, 185.0797. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%; *M*, 185.0840); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3296, 2851, 2818 and 1676; δ_H(250 MHz; $CDCl_3$) 2.56 (2 H, m), 2.86 (4 H, m), 7.35 (1 H, d, *J* 8.4), 7.68 (1 H, dd, *J* 1.6 and 6.8), 7.97 (1 H, s), 8.34 (1 H, s, NH) and 10.00 (1 H, s, CHO); δ_C(62.5 MHz; $CDCl_3$) 24.28 (CH_2), 25.83 (CH_2), 28.50 (CH_2), 111.70 (CH), 121.33 (CH), 121.41 (C), 123.23 (CH), 124.50 (C), 129.25 (C), 144.47 (C), 145.69 (C) and 192.74 (CHO); *m/z* 185 (M^+, 100%), 173 (55), 156 (30) and 128 (25).

7-(2,2,5,5-Tetramethyl-3-oxotetrahydro-4-furylidene)-1,2,3,4-tetrahydrocyclopenta[*b*]indole 8

To a mixture of the indole **7** (62 mg, 0.38 mmol) and 2,2,5,5-tetramethyltetrahydrofuran-3-one (120 mg, 0.76 mmol) in methanol (5 cm^3) was added 10% aqueous sodium hydroxide (10 cm^3). The system was stirred under reflux for 2 h. After cooling, the mixture was extracted with dichloromethane, and the extract dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to chromatography (silica, light petroleum–ether, 1:1) to give the *title compound* **8** as two alkene isomers:

Minor isomer (8 mg, 8%) as a yellow oil (Found: M^+, 309.1741. $C_{20}H_{23}NO_2$ requires *M*, 309.1728); $\nu_{max}(film)/cm^{-1}$ 3342 and 1701; δ_H(250 MHz; $CDCl_3$) 1.36 (6 H, s), 1.54 (6 H, s), 2.55 (2 H, m), 2.86 (4 H, m), 6.79 (1 H, s), 7.29 (1 H, dd, *J* 2.3 and 8.6), 7.94 (1 H, dd, *J* 1.7 and 6.8), 8.01 (1 H, s, NH) and 8.27 (1 H, d, *J* 1.1); δ_C(62.5 MHz; $CDCl_3$) 24.18 (CH_2), 25.80 (CH_2), 26.35 (CH_3), 26.63 (CH_3), 28.53 (CH_2), 29.00 (CH_3), 31.71 (CH_3), 79.91 (C), 110.81 (CH), 111.33 (CH), 122.69 (CH), 123.17 (CH), 123.68 (CH), 124.62 (CH), 138.50 (CH), 141.55 (CH) and 201.51 (CO); *m/z* 309 (M^+, 35%), 294 (100), 223 (25) and 43 (40).

Major isomer (23 mg, 22%) as a yellow solid, mp 110 °C (decomp.) (Found: M^+, 309.1728. $C_{20}H_{23}NO_2$ requires *M*, 309.1728); $\nu_{max}(film)/cm^{-1}$ 3285 and 1712; δ_H(250 MHz; $CDCl_3$) 1.36 (6 H, s), 1.68 (6 H, s), 2.57 (2 H, m), 2.82 (4 H, m), 7.30 (2 H, s), 7.64 (1 H, s), 7.67 (1 H, s) and 8.22 (1 H, s, NH); δ_C(62.5 MHz; $CDCl_3$) 24.25 (CH_2), 25.87 (CH_2), 26.23 (CH_3), 28.62 (CH_2), 29.08 (CH_3), 79.86 (C), 80.02 (C), 111.45 (CH), 120.56 (C), 122.83 (CH), 123.74 (CH), 124.90 (C), 125.02 (C), 133.04 (C), 136.15 (C), 138.69 (CH), 141.70 (C), 145.32 (C) and 207.60 (CO); *m/z* 309 (M^+, 35%), 294 (100), 223 (23) and 43 (43).

1-Benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-2-carboxylic acid 10

Aqueous potassium hydroxide (5 mol dm^{-3}; 30 cm^3) was added to a stirred solution of ethyl 1-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-2-carboxylate **9**[11] (4.04 g, 15.0 mmol) in tetrahydrofuran (30 cm^3) and methanol (30 cm^3) and the mixture heated under reflux for 4 h. After cooling to room temperature, the mixture was diluted with water, extracted with ether, and this extract was discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The combined extracts were washed with water and brine, dried ($MgSO_4$), and evaporated and the residue was recrystallised (ether–light petroleum) to give the *title compound* **10** (3.24 g, 90%), mp 154–156 °C (decomp.) (Found: C, 74.45; H, 6.2; N, 6.0. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3428 and 1641; δ_H(250 MHz; $CDCl_3$) 2.40 (2 H, m), 2.61 (4 H, m), 5.47 (2 H, s, CH_2Ph), 6.68 (1 H, s, 3-H), 7.08 (2 H, m) and 7.28 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 24.77 (CH_2), 24.96 (CH_2), 28.46 (CH_2) 49.93 (CH_2), 113.16 (CH), 126.35 (C), 126.76 (CH), 126.98 (CH), 128.39 (CH), 138.66 (C), 147.17 (C), 162.95 (C) and 201.59 (CO_2H); *m/z* 241 (M^+, 19%), 197 (23) and 91 (100).

1-Benzyl-1,4,5,6-tetrahydrocyclopent[*b*]pyrrole 11

The acid **10** (2.74 g, 11.35 mmol) was heated under nitrogen until it melted and evolution of carbon dioxide ceased. After cooling to room temperature, the residue was chromatographed (silica, light petroleum–ether, 5:1) to give the *title compound* **11** (2.22 g, 99%) as a pale yellow oil (Found: M^+, 197.1204. $C_{14}H_{15}N$ requires *M*, 197.1204); $\nu_{max}(film)/cm^{-1}$ 3096, 3063, 3030, 2946, 2901 and 2853; δ_H(250 MHz; $CDCl_3$) 2.33 (2 H, m), 2.42 (2 H, m), 2.53 (2 H, m), 4.93 (2 H, s, CH_2Ph), 5.93 (1 H, d, *J* 2.7, 2-H), 6.55 (1 H, d, *J* 2.7, 3-H), 7.11 (2 H, m) and 7.30 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 24.51 (CH_2), 25.68 (CH_2), 29.22 (CH_2), 51.87 (CH_2), 103.19 (2-C), 123.41 (3-C), 126.50 (C), 127.01 (CH), 127.42 (CH), 128.65 (CH) and 138.29 (C); *m/z* 197 (M^+, 40%) and 91 (100).

Ethyl 2-(1-benzyl-1,4,5,6-tetrahydrocyclopent[*b*]pyrrol-2-yl)-2-oxoethanoate 12

A solution of pyridine (260 mg, 3.29 mmol) in dry dichloromethane (6 cm^3) was added dropwise to a stirred solution of ethyl (chlorocarbonyl)methanoate (412 mg, 3.02 mmol) in dry dichloromethane (6 cm^3) at −78 °C under nitrogen. A solution of the pyrrole **11** (541 mg, 2.74 mmol) in dry dichloromethane (6 cm^3) was added dropwise to it and the solution allowed to warm slowly to room temperature. After being stirred for 48 h, the solution was washed with dilute hydrochloric acid, water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica, light petroleum–ether, 1:2) to give the *title compound* **12** (734 mg, 90%), mp 63–64 °C (Found: C, 72.5; H, 6.4; N, 4.7. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1732 and 1631; δ_H(250 MHz; $CDCl_3$) 1.37 (3 H, t, *J* 7.1, CH_2CH_3), 2.41 (2 H, m), 2.63 (4 H, m), 4.35 (2 H, q, *J* 7.1, CH_2CH_3), 5.53 (2 H, s, CH_2Ph), 7.04 (1 H, s, 3-H), 7.14 (2 H, m) and 7.24 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 14.04 (CH_3), 24.52 (CH_2), 24.77 (CH_2), 28.51 (CH_2), 51.00 (CH_2), 61.76 (CH_2), 119.65 (CH), 127.03 (CH), 127.37 (CH), 128.53 (CH), 129.43 (C), 130.59, 137.36, 153.96, 172.85 and 201.47 (CO_2Et); *m/z* 297 (M^+, 15%), 224 (100) and 91 (100).

Methyl 1-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrol-2-ylacetate 13

To a solution of the ester **12** (4.38 g, 14.73 mmol) in tetrahydrofuran (90 cm^3) and methanol (10 cm^3) was added aqueous potassium hydroxide (2 mol dm^{-3}; 75 cm^3) dropwise with stirring. The mixture was stirred for 1 h, diluted with water, extracted with ether, and this extract was discarded. The aqueus phase was acidified and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue recrystallised (ethyl acetate–light petroleum) to give 2-(1-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrol-2-yl)-2-oxoethanoic acid (3.85 g, 97%), mp 133–136 °C (Found: C, 71.2; H, 5.6; N, 5.2. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3289, 1755 and 1607; δ_H(250 MHz; $CDCl_3$) 2.44 (2 H, m), 2.68 (4 H, m), 5.53 (2 H, s, CH_2Ph), 7.06 (2 H, m), 7.30 (3 H, m) and 7.89 (1 H, s, 3-H); δ_C(62.5 MHz; $CDCl_3$) 24.54 (CH_2), 28.51 (CH_2), 51.40 (CH_2), 123.47 (CH), 126.51 (CH), 127.63 (CH), 128.76 (CH), 129.97, 131.34, 137.03, 157.69, 161.08 and 167.55; *m/z* 269 (M^+, 10%), 224 (40) and 91 (100).

A mixture of the above keto acid (1.58 g, 5.87 mmol), powdered potassium hydroxide (2.14 g, 38.14 mmol) and hydrazine hydrate (0.57 cm^3, 11.73 mmol) in ethanol (5 cm^3) was heated under nitrogen at 80 °C (oil bath) for 1 h and then at 150 °C for 1 h. After cooling to room temperature, the mixture was diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dry ether (10 cm^3) and ethereal diazomethane was added to the solution until evolution of nitrogen ceased. The solution was then evaporated and the residue chromatographed (silica, light petroleum–ether, 4:1) to give the *title compound* **13** (1.49 g, 94%) as a yellow oil (Found: C, 75.5; H, 7.0; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%); $\nu_{max}(film)/cm^{-1}$ 1738; δ_H(250 MHz; $CDCl_3$) 2.35 (2 H, m), 2.50 (2 H, m), 2.63 (2 H, m), 3.49 (2 H, s), 3.55 (3 H, s), 5.01 (2 H, s, CH_2Ph), 5.89 (1 H, s, 3-H), 6.98 (2 H, m) and 7.26 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 24.98 (CH_2), 25.77 (CH_2), 28.57 (CH_2), 33.32 (CH_2), 48.86 (CH_2), 52.00 (CH_3), 104.31 (CH), 125.01 (C), 126.27 (CH), 126.95 (CH), 127.21 (C), 128.65 (CH), 138.23 (C), 139.12 (C) and 171.29 (CO); *m/z* 269 (M^+, 20%), 210 (58) and 91 (100).

Methyl 3-acetyl-1-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]-pyrrol-2-ylacetate 15

A solution of acetyl chloride (64 mg, 0.81 mmol) and titanium(IV) chloride (0.27 cm^3, 2.43 mmol) in dry dichloromethane (3 cm^3) was stirred under nitrogen at 0 °C for 10 min after which a solution of the pyrrole **13** (109 mg, 0.40 mmol) in dry dichloromethane (2 cm^3) was added dropwise to it. After the mixture had been allowed to warm to room temperature it was stirred for 24 h and then poured into water and extracted with dichloromethane. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica, light petroleum–ether, 1:4) to give the *title compound* **15** (71 mg, 56%), mp 118–119 °C (Found: C, 73.1; H, 6.8; N, 4.5. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.8; N, 4.5%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1727 and 1648; δ_H(250 MHz; $CDCl_3$) 2.36 [3 H, s, (CO)CH_3], 2.40 (2 H, m), 2.52 (2 H, m), 2.84 (2 H, m), 3.60 (3 H, s, CO_2CH_3), 4.04 (2 H, s), 4.99 (2 H, s, CH_2Ph), 6.99 (2 H, m) and 7.31 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 24.81 (CH_2), 27.71 (CH_2), 27.89 (CH_2), 29.76 [(CO)CH_3], 31.71 (CH_2), 48.68 (CH_2), 51.98 (CO_2CH_3), 118.37 (C), 126.30 (CH), 126.42 (C), 127.64 (CH), 128.78 (CH), 132.82 (C), 136.42 (C), 138.38 (C), 170.73 (CO) and 195.20 (CO); *m/z* 311 (M^+, 20%), 279 (40), 252 (25), 188 (25) and 91 (100).

4-Benzyl-8-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]pyrano-[3,4-*d*]pyrrol-6-one 16

To a solution of the ester **15** (193 mg, 0.62 mmol) in tetrahydrofuran (5 cm^3) and methanol (1 cm^3) was added aqueous potassium hydroxide (2 mol dm^{-3}; 4 cm^3) dropwise with stirring. The mixture was stirred at room temperature for 2 h after which it was diluted with water and extracted with ether and this extract was discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate and the combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue recrystallised (ethyl acetate–light petroleum) to give 3-*acetyl*-1-*benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylacetic acid* (183 mg, 99%), mp 170–172 °C (decomp.) (Found: M^+, 297.1365. $C_{18}H_{19}NO_3$

requires M, 297.1365); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1711 and 1643; δ_H(250 MHz; $CDCl_3$) 2.46 (2 H, m), 2.48 [3 H, s, (CO)CH_3], 2.54 (2 H, m), 2.86 (2 H, m), 3.76 (2 H, s), 5.14 (2 H, s, CH_2Ph), 7.01 (2 H, m) and 7.31 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 24.79 (CH_2), 27.23 (CH_2), 27.85 (CH_2), 28.72 (CH_3), 34.84 (CH_2), 48.75 (CH_2), 118.98 (C), 126.23 (CH), 126.90 (C), 127.89 (CH), 128.94 (CH), 133.27 (C), 135.82 (C), 139.69 (C), 169.91 (CO) and 199.19 (CO); m/z 297 (M^+, 5), 253 (85), 238 (25), 162 (30) and 91 (100).

To a solution of the above keto acid (154 mg, 0.52 mmol) and triethylamine (0.22 cm^3, 1.55 mmol) in dry tetrahydrofuran (10 cm^3) at 0 °C under nitrogen was added isobutyl chloroformate (106 mg, 0.78 mmol) in dry tetrahydrofuran (5 cm^3) dropwise with stirring. The mixture was then allowed to warm to room temperature after which it was stirred overnight. After this, the mixture was poured into brine and extracted with ethyl acetate and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica, ether–methanol, 19:1) to give the *title compound* **16** (133 mg, 92%), mp 158–161 °C (Found: C, 77.1; H, 6.05; N, 4.95. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1685; δ_H(250 MHz; $CDCl_3$) 2.43 (3 H, s, CH_3), 2.46 (2 H, m), 2.57 (2 H, m), 2.74 (2 H, m), 4.81 (2 H, s, CH_2Ph), 5.48 (1 H, s), 7.14 (2 H, m) and 7.30 (3 H, m); δ_C(62.5 MHz; $CDCl_3$) 18.16 (CH_3), 25.05 (CH_2), 27.52 (CH_2), 48.15 (CH_2), 81.92 (CH), 116.52 (C), 126.85 (CH), 127.96 (CH), 128.89 (CH), 135.82, 150.14, 157.78 and 164.62; m/z 279 (M^+, 5%), 91 (20) and 44 (100).

Diels–Alder reactions

Dimethyl 4-benzyl-8-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]-indole-6,7-dicarboxylate 17

A mixture of the pyranopyrrolone **16** (55 mg, 0.20 mmol) and dimethyl acetylenedicarboxylate (56 mg, 0.39 mmol) in chlorobenzene (10 cm^3) was refluxed under nitrogen for 4 h. The solvent was evaporated and the residue chromatographed (silica, light petroleum–ether, 1:2) to give the *title compound* **17** (66 mg, 89%), mp 182–184 °C (Found: C, 72.9; H, 6.1; N, 3.7. $C_{23}H_{23}NO_4$ requires C, 73.2; H, 6.1; N, 3.7%); ν_{max}(Nujol)/cm^{-1} 1718 and 1250; δ_H(250 MHz; $CDCl_3$) 7.78 (1 H, s, 5-H), 7.29–7.26 (3 H, m), 7.03–7.00 (2 H, m), 5.27 (2 H, s, CH_2Ph), 3.94 (3 H, s, CO_2Me), 3.85 (3 H, s, CO_2Me), 3.04 (2 H, t, J 7), 2.74 (2 H, t, J 7), 2.55 (3 H, s, 8-Me) and 2.55–2.45 (2 H, m); m/z 377 (M^+, 66%), 346 (21) and 91 (100).

4-Benzyl-8-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole 21

A mixture of the pyranopyrrolone **16** (43 mg, 0.15 mmol) and phenyl vinyl sulfoxide (117 mg, 0.77 mmol) in chlorobenzene (1 cm^3) was refluxed under nitrogen for 24 h and then evaporated. The residue was chromatographed (silica, light petroleum–dichloromethane, 5:1) to give the *title compound* **21** (19 mg, 47%), mp 71–73 °C (Found: M^+, 261.1517. $C_{19}H_{19}N$ requires M, 261.1517); $\nu_{max}(CHCl_3)/cm^{-1}$ 1450, 1426, 1350 and 696; δ_H(250 MHz; $CDCl_3$) 7.31–7.17 (3 H, m), 7.09 (2 H, d, J 8), 7.04–6.92 (2 H, m), 6.82 (1 H, d, J 7), 5.20 (2 H, s, CH_2Ph), 3.05 (2 H, t, J 6.9), 2.75 (2 H, t, J 6.9), 2.59 (3 H, s, 8-Me) and 2.51 (2 H, quintet, J 6.9, $CH_2CH_2CH_2$); m/z 261 (M^+, 100%), 218 (12), 170 (31) and 91 (55).

Mixture of ethyl 4-benzyl-8-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-7-carboxylate 19 and ethyl 4-benzyl-8-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-6-carboxylate 18

A mixture of ethyl propiolate (0.07 cm^3, 0.7 mmol) and the pyranopyrrole **16** (50 mg, 0.18 mmol) in chlorobenzene (5 cm^3) was refluxed under nitrogen for 12 h after which the mixture was evaporated under reduced pressure to give the *title compounds* **18** and **19** (1.8:1 mixture) (53 mg, 89%) as an orange semi-solid (Found: M^+, 333.1734; $C_{22}H_{23}NO_2$ requires M, 333.1734); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3062, 3031, 2936 and 1702; δ_H(250 MHz; $CDCl_3$) 1.40 (6 H, 2 × t, J 7.1, 2 × CH_2CH_3), 2.51 (4 H, m), 2.59 (3 H, s, CH_3), 2.72 (4 H, m), 2.86 (3 H, s, CH_3), 3.02 (4 H, m), 4.32 (4 H, 2 × q, J 7.1, 2 × CH_2CH_3), 5.17 (2 H, s, CH_2Ph), 5.25 (2 H, s, CH_2Ph), 7.06 (4 H, m), 7.26 (6 H, m), 7.54 (1 H, s), 7.67 (1 H, d, J 8.7) and 7.83 (1 H, s); δ_C(62.5 MHz; $CDCl_3$) 14.41 (CH_3), 17.68 (CH_3), 18.87 (CH_3), 24.76 (CH_2), 24.98 (CH_2), 25.85 (CH_2), 26.94 (CH_2), 28.31 (CH_2), 28.47 (CH_2), 48.30 (CH_2), 60.07 (CH_2), 60.40 (CH_2), 107.04 (CH), 109.79 (CH), 119.00, 119.55, 120.30, 120.56 (CH), 122.22, 123.40 (CH), 126.48 (CH), 126.56 (CH), 127.45 (CH), 127.80, 128.69 (CH), 130.00, 134.05, 134.55, 137.50, 140.20, 147.05, 149.10, 167.00 (CO) and 169.00 (CO); m/z 333 (M^+, 75%), 288 (10) and 91 (100). The residue was subjected to chromatography (silica, light petroleum–ether, 2:1) to give the ester **19** (5 mg), δ_H(250 MHz; $CDCl_3$) 1.38 (3 H, t, J 7.1, CH_2CH_3), 2.51 (2 H, m), 2.70 (2 H, m), 2.87 (3 H, s, CH_3), 3.09 (2 H, m), 4.30 (2 H, q, J 7.1, CH_2CH_3), 5.21 (2 H, s, CH_2Ph), 7.06 (2 H, m), 7.25 (4 H, m) and 7.68 (1 H, d, J 8.7).

Ethyl 4-benzyl-8-methyl-6-trimethylsilyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-7-carboxylate 20

A mixture of ethyl 3-(trimethylsilyl)propynoate (0.05 cm^3, 0.3 mmol) and the pyranopyrrole **16** (25 mg, 0.09 mmol) in chlorobenzene (5 cm^3) was refluxed under nitrogen for 48 h after which it was evaporated under reduced pressure. The residue was subjected to chromatography (silica, light petroleum–ether, 3:1) to give the *title compound* **20** (19 mg, 53%) as a brown viscous oil (Found: M^+, 405.2124; $C_{25}H_{31}NO_2Si$ requires M, 405.2124; ν_{max}(film)/cm^{-1} 3030, 2954 and 1709; δ_H(250 MHz; $CDCl_3$) 0.14 [9 H, s, $(CH_3)_3$] 1.29 (3 H, t, J 7.1, CH_2CH_3), 2.40 (2 H, m), 2.51 (3 H, s, CH_3), 2.70 (2 H, m), 2.95 (2 H, m), 4.25 (4 H, q, J 7.1, CH_2CH_3), 5.11 (2 H, s, CH_2Ph), 6.97 (2 H, m) and 7.16 (4 H, m); δ_C(62.5 MHz; $CDCl_3$) 0.31 [$(CH_3)_3$], 14.26 (CH_3), 16.91 (CH_3), 24.89 (CH_2), 26.44 (CH_2), 28.44 (CH_2), 48.35 (CH_2), 60.63 (CH_2), 114.15 (CH), 118.95 (C), 126.77 (CH), 127.45 (CH), 128.07 (CH), 129.16 (CH), 129.27 (CH), 129.94 (C), 137.62 (C), 140.68 (C), 147.01 (C) and 171.95 (CO); m/z 405 (M^+, 3%), 390 (15), 91 (100), 84 (20) and 49 (20).

Ethyl 4-benzyl-8-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-7-carboxylate

The indole **20** (16 mg) was refluxed in trifluoroacetic acid (1 cm^3) and water (0.5 cm^3) under nitrogen for 2 h after which the mixture was diluted with water and extracted with ether. The combined ether extracts were washed with aqueous sodium hydrogen carbonate until the washings remained basic, and then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to chromatography (silica, light petroleum–ether, 3:1) to give the title compound (2 mg, 15%) as a yellow oil, data as given for **19** above.

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