Synthesis of inverto-yuehchukene and its 10-(indol-3′-yl) isomer. X-Ray structure of (4a*RS*,10a*RS*)-1,1,3-trimethyl-1,2,4a,5,10,10a-hexahydroindene[1,2-*b*]indol-10-one

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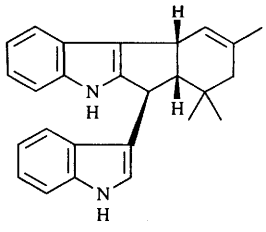
A total synthesis of inverto-yuehchukene 4 and its 10-(indo-3′-yl) isomer 7 is described. The key tetracyclic ketone intermediate 13 was synthesized by a coupling reaction between 3-indolylzinc reagent and acid chloride 11, followed by Nazarov cyclization of the divinyl ketone 12. The indol-2-yl moiety present in inverto-yuehchukene 4 was introduced by palladium(0)-catalysed cross-coupling between indol-2-ylzinc reagent and the acetate 16.

Introduction

Yuehchukene (YCK) **1**,[1,2] a naturally occurring bis-indole shown to exhibit potent anti-implantation activity in rat, was characterized as the dimer of 3-didehydroprenylindole **2**.[3] The latter compound has also been isolated from the root bark of *Merrillia caloxylon* (Ridley) Swingle.[4]



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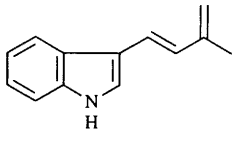
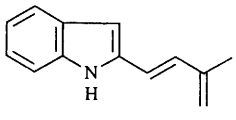


2

By analogy, dimerization of 2-didehydroprenylindole **3** would lead to structure **4** which we named inverto-yuehchukene (I-YCK). Such dimerization is analogous to the biosynthesis of borreverine **5**, from the 2-prenyltryptamine **6**.[5]



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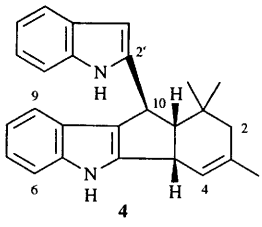

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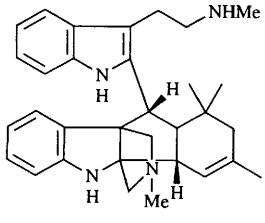

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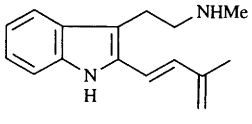
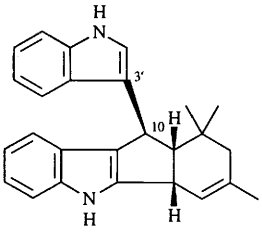


6

As part of our current structure–activity study on YCK,[6] we decided to synthesize I-YCK. In this paper we report a total synthesis of I-YCK **4** and its 10-(3′-indolyl) isomer **7**.

The synthetic strategy to I-YCK **4** is illustrated by the retrosynthetic analysis shown in Scheme 1. I-YCK may be disconnected to give the precursor (8) and two indole moieties.



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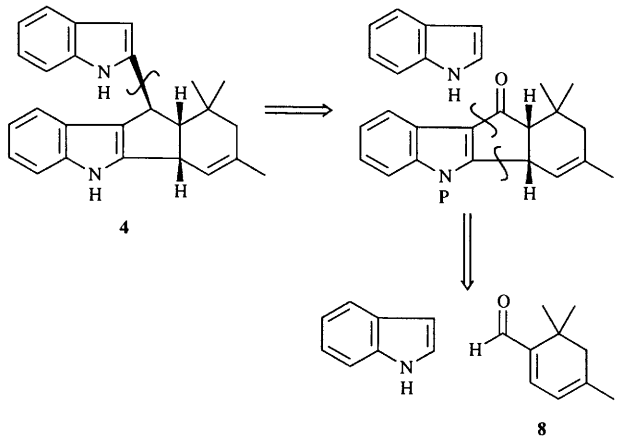
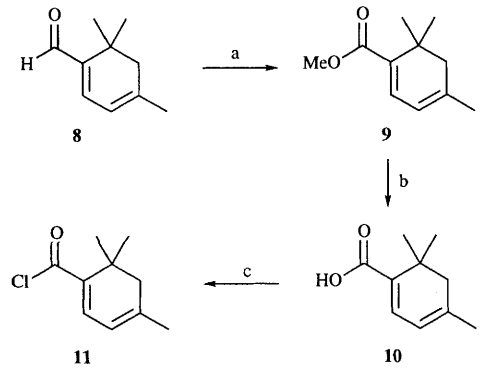


Scheme 1

The aldehyde **8**, prepared by base-catalysed dimerization of commercially available 3,3-dimethylacrolein,[7] was converted into the acid chloride **11** in a three-step sequence (Scheme 2). Thus, the aldehyde **8** was first oxidized by activated manganese dioxide in methanol in the presence of sodium cyanide[8] to the methyl ester **9**, which on saponification to acid **10**, followed by treatment with oxalyl dichloride,[9,10] afforded the acid chloride **11** in 45% overall yield.

The acid chloride **11** was treated with indol-3-yl Grignard reagent[11] whereby the divinyl ketone **12** was obtained in 31% yield with an appreciable amount of the acid **10**, resulting from hydrolysis of the acid chloride.[12] However, when indol-3-yl-zinc reagent or the zinc salt of indole,[12] prepared by trans-metallation of the Grignard reagent with anhydrous zinc chloride, was used instead of the Grignard reagent, the yield of the ketone **12** increased to 80% (Scheme 3).

Nazarov cyclization[13] of the divinyl ketone **12** in a refluxing



Scheme 2 *Reagents and conditions:* a, MnO_2, NaCN, MeOH, room temp., 2 days, 64%; b, KOH, EtOH, reflux, 1 d, 88%; c, $(COCl)_2$, C_6H_6, room temp. 2 h, 80%

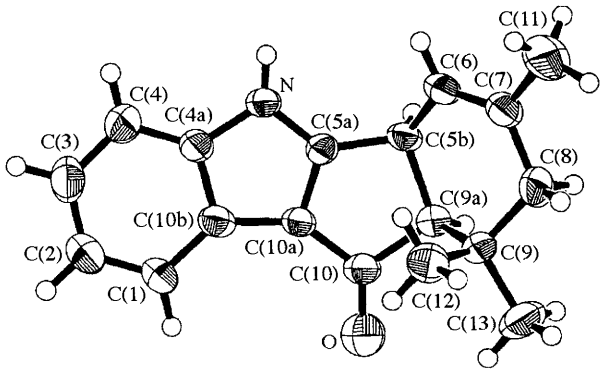


Fig. 1 X-Ray structure of compound **13** with crystallographic numbering scheme

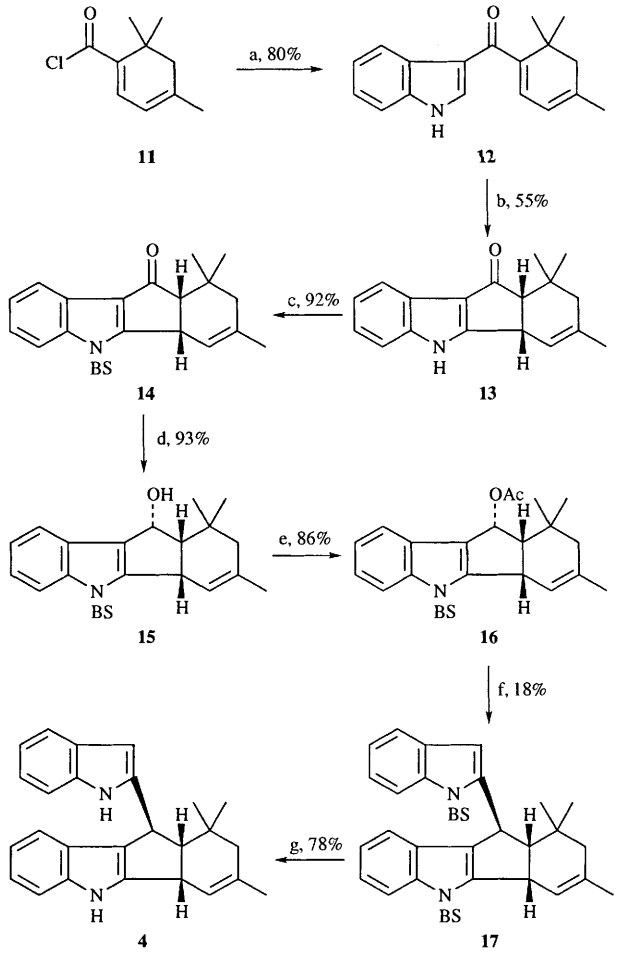
conc. hydrochloric acid–1,4-dioxane mixture[14] gave the tetracyclic ketone **13** in 55% yield. The stereochemistry at the C/D ring junction was assigned as *cis* based on the value of the observed vicinal coupling constant between 4a-H and 10a-H, *viz.* 6.59 Hz. The stereochemical assignment was confirmed by X-ray crystallography (Fig. 1).

To complete the synthesis of I-YCK, it requires stereoselective introduction, at C-10, of an indol-2-yl moiety *syn* to the hydrogen atoms at the C/D ring junction. To this end, the ketone **14**, an N-protected form of ketone **13**, was reduced stereoselectively with sterically demanding Superhydride[15] (lithium triethylborohydride) to give the 10α alcohol **15**. Conversion of the alcohol **15** into its acetate derivative **16** was achieved by reaction with acetic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP) and triethylamine (TEA).[16]

Our original intention to introduce the indol-2-yl moiety at C-10 by S_N2 displacement of the acetate with a number of metallated indole-2-anions including Li^+, Mg^{2+}, Cu^+ and Zn^{2+}, was unsuccessful. Subsequently, across-coupling reaction[17] between the acetate **16** and [*N*-(phenylsulfonyl)indol-2-yl]zinc[zinc(*N*-Bs-indol-2-yl) chloride] in the presence of the Pd^0 catalyst generated *in situ*[18] from bis(triphenylphosphine)palladium(II) chloride[19] and diisobutyl aluminium hydride (DIBAH) was attempted, whereby the desired I-YCK **17** was obtained albeit in low yield (18%). Attempts to improve the yield by using $PdCl_2$(dppf),†[,20] and $Pd(Ph_3P)_4$[21] did not prevail. Finally, removal of the *N*-phenylsulfonyl group with sodium amalgam in methanol and disodium hydrogen phosphate buffer[22] afforded the title compound **4** in 78% yield (Scheme 3).

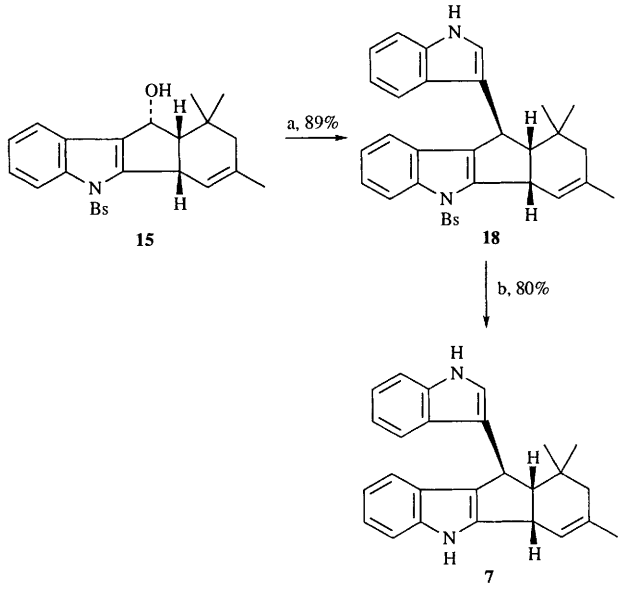
On the other hand, treatment of the alcohol **15** with indole in the presence of boron trifluoride–diethyl ether[23] afforded the

† Ligand dppf = bis(diphenylphosphino)ferrocene.



Scheme 3 *Reagents and conditions:* a, (i) indole, EtMgBr, (ii) $ZnCl_2$; b, conc. HCl, 1,4-dioxane, reflux 4 h; c, BuLi, BsCl, −78 °C; d, Superhydride, THF, 0 °C, 15 min; e, Ac_2O, DMAP, TEA, CH_2Cl_2, rt, 0.5 h, f, zinc (*N*-Bs-indol-2-yl) chloride, $Pd(PPh_3)_2Cl_2$, DIBAH, THF, reflux, 12 h; g, Na/Hg, aq. Na_2HPO_4, Et_2O–MeOH, rt

indol-3-yl coupling product **18** which after N-deprotection gave the 10-(indol-3′-yl) isomer of I-YCK (compound **7**) in 80% yield (Scheme 4).



Scheme 4 *Reagents and conditions:* a, indole, BF_3·Et_2O, Et_2O, 0 °C; b, Na/Hg, Na_2HPO_4, Et_2O–MeOH, rt

The biological activity of both I-YCK **4** and its isomer **7** will be reported elsewhere.

Experimental

Mps were measured on a 'LiuKam' heating stage for crystal melting point studies adapted to a Zeiss microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FIS-7IR spectrophotometer. NMR spectra were recorded on a JEOL FX-9OQ or a GSX-270 spectrometer for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were recorded on an Hitachi RMS-4 or a high-resolution Finnigan MAT-95 mass spectrometer. UV spectra were recorded on a Shimadzu UV 240 spectrophotometer. TLC was performed using Merck pre-coated silica gel F-254 plates (thickness 0.25 mm). Column chromatography was carried out with Kieselgel 60 (Merck) as the stationary phase. Analytical HPLC was performed on a Beckmann Model 331 HPLC System with Model 163 variable-wavelength UV–VIS detector. Organic extracts were dried over anhydrous magnesium sulfate and evaporated at aspirator pressure on a rotary evaporator. Light petroleum (LP) refers to the fraction boiling in the range 40–60 °C and was redistilled before use. All reactions requiring anhydrous conditions were conducted in oven-dried apparatus at 120 °C and under a static atmosphere of dry nitrogen or argon. New compounds whose elemental compositions were established through accurate mass determination were shown to be homogeneous by spectroscopic and chromatographic methods. All compounds described are racemic.

4,6,6-Trimethylcyclohexa-1,3-dienecarbaldehyde 8

To a suspension of powdered KOH (2.24 g, 0.04 mol) in sodium-dried diethyl ether (200 cm^3) stirred at 0 °C under N_2 was slowly added 3-methylbut-2-enal (40 cm^3, 0.42 mol) during a 15 min period. The resulting yellow mixture was stirred at 0 °C for 2.75 h. The organic layer was washed successively with water (50 cm^3 × 6) and saturated brine (50 cm^3), and dried over anhydrous $MgSO_4$. Removal of solvent and purification of the crude product by vacuum distillation afforded aldehyde **8** (10.40 g, 33%) as a yellow viscous liquid (bp 58–70 °C/5 mmHg; lit.,[7] 64–72 °C/10 mmHg); ν_{max}(neat)/cm^{-1} 2700 (CH of aldehyde), 1672 (C=O), 1637 (C=C) and 1600; δ_H(90 MHz) 1.20 (6 H, s, 2 × CH_3), 1.90 (3 H, d, *J* 0.88, 4-CH_3), 2.12 (2 H, m, 5-H_2), 5.98 (1 H, m, 3-H), 6.61 (1 H, d, *J* 5.68, 2-H) and 9.40 (1 H, s, CHO); δ_C(22.5 MHz) 23.97 (4-CH_3), 26.08 (6-CH_3), 32.77 (C-6), 46.07 (C-5), 118.67 (C-3), 142.53 (C-4), 144.70 (C-2), 146.92 (C-1) and 192.91 (C=O); *m/z* 150 (M^+).

Methyl 4,6,6-trimethylcyclohexa-1,3-dienecarboxylate 9

Manganese dioxide (120 g) was activated by azeotropic distillation with anhydrous benzene (600 cm^3) for 4 h to remove trapped water. The benzene was replaced by methanol (600 cm^3). Sodium cyanide (16.4 g, 335 mmol), glacial acetic acid (6.0 g, 100 mmol) and the aldehyde **8** (10 g, 67 mmol) were added to the suspension of manganese dioxide in methanol (600 cm^3). The resulting mixture was stirred at room temperature until reaction was complete in 2 days. The manganese dioxide was removed by filtration and the filtration cake was washed with diethyl ether (1000 cm^3). The filtrate was evaporated to dryness and water (200 cm^3) was added. The aqueous layer was extracted with diethyl ether (200 cm^3 × 3). The organic extracts were combined, washed with brine (100 cm^3), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by column chromatography (SiO_2; Et_2O–LP 4:96) afforded the methyl ester **9** (7.70 g, 64%) as a yellow liquid, ν_{max}(neat)/cm^{-1} 1690 (C=O), 1632 (C=C), 1604 and 1568; δ_H(90 MHz) 1.18 (6 H, s, 2 × CH_3), 1.84 (3 H, d, *J* 1.09, 4-CH_3), 2.08 (2 H, m, 5-H_2), 3.70 (3 H, s, OCH_3), 5.75 (1 H, m, 3-H) and 6.80 (1 H, d, *J* 5.91, 2-H); δ_C(22.5 MHz) 23.70 (4-CH_3), 26.21 (6-CH_3), 33.44 (C-6), 46.53 (C-5), 50.90 (OCH_3), 118.29 (C-3), 133.32 (C-2), 143.04 and 144.56 (C-1 and -4) and 167.78 (C=O); *m/z* 180 (M^+).

4,6,6-Trimethylcyclohexa-1,3-dienecarboxylic acid 10

To a solution of potassium hydroxide (2.92 g) in ethanol (95%; 280 cm^3) was added the methyl ester **9** (7.0 g, 38.9 mmol). The resulting mixture was refluxed for 1 day, cooled and treated with dil. HCl (2 mol dm^{-3}; 100 cm^3). The aqueous solution was extracted with ethyl acetate (300 cm^3 × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. Recrystallization of the residue from diethyl ether–light petroleum afforded acid **10** (5.70 g, 88%) as crystals, mp 112–114 °C; ν_{max}(Nujol)/cm^{-1} 3465–2520 (OH), 1671 (C=O), 1634 (C=C) 1569; λ_{max}(EtOH)/nm 295; δ_H(90 MHz; $CDCl_3$) 1.20 (6 H, s, 2 × CH_3), 1.87 (3 H, s, 4-CH_3), 2.11 (2 H, m, 5-H), 5.81 (1 H, m, 3-H), 7.01 (1 H, d, *J* 5.69, 2-H) and 10.81 (1 H, br s, CO_2H); δ_C(22.5 MHz; $CDCl_3$) 23.84 (4-CH_3), 26.22 (6-CH_3), 33.26 (C-6), 46.72 (C-5), 118.40 (C-3), 132.43 (C-4), 135.84 (C-2), 144.78 (C-1) and 173.41 (C=O); *m/z* 166 (M^+).

4,4,6-Trimethylcyclohexa-1,3-dienecarbonyl chloride 11

To a solution of the acid **10** (230 mg, 1.40 mmol) in anhydrous benzene (12 cm^3) was added freshly distilled oxalyl dichloride (0.18 cm^3, 2.1 mmol). The resulting mixture was stirred at room temperature for 2 h. Benzene and excess of oxalyl dichloride were distilled off at atmospheric pressure. The crude product was purified by fractional distillation at reduced pressure to afford acid chloride **11** (207 mg, 80%) as a viscous liquid, bp 62–64 °C/0.5 mmHg; ν_{max}(neat)/cm^{-1} 1740 (C=O). The acid chloride **11** was immediately used in the next step without further purification.

Indol-3′-yl 4,6,6-trimethylcyclohexa-1,3-dienyl ketone 12

To magnesium turnings (1.04 g, 42.8 mmol) in anhydrous diethyl ether (10 cm^3) under N_2, at room temperature was added ethyl bromide (3.34 cm^3, 44.7 mmol) as a solution in anhydrous diethyl ether (6 cm^3). After all the magnesium had dissolved, a solution of indole (4.10 g, 35.0 mmol) in anhydrous benzene (40 cm^3) was added. When the evolution of bubbles had ceased, anhydrous benzene (60 cm^3) was added and the resulting green mixture was stirred for 10 min at room temperature, after which a mixture of zinc chloride (4.50 g, 33.0 mmol) in anhydrous diethyl ether (35 cm^3) was added and the whole was stirred for 30 min until a milky solution was formed. This milky solution was added to a solution of the acid chloride **11** (5.0 g, 30.1 mmol) in anhydrous benzene (60 cm^3) under N_2 at 5 °C. The reaction mixture was stirred for 2 h at 5 °C, quenched by being poured into saturated aq. NH_4Cl (50 cm^3), and extracted with acetone (100 cm^3 × 3). The organic layer was separated, and washed successively with aq. sodium hydrogen carbonate (5%, 80 cm^3), water (80 cm^3), brine (80 cm^3), and dried over anhydrous $MgSO_4$. The concentrated extract was purified by column chromatography (SiO_2; Et_2O–LP 3:7) and recrystallization from acetone to afford *compound* **12** (6.40 g, 80%) as crystals, mp 206–207 °C (Found: C, 81.5; H, 7.0; N, 5.2. $C_{18}H_{19}NO$ requires C, 81.48; H, 7.22; N, 5.28%); ν_{max}(Nujol)/cm^{-1} 3260 (NH), 1640 (C=C), 1586 (C=O), 1511, 1188 and 1133; λ_{max}(EtOH)/nm 269 and 311; δ_H(270 MHz; [$^2H_6$]acetone) 1.24 (6 H, s, 2 × CH_3), 1.88 (3 H, d, *J* 0.98, 4-CH_3), 2.14 (2 H, s, 5-H_2), 5.85 (1 H, m, 3-H), 6.35 (1 H, d, *J* 5.35, 2-H), 7.21 (2 H, m, 5′- and 6′-H), 7.49 (1 H, m, 4′-H), 7.86 (1 H, m, 2′-H), 8.34 (1 H, m, 7′-H) and 10.98 (1 H, br s, NH); δ_C(67.5 MHz) 23.88 (4-CH_3), 26.10 (6-CH_3), 35.13 (C-6), 46.27(C-5), 111.30, 118.34, 118.73, 122.35, 122.47, 123.60, 126.24, 130.81, 132.81, 136.54, 141.45, 143.26 and 193.29 (C=O); *m/z* 265 (M^+);

(4a*RS*,10a*RS*)-1,1,3-Trimethyl-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indol-10-one 13

To a solution of the divinyl ketone **12** (2.73 g, 10.3 mmol) in 1,4-dioxane (100 cm^3) was added conc. hydrochloric acid (100 cm^3) and the resulting brown mixture was refluxed for 4 h. On cooling of the solution, saturated aq. sodium carbonate was

added until the reaction mixture was alkaline towards pH paper (pH = 8). The aqueous solution was extracted with CH_2Cl_2 (100 cm^3 × 4). The combined extract was washed successively with water (80 cm^3 × 2) and brine (80 cm^3), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (SiO_2; Et_2O–LP 6:4) and by recrystallization in CH_2Cl_2–Et_2O to afford ketone **13** (1.50 g, 55%) as yellow rectangular crystals, mp 225 °C (Found: C, 81.4; H, 6.8; N, 5.2. $C_{18}H_{19}NO$ requires C, 81.48; H, 7.22; N, 5.28%); ν_{max}(Nujol)/cm^{-1} 3226 (NH), 1681 (C=O), 1619 (C=C), 1216, 1154 and 1062; λ_{max}(EtOH)/nm 214, 240, 264 and 295; δ_H[270 MHz; $(CD_3)_2SO$] 0.79 (3 H, s, 1-CH_3), 1.22 (3 H, s, 1-CH_3), 1.67 (1 H, d, *J* 16.87, 2-H), 1.69 (3 H, s, 3-CH_3), 1.89 (1 H, d, *J* 16.12, 8-H), 2.80 (1 H, d, *J* 6.59, 10a-H), 3.99 (1 H, br s, 4a-H), 5.74 (1 H, s, 4-H), 7.12–7.68 (4 H, m, ArH) and 12.14 (1 H, br s, NH); δ_C[22.5 MHz; $(CD_3)_2SO$] 23.46, 23.78 (1- and 3-CH_3), 29.09 (1-CH_3), 32.75 (C-1), 35.74 (C-4a), 43.91 (C-2), 59.16 (C-10a), 112.52, 117.26, 118.12, 119.64, 120.91, 121.43, 122.76, 134.16, 141.85, 167.02 and 195.43 (C=O); *m/z* 265 (M^+).

(4a*RS*,10a*RS*)-1,1,3-Trimethyl-5-(phenylsulfonyl)-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indol-10-one 14

To a solution of the ketone **13** (1.50 g, 5.66 mmol) in anhydrous tetrahydrofuran (THF) (30 cm^3) at −78 °C under N_2 was added butyllithium (1.6 mol dm^{-3} solution in pentane; 4.0 cm^3, 6.40 mmol). After stirring of the resulting red solution for 15 min at −78 °C, a solution of benzenesulfonyl chloride (0.95 cm^3, 7.40 mmol) in anhydrous THF (5 cm^3) was added. The mixture was allowed to warm to 0 °C during 1.5 h, quenched with water (30 cm^3) and extracted with CH_2Cl_2 (30 cm^3 × 3). The combined extract was washed successively with water (20 cm^3) and brine (20 cm^3) and dried over anhydrous $MgSO_4$. Purification of the crude product by column chromatography (SiO_2; Et_2O–LP 1:3) afforded *compound* **14** (2.11 g, 92%) as crystals, mp 69 °C (Found: C, 70.8; H, 5.8; N, 3.33. $C_{24}H_{23}NO_3S$ requires C, 71.09; H, 5.72; N, 3.45%); ν_{max}(Nujol)/cm^{-1} 1701 (C=O), 1644 (C=C), 1372 (S=O, asym) and 1182 (S=O, sym); δ_H(90 MHz) 1.12 (3 H, s, 1-CH_3), 1.43 (3 H, s, 1-CH_3), 1.63 (3 H, s, 3-CH_3), 1.62 (1 H, d, *J* 16.84, 2-H), 2.00 (1 H, d, *J* 17.51, 2-H), 2.91 (1 H, dd, *J* 5.68 and 1.53, 10a-H), 4.36 (1 H, br s, 4a-H), 5.93 (1 H, br s, 4-H) and 7.20–8.00 (9 H, m, ArH); δ_C(22.5 MHz) 24.13 (3-CH_3), 26.54 (1-CH_3), 28.96 (1-CH_3), 33.67 (C-1), 39.47 (C-4a), 41.55 (C-2), 60.59 (C-10a), 114.36, 119.05, 121.21, 122.92, 124.71, 124.92, 125.52, 126.79, 129.58, 134.43, 135.43, 138.22, 140.42, 166.85 and 197.19 (C=O); *m/z* 405 (M^+).

(4a*RS*,10*SR*,10a*RS*)-1,1,3-Trimethyl-5-(phenylsulfonyl)-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indol-10-ol 15

To a solution of the ketone **14** (200 mg, 0.49 mmol) in anhydrous THF (4 cm^3) at 0 °C under N_2 was added Superhydride (1.0 mol dm^{-3} solution in THF; 1.5 cm^3, 1.5 mmol) in portions during a 30 min period. After stirring of the mixture for 15 min, water (4 cm^3) and diethyl ether (4 cm^3) were added, and the organic layer was separated. The aqueous layer was further extracted with diethyl ether (4 cm^3 × 2). The combined extract was washed successively with water (3 cm^3) and brine (3 cm^3), dried over anhydrous $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (SiO_2; Et_2O–LP 3:7) gave compound **15** (186 mg, 93%) as an amorphous solid, mp 190 °C (Found: C, 70.4; H, 5.9; N, 3.4. $C_{24}H_{25}NO_3S$ requires C, 70.73; H, 6.18; N, 3.44%); ν_{max}($CHCl_3$)/cm^{-1} 3395 (OH), 1364 (S=O, asym), 1178 (S=O, sym); δ_H(270 MHz) 1.14 (3 H, s, 1-CH_3), 1.31 (3 H, s, 1-CH_3), 1.63 (3 H, s, 3-CH_3), 1.67 (1 H, d, 2-H), 2.37 (1 H, m, 10a-H), 2.48 (1 H, d, *J* 17.82, 2-H), 3.95 (1 H, br s, 4a-H), 5.09 (1 H, dd, *J* 10.74, 5.62, 10-H), 5.86 (1 H, s, 4-H) and 7.19–8.03 (9 H, m, ArH); δ_C(67.5 MHz) 24.05 (3-CH_3), 27.15 (1-CH_3), 30.97 (1-CH_3), 32.10 (C-1), 39.91 (C-4a), 41.81 (C-2), 56.17 (C-10a), 71.04 (C-10), 114.61, 119.53, 120.41, 123.89, 124.10, 125.72, 126.50, 127.56, 129.30, 133.84, 134.08, 138.45, 139.93 and 148.47; *m/z* 407 (M^+).

(4a*RS*,10*SR*,10a*RS*)-1,1,3-Trimethyl-5-(phenylsulfonyl)-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indol-10-yl acetate 16

A mixture of the alcohol **15** (100 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (4 cm^3) containing DMAP (46.0 mg, 0.37 mmol), TEA (0.06 cm^3, 0.44 mmol) and acetic anhydride (0.036 cm^3, 0.37 mmol) was stirred at room temperature for 0.5 h, after which aq. copper(II) sulfate (3 cm^3) was added. The solution was extracted with CH_2Cl_2. Work-up and purification of the crude product by column chromatography (SiO_2; Et_2O–LP 2:8) afforded the acetate **16** (96 mg, 86%) as crystals, mp 175–176 °C; ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O), 1620 (C=C), 1365 (S=O, asym) and 1170 (S=O, sym); δ_H(270 MHz) 1.12 (3 H, s, 1-CH_3), 1.25 (3 H, s, 1-CH_3), 1.63 (1 H, d, 2-H), 1.68 (3 H, s, 3-CH_3), 1.98 (3 H, s, Ac), 2.39 (1 H, d, *J* 7.09, 2-H), 2.63 (1 H, m, 10a-H), 4.01 (1 H, br s, 4a-H), 5.84 (1 H, s, 4-H), 6.11 (1 H, d, *J* 6.10, 10-H) and 7.15–7.99 (9 H, m, ArH); δ_C(67.5 MHz) 21.44 (CH_3CO), 24.14 (3-CH_3), 27.17 (1-CH_3), 30.90 (1-CH_3), 32.06 (C-1), 40.11 (C-4a), 41.90 (C-2), 54.35 (C-10a), 71.89 (C-10), 114.26, 118.47, 120.96, 123.90, 124.09, 124.39, 125.72, 126.49, 126.55, 129.31, 133.88, 138.37, 139.72, 149.35 and 170.97 (C=O); *m/z* (rel. int.) 449 (8, M^+), 389 (73, $M^+ - CH_3CO_2H$), 374 (81, $M^+ - CH_3CO_2H - CH_3$), 248 (77, $M^+ - CH_3CO_2H - C_6H_5SO_2$), 232 (100, $M^+ - CH_3CO_2H - C_6H_5SO_2 - CH_3 - H$) and 218 (64, $M^+ - CH_3COO_2H - C_6H_5SO_2 - CH_3 - CH_3$).

(4a*RS*,10*RS*,10a*SR*)-1,1,3-Trimethyl-5-(phenylsulfonyl)-10-[1′-(phenylsulfonyl)indol-3′-yl]-1,2,4a,5,10,10a-hexahydroindeno-[1,2-*b*]indole 17

To a solution of *N*-(phenylsulfonyl)indole (164 mg, 0.63 mmol) under Ar at −20 °C was added Bu^{t}Li (1.7 mol dm^{-3}; 0.5 cm^3, 0.84 mmol) as a solution in anhydrous THF (2 cm^3). The resulting brown solution was stirred at −20 °C for 15 min and at room temperature for another 15 min before being cooled to −78 °C. Anhydrous zinc chloride (88 mg, 0.64 mmol) was added and the resulting solution was stirred and allowed to warm to room temperature in 1.5 h. This freshly prepared *N*-(phenylsulfonyl)indol-2-yl zinc reagent was added to a mixture of the acetate **16** (95 mg, 0.21 mmol) and Pd^0 catalyst (0.01 mmol), prepared *in situ* by addition of DIBAH (1.0 mol dm^{-3}; 0.02 cm^3, 0.02 mmol) to $Pd(Ph_3P)_2Cl_2$ (7 mg, 0.01 mmol) in anhydrous THF (2 cm^3). After refluxing of the final brown mixture for 12 h under Ar, aq. NH_4Cl (3 cm^3) was added to quench the reaction. The aqueous solution was extracted with diethyl ether and acetone. Work-up and purification of the crude product by column chromatography (SiO_2; LP–Et_2O 9:1) afforded compound **17** (25 mg, 18%) as a solid (25 mg, 18%); ν_{max}($CHCl_3$)/cm^{-1} 1606, 1453, 1372 (S=O, asym), 1179 (S=O, sym), 1092 and 756; δ_H(270 MHz; C_6D_6) 0.82 (3 H, s, 1-CH_3), 1.04 (3 H, s, 1-CH_3), 1.48 (1 H, d, *J* 17.58, 2-H), 1.62 (3 H, s, 3-CH_3), 2.24 (1 H, d, *J* 17.58, 2-H), 3.22 (1 H, m, 10a-H), 4.38 (1 H, dd, *J* 8.79 and 1.71, 10-H), 4.55 (1 H, br s, 4a-H) and 6.30–8.33 (19 H, m, ArH); δ_C(67.5 MHz; C_6D_6) 24.26 (3-CH_3), 28.97 (1-CH_3), 29.26 (1-CH_3), 33.54 (C-1), 37.28 (C-4a), 40.95 (C-2), 42.33 (C-10), 60.29 (C-10a), 111.54, 115.42, 118.83, 119.53, 119.69, 121.80, 121.95, 122.16, 123.94, 126.58, 127.04, 128.75, 128.83, 128.92, 128.99, 129.10, 130.12, 132.75, 133.20, 136.89, 139.41, 141.39 and 144.90; *m/z* (rel. int.) 366 (0.7, M^+).

(4a*RS*,10*RS*,10a*SR*)-10-(Indol-2′-yl)-1,1,3-trimethyl-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indole, I-YCK 4

A mixture of bis-sulfonamide **17** (17.8 mg, 0.028 mmol) in anhydrous diethyl ether (1 cm^3) and anhydrous methanol (2 cm^3) containing disodium hydrogen phosphate (0.45 g) and sodium amalgam (5%; 0.45 g) was stirred at room temperature until all sodium amalgam had become liquid mercury. Water (2 cm^3) was added and the residue was washed by diethyl ether (2 cm^3 × 4). Combined supernatant was washed with brine (3 cm^3), dried over anhydrous $MgSO_4$ and concentrated. Column chromatography (SiO_2; Et_2O–LP 1:3) of the residue afforded

Table 1 Selected torsion angles (°) in compound **13**

H(5b)–C(5b)–C(9a)–H(9a)	19.35
H(5b)–C(5b)–C(9a)–C(9)	138.35
C(6)–C(5b)–C(9a)–H(9a)	−102.46
H(6a)–C(5b)–C(9a)–H(10)	−98.50
C(5a)–C(5b)–C(9a)–H(10a)	130.38

I-YCK **4** (8.0 mg, 78%) as an amorphous solid, mp 86 °C (decomp.) (Found: M^+, 366.2097. $C_{26}H_{26}N_2$ requires *M*, 366.2096); $\nu_{max}(CHCl_3)/cm^{-1}$ 3403 (NH), 1619 (C=C), 1454, 1259, 1088 and 737; $\lambda_{max}(EtOH)/cm^{-1}$ 225 and 285; δ_H(270 MHz; C_6D_6) 0.80 (3 H, s, 1-CH_3), 1.10 (3 H, s, 1-CH_3), 1.67 (3 H, s, 3-CH_3), 1.69 (1 H, d, *J* 17.58, 2-H), 2.20 (1 H, d, *J* 17.58, 2-H), 3.12 (1 H, m, 10a-H), 3.92 (1 H, br s, 4a-H), 4.55 (1 H, dd, *J* 7.20 and 1.22, 10-H), 5.53 (1 H, br s, 4-H) 6.80–7.94 (11 H, m, NH and ArH); δ_C(67.5 MHz; C_6D_6) 24.42 (3-CH_3), 28.02 (1-CH_3), 29.49 (1-CH_3), 33.45 (C-1), 36.89 (C-4a), 39.62 (C-10), 41.93 (C-2), 62.04 (C-10a), 111.47, 111.59, 119.23, 119.53, 119.78, 119.89, 120.77, 120.88, 121.05, 121.78, 121.95, 125.37, 127.43, 128.64, 132.75, 136.91, 141.03 and 143.46.

(4a*RS*,10*SR*,10a*RS*)-10-(Indol-3′-yl)-1,1,3-trimethyl-5-(phenylsulfonyl)-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indole 18

To a mixture of the alcohol **15** (100 mg, 0.25 mmol) and indole (30 mg, 0.26 mmol) in diethyl ether (5 cm^3) at 0 °C under N_2 was added boron trifluoride–diethyl ether (0.038 cm^3, 0.31 mmol). After stirring of the resulting orange solution at 0 °C for 0.5 h water (3 cm^3) was added. Work-up and purification of the crude product by column chromatography (SiO_2; Et_2O–LP 3:7) afforded sulfonamide **18** (98.8 mg, 89%) as an amorphous solid, mp 207 °C (Found: M^+, 506.1768. $C_{32}H_{30}N_2O_2S$ requires *M*, 506.2028); ν_{max}(Nujol)/cm^{-1} 3465 (NH), 1362 (S=O, asym) and 1177 (S=O, sym); δ_H(270 MHz, C_6D_6) 0.82 (3 H, s, 1-CH_3), 1.03 (3 H, s, 1-CH_3), 1.48 (1 H, d, *J* 17.09, 2-H), 1.61 (3 H, s, 3-CH_3), 2.25 (1 H, d, *J* 17.09, 2-H), 3.24 (1 H, m, 10a-H), 4.39 (1 H, dd, *J* 1.71 and 8.55, 10-H), 4.54 (1 H, br s, 4a-H), 6.30 (1 H, s, 4-H) and 6.44–8.33 (15 H, m, NH and ArH); δ_C(67.5 MHz; C_6D_6) 24.25 (3-CH_3), 28.96 (3-CH_3), 29.26 (1-CH_3), 33.52 (C-1), 37.28 (C-4a), 40.94 (C-2), 42.31 (C-10), 60.26 (C-10a), 111.57, 115.39, 118.77, 119.52, 119.55, 119.67, 121.78, 121.93, 122.19, 123.92, 123.95, 126.56, 127.02, 128.32, 129.10, 130.15, 132.77, 133.23, 136.91, 139.35, 141.37 and 144.87.

(4a*RS*,10*SR*,10a*RS*)-10-(Indol-3′-yl)-1,1,3-trimethyl-1,2,4a,5,10,10a-hexahydroindeno[1,2-*b*]indole 7

By the same procedure as in the preparation of compound **4**, reaction of the sulfonamide **18** (95.0 mg, 0.19 mmol) with sodium amalgam gave, after chromatography, *compound* **7** (55.6 mg, 80%) as an amorphous solid, mp 85 °C (decomp.) (Found: M, 366.2210. $C_{26}H_{26}N_2$ requires *M*, 366.2096); $\nu_{max}(CHCl_3)/cm^{-1}$ 3407 (NH), 1618 (C=C), 1161, 1096, 1017 and 742; λ_{max}(EtOH)/nm, 222, 240 and 291; δ_H(270 MHz; C_6D_6) 0.85 (3 H, s, 1-CH_3), 1.12 (3 H, s, 1-CH_3), 1.54 (1 H, d, *J* 16.85, 2-H), 1.69 (3 H, s, 3-CH_3), 2.15 (1 H, d, *J* 17.09, 2-H), 3.11 (1 H, m, 10a-H), 3.76 (1 H, br s, 4a-H), 4.63 (1 H, d, *J* 5.86, 10-H), 5.46 (1 H, br s, 4-H) and 6.49–7.76 (11 H, m, NH and ArH); δ_C(67.5 MHz) 24.20 (3-CH_3), 27.92 (1-CH_3), 29.25 (1-CH_3), 33.23 (C-1), 36.35 (C-4a), 39.35 (C-10), 41.56 (C-2), 61.09 (C-10a), 111.04, 111.27, 118.60, 118.97, 119.35, 119.40, 119.93, 120.42, 120.91, 121.55, 121.63, 124.62, 127.17, 133.15, 136.45, 140.44 and 143.83.

X-Ray study of compound 13

Crystal data. $C_{18}H_{19}NO$, pale yellow rectangular crystals from methylene dichloride–diethyl ether, *M* = 265.36, monoclinic, space group $P2_1/c$ (No. 14), *a* = 10.800(1), *b* = 13.737(2), *c* = 9.887(1) Å, β = 98.36(2)°, *V* = 1451.2(8) $Å^3$, *Z* = 4, D_c = 1.214 g cm^{-3}, μ(Mo-Kα) = 0.697 cm^{-1}, *F*(000) = 568, *T* = 297 K. Crystal size: 0.15 × 0.1 × 0.25 mm. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromatized Mo-Kα radiation (λ = 0.710 73 Å) using the ω–2θ scanning technique with variable scan width (1.00 + 0.35 tan θ)°. Reflections in the range of $2\theta_{max}$ = 50° *h*: 0–13; *k*: 0–16; *l*: −11 to 11 with 3 standard reflections measured every 2 hours. A total of 3124 independent reflections were obtained of which 1407 with $F_o > 3\sigma F_o$ were considered to be observed and used in subsequent calculations.‡

Solution and refinement. The structure was solved by direct methods with MULTAN 82[24] from which all the non-hydrogen atoms were located. Positions of the hydrogen atoms were revealed in Fourier difference maps at a later stage; however, only those bonded to C(6a), C(9a) and the methyl carbon atoms were taken from the difference map and all others were generated geometrically (C–H = 0.95 Å). All hydrogen parameters except those for 5b-H and 9a-H were not refined. In the final least-squares cycle, a list of 184 parameters were adjusted: atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms, atomic co-ordinates for 5b-H and 9a-H, an extinction coefficient, and a scale factor. The refinement was by full-matrix least-squares and the quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = 4F_o/[\sigma^2(F_o^2) + (0.050\ F_o^2)^2]$. Atomic scattering factors were obtained from ref. 25. Calculations were carried out on a MicroVAX computer using the Structure Determination Package (SDP).[26] The final *R* values were: *R* = 0.066, R_w = 0.081 and the 'goodness of fit', $[\Sigma w(|F_o| - |F_c|)^2/(m - s)]^{\frac{1}{2}}$ = 2.03, where *m* is the number of measurements and *s* is the number of parameters. In the final Fourier difference map, the residual electron densities were between −0.43 and 0.41 e $Å^{-3}$ respectively. The ORTEP drawing of the molecule (Fig. 1) shows thermal ellipsoids at the 50% probability level and the numbering scheme. Selected torsion angles are given in Table 1. Tables of fractional atomic coordinates, bond lengths and angles, and thermal parameters are available on request from the Cambridge Crystallographic Data Centre.§

‡ The X-ray crystallography was carried out by Dr T. F. Lai, Department of Chemistry, The University of Hong Kong.

§ *Supplementary material* (see Instructions for Authors, section 5.6.3, January issue): Tables of fractional atomic coordinates, hydrogen-atom parameters, thermal parameters, and bond lengths and angles are available on request from the Cambridge Crystallographic Data Centre.

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