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SYNTHESIS OF CYCLOPENT[b]INDOLONES

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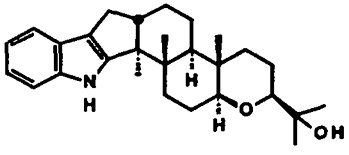
Abstract: A number of cyclopent[b]indol-1-ones as well as -3-ones have been synthesized, using a new methodology involving intramolecular ring closure of α,β-unsaturated acylindoles. In some cases 1,2,3,4-tetrahydrocarbazol-4-ones were obtained. This methodology was used in the syntheses of the indole alkaloid yuehchukene and the carbazole alkaloid analogue demethoxycarbazomycin B.

The isolation and identification of alkaloids containing a cyclopent[b]indole unit is proceeding rapidly. This group includes a large number of tremorgenic mycotoxins[1] such as the penitrems, the janthitrems, the lolitrems, paxilline, paspaline[2] etc., here exemplified by the structure of paspaline (1). Another natural product with a cyclopent[b]indole unit is the monoterpenoid alkaloid yuehchukene (2) which has recently been isolated[3] from the roots of *Murraya paniculata*. Yuehchukene is reported to possess strong antiimplantation activity in rats[4] and has been synthesized by several groups.[5-10] Some reduced cyclopent[b]indoles have also been reported, *e.g.* polyveoline[11] (3) and borreverine.[12]



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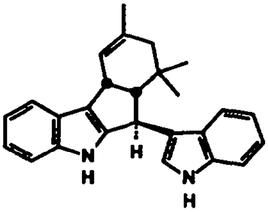

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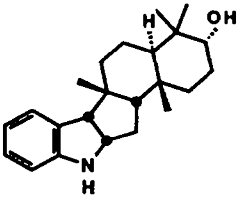

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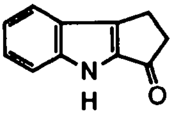
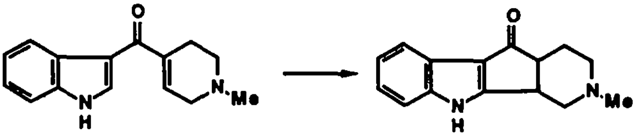
In the search for an attractive synthetic strategy for the cyclopent[b]indole alkaloids we focused our interest on cyclopent[b]indolones, where the carbonyl group could serve as a synthetic handle for further elaborations. Since Manske synthesized 1,2,3,4-tetrahydrocyclopent[b]indol-3-one (**4**) in 1931[13] several reports on synthesized cyclopent[b]indolones have been published.



4

However, only a few of the approaches are of preparative relevance, the most useful being ring closure of indole-3-propanoic acids or their derivatives,[14-19] Fischer indolization,[13,20] and DDQ oxidation of cyclopent[b]indoles.[21-23] None of these methods, however, seemed to be suitable for the preparation of more complex and/or sensitive structures. Joule recently cyclized **5** to **6** in refluxing aqueous hydrochloric acid.[24,25] This methododology seemed to be more promising, although it had to be modified and the scope and limitation had to be defined.

We now present full details of our work in this area.[26]

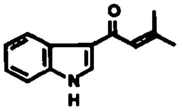
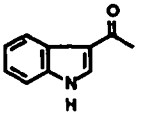
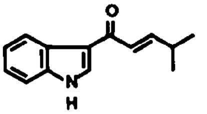
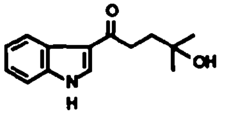
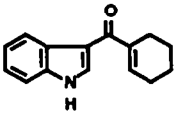
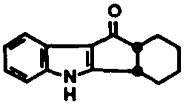
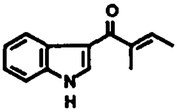
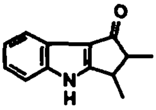
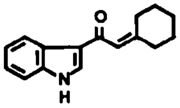


5 **6**

As the first step in the synthesis of cyclopent[b]indol-1-ones, α,β-unsaturated acid chlorides were reacted with the zinc salt of indole to give the corresponding 3-acylindoles.[27] The indole Grignard reagent was used during our preliminary work[26] but the yields were considerably lower. The α,β–unsaturated 3-acylindoles were then treated with conc. aq. HCl in refluxing dioxane (Table 1), yielding annulated products in some cases (entries 3 and 4).

However, in other cases competing reactions were predominating; *retro* aldol condensations gave 3-acetylindole and the corresponding ketone (entries 1 and 5), or double-bond migration followed by hydration yielded a tertiary alcohol (entry 2).

Table 1: Cyclization of α,β-unsaturated 3-acylindoles in dioxane/HCl

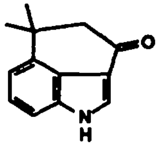
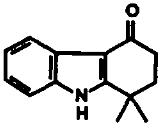
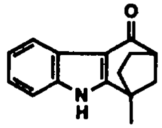
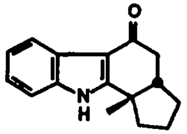
Entry	Acylindole	Product	Isolated yields (%)
1	 **7**	 **8**	50
2	 **9**	 **10**	41
3	 **11**	 **12**[a]	80
4	 **13**	 **14a+14b**	68[b]
5	 **15**	**8**	81

a) Stereochemistry of the ring junction determined as *cis* by NOE difference experiments.

b) The product was isolated as a 20/80 mixture of the *cis* and *trans* isomers.

We therefore looked for a complementary method using anhydrous conditions. Unfortunately, HCl (g) in dry dioxane or acetonitrile at reflux gave no ring closure, and trifluoroacetic acid (TFA) in refluxing acetonitrile gave cyclopent[b]indol-1-ones only in low yields. Other systems such as sulfuric acid/dioxane or polyphosporic acid (PPA) gave also poor yields of annulated products. However, heating in a $AlCl_3$/NaCl melt[28] gave interesting results (Table 2).

Table 2: Cyclization of α,β-unsaturated 3-acylindoles in $AlCl_3/NaCl$ melts.

Entry	Acylindole	Product	Isolated yields (%)
1	7	 16	53
2	9	 17	65
3	11	 18	52
4	13	14a+14b	15[a]
5	15	 19[b]	40

a) The product was isolated as a 45/55 mixture of the *cis*- and *trans*-isomers.

b) The stereochemistry of the ring junction was indicated as *cis* by a 13% NOE of the methine proton upon irradiation of CH_3.

Interestingly, cyclization of **7** in a $AlCl_3/NaCl$ melt gave **16**, and not the regioisomer **20** (entry 1). This conclusion is based on the following decoupling experiments: ^{1}H-NMR of **16** shows a doublet at 7.74 ppm with a coupling constant of 2.8 Hz. Irradiation of the N-H signal at 9.51 ppm converts this doublet to a singlet, thus identifying it as 2-H in **16**. Similar irradiation of the N-H signal of **20** induces virtually no change of the spectrum. Further structural evidence for **16** and **20** was obtained from NOE difference spectra where the methyl protons were irradiated. For **16**, a 22% enhancement of a downfield signal, H-5, was observed. In contrast, the corresponding experiment for **20** gave only a 4% NOE for the N-H proton. Magnetization transfer from the methyl protons *via* long-range C-H couplings in a selective INEPT experiment[29] occurs to C-4 in **16**, whereas for **20**, the C-2 signal is obtained.

16

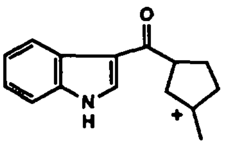
20

Scheme 1: Structurally important nuclear Overhauser enhancements for **16** and **20**. The atoms are numbered as indicated for better comparability.

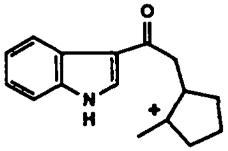
This facile access to the 3-oxo-1,3,4,5-tetrahydrobenz[cd]indole ring system is quite interesting due to the relation between **16** and the pharmacologically interesting ergot alkaloids[30] as well as the recently reported hapalindoles.[31] Direct electrophilic ring closure onto the 4-position of the indole nucleus (unsubstituted in the 2-position) has, to our knowledge, previously only been reported by one research group.[32] We can thus confirm that powerful electron-withdrawing substituents at the indolic 3-position *can*, at least in some cases, induce electrophilic annulation onto the 4-position without the need of blocking the 1-position and/or changing the oxidation state of the pyrrole ring.[33] This concept might have some interesting applications.

The regioisomer of **16**, *i. e.* the cyclopent[b]indole isomer **20**, was obtained in low yield by heating **7** in phosphoric acid trimethylsilyl ester (PPSE)[34-36] while heating in sulphuric acid/dioxane gave a mixture of **16** and **20**. The tricyclic indole **16** was the only compound with a cycloalkan[cd]indolone ring system we were able to isolate, although minor fractions, containing mixtures where cycloalkan[cd]indolones could be detected with ^{1}H NMR, usually were obtained from the $AlCl_3$/NaCl melts.

Annulations in $AlCl_3$/NaCl melts were in some cases accompanied by ring contraction (entries 3 and 5) and in one case double bond migration prior to ring closure was encountered (entry 2). Apparently the structures of the products seem to be derived from nucleophilic attack on the most stable cation, *e.g.* **18a** and **19a**.

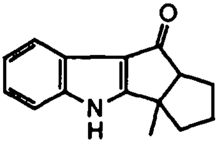


18a



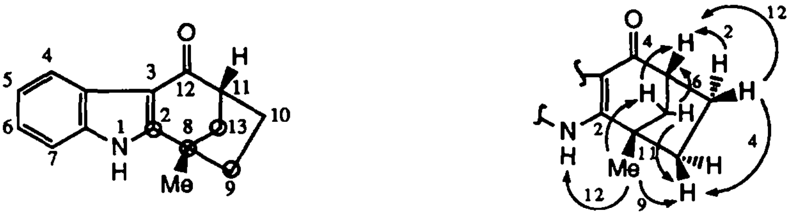
19a

Alkyl groups are known to migrate under the given conditions[37] and the high stability of the 1-methyl-1-cyclopentyl cation is well documented.[38] Therefore, mechanistically the $AlCl_3/NaCl$ induced annulations may be regarded as intramolecular alkylations rather than acid-catalyzed Michael additions or Nazarov[39] cyclizations. Furthermore, we propose the cycloalkan[b]indolones to be derived *via* direct alkylation at the indolic 2-position, rather than alkylation at the 3-position followed by migration of the alkyl substituent. If the latter alternative is considered, the intermediate spiroindolenine intermediate could, at least theoretically, give the isomeric cycloalkan[b]indol-3-ones, after migration of the acyl group instead of the alkyl group. Indeed, preferential acetyl migration has been supposed in the acetylation of 3-methylindole.[40] However, UV-spectra indicate the position of the carbonyl groups at the indolic 3-position and not the 2-position, since they are significantly different for a 3-acylindole and the corresponding 2-isomer.[16,21,41,42] For **12**, **18**, and **19** this was verified by the observation of an NOE between the N-H proton and protons in the aliphatic part of the molecules.



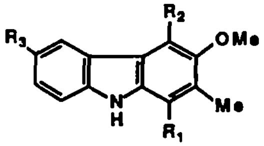
21

The fused bicyclic ketone **18** was, based upon chemical considerations, given the incorrect structure **21** in our preliminary communication.[26] However, a reinvestigation of the spectral data established the molecular structure to be the one of **18**, which is likely to be formed *via* the intermediate cation **18a** and not, as previously assumed, *via* a cation similar to **19a**. The structure of **18** is deduced from its NMR spectra by the following considerations. The methine proton is coupled to one proton each of two methylene groups. One pair of these methylene protons consists of a doublet (J=11.1 Hz) and a double doublet (J=4.9 Hz, 11.1 Hz), identifying them as being located in the methylene bridge (C-13), which is corroborated by NOEs upon irradiation of the methyl protons. As can be shown by a model, the methine proton assumes a 90 degree dihedral angle with two of the four neighbouring protons, resulting in signal a double doublet (J=4.9 Hz, 7.5 Hz). In addition, a selective INEPT experiment, where magnetization is transferred from protons to coupled carbons over two or three bonds,[29] showed magnetization transfer from the methyl protons to two non-protonated and two CH_2 carbons, which in additional experiments were identified as C-2, C-8, C-9 and C-13. For the isomer **21**, magnetization transfer to only one CH_2 carbon would be possible. Further decoupling, NOE , selective INEPT, and HMQC[43] experiments provided the complete assignment of all proton and carbon signals, which was in accordance with structure **18**. It should be noted that also the UV spectrum of **18** resembles those of the other cyclohexanone rather than the cyclopentanone derivatives.

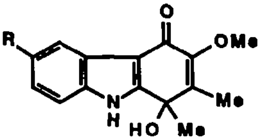


Scheme 2: Structurally significant NOEs for **18** (numbers on arrows show NOEs in %). Also indicated are the carbons (encircled) which appear in the selective INEPT experiment with the pulses on the methyl protons.

The facile synthesis of the tetrahydrocarbazol-4-one **17** induced us to study a new approach to 1,2 dimethyl carbazoles such as the carbazomycins (**22**), produced by the actinomycete *Streptoverticillium ehimence*,[44] *via* the dienone-phenol rearrengement.[45]

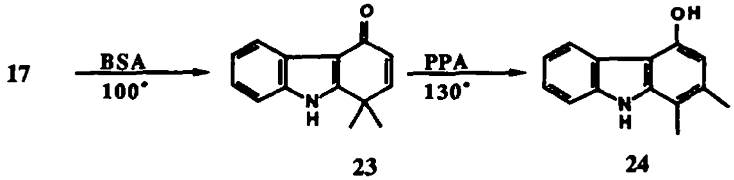


Carbazomycin A (**22a**)	R_1=Me	R_2=OMe	R_3=H
Carbazomycin B (**22b**)	R_1=Me	R_2=OH	R_3=H
Carbazomyzin C (**22c**)	R_1=Me	R_2=OH	R_3=OMe
Carbazomycin D (**22d**)	R_1=Me	R_2=OMe	R_3=OMe
Carbazomycin E (**22e**)	R_1=CHO	R_2=OH	R_3=H
Carbazomycin F (**22f**)	R_1=CHO	R_2=OH	R_3=OMe



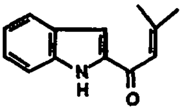
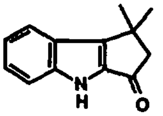
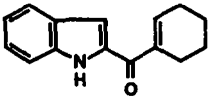
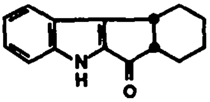
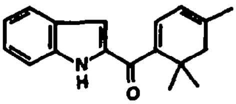
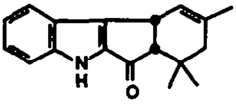
Carbazomycin G (**22g**)	R=H
Carbazomycin H (**22h**)	R=OMe

Thus, treating **17** with benzeneseleninic anhydride[46] (BSA) in chlorobenzene at 100° C for 1.25 h gave **23** in 54% yield. Rearrangement of **23** in PPA at 130° for 25 min gave the new compound 1,2-dimethyl-4-hydroxy-9*H*-carbazole (**24**) (demethoxycarbazomycin B) in 38% yield. Attempts to hydroxylate **24** using copper-catalyzed activation of molecular oxygen[47] in acetonitrile or benzeneseleninic anhydride[48] in THF were, in our hands, unsuccessful. Similar difficulties have recently been reported[49] by Moody in connection with attempted hydroxylations of the isomer 1,2-dimethyl-3-hydroxycarbazole. Thus, several attempts to introduce the extra hydroxyl group at C-4 using oxidants such as manganese (IV) oxide, Fremy's salt, dibenzoyl peroxide, or benzoyl *tert*-butyl nitroxide resulted in either complete decomposition of the substrate or in the formation of dimeric products.[49]



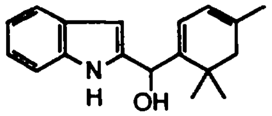
In the synthesis of the regioisomeric cyclopent[b]indol-3-ones, which required ready availability of unsaturated 2-acylindoles, a different acylation method was needed. The Katritzky method[50] for functionalization of indole at the 2-position, with carbon dioxide used as both an *N*-protecting- and an anion-stabilizing group, worked well. Thus, α,β–unsaturated acid chlorides or -esters reacted with the dianion derived from indole and carbon dioxide to give the corresponding 2-acylindoles (Table 3). In one case (entry 3) the corresponding aldehyde was more readily available[51] and thus oxidation (of the alcohol 29) was required.

Table 3: Cyclization of 2-acylindoles[a]

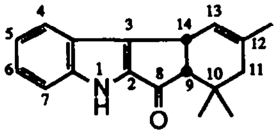
Entry	Acylindole		Product		Isolated yields (%)
1		25		26	54
2		27		28[b]	73
3		30		31[b]	96

a) Reaction conditions: 25, heated in PPA; 27, refluxed in dioxane/conc. HCl; 30, refluxed in acetonitrile/TFA.

b) The assignment of the stereochemistry was based on NOE measurements. The atom numbering (made for the NMR discussion) is the same for 28 and 31 and is shown below.



29



31

Since the 3-position is by far the most reactive in electrophilic reactions of indole[52] we expected ring closure of unsaturated 2-acylindoles to proceed more smoothly than for the corresponding 3-acylindoles. That was indeed the case. The comparatively mild conditions used in the synthesis of the yuehchukene precursor **31** as well as the high yield demonstrates the usefulness of the methodology in natural product synthesis.[5]

Experimental Section

Melting points were determined on a calibrated Reichert WME Kofler hot stage. NMR spectra were recorded for $CDCl_3$ or DMSO-d_6 solutions on a Bruker WP-200 and a Varian XL-300 spectrometer, ^1H at 200 and 300 MHz and ^{13}C at 50 and 75.4 MHz, respectively. HMQC (for 1-bond heteronuclear correlation),[43] selective INEPT[29] and NOE difference spectra[53] were recorded on the Varian instrument using software supplied by the manufacturer. Samples were degassed by the freeze-pump-thaw technique prior to NOE experiments. Chemical shifts are reported relative to tetramethylsilane. IR spectra were obtained using a Perkin Elmer 257 or a Perkin Elmer 1710 IR FT instrument. Mass spectra were obtained with an LKB-9000 or a Finnigan 4500 spectrometer. High resolution mass spectra (HRMS) were obtained on a Kratos MS25RF instrument. UV spectra were measured on ethanol solutions using a Hewlett Packard 8451A spectrophotometer. Flash chromatography[54] was performed with the solvents indicated using Merck silica gel 60 (particle size 0.040-0.063 mm). The unsaturated 3-acylindoles used as starting materials were prepared according to a new method.[27]

Attempted Cyclization of 7 in HCl/dioxane.

HCl (20 mL, conc. aq.) was added to a solution of 7 (0.50 g) in dioxane (20 mL) and the mixture refluxed for 1.5 h. The cooled mixture was neutralized (Na_2CO_3) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The dark residue triturated with CH_2Cl_2 gave 0.20 g (50%) of 3-acetylindole (**8**), identical (^1H NMR, IR, mp) with a sample prepared by acetylation of the zinc salt of indole[27] as well as following a literature method.[55]

Attempted Cyclization of 9 in HCl/dioxane.

HCl (20 mL, conc. aq.) was added to a solution of 9 (0.50 g) in dioxane (20 mL) and the mixture was refluxed for 2h. The mixture was cooled, neutralized (Na_2CO_3), and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to give a brown oil. Trituration with ether gave the alcohol **10**, 0.22 g (41%).

Mp 124-125° C; ^1H NMR ($CDCl_3$) δ 1.28 (s, 6H), 1.96 (t, J=7.3 Hz, 2H), 3.08 (t, J=7.3 Hz, 2H), 7.2-7.5 (m, 3H), 7.95 (d, J=2.9 Hz, 1H), 8.4 (m, 1H) ppm; IR (KBr) 3423, 3275, 1640; mass spectrum, m/z 231 (M^+), 144 (base peak).

Preparation of 12 by Cyclization of 11 in HCl/dioxane.

HCl (10 mL, conc. aq.) was added to a solution of **11** (0.20 g) in dioxane (10 mL) and the mixture refluxed for 2h. The mixture was cooled, neutralized (Na_2CO_3), and extracted with CH_2Cl_2. The organic phase was separated and washed with brine, dried ($MgSO_4$) and evaporated. The dark, solid residue triturated with ether gave 0.16 g (80%) of the *cis*-ketone **12** as light brown crystals, which were further purified by sublimation (230° C in bath, 10 mm Hg).

Mp 218-220° C; ^1H NMR ($CDCl_3$) δ 1.4-1.65 (m, 5H), 1.8-2.0 (m, 2H), 2.1 (m, 1H), 3.06 (m, 1H, (C=O)-CH), 3.45 (m, 1H, N-C-CH), 7.2 (m, 1H), 7.4 (m, 1H), 7.9 (m, 1H), 11.14 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 20.4 (t), 20.5 (t), 23.2 (t), 26.7 (t), 34.4 (d), 52.0 (t), 112.4 (d), 118.8 (s), 120.8 (d), 121.7 (s), 121.9 (d), 123.2 (d), 142.4 (s), 170.4 (s), 198.4 (s) ppm; IR (KBr) 3200, 1655 cm^{-1}; UV λ_{max} 238 nm (ε 17 000), 262 (17 800), 292 (7 800); mass spectrum, m/z 225 (M^+, base peak); HRMS calcd. for $C_{15}H_{15}NO$ (M^+) 225.1154, found 225.1146. NOE: {N-C-C$\underline{H}$} - (CO)-CH, 12%; {(CO)-C$\underline{H}$} - N-C-CH, 14%; {NH} - N-C-CH, 3%; H-7, 9%.

Preparation of 14a/14b by Cyclization of 13 in HCl/dioxane.

HCl (10 mL, conc. aq.) was added to a solution of **13** (0.25 g) in dioxane (10 mL) and the reaction mixture refluxed for 1.75 h. After cooling, followed by neutralization (Na_2CO_3) and extraction with CH_2Cl_2, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography (CH_2Cl_2/MeOH, 100:2) gave 0.17 g (68%) of a (20/80) mixture of the *cis/trans* isomers **14a** and **14b**.

Mp 174-179° C; ^1H NMR ($CDCl_3$) δ *cis*-isomer **14a**: 1.28 (d, J=7.6 Hz, 3H), 1.34 (d, J=7.6 Hz, 3H), 3.19 (dq, J=7.6 Hz, 7.4 Hz, 1H), 3.57 (dq, J=7.6 Hz, 7.4 Hz, 1H), 7.2-7.5 (m, 3H), 7.9 (m, 1H) ppm, *trans*-isomer **14b**: 1.39 (d, J=7.5 Hz, 3H), 1.48 (d, J=7.1 Hz, 3H), 2.62 (dq, J=7.5 Hz, 2.7 Hz, 1H), 3.03 (dq, J=7.1 Hz, 2.7 Hz, 1H), 7.2-7.5 (m, 3H), 7.9 (m, 1H) ppm.

Attempted Cyclization of 15 in HCl/dioxane.

HCl (10 mL, conc. aq.) was added to a solution of **15** (0.25 g) in dioxane (10 mL) and the reaction mixture refluxed for 2h. The mixture was cooled, neutralized (Na_2CO_3) and extracted with CH_2Cl_2. The organic phase was separated, washed with brine, dried ($MgSO_4$) and evaporated. The resulting dark oil was purified by flash cromatography (CH_2Cl_2/MeOH, 100:1) yielding 0.140 g (84%) of 3-acetylindole (**8**), identified by comparison with an authentic sample.[27,55]

Preparation of 16 by Cyclization of 7 in $AlCl_3$/NaCl.

Compound 7 (1.5 g) was added to a melt of $AlCl_3$ (16 g) and NaCl (4 g) at 125° C. The reaction mixture was stirred for 3 min, poured onto ice and extracted with CH_2Cl_2. The organic phase was separated and washed with $NaHCO_3$ (sat. aq.), water and finally brine. Drying ($MgSO_4$) and evaporation gave a dark oil which was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give 0.80 g (53%) of the ketone **16** as a "foam". Trituration with ether gave light yellow crystals.

Mp 172-173° C; ^1H NMR ($CDCl_3$) δ 1.41 (s, 6H, $2CH_3$), 2.74 (s, 2H, CH_2), 7.15 (m, 1H, H-5), 7.23 - 7.3 (m, 2H, H-6, H-7), 7.70 (d, J=2.8 Hz, 1H, H-2), 9.51 (s, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ 29.3 (CH_3), 39.1 (C-8), 55.7 (CH_2), 109.5 (C-7), 114.3 (C-3), 116.0 (C-5), 123.6 (C-2), 124.5 (C-6), 127.7 (C-3a), 133.8 (C-7a), 138.8 (C-4), 194.6 (C=O) ppm; IR (KBr) 3166, 1649 cm^{-1}; UV λ_{max} 246 nm (ε 8 300), 312 (8 850); mass spectrum, m/z 199 (M^+), 184 (base peak); HRMS calcd. for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0985.

Preparation of 20 by Cyclization of 7 in PPSE.

Hexamethyldisiloxane (1.7 mL) was added to a suspension of P_2O_5 (0.71 g) in dry CH_2Cl_2 (10 mL). After refluxing for 30 min, the solvent was distilled off (160° C in bath). Compound 7 (0.20 g) was added to the hot (160° C) mixture, stirred for 5 min, cooled, quenched with water, and extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ (sat. aq.) and brine, dried ($MgSO_4$) and evaporated. The crude product was filtered through a short flash column (CH_2Cl_2/MeOH, 95:5) to give 50 mg (25%) of the ketone **20**.

Mp 211-212° C; ^1H NMR ($CDCl_3$) δ 1.55 (s, 6H, $2CH_3$), 2.93 (s, 2H, CH_2), 7.23 (m, 2H, H-5, H-6), 7.44 (m, 1H, H-7), 7.86 (m, 1H, H-4), 10.5 (s, 1H, N-H) ppm; ^{13}C NMR ($CDCl_3$) δ 27.9 (CH_3), 36.0 (C-8), 57.8 (CH_2), 112.5 (C-7), 118.5 (C-3), 120.9 (C-4), 121.3 (C-3a), 122.4 (C-5), 123.8 (C-6), 142.4 (C-7a), 175.1 (C-2), 195.3 (C=O) ppm; IR (KBr) 3221, 1659 cm^{-1}; UV λ_{max} 238 nm (ε 18 800), 260 (20 100), 292 (9 440); mass spectrum, m/z 199 (M^+), 184 (base peak); HRMS calcd. for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0995.

Preparation of 16 and 20 by Cyclization of 7 in H_2SO_4/dioxane.

H_2SO_4 (5 mL, conc.) was added to a solution of 7 (0.50 g) in dry dioxane (25 mL) whereupon the resulting red mixture was refluxed for 5h. The reaction mixture was cooled, neutralized (Na_2CO_3) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5), yielding 70 mg (14%) of a 46/54 mixture (according to ^1H NMR) of **16** and **20**.

Preparation of 17 by Cyclization of 9 in $AlCl_3$/NaCl.

Compound **9** (2.0 g) was added to a melt of $AlCl_3$ (16 g) and NaCl (4 g) at 130° C. The reaction mixture was stirred for 3 min, poured onto ice and extracted with CH_2Cl_2. The organic phase was separated and washed with $NaHCO_3$ (sat. aq.) and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 100:1) which gave 1.35 g (65%) of the ketone **17**. The product could be further purified by trituration with diisopropyl ether.

Mp 262-263° C; ^1H NMR ($CDCl_3$) δ 1.48 (s, 6H), 2.09 (t, J=6.2 Hz, 2H), 2.68 (t, J=6.2 Hz, 2H), 7.2-7.4 (m, 3H), 8.25 (m, 1H) ppm; IR (KBr) 3180, 1620 cm^{-1}; UV λ_{max} 242 nm (ε 16 600), 264 (12 500), 296 (11 500); mass spectrum, m/z 213 (M^+), 198 (base peak).

Preparation of 18 by Cyclization of 11 in $AlCl_3$/NaCl.

Compound **11** (0.40 g) was added to a melt of $AlCl_3$ (6 g) and NaCl (1.5 g) at 135° C and the mixture was stirred for 5 min, poured onto ice and extracted with CH_2Cl_2. The organic layer was separated, washed with $NaHCO_3$ (sat. aq.) and brine, dried ($MgSO_4$) and evaporated to give a brown solid. Flash chromatography (CH_2Cl_2/MeOH, 100:2) gave 0.21 g (52%) of the ketone **18**. An analytical sample was obtained by crystallization from CH_2Cl_2/MeOH or sublimation (250° C in bath, 10 mm Hg).

Mp 259-261° C; ^1H NMR ($CDCl_3$) δ 1.67 (s, 3H), 1.7-2.4 (m, 6H), 3.09 (dd, J=5.0 Hz, 7.5 Hz, 1H), 7.2-7.4 (m, 3H), 8.15 (m, 1H) ppm; (DMSO-d_6) δ 1.48 (m, 1H, H-10), 1.62 (s, 3H, CH_3), 1.66 (m, 1H, H-9), 1.73 (dd, J=4.9 Hz, 11.1 Hz, H-10), 1.89 (ddd, J=5.9 Hz, 10.8 Hz, 12.1 Hz, 1H, H-9), 2.03 (d, J=11.1 Hz, H-13), 2.25 (m, 1H, H-13), 2.83 (dd, J=4.9 Hz, 7.5 Hz, 1H, H-11), 7.13 (m, 2H, H-5, H-6), 7.42 (m, 1H, H-7), 7.85 (m, 1H, H-4), 11.80 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ 20.1 (q), 27.3 (C-10), 37.8 (C-9), 42.6 (C-8), 48.4 (C-13), 50.8 (C-11), 108.1 (C-3), 111.5 (C-7), 119.35 (C-4), 120.9 (d), 121.6 (d), 124.2 (s), 135.5 (s), 159.25 (C-2), 195.6 (s) ppm; IR (KBr) 3200, 1630 cm^{-1}; UV λ_{max} 242 nm (ε 16 100), 266 (12 900), 296 (8 930); mass spectrum, m/z 225 (M^+, base peak); HRMS calcd. for $C_{15}H_{15}NO$ (M^+) 225.1154, found 225.1142.

Preparation of 14a/14b by Cyclization of 13 in $AlCl_3$/NaCl.

Compound **13** (0.50 g) was added to a melt of $AlCl_3$ (8 g) and NaCl (2 g) at 130° C and the mixture was stirred for 4 min. The reaction mixture was poured onto ice and extracted with CH_2Cl_2, the organic phase was washed with $NaHCO_3$ (sat. aq.), brine, dried ($MgSO_4$) and evaporated. Flash chromatography (CH_2Cl_2/MeOH, 100:2) gave 75 mg (15%) solid as a (45/55) mixture of the *cis/trans isomers* **14a** and **14b**, as indicated by ^{1}H NMR (see under "**Preparation of 14a/14b by ...**" above).

Preparation of 19 by Cyclization of 15 in $AlCl_3$/NaCl.

Compound **15** (0.25 g) was added to a melt of $AlCl_3$(6 g) and NaCl (1.5 g) at 130° C. The reaction mixture was stirred for 5 min and poured onto ice, followed by extraction with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ (sat. aq.), brine, dried ($MgSO_4$) and evaporated. Flash chromatography (CH_2Cl_2/MeOH, 100:2) gave 0.10 g (40%) of the ketone **19** as white crystals.

Mp 224-227° C; ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 3H), 1.5-2.5 (m, 7H), 2.58 (dd, J=17.0 Hz, 3.6 Hz, 1H), 2.84 (dd, J=17.0 Hz, 5.2 Hz, 1H), 7.2-7.4 (m, 3H), 8.2 (m, 1H) ppm; (DMSO-d_6) δ 1.32-1.50 (m, 2H), 1.54 (s, 3H, CH_3), 1.6-2.0 (m, 4H), 2.27 (m, 1H, methine-H), 2.33 (m, 1H, CO-CH_2-α), 2.73 (dd, J=5Hz, 17Hz, 1H, CO-CH_2-β), 7.14 (m, 2H, H-5, H-6), 7.40 (m, 1H, H-7), 7.96 (m, 1H, H-4), 11.80 (s, 1H, N-H) ppm; ^{13}C NMR (DMSO-d_6) δ 22.2 (t), 25.2 (q), 29.9 (t), 39.1 (t), 39.4 (t), 42.7 (s), 46.3 (d), 110.3 (s), 111.6 (d), 120.4 (d), 121.5 (d), 122.4 (d), 124.4 (s), 136.4 (s), 156.5 (s), 192.0 (s) ppm; IR (KBr) 3214, 1632 cm^{-1}; UV λ_{max} 242 nm (ε 16 300), 266 (11 400), 296 (10 800); mass spectrum, m/z 239 (M^+, base peak); HRMS calcd. for $C_{16}H_{17}NO$ (M^+) 239.1310, found 239.1309.

Dienone 23.

Benzeneseleninic anhydride (2.20 g, 6.10 mmol) was added to a solution of **17** (1.30 g, 6.10 mmol) in hot chlorobenzene (40 mL). The mixture was kept at 100-110° C for 1.25 h and allowed to cool. The precipitate formed was collected and washed repeatedly with ether. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 100:2) which gave 0.70 g (54%) of the dienone **23** as white crystals.

Mp 270-274° C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 6H), 6.21 (d, J=10.0 Hz, 1H), 6.62 (d, J=10.0 Hz, 1H), 7.1-7.5 (m, 3H), 8.2 (m, 1H) ppm; IR (KBr) 3190, 1640 cm^{-1}; mass spectrum, m/z 211 (M^+), 196 (base peak).

Carbazole 24.

A solution of **23** (0.117 g) in polyphosphoric acid (10 mL) was heated at 130° C with stirring for 25 min and poured onto water. The mixture was extracted with CH_2Cl_2, the organic phase was separated, repeatedly washed with $NaHCO_3$ (sat. aq.), brine, dried ($MgSO_4$) and evaporated. Filtration through a short flash column (CH_2Cl_2/MeOH, 100:2) gave 47 mg (38%) of carbazole **24** as whitish crystals.

Mp 235-240° C (dec.); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.39 (s, 3H), 6.44 (s, 1H), 7.2-7.4 (m, 3H), 8,20 (m, 1H) ppm; IR (KBr) 3470, 3362 cm^{-1}; mass spectrum, m/z 211 (M^+, base peak); HRMS calcd. for $C_{14}H_{13}NO$ (M^+), found 211.0997.

2-Acylindole 25.

Butyllithium (2.5 M, 4.2 mL) was added dropwise to a solution of indole (1.17 g, 10.0 mmol) in dry THF (20 mL) at -78° C under nitrogen. The resulting suspension was kept at -78° C for 30 min, CO_2 (g) was bubbled through the mixture for 10 min, and the clear solution was allowed to stand for additional 10 min. The solvent was evaporated (0° C, 1 mm Hg), the crystalline residue dissolved in 20 mL THF, cooled to -78° C, and t-butyllithium (1.7 M, 6.2 mL) added dropwise. After having held the resulting yellow solution at -78° C for 1h, ethyl 3,3-dimethylacrylate (1.28 g, 10.0 mmol) was added. The reaction mixture was kept at -78° C for 2 h, then water (1 mL) was added and the solution allowed to reach room temperature. It was then poured into NH_4Cl (sat. aq., 50 mL) under stirring, ether (50 mL) was added and the organic phase separated, washed with brine, dried ($MgSO_4$) and evaporated. The solid residue was purified by flash chromatography (hexane/ether, 3:1) yielding 0.85 g (43%) of 2-acylindole **25**.

Mp 161-162° C; ^1H NMR ($CDCl_3$) δ 2.03 (br s, 3H), 2.33 (br s, 3H), 6.79 (br s, 1H), 7.1-7.8 (m, 5H) ppm; IR (KBr) 3295, 1651 cm^{-1}; mass spectrum, m/z 199 (M^+, base peak).

Preparation of 26 by Cyclization of 25.

The acylindole **25** (0.25 g) was added to polyphosphoric acid (15 mL) at 110° C, stirred for 3 min, and poured into a mixture of NH_3 (conc. aq., 40 mL) and ice (40 g). Extraction with ether followed by washing of the organic phase with brine, drying ($MgSO_4$) and evaporation gave a solid residue. Trituration with diisopropyl ether gave 0.135 g (54%) of the ketone **26** as white crystals.

Mp 162-164° C; ^1H NMR ($CDCl_3$) δ 1.58 (s, 6H), 2.89 (s, 2H), 7.1-7.8 (m, 4H) ppm; IR (KBr) 3201, 1671 cm^{-1}; UV λ_{max} 234 nm (ε 15 800), 300 (21 800); mass spectrum, m/z 199 (M^+), 184 (base peak); HRMS calcd. for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0997.

2-Acylindole 27.

Following the procedure in the synthesis of **25** on a 10 mmol scale, using 1-cyclohexene-1-carbonyl chloride as the electrophile, a solid residue was obtained. Trituration with ether gave 1.52 g (68%) of 2-acylindole **27**.

Mp 152-153° C; ^1H NMR ($CDCl_3$) δ 1.7-1.8 (m, 4H), 2.34 (m, 2H), 2.48 (m, 2H), 7.08 (m, 1H), 7.1-7.7 (m, 5H) ppm; IR (KBr) 3317, 1607 cm^{-1}; mass spectrum, m/z 225 (M^+, base peak).

Preparation of 28 by Cyclization of 27.

HCl (conc. aq., 30 mL) was added to a solution of **27** (2.77 g) in dioxane (30 mL) and the mixture refluxed for 30 min, then allowed to cool and neutralized with NaOH (aq., 40%). The organic solvent was evaporated and CH_2Cl_2 (150 mL) added, the organic layer separated, washed with brine, dried ($MgSO_4$), and evaporated. The crystalline residue was triturated with ether which gave 2.18 g (79%) of the ketone **28** as whitish crystals.

Mp 198-200° C; ^{1}H NMR ($CDCl_3$) δ 1.4-1.6 (m, 5H), 1.85 - 2.05 (m, 2H), 2.25 (m, 1H, H-13β), 3.1 (m, 1H, coalescing to d, J=6.3 Hz, by irradiation at 2.0 ppm, H-9), 3.7 (m, 1H, H-14), 7.17 (dd, J=7 Hz, 8 Hz, 1H, H-5), 7.38 (dd, J=7 Hz, 8.5 Hz, 1H, H-6), 7.55 (d, J=8.5 Hz, 1H, H-7), 7.72 (d, J=8 Hz, 1H, H-4), 9.62 (s, 1H, NH) ppm. IR (KBr) 3159, 1663 cm^{-1}; UV λ_{max} 234 nm (ε 17 200), 302 (21 800); mass spectrum, m/z 225 (M^+, base peak); HRMS calcd. for $C_{15}H_{15}NO$ (M^+) 225.1154, found 225.1187. NOE difference spectra: {NH} - H-7, 6%; {H-4} - H-5, 10%; {H-14} - H-9, 10%, H-13β, 4%; {H-9} - H-14, 12%, H-10β, 6%.

Alcohol 29.

The procedure used in the synthesis of **25** was repeated on a 50 mmol scale, using 4,6,6-trimethylcyclohexa-1,3-dien-1-carbaldehyde[51] as the electrophile. The crude product thus obtained was triturated with pentane yielding 9.5-11.2 g (71-84%) of the alcohol **29**.

Mp 120-121° C; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H), 1.10 (s, 3H), 1.81 (s, 3H), 2.00 (br s, 2H), 5.57 (br s, 1H), 5.72 (m, 1H), 6.09 (d, J=5.5 Hz, 1H), 6.45 (br s, 1H), 7.0-7.6 (m, 4H) ppm; IR (KBr) 3430, 3279 cm^{-1};. mass spectrum, m/z 267 (M^+), 234 (base peak).

Ketone 30.

MnO_2 (27 g)[56] was added to a solution of **29** (13.0 g, 48.7 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred for 1h, when an additional portion of MnO_2 (27 g) was added. After one more hour, the mixture was filtered through Celite and the solvent evaporated. The resulting solid was triturated with pentane and the crystals collected. 11.2 g (87%) of the ketone **30** was obtained as light yellow crystals.

Mp 137-138° C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 6H), 1.92 (s, 3H), 2.18 (br s, 2H), 5.88 (m, 1H), 6.74 (d, J=5.7 Hz, 1H), 7.03 (br s, 1H), 7.1-7.7 (m, 4H) ppm; IR (KBr) 3302, 1603 cm^{-1}; mass spectrum, m/z 265 (M^+), 144 (base peak).

Preparation of 31 by Cyclization of 30.

Trifluoroacetic acid (6.6 g, 58 mmol) was added to a solution of **30** (10.27 g, 38.8 mmol) in acetonitrile (100 mL) and the mixture refluxed for 2.5 h. After cooling, the crystals were filtered and washed with ether, yielding 9.89 g (96%) of the yuehchukene precursor 31.

Mp 250-251° C (lit.[9] 220-223° C); ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.29 (s, 3H), 1.70 (br s, 3H), 1.73 (d, J=15.8 Hz,1H), 1.96 (d, J=15.8 Hz, 1H), 2.85 (d, J=5.9 Hz, 1H), 4.05 (br s, 1H, coalescing to d, J=5.9 Hz on irradiation at 5.9), 5.90 (br s, 1H), 7.1-7.8 (m, 4H) ppm; ^{1}H NMR (DMSO-d_6) δ 0.82 (s, 3H, CH_3), 1.2 (s, 3H, CH_3), 1.66 (s, 3H, C=C-CH_3), 1.68 (d, J=16.3 Hz, 1H, $CH_2\alpha$), 1.88 (d, J=16.3 Hz, 1H, $CH_2\beta$), 2.83 (d, J=6.0 Hz, 1H, H-9; reduced to a singlet upon decoupling at 3.99 ppm), 3.99 (br s, 1H, H-14), 5.92 (s, 1H, H-13), 7.11 (dd, J=7, 8 Hz, 1H, H-5), 7.32 (dd, J=7, 8 Hz, 1H, H-6), 7.41 (d, J=8 Hz, 1H, H-7), 7.83 (d, J=8 Hz, 1H, H-4), 11.55 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 23.7 (q), 23.8 (q), 28.9 (q), 33.3 (s), 35.3 (d), 43.8 (t), 59.1 (d), 113.6 (d), 119.9 (d), 120.0 (d), 121.7 (d), 122.0 (d), 126.3 (d), 132.2 (s), 138.1 (s), 143.4 (s), 145.0 (s), 194.7 (s) ppm. NOE difference spectra: {H-9} - H-14, 20%; {H-13} - H-14, 9%; H-4, 10%; C=C-CH$_3$, 7%; {H-14} - H-9, 15%; H-4, 0.5%; IR (KBr) 3275, 1657 cm^{-1}; UV λ_{max} 234 nm (ε 16 500), 304 (21 900); mass spectrum, m/z 265 (M$^+$), 250 (base peak); HRMS calcd. for $C_{18}H_{19}NO$ (M$^+$) 265.1467, found 265.1468.

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