Reactivity of β-Carbolines and Cyclopenta[*b*]indolones Prepared from the Intramolecular Cyclization of 5(4*H*)-Oxazolones Derived from L-Tryptophan

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4-(1*H*-Indol-3-ylmethyl)-2-trichloromethyl-1,3-oxazol-5(4*H*)-one (**4**) was shown to undergo an intramolecular reaction in the presence of TFA, to afford a β-carboline **5** and a cyclopenta[*b*]indolone **6** by nucleophilic addition at C-2 and C-5, respectively. The distribution of these two products was found to be dependent on the reaction temperature, with lower temperatures favouring the formation of the β-carboline **5**. Subsequent reactions performed on the β-carboline **5** led to the formation of canthine and canthin-6-one derivatives. These syntheses both involved methyl 1-formyl-β-carboline-3-carboxylate (**20**), a useful precursor which was prepared in 54% yield, by a four-step procedure, from readily available L-tryptophan. The cyclopenta[*b*]indolone **6** readily underwent oxidative deamidation to afford cyclopenta[*b*]indole-2,3-dione (**37**), while substitution by alcohols afforded the alkoxy derivatives **40** and **41**.

Introduction

The importance of β-carbolines as biologically active compounds is well documented, and this ensures that they remain as targets of modern organic synthesis.[1] New β-carbolines are continually being isolated from natural sources,[2] and these compounds subsequently become targets for total synthesis.[3,4] Recently, β-carbolines have undergone evaluation as photochemical DNA-cleavage agents, and β-carboline−carbohydrate hybrids were found to cleave DNA at the guanine site upon radiation with UV light. This is in addition to their already known property as DNA intercalators.[5] Recently, endogenously formed β-carbolines, ''mammalian alkaloids'', have come under increasing scrutiny in connection with Parkinson's disease.[6] The biosynthesis of tetrahydro-β-carbolines from tryptamines and aldehydes involves a Pictet−Spengler reaction;[7] it was recently discovered that the potent dopaminergic neurotoxin 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline forms in humans after therapeutic administration of chloral hydrate or exposure to trichloroethylene, presumably by Pictet−Spengler condensation of the latter reagent with biogenic tryptamine.[8]

The Pictet−Spengler reaction is the most commonly employed synthetic route towards β-carbolines, but in this method, the reaction product is the tetrahydro-β-carboline, which requires subsequent oxidation. The Bischler−Napieralski reaction provides a valuable alternative pathway for the preparation of β-carbolines, but in this case, N_b-acyltryptophan derivatives usually undergo intramolecular cyclization to form 3,4-dihydro-β-carbolines. However, there are examples in which N_b-acyltryptophan esters have been converted into fully aromatic β-carbolines directly.[1] 5(4*H*)-Oxazolones and their unsaturated derivatives are recognized as synthetically important reagents, especially for the formation of heterocyclic compounds.[9,10] Unsaturated 5(4*H*)-oxazolones have been used in modified intermolecular Pictet−Spengler reactions as ''arylacetaldehyde equivalents''. These compounds are hydrolysed to arylpyruvic acid, which is the reactive species.[11] 5(4*H*)-Oxazolones prepared from tryptophan or *C*-terminal tryptophan-containing peptides have been used for the preparation of β-carbolines by treatment with TFA. The oxazolone ring gives enhanced reactivity over the corresponding noncyclized N_b-acyltryptophan derivatives, but, as in the case of the Bischler−Napieralski reaction, these compounds give the corresponding 3,4-dihydro-β-carbolines.[12] The trifluoromethyl-5(4*H*)-oxazolone **1**, however, which can be considered as an activated form of an N_b-acyltryptophan derivative, gave the 1-trifluoromethyl-β-carboline **2** directly, in 39% yield (Scheme 1).[10]

The trifluoromethyl-5(4*H*)-oxazolone **1** is readily prepared from L-tryptophan in high yield and requires no purification. Given the simplicity of this reaction, and that of the subsequent one-pot transformation to the β-carboline **2**, we have reinvestigated this earlier work in an effort to develop a higher-yielding procedure for preparing β-carbolines. We chose the trichloromethyl-5(4*H*)-oxazolone **4** as

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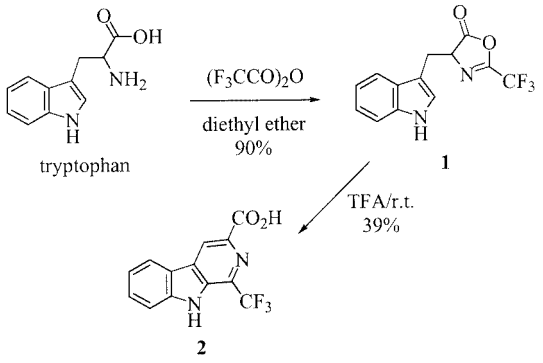


Scheme 1

our starting oxazolone, since the corresponding β-carboline would contain a 1-trichloromethyl substituent, which could serve as a precursor to an aldehyde, and provide a handle for the subsequent formation of canthine and canthinone derivatives. There are numerous recent reports of compounds containing the parent structure **3**, and whilst the active area of canthine synthesis has been dominated by intramolecular Diels–Alder reactions,[13] the more traditional Pictet–Spengler condensation has also been involved.[14] There are far fewer reports of canthines or canthinones possessing an acid or ester group at the C-2 position of structure **3** (Figure 1). We intended to apply a recently described methodology to the preparation of such compounds.

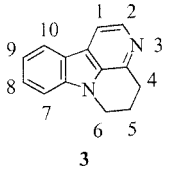
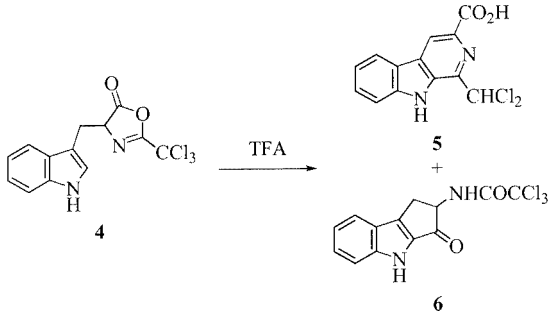


Figure 1. The canthine parent structure **3** with partial numbering

Results and Discussion

Preparation and Reactivity of Oxazolone 4

The 2-(trichloromethyl)oxazolone **4** was prepared in high yield from tryptophan, using a slightly modified literature procedure[10] which required no purification, and was then subjected to various reaction conditions as shown in Table 1. We were surprised to find that the reaction of the oxazolone **4** with TFA afforded the 1-dichloromethyl-β-carboline **5**, rather than the expected 1-trichloromethyl derivative (Scheme 2). However, we reasoned that this product would also serve our purposes well. While **5** is the first reported β-carboline with such a substituent, a number of tetrahydro-β-carboline derivatives with either a trichloromethyl or a dichloromethylene substituent at the C-1 position have been prepared recently.[8b][8c] We were equally surprised to isolate the cyclopenta[*b*]indolone **6** from the same reaction, since the trifluoro analogue was not mentioned as a product from the corresponding reaction of the (trifluoromethyl)oxazolone **1**.[10] The cyclopenta[*b*]indolone **6** could be a useful precursor in the synthesis of natural products containing the cyclopenta[*b*]indolone unit (see later), and so we set about optimizing the reaction conditions for the preparation of each of these compounds.



Scheme 2

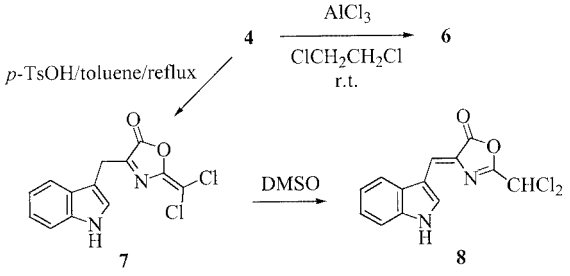
We initially treated the oxazolone **4** with TFA at room temperature, followed by an aqueous work-up,[10] but this procedure gave an unsatisfactory reaction as N_b-(trichloroacetyl)tryptophan was isolated.[15] This product results from the hydrolysis of the oxazolone **4**, and does not form either of the two desired products when subjected to further treatment with TFA. Furthermore, the separation of products **5**, **6**, and N_b-(trichloroacetyl)tryptophan was laborious, and therefore, we developed non-aqueous work-up conditions whereby the β-carboline **5** was consistently collected in an almost analytically pure state, without the need for further purification. We found that the most important aspect of these reactions is the reaction temperature at the point of mixing, and thus, after an initial low reaction tem-

Table 1. Reactions of oxazolone **4**

Entry	Conditions	Yield β-Carboline **5**	Yield Cyclopenta[*b*]indolone **6**
1	TFA/Δ/15 min (Procedure A)	35%	45%
2	TFA/0 °C/1 h, then room temp./24 h	77%	15%
3	TFA/−15 °C/1 h, then room temp./24 h (Procedure B)	87%	4%
4	*p*TsOH/toluene/Δ	–	–
5	HCl/MeOH/Δ	–	–
6	$AlCl_3$/Cl(CH_2)$_2$Cl	–	43%
7	H_2O/THF or H_2O/dioxane	–	–

perature, the resulting red reaction solution can be left at room temperature until complete reaction has occurred. Under these conditions, the β-carboline **5** is formed almost exclusively (Table 1, Entries 2 and 3). In contrast, at high initial reaction temperatures, the reaction goes to completion quickly, and there is a slight preference for formation of the cyclopenta[*b*]indolone **6** (Table 1, Entry 1).

The reaction of the oxazolone **4** with TFA is sluggish at temperatures close to −15 °C, the freezing point of neat TFA. However, the use of co-solvent systems, such as TFA in toluene or dichloromethane,[16] also gave little reaction below −15 °C, while above this temperature, there was no further enhancement of the preferential formation of the β-carboline **5**. At the other end of the scale, heating oxazolone **4** at reflux in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid led to the formation of a different product, to which the known structure **7** was assigned (Scheme 3),[10] but neither of the two desired products were formed (Table 1, Entry 4). Furthermore, treatment of product **7** with TFA did not afford either of the two desired products. Product **7** underwent tautomerism to the known conjugated oxazolone **8**[10] when dissolved in deuterated dimethyl sulfoxide.



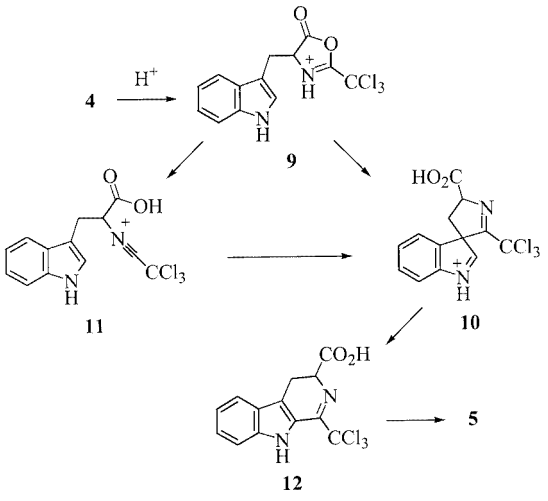
Scheme 3

Stirring of the oxazolone **4** in methanolic hydrogen chloride at room temperature simply resulted in hydrolysis to N_b-(trichloroacetyl)tryptophan methyl ester,[17] i.e. the methyl ester of N_b-(trichloroacetyl)tryptophan, in low yield (Table 1, Entry 5). Under Friedel−Crafts conditions, the oxazolone **4** reacted with aluminium trichloride to afford the cyclopenta[*b*]indolone **6** in 43% yield (Table 1, Entry 6, Scheme 3). This reaction is analogous to the reported preparation of the corresponding trifluoro analogue from the (trifluoromethyl)oxazolone **1**.[10] The reaction also produced baseline material, but the β-carboline **5** was not observed. Dissolution of the oxazolone **4** in aqueous solutions of DMSO, dioxane, or THF is sufficient to hydrolyse the oxazolone, and in fact, we prepared N_b-(trichloroacetyl)-tryptophan in quantitative yield, simply by heating the oxazolone **4** at reflux in aqueous THF (Table 1, Entry 7). Interestingly, the (trifluoromethyl)oxazolone **1** undergoes isomerisation, and not ring hydrolysis, when treated under similar conditions.[10]

Preliminary NMR-spectroscopic examinations of the reaction of the oxazolone **4** with deuterated TFA were conducted at both room temperature and below −10 °C, and the results were consistent with our findings that the outcome of this reaction was dependent on the initial reaction temperature. The formation of the cyclopenta[*b*]indolone **6** is completed early on at either temperature, and this product can be observed along with a number of transient intermediates. However, at both temperatures, for the majority of the time, apart from cyclopenta[*b*]indolone **6** and the slow-forming β-carboline **5**, a single intermediate was observed under the course of the reaction. This intermediate was tentatively assigned the structure of the 3,4-dihydro-β-carboline **12**, or the salt thereof, based on NMR-spectroscopic evidence and the fact that at room temperature intermediate **12** is slowly converted into the β-carboline **5** over a number of days, and not at all to the cyclopenta[*b*]indolone **6**. The ^{1}H NMR (300 MHz, CF_3CO_2D) spectrum of intermediate **12** [δ = 3.66 (m, 2 H, CH_2CH), 5.04 (m, 1 H, CH_2C*H*), 7.03, 7.25, 7.37, 7.45 (each m, 1 H, aryl C*H*) ppm] contains four complex aromatic signals, most likely indicating that substitution has occurred at C-2 of the tryptophan indolic ring. Alkyl signals appropriate for the proposed 3,4-dihydro-β-carboline species were also observed. The ^{13}C NMR (75.4 MHz, CF_3CO_2D) spectrum of intermediate **12** [δ = 25.17 (*C*-4), 58.30 (*C*-3), 90.17 (*C*Cl_3), 116.36 (aryl *C*H), 124.76, 127.19 (aryl *C*H), 127.60, 136.48 (aryl *C*), 137.99 (aryl *C*H), 148.28 (aryl *C*), 161.39 (*C*-1), 174.63 (*C*O_2H) ppm, the signal for one quaternary carbon is obscured] confirmed the presence of only four aromatic CH carbon atoms, whilst the downfield shift of the proposed carboxylic acid carbonyl signal indicated a lack of conjugation with this carbon atom and hence suggested the 3,4-dihydro-β-carboline species. This assignment was corroborated by the presence of appropriate methylene and methine signals. A quaternary carbon signal at δ = 90.17 ppm was suggestive of a trichloromethyl rather than a dichloromethyl substituent at C-1.

Dissolution of the oxazolone **4** in TFA is an exothermic process, and these oxazolones are known to be highly susceptible to isomerism,[10] which may account for the transient intermediates observed. Oxazolone **4** can be thought of as an imidoyl derivative, which presumably undergoes protonation to form the imidoyl salt **9** (Scheme 4). This salt probably participates in the same way as other imidoyl derivatives do in the Bischler−Napieralski reaction: nucleophilic addition at C-2 of the oxazolone ring, presumably with cyclization by *ipso* attack at the C-3 position of the indole ring, and with oxazolone ring-opening to form the five-membered spirocyclic indolenine intermediate **10**;[18] but possibly proceeding through an intermediate nitrilium salt **11**.[19] Spirocyclic indolenine intermediate **10** then undergoes a 1,2-shift to give the 2,3-dihydro-β-carboline **12**. Oxidation to the β-carboline **5** is accompanied by loss of a chlorine atom, presumably as hydrogen chloride, a reaction which may be facilitated by the presumed lability of the 3-H proton. The related 1-trichloromethyl-2,3-dihydro-β-carboline, unsubstituted at C-3, has been reported to be unstable.[8c] The air oxidation of the 2,3-dihydro-β-carboline **12** is relatively slow compared to the preceeding steps involving the highly reactive imidoyl or nitrilium salts, and this compares well with the reported air oxidation of the

3,4-dihydro-β-carboline xestomanzamine B to the β-carboline xestomanzamine A.[4] A mechanism for the aromatization of 3,4-dihydro-β-carbolines under mildly basic conditions has been described.[20]



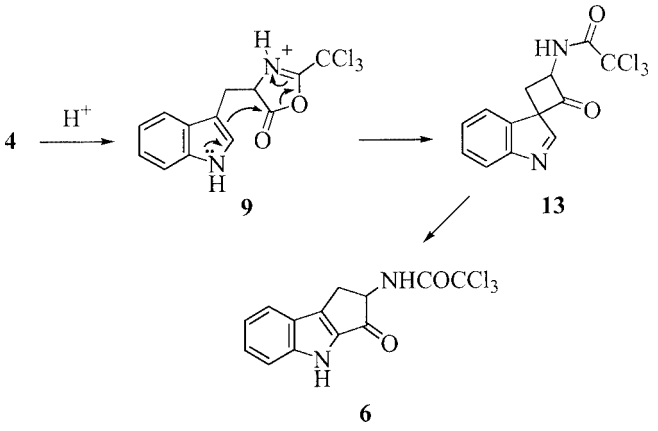
Scheme 4

In an attempt to rationalize the reported yield (39%), it has been proposed that during the formation of the trifluoromethyl-β-carboline **2**, some of the starting material might be acting as an oxidizing agent,[10] however, in our hands, the reaction gave the trifluoromethyl-β-carboline **2** in 56% yield, along with a low yield of the corresponding cyclopenta[*b*]indolone.

The Pictet−Spengler reaction of tryptophan with chloral apparently failed at the bench,[21] however, it might still be possible that this reaction proceeds in vivo. If this were the case, then like 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (as discussed above),[8] 1-trichloromethyl-3,4-dihydro-β-carboline-3-carboxylate (**12**) and possibly even 1-dichloromethyl-β-carboline-3-carboxylate (**5**) could be novel endogenous mammalian alkaloids present after administration of chloral hydrate or exposure to trichloroethylene.

We could not identify any intermediates likely to be involved in the formation of the cyclopenta[*b*]indolone **6** by NMR spectroscopy. However, the mechanism is clearly different from the formation of the β-carboline, since the C-5 atom of the oxazolone becomes the C-3 atom of the cyclopenta[*b*]indolone **6**. Presumably, the same imidoyl tryptophanate **9** is involved, but reacts at C-5 with ring opening (Scheme 5), possibly via a four-membered spirocyclic indolenine intermediate **13**, which then undergoes a 1,2-shift to give the cyclopenta[*b*]indolone **6**.

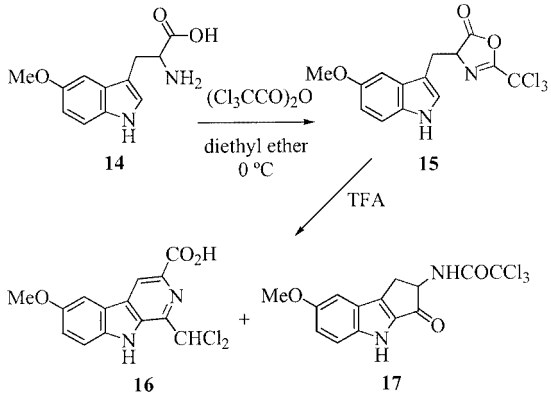
Similar four-membered spirocyclic indolenine intermediates in the formation of cyclopenta[*b*]indolones have been proposed by other workers.[22,23] In this way, the imidoyl tryptophanate **9** participates as an activated carboxylic acid, and we note that there are several examples in the literature where the carboxylic acid carbonyl group of N_b-acyltryptophan derivatives have undergone ring-closure to give cyclopenta[*b*]indolones,[24] although these have normally required the use of Friedel−Crafts acylation conditions.[10,25]



Scheme 5

A comparison of the two proposed mechanisms could account for the distribution of the β-carboline **5** and the cyclopenta[*b*]indolone **6** products at different temperatures, since the formation of the four-membered spirocyclic indolenine intermediate **13** would require somewhat more energy than the formation of the five-membered spirocyclic indolenine intermediate **10**. We note that in comparison to other N_b-acyltryptophan derivatives undergoing the Bischler−Napieralski reaction, the iminium ion generated from L-tryptophan present here has restricted mobility, being locked in an otherwise planar oxazolone ring, itself tethered by a single methylene bridge to the indole moiety to which the iminium ion reacts, and containing a bulky trichloromethyl substituent at C-2.

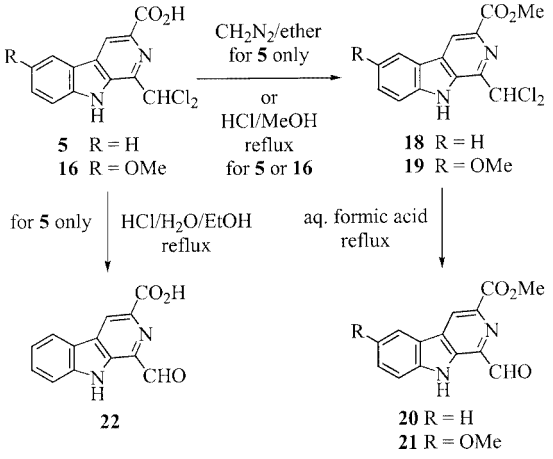
In an effort to extend the above reaction using benzenoid-substituted tryptophan derivatives, oxazolone **15** was prepared in 71% yield from 5-methoxytryptophan (**14**) (Scheme 6). Addition of the oxazolone **15** to refluxing TFA gave the 6-methoxy-β-carboline **16** and the 7-methoxycyclopenta[*b*]indolone **17** in 27% and 15% yields, respectively. At lower temperature, the 6-methoxy-β-carboline **16** and the 7-methoxycyclopenta[*b*]indolone **17** were formed in 63% and 2.3% yields, respectively. The lower yield of the 6-methoxy-β-carboline **16** was due, in part, to the higher solubility of this product in toluene. We note once again that a 2-(trichloromethyl)oxazolone has given rise to a 1-dichloromethyl-β-carboline.



Scheme 6

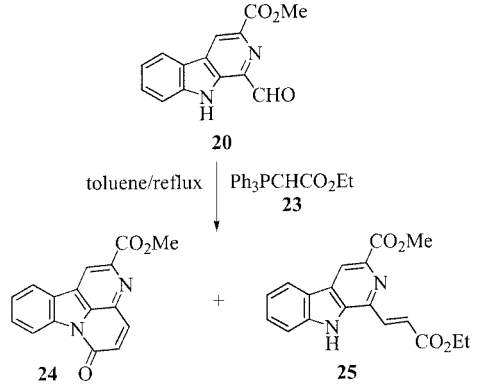
Preparation of Canthine and Canthinone Derivatives

The β-carboline **5** was conveniently converted quantitatively into its methyl ester **18** by stirring in freshly prepared ethereal diazomethane, or, alternatively, with hydrogen chloride in methanol in 86% yield (Scheme 7). The corresponding conversion of the 6-methoxy-β-carboline **16** to the methyl ester **19** was achieved in 58% yield. The conversion of the β-carboline **5** to the 1-formyl-β-carboline **22** was achieved in quantitative yield by heating at reflux in aqueous ethanolic HCl. However, this reaction could be problematic due to the relatively low solubility of the product. The corresponding conversion of the methyl ester **18** also proceeded readily on a small scale, however the work-up was also troublesome. Fortunately, the use of aqueous formic acid provided a relatively easy work-up, and afforded the aldehyde[26] **20** in 78% yield. Similarly, the methyl ester **19** was converted into **21** in 82% yield.



Scheme 7

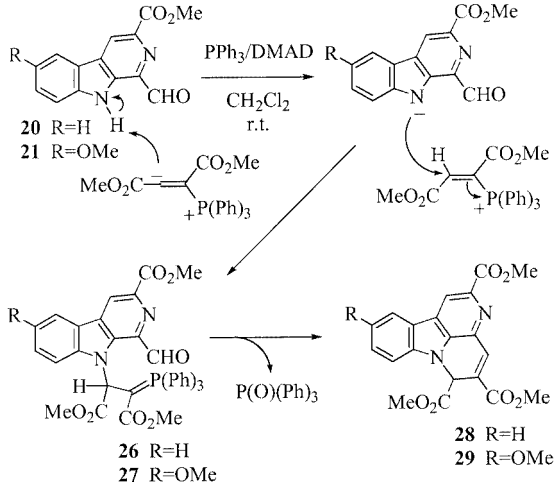
With the aldehydes **20** and **21** in hand, their conversion to tetracyclic compounds possessing the canthine parent structure (**3**, Figure 1) was examined. Treatment of the aldehyde **20** with the phosphorane **23** furnished two products: the known 2-(methoxycarbonyl)canthin-6-one derivative **24**,[26–27] and the previously unknown noncyclized β-carbolinepropenoate **25**, which were separable by recrystallization (Scheme 8).



Scheme 8

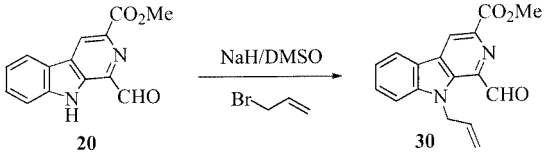
Both NH and ethyl ester resonances were observed in the ^{1}H NMR spectrum of the noncyclized β-carbolinepropenoate **25**, which was present purely as the *trans* isomer, with olefinic protons 4-H and 5-H exhibiting equal coupling constants of 15.4 Hz. Presumably, the *cis* isomer undergoes spontaneous intramolecular cyclization onto the adjacent nitrogen atom.

Using an approach that has recently been described for the construction of various heterocycles,[28–30] the aldehydes **20** and **21** were each treated with dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphane to give the substituted unsaturated canthine derivatives **28** and **29**, respectively (Scheme 9). Presumably,[28,29] a 1:1 adduct is formed between triphenylphosphane and DMAD. This deprotonates the β-carboline, and the so-formed species subsequently attacks the 1:1 adduct to form phosphorane **26** or **27**. Cyclization is then accomplished by an intramolecular Wittig reaction (Scheme 9).



Scheme 9

We expect that these functionalized canthine derivatives ought to be useful for the preparation of more complicated canthine derivatives, including natural products or their analogues. In connection with some other routes towards canthine derivatives which we are currently pursuing, the aldehyde **20** was *N*-alkylated with allyl bromide in 95% yield to give the *N*-allyl-1-formyl derivative **30** (Scheme 10).

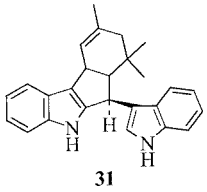


Scheme 10

Reactivity of Cyclopenta[*b*]indolone 6

The preparation and further transformations of cyclopenta[*b*]indolones, especially towards yuehchukene and its

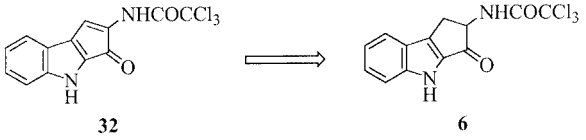
analogues, is of ongoing interest in our group.[31] Yuehchukene (**31**, Figure 2) is a bis(indole) alkaloid isolated from the root of *Murraya Paniculata*, as well as other members of the genus.[32]



31

Figure 2. Yuehchukene

Yuehchukene induces weak estrogenic activity, and interest in the biological activity of this compound has maintained ongoing biological testing.[33] Interest in yuehchukene analogues, as well as other biologically active compounds containing the cyclopenta[*b*]indolone unit, has ensured that cyclopenta[*b*]indolones remain an active area of research.[34] We envisioned that cyclopenta[*b*]indolone **6** could be a useful precursor in the synthesis of natural products containing the cyclopenta[*b*]indolone unit, and we briefly examined its conversion into the cyclopentadienone derivative **32** (Scheme 11), which ought to be a highly reactive, synthetically useful intermediate.



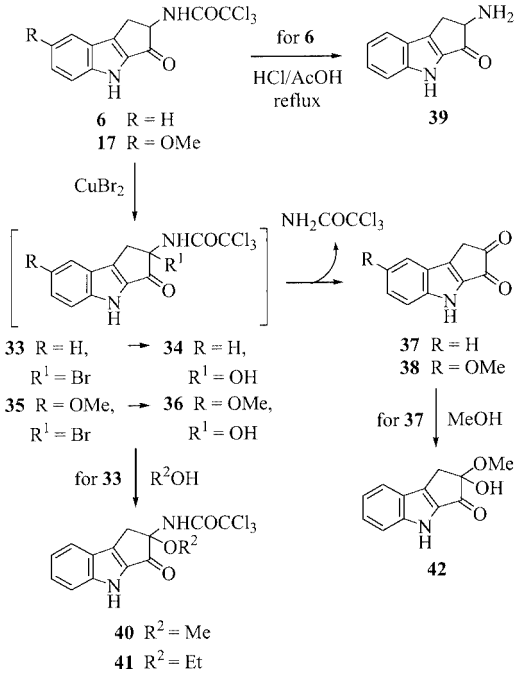
32 **6**

Scheme 11

Substituted cyclopentenones and indan-1-ones have been converted into their corresponding cyclopentadienone and indenone derivatives, respectively, by the elimination of an appropriate leaving group.[35–38] However, such reactions have not been reported for examples containing an amide substituent positioned similarly to that in our compounds. The introduction of a double bond adjacent to a cyclic ketone has also been achieved using various oxidants, notably 2-iodoxybenzoic acid (IBX)[39] and selenium reagents, such as selenium dioxide[26] and benzeneseleninic anhydride.[40]

Attempted oxidation of cyclopenta[*b*]indolone **6** with freshly prepared IBX,[41] DDQ, manganese dioxide, palladium on carbon, selenium dioxide, or benzeneseleninic anhydride, in various solvents, led to slow decomposition of the starting material and the formation of complex mixtures or otherwise no reaction at all. In some cases, the dione **37** was formed, but it could not be isolated in a pure state.

Treatment of cyclopenta[*b*]indolone **6** with copper(II) bromide in ethyl acetate afforded dione **37** in good yield after repeated chromatography to remove α,α,α-trichloroacetamide (Scheme 12).



Scheme 12

Interestingly, while the ^{1}H NMR spectrum ([D$_6$]DMSO) of pure α,α,α-trichloroacetamide contains a single broad resonance at δ = 8.36 ppm due to the amide NH$_2$ protons, the same amide protons show two broad resonances at δ = 8.40 and 8.29 ppm in the ^{1}H NMR spectrum ([D$_6$]DMSO) of a mixture of dione **37** and α,α,α-trichloroacetamide. Addition of further equivalents of α,α,α-trichloroacetamide indicated that there was a strong association between the two compounds, which could explain the difficulty in removing the by-product. It is likely that in solution, dione **37** and α,α,α-trichloroacetamide form 1:1 hydrogen-bonded adducts, which may undergo dimerization.

The NMR-spectroscopic data of dione **37** was in agreement with the given NMR-spectroscopic data of the 1-^{13}C isotopically labelled derivative of the dione **37**, 2,3-dioxo-[1-^{13}C]cyclopenta[*b*]indole, which has been prepared by deamination of [1-^{13}C]**39** hydrochloride by treatment with NBS followed by triethylamine.[22] Hydrolysis of the cyclopenta[*b*]indolone **6** afforded the amine **39** in 49% yield as its hydrochloride salt,[10,25] a compound known to exhibit anti-inflammatory activity and also to act on the central nervous system.[25]

When the ^{1}H NMR spectrum of dione **37** was recorded in deuterated methanol, partial formation (approximately 39%) of the hemiketal **42** was observed (Scheme 12), whereas complete formation of the hemiketal of 1,2-indandione reportedly occurs upon dissolution in methanol.[42] In both cases, substitution occurs at C-2, as is evident by the resulting non-equivalence of the methylene protons, which show a pair of doublets.

Attempted bromination of the cyclopenta[*b*]indolone **6** with *N*-bromosuccinimide and AIBN in carbon tetra-

chloride failed. Treatment of the cyclopenta[*b*]indolone **6** with copper(II) bromide in refluxing chloroform gave a low yield of the dione **37**, but the ethoxy derivative **41** was recovered in moderate yield (Scheme 12). This product presumably forms as a result of nucleophilic attack on the brominated intermediate **33** by residual ethanol, and indeed, when absolute ethanol was used, a similar result was observed. The corresponding reaction in refluxing methanol gave the methoxy derivative **40** in high yield, but little of the dione **37** formed (Scheme 12). The ^{1}H NMR spectra of the alkoxy derivatives **40** and **41** both contained two sets of doublets, representing the C-2 methylene protons of these chiral products. Dione **37** is not likely to be involved in the formation of the latter products, since heating of a solution of a 1:2 adduct of α,α,α-trichloroacetamide/dione **37** in methanol failed to afford the methoxy derivative **40**.

Treatment of the cyclopenta[*b*]indolone **6** with copper(II) bromide in isopropyl alcohol produced only the dione **37**, indicating that oxidative deamidation was successful in this solvent but nucleophilic attack by isopropyl alcohol was not, and not surprisingly, the use of isobutyl alcohol as the solvent also failed to give the corresponding isobutoxy derivative.

Oxidations of *N*-acyl-α-amino ketones to α-dicarbonyl compounds with bromine have been reported,[43] and more recently the bromine-catalysed free-radical oxidation of acetamides by hydrogen peroxide has been described.[44] Presumably, α-hydrogen abstraction followed by bromination occurs to give the α-bromo intermediates **33** and **35**, which then undergo oxidation to the dienones via the hydroxy intermediates **34** and **36**, respectively. Alternatively, reaction with the alcohol affords the alkoxy derivatives **40** and **41**.

The 7-methoxycyclopenta[*b*]indolone **17** underwent a similar reaction upon treatment with copper(II) bromide in refluxing ethyl acetate, and afforded the corresponding 7-methoxydione **38** in 73% yield (Scheme 12). It is interesting to note the lack of interference between this product and residual α,α,α-trichloroacetamide in this case.

The diones **37** and **38** could serve as valuable synthetic intermediates themselves, prepared in three steps from L-tryptophan. Attempted reactions of the dione **37** with 3,5-dimethoxyaniline, in a similar manner to the reported reactions of 3,5-dimethoxyaniline with ninhydrin[45] or 1,2-indanedione,[46] have so far failed.

Attempted eliminations of alcohol from either alkoxy derivative **40** or **41** as a route to the elusive cyclopentadienone **32**, either by treatment with *p*-toluenesulfonic acid in refluxing toluene,[47] or using alternative acidic conditions, have so far been unsuccessful.

Conclusions

The preparation of the 1-dichloromethyl-β-carboline **5** has been optimized to give this product in two steps from readily available L-tryptophan in high yield and purity, without the need for chromatographic purification. Furthermore, we have shown that the product can be easily converted into the synthetically useful aldehyde **20**, itself produced in this work by a four-step procedure in 54% yield from readily available L-tryptophan. We have further elaborated intermediate **20** into both canthine and canthinone derivatives. We have examined the scope of this procedure using 5-methoxytryptophan, and hope to evaluate other substituted tryptophan analogues. Clearly, this procedure is a convenient method for the preparation of β-carbolines with a synthetically useful substituent at the C-1 position.

We have only briefly examined the mechanism for the formation of the β-carboline **5** and the cyclopenta[*b*]indolone **6** from the 2-(trichloromethyl)oxazolone **4**. However, we feel that it would be interesting to examine this reaction in more detail, along with a comparative study of the corresponding reaction involving the 2-(trifluoromethyl)oxazolone **1**, which does not involve loss of hydrogen fluoride.

We have briefly examined the reactivity of the cyclopenta[*b*]indolone **6**, which underwent oxidative deamidation with copper(II) bromide readily, to give the potentially useful dienone **37**.

Experimental Section

General Remarks: NMR spectra were recorded with a Bruker DPX 300 (300 MHz) spectrometer, at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C, and chemical shifts are reported in δ units. For ^{1}H NMR spectra, the peak due to residual $CHCl_3$ (δ = 7.26 ppm), MeOH (δ = 3.31 ppm) or the central peak of DMSO (δ = 2.50 ppm), were used as the internal references. ^{1}H NMR spectroscopic data are recorded as follows: chemical shift δ {multiplicity, coupling constant(s) *J* [Hz], relative integral, assignment (where possible)}. Protons attached to heteroatoms were confirmed using D_2O exchange experiments. For ^{13}C NMR spectra, the central peak of the multiplets of $CHCl_3$ triplet (δ = 77.0 ppm) or DMSO (δ = 39.51 ppm) were used as the references for proton-decoupled ^{13}C NMR spectra. ^{13}C NMR spectroscopic data are recorded as follows: chemical shift δ (protonicity, where the assignment of protonicity was aided by decoupling and DEPT experiments). Infrared spectra were recorded with a Perkin−Elmer 1600 Fourier Transform Infrared Spectrophotometer as KBr discs. MS (ESI) data were obtained using a Perkin−Elmer API 150 EX spectrometer. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were measured with a Büchi B-545 apparatus and are uncorrected. HRMS determinations (FAB) were performed by Einar Nilsson, University of Lund, Sweden. Chromatography was performed using Merck Silica Gel 60. All solvents were purified by distillation or otherwise were analytical grade and used as received.

4-(1*H*-Indol-3-ylmethyl)-2-(trichloromethyl)-1,3-oxazol-5(4*H*)-one (4): Trichloroacetic anhydride (10 mL, 55 mmol) was added to a stirred suspension of L-tryptophan (5.10 g, 25.0 mmol) in diethyl ether (150 mL), cooled with a salt/ice slurry, over 15 min. Stirring was continued with cooling for 1 h before the resulting solution was kept in a freezer (−25 °C) overnight. *n*-Hexane was then added, and the mixture was partially concentrated in vacuo to induce further precipitation. The resulting precipitate was filtered and washed with *n*-hexane to give the title compound (6.62 g, 80%) as a white powder. M.p. 116 °C (ref.[10] m.p. 158−170 °C).[48] The compound was protected from light and stored in a freezer.

Treatment of 4-(1*H*-Indol-3-ylmethyl)-2-(trichloromethyl)-1,3-oxazol-5(4*H*)-one (4) with TFA. (a) Procedure A: Solid oxazolone **4** (3.03 g, 9.14 mmol) was added portionwise over 1 min to a stirred refluxing solution of TFA (20 mL), and heating at reflux was continued for 15 min. Anhydrous toluene (25 mL) was then added, and the TFA was distilled off. Once the temperature of the distillate had risen above 105 °C, the resulting precipitate was filtered hot, washed twice with a little hot toluene and then with excess *n*-hexane, then dried to give 1-(dichloromethyl)-9*H*-β-carboline-3-carboxylic acid (**5**, 1.07 g, 35%) as a white powder (see below for details). The filtrate was concentrated in vacuo and the remaining residue was dissolved in ethyl acetate and washed sequentially with 0.5 M HCl, 0.5 M NaOH twice, brine, then dried ($MgSO_4$) and the solvents were evaporated in vacuo to give 2,2,2-trichloro-*N*-(1,2,3,4-tetrahydro-3-oxocyclopenta[*b*]indol-2-yl)acetamide (**6**, 1.20 g, 45%) as a white powder (see below for details). **(b) Procedure B:** Oxazolone **4** (10.04 g, 30.0 mmol) was added to a solution of TFA (50 mL), which had been equilibrated in a salt/ice slurry at approximately −15 °C. The mixture was stirred with continued cooling for 1 h before the resulting blood-red solution was stoppered and stirred at room temperature for 24 h. The solution was then heated to reflux, and reflux was continued for a further 10 min before dry toluene (90 mL) was added, and the TFA was distilled off. Once the temperature of the distillate had risen above 105 °C, the resulting precipitate was filtered hot, washed twice with a little hot toluene, then with excess *n*-hexane, and then dried to give 1-(dichloromethyl)-9*H*-β-carboline-3-carboxylic acid (**5**, 7.79 g, 87%) as a white powder (see below for details). The filtrate was concentrated in vacuo and the remaining residue was dissolved in ethyl acetate and washed sequentially with 0.5 M HCl, saturated $NaHCO_3$ solution, brine, then dried ($MgSO_4$) and the solvents were evaporated in vacuo to give a dark solid. Purification by flash column chromatography (ethyl acetate) gave 2,2,2-trichloro-*N*-(1,2,3,4-tetrahydro-3-oxocyclopenta[*b*]indol-2-yl)acetamide (**6**, 0.446 g, 4%) as a white powder (see below for details).

1-(Dichloromethyl)-9*H*-β-carboline-3-carboxylic Acid (5): M.p. (darkening at 220 °C) > 360 °C. IR (KBr): $\tilde{\nu}$ = 3263, 1741, 1626, 1594, 1393, 968, 719 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 7.35 (t, *J* = 7.5 Hz, 1 H, aryl C*H*), 7.65 (t, *J* = 8.2 Hz, 1 H, aryl C*H*), 7.76 (s, 1 H, C*H*Cl$_2$), 7.79 (d, *J* = 8.2 Hz, 1 H, aryl C*H*), 8.43 (d, *J* = 7.9 Hz, 1 H, aryl C*H*), 9.01 (s, 1 H, 4-*H*), 12.21 (s, 1 H, N*H*), 12.97 (br. s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 70.31 (*C*HCl$_2$), 112.84, 119.09 (aryl *C*H), 120.74 (aryl *C*), 120.86, 122.21, 129.43 (aryl *C*H), 130.71, 132.44, 136.10, 138.97, 141.40 (aryl *C*), 166.25 (*C*O$_2$H) ppm. ESI MS: *m*/*z* = 297 [M + 1, $^{35}Cl^{37}Cl$], 295 [M + 1, $^{35}Cl^{35}Cl$] and [M − 1, $^{35}Cl^{37}Cl$], 293 [M − H, $^{35}Cl^{35}Cl$]. $C_{13}H_8Cl_2N_2O_2$ (295.1): calcd. C 52.91, H 2.73, N 9.49; found C 52.90, H 2.64, N 9.28.

2,2,2-Trichloro-*N*-(1,2,3,4-tetrahydro-3-oxocyclopenta[*b*]indol-2-yl)-acetamide (6): M.p. 231−233 °C. IR (KBr): $\tilde{\nu}$ = 3346, 3265, 1686, 1516, 1325, 1240, 825, 745 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.97 (dd, *J* = 16.1, 3.3 Hz, 1 H, C*H*$_2$CH), 3.56 (dd, *J* = 16.1, 6.9 Hz, 1 H, C*H*$_2$CH), 4.80 (m, 1 H, CH$_2$C*H*), 7.15 (t, *J* = 7.8 Hz, 1 H, aryl C*H*), 7.38 (t, *J* = 8.0 Hz, 1 H, aryl C*H*), 7.48 (d, *J* = 8.3 Hz, 1 H, aryl C*H*), 7.74 (d, *J* = 8.0 Hz, 1 H, aryl C*H*), 9.57 (d, *J* = 8.1 Hz, 1 H, N*H*CO), 11.82 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 27.31 (*C*H$_2$), 59.58 (*C*H), 113.67, 120.25, 121.50 (aryl *C*H), 122.77 (aryl *C*), 127.05 (aryl *C*H), 136.62, 141.22, 143.53 (aryl *C*), 161.60 (*C*ONH), 189.38 (*C*O) ppm.[49] ESI MS: *m*/*z* = 333 [M + 1, $^{35}Cl^{35}Cl^{37}Cl$] and [M − 1, $^{35}Cl^{37}Cl^{37}Cl$], 331 [M + 1, $^{35}Cl^{35}Cl^{35}Cl$] and [M − 1, $^{35}Cl^{35}Cl^{37}Cl$], 329 [M − 1, $^{35}Cl^{35}Cl^{35}Cl$]. $C_{13}H_9Cl_3N_2O_2$ (331.6): calcd. C 47.09, H 2.74, N 8.45; found C 47.13, H 2.68, N 8.37.

Treatment of 2-Trichloromethyl-4-(3-indolylmethyl)-5(4*H*)-oxazolone (4) with Aluminium Trichloride: The oxazolone **4** (0.500 g, 1.51 mmol) was added all at once to a stirred mixture of aluminum chloride (0.60 g, 4.5 mmol) in anhydrous dichloroethane (13 mL), and stirring was continued at room temperature under argon for 2 h. The resulting mixture was diluted with ethyl acetate and washed sequentially with dilute hydrochloric acid, water, a saturated sodium carbonate solution, brine, and then dried ($MgSO_4$) and the solvents were evaporated in vacuo. The remaining residue was purified by flash column chromatography (chloroform) to give 2,2,2-trichloro-*N*-(1,2,3,4-tetrahydro-3-oxocyclopenta[*b*]indol-2-yl)acetamide (**6**, 0.214 g, 43%) as a pale yellow powder.

Treatment of 4-(1*H*-Indol-3-ylmethyl)-2-(trifluoromethyl)-1,3-oxazol-5(4*H*)-one (1) with TFA: According to Procedure A for the treatment of the oxazolone **4** with TFA, the oxazolone **1** (1.00 g, 3.55 mmol) afforded the β-carboline **2** (0.294 g, 30%) as a pale yellow powder. M.p. 281−283 °C (ref.[10] m.p. 214−216 °C). The corresponding cyclopenta[*b*]indolone (82 mg, 8%) was recovered as a white powder. M.p. 200 °C (dec.) [ref.[10] m.p. 204 °C (dec.)]. Further processing of the mother liquor returned additional β-carboline **2** (0.255 g, 26%), collected in an impure state along with additional cyclopenta[*b*]indolone (37 mg, 4%).

***N*$_b$-(Trichloroacetyl)tryptophan Methyl Ester:** Concentrated hydrochloric acid (5 drops) was added to a stirred solution of the oxazolone **4** (1.07 g, 3.23 mmol), heated at reflux, and reflux was continued for 1 h. The mixture was cooled, then cooled further with ice, before the resulting precipitate was filtered and washed with a little chilled methanol and dried to give the title compound (0.532 g, 45%) as a white powder. M.p. 177−178 °C (ref.[17] m.p. 176−178 °C).

2-Dichloromethylene-4-(1*H*-indol-3-ylmethyl)-1,3-oxazol-5(2*H*)-one (7): Solid oxazolone **4** (1.044 g, 3.15 mmol) was added, all at once, to a stirred and refluxing solution of toluene (20.0 mL), containing a catalytic quantity of *p*TsOH, and heating at reflux was continued for 1 h. The mixture was then cooled before it was concentrated in vacuo and the remaining residue was purified by flash column chromatography (dichloromethane). Crystallization occurred in a number of the fractions off the column and the title compound (0.268 g, 29%) was collected qualitatively as red crystals. M.p. 116 °C (dec.) (ref.[10] m.p. 124 °C).

4-[(5-Methoxy-1*H*-indol-3-yl)methyl]-2-(trichloromethyl)-1,3-oxazol-5(4*H*)-one (15): Trichloroacetic anhydride (1.45 g, 4.70 mmol) was added to a stirred suspension of 5-methoxy-L-tryptophan (**14**) (0.501 g, 2.14 mmol) in diethyl ether (23 mL) cooled with an iced water bath and under argon over 15 min. Stirring was continued with cooling for 1 h before the resulting precipitate was filtered and washed with chilled ether (15 mL), then excess *n*-hexane, and dried to give the title compound (0.548 g, 71%) as a white powder. M.p. 92 °C (colour change),[50] m.p. 95−96 °C. IR (KBr): $\tilde{\nu}$ = 3448, 3254, 1838, 1694, 1522, 1487, 1218, 1168, 1077, 1057, 1011, 967, 895, 827, 806, 679 cm^{-1}. ^1H NMR (CDCl$_3$): δ = 3.55 (m, 2 H, C*H*$_2$CH), 3.87 (s, 3 H, OC*H*$_3$), 5.09 (m, 1 H, CH$_2$C*H*), 6.89 (dd, *J* = 8.9, 2.3 Hz, 1 H, 6′-H), 7.01 and 7.10 (d, *J* = 2.3 Hz, each 1 H, 2′-H and 4′-H), 7.27 (d, *J* = 8.9 Hz, 1 H, 8′-H), 8.11 (br. s, 1 H, N*H*) ppm. ESI MS: *m*/*z* = 363 [M + 1, $^{35}Cl^{35}Cl^{37}Cl$]. HRMS: calcd. for $C_{14}H_{11}{}^{35}Cl_3N_2O_3$ [M]$^+$ 359.9835; found 359.9844. The compound was protected from light and stored in a freezer.

Treatment of Oxazolone 15 with TFA: According to Procedure A for the treatment of the oxazolone **4** with TFA, the oxazolone **15**

(0.200 g, 0.553 mmol) afforded the β-carboline **16** (48 mg, 27%) as a bright yellow powder (see below for details). The cyclopenta-[*b*]indolone **17** (29 mg, 15%) was recovered as a white powder (see below for details). According to Procedure B for the treatment of the oxazolone **4** with TFA, the oxazolone **15** (1.000 g, 2.77 mmol) afforded the β-carboline **16** (0.566 g, 63%) as a bright yellow powder (see below for details). The cyclopenta[*b*]indolone **17** (0.023 g, 2.3%) was recovered as a cream-coloured powder (see below for details).

1-(Dichloromethyl)-6-methoxy-9*H*-β-carboline-3-carboxylic Acid (16): M.p. (darkening at > 210 °C) > 360 °C. IR (KBr): $\tilde{\nu}$ = 3223, 1764, 1684, 1509, 1223, 1199, 1148, 939, 818, 705 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 3.88 (s, 3 H, OC*H*$_3$), 7.29 (t, *J* = 8.9, 2.4 Hz, 1 H, 7-H), 7.69 (d, *J* = 8.9 Hz, 1 H, 8-H), 7.73 (s, 1 H, C*H*Cl$_2$), 8.04 (d, *J* = 2.4 Hz, 1 H, 5-H), 9.03 (s, 1 H, 4-H), 12.04 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 55.69 (O*C*H$_3$), 70.38 (*C*HCl$_2$), 103.85, 113.70, 119.36, 119.55 (aryl *C*H), 121.30, 130.49, 132.71, 135.40, 136.15, 138.95 (aryl C), 154.39 (C-6), 166.25 (*C*O$_2$H) ppm. ESI MS: *m*/*z* = 325 [M − 1, $^{35}Cl^{37}Cl$], 323 [M − 1, $^{35}Cl^{35}Cl$]. HRMS: calcd. for $C_{14}H_{10}{}^{35}Cl_2N_2O_3$ $[M]^+$ 324.0068; found 324.0071.

2,2,2-Trichloro-*N*-(1,2,3,4-tetrahydro-7-methoxy-3-oxocyclopenta-[*b*]indol-2-yl)acetamide (17): M.p. 225−228 °C. IR (KBr): $\tilde{\nu}$ = 3283, 3207, 1713, 1676, 1530, 1497, 1212, 1089, 1013, 817 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.93 (dd, *J* = 16.0, 3.4 Hz, 1 H, C*H*$_2$CH), 3.53 (dd, *J* = 16.0, 7.0 Hz, 1 H, C*H*$_2$CH), 3.79 (s, 3 H, OC*H*$_3$), 4.80 (m, 1 H, CH$_2$C*H*), 7.04 (dd, *J* = 9.0, 2.4 Hz, 1 H, 6-H), 7.19 (d, *J* = 2.4 Hz, 1 H, 8-H), 7.38 (d, *J* = 9.0 Hz, 1 H, 5-*H*), 9.54 (d, *J* = 8.1 Hz, 1 H, N*H*CO), 11.67 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 27.30 (*C*H$_2$CH), 55.37 (O*C*H$_3$), 59.53 (CH$_2$*C*H), 92.44 (*C*Cl$_3$), 101.55, 114.50, 118.40 (aryl *C*H), 122.91, 136.88, 138.86, 140.41 (aryl *C*), 153.84 (*C*-7), 161.54 (*C*ONH), 189.15 (*C*O) ppm. ESI MS: *m*/*z* = 363 [M + 1, $^{35}Cl^{35}Cl^{37}Cl$], 361 [M + 1, $^{35}Cl^{35}Cl^{35}Cl$]. $C_{14}H_{11}Cl_3N_2O_3$ (361.6): calcd. C 46.50, H 3.07, N 7.75; found C 46.65, H 3.02, N 8.15.

Methyl 1-(Dichloromethyl)-9*H*-β-carboline-3-carboxylate (18). (a) Procedure A: A suspension of the β-carboline-3-carboxylic acid **5** (7.21 g, 24.4 mmol) in excess ethereal diazomethane was stirred for 2 d before the solvent was allowed to evaporate and the resulting powder was dried to give the title compound (7.54 g, 100%) as an off-white powder. M.p. (darkening at 220 °C) > 360 °C. IR (KBr): $\tilde{\nu}$ = 3337, 1720, 1502, 1435, 1356, 1257, 725 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 3.94 (s, 3 H, OC*H*$_3$), 7.37 and 7.66 (t, *J* = 7.6 Hz, each 1 H, aryl C*H*), 7.78−7.81 (m, 2 H, C*H*Cl$_2$ and aryl C*H*), 8.46 (d, *J* = 7.9 Hz, 1 H, aryl C*H*), 9.03 (s, 1 H, 4-*H*), 12.27 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 52.22 (CO$_2$*C*H$_3$), 70.07 (*C*HCl$_2$), 112.83, 119.24 (aryl *C*H), 120.69 (aryl *C*), 120.92, 122.27, 129.51 (aryl *C*H), 130.35, 132.40, 135.28, 139.20, 141.36 (aryl *C*), 165.35 (*C*O$_2$CH$_3$) ppm. ESI MS: *m*/*z* = 311 [M + 1, $^{35}Cl^{37}Cl$], 309 [M + 1, $^{35}Cl^{35}Cl$] and [M − 1, $^{35}Cl^{37}Cl$], 307 [M − 1, $^{35}Cl^{35}Cl$]. $C_{14}H_{10}Cl_2N_2O_2$ (309.1): calcd. C 54.39, H 3.26, N 9.06; found C 54.24, H 3.29, N 8.97. **(b) Procedure B:** Anhydrous hydrogen chloride was bubbled through a solution of β-carboline-3-carboxylic acid **5** (3.07 g, 10.4 mmol) in methanol (100 mL) for 20 min, after which time, the hot solution was heated at reflux for a further 3 h. The solvent was then evaporated in vacuo, and the remaining mixture was dissolved in ethyl acetate and washed with a saturated sodium carbonate solution, dried (MgSO$_4$), and then passed through a short column of silica gel (ethyl acetate) to give the title compound (2.78 g, 86%) as an off-white powder.

Methyl 1-(Dichloromethyl)-6-methoxy-9*H*-β-carboline-3-carboxylate (19): According to Procedure B for the methylation of the β-carboline **5** to the β-carboline **18**, the β-carboline **16** (0.252 g, 0.775 mmol) afforded a residue, which was purified by flash column chromatography (25% *n*-hexane/chloroform) to give the title compound (0.153 g, 58%) as a pale yellow powder. M.p. 189−190 °C. IR (KBr): $\tilde{\nu}$ = 3299, 1697, 1679, 1502, 1474, 1440, 1333, 1212, 719 cm^{-1}. ^1H NMR (CDCl$_3$): δ = 3.95 and 4.06 (s, each 3 H, OC*H*$_3$), 7.18 (s, 1 H, C*H*Cl$_2$), 7.31 (dd, *J* = 8.9, 2.5 Hz, 1 H, 7-*H*), 7.57 (d, *J* = 8.9 Hz, 1 H, 8-H), 7.63 (d, *J* = 2.5 Hz, 1 H, 5-H), 8.91 (s, 1 H, 4-H), 9.02 (s, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$): δ = 52.95 (CO$_2$*C*H$_3$), 55.95 (O*C*H$_3$), 71.18 (*C*HCl$_2$), 103.23, 113.22, 119.52, 120.24 (aryl *C*H), 121.80, 131.62, 133.70, 134.69, 135.76, 139.57 (aryl *C*), 155.32 (*C*-6), 165.68 (*C*O$_2$CH$_3$) ppm. ESI MS: *m*/*z* = 341 [M + 1, $^{35}Cl^{37}Cl$], 339 [M + 1, $^{35}Cl^{35}Cl$] and [M − 1, $^{35}Cl^{37}Cl$], 337 [M − 1, $^{35}Cl^{35}Cl$]. $C_{15}H_{12}Cl_2N_2O_3$ (339.2): calcd. C 53.12, H 3.57, N 8.26; found C 53.06, H 3.68, N 8.18.

Methyl 1-Formyl-9*H*-β-carboline-3-carboxylate (20):[26] Compound **18** (0.500 g, 1.62 mmol) was heated at reflux in 10% water/formic acid (10 mL) for 3 h. The resulting dark mixture was poured onto crushed ice, and saponified with a limited amount of 2 M NaOH, and then neutralized with a saturated NaHCO$_3$ solution. The resulting mixture was extracted with dichloromethane, and the organic extract was washed with water, dried (MgSO$_4$), and the solvents were evaporated in vacuo to give the title compound (0.320 g, 78%) as a yellow powder. M.p. 242−244 °C (ref.[26] m.p. 244−246 °C).

Methyl 1-Formyl-6-methoxy-9*H*-β-carboline-3-carboxylate (21): According to the procedure for the hydrolysis of β-carboline **18** to β-carboline **20**, β-carboline **19** (0.116 g, 0.342 mmol) afforded the title compound (0.080 g, 82%) as a yellow powder. M.p. 246 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3378, 2831, 1708, 1683, 1500, 1472, 1438, 1362, 1316, 1300, 1272, 1229, 1217, 1202, 1122, 1095, 1026, 988, 816, 724, 712, 646, 626 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 3.88 and 3.96 (s, each 3 H, OC*H*$_3$), 7.27 (dd, *J* = 8.9, 2.3 Hz, 1 H, 7-H), 7.71 (d, *J* = 8.9 Hz, 1 H, 8-H), 8.07 (d, *J* = 2.3 Hz, 1 H, 5-H), 9.18 (s, 1 H, 4-H), 10.25 (s, 1 H, C*H*O), 12.30 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 52.21 (CO$_2$*C*H$_3$), 55.64 (O*C*H$_3$), 104.08, 114.21, 119.56 (aryl *C*H), 120.69 (aryl *C*), 121.61 (aryl *C*H), 131.36, 134.94, 135.32, 135.96, 137.06 (aryl *C*), 154.67 (C-6), 165.30 (*C*O$_2$CH$_3$), 194.17 (*C*HO) ppm. ESI MS: *m*/*z* = 285 [M + 1], 283 [M − 1]. $C_{15}H_{12}N_2O_4{}^3/_2H_2O$ (311.3): calcd. C 57.88, H 4.86, N 9.00; found C 57.88, H 4.79, N 8.86.

1-Formyl-9*H*-β-carboline-3-carboxylic Acid (22): A suspension of the β-carboline-3-carboxylic acid **5** (0.504 g, 1.71 mmol) in ethanol/2 M HCl (1:1), 30 mL) was heated at reflux for 1 h. The more volatile solvent was then evaporated in vacuo, and the resulting mixture was saponified with 2 M NaOH. The basic solution was then acidified with excess glacial acetic acid and extracted with ethyl acetate. The organic extract was dried (MgSO$_4$) and the solvents were evaporated in vacuo to give the title compound (0.407 g, 99%) as a yellow powder. M.p. 247−248 °C. IR (KBr): $\tilde{\nu}$ = 3329, 2875, 1750, 1680, 1375, 1249, 959, 743 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 7.38 (t, *J* = 7.8 Hz, 1 H, aryl C*H*), 7.65 (t, *J* = 8.2 Hz, 1 H, aryl C*H*), 7.83 (d, *J* = 8.2 Hz, 1 H, aryl C*H*), 8.47 (d, *J* = 7.8 Hz, 1 H, aryl C*H*), 9.17 (s, 1 H, 4-H), 10.28 (s, 1 H, C*H*O), 12.42 (s, 1 H, N*H*), 13.02 (br. s, 1 H, CO$_2$*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 113.41 (aryl *C*H), 120.18 (aryl *C*), 121.23, 121.34, 122.40, 129.57 (aryl *C*H), 131.62, 134.71, 135.15, 137.63, 142.46 (aryl *C*), 166.25 (*C*O$_2$H), 194.33 (*C*HO) ppm. ESI MS: *m*/*z* = 241 [M + 1], 239 [M − 1]. $C_{13}H_8N_2O_3$ (240.2): calcd. C 65.00, H 3.36, N 11.66; found C 65.10, H 3.42, N 11.58.

Reaction of Methyl 1-Formyl-9*H*-β-carboline-3-carboxylate (20) with the Phosphorane 23: A mixture of the aldehyde **20** (0.411 g, 1.62 mmol) and the phosphorane **23** (0.621 g, 1.78 mmol) in toluene (10 mL) was heated at reflux for 2 h. The resulting mixture was cooled and then concentrated in vacuo. The remaining solid residue was recrystallized from *n*-butanol to give a 1:1 mixture of canthin-6-one **24** and β-carboline **25** (330 mg) as a pale yellow powder, free from triphenylphosphane oxide. Recrystallization of the mixture from chloroform gave methyl 1-[3-ethoxy-3-oxoprop-1-enyl]-9*H*-β-carboline-3-carboxylate (**25**, 0.178 g, 34%) as a pale yellow powder; m.p. 246−248 °C (see below for details). The filtrate was then processed further and methyl 6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (**24**) was obtained as a white powder (0.130 g, 29%). M.p. 247−249 °C (ref.[27] m.p. 249−250 °C).

Methyl 1-[3-Ethoxy-3-oxoprop-1-enyl]-9*H*-β-carboline-3-carboxylate (25): M.p. 246−248 °C. IR (KBr): $\tilde{\nu}$ = 3340, 1718, 1500, 1427, 1327, 1298, 1246, 1168, 1036, 752 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.32 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 3.94 (s, 3 H, OC*H*$_3$), 4.28 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 7.15 (d, *J* = 15.4 Hz, 1 H, propenyl C*H*), 7.35 (t, *J* = 7.9 Hz, 1 H, aryl C*H*), 7.66 (m, 2 H, aryl C*H*), 8.36 (d, *J* = 15.4 Hz, 1 H, propenyl C*H*), 8.43 (d, *J* = 7.9 Hz, 1 H, aryl C*H*), 8.95 (s, 1 H, 4-*H*), 12.55 (br. s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 14.19 (CO$_2$CH$_2$*C*H$_3$), 52.16 (CO$_2$*C*H$_3$), 60.36 (CO$_2$*C*H$_2$CH$_3$), 112.41, 118.35, 120.67 (aryl *C*H), 120.88 (aryl *C*), 122.07, 122.37, 129.24 (aryl *C*H), 129.77, 135.34, 136.37, 136.79 (aryl *C*), 138.28 (aryl *C*H), 141.24 (aryl *C*), 165.67, 165.87 (*C*O$_2$CH$_3$ and *C*O$_2$CH$_2$CH$_3$) ppm. ESI MS: *m*/*z* = 325 [M + 1], 323 [M − 1]. C$_{18}$H$_{16}$N$_2$O$_4$ (324.3): calcd. C 66.66, H 4.97, N 8.64; found C 66.54, H 4.87, N 8.56.

Trimethyl 6*H*-Indolo[3,2,1-*de*][1,5]naphthyridine-2,5,6-tricarboxylic Acid (28): A solution of dimethyl acetylenedicarboxylate (0.305 g, 2.15 mmol) in dichloromethane (5 mL) was added to a stirred suspension of the aldehyde **20** (0.500 g, 1.97 mmol) and triphenylphosphane (0.566 g, 2.16 mmol) in dichloromethane (25 mL), cooled with a salt/ice slurry, over 7 min. Stirring was continued at ambient temperature for 20 h before the solvent was evaporated in vacuo, and the remaining red residue was purified by flash column chromatography (dichloromethane) to give the title compound (0.665 g, 89%) as a bright yellow powder. M.p. 203−206 °C. IR (KBr): $\tilde{\nu}$ = 1749, 1704, 1631, 1436, 1374, 1256, 1229, 757 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 3.62, 3.88, 3.91 (s, each 3 H, OC*H*$_3$), 6.56 (s, 1 H, 6-H), 7.42 (t, *J* = 7.4 Hz, 1 H, aryl C*H*), 7.68 (t, *J* = 7.7 Hz, 1 H, aryl C*H*), 7.78 (d, *J* = 8.3 Hz, 1 H, aryl C*H*), 7.82 (s, 1 H, 4-H), 8.40 (d, *J* = 7.9 Hz, 1 H, aryl C*H*), 8.78 (s, 1 H, 1-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 52.20, 52.79, 53.16 (CO$_2$*C*H$_3$), 56.56 (C-6), 111.95, 119.87 (aryl *C*H), 121.66 (aryl *C*), 121.93, 123.35 (aryl *C*H), 125.13, 128.89 (aryl *C*), 129.22, 133.64 (aryl *C*H and C-4), 134.80, 135.37, 138.82, 140.62 (aryl *C*), 164.34, 165.47, 167.40 (*C*O$_2$CH$_3$) ppm. ESI MS: *m*/*z* = 381 [M + 1], 379 [M − 1]. C$_{20}$H$_{16}$N$_2$O$_6$ (380.4): calcd. C 63.16, H 4.24, N 7.37; found C 63.25, H 4.27, N 7.29.

Trimethyl 9-Methoxy-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2,5,6-tricarboxylic Acid (29): According to the procedure for the preparation of the canthine **28** from the aldehyde **20**; aldehyde **21** (40 mg, 0.14 mmol), triphenylphosphane (37 mg, 0.14 mmol) and dimethyl acetylenedicarboxylate (20 mg, 0.14 mmol) afforded the title compound (44 mg, 76%) as a bright yellow powder. M.p. 186−189 °C. IR (KBr): $\tilde{\nu}$ = 1738, 1709, 1478, 1438, 1221, 782 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ = 3.68 (s, 3 H, OC*H*$_3$), 3.93 (s, 6 H, OC*H*$_3$), 4.05 (s, 3 H, OC*H*$_3$), 6.32 (s, 1 H, 6-H), 7.29−7.32 (m, 1 H, aryl C*H*), 7.58−7.61 (m, 2 H, aryl C*H*), 8.17 (s, 1 H, 4-H), 8.70 (s, 1 H, 1-H) ppm. ^{13}C NMR (CDCl$_3$): δ = 52.83, 53.20, 55.93, 57.23 (*C*-6 and CO$_2$*C*H$_3$), 104.92, 112.28, 118.84, 119.99 (aryl *C*H), 123.03, 125.70, 127.88, 133.38 (aryl *C*), 135.53 (C-4), 135.72, 135.94, 136.00, 138.95 (aryl *C*), 155.62 (C-9), 165.00, 166.32, 167.22 (*C*O$_2$CH$_3$) ppm. ESI MS: *m*/*z* = 411 [M + 1], 409 [M − 1]. HRMS: calcd. for C$_{21}$H$_{18}$N$_2$O$_7$ [M + H]$^+$ 411.1192; found 411.1192.

Methyl 1-Formyl-9-(prop-1-enyl)-9*H*-β-carboline-3-carboxylate (30): Sodium hydride (60% suspension, 60 mg, 1.5 mmol), prewashed with light petroleum ether, was added to a stirred solution of aldehyde **20** (0.250 g, 0.983 mmol) in DMSO (15 mL). The red mixture was stirred at room temperature under nitrogen for 2 h. After this time, allyl bromide (0.10 mL, 1.2 mmol) was added, and stirring was continued at room temperature for a further 2 h. The orange solution was then heated to a maximum of 80 °C over 20 min, and then cooled. The solution was then diluted with ethyl acetate and washed twice with water, then once with brine, dried (MgSO$_4$), and the solvents were evaporated in vacuo to give the title compound (0.275 g, 95%) as a white powder. M.p. 118−123 °C. IR (KBr): $\tilde{\nu}$ = 1711, 1447, 1372, 1265, 1126, 936, 752 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ = 4.10 (s, 3 H, OC*H*$_3$), 4.81 (dd, *J* = 9.0, 1.0 Hz, 1 H, CH=C*H*$_2$), 5.11 (dd, *J* = 5.7, 1.0 Hz, 1 H, CH=C*H*$_2$), 5.55 (m, 2 H, C*H*$_2$), 5.96 (m, 1 H, C*H*=CH$_2$), 7.44 (t, *J* = 7.8 Hz, 1 H, aryl C*H*), 7.58 (d, *J* = 8.4 Hz, 1 H, aryl C*H*), 7.70 (t, *J* = 8.3 Hz, 1 H, aryl C*H*), 8.24 (d, *J* = 7.8 Hz, 1 H, aryl C*H*), 9.05 (s, 1 H, 4-*H*), 10.36 (s, 1 H, C*H*O) ppm. ^{13}C NMR (CDCl$_3$): δ = 49.13 (*C*H$_2$), 52.88 (CO$_2$*C*H$_3$), 111.11 (aryl *C*H), 116.67 (CH=*C*H$_2$), 120.61 (aryl *C*H), 121.12 (aryl *C*), 121.53, 121.85, 129.89 (aryl *C*H), 132.56 (*C*H=CH$_2$), 133.03, 136.09, 137.01, 137.18, 142.89 (aryl *C*), 165.57 (*C*O$_2$CH$_3$), 193.19 (*C*HO) ppm. ESI MS: *m*/*z* = 295 [M + 1], 293 [M − 1]. C$_{17}$H$_{14}$N$_2$O$_3$ (294.3): calcd. C 69.38, H 4.79, N 9.52; found C 69.34, H 4.72, N 9.48.

1,4-Dihydrocyclopenta[*b*]indole-2,3-dione (37): Copper(II) bromide (0.653 g, 2.92 mmol) was added, all at once, to a refluxing solution of **6** (0.400 g, 1.21 mmol) in ethyl acetate (25 mL). Heating at reflux was continued for 2 h. The mixture was cooled, and then washed with a dilute NaCl solution, then brine, dried (MgSO$_4$), and the solvents were evaporated in vacuo to give a solid. Purification by percolation column chromatography (ethyl acetate) gave the title compound (0.354 g, 72%) as a pale orange powder. M.p. 254−256 °C. IR (KBr): $\tilde{\nu}$ = 3203, 1763, 1676, 1504, 1250, 1221, 833, 739 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 3.61 (s, 2 H, C*H*$_2$), 7.20 (m, 1 H, aryl C*H*), 7.50 (m, 2 H, aryl C*H*), 7.79 (d, *J* = 7.9 Hz, 1 H, aryl C*H*), 12.27 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 32.43 (*C*H$_2$), 113.80, 121.19, 122.78 (aryl *C*H), 122.87 (aryl *C*), 129.71 (aryl *C*H), 140.05, 140.62, 142.17 (aryl *C*), 174.73 (C-2), 200.40 (C-3) ppm. ESI MS: *m*/*z* = 186 [M + 1], 184 [M − 1]. C$_{11}$H$_7$NO$_2$ (185.2): calcd. C 71.35, H 3.81, N 7.56; found C 71.42, H 3.76, N 7.51.

7-Methoxy-1,4-dihydrocyclopenta[*b*]indole-2,3-dione (38): According to the procedure for the preparation of the cyclopenta[*b*]indol-2,3-dione **37** from the cyclopenta[*b*]indolone **6**; the cyclopenta-[*b*]indolone **17** (30 mg, 0.083 mmol) and copper(II) bromide (45 mg, 0.20 mmol) afforded a motley orange solid, which was purified by flash column chromatography (50% *n*-hexane/ethyl acetate) to give the title compound (13 mg, 73%) as a pale orange powder. M.p. (darkening at > 190 °C) > 222 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3314, 1751, 1690, 1512, 1266, 1219, 1018, 830 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 3.59 (s, 2 H, C*H*$_2$), 3.80 (s, 3 H, OC*H*$_3$), 7.16 (dd, *J* = 9.0, 2.3 Hz, 1 H, 6-H), 7.23 (d, *J* = 2.3 Hz, 1 H, 8-H), 7.42 (d, *J* = 9.0 Hz, 1 H, 5-H), 12.17 (br. s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 32.50 (*C*H$_2$), 55.41 (O*C*H$_3$), 101.97, 114.75, 121.76 (aryl *C*H), 123.11, 137.75, 139.06, 140.92 (aryl *C*), 154.40 (C-7), 174.48 (C-2), 200.61 (C-3) ppm. ESI MS: *m*/*z* = 216

[M + 1], 214 [M − 1]. HRMS: calcd. for $C_{12}H_9NO_3$ [M + H]$^+$ 216.0661; found 216.0667.

2-Amino-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (39) Monohydrochloride: A suspension of **6** (0.250 g, 0.754 mmol) in concentrated hydrochloric acid/glacial acetic acid (2:3, 3.0 mL) was heated at reflux for 20 h, and then allowed to stand at ambient temperature for several hours. The resulting precipitate was filtered, washed several times with glacial acetic acid, then with diethyl ether, and dried, to give the title compound (83 mg, 49%) as a dark powder. M.p. > 400 °C (ref.[10] m.p. > 280 °C).

2,2,2-Trichloro-*N*-(2-methoxy-1,2,3-trihydro-3-oxocyclopenta[*b*]-indol-2-yl)acetamide (40): A solution of **6** (0.302 g, 0.911 mmol) and copper(II) bromide (0.450 g, 0.201 mmol) in methanol (20 mL) was heated at reflux for 3 h, after which time, the solution was concentrated in vacuo and the remaining residue purified by percolation column chromatography (2.5% MeOH/CH_2Cl_2) to give the title compound (0.266 g, 81%) as a white powder. M.p. 165−166 °C. IR (KBr): $\tilde{\nu}$ = 3319, 1684, 1489, 1330, 1244, 1080, 822, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.47 (s, 3 H, OCH_3), 3.73 and 3.80 (d, J = 17.4 Hz, each 1 H, CH_2), 7.22 (m, 1 H, aryl C*H*), 7.47 (m, 2 H, aryl C*H*), 7.67−7.72 (m, 2 H, aryl C*H* and N*H*CO), 8.71 (br. s, 1 H, N*H*) ppm. ^{1}H NMR ([D$_6$]DMSO): δ = 3.36−3.62 (m, 5 H, CH_2 and OCH_3), 7.16 (t, J = 7.4 Hz, 1 H, aryl C*H*), 7.41 (t, J = 7.5 Hz, 1 H, aryl C*H*), 7.48 (d, J = 8.3 Hz, 1 H, aryl C*H*), 7.74 (d, J = 8.0 Hz, 1 H, aryl C*H*), 9.56 (s, 1 H, N*H*CO), 11.91 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 34.90 (*C*H$_2$), 51.71 (O*C*H$_3$), 93.17 (*C*-2), 113.59, 120.39, 121.70 (aryl *C*H), 122.45 (aryl *C*), 127.57 (aryl *C*H), 134.68, 140.30, 143.60 (aryl *C*), 160.84 (*C*ONH), 184.43 (C-3) ppm.[49] ESI MS: *m*/*z* = 363 [M + 1, ^{35}Cl^{35}Cl^{37}Cl], 361 [M + 1, ^{35}Cl^{35}Cl^{35}Cl] and [M − 1, ^{35}Cl^{35}Cl^{37}Cl], 359 [M − 1, ^{35}Cl^{35}Cl^{35}Cl]. $C_{14}H_{11}Cl_3N_2O_3$ (361.6): calcd. C 46.50, H 3.07, N 7.75; found C 46.38, H 2.98, N 7.62.

2,2,2-Trichloro-*N*-(2-ethoxy-1,2,3-trihydro-3-oxocyclopenta[*b*]indol-2-yl)acetamide (41): A solution of **6** (1.03 g, 3.11 mmol) and copper(II) bromide (1.61 g, 0.201 mmol) in chloroform (100 mL) (containing < 1% ethanol) was heated at reflux for 24 h, after which time, the solution was concentrated in vacuo and the remaining residue purified by percolation column chromatography (2.5% MeOH/CH_2Cl_2) to give the title compound (0.476 g, 41%) as a white powder. M.p. 180−181 °C. IR (KBr): $\tilde{\nu}$ = 3251, 1730, 1666, 1480, 1333, 1222, 1056, 821, 746 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.08 (t, J = 7.0 Hz, 3 H, CH$_2$CH_3), 3.39 and 3.46 (d, J = 16.6 Hz, each 1 H, CH$_2$), 3.72 (q, J = 7.0 Hz, 2 H, CH_2CH$_3$), 7.15 (t, J = 7.1 Hz, 1 H, aryl C*H*), 7.41 (t, J = 7.5 Hz, 1 H, aryl C*H*), 7.48 (d, J = 8.4 Hz, 1 H, aryl C*H*), 7.74 (d, J = 8.0 Hz, 1 H, aryl C*H*), 9.52 (s, 1 H, N*H*CO), 11.90 (s, 1 H, N*H*) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 15.22 (CH$_2$*C*H$_3$), 35.38 (*C*H$_2$), 59.53 (*C*H$_2$CH$_3$), 93.19 (C-2), 113.66, 120.46, 121.77 (aryl *C*H), 122.56 (aryl *C*), 127.60 (aryl *C*H), 134.82, 140.26, 143.63 (aryl *C*), 160.79 (*C*ONH), 184.80 (*C*-3) ppm.[49] ESI MS: *m*/*z* = 377 [M − 1, ^{35}Cl^{37}Cl^{37}Cl] and [M + 1, ^{35}Cl^{35}Cl^{37}Cl], 375 [M + 1, ^{35}Cl^{35}Cl^{35}Cl] and [M − 1, ^{35}Cl^{35}Cl^{37}Cl], 373 [M − 1, ^{35}Cl^{35}Cl^{35}Cl]. $C_{15}H_{13}Cl_3N_2O_3$ (375.6): calcd. C 47.96, H 3.49, N 7.46; found C 48.12, H 3.40, N 7.35.

Formation of the Hemiketal 42 of 1,4-Dihydrocyclopenta[*b*]indole-2,3-dione (37): A solution of the dione **37** in CD_3OD was observed to have undergone 39% conversion into the hemiketal **42**. **Dione 37:** ^{1}H NMR (CD_3OD): δ = 3.66 (s, 2 H, CH_2), 7.24 (m, 1 H, aryl C*H*), 7.53 (m, 2 H, aryl C*H*), 7.81 (d, J = 8.2 Hz, 1 H, aryl C*H*) ppm. **Hemiketal 42:** ^{1}H NMR (CD_3OD): δ = 3.17 and 3.39 (d, J = 16.3 Hz, each 1 H, CH_2), 7.16 (t, J = 7.5 Hz, 1 H, aryl C*H*), 7.40 (t, J = 7.7 Hz, 1 H, aryl C*H*), 7.49 (d, J = 8.5 Hz, 1 H, aryl C*H*), 7.70 (d, J = 8.1 Hz, 1 H, aryl C*H*) ppm.

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[50] Oxazolone **15** was isolated in high purity, but its low stability rendered the compound unsuitable for full characterization. Furthermore, the colour change observed during the melting point measurement was most likely due to isomerization.

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