A versatile synthetic route to the anti-implantation agent, yuehchukene, and its analogues

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A detailed study directed toward the development of a versatile synthetic route to the interesting dimeric natural product yuehchukene (**1**) and its epimer, 6a-*epi*-yuehchukene (**2**), has been completed. Due to the anti-implantation activity associated with **1**, it was important to provide a synthetic strategy not only to **1**, but to a family of yuehchukene analogues that, hopefully, would reveal superior chemical stability and (or) elevated biological activity. The experiments described herein and which utilize the readily available and inexpensive isophorone (**6**) satisfy these requirements.

Key words: yuehchukene synthesis, yuehchukene analogues, anti-implantation activity.

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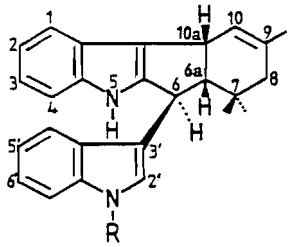
On a réalisé une étude détaillée entreprise dans le but de développer une voie de synthèse versatile du yuehchukène (**1**) et de son épimère, le 6a-*épi*-yuehchukène (**2**), des produits naturels dimères intéressants. Compte tenu de l'activité anti-implantation associée au composé **1**, il était important de proposer une stratégie de synthèse qui ne conduirait pas seulement à **1**, mais à une famille d'analogues du yuehchukène qui pourraient éventuellement posséder une stabilité chimique supérieure et (ou) une activité biologique plus grande. Les expériences décrites dans ce travail, qui utilisent l'isophorone (**6**) (un produit facilement disponible et peu coûteux) comme produit de départ, satisfont à ces critères.

Mots clés : synthèse du yuehchukène, analogue du yuehchukène, activité anti-implantation.

[Traduit par la rédaction]

The genus *Murraya*, of the plant family *Rutacaea*, occurs throughout tropical and sub-tropical east Asia, from China and India in the north through to New Caledonia and northeastern Australia in the south. Chemically, *Murraya* species are characterized by the occurrence of carbazole, furoquinoline, and acridone alkaloids (1–4), coumarins (5, 6), and flavanoids (7). Yuehchukene (**1**), a novel type of dimeric indole natural product, was recently isolated in racemic form, in trace quantities (<18 ppm), from the roots of *M. paniculata* (8). Its name derives from the word yueh-chu, which is the name of the plant in Chinese.

Owing to the low yield of **1**, a survey of other *Murraya* species was carried out (2, 9) but the problem of low yield persisted.



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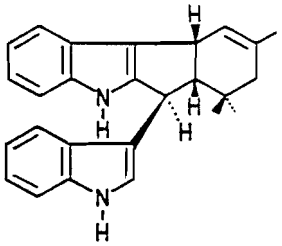

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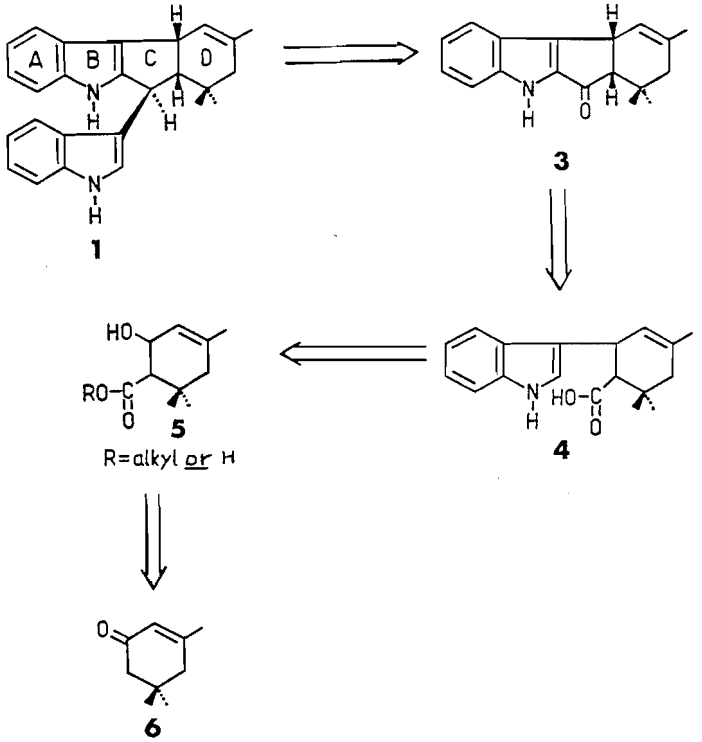
The most interesting feature about yuehchukene is its biological activity. Crude extracts of *M. paniculata* have been used in China as an astringent and antidysenteric (10–12). They also showed strong cardiac depressant and antispasmodic activity (13) but the most interesting results came from the studies of Kong *et al.* (8, 11, 14, 15), which revealed that **1** possessed strong anti-implantation activity in rats. To fully exploit the pharmacological potential of this molecular system, it was considered appropriate to develop a versatile stereoselective synthetic route that, in addition to **1**, would also allow preparation of closely related analogues. The present study describes results that satisfy these objectives. A preliminary account of a portion of this study has appeared (16).



SCHEME 1. Retrosynthetic analysis for the synthesis of yuehchukene (**1**) and its analogues.

A retrosynthetic analysis was planned according to Scheme 1. The assembly of the target molecule was strategically envisaged so as to facilitate the required variations for the preparation of

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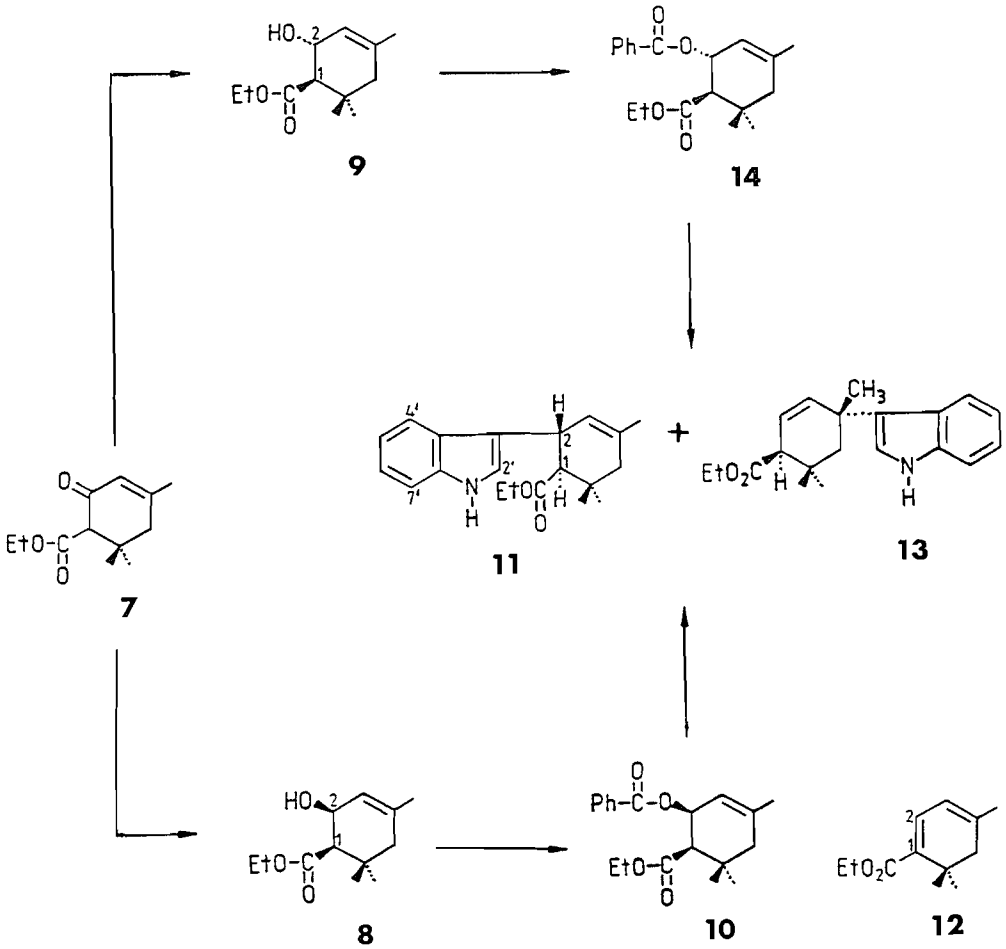


SCHEME 2. Conversion of keto-ester **7** to indole intermediates **11** and **13**.

desired analogues. Thus, for instance, the indole groups could be differently substituted or, even more interestingly, the protons at C-6a and C-10a in ketone **3** could have an *anti* relationship to produce a *trans* junction of rings C and D, thus providing the isomer, 6a-*epi*-yuehchukene (**2**). This strategy also has the advantage of starting from commercially inexpensive isophorone (**6**).

The initial studies were performed with the known keto-ester (**7**), available via condensation of mesityl oxide and ethyl acetoacetate (17), since it was envisaged (see later) that **7** could be subsequently available from **6** (Scheme 2). The keto-ester **7** was reduced with sodium borohydride in methanol to give *cis*-hydroxyester **8** in 71% yield and the epimeric alcohol **9** in 23% yield. The stereochemistry at C-1 and C-2 in these isomers was readily available from the ^{1}H NMR spectra (see Experimental).

The next transformation required an activation of the hydroxyl group of **8** to facilitate its displacement by the indole moiety (see Scheme 1). Treatment of hydroxyester **8** with *p*-toluenesulfonyl chloride in the presence of various bases (DMAP, pyridine, Et_3N) gave the undesired product **12** as a result of overall elimination of water. Fortunately, the desired activation of the hydroxyl group could be achieved by treatment of **8** with benzoyl chloride and DMAP (18) in dichloromethane at 5°C to obtain the allylic benzoate **10** as an oil (85% yield).

Having in hand **10**, the nucleophilic substitution of the benzoate group was attempted by utilizing indolylmagnesium iodide in ether at 5°C. The desired indole-ester **11** was obtained in 42% yield along with the isomer **13** (31%).

The indole-ester **11** revealed particularly informative spectra and its structure was readily available from spectral analysis. The IR spectrum shows the characteristic sharp absorption band of N-H at 3480 cm^{-1} and the intense band of the carbonyl group at 1730 cm^{-1}. The mass spectrum reveals the molecular ion and the base peak at m/z 311. Finally, the ^{1}H NMR spectrum shows the proton at C-1 at 2.67 ppm as a doublet with a J value of 12 Hz due to the coupling with the proton at C-2, which in turn appears at 3.90 ppm as a multiplet. Irradiation of the latter signal simplified the doublet at 2.67 ppm to a singlet. Owing to the large coupling constant between these two protons (12 Hz), the *trans* stereochemistry was assigned. The proton at C-2′ appears at 6.99 ppm as a doublet with a J value of 3.2 Hz due to the coupling with the N-H proton, which appears at 7.92 ppm as a broad signal. The coupling was again corroborated by double resonance experiments. The signals of the other aromatic protons are sufficiently resolved so that assignments could also be made (see Experimental).

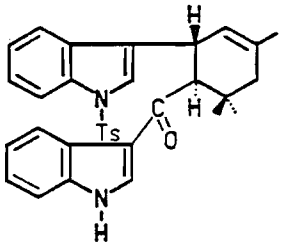
The product **13** was characterized mainly by ^{1}H NMR spectroscopy. Its IR spectrum shows the bands corresponding to N-H and C=O at 3480 and 1730 cm^{-1}. The ^{1}H NMR spectrum displays the vinylic protons as two pairs of doublet of doublets at 5.79 (J = 10 and 4 Hz) and 6.05 ppm (J = 10 and 2 Hz) being both coupled with the proton at C-1, which appears at 2.95 ppm as a doublet of doublets (J = 4 and 2 Hz). These assignments were corroborated by double resonance experiments. The stereochemistry shown in **13** was assigned later by correlation with another intermediate, the indole-acid **32** (Scheme 4) discussed later.

Following similar transformations to those described above,

the minor *trans*-hydroxyester **9** (Scheme 2) was transformed to *trans*-benzoate **14** and, in turn, to the compounds **11** and **13** with practically the same yields and same ratio of **11**/**13** as obtained with **8** as starting material. Therefore, it seems that a carbocation intermediate or a similar species is involved in the overall conversion of **10** and **14** to the final products. An alternative rationale could involve **12** as an intermediate followed by 1,4- and 1,6-conjugate addition of the Grignard reagent.

The next step required the hydrolysis of **11** to the corresponding acid in accord with the retrosynthetic analysis (see **4**, Scheme 1). Unfortunately, treatment of **11** with either aqueous sodium hydroxide in refluxing ethanol or trimethylsilyl iodide in refluxing acetonitrile (19) did not afford the desired product; the starting material was recovered unchanged and direct cyclization of **11** to **3** also failed.

An alternative route to the yuehchukene system from ester **11** could involve initial attachment of the other indole unit and then subsequent cyclization. For this purpose, **11** was converted to its *N*-tosyl derivative and the latter was reacted with indolylmagnesium iodide in an effort to obtain the ketone **15** but only unreacted **11** was recovered even though similar reaction of **11** with *n*-butyllithium did afford the expected product **16**.



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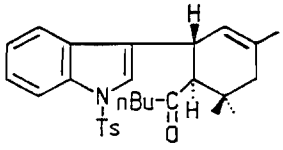

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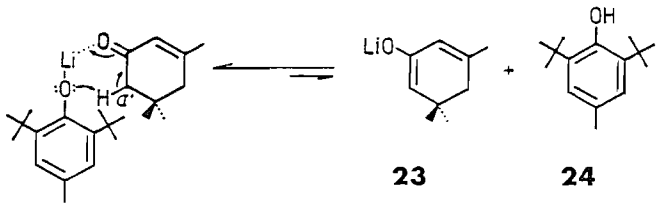
In view of the above, reconsideration of the synthetic strategy in terms of the corresponding acid **5** (Scheme 1) was made. The hydroxyester **8** could be hydrolyzed to the corresponding acid **18** (NaOH, room temperature, 5 days, 75% yield) but the low yield (16%) in the original preparation of **7** according to the literature procedure (17) demanded a superior synthetic route to **17**. A solution to this objective is now provided (Scheme 3).

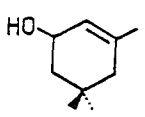
The readily available and inexpensive isophorone (**6**), when treated with lithium 2,6-di-*tert*-butyl-4-methylphenoxide and carbon dioxide gas in diethyl ether at room temperature (20), gave keto-acid **17**. This product turned out to be too unstable for isolation after the acidic work-up of the reaction mixture, so reduction with sodium borohydride was performed *in situ* on the salt **19** to give, upon acidification, *cis*-hydroxy acid **18** in 46% overall yield. Small quantities (about 5%) of the corresponding *trans*-hydroxy acid **21** were also obtained. Since the remainder was recovered isophorone **6**, the effective yield in the overall conversion from **6** to **18** was 90%.

Several aspects of this transformation are worthy of comment. First of all, this appears to be the first case of a kinetic carboxylation of an α,β-unsaturated ketone under these mild conditions, although carboxylation of simple ketones with these reagents has been reported (20). Perhaps the reason that such a mild base (pK_a of conjugated acid = 12.3) (21) was capable of abstracting the α′ proton ($pK_a \simeq 20$) (**22** → **23** + **24**) is, in part, due to the complex-induced proximity effect (CIPE) (22), which refers to the chelation of the metal (lithium, in this case) to the carbonyl oxygen making the α′ proton more acidic and, at the same time, placing the base closer to the same proton. The reason for using such a bulky base was to prevent its carboxylation under the conditions of the reaction (20).



22 **23** **24**

The fact that isophorone (**6**), and *not* alcohol **25**, was recovered from the "one-pot" double transformation suggests that the carboxylation step was complete, thereby giving the products **19** and **20**. Sodium borohydride reacted only with **19** to give **18** while **20** decomposed back to **6** during the acidic work-up of the reaction mixture.



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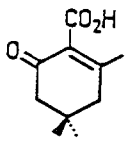

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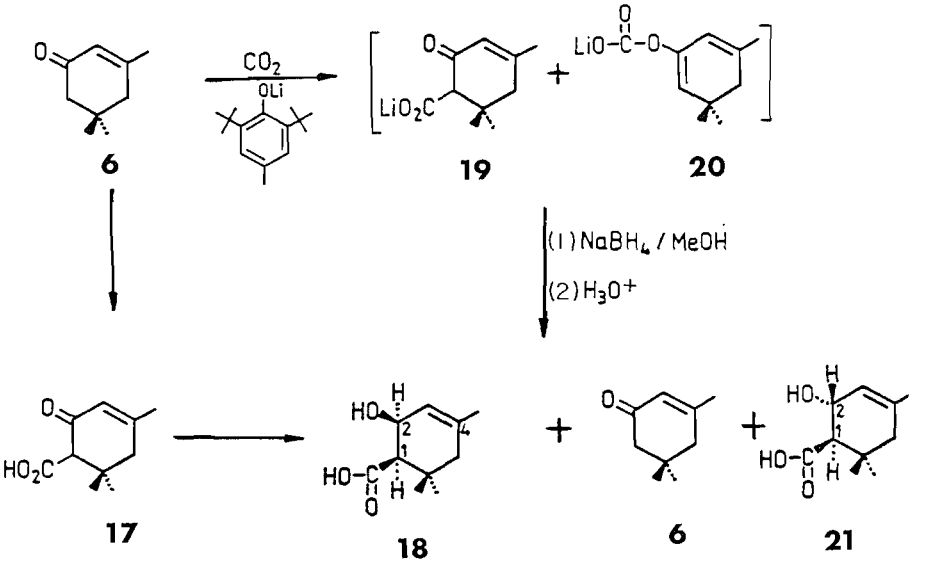
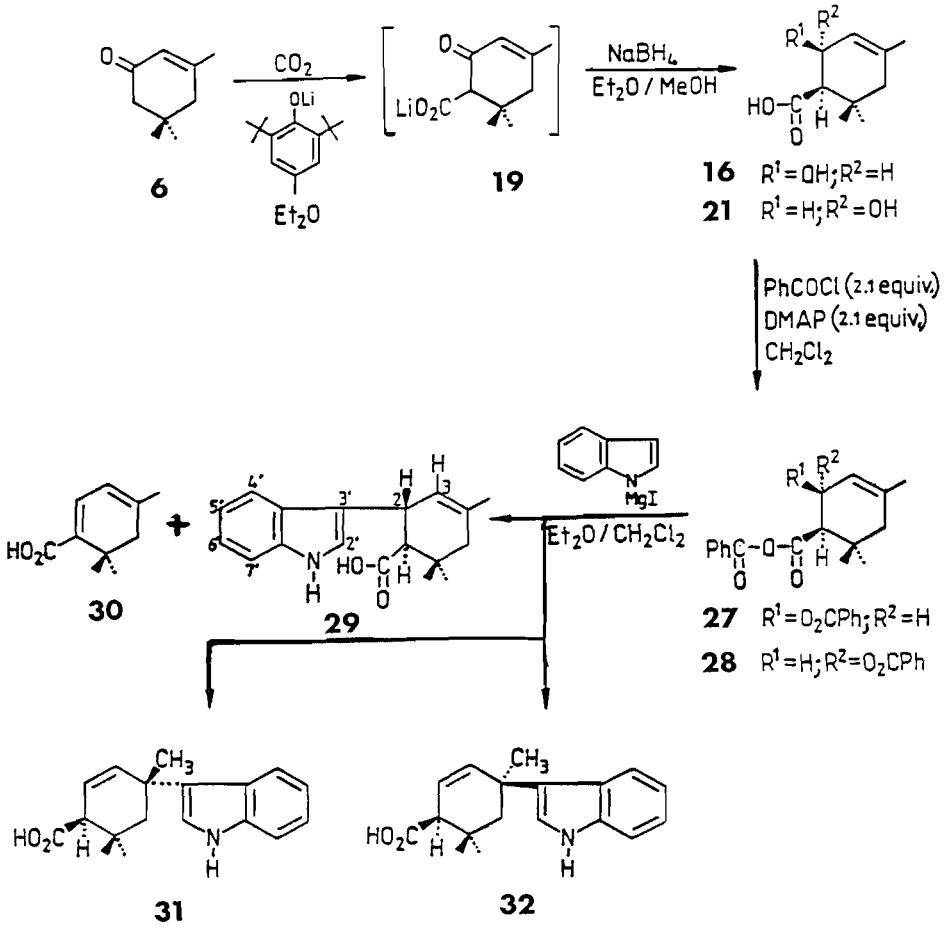
It should be noted that direct carboxylation with methylmagnesium carbonate[2] or bromomagnesium ureide – carbon dioxide adducts (24) affords mainly the undesired acid **26**.

The next step was the activation of the hydroxyl functionality in **18** in order to provide a good leaving group for subsequent nucleophilic displacement (Scheme 4). Thus, treatment of **18** with 2.1 equivalents of benzoyl chloride and DMAP in dichloromethane at 5°C furnished the unstable ester-anhydride **27**, which was obtained as a crude liquid and was not further purified. Treatment of **27** with indolylmagnesium iodide from 5 to 25°C gave rise to the long-desired indole-acid **29** (40% yield) as colorless crystals (mp 173–174°C). Careful purification of the crude mixture also gave by-products **30** (15%), **31** (26%), and **32** (3%). The structure and stereochemistry of **29** could be readily assigned from a detailed analysis of its spectroscopic properties. Apart from the mass spectrum, which provided the correct molecular ion (*m*/*z* 283), the ^1H NMR spectrum was particularly informative. The *gem*-dimethyl group protons appear as singlets at 1.08 and 1.14 ppm and the protons of the vinylic methyl group at 1.71 as a broad singlet. The AB system corresponding to the protons at C-5 appears at 1.76 and 2.15 ppm with a *J* value of 16 Hz. The hydrogen at C-2 appears at 3.93 ppm as a doublet with a *J* value of 10 Hz caused by the *trans* coupling with the proton at C-1, which appears at 2.71 ppm as a doublet. These assignments were corroborated by double resonance experiments. Thus, irradiation of the proton at C-2 causes the proton at C-1 to become a singlet, and irradiation of the proton at C-1 changes the signal of the proton at C-2 from doublet to singlet. The vinylic proton appears at 5.47 ppm as a broad singlet. The protons at C-2 and C-3 show only a small coupling to each other since a molecular model of **29** reveals that the dihedral angle between them is nearly 90°C. The proton at position 2′ of the indole moiety appears at 6.94 ppm as a doublet with a small *J* value of 2 Hz because of its coupling to the proton on the nitrogen atom (7.77 ppm), the latter also corroborated by decoupling experiments. The signals of the other aromatic protons were also identified. These assignments were based on nOe-difference and double resonance experiments. Irradiation at the N-H proton resonance enhances both the signal at 6.94

[2]J. P. Kutney and H. Kurobe. Unpublished results.



SCHEME 3. Conversion of isophorone (**6**) to hydroxy acids **18** and **21**.



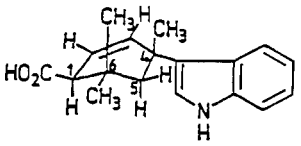
SCHEME 4. Overall sequence from isophorone (**6**) to indole intermediates **29**, **31**, and **32**.

ppm and the doublet at 7.33 ppm. Since the signal at 6.94 ppm had already been assigned to the aromatic proton at C-2′, the signal at 7.33 ppm must correspond to the proton at C-7′, and this was confirmed by a second nOe experiment. Irradiation at 5.47 ppm, which is the signal corresponding to the vinylic proton, increases the signals of only two aromatic protons: the signal at 6.94 ppm (proton at C-2′) and the doublet at 7.62 ppm. As can be seen from models, the only aromatic protons that are in proximity with the vinylic proton when the C-2—C-3′ bond is rotated are those at C-2′ and C-4′. Therefore, the doublet at 7.62 ppm was assigned to the proton at C-4′. The knowledge of the chemical shifts of the protons at C-4′ and C-7′ permitted the assignment of the signals of the protons at C-5′ and C-6′ by double resonance experiments. Thus, decoupling of the proton at C-4′ simplified only the signal at 7.08 ppm to a doublet. Therefore, the signal at 7.08 ppm (doublet of doublets, $J = 8,8$

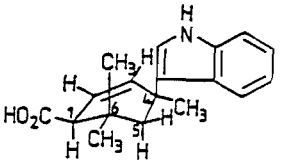
Hz, in the normal spectrum) corresponds to the proton at C-5′ and the signal at 7.17 ppm (doublet of doublets, J = 8,8 Hz) is assigned to the proton at C-6′.

The by-product diene **30**, obviously the result of base-catalyzed elimination, is readily characterized from its IR (3200–2800 and 1679 cm^{-1}) and typical homoannular diene UV absorption (λ_{max} 290 nm) spectra.

The isomeric nature of the interesting by-product indole-acids **31** and **32** was shown by the identical molecular ion peaks (*m/z* 283) in their mass spectra and their similarity in the ^1H NMR spectra. The stereochemistry of both compounds was determined on the basis of nOe-difference experiments. As a result of these experiments, the 3-dimensional structures of the main conformers of **31** and **32** are shown in **31A** and **32A**.



31A



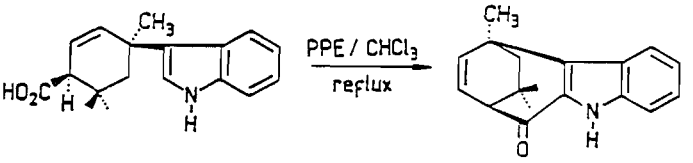
32A

The stereochemistry of **31** was determined as follows. Irradiation of the singlet due to the protons of the methyl group at C-4 (1.58 ppm) enhances the singlet due to the β-methyl group at C-6 (1.10 ppm) and the signals due to the vinylic proton at C-3 (6.06 ppm) and the β-proton at C-5 (1.99 ppm). Irradiation of the signal due to the other methyl group at C-6, namely, the α-methyl (0.95 ppm), enhances the signal of the axial proton at C-1 and both doublets due to the protons at C-5 (1.99 and 2.25 ppm). Finally, irradiation of the signal due to the proton at C-1 enhances the signal corresponding to the protons of the α-methyl at C-6 (but not the signal due to the β-methyl), the doublet of the α-proton at C-5 (2.25 ppm), and the signal of the vinylic proton at C-2. Therefore, these results indicate that the methyl group at C-4 has an *anti* relationship to the proton at C-1 in **31**. The stereochemistry of **32**, which could also be determined from the same results, was confirmed by the following experiments. Irradiation at 0.60 ppm, which is the signal due to one of the methyl groups at C-6, enhances both the doublet of the proton at C-2′ (6.92 ppm) and the doublet of the β-proton at C-5 (2.52 ppm). Therefore, the singlet at 0.60 ppm was assigned to the β-methyl group. Irradiation of the signal due to the other methyl group (1.13 ppm) namely, the α-methyl at C-6, enhances the signal of the axial proton at C-1 (3.02 ppm) and both doublets due to the protons at C-5 (1.73 and 2.52 ppm). Finally, irradiation of the signal of the proton at C-1 enhances both the singlet due to the α-methyl group at C-6 and the doublet due to the α-proton at C-5 (1.73 ppm). Therefore, the structure of **32** was confirmed to be as shown in **32A**.

The indole-acid **31** was transformed into the ester **13** discussed earlier (Scheme 2) under the neutral conditions of ethanol, triphenylphosphine, and diethylazodicarboxylate (25). The above NMR data were therefore also utilized to assign the structure and stereochemistry to ester **13**.

Additional quantities of the crucial intermediate **29** could be obtained when the *trans* benzoate **28**, obtained from esterification of the hydroxy acid **21** (Scheme 4), was treated with indolylmagnesium iodide. The reaction mixture with the same product ratio as obtained with the *cis* isomer **27** was obtained. This result again suggests a carbocationic intermediate is involved in the conversion to **29**, **31**, and **32**. Thus for preparative purposes, the mixture of alcohols **18** and **21** is directly converted to **27** and **28** and the latter, without isolation, is treated with the Grignard reagent to afford **29**, **31**, and **32**.

With indole-acid **29** on hand, the strategy outlined in Scheme 1 (**4** → **3**) was again considered. Intramolecular cyclization of **29** with either polyphosphoric acid (26) or polyphosphoric ester (PPE) (27) met with failure even though the indole-acid **32** underwent facile cyclization with PPE in chloroform to afford ketone **33** in 55% yield. The structure proof of **33** is presented later in this discussion.



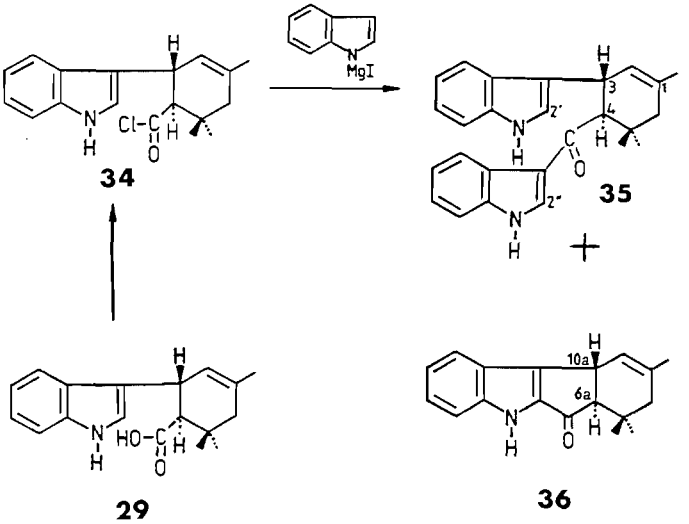
32 **33**

Conversion of **29** into the corresponding acid chloride **34** and attempts to achieve an intramolecular Friedel–Crafts acylation under conditions ($ZnCl_2$, nitrobenzene) reported for acylation at position 2 of 3-substituted indoles (28) also failed.

On the other hand, reaction of **34** with indolylmagnesium iodide under careful conditions (initially at −50°C and then at −5°C) afforded the expected product **35** (18% yield) and, somewhat surprisingly, the previously desired ketone **36** (25% yield) (Scheme 5).

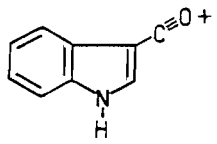
The most pertinent features in the mass spectrum of **35** are the molecular ion (*m/z* 382) and the base peak at *m/z* 144 corresponding to the fragment ion **a**. The ^1H NMR spectrum displays at 3.54 ppm the proton at C-4 as a doublet with a J value of 10 Hz, revealing a *trans* stereochemical relationship with the proton at C-3, which appears as a multiplet at 4.14 ppm. Also, integration of the aromatic proton region shows the presence of two indole systems with the proton at C-2′ appearing at 6.85 ppm as a doublet (J = 2 Hz) and the N-H protons at 7.59 and 7.98 ppm as broad signals. The proton at C-2″ appears downfield of 7.0 ppm due to the presence of the carbonyl group at the position 3″.

The IR spectrum of the crystalline ketone **36** (mp 129–131°C) shows the N-H absorption at 3464 cm^{-1} and the conjugated carbonyl group at 1683 cm^{-1}. The mass spectrum displays the molecular ion at *m/z* 265 and the base peak at *m/z* 250 due to the easy loss of a methyl radical. The ^1H NMR spectrum shows the N-H proton at 8.73 ppm and, most importantly, no aromatic



34 **35** **29** **36**

SCHEME 5. Conversion of indole-acid **29** to the ketones **35** and **36**



a

signals upfield of 7.0 ppm, thereby confirming the absence of the aromatic proton at C-2′ in the heterocyclic ring. Finally, the *trans* relationship between the protons at carbons 6a and 10a was assigned by X-ray diffraction analysis of the molecule. The results are presented in Fig. 1.

Efforts to increase the yield of **36** are summarized in Table 1. Careful monitoring revealed that the reaction only occurs at a temperature of −15°C or higher, giving both products in about the same ratio (expts. 1 and 2). When acid chloride **34** was added into indolylmagnesium iodide (expts. 1–4) there was a tendency to give a higher ratio of products **35**/**36** as the equivalents of the Grignard reagent were increased. On the other hand, when the addition was reversed (expts. 5–7), the yield of ketone **36** could be improved as the length of time for the addition of indolylmagnesium iodide was increased from 3 to 8 h. Therefore, it appears from these results that the abstraction of a proton from the nitrogen atom is faster than the addition of indolylmagnesium iodide to the carbonyl group, but the intramolecular cyclization is slow. When there is an excess of the Grignard reagent, compound **35** is predominantly formed (expt. 3). On the other hand, the ratio **36**/**35** is maximum when acid chloride **34** is maintained in excess (expts. 6 and 7).

Since ketone **36** was apparently formed by the behaviour of indolylmagnesium iodide acting as a base, attempts were made to increase even further the yield of **36** by utilizing a hindered base (LDA). Table 2 shows the results. Addition of 1.2 equivalents of LDA at −15°C gave only 15% of ketone **36** along with recovered indole-acid **29** (expt. 1). Increasing both the amount of LDA (to 2.5 equivalents) and the length of time for its addition (to 7 h, expt. 3) raised the yield by a factor of 2, although this was still low. On the other hand, increasing the temperature to 20°C did not give any **36** but rather the next expected intermediate, *cis*-ketone **37** (Scheme 6). Since the yield of both **37** and **29** was almost the same as the yield of **36** and **29** when the conditions of the reaction were the same (except for the temperature) (expts. 3 and 4), it seems that no further cyclization took place on warming but only the epimerization of **36** occurred. Furthermore, in a separate experiment, *trans*-ketone **36** was epimerized to *cis*-ketone **37** (85% yield) in the presence of LDA (−15 to 20°C) (Scheme 6).

The spectroscopic characteristics of crystalline *cis*-ketone **37** are, as expected, quite similar (but not identical) to those of *trans*-ketone **36**. Perhaps most noteworthy is that the coupling constant between the protons at carbons 6a and 10a in the ^{1}H NMR spectra of both compounds is the same (6 Hz). The most pronounced difference is their melting points: 129–131°C for **36** and 220–223°C for **37**.

In attempting to optimize the yield of the epimerization reaction, it was found that sodium methoxide in refluxing THF–MeOH gives the thermodynamically more stable *cis*-ketone **37** in quantitative yield.

In summary, the indole-acid **29**, via the routes outlined in Schemes 5 and 6, affords a potentially attractive entry into *both* the natural yuehchukene (**1**) and unnatural 6a-*epi*-yuehchukene (**2**) series.

The overall strategy (**3** → **1**, Scheme 1) in attaching the second indole unit onto the carbonyl function of the *trans*-

TABLE 1.

Expt.	Equiv. of Grignard	Temperature (°C)	Length of addition of Grignard[a] (h)	Yield (%) 36	35
1	3.5	−50 to 5	—	25	18
2	5.0	−50 to 5	—	23	20
3	20.0	−50 to 5	—	08	40
4	3.5	−50 to 15	—	24	17
5	3.5	−15 to 20	3.0	29	16
6	3.5	−15 to 20	8.0	46	14
7	3.5	−15 to 20	14.0	46	19

[a]Acid chloride was added into Grignard, expts. 1–4, in 0.5 h.

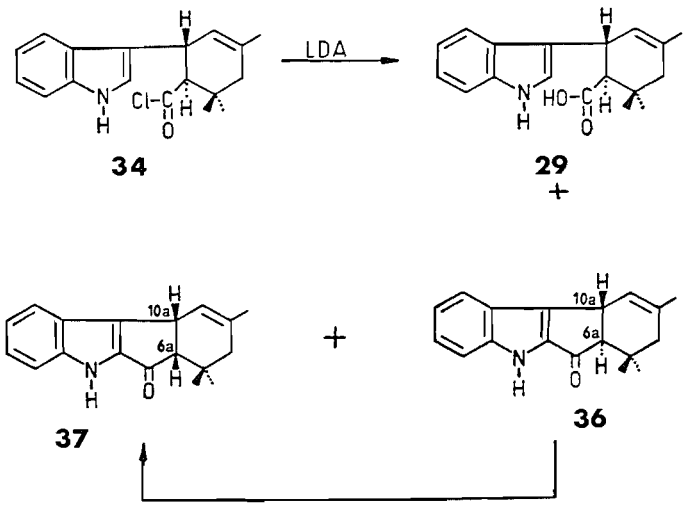
TABLE 2.

Expt.	Equiv. of of LDA	Temperature (°C)	Length of addition of LDA (h)	Yield (%) 29	36	37
1	1.2	−15	0.3	50	15	—
2	2.0	−15	0.3	43	20	—
3	2.5	−15	7.0	27	30	—
4	2.5	−15 to 20	7.0	26	—	27

ketone **36** and, thereby, an entry into the natural series was now considered. The successful route to **1** is outlined in Scheme 7.

Mild hydride reduction ($NaBH_4$/MeOH) was unsuccessful in the conversion **37** → **38** but, fortunately, the more reactive reagent $LiAlH_4$ did reduce the ketone functionality to give alcohol **38** as the main product (65% yield), along with the epimeric alcohol **39** as a minor component (35%). Lithium tri-*sec*-butylborohydride (L-Selectride) (29) gave, as expected, only alcohol **38** but, unfortunately, in lower yield (50%).

The ^{1}H NMR spectrum of **38** displays, at 5.06 ppm, the signal of the hydrogen at C-6 as a broad signal, which becomes a distinct doublet (J = 6 Hz) only after exchange of the O-H proton with D_2O. This latter result shows that the proton at C-6 is coupled with both the O-H proton and the proton at C-6a. The O-H proton appears at 2.6–2.7 ppm and overlaps with the signals of the vinylic methyl group and one of the protons at C-8. On the other hand, the ^{1}H NMR spectrum of **39** shows the signal



SCHEME 6. Conversion of acid chloride **34** to the ketones **36** and **37**.

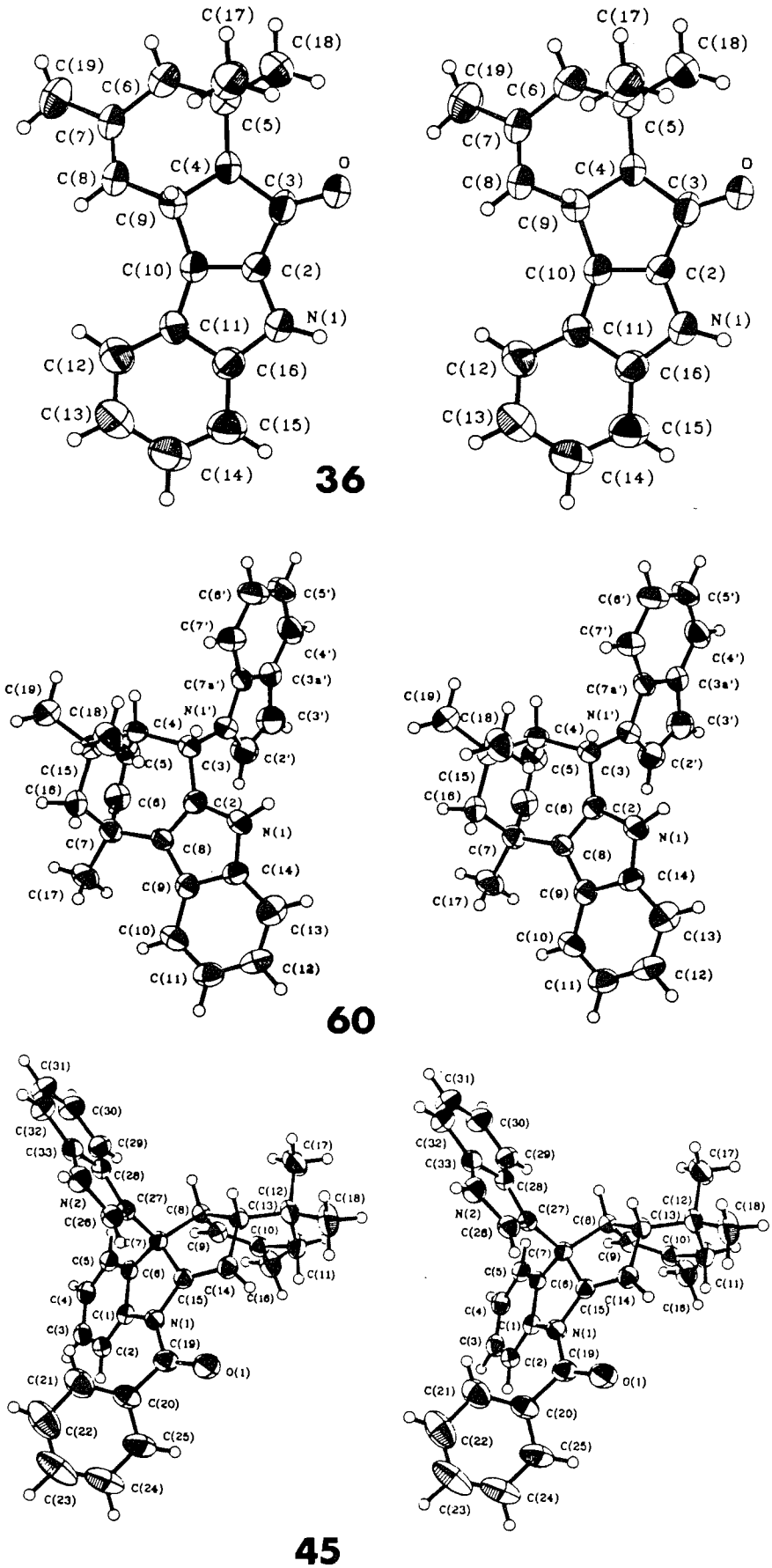
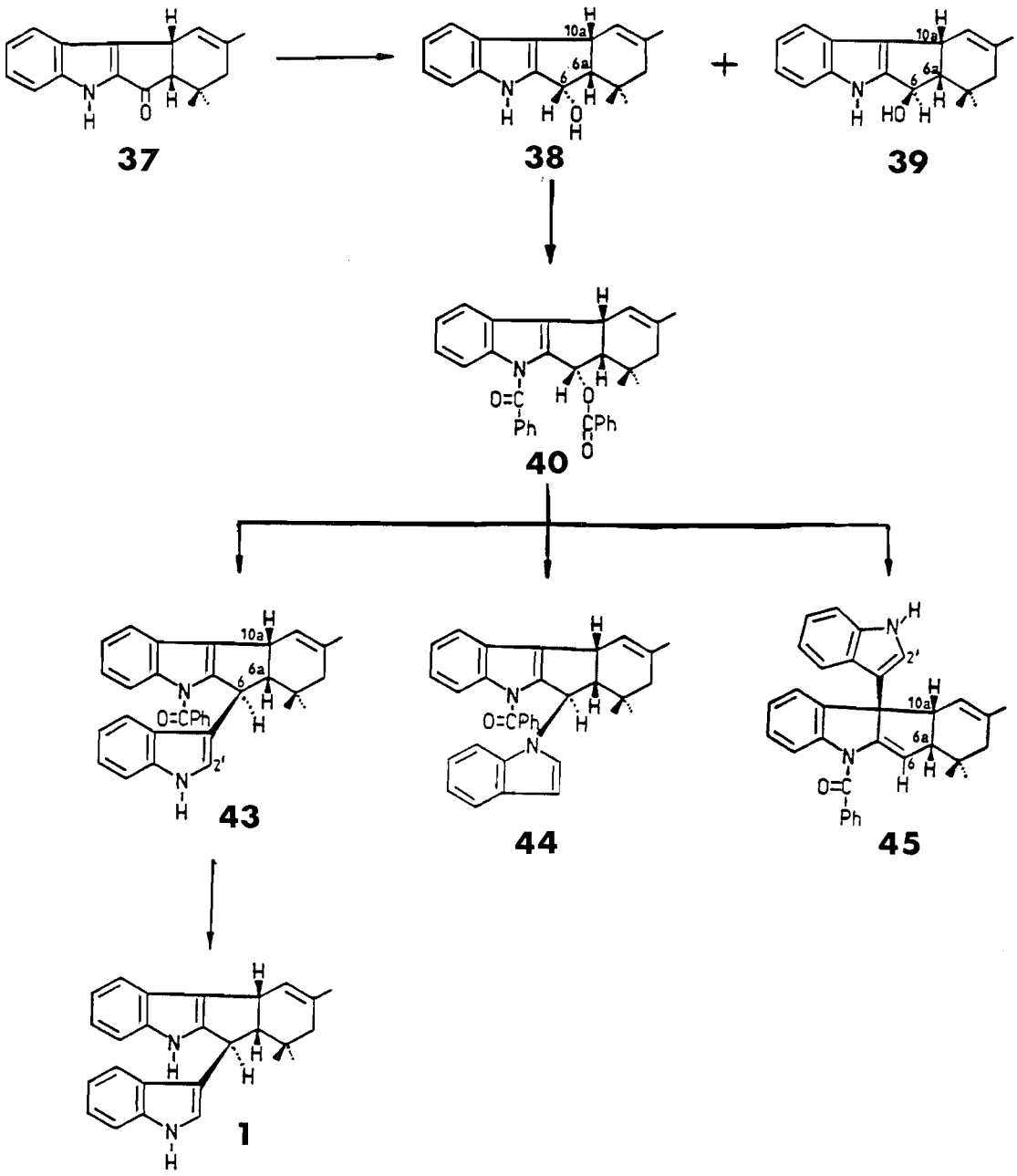


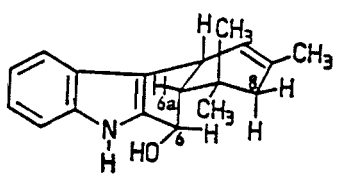
FIG. 1. Stereoviews of **36** (top), **60** (middle), and **45** (bottom) showing crystallographic atom numbering schemes;[5] 50% probability thermal ellipsoids are shown for the non-hydrogen atoms. Both structures contain equal numbers of both enantiomers, those depicted above being chosen at random.



SCHEME 7. The synthesis of yuehchukene (**1**) and related analogues from ketone **37**.

of the proton at C-6, at 5.12 ppm as a doublet (J = 6 Hz) due to coupling with only the proton at C-6a, thus revealing no coupling with the O-H proton.

The distinction between the two alcohols was established by nOe-difference experiments performed with alcohol **39**. Thus, irradiation at the signal of the proton at C-6 did not affect the signal of the proton at C-6a but did show an effect on the signals of the protons of the methyl groups at C-7 and one of the protons at C-8. The conformational structure of **39**, shown as **39A**, shows the proximity between protons at C-6 and C-8. Therefore

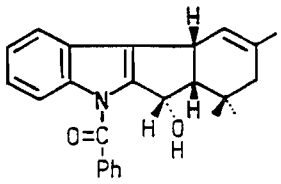


39A

the hydroxyl group in **39** bears a *cis* relationship to the proton at C-6a.

The next transformation involved a dibenzoylation of **38** using 4 equivalents of benzoyl chloride, 1.2 equivalents of DMAP, and 4 equivalents of triethylamine (18) in dichloromethane, to give rise to compound **40** as white crystals (76% yield). Its structure and stereochemistry were readily ascertained from the informative spectroscopic data (see Experimental). Addition of only one equivalent of benzoyl chloride to alcohol **38** gave rise to the chemoselective formation of compound **41** (and not **42**).

To complete the synthetic route, nucleophilic displacement of the benzoate group in **40** was appropriate. Reaction of **40** with indolylmagnesium iodide in ether–dichloromethane solution at 5°C afforded the expected benzoylyuehchukene (**43**) as a white foam (40% yield) but, in addition, two other isomeric compounds subsequently assigned the structures **44** (18% yield) and **45** (30% yield) (Scheme 7).



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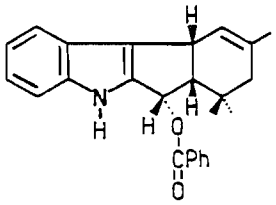

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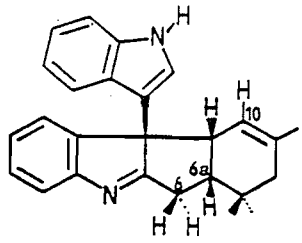


46

Benzoylyuehchukene (**43**) was characterized by IR, MS, and ^{1}H NMR spectroscopy. The IR spectrum reveals the N-H and carbonyl absorptions at 3480 and 1681 cm^{-1}, respectively. The mass spectrum shows the molecular ion at m/z 470 and the base peak at m/z 105 corresponding to the relatively stable cation PhC≡O$^+$. The ^{1}H NMR spectrum shows the proton at C-6 at 4.12 ppm as a doublet with a J value of 4 Hz. As expected, this chemical shift is at consideraly higher field than that of the starting benzoate **40** (6.39 ppm). The N-H proton appears at 7.73 ppm as a broad signal and the signal of the hydrogen at C-2′ of the heterocyclic ring of the newly incorporated indole appears at 6.15 ppm as a doublet with a J value of 2 Hz. This latter assignment was corroborated by decoupling the signal corresponding to the proton on the nitrogen atom, with the resulting collapse of the doublet at 6.15 ppm into a singlet. Finally, the structural assignment was firmly established when **43** was treated with sodium methoxide in methanol at 5°C to afford (±)-yuechchukene (**1**) in 90% yield. The synthetic material was identical with the racemic natural product isolated from the plant.

Compound **44**, formed by N-alkylation rather than C-alkylation, reveals in its IR spectrum the typical amide absorption at 1685 cm^{-1} and the mass spectrum displays the molecular ion at m/z 470, the base peak at 105, and an intense peak (relative intensity = 50%) at 354, not observed in **43** and due to the facile loss of indole from the molecular ion. The ^{1}H NMR spectrum shows the proton at C-6 at 5.53 ppm as a broad signal. The proton at C-2′ appears at 6.29 ppm as a doublet with a J value of 3.5 Hz. The result shows the coupling of the latter with the proton at C-3′, appearing at 6.48 ppm as a doublet with the same J value. Double resonance experiments confirm this assignment.

The stereochemistry at C-6 in **44** was assigned on the basis of nOe experiments. Thus, irradiation of the signal due to the proton at C-6a (2.85 ppm) shows enhancement of both the signal of the proton at C-10a (4.08 ppm) and the signal of the proton at C-2′ (6.29 ppm) but it does not affect the signal due to the proton at C-6 (5.53 ppm). Also, irradiation of the signal due to the proton at C-6 does not affect the proton at C-10a, but only the aromatic protons at C-2′ and possibly at C-7′. Therefore, the newly incorporated indole moiety was assigned to be in a *cis* relationship with the proton at C-6a.

The unexpected compound **45** was characterized by IR, MS, ^{1}H NMR, and X-ray analysis (Fig. 1).

Since deprotection of **44** affords a new analogue of yuehchukene, which is one of the objectives of this project, that transformation was also carried out. Thus, treatment of **44** with sodium methoxide in methanol gave compound **46** in 97% yield. During this conversion, there was concomitant migration of the double bond to the more stable imine form. The IR spectrum of this unstable yellowish oil shows the N-H absorption at 3477 cm^{-1} and the mass spectrum displays the molecular ion as the base peak at m/z 366. The ^{1}H NMR spectrum shows the protons at C-6 and at C-6a as an ABC system. The C-6 protons appear at 2.29 ppm (doublet of doublets, J = 8, 18 Hz) and 2.83 ppm (doublet of doublets, J = 10, 18 Hz) while C-6a appears at 2.64 (multiplet). These assignments were corroborated by double resonance experiments. When the signal at 2.64 ppm was decoupled, both C-6 signals became doublets, showing that only *geminal* coupling exists with these protons. Also, the spectrum shows only one vinylic proton signal (4.72 ppm) (and not two as in **45**) corresponding to C-10, thereby establishing the proposed migration of the double bond to form the imine structure.

As noted earlier, the main objective of this study was to develop a versatile synthetic route that would afford not only an approach to the natural product but *also* to new analogues, which may portray similar efficacy as contraceptive agents but with lower toxicity, when evaluated in the pharmacological screening program.

With the above results in hand (Scheme 7), it was natural to consider the corresponding *trans*-ketone **36** so as to complete the synthesis of 6a-*epi*-yuehchukene (**2**). Unfortunately the corresponding intermediates in this series revealed a high degree of instability and low yields in the conversions so new chemistry had to be developed.

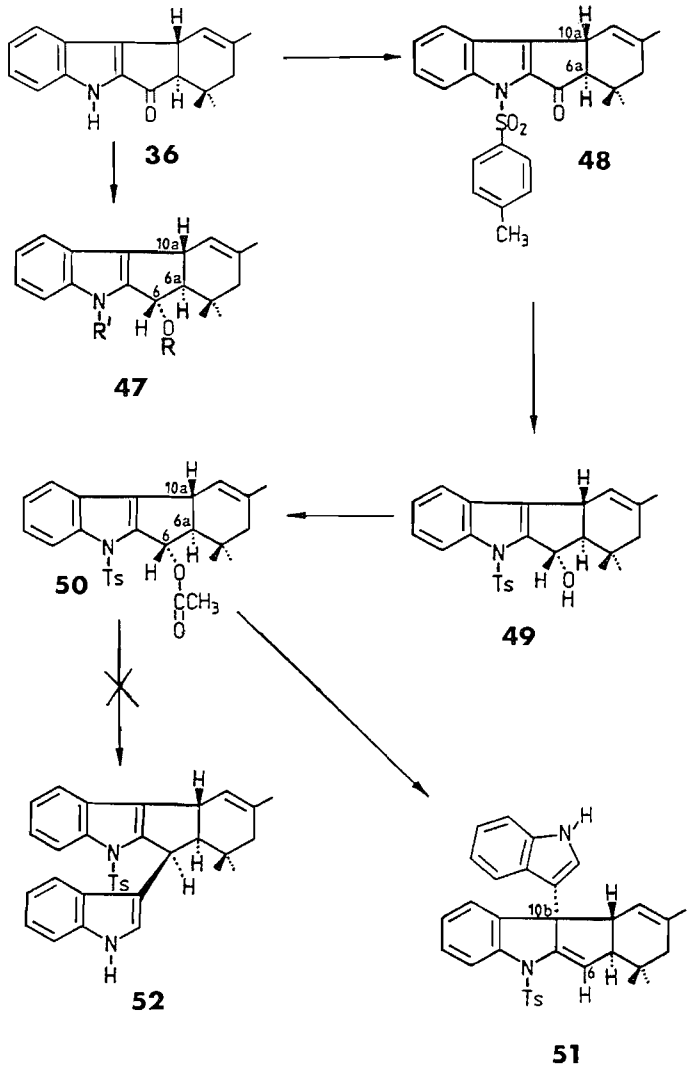
Although reduction of **36** ($LiAlH_4$, ether, 5°C) (Scheme 8) did afford the desired alcohol **47** (R = R′ = H′) in 90% yield, the subsequent conversion to the dibenzoyl derivative **47** (R = R′ = COPh) for further elaboration to the *epi*-yuehchukene system (compare **40** → **43**, Scheme 7), met with little success. Treatment of **47** (R = R′ = H) with various concentrations of benzoyl chloride afforded a low yield (15%) of the *O*-benzoyl derivative **47** (R = COPh; R′ = H) and extensive decomposition. The desired dibenzoyl derivative was never obtained.

To increase the stability of the intermediates, it was decided to protect the indole ring at an earlier stage of the synthetic route. The first choice was the *p*-toluenesulfonyl functionality since this group was expected to decrease the reactivity of the indole unit because of its electron-withdrawing properties.

Ketone **36** was converted to its tosyl derivative **48** in 90% yield by using *p*-toluenesulfonyl chloride in the presence of sodium hydride (Scheme 8). Reduction of **48** proceeded smoothly to the alcohol **49** (90% yield).

The stereochemistry at C-6 in **49** was assigned on the basis of nOe-difference experiments. Irradiation of the signal due to the proton at C-10a (3.38 ppm) enhances the signal of the proton at C-6 (5.27 ppm). This experiment also served to assign the β-methyl group at C-7 (1.05 ppm). Irradiation of the protons of this β-methyl group enhances both the signal of the proton at C-6 and that of the proton at C-10a, but shows no effect on the signal due to the proton at C-6a (2.42 ppm). Therefore, the stereochemistry at C-6 was assigned to have the O-H group and the proton at C-6a in a *cis*-relationship.

Treatment of alcohol **49** with acetic anhydride and DMAP in CH_2Cl_2 at room temperature gave acetate **50** in 75% yield. The use of acetic anhydride, instead of benzoyl chloride as used in the previous study, was an attempt to increase further the stability of the ester.



SCHEME 8. Conversion of ketone **36** to indoline **51**.

The next transformation in the sequence involved nucleophilic displacement of the acetate group by indolylmagnesium iodide. Unfortunately, the expected derivative of 6a-*epi*-yuehchukene (**52**, Scheme 8) could not be observed. Instead, the isomer **51** was obtained in 40% yield and characterized by the usual spectroscopic data (see Experimental).

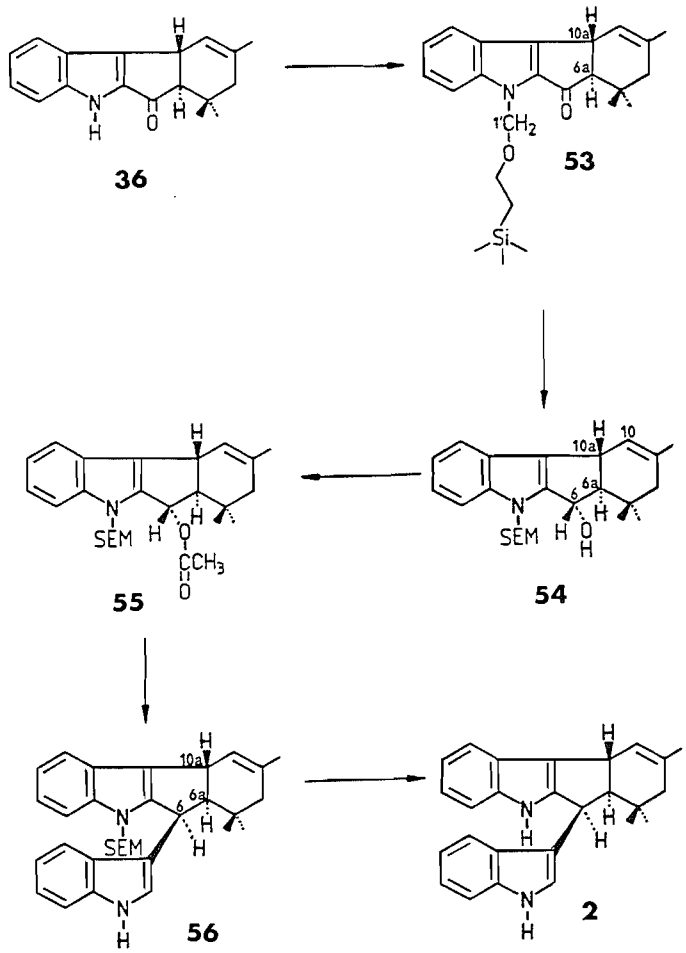
It thus appears that, in this reaction, the approach of indolylmagnesium iodide to the C-6 carbon atom is considerably hindered by the axial methyl at C-7 and also, perhaps, by the bulky tosyl group. On the basis of this result, it was thought that perhaps the approach of the nucleophile might be easier with a less bulky protecting group on the indole system. Trimethylsilylethoxymethyl chloride (SEM-Cl) was chosen as another alternative to protect the indole moiety. SEM-Cl has not been previously utilized for the protection of the indole system, although it is usually employed to protect alcohols (30). However, it has been used for the protection of the pyrrole group (31) and it was felt that its applicaction in this study might prove fruitful. It was also anticipated that the introduction of this protecting group should increase the reactivity of the indole functionality when compared with the tosyl group. Scheme 9 summarizes the successful route.

Treatment of *trans*-ketone **36** with 1.5 equivalents of SEM-Cl in the presence of sodium hydride funished compound **53**. This unstable product was usually used *in situ* for the next reaction, but in one study it was isolated in a pure form (93% yield) to be characterized by IR, MS, and ^{1}H NMR spectroscopy. The infrared spectrum displays the absorption of the carbonyl group at 1695 cm^{-1} while the mass spectrum reveals the molecular ion at m/z 395 and the base peak at m/z 73 corresponding to the ratio $(CH_3)_3Si^+$. The ^{1}H NMR spectrum displays, at −0.1 ppm, a singlet that integrates for 9 protons and is due to the trimethylsilyl group; at 0.86 ppm, a multiplet corresponding to the protons of the methylene carbon bonded to the silicon; at 3.52 ppm, another multiplet due to the adjacent methylene carbon; and at 5.61 and 5.69 ppm, an AB system, with a coupling constant of 11.5 Hz, corresponding to the diastereotopic protons of the methylene carbon attached to the nitrogen atom.

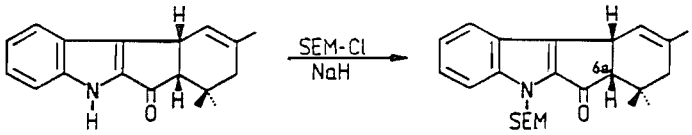
That neither **36** nor **53** epimerized at C-6a, during the reaction conditions employed, was proved by obtaining a different product from the corresponding *cis*-ketone **37**, namely, compound **57**. In fact, the amount of sodium hydride was critical for the exclusive formation of **53**, especially with THF as the solvent. Any excess of sodium hydride in the conversion of **36** to **53** led to variable quantities of **57** as a by-product.

Treatment of ketone **53** in a pure form, or *in situ*, with $LiAlH_4$ at 5°C, or with DIBAL at −78°C (32), gave **54** as a single alcohol in 80–85% yield (67% overall for the one-pot reaction from **36** to **54**). The product, isolated as an oil, was then subjected to the usual spectroscopic measurements.

The stereochemistry at C-6 was again established on the basis of nOe-difference experiments. Irradiation of the signal due to



SCHEME 9. The synthesis of 6a-*epi*-yuehchukene (**2**) from ketone **36**.

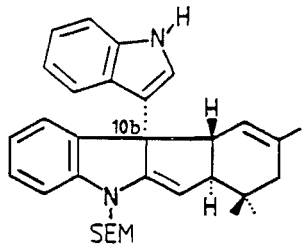


37 57

the proton at C-6 (5.12 ppm) enhances the signal of the proton at C-10a (3.41 ppm). Also, irradiation of the β-methyl at C-7 (1.03 ppm), which was assigned by irradiation of the signal due to the proton at C-10a, enhances both the signal of the proton at C-6 and that of the proton at C-10a, but not the one at C-6a. Therefore, the O-H group and the proton at C-6a were assigned to be in a *cis* relationship.

Treatment of alcohol **54** with an excess of acetic anhydride, DMAP, and triethylamine in dichloromethane at 20°C gave the corresponding acetate **55** (86% yield) as a colorless oil.

In the next step, the crucial displacement of the acetate group by indolylmagnesium iodide was attempted. Fortunately, treatment of acetate **55** with this reagent in ether–dichloromethane at 5°C furnished SEM-6a-*epi*-yuehchukene (**56**) as a white foam after isolation, and in 36% yield. Although this yield is apparently low, it might be considered quite satisfactory, firstly, because the other routes could not give the desired product and, secondly, because the newly incorporated indole still bears the strong 1,3 diaxial-like interaction with the β-methyl at C-7. The isomeric product **58**, in which the indole group is attached to the C-10b, was not observed in this case.



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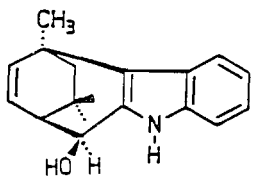
The structure of SEM-6a-*epi*-yuehchukene (**56**), including its stereochemistry, was characterized by IR, MS, and mainly ^{1}H NMR spectroscopy. The IR spectrum shows the N-H band at 3414 cm^{-1} and the mass spectrum gives the correct molecular ion at *m/z* 496. The ^{1}H NMR spectrum shows the proton at C-6 at 4.78 ppm, as a doublet, with a *J* value of 6 Hz because of its coupling with the proton at C-6a (2.70 ppm, dd, J = 11, 6 Hz). This analysis was corroborated by double resonance experiments. The β-methyl group at C-7 (assigned by nOe experiments, *vide supra*) appears as a broad singlet with the usual chemical shift of 0.34 ppm. The magnetic anisotropic effects of the newly incorporated indole group are probably the cause of this shielding.

The nOe-difference experiments provided the important data to establish the stereochemistry at C-6. Thus, irradiation of the signal due to the proton at C-6 enhances the signal of the proton at C-6a (2.70 ppm) but not the signal of the proton at C-10a (4.06 ppm). Also, irradiation of the signal due to the α-methyl group (1.13 ppm) (assigned by the enhancement of the β-methyl group when irradiating the signal due to the proton at C-10a) enhances both the signal of the proton at C-6a and the signal due to the proton at C-6. Therefore, the protons at C-6a and C-6 were assigned to bear a *cis* relationship.

Finally, the total synthesis of 6a-*epi*-yuehchukene (**2**) was accomplished by treatment of **56** with tetra-*n*-butylammonium fluoride in THF–HMPA at 40°C for 1 day to give **2** as a white foam (89% yield). Both the solvent and the reaction temperature were critical for the success of this reaction. Without HMPA, the reaction is much slower and apparently decomposition starts to take place. At 25–30°C there is no reaction and above 45°C decomposition of the reactant and (or) the product is a serious problem. On the other hand, deprotection of the indole system using lithium tetrafluoroborate in acetonitrile (33) led only to decomposition of **56**.

The IR spectrum of **2** displays the N-H absorption at 3400 cm^{-1}, the mass spectrum the molecular ion at *m/z* 366, and in the ^{1}H NMR spectrum the protons at each nitrogen atom appear at different chemical shifts. One of these broad signals appears at 8.89 ppm while the other is present at 9.10 ppm.

More recently, experiments designed to complete the structure elucidation of ketone **33**, mentioned earlier, were completed. Ketone **33**, upon reduction with lithium aluminum hydride, afforded alcohol **59** isolated as an oil. The latter was then converted to the corresponding benzoate, which, without purification, was treated directly with an ethereal solution of indolylmagnesium iodide. The resulting crystalline product, obtained by the expected nucleophilic displacement of the benzoate group, was subjected to X-ray analysis, which provided the structural assignment **60** to this compound (Fig. 1). On the basis of this assignment, it is clear that the structures of **59** and **33** are firmly established.



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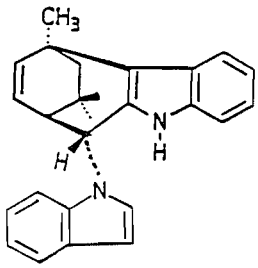

60

In spite of numerous frustrations and unanticipated difficulties in what appeared initially to be a rather straightforward series of objectives, the routes described are sufficiently versatile to provide a series of novel analogues of yuehchukene for appropriate biological screening within the anti-implantation area. It should be emphasized that many of the difficulties encountered are clearly due to the high chemical reactivity and (or) instability of the indolic intermediates. Unfortunately, the compounds are often unstable to air, acidic reagents, and (or) in various solvents normally employed in obtaining the spectral data. The natural product yuehchukene, for example, as well as its isomer **2**, are highly unstable unless kept in the cold under an inert atmosphere, and a similar situation prevails with a number of the intermediates obtained. In fact, it should be noted that yuehchukene instability is presenting a considerable problem in formulation studies involving extensive tests in animals. It is hoped that some of the intermediates, for example, the *N*-benzoyl derivative of natural yuehchukene (**43**) or the SEM derivative of 6a-*epi*-yuehchukene (**56**), which are more stable, will prove to be active in the anti-implantation screening tests.

Yuehchukene (**1**) has previously been synthesized in low yield by acid-induced dimerization of 3-isoprenylindole (35, 36) and via a different route (37). Neither study offers the versatility to prepare a "family" of yuehchukene analogues provided in the present study.

Experimental

Melting points were determined on a Nalge melting point apparatus and were uncorrected. The infrared spectra were recorded on Perkin–Elmer 710B and 1710 (Fourier transform IR) spectrometers either in chloroform solution (using sodium chloride cells of 0.1 mm path length) or as a neat liquid film. The ultraviolet spectra were recorded on a Cary 15 spectrometer, the extinction coefficients (log ε_{max}) are given in parentheses, and the wavelength(s) of the maxima in nanometers. The mass spectra were recorded on AEI-MS-9 (low resolution) or Kratos-MS-50 (high resolution) spectrometers. The ^{1}H NMR spectra were recorded on either Bruker WH-400 or Varian XL-300 spectrometers unless otherwise stated, in $CDCl_3$ solution, and the chemical shifts are reported in ppm relative to tetramethylsilane (internal standard). The optical rotations were recorded on a Perkin–Elmer 141 automatic polarimeter in a 10-cm cell at ambient temperature using the solvent and concentrations (g/100 mL) indicated in parentheses following the recorded rotation values. The elemental analyses were determined by Mr. P. Borda, Microanalytical Laboratory, The University of British Columbia. The X-ray diffraction analysis were performed by Dr. S. Rettig on a Rigaku AFC6 diffractometer. Column chromatography (34) was performed using 230–400 mesh silica gel supplied by E. Merck Co. Gas–liquid chromatography was performed on a Hewlett Packard model 5890 gas chromatograph, using a flame ionization detector and a 25 m × 0.21 mm fused silica capillary column: DB1701.

Ethyl 2β-hydroxy-4,6,6-trimethylcyclohex-3-ene-1β-carboxylate **8** *and ethyl 2α-hydroxy-4,6,6-trimethylcyclohex- 3-ene-1β-carboxylate* **9**

To a solution of keto-ester **7** (500 mg, 2.38 mmol) in methanol (10 mL) at room temperature under nitrogen, sodium borohydride (74 mg, 2.40 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. Water (3 mL) and ammonium chloride (3 mL, sat. aq.) were added, and methanol was evaporated *in vacuo*. The residue was extracted with ether (3×, 10 mL) and the organic solution was washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a yellow oil. Purification by flash chromatography using hexanes/ether (7:3, v/v) gave *cis*-hydroxyester **8** (358 mg, 71%) and *trans*-hydroxyester **9** (116 mg, 23%) as colorless liquids. *cis*-Hydroxyester **8**: IR ν_{max} ($CHCl_3$): 3450, 2920, 1740 cm^{-1}. ^{1}H NMR (80 MHz) δ: 1.15 (3H, s, C6-CH_3), 1.22 (3H, s, C6-CH_3), 1.42 (3H, t, J = 7, C2′-H), 1.66 (1H, d, J = 17, C5-H), 1.72 (3H, brs, C4-CH_3), 2.07 (1H, d, J = 17, C5-H), 2.34 (1H, brs, O-H), 2.65 (1H, d, J = 6, Cl-H), 4.12 (2H, q, J = 7, Cl′-H), 4.40 (1H, m, C2-H), 5.42 (1H, brs, C3-H). MS *m/z*: 212 (M$^+$), 197, 194, 83. High resolution mass measurement, calcd. for $C_{12}H_{20}O_3$: 212.1412; found: 212.1408. Anal. calcd. for $C_{12}H_{20}O_3$: C 67.88, H 9.50; found: 67.73, H 9.48.

trans-Hydroxyester **9**: IR ν_{max} ($CHCl_3$): 3400, 2960, 1725 cm^{-1}. ^{1}H NMR (80 MHz) δ: 1.00 (3H, s, C6-CH_3), 1.05 (3H, s, C6-H), 1.30 (3H, t, J = 6, C2′-H), 1.59 (1H, d, J = 17, C5-H), 1.60 (1H, brs, O-H), 1.70 (3H, brs, C4-CH_3), 2.02 (1H, d, J = 17, C5-H), 2.25 (1H, d, J = 10, Cl-H), 4.20 (2H, d, J = 6, Cl′-H), 4.54 (1H, m, C2-H), 5.42 (1H, brs, C3-H). MS *m/z*: 212 (M$^+$), 197, 194, 121. High resolution mass measurement, calcd. for $C_{12}H_{20}O_3$: 212.1412; found: 212.1410. Anal. calcd. for $C_{12}H_{20}O_3$: C 67.88, H 9.50; found: C 67.66, H 9.62.

Ethyl 2β-benzoxy-4,6,6-trimethylcyclohex-3-ene-1β-carboxylate **10**

To a solution of hydroxyester **8** (300 mg, 1.43 mmol) and dimethylaminopyridine (DMAP, 189 mg, 1.54 mmol) in methylene dichloride (10 mL) at 5°C under nitrogen was added benzoyl chloride (0.18 mL, 1.54 mmol). The reaction mixture was stirred at 5°C for 3 h and then poured into water (10 mL) and the layers were separated. The aqueous phase was extracted with methylene dichloride (10 mL twice) and the combined organic phases were dried over sodium sulfate, filtered, and evaporated *in vacuo* to give a pale yellow oil. This crude product was purified by flash chromatography using hexanes/ether (9:1, v/v) to afford benzoate **10** (380 mg, 85%) as a colorless oil: IR ν_{max} ($CHCl_3$): 2975, 1725, 1610 cm^{-1}. ^{1}H NMR δ: 1.05 (3H, t, J = 6, C2′-H), 1.11 (3H, s, C6-CH_3), 1.15 (3H, s, C6-CH_3), 1.73 (1H, d, J = 18, C5-H), 1.76 (3H, brs, C4-CH_3), 2.26 (1H, d, J = 18, C5-H), 2.87 (1H, d, J = 6.7, Cl-H), 4.01 (2H, q, J = 6, Cl′-H), 5.51 (1H, brs, C3-H), 5.80 (1H, m, C2-H), 7.40 (2H, dd, J = 7.6, 7.6, C3″ and C5″-H), 7.53 (1H, tt, J = 7.6, 1.3, C4″-H), 8.10 (2H, dd, J = 7.6, 1.3, C2″ and C6″-H). MS *m/z*: 316 (M$^+$), 211, 194, 105. High resolution mass measurement, calcd. for $C_{19}H_{24}O_4$: 316.1675; found: 316.1667. Anal. calcd. for $C_{19}H_{24}O_4$: C 72.11, H 7.65; found: C 71.81, H 7.82.

Ethyl 2α-benzoxy-4,6,6-trimethylcyclohex-3-ene-1β-carboxylate **14**

Following the same conditions as above, *trans*-hydroxyester **9** (105 mg, 0.50 mmol) gave *trans*-benoate **14** (128 mg, 82%): IR ν_{max} ($CHCl_3$): 2980, 1730, 1710, 1605 cm^{-1}. ^{1}H NMR δ: 1.08 (3H, s, C6-CH_3), 1.09 (3H, s, C6-CH_3) 1.18 (3H, t, J = 7, C2′-H), 1.71 (3H, brs, C4-CH_3), 1.77 (1H, d, J = 18, C5-H), 2.09 (1H, d, J = 18, C5-H), 2.70 (1H, d, J = 10, C1-H), 4.13 (2H, q, J = 7, C1′-H), 5.52 (1H, brs, C3-H), 5.83 (1H, brd, J = 10, C2-H), 7.39 (2H, dd, J = 8, 8, C3″ and C5″-H), 7.52 (1H, t, J = 8, C4″-H), 8.00 (2H, d, J = 8, C2″-H and C6″-H). MS *m/z*: 316 (M$^+$), 271, 211, 165, 105. High resolution mass measurement, calcd. for $C_{19}H_{24}O_4$: 316.1675; found: 316.1662. Anal. calcd. for $C_{19}H_{24}O_4$: C 72.11, H 7.65; found: C 71.88, H 7.80.

Ethyl 2α-(3-indoyl)-4,6,6-trimethylcyclohex-3-ene-1β-carboxylates **11** *and* **13**

To a suspension of magnesium (116 mg, 4.80 mmol) in dry ether (5 mL) at room temperature under nitrogen, was added methyl iodide (0.3 mL, 4.80 mmol) dropwise. After stirring for 30 min, a solution of indole (590 mg, 5.10 mmol) in dry ether (5 mL) was added at 5°C. The mixture was stirred for 1 h at room temperature, then dichloromethane (3.5 mL) was added to bring the complex into solution. This freshly prepared solution of indolylmagnesium iodide (about 4.80 mmol) was added dropwise to a solution of benzoate **10** (500 mg, 1.61 mmol) in dry ether (10 mL) at 5°C. The reaction mixture was stirred for 2 h at 5°C and for 1 h at room temperature, and then decomposed with ammonium chloride (5 mL, sat. aq.). The layers were separated and the aqueous phase was extracted with dichloromethane (3×, 10 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a brown residue. Purification by flash chromatography using hexanes/ether (8:2, v/v) gave indole-ester **11** (206 mg, 42%) and with further elution the isomer **13** (158 mg, 31%) as pale yellow liquids. Indole-ester **11**: UV λ_{max} (log ε) (MeOH): 224 (4.50), 280 (3.78) nm. IR ν_{max} ($CHCl_3$): 3480, 2960, 1730 cm^{-1}. ^{1}H NMR δ: 0.99 (3H, t, J = 8, C2′-H), 1.03 (3H, s, C6-CH_3), 1.14 (3H, s, C6-CH_3), 1.73 (3H, brs, CR-CH_3), 1.74 (1H, d, J = 16, C5-H), 2.15 (1H, d, J = 16, C5-H), 2.67 (1H, d, J = 12, C1-H), 3.90 (1H, m, C2-H), 3.90 (2H, q, J = 8, C1′-H), 5.48 (1H, brs, C3-H), 6.99 (1H, d, J = 3.2, C2″-H), 7.06 (1H, dd, J = 8, 8, C5″-H), 7.15 (1H, dd, J = 8, 8, C6″-H), 7.31 (1H, d, J = 8, C7″-H), 7.61 (1H, d, J = 8, C4″-H), 7.92 (1H, brs, N-H). MS *m/z*: 311 (M$^+$), 296, 238, 222. High resolution mass measurement, calcd. for $C_{20}H_{25}NO_2$: 311.1885; found: 311.1879. Anal. calcd. for $C_{20}H_{25}NO_2$: C 77.14, H 8.09, N. 4.50; found: C 76.99, H 8.26, N 4.60.

Indole-ester **13**: UV λ_{max} (log ε) (MeOH): 225 (4.53), 283 (3.71) nm. IR ν_{max} ($CHCl_3$): 3480, 2980, 1730, 1635 cm^{-1}. ^{1}H NMR (80 MHz) δ: 0.75 (3H, s, C6-CH_3), 1.00 (3H, s, C6-CH_3), 1.27 (3H, t, J = 6, C2′-H), 1.58 (3H, s, C4-CH_3), 1.95 (1H, d, J = 14, C5-H), 2.25 (1H, d, J = 14, C5-H), 2.95 (1H, dd, J = 4, 2, C1-H), 4.20 (2H, q, J = 6, C1′-H), 5.79 (1H, dd, J = 10, 4, C2 or C3-H), 6.05 (1H, dd, J = 10, 2, C2 or C3-H), 6.95 (1H, d, J = 2.5, C2″-H), 7.06 (1H, dd, J = 8, 8, Ar-H), 7.15 (1H, dd, J = 8, 8, Ar-H), 7.23 (1H, d, J = 8, C7″-H), 7.74 (1H, d, J = 8, C4″-H), 7.93 (1H, brs, N-H). MS *m/z*: 311 (M$^+$), 296, 238, 117. High resolution mass measurement, calcd. for $C_{20}H_{25}NO_2$: 311.1885; found: 311.1880. Anal. calcd. for $C_{20}H_{25}NO_2$: C 77.14, H 8.09, N 4.50; found: C 76.96, H 8.22, N 4.39.

2β-Hydroxy-4,6,6-trimethylcyclohex-3-ene-1β-carboxylic acid ***18*** *and 2α-hydroxy-4,6,6-trimethylcyclohex-3-ene-1β-carboxylic acid* ***21***

To a solution of 2,6-di-*tert*-butyl-4-methylphenol (231.8 g, 1.05 mmol) in dry ether (2.75 L) at −78°C under nitrogen was added dropwise a solution of *n*-butyllithium (0.625 L, 1.0 mol, 1.6 M in hexane). The suspension of white solid was warmed to room temperature and carbon dioxide gas was passed through the mixture for 10–12 min. A solution of isophorone **6** (50.05 mL, 0.33 mol) in dry ether (0.23 L) was then added with the precipitate dissolving completely. CO_2 was bubbled through the solution until no more absorption occurred. A positive pressure of CO_2 was then installed by connecting CO_2-filled balloons to the reaction flask. The stirring was continued for 4 days at room temperature. The reaction mixture was then cooled to 0°C, the balloons were removed, and a nitrogen flow was connected. To the lithium salt of the β-keto-acid **19** was added sodium borohydride (11.4 g, 0.37 mol) in methanol (0.5L) in three portions. After 2.5 h of stirring at 0°C, additional sodium borohydride (11.4 g, 0.37 mol) in methanol (0.5L) was added. The ice bath was removed and the stirring was continued for 3 h. The solvent was evaporated *in vacuo* and the residue was dissolved in ether (1.2 L) and water (1 L). After separating the layers, the aqueous phase was washed with ether (2×, 0.5 L) and acidified very carefully with HCl (10% aq.) to pH 5.5 at 5°C. Extraction with ethyl acetate (3×, 300 mL) followed by drying over sodium sulfate, filtration, and evaporation *in vacuo* gave a crude pale yellow solid. Crystallization from ether/hexane furnished *cis*-hydroxy acid **18** (28 g, 46%) as colorless crystals. Crystallization of the evaporated mother liquor with chloroform yielded *trans*-hydroxy acid **21** (2.5 g, 4%). *cis*-Hydroxy acid **18**: mp 115–118°C (ether/hexane). IR ν_{max} ($CHCl_3$): 3350–2500, 3010, 2970, 1718 cm^{-1}. ^1H NMR δ: 1.05 (3H, s, C6-CH_3), 1.15 (3H, s, C6-CH_3), 1.70 (1H, d, J = 17.5, C5-H), 1.73 (3H, brs, C4-CH_3), 2.07 (1H, d, J = 17.5, C5-H), 2.69 (1H, d, J = 6, C1-H), 4.45 (1H, brs, C2-H), 5.45 (1H, brs, C3-H). MS *m/z*: 184 (M^+), 166, 151, 121, 83. High resolution mass measurement, calcd. for $C_{10}H_{16}O_3$: 184.1100; found: 184.1099. Anal. calcd. for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 65.45, H 8.65.

trans-Hydroxy acid ***21****:* mp 186–188°C ($CHCl_3$). IR ν_{max} (KBr): 3375, 3200–2300, 2950, 1710, 1635 cm^{-1}. ^1H NMR δ: 0.98 (3H, s, C6-CH_3), 1.08 (3H, s, C6-CH_3), 1.64 (1H, d, J = 17, C5-H), 1.69 (3H, brs, C4-CH_3), 2.01 (1H, d, J = 17, C5-H), 2.24 (1H, d, J = 10, C1-H), 4.48 (1H, m, C2-H), 5.41 (1H, brs, C3-H), MS *m/z*: 184 (M^+), 166, 151, 83. High resolution mass measurement, calcd. for $C_{10}H_{16}O_3$: 184.1100; found: 184.1102. Anal. calcd. for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 64.89, H 8.66.

2β-Benzoxy-4,6,6-trimethylcyclohex-3-ene-1β-carboxylic benzoic anhydride ***27***

To a suspension of hydroxy acid **18** (20 g, 0.109 mol) in methylene dichloride (450 mL) was added dimethylaminopyridine (28 g, 0.228 mol) at room temperature. The mixture was stirred 10 min, then was cooled to 0–5°C under nitrogen. Benzoyl chloride (26.5 mol, 0.228 mol) was added and the stirring was continued for 4.5 h at 0–5°C. An aliquot (0.5 mL) was taken from the reaction mixture and was determined by GC to contain 72% product with no hydroxy acid. The reaction mixture was poured into water (200 mL), and the layers were separated. The aqueous phase was extracted with methylene dichloride (2×, 100 mL) and the combined organic phases were dried over sodium sulfate, filtered, and evaporated *in vacuo* to give **27** as a yellow oil that was used without further purification for the next reaction.

Compound **27**: IR ν_{max} ($CHCl_3$): 2960, 1795, and 1725 cm^{-1}. ^1H NMR δ: 1.22 (3H, s, C6-CH_3), 1.31 (3H, s, C6-CH_3), 1.78 (3H, brs, C4-CH_3), 1.80 (1H, d, J = 17, C5-H), 2.30 (1H, d, J = 17, C5-H), 3.10 (1H, d, J = 6, C1-H), 5.58 (1H, m, C3-H), 5.82–6.05 (1H, m, C2-H), 7.17–8.30 (10H, m, Ar-H).

2α-(3-Indolyl)-4,6,6-trimethylcyclohex-3-ene-1β-carboxylic acid ***29***

To a suspension of magnesium (10.6 g, 0.44 mol) in dry ether (212 mL) at room temperature under nitrogen was added dropwise a solution of methyl iodide (27.2 mL, 0.44 mol) in dry ether (81.5 mL). After stirring for 30 min a solution of indole (54.4 g, 0.47 mol) in dry ether (330 mL) was added at 5°C. The mixture was stirred for 1 h at room temperature, then dichloromethane (213 mL) was added to bring the complex into solution. This freshly prepared solution of indolylmagnesium iodide (about 0.44 mol) was added dropwise to a solution of the crude benzoate **27** (38 g) in dry ether (203 mL) at 5°C. The reaction mixture was stirred for 2 h at 5°C, for 1 h at room temperature, and then decomposed with ammonium chloride (700 mL, sat. aq.). The layers were separated and the aqueous phase was extracted with ethyl acetate (3×, 200 mL). The combined organic layers were washed with water (800 mL), brine (800 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was dissolved in ether (500 mL) and 3-benzoylindole was separated by filtration. The resulting solution was extracted with sodium hydroxide solution (3×, 150 mL, 5% aq.) and the combined aqueous layers were cooled to below 10°C and acidified with hydrochloric acid (10% aq.) to pH 5. Extraction with ethyl acetate (3×, 300 mL) followed by washings with water (400 mL), and brine (400 mL), drying over sodium sulfate, and evaporation *in vacuo* yielded a crude foam (20 g). Purification by flash chromatography using hexanes/ethyl acetate (7:3, v/v) gave a mixture (14.36 g) of indole-acid **29** and compound **31** in a ratio 6:4 in favor of indole-acid **29** (i.e., 40% yield) as determined by ^1H NMR. Compounds **32** (0.64 g, 3%) and **30** (1.9 g, 15%) were also obtained from the column. Further purification of the mixture of **29** and **31** by flash chromatography using chloroform/hexanes (6.5:3.5, v/v) afforded indole-acid **29** (6.5 g, 30%), although always accompanied by some decomposition. Since there is no detriment to the yield of the next step in using the mixture of products, this last purification was usually avoided.

Indole-acid **29**: mp 173–174°C (ether–hexane). UV λ_{max} (log ε) (MeOH): 222 (4.51), 282 (3.76) nm. IR ν_{max} : 3480, 3400–2450, 3020, 2980, 1710, 1630 cm^{-1}. ^1H NMR δ: 1.08 (3H, s, C6-CH_3), 1.14 (3H, s, C6-CH_3), 1.71 (3H, brs, C4-CH_3), 1.76 (1H, d, J = 16, C5-H), 2.15 (1H, d, J = 16, C5-H), 2.71 (1H, d, J = 10, C1-H), 3.93 (1H, brd, J = 10, C2-H), 5.47 (1H, brs, C3-H), 6.94 (1H, d, J = 2, C2′-H), 7.08 (1H, dd, J = 8, 8, C5′-H), 7.17 (1H, dd, J = 8, 8, C6′-H), 7.33 (1H, d, J = 8, C7′H), 7.62 (1H, d, J = 8, C4′-H), 7.77 (1H, bs, N-H). MS *m/z*: 283 (M^+), 222, 182, 168. High resolution mass measurement, calcd. for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1573. Anal. calcd. for $C_{18}H_{21}NO_2$: C 76.30, H 7.47, N 4.94; found: C 76.49, H 7.42, N 4.90.

Compound **31**: UV λ_{max} (log ε) (MeOH): 222 (4.49), 281 (3.79) nm. IR ν_{max} ($CHCl_3$): 3500–2450, 3400, 3025, 2940, 1700, 1660 cm^{-1}. ^1H NMR δ: 0.95 (3H, s, C6-CH_3), 1.10 (3H, s, C6-CH_3), 1.58 (3H, s, C4-CH_3), 1.99 (1H, d, J = 16, C5-H), 2.25 (1H, d, J = 16, C5-H), 3.02 (1H, dd, J = 3, 2, C1-H), 5.85 (1H, dd, J = 10, 3, C2-H), 6.06 (1H, dd, J = 10, 2, C3-H), 6.94 (1H, d, J = 2, C2′-H), 7.10 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.18 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.36 (1H, d, J = 8, C7′-H), 7.74 (1H, d, J = 8, C4′-H), 7.89 (1H, brs, N-H). MS *m/z*: 283 (M^+), 268, 222, 117. High resolution mass measurement, calcd. for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1574. Anal. calcd. for $C_{18}H_{21}NO_2$: C 76.30, H 7.47, N 4.94; found: C 76.50, H 7.52, N 4.83.

Compound **32**: UV λ_{max} (log ε) (MeOH): 223 (4.54), 283 (3.70) nm. IR ν_{max} ($CHCl_3$): 3400, 3400–2700, 3029, 2962, 1700, 1660 cm^{-1}. ^1H NMR δ: 0.60 (3H, s, C6-CH_3), 1.13 (3H, s, C6-CH_3), 1.51 (3H, brs, C4-CH_3), 1.73 (1H, d, J = 14, C5-H), 2.52 (1H, dd, J = 14, 1, C5-H), 3.02 (1H, m, C1-H), 5.82 (1H, dd, J = 10, 2, C2-H), 6.13 (1H, ddd, J = 10, 2, 1, C3-H), 6.92 (1H, d, J = 2, C2′-H), 7.10 (1H, ddd, J = 7.5, 7.5, 1, Ar-H), 7.18 (1H, ddd, J = 7.5, 7.5, 1, Ar-H), 7.36 (1H, d, J = 7.5, C7′H), 7.82 (1H, d, J = 7.5, C4′-H), 7.90 (1H, brs, N-H). MS *m/z*: 283 (M^+), 268, 117. High resolution mass measurement, calcd. for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1574.

Compound **30**: mp 115–117°C (ether/hexane). UV λ_{max} (log ε) (MeOH): 290 (4.1) nm. IR ν_{max} ($CHCl_3$): 3200–2800, 3048, 2959, 1680, 1642 cm^{-1}. ^1H NMR δ: 1.20 (6H, s, C6-CH_3), 1.85 (3H, brs, C4-CH_3), 2.13 (2H, s, C5-H), 5.81 (1H, dq, J = 6.5, 1.2, C3-H), 7.00 (1H, d, J = 6.5, C2-H). MS *m/z*: 166 (M^+), 151, 107. High resolution mass measurement, calcd. for $C_{10}H_{14}O_2$: 166.0994; found: 166.0995. Anal. calcd. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.33, H 8.40.

6-Oxo-7,7-9-trimethyl-5,6,6aα,7,8,10aβ-hexahydroindeno-[2,1-b]indole ***36***

Method A

To a solution of indole-acid **29** (450 mg, 1.6 mmol) in benzene (10

mL) at 0°C under nitrogen was added oxalyl chloride (0.21 mL, 2.4 mmol). After stirring for 24 h at room temperature, the solvent was removed *in vacuo* to give a dark residue, which was diluted with dry benzene (5 mL) and, again, the solvent was removed *in vacuo*. The acid chloride **34** was then dissolved in ether (10 mL) and a solution of indolylmagnesium iodide (3.5 equiv., prepared as described above, see experiment on compound **29**) in ether (8 mL), and dichloromethane (3.1 mL) was added dropwise for 8 h at −15°C under nitrogen. The reaction mixture was stirred for 14 h at room temperature, followed by quenching with ammonium chloride (10 mL, sat. aq.) and extraction with dichloromethane (3×, 10 mL). The organic phase was washed with sodium bicarbonate (10 mL, sat. aq.) and brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a dark oil. This crude product was purified by flash chromatography using hexanes/ether (8.5:1.5, v/v) to give *trans*-ketone **60** (194 mg, 46% overall) as a pale yellow powder. Further elution using hexanes/ether (6.5:3.5, v/v) furnished **35** (85 mg, 14%) as a yellowish foam.

Method B

To a solution of the acid chloride **34** (prepared from indole-acid **29** (198 mg, 0.7 mmol) as in Method A), in dry tetrahydrofuran (4 mL) at −15°C under nitrogen, was added dropwise a solution of lithium diisopropylamide in tetrahydrofuran prepared from diisopropylamine (0.25 mL, 1.75 mmol) for 7 h. After this time, the reaction mixture was further stirred for 1.5 h at −15°C and then quenched by the addition of ice (about 1 g) and ammonium chloride (2 mL, sat. aq.). After extraction with ethyl acetate (3×, 10 mL), the organic phase was washed with water/brine (10 mL, 1:1, v/v), brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a brown oil. Purification by flash chromatography using hexanes/ether (8.5:1.5, v/v) afforded pure *trans*-ketone **36** (55.6 mg, 30%). Further elution using hexanes/ether (6:4, v/v) recovered indole-acid **29** (53 mg, 27%).

trans-Ketone **36**: mp 129–131°C (acetone/hexane). UV λ_{max} (log ε) (MeOH): 232 (4.26), 307 (4.23) nm. IR ν_{max} ($CHCl_3$): 3464, 3040, 2960, 1683, 1625 cm^{-1}. ^1H NMR δ: 1.14 (3H, s, C7-CH_3), 1.47 (3H, s, C7-CH_3), 1.75 (3H, brs, C9-CH_3), 1.97 (1H, d, J = 18, C8-H), 2.07 (1H, d, J = 18, C8-H), 2.84 (1H, d, J = 6, C6a-H), 3.99 (1H, m, C10a-H), 6.24 (1H, brs, C10-H), 7.18 (1H, ddd, J = 8, 8, 1, Ar-H), 7.35 (1H, ddd, J = 8, 8, 1, Ar-H), 7.44 (1H, d, J = 8, Ar-H), 7.80 (1H, d, J = 8, Ar-H), 8.73 (1H, brs, N-H). MS m/z: 265 (M^+), 250, 222. High resolution mass measurement, calcd. for $C_{18}H_{19}NO$: 265.1466: found: 265.1466. Anal. calcd. for $C_{18}H_{19}NO$: C 81.48, H 7.22, N 5.28; found: C 81.16, H 7.09, N 5.23.

Compound **35**: UV λ_{max} (log ε) (MeOH): 219 (4.56) nm. IR ν_{max} ($CHCl_3$): 3465, 3025, 2960, 1637 cm^{-1}. ^1H NMR δ: 0.93 (3H, s, C5-CH_3), 1.27 (3H, s, C5-CH_3), 1.79 (1H, d, J = 18, C6-H), 1.80 (3H, brs, C1-CH_3), 2.30 (1H, d, J = 18, C6-H), 3.54 (1H, d, J = 10, C4-H), 4.14 (1H, m, C3-H), 5.59 (1H, brs, C2-H), 6.85 (1H, d, J = 2, C2′-H), 7.05–7.14 (3H, m, Ar-H), 7.15–7.24 (4H, m, Ar-H), 7.59 (1H, brs, N-H), 7.74 (1H, d, J = 8, Ar-H), 7.98 (1H, brs, N-H), 8.40 (1H, d, J = 8, Ar-H). MS m/z: 382 (M^+), 238, 144. High resolution mass measurement, calcd. for $C_{26}H_{26}N_2O$: 382.2044; found: 382.2042.

6-Oxo-7,7,9-trimethyl-5,6,6aβ,7, 8,10Aβ-hexahydroindeno-[2,1-b]indole ***37***

Method A

To a solution of *trans*-ketone **36** (430 mg, 1.6 mmol) in dry tetrahydrofuran (6 mL) and dry methanol (15 mL) at room temperature under nitrogen was added sodium methoxide (10 mL, 0.03 M in methanol). The reaction mixture was refluxed for 1 h, cooled to room temperature, and then water (2 mL) and ammonium chloride (5 mL, sat. aq.) were added. The organic solvent was evaporated *in vacuo* and the resulting residue was extracted with methylene chloride. The organic phase was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo* to yield a yellow solid. Recrystallization of this powder from acetone/hexane gave pure *cis*-ketone **37** (426 mg, 99%) as pale yellow crystals.

Method B

To a solution of *trans*-ketone **36** (24.6 mg, 0.093 mmol) in dry tetrahydrofuran (3 mL) at −15°C under nitrogen was added dropwise a solution of lithium diisopropylamide in tetrahydrofuran (prepared from diisopropylamine (0.03 mL, 0.21 mmol)). The reaction was warmed to room temperature and stirred for 2.5 h. Ice (about 0.5 g) and ammonium chloride (4 mL, sat. aq.) were added, followed by extraction with ethyl acetate (3×, 5 mL). The organic phase was washed with water/brine (7 mL, 1:1, v/v), brine (7 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a yellow solid. Crystallization from hexane/acetone furnished *cis*-ketone **24** (21 mg, 85%) as pale yellow crystals.

Method C

To a solution of acid chloride **34** (prepared from indole-acid **29** (281.5 mg, 0.99 mmol)) in dry tetrahydrofuran (5.6 mL) at −15°C under nitrogen was added dropwise a solution of lithium diisopropylamide in tetrahydrofuran (prepared from diisopropylamine (0.35 mL, 2.48 mmol)) for 7 h. After completion of the addition, the reaction mixture was allowed to reach room temperature. After stirring for 14 h, ice (about 1 g) and ammonium chloride (10 mL, sat. aq.) were added, followed by extraction with ethyl acetate (3×, 10 mL). The organic phase was washed with water/brine (10 mL, 1:1 v/v), brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a brown oil. Purification by flash chromatography using hexanes/ether (8.5:1.5, v/v) furnished *cis*-ketone **37** (71.2 mg, 27%) and further elution using hexanes/ether (6:4, v/v) returned indole-acid **29** (73.2 mg, 26%).

cis-Ketone **37**: mp 220–223°C (acetone/hexane). UV λ_{max} (log ε) (MeOH): 227 (4.29), 302 (4.25) nm. IR ν_{max} ($CHCl_3$): 3464, 3021, 2831, 1676, 1620 cm^{-1}. ^1H NMR δ: 0.92 (3H, s, C7-CH_3), 1.27 (3H, s, C7-CH_3), 1.69 (3H, brs, C9-CH_3), 1.76 (1H, d, J = 16.5, C8-H), 1.96 (1H, d, J = 16.5, C8-H), 2.89 (1H, d, J = 6, C6a-H), 4.05 (1H, m, C10a-H), 5.90 (1H, brs, C10-H), 7.18 (1H, ddd, J = 9, 8, 1.5, Ar-H), 7.36 (1H, ddd, J = 10, 9, 1.5, Ar-H), 7.48 (1H, dd, J = 10, 1.5, Ar-H), 7.79 (1H, dd, J = 8, 1.5, Ar-H), 9.75 (1H, brs, N-H). MS m/z: 265 (M^+), 250, 222. High resolution mass measurement, calcd. for $C_{18}H_{19}NO$: 265.1466; found: 265.1473. Anal. calcd. for $C_{18}H_{19}NO$: C81.48, H 7.22, N 5.28; found: C 81.19, H 7.10, N 5.10.

6α-Hydroxy-7,7,9-trimethyl-5,6α,6aβ-7,8,10aβ-hexahydroindeno-[2,1-b]indole ***38*** *and 6β-hydroxy-7,7,9-trimethyl-5,6α,6aβ-7,8,10aβ-hexahydroindeno[2,1-b]indole* ***39***

Method A

To a solution of *cis*-ketone **37** (1.02 g, 3.85 mmol) in dry THF (40 mL) at 0°C under nitrogen was added lithium aluminum hydride (about 0.14 g, 4.0 mmol). After stirring for 1 h at 0.5°C and 1 h at room temperature, wet ether (15 mL, sat. aq.), sodium hydroxide (30 mL, 15% aq.), and water (10 mL) were slowly added. The mixture was extracted with ether (5×, 15 mL) and the organic phase was washed with water/brine (100 mL, 1:1, v/v), brine (50 mL), dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield a yellow solid. Purification by flash chromatography using hexanes/ether (8.5:1.5, v/v) afforded pure crystals of alcohol **38** (1.27 g, 65%) and further elution with hexanes/ether (7.5:2.5, v/v) afforded alcohol **39** (0.68 g, 35%) as a crystalline solid.

Method B

To a solution of L-selectride (0.24 mL, 0.24 mmol, 1 M in tetrahydrofuran) at −78°C under nitrogen was added a solution of *cis*-ketone **37** (21.7 mg, 0.08 mmol) in dry tetrahydrofuran (1.5 mL). The reaction mixture was stirred for 1 h at −78°C, 2 h at 0°C, and 1 h at room temperature. The reaction was then cooled to 0°C and a further portion of L-selectride (0.24 mL, 0.24 mmol, 1 M in tetrahydrofuran) was added. After stirring at room temperature overnight, water (0.1 mL), sodium hydroxide (0.3 mL, 3 M), and H_2O_2 (0.22 mL, 30% aq.) were added at 0°C. The mixture was stirred for 2 h at room temperature and then diluted with dichloromethane (5 mL). The aqueous layer was treated with excess of solid sodium chloride and extracted with dichloromethane (3×, 5 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a yellow oil. Purification by flash chromatography using hexanes/ether (8.5:1.5, v/v) gave unreacted *cis*-ketone **37** (8 mg, 36%), and alcohol **38** (11 mg, 50.3%).

Alcohol **38**: mp 159–162°C (ether/hexane). UV λ_{max} (log ε) (MeOH): 224 (4.50), 282 (3.85) nm. IR ν_{max} ($CHCl_3$): 3571, 3470, 3250, 2958, 1669 cm^{-1}. ^1H NMR δ: 1.12 (3H, s, C7-CH_3), 1.34 (3H, s, C7-CH_3), 1.63 (3H, brs, C9-CH_3), 1.70 (1H, d, J = 16.6, C8-H), 2.44 (2H, m, C6a-H and C8-H), 2.65 (1H, brs, O-H), 3.72 (1H, m, C10a-H), 5.06 (1H, m, C6-H), 5.75 (1H, brs, C10-H), 7.10–7.30 (2H, m, C2-H and C3-H), 7.38 (1H, d, J = 7, C4-H), 7.64 (1H, d, J = 7, C1-H), 8.17 (1H, brs, N-H). MS m/z: 267 (M^+), 249, 234, 219. High resolution mass measurement, calcd. for $C_{18}H_{21}NO$: 267.1623; found: 267.1629. Anal. calcd. for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24; found: C 80.50, H 8.18, N 4.96.

Alcohol **39**: mp 149–150°C (ether/hexane). UV λ_{max} (log ε) (MeOH): 227 (4.48), 282 (3.88) nm. IR ν_{max} ($CHCl_3$): 3587, 3470, 3350, 3019, 2961 cm^{-1}. ^1H NMR δ: 1.06 (3H, s, C7-CH_3), 1.18 (3H, s, C8-CH_3), 1.56 (3H, brs, C9-CH_3), 1.60 (1H, d, J = 17, C8-H), 2.02 (1H, d, J = 17, C8-H), 2.03 (1H, brs, O-H), 2.37 (1H, dd, J = 6.6, 6.6, C6a-H), 3.86 (1H, m, C10a-H), 5.12 (1H, d, J = 6.6, C6-H), 5.56 (1H, brs, C10-H), 7.11 (1H, dd, J = 7.3, 7.3, Ar-H), 7.15 (1H, dd, J = 7.3, 7.3, Ar-H), 7.27 (1H, d, J = 7.3, C4-H), 7.55 (1H, d, J = 7.3, C1-H), 8.18 (1H, brs, N-H), MS m/z: 267 (M^+), 249, 234, 219. High resolution mass measurement, calcd. for $C_{18}H_{21}NO$: 267.1623; found: 267.1616.

5-Benzoyl-6α-benzoxy-7,7,9-trimethyl-5, 6α-6aβ,7,8,10aβ-hexahydroindeno[2,1-b]indole ***40***

To a solution of alcohol **38** (697 mg, 2.61 mmol), dimethyl aminopyridine (382 mg, 3.13 mmol), and triethylamine (7 mL) in dichloromethane (57 mL) at room temperature under nitrogen was added benzoyl chloride (1.21 mL, 10.44 mmol). After 1 day at reflux, the reaction mixture was cooled to room temperature and water (30 mL) was added. The organic phase was washed with sodium bicarbonate (30 mL, 10% aq.), water (30 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a pale yellow foam. Purification by flash chromatography using hexanes/ethyl acetate (9.3:0.7, v/v) gave **40** (942 mg, 76%) as white crystals.

Compound **40**: mp 171–174°C (ether/hexane). UV λ_{max} (log ε) (MeOH): 225 (4.27), 260 (4.02) nm. IR ν_{max} ($CHCl_3$): 3010, 2959, 1718, 1684, 1603 cm^{-1}. ^1H NMR δ: 1.03 (3H, s, C7-CH_3), 1.12 (3H, s, C7-CH_3), 1.54 (1H, d, J = 17, C8-H), 1.67 (3H, brs, C9-CH_3), 2.09 (1H, d, J = 17, C8-H), 2.74 (1H, dd, J = 5.5, 5.5, C6a-H), 3.84 (1H, m, C10a-H), 5.73 (1H, brs, C10-H), 6.40 (1H, d, J = 5.5, C6-H), 7.20–7.80 (14H, m, Ar-H). MS m/z: 475 (M^+), 353, 338, 105. High resolution mass measurement, calcd. for $C_{32}H_{29}NO_3$: 475.2147; found: 475.2145. Anal. calcd. for $C_{32}H_{29}NO_3$: C 80.82, H 6.15, N 2.94; found: C 80.80, H 6.13, N 2.89.

5-Benzoyl-6β-(3-indolyl)-7,7,9-trimethyl -5,6β,6aβ,7,8,10aβ-hexahydroindeno[2,1-b]indole ***43***

To a solution of indolylmagnesium iodide (for preparation, see experiment on compound **29**), in dry ether (1.8 mL) and dry dichloromethane (0.5 mL) at 0–5°C under nitrogen, was added dropwise a solution of benzoate **40** (169 mg, 0.35 mmol) in dry ether (1.2 mL) and dry dichloromethane (0.8 mL). After stirring for 2 h at 0–5°C and 3 h at room temperature, water (1 mL) and ammonium chloride (4 mL, sat. aq.) were added, followed by extraction with dichloromethane (2×, 10 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a brown oil. Purification by flash chromatography using hexanes/ether (8:2, v/v) furnished, in order of increasing polarity, the N-substituted compound **44** (29 mg, 18%), as an oil, benzoylyuehchukene **43** (66.1 mg, 40%) as a foam, and indoline **45** (50.7 mg, 30%) as white crystals.

Benzoylyuehchukene **43**: UV λ_{max} (MeOH): 226, 263 nm. IR ν_{max} (film): 3481, 3020, 2961, 1681, 1603 cm^{-1}. ^1H NMR δ: 0.88 (3H, s, C7-CH_3), 1.05 (3H, s, C7-CH_3), 1.72 (3H, brs, C9-CH_3), 1.76 (1H, d, J = 16, C8-H), 1.95 (1H, d, J = 16, C8-H), 2.74 (1H, dd, J = 7, 4, C6a-H), 3.95 (1H, m, C10a-H), 4.12 (1H, brd, J = 4, C6-H), 5.86 (1H, brs, C10-H), 6.15 (1H, d, J = 2.5, C2′-H), 6.82–6.92 (2H, m, Ar-H), 7.03–7.10 (1H, m, Ar-H), 7.12–7.35 (7H, m, Ar-H), 7.44 (1H, m, Ar-H), 7.61 (1H, d, J = 8, Ar-H), 7.72 (1H, brs, N-H), 7.82 (1H, d, J = 8, Ar-H). MS m/z: 470 (M^+), 455, 365, 105. High resolution mass measurement, calcd. for $C_{33}H_{30}N_2O$: 470.2357; found: 470.2353.

Compound **44**: UV λ_{max} (log ε) (MeOH): 207 (5.71), 253 (4.37) nm. IR ν_{max} (film): 3010, 2959, 1685, 1603 cm^{-1}. ^1H NMR δ: 0.85 (3H, s, C7-CH_3), 1.08 (3H, s, C7-CH_3), 1.73 (3H, s, C9-CH_3), 1.82 (1H, d, J = 16.5, C8-H), 1.98 (1H, d, J = 16.5, C8-H), 2.85 (1H, m, C6a-H), 4.08 (1H, m, C10a-H), 5.53 (1H, m, C6-H), 5.84 (1H, brs, C10-H), 6.92 (1H, d, J = 3.5, C2′-H), 6.48 (1H, d, J = 3.5, C3′-H), 6.69 (1H, d, J = 8, C7′-H), 6.93 (1H, dd, J = 7, 7, Ar-H), 6.98 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.11–7.29 (5H, m, Ar-H), 7.32 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.41–7.52 (2H, m, Ar-H), 7.61 (1H, m, Ar-H), 7.68 (1H, d, J = 8, C1-H). MS m/z: 470 (M^+), 354, 105. High resolution mass measurement, calcd. for $C_{33}H_{30}N_2O$: 470.2357; found: 470.2355. Anal. calcd. for $C_{33}H_{30}N_2O$: C 84.22, H 6.43, N 5.96; found: C 84.06, H 6.20, N 6.12.

Indoline **45**: mp 250–252°C (acetone/hexane). UV λ_{max} (log ε) (MeOH): 224 (4.66), 282 (4.23) nm. IR ν_{max} ($CHCl_3$): 3477, 3009, 2960, 1650 160 cm^{-1}. ^1H NMR δ: 0.78 (3H, s, C7-CH_3), 1.40 (1H, d, J = 17, C8-H), 1.56 (3H, brs, C9-CH_3), 1.81 (1H, d, J = 17, C8-H), 2.72 (1H, brd, J = 5, C6a-H), 3.64 (1H, m, C10a-H), 5.11 (1H, brs, C6-H or C10-H), 5.36 (1H, brs, C6-H or C10-H), 6.97–7.05 (2H, m, Ar-H), 7.15 (1H, d, J = 2.5, C2′-H), 7.12–7.24 (2H, m, Ar-H), 7.23–7.32 (1H, m, Ar-H), 7.34 (1H, dd, J = 7.5, 1, Ar-H), 7.42 (2H, dd, J = 8, 8, Ar-H), 7.51 (1H, brdd, J = 8, 8, Ar-H), 7.58 (3H, m, Ar-H), 7.91 (1H, d, J = 8, Ar-H), 7.97 (1H, brs, N-H). MS m/z: 470 (M^+), 365, 105. High resolution mass measurement, calcd. for $C_{33}H_{30}N_2O$: 470.2357; found: 470.2354. Anal. calcd. for $C_{33}H_{30}N_2O$: C 84.22, H 6.43, N 5.96; found: C 84.15, H 6.44, N 5.84.

Yuehchukene ***1***

To a solution of benzoylyuehchukene **43** (200 mg, 0.43 mmol) in dry methanol (5 mL) at 5°C under nitrogen, was added sodium methoxide (freshly prepared from sodium (about 23 mg, 1 mmol) and methanol (4 mL)). After stirring at 5°C for 4 h, water (1 mL) and ammonium chloride (3 mL, sat. aq.) were added. The organic solvent was evaporated *in vacuo* and the residue was extracted with ethyl acetate (4×, 5 mL). The organic phase was washed with water (5 mL), brine (5 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a brown oil. This crude product was purified by flash chromatography using hexanes/ether (8.5:1.5, v/v) to give the synthetic yuehchukene **1** (140.3 mg, 90%) as a white foam.

Yuehchukene **1**: UV λ_{max} (MeOH): 225, 283. IR ν_{max} ($CHCl_3$): 3400, 2955, 1618 cm^{-1}: ^1H NMR δ: 0.86 (3H, s, C7-CH_3), 1.10 (3H, s, C7-CH_3), 1.63 (1H, d, J = 17, C8-H), 1.66 (3H, brs, C9-CH_3), 2.28 (1H, d, J = 17, C8-H), 3.15 (1H, dd, J = 8.5, 8.5, C6A-H), 4.02 (1H, m, C10a), 4.56 (1H, d, J = 8.5), 5.70 (1H, brs, C10-H), 6.98–7.12 (5H, m, Ar-H), 7.38 (1H, d, J = 8, Ar-H), 7.44 (1H, d, J = 8, Ar-H), 7.48 (1H, brs, N-H), 7.57 (1H, d, J = 8, Ar-H), 8.00 (1H, brs, N-H). MS m/z: 366 (M^+), 351, 254. High resolution mass measurement, calcd. for $C_{26}H_{26}N_2$: 366.2095; found: 366.2096.

Samples of synthetic **1** and natural **1** were compared by TLC, NMR, and IR spectra, and shown to be identical.

6α-Hydroxy-7,7,9-trimethyl-5,6α,6aα7,8, 10aβ-hexahydroindeno-[2,1-b]indole ***47***

To a suspension of lithium aluminum hydride (about 29 mg, 2 mmol) in tetrahydrofuran (1 mL) at 0°C under nitrogen was added a solution of *trans*-ketone **36** (212 mg, 0.80 mmol) in tetrahydrofuran (2 mL). After stirring for 2 h at 0°C, the reaction was quenched with wet ether (0.5 mL, sat. aq.), sodium hydroxide (0.5 mL, 15% aq.), and water (1 mL). After filtration through Celite, the filtrate was evaporated *in vacuo* to give a residue that was diluted with ether (5 mL). This ethereal solution was washed with brine (5 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography using hexanes/ether (8:2, v/v) to give alcohol **47** (192 mg, 90%).

Alcohol **47**: UV λ_{max} (log ε) (MeOH): 223 (4.49), 282 (4.07) nm. IR ν_{max} ($CHCl_3$): 3685, 3466, 3020, 1621 cm^{-1}. ^1H NMR δ: 1.06 (3H, s, C7-CH_3), 1.24 (3H, s, C7-CH_3), 1.60 (1H, brs, O-H), 1.71 (3H, brs, C9-CH_3), 1.84 (1H, d, J = 18, C8-H), 2.04 (1H, d, J = 18, C8-H), 2.18 (1H, dd, J = 8.5, 8.5, C6a-H), 3.45–3.56 (1H, m, C10a), 5.08

(1H, d, J = 8.5, C6-H), 6.15 (1H, brs, C10-H), 7.09 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.13 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.33 (1H, dd, J = 8, 1.5, Ar-H), 7.62 (1H, dd, J = 8, 1.5, Ar-H), 8.10 (1H, brs, N-H). MS m/z: 267 (M^+), 249, 234, 117. High resolution mass measurement, calcd. for $C_{18}H_{21}NO$: 267.1623; found: 267.1623.

*6-Oxo-5-(*p*-toluenesulfonyl)-7,7,9-trimethyl-5,6,6aα,7,8,10aβ-hexahydroindeno[2,1-b]indole* **48**

To a solution of *trans*-ketone **36** (600 mg, 2.26 mmol) in dichloromethane (5 mL) at 0°C under nitrogen was added sodium hydride (90 mg, 2.3 mmol, 60% dispersion in oil). After stirring for 10 min at room temperature, *p*-toluenesulfonyl chloride (450 mg, 2.4 mmol) was added to the reaction mixture at 0°C. The reaction was stirred for 2 h at room temperature, then quenched with ammonium chloride (5 mL, sat. aq.), and diluted with dichloromethane (5 mL). The organic phase was washed with brine (5 mL), dried over sodium hydroxide, filtered, and evaporated *in vacuo* to yield a yellow solid. Purification by flash chromatography using hexanes/ether (9:1, v/v) furnished tosyl-ketone **48** (853 mg, 90%) as pale yellow crystals.

Tosyl-ketone **48**: mp 123–124°C (acetone/hexane). UV λ_{max} (log ε) (MeOH): 297 (4.21), 243 (4.23), 222 (4.28) nm. IR ν_{max} ($CHCl_3$): 3032, 2959, 1713, 1605, 1381, 1123 cm^{-1}. ^1H NMR δ: 1.08 (3H, s, C7-CH_3), 1.44 (3H, s, C7-CH_3), 1.71 (3H, brs, C9-CH_3), 1.92 (1H, d, J = 18, C8-H), 2.04 (1H, d, J = 18, C8-H), 2.36 (3H, s, Ar-CH_3), 2.81 (1H, d, J = 8, C6a-H), 3.77–3.84 (1H, m, C10a), 6.12 (1H, brs, C10-H), 7.25 (2H, d, J = 8, C3′-H and C5′-H), 7.33 (1H, dd, J = 8, 8, Ar-H), 7.50 (1H, dd, J = 8, 8, Ar-H), 7.74 (1H, d, J = 8, Ar-H), 8.04 (2H, d, J = 8, C2′-H and C6′-H), 8.28 (1H, d, J = 8, Ar-H). MS m/z: 419 (M^+), 404, 263, 248. High resolution mass measurement, calcd. for $C_{25}H_{25}NO_3S$: 419.1555; found: 419.1556. Anal. calcd. for $C_{25}H_{25}NO_3S$: C 71.57, H 6.01, N 3.34; found: C 71.23, H 6.09, N 3.44.

*6α-Hydroxy-5-(*p*-toluenesulfonyl)-7,7,9-trimethyl-5,6α,6aα,7,8,-10aβ-hexahydroindeno[2,1-b]indole* **49**

To a suspension of lithium aluminum hydride (about 72 mg, 2 mmol) in tetrahydrofuran (2 mL) at 0°C under nitrogen was added a solution of tosyl ketone **48** (800 mg, 1.91 mmol) in tetrahydrofuran (4 mL). After stirring for 2 h at 0°C, the reaction was quenched with wet ether (1 mL, sat. aq.), sodium hydroxide (1 mL, 15% aq.), and water (2 mL). After filtration through Celite, the filtrate was evaporated *in vacuo* to give a residue that was diluted with ether (10 mL). This ethereal solution was washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography using hexanes/ether (8.5:1.5, v/v) to give alcohol **49** (691 mg, 86%) as colorless needles.

Alcohol **49**: mp 118–119°C (ether/hexane). UV λ_{max} (log ε) (MeOH): 222 (4.43), 258 (4.40) nm. IR ν_{max} 3563, 3010, 2962, 1599, 1381, 1123 cm^{-1}. ^1H NMR δ: 1.05 (3H, s, C7-βCH$_3$), 1.28 (3H, s, C7-αCH$_3$), 1.70 (3H, brs, C9-H), 1.88 (1H, d, J = 17.5, C8-H), 2.09 (1H, d, J = 17.5, C8-H), 2.33 (3H, s, Ar-CH_3), 2.42 (1H, dd, J = 10, 8.5, C6a-H), 3.38 (1H, m, C10a), 4.10 (1H, d, J = 2, O-H), 5.27 (1H, ddd, J = 8.5, 2, 2, C6-H), 6.04 (1H, brs, C10-H), 7.19–7.34 (4H, m, Ar-H), 7.54 (1H, d, J = 7, C1-H), 7.84 (2H, d, J = 9, C2′-H and C6′-H), 7.91 (1H, dd, J = 8, 1.5, C4-H). MS m/z: 421 (M^+), 406, 251, 91. High resolution mass measurement, calcd. for $C_{25}H_{27}NO_3S$: 421.1711; found: 421.1715. Anal. calcd. for $C_{25}H_{27}NO_3S$: C 71.23, H 6.46, N 3.32; found: C 71.20, H 6.47, N 3.46.

*6α-Acetoxy-5-(*p*-toluenesulfonyl)-7,7,9-trimethyl-5,6α,6aα,7,8,10aβ-hexahydroindeno[2,1-b]indole* **50**

To a solution of alcohol **49** (100 mg, 0.24 mmol) and *N,N*-dimethylaminopyridine (37 mg, 0.31 mmol) in dichloromethane (5 mL) at room temperature was added acetic anhydride (0.027 mL, 0.29 mmol). The reaction mixture was stirred for 3 days at room temperature, then diluted with dichloromethane (5 mL) and washed with water (10 mL). The organic phase was washed with brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a yellow foam. This crude product was purified by flash chromatography using hexanes/ether (8:2, v/v) to obtain acetate **50** (82.5 mg, 75%) as a white foam.

Acetate **50**: UV λ_{max} (log ε) (MeOH): 221 (4.41), 257 (4.21) nm. IR ν_{max} ($CHCl_3$): 3019, 2960, 1739, 1599, 1373, 1170 cm^{-1}. ^1H NMR δ: 1.07 (3H, s, C7-CH_3), 1.09 (3H, s, C7-CH_3), 1.71 (3H, brs, C9-CH_3), 1.86 (1H, d, J = 17, C8-H), 2.04 (1H, d, J = 17, C8-H), 2.15 (3H, s, O=C-CH_3), 2.33 (3H, s, Ar-CH_3), 2.53 (1H, dd, J = 10, 9, C6a-H), 3.37–3.45 (1H, m, C10a-H), 6.05 (1H, brs, C10-H), 6.67 (1H, dd, J = 9, 2.5, C6-H), 7.20–7.32 (4H, m, Ar-H), 7.54 (1H, d, J = 8, C1-H), 7.81 (2H, d, J = 8, C2′-H and C6′-H), 8.04 (1H, d, J = 8, C4′-H). MS m/z: 463 (M^+), 403, 388, 308, 248. High resolution mass measurement, calcd. for $C_{27}H_{29}NO_4S$: 463.1817; found: 463.1818. Anal. calcd. for $C_{27}H_{29}NO_4S$: C 69.96, H 6.30, N 3.02; found: C 69.56, H 6.32, N 2.88.

*10bα-(3-Indolyl)-5-(*p*-toluenesulfonyl)-7,7,9-trimethyl-5,6aα,-7,8,10aβ,10bα-hexahydroindeno[2,1-b]indole* **51**

To a solution of indolymagnesium iodide in dry ether (12 mL) and dichloromethane (4 mL) at 0–5°C under nitrogen was added a solution of acetate **50** (540 mg, 1.17 mmol) in ether (7 mL). After stirring for 17 h at 5°C, the reaction mixture was quenched with ammonium chloride (8 mL, sat. aq.) and extracted with dichoromethane (3×, 8 mL). The organic phase was washed with water (8 mL), brine (8 mL), dried over sodium sulfate, and evaporated *in vacuo* to yield a brown oil. Purification by flash chromatography using hexanes/ether (7:3, v/v) gave compound **51** (250 mg, 41%) as a white powder.

Compound **51**: mp 207–208°C (acetone/hexanes). UV λ_{max} (log ε) (MeOH): 226 (4.73), 270 (4.08) nm. IR ν_{max} ($CHCl_3$): 3470, 2960, 1650, 1370, 1170 cm^{-1}. ^1H NMR δ: 0.71 (3H, s, C7-CH_3), 1.06 (3H, s, C7-CH_3), 1.54 (3H, brs, C9-CH_3), 1.63 (1H, d, J = 17, C8-H), 1.79 (1H, d, J = 17, C8-H), 2.33 (3H, s, Ar-CH_3), 2.76 (2H, m, C6a-H and C10a-H), 5.87 (1H, brs, C6-H or C10-H), 5.94 (1H, brs, C6-H or C10-H), 6.97–7.30 (8H, m, Ar-H), 7.25 (1H, d, J = 8, Ar-H), 7.59 (1H, d, J = 8, Ar-H), 7.65 (1H, d, J = 8, Ar-H), 7.76 (2H, d, J = C2′-H and C6′-H), 7.90 (1H, brs, N-H). MS m/z: 520 (M^+), 403, 388, 365. High resolution mass measurement, calcd. for $C_{33}H_{32}N_2O_2S$: 520.2184; found: 520.2179

6-Oxo-7,7,9-trimethyl-5-trimethylsilylethoxymethyl-5,6,6aα,7,8,-10aβ-hexahydroindeno-[2,1-b]indole **53**

To a solution of *trans*-ketone **36** (31 mg, 0.12 mmol) in dichloromethane (4 mL) at 0°C under nitrogen was added sodium hydride (4.5 mg, 0.15 mmol, 80% dispersion in oil). After stirring at 0°C for 1 h, 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl), (0.03 mL, 0.175 mmol) was added and the stirring was continued for 40 min. Water (2 mL) and ammonium chloride (4 mL, sat. aq.) were added and the mixture was extracted with dichloromethane (3×, 4 mL). The organic phase was washed with water (6 mL), brine (6 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a yellow liquid. The product was immediately purified by flash chromatography using hexanes/ether (9.7:0.3, v/v) to obtain *trans*-SEM-ketone **53** (43 mg, 93%) as a yellow oil. This product turned out to be very unstable so it was usually utilized without purification for the next reaction. IR ν_{max} (film): 2954, 1695, 1615 cm^{-1}. ^1H NMR δ: −0.1 (9H, s, Si-$(CH_3)_3$), 0.86 (2H, m, C4′-H), 1.10 (3H, s, C7-CH_3), 1.42 (3H, s, C7-CH_3), 1.72 (3H, brs, C9-CH_3), 1.93 (1H, d, J = 17, C8-H), 2.03 (1H, d, J = 17, C8-H), 2.79 (1H, d, J = 7, C6a-H), 3.52 (2H, m, C3′-H), 3.94 (1H, m, C10a), 5.61 (1H, d, J = 11.5, C1′-H), 5.69 (1H, d, J = 11.5, C1′-H), 6.23 (1H, brs, C10-H), 7.19 (1H, dd, J = 8, 8, Ar-H), 7.36 (1H, dd, J = 8, 8, Ar-H), 7.53 (1H, d, J = 8, Ar-H), 7.77 (1H, d, J = 8, Ar-H). MS m/z: 395 (M^+), 73.

6α-Hydroxy-7,7,9-trimethyl-5-trimethylsilylethoxymethyl-5,6α,-6aβ,7,8,10aβ-hexadroindeno[2,1-b]indole **54**

Method A

To a solution of SEM-*trans*-ketone **53** (29.4 mg, 0.074 mmol) in dry toluene (2.5 mL) at −78°C under nitrogen was added diisobutylaluminium hydride (DIBAL) (0.11 mL, 0.11 mmol, 1 M in hexane). After stirring for 1 h at −78°C, solid ammonium chloride (about 20 mg) was added. The temperature was raised to 0°C, then water (2 mL) and ammonium chloride (5 mL, sat. aq.) were added. Careful extraction with ether (4×, 5 mL) followed by washing with brine (15 mL), drying

over sodium sulfate, filtration, and evaporation *in vacuo* yielded a yellow oil, which was purified by flash chromatography using hexanes/ether (8:2, v/v) to give alcohol **54** (19.4 mg, 80% based on recovered ketone) and unreacted **53** (5.2 mg).

Method B

To a suspension of sodium hydride (13.6 mg, 0.45 mmol, 80% dispersion in oil) (prewashed twice with dry ether (1 mL) in dry tetrahydrofuran (1 mL) at 0°C under nitrogen), was added *trans*-ketone **36** (100 mg, 0.38 mmol) in dry tetrahydrofuran (1.5 mL). After stirring for 40 min, SEM-Cl (0.073 mL, 0.415 mmol) was added and the reaction stirred for 2.5 h at 0°C. Lithium aluminium hydride (about 36 mg, 1 mmol) was then added and, after 30 min at the same temperature, the reaction was quenched with ice (about 0.5 g), and sodium hydroxide (4 mL, 15% aq.). Exhaustive extraction with ether (5×, 5 mL) followed by washing with water/brine (10 mL, 1:1, v/v), brine (10 mL), drying over sodium sulfate, filtration, and evaporation *in vacuo* yielded a yellow oil. Purification by flash chromatography using hexanes/ether (8:2, v/v) furnished pure alcohol **54** (100.2 mg, 67% overall). UV λ_{max} (log ε) (MeOH): 230 (4.44), 280 (3.89) nm. IR ν_{max} (film): 3440, 2960, 1660 cm^{-1}. ^1H NMR δ: −0.07 (9H, s, $Si(CH_3)_3$), 0.81–0.90 (2H, m, C4′-H), 1.03 (3H, s, C7-βCH_3), 1.21 (3H, s, C7-αCH_3), 1.70 (3H, brs, C9-CH_3), 1.84 (1H, d, J = 17, C8-H), 2.03 (1H, d, J = 17, C8-H), 2.10 (1H, dd, J = 9, 9, C6a-H), 3.30 (1H, d, J = 9, Hz, O-H), 3.41 (1H, m, C10a-H), 3.46–3.58 (2H, m, C3′-H), 5.12 (1H, ddd, J = 9, 9, 2, C6-H), 5.41 (1H, d, J = 11, C1′-H), 5.58 (1H, d, J = 11, C1′-H), 6.15 (1H, brs, C10-H), 7.06 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.13 (1H, ddd, J = 8, 8, 1.5, Ar-H), 7.44 (1H, d, 8, C4-H), 7.57 (1H, d, J = 8, C1-H). MS m/z: 397 (M^+), 379, 73. High resolution mass measurement, calcd. for $C_{24}H_{35}NO_2Si$: 397.2437; found: 397.2443. Anal. calcd. for $C_{24}H_{35}NO_2Si$: C 72.50, H 8.87, N 3.52; found: C 73.00, H 9.00, N 3.24.

6α-Acetoxy-7,7,9-trimethyl-5-trimethylsilylethoxymethyl-5,6α,5aα,7,8,10aβ-hexahydroindeno[2-1-b]indole **55**

Method A

To a solution of alcohol **54** (46.5 mg, 0.12 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (21.4 mg, 0.18 mmol) in dichloromethane (1.5 mL) at 0–5°C under nitrogen were added acetic anhydride (0.094 mL, 1 mmol) and triethylamine (0.147 mL, 1.05 mmol). The reaction mixture was stirred for 2 h at room temperature, then water (5 mL) and dichloromethane (5 mL) were added and the layers separated. The organic phase was washed with brine (5 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a yellow oil. This crude product was purified by flash chromatography using hexanes/ether (9.5:0.5, v/v) to obtain acetate **55** (44 mg, 86%) as a colorless oil.

Method B

To a suspension of sodium hydride (37.3 mg, 1.24 mmol, 80% dispersion in oil) (prewashed twice with dry ether (1 mL) in dry tetrahydrofuran (2 mL)) at 0°C under nitrogen was added *trans*-ketone **36** (300 mg, 1.13 mmol) in dry tetrahydrofuran (3 mL). The mixture was stirred for 40 min at 0°C, then 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) (0.22 mL, 1.24 mmol) was added. Stirring was continued at 0°C for 2.5 h and then the reaction mixture was cooled to −15°C. Diisobutylaluminum hydride (DIBAL) (2.26 mL, 2.26 mmol, 1 M in hexane) was added and after 1 h at −15°C acetic anhydride (0.32 mL, 3.4 mmol) was added dropwise. After stirring for 16 h at 0°C the reaction mixture was poured into sodium bicarbonate (10 mL, sat. aq.), followed by extraction with ether (3×, 10 mL). The organic phase was washed with brine (20 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a dark oil. This crude product was purified by flash chromatography using hexanes/ether (9.5:0.5 v/v) to obtain acetate **55** (250.1 mg, 50.3% overall).

Acetate **55**: UV λ_{max} (log ε) (MeOH): 227 (4.49), 280 (3.94) nm. IR ν_{max} (film): 2955, 1737, 1659 cm^{-1}. ^1H NMR (CD_3CN) δ: −0.09 (9H, s, Si-$(CH_3)_3$), 0.77–0.90 (2H, m, C4′-H), 1.04 (6H, s, C7-CH_3), 1.71 (3H, brs, C9-CH_3), 1.87 (1H, d, J = 17, C8-H), 2.04 (1H, d, J = 17, C8-H), 2.11 (3H, s, O=C-CH_3), 2.50 (1H, dd, J = 10, 10, C6a-H), 3.43 (2H, dd, J = 9, 9, C3′-H), 3.50 (1H, m, C10a), 5.29 (1H, d, J = 11, C1′-H), 5.33 (1H, d, J = 11, C1′-H), 6.18 (1H, brs, C10-H), 6.43 (1H, d, J = 10, C6-H), 7.10 (1H, brdd, J = 8, 8, Ar-H), 7.18 (1H, brdd, J = 8, 8, Ar-H), 7.46 (1H, d, J = 8, C4-H), 7.62 (1H, d, J = 8, C1-H). MS m/z: 439 (M^+), 379, 75, 73. High resolution mass measurement, calcd. for $C_{26}H_{37}NO_3Si$: 439.2542; found: 439.2549.

6β-(3-Indolyl)-7,7,9-trimethyl-5-trimethysilylethoxymethyl-5,6β,6aα,7,8,10aβ-hexahydroindeno[2,1-b]indole **56**

To a solution of indolylmagnesium iodide (prepared as above) in dry ether (5.5 mL) and dichloromethane (1.6 mL) at 0–5°C under nitrogen was added a solution of acetate **55** (492 mg, 1.12 mmol) in dry ether (3.7 mL). The reaction mixture was stirred for 2.5 h at 0–5°C, then water (3 mL) and ammonium chloride (5 mL, sat. aq.) were added. After extraction with ether (2×, 10 mL), the organic phase was washed with sodium bicarbonate (10 mL, sat. aq.), brine (10 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a brown viscous oil. This crude product was purified by flash chromatography using hexanes/ethyl acetate (96.5:3.5, v/v) to furnish SEM-*trans*-yuehchukene **56** (201 mg, 36%) as a pale yellow foam. UV λ_{max} (log ε) (MeOH): 223 (4.7), 280 (4.14) nm. IR ν_{max} (film): 3414, 3055, 2952, 1657 cm^{-1}. ^1H NMR (CD_3CN) δ: −0.16 (9H, s, $Si(CH_3)_3$), 0.34 (3H, brs, C7-βCH_3), 0.44–0.73 (2H, m, C4′-H), 1.13 (3H, m, C7-α-CH_3), 1.67 (1H, d, J = 17, C8-H), 1.70 (3H, s, CH_3), 2.05 (1H, d, J = 17, C8-H), 2.70 (1H, dd, J = 11, 6, C6a-H), 3.05–3.32 (2H, m, C3′-H), 4.06 (1H, m, C10a-H), 4.78 (1H, d, J = 6, C6-H), 4.98 (1H, brd, J = 11, C1′-H), 5.19 (1H, d, J = 11, C1′-H), 6.25 (1H, brs, C10-H), 6.30–7.85 (9H, m, Ar-H), 9.15 (1H, brs, N-H). MS m/z: 496 (M^+), 481, 75. High resolution mass measurement, calcd. for $C_{32}H_{40}N_2OSi$: 496.2909; found: 496.2908. Anal. calcd. for $C_{32}H_{40}N_2OSi$: C 77.37, H 8.12, N 5.64; found: C 77.10, H 8.21, N 5.40.

6a-epi-*Yuehchukene* **2**

To a solution of SEM-*trans*-yuehchukene **56** (46 mg, 0.093 mmol) in dry tetrahydrofuran (1 mL) at room temperature under nitrogen were added tetra-*n*-butylammonium fluoride (1.85 mL, 1.85 mmol, 1 M in tetrahydrofuran) and hexamethylphosphoramide (HMPA) (0.7 mL). The temperature was increased to 40–45°C and the reaction mixture was maintained at this condition for 1 day. Then a further portion of tetra-*n*-butylammonium fluoride (1 mL, 1 mmol, 1 M in the tetrahydrofuran) and hexamethylphosphoramide (0.6 mL) was added and the stirring at 40–45°C was continued for another day. Water (2 mL) and ammonium chloride (5 mL, sat. aq.) were added and the mixture was extracted with ether (3×, 6 mL). The organic phase was washed with brine, dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a yellow oil. This crude product was purified by flash chromatography using hexanes/ether (9:1, v/v) to obtain *trans*-yuehchukene **2** (30.2 mg, 89%) as a white foam. UV λ_{max} (log ε) (MeOH): 324 (4.63), 280 (4.03) nm. IR ν_{max} (film): 3400, 2920, 1655 cm^{-1}. ^1H NMR (CD_3CN) δ: 0.32 (3H, s, C7-βCH_3), 1.15 (3H, s, C7-αCH_3), 1.67 (1H, d, J = 17, C8-H), 1.69 (3H, s, C9-CH_3), 2.05 (1H, d, J = 17, C8-H), 2.69 (1H, dd, J = 10, 7, C6a-H), 4.01 (1H, brd, J = 10, C10a-H), 4.70 (1H, d, J = 7, C6-H), 6.26 (1H, brs, C10-H), 6.70–7.17 (6H, m, Ar-H), 7.29 (1H, dd, J = 7, 3, Ar-H), 7.34 (1H, d, J = 8, Ar-H), 7.66 (1H, brd, J = 8, Ar-H), 8.89 (1H, brs, N-H), 9.10 (1H, brs, N-H). MS m/z: 366 (M^+), 351, 142. High resolution mass measurement, calcd. for $C_{26}H_{26}N_2$: 366.2095; found: 366.2090.

10α-Methyl-6-oxo-5,6,7β,10β-tetrahydro-7β, 10β-(1-1-dimethylethano)-cyclohept[b]indole **33**

To a solution of indole-acid **28** (400 mg, 1.41 mmol) in dry chloroform (70 mL) at room temperature under nitrogen was added polyphosphate ester (PPE) (1.5 mL). The reaction mixture was refluxed for 1 h, followed by cooling and addition of water (20 mL). The organic phase was then washed with sodium bicarbonate (25 mL, sat. aq.), water (25 mL), brine (25 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield a viscous oil. The crude product was purified on a short silica gel column using hexanes/ether (8.5:1.5, v/v) to give pure ketone **33** (190 mg, 55%) as colorless prisms. UV λ_{max} (log ε) (MeOH): 237 (4.33), 314 (4.32) nm. IR λ_{max} (KBr): 3300, 3060, 2960, 1620, 1601 cm^{-1}. ^1H NMR δ: 1.00 (3H, s,

C1′-CH_3), 1.18 (3H, s, C1′-CH_3), 1.63 (1H, d, J = 15, C2′-H), 1.97 (3H, s, C10-CH_3), 2.01 (1H, d, J = 15, C2′-H), 3.29 (1H, d, J = 7, C7-H), 6.18 (1H, dd, J = 8, 7, C8-H), 6.45 (1H, d, J = 8, C9-H), 7.10 (1H, dd, J = 8, 6, Ar-H), 7.29 (1H, dd, J = 8, 6, Ar-H), 7.38 (1H, d, J = 8, Ar-H), 8.04 (1H, d, J = 8, Ar-H), 8.86 (1H, brs, N-H). MS m/z: 265 (M^+), 250, 237, 209, 181. High resolution mass measurement, calcd. for $C_{18}H_{19}NO$: 265.1466; found: 265.1465. Anal. calcd. for $C_{18}H_{19}NO$: C 81.48, H 7.22, N 5.28; found: C 81.39, H 7.40, N 5.24.

6α-Hydroxy-10-α methyl 5,6,7β,10β-tetrahydro-7β,10β-(1,1-dimethylethano)-cyclohept[b]indole ***59***

To a suspension of lithium aluminium hydride (29 mg, 0.76 mmol) in 5 mL of tetrahydrofuran at −40°C, the cooled solution of ketone **33** (200 mg, 0.75 mmol) in 5 mL tetrahydrofuran was added. The reaction was stirred for 1 h at −40°C. Then the reaction mixture was quenched with 1 mL of H_2O, warmed up to room temperature, diluted with water, and extracted with dichloromethane. The organic layer was dried with sodium sulfate, evaporated to dryness, and purified on a silica gel column using hexane/ether (8.5:1.5, v/v) to give unreacted ketone **33** (23 mg, 12%) and one alcohol **59** (142 mg, 71%). ^{1}H NMR δ: 1.06 (3H, s), 1.17 (3H, s), 1.55 (1H, d, J = 15), 1.08 (3H, s), 2.23 (1H, bs), 2.42 (1H, dd, J = 3, 6), 4.96 (1H, s), 6.18 (1H, dd, J = 6, 8), 6.26 (1H, d, J = 8), 7.02 (1H, dd, J = 6, 8), 7.09 (1H, dd, J = 6, 8), 7.31 (1H, d, J = 8), 7.87 (1H, *d*, J = 8), 8.42 (1H, b). MS m/z: 267 (M^+) (100%), 252, 234. High resolution mass measurement, calcd. for $C_{18}H_{21}NO$: 267.1623; found: 267.1620.

6β-(N-Indolyl)-10α-methyl-5,6,7β,10β-tetrahydro-7β,10β-(1,1-dimethylethano)-cyclohept[b]indole ***60***

To a solution of alcohol **59** (140 mg, 0.522 mmol), dimethylaminopyridine (77 mg, 0.626 mmol), and triethylamine (1.4 mL) in dichloromethane (12 mL) at room temperature under nitrogen was added benzoyl chloride (0.25 mL, 2.1 mmol). After 18 h of reflux, the reaction mixture was cooled to room temperature and water (30 mL) was added. The organic phase was washed with sodium bicarbonate (10% aq.) and water, dried over sodium sulfate, filtered, and evaporated to dryness to yield crude benzoate of the alcohol **59**. Then, without futher purification, the crude benzoate was dissolved in a mixture of dry ethyl ether (2 mL) and dichloromethane (1 mL), and added dropwise to a solution of indolylmagnesium iodide (for preparation, see Experimental for compound **29**) in a mixture of ethyl ether (3 mL) and dichloromethane (1 mL). After stirring for 2 h at 0–5°C and 2 h at room temperature, water (2 mL) and ammonium chloride (6 mL, sat. aq.) were added, followed by extraction with dichloromethane (3 × 10 mL). The organic phase was washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered, and evaporated to yield a brown oil. Flash chromatography on silica gel employing hexanes/ether (8:2) as eluent gave 124 mg (64.5%, calcd. based on alcohol **59**) of the compound **60**, as white crystals; mp 124–124.5°C. ^{1}H NMR δ: 1.11 (3H, s), 1.30 (3H, s), 1.54 (1H, d, J = 12), 1.92 (3H, s), 2.05 (1H, d, J = 12), 2.73 (1H, dd, J = 8, 4), 5.57 (1H, dd, J = 8, 8), 5.99 (1H, d, J = 4), 6.31 (1H, d, J = 8), 6.34 (1H, d, J = 4), 6.64 (1H, d, J = 4), 7.0–7.3 (5H, m), 7.42 (1H, d, J = 8), 7.59 (1H, d, J = 6), 7.7 (1H, s, b), 7.93 (1H, d, J = 8). MS m/z: 366 (M^+), 250, 194. High resolution mass measurement, calcd. for $C_{26}H_{26}N_2$: 366.2096; found: 366.2107.

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TABLE 3. Crystallographic data[a]

Compound	**36**	**60**·½ CH_2Cl_2	**45**·C_3H_6O
Formula	$C_{18}H_{19}NO$	$C_{26.5}H_{27}ClN_2$	$C_{36}H_{36}N_2O_2$
FW	265.35	408.97	528.69
Crystal size, mm	0.05 × 0.19 × 0.25	0.25 × 0.25 × 0.42	0.22 × 0.35 × 0.56
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	$P\bar{1}$	$Fdd2$	$P2_1/n$
a, Å	8.2249(9)	19.242(1)	9.5050(3)
b, Å	12.845(1)	56.193(3)	21.9825(9)
c, Å	7.8662(8)	8.1466(5)	14.0170(4)
α, deg	85.58(1)	90	90
β, deg	113.207(8)	90	94.981(4)
γ, deg	107.076(9)	90	90
V, Å^3	731.2(1)	8808(1)	2917.7(2)
Z	2	16	4
ρ_{calc}, g/cm^3	1.205	1.234	1.204
$F(000)$	284	3472	1128
$\mu/(CuK_\alpha)$, cm^{-1}	5.43	16.36	5.44
Transmission factors		0.587–0.714	0.787–0.891
Scan type	ω–2θ	ω–2θ	ω–2θ
Scan range, deg in ω	0.85 + 0.14 tan θ	0.55 + 0.14 tan θ	0.70 + 0.14 tan θ
Scan speed, deg/min	1.3–10.0	0.9–10.0	1.1–10.0
Data collected	$\pm h, +k, \pm l$	$\pm h, +k, \pm l$	$\pm h, +k, \pm l$
$2\theta_{max}$, deg	150	150	150
Cryst. decay	Negligible	Negligible	Negligible
No. of unique reflections	3004	2430	5986
No. of reflections with $I \geq n\sigma(I)$	911 (n = 2)	1342 (n = 3)	4290 (n = 3)
No. of variables	181	264	482
R	0.054	0.062	0.043
R_w	0.048	0.070	0.051
gof	1.62	2.39	0.96
Max Δ/σ (final cycle)	0.002	0.28	0.30
Residual density e/Å^3	−0.22 to +0.36	−0.26 to +0.91	−0.20 to +0.28

[a]Temperature 294 K, Enraf–Nonius CAD4-F diffractometer, Cu-K_α radiation ($\lambda(K_{\alpha 1})$ = 1.54056, $\lambda(K_{\alpha 2})$ = 1.54439 Å), nickel filter, takeoff angle 3.0°, aperture (4.0 × 2.0) + 1.0 tan θ mm at a distance of 173 mm from the crystal, scan extended by 25% on each side for background measurement, $\sigma^2(I) = [C + 2B + (0.040(C - B))^2]$ with C = scan count, B = normalized total background count, function minimized $\Sigma w(|F_o| - |F_c|)^2$ where $w = 4F_o^2/\sigma^2(F_o^2)$, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$, and gof = $[\Sigma(|F_o| - |F_c|)^2/(m-n)]^{1/2}$. Values given for R, R_w, and gof are based on those reflections with $I \geq n\sigma(I)$.

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Appendix

X-ray crystallographic analyses of ***36****,* ***60***·½ CH_2Cl_2*, and* ***45***·C_3H_6O

Crystallographic data for the three compounds appear in Table 3. The final unit-cell parameters were obtained by least squares on the setting angles for 25 reflections with 2θ = 32.3–50.4° for **36**, 40.1–88.0° for **60**, and 80.2–94.0° for **45**. The intensities of three standard reflections, measured every hour of X-ray exposure time throughout the data collections, remained essentially constant for all three compounds. The data were processed[3] and corrected for Lorentz and polarization effects, and absorption for **60**·½CH_2Cl_2 and **45**·C_3H_6O (analytical method).

The structure analysis of **36** was initiated in the centrosymmetric space group $P\bar{1}$ on the basis of E-statistics, the choice being confirmed by subsequent calculations. The structures were solved by direct methods, the coordinates of the non-hydrogen atoms being determined from E-maps and subsequent difference Fourier syntheses. The asymmetric unit of **60** contains one half of a dichloromethane solvate molecule (situated on a crystallographic twofold rotation axis), and the asymmetric unit of **45** contains an acetone solvate molecule. All non-hydrogen atoms (except for the carbon atom of the dichloromethane molecule in **60**·½CH_2Cl_2) were refined with anisotropic thermal parameters. Hydrogen atoms were fixed in idealized positions (C(sp^2)—H = 0.97, C(sp^3)—H = 0.98, N—H = 0.92 Å, $U_H \propto U_{bonded\ atom}$) except for **45**·$C_3H_6O$ where all hydrogen atoms except those associated with the acetone molecule were refined with isotropic thermal parameters. Neutral atom scattering factors and anomalous dispersion corrections for the non-hydrogen atoms were taken from the International Tables for X-ray Crystallography (23). A parallel refinement of the structure of **60**·½CH_2Cl_2 having the opposite polarity gave slightly higher residuals, the R_w factor ratio being 1.005. Final atomic coordinates and equivalent isotropic thermal parameters

[3]Computer programs used include locally written programs for data processing and locally modified versions of the following: MULTAN80, multisolution program by P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson; ORFLS, full-matrix least-squares, and ORFFE, function and errors, by W. R. Busing, K. O. Martin, and H. A. Levy; FORDAP, Patterson and Fourier syntheses, by A. Zalkin; ORTEP II, illustrations, by C. K. Johnson.

TABLE 4. Final position (fractional × 10^4, Cl and **45** × 10^5) and isotropic thermal parameters ($U \times 10^3$ Å^2) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*	U_{eq}/U_{iso}
		36		
O	7944(5)	−1570(3)	9787(5)	72
N(1)	8806(5)	404(3)	7210(5)	63
C(2)	7509(7)	−598(4)	6957(7)	51
C(3)	7088(7)	−1462(4)	8146(7)	54
C(4)	5321(6)	−2256(4)	6831(6)	50
C(5)	4626(7)	−3452(4)	7186(6)	54
C(6)	2749(7)	−3903(4)	5558(7)	72
C(7)	2440(7)	−3419(4)	3682(7)	63
C(8)	3646(7)	−2547(4)	3410(6)	60
C(9)	5449(7)	−2059(4)	4923(6)	55
C(10)	6560(6)	−885(4)	5130(7)	51
C(11)	7266(6)	−34(4)	4132(7)	53
C(12)	6927(7)	120(5)	2261(7)	70
C(13)	7947(8)	1051(5)	1771(7)	74
C(14)	9295(8)	1839(5)	3124(9)	78
C(15)	9684(7)	1712(5)	4979(9)	71
C(16)	8649(7)	762(4)	5472(8)	56
C(17)	5977(8)	−4069(4)	7240(7)	79
C(18)	4365(7)	−3591(4)	9010(7)	79
C(19)	637(8)	−3953(5)	2178(7)	100
		60		
Cl	3242(6)	2471(1)	909(15)	334
N(1)	5040(3)	2295(1)	3408	47
N(1′)	4417(3)	1804(1)	2950(11)	44
C(2)	5362(4)	2091(1)	2848(12)	41
C(3)	5122(3)	1854(1)	3463(13)	42
C(4)	5632(4)	1651(1)	2975(13)	44
C(5)	5605(4)	1621(1)	1150(14)	55
C(6)	5956(4)	1776(1)	278(13)	51
C(7)	6392(3)	1969(1)	1065(12)	43
C(8)	5902(3)	2149(1)	1833(13)	39
C(9)	5915(4)	2410(1)	1797(13)	41
C(10)	6336(4)	2583(1)	1011(13)	51
C(11)	6202(4)	2821(1)	1329(14)	54
C(12)	5661(5)	2892(1)	2291(15)	56
C(13)	5226(4)	2733(1)	3043(13)	58
C(14)	5367(4)	2490(1)	2779(12)	44
C(15)	6379(4)	1680(1)	3613(14)	52
C(16)	6809(3)	1845(1)	2424(14)	52
C(17)	6889(4)	2072(1)	−183(14)	63
C(18)	6382(4)	1782(2)	5406(15)	67
C(19)	6713(4)	1434(1)	3644(15)	70
C(2′)	4099(4)	1873(2)	1531(15)	63
C(3′)	3470(4)	1769(2)	1403(16)	69
C(3a′)	3370(4)	1622(1)	2806(14)	49
C(4′)	2843(4)	1473(2)	3361(15)	62
C(5′)	2935(4)	1353(1)	4838(16)	61
C(6′)	3533(5)	1379(1)	5736(14)	62
C(7′)	4075(4)	1527(1)	5212(14)	52
C(7a′)	3978(4)	1647(1)	3743(13)	42
C(s)	2500	2500	−333(93)	290(22)
		45		
O(1)	65798(19)	19109(8)	53527(12)	64
N(1)	52267(17)	13169(8)	43325(11)	36
N(2)	33115(20)	21329(9)	13944(14)	47
C(1)	43926(19)	7743(9)	41672(14)	33
C(2)	35945(21)	4714(10)	47966(15)	38
C(3)	30057(21)	−848(10)	45124(16)	41
C(4)	32036(21)	−3288(10)	36268(16)	42
C(5)	40042(21)	−182(10)	29964(15)	37
C(6)	46082(19)	5327(8)	32671(13)	32
C(7)	55266(19)	9739(9)	27523(13)	31
C(8)	69054(20)	7685(9)	23070(14)	34
C(9)	74821(21)	1810(9)	27238(14)	37
C(10)	87640(22)	1059(10)	31654(15)	40
C(11)	98017(23)	6207(11)	32831(19)	48
C(12)	94944(21)	11387(10)	25690(16)	44
C(13)	79195(20)	13132(9)	25536(15)	37
C(14)	74525(22)	15359(10)	34997(15)	39
C(15)	61599(19)	13384(9)	35944(13)	33
C(16)	92445(30)	−4934(12)	35854(23)	56
C(17)	98113(31)	9328(16)	15630(21)	61
C(18)	104447(29)	16819(14)	28613(27)	64
C(19)	54489(24)	16575(10)	51581(15)	43
C(20)	42433(26)	17511(10)	57496(17)	48
C(21)	29102(31)	18833(13)	53345(24)	66
C(22)	18542(43)	20358(15)	59198(34)	88
C(23)	21288(52)	20347(14)	68999(33)	92
C(24)	34365(50)	18986(16)	73036(82)	84
C(25)	45146(37)	17645(13)	67390(20)	65
C(26)	41653(22)	19430(10)	21789(16)	40
C(27)	45936(20)	13611(9)	20535(13)	34
C(28)	39466(20)	11693(10)	11326(14)	38
C(29)	39375(25)	6296(11)	6057(16)	47
C(30)	31616(29)	6030(14)	−2760(18)	60
C(31)	24045(29)	11053(15)	−6398(19)	63
C(32)	23826(26)	16403(14)	−1436(18)	56
C(33)	31578(22)	16678(10)	7466(15)	43
O(2))	32408(56)	33502(19)	30111(32)	210
C(34)	29392(56)	36405(23)	36647(31)	111
C(35)	35960(48)	42373(23)	38698(29)	115
C(36)	17811(69)	34679(28)	42737(40)	162

(U_{eq} = 1/3 trace of diagonalized *U*), bond lengths, and bond angles appear in Tables 2–4, respectively. Hydrogen atom parameters, anisotropic thermal parameters, torsion angles, and measured and calculated structure factor amplitudes for the three structures are provided as supplementary material.[4]

Discussion of crystal structures

The crystal structure of compound **36** consists of centrosymmetric hydrogen-bonded dimers (N(1)—H(N)···O(2-*x*,-*y*,2-*z*), H···O = 2.00, N···O = 2.864(5) Å, N—H···O = 157°). The junction between the cyclohexene and cyclopentanone rings (at C(4)—C(8)) is *trans* (see Fig. 1).[5] The indole moiety is planar to within 0.030(7) Å. The five-membered C(2–4),C(9–10) ring has a slightly distorted C(4)-envelope conformation, and the C(4–9) cyclohexene ring has a semiplanar conformation with C(4) displaced from the approximate plane of the other five

[4]Supplementary material mentioned in the text may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0R6.

Tables of hydrogen atom coordinates, and of bond lengths and angles involving hydrogen atoms, have also been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

[5]The crystallographic atom numbering shown in Fig. 1, which differs from that shown in schemes above, is employed in this section. Atom labels in Tables 4–7 correspond to those in Fig. 1.

TABLE 5. Bond lengths (Å) with estimated standard deviations in parentheses

Bond	Length (Å)	Bond	Length (Å)
		36	
O—C(3)	1.223(5)	C(7)—C(8)	1.328(6)
N(1)—C(2)	1.380(5)	C(7)—C(19)	1.490(6)
N(1)—C(16)	1.377(5)	C(8)—C(9)	1.481(6)
C(2)—C(3)	1.448(6)	C(9)—C(10)	1.500(6)
C(2)—C(10)	1.356(5)	C(10)—C(11)	1.416(6)
C(3)—C(4)	1.528(6)	C(11)—C(12)	1.395(6)
C(4)—C(5)	1.520(6)	C(11)—C(16)	1.411(6)
C(4)—C(9)	1.543(6)	C(12)—C(13)	1.372(6)
C(5)—C(6)	1.548(6)	C(13)—C(14)	1.402(7)
C(5)—C(17)	1.532(7)	C(14)—C(15)	1.373(6)
C(5)—C(18)	1.522(6)	C(15)—C(16)	1.394(6)
C(6)—C(7)	1.512(6)		
		60	
Cl—C(s)	1.76(4)	C(9)—C(10)	1.419(10)
N(1)—C(2)	1.382(8)	C(9)—C(14)	1.397(10)
N(1)—C(14)	1.361(8)	C(10)—C(11)	1.386(10)
N(1′)—C(3)	1.448(9)	C(11)—C(12)	1.362(11)
N(1′)—C(2′)	1.364(11)	C(12)—C(13)	1.370(11)
N(1′)—C(7a′)	1.381(9)	C(13)—C(14)	1.407(10)
C(2)—C(3))	1.493(9)	C(15)—C(16)	1.574(11)
C(2)—C(8))	1.368(9)	C(15)—C(18)	1.568(14)
C(3)—C(4)	1.557(10)	C(15)—C(19)	1.527(10)
C(4)—C(5)	1.497(12)	C(2′)—C(3′)	1.348(11)
C(4)—C(15)	1.538(11)	C(3′)—C(3a′)	1.421(12)
C(5)—C(6)	1.313(10)	C(3a′)—C(4′)	1.393(11)
C(6)—C(7)	1.512(10)	C(3a′)—C(7a′)	1.403(10)
C(7)—C(8)	1.520(10)	C(4′)—C(5′)	1.389(13)
C(7)—C(16)	1.534(11)	C(5′)—C(6′)	1.372(12)
C(7)—C(17)	1.511(10)	C(6′)—C(7′)	1.399(11)
C(8)—C(9)	1.468(10)	C(7′)—C(7a′)	1.387(10)
		45	
O(1)—C(19)	1.220(3)	C(12)—C(17)	1.536(3)
N(1)—C(1)	1.440(2)	C(12)—C(18)	1.531(3)
N(1)—C(15)	1.421(2)	C(13)—C(14)	1.516(3)
N(1)—C(19)	1.379(2)	C(14)—C(15)	1.321(3)
N(2)—C(26)	1.374(3)	C(19)—C(20)	1.486(3)
N(2)—C(33)	1.367(3)	C(20)—C(21)	1.379(4)
C(1)—C(2)	1.383(3)	C(20)—C(25)	1.389(4)
C(1)—C(6)	1.400(3)	C(21)—C(22)	1.391(4)
C(2)—C(3)	1.388(3)	C(22)—C(23)	1.376(5)
C(3)—C(4)	1.380(3)	C(23)—C(24)	1.354(5)
C(4)—C(5)	1.394(3)	C(24)—C(25)	1.380(4)
C(5)—C(6)	1.379(3)	C(26)—C(27)	1.359(3)
C(6)—C(7)	1.527(3)	C(27)—C(28)	1.444(3)
C(7)—C(8)	1.566(3)	C(28)—C(29)	1.397(3)
C(7)—C(15)	1.508(2)	C(28)—C(33)	1.409(3)
C(7)—C(27)	1.523(3)	C(29)—C(30)	1.384(3)
C(8)—C(9)	1.501(3)	C(30)—C(31)	1.391(4)
C(8)—C(13)	1.557(3)	C(31)—C(32)	1.367(4)
C(9)—C(10)	1.328(3)	C(32)—C(33)	1.394(3)
C(10)—C(11)	1.501(3)	O(2)—C(34)	1.172(5)
C(10)—C(16)	1.498(3)	C(34)—C(35)	1.470(6)
C(11)—C(12)	1.527(3)	C(34)—C(36)	1.499(7)
C(12)—C(13)	1.544(3)		

atoms of the ring (see Table 7). There is evidence of considerable steric strain at the junction of the two five-membered rings. The (N(1),C(3)]C(2)—C(10)[C(4),C(11)) grouping is significantly non-planar (maximum deviation from the mean plane is 0.091(6) Å) and there is substantial angular distortion about both C(2) and C(10) (see Table 6). The short C(2)—C(3) distance of 1.448 Å is indicative of conjugation between the indole and carbonyl groups, while the C(3)—C(4) bond of 1.528 Å is long for a $C(sp^2)$—$C(sp^3)$ single bond. The detailed molecular geometry reflects both steric and electronic effects but is generally as expected.

Compound **60** crystallizes as a hemi-dichloromethane solvate with the CH_2Cl_2 molecule situated on a crystallographic C_2 axis. The crystal structure consists of well-separated molecules of **60** and CH_2Cl_2, the shortest intermolecular distances between non-hydrogen atoms being N(1)···C(11)$(1 - x, 1/2 - y, 1/2 + z)$ = 3.44(1) Å. The molecule **60** consists of a substituted indolo[2,3-*b*]bicyclo[3.2.2]non-6-ene ring system (Fig. 1). The indole moiety fused to the bicyclic system is planar within 0.03(1) Å, and both the 1-indolyl substituent at C(3) and the C(4)–C(5)=C(6)–C(7) group are planar within experimental error. As expected, there is less strain at the junction between the fused indole moiety and the seven-membered ring(s) of the bicyclo[3.2.2.] nonene system in **60** than at the corresponding junction between two five-membered rings in **36**. Bond lengths and angles (Tables 3 and 4) are generally as expected, with steric lengthening of some bonds between substituted atoms (e.g., C(3)—C(4) = 1.557, C(7)—C(8) = 1.520, C(15)—C(16) = 1.574, and C(15)—C(18) = 1.568 Å).

The solid state structure of **45**·Me_2CO consists of molecules of **45** linked into infinite chains by N—H···O hydrogen bonds (N(2)—H(N2)···O(1)$(x - 1/2, 1/2 - y, z - 1/2)$, H···O = 2.25(3), N···O = 2.974(2) Å, N—H···O = 144(2)°) and well-separated acetone solvate molecules. The junction between the cyclopentene and cyclohexene rings (at C(8)—C(13)) is *cis* (see Fig. 1). Within the central system of four fused rings, the five-membered heterocyclic ring has a distorted C(15)-envelope conformation, the cyclopentene ring has a C(8)-envelope conformation, the cyclohexene ring has a semiplanar conformation with C(12) displaced from the approximate plane of the other five ring atoms, and the C(1–6) aromatic ring is planar within experimental error. The 3-indolyl substituent at C(7) and the phenyl group at C(19) are planar to within 0.014(2) Å and experimental error, respectively. The geometry about N(1) is nearly planar, the bond lengths involving this atom being consistent with interactions of N(1) with the three adjacent π-systems (the C(1–6) aromatic ring, the carbonyl group, and the C(14)=C(15) double bond). The angle between normals to the N(1) coordination group and the C(19)-carbonyl group mean planes (usually near zero for amides) is 29°. A weak intramolecular C—H···O interaction may be at least partially responsible for this (C(14)—H(14)···O, H···O = 2.51(2), C···O = 2.913(3) Å, C—H···O = 107(2)°). The C(20–25) phenyl ring is twisted 43° out of the plane of the carbonyl group. Strain in the fused ring system is indicated by a 0.140(2) Å deviation of N(1) from the C(1–6) mean plane, a significant non-planarity about the C(14)=C(15) double bond, and the lengthening of several intra-annular bonds (C(6)—C(7) = 1.527, C(7)—C(8) = 1.566, C(8)—C(13) = 1.557, and C(12)-C(13) = 1.544 Å). Remaining aspects of the molecular geometry (Tables 5–7) are as expected.

TABLE 6. Bond angles (deg) with estimated standard deviations in parentheses

Bonds	Angle (deg)	Bonds	Angle (deg)
	36		
C(2)—N(1)—C(16)	106.6(4)	C(8)—C(7)—C(19)	122.3(5)
N(1)—C(2)—C(3)	135.5(5)	C(7)—C(8)—C(9)	120.7(4)
N(1)—C(2)—C(10)	110.9(4)	C(4)—C(9)—C(8)	111.0(4)
C(3)—C(2)—C(10)	113.1(4)	C(4)—C(9)—C(10)	102.0(4)
O—C(3)—C(2)	129.6(5)	C(8)—C(9)—C(10)	125.7(4)
O—C(3)—C(4)	127.3(5)	C(2)—C(10)—C(9)	109.0(4)
C(2)—C(3)—C(4)	103.1(4)	C(2)—C(10)—C(11)	107.4(4)
C(3)—C(4)—C(5)	124.4(4)	C(9)—C(10)—C(11)	141.9(5)
C(3)—C(4)—C(9)	103.7(4)	C(10)—C(11)—C(12)	134.3(5)
C(5)—C(4)—C(9)	113.8(4)	C(10)—C(11)—C(16)	106.0(5)
C(4)—C(5)—C(6)	105.9(4)	C(12)—C(11)—C(16)	119.7(5)
C(4)—C(5)—C17)	110.7(4)	C(11)—C(12)—C(13)	118.8(5)
C(4)—C(5)—C(18)	111.4(4)	C(12)—C(13)—C(14)	120.6(5)
C(6)—C(5)—C(17)	110.4(4)	C(13)—C(14)—C(15)	122.3(5)
C(6)—C(5)—C(18)	109.8(4)	C14)—C(15)—C(16)	116.9(5)
C(17)—C(5)—C(18)	108.6(4)	N(1)—C(16)—C(11)	109.1(5)
C(5)—C(6)—C(7)	119.2(4)	N(1)—C(16)—C(15)	129.1(5)
C(6)—C(7)—C(8)	122.5(4)	C(11)—C(16)—C(15)	121.7(5)
C(6)—C(7)—C(19)	115.1(5)		
	60		
C(2)—N(1)—C(14)	109.6(6)	C(9)—C(10)—C(11)	118.1(7)
C(3)—N(1′)—C(2′)	127.5(7)	C(10)—C(11)—C(12)	122.1(7)
C(3)—N(1′)—C(7a′)	124.3(7)	C(11)—C(12)—C(13)	122.2(7)
C(2′)—N(1′)—C(7a′)	107.6(6)	C(12)—C(13)—C(14)	116.6(8)
N(1)—C(2)—C(3)	119.3(6)	N(1)—C(14)—C(9)	107.9(6)
N(1)—C(2)—C(8)	109.9(6)	N(1)—C(14)—C(13)	129.2(7)
C(3)—C(2)—C(8)	130.6(6)	C(9)—C(14)—C(13)	122.8(7)
N(1′)—C(3)—C(2)	111.5(6)	C(4)—C(15)—C(16)	110.3(7)
N(1′)—C(3)—C(4)	111.9(6)	C(4)—C(15)—C(18)	110.9(7)
C(2)—C(3)—C(4)	111.9(6)	C(4)—C(15)—C(19)	107.5(7)
C(3)—C(4)—C(5)	108.4(7)	C(16)—C(15)—C(18)	111.0(7)
C(3)—C(4)—C(15)	115.1(6)	C(16)—C(15)—C(19)	108.8(6)
C(5)—C(4)—C(15)	112.3(7)	C(18)—C(15)—C(19)	108.2(7)
C(4)—C(5)—C(6)	116.3(8)	C(7)—C(16)—C(15)	115.8(6)
C(5)—C(6)—C(7)	122.1(7)	N(1′)—C(2′)—C(3′)	110.2(8)
C(6)—C(7)—C(8)	107.9(5)	C(2′)—C(3′)—C(3a′)	108.0(8)
C(6)—C(7)—C(16)	105.8(6)	C(3′)—C(3a′)—C(4′)	135.1(8)
C(6)—C(7)—C(17)	109.9(7)	C(3′)—C(3a′)—C(7a′)	105.6(7)
C(8)—C(7)—C(16)	109.3(6)	C(4′)—C(3a′)—C(7a′)	119.3(8)
C(8)—C(7)—C(17)	114.4(6)	C(3a′)—C(4′)—C(5′)	118.7(8)
C(16)—C(7)—C(17)	109.2(6)	C(4′)—C(5′)—C(6′)	121.1(7)
C(2)—C(8)—C(7)	124.1(6)	C(5′)—C(6′)—C(7′)	121.7(8)
C(2)—C(8)—C(9)	105.3(6)	C(6′)—C(7′)—C(7a′)	116.9(8)
C(7)—C(8)—C(9)	130.5(6)	N(1′)—C(7a′)—C(3a′)	108.6(7)
C(8)—C(9)—C(10)	134.7(7)	N(1′)—C(7a′)—C(7′)	129.2(7)
C(8)—C(9)—C(14)	107.2(7)	C(3a′)—C(7a′)—C(7′)	122.3(7)
C(10)—C(9)—C(14)	118.1(7)	Cl—C(s)—Cl*	110(4)
	45		
C(1)—N(1)—C(15)	106.27(15)	C(8)—C(13)—C(14)	102.7(2)
C(1)—N(1)—C(19)	128.8(2)	C(12)—C(13)—C(14)	115.2(2)
C(15)—N(1)—C(19)	122.2(2)	C(13)—C(14)—C(15)	109.1(2)
C(26)—N(2)—C(33)	109.0(2)	N(1)—C(15)—C(7)	108.68(15)
N(1)—C(1)—C(2)	128.4(2)	N(1)—C(15)—C(14)	136.8(2)
N(1)—C(1)—C(6)	109.7(2)	C(7)—C(15)—C(14)	114.1(2)
C(2)—C(1)—C(6)	121.5(2)	O(1)—C(19)—N(1)	120.2(2)
C(1)—C(2)—C(3)	118.1(2)	O(1)—C(19)—C(20)	121.3(2)
C(2)—C(3)—C(4)	121.1(2)	N(1)—C(19)—C(20)	118.3(2)
C(3)—C(4)—C(5)	120.3(2)	C(19)—C(20)—C(21)	121.3(2)
C(4)—C(5)—C(6)	119.5(2)	C(19)—C(20)—C(25)	118.3(2)
C(1)—C(6)—C(5)	119.4(2)	C(21)—C(20)—C(25)	120.1(3)
C(1)—C(6)—C(7)	108.6(2)	C(20)—C(21)—C(22)	119.1(3)

TABLE 6 (*concluded*)

Bonds	Angle (deg)	Bonds	Angle (deg)
C(5)—C(6)—C(7)	132.0(2)	C(21)—C(22)—C(23)	120.3(4)
C(6)—C(7)—C(8)	122.5(2)	C(22)—C(23)—C(24)	120.4(3)
C(6)—C(7)—C(15)	99.98(15)	C(23)—C(24)—C(25)	120.5(4)
C(6)—C(7)—C(27)	109.51(15)	C(20)—C(25)—C(24)	119.6(4)
C(8)—C(7)—C(15)	100.03(15)	N(2)—C(26)—C(27)	110.2(2)
C(8)—C(7)—C(27)	111.44(15)	C(7)—C(27)—C(26)	127.4(2)
C(15)—C(7)—C(27)	112.1(2)	C(7)—C(27)—C(28)	126.2(2)
C(7)—C(8)—C(9)	112.5(2)	C(26)—C(27)—C(28)	106.3(2)
C(7)—C(8)—C(13)	102.31(15)	C(27)—C(28)—C(29)	134.7(2)
C(9)—C(8)—C(13)	112.1(2)	C(27)—C(28)—C(33)	106.7(2)
C(8)—C(9)—C(10)	125.3(2)	C(29)—C(28)—C(33)	118.6(2)
C(9)—C(10)—C(11)	121.7(2)	C(28)—C(29)—C(30)	119.1(2)
C(9)—C(10)—C(16)	121.9(2)	C(29)—C(30)—C(31)	120.8(3)
C(11)—C(10)—C(16)	116.4(2)	C(30)—C(31)—C(32)	121.8(2)
C(10)—C(11)—C(12)	113.8(2)	C(31)—C(32)—C(33)	117.5(2)
C(11)—C(12)—C(13)	108.9(2)	N(2)—C(33)—C(28)	107.7(2)
C(11)—C(12)—C(17)	109.9(2)	N(2)—C(33)—C(32)	130.2(2)
C(11)—C(12)—C(18)	109.3(2)	C(28)—C(33)—C(32)	122.1(2)
C(13)—C(12)—C(17)	109.1(2)	O(2)—C(34)—C(35)	120.7(6)
C(13)—C(12)—C(18)	111.0(2)	O(2)—C(34)—C(36)	123.3(6)
C(17)—C(12)—C(18)	108.5(2)	C(35)—C(34)—C(36)	115.8(4)
C(8)—C(13)—C(12)	113.1(2)		

TABLE 7. Intra-annular torsion angles (deg) with standard deviations in parentheses

Atoms	Value (deg)
36	
C(10)—C(2)—C(3)—C(4)	−15.2(6)
C(2)—C(3)—C(4)—C(9)	27.2(5)
C(3)—C(4)—C(9)—C(10)	−29.1(5)
C(4)—C(9)—C(10)—C(2)	21.0(5)
C(3)—C(2)—C(10)—C(9)	−4.0(6)
C(9)—C(4)—C(5)—C(6)	−55.5(5)
C(4)—C(5)—C(6)—C(7)	30.9(6)
C(5)—C(6)—C(7)—C(8)	−6.9(8)
C(6)—C(7)—C(8)—C(9)	5.3(8)
C(7)—C(8)—C(9)—C(4)	−28.8(7)
C(5)—C(4)—C(9)—C(8)	56.7(5)
60	
C(8)—C(2)—C(3)—C(4)	6.9(11)
C(2)—C(3)—C(4)—C(5)	−67.4(8)
C(3)—C(4)—C(5)—C(6)	78.7(9)
C(4)—C(5)—C(6)—C(7)	2.9(12)
C(3)—C(2)—C(8)—C(7)	0.8(12)
C(5)—C(6)—C(7)—C(8)	−71.1(9)
C(6)—C(7)—C(8)—C(2)	49.8(10)
C(8)—C(2)—C(3)—C(4)	6.9(11)
C(2)—C(3)—C(4)—C(15)	59.3(9)
C(3)—C(4)—C(15)—C(16)	−83.9(8)
C(4)—C(15)—C(16)—C(7)	8.5(9)
C(8)—C(7)—C(16)—C(15)	67.0(8)
C(16)—C(7)—C(8)—C(2)	−64.8(9)
C(3)—C(2)—C(8)—C(7)	0.8(12)

TABLE 7 (*concluded*)

Atoms	Value (deg)
C(15)—C(4)—C(5)—C(6)	−49.6(10)
C(4)—C(5)—C(6)—C(7)	2.9(12)
C(5)—C(6)—C(7)—C(16)	45.8(9)
C(6)—C(7)—C(16)—C(15)	−48.9(8)
C(4)—C(15)—C(16)—C7)	8.5(9)
C(5)—C(4)—C(15)—C(16)	40.7(9)
45	
C(15)—N(1)—C(1)—C(6)	−10.8(2)
N(1)—C(1)—C(6)—C(7)	−6.0(2)
C(1)—C(6)—C(7)—C(15)	19.0(2)
C(6)—C(7)—C(15)—N(1)	−25.9(2)
C(1)—N(1)—C(15)—C(7)	23.7(2)
C(15)—C(7)—C(8)—C(13)	−31.9(2)
C(7)—C(8)—C(13)—C(14)	32.1(2)
C(8)—C(13)—C(14)—C(15)	−20.0(2)
C(13)—C(14)—C(15)—C(7)	−1.4(2)
C(8)—C(7)—C(15)—C(14)	21.9(2)
C(13)—C(8)—C(9)—C(10)	−6.9(3)
C(8)—C(9)—C(10)—C(11)	−0.7(3)
C(9)—C(10)—C(11)—C(12)	−21.3(3)
C(10)—C(11)—C(12)—C(13)	48.6(3)
C(11)—C(12)—C(13)—C(8)	−56.8(2)
C(9)—C(8)—C(13)—C(12)	36.1(2)