A GENERAL APPROACH TO THE TOTAL SYNTHESIS OF YUEHCHUKENE AND ITS
ANALOGUES. A NOVEL ANTI-IMPLANTATION AGENT

by

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ABSTRACT

This thesis concerns a general approach to the total synthesis of yuehchukene 2 and its analogues. Yuehchukene has a potent anti-implantation activity. It also lacks the estrogenic side effect of most compounds with similar biological activity. However, it is somewhat unstable and this could bring some problems when administered to humans.

Development of a versatile synthesis of yuehchukene capable of producing a variety of analogous structures in order to fully exploit the pharmacological properties of this novel molecular system and/or to make a more stable product without losing its biological properties was the central objective of this project. Specifically, the total synthesis of yuehchukene 2 and its analogue 6a-epi-yuehchukene 25 are described.

After some preliminary studies, it was found that a kinetic carboxylation (lithium 2,6-di-tert-butyl-4-methylphenoxide, CO₂) of isophorone 26 followed by a reduction (NaBH₄) produced stereoselectively cis-hydroxyacid 46 in good yield. The latter was transformed into indoleacid 48 by dibenzoylation (PhCOCl, DMAP) and treatment with indolylmagnesium iodide. The key intermediate trans-ketone 60 was obtained by treatment of 48 with oxalyl chloride followed by indolylmagnesium iodide. Epimerization of 60 to the more stable cis-ketone 24 was accomplished quantitatively under basic conditions (MeONa/MeOH, reflux). Reduction (LiAlH₄) and dibenzoylation (PhCOCl, DMAP, Et₃N) of 24 furnished the benzoate 68 which was subjected to a nucleophilic substitution with indolylmagnesium iodide to give N-benzoyl yuehchukene 69. The latter transformation also gave the interesting compound 75 which was submitted to an X-Ray diffraction analysis. The total synthesis of yuehchukene 2 was then achieved by methanolysis (NaOMe/MeOH).
As far as the synthesis of 6a-epi-yuehchukene 25 is concerned, it was found that, after a thorough study, it was best to transform trans-ketone 60 into its SEM-derivative 85 (SEM-Cl, NaH). The latter was reduced (DIBAL) and acetylated (Ac₂O, DMAP, Et₃N) to produce stereoselectively the acetate 87 which, by treatment with indolylmagnesium iodide, furnished SEM-trans-yuehchukene 88. The newly incorporated indole group bears a 1,3-diaxial-like interaction with the β-methyl group at C-7. Unlike 88, tosylacetate 82 gave the compound 84. Finally, the total synthesis of 6a-epi-yuehchukene was accomplished by deprotection of the indole system. Various compounds from this study are now under investigation at WHO and in Hong Kong but, unfortunately, biological results are unavailable at present.
60 \( R = H \)
85 \( R = \text{SEM} \)

68

75

82 \( R = \text{Ts} \)
87 \( R = \text{SEM} \)

84


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The following is a list of abbreviations that have been used throughout this thesis:

- **Ac** = acetate
- **brs** = broad singlet
- **brd** = broad doublet
- **brdd** = broad doublet of doublets
- **CIPE** = complex-induced proximity effect
- **d** = doublet
- **dd** = doublet of doublets
- **ddd** = doublet of doublets of doublets
- **DMAP** = 4-dimethylaminopyridine
- **dq** = doublet of quartets
- **dt** = doublet of triplets
- **dtq** = doublet of triplets of quartets
- **DIBAL** = di-iso-butylaluminum hydride
- **ether** = diethylether
- **GC** = gas liquid chromatography
- **h** = hour
- **[H]** = reduction
- **HMPA** = hexamethylphosphoramide
- **IR** = infrared
- **M.** = *Murraya*
- **m** = multiplet
- **MMC** = methylmagnesium carbonate
- **MS** = mass spectroscopy
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<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
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<td>PD</td>
<td>pregnancy day</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
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<td>PPE</td>
<td>polyphosphate ester</td>
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<td>sat. aq.</td>
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<tr>
<td>SEM</td>
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1. INTRODUCTION

1.1. GENERAL REMARKS

The genus *Murraya*, of the plant family *Rutaceae*, 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. Several species are widespread in the area, notably *M. paniculata*, *M. koenigii* and *M. exotica*, but others are often very localized in their distribution.\(^1\)

Chemically *Murraya* species are characterized by the occurrence of carbazole alkaloids which are, to date, restricted to the *Rutaceae*\(^2\). Murrayanine 1 is a typical example:

![Murrayanine](image)

In addition to carbazoles, *Murraya* species have been reported to contain furoquinoline and acridone alkaloids\(^3,4\) and are also a good source of coumarins\(^5,6\) and flavonoids\(^7\).

Recently yuehchukene 2, a novel type of dimeric indole natural product, has been isolated from the roots of *Murraya paniculata* in trace quantities (<18 ppm)\(^8\). Its name derives from the word yueh-chu which is the name of the plant in Chinese.
Species | Yuehchukene (ppm) | Girinimbine | 8-Prenylated coumarins
---|---|---|---
*M. paniculata* | 13.9 | - | +
*M. alata* | 20.6 | - | - +
*M. exotica* | 26.1 | - | +
*M. crenulata* | - | + | -
*M. euchrestifolia* | - | + | -
*M. koenigii* | - | + | -
*M. microphylla* | - | + | -
*M. siamensis* | - | + | -

**TABLE 1**
Owing to the low yield of 2, a survey of the roots of other Murraya species was carried out in an attempt to find better sources. To date, this survey has encompassed eight of the thirteen species within the genus and the results are summarized in Table 1.

Only three species contained yuehchukene. *M. exotica* was found to contain the highest average yield of yuehchukene, although still in low yield, and *M. alata* showed a content second to that of *M. exotica*. These three species were also found to be sources of the 8-prenylated coumarins 3-8 (Figure 1). However, the other five species did not produce detectable amounts of yuehchukene nor coumarins. Instead each of them yielded mainly the carbazole girinimbine 10.

![Murraya species chemical structure](image)

**10**

Apparently, there was no overlap between these two groups of species and, therefore, this study also served to establish a chemotaxonomic division of Murraya species.

Search of the stem bark of *M. paniculata* also revealed amounts of yuehchukene 2 although in even lower yield (about 5 ppm).
FIGURE 1
1.2. PHARMACOLOGY

The most interesting feature about yuehchukene is its biological activity. In fact, it had previously escaped notice because of its low concentration and instability under normal laboratory conditions and was found only because of the marked biological activity of a crude extract from the roots of *Murraya paniculata*[^1^].

In China it was already known that roots of *M. paniculata* and *M. exotica* appear to help in the treatment of numerous ailments including headache, toothache, and rheumatism[^9^]. The leaves, bark and fruit of *M. paniculata* are used as an astringent and antidysenteric[^12^]. Petroleum ether extracts of the leaves of *M. paniculata* show strong cardiac depressant activity to frog heart, and antispasmodic activity on rat intestine[^13^].

As far as plant materials for fertility control are concerned, quite a number of Chinese plants are known to have different fertility regulating properties[^1^]. However, there was no record ascribing any *Murraya* species the property of fertility control in humans[^1^]. Originally, as a part of a program of the World Health Organization (WHO) to develop research on plants alleged to have fertility regulation properties, Kong et al[^8^] were pursuing the isolation of an active compound from the roots of *M. paniculata* with presumed ecbolic properties when they observed a crude extract with strong anti-implantation activity in rats. A laborious process of isolation of the active compound yielded the unstable natural product yuehchukene in minute amounts.

Yuehchukene was administered to rats from pregnancy day 1 to pregnancy day 6 (PD[^1^]^-^[^6^]) at 2 mg/kg and autopsied on pregnancy day 16. It was found to be 100% active. The experimental rats maintained the same growth rate as the control rats until pregnancy day 10 when fetal development caused an abrupt rise
in the body weight of the pregnant rats of the control while the experimental group remained at the same level until autopsy.

Table 2 shows the results of a complete study to afford a precise timing to the anti-implantation effect.

Thus, when yuehchukene was administered at 2 mg/kg during PD\textsubscript{1-6} or at 2.5 mg/kg on PD\textsubscript{1-2} or PD\textsubscript{3-4}, it was 100% effective; whereas when administered at 2.5 mg/kg on PD\textsubscript{5-6} or PD\textsubscript{7-8} all rats were pregnant. A subsequent experiment (No.6 in Table 2) showed that at a dose of 3 mg/kg on PD\textsubscript{2} only, yuehchukene was also 100% active.

As a second feature and perhaps with the same importance, the natural product lacks estrogenic activity, a problematic side effect of most anti-implantation compounds\textsuperscript{11}.

The fact that yuehchukene would need to be taken only post-intercourse during the fertile period, and therefore capable of being unambiguously timed, is an advantage over other contraceptive compounds. It would eventually be more accessible economically and more convenient to use than, for example, the anti-ovulatory pill. However, the fact that yuehchukene is relatively unstable might give some problems when administered to humans.

1.3. STRUCTURE ELUCIDATION

The structure of this white amorphous powder (m.p. 127\textdegree{}C) was elucidated by UV, MS, IR, \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR, and by X-Ray crystallography of its monoacetylated derivative\textsuperscript{15}.

The UV spectrum reveals the presence of an indole functionality ($\lambda_{\text{max}}$ 225, 283, 292 nm); its mass spectrum displays a molecular ion, which is
also the base peak, at \( m/z \) 366 and a peak at 351 due to a facile loss of a methyl radical; the IR spectrum shows absorptions at 3400 and 1618 cm\(^{-1}\) for the N-H and the olefinic stretching frequencies, respectively; and the \(^1\)H-NMR spectrum reveals all 26 protons, the major features being 3 methyl groups (\( \delta 0.86, 1.10, 1.66 \)), an olefinic proton (\( \delta 5.70 \), broad), 2 N-H systems (\( \delta 7.58 \) and \( \delta 8.00 \)) exchangeable with D\(_2\)O, nine protons in the aromatic zone, and an AMX system for the protons at C-6 (\( \delta 4.56 \) d, \( J=8.5 \)Hz) (see Figure 2), C-6a (\( \delta 3.15 \), dd, \( J=8.5,7 \)Hz) and C-10a (\( \delta 4.02 \), m) as determined by decoupling experiments. \(^1\)C-NMR further supports the assignment as it shows a triplet for C-8 at \( \delta 41.03 \), and singlet
for C-7 at δ33.41$^8$.

Finally, acetylation of yuehchukene gave a crystalline mono-N-acetyl derivative. An X-Ray diffraction study revealed it to be compound 11$^{15}$ (Figure 2). To prove that no rearrangement had occurred during acetylation, 11 was subjected to hydrolysis which gave yuehchukene 2 back$^{16}$.

The lack of optical activity ($[\alpha]_D^0=0^\circ$)$^8$ and the absence of a Cotton effect in its ORD spectrum$^{16}$ indicates that yuehchukene occurs naturally as a racemic modification.

**FIGURE 2$^+$**

\[2 \ R=H \]

\[11 \ R=Ac\]

$^+$The numbering system is in accord with the International Union of Pure and Applied Chemistry (IUPAC)$^{17}$ rule system. For clarity, the numbers corresponding to the indole substituent at C-6 are primed, and the same will apply for other substituents of other compounds throughout this thesis, especially when assigned by $^1$H-NMR spectroscopy.
1.4. BIOGENETIC CONSIDERATIONS

The fact that the natural product occurs as a racemic modification implies that its biosynthesis is not enantioselective, which is contrary to the usual pattern in nature.

Specifically, it has been suggested that it is formed from a non-enantioselective Diels-Alder cycloaddition of two units of 3-isoprenylindole 12 as shown in Scheme 1\(^8,18\).

![Scheme 1](image-url)
Thus, the Diels-Alder cycloaddition would proceed with an endo transition state giving a cis stereochemistry between protons at C-6a and C-10a (see intermediate 13). In the final step the intramolecular cyclization would proceed to give the more stable configuration at C-6.

The first record of dimers of this type in the Rutaceae family were for coumarins, a typical example being mexolide 15 (M. paniculata and M. exotica) (Scheme 2), the formation of which can be envisaged through the condensation of two molecules of the diene 14\(^1\),\(^9\). In all examples of coumarin dimers from the Rutaceae family the mode of cyclization is the same, with the variation in structure arising only from differing substitution patterns on the coumarin nucleus.

![Scheme 2](image)

The first report for a Diels-Alder nitrogen-containing dimer in the Rutaceae occurred in 1978\(^2\),\(^0\). Since that time a total of about 20 compounds have been reported\(^2\),\(^1\). Figure 3 shows the 4 different groups in which these natural products can be arranged according to their nitrogen-containing moiety. Each group is represented by
Group: Tyrosine

Alfileramine

Group: Tryptophan

Borreverine

Group: Indole

Yuehchukene

Group: 2-Quinolone

Pteledimerine

FIGURE 3
a typical example. In the indole group, yuehchukene 2 is the only known example.

The biosynthetic pathway for the formation of 3-isoprenylindole 12 has not been investigated, although there is some indication that 3-(3-methyl-2-butenyl)indole 16 might be a precursor (Scheme 3). As has been proposed for the biosynthesis of prenylated coumarins and quinoline alkaloids of the same plant family\textsuperscript{2}, the 3-methyl-2-butenyl group would undergo epoxidation, hydration and dehydration to form 3-isoprenylindole 12. Furthermore, 16, as a possible precursor, is supported by the recent isolation of the prenylindoles paniculidine A 17 and paniculidine B 18 (Figure 4) from the root bark of \textit{M. paniculata}\textsuperscript{2,2}.

\begin{center}
\textbf{SCHEME 3}
\end{center}
1.5. SYNTHETIC CONSIDERATIONS

The interesting features of yuehchukene 2 (see Section 1.2) have made it a target molecule for synthesis, especially because it occurs in the plant in small quantities (see Section 1.1).

The same group that isolated, characterized and studied the biological activity also developed a biomimetic synthesis of yuehchukene\textsuperscript{18}. The approach was based on the preparation of 3-isoprenylindole and its subsequent acid catalyzed Diels-Alder cycloaddition to 2 as shown in Scheme 4.

Thus, the N-\textit{p}-toluenesulfonyl derivative of 3-formylindole 19 was treated with the Grignard reagent derived from 3-chloro-2-methylprop-1-ene to give alcohol 20 in 80\% yield. Deprotection and dehydration was then carried out with ethanolic sodium hydroxide at 50\textdegree C to give 3-isoprenylindole in 70\% yield. Having in hand 12, the Diels-Alder cyclization was carried out utilizing catalytic amounts of trifluoroacetic acid at 50-60\textdegree C. Yuehchukene 2 was then obtained, albeit in only 10\% yield.

This biomimetic synthesis ruled out the possibility that samples of natural
SCHEME 4
yuehchukene contained a concealed potent anti-implantation compound since the synthetic racemic yuehchukene proved to have the same biological activity as the natural product.

Since Kong's synthesis, Wenkert et al.² ³ have developed a similar approach for the synthesis of 3-isoprenylindole. Their pathway is shown in Scheme 5.

N-benzenesulfonyl-3-bromoindole 21, the product of the base promoted reaction of 3-bromoindole with benzenesulfonyl chloride, was subjected to a metal-halogen exchange with tert-butyl lithium at -95°C and, subsequentially, with cuprous cyanide. The corresponding cuprate 22 was then immediately treated with 3-methyl-2-butenoyl chloride to form ketone 23 in 67% yield from 21. Lithium aluminum hydride reduction and base-promoted deprotection and dehydration afforded 3-isoprenylindole 12.

Development of a versatile stereoselective synthesis of yuehchukene capable of producing a variety of analogous structures in order to fully exploit the pharmacological potentials of this novel molecular system and/or to make a more stable product without losing its biological properties became, at this stage, highly desirable.

A retrosynthetic analysis was planned according to Scheme 6. The assembly of the target molecule was strategically envisaged so as to facilitate the required variations for the preparation of 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 24 could have an anti relationship to produce a trans junction of rings C and D in yuehchukene. This would give 6a-epi-yuehchukene 25 (also named trans-yuehchukene in this thesis). This strategy also has the advantage of starting from commercially inexpensive isophorone 26.
SCHEME 5

\[
\text{Br} \xrightarrow{\text{PHSO}_2\text{Cl}} \text{KOH} \rightarrow \text{Br} \xrightarrow{\text{SO}_2\text{Ph}} 21
\]

\[1)^{t-\text{BuLi}} \rightarrow -95^\circ\text{C} \rightarrow 2)^{\text{CuCN}}
\]

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{Cu(CN)Li}} & & \\
\text{Br} & \xrightarrow{\text{SO}_2\text{Ph}} & & \\
\text{Cu(CN)Li} & \rightarrow & & \\
\text{SO}_2\text{Ph} & \rightarrow & & \\
\text{LiAlH}_4 & \rightarrow & & \\
\end{align*}
\]

\[
\text{OH} \xrightarrow{\text{KOH/EtOH}} \rightarrow \text{H} \xrightarrow{\text{KOH/EtOH}} 12
\]

\[
\begin{align*}
\text{SO}_2\text{Ph} & \rightarrow & & \\
\text{SO}_2\text{Ph} & \rightarrow & & \\
\end{align*}
\]
SCHEME 6
Our goals were, firstly, another total synthesis of yuehchukene itself, with the concomitant possibility of improving the previous biomimetic synthesis, and secondly, the synthesis of an analogue.

Thus, this work has been divided into two parts:

1. Total Synthesis of (±)-Yuehchukene
2. Total Synthesis of (±)-6a-Epi-Yuehchukene.
2. RESULTS AND DISCUSSION

2.1. TOTAL SYNTHESIS OF (±)-YUEHCHUKENE

2.1.1. Indoleacid 48

As pointed out at the end of the last chapter, the first step consisted in
the functionalization of isophorone 26. Thus, at first, a direct methoxycarbonylation
of isophorone 26 was attempted to obtain ketoester 27.

\[
\begin{align*}
\text{CH}_3\text{O}-\text{C} & \\
\text{O} & \\
\end{align*}
\]

27

Unfortunately, the kinetic enolate 28 (see Scheme 7), generated with LDA
at -78°C, gave the O-acylated compound 29 as the only product with methyl
chloroformate in either THF or diethyl ether. On the other hand, 28 did not react
with methyl carbonate in THF. Isophorone 26 was recovered after the addition of
aqueous ammonium chloride.

Diene 29 was characterized by both IR and \(^1\)H-NMR. The IR spectrum
shows only one carbonyl absorption at 1765 cm\(^{-1}\) which corresponds to the
carbonyl of the carbonate group, and the \(^1\)H-NMR spectrum displays the two
vinyllic protons at 5.10 and 5.52 and the signal corresponding to the protons at
C-4 at δ2.05. This last signal appears as doublet of quartets ($J=1.5, 1.5$ Hz) because of its coupling with the vinylic proton at C-6 and the protons of the vinilyc methyl group at C-5.

In order to continue with the approach, a published route was momentarily chosen to prepare the required ester$^2$*, although in low yield (16%). Condensation of mesityl oxide and ethyl acetoacetate (Scheme 8) in the presence of zinc chloride gave the desired product 30 (ethyl ester instead of methyl ester as in 27) along
with the isomer 31 (32%) and isophorone 26 (10%).

Having ketoester 30 at hand, the route presented in scheme 9 was followed to obtain indole-ester 34. Thus, ketoester 30 was reduced with sodium borohydride in methanol to give cis-hydroxyester 32 in 71% yield. The epimeric alcohol 35 was also obtained in 23% yield. The approximate ratio of 3:1 in favor of the cis isomer 32 indicates preferential approach of NaBH₄ to the less hindered face of 30.
The IR spectra of both products reveal absorption bands of the hydroxyl and carbonyl groups at 3450 and 1740 cm$^{-1}$ for 32, and 3400 and 1725 cm$^{-1}$ for 35. As expected, the differentiation of the alcohols was readily made by $^1$H-NMR. It is well known that the relationship between protons at contiguous carbons in a 6-membered ring can be determined by the value of the coupling constant between them in its $^1$H-NMR spectrum$^{25}$; thus, the $J$ value between protons in an anti-periplanar relationship (axial-axial) has a typical value of 8-12 Hz, whereas that between protons in a syn-clinal relationship (equatorial-axial) is typically...
Results and Discussion / 23

2-5 Hz. The chemical shifts of protons at C-1 (doublet) and C-2 (multiplet) in 32 (see Scheme 9) appear at δ2.65 and 4.40, respectively, with a coupling constant between them of 6 Hz, whereas the signals of protons at C-1 (doublet) and C-6 (multiplet) in 35 appear at δ2.25 and 4.54 with a coupling constant of 10 Hz. Clearly, from these values, it is possible to deduce that the carboethoxy and the hydroxyl groups in 32 are in a cis relationship, whereas in 35 they are in a trans relationship. The assignments of the chemical shifts were proved by double resonance experiments; thus, irradiation at the signal of the proton at C-2 of 32 (δ4.40) simplified to a singlet the signal of the proton at C-1 (δ2.65); the same result was observed in the case of 35.

The ¹H-NMR spectrum of 32 also shows the signals of the gem-dimethyl group at C-6 at δ1.15 and 1.22 as singlets; the protons at the vinylic methyl group at δ1.72 as a broad singlet; the signals corresponding to the protons of the ethyl group at δ1.42 and 4.12 as triplet and quartet, respectively; the protons at C-4 as an AB system at δ1.66 and 2.07 with a coupling constant of 17 Hz; the O-H proton at δ2.34 as a broad signal which disappears in the presence of D₂O; and, finally, the vinylic proton at δ5.42 as a broad singlet.

The next transformation required an activation of the hydroxyl group of 32 so as to facilitate its displacement by the indole moiety (see Scheme 6, retrosynthetic analysis). Treatment of hydroxyester 32 with p-toluenesulfonyl chloride in the presence of various bases (DMAP, pyridine, Et₃N) gave the undesired product 36 as a result of overall elimination of water.

Fortunately, the desired activation of the hydroxyl group could be achieved by treatment of 32 with benzoyl chloride and DMAP²⁶ in dichloromethane at 5°C to obtain the allylic benzoate 33 as an oil in 85% yield (Scheme 9).
Its IR spectrum shows a broad absorption centered at 1725 cm\(^{-1}\) due to both carbonyl groups while the mass spectrum reveals the molecular ion at m/z 316 and the base peak at m/z 105 due to the relatively stable cation Ph\(\text{C}^{\text{\@}}\text{O}\). As expected\(^2\), the proton at C-2, in its \(^1\text{H}-\text{NMR}\) spectrum, is shifted to lower field by about 1.3 ppm with respect to the corresponding proton in hydroxyester 32; it appears at \(\delta 5.80\) as a multiplet. The spectrum also shows clearly the signals corresponding to the aromatic protons. Thus, the protons at the \textit{ortho} position appear at \(\delta 8.10\) as a doublet of doublets with \(J\) values of 7.6 and 1.3 Hz; the proton at the \textit{para} position at \(\delta 7.53\) as a triplet of triplets with \(J\) values of 7.6 and 1.3 Hz; and the protons at the \textit{meta} position at \(\delta 7.40\) as a doublet of doublets with both \(J\) values equal to 7.6 Hz.

Having in hand 33, the nucleophilic substitution of the benzoate group was attempted by utilizing indolylmagnesium iodide 37 (Figure 5) in ether at 5\(^\circ\)C. The desired indole-ester 34 (see Scheme 9) was obtained in 42% yield along with the isomer 39 (31%).

The choice of the activated indole as indolylmagnesium iodide 37 rather than indolylithium or sodium 38 was based on the known behavior of these
activated indoles towards electrophiles. The tendency is that the magnesium salt is the one which gives the highest ratio of C to N alkylation. On the other hand, indolylsodium (M=Na) is the nucleophile which gives the lowest C/N ratio. The solvent of the reaction is also important; thus, diethylether gives higher
C/N ratio than THF²⁷.

Indole-ester 34 was characterized by IR, MS and $^1$H-NMR spectra. 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 δ2.67 as a doublet with a $J$ value of 12 Hz due to the coupling with the proton at C-2 which appears at δ3.90 as a multiplet. Irradiation of the latter signal simplified the doublet at δ2.67 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 δ6.99 as a doublet with a $J$ value of 3.2 Hz due to the coupling with the N-H proton, which appears at δ7.92 as a broad signal. The coupling was again corroborated by double resonance experiments. The signals of the other aromatic protons are sufficiently resolved so as to assign each one of them. These assignments are based on the known chemical shifts of the protons of the posterior intermediate indoleacid 48 (see Scheme 15, p33) and are presented in Table 3.

The product 39 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 δ5.79 ($J$=10 and 4 Hz) and δ6.05 ($J$=10 and 2 Hz) being both coupled with the proton at C-1 which appears at δ2.95 as a doublet of doublets ($J$=4 and 2 Hz). These assignments were corroborated by double resonance experiments.

The stereochemistry of the molecule was assigned later by correlation with a posterior intermediate, namely, acid 57 (see p.39). This compound, which was
<table>
<thead>
<tr>
<th>Position</th>
<th>Chemical shift (δ)</th>
<th>Multiplicity</th>
<th>Coupling constant (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4'</td>
<td>7.61</td>
<td>doublet</td>
<td>8</td>
</tr>
<tr>
<td>5'</td>
<td>7.06</td>
<td>doublet of doublets</td>
<td>8,8</td>
</tr>
<tr>
<td>6'</td>
<td>7.15</td>
<td>doublet of doublets</td>
<td>8,8</td>
</tr>
<tr>
<td>7'</td>
<td>7.31</td>
<td>doublet</td>
<td>8</td>
</tr>
</tbody>
</table>

**TABLE 3**

obtained from a different approach and has a known stereochemistry (*vide supra*), was transformed into the ester 39 under the neutral conditions of ethanol, triphenylphosphine and diethylazodicarboxylate\(^2\,^9\) (Scheme 10).
Following similar transformations to those described above, the minor
trans-hydroxyester 35 (see Scheme 11) was transformed to trans-benzoate 40 and, in
turn, to the compounds 34 and 39 with practically the same yields and same ratio
of 34/39 as obtained with 33 as starting material. Therefore, it seems that a
carbocation intermediate or a similar species is involved in the overall conversion of
33 and 40 to the final products.

The next step required the hydrolysis of indole-ester 34 to the corresponding acid in accord with the retrosynthetic analysis (see Scheme 6).
Unfortunately, treatment of 34 with either aqueous sodium hydroxide in refluxing ethanol or trimethylsilyl iodide in refluxing acetonitrile did not afford the desired product 41 (Scheme 12); the starting material 34 was recovered unchanged.

Attempts to achieve a direct cyclization of 34 to ketone 42 (and thus obtain a more advanced intermediate) with one equivalent of potassium hydride in THF or dioxane, or one equivalent of LDA in THF also failed (Scheme 13). 34 was again recovered unchanged.

A direct conversion of ester 43 (see Scheme 14) to ketone 44 by reaction with indolylmagnesium iodide was also attempted. Although this route would give a
SCHEME 11
trans stereochemistry of rings C and D in 45, as opposed to the cis stereochemistry of yuehchukene 2, it would provide a synthesis of an analogue of yuehchukene which is one of the objectives of this project. A possible epimerization of either 43 or 44 could allow enter into the cis series.
Treatment of indole-ester 34 with $p$-toluenesulfonyl chloride in the presence of potassium hydride afforded the N-tosyl derivative 43 in 90% yield. The IR spectrum of the latter shows the expected disappearance of the N-H band while in the $^1$H-NMR spectrum the presence of a singlet at $\delta$2.34 due to the methyl of the tosyl group was clearly evident.

In the next reaction, tosylester 43 was treated with indolylmagnesium iodide. Unfortunately, refluxing in either diethyl ether or THF did not yield ketone 44. The starting material was again recovered. With the more reactive nucleophile, $n$-butyllithium, ketone 44a was obtained, but the latter was of little value to the objectives of the project.

As a possible solution to all these negative results, it was planned to make the required changes to the cumbersome ester group in an earlier stage of the sequence. The new strategy is described in Scheme 15.

Fortunately, hydrolysis of the ester functionality could be indeed accomplished by treatment of hydroxyester 32 with aqueous sodium hydroxide in ethanol at room temperature for 5 days to give hydroxyacid 46 in 75% yield after the usual acidic work-up of the reaction mixture.
The IR spectrum of this crystalline product (m.p. 115-118°C) shows a broad band from 3550 to 2800 cm\(^{-1}\) due to the hydroxyl groups and the mass spectrum contains the desired molecular ion at m/z 184.

The various difficulties presented in the route stimulated a simultaneous consideration of an alternative strategy, namely, the direct carboxylation of isophorone 26 (see Scheme 16). It was felt that this approach might allow preparation of 46, via ketoacid 49, in a more direct and, hopefully, better yielding sequence.
Treatment of isophorone 26 with lithium 2,6-di-tert-butyl-4-methylphenoxide 50 (Figure 6) and carbon dioxide gas in diethyl ether at room temperature gave ketoacid 49. 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 49a to give, upon acidification, cis-hydroxyacid 46 in 46% overall yield. Small quantities (about 5%) of the corresponding trans-hydroxyacid 51 were also obtained. Since the remainder was recovered isophorone 26, the effective yield in the overall conversion from 26 to 46 was 90%.

The ¹H-NMR spectra of 46 and 51 provided again the crucial data to distinguish these isomers. The signals of the protons at C-1 (doublet) and C-2 (multiplet) in 46 appear at δ2.69 and 4.45, respectively, with a coupling constant between them of 6 Hz; on the other hand, the signals of the same protons in 51 appear at δ2.24 and 4.48, respectively, with a coupling constant of 10 Hz. As in the case of the esters 32 and 35 (see Scheme 9), it is possible to deduce, from these J values, that the carboxyl and the hydroxyl groups in 46 are in a cis relationship, whereas in 51, they are in a trans relationship. The assignments of the
chemical shifts were proved by double resonance experiments.

Several remarks are worth noting of this transformation (see Scheme 16). First of all, this appears to be the first case of a kinetic carboxylation of an \( \alpha, \beta \)-unsaturated ketone under these mild conditions, although carboxylation of simple ketones with these reagents has been reported before.\(^3\text{1} \). Perhaps the reason that such a mild base (pK\( _a \) of conjugated acid=12.3\(^3\text{2} \)) was capable of abstracting the \( \alpha' \) proton (pK\( _a \approx 20 \)) (see Figure 7) is, in part, due to the complex-induced
FIGURE 7

SCHEME 17
proximity effect (CIPE)\textsuperscript{33} which refers to the chelation of the metal (lithium, in this case) to the carbonyl oxygen making the $\alpha'$ 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\textsuperscript{31}.

The fact that isophorone 26 and not alcohol 52 was recovered from the "one-pot" double transformation suggests that the carboxylation step was complete, thereby giving the products 49a and 53 (Scheme 17). Sodium borohydride reacted only with 49a to give 46 while 53 decomposed back to isophorone 26 during the acidic work-up of the reaction mixture.

\[
\begin{align*}
\text{HO} & \\
\text{52}
\end{align*}
\]

The stereoselectivity of the reduction of 49a results from the approach of sodium borohydride to the more open face (Figure 8), perhaps because of both steric hindrance and electrostatic repulsion with the negatively charged carboxylate.

Finally, this regioselective carboxylation of isophorone turned out to be quite useful, on the one hand, because, as mentioned before, methoxycarbonylation with either methyl chloroformate or methyl carbonate (see Scheme 7) did not lead to the desired product; and, on the other hand, direct carboxylation using methylmagnesium carbonate (MMC)\textsuperscript{34} or bromomagnesium ureide-carbon dioxide
adducts (e.g. 54) gives mainly the undesired acid 55 from isophorone 26 (Scheme 18). Furthermore, this route provides cis-hydroxyacid 46 more readily and with better yield than the previous route (see Scheme 8, and first reaction in Scheme 15)
The next step was the activation of the hydroxyl functionality in 46 in order to provide a good leaving group for subsequent nucleophilic displacement (see Scheme 15). Thus, treatment of hydroxyacid 46 with 2.1 equivalents of benzoyl chloride and DMAP in dichloromethane at 5°C furnished the unstable ester-anhydride 47, which was obtained as a crude liquid and was not further purified.

Treatment of 47 with indolylmagnesium iodide 37 from 5 to 25°C gave rise to the long desired indoleacid 48 in 40% yield as colorless crystals (m.p. 173-174°C). Careful purification of the crude mixture also gave byproducts 56 (15%), 57 (26%) and 58 (3%) (Figure 9).

![Figure 9](image_url)
The IR spectrum of 48 shows at 3480 cm\(^{-1}\) the characteristic sharp N-H absorption of indole, from 3550 to 2450 cm\(^{-1}\) the broad band of the carboxyl hydroxyl group, and at 1710 cm\(^{-1}\) the absorption due to the stretching frequency of the carbonyl group. The mass spectrum gives the correct molecular ion at m/z 283. The \(^1\)H-NMR spectrum (Figure 10) displays the gem-dimethyl group as singlets at δ1.08 and 1.14, 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 appear at δ1.76 and 2.15 with a J value of 16 Hz. The hydrogen at C-2 appears at δ3.93 as a doublet with a J value of 10 Hz caused by the \textit{trans} coupling with the proton at C-1, which appears at δ2.71 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 a singlet. The vinylic proton appears at δ5.47 as a broad singlet. The protons at C-2 and C-3 show hardly any coupling to each other (see Figure 10) probably because, according to a model of the compound (Figure 11), the dihedral angle between them is nearly 90° and therefore, according to the Karplus equation\(^2\)\(^5\), they should show a minimal coupling.

\[\text{FIGURE 11}\]
The proton at position 2' of the indole moiety appears at δ6.94 as a doublet with a small $J$ value of 2 Hz because of its coupling to the proton on the nitrogen atom (δ7.77), 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. Figure 10 shows the spectrum of indoleacid 48 and the results from NOE and double resonance experiments, and Table 4 presents the corresponding assignments. Irradiation at δ7.77 (Figure 10a), which is the signal corresponding to the N-H proton, enhances both the signal at δ6.94 and the doublet at 7.33. The signal at δ6.94 had already been assigned to the aromatic proton at C-2', therefore, the signal at δ7.33 should correspond to the proton at C-7'. This was confirmed by the second NOE experiment (Figure 10b): irradiation at δ5.47, which is the signal corresponding to the vinylic proton, increases the signals of only two aromatic protons: the signal at δ6.94 (proton at C-2') and the doublet at 7.62. 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 δ7.62 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' (Figure 10c) simplified only the signal at δ7.08 to a doublet. Therefore, the signal at δ7.08 (doublet of doublets, $J=8.8$ Hz, in the normal spectrum) corresponds to the proton at C-5' and the signal at δ7.17 (doublet of doublets, $J=8.8$ Hz) is assigned to the proton at C-6'.

†When freezing the conformation of the indole system as in 81 (p. 77), it will be noted that irradiation at the vinylic proton also enhances the signal of the proton at C-4'.
Figure 10. $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of indoleacid 48, NOE-difference experiments (Figures 10a and 10b) and double resonance experiments (Figure 10c).

a) irradiation at 7.77 ppm.

b) irradiation at 5.47 ppm.

c) homonuclear spin decoupling at 7.62 ppm.
The byproduct diene 56 (see Figure 9) was characterized mainly by IR and UV spectroscopy. The infrared spectrum reveals the broad band of the acid functionality from 3200 to 2800 cm\(^{-1}\) and the carbonyl absorption at 1679 cm\(^{-1}\), the latter suggesting conjugation of the carbonyl of the acid with at least one double bond. Its UV spectrum (\(\lambda_{\text{max}} = 290\) nm) confirms the extra conjugation. The predicted value according to Woodward's rules\(^{36}\) is 286 nm (Figure 12).
Acid α,β-disubstituted double bond extending conjugation homodiene component
\[ \lambda_{\text{max calc.}} = 286 \text{ nm} \]

**FIGURE 12**

Finally, the characterization of the products 57 and 58 (see Figure 9) was as follows. In the IR spectra of both compounds, the N-H and C=O absorptions appear at 3400 and 1700 cm\(^{-1}\), respectively. The O-H bands appear from 3500-2450 cm\(^{-1}\) in 57 and 3400-2700 cm\(^{-1}\) in 58. In the mass spectra the molecular ion of both compounds appear at m/z 283. The \(^1\)H-NMR spectra were also similar. The spectrum of 57 shows the vinylic protons as two pairs of a doublet of doublets at \(\delta\) 6.06 (J=10 and 2 Hz) and \(\delta\) 5.85 (J=10 and 3 Hz) being both coupled with the proton at C-1, which appears at \(\delta\) 3.02 as a doublet of doublets (J=3 and 2 Hz). These assignments were corroborated by double resonance experiments. The spectrum of 58 shows the vinylic protons at \(\delta\) 6.13 (broad doublet, J=10 Hz) and at \(\delta\) 5.82 (doublet of doublets, J=2 and 10 Hz).

The stereochemistry of both compounds was determined on the basis of NOE-difference experiments. Figure 13 shows the 3-dimensional structures of the main conformers of 57 and 58, as a result from these experiments.
The stereochemistry of 57 was determined as follows. Irradiation of the singlet due to the protons of the methyl group at C-4 (δ1.58) enhances the singlet due to the β-methyl group at C-6 (δ1.10) and the signals due to the vinylic proton at C-3 (δ6.06) and the β-proton at C-5 (δ1.99). Irradiation of the signal due to the other methyl group at C-6, namely, the α-methyl (δ0.95), enhances the signal of the axial proton at C-1 and both doublets due to the protons at C-5 (δ1.99 and 2.25). 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 (δ2.25), 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 57. The stereochemistry of 58, which could also be determined from the same results, was confirmed by the
following experiments. Irradiation at δ0.60, which is the signal due to one of the methyl groups at C-6, enhances both the doublet of the proton at C-2' (δ6.92) and the doublet of the β-proton at C-5 (δ2.52). Therefore, the singlet at δ0.60 was assigned to the β-methyl group (see Figure 13). Irradiation of the signal due to the other methyl group (δ1.13), namely, the α-methyl at C-6, enhances the signal of the axial proton at C-1 (δ3.02) and both doublets due to the protons at C-5 (δ1.73 and 2.52). 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 (δ1.73). Therefore, the structure of 58 was confirmed to be as shown in Figure 13.

As mentioned before, these results were also the base to assign the stereochemistry of the ester 39 (see scheme 10).

As in the case with 40 (see Scheme 11), treatment of the trans-benzoate 59 with indolylmagnesium iodide gave the same products and with the same ratio as obtained with the cis-benzoate 47 (Scheme 19). This result again suggests that a carbocation or a similar species is an intermediate in the reaction.

In summary, Scheme 20 presents the best route to obtain the required indoleacid 48 from isophorone 26. Obviously, owing to the above-mentioned results, hydroxyacids 46 and 51 were not separated as in the preparative experiments since they afforded the same end products in the overall conversion.
\[ \text{SCHEME 19} \]
**Results and Discussion**

PhCOCl (2.1 equiv)  
DMAP (2.1 equiv)  
CH₂Cl₂

\[ \text{PhCOCl} \quad \text{DMAP} \quad \text{CH₂Cl₂} \]

**Scheme 20**
2.1.2. Cis-ketone 24

Having indoleacid 48 at hand, the approach was now centered on its intramolecular cyclization:

\[ \text{SCHEME 21} \]

As far as the synthesis of yuehchukene is concerned, the required stereochemistry of rings C and D demands a cis relationship of the protons at C-6a and C-10a (see 24, Scheme 6, p.17). Based on the observed tendency\(^{3,7}\) that cis-1-hydrindanones (for example, 62) are thermodynamically more stable than

\[ \text{SCHEME 22} \]
trans-1-hydridanones, it was anticipated that the cis-ketone 24 might be prepared from the trans-ketone 60 (Scheme 22).

Unfortunately, neither PPA\textsuperscript{3b} nor PPE\textsuperscript{39} could cause the desired cyclization of indoleacid 48 to ketone 60 (Scheme 23), even though compound 58 underwent smooth cyclization with PPE in CHCl\textsubscript{3} to give ketone 63 in 55\% yield.

\[\text{SCHEME 23}\]
Conversion of 48 into acid chloride 64 (Scheme 24) with oxalyl chloride in benzene, and then intramolecular Friedel-Crafts acylation with zinc chloride in nitrobenzene following the same conditions as reported for acylation at position 2 of 3-substituted indoles\(^4^0\), failed as well.

SCHEME 24
After these discouraging results, it was decided to consider an intermolecular acylation, rather than the above-noted reactions, and then continue the route as shown in Scheme 25.

\[ \text{SCHEME 25} \]
Addition of acid chloride 64 into an ether-dichloromethane solution of indolylmagnesium iodide (3.5 equiv.) at \(-50^\circ\text{C}\) and then raising the temperature to 5\(^\circ\text{C}\) afforded the expected product 65 in 18% yield, and somewhat surprisingly, the previously desired ketone 60 in 25% yield (Scheme 26).

**SCHEME 26**

The IR spectrum of 65 shows the N-H absorption at 3465 cm\(^{-1}\) and the C=O stretching frequency at 1637 cm\(^{-1}\), the latter being characteristic of 3-acylindole systems. The mass spectrum gives the molecular ion at m/z 382 and the base peak at m/z 144 corresponding to the fragment cation a.

Finally, the \(^1\text{H-NMR}\) spectrum displays at \(\delta3.54\) the proton at C-4 (see Scheme 25) 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 δ4.14. Also, integration of
the aromatic proton region shows the presence of two indole systems with the
proton at C-2' appearing at δ6.85 as a doublet (J=2 Hz) and the N-H protons at
δ7.59 and 7.98 as broad signals. The proton at C-2'' appears downfield of δ7.0
due to the presence of the carbonyl group at the position 3''.

The IR spectrum of the crystalline ketone 60 (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 δ8.73 and, most importantly, no aromatic 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 Figure 14.

FIGURE 14
Although the yield of either 60 or 65 was low, the outcome of the transformation was stimulating to evaluate reaction parameters in order to obtain an increased yield of ketone 60. Table 5 shows the results of the reaction under different conditions. Careful monitoring revealed that the reaction only occurs at a temperature of -15°C, or higher, giving both products in about the same ratio (runs 1 and 2). When acid chloride 64 was added into indolylmagnesium iodide (runs 1 to 4) there was a tendency to give a higher ratio of products 65/60 as the equivalents of the "Grignard reagent" were increased. On the other hand, when the addition was reversed (runs 5 to 7), the yield of ketone 60 could be improved as the length of the addition of indolylmagnesium iodide was increased from 3 to 8 hours. 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, and when there is an excess of the "Grignard reagent" 37, compound 65 is predominantly formed (run 3). On the other hand, the ratio 60/65 is maximum when acid chloride 64 is maintained in excess (runs 6 and 7).

Since ketone 60 was apparently formed by the behavior of indolylmagnesium iodide acting as a base, attempts were made to increase even further the yield of ketone 60 by utilizing the hindered base LDA. Table 6 shows the results. Addition of 1.2 equivalents of LDA at -15°C gave only 15% of ketone 60 along with recovered indoleacid 48 (run 1). Increasing both the amount of LDA (to 2.5 equivalents) and the length of its addition (to 7 h, run 3) raised the yield by a factor of 2, although this was still low. On the other hand, increasing the temperature up to 20°C did not give any 60 but the next expected intermediate cis-ketone 24 (see Scheme 22). Since the yield of both 24 and 48 were almost
Acid chloride was added into 37 in runs 1 to 4 in 0.5 h.

<table>
<thead>
<tr>
<th>Run</th>
<th>Equivalents of 37</th>
<th>Temperature (°C)</th>
<th>Length of addition of 37 (h)</th>
<th>Yield (¹/₁) 60 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>-50 to 5</td>
<td>-</td>
<td>25 18</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>-50 to 5</td>
<td>-</td>
<td>23 20</td>
</tr>
<tr>
<td>3</td>
<td>20.0</td>
<td>-50 to 5</td>
<td>-</td>
<td>08 40</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>-50 to 15</td>
<td>-</td>
<td>24 17</td>
</tr>
<tr>
<td>5</td>
<td>3.5</td>
<td>-15 to 20</td>
<td>3.0</td>
<td>29 16</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>-15 to 20</td>
<td>8.0</td>
<td>46 14</td>
</tr>
<tr>
<td>7</td>
<td>3.5</td>
<td>-15 to 20</td>
<td>14.0</td>
<td>46 19</td>
</tr>
</tbody>
</table>

TABLE 5
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TABLE 6

<table>
<thead>
<tr>
<th>Run</th>
<th>Equivalents of LDA</th>
<th>Temperature (°C)</th>
<th>Length of addition of LDA (h)</th>
<th>Yield (%) 48 60 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>-15</td>
<td>0.3</td>
<td>50 15 --</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>-15</td>
<td>0.3</td>
<td>43 20 --</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>-15</td>
<td>7.0</td>
<td>27 30 --</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>-15 to 20</td>
<td>7.0</td>
<td>26 -- 27</td>
</tr>
</tbody>
</table>

**64** → LDA → **48**

**60** - H6αα

**24** - H6αβ
the same as the yield of 60 and 48 when the conditions of the reaction were the same (except for the temperature) (runs 3 and 4), it seems that no further cyclization took place on warming but only the epimerization of 60 occurred. Furthermore, in a separate experiment, trans-ketone 60 was epimerized to cis-ketone 24 in the presence of LDA (-15 to 20°C) in 85% yield (Scheme 27).

The spectroscopic characteristics of crystalline cis-ketone 24 are, as expected, quite similar (but not identical) to those of trans-ketone 60. Perhaps most noteworthy is that the coupling constant between the protons at carbons 6a and 10a in the ¹H-NMR spectra of both compounds is the same (6 Hz). The most pronounced difference is their melting points: 129-131°C for 60 and 220-223°C for 24.

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 24 in quantitative yield (Scheme 27).

In summary, Scheme 28 shows the most desirable route to the cis-ketone 24 from indoleacid 48.
2.1.3. Yuehchukene 2

The next objective in the strategy involved the transformation of the ketone functionality in 24 into an appropriate leaving group, in order to subsequently perform an attachment of the other indole moiety present in the natural product by an overall nucleophilic substitution reaction (see Scheme 6, retrosynthetic analysis).

The approach that was followed to accomplish these transformations is presented in Scheme 29.
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Scheme 29

24 → 67 → 69 → 68
Mild hydride reduction (NaBH$_4$/MeOH) was unsuccessful in the first conversion, but, fortunately, the more reactive reagent LiAlH$_4$ did reduce the ketone functionality to give alcohol 67 (Scheme 29) as the main product in 65% yield, along with the epimeric alcohol 70 as a minor component (35%).

Lithium tri-sec-butylborohydride (L-Selectride) gave, as expected, only alcohol 67 but, unfortunately, in lower yield (50%). The remainder of the reaction mixture in the latter conversion was unreacted 24. Even an excess of L-Selectride gave the same result. This outcome suggests that 24 was perhaps being transformed into the enolate 71, which, in the acidic work-up, would regenerate ketone 24 (Scheme 30).

Both alcohols (67 and 70) reveal the characteristic O-H frequency in their IR spectra. The $^1$H-NMR spectrum of 67 displays, at $\delta$5.06, the signal of the hydrogen at C-6 as a broad signal which becomes a distinct doublet ($J=6$ Hz) only after exchange of the O-H proton with D$_2$O. 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 $\delta$2.6-2.7 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
Results and Discussion

24

L-Selectride

24

Scheme 30

of 70 shows the signal of the proton at C-6, at $\delta 5.12$, as a doublet ($J=6$ Hz) due to coupling with only the proton at C-6a with apparently no coupling with the O-H proton.

The distinction between the two alcohols was established by NOE-difference experiments performed with alcohol 70. 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 70, presented in Figure 15, shows the proximity between protons at C-6 and C-8.

![Figure 15](image)

**FIGURE 15**

Therefore, the hydroxyl group in 70 bears an *cis* relationship to the proton at C-6a.

The fact that L-Selectride gave only alcohol 67 is also in accordance with the previous assignment since this bulky reagent is known to approach quite selectively from the more open face of a carbonyl group (which is, of course, the β-face of ketone 24, see Scheme 29).

The next transformation involved a dibenzoylation of 67 using 4 equivalents of benzoyl chloride, 1.2 equivalents of DMAP and 4 equivalents of triethylamine in dichloromethane, to give rise to compound 68 (see Scheme 29) as white crystals (76% yield).

Its IR spectrum does not present peaks above 3200 cm⁻¹ but, instead, two distinguishable carbonyl bands: at 1718 cm⁻¹ corresponding to the aromatic
ester, and at 1684 cm$^{-1}$ corresponding to the amide. The mass spectrum shows the correct molecular ion at m/z 475 with the base peak at 105 due to the formation of the relatively stable cation PhC=O$. In its $^1$H-NMR spectrum, the proton at C-6 was shifted, as expected$^{25}$, to lower field by about 1.3 ppm. It appeared at δ6.40 as a doublet with a $\nu$ value of 5.5 Hz due to coupling with the proton at C-6a, and it was distinguished from the vinylic proton (δ5.73, broad singlet) by double resonance experiments. Decoupling of the proton at C-6a (δ2.72, doublet of doublets, $\nu$=5.5,5.5 Hz) changed the signal of the proton at C-6 from a doublet to a singlet.

Addition of only one equivalent of benzoyl chloride to alcohol 67 gave rise to the chemoselective formation of compound 72 (and not compound 73).

![Chemical structures](image)

72
73

Its characterization was made mainly from $^1$H-NMR spectroscopy. The signal of the proton at C-6 appears at δ4.92, as a doublet of doublets ($\nu$=6.6 Hz). This chemical shift is very similar to that in alcohol 67 (δ5.06) and quite different from the one in compound 68 (δ6.40). Furthermore, the doublet of doublets implies
coupling with both the O-H proton and the proton at C-6a. Finally, the O-H proton appears at δ2.40, a position quite different from the normal chemical shift of an indolic proton (δ8.17 in alcohol 67).

The next transformation was the important displacement of the benzoate group by indolylmagnesium iodide. Benzoate 68 was treated with the "Grignard reagent" in ether-dichloromethane solution at 5°C to obtain benzoylyuechukene 69 as a white foam and in 40% yield. Isomers 74 and 75 (Figure 16) were also formed in 18 and 30% yield, respectively.

Benzoylyuechukene 69 was characterized by IR, MS, and ¹H-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 ¹H-NMR spectrum shows the proton at C-6 at δ4.12 as a doublet with a J value of 4 Hz. As expected, this chemical shift is at considerably higher field than that of the starting benzoate 68 (δ6.39). The N-H proton appears at δ7.73 as a broad signal and the signal of the hydrogen at C-2' of the heterocyclic ring of the newly incorporated indole appears at δ6.15 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 δ6.15 into a singlet.

Usually the proton at C-2 in the indole functionality appears within the range 6.6-6.9 ppm, so it was somewhat surprising to find the occurrence of such a proton at δ6.15 in this case. However, a model of the compound (Figure 17) shows that such a proton might well be shielded by the magnetic anisotropic effects of the benzoyl group. The stereochemistry at C-6 was determined by the
FIGURE 16

FIGURE 17
conversion to the target molecule yuehchukene 2 in the next step.

Compound 74, formed by N-alkylation rather than C-alkylation, presents in its IR spectrum the carbonyl absorption at 1685 cm$^{-1}$ and no band above 3100 cm$^{-1}$. 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 which was not observed in 69 and is due to the facile loss of indole from the molecular ion. The $^1$H-NMR (Figure 18) spectrum shows the proton at C-6 at $\delta$5.53 as a broad signal. The proton at C-2' appears at $\delta$6.29 as a doublet with a $J$ value of 3.5 Hz. This result shows the coupling of the latter with the proton at C-3' that appears at $\delta$6.48 as a doublet with the same $J$ value. Double resonance experiments confirm this proposal (see Figure 18a). The unusual assignment of the proton at C-2' at such a high field is again based on the shielding of the benzoyl group.

The stereochemistry at C-6 in 74 was assigned on the basis of NOE experiments. Thus, irradiation of the signal due to the proton at C-6a ($\delta$2.85, see Figure 18b) shows enhancement of both the signal of the proton at C-10a ($\delta$4.08) and the signal of the proton at C-2' ($\delta$6.29), but it does not affect the signal due to the proton at C-6 ($\delta$5.53). Also, irradiation of the signal due to the proton at C-6 (see Figure 18c) 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 75 (Figure 16) was characterized by IR, MS, $^1$H-NMR, and X-Ray analysis. The IR spectrum shows the sharp band due to the N-H stretching frequency at 3477 cm$^{-1}$ and the carbonyl absorption at
Figure 18.- $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of compound 74, double resonance experiments (Figure 18a) and NOE-difference experiments (Figures 18b and 18c).

a) homonuclear spin decoupling at 6.29 ppm.
b) irradiation at 2.85 ppm.
c) irradiation at 5.53 ppm.
1650 cm\(^{-1}\). The latter value, which is lower than that in both 69 (1681 cm\(^{-1}\)) and 74 (1685 cm\(^{-1}\)), shows that the unshared pair of electrons on the nitrogen atom interact more with the carbonyl group than when those electrons participate in the aromaticity of the indole system. The mass spectrum also displays the molecular ion at m/z 470 and the base peak at 105. The \(^1\)H-NMR spectrum shows the N-H proton at \(\delta 7.97\) as a broad signal and the proton at C-2' at \(\delta 7.15\) as a doublet with a \(J\) value of 2.5 Hz. Both vinylic protons appear as singlets at \(\delta 5.11\) and 5.36 ppm. The proton at C-6a which appears as a doublet at \(\delta 2.72\) collapses into a singlet on irradiation of the signal at C-10a, thereby establishing that there is no coupling between the protons at C-6a and C-6. All of these assignments were corroborated and the stereochemistry at C-10b was established by an X-ray diffraction analysis of the colorless crystalline compound 75 (m.p. = 250-252\(^0\)) as shown in Figure 19. X-ray analysis established the dihedral angle between the hydrogen atoms at C-6a and at C-6 to be 91\(^0\), in accord with the \(J=0\) between these protons in the \(^1\)H-NMR spectrum (\textit{vide infra}).

Finally, completion of the total synthesis of (±)-yuehchukene was successfully accomplished by facile methanolysis of N-benzoylyuehchukene 69 using sodium methoxide in methanol at 5\(^0\)C to give the pure alkaloid 2 in 90% yield (Scheme 29). This final product presents identical spectroscopic data (IR, MS, \(^1\)H-NMR, and UV) as the natural yuehchukene (see Section 3, Introduction).

Since deprotection of 75 affords a new analogue of yuehchukene, which is one of the objectives of this project, that transformation was also carried out. Thus, treatment of 75 with sodium methoxide in methanol gave compound 76 (Scheme 31) in 97% yield. During this conversion, there was concomitant migration of the double bond to the more stable imine form\(^a\). The IR spectrum of this unstable
FIGURE 19

SCHEME 31

$75 \xrightarrow{\text{MeONa, MeOH, Reflux, 97\%}} 76$
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. Table 7 shows the chemical shifts and coupling constants of these protons. These assignments were corroborated by double resonance experiments. When the signal at $\delta$2.64 was decoupled both signals corresponding to the hydrogens at C-6 became doublets, showing that only geminal coupling exists with these protons. Also, the spectrum

\[
\begin{array}{cccc}
\text{Position} & \text{Chemical shift (δ)} & \text{Multiplicity} & \text{Coupling constant (Hz)} \\
6a \text{ or } 6\beta & 2.29 & \text{doublet of doublets} & 8,18 \\
6a & 2.64 & \text{multiplet} & - \\
6a \text{ or } 6\beta & 2.83 & \text{doublet of doublets} & 10,18 \\
\end{array}
\]

TABLE 7
shows only one vinylic proton signal (δ4.72) (and not two as in 75) corresponding to C-10, thereby establishing the proposed migration of the double bond to form the imine structure 76.

Finally, to end the first part of the project, compounds 69, 74, 75, 76 and yuehchukene 2 were prepared in 100-250 mg scale for pharmacological testing. These samples have already been submitted but, unfortunately, results are not available at present.
2.2. TOTAL SYNTHESIS OF (±)-6a-EPi-YUEHCHUKENE

As mentioned before, the main objective of our project was to develop a versatile approach so as to synthesize new analogues of the natural product yuehchukene. Thus, this second part deals with the total synthesis of the isomer 6a-epi-yuehchukene 25. Originally, the approach presented in Scheme 32 was followed.

Trans-ketone 60, which was one of the key intermediates in the previous synthesis, was reduced with LiAlH₄ in ether at 5°C to give 77 in 90% yield as the only product. Its IR spectrum shows two bands for the O-H, at 3685 cm⁻¹ (sharp) and at 3200 cm⁻¹ (broad). The N-H absorption appears at 3466 cm⁻¹. The \(^1\)H-NMR spectrum shows the proton at C-6 at 65.08 as a doublet with a J value of 8.5 Hz on account of its coupling with the proton at C-6a (62.18, doublet of doublets, J=8.5,8.5 Hz), as corroborated by double resonance experiments. The
SCHEME 32
value of this coupling was the basis on which the assignment of the stereochemistry at C-6 was made. The related alcohols 81 and 86 (see Schemes 33 and 35, p. 77 and 83) with known stereochemistry (*vide supra*) have a coupling constant for the same protons (*i.e.* protons at C-6 and C-6a) of 8.5 and 9 Hz, respectively. Therefore, due to the close similarity of this value in the three alcohols, 77 was assigned to have the hydroxyl group and the proton at C-6a in a *cis* relationship. Furthermore, if the proton at C-6 had an *α* orientation (in the structure presented in Scheme 32), it would have a dihedral angle with the proton at C-6a of approximately 40° and, therefore, the expected *J* value would be 5-6 Hz according with the Karplus equation\(^2\), while the expected value in 77 would be 8-9 Hz.

The next step required the conversion of the hydroxyl group to the benzoate functionality. Treatment of 77 with one equivalent of benzoyl chloride and DMAP gave benzoate 78 in only 15% yield. Apparently, the remainder of the reaction mixture represented products of decomposition. Treatment of 77 with two equivalents of benzoyl chloride to try to form the dibenzoylated product 79 (as in the approach to yuehchukene) did not improve the yield. Apparently, in this transformation, O-benzyolation occurs faster than N-benzyolation (as opposed to the behavior of alcohol 67, see p. 64) to form 78 and this decomposes quite readily under the conditions of the reaction regardless of the amount of benzoyl chloride used.

The IR spectrum of 78 shows the sharp N-H absorption at 3460 cm\(^{-1}\) and the carbonyl band at 1710 cm\(^{-1}\). The \(^1\)H-NMR spectrum shows the broad singlet of the N-H proton at δ8.45 and the expected deshielding of the proton at C-6 to δ5.94.
In order to increase the stability of the intermediates, it was decided to protect the indole ring in 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 on account of its electron-withdrawing properties. The route followed is shown in Scheme 33.

Ketone 60 was converted to its tosyl derivative 80 in 90% yield by using p-toluenesulfonyl chloride in the presence of sodium hydride. Its IR spectrum does not show any band above 3100 cm\(^{-1}\) but, instead, two strong absorptions at 1123 and 1381 cm\(^{-1}\) due to the sulfonyl group.

The N-tosylketone 80 was reduced with LiAlH\(_4\) in THF at 0°C to give stereoselectively alcohol 81 in 90% yield. As in the case with 77, no other alcohol was observed in the reaction mixture. The IR spectrum reveals the O-H absorption at 3563 cm\(^{-1}\). The \(^1\)H-NMR spectrum (Figure 20) shows the signal of the proton at C-6 at \(\delta 5.27\) as a doublet of doublets of doublets with \(J\) values of 8.5, 2 and 2 Hz. This splitting pattern is due to the coupling of this proton with the proton at C-6a (\(\delta 2.42, \text{dd, } J = 10, 8.5 \text{ Hz}\)), coupling with the O-H proton (\(\delta 4.10, \text{d, } J = 2 \text{ Hz}\)).
SCHEME 33

60 \rightarrow 80

60 \rightarrow 82 \rightarrow 81
and a long distance coupling (2 Hz) with the hydrogen at C-10a (δ3.38, m). All these assignments were corroborated by exchange of the O-H proton with D₂O and/or double resonance experiments.

The stereochemistry at C-6 was assigned on the basis of NOE-difference experiments. Figure 20 shows the spectrum and the affected signals after the experiment. Irradiation of the signal due to the proton at C-10a (δ3.38) enhances the signal of the proton at C-6 (Figure 20a). This experiment also served to assign the β-methyl group at C-7 (δ1.05). Irradiation of the protons of this β-methyl group (Figure 20b) enhances both the signal of the proton at C-6 and that of the proton at C-10a, but hardly affects the signal due to the proton at C-6a (δ2.42) in comparison with the enhancement produced, to this signal, by irradiation of the protons of the α-methyl group (Figure 20c). Therefore, the stereochemistry at C-6 was assigned to have the O-H group and the proton at C-6a in a cis relationship. On the other hand, Figure 20d shows that irradiation of the vinylic proton does influence the signal due to the aromatic proton at C-1 (compare indoleacid 48 p. 41) presumably because of its proximity.

Treatment of alcohol 81 with 1.2 equivalents of acetic anhydride and 1.3 equivalents of DMAP in CH₂Cl₂ at room temperature gave acetate 82 in 75% yield. Thus, this product was obtained in a far better yield than the analogue 78 (15-20%). The use of acetic anhydride instead of benzoyl chloride used in the previous study was to attempt to increase further the stability of the ester.

The infrared spectrum of acetate 82 shows the carbonyl absorption at 1739 cm⁻¹; the mass spectrum reveals the molecular ion at m/z 463; and the ¹H-NMR spectrum shows the methyl group of the acetate at δ2.15 as a singlet.

The next transformation in the sequence involved nucleophilic displacement
Figure 20. $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of alcohol 81 and NOE-difference experiments.

a) irradiation at 3.38 ppm.
b) irradiation at 1.05 ppm.
c) irradiation at 1.28 ppm.
d) irradiation at 6.04 ppm.
of the acetate group by indolylmagnesium iodide. Unfortunately, the expected
derivative of \textit{trans}-yuehchukene 83 (Scheme 34) could not be observed. Instead, the
isomer 84 was obtained in 40\% yield.
Indoline 84 was characterized by IR, MS, $^1$H-NMR and X-Ray diffraction analysis. The IR spectrum shows the N-H absorption at 3460 cm$^{-1}$ and the mass spectrum reveals the molecular ion at m/z 520. In the $^1$H-NMR spectrum, the vinylic protons appear as broad singlets at δ5.87 and 5.94 singlets, thereby suggesting that the dihedral angles between these protons and the adjacent methine protons (i.e. those at C-6a and C-10a) are near 90°. These assignments were confirmed and the stereochemistry at C-10b was assigned by X-Ray diffraction analysis of this crystalline product (m.p. 207-208°C) (Figure 21).

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. Figure 22 shows the three dimensional structure of what was the expected product 83. The strong interactions noted above are evident.

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. In this instance, the carbon atom C-1' in 85 (see Scheme 35) would be attached to only two hydrogens and a primary alkyl group, whereas, in the tosyl case, the sulfur atom is attached to two oxygens and an aryl group. Clearly, in the former case, the SEM group would give less steric demand.

SEM-Cl has not been previously utilized for the protection of the indole system, although it is usually employed to protect alcohols. However, it has been used for the protection of the pyrrole group, and it was felt that its application 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.
FIGURE 21

FIGURE 22
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Scheme 35
compared with the tosyl group (and, therefore, increase the instability of the intermediates). However, the indole system would lack the weakly acidic indolic hydrogen atom, and the latter would not interfere with the formation of the subsequent intermediates (compare acetate 78, Scheme 32). Scheme 35 shows the route followed in the laboratory.

Treatment of trans-ketone 60 with 1.5 equivalents of SEM-chloride in the presence of sodium hydride furnished compound 85. 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$^{-1}$ and no band above 3100 cm$^{-1}$. The mass spectrum reveals the molecular ion at m/z 395 and the base peak at m/z 73 corresponding to the cation ($\text{CH}_3)_3\text{Si}^\oplus$.

The $^1$H-NMR spectrum displays at $\delta$-0.1, a singlet which integrates for 9 protons and is due to the trimethylsilyl group; at $\delta$0.86, a multiplet corresponding to the protons of the methylene carbon bonded to the silicon; at $\delta$3.52, another multiplet due to the adjacent methylene carbon, and at $\delta$5.61 and 5.69, 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 60 nor 85 epimerized at C-6a, during the reaction conditions employed, was proved by obtaining a different product from the corresponding cis-ketone 24, namely, compound 89, as shown in Scheme 36.

In fact, the amount of sodium hydride was critical for the exclusive formation of 85, especially with THF as the solvent. Any excess of sodium hydride in the conversion of 60 to 85 led to variable quantities of 89 as a byproduct.
Treatment of ketone 85 in a pure form, or in situ, with LiAlH₄ at 5°C, or with Dibal at -78°C⁸, gave 86 as a single alcohol in 80-85% yield (67% overall for the "one-pot" reaction from 60 to 86). 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 the proton at C-6 (δ5.12) enhances the signal of the proton at C-10a (δ3.41). Also, irradiation of the β-methyl at C-7 (δ1.03), 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 86 with an excess of acetic anhydride, DMAP and triethylamine in dichloromethane at 20°C, gave the corresponding acetate 87 (86% yield) as a colorless oil. This product was readily characterized by virtue of the
carbonyl absorption at 1737 cm\(^{-1}\) in its IR spectrum, the molecular ion at m/z 439 in its mass spectrum, and the singlet due to the protons of the methyl group of acetate at \(\delta 2.11\) and the expected deshielding of proton at C-6 to 6.43 ppm in its \(^1\)H-NMR spectrum.

In the next step, the crucial displacement of the acetate group by indolylmagnesium iodide was attempted. Fortunately, treatment of acetate 87 with the "Grignard reagent" in ether/dichloromethane at 5\(^\circ\)C furnished SEM-trans-yuehchukene 88 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 \(\beta\)-methyl at C-7 (Figure 23).

![Figure 23](image)

**FIGURE 23**

The isomeric product 90 in which the indole group is attached to the C-10b was not observed in this case.
The structure of SEM-trans-yuechukene 88, 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 $\delta$4.78, as a doublet, with a $J$ value of 6 Hz because of its coupling with the proton at C-6a ($\delta$2.70, dd, $J$=11.6 Hz). This analysis was corroborated by double resonance experiments. The $\beta$-methyl group at C-7 (assigned by NOE experiments, vide supra) appears as a broad singlet with the unusual chemical shift of $\delta$0.34. Probably, the magnetic anisotropic effects of the newly incorporated indole group are the cause of this shielding.

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 ($\delta$2.70), but not the one of the proton at C-10a ($\delta$4.06). Also, irradiation of the signal due to the $\alpha$-methyl group ($\delta$1.13) (assigned by the enhancement of the $\beta$-methyl group when irradiating of 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 trans-yuehchukene 25 (see Scheme 35) was accomplished by treatment of 88 with tetra-n-butylammonium fluoride in THF-HMPA at 40°C for one day to give 25 as a white foam in 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 notorious. On the other hand, deprotection of the indole system using lithium tetrafluoroborate in acetonitrile led only to decomposition of the starting SEM-trans-yuehchukene 88.

The IR spectrum of trans-yuehchukene 25 displays the N-H absorption at 3400 cm\(^{-1}\), the mass spectrum the molecular ion at m/z 366, and the \(^1\)H-NMR spectrum the protons at each nitrogen atom at different chemical shifts. One of these broad signals appears at δ8.89 while the other is present at δ9.10.

Having established the way to obtain this isomer of the natural product, the synthesis was repeated in a larger scale to obtain a sample of 100 mg of trans-yuehchukene 25 for pharmacological testing.

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 25, 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 at the World Health Organization (WHO), where extensive tests in animals are currently underway. It is hoped that some of the intermediates, for example the N-benzoyl derivative of natural yuehchukene (69, Scheme 29) or the SEM derivative of trans-yuehchukene (88, Scheme 35), which are more stable, will prove to be active in the anti-implantation screening tests.

Various compounds from the above study are now under investigation at WHO and in Hong Kong but, unfortunately, biological results are still unavailable.
3. EXPERIMENTAL

3.1. GENERAL
Melting points (with the recrystallization solvents given in brackets) were determined using a Nalge melting point apparatus and are uncorrected. The infrared spectra were recorded on Perkin Elmer 710, 710B, and 1710 spectrometers in chloroform solution (using NaCl cells of 0.1 mm path length) or as thin film (using NaCl cells), or as KBr pellets. The ultraviolet spectra were recorded on a Cary 15 spectrometer using 1 cm quartz cells. The mass spectra were recorded on AEI-MS-9 (low resolution) or KRATOS-MS-50 (high resolution) spectrometers, employing the electron impact ionization method. The $^1$H-NMR spectra were recorded on Bruker WH-400, Varian XL-300 or Bruker WP-80 spectrometers and the chemical shifts are reported in ppm relative to tetramethylsilane (internal standard). The structures presented after each title may have primed numbers for the substituents to facilitate the $^1$H-NMR assignments. The molecular formulae were determined using combustion analysis by Mr P. Borda, Microanalytical Laboratory, University of British Columbia. Previously known compounds, some byproducts, or very unstable intermediates may not have the determination of molecular formula. Column chromatography was performed using columns of silica gel (Merck art. 9385) with nitrogen gas pressure to obtain a suitable flow rate and will be referred to as "flash chromatography". Unless otherwise stated, all reactions were monitored by thin layer chromatography (TLC) analyses, which were carried out on commercial aluminum-backed silica gel plates (Merck art. 5554). Visualization was accomplished with ultraviolet light and/or by spraying with 5% ammonium molibdate-10% aqueous sulfuric acid, followed by heating. Gas-liquid chromatography (GC) was performed on a Hewlett-Packard model
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5890 gas chromatograph, using a flame ionization detector and a 25 m X 0.21 mm fused silica capillary column coated with cross-linked SE-54. Anhydrous ether and tetrahydrofuran were prepared by distillation from a mixture containing sodium and benzophenone. Anhydrous dichloromethane, chloroform and pentane were prepared by distillation from phosphorous pentoxide. Anhydrous methanol and ethanol were prepared by distillation from magnesium. Anhydrous benzene, toluene, HMPA and isopropylamine were prepared by distillation from calcium hydride.

3.2. METHYL 3,3,5-TRIMETHYL-1,5-CYCLOHEXADIENYL CARBONATE 29

To a solution of dry isopropylamine (5.7 mL, 0.04 mol) in dry THF (50 mL) at -78°C under N₂ was added dropwise n-butyllithium (25 mL, 0.04 mol, 1.6M in hexane). The mixture was warmed to -15°C, stirred for 0.5 h and then recooled to -78°C. To this cold solution of LDA was added dropwise isophorone (5 g, 0.036 mol) in THF (20 mL). The mixture was stirred for 0.25 h at -78°C and then a solution of methyl chloroformate (3.1 mL, 0.04 mol) in THF (20 mL) was added dropwise. The reaction mixture was maintained at -78°C for 0.5 h and then warmed to -30°C for 1 h. Ice (about 2 g) and NH₄Cl (25 mL, sat. aq.) were
added and the layers were separated. After the aqueous phase was extracted with ethyl acetate (2X, 25 mL), the combined organic phases were washed with water/brine (60 mL, 1:1, v/v), brine (60 mL), dried over Na₂SO₄, filtered, and evaporated in vacuo to yield a yellow oil. Purification by flash chromatography using hexanes/ether (9:1, v/v) afforded carbonate 29 (5.89 g, 83%) as a colorless oil.

The physical properties of 29 are as follows:

UV λ_max. (log ε) (MeOH): 259(4.08) nm.

IR ν_max (film): 2960(C-H, stretch), 1765(C=O, stretch), 1660 and 1620(C=C, stretch) cm⁻¹.

¹H-NMR (80 MHz, CDCl₃) δ: 1.05(6H, s, C₃-CH₃), 1.83(3H, brs, C₅-CH₃), 2.05(2H, dq, J=1.5, 1.5 Hz, C₄-H), 3.85(3H, s, OCH₃), 5.10(1H, brs, C₂-H), 5.52(1H, dtq, J=1.5, 1.5, 1.5 Hz, C₆-H).

MS m/z: 196(M⁺), 181, 165. High resolution mass measurement: calculated for C₁₁H₁₆O₃: 196.1099; found: 196.1096.

3.3. ETHYL 2-OXO-4,6,6-TRIMETHYLCYCLOHEX-3-ENE-1-CARBOXYLATE 30

To a solution of mesityl oxide (10 g, 0.102 mol) and ethyl acetoacetate (13.2 g, 0.102 mol) in pentane/benzene (100 mL, 1:1, v/v) at room temperature under N₂
was added anhydrous zinc chloride (2.73 g, 0.02 mol). The mixture was refluxed for
5 h, cooled to room temperature and poured into NaHCO₃ (100 mL, sat. aq.).
After separation of the layers, the organic phase was washed with water (50 mL),
brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to yield a
yellow oil. Purification by flash chromatography using hexanes/ether (8:2, v/v) gave
ketoester 30 (3.5 g, 16%), and further elution the isomeric compound 31 (7.0 g,
32%) and isophorone 26 (2.3 g, 10%).
The physical properties of 30 are as follows:
UV \( \lambda_{\text{max}} \) (EtOH): 237 nm.
IR \( \nu_{\text{max}} \) (CHCl₃): 2960(C-H, stretch), 1740(C = O of ester, stretch), 1675(C = O of
ketone, stretch), 1640(C = C, stretch) cm⁻¹
\(^1\)H-NMR (80 MHz, CDCl₃) \( \delta \): 1.12(3H, s, C₆-CH₃), 1.17(3H, s, C₆-CH₃), 1.30(3H, t, J = 7
Hz, C₂'-H), 2.00(3H, brs, C₄-CH₃), 2.04(1H, d, J = 18 Hz, C₅-H), 2.56(1H, d, J = 18 Hz, C₅-H),
3.15(1H, s, C₁-H), 4.17(2H, q, J = 7 Hz, C₁'-H), 5.94(1H, m, C₃-H).
MS m/z: 210(M⁺), 195, 82. High resolution mass measurement: calculated for

The physical properties of 31 are as follows:
UV \( \lambda_{\text{max}} \) (EtOH): 235 nm.
IR \( \nu_{\text{max}} \) (CHCl₃): 2960(C-H, stretch), 1725(C = O of ester, stretch), 1670(C = O of
ketone, stretch) cm⁻¹
\(^1\)H-NMR (80 MHz, CDCl₃) \( \delta \): 1.07(6H, s, C₆-CH₃), 1.30(3H, t, J = 7 Hz, C₂'-H),
1.95(3H, brs, C₂-CH₃), 2.05(1H, d, J = 16 Hz, C₅-H), 2.77(1H, d, J = 16 Hz, C₅-H),
2.95(1H, brs, C₁-H), 4.20(2H, q, J = 7 Hz, C₁'-H), 5.97(1H, brs, C₃-H).
MS m/z: 210(M⁺), 195, 98. High resolution mass measurement: calculated for
To a solution of ketoester 30 (500 mg, 2.38 mmol) in MeOH (10 mL) at room temperature under N₂ was added NaBH₄ (74 mg, 2.40 mmol). The reaction mixture was stirred at room temperature for 2 h. Water (3 mL) and NH₄Cl (3 mL, sat. aq.) were added, and MeOH was evaporated in vacuo. The residue was extracted with ether (3X, 10 mL) and the organic solution was washed with water (15 mL), brine (15 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to yield a yellow oil. Purification by flash chromatography using hexanes/ether (7:3, v/v) gave cis-hydroxyester 32 (358 mg, 71%) and trans-hydroxyester 35 (116 mg, 23%) as colorless liquids.

The physical properties of 32 are as follows:

IR ν max. (CHCl₃): 3450(O-H, stretch), 2920(C-H, stretch), 1740(C=O, stretch) cm⁻¹.

¹H-NMR (80 MHz, CDCl₃) δ: 1.15(3H, s, C₆-CH₃), 1.22(3H, s, C₆-CH₃), 1.42(3H, t, J = 7 Hz, C₂'-H), 1.66(1H, d, J = 17 Hz, C₅-H), 1.72(3H, brs, C₄-CH₃), 2.07(1H, d, J = 17 Hz, C₅-H), 2.34(1H, brs, O-H), 2.65(1H, d, J = 6 Hz, C₁-H), 4.12(2H, q, J = 7 Hz, C₁'-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: calculated for C₁₂H₂₀O₃: 212.1412; found: 212.1408.
Elemental analysis: calculated for $C_{12}H_2O_3$: C 67.88, H 9.50; found: C 67.73, H 9.48.

The physical properties of 35 are as follows:

IR $\nu_{max}$ (CHCl$_3$): 3400(O-H, stretch), 2960(C-H, stretch), 1725(C=O, stretch) cm$^{-1}$.

$^1$H-NMR (80 MHz, CDCl$_3$) $\delta$: 1.00(3H, s, C6-CH$_3$), 1.05(3H, s, C6-H), 1.30(3H, t, $\delta$=6 Hz, C2'-H), 1.59(1H, d, $\delta$=17 Hz, C5-H), 1.60(1H, brs, O-H), 1.70(3H, brs, C4-CH$_3$), 2.02(1H, d, $\delta$=17 Hz, C5-H), 2.25(1H, d, $\delta$=10 Hz, C1-H), 4.20(2H, d, $\delta$=6 Hz, C1'-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: calculated for $C_{12}H_2O_3$: 212.1412; found: 212.1410.

Elemental analysis: calculated for $C_{12}H_2O_3$: C 67.88, H 9.50; found: C 67.66, H 9.62.

3.5. ETHYL 4,6,6-TRIMETHYLCYCLOHEXA-1,3-DIENE-1-CARBOXYLATE 36

![Diagram of 4,6,6-Trimethylcyclohexa-1,3-diene-1-carboxylate](image)

To a solution of hydroxyester 32 (155 mg, 0.74 mmol) in CH$_2$Cl$_2$ (5 mL) at 5°C under N$_2$ was added $p$-toluenesulfonyl chloride (139 mg, 0.74 mmol). After stirring to complete solution at 5°C, DMAP (91 mg, 0.74 mmol) was added. The reaction
mixture was stirred at 5°C for 2 h and then was poured into water and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2X, 5 mL) and the combined organic phases were dried over Na₂SO₄, filtered and evaporated in vacuo to give diene 36 (167 mg, 94%) as a pale yellow crude oil.

The physical properties of 36 are as follows:

UV λ<sub>max.</sub> (MeOH): 289 nm.

IR ν<sub>max.</sub> (CHCl₃): 2970 (C-H, stretch), 1705 (C=O, stretch), 1650 (C=C, stretch) cm⁻¹.

¹H-NMR (80 MHz, CDCl₃) δ: 1.20 (6H, s, C₆-CH₃), 1.30 (3H, t, /=7 Hz, C₂'-H), 1.85 (3H, brs, C₄-CH₃), 2.10 (2H, m, C₅-H), 4.20 (2H, q, /=7 Hz, C₁'-H), 5.78 (1H, C₃-H), 6.81 (1H, d, /=6 Hz, C₂-H). MS m/z: 194 (M⁺), 179, 149, 121. High resolution mass measurement: calculated for C₁₂H₁₆O₂: 194.1306; found: 194.1302.

3.6. ETHYL 2β-BENZOXY-4,6,6-TRIMETHYL CYCLOHEX-3-ENE-1β-CARBOXYLATE 33

To a solution of hydroxyester 32 (300 mg, 1.43 mmol) and DMAP (189 mg, 1.54 mmol) in CH₂Cl₂ (10 mL) at 5°C under N₂ was added benzoyl chloride (0.18 mL, 1.54 mmol). The reaction mixture was stirred at 5°C for 3 h and then was poured into water (10 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2X, 10 mL) and the combined organic phases were dried
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over Na₂SO₄, 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 33 (380 mg, 85%) as a colorless oil.

The physical properties of 33 are as follows:

IR ν_max. (CHCl₃): 2975(C-H, stretch), 1725(broad, C=O, stretch), 1610(C=C, stretch) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 1.05(3H, t, /=6 Hz, C₂'-H), 1.11(3H, s, C₆-CH₃), 1.15(3H, s, C₆-CH₃), 1.73(1H, d, /=18 Hz, C₅-H), 1.76(3H, brs, C₄-CH₃), 2.26(1H, d, /=18 Hz, C₅-H), 2.87(1H, d, /=6.7 Hz, C₁-H), 4.01(2H, q, /=6 Hz, C₁'-H), 5.51(1H, brs, C₃-H), 5.80(1H, m, C₂-H), 7.40(2H, dd, /=7.6, 7.6 Hz, C₃" and C₅"-H), 7.53(1H, tt, /=7.6, 1.3 Hz, C₄"-H), 8.10(2H, dd, /=7.6, 1.3 Hz, C₂" and C₆"-H).

MS m/z: 316(M⁺), 211, 194, 105. High resolution mass measurement: calculated for C₁₉H₂₃O₄: 316.1675; found: 316.1667.

Elemental Analysis: calculated for C₁₉H₂₃O₄: C 72.11, H 7.65; found: C 71.81, H 7.82.

3.7. ETHYL 2α-BENZOXY-4,6,6-TRIMETHYL CYCLOHEX-3-ENE-1β-CARBOXYLATE 40

Following the same conditions as above trans-hydroxyester 35 (105 mg, 0.50 mmol)
gave trans-benzoate 40 (128 mg, 82%).

The physical properties of 40 are as follows:

\[ \text{IR } \nu_{\text{max}} \left( \text{CHCl}_3 \right): 2980(\text{C-H, stretch}), 1730(\text{C=O of ethyl ester, stretch}), 1710(\text{C=O of aromatic ester, stretch}), 1605(\text{C=C, stretch}) \text{ cm}^{-1}. \]

\[ ^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3 \delta : 1.08(3H, s, C_6-\text{CH}_3), 1.09(3H, s, C_6-\text{CH}_3), \]

1.18(3H, t, J = 7 Hz, C2'-H), 1.71(3H, brs, C4-CH3), 1.77(1H, d, J = 18 Hz, C5-H),

2.09(1H, d, J = 18 Hz, C5-H), 2.70(1H, d, J = 10 Hz, C1-H), 4.13(2H, q, J = 7 Hz, C1'H),

5.52(1H, brs, C3-H), 5.83(1H, brd, J = 10 Hz, C2-H), 7.39(2H, dd, J = 8, 8 Hz, C3'' and C5''-H),

7.52(1H, t, J = 8 Hz, C4''-H), 8.00(2H, d, J = 8 Hz, C2''-H and C6''-H).

\[ \text{MS } m/z: 316(\text{M}^+), 271, 211, 165, 105. \] High resolution mass measurement: calculated for \( C_{19}H_{20}O_4 \): 316.1675; found: 316.1662.

Elemental analysis: calculated for \( C_{19}H_{20}O_4 \): C 72.11, H 7.65; found: C 71.88, H 7.80.

3.8. ETHYL 2α-(3-INDOLYL)-4,6,6-TRIMETHYLCYCLOHEX-3-ENE-1β-CARBOXYLATE 34

![Chemical structure of 34 and 39](image)

To a suspension of magnesium (116 mg, 4.80 mmol) in dry ether (5 mL) at room temperature under \( N_2 \) was added dropwise methyl iodide (0.3 mL, 4.80 mmol).
After stirring for 30 minutes, 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 33 (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 1 h at room temperature and then decomposed with NH₄Cl (5 mL, sat. aq.). The layers were separated and the aqueous phase was extracted with dichloromethane (3X, 10 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuo to yield a brown residue. Purification by flash chromatography using hexanes/ether (8:2, v/v) gave indole-ester 34 (206 mg, 42%) and with further elution the isomer 39 (158 mg, 31%) as pale yellow liquids.

The physical properties of 34 are as follows:

**UV** $\lambda_{max}$ (MeOH): 224, 280 nm.

**IR** $\nu_{max}$ (CHCl₃): 3480(N-H, stretch), 2960(C-H, stretch), 1730(C = O, stretch) cm⁻¹.

$^1$H-NMR (400 MHz, CDCl₃) δ: 0.99(3H, t, /=8 Hz, C₂'-H), 1.03(3H, s, C₆-CH₃), 1.14(3H, s, C₆-CH₃), 1.73(3H, brs, C₄-CH₃), 1.74(1H, d, /=16 Hz, C₅-H), 2.15(1H, d, /=16 Hz, C₅-H), 2.67(1H, d, /=12 Hz, C₁-H), 3.90(1H, m, C₅-H), 3.90(2H, q, /=8 Hz, C₁'-H), 5.48(1H, brs, C₃-H), 6.99(1H, d, /=3.2 Hz, C₂''-H), 7.06(1H, dd, /=8,8 Hz, C₅''-H), 7.15(1H, dd, /=8,8 Hz, C₆''-H), 7.31(1H, d, /=8 Hz, C₇''-H), 7.61(1H, d, /=8 Hz, C₄''-H), 7.92(1H, brs, N-H).

**MS** m/z: 311(M⁺), 296, 238, 222. High resolution mass measurement: calculated for C₂₀H₂₅NO₂: 311.1885; found: 311.1879.

Elemental analysis: calculated for C₂₀H₂₅NO₂: C 77.14, H 8.09, N 4.50; found:
The physical properties of 39 are as follows:

**UV** $\lambda_{\text{max.}}$ (log $\epsilon$) (MeOH): 225(4.53), 283(3.71) nm.

**IR** $\nu_{\text{max.}}$ (CHCl$_3$): 3480(N-H), 2980(C-H, stretch), 1730(C=O, stretch), 1635(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (80 MHz, CDCl$_3$) $\delta$: 0.75(3H,s,C6-CH$_3$), 1.00(3H,s,C6-CH$_3$), 1.27(3H,t,$\pm$6 Hz,C2'-H), 1.58(3H,s,C4-CH$_3$), 1.95(1H,d,$\pm$14 Hz,C5-H), 2.25(1H,d,$\pm$14 Hz,C5-H), 2.95(1H,dd,$\pm$4.2 Hz,C1-H), 4.20(2H,q,$\pm$6 Hz,C1'-H), 5.79(1H,dd,$\pm$10.4 Hz,C2 or C3-H), 6.05(1H,dd,$\pm$10.2 Hz,C2 or C3-H), 6.95(1H,d,$\pm$2.5 Hz,C2''-H), 7.06(1H,dd,$\pm$8.8 Hz,Ar-H), 7.15(1H,dd,$\pm$8.8 Hz,Ar-H), 7.23(1H,d,$\pm$8 Hz,C7''-H), 7.74(1H,d,$\pm$8 Hz,C4''-H), 7.93(1H,brs,N-H).

**MS** m/z: 311(M$^+$), 296, 238, 117.

Elemental analysis: calculated 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.

### 3.9. Ethyl 2a-(1-p-Toluenesulfonyl-3-indolyl)-4,6,6-trimethyl cyclohex-3-ene-1β-carboxylate 43
To a solution of indole-ester 34 (220 mg, 0.71 mmol) in THF (5 mL) at 0°C under N₂ was added potassium hydride (81 mg, 0.71 mmol, 35% dispersion in oil) followed by p-toluenesulfonyl chloride (149 mg, 0.78 mmol). The reaction mixture was stirred for 3 h at 0-5°C, and then water (1 mL) and NH₄Cl (2 mL, sat. aq.) were added. After evaporation of THF in vacuo, the mixture was extracted with ether (3X, 5 mL) and the organic solution was washed with water (10 mL), brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to yield a yellow oil. Purification by flash chromatography using hexanes/ether (8:2, v/v) gave tosylester 43 (296 mg, 90%) as a pale yellow foam.

The physical properties of 43 are as follows:

UV \( \lambda_{\text{max}} \) (log \( \varepsilon \)) (MeOH): 214(4.43), 250(4.05) nm.

IR \( \nu_{\text{max}} \) (CHCl₃): 2970(C-H, stretch), 1720(C=O, stretch), 1605(C=C, stretch) cm⁻¹.

\(^1\)H-NMR (400 MHz, CDCl₃) 6: 0.96(3H, t, /=6 Hz, C2'-H), 1.03(3H, s, C6-CH₃), 1.11(3H, s, C6-CH₃), 1.71(3H, brs, C4-CH₃), 1.75(1H, d, /=16 Hz, C5-H), 2.13(1H, d, /=16 Hz, C5-H), 2.34(3H, s, Ar-CH₃), 2.59(1H, d, /=9 Hz, C1-H), 3.73-3.95(3H, m, C1'-H and C2-H), 5.35(1H, brs, C3-H), 7.17-7.30(4H, m, Ar-H), 7.36(1H, s, C2"-H), 7.52(1H, d, /=8 Hz, Ar-H), 7.70(2H, d, /=8 Hz, Ar-H), 7.95(1H, d, /=8 Hz, Ar-H).


Elemental analysis: calculated for C₂₇H₃₁NSO₄: C 69.65, H 6.72, N 3.01; found: C 69.43, H 6.90, N 2.94.
3.10.  3α-(1-ρ-TOLUENSULFONYL-3-INDOLYL)-1,5,5-TRIMETHYL-
4β-PENTANOYL-1-CYCLOHEXENE 44A

To a solution of tosylester 43 (76 mg, 0.16 mmol) in THF (2 mL) at -78°C under
N₂ was added dropwise n-butyllithium (0.11 mL, 0.18 mmol, 1.6M in hexane). The
reaction mixture was stirred for 0.5 h at -78°C and then warmed to 0°C for 0.5
h. After addition of ice (about 0.5 g) and NH₄Cl (2 mL, sat. aq.), the reaction
mixture was extracted with ethyl acetate (3X, 5 mL) and the resulting organic
solution was washed with water (10 mL), brine (10 mL), dried over Na₂SO₄, filtered
and concentrated in vacuo to yield a yellow oil. Purification by flash
chromatography using hexanes/ether (8:2, v/v) gave ketone 44a (35 mg, 45%).

The physical properties of 44a are as follows:

UV λ_max. (MeOH): 225, 285 nm.

IR ν_max. (CHCl₃): 2960(C-H, stretch), 1705(C=O, stretch), 1600(C=C, stretch) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 0.56(3H, t, /=7 Hz, C5'-H), 0.76-1.04(4H, m, C3'-H and
C4'-H), 0.98(3H, s, C5-CH₃), 1.06(3H, s, C5-CH₃), 1.69(1H, d, /=17 Hz, C6-H),
1.72(3H, brs, C1-CH₃), 2.07-2.18(3H, m, 2XC2'-H and 1XC6-H), 2.33(3H, s, Ar-CH₃),
2.80(1H, d, /=10 Hz, C4-H), 3.84(1H, m, C3-H), 5.31(1H, brs, C2-H), 7.16-7.23(3H, m, Ar-H),
7.25-7.32 (2H, m, Ar-H), 7.48 (1H, d, J = 8 Hz, Ar-H), 7.73 (2H, d, J = 8 Hz, Ar-H),
7.95 (1H, d, J = 8 Hz, Ar-H).

MS m/z: 477 (M+), 420, 392, 322.

3.11. 2β-HYDROXY-4,6,6-TRIMETHYLICYCLOHEX-3-ENE-1β-CARBOXYLIC ACID 46

3.11.1. Method A
To a solution of hydroxyester 32 (600 mg, 2.83 mmol) in EtOH (10 mL) at room
temperature was added NaOH (5 mL, 10% aq). After stirring the reaction mixture
for 5 days the organic solvent was evaporated in vacuo. The residue was diluted
with water (5 mL) and the resulting solution was washed with ether. The aqueous
phase was carefully acidified with HCl (10% aq.) to pH 5.5 at 5°C. Extraction with
ethyl acetate (3X, 8 mL) followed by drying over Na2SO4, filtration and evaporation
in vacuo gave a pale yellow solid. Crystallization from ether/hexane furnished
cis-hydroxyacid 46 (391 mg, 75%) as colorless crystals.
3.11.2. Method B

To a solution 2,6-di-tert-butyl-4-methylphenol (231.8 g, 1.05 mol) in dry ether (2.75 L) at -78°C under N₂ was added dropwise a solution of n-butyllithium (0.625 L, 1.0 mol, 1.6M in hexane). The suspension of white solid was warmed to room temperature and carbon dioxide gas was passed through the mixture for 10-12 minutes. A solution of isophorone 26 (50.05 mL, 0.33 mol) in dry ether (0.23 L) was then added with the precipitate dissolving completely. CO₂ was bubbled through the solution until no more absorption occurred. A positive pressure of CO₂ was then installed by connecting CO₂-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 this salt of the β-ketoacid 27 was added sodium borohydride (11.4 g, 0.37 mol) in methanol (0.5 L) in three portions. After 2.5 h of stirring at 0°C additional sodium borohydride (11.4 g, 0.37 mol) in methanol (0.5 L) 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 (2X, 0.5 L) and then acidified very carefully with HCl (10% aq) to pH 5.5 at 5°C. Extraction with ethyl acetate (3X, 300 mL) followed by drying over Na₂SO₄, filtration and evaporation in vacuo gave a crude pale yellow solid. Crystallization from ether/hexane furnished cis-hydroxyacid 46 (28 g, 46%) as colorless crystals. Crystallization of the evaporated mother liquor with chloroform yielded trans-hydroxyacid 51 (2.5 g, 4%).

The physical characteristics of 46 are as follows:

m.p. = 115-118°C (ether/hexane).
IR \( \nu_{\text{max.}} \) (CHCl\(_3\)): 3350-2500(O-H,stretch), 3010 and 2970(C-H,stretch), 1718(C=O,stretch) cm\(^{-1}\).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \): 1.05(3H,s,C6-CH\(_3\)), 1.15(3H,s,C6-CH\(_3\)), 1.70(1H,d,J=17.5 Hz, C5-H), 1.73(3H,brs,C4-CH\(_3\)), 2.07(1H,d,J=17.5 Hz, C5-H), 2.69(1H,d,J=6 Hz, 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: calculated for C\(_{10}\)H\(_{16}\)O\(_3\): 184.1100; found: 184.1099.

Elemental analysis: calculated for C\(_{10}\)H\(_{16}\)O\(_3\): C 65.19, H 8.75; found: C 65.45, H 8.65.

The physical properties of 51 are described in section 3.12.

3.12. 2\(\alpha\)-HYDROXY-4,6,6-TRIMETHYLCYCLOHEX-3-ENE-1\(\beta\)-CARBOXYLIC ACID 51

Following the same conditions as reaction 3.11.1, trans-hydroxyester 35 (223 mg, 1.05 mmol) gave trans-hydroxyacid 51 (157 mg, 81%).

The physical characteristics of 51 are as follows:

m.p. = 186-188\(^\circ\)C (CHCl\(_3\)).

IR \( \nu_{\text{max.}} \) (KBr): 3375(O-H,stretch), 3200-2300(O-H,stretch), 2950 (C-H,stretch),
1710(C=O, stretch), 1635(C= C, stretch) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 0.98(3H, s, C6-CH₃), 1.08(3H, s, C6-CH₃),
1.64(1H, d, /=17 Hz, C5-H), 1.69(3H, brs, C4-CH₃), 2.01(1H, d, /=17 Hz, C5-H),
2.24(1H, d, /=10 Hz, 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: calculated for
C₁₀H₁₆O₃: 184.1100; found: 184.1102.

Elemental analysis: calculated for C₁₀H₁₆O₃: C 65.19, H 8.75; found:
C 64.89, H 8.66.

3.13. 2β-BENZOXY-4,6,6-TRIMETHYLCYCLOHEX-3-ENE-1β-CARBOXYLIC BENZOIC
ANHYDRIDE 47

To a suspension of hydroxyacid 46 (20 g, 0.109 mol) in CH₂Cl₂ (450 mL) was
added DMAP (28 g, 0.228 mol) at room temperature. The mixture was stirred 10
minutes, then was cooled to 0-5°C under N₂. Benzoyl chloride (26.5 mL, 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 hydroxyacid. The reaction mixture was poured into water (200
mL), and the layers were separated. The aqueous phase was extracted with CH₂Cl₂.
(2X, 100mL) and the combined organic phases were dried over Na$_2$SO$_4$, filtered and evaporated *in vacuo* to give 47 as a yellow oil and was used without further purification for the next reaction.

The physical properties of 47 are as follows:

IR $\nu_{\text{max}}$ (CHCl$_3$): 2960 (C-H, stretch), 1795 and 1725 (C=O, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 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, $\delta$=17 Hz, C5-H), 2.30 (1H, d, $\delta$=17 Hz, C5-H), 3.10 (1H, d, $\delta$=6 Hz, C1-H), 5.58 (1H, m, C3-H), 5.82-6.05 (1H, m, C2-H), 7.17-8.30 (10H, m, Ar-H).

3.14. 2α-(3-INDOLYL)-4,6,6-TRIMETHYLCYCLOHEX-3-ENE-1β-CARBOXYLIC ACID 48

To a suspension of magnesium (10.6 g, 0.44 mol) in dry ether (212 mL) at room temperature under N$_2$ was added dropwise a solution of methyl iodide (27.2 mL, 0.44 mol) in dry ether (81.5 mL). After stirring for 30 minutes 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 mole) was added dropwise to a solution of the crude benzoate
47 (38 g) in dry ether (203 mL) at 5°C. The reaction mixture was stirred for 2 h at 5°C, 1 h at room temperature and then decomposed with NH₄Cl (700 mL, sat. aq.). The layers were separated and the aqueous phase was extracted with ethyl acetate (3X, 200mL). The combined organic layers were washed with water (800 mL), brine (800 mL), dried over Na₂SO₄, 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 NaOH (3X, 150mL, 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 (3X, 300mL) followed by washings with water (400 mL) and brine (400 mL), drying over Na₂SO₄, 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 indoleacid 48 and compound 57 in a ratio 6:4 in favor of indoleacid 48 (i.e. 40% yield) as determined by ¹H-NMR. Compounds 58 (0.64 g, 3%) and 56 (1.9 g, 15%) were also obtained from the column. Further purification of the mixture of 48 and 57 by flash chromatography using chloroform/hexanes (6.5:3.5, v/v) afforded indoleacid 48 (6.5 g, 30%), although always accompanied with some decomposition. Since there was no detriment to the yield of the next step in using the mixture of products, this last purification was usually avoided.

The physical properties of 48 are as follows:

m.p. = 173-174°C (ether-hexane).

UV λmax. (log ε) (MeOH): 222(4.51), 282(3.76) nm.

IR νmax. (CHCl₃): 3480(N-H,stretch), 3400-2450(O-H,stretch), 3020 and 2980(C-H,stretch), 1710(C=O,stretch), 1630(C=C,stretch) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 1.08(3H,s,C6-CH₃), 1.14(3H,s,C6-CH₃),
1.71(3H, brs, C4-CH$_3$), 1.76(1H, d, J= 16 Hz, C5-H), 2.15(1H, d, J= 16 Hz, C5-H),
2.71(1H, d, J= 10 Hz, C1-H), 3.93(1H, brd, J= 10 Hz, C2-H), 5.47(1H, brs, C3-H),
6.94(1H, d, J= 2 Hz, C2'-H), 7.08(1H, dd, J= 8, 8 Hz, C5'-H), 7.17(1H, dd, J= 8, 8 Hz, C6'-H),
7.33(1H, d, J= 8 Hz, C7'-H), 7.62(1H, d, J= 8 Hz, C4'-H), 7.77(1H, brs, N-H).

MS m/z: 283(M$^+$), 222, 182, 168. High resolution mass measurement: calculated for
C$_{11}$H$_{21}$N$_2$: 283.1572; found: 283.1573.

Elemental analysis: calculated for C$_{11}$H$_{21}$N$_2$: C 76.30, H 7.47, N 4.94; found:
C 76.49, H 7.42, N 4.90.

The physical properties of 57 are as follows:

UV $\lambda_{max}$. (log $\epsilon$) (MeOH): 222(4.49), 281(3.79) nm.

IR $\nu_{max}$. (CHCl$_3$): 3500-2450(O-H, stretch), 3400(N-H, stretch), 3025 and
2940(C-H, stretch), 1700(C=O, stretch), 1660(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 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 Hz, C5-H), 2.25(1H, d, J= 16 Hz, C5-H),
3.02(1H, dd, J= 3, 2 Hz, C1-H), 5.85(1H, dd, J= 10, 3 Hz, C2-H), 6.06(1H, dd, J= 10, 2 Hz, C3-H),
6.94(1H, d, J= 2 Hz, C2'-H), 7.10(1H, ddd, J= 8, 8, 1.5 Hz, Ar-H),
7.18(1H, ddd, J= 8, 8, 1.5 Hz, Ar-H), 7.36(1H, d, J= 8 Hz, C7'-H), 7.74(1H, d, J= 8 Hz, C4'-H),
7.89(1H, brs, N-H).

MS m/z: 283(M$^+$), 268, 222, 117. High resolution mass measurement: calculated for
C$_{11}$H$_{21}$N$_2$: 283.1572; found: 283.1574.

Elemental analysis: calculated for C$_{11}$H$_{21}$N$_2$: C 76.30, H 7.47, N 4.94; found:
C 76.50, H 7.52, N 4.83.

The physical properties of 58 are as follows:

UV $\lambda_{max}$. (log $\epsilon$) (MeOH): 223(4.54), 283(3.70) nm.
IR $\nu_{\text{max}}$ (CHCl$_3$): 3400(N-H, stretch), 3400-2700(O-H, stretch), 3029 and 2962(C-H, stretch), 1700(C=O, stretch), 1660(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 0.60(3H, s, C$_6$-CH$_3$), 1.13(3H, s, C$_6$-CH$_3$), 1.51(3H, brs, C$_4$-CH$_3$), 1.73(1H, d, $J$ = 14 Hz, C$_5$-H), 2.52(1H, dd, $J$ = 14.1 Hz, C$_5$-H), 3.02(1H, m, C$_1$-H), 5.82(1H, dd, $J$ = 10.2 Hz, C$_2$-H), 6.13(1H, ddd, $J$ = 10.2, 1 Hz, C$_3$-H), 6.92(1H, d, $J$ = 2 Hz, C$_2'$-H), 7.10(1H, ddd, $J$ = 7.5, 7.5, 1 Hz, Ar-H), 7.18(1H, ddd, $J$ = 7.5, 7.5, 1 Hz, Ar-H), 7.36(1H, d, $J$ = 7.5 Hz, C$_7'$-H), 7.82(1H, d, $J$ = 7.5 Hz, C$_4'$-H), 7.90(1H, brs, N-H).

MS m/z: 283(M$^+$), 268, 117. High resolution mass measurement: calculated for C$_{18}$H$_{21}$N$_2$: 283.1572; found: 283.1574.

The physical properties of 56 are as follows:

m.p. = 115-117°C (ether/hexane).

UV $\lambda_{\text{max}}$ (MeOH): 290 nm.

IR $\nu_{\text{max}}$ (CHCl$_3$): 3200-2800(O-H, stretch), 3048 and 2959(C-H, stretch), 1680(C=O, stretch), 1642(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 1.20(6H, s, C$_6$-CH$_3$), 1.85(3H, brs, C$_4$-CH$_3$), 2.13(2H, s, C$_5$-H), 5.81(1H, dq, $J$ = 6.5, 1.2 Hz, C$_3$-H), 7.00(1H, d, $J$ = 6.5 Hz, C$_2$-H).

MS m/z: 166(M$^+$), 151, 107. High resolution mass measurement: calculated for C$_{10}$H$_{14}$O$_2$: 166.0994; found: 166.0995.

Elemental analysis: calculated for C$_{10}$H$_{14}$O$_2$: C 72.26, H 8.49; found: C 72.33, H 8.40.
3.15. ETHYL 4α-(3-INDOLYL)-4β,6,6-TRIMETHYLCYCLOHEX-2-ENE-1β-CARBOXYLATE 39

To a solution of acid 57 (118 mg, 0.42 mmol) in THF (5 mL) at room temperature under N₂ were added dry ethanol (0.027 mL, 0.462 mmol) and triphenylphosphine (121 mg, 0.462 mmol). To the resulting solution was added dropwise diethylazodicarboxylate (0.073 mL, 0.462 mmol) and the reaction mixture was maintained at room temperature for one day. Evaporation of the solvent in vacuo and purification by flash chromatography using hexanes/ether (7.5:2.5, v/v) afforded ester 39 (106 mg, 82%).

The physical properties of this product resulted identical to those described in Section 3.8.
3.16. 6-OXO-7,7,9-TRIMETHYL-5,6,6a,7,8,10a,β-HEXAHYDROINDENO[2,1-b]INDOLE 60

3.16.1. Method A

To a solution of indole acid 48 (450 mg, 1.6 mmol) in benzene (10 mL) at 0° under N₂ 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 64 was then dissolved in ether (10 mL) and a solution of indolylmagnesium iodide (3.5 equiv., for preparation see section 3.8) in ether (8 mL) and dichloromethane (3.1 mL) was added dropwise for 8 h at -15°C under N₂. The reaction mixture was stirred for 14 h at room temperature followed by quenching with NH₄Cl (10 mL, sat. aq.) and extraction with dichloromethane (3X, 10 mL). The organic phase was washed with NaHCO₃ (10 mL, sat. aq.) and brine (10 mL), dried over Na₂SO₄, 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 65 (85 mg, 14%) as a yellowish foam.

3.16.2. Method B
To a solution of the acid chloride (prepared from indoleacid 48 (198 mg, 0.7 mmole) as in method A) in dry THF (4 mL) at -15°C under N2 was added dropwise a solution of LDA in THF (prepared from diisopropylamine (0.25 mL, 1.75 mmol) as described in section 3.2) 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 NH4Cl (2 mL, sat. aq.). After extraction with ethyl acetate (3X, 10 mL), the organic phase was washed with water/brine (10 mL, 1:1, v/v), brine (10 mL), dried over Na2SO4, 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 60 (55.6 mg, 30%). Further elution using hexanes/ether (6:4, v/v) recovered indoleacid 48 (53 mg, 27%).
The physical properties of 60 are as follows:
m.p. = 129-131°C (acetone/hexane).
IR νmax (CHCl3): 3464(N-H, stretch), 3040 and 2960(C-H, stretch), 1683(C=O, stretch), 1625(C=C, stretch) cm⁻¹.
1H-NMR (400 MHz, CDCl3) δ: 1.14(3H,s,C7-CH3), 1.47(3H,s,C7-CH3), 1.75(3H,brs,C9-CH3), 1.97(1H,d,J= 18 Hz,C8-H), 2.07(1H,d,J= 18 Hz,C8-H), 2.84(1H,d,J= 6 Hz,C6a-H), 3.99(1H,m,C10a-H), 6.24(1H,brs,C10-H), 7.18(1H,ddd,J= 8,8.1 Hz,Ar-H), 7.35(1H,ddd,J= 8,8.1 Hz,Ar-H), 7.44(1H,d,J= 8 Hz,Ar-H), 7.80(1H,d,J= 8 Hz,Ar-H), 8.73(1H,brs,N-H).
Experimental

MS m/z: 265(M+), 250, 222. High resolution mass measurement: calculated for C_{18}H_{19}NO: 265.1466; found: 265.1466.

Elemental analysis: calculated 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.

The physical properties of 65 are as follows:

UV $\lambda_{\text{max}}$ (log $\epsilon$) (MeOH): 219(4.56) nm.

IR $\nu_{\text{max}}$ (CHCl$_3$): 3465(N-H, stretch), 3025 and 2960(C-H), 1637(C=O, stretch) cm$^{-1}$.

$^1$H-NMR (400MHz, CDCl$_3$) δ: 0.93(3H,s,C5-CH$_3$), 1.27(3H,s,C5-CH$_3$), 1.79(1H,d,$\delta$=18 Hz,C6-H), 1.80(3H,brs,C1-CH$_3$), 2.30(1H,d,$\delta$=18 Hz,C6-H), 3.54(1H,d,$\delta$=10 Hz,C4-H), 4.14(1H,m,C3-H), 5.59(1H,brs,C2-H), 6.85(1H,d,$\delta$=2 Hz,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,$\delta$=8 Hz,Ar-H), 7.98(1H,brs,N-H), 8.40(1H,d,$\delta$=8 Hz,Ar-H).

MS m/z: 382(M$^+$), 238, 144. High resolution mass measurement: calculated for C$_{26}$H$_{26}$N$_2$O: 382.2044; found: 382.2042.

3.17. 6-OXO-7,7,9-TRIMETHYL-5,6,6aβ,7,8,10αβHEXAHYDROINDENO[2,1-b]INDOLE 24

![Chemical Structure Image]
3.17.1. Method A

To a solution of trans-ketone 60 (430 mg, 1.6 mmol) in dry THF (6 mL) and dry MeOH (15 mL) at room temperature under N\textsubscript{2} was added sodium methoxide (10 mL, 0.03M in MeOH). The reaction mixture was refluxed for 1 h, cooled to room temperature and then water (2 mL) and NH\textsubscript{4}Cl (5 mL, sat. aq.) were added. The organic solvent was evaporated in vacuo and the resulting residue was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic phase was washed with water (10 mL), brine (10 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and evaporated in vacuo to yield a yellow solid. Recrystallization of this powder from acetone/hexane gave pure cis-ketone 24 (426 mg, 99%) as pale yellow crystals.

3.17.2. Method B

To a solution of trans-ketone 60 (24.6 mg, 0.093 mmol) in dry THF (3 mL) at -15°C under N\textsubscript{2} was added dropwise a solution of LDA in THF (prepared from diisopropylamine (0.03 mL, 0.21 mmole) as described in section 3.2). The reaction was warmed to room temperature and stirred for 2.5 h. Ice (about 0.5 g) and NH\textsubscript{4}Cl (4 mL, sat. aq.) were added followed by extraction with ethyl acetate (3X, 5 mL). The organic phase was washed with water/brine (7 mL, 1:1, v/v), brine (7 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, 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.
3.17.3. Method C

To a solution of acid chloride 64 (prepared from indoleacid 48 (281.5 mg, 0.99 mmol) as described in section 3.16.1) in dry THF (5.6 mL) at -15° under N₂ was added dropwise a solution of LDA in THF (prepared from diisopropylamine (0.35 mL, 2.48 mmol) as described in section 3.2) 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 NH₄Cl (10 mL, sat. aq.) were added followed by extraction with ethyl acetate (3X, 10 mL). The organic phase was washed with water/brine (10 mL, 1:1, v/v), brine (10 mL), dried over Na₂SO₄, 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 24 (71.2 mg, 27%) and further elution using hexanes/ether (6:4, v/v) returned indoleacid 48 (73.2 mg, 26%). The physical properties of 24 are as follows: m.p. = 220-223° C (acetone/hexane).

UV λ_max. (log ε) (MeOH): 227(4.29), 302 (4.25) nm.

IR ν_max. (CHCl₃): 3464(N-H, stretch), 3021 and 2831(C-H, stretch), 1676(C=O, stretch), 1620(C=C, stretch) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ: 0.92(3H, s, C7-CH₃), 1.27(3H, s, C7-CH₃), 1.69(3H, brs, C9-CH₃), 1.76(1H, d, J= 16.5 Hz, C8-H), 1.96(1H, d, J= 16.5 Hz, C8-H), 2.89(1H, d, J= 6 Hz, C6a-H), 4.05(1H, m, C10a-H), 5.90(1H, brs, C10-H), 7.18(1H, ddd, J= 9, 8, 1.5 Hz, Ar-H), 7.36(1H, ddd, J= 10, 9, 1.5 Hz, Ar-H), 7.48(1H, dd, J= 10, 1.5 Hz, Ar-H), 7.79(1H, dd, J= 8, 1.5 Hz, Ar-H), 9.75(1H, brs, N-H),

MS m/z: 265(M⁺), 250, 222. High resolution mass measurement: calculated for C₁₈H₁₉NO: 265.1466; found: 265.1473.

Elemental analysis: calculated for C₁₈H₁₉NO: C 81.48, H 7.22, N 5.28; found: C 81.19, H 7.10, N 5.10.
3.18. Method A

To a solution of cis-ketone 24 (1.02 g, 3.85 mmol) in dry THF (40 mL) at 0°C under N₂ was added LiAlH₄ (about 0.14 g, 4.0 mmole). After stirring for 1 h at 0-5°C and 1 h at room temperature, wet ether (15 mL, sat. aq.), NaOH (30 mL, 15% aq.), and water (10 mL) were slowly added. The mixture was extracted with ether (5X, 15 mL) and the organic phase was washed with water/brine (100 mL, 1:1, v/v), brine (50 mL), dried over MgSO₄, 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 67 (1.27 g, 65%) and further elution with hexanes/ether (7.5:2.5, v/v) afforded alcohol 70 (0.68 g, 35%) as a crystalline solid.
3.18.2. Method B

To a solution of L-Selectride (0.24 mL, 0.24 mmol, 1M in THF) at -78°C under N₂ was added a solution of cis-ketone 24 (21.7 mg, 0.08 mmol) in dry THF (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, 1M in THF) was added. After stirring at room temperature overnight, water (0.1 mL), NaOH (0.3 mL, 3M) and H₂O₂ (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 NaCl and extracted with dichloromethane (3X, 5 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and evaporated in vacuo to yield a yellow oil.

Purification by flash chromatography using hexanes/ether (8.5:1.5, v/v) gave alcohol 67 (11 mg, 50.3%) and recovered cis-ketone 24 (8 mg, 36%).

The physical properties of 67 are as follows:

m.p. = 159-162°C (ether/hexane).

UV λmax. (log ε) (MeOH): 224(4.50), 282(3.85) nm.

IR νmax. (CHCl₃): 3571(free O-H, stretch), 3470(N-H, stretch), 3250(hydrogen bonded O-H), 2958(C-H, stretch), 1669(C=C, stretch) cm⁻¹.

¹H-NMR (300 MHz, CDCl₃) δ: 1.12(3H, s, C7-CH₃), 1.34(3H, s, C7-CH₃), 1.63(3H, brs, C9-CH₃), 1.70(1H, d, J=16.6 Hz, 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 Hz, C4-H), 7.64(1H, d, J=7 Hz, C1-H), 8.17(1H, brs, N-H).

MS m/z: 267(M⁺), 249, 234, 219. High resolution mass measurement: calculated for
C_{18}H_{21}NO: 267.1623; found: 267.1629.

Elemental analysis: calculated 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.

The physical properties of 70 are as follows:

m.p. = 149-150°C (ether/hexane).

UV $\lambda_{\text{max}}$ (log $e$) (MeOH): 227(4.48), 282(3.88) nm.

IR $\nu_{\text{max.}}$ (CHCl$_3$): 3587 (free O-H, stretch), 3470 (N-H, stretch), 3350 (hydrogen bonded O-H), 3019 and 2961 (C-H, stretch) cm$^{-1}$.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 1.06 (3H, s, C7-CH$_3$), 1.18 (3H, s, C7-CH$_3$), 1.56 (3H, brs, C9-CH$_3$), 1.60 (1H, d, $J$ = 17 Hz, C8-H), 2.02 (1H, d, $J$ = 17 Hz, C8-H), 2.03 (1H, brs, O-H), 2.37 (1H, dd, $J$ = 6.6, 6.6 Hz, C6a-H), 3.86 (1H, m, C10a-H), 5.12 (1H, d, $J$ = 6.6 Hz, C6-H), 5.56 (1H, brs, C10-H), 7.11 (1H, dd, $J$ = 7.3, 7.3 Hz, Ar-H), 7.15 (1H, dd, $J$ = 7.3, 7.3 Hz, Ar-H), 7.27 (1H, d, $J$ = 7.3 Hz, C4-H), 7.55 (1H, d, $J$ = 7.3 Hz, C1-H), 8.18 (1H, brs, N-H).

MS m/z: 267 (M$^+$), 249, 234, 219. High resolution mass measurement: calculated for C_{18}H_{21}NO: 267.1623; found: 267.1616.
3.19. 5-BENZOYL-6α-BENZOXY-7,7,9-TRIMETHYL-5,6α,6αβ,7,8,10αβ-
HEXAHYDROINDENO[2,1-b]INDOLE 68

To a solution of alcohol 67 (697 mg, 2.61 mmol), DMAP (382 mg, 3.13 mmol) and triethylamine (7 mL) in CH₂Cl₂ (57 mL) at room temperature under N₂ 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 NaHCO₃ (30 mL, 10% aq), water (30 mL), dried over Na₂SO₄, 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 68 (942 mg, 76%) as white crystals.

The physical properties of 68 are as follows:
m.p. = 171-174°C (ether/hexane).
UV λmax. (log ε) (MeOH): 225(4.27), 260(4.02) nm.
IR νmax. (CHCl₃): 3010 and 2959(C-H, stretch), 1718(C=O of ester, stretch),
1684(C=O of amide, stretch), 1603(C=C, stretch) cm⁻¹.
¹H-NMR (400 MHz, CDCl₃) δ: 1.03(3H,s,C7-CH₃), 1.12(3H,s,C7-CH₃).
1.54(1H,d,J=17 Hz,C8-H), 1.67(3H,brs,C9-CH₃), 2.09(1H,d,J=17 Hz,C8-H),
2.74(1H,dd,J=5.5,5.5 Hz,C6a-H), 3.84(1H,m,C10a-H), 5.73(1H,brs,C10-H),
6.40(1H,d,J=5.5 Hz,C6-H), 7.20-7.80(14H,m,Ar-H).

MS m/z: 475(M⁺), 353, 338, 105. High resolution mass measurement: calculated for
C₃₂H₂₉NO₃: 475.2147; found: 475.2145.
Elemental analysis: calculated for C₃₂H₂₉NO₃: C 80.82, H 6.15, N 2.94; found:
C 80.80, H 6.13, N 2.89.

3.20. 5-BENZOYL-6α-HYDROXY-7,7,9-TRIMETHYL-5,6α,6β,7,8,10αβ-
HEXAHYDROINDENO[2,1-b]INDOLE 72

To a solution of alcohol 67 (82 mg, 0.31 mmol), DMAP (45.4 mg, 0.37 mmol) in
CH₂Cl₂ (5 mL) at room temperature under N₂ was added benzoyl chloride (0.043
mL, 0.37 mmol). After 3 h at reflux, the reaction mixture was cooled to room
temperature and water (5 mL) was added. The organic phase was washed with
NaHCO₃ (5 mL, 10% aq), dried over Na₂SO₄, filtered, and evaporated in vacuo
to yield a pale yellow foam. Purification by flash chromatography using hexanes/ethyl
acetate (9:1, v/v) gave 72 (85 mg, 74%) as a colorless foam.
The physical properties of 72 are as follows:

UV \( \lambda_{\text{max}} \) (MeOH): 224, 262 nm.

IR \( \nu_{\text{max}} \) (CHCl\(_3\)): 3564(O-H, stretch), 3013 and 2961(C-H, stretch), 1679(C=O, stretch), 1602(C=C, stretch) cm\(^{-1}\).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \): 1.10(3H, s, C7-CH\(_3\)), 1.25(3H, s, C7-CH\(_3\)), 1.61(1H, d, /=17 Hz, C8-H), 1.65(3H, brs, C9-CH\(_3\)), 2.40(1H, brs, O-H), 2.46(1H, dd, /=6.6 Hz, C6a-H), 2.54(1H, d, /=17 Hz, C8-H), 3.71(1H, m, C10a-H), 4.92(1H, dd, /=6.6 Hz, C6-H), 5.63(1H, brs, C10-H), 7.10-7.81(9H, m, Ar-H).

MS m/z: 371(M\(^+\)), 356, 338, 105.

3.21. 5-BENZOYL-6\(\beta\)-(3-INDOLYL)-7,7,9-TRIMETHYL-5,6\(\beta\),6\(a\)\(\beta\),7,8,10a\(\beta\)-HEXAHYDROINDENO[2,1-b]INDOLE 69

\[\text{69}\]

\[\text{74}\]

\[\text{75}\]
To a solution of indolylmagnesium iodide (1.09 mmol, for preparation see section 3.8) in dry ether (1.8 mL) and dry dichloromethane (0.5 mL) at 0-5°C under N₂ was added dropwise a solution of benzoate 68 (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 NH₄Cl (4 mL, sat. aq.) were added, followed by extraction with dichloromethane (2X, 10 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over Na₂SO₄, 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 74 (29 mg, 18%), as an oil, benzoylyuehchukene 69 (66.1 mg, 40%) as a foam, and indoline 75 (50.7 mg, 30%) as white crystals.

The physical properties of 69 are as follows:

UV \( \lambda_{\text{max}} \) (MeOH): 226, 263 nm.

IR \( \nu_{\text{max}} \) (film): 3481(N-H, stretch), 3020 and 2961(C-H, stretch), 1681(C = 0, stretch), 1603(C = C, stretch) cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \): 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,/=16 Hz,C8-H), 1.95(1H,d,/=16 Hz,C8-H), 2.74(1H,dd,/=7.4 Hz,C6a-H), 3.95(1H,m,C10a-H), 4.12(1H,brd,/=4 Hz,C6-H), 5.86(1H,brs,ClO-H), 6.15(1H,d,/=2.5 Hz,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,/=8 Hz,Ar-H), 7.72(1H,brs,N-H), 7.82(1H,d,/=8 Hz,Ar-H).

MS m/z: 470(M⁺), 455, 365, 105. High resolution mass measurement: calculated for C\(_{33}\)H\(_{30}\)N\(_2\)O: 470.2357; found: 470.2353.
The physical properties of 74 are as follows:

UV $\lambda_{\text{max}}$, ($\log e$) (MeOH): 207(5.71), 253(4.37) nm.

IR $\nu_{\text{max}}$, (film): 3010 and 2959(C-H, stretch), 1685(C=O, stretch), 1603(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 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 Hz, C8-H), 1.98(1H, d, $J$=16.5 Hz, 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), 6.29(1H, d, $J$=3.5 Hz, C2'-H), 6.48(1H, d, $J$=3.5 Hz, C3'-H), 6.69(1H, d, $J$=8 Hz, C7'-H), 6.93(1H, dd, $J$=7.7 Hz, Ar-H), 6.98(1H, ddd, $J$=8.8, 1.5 Hz, Ar-H), 7.11-7.29(5H, m, Ar-H), 7.32(1H, ddd, $J$=8.8, 1.5 Hz, Ar-H), 7.41-7.52(2H, m, Ar-H), 7.61(1H, m, Ar-H), 7.68(1H, d, $J$=8 Hz, C1-H).

MS m/z: 470(M$^+$), 354, 105. High resolution mass measurement: calculated for C$_{33}$H$_{30}$N$_2$O: 470.2357; found: 470.2355.

Elemental analysis: calculated for C$_{33}$H$_{30}$N$_2$O: C 84.22, H 6.43, N 5.96; found: C 84.06, H 6.20, N 6.12.

The physical properties of 75 are as follows:

m.p. = 250-252°C (Acetone/hexane).

UV $\lambda_{\text{max}}$, ($\log e$) (MeOH): 224(4.66), 282(4.23) nm.

IR $\nu_{\text{max}}$, (CHCl$_3$): 3477(N-H, stretch), 3009 and 2960(C-H, stretch), 1650(C=O, stretch), 1601(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.78(3H, s, C7-CH$_3$), 0.89(3H, s, C7-CH$_3$), 1.40(1H, d, $J$=17 Hz, C8-H), 1.56(3H, brs, C9-CH$_3$), 1.81(1H, d, $J$=17 Hz, C8-H), 2.72(1H, brd, $J$=5 Hz, 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 Hz, 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 Hz, Ar-H), 7.41-7.52(2H, m, Ar-H), 7.61(1H, m, Ar-H), 7.68(1H, d, $J$=8 Hz, C1-H).
7.42(2H,dd,J=8.8 Hz,Ar-H), 7.51(1H,brdd,J=8.8 Hz,Ar-H), 7.58(3H,m,Ar-H),
7.91(1H,d,J=8 Hz,Ar-H), 7.97(1H,brs,N-H).

MS m/z: 470(M⁺), 365, 105. High resolution mass measurement: calculated for
C₃₃H₃₀N₂O: 470.2357; found: 470.2354.

Elemental analysis: calculated for C₃₃H₃₀N₂O: C 84.22, H 6.43, N 5.96; found:
C 84.15, H 6.44, N 5.84.

3.22. YUEHCHUKENE 2

To a solution of benzoyluehchukene 69 (200 mg, 0.43 mmol) in dry methanol
(5 mL) at 5°C under N₂ 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 NH₄Cl (3 mL, sat. aq.) were added. The organic solvent
was evaporated in vacuo and the residue was extracted with ethyl acetate
(4X, 5 mL). The organic phase was washed with water (5 mL), brine (5 mL), dried
over Na₂SO₄, 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 2 (140.3 mg, 90%) as a white foam. The physical properties of synthetic yuehchukene 2 are as follows:

**UV** $\lambda_{\text{max}}$ (MeOH): 225, 283.

**IR** $\nu_{\text{max}}$ (CHCl$_3$): 3400 (N-H, stretch), 2955 (C-H, stretch), 1618 (C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.86 (3H, s, C7-CH$_3$), 1.10 (3H, s, C7-CH$_3$), 1.63 (1H, d, /= 17 Hz, C8-H), 1.66 (3H, brs, C9-CH$_3$), 2.28 (1H, d, /= 17 Hz, C8-H), 3.15 (1H, dd, /= 8.5, 8.5 Hz, C6a-H), 4.02 (1H, m, C10a), 4.56 (1H, d, /= 8.5 Hz), 5.70 (1H, brs, C10-H), 6.98-7.12 (5H, m, Ar-H), 7.38 (1H, d, /= 8 Hz, Ar-H), 7.44 (1H, d, /= 8 Hz, Ar-H), 7.48 (1H, brs, N-H), 7.57 (1H, d, /= 8 Hz, Ar-H), 8.00 (1H, brs, N-H).

MS m/z: 366 (M$^+$), 351, 254. High resolution mass measurement: calculated for C$_{26}$H$_{26}$N$_2$: 366.2095; found: 366.2096.

**3.23. 10bβ-(3-INDOLYL)-7,7,9-TRIMETHYL-6,6aβ,7,8,10aβ,10bβ-HEXAHYDROINDENO [2,1-b]INDOLE 76**

![Chemical Structure](image)

To a solution of 75 (175 mg, 0.37 mmol) in dry THF (3 mL) and dry methanol (5 mL) at room temperature under N$_2$ was added sodium methoxide (freshly
prepared from sodium (about 23 mg, 1.0 mmole) and methanol (4 mL). The reaction mixture was refluxed for 4 h and then water (2 mL) and NH$_4$Cl (3 mL, sat. aq.) were added. The solvent was evaporated in vacuo and the residue was extracted with ethyl acetate (4X, 5 mL). The organic phase was washed with water (5 mL), brine (5 mL), dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo to yield a yellow oil. This crude product was purified by flash chromatography using hexanes/ethyl acetate (7.5:2.5, v/v) to give 76 (132 mg, 97%) as a pale yellow oil.

The physical properties of 76 are as follows:

UV $\lambda_{max.}$ (log $\epsilon$) (MeOH): 218(4.6), 270(3.89) nm.

IR $\nu_{max.}$ (CHCl$_3$): 3477(N-H, stretch), 3009 and 2960(C-H, stretch)

1619(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.88(3H, s, C7-CH$_3$), 0.90(3H, s, C7-CH$_3$), 1.45(3H, brs, C9-CH$_3$), 1.48(1H, d, $J=18$ Hz, C8-H), 2.00(1H, d, $J=18$ Hz, C8-H), 2.29(1H, dd, $J=18$, 8 Hz, C6-H), 2.64(1H, m, C6a-H), 2.83(1H, dd, $J=18$, 10 Hz, C6-H), 3.61(1H, m, C10a-H), 4.72(1H, brs, C10-H), 7.0-7.54(9H, m, Ar-H), 8.25(1H, brs, N-H).

MS m/z: 366(M$^+$), 245, 218. High resolution mass measurement: calculated for C$_{26}$H$_{26}$N$_2$: 366.2095; found: 366.2093.
3.24. 6-OXO-7,7,9-TRIMETHYL-5-TRIMETHYLSILYLETHOXYMETHYL-5,6,6a,7,8,10a,β-
HEXAHYDROINDENO-[2,1-b]INDOLE 85

To a solution of trans-ketone 60 (31 mg, 0.12 mmol) in dichloromethane (4 mL) at
0°C under N₂ was added sodium hydride (4.5 mg, 0.15 mmol, 80% dispersion in
oil). After stirring at 0°C for 1 h, SEM-Cl (0.03 mL, 0.175 mmol) was added and
the stirring was continued for 40 minutes. Water (2 mL) and NH₄Cl (4 mL, sat.
aq.) were added and the mixture was extracted with dichloromethane (3X, 4mL).
The organic phase was washed with water (6 mL), brine (6 mL), dried over
Na₂SO₄, 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 85 (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.

The physical properties of 85 are as follows:

IR νmax. (film): 2954(C-H), 1695(C=O,stretch), 1615(C=C,stretch) cm⁻¹.
Experimental / 129

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: -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 Hz,C8-H),
2.03(1H,d,$J$= 17 Hz,C8-H), 2.79(1H,d,$J$= 7 Hz,C6a-H), 3.52(2H,m,C3'-H),
3.94(1H,m,C10a), 5.61(1H,d,$J$=11.5 Hz,C1'-H), 5.69(1H,d,$J$=11.5 Hz,C1'-H),
6.23(1H,brs,C10-H), 7.19(1H,dd,$J$=8,8 Hz,Ar-H), 7.36(1H,dd,$J$=8,8 Hz,Ar-H),
7.53(1H,d,$J$=8 Hz,Ar-H), 7.77(1H,d,$J$=8 Hz,Ar-H).
MS m/z: 395(M$^+$), 73.

3.25. 6-OXO-7,7,9-TRIMETHYL-5-TRIMETHYLSILYLETHOXYMETHYL-5,6,6a$\beta$,7,8,10a$\beta$-
HEXAHYDROINDENO-[2,1-b]INDOLE 89

Following the same conditions as reaction 3.24, cis-ketone 24 (23 mg, 0.09 mmol)
gave the unstable cis-SEM-ketone 89 (24 mg, 70%) which was immediately submitted
for characterization. The physical properties of 89 are as follows:
UV $\lambda_{max}$ (MeOH): 230, 300 nm.
IR $\nu_{max}$ (film): 2960(C-H,stretch), 1700(C=O,stretch), 1660(C=C,stretch) cm$^{-1}$.
$^1$H-NMR (270 Mz, CDCl$_3$) $\delta$: -0.08(9H,s,Si-(CH$_3$)$_3$), 0.80-0.90(2H,m,C4'-H),
0.92(3H,s,C7-CH$_3$), 1.30(3H,s,C7-CH$_3$), 1.70(3H,brs,C9-CH$_3$), 1.73(1H,d,$J$=17 Hz,C8-H),
1.95(1H,d,J=17 Hz,C8-H), 2.88(1H,d,J=5.5 Hz,C6a-H), 3.51(2H,m,C3'-H), 3.99(1H,m,C10a), 5.65(1H,d,J=11.5 Hz,C1'-H), 5.74(1H,d,J=11.5 Hz,C1'-H), 5.88(1H,brs,C10-H), 7.23(1H,dd,J=7.5,7.5 Hz,Ar-H), 7.41(1H,dd,J=7.5,7.5 Hz,Ar-H), 7.56(1H,d,J=7.5 Hz,Ar-H), 7.79(1H,d,J=7.5 Hz,Ar-H).

MS m/z: 395(M^+), 73. High resolution mass measurement: calculated for C_{24}H_{33}NO Si: 395.2280; found: 395.2278.

3.26. 6α-HYDROXY-7,7,9-TRIMETHYL-5-TRIMETHYLSILYLETHOXYMETHYL-5,6α,6αβ,7,8,10αβ-HEXAHYDROINDENO[2,1-b]INDOLE 86

3.26.1. Method A

To a solution of SEM-trans-ketone 85 (29.4 mg, 0.074 mmol) in dry toluene (2.5 mL) at -78°C under N_2 was added DIBAL (0.11 mL, 0.11 mmol, 1M in hexane). After stirring for 1 h at -78°C solid NH_4Cl (about 20mg) was added. The temperature was raised to 0°C, then water (2 mL) and NH_4Cl (5 mL, sat. aq.) were added. Careful extraction with ether (4X, 5mL) followed by washing with brine (15 mL), drying over Na_2SO_4, 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 86 (19.4 mg, 80% based on recovered ketone) and unreacted 85 (5.2 mg).

3.2.6.2. 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 THF (1 mL) at 0°C under N2 was added trans-ketone 60 (100 mg, 0.38 mmol) in dry THF (1.5 mL). After stirring for 40 minutes, SEM-Cl (0.073 mL, 0.415 mmol) was added and the reaction stirred for 2.5 h at 0°C. LiAlH4 (about 36 mg, 1 mmol) was then added and after 30 minutes at the same temperature the reaction was quenched with ice (about 0.5 g), and NaOH (4 mL, 15% aq.) . Exhaustive extraction with ether (5X, 5mL) followed by washing with water/brine (10 mL, 1:1, v/v), brine (10 mL), drying over Na2SO4, filtration, and evaporation in vacuo yielded a yellow oil. Purification by flash chromatography using hexanes/ether (8:2, v/v) furnished pure alcohol 86 (100.2 mg, 67% overall).

The physical properties of 86 are as follows:

UV \( \lambda_{\text{max}} \) (log \( e \)) (MeOH): 230(4.44), 280(3.89) nm.

IR \( \nu_{\text{max}} \) (film): 3440(O-H, stretch), 2960(C-H, stretch), 1660(C=C, stretch) cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CD3CN) \( \delta \): -0.07(9H, s, Si-(CH3))3, 0.81-0.90(2H, m, C4'-H), 1.03(3H, s, C7-CH3), 1.21(3H, s, C7-CH3), 1.70(3H, brs, C9-CH3), 1.84(1H, d, J=17 Hz, C8-H), 2.03(1H, d, J=17 Hz, C8-H), 2.10(1H, dd, J=9,9 Hz, 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 Hz, C6-H), 5.41(1H, d, J=11 Hz, C1'-H), 5.58(1H, d, J=11 Hz, C1'-H), 6.15(1H, brs, C10-H), 7.06(1H, ddd, J=8,8,1.5 Hz, Ar-H), 7.13(1H, ddd, J=8,8,1.5 Hz, Ar-H), 7.44(1H, d, 8 Hz, C4-H), 7.57(1H, d, J=8 Hz, C1-H).

MS m/z: 397(M+), 379, 73. High resolution mass measurement: calculated for
C_{24}H_{35}NO_{2}Si: 397.2437; found: 397.2443.

Elemental analysis: calculated for C_{24}H_{35}NO_{2}Si: C 72.50, H 8.87, N 3.52; found: C 73.00, H 9.00, N 3.24.

3.27. 6α-ACETOXY-7,7,9-TRIMETHYL-5-TRIMETHYLSILYLETHOXYMETHYL-
5,6α,6aa,7,8,10αβ-HEXAHYDROINDENO[2,1-b]INDOLE 87

![Chemical Structure](attachment:image.png)

3.27.1. Method A

To a solution of alcohol 86 (46.5 mg, 0.12 mmol) and DMAP (21.4 mg, 0.18 mmol) in dichloromethane (1.5 mL) at 0-5°C under N\textsubscript{2} were added acetic anhydride (0.094 mL, 1 mmole) 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 Na\textsubscript{2}SO\textsubscript{4}, 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 87 (44 mg, 86%)
3.27.2. 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 THF (2 mL) at 0°C under N₂ was added trans-ketone 60 (300 mg, 1.13 mmole) in dry THF (3 mL). The mixture was stirred for 40 minutes at 0°C, then 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. DIBAL (2.26 mL, 2.26 mmol, 1M 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 NaHCO₃ (10 mL, sat. aq.) followed by extraction with ether (3X, 10 mL). The organic phase was washed with brine (20 mL), dried over Na₂SO₄, 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 87 (250.1 mg, 50.3% overall).

The physical properties of 87 are as follows:

UV λ<sub>max</sub> (log ε) (MeOH): 227(4.49), 280(3.94) nm.

IR ν<sub>max</sub> (film): 2955(C-H, stretch), 1737(C=O, stretch), 1659(C=C, stretch) cm<sup>-1</sup>.

¹H-NMR (400 MHz, CD₃CN) δ: -0.09(9H, s, Si-(CH₃)₃), 0.77-0.90(2H, m, C4'-H), 1.04(6H, s, C7-CH₃), 1.71(3H, brs, C9-CH₃), 1.87(1H, d, J=17 Hz, C8-H), 2.04(1H, d, J=17 Hz, C8-H), 2.11(3H, s, O=C-CH₃), 2.50(1H, dd, J=10, 10 Hz, C6a-H), 3.43(2H, dd, J=9, 9 Hz, C3'-H), 3.50(1H, m, C10a), 5.29(1H, d, J=11 Hz, C1'-H), 5.33(1H, d, J=11 Hz, C1'-H), 6.18(1H, brs, C10-H), 6.43(1H, d, J=10 Hz, C6-H), 7.10(1H, brdd, J=8, 8 Hz, Ar-H), 7.18(1H, brdd, J=8, 8 Hz, Ar-H), 7.46(1H, d, J=8 Hz, C4-H), 7.62(1H, d, J=8 Hz, C1'-H).
Experimental / 134

MS m/z: 439(M⁺), 379, 75, 73. High resolution mass measurement: calculated for C₂₆H₃₇NO₃Si: 439.2542; found: 439.2549.

3.28. 6β-(3-INDOLYL)-7,7,9-TRIMETHYL-5-TRIMETHYLSILYLETHOXYMETHYL-5,6β,6a,7,8,10a β-HEXAHYDROINDENO[2,1-b]INDOLE 88

To a solution of indolylmagnesium iodide (3.36 mmol, for preparation see section 3.8) in dry ether (5.5 mL) and dichloromethane (1.6 mL) at 0-5°C under N₂ was added a solution of acetate 87 (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 NH₄Cl (5 mL, sat. aq.) were added. After extraction with ether (2X, 10mL), the organic phase was washed with NaHCO₃ (10 mL, sat. aq.), brine (10 mL), dried over Na₂SO₄, 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 88 (201 mg, 36%) as a pale yellow
foam.

The physical properties of 88 are as follows:

UV $\lambda_{\text{max}}$ (log $\epsilon$) (MeOH): 223(4.7), 280(4.14) nm.

IR $\nu_{\text{max}}$ (film): 3414(N-H, stretch), 3055 and 2952(C-H, stretch), 1657(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CD$_3$CN) $\delta$: -0.16(9H, s, Si(CH$_3$)$_3$), 0.34(3H, brs, C7- $\beta$CH$_3$), 0.44-0.73(2H, m, C4'-H), 1.13(3H, m, C7- $\alpha$CH$_3$), 1.67(1H, d, $J= 17$ Hz, C8-H), 1.70(3H, s, CH$_3$), 2.05(1H, d, $J= 17$ Hz, C8-H), 2.70(1H, dd, $J= 11.6$ Hz, C6a-H), 3.05-3.32(2H, m, C3'-H), 4.06(1H, m, C10a-H), 4.78(1H, d, $J= 6$ Hz, C6-H), 4.98(1H, brd, $J= 11$ Hz, C1'-H), 5.19(1H, d, $J= 11$ Hz, 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: calculated for C$_{32}$H$_{40}$N$_2$O$^+$Si: 496.2909; found: 496.2908.

Elemental analysis: calculated for C$_{32}$H$_{40}$N$_2$O$^+$Si: C 77.37, H 8.12, N 5.64; found: C 77.10, H 8.21, N 5.40.

3.29. 6A-EP/-YUEHCHUKENE 25
To a solution of SEM-trans-yuechukene \(88\) (46 mg, 0.093 mmol) in dry THF (1 mL) at room temperature under \(N_2\) were added tetra-n-butylammonium fluoride (1.85 mL, 1.85 mmol, 1M in THF) and HMPA (0.7 mL). The temperature was increased to 40-45° and the reaction mixture was maintained at this condition for 1 day. Then a further portion of tetra-n-butylammonium fluoride (1 mL, 1 mmole, 1M in THF) and HMPA (0.6 mL) was added and the stirring at 40-45°C was continued for another day. Water (2 mL) and \(\text{NH}_4\text{Cl}\) (5 mL, sat. aq.) were added and the mixture was extracted with ether (3X, 6mL). The organic phase was washed with brine, dried over \(\text{Na}_2\text{SO}_4\), 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-yuechukene \(25\) (30.2 mg, 89%) as a white foam.

The physical properties of \(25\) are as follows:

UV \(\lambda_{\text{max}}\) (log \(e\)) (MeOH): 324(4.63), 280(4.03) nm.

IR \(\nu_{\text{max}}\) (film): 3400(N-H,stretch), 2920(C-H,stretch), 1655(C=C,stretch) cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CD\(_3\)CN) \(\delta\): 0.32(3H,s,C7-\(\beta\)CH\(_3\)), 1.15(3H,s,C7-\(\alpha\)CH\(_3\)), 1.67(1H,d,\(J=17\) Hz,C8-H), 1.69(3H,s,C9-CH\(_3\)), 2.05(1H,d,\(J=17\) Hz,C8-H), 2.69(1H,dd,\(J=10,7\) Hz,C6a-H), 4.01(1H,brd,\(J=10\) Hz,C10a-H), 4.70(1H,d,\(J=7\) Hz,C6-H), 6.26(1H,brs,C10-H), 6.70-7.17(6H,m,Ar-H) 7.29(1H,dd,\(J=7,3\) Hz,Ar-H), 7.34(1H,d,\(J=8\) Hz,Ar-H), 7.66(1H,brd,\(J=8\) Hz,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: calculated for \(C_{26}H_{26}N_2\): 366.2095; found: 366.2090.
To a suspension of LiAlH₄ (about 29 mg, 2 mmol) in THF (1 mL) at 0°C under N₂ was added a solution of trans-ketone 60 (212 mg, 0.80 mmol) in THF (2 mL). After stirring for 2 h at 0°C the reaction was quenched with wet ether (0.5 mL, sat. aq.), NaOH (0.5 mL, 15% aq.) and water (1 mL). After filtration through celite, the filtrate was evaporated in vacuo to give a residue which was diluted with ether (5 mL). This ethereal solution was washed with brine (5 mL), dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product was purified by flash chromatography using hexanes/ether (8:2, v/v) to give alcohol 77 (192 mg, 90%).

The physical properties of 77 are as follows:

UV λmax. (log ε) (MeOH): 223(4.49), 282(4.07) nm.

IR νmax. (CHCl₃): 3685(free O-H,stretch), 3466(N-H,stretch), 3020(C-H,stretch), 1621(C=C,stretch) cm⁻¹.

¹H-NMR (300 MHz, CDCl₃) δ: 1.06(3H,s,C7-CH₃), 1.24(3H,s,C7-CH₃), 1.60(1H,brs,O-H), 1.71(3H,brs,C9-CH₃), 1.84(1H,d,J=18 Hz,C8-H), 2.04(1H,d,J=18 Hz,C8-H), 2.18(1H,dd,J=8.5,8.5 Hz,C6a-H), 3.45-3.56(1H,m,C10a),
5.08(1H, d, J = 8.5 Hz, C6-H), 6.15(1H, brs, C10-H), 7.09(1H, ddd, J = 8.8, 1.5 Hz, Ar-H),
7.13(1H, ddd, J = 8.8, 1.5 Hz, Ar-H), 7.33(1H, dd, J = 8.1.5 Hz, Ar-H),
7.62(1H, d, J = 8.1.5 Hz, Ar-H), 8.10(1H, brs, N-H).

MS m/z: 267(M^+), 249, 234, 117. High resolution mass measurement: calculated for C_{18}H_{21}NO: 267.1623; found: 267.1623.

3.31. 6a-BENZOXY-7,7,8-TRIMETHYL-5,6a,6aa,7,8,10a^-HEXAHYDROINDENO[2,1-b]INDOLE 78

To a solution of alcohol 77 (156 mg, 0.58 mmol) and DMAP (72 mg, 0.60 mmol) in CH2Cl2 (5 mL) at 0-5°C under N2 was added benzoyl chloride (0.056 mL, 0.6 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with dichloromethane (5 mL) and washed with water (10 mL). The organic phase was washed with brine (10 mL), dried over Na2SO4, filtered and evaporated in vacuo to yield a brown oil. Purification by flash chromatography using hexanes/ether (8:2, v/v) gave benzoate 78 (27 mg, 15%) as pale yellow foam.
The physical properties of 78 are as follows:

UV $\lambda_{\text{max.}}$ (log $\varepsilon$) (MeOH): 226(4.52), 272(3.86) nm.

IR $\nu_{\text{max.}}$ (CHCl$_3$): 3460(N-H, stretch), 3010 and 2960(C-H, stretch),
1710(C=O, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, (CDCl$_3$) $\delta$: 1.09(3H, s, C7-CH$_3$), 1.26(3H, s, C7-CH$_3$),
1.75(3H, brs, C9-CH$_3$), 1.95(1H, d, $\delta$= 18 Hz, C8-H), 2.16(1H, d, $\delta$= 18 Hz, C8-H),
2.80(1H, dd, $\delta$= 10, 10 Hz, C6a-H), 3.66(1H, m, C10a-H), 5.94(1H, dd, $\delta$= 10.2 Hz, C6-H),
6.22(1H, brs, C10-H), 7.10(1H, brd, $\delta$= 8.8 Hz, Ar-H), 7.15(1H, brdd, $\delta$= 8.8 Hz, Ar-H),
7.33(1H, brd, $\delta$= 8 Hz, Ar-H), 7.47(2H, dd, $\delta$= 8.8 Hz, C5'-H and C7'-H),
7.59(1H, tt, $\delta$= 8.15 Hz, C6'-H), 7.64(1H, brd, $\delta$= 8 Hz, Ar-H), 8.10(2H, dd, $\delta$= 8.15 Hz, C4'-H
and C8'-H), 8.45(1H, brs, N-H).

MS m/z: 371(M$^+$), 356, 234. High resolution mass measurement: calculated for
C$_{26}$H$_{25}$N$_2$: 371.1885; found: 371.1880.

3.32. 6-OXO-P-TOLUENESULFONYL)-7,7,9-TRIMETHYL-5,6,6a,a,7,8,10a-β-
HEXAHYDROINDENO[2,1-b]INDOLE 80

To a solution of trans-ketone 60 (600 mg, 2.26 mmol) in dichloromethane (5 mL) at 0°C under N$_2$ was added sodium hydride (90 mg, 2.3 mmol, 60% dispersion in
oil). After stirring for 10 minutes 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 \( \text{NH}_4\text{Cl} \) (5 mL, sat. aq.) and diluted with dichloromethane (5 mL). The organic phase was washed with brine (5 mL), dried over \( \text{Na}_2\text{SO}_4 \), filtered and evaporated in vacuo to yield a yellow solid. Purification by flash chromatography using hexanes/ether (9:1, v/v) furnished tosyl-ketone 80 (853 mg, 90%) as pale yellow crystals.

The physical properties of 80 are as follows:

m.p. = 123-124°C (acetone/hexane).

UV \( \lambda_{\text{max}} \) (log \( e \)) (MeOH): 297(4.21), 243(4.23), 222(4.28) nm.

IR \( \nu_{\text{max}} \) (CHCl\(_3\)): 3032 and 2959(C-H, stretch), 1713(C=O, stretch), 1605(C=C, stretch), 1381 and 1123(SO\(_2\), stretch) cm\(^{-1}\).

\( ^1\text{H}-\text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \): 1.08(3H, s, C7-CH\(_3\)), 1.44(3H, s, C7-CH\(_3\)), 1.71(3H, brs, C-9-CH\(_3\)), 1.92(1H, d, \( J=18 \) Hz, C8-H), 2.04(1H, d, \( J=18 \) Hz, C8-H), 2.36(3H, s, Ar-CH\(_3\)), 2.81(1H, d, \( J=8 \) Hz, C6a-H), 3.77-3.84(1H, m, Cl0a), 6.12(1H, brs, C10-H), 7.25(2H, d, \( J=8 \) Hz, C3'-H and C5'-H), 7.33(1H, dd, \( J=8,8 \) Hz, Ar-H), 7.50(1H, dd, \( J=8,8 \) Hz, Ar-H), 7.74(1H, d, \( J=8 \) Hz, Ar-H), 8.04(2H, d, \( J=8 \) Hz, C2'-H and C6'-H), 8.28(1H, d, \( J=8 \) Hz, Ar-H).

MS m/z: 419(M\(^+\)), 404, 263, 248. High resolution mass measurement: calculated for \( \text{C}_2\text{H}_2\text{SNO}_3\text{S} \): 419.1555; found: 419.1556.

Elemental analysis: calculated for \( \text{C}_2\text{H}_2\text{SNO}_3\text{S} \): C 71.57, H 6.01, N 3.34; found: C 71.23, H 6.09, N 3.44.
3.33. 6α-HYDROXY-5-(p-TOLUENESULFONYL)-7,7,9-TRIMETHYL-5,6a,6aa,7,8,10Aβ-
HEXAHYDROINDENO[2,1-b]INDOLE 81

To a suspension of LiAlH₄ (about 72 mg, 2 mmol) in THF (2 mL) at °C under N₂
was added a solution of tosylketone 80 (800 mg, 1.91 mmol) in THF (4 mL).
After stirring for 2 h at 0°C the reaction was quenched with wet ether (1 mL,
sat. aq.), NaOH (1 mL, 15% aq.) and water (2 mL). After filtration through celite,
the filtrate was evaporated in vacuo to give a residue which was diluted with ether
(10 mL). This ethereal solution was washed with brine (10 mL), dried over
Na₂SO₄, 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 81 (691 mg, 86%)
as colorless needles.

The physical properties of 81 are as follows:
m.p. = 118-119°C (ether/hexane).
UV λ_max. (log ε) (MeOH): 222(4.43), 258(4.40) nm.
IR ν_max. (CHCl₃): 3563(O-H, stretch), 3010 and 2962(C-H, stretch), 1599(C=C, stretch),
1381 and 1123(SO₂, stretch) cm⁻¹.
¹H-NMR (400 MHz, CDCl₃) δ: 1.05(3H,s,C7-βCH₃), 1.28(3H,s,C7-αCH₃),
1.70(3H, brs, C9-H), 1.88(1H, d, J = 17.5 Hz, C8-H), 2.09(1H, d, J = 17.5 Hz, C8-H), 2.33(3H, s, Ar-CH₃), 2.42(1H, dd, J = 10.8, 5 Hz, C6a-H), 3.38(1H, m, C10a), 4.10(1H, d, J = 2 Hz, O-H), 5.27(1H, ddd, J = 8.5, 2, 2 Hz, C6-H), 6.04(1H, brs, C10-H), 7.19-7.34(4H, m, Ar-H), 7.54(1H, d, J = 7 Hz, C1-H), 7.84(2H, d, J = 9 Hz, C2'-H and C6'-H), 7.91(1H, dd, J = 8.15 Hz, C4-H).

MS m/z: 421 (M⁺), 406, 251, 91. High resolution mass measurement: calculated for C₂₅H₂₇NO₃S: 421.1711; found: 421.1715.
Elemental analysis: calculated for C₂₅H₂₇NO₃S: C 71.23, H 6.46, N 3.32; found: C 71.20, H 6.47, N 3.46.

3.34. 6a-ACETOXY-5-(p-TOLUENESULFONYL)-7,7,9-TRIMETHYL-5,6a,6aa,7,8,10aβ-HEXAHYDROINDENO[2,1-b]INDOLE 82

To a solution of alcohol 81 (100 mg, 0.24 mmol) and DMAP (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 Na$_2$SO$_4$, 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 82 (82.5 mg, 75%) as a white foam.

The physical characteristics of 82 are as follows:

UV $\lambda_{\text{max.}}$ (log $e$) (MeOH): 221(4.41), 257(4.21) nm.

IR $\nu_{\text{max.}}$ (CHCl$_3$): 3019 and 2960(C-H, stretch), 1739(C=O, stretch), 1599(C=C, stretch), 1373 and 1170(SO$_2$, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 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, $J=17$ Hz, C8-H), 2.04(1H, d, $J=17$ Hz, C8-H), 2.15(3H, s, O= C-CH$_3$), 2.33(3H, s, Ar-CH$_3$), 2.53(1H, dd, $J=10.9$ Hz, C6a-H), 3.37-3.45(1H, m, C10a-H), 6.05(1H, brs, C10-H), 6.67(1H, dd, $J=9.2.5$ Hz, C6-H), 7.20-7.32(4H, m, Ar-H), 7.54(1H, d, $J=8$ Hz, C1-H), 7.81(2H, d, $J=8$ Hz, C2'-H and C6'-H), 8.04(1H, d, $J=8$ Hz, C4'-H).

MS m/z: 463(M$^+$), 403, 388, 308, 248. High resolution mass measurement: calculated for C$_{27}$H$_{29}$NO$_4$S: 463.1817; found: 463.1818.

Elemental analysis: calculated for C$_{27}$H$_{29}$NO$_4$S: C 69.96, H 6.30, N 3.02; found: C 69.56, H 6.32, N 2.88.
To a solution of indolylmagnesium iodide (3.51 mmol, for preparation see section 3.8) in dry ether (12 mL) and dichloromethane (4 mL) at 0-5°C under N\textsubscript{2} was added a solution of acetate 81 (540 mg, 1.17 mmol) in ether (7 mL). After stirring for 17 h at 5°C, the reaction mixture was quenched with NH\textsubscript{4}Cl (8 mL, sat. aq.) and extracted with dichloromethane (3X, 8mL). The organic phase was washed with water (8 mL), brine (8 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and evaporated in vacuo to yield a brown oil. Purification by flash chromatography using hexanes/ether (7:3, v/v) gave compound 84 (250 mg, 41%) as a white powder.

The physical properties of 84 are as follows:
m.p. = 207-208°C (acetone/hexanes).

UV \lambda_{max} (log ε) (MeOH): 226(4.73), 270(4.08) nm.

IR \nu_{max} (CHCl\textsubscript{3}): 3470(N-H,stretch), 2960(C-H,stretch), 1650(C=C,stretch), 1370 and 1170(SO\textsubscript{2},stretch) cm\textsuperscript{-1}.

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \delta: 0.71(3H,s,C7-CH\textsubscript{3}), 1.06(3H,s,C7-CH\textsubscript{3}),
1.54(3H, brs, C9-CH$_3$), 1.63(1H, d, J = 17 Hz, C8-H), 1.79(1H, d, J = 17 Hz, 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 Hz, Ar-H),
7.59(1H, d, J = 8 Hz, Ar-H), 7.65(1H, d, J = 8 Hz, Ar-H), 7.76(2H, d, J = 8 Hz, C2'-H and C6'-H),
7.90(1H, brs, N-H).

MS m/z: 520(M$^+$), 403, 388, 365. High resolution mass measurement: calculated for
C$_{33}$H$_{32}$N$_2$O$_2$S: 520.2184; found: 520.2179.

3.36. 10a-METHYL-6-OXO-5,6,7β,10β-TETRAHYDRO-7β,10β-(1,1-DIMETHYLETHANO)-CYCLOHEPT[b]INDOLE 63

![Chemical Structure](image)

To a solution of indoleacid 58 (400 mg, 1.41 mmol) in dry chloroform (70 mL) at
room temperature under N$_2$ 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 NaHCO$_3$ (25 mL, sat. aq.),
water (25 mL), brine (25 mL), dried over Na$_2$SO$_4$, filtered, and evaporated
in vacuo to yield a viscous oil. This crude product was purified on a short
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silica-gel column using hexanes/ether (8.5:1.5, v/v) to give pure ketone 63 (190 mg, 55%) as colorless prisms.

The physical properties of 63 are as follows:

UV $\lambda_{\text{max}}$ (log $\epsilon$) (MeOH): 237(4.33), 314(4.32) nm.

IR $\nu_{\text{max}}$ (KBr): 3300(N-H, stretch), 3060 and 2960(C-H, stretch), 1620(C=O, stretch), 1601(C=C, stretch) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 1.00(3H,s, C1'-CH$_3$), 1.18(3H,s, C1'-CH$_3$), 1.63(1H,d, $\gamma=15$ Hz, C2'-H), 1.97(3H,s, C10-CH$_3$), 2.01(1H,d, $\gamma=15$ Hz, C2'-H), 3.29(1H,d, $\gamma=7$ Hz, C7-H), 6.18(1H,dd, $\gamma=8$, $\gamma=7$ Hz, C8-H), 6.45(1H,d, $\gamma=8$ Hz, C9-H), 7.10(1H,dd, $\gamma=8$, $\gamma=6$ Hz, Ar-H), 7.29(1H,dd, $\gamma=8$, $\gamma=6$ Hz, Ar-H), 7.38(1H,d, $\gamma=8$ Hz, Ar-H), 8.04(1H,d, $\gamma=8$ Hz, Ar-H), 8.86(1H, brs, N-H).

MS m/z: 265(M$^+$), 250, 237, 209, 181. High resolution mass measurement: calculated for C$_{18}$H$_{19}$NO: 265.1466; found: 265.1465.

Elemental analysis: calculated 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.
4. REFERENCES


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