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SYNTHESIS OF YUEHCHUKENE AND SOME ANALOGUES A GENERAL APPROACH

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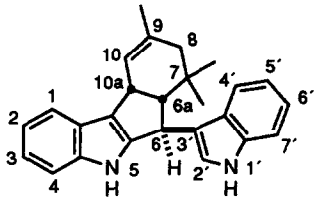
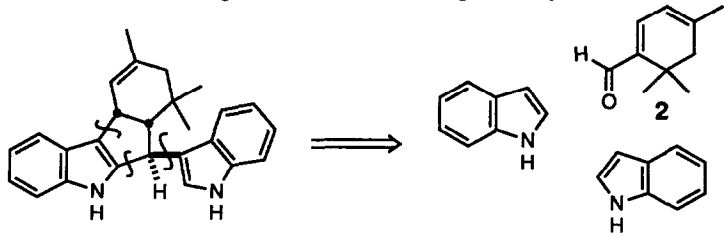
Abstract: Yuehchukene and a number of structural analogues have been synthesized by intramolecular ring closure of α,β-unsaturated 2-acylindoles in the key step. Reduction of the resulting cyclopent[b]indol-3-one derivatives, followed by acid-catalyzed incorporation of a second indole unit, gave the title compounds.

The bis-indole alkaloid, yuehchukene (**1**), has been isolated from the roots of *Murraya paniculata*[1] and later[2] also from other species. The alkaloid, which is racemic, possesses strong anti-implantation activity in rats[3] as well as in mice,[4] and moderate activity in Guinea pigs.[5] Due to this biological activity and the paucity of naturally derived material (10-52 ppm), yuehchukene has been a target for synthesis by a number of research groups[6] and syntheses of analogues have been published[6c,6d,7] as well. We here report full details[8] on our synthesis of yuehchukene as well as some analogues.



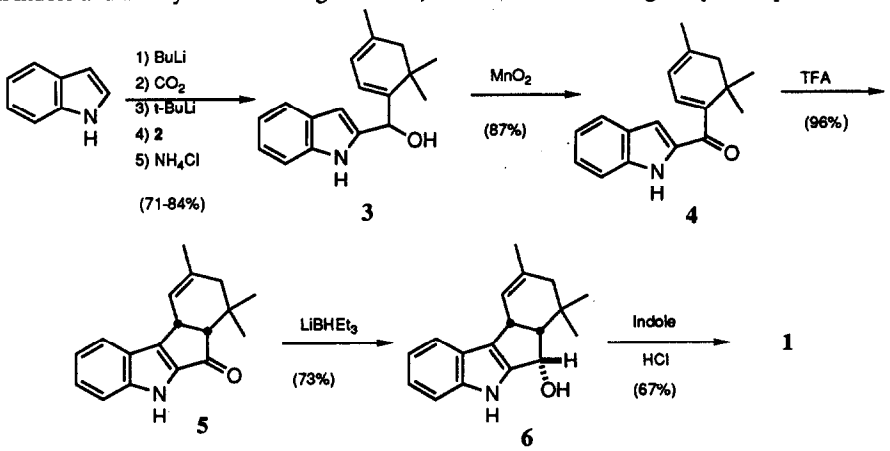
1

Our strategy is illustrated by the simple retrosynthetic analysis in Scheme 1. Compound **1** may be disconnected to give the terpenoid precursor **2** and the two indole moieties, which makes it possible to vary all three of these units in order to make a large number of derivatives potentially available.



Scheme 1

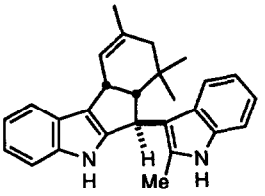
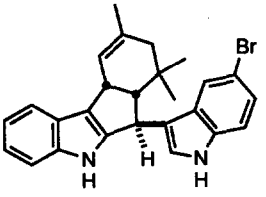
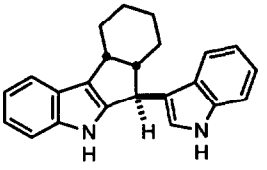
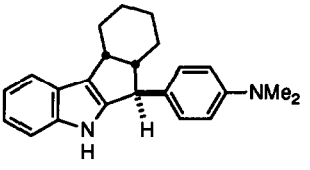
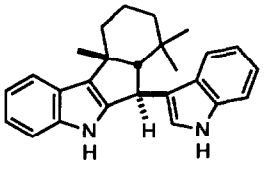
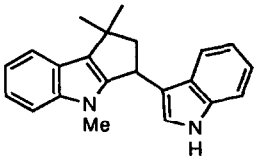
The readily available aldehyde **2**, easily made by base-catalyzed dimerization of 3,3-dimethylacrolein,[9] was chosen as starting material. Katritzky's CO_2-protection method[10] for 2-functionalization of indoles was then used, which resulted in the alcohol **3** (Scheme 2). Oxidation with MnO_2 gave the unsaturated ketone **4**, which was cyclized to the *cis*-hexahydroindeno[2,1-b]indol-6-one **5** in nearly quantitative yield, using the methodology previously developed in our laboratory.[11] The optimum conditions were a slight excess of trifluoroacetic acid (TFA) in refluxing acetonitrile. Other reagents such as *e.g.* $BF_3 \cdot Et_2O$ and $SnCl_4$ also gave **5**, albeit in lower yields. The ketone **5** was reduced to the α-alcohol **6** with complete stereoselectivity using $LiBHEt_3$ (Superhydride®).[12] In the final step **6** was condensed with indole under acidic conditions, which gave **1** as the only diastereomer. Spectroscopic data were in full agreement with those published.[1] The overall yield of **1** (from indole and aldehyde **2** as starting materials) is 34% which is the highest yield reported so far.



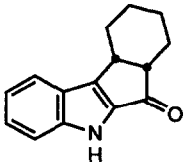
Scheme 2

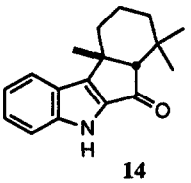
Thus, this approach seemed promising and the analogues listed in the Table illustrates the potential. In the first step carboxylic acid derivatives (*e.g.* esters, acid chlorides, and *N,N*-dimethylamides) are normally preferred instead of aldehydes as electrophiles (entries 3, 4, and 6), thereby excluding the oxidation step. However, sometimes the aldehydes are more readily available (entries 1, 2, and 5) justifying an extra step. The annulation step gives, as previously reported,[11] exclusively products with *cis*-configuration, and **5** has indeed been shown to be thermodynamically more stable than the corresponding *trans*-isomer.[6d] Hydride reductions of the indeno[2,1-b]indol-6-one derivatives to the corresponding alcohols are highly dependent upon the steric hindrance in the substrates. Thus, sodium borohydride which is sufficient for reducing **13**, does not reduce **5** and $LiBHEt_3$ (which reduces **5**) is not able to reduce **14** in THF. We used $LiAlH_4$ in the reduction of **14** which gave the β-alcohol **15b** in 52% yield, but also the α-epimer **15a** (12%) and **16** (17%), where complete reduction of the carbonyl group had taken place. It is well known[13] that 3-acylindoles are completely reduced by $LiAlH_4$ to the corresponding 3-alkylindoles, because of the strong conjugation with the nitrogen. However, this seems to be the first example of a 2-acylindole undergoing similar reduction with alkali metal hydrides.

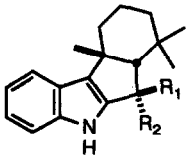
Table: Synthesized yuehchukene analogues

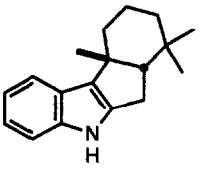
Entry	Nr	Structure[a]	Number of steps[b]	Overall yield[b] (%)
1	**7**		5	47
2	**8**		5	17
3	**9**		4	21
4	**10**		4	17
5	**11**		5	29
6	**12**		4	31

a) The relative stereochemistry of compounds **9** and **11** were determined by NOE difference experiments. b) From indole (entries 1-5) resp. 1-methylindole (entry 6).


13

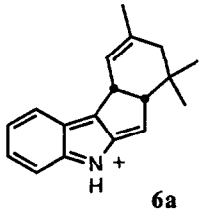

14


15a: R_1 =H, R_2=OH
15b: R_1=OH, R_2=H


16

Hydride attack takes place preferentially from the least hindered side of the carbonyl and gave, in the reductions of **5** and **13**, the expected α-alcohols with 100 % diastereoselectivity. However, in the $LiAlH_4$-reduction of **14** the β-alcohol was obtained as the major epimer. The relative configurations of the hydroxyl groups were determined by NOE (see Experimental Section).

The acid-catalyzed condensation between the indole alcohols and indoles was inspired from Büchi's work on the *Voacanga* bis-indole alkaloids.[14] Resonance-stabilized iminium ions such as *e.g.* **6a** are assumed as intermediates. Hence, the relative configuration of the hydroxyl group in the precursor alcohols is unimportant with regard to the condensation reaction (as shown in the condensation of β-alcohol **15b** with indole).


6a

The reaction is relatively general, taking place with indole, 2-methylindole, 5-bromoindole, and even *N,N*-dimethylaniline as nucleophiles. However, less nucleophilic partners such as 5-nitroindole, 1,2,3-trimethoxybenzene, and 1,2,4-trimethoxybenzene failed to react. Under these acidic conditions (but in the absence of strong nucleophiles), the indolic alcohols quickly decomposed, producing complex mixtures. The condensations were completely stereoselective and no diastereomers could be detected from the reaction mixtures. NOE experiments on **9** and **11** confirmed the relative configurations at the chiral centers.

The success of the method is the result of: i) An efficient method for functionalization of indoles at the 2-position under mild conditions.[10] ii) The relative ease with which α,β-unsaturated 2-acylindoles undergo cyclization to the 3-position with the resulting *cis*-stereochemistry.[11] iii) The facile acid-catalyzed condensation between alcohols of type **6** and non-deactivated indoles, with total stereoselectivity. In conclusion, yuehchukene (**1**) has been synthesized in 34% overall yield, using a quite general procedure. The usefulness was demonstrated by the synthesis of a number of structural analogues.

Experimental Section

Melting points[15] were determined on a calibrated Reichert WMW Kofler hot stage. NMR spectra were recorded on a Bruker AM 400 (400 MHz), AM 250 (250 MHz), or Varian XL-300 (300 MHz) spectrometer. Samples were degassed by the freeze-pump-thaw technique prior to NOE experiments. Chemical shifts are reported relative to tetramethylsilane. IR spectra were recorded on either a Perkin Elmer 1710 FTIR or Perkin Elmer 1600 FTIR instrument. Mass spectra were obtained with a Finnigan MAT INCOS instrument (EI, 70 eV). High resolution mass spectra (HRMS) were obtained on a Kratos MS 25 instrument. Flash chromatography[16] was performed using Merck silica gel 60 (particle size 0.040-0.063 mm). All compounds are racemic.

(6α,6aβ,10aβ)-5,6,6a,7,8,10a-Hexahydro-7,7,9-trimethylindeno[2,1-b]indol-6-ol (6). $LiBHEt_3$ (1.0 M, 25 mL) was added in three portions during 2 h to a solution of ketone **5**[11] (1.50 g, 5.66 mmol) in dry THF (35 mL) under nitrogen. After one more hour water (25 mL) was added and the mixture was poured into ether (50 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated. The solid residue was recrystallized from ethanol/water which gave 1.10 g (73 %) of **6** as white needles.

Mp 208-210 °C (dec.) (lit.[6d] 159-162 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.07 (s, 3H, β-CH_3), 1.31 (s, 3H, α-CH_3), 1.55 (s, 3H, C=C-CH_3), 1.54 (d, J=17 Hz, 1H, β-H-8), 2.40 (m, 1H, H-6a), 2.59 (d, 17 Hz, α-H-8), 2.88 (s, 1H, OH), 3.63 (m, 1H, H-10a), 5.07 (d, J=6.0 Hz, 1H, H-6), 5.62 (br s, 1H, H-10), 7.0-7.1 (m, 2H), 7.3-7.6 (m, 2H) ppm. NOE difference spectra: {H-6} - H-6a, 9%; OH, 6%; {H-6a} - H-6, 12%; H-10a, 11%; {H-10a} - H-10, 6%; H-6a, 8%; β-CH_3, 1%; {OH} - H-8a, 2%; 6-H, 5%; {α-H-8} - OH, 10%; β-H-8, 28%; {β-CH_3} - H-10a, 9%; H-6a, 9%; α-H-8, 4%; {α-CH_3} - H-6, 8%; OH, 3%; α-H-8, 6%; H-6a, 6%; IR (KBr) 3531, 3266 cm^{-1}; mass spectrum, m/z 267 (M^+, base peak).

Yuehchukene (1).

Indole (76 mg, 0.65 mmol) and alcohol **6** (174 mg, 0.65 mmol) were dissolved in a mixture of CH_2Cl_2 (5 mL) and methanol (5 mL) and HCl (conc. aq., 1 drop) was added to the stirred solution. After 10 min ether (10 mL) was added and the solution was washed with $NaHCO_3$ (sat. aq.), water, and brine, dried ($MgSO_4$) and evaporated. The dark residue was purified by flash chromatography (hexane/ether, 8:2) yielding 160 mg (67 %) of **1** as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.08 (s, 3H), 1.61 (d, J=17 Hz, 1H), 1.65 (s, 3H), 2.26 (d, J=17 Hz, 1H), 3.13 (m, 1H), 4.01 (br s, 1H), 4.53 (d, J=8.4 Hz, 1H), 5.69 (br s, 1H), 6.9-7.6 (m, 10 H), 7.85 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 (q), 28.8 (q), 29.0 (q), 33.4 (s), 37.5 (d), 38.2 (d), 40.9 (t), 53.3 (s), 60.8 (d), 111.1 (d), 111.6 (d), 118.2 (d), 118.3 (s), 119.2 (d), 119.4 (d), 120.4 (s), 120.4 (d), 122.0 (d), 122.2 (d), 122.9 (d), 124.1 (s), 126.7 (s), 130.1 (s), 136.3 (s), 140.1 (s), 145.1 (s) ppm; IR (KBr) 3404 cm^{-1}; mass spectrum, m/z 366 (M^+, base peak); HRMS calcd. for $C_{26}H_{26}N_2$ (M^+) 366.2096, found 366.21030.

(6α,6aα,10aα)-5,6,6a,7,8,10a-Hexahydro-6-(1*H*-2-methylindol-3-yl)-7,7,9-trimethylindeno[2,1-b]indole (7).

Following the procedure in the previous experiment on a 0.75 mmol scale, but using 2-methylindole as the nucleophile, a brown, solid residue was obtained. Flash chromatography (hexane/ether, 8:2) gave 260 mg (91 %) of **7** as an amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.06 (s, 3H), 1.64 (d, J=17 Hz, 1H), 1.67 (s, 3H), 2.31 (d, J=17 Hz, 1H), 3.26 (m, 1H), 4.0 (m, 1H), 4.51 (d, J=8.6 Hz, 1H), 5.68 (br s, 1H), 6.9-7.3 (m, 8H), 7.45 (br s, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.75 (br s, 1H) ppm; IR (KBr) 3397 cm^{-1}; mass spectrum, m/z 380 (M^+, base peak); HRMS calcd. for $C_{27}H_{28}N_2$ (M^+) 380.22525, found 380.22570.

(6α,6aα,10aα)-5,6,6a,7,8,10a-Hexahydro-6-(1*H*-5-bromoindol-3-yl)-7,7,9-trimethylindeno[2,1-b]indole (8).

Using the same procedure as above on a 0.655 mmol scale, using 5-bromoindole as the nucleophile, a dark residue was obtained. Flash chromatography (hexane/ether, 8:2) followed by (hexane/EtOAc, 8:2) gave 96 mg (33 %) of **8** as an amorphous solid and 45 mg of 5-bromoindole.

^{1}H NMR (250 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.10 (s, 3H), 1.61 (d, J=18 Hz, 1H), 1.65 (s, 3H), 2.25 (d, J=18 Hz, 1H), 3.11 (m, 1H), 4.0 (m, 1H), 4.51 (d, J=8.5 Hz, 1H), 5.68 (br s, 1H), 7.0-8.1 (m, 9H) ppm; IR (KBr) 3397 cm^{-1}; mass spectrum, m/z 444/446 (M^+), 234 (base peak); HRMS calcd. for $C_{26}H_{25}BrN_2$ (M^+) 444.12011, found 444.11590.

(6α,6aβ,10aβ)-5,6,6a,7,8,9,10,10a-Octahydroindeno[2,1-b]indol-6-ol.

Ketone **13** (1.50 g, 6.67 mmol) was partially dissolved in hot methanol (60 mL) whereafter $NaBH_4$ (1.26 g, 33 mmol) was added in portions during 5 min. The reaction mixture was stirred for 1 h without heating and water (25 mL) was then added. The methanol was replaced (*via* evaporation) with CH_2Cl_2 (50 mL) and the organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (hexane:EtOAc, 60:40) which gave 1.01 g (67 %) product as white needles.

Mp 128-131 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 1.8-2.4 (m, 8H), 3.18 (m, 1H, H-6a), 3.54 (m, 1H, H-10a), 4.36 (d, J=6.3 Hz, 1H, OH), 5.56 (dd, J=6.0 Hz, 6.3 Hz, 1H, H-6), 7.35-7.5 (m, 2H), 7.8 (m, 1H), 7.9 (m, 1H), 10.4 (br s, 1H, NH) ppm. NOE difference spectra: {H-6} - OH, 3%; H-6a, 5%; {OH} - H-6, 14%; {H-10a} - H-6, 9%; H-6a, 4%; {H-6a} - H-6, 16%; H-10a, 8%; IR (KBr) 3550, 3241 cm^{-1}; mass spectrum, m/z 227 (M^+), 130 (base peak).

(6α,6aα,10aα)-5,6,6a,7,8,9,10,10a-Octahydro-6-(1*H*-indol-3-yl)-indeno[2,1-b]indole (9).

Indole (206 mg, 1.76 mmol) and the alcohol obtained in the previous experiment (400 mg, 1.76 mmol) was dissolved in a mixture of CH_2Cl_2 (5 mL) and MeOH (5 mL) whereafter HCl (conc. aq., 1 drop) was added to the stirred solution. The reaction mixture was allowed to stand for 15 min when CH_2Cl_2 (15 mL) was added and the solution extracted with Na_2CO_3 (sat. aq., 10 mL), washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography (hexane/ether, 8:2) of the residue gave 330 mg (58 %) of the product as a white, amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8-1.9 (m, 7H), 2.1 (m, 1H, H-7β), 3.0 (m, 1H, H-6a), 3.3 (m, 1H, H-10a),

4.42 (d, J=8.6 Hz, 1H, H-6), 7.0-7.6 (m, 8H), 7.7 (br s, 1H), 8.0 (br s, 1H) ppm. NOE difference spectra: {H-6} - H-2', 5%; {H-6a} - H-10a, 7%; H-7β, 5%; {H-10a} - H-6a, 14%; {H-7β} - H-6a, 9%; H-6, -1% (*via* H-7α); IR (KBr) 3405 cm^{-1}; mass spectrum, m/z 326 (M^+, base peak); HRMS calcd. for $C_{23}H_{22}N_2$ (M^+) 326.1783, found 326.17990.

(6α,6aα,10aα)-5,6,6a,7,8,9,10,10a-Octahydro-6-(*N,N*-dimethylbenzenamin-4-yl)-indeno[2,1-b]indole (10).

N,N-Dimethylaniline (121 mg, 1.0 mmol) and the alcohol used in the previous experiment (227 mg, 1.0 mmol) was dissolved in methanol (5 mL) and HCl (conc. aq., 1 drop) added to the stirred mixture, which was allowed to stand over night and then diluted with ether (20 mL) and extracted with Na_2CO_3 (sat. aq., 10 mL), washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography (hexane/ether, 8:2) gave 153 mg (46 %) of the product as a white amorphous solid.

^1H NMR (250 MHz, $CDCl_3$) δ 0.8-1.9 (m, 7H), 2.1 (m, 1H), 2.7 (m, 1H), 3.2 (m, 1H), 4.03 (d, J=8.6 Hz, 1H, H-6), 6,71 (d, J=8.8 Hz, 2H), 7.09 (d, J=8.8 Hz, 2H), 7.1 (m, 2H), 7.25 (m, 1H), 7.55 (m, 1H), 7.75 (br s, 1H) ppm; IR (KBr) 3403 cm^{-1}; mass spectrum, m/z 330 (M^+, base peak); HRMS calcd. for $C_{23}H_{26}N_2$ (M^+) 330.2096, found 330.20866.

α-(2,6,6-Trimethylcyclohex-1-en-1-yl)-1*H*-indole-2-methanol.

Butyllithium (2.5 M, 10.5 mL) was added dropwise to a solution of indole (2.925 g, 25.0 mmol) in dry THF (45 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 45 mL THF, cooled to -78 °C, and t-butyllithium (1.7 M, 15.4 mL) added dropwise. After having held the resulting yellow solution at -78 °C for 1h, β-cyclocitral[17] (3.80 g, 25.0 mmol) was added. The reaction mixture was kept at -78 °C for 1.75 h, then water (2.5 mL) was added and the solution allowed to reach room temperature. It was then poured into NH_4Cl (sat. aq., 100 mL) under stirring, ether (75 mL) was added and the organic phase separated, washed with brine, dried ($MgSO_4$) and evaporated. The resulting oil crystallized after one night in the refrigerator and was then triturated with pentane which gave 4.80 g (71 %) white crystals.

Mp 107-109 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.20 (s, 3H), 1.52 (s, 3H), 1.5-1.7 (m, 4H), 2.0 (m, 2H), 5.56 (br s, 1H), 6.2 (br s, 1H), 7.0-7.2 (m, 2H), 7.35 (m, 1H), 7.5 (m, 1H) ppm; IR (KBr) 3533, 3346 $cm.^{-1}$

1*H*-Indol-2-yl(2,6,6-trimethylcyclohex-1-en-1-yl)-methanone.

MnO_2 (5.7 g) was added to a solution of the alcohol obtained in the previous experiment (1.84 g, 6.83 mmol) in CH_2Cl_2 (25 mL) under nitrogen. The reaction mixture was stirred for 2 h, when an additional portion of MnO_2 (5.7 g) was added. After an additional 1.5 hour, the mixture was filtered through Celite, and the solvent evaporated. The resulting solid was triturated with pentane which gave 1.68 g (92 %) of the ketone as an off-white precipitate.

Mp 157-158 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.1 (br, 6H), 1.56 (s, 3H), 1.5-1.6 (m, 2H), 1.7-1.9 (m, 2H), 2.1 (m, 2H), 7.0 (br s, 1H), 7.15 (m, 1H), 7.35 (m, 1H), 7.45 (m, 1H), 7.7 (m, 1H) ppm; IR (KBr) 3307, 1608 $cm.^{-1}$

***cis*-6a,7,8,9,10,10a-Hexahydro-7,7,10a-trimethylindeno[2,1-b]indol-6(5*H*)-one (14).** Trifluoroacetic acid (1.55 g, 13.6 mmol) was added to a solution of the ketone obtained in the previous experiment (1.81 g, 6.79 mmol) in CH_3CN (15 mL) and the mixture was refluxed for 4.5 h. The reaction mixture was allowed to cool and the crystals collected. The yield was 1.52 g (84 %) of white flakes. Slow evaporation of the mother liquid gave an additional 0.170 g (9 %) product.

Mp 209-210 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.87 (s, 3H), 1.24 (s, 3H), 1.3-2.1 (m, 6H), 1.47 (s, 3H), 2.34 (s, 1H), 7.1 (m, 1H), 7.3 (m, 1H), 7.4 (m, 1H),7.75 (m, 1H) ppm; IR (KBr) 3169, 1660 cm.$^{-1}$

Reduction of ketone 14.

A solution of **14** (425 mg, 1.59 mmol) in dry THF (15 mL) under nitrogen was cooled to 0 °C, whereafter $LiAlH_4$ (106 mg, 2.80 mmol) was added in portions during 5 min. The mixture was stirred for 3 h and then water (3 mL) was added dropwise and it was then poured into NH_4Cl (sat. aq., 30 mL). EtOAc (30 mL) was added, the organic layer separated and the water phase extracted with EtOAc (20 mL). The combined organic extracts was washed with water followed by brine, dried ($MgSO_4$), and evaporated. Flash chromatography (CH_2Cl_2/ether, 9:1) of the solid residue gave in the first fractions **16** (41 mg, 12 %) and in later fractions **15a** (50 mg, 12 %) and **15b** (220 mg, 51 %) respectively.

***cis*-5,6,6a,7,8,9,10,10a-Octahydro-7,7,10a-trimethylindeno[2,1-b]indole (16).**

Mp 90-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.18 (s, 3H), 1.2-1.7 (m, 5H), 1.69 (s, 3H), 1.95 (m, 1H), 2.34 (t, J=8 Hz, 1H), 2.75 (d, J=8 Hz, 2H), 7.1 (m, 2H), 7.3 (m, 1H), 7.55 (m, 1H), 7.7 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (t), 26.5 (q), 28.7 (t), 29.7 (q), 31.1 (q), 32.8 (s), 35.6 (t), 36.5 (t), 41.9 (s), 61.7 (d), 111.4 (d), 117.8 (d), 119.2 (d), 120.2 (d), 123.8 (s), 129.8 (s), 139.4 (s), 139.9 (s) ppm; IR (KBr) 3388 cm^{-1}; mass spectrum, m/z 253 (M^+), 238 (base peak).

(6α,6aα,10aα)-5,6,6a,7,8,9,10,10a-Octahydro-7,7,10a-trimethylindeno[2,1-b]indol-6-ol (15a).

Mp 140-150 °C (dec.); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.19 (s, 3H, β-CH_3), 1.34 (s, 3H, α-CH_3), 1.65 (s, 3H, CH_3-10a), 1.2-1.9 (m, 6H), 2.01 (d, J=5.4 Hz, 1H, H-6a), 3.49 (d, J=6.2 Hz, 1H, OH), 5.10 (dd, J=6.2 Hz, 5.4 Hz, 1H, H-6), 6.95 (m, 1H), 7.05 (m, 1H), 7.4 (m, 1H), 7.6 (m, 1H), 9.8 (br s, 1H) ppm. NOE difference spectra: {H-6} - OH, 6%; H-6a, 8%; {H-6a} - H-6, 3%; {CH_3-10a} - H-6a, 14%; H-1, 7%; β-CH_3, 6%; {β-CH_3} - H-6a, 8%; IR (KBr) 3574, 3255 cm^{-1}; mass spectrum, m/z 269 (M^+), 254 (base peak).

(6α,6aα,10aα)-5,6,6a,7,8,9,10,10a-Octahydro-7,7,10a-trimethylindeno[2,1-b]indol-6-ol (15b).

Mp 165-176 °C (dec.); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.18 (s, 3H, β-CH_3), 1.20 (s, 3H, α-CH_3), 1.68 (s, 3H, CH_3-10a), 1.2-2.0 (m, 6H), 2.11 (d, J=7.4 Hz, 1H, H-6a), 3.97 (d, J=7.9 Hz, 1H, OH), 5.11 (dd, J=7.4 Hz, 7.9 Hz, 1H, H-6), 6.95 (m, 1H), 7.05 (m, 1H), 7.35 (m, 1H), 7.5 (m, 1H), 9.7 (br s, 1H) ppm. NOE difference spectra: {H-6} - OH, 8%; {OH} - H-6, 7%; H-6a, 5%; {CH_3-10a} - H-6a, 10%; H-1, 8%; β-CH_3, 5%; IR (KBr) 3484, 3247 cm^{-1}; mass spectrum, m/z 269 (M^+), 254 (base peak).

(6α,6aα,10aα)-5,6,6a,7,8,9,10,10a-Octahydro-6-(1*H*-indol-3-yl)-7,7,10a-trimethylindeno[2,1-b]indole (11).

To a solution of indole (152 mg, 1.30 mmol) and β-alcohol **15b** (350 mg, 1.30 mmol) in a mixture of CH_2Cl_2 (5 mL) and MeOH (5 mL) HCl (conc. aq., 3 drops) was added under stirring. After 15 min ether (25 mL) was added and the solution washed with $NaHCO_3$ (sat. aq.), water, and brine, and finally dried ($MgSO_4$) and evaporated. Flash chromatography (hexane/ether, 8:2) gave 368 mg (77 %) of **11** as an amorphous solid.

^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H, α-CH_3), 1.10 (s, 3H, β-CH_3), 1.1-2.1 (m, 6H), 1.80 (s, 3H, CH_3-10a), 2.81 (d, J=9.1 Hz, 1H, H-6a), 4.56 (d, J=9.1 Hz, 1H, H-6), 7.0-7.6 (m, 9H), 7.95 (br s, 1H, NH) ppm. NOE difference spectra: {H-6} - H-6a, <2%; {H-6a} - H-2´, 7%; H-4´, 8%; {CH_3-10a} - H-1, 16%; H-6a, 12%; IR (KBr) 3403 cm^{-1}; mass spectrum, m/z 368 (M^+, base peak); HRMS calcd. for $C_{26}H_{28}N_2$ (M^+) 368.22525, found 368.22385.

1,2,3,4-Tetrahydro-1,1,4-trimethylcyclopent[b]indol-3-ol.

$NaBH_4$ (182 mg, 4.83 mmol) was added to a solution of 1,1,4-trimethylcyclopent[b]indol-3(2H)-one[18] (286 mg, 1.21 mmol) in warm (55 °C) MeOH (10 mL). The mixture was stirred for 1 h, water (10 mL) was added followed by ether (30 mL) and the organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography (hexane/EtOAc, 7:3) which gave 200 mg (69 %) of the alcohol as colourless prisms.

Mp 105-107 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.50 (s, 3H), 1.9 (br s, 1H), 2.12 (dd, J=13.9, 2.9 Hz, 1 H), 2.71 (dd, J=13.9, 6.2 Hz, 1H), 3.69 (s, 3H), 5.3 (br s, J=6.2, 2.9 Hz, 1H), 7.05 (m, 1H), 7.2 (m, 2H), 7.5 (m, 1H) ppm; IR (KBr) 3242 cm^{-1}; mass spectrum, m/z 215 (M^+), 200 (base peak).

1,2,3,4-Tetrahydro-1,1,4-trimethyl-3-(1*H*-indol-3-yl)-cyclopent[b]indole (12).

HCl (conc. aq., 1 drop) was added to a solution of indole (56 mg, 0.48 mmol) and the alcohol obtained in the previous experiment (115 mg, 0.48 mmol) in MeOH (2.5 mL). The reaction mixture was stirred for 15 min and poured into $NaHCO_3$ (sat. aq., 10 mL). Ether (15 mL) was added, the organic phase separated and washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography (hexane/ether, 7:3) gave 140 mg (86 %) of **12** as an amorphous solid.

^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.49 (s, 3H), 2.46 (dd, J=12.8, 6.2 Hz, 1H), 2.83 (dd, J=12.8, 8.0 Hz, 1H), 3.37 (s, 3H), 4.78 (dd, J=8.0, 6.2 Hz, 1H), 6.91 (d, J=2.4 Hz, 1H), 7.0-7.6 (m, 8H), 7.95 (br s, 1H) ppm; IR (KBr) 3405 cm^{-1}; mass spectrum, m/z 314 (M^+), 299 (base peak); HRMS calcd. for $C_{22}H_{22}N_2$ (M^+) 314.1783, found 314.17871.

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