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Application of a catalytic palladium biaryl synthesis reaction, via C–H functionalization, to the total synthesis of Amaryllidaceae alkaloids

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Abstract—The total synthesis of the Amaryllidaceae alkaloids dehydroanhydrolycorine, hippadine, pratosine, anhydrolycorine, assoanine, anhydrolycorin-7-one and oxoassoanine was achieved from the appropriate *N*-benzylisatin precursors using an intramolecular, palladium catalyzed, dehydrohalogenation, biaryl synthesis reaction to establish the carbon skeleton of the natural products. In order to avoid the formation of regioisomers in the cyclization reactions it was found necessary to incorporate the halogen on the benzyl group. Borane reduction of the 7*H*-pyrrolo[3,2,1-*de*]phenanthridine-4,5-dione derivatives gave 7*H*-pyrrolo[3,2,1-*de*]- and 4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]-phenanthridines (dehydroanhydrolycorine, dehydroassoanine, anhydrolycorine and assoanine). The former were readily reduced to the latter with $NaCNBH_3$ to give anhydrolycorine and assoanine. These compounds were then oxidized to anhydrolycorin-7-one and oxoassoanine whilst the same mixtures of borane reduction products could be oxidized to give hippadine and pratosine.

1. Introduction

The Amaryllidaceae alkaloids constitute a structurally diverse group of almost 200 alkaloids isolated from the majority of the genera of the family Amaryllidaceae.[1] The structures have been classified into mainly seven groups. Many of these alkaloids possess significant biological activity and this has in many ways, as well as the structural diversity, stimulated synthetic efforts and the pursuit of new synthetic methodologies. A sub-group of the lycorine structure is represented in Figure 1. This sub-group has either a pyrrolo[3,2,1-*de*]phenanthridine (**1**) or a dihydropyrrolo[3,2,1-*de*]phenanthridine (**2**) skeleton where R_{1-4} may be a hydroxy, methoxy or a fused methylenedioxy ring (R_2/R_3). Positively charged quaternary nitrogen (X=H: vasconine and tortuesine) and neutral zwitterionic ($R_1=O^-$, X=H: ungeremine, criasbetaine and zeflabetaine) compounds have also been isolated.[1]

The use of palladium, in catalytic or stoichiometric quantities, has become an indispensable tool for the synthesis of heterocyclic compounds.[2] The synthetic strategies that have been developed for the synthesis of the pyrrolophenanthridine alkaloids are no exception. All of these strategies, that use palladium, have in common the synthesis of the biaryl linkage between a phenyl group and an indole or indoline derivative. Suzuki aryl–aryl cross couplings have been employed for the synthesis of ungeramine, hippadine (**1b**), anhydrolycorinone (**2b**) and oxoassoanine (**2d**).[3] Stille cross couplings using a 7-stannylindoline derivative were investigated by Iwao and Watanabe for the synthesis of **1b**, **2b**, **2d** and pratosine (**1d**).[4] These authors also transformed anhydrolycorine (**2a**) into kalbretorine (**1g**) via a directed *ortho* lithiation followed by boration and oxidation. Grigg and co-workers used a $Pd(OAc)_2/(Me_3Sn)_2$ system to prepare **1b** in a cyclization between two aryl iodides.[5]

A few examples of the use of palladium for the cyclization of *N*-benzoylindole derivatives are known. These cyclizations are dependant upon the structure of the substrate. Itahara observed that the $Pd(OAc)_2$ oxidative cyclization occurred at C-2 of the indole resulting in the formation of isoindolo[2,1-*a*]indole derivatives.[6] Black and co-workers obtained similar results for the oxidative cyclization of *N*-piperonylindole and methoxybenzoylindole derivatives

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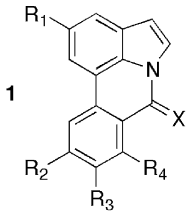
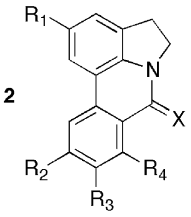


a $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = 2H; Dehydroanhydrolycorine
b $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = O; Hippadine
c $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = 2H; Dehydroassoanine
d $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = O; Pratosine
e $R_1 = R_4 = H$; $R_2 = OCH_3$; $R_3 = OH$; X = O; Pratorinine
f $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = OCH_3$; X = O; Pratorimine
g $R_1 = H$; $R_2/R_3 = -OCH_2O-$; $R_4 = OH$; X = O; Kalbretorine
h $R_1 = H$; $R_2/R_3 = -OCH_2O-$; $R_4 = OCH_3$; X = O; *O*-Methylkalbretorine



a $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = 2H; Anhydrolycorine
b $R_1 = R_4 = H$; $R_2/R_3 = -OCH_2O-$; X = O; Anhydrolycorin-7-one
c $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = 2H; Assoanine
d $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; X = O; Oxoassoanine

Figure 1. Generalized structures for pyrrolo[3,2,1-*de*]phenanthridine (**1**) and dihydropyrrolo[3,2,1-*de*]phenanthridine (**2**) alkaloids (**1c** is unknown as a natural product).

using stoichiometric quantities of $Pd(OAc)_2$.[7] Later these workers anticipated that activation of the benzo-ring of the indole nucleus with methoxy groups (4,6-disubstituted) would allow regioselective C-7 cyclization to occur in preference to C-2 cyclization. In addition, it was shown that the desired C-7 regioselectivity could be guaranteed by oxidative cyclization of *N*-benzoylindolines and subsequent oxidation to the pyrrolophenanthridinone.[8] Grigg and co-workers favoured the investigation of catalytic methods and observed that the Heck reaction[9] of *N*-(2-iodobenzoyl)-indole, and the 3-methylindole derivative, resulted in cyclization at C-2 of the indole nucleus when they used 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3, in the presence of K_2CO_3 and Et_4NCl, in refluxing acetonitrile.[10] Other investigations have also revealed the preference for cyclization at C-2 when the halogen was bonded to the *N*-benzoyl or *N*-benzyl fragment of the indole substrate.[11]

Harayama and co-workers have recently investigated the palladium catalyzed cyclizations of *N*-2-halobenzylindolines. They found that these reactions gave mixtures of the cyclized dihydropyrrolophenanthridine and oxidized dihydropyrrolophenanthridinone as well as the reduced benzylindoline and oxidized benzylindole.[12] Knölker has reported the palladium catalyzed cyclization of *N*-2-iodo-3,4-methylenedioxybenzyltetrahydroindole under air to give **2b** in 29% yield.[13]

Nucleophilic substitution of either *ortho*-methoxy or *ortho*-iodo aromatic substituents in aryloxazolines or benzaldimines, respectively, have been investigated as a means for the construction of the biaryl linkage. In the former case, Hutchings and Meyers required 5 steps to obtain **2d** in moderate overall yield by coupling a bromoindoline Grignard reagent with the appropriate oxazoline followed by subsequent transformations.[14] Similar procedures were later applied to the synthesis of **2b** and dihydrokalbretorine, DDQ oxidation of these compounds yielded **1b**, **1d** and **1g**.[15] In the latter case, Flippin and co-workers prepared vasconine by coupling an indolinylcopper reagent with the appropriate *ortho*-iodobenzaldimine in an Ullmann type biaryl synthesis. Vasconine was then transformed into assoanine (**2c**) and **2d**.[16] A similar methodology was applied later to the synthesis of the pyrrolophenanthridinium alkaloids tortuosine, criasbetaine, and ungeremine.[17] Harrowven and co-workers have made use of an intramolecular Ullmann type coupling reaction to give **1a** which was then oxidized to **1b**.[18]

Other notable methods for the synthesis of these alkaloids include radical cyclizations[19] and intramolecular cycloaddition reactions.[20]

2. Results and discussion

Our approach to the synthesis of the natural products **1** and **2** was based upon the early construction of the entire carbon framework. It was envisaged that benzylation of isatin and subsequent palladium catalyzed synthesis of the biaryl linkage would result in the obtention of the appropriate carbon skeleton.[21] Subsequent reduction and oxidation reactions would be utilized to finish the syntheses of the natural products **1**(**a**, **b** and **d**), **2**(**a**–**d**) as well as the unknown **1c** and analogous derivatives (Fig. 2).

In previous studies of the reactivity of isatin (**3**),[22] we have demonstrated that these compounds may be considered as masked indoles. The reduction of **3** and its' derivatives to indoles in high yields by THF solutions of $BH_3 \cdot THF$ has some distinct advantages over the use of other hydride reagents,[23] though, as of yet, has been rarely exploited for natural product synthesis.[23c,24] Therefore, the synthetic approach for the formation of the biaryl bond using an *N*-benzyl isatin derivative followed by $BH_3 \cdot THF$ reduction of the dioxindole nucleus guarantees the construction of the pyrrolo[3,2,1-*de*]phenanthridine skeleton (**1**) and avoids the problem of regioselective cyclization at C-7 of the indole nucleus.[6–8,10,11]

The *N*-benzylisatin derivatives (**5**) used in this study were readily prepared from the appropriate **3** and benzyl chloride (**4**) in the presence of K_2CO_3 and NaI in DMF or by the use of CaH_2 and DMF (Table 1) (Scheme 1).[25,26]

A previous study had revealed the necessity to transform the keto-carbonyl group of **5** into the *spiro*-dioxolane **6** to facilitate formation of the biaryl linkage by palladium catalysis.[26,27] The dioxolanes **6** were prepared by acid

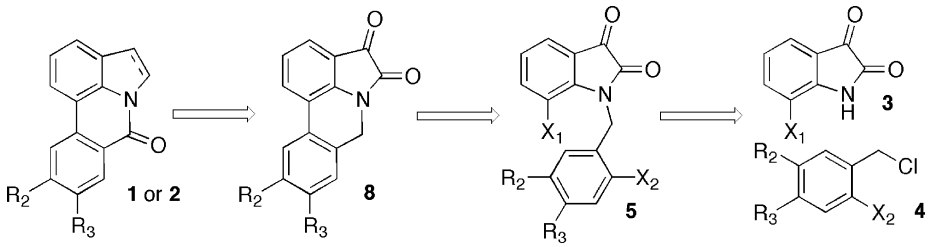
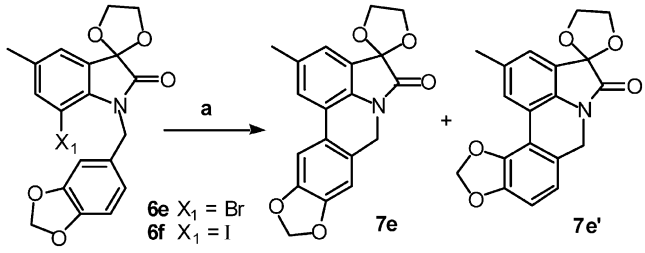


Figure 2. Retroanalysis for the synthesis of pyrrolo- and dihydropyrrolo-[3,2,1-*de*]phenanthridinones: R_2/R_3=H or –OCH_3 or –OCH_2O–; when X_1=I or Br, X_2=H; when X_1=H, X_2=I or Br.

catalysis with azeotropic removal of water using ethylene glycol and toluene. With the appropriate substrates in hand, previously determined conditions for the palladium catalyzed synthesis of the biaryl linkage were applied.[26] The substrate (0.1 M in DMF) was heated in the presence of 10 mol% $Pd(OAc)_2$, 1.0 mol equiv of Bu_4NBr, and 5 mol equiv of KOAc (oil bath temperature 100 °C). No particular precautions, such as an inert atmosphere, or anhydrous DMF, were required and the cyclizations were routinely performed exposed to the atmosphere. The oxopyrrolophenanthridine derivatives (**7**) were obtained in greater than 85% yield from the respective iodide substrates (**6a**, **c**, and **d**) after workup and purification. The bromide **6b** required a considerably longer reaction time and gave a less satisfactory yield (Table 2).

When compounds **6e** and **6f** were treated under the aforementioned palladium catalyzed reaction conditions, two regioisomeric products were obtained as a more or less 1:3 mixture (Eq. 1). The principal isomer was separated by repeated crystallization from MeOH and identified as **7e**′. Subjection of **6g** to the biaryl forming reaction gave a good yield (43%) of **7e** at 46% conversion of the substrate. Thus with an unambiguous method for the regiospecific synthesis of **7e** and the purification of **7e**′ from the mixture it was possible to assign all the signals in the ^1H and ^{13}C NMR spectra of the mixtures of **7e** and **7e**′. It is interesting to note that the regioselectivity of these reactions is opposite to that previously observed by Black and co-workers,[8] and is consistent with that recently reported by Harayama and colleagues in similar palladium catalyzed biaryl forming reactions.[28]

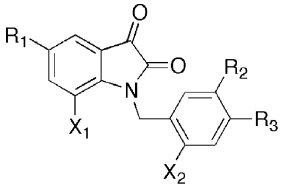


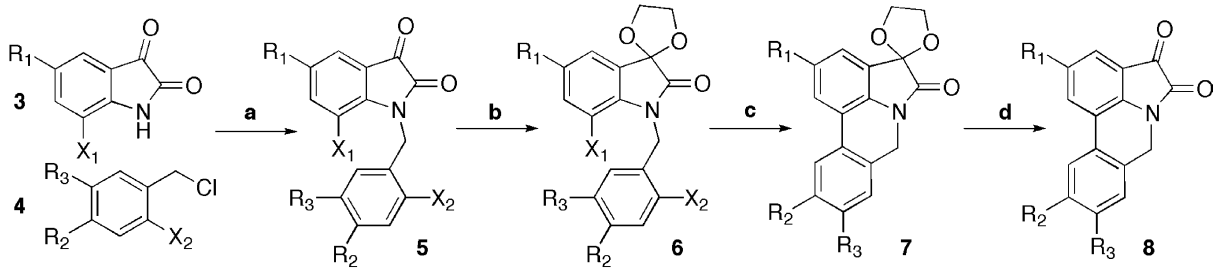
(1)

a 10 mol% $Pd(OAc)_2$, Bu_4NBr, KOAc, DMF.

The reaction mechanism for formation of the biaryl bond is presently debatable and it is possible to envisage a number of scenarios (Fig. 3).[29] Initial oxidative addition of an in situ generated anionic Pd(0) species to the aryl halide would give $ArPd(II)OAcS_2$ (where S is a solvent molecule).[30] This Pd(II) complex could evolve giving rise to the formation of an η^2-arene complex by loss of one of the ligating solvent molecules.[31] Such an η^2-arene complex can be envisioned as a precursor to any of the proposed scenarios (Fig. 3) that

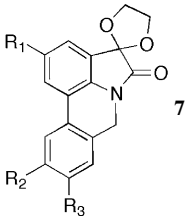
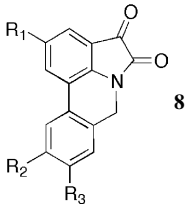
Table 1. Substrates used in this study

Compound		R_2/R_3	R_1	X_1	X_2
	**5a**	H	CH_3	I	H
	5b	–OCH_2O–	H	H	Br
	5c	–OCH_2O–	H	H	I
	5d	OCH_3	H	H	I
	5e	–OCH_2O–	CH_3	Br	H
	5f	–OCH_2O–	CH_3	I	H
	5g	–OCH_2O–	CH_3	H	Br



Scheme 1. For identification of the substituents see Table 1: (a) DMF, K_2CO_3, NaI; (b) $(CH_2OH)_2$, toluene, H_2SO_4; (c) sub. 0.1 M in DMF, 10 mol% $Pd(OAc)_2$, 1 equiv Bu_4NBr, 5 equiv KOAc, 100 °C; (d) 6 N HCl/THF (1:1, v/v) reflux.

Table 2. Cyclization and dioxolane hydrolysis reaction products

Product		R_2/R_3	R_1	Yield (%), [Reac. Time, hrs] mp (°C)	Product		Yield mp (°C)
 **7**	**6a→7a**	H	CH_3	98 [3], 191–3	 **8**	**8a**	96, 237–8
	6b→7b	$-OCH_2O-$	H	69 [24]		**8b**	92, 235–7
	6c→7b	$-OCH_2O-$	H	95 [5], 226–8			
	6d→7d	OCH_3	H	87 [10], 188–190		**8d**	87, 240–2
	6e→7e/7e′	$-OCH_2O-$	CH_3	42[a] [16]			
	6f→7e/7e′	$-OCH_2O-$	CH_3	97[b] [6]			
	6g→7e	$-OCH_2O-$	CH_3	43 [29][c], 243–5			

[a] A mixture of two regioisomers (1:3.2) as determined by ^1H NMR.
[b] A mixture of two regioisomers (1:3.0) as determined by ^1H NMR, mp of **7e′** is 217–9 °C.
[c] 20 mol% PPh_3 in place of the Bu_4NBr.

result in C–H functionalization.[32] Alternatively, the formation of an η^1-arene complex, as an intermediate, may precede the formation of the palladacycle.[33] In the first scenario, the η^2-arene complex (or the η^1-arene complex) would evolve by addition of the σ-Pd–C aryl bond to the aromatic ring in a Heck type reaction giving rise to a *trans* disposed arrangement of the Pd and hydrogen to be eliminated. In Heck reactions such eliminations occur in a *syn* manner. In order to regenerate Pd(0) it would be necessary for a base to abstract the proton, resulting in aromatization of the benzoid ring and the elimination of Pd(0) or for stereomutation of the π-allyl palladium to occur resulting in a *cis* relationship with respect to the hydrogen to be eliminated.[10,34] The second scenario proposes that the reaction mechanism passes via a classical aromatic electrophilic substitution to give a *cis*-diarylpalladium species that would eliminate Pd(0) forming the biaryl bond. Such a mechanism may or may not include a σ-complex intermediate of finite lifetime and is expected to show a normal aryl-substituent effect where electron releasing groups increase the rate of reaction.[35] However, such substituent effects have been called into question.[36] The third scenario is that an η^2-arene (or an η^1-arene) aryl-Pd complex precedes an agostic interaction between the palladium and the carbon–hydrogen bond.[37] An agostic effect may possibly represent a transition state for C–H activation which ultimately results in the formation of the *cis*-diarylpalladium (II) species.[33,36,38]

The dioxolane products **7**(**a**, **b** and **d**) were hydrolyzed in refluxing 50% aqueous 6 N HCl/THF for 5 h. Evaporation of the THF resulted in the precipitation of the dark red/purple compounds **8** in greater than 85% yield. Rigby and Mateo reported an alternative method for what was claimed to be the synthesis of compound **8b**.[39] Both the physical and the spectroscopic properties detailed for compound **8b** as prepared by Rigby and Mateo are inconsistent with those obtained in this study.

With compounds **8** in hand, attention was turned to

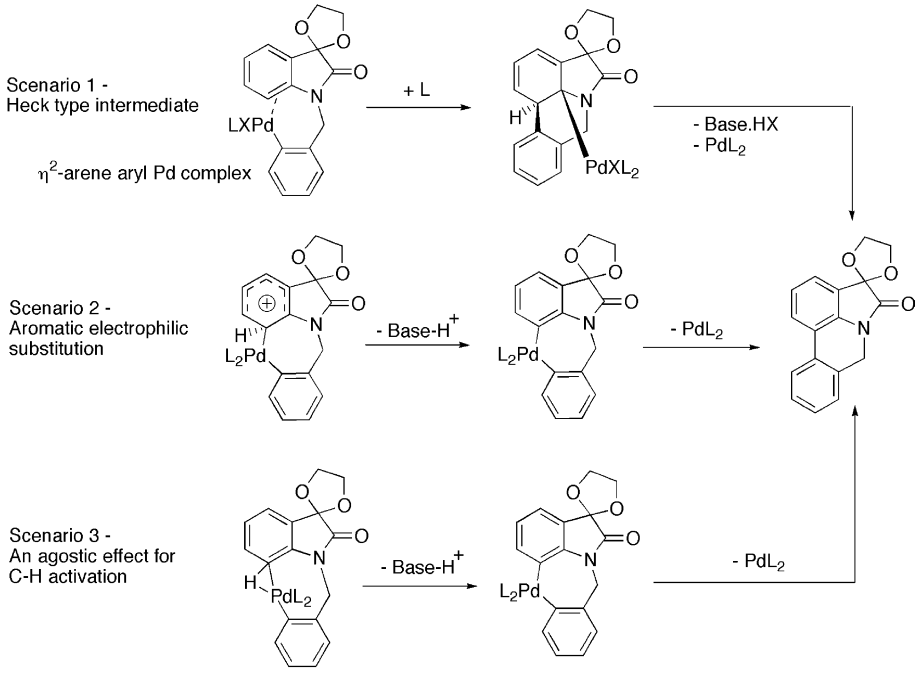
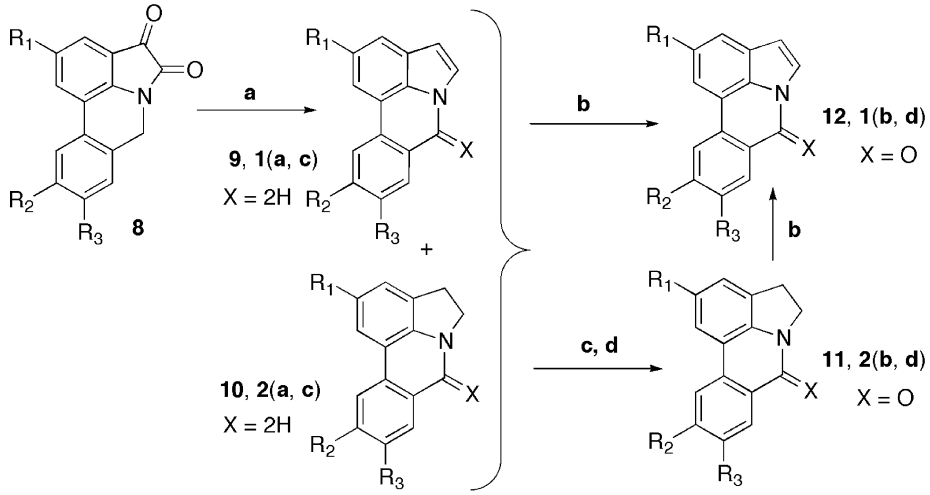


Figure 3. Reaction mechanism scenarios. In all three cases equivalent scenarios may be envisioned where the halogen would have initially been bonded to the oxindole system. No distinction is implied by the ligand (L) as to whether it is an anionic or neutral ligand and indeed L_2 could be a combination of such ligands (scenarios 2 and 3).



Scheme 2. Reduction of compounds **8**: (a) $BH_3 \cdot THF$ (3 mol equiv); (b) oxidation; (c) $NaCNBH_3$, AcOH; (d) $KMnO_4$, NaOH, CH_2Cl_2 (compounds **9**, **10**, **11** and **12**: $R_1 = CH_3$, $R_2, = R_3 = H$).

investigate the reduction reaction employing $BH_3 \cdot THF$. A solution of $BH_3 \cdot THF$ was added to THF solutions of compounds **8**. The reactions were maintained at room temperature for 3 h then hydrolyzed. Normal workup of the hydrolyzed reactions gave the crude products. In the case of **8a**, compound **9** could be obtained in up to 92% yield. This compound was characterized spectroscopically, the vinylic indole proton signals being observed at 6.43 and 7.07 ppm as doublets ($J = 2.9$ Hz). In contrast to **8a**, the reduction of both **8b** and **8d** with $BH_3 \cdot THF$ gave a mixture of the respective **1a/2a** and **1c/2c**. In the case of the reaction of **8b** the mixture was quantified as being a 7:3 ratio of **1a**:**2a**. These compounds were unambiguously identified in the ^1H NMR spectrum from the presence of the vinylic indole CH doublets in **1a** (6.50 and 7.07 ppm, $J = 2.8$ Hz) and the presence of the two vicinial CH_2 triplets in **2a** (3.00 and 3.30 ppm, $J = 7.8$ Hz). The obtention of substantial quantities of compounds **2** (**a** and **c**) was unexpected based upon our previous experience of the reduction of dioxindole derivatives.[23] The mixtures of **1a/2a** and **1c/2c** could not be chromatographically separated without substantial losses and were found to darken when exposed to the atmosphere at room temperature for any appreciable time. This is most likely due to oxidation of the samples as both anhydrolycorine (**2a**) and assoanine (**2c**) are known to undergo autoxidation in the presence of air and acid.[19c] However, the obtention of a mixture was not seen as a drawback, but rather, the mixture could be used to obtain either compounds **1** (X=O) or **2** (X=O), Figure 1. Compounds **1** (X=O) could, in principle, be obtained by oxidation of either **1** (X=2H) or **2** (X=2H), whilst compounds **2** (X=O) could be obtained by reduction of **1** (X=2H) to **2** (X=2H) followed by oxidation to give **2** (X=O), Figure 1 and Scheme 2.

Compound **9** was reduced with $NaCNBH_3$ in AcOH at room temperature to give **10** in 54% yield.[40] This product readily decomposed on exposure to the atmosphere but was characterized by ^1H NMR which revealed the presence of two triplets at 2.98 and 3.32 ppm ($J = 7.8$ Hz). As a consequence of the instability of **10** it was decided to try reducing **8a** to give **10**, via the sequence (i) $BH_3 \cdot THF$, (ii) $NaCNBH_3$, AcOH, and to directly oxidize crude **10** to give **11** (Scheme 2). When **8a** was reduced to **10**, in this manner, and then directly oxidized with oxone®, in a mixture of water/acetone and $NaHCO_3$, compound **11** was obtained with a global yield of 30%. The structure of **11** was confirmed spectroscopically. The introduction of the amide carbonyl was observed in the IR (1641 cm^{-1}) and in the ^{13}C NMR (160.1 ppm) and by the disappearance of the C-7 methylene hydrogens. The presence of the indoline methylene groups (C4/C5) was confirmed by the two triplets at 3.38 and 4.47 ppm ($J = 8.2$ Hz). An accurate mass measurement of the molecular ion was consistent with that expected for the structure of **11**.

When compound **8b** was subjected to the same sequence of reactions, with the aim of obtaining anhydrolycorin-7-one (**2b**), an amorphous colourless solid of relatively high melting point (227–243 °C) was obtained. It is suspected that this solid was a mixture of 4,5-dihydropyrrolo-9,10-methylenedioxyphenanthridinium salts though the solid could not be properly characterized. Treatment of this amorphous solid with $KMnO_4$ under basic conditions gave **2b** in a global yield (from **8b**) of 31%, Scheme 3. However, when **8b** was reduced to **2a** then oxidized with $KMnO_4$, anhydrolycorin-7-one (**2b**) was obtained in a global yield of 75%. Applying the same three reaction sequence to **8d** gave oxoassoanine (**2d**) in a global yield of 72%. The spectroscopic and melting point data were found to be consistent with published data.[15,19g,41]

Having secured the syntheses of anhydrolycorin-7-one (**2b**) and oxoassoanine (**2d**) via the air unstable anhydrolycorine (**2a**) and assoanine (**2c**), a formal synthesis of hippadine (**1b**) and pratosine (**1d**), via oxidation with DDQ, was also complete.[4,15,19d,42] However, with the mixtures of **1a/2a** and **1c/2c** it was envisaged that a one pot oxidation could lead to the pyrrolophenanthridinones **1b** and **1d**. Initially, **9** was treated with MnO_2–SiO_2 in refluxing benzene. The volatiles were removed and the solid residue was chromatographed resulting in the isolation of **12** in 53% yield (Scheme 2). Treatment of the mixtures **1a/2a** and **1c/2c**, in a similar manner, resulted in the partial oxidation of the mixtures

where **1b** (35% yield) and **1d** (36% yield) were the only eluted products from the respective reactions. These products were recrystallized from MeOH before spectroscopic analysis. Further elution of the column, in the case of the synthesis of **1b**, using MeOH, resulted in the obtention of an amorphous solid. This solid was treated with $KMnO_4$ under basic conditions resulting in the obtention of **2b** in 21% yield after workup. The products **1b** and **1d** gave compatible analyses with those reported in the literature.[15,41,42]

In conclusion, the natural products **1** (**a**, **b**, **d**) and **2** (**a**, **b**, **c**, and **d**) have been prepared in a concise manner from *N*-benzylisatin derivatives via a palladium catalyzed dehydrohalogenation aryl–aryl coupling reaction. The reaction conditions are based upon those developed by Jeffery[43] for the Heck reaction and permit that the palladium catalyzed reactions occur under milder conditions than those originally reported in similar biaryl coupling reactions.[44] The cyclization of a *meta*-substituted *N*-benzyl-7-haloisatin derivative resulted in a mixture of regioisomers and is therefore only a regioselective route to the natural products or analogues. The syntheses were completed through the use of combined reduction ($BH_3 \cdot THF$ and $NaCNBH_3$) and oxidation ($KMnO_4$) reactions or by oxidation of the products obtained from the borane reduction of the respective **8**. In the case of **2b** and **2d**, global yields of the order of 50% were obtained through a sequence of seven reactions starting from the respective isatin **3** and benzyl chloride **4**.

3. Experimental

3.1. General

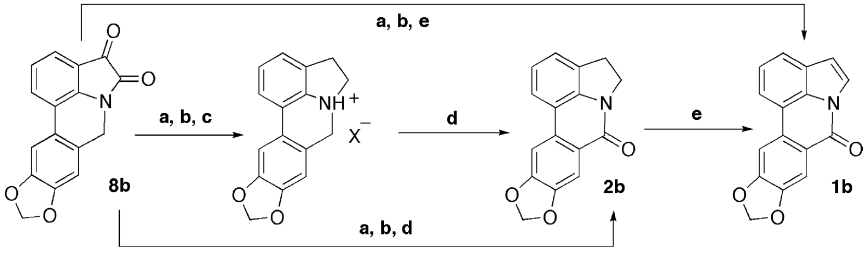
DMF was used as received or distilled under reduced pressure. All other solvents were distilled over standard drying agents under nitrogen before use. 7-Bromo-5-methylisatin was prepared by bromination of 5-methylisatin in 95% ethanol with bromine; 7-iodo-5-methylisatin was prepared by iodination using aqueous $KICl_2$;[45] the benzyl chlorides were prepared by reaction of the respective benzyl alcohol (2-iodo-4,5-methyenedioxybenzyl alcohol,[46] 2-bromo-4,5-methyenedioxybenzyl alcohol,[47] 2-iodo-4,5-dimethoxybenzyl alcohol[48]) with $SOCl_2$ in CH_2Cl_2. MnO_2–SiO_2[49] was prepared according to the indicated literature procedure. All other starting materials were obtained from commercial suppliers and were generally used without further purification. Melting points were determined on a Mel-Temp II-Laboratory Devices Inc, capillary apparatus and are reported as uncorrected values. Column chromatography was performed using silica gel (70–230 mesh, Merck). ^1H and ^{13}C NMR spectra were recorded using Bruker (200 and 300 MHz) spectrometers. The PENDANT pulse sequence was used to distinguish C, CH, CH_2 and CH_3 in the ^{13}C NMR.[50] Mass spectra were obtained by electron impact (70 eV) on a VG Autospec or Hewlett–Packard (GC-MS) spectrometers. Infra-red spectra were recorded using a Perkin–Elmer 1600 FT-IR as KBr discs or films.

3.2. *N*-Benzylisatins

A mixture of the respective isatin (10.0 mmol) and K_2CO_3 (2.00 g, 14.5 mmol) in DMF (10 ml) was stirred with heating (40–60 °C) for 1 h. To the resulting dark coloured suspension were added, the benzyl chloride (11.0 mmol) and KI (0.33 g, 2.0 mmol). Stirring and heating (40–60 °C) were continued until TLC revealed that the reaction had completed. The reaction mixture was hydrolysed with aqueous hydrochloric acid (100 ml, 0.2 mol l^{-1}), extracted with ethyl acetate (4×20 ml) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by filtration through a short column of silica using CH_2Cl_2. Recrystallization from ethyl acetate/hexane (1:1) gave analytically pure samples.

3.2.1. 1-Benzyl-7-iodo-5-methyl-indole-2,3-dione (5a). Red crystals, 89–94%, mp 145–147 °C. IR (ν_{max}, cm^{-1}): 3052, 2919, 1737, 1612, 1559, 1476, 1436, 1332, 1133, 879, 767, 731. MS (% rel. int.): 377(M^+, 54), 320(6), 286(94), 230(14), 193(9), 165(10), 103(28), 91(100). ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 5.42 (s, 2H, CH_2-benzyl), 7.18–7.29 (m, 5H, CH-phenyl), 7.42 (d, 1H, J=1.6 Hz, H-4), 7.74 (d, 1H, J=1.6 Hz, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.1 (CH_3), 43.69 (CH_2-benzyl), 73.8 (C-7), 120.7 (C), 126.2 (CH), 126.5 (2×CH), 127.6 (CH), 128.9 (2×CH), 136.0 (C), 136.1 (C), 148.8 (C), 151.2 (CH), 159.4 (C-2), 182.9 (C-3). Anal. for $C_{16}H_{12}INO_2$: C 50.95; H 3.21; N 3.71 (calcd); C, 50.91; H, 3.18; N 3.49 (found).

3.2.2. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-indole-2,3-dione (5b). Orange crystals, 87–91%, mp 191–192 °C. IR (ν_{max}, cm^{-1}): 3080, 3057, 2924, 2890, 1746, 1732, 1610, 1498, 1471, 1433, 1365, 1346, 1279, 1244, 1175, 1113, 1036, 929, 877, 860, 756. ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (s, 2H, CH_2-benzyl), 5.96 (s, 2H, OCH_2O), 6.69 (s, 1H, H-6′), 6.81 (d, 1H, J=7.6 Hz, H-7), 7.04 (s, 1H, H-3′), 7.13 (t, 1H, J=7.6 Hz, H-5), 7.53 (t, 1H, J=7.6 Hz, H-6), 7.64 (d, 1H, J=7.6 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 44.1 (CH_2-benzyl), 102.3 (OCH_2O), 108.2 (CH), 111.4 (CH), 113.1 (CH), 113.6 (C), 117.9 (C), 124.3 (CH), 125.7



Scheme 3. Obtention of anhydrolycorinone (**2b**) and hippadine (**1b**). (a) $BH_3 \cdot THF$ (3 mol equiv); (b) $NaCNBH_3$, AcOH; (c) Oxone™, $NaHCO_3$, H_2O/acetone; (d) $KMnO_4$, NaOH, CH_2Cl_2; (e) MnO_2–SiO_2, benzene, reflux.

(CH), 126.7 (C), 138.8 (CH), 148.4 (C), 148.6 (C), 150.6 (C), 158.6 (C-2), 183.2 (C-3).

3.2.3. 1-(2′-Iodo-4′,5′-methylenedioxybenzyl)-indole-2,3-dione (5c). Orange crystals, 84–92%, mp 191–193 °C. IR (ν_{max}, cm^{-1}): 3076, 2886, 1746, 1732, 1610, 1495, 1471, 1432, 1362, 1347, 1243, 1174, 1035, 927, 756. ^1H NMR (200 MHz, $CDCl_3$): δ 4.91 (s, 2H, CH_2-benzyl), 5.95 (s, 2H, OCH_2O), 6.65 (s, 1H, H-6′), 6.74 (d, 1H, $J=7.5$ Hz, H-7), 7.14 (t, 1H, $J=7.5$ Hz, H-5), 7.29 (s, 1H, H-3′), 7.52 (t, 1H, $J=7.5$ Hz, H-6), 7.64 (d, 1H, $J=7.5$ Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 49.2 (CH_2-benzyl); 85.9 (C-2′), 102.2 (OCH_2O), 107.7 (CH), 111.7 (CH), 117.9 (C), 119.1 (CH), 124.4 (CH), 125.7 (CH), 129.6 (C), 138.8 (CH), 148.6 (C), 149.4 (C), 150.6 (C), 158.6 (C-2), 183.1 (C-3). Anal. for $C_{16}H_{10}INO_4$: C, 47.20; H, 2.48; N, 3.44 (calcd); C, 46.97; H, 2.54; N, 3.27 (found).

3.2.4. 1-(2′-Iodo-4′,5′-dimethoxybenzyl)-indole-2,3-dione (5d). Orange crystals, 90–92%, 173–174 °C. IR (ν_{max}, cm^{-1}): 3079, 2997, 2941, 2837, 1740, 1614, 1504, 1469, 1443, 1345, 1251, 1213, 1162, 1023, 873, 752. MS (% rel. int.): 423(M^+, 7), 296(100), 277(50). ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.95 (s, 2H; CH_2-benzyl), 6.70 (s, 1H, H-5′), 6.82 (d, 1H, $J=7.5$ Hz, H-7), 7.15 (t, 1H, $J=7.5$ Hz, H-5), 7.27 (s, 1H, H-2′), 7.51 (t, 1H, $J=7.5$ Hz, H-6), 7.63 (d, 1H, $J=7.5$ Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 49.1 (CH_2-benzyl), 56.2 (CH_3O), 56.4 (CH_3O), 86.4 (C-2′), 110.8 (CH), 112.0 (CH), 117.9 (C), 121.9 (CH), 124.3 (CH), 125.6 (CH), 128.9 (C), 138.8 (CH), 149.7 (C), 150.3 (C), 150.7 (C), 158.7 (C-2), 183.2 (C-3). Anal. for $C_{17}H_{14}INO_4$: C, 48.25; H, 3.33; N, 3.31 (calcd); C, 48.15; H, 3.39; N, 3.42 (found).

3.2.5. 7-Bromo-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2,3-dione (5e). Orange crystals, 85%, mp 157–159 °C. IR (ν_{max}, cm^{-1}): 3061, 2929, 2884, 2790, 1741, 1731, 1619, 1571, 1503, 1480, 1448, 1326, 1248, 1158, 1135, 1037, 928, 816, 801. MS (% rel. int.): 375/373(M^+, 20/21), 240/238(28), 135(100). ^1H NMR (200 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 5.31 (s, 2H, CH_2-benzyl), 5.94 (s, 2H, OCH_2O), 6.75 (m, 3H, H-2′, H-5′ and H-6′), 7.43 (s, 1H, H-4), 7.49 (s, 1H, H-6). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.3 (CH_3), 44.4 (CH_2-benzyl), 101.3 (OCH_2O), 104.2 (C-7), 107.5 (CH), 108.6 (CH), 120.2 (CH), 121.0 (C), 125.6 (CH), 130.0 (C), 135.8 (C), 144.3 (CH), 145.5 (C), 147.3 (C), 148.2 (C), 159.3 (C-2), 182.7 (C-3).

3.2.6. 7-Iodo-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2,3-dione (5f). Orange Crystals, 83%, 165–166 °C. IR (ν_{max}, cm^{-1}): 3059, 2925, 2883, 2789, 1731, 1616, 1502, 1478, 1446, 1326, 1247, 1155, 1137, 1037, 928, 808, 711. ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 5.36 (s, 2H, CH_2-benzyl), 5.94 (s, 2H, OCH_2O), 6.69–6.77 (m, 3H, H-2′, H-5′ and H-6′), 7.46 (s, 1H, H-4), 7.79 (s, 1H, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.1 (CH_3), 43.3 (CH_2-benzyl), 73.8 (C-7), 101.3 (OCH_2O), 107.3 (CH), 108.6 (CH), 120.0 (CH), 120.8 (C), 126.3 (CH), 129.7 (C), 136.0 (C), 147.2 (C), 148.2 (C), 148.7 (C), 151.2 (CH), 159.4 (C-2), 182.7 (C-3).

3.2.7. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-5-methyl-indole-2,3-dione (5g). Orange crystals, 74%, mp 223–225 °C. IR (ν_{max}, cm^{-1}): 3036, 2980, 2957, 2907, 1736, 1623, 1595, 1503, 1482, 1440, 1359, 1340, 1236, 1113, 1035, 930, 864, 837, 780. ^1H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 4.94 (s, 2H, CH_2-benzyl), 5.95 (s, 2H, OCH_2O), 6.68 (s, 1H, H-6′), 6.69 (d, 1H, $J=7.6$ Hz, H-7), 7.04 (s, 1H, H-3′), 7.33 (d, 1H, $J=7.6$ Hz, H-6), 7.45 (s, 1H, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.9 (CH_3), 44.1 (CH_2-benzyl), 102.2 (OCH_2O), 108.2 (CH), 111.2 (CH), 113.1 (CH), 113.5 (C), 117.9 (C), 126.0 (CH), 126.8 (C), 134.2 (C), 139.2 (CH), 148.3 (C), 148.4 (C), 148.5 (C), 158.7 (C-2), 183.4 (C-3).

3.3. *N*-Benzylisatin ethylenedioxy ketals

The appropriate *N*-benzylisatin (10.0 mmol), ethyleneglycol (10 ml), *p*-toluenesulfonic acid (a few crystals) and toluene (30 ml) were refluxed ($\approx$5 h) with azeotropic removal of water until TLC revealed complete reaction.

On complete reaction the solvent was removed under vacuum, and the residue was treated with aqueous sodium bicarbonate (5%, 30 ml) and extracted with ethyl acetate (4×15 ml). The organic phase was dried with anhydrous sodium sulfate, the solvent removed under reduced pressure and the crude product purified by silica gel column chromatography using CH_2Cl_2 as eluent. The products were recrystallized from ethyl acetate/hexane (1:4).

3.3.1. 1-Benzyl-3,3-ethylenedioxy-7-iodo-5-methyl-indole-2-one (6a). Colourless crystals, 84–94%, 146–147 °C. IR (ν_{max}, cm^{-1}): 3085, 3058, 3030, 2970, 2946, 2905, 1737, 1623, 1567, 1471, 1438, 1414, 1299, 1154, 1038, 999, 945, 866, 725. MS (% rel. int.): 421(M^+, 25), 330(100), 286(37), 91(63). ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 4.31–4.39 (m, 2H, ketal), 4.54–4.62 (m, 2H, ketal), 5.33 (s, 2H, CH_2-benzyl), 7.15–7.32 (m, 6H, H-4 and 5×CH-phenyl), 7.54 (s, 1H, C-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3 (CH_3), 43.3 (CH_2-benzyl), 66.2 (2×CH_2-ketal), 72.4 (C-7), 101.1 (C-3), 126.0 (CH), 126.4 (2×CH), 127.2 (CH), 128.8 (2×CH), 135.3 (C), 136.8 (C), 142.1 (C), 144.5 (CH), 174.6 (C-2).

3.3.2. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-3,3-ethylenedioxy-indole-2-one (6b). Colourless crystals, 82%, mp 175–177 °C. IR (ν_{max}, cm^{-1}): 3108, 3050, 2979, 2910, 1734, 1621, 1499, 1481, 1468, 1424, 1366, 1321, 1243, 1185, 1131, 1043, 959, 933, 872, 831, 750. ^1H NMR (200 MHz, $CDCl_3$): δ 4.32–4.44 (m, 2H, ketal), 4.55–4.67 (m, 2H, ketal), 4.83 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.62 (s, 1H, H-6′), 6.67 (d, 1H, $J=7.5$ Hz, H-7), 7.02 (s, 1H, H-3′), 7.08 (dt, 1H, $J=1.2$, 7.5 Hz, H-5), 7.29 (dt, 1H, $J=1.2$, 7.5 Hz, H-6), 7.40 (dd, 1H, $J=1.2$, 7.5 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 43.4 (CH_2-benzyl), 66.1 (2×CH_2-ketal), 102.0 (OCH_2O), 102.4 (C-3), 108.0 (CH), 109.9 (CH), 112.9 (CH), 113.3 (C), 123.8 (CH), 124.1 (C), 125.1 (CH), 127.4 (C), 131.9 (CH), 143.6 (C), 148.1 (C), 148.2 (C), 173.8 (C-2).

3.3.3. 1-(2′-Iodo-4′,5′-methylenedioxybenzyl)-3,3-ethylenedioxy-indole-2-one (6c). Colourless crystals, 88–95%, mp 191–193 °C. IR (ν_{max}, cm^{-1}): 3095, 3043, 2975, 2906, 1731, 1622, 1497, 1478, 1467, 1422, 1362, 1247, 1185, 1129, 1044, 960, 931, 750. ^1H NMR (300 MHz,

$CDCl_3$): δ 4.33–4.45 (m, 2H, ketal), 4.55–4.67 (m, 2H, ketal), 4.77 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.59 (s, 1H, H-6′), 6.62 (d, 1H, J=7.6 Hz, H-7), 7.09 (t, 1H, J=7.6 Hz, H-5), 7.27 (s, 1H, H-3′), 7.29 (t, 1H, J=7.6 Hz, H-6), 7.40 (d, 1H, J=7.6 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 48.6 (CH_2-benzyl), 66.1 (2×CH_2-ketal), 85.6 (C-2′), 102.0 (OCH_2O), 102.5 (C-3), 107.7 (CH), 110.2 (CH), 118.9 (CH), 123.8 (CH), 124.1 (C), 125.1 (CH), 130.4 (C), 132.0 (CH), 143.6 (C), 148.3 (C), 149.3 (C), 173.7 (C-2). Anal. for $C_{18}H_{14}INO_5$: C, 47.91; H, 3.13; N, 3.10 (calcd); C, 48.23; H, 3.31; N, 3.23 (found).

3.3.4. 1-(2′-Iodo-4′,5′-dimethoxybenzyl)-3,3-ethylenedioxy-indole-2-one (6d). Colourless crystals, 93–94%, mp 130–131 °C. IR (ν_{max}, cm^{-1}): 3088, 2966, 2906, 2842, 1721, 1617, 1507, 1464, 1445, 1372, 1250, 1211, 1161, 1126, 1022, 946, 865, 762. MS (% rel. int.): 467(M^+, 2), 340(100), 277(22), 190(73), 146(37). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 4.34–4.38 (m, 2H, ketal), 4.61–4.66 (m, 2H, ketal), 4.81 (s, 2H, CH_2-benzyl), 6.59 (s, 1H, H-6′), 6.65 (d, 1H, J=7.6 Hz, H-7), 7.10 (t, 1H, J=7.6 Hz, H-5), 7.23 (s, 1H, H-3′), 7.25 (t, 1H, J=7.6 Hz, H-6), 7.39 (d, 1H, J=7.6 Hz, H-4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 48.2 (CH_2-benzyl), 56.0 (CH_3O), 56.4 (CH_3O), 66.1 (2×CH_2-ketal), 85.8 (C-2′), 102.6 (C-3), 110.3 (2×CH), 121.8, 123.8, 124.1, 125.0, 129.6, 131.9, 143.6 (C), 149.2 (C), 150.1 (C), 173.9 (C-2).

3.3.5. 7-Bromo-3,3-ethylenedioxy-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2-one (6e). Colourless crystals, 98%, mp 115–116 °C. IR (ν_{max}, cm^{-1}): 2974, 2901, 1732, 1625, 1500, 1479, 1444, 1304, 1244, 1156, 1039, 1000, 942, 916, 858, 798. MS (% rel. int.): 419/417(M^+, 14/15), 284/282(100/98), 238/240(35), 135(91), 103(18), 77(41). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 4.22–4.38 (m, 2H, ketal), 4.53–4.64 (m, 2H, ketal), 5.18 (s, 2H, CH_2-benzyl), 5.90 (s, 2H, OCH_2O), 6.66–6.74 (m, 3H, H-2′, H-5′, H-6′), 7.16 (s, 1H, H-4), 7.24 (s, 1H, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.5 (CH_3), 43.9 (CH_2-benzyl), 66.2 (2×CH_2-ketal), 101.4 (C-3), 102.8 (C and OCH_2O), 107.3 (CH), 108.5 (CH), 119.8 (CH), 125.2 (CH), 127.4 (C), 130.8 (C), 135.1 (C), 137.5 (CH), 138.9 (C), 146.9 (C) 148.0 (C), 174.4 (C-2).

3.3.6. 3,3-Ethylenedioxy-7-iodo-1-(3′,4′-methylenedioxybenzyl)-5-methyl-indole-2-one (6f). Colourless crystals, 90–92%, mp 129–131 °C. IR (ν_{max}, cm^{-1}): 2970, 2944, 2891, 1733, 1619, 1492, 1473, 1437, 1328, 1243, 1154, 1037, 1001, 948, 854, 813, 737. MS (% rel. int.): 465(M^+, 13), 330(100), 286(30), 135(39), 77(14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 4.31–4.36 (m, 2H, ketal), 4.57–4.62 (m, 2H, ketal), 5.23 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.64 (d, 1H, J=8.0 Hz, H-5′), 6.69 (s, 1H, H-2′), 6.74 (d, 1H, J=8.0 Hz, H-6′), 7.20 (d, 1H, J=1.0 Hz, H-6), 7.56 (d, 1H, J=1.0 Hz, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3 (CH_3), 43.0 (CH_2-benzyl), 66.1(2×CH_2-ketal), 72.4 (C-7), 101.1 (C-3), 101.2 (OCH_2O), 107.2 (CH), 108.5 (CH), 119.6 (CH), 126.0 (CH), 127.2 (C), 130.5 (C), 135.3 (C), 142.0 (C), 144.5 (CH), 146.8 (C), 148.1 (C), 174.6 (C-2).

3.3.7. 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-3,3-ethylenedioxy-5-methyl-indole-2-one (6g). Colourless crystals, 89%, mp 218–220 °C. IR (ν_{max}, cm^{-1}): 3073, 2964, 2904, 1733, 1635, 1605, 1500, 1484, 1429, 1359, 1300, 1273, 1239, 1181, 1112, 1036, 998, 932, 853, 821, 736. MS (% rel. int.): 419/417(M^+, 1/1), 338(86), 238(23), 215(14), 204(100), 160(47), 104(16), 77(12). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 4.34–4.37 (m, 2H, ketal), 4.60–4.63 (m, 2H, ketal), 4.81 (s, 2H, CH_2-benzyl), 5.92 (s, 2H, OCH_2O), 6.55 (d, 1H, J=8.0 Hz, H-7), 6.60 (s, 1H, H-6′), 7.01 (s, 1H, H-3′), 7.08 (dd, 1H, J=1.0, 8.0 Hz, H-6), 7.22 (d, 1H, J=1.0 Hz, H-4). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1 (CH_3), 43.5 (CH_2-benzyl), 66.1 (2×CH_2-ketal), 102.1 (OCH_2O), 102.6 (C-3), 108.0 (CH), 109.8 (CH), 112.9 (CH), 113.3 (C), 124.0 (C), 125.8, 127.6, 132.2, 133.6, 141.2 (C-7a), 148.1 (C), 148.2 (C), 173.8 (C-2). Anal. for $C_{19}H_{16}BrNO_5$: C, 54.56; H, 3.86; N, 3.35 (calcd); C, 54.80; H, 4.01; N, 3.46 (found).

3.4. Palladium catalysed coupling reactions

The appropriate *N*-benzylisatin ketal (1.0 mmol), $Pd(OAc)_2$ (23.0 mg, 0.1 mmol), Bu_4NBr (322 mg, 1.1 mmol), KOAc (490.0 mg, 5.0 mmol) and DMF (10 ml) were heated on an oil bath (100 °C, bath temp) in a round bottom flask and the reaction accompanied by TLC. On complete reaction, distilled water (50 ml) was added to the reaction mixture which was then extracted with ethyl acetate (4×15 ml). The organic phase was dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (4:1) as eluent. Products could be recrystallized from MeOH/H_2O.

3.4.1. 4,4-Ethylenedioxy-6,7-dihydro-2-methyl-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7a). White crystals, 96–98%, 191–193 °C. IR (ν_{max}, cm^{-1}): 3058, 2975, 2954, 2889, 1719, 1636, 1500, 1449, 1349, 1268, 1204, 1054, 1029, 1000, 949, 864, 774, 741. MS (% rel. int.): 293(M^+, 33), 264(100), 220(29), 193(27), 192(22), 165(17), 110(31), 96(29), 82(28). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.29–4.34 (m, 2H, ketal), 4.57–4.61 (m, 2H, ketal), 4.91 (s, 2H, H-7), 7.07 (s, 1H, H-3), 7.12 (d, 1H, J=7.3 Hz, H-8), 7.23 (t, 1H, J=7.3 Hz, H-9), 7.29 (t, 1H, J=7.3 Hz, H-10), 7.45 (s, 1H, H-1), 7.70 (d, 1H, J=7.3 Hz, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.6 (CH_3), 42.4 (CH_2-benzyl), 66.0 (2×CH_2-ketal), 103.4 (C), 117.2 (C), 122.4 (CH), 122.7 (C), 124.6 (CH), 125.1 (CH), 127.8 (CH), 128.1 (CH), 128.3 (C), 128.5 (CH), 128.9 (C), 133.3 (C), 137.1 (C), 172.9 (C-5). Anal. for $C_{18}H_{15}NO_3$: C 73.71, H 5.15, N 4.76 (calcd); C 73.23, H 5.04, N 4.62 (found).

3.4.2. 4,4-Ethylenedioxy-6,7-dihydro-9,10-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7b). White crystals, 69–95%, 226–228 °C (decomp.). IR (ν_{max}, cm^{-1}): 3047, 2969, 2900, 1716, 1638, 1508, 1475, 1369, 1238, 1188, 1153, 1042, 1020, 939, 885, 787, 744. MS (% rel. int.): 323(M^+, 42), 294(100), 250(37), 223(27), 222(18), 164(23), 138(14), 124(30), 110(14), 96(43), 82(39), 69(25). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.31–4.39 (m, 2H, ketal), 4.54–4.61 (m, 2H, ketal), 4.88 (s, 2H, H-7), 6.00 (s, 2H, OCH_2O), 6.61 (s, 1H, H-8), 7.03 (t, 1H, J=7.6 Hz, H-2), 7.18 (s, 1H, H-11), 7.19 (d, 1H, J=7.6 Hz, H-3), 7.49 (d, 1H, J=7.6 Hz, H-1). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 42.9 (CH_2-benzyl), 66.0 (2×CH_2-ketal), 101.8 (OCH_2O), 102.9

(CH), 103.5 (C), 107.8 (CH), 117.8 (C), 122.3 (C), 122.6 (C), 122.7 (C), 123.7 (CH), 123.80 (CH), 123.85 (CH), 139.0 (C), 148.1 (C), 148.3 (C), 173.1 (C-5). HRMS for $C_{18}H_{13}NO_5$: 323.0794 (calcd); 323.0796 (found).

3.4.3. 4,4-Ethylenedioxy-6,7-dihydro-9,10-dimethoxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7d). White crystals, 81–87%, mp 188–190 °C. IR (ν_{max}, cm^{-1}): 3067, 2966, 2909, 2839, 1719, 1635, 1613, 1531, 1467, 1407, 1358, 1255, 1217, 1185, 1149, 1048, 1002, 940, 854, 780, 737. MS (% rel. int.): 339(M^+, 42), 310(100), 266(21), 239(28). ^1H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 4.31–4.39 (m, 2H, ketal), 4.54–4.65 (m, 2H, ketal), 4.88 (s, 2H, H-7), 6.60 (s, 1H, H-8), 7.03 (t, 1H, J=7.5 Hz, H-2), 7.16 (s, 1H, H-11), 7.18 (d, 1H, J=7.5 Hz, H-3), 7.53 (d, 1H, J=7.5 Hz, H-1). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 42.4 (C-7), 56.20 and 56.21(2×CH_3O), 66.0 (2×CH_2-ketal), 103.4 (C), 105.4 (CH), 110.3 (C-H), 117.8 (C), 120.8 (C), 121.4 (C) 122.6 (C), 123.5 (CH), 123.6 (CH), 123.7 (CH), 139.0 (C), 148.9 (C), 149.6 (C), 173.1 (C-5). HRMS for $C_{19}H_{17}NO_5$: 339.1107 (calcd); 339.1107 (found).

3.4.4. 4,4-Ethylenedioxy-6,7-dihydro-2-methyl-9,10-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7e). White crystals, 24–43%, 243–245 °C. IR (ν_{max}, cm^{-1}): 3064, 2972, 2905, 2856, 1713, 1640, 1501, 1470, 1391, 1363, 1239, 1199, 1154, 1052, 1031, 997, 946, 931, 864, 848, 830, 748. MS (% rel. int.): 337(M^+, 34), 308(100), 264(24), 237(26), 131(16), 103(13). ^1H NMR (200 MHz, $CDCl_3$/DMSO-d_6): δ 2.27 (s, 3H, CH_3), 4.20–4.26 (m, 2H, ketal), 4.42–4.49 (m, 2H, ketal), 4.77 (s, 2H, H-7), 5.93 (s, 2H, OCH_2O), 6.56 (s, 1H, H-8), 6.93 (s, 1H, H-3), 7.14 (s, 1H, H-1), 7.52 (s, 1H, H-11). ^{13}C NMR (50.3 MHz, $CDCl_3$/DMSO-d_6): δ 20.8 (CH_3), 42.0 (C-7), 65.2 (2×CH_2-ketal), 101.0 (OCH_2O), 102.0 (CH), 102.9 (C), 107.0 (CH), 116.7 (C), 121.5 (C), 121.8 (C), 122.0 (C), 123.4 (CH), 123.5 (CH), 132.5 (C), 147.4 (C), 147.5 (C), 172.1 (C-5). Anal. for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15 (calcd.); C 67.59, H 4.53, N 4.27 (found).

3.4.5. 4,4-Ethylenedioxy-6,7-dihydro-2-methyl-10,11-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-5-one (7e′). White crystals, 74%, 217–219 °C. IR (ν_{max}, cm^{-1}): 3032, 2968, 2904, 1724, 1635, 1506, 1494, 1463, 1442, 1366, 1272, 1247, 1198, 1111, 1064, 1022, 948, 927, 869, 794, 711. MS (% rel. int.): 337(M^+, 28), 308(100), 264(25), 237(21). ^1H NMR (200 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 4.25–4.31 (m, 2H, ketal), 4.36–4.42 (m, 2H, ketal), 4.81 (s, 2H, H-7), 6.18 (s, 2H, OCH_2O), 6.80 (d, 1H; J=8.0 Hz, H-8), 6.89 (d; 1H; J=8.0 Hz, H-9), 7.14 (s, 1H, H-3), 7.74 (s, 1H, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 21.6 (CH_3), 42.7 (C-7), 66.2 (2×CH_2-ketal), 102.3, 103.2, 108.7, 112.0, 115.1, 121.4, 123.1, 123.6, 125.5, 128.4, 133.2, 137.0, 144.7, 147.6, 172.6 (C-5). Anal. for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15 (calcd.); C 67.59, H 4.53, N 4.27 (found).

3.5. 6,7-Dihydro-pyrrolo[3,2,1-*de*]phenanthridin-4,5-diones

4,4-Ethylenedioxy-6,7-dihydro-pyrrolo[3,2,1-*de*]phenanthridin-5-ones (3 mmol), THF (10.0 ml) and aqueous HCl (6 mol l^{-1}, 10.0 ml) were heated at reflux for 5 h. The THF was removed under reduced pressure resulting in the precipitation of red crystals. These were removed by filtration, washed with distilled water and air dried.

3.5.1. 6,7-Dihydro-2-methyl-pyrrolo[3,2,1-*de*]phenanthridin-4,5-dione (8a). Dark red crystals, 94–96%, mp 237–238 °C. IR (ν_{max}, cm^{-1}): 3059, 2920, 2862, 1731, 1626, 1491, 1355, 1305, 1122, 767. MS (% rel. int.): 249(M^+, 47), 220(100), 193(34), 192(35), 165(27), 110(21), 95(41). ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 5.01 (s, 2H, H-7), 7.15 (d, 1H, J=7.2 Hz, H-8), 7.22 (s, 1H, H-3), 7.31 (td, 1H, J=1.3, 7.2 Hz, H-9), 7.36 (t, 1H, J=7.2 Hz, H-10), 7.67 (s, 1H, H-1), 7.74 (dd, 1H, J=1.3, 7.2 Hz, H-11). ^1H NMR (300 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 4.94 (s, 2H, H-7), 7.22 (s, 1H, H-3), 7.29–7.36 (m, 3H, H-8, H-9 and H-10), 7.93 (d, 1H, J=7.8 Hz, H-11), 7.95 (s, 1H, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 21.0 (CH_3), 42.3 (C-7), 116.7 (C), 118.2 (C), 123.1 (CH), 124.5 (CH), 127.2 (C), 128.4 (CH), 128.6 (CH), 129.4 (CH), 129.5 (C), 131.3 (CH), 133.3 (C), 144.9 (C), 158.2 (C-5), 183.7 (C-4). Anal. for $C_{16}H_{11}NO_2$: C 77.10, H 4.45, N 5.62 (calcd.); C 77.19, H 4.41, N 5.71 (found).

3.5.2. 6,7-Dihydro-9,10-methylenedioxy-pyrrolo[3,2,1-*de*]phenanthridin-4,5-dione (8b). Dark red crystals, 92%, mp 235–237 °C. IR (ν_{max}, cm^{-1}): 3053, 2919, 2852, 2780, 1732, 1632, 1598, 1507, 1476, 1426, 1388, 1356, 1308, 1239, 1201, 1036, 1020, 927, 867, 775. MS (% rel. int.): 279(M^+, 53), 250(100), 223(25), 164(15). ^1H NMR (200 MHz, Acetone-d_6): δ 5.00 (s, 2H, H-7), 6.09 (s, 2H, OCH_2O), 6.90 (s, 1H, H-8), 7.11 (t, 1H, J=7.7 Hz, H-2), 7.35 (d, 1H, J=7.7 Hz, H-3), 7.48 (s, 1H, H-11), 7.99 (d, 1H, J=7.7 Hz, H-1). ^1H NMR (200 MHz, CD_3CN): δ 5.48 (s, 2H, H-7), 6.58 (s, 2H, OCH_2O), 7.33 (s, 1H, H-8), 7.63 (t, 1H, J=7.6 Hz, H-2), 7.90 (d, 1H, J=7.6 Hz, H-3), 7.91 (s, 1H, H-11), 8.40 (d, 1H, J=7.6 Hz, H-1). ^1H NMR (200 MHz, DMSO-d_6): δ 4.89 (s, 2H, H-7), 6.08 (s, 2H, OCH_2O), 6.94 (s, 1H, H-8), 7.04 (t, 1H, J=7.6 Hz, H-2), 7.33 (d, 1H, J=7.6 Hz, H-3), 7.58 (s, 1H, H-11), 8.01 (d, 1H, J=7.6 Hz, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 42.6 (C-7), 102.1 (OCH_2O), 103.5 (CH), 108.4 (CH), 116.5 (C), 118.8 (C), 121.2 (C), 123.3 (CH), 123.6 (C), 123.8 (CH), 130.5 (CH), 146.5 (C), 148.1 (C), 148.5 (C), 158.3 (C-5), 183.6 (C-4). HRMS for $C_{16}H_9NO_4$: 279.0532 (calcd); 279.0532 (found).

3.5.3. 6,7-Dihydro-9,10-dimethoxy-pyrrolo[3,2,1-*de*]-phenanthridin-4,5-dione (8d). Dark red crystals, 86–92%, mp 240–242 °C. IR (ν_{max}, cm^{-1}): 3028, 2989, 2924, 2856, 1743, 1726, 1625, 1610, 1525, 1465, 1444, 1359, 1259, 1219, 1147, 1057, 976, 861, 779, 754, 742. MS (% rel. int.): 295(M^+, 89), 266(100), 239(24), 213(16), 196(10), 153(14), 127(14). ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.99 (s, 2H, H-7), 6.71 (s, 1H, H-8), 7.07 (t, 1H, J=7.7 Hz, H-2), 7.26 (s, 1H, H-11), 7.32 (d, 1H, J=7.7 Hz, H-3), 7.85 (d, 1H, J=7.7 Hz, H-1). ^1H NMR (200 MHz, DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.90 (s, 2H, H-7), 6.94 (s, 1H, H-8), 7.06 (t, 1H, J=7.5 Hz, H-3), 7.33 (d, 1H, J=7.5 Hz, H-3), 7.46 (s, 1H, H-11), 8.10 (d, 1H, J=7.5 Hz, H-1). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 42.2 (C-7), 56.1 (OCH_3), 56.3 (OCH_3), 106.6 (CH), 111.5 (CH), 116.5 (C), 119.0 (C),

119.5 (C), 121.8 (C), 123.0 (CH), 123.7 (CH), 130.5 (CH), 146.5 (C), 149.1 (C), 150.1 (C), 158.3 (C-5), 183.7 (C-4). Anal. for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74 (calcd.); C 69.11, H 4.46, N 4.81 (found).

3.6. Alkaloids

3.6.1. Reduction with BH_3–THF. The appropriate pyrrolophenanthridin-4,5-dione (1.0 mmol) was dissolved in anhydrous THF (5 ml) and cooled on an ice water bath under a slowly flowing nitrogen atmosphere. A solution of $BH_3\cdot$THF (1 mol l^{-1}, 3.0 mmol) was added dropwise by syringe to the stirred reaction. The reaction was monitored by TLC and on complete reaction aqueous HCl (3.0 mol l^{-1}, 3 ml) was added dropwise. The mixture was subsequently neutralized with aqueous NaOH (10%), saturated aqueous NaCl was added and the mixture extracted with CH_2Cl_2(3×15 ml). The organic phase was further washed with water (1×15 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was chromatographed on a silica gel column using dichloromethane/hexane (2:1) as eluent.

3.6.1.1. 6,7-Dihydro-2-methyl-pyrrolo[3,2,1-*de*]-phenanthridine (9). White crystals, 90–92%, mp 135–137 °C. IR (ν_{max}, cm^{-1}): 3099, 3031, 2919, 2857, 1508, 1451, 1385, 1329, 1271, 1210, 854, 778, 755, 714. MS (% rel. int.): 219(M^+, 54), 218(100), 108(23). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 5.50 (s, 2H, H-7), 6.43 (d, 1H, J=2.9 Hz, H-4), 7.07 (d, 1H, J=2.9 Hz, H-5), 7.14 (d, 1H, J=7.5 Hz, H-8), 7.21–7.32 (m, 4H, H-1, H-3, H-9, H-10), 7.89 (d, 1H, J=7.5 Hz, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.1 (CH_3), 48.0 (C-7), 102.0 (CH), 115.4 (CH), 118.1 (C), 120.4 (CH), 122.8 (CH), 126.2 (CH), 126.4 (C), 127.4 (CH), 127.8 (CH), 127.9 (CH), 129.7 (C), 130.3 (C), 130.5 (C), 132.2 (C). HRMS for $C_{16}H_{13}N$: 219.1048 (calcd); 219.1050 (found).

3.6.2. Reduction with $NaCNBH_3$–AcOH. To the crude product (~1 mmol) from the $BH_3\cdot$THF reduction reaction was added $NaCNBH_3$ (189.0 mg, 3 mmol) and the mixture was cooled to 10 °C. Acetic acid (3 ml) was added dropwise and the mixture was stirred at room temperature. After 3 h, the mixture was cooled on an ice bath, neutralized with aqueous NaOH (10%) and extracted with dichloromethane (4×15 ml). Evaporation of the solvent under reduced pressure gave the crude product. This was quickly filtered through a short column of silica eluting with CH_2Cl_2. Evaporation of the solvent gave the product.

3.6.2.1. 4,5,6,7-Tetrahydro-2-methyl-pyrrolo[3,2,1-*de*]phenanthridine (10). A semi-solid material that rapidly darkened when exposed to the atmosphere. ^{1}H NMR (200 MHz, $CDCl_3$): 2.31 (s, 3H, CH_3), 2.98 (t, 2H, J=7.8 Hz, H-4,), 3.32 (t, 2H, J=7.8 Hz, H-5), 4.10 (s, 2H, H-7), 6.88 (s, 1H, H-3), 7.11–7.33 (m, 4H, H-1, H-8, H-9, H-10), 7.66 (d, 1H, J=7.4 Hz, H-11).

3.6.3. Reduction with $NaCNBH_3$ and subsequent oxidation with Oxone™. To the crude product from the reduction reaction using $BH_3\cdot$THF (~1 mmol) was added $NaCNBH_3$ (189.0 mg, 3 mmol) and the mixture cooled to 10 °C. Acetic acid (3 ml) was added dropwise and the mixture was stirred at room temperature. After 3 h, the mixture was cooled on an ice bath, neutralized with aqueous NaOH (10%) and extracted with dichloromethane (4×15 ml).

The solvent was removed under reduced pressure, $NaHCO_3$ (252.0 mg, 3 mmol) and acetone (3.0 ml) were added. Oxone® (650.0 mg, 1.0 mmol) was slowly added to the mixture and stirred to room temperature. After 30 min, isopropanol (1 ml) was added, and solvent was removed under vacuum. The residue was chromatographed on silica gel column using heptane/dichloromethane (1:1) as eluent and the product recrystallized from methanol/water (1:1).

3.6.3.1. 4,5-Dihydro-2-methyl-pyrrolo[3,2,1-*de*]-phenanthridin-7-one (11). White crystals, 32%, mp 197–200 °C. IR (ν_{max}, cm^{-1}): 3069, 3030, 2964, 2915, 2856, 1641, 1624, 1600, 1504, 1366, 1344, 1287, 1181, 1032, 888, 854, 766, 722, 689. MS (% rel. int.): 235(M^+, 100), 234(99), 219(20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.38 (t, 2H, J=8.2 Hz, H-4), 4.47 (t, 1H, J=8.2 Hz, H-5), 7.15 (s, 1H, H-3), 7.57 (td, 1H, J=1.0, 7.8 Hz, H-10), 7.70 (s, 1H, H-1), 7.74 (td, 1H, J=1.0, 7.8 Hz, H-9), 8.18 (d, 1H, J=7.8 Hz, H-8), 8.54 (dd, 1H, J=1.0, 7.8 Hz, H-11). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9 (CH_3), 27.5 (C-4), 46.8 (C-5), 116.6 (C), 120.0 (CH), 122.2 (CH), 126.0 (CH), 127.6 (C), 127.9 (CH), 128.6 (CH), 131.0 (C), 132.1 (CH), 133.3 (C), 134.0 (C), 138.0 (C), 160.1 (C-7). HRMS for $C_{16}H_{13}NO$: 235.0997 (calcd); 235.0994 (found).

3.6.4. Reduction with $NaCNBH_3$ and subsequent oxidation with $KMnO_4$. To the crude product (~1 mmol) from the $BH_3\cdot$THF reduction reaction was added $NaCNBH_3$ (189.0 mg, 3.0 mmol) and the mixture was cooled to 10 °C. Acetic acid (3 ml) was added dropwise and the mixture was stirred at room temperature. After 3 h, the mixture was cooled on an ice bath, neutralized with aqueous NaOH (10%) and extracted with dichloromethane (4×15 ml).

The organic phase was concentrated (~10 ml), aqueous NaOH (3 mol l^{-1}, 10 ml) and $KMnO_4$ (316.0 mg, 2.0 mmol) were added. The suspension was stirred vigorously at room temperature for 2 h, filtered through Celite and extracted with dichloromethane (3×15 ml). The organic phase was washed with aqueous Na_2SO_3 (5% w/v, 15 ml), with distilled water (1×15 ml) and dried over Na_sSO_4. The solvent was removed under vacuum. The residue was chromatographed on a silica gel column using dichloromethane/methanol (9:1) as eluent and the product was recrystallized from methanol/water (1:1).

3.6.4.1. 4,5-Dihydro-9,10-dimethoxy-pyrrolo[3,2,1-*de*]phenanthridin-7-one (Oxoassoanine) (2d). White crystals, 68–75%, mp 267–268 °C (lit.: 266–269[15]; 266–267[19g] °C). IR (ν_{max}, cm^{-1}): 3063, 3016, 3005, 2839, 1644, 1607, 1521, 1478, 1436, 1364, 1303, 1273, 1210, 1125, 1030, 870, 777, 766. MS (% rel. int.): 281(M^+, 100), 280(31), 266(12), 238(20). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.43 (t, 2H, J=8.2 Hz, H-4), 4.04 (s, 3H, OCH_3), 4.08 (s, 3H, CH_3), 4.44 (t, 2H, J=8.2 Hz, H-5), 7.21 (t, 1H, J=7.5 Hz, H-2), 7.30 (d, 1H, J=7.5 Hz, H-3), 7.52 (s, 1H,

H-8), 7.80 (d, 1H, J=7.5 Hz, H-1), 7.93 (s, 1H, H-11). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.6 (C-4), 46.7 (C-5), 56.3 (OCH_3), 56.4 (OCH_3), 103.1 (CH), 108.9 (CH), 116.9 (C), 119.3 (CH), 121.5 (C), 123.3 (CH), 123.7 (CH), 128.6 (C), 131.1 (C), 139.5 (C), 149.8 (C), 153.0 (C), 159.8 (C-7).

3.6.4.2. 4,5-Dihydro-9,10-methylenedioxy-pyrrolo-[3,2,1-*de*]phenanthridin-7-one (Anhydrolycorin-7-one) (2b). White crystals, 75%, mp 228–229 °C (lit.: 231–232[19g]; 230–231[20e,g]; 228–230[41] °C). IR (ν_{max}, cm^{-1}): 3057, 2968, 2908, 1643, 1614, 1587, 1505, 1484, 1468, 1393, 1370, 1352, 1257, 1035, 933, 857, 763. MS (% rel. int.): 265(M$^+$, 100), 264(92), 234(7), 206(18), 178(19). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.42 (t, 2H, J=8.2 Hz, H-4), 4.47 (t, 2H, J=8.2 Hz, H-5), 6.13 (s, 2H, OCH_2O), 7.19 (t, 1H, J=7.7 Hz, H-2), 7.29 (d, 1H, J=7.7 Hz, H-3), 7.53 (s, 1H, H-8), 7.73 (d, 1H, J=7.7 Hz, H-1), 7.90 (s, 1H, H-11). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.6 (C-4), 46.6 (C-5), 101.0 (CH), 102.2 (OCH_2O), 106.9 (CH), 116.9 (C), 119.5 (CH), 123.1 (C), 123.4 (CH), 123.9 (CH), 130.7 (C), 131.0 (C), 139.4 (C), 148.5 (C) 151.9 (C), 159.6 (C-7).

3.6.5. Oxidation with MnO_2–SiO_2. To the crude product ($\sim$1 mmol) from the BH_3·THF reduction reaction was added MnO_2–SiO_2 (3.0 mmol of MnO_2) and solvent (15 ml of anhydrous benzene or THF). The suspension was heated under reflux for 4 h, the solvent was removed and the residue was chromatographed on a short silica gel column using dichloromethane/methanol (20:1) as eluent. The solids were recrystallized from methanol.

3.6.5.1. 9,10-Methylenedioxy-pyrrolo[3,2,1-*de*]-phenanthridin-7-one (Hippadine) (1b). White crystals, 35%, mp 217–218 °C (lit.: 217–218[15,41] °C). IR (ν_{max}, cm^{-1}): 3148, 2958, 2920, 2850, 1672, 1618, 1526, 1479, 1458, 1392, 1365, 1312, 1285, 1243, 1118, 1029, 932, 878, 801, 765, 722. MS (% rel. int.): 263(M$^+$, 100), 205(6), 177(24), 150(12). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.15 (s, 2H, OCH_2O), 6.88 (d, 1H, J=3.4 Hz, H-4), 7.45 (t, 1H, J=7.7 Hz, H-2), 7.61 (s, 1H, H-11), 7.73 (d, 1H, J=7.7 Hz, H-3), 7.88 (d, 1H, J=7.7 Hz, H-1), 7.95 (s, 1H, H-8), 8.02 (d, 1H, J=3.4 Hz, H-5). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 101.8 (CH), 102.5 (OCH_2O), 108.1 (CH), 110.9 (CH), 116.8 (C), 118.5 (CH), 122.6 (C), 122.7 (CH), 123.7 (CH), 124.1 (CH), 128.5 (C), 131.1 (C), 131.7 (C), 148.6 (C), 152.7 (C), 158.3 (C-7).

3.6.5.2. 9,10-Dimethoxy-pyrrolo[3,2,1-*de*]phenanthridin-7-one (Pratosine) (1d). White crystals, 32–36%, mp 233–234 °C (lit.: 234–235[15] °C). IR (ν_{max}, cm^{-1}): 3149, 3111, 3006, 2936, 2836, 1668, 1603, 1529, 1509, 1440, 1363, 1314, 1273, 1213, 1142, 1105, 1001, 870, 765. MS (% rel. int.): 279(M$^+$, 100), 264(16), 236(37), 221(14), 193(15), 165(15). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.05 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 6.88 (d, 1H, J=3.4 Hz, H-4), 7.45 (t, 1H, J=7.6 Hz, H-2), 7.58 (s, 1H, H-11), 7.73 (d, 1H, J=7.6 Hz, H-3), 7.91 (d, 1H, J=7.6 Hz, H-1), 7.94 (s, 1H, H-8), 8.03 (d, 1H, J=3.4 Hz, H-5). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 56.4(2×OCH_3), 103.8 (CH), 110.1 (CH), 110.8 (CH), 116.8 (C), 118.2 (CH), 120.8 (C), 122.5 (CH), 123.6 (CH), 124.0 (CH), 128.6 (C), 129.5 (C), 131.2 (C), 149.7 (C), 153.7 (C), 158.5 (C-7).

3.6.5.3. 2-Methyl-pyrrolo[3,2,1-*de*]phenanthridin-7-one (12). White crystals, 40–53%, mp 157–158 °C. IR (ν_{max}, cm^{-1}): 3132, 3099, 3073, 2922, 2858, 1676, 1634, 1595, 1484, 1449, 1385, 1353, 1304, 1292, 1174, 1151, 847, 787, 759, 728, 691. MS (% rel. int.): 233(M$^+$, 100), 232(80), 204(10), 176(9). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 6.83 (d, 1H, J=3.6 Hz, H-4), 7.55 (s, 1H, H-3), 7.60 (td, 1H, J=1.1, 8.0 Hz, H-9), 7.78 (td, 1H, J=1.1, 8.0 Hz, H-10), 7.82 (s, 1H, H-1), 8.00 (d, 1H, J=3.6 Hz, H-5), 8.24 (d, 1H, J=8.0 Hz, H-11), 8.59 (dd, 1H, J=1.1, 8.0 Hz, H-8). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.2 (CH_3), 111.0 (CH), 116.3 (C), 119.6 (CH), 122.7 (CH), 123.5 (CH), 123.6 (CH), 127.3 (C), 128.1 (CH), 128.7 (C), 129.7 (CH), 130.1 (C), 133.1 (CH), 133.9 (C), 134.6 (C), 158.8 (C-7). HRMS for $C_{16}H_{11}NO$: 233.0841 (calcd); 233.0848 (found).

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