Antifertility Agents: A Synthetic Entry to Yuehchukene Analogues; Stereoselective Synthesis of 7,7-Bis-nor-yuehchukene *via* 9-Methyl-6-oxo-6aβ-7,8,10aβ-tetrahydroindeno[2,1-*b*]indole

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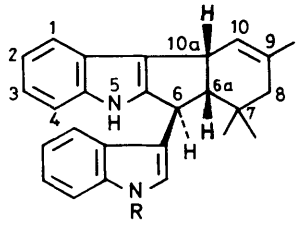
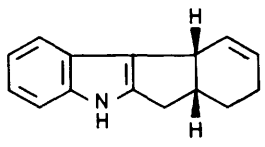
Intermolecular Diels–Alder reaction and polyphosphate ester-catalysed intramolecular acylation are used in a synthetic approach to 9-methyl-6-oxo-6aβ-7,8,10aβ-tetrahydroindeno[2,1-*b*]indole (**15**), the basic structure of the antifertility agent yuehchukene (**1**). Stereoselective conversion of (**15**) into 7,7-bis-nor-yuehchukene (**19**) is also described.

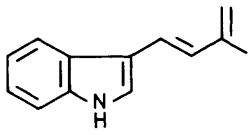
Yuehchukene (YCK) (**1**), first isolated from the root bark of *Murraya paniculata* (L.) Jack,[1] is a bis-indole alkaloid and its structure was determined by *X*-ray analysis[2] of its monoacetate derivative (**2**). New natural sources of YCK from indigenous plants in S.E. Asia and Australia have also been identified.[3] The basic structural unit of YCK is the tetracyclic 6a,7,8,10a-tetrahydroindeno[2,1-*b*]indole (**3**) which is a new structural feature in naturally occurring indole compounds. YCK differs from other bis-indole alkaloids in that it lacks a $[CH_2]_2N$ moiety at the 3-position of indole and thus biogenetically is not derived from tryptophan. YCK may be regarded as the product of dimerization of 3-dehydroprenylindole (**4**) and has, in fact, been synthesized[4] by acid-catalysed dimerization of (**4**). YCK



(**1**) R = H
(**2**) R = Ac



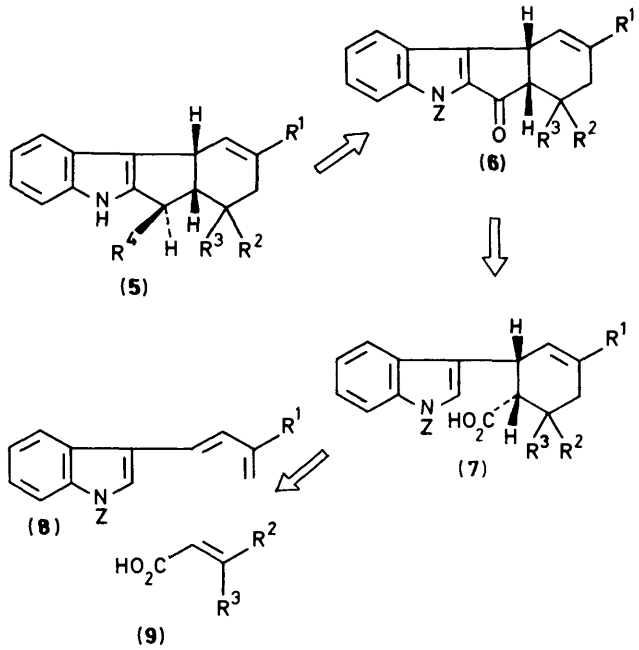
(**3**)



(**4**)

has been shown to exhibit potent anti-implanation activity in rates and is a potential fertility regulating agent.[5] In order to carry out both an in-depth pharmacological evaluation and a structure–activity relationship study, it became necessary to synthesize a number of YCK analogues. Since the tetracycle (**3**) is regarded as the basic structural unit of YCK, in the first phase of study, this unit should be retained. We thus investigated a synthetic entry to the tetracycle (**3**) which would provide access to YCK analogues with possible variations of substituents at C-6, -7, and -9.

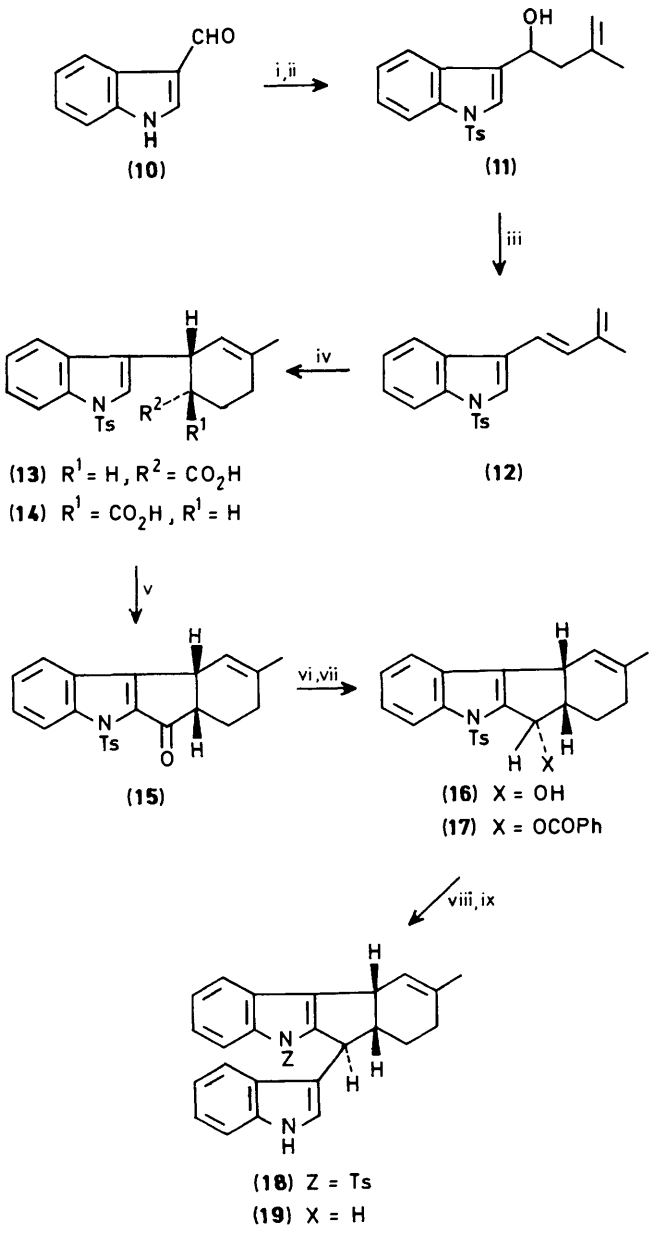
The present approach, according to the retrosynthetic analysis shown in Scheme 1, involves two key stages: (i) formation of the indol-3-ylcyclohexenecarboxylic acid (**7**) by



Scheme 1.

intermolecular Diels–Alder reaction of the diene (**8**) with appropriate acrylic acid derivatives (**9**), and (ii) subsequent intramolecular acylation of the acid (**7**) to afford the key tetracyclic intermediate (**6**). It is especially interesting to investigate the effect of the gem-dimethyl group at C-7 on the biological activity and thus we set 7,7-bis-nor-YCK (**5**; R^1 = Me, R^2 = R^3 = H, R^4 = indol-3-yl) (**19**) as the first target molecule to be synthesized by this new approach. We report herein the synthesis of (**19**).

The starting material for the present synthesis (Scheme 2) was indole-3-carbaldehyde (**10**) which was converted into the alcohol (**11**) by our established procedure.[4] The requisite diene (**12**) was obtained in 50% yield by dehydrating the alcohol (**11**) with methanesulphonyl chloride and triethylamine in THF. The diene (**12**) underwent Diels–Alder addition with acrylic acid in refluxing benzene to give a 4:1 epimeric mixture of the adduct carboxylic acids (**13**) and (**14**) in 79% yield which were separated by chromatography. Although spectral data of (**13**) and (**14**) were in good agreement with their structures, differentiation of



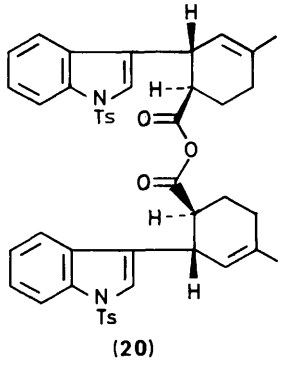
Scheme 2. *Reagents:* i, NaH–*p*-TsCl, DME; ii, CH_2CMeCH_2MgCl, THF; iii, MsCl, Et_3N, THF; iv, CH_2CHCO_2H, C_6H_6; v, PPE, $CHCl_3$; vi, $Li(MeO)_3AlH$, THF; vii, DMAP, Et_3N, PhCOCl; viii, indolylMgBr, C_6H_6; ix, Na–Hg, Na_2HPO_4, MeOH

these two epimers by ^1H n.m.r. was not possible since both exhibited a similar coupling constant for the two methine hydrogens. The assignment of structure (**13**) to the major product and (**14**) to the minor product was based on the Alder *endo* rule[6] and our subsequent study.

Intramolecular acylation at the indole 2-position with carboxylic acid to give a cyclic ketone by warming in polyphosphoric acid (PPA) is well documented.[7] However when either (**13**) or (**14**) was heated with PPA or PPA–xylene, no intramolecular acylation took place and starting materials were recovered unchanged.

Polyphosphate ester[8] (PPE), an established reagent for cyclodehydration in the synthesis of dihydroisoquinoline,[9] has recently been applied to effect cyclodehydration between indole and a carboxylic acid.[10] Treatment of the acid (**13**) with PPE in refluxing chloroform gave the desired tetracyclic ketone (**15**) in 60% yield. Although all the spectral results supported the structural assignment (**15**), the stereochemistry at the ring junction could not be confirmed from a coupling constant analysis of ^1H n.m.r. data. According to the vicinal Karplus correlation,[11] the coupling constants between 10a-H and 6a-H of a *cis*-and *trans*-fused ring for the present system should be 8—10 Hz and 2—3 Hz respectively. The observed coupling constant between 10a-H and 6a-H in (**15**) was 5.5 Hz and thus shed no light on our tentative assignment of stereochemistry at the ring junction.

It is pertinent that similar treatment of the epimeric acid (**14**) with PPE gave no intramolecular acylation product, intermolecular dehydration occurring instead to afford the anhydride (**20**) in 95% yield.



(**20**)

Having prepared the tetracyclic ketone (**15**), the key synthetic intermediate for (**19**), we then examined the stereoselective introduction of the indol-3-yl moiety at C-6. Initially, it was intended to introduce indol-3-yl moiety by nucleophilic addition to the ketone (**15**). Consideration of molecular models reveals that the tetracyclic ketone (**15**) is 'bent' so that delivery of the required indole moiety must occur from the β-face thereby providing the correct stereochemistry at the newly created chiral centre. However, attempts to induce the ketone (**15**) to react with indolylmagnesium bromide or 3-lithiated *N*-tosylindole[12] gave no addition product, starting ketone being recovered unchanged. This was probably due to the facile enolization[13] of (**15**).

Since direct nucleophilic addition of the indole moiety to C-6 of compound (**15**) was not possible, we turned to the bimolecular nucleophilic substitution approach. This required stereoselective conversion of the carbonyl function of (**15**) into a sterically hindered 6α-leaving group. Reduction of the ketone (**15**) with lithium triethoxyaluminium hydride[14] in THF afforded the 6α-hydroxy derivative (**16**) in 75% yield. The ratio of 6α- to 6β-alcohol was 97.6:2.4 by h.p.l.c. analysis.

Attempts to convert the alcohol (**16**) into its mesyl or tosyl derivatives resulted in a complex and intractable mixture of products. Clearly, after their formation, the great mobility of the mesyloxy and tosyl groups resulted in their undergoing both elimination and further rearrangement. Preparations of the benzoyloxy derivative[15] which undergoes elimination only with difficulty was, therefore, attempted. Since the 6α-hydroxy group is sterically hindered, benzoyl chloride was inactive and, therefore, benzoyl trifluoromethanesulphonate (benzoyl triflate), a highly efficient benzoylating reagent for sterically congested secondary and tertiary hydroxy groups,[16] was employed. Treatment of the alcohol (**16**) with this reagent in anhydrous dichloromethane at −60 °C afforded the benzoate (**17**) in 80% yield. The latter was also obtained in (85%) by treating the alcohol (**16**) with benzoyl chloride–triethylamine in

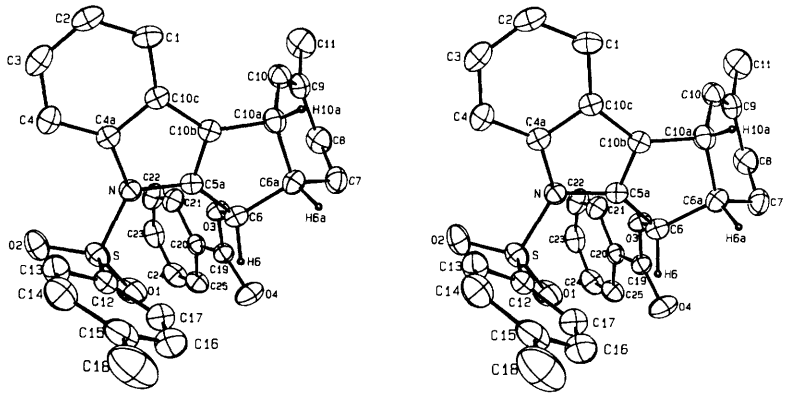


Figure. A stereoscopic view of the benzoate (**17**). Thermal ellipsoids of the non-hydrogen atoms are drawn at 30% probability level

the presence of stoicheiometric amount of 4-(dimethylamino)-pyridine,[17] an active esterification catalyst.

In order to ascertain the stereochemical assignment of the benzoate (**17**), *X*-ray diffraction study on this compound was performed. This investigation (Figure) showed that rings C and D were *cis*-fused and the benzoate group lay on the opposite side to the ring junction hydrogens. Thus the structure of the benzoate (**17**) was established unambiguously and our earlier stereochemical assignments for compounds (**13**)—(**16**) were confirmed.

Bimolecular nucleophilic displacement of the 6α-benzoate group in (**17**) with the indol-3-yl moiety was readily achieved by treating (**17**) with the indolyl Grignard reagent in benzene, to give (**18**) in 70% yield. Finally, detosylation of (**18**) with sodium amalgam in methanol in the presence of disodium hydrogen phosphate buffer[18] afforded 7,7-bis-nor-YCK (**19**) in 75% yield.[19]

Experimental

M.p.s were measured on a Reichert Kofler-block apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 577 spectrophotometer and calibrated with styrene. N.m.r. spectra were recorded on a JEOL FX-90Q and a Bruker WM-400 spectrometer in deuteriochloroform unless otherwise stated with tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi RMS-4 and VG 70-70F high resolution mass spectrometers. U.v. spectra are recorded on a Shimdazu UV240 spectrophotometer. Thin layer chromatography was performed using Merck pre-coated silica gel F-254 plates (thickness 0.25 mm). Flash chromatography was carried out with Kieselgel 60 (Merck) as the stationary phase.[20] Analytical h.p.l.c. was performed on a Beckmann Model 331 HPLC System with Model 163 variable wavelength u.v.–vis. detector. Organic extracts were dried over anhydrous sodium sulphate and evaporated at aspirator pressure using a rotary evaporator. Ether refers to diethyl ether and light petroleum refers to the fraction with b.p. 40—60 °C and was redistilled before use. All reactions requiring anhydrous conditions were conducted in apparatus dried in oven at 120 °C and under static atmosphere of dry 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.

(E)-3-(3-*Methylbutadienyl*)-1-*tosylindole* (**12**).—To a solution of the alcohol (**11**) (24 g, 68 mmol) in anhydrous THF (270 ml) stirred under argon at −60 °C was added triethylamine (28.4 ml, 203 mmol) and mesyl chloride (7.8 ml, 100 mmol). The resulting solution was warmed to room temperature in 1.5 h and a white solid formed during this period. The reaction mixture was stirred at room temperature for a further 0.5 h and then heated under gentle reflux for 20 min. The precipitate was filtered off and discarded and the filtrate was concentrated to give a brown viscous liquid. Chromatography on silica gel with dichloromethane–light petroleum (3:7) as eluant yielded the diene (**12**) (13.7 g, 60%) as a pale yellow viscous liquid (Found: C, 71.4; H, 5.6; N, 4.0. $C_{20}H_{19}NO_2S$ requires C, 71.2; H, 5.7; N, 4.15%); $\lambda_{max.}$(EtOH) 205, 229, 249, 268, 284, and 294 nm; $\nu_{max.}$(film) 1 598 (C=C), 1 280, 1 220, 1 120, 970, and 810 cm^{-1}; δ_H(90 MHz) 8.2—6.9 (9 H, m, ArH), 6.56, 6.97 (2 H, ABq, *J* 16.2 Hz, CH=CH), 5.11 (2 H, m, $=CH_2$), 2.13 (3 H, s, C_6H_4*Me*), and 1.96 (3 H, s, Me); δ_C(22.5 MHz) 144.9, 142.0, 135.7, 135.3, 133.0, 129.9, 129.2, 126.8, 125.0, 123.6, 123.5, 120.9, 120.3, 119.0, 117.1, 113.8, 21.4 (C_6H_4*Me*), and 18.3 (Me); *m/z* 337 (M^+).

4-*Methyl*-2-(1′-*tosylindol*-3′-*yl*)*cyclohex*-3-*ene carboxylic Acids* (**13**) *and* (**14**).—To freshly distilled acrylic acid (2.2 ml, 30 mmol) in benzene (2 ml) heated under reflux was added dropwise the diene (**12**) (5 g, 14.8 mmol) in benzene (8 ml). The progress of the reaction was monitored by t.l.c. After all the diene (**12**) had reacted (*ca.* 3 h), benzene was replaced by ether (100 ml). The reaction mixture was filtered and the filtrate was washed with saturated aqueous sodium hydrogen carbonate and brine, dried, and evaporated to dryness. Chromatography of the residue on silica gel with ether–light petroleum (1:1) as eluant gave first (**13**) (3.83 g, 63%) and further elution furnished (**14**) (0.79 g, 16%) as a colourless solids. Recrystallization of (**13**) from ether–light petroleum gave an analytical sample, m.p. 158—159 °C (Found: C, 67.8; H, 6.1%; M^+, 409.1342. $C_{23}H_{23}NO_4S$ requires C, 67.5; H, 5.7%; *M*, 409.1347); $\lambda_{max.}$(EtOH) 205, 215, 253, 282sh, and 290sh; $\nu_{max.}$(KBr) 3 350br (OH, H-bonded), 1 710s (C=O), 1 596 (C=C), 1 280, 1 180, 970, and 810 cm^{-1}; δ_H(400 MHz) 7.85 (1 H, d, *J* 8.0 Hz, 1-H), 7.61 (2 H, d, *J* 8.0 Hz, ArH), 7.48 (1 H, d, *J* 8.0 Hz, 4-H), 7.29 (1 H, s, 2′-H), 7.14 (2 H, d, *J* 8.0 Hz, ArH), 7.07, 7.19 (2 H, 2t, *J* 8.0 Hz, 5′-H 6′-H), 5.47 (1 H, d, br, *J* 3.5 Hz, 3-H), 4.02 (1 H, s, br, 2-H), 2.77 (1 H, m, 1-H), 2.28 (3 H, s, C_6H_4*Me*), 2.12 (2 H, m, CH_2), and 1.79 (5 H, s + m, Me, CH_2), $J_{2,3}$ 3.5 Hz, $J_{1,2}$ 4.5 Hz, $J_{1,6}$ 4.5 Hz, 10.5 Hz; δ_C(100 MHz) 178.63 (s), 144.60 (s), 135.40 (s), 135.31 (s), 134.86 (s), 130.78 (s), 129.69 (d), 126.56 (d), 126.04 (d), 124.40 (d), 122.80 (d), 122.63 (s), 121.92 (d), 120.01 (d), 113.59 (d), 43.53 (d), 33.74 (d), 29.23 (t), 23.41 (q), 21.43 (q), and 20.19 (t).

For (**14**): m.p. 115—116 °C (Found: *m/z* 409.1342. $C_{23}H_{23}NO_4S$ requires *m/z* 409.1347); $\lambda_{max.}$(EtOH) 204, 216, 253, 283sh, and 290sh nm; $\nu_{max.}$(Nujol) 3 340br (OH, H-bonded), 1 710s (C=O), 1 596 (C=C), 1 100, 950, and 785 cm^{-1}; δ_H(90 MHz) 8.0—

7.0 (10 H, m, ArH, OH), 5.40 (1 H, s, br, 3-H), 3.95 (1 H, s, br, 2-H), 2.74 (1 H, dt, br, 1-H), 2.28 (3 H, s, Ar*Me*), 2.0 (4 H, m, CH_2CH_2) and 1.75 (3 H, s, Me), $J_{1,2}$ 6.1 Hz, $J_{1,6}$ 6.3 Hz; δ_C(22.5 MHz) 180.9 (CO_2H), 144.0, 135.7, 135.3, 134.9, 129.7, 126.7, 125.2, 124.7, 124.1, 123.1, 121.4, 119.8, 113.9, 44.5, 34.8, 28.3, 24.0, 23.5 (Me), and 21.5 (ArMe).

(1R,2S)-4-*Methyl*-2-(1-*tosylindol*-3-*yl*)*cyclohex*-3-*enecarboxylic Acid Anhydride* (**20**).—A solution of compound (**14**) (4 g, 9.8 mmol) and polyphosphate ester (8 g) in anhydrous chloroform (400 ml) was refluxed for 0.5 h. The solution was cooled and ether was added. The organic layer was washed with water and brine, dried, and evaporated to dryness. Chromatography of the residue on silica gel with ether–light petroleum (2:3) as eluant afforded the anhydride (**20**) (3.6 g, 92%) as a white solid, m.p. 186—187 °C (Found: C, 69.2; H, 5.8. $C_{46}H_{44}N_2O_7S_2$ requires C, 69.0; H, 5.5%); $\nu_{max.}$(Nujol) 1 817s, 1 743m (C=O), 1 598, 850, and 780 cm^{-1}; δ_H(90 MHz) 8.0—7.0 (18 H, m, ArH), 5.37 (2 H, s, br, 10 and 10′-H), 3.82 (2 H, s, br, 10a- and 10a′-H), 2.70 (2 H, m, 6a- and 6a′-H), 2.29 (6 H, s, 2 Ar*Me*), and 1.96 (8 H, m, 4 CH_2), and 1.73 (6 H, s, 2 Me); δ_C(22.5 MHz), 170.6 (C=O), 135.6, 135.3, 134.9, 129.5, 129.1, 126.8, 124.4, 124.2, 123.1, 122.9, 121.2, 119.8, 113.8, 45.9, 39.5, 28.2, 23.7, 23.4, and 21.5.

9-*Methyl*-6-*oxo*-5-*tosyl*-6aβ,7,8,10aβ-*tetrahydroindeno*-[2.1-b]*indole* (**15**).—To a solution of the acid (**13**) (4 g, 9.8 mmol) in anhydrous chloroform (30 ml) was added a solution of polyphosphate ester (8.4 g) in chloroform (10 ml). The resulting solution was heated under gentle reflux for 0.5 h after which it was poured into cold water and extracted with ether. The extract was washed with water and saturated brine, dried, and evaporated to dryness. Chromatography on silica gel with ether–light petroleum (3:7) as eluant gave the ketone (**15**) (2.29 g, 60%), m.p. 145—146 °C (from ether–light petroleum) (Found: C, 70.6; H, 5.6%; M^+, 391.1257. $C_{23}H_{21}NO_3S$ requires C, 70.6; H, 5.4%; *M*, 391.1242); $\lambda_{max.}$(EtOH) 202, 223, 242, and 292 nm; $\nu_{max.}$(KBr) 1 702s (C=O), 1 597 (C=C), 1 160, 1 110, 1 000, 970, 720, and 650 cm^{-1}; δ_H(400 MHz) 8.33 (1 H, d, *J* 8.0 Hz, 1-H), 8.02 (2 H, d, *J* 8.0 Hz, ArH), 7.71 (1 H, d, *J* 8.0 Hz, 4-H), 7.53, 7.35 (2 H, 2 t, *J* 8.0 Hz, 2- and 3-H), 7.23 (2 H, d, *J* 8.0 Hz, ArH), 5.70 (1 H, s, br, 10-H), 3.93 (3 H, s, br, 10a-H), 3.18 (1 H, dt, *J* 5.5 Hz, 6a-H), 2.35 (3 H, s, $ArCH_3$), 2.13 (1 H, m, 7-H), 1.86 (3 H, m, 7-H, 2 8-H), and 1.62 (3 H, s, Me), $J_{10a,a}$ 5.5 Hz, $J_{7,7}$ 12 Hz, $J_{6a,7}$ 5.5 Hz, $J_{7,8}$ 4.5 Hz; δ_C(75 MHz) 192.50 (s), 155.62 (s), 145.11 (s), 137.59 (s), 135.72 (s), 129.96 (s), 129.78 (d), 129.17 (d), 127.50 (d), 124.40 (s), 123.88 (d), 121.90 (d), 118.60 (d), 115.75 (d), 51.32 (d), 34.42 (d), 27.20 (t), 24.13 (t), 24.06 (q), and 21.60 (q).

6α-*Hydroxy*-9-*methyl*-5-*tosyl*-6aβ,7,8,10aβ-*tetrahydroindeno*[2,1-b]*indole* (**16**).—To a suspension of lithium aluminium hydride (0.76 g, 20 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C was added dropwise a solution of methanol (0.6 ml, 15 mmol) in tetrahydrofuran (5 ml). A solution of compound (**15**) (2 g, 5 mmol) in tetrahydrofuran (15 ml) was added to the freshly prepared solution of lithium trimethoxyaluminium hydride and the mixture was stirred at room temperature for 0.5 h. Work-up and chromatography on silica gel with ether–light petroleum (1:3) gave the alcohol (**16**) (1.5 g, 75%) as a white solid, m.p. 165—166 °C (from ether–light petroleum) (Found: C, 70.3; H, 6.05; N, 3.4. $C_{23}H_{23}NO_3S$ requires C, 70.2; H, 5.9; N, 3.55%); $\lambda_{max.}$(EtOH) 202, 220, and 257 nm; $\nu_{max.}$(Nujol) 3 590s (OH), 1 596 (C=C), 1 070, and 790 cm^{-1}; δ_H(90 MHz) 8.0—7.0 (9 H, m, ArH, OH), 5.76 (1 H, s, br, 10-H), 5.54 (1 H, dd, *J* 7.0, 0.88 Hz, 6-H), 3.55 (1 H, s, br, 10a-H), 3.12 (1 H, m, 6a-H), 2.31 (3 H, s, C_6H_4Me), 2.02 (4 H, m, CH_2CH_2), and 1.69 (3 H, s, Me), $J_{10a,6a}$ 6.1 Hz, $J_{6,6a}$ 7 Hz; δ_C(22.5 MHz) 144.9, 142.6, 140.1, 136.2, 135.3, 130.8, 129.9, 126.9, 124.5, 123.6, 120.1, 114.5, 72.2, 44.8, 37.3, 28.8, 23.9, 21.5, and 21.4; *m/z* 393 (M^+) and 375.

6α-*Benzoyloxy*-9-*methyl*-5-*tosyl*-6aβ,7,8,10aβ-*tetrahydroindeno*[2,1-b]*indole* (**17**).—To a solution of compound (**16**) (2.0 g, 5.1 mmol) in chloroform (20 ml) was added 4-dimethylaminopyridine (683 mg, 5.6 mmol), triethylamine (0.79, 5,6 mmol), and benzoyl chloride (0.65 ml, 5.6 mmol). The resulting solution was heated under gentle reflux for 0.5 h. The solution was poured into a aqueous copper sulphate and the mixture extracted with dichloromethane. The extract was washed with water, dried, and evaporated to dryness and the residues chromatographed on silica gel with ether–light petroleum (1:4) to give the benzoate (**17**) (2.15 g, 85%) as a white solid, m.p. 160—161 °C (from ether–light petroleum) (Found: C, 72.6; H, 5.5; N, 3.1%. $C_{30}H_{27}NO_3S$ requires C, 72.4; H, 5.5; N, 2.8%); $\lambda_{max.}$(EtOH) 201, 222, and 258 nm; $\nu_{max.}$(Nujol) 1 740 (C=O), 1 597 (C=C), 1 250, 1 075, 895, and 680 cm^{-1}; δ_H(400 MHz) 8.1—7.0 (13 H, m, ArH), 7.04 (1 H, d, *J* 3 Hz, 6-H), 5.81 (1 H, s, br, 10-H), 3.72 (1 H, s, br, 10a-H), 3.38 (1 H, m, 6a-H), 2.27 (3 H, s, C_6H_4Me), 1.99, 1.87 (4 H, 2m, 27-H, 28-H), and 1.68 (3 H, s, Me), $J_{6a,10a}$ 7.0 Hz, $J_{6,6a}$ 3.0 Hz; δ_C(75 MHz) 165.9 (s, 144.6 (s), 140.5 (s), 138.1 (s), 134.6 (s), 133.6 (s), 132.9 (d), 130.1 (s), 129.9 (d), 129.8 (d), 129.6 (d), 128.3 (d), 126.7 (d), 125.6 (s), 125.0 (d), 123.4 (d), 120.4 (d), 120.0 (d), 114.7 (d), 74.0 (d), 44.1 (d), 37.0 (d), 27.6 (t), 24.0 (q), 22.0 (t), and 21.4 (q); *m/z* 497 (M^+), 392, 375, and 342.

Alternative procedure to Compound (**17**).—To a solution of compound (**16**) (0.95 g, 2.4 mmol) in anhydrous dichloromethane (8 ml) and pyridine (0.61 ml, 7.3 mmol) at −80 °C was added benzoyl triflate (0.85 ml, 4.8 mmol). The mixture was stirred at −60 °C for 0.5 h and kept at room temperature for a further 1 h. Water and dichloromethane were added to quench the reaction. The organic layer was separated, washed with water, dried, and evaporated to dryness and the residue chromatographed to give (**17**) (0.96 g, 80%).

6β-*Indol*-3′-*yl*-9-*methyl*-5-*tosyl*-6aβ,7,8,10aβ-*tetrahydroindeno*-[2.1-b]*indole* (**18**).—To a suspension of magnesium turnings (72.4 mg, 3.0 mmol) in anhydrous ether (3 ml) was added bromoethane (0.21 ml, 2.8 mmol) in ether (1 ml). After reaction had ceased, indole (0.33 g, 2.8 mmol) in anhydrous benzene (6 ml) was added. Ether was distilled off and benzene (6 ml) was added. This freshly prepared solution of indolylmagnesium bromide in benzene was added to a suspension of the benzoate (**17**) in benzene (6 ml) and the mixture was stirred at room temperature for 0.5 h. It was then poured into aqueous ammonium chloride and extracted with ether. The extract was washed with water and brine, dried, and evaporated to dryness. Flash chromatography on silica gel with ether–light petroleum (3:7) as eluant gave (**18**) (0.87 g, 70%) as a white solid, m.p. 90 °C (decomp.) (Found: M^+, 492.1865. $C_{31}H_{28}N_2O_2S$ requires *M*, 492.1871); $\lambda_{max.}$(EtOH) 203, 222, and 264 nm; $\nu_{max.}$(Nujol) 3 400s (NH), 1 597 (C=C), 1 230, 1 210, 1 090, 990, 890, and 785 cm^{-1}; δ_H(90 MHz) 8.11—6.58 (12 H, m, ArH), 7.85 (1 H, s, br, NH), 6.59 (1 H, d, *J* 2.2 Hz, 2′-H), 5.58 (1 H, s, br, 10-H), 4.62 (1 H, s, br, 6-H), 3.83 (1 H, s, br, 10a-H), 2.88 (1 H, m, 6a-H), 2.18 (3 H, s, C_6H_4Me), 1.92 (4 H, m, CH_2CH_2) and 1.69 (3 H, s, Me), $J_{6a,10a}$ 6.6 Hz, $J_{2',6}$ 2.2 Hz; δ_C(22.5 MHz) 144.1, 143.8, 140.7, 136.7, 135.6, 129.2, 127.0, 126.5, 123.6, 123.3, 121.8, 121.0, 120.4, 120.1, 119.5, 119.4, 117.8, 114.9, 111.2, 50.6 (C-6), 45.2 (C-6a), 38.2 (C-10a), 29.0, 27.6, 24.0 (9-Me), and 21.4 (C_6H_4Me).

6β-*Indol*-3′-*yl*-9-*methyl*-6aβ,7,8,10aβ-*tetrahydroindeno*-[2.1-b]*indole* (**19**).—A mixture of compound (**18**) (0.6 g) in anhydrous ether (10 ml) and methanol (20 ml), disodium hydrogen phosphate (10 g), and sodium amalgam (5%; 5 g) was

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for non-hydrogen atoms in compound (**17**), with e.s.d.s in parentheses

Atom	*x*	*y*	*z*
S	6 489(6)	995(6)	3 950(6)
O(1)	6 387(2)	903(2)	2 774(2)
O(2)	6 585(2)	−119(2)	4 933(2)
O(3)	3 507(1)	2 910(1)	1 615(1)
O(4)	4 542(2)	2 449(2)	38(1)
N	5 138(2)	2 228(2)	4 050(2)
C(1)	3 469(2)	4 592(2)	5 666(2)
C(2)	3 777(2)	3 833(3)	6 832(2)
C(3)	4 577(2)	2 498(3)	7 125(2)
C(4)	5 101(2)	1 857(2)	6 274(2)
C(4a)	4 789(2)	2 617(2)	5 105(2)
C(5a)	4 576(2)	3 395(2)	3 112(2)
C(6)	4 386(2)	3 647(2)	1 815(2)
C(6a)	3 730(2)	5 194(2)	1 429(2)
C(7)	2 738(3)	5 777(3)	337(2)
C(8)	1 363(3)	5 681(3)	565(2)
C(9)	864(2)	6 023(2)	1 665(2)
C(10)	1 684(2)	5 993(2)	2 529(2)
C(10c)	3 991(2)	3 977(2)	4 786(2)
C(10a)	3 160(2)	5 639(2)	2 530(2)
C(10b)	3 889(2)	4 422(2)	3 516(2)
C(11)	−607(3)	6 390(4)	1 753(3)
C(12)	7 818(2)	1 585(2)	4 126(2)
C(13)	8 441(2)	1 285(2)	5 233(2)
C(14)	9 487(3)	1 755(3)	5 379(3)
C(15)	9 914(2)	2 525(2)	4 424(3)
C(16)	9 271(3)	2 796(3)	3 325(3)
C(17)	8 240(3)	2 337(3)	3 164(2)
C(18)	11 025(3)	3 056(3)	4 563(4)
C(19)	3 762(2)	2 285(2)	758(2)
C(20)	2 971(2)	1 367(2)	803(2)
C(21)	2 023(2)	1 275(2)	1 601(2)
C(22)	1 290(3)	431(3)	1 596(3)
C(23)	1 529(3)	−358(3)	809(3)
C(24)	2 469(3)	−270(3)	17(3)
C(25)	3 180(2)	594(2)	7(2)

Table 2. Selected torsion angles (°)

H(6)–C(6)–C(6a)–H(6a)	−36.9(2.5)
H(6)–C(6)–C(6a)–C(7)	83.8(1.8)
H(6)–C(6)–C(6a)–C(10a)	−147.2(1.8)
H(6a)–C(6a)–C(10a)–H(10a)	20.6(2.5)
H(6a)–C(6a)–C(10a)–C(10)	147.9(1.9)
H(6a)-C(6a)–C(10a)–C(10b)	−90.6(1.9)

stirred at room temperature. The progress of the reaction was monitored with t.l.c. After the reaction was complete, water was added. Work-up and flash chromatography on silica gel with ether–light petroleum (3:7) gave the title compound (**19**) (0.31 g, 75%) as a white solid, m.p. 121 °C (decomp.) (Found: M^+, 338.1791. $C_{24}H_{22}N_2$ requires *M*, 338.1783); $\lambda_{max.}$(EtOH) 203, 224, 281, and 289sh nm; $\nu_{max.}$(Nujol) 3 395s (NH), 1 070, 990, and 742s cm^{-1} (NH); δ_H(90 MHz, C_6D_6) 7.8—6.3 (8 H, m, ArH), 6.34 (1 H, d, *J* 2.6 Hz, 2'-H), 5.95 (1 H, br s, 10-H), 4.38 (1 H, d, *J* 6.6 Hz, 6-H), 3.94 (1 H, br s, 10a-H), 3.17 (1 H, m, 6a-H), 1.89 (4 H, m, CH_2CH_2), and 1.64 (3 H, s, Me); δ_C(22.5 MHz, C_6D_6) 144.2, 141.1, 137.1, 132.4, 127.5, 126.5, 125.2, 124.4, 122.4, 121.8, 121.0, 119.9, 119.7, 119.0, 117.5, 112.0, 111.5, 52.0 (C-6), 40.1 (C-6a), 38.8 (C-10a), 27.4, 25.2, and 24.2.

X-Ray Study of Compound (**17**).—*Crystal data.* $C_{30}H_{27}NO_4S$, colourless prisms from diethyl ether–light petroleum, *M* = 497.6. Triclinic, space group $P\bar{1}$, *a* = 10.648(3), *b* = 10.911(2), *c* = 11.785(3) Å, α = 74.86(2), β = 89.87(2), γ = 71.71(2)°, *U* = 1 250.3(7) Å^3, *Z* = 2, D_c = 1.323 g cm^{-3}, μ(Mo-K_α) = 1.58 cm^{-1}. Crystal size: 0.32 × 0.21 × 0.15 mm. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-K_α radiation (0.710 73 Å) using the ω–2θ scanning technique with variable scan width of 0.60 + 0.35 tanθ deg. All reflections within the $(h, \pm k, \pm l)$ quadrants extending to 2θ = 50° were measured. A total of 4 352 independent reflections were obtained of which 3 170 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 [21] from which all the non-hydrogen atoms were located. Positions of the hydrogen atoms were revealed in difference maps at a later stage; however, only those bonded to C(6), C(6a), C(10a), 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 H(6), H(6a), and H(10a) were not refined. In the final least-squares cycle, a list of 335 parameters were adjusted: atomic co-ordinates and anisotropic thermal parameters for all non-hydrogen atoms, atomic co-ordinates for H(6), H(6a), and H(10a), 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 $w = 4F_o^2/[\sigma(F_o^2) + (0.055F_o^2) + (0.055F_o^2)]$. Atomic scattering factors were obtained from reference 22. Calculations were carried out on a MicroVax II computer using the Structure Determination Package (SDP).[23] The final *R* values were: *R* = 0.043, R_w = 0.058 and the 'goodness of fit', $[\Sigma w(|F_o| - |F_c|)^2/(m-s)]^{\frac{1}{2}}$ = 1.43, where *m* is the number of measurements and *s* is the number of parameters. In the final difference Fourier map, the residual electron densities were between −0.26 and 0.23 e Å^{-3}. Fractional atomic co-ordinates are given in Table 1, and selected torsion angles in Table 2. Tables of bond lengths, bond angles, and thermal parameters are available on request from the Cambridge Crystallographic Data Centre.*

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