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Cyclopropenones in the synthesis of indolizidine, pyrrolo[2,1-*a*] isoquinoline and indolizino[8,7-*b*]indole alkaloids

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ABSTRACT

An attempted synthesis of the indolizidine natural product castanospermine resulted in the successful addition of cyclopropenone to a sugar-derived poly-hydroxylated cyclic imine to give an indolizidinone product, but with the installation of an extra hydroxy group at the castanospermine *8a*-bridgehead position. This was also observed in our previous approach to the australine and hyacinthacine pyrrolizidine natural products. The same oxidative phenomenon occurred during the synthesis of pyrrolo[1,2-*a*] isoquinolines from the reaction of aldimine dihydroisoquinolines with cyclopropenones, whereas ketimine based dihydroisoquinolines gave pyrrolo[1,2-*a*]isoquinolines without bridgehead oxidation. These results may have some significance for the origins of the bridgehead hydroxy natural products jenamidine B_1/B_2, clazamycin A/B and legonmycin A/B. The precursor cyclic aldimine for the synthesis of the indolizino[8,7-*b*]indoles gave dimeric indolizino[8,7-*b*]indoles, whereas the corresponding cyclic ketimines behaved as expected and gave the indolizino[8,7-*b*]indole core after reaction with cyclopropenones.

1. Introduction

Pyrrolo-fused alkaloids (see Fig. 1) with a nitrogen atom at the ring junction are a large and diverse class of natural products. Of particular interest to our research are the poly-hydroxylated indolizidines [1,2] such as the antiviral and glycosidase inhibiting iminosugar castanospermine **1** [1,3,4], and the poly-hydroxylated pyrrolizidines [1,5] such as the glycosidase inhibitor hyacinthacine A_2 **2** [1,6,7] and the glucosidase inhibitor australine **3** [1,8,9]. The pyrrolizidinone class of alkaloid natural products is also of interest and includes the marine-derived bohemamine **4** and related analogues [10], the antiproliferative jenamidines A_1/A_2 **5** [11] and jenamidines B_1/B_2 **6** [11]. There is also great literature interest in the pyrroloisoquinolines such as the antitumour compound crispine **7** [12–15], and the indolizinoindoles including the potent anti-Leishmania, antinociceptive harmicine **8** [15–17].

Within the pyrrolizidinone class there is a sub-set of natural products that are distinguished by the presence of a bridgehead hydroxy group such as that present in bohemamine D **9** [10], jenamidine C **10** [11], the related antitumour imino clazamycins A and B **11** [18], and the recently identified legonmycins A and B **12** and **13** [19], as well as jenamidines B_1/B_2 **6** [11], from above. These latter species (**6**, **9**–**13**) are rare amongst the pyrrolizidine natural products in that they are alkaloid natural products of bacterial origin rather that plant origin. It is of interest that the biosynthesis of these bacterial natural products has recently attracted attention [19,20] and that it was established that the bridgehead-OH species (**6**, **9**, **10**, **12** and **13**) are derived from a late stage biosynthetic oxidation of the corresponding naturally occurring bridgehead-H species, such as compounds **5**, **14** and **15**, the biosynthetic origins of which were also elucidated. Our own work [21,22], and that of others [23–26] (as discussed later) suggests that an additional origin for the bridgehead-OH species is worthy of consideration whereby aerial oxidation might be responsible for the conversion of the bridgehead-H alkaloid into the bridgehead-OH alkaloid.

In previous work, we have shown that a range of 5- and 6-membered ring cyclic aldimines **16** (n = 1 or 2, Scheme 1) undergo reaction with cyclopropenones **17** to produce the fused bicyclic bridgehead-OH species **18** (with X-ray crystallographic

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[1] Dedicated to Professor Richard Taylor in celebration of his 70th birthday.

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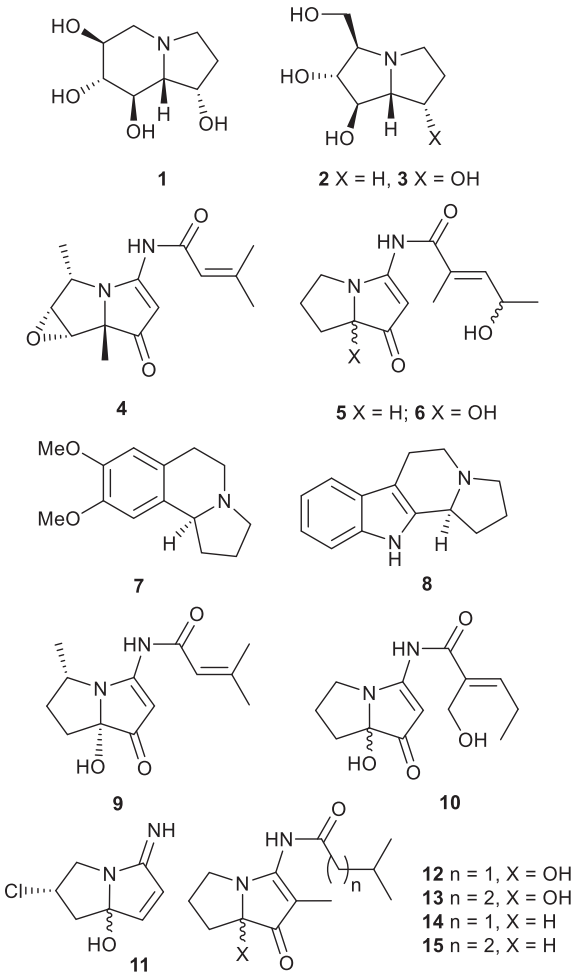
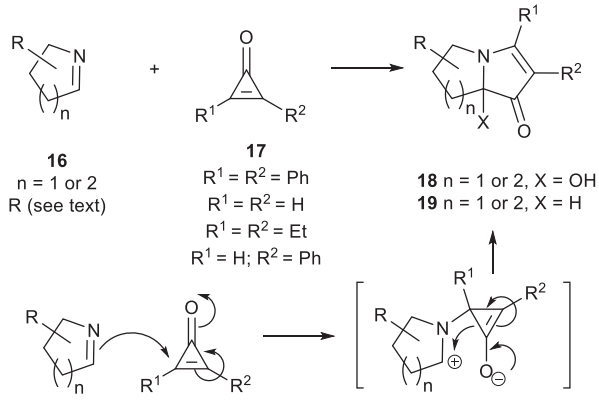


Fig. 1. Pyrrolo-fused alkaloids.



Scheme 1. The synthesis of bridgehead hydroxy-pyrrolizidinones [22].

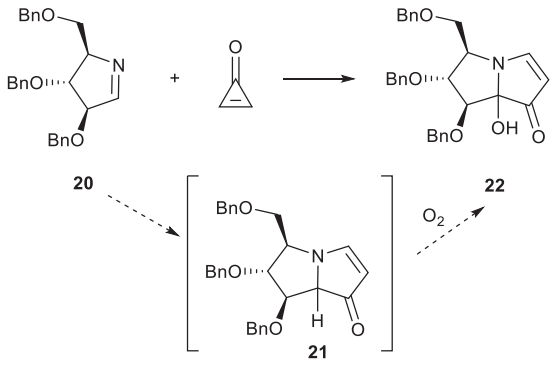
confirmation) rather than the expected bridgehead-H species **19** [22]. As shown in Scheme 1, we proposed that the reaction proceeded via the expected [21] regioselective formal [3 + 2]-cycloaddition process to produce species **19** which then underwent oxidation. We observed this process in a total of nine examples. A particular highlight of our approach is the ability to install with ease the bridgehead-OH and pyrrolizidinone ring that is present at the core of the clazamycin, jenamidine, bohemamine and legonmycin natural products **6** and **9**–**13**. Although we noted at the time [22] that this observation may account for the origins of the jenamidine B_1/B_2 bridgehead-OH moiety (by aerial oxidation of jenamidine A_1/A_2), we feel that a reiteration of this is worthwhile given the more recent biosynthetic reports [19,20]. It is notable that during the isolation of legonmycins A and B **12/13**, the presence of the corresponding non-hydroxy systems **14/15** was observed [19]. It is possible in each of these cases that an alternative or additional pathway for the formation of the bridgehead-OH compound could be the aerial oxidation of the bridgehead-H species.

During our original work [22], we attempted an approach to the hyacinthacine and australine natural products **2** and **3** starting from the imine **20** and cyclopropenone (Scheme 2). We found that oxidation led to the pyrrolizidinone **22** as the only isolable product, and were unable to isolate the proposed intermediate **21**. In some much earlier work [27], Eicher had shown that pyrroloisoquinolines could be accessed from the reaction of cyclic ketimines and diphenylcyclopropenone (DPCP), but observed only the expected bridgehead-H outcome with the single cyclic aldimine that was studied, and reported no additional oxidation. On the basis of this rich history, and the ongoing interest in these heterocyclic systems, we are continuing to explore cyclopropenone based routes for the synthesis of natural products. In this manuscript, we will discuss the results of our attempts to access compounds **1**, **7, 8** and analogues via the reaction of cyclic aldimines and ketimines with cyclopropenones.

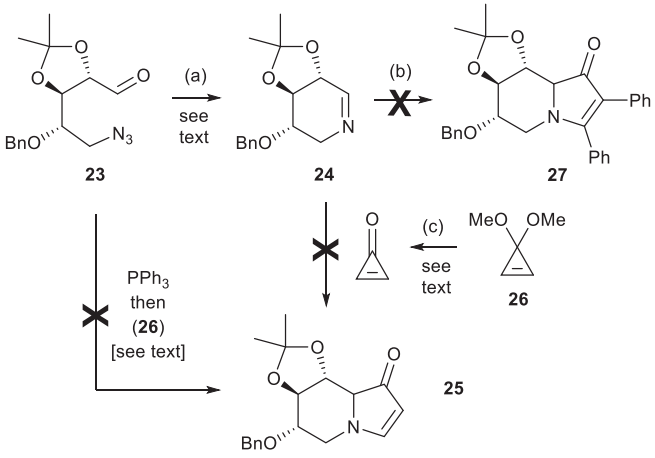
2. Results and discussion

The natural product that we targeted first was castanospermine **1**. In order to access this, we attempted to produce the imine **24** from the previously reported [28] azide **23**, as shown in Scheme 3. We subjected the azido-aldehyde **23** to a two-step Staudinger aza-Wittig ring closure to give the unstable and previously unreported cyclic aldimine **24**. All attempts to produce indolizidine **25** from the reaction of imine **24** with the parent unsubstituted cyclopropenone [29] were unsuccessful, an outcome that we attribute to a combination of the instability of the imine **24** together with the instability of cyclopropenone, which was generated in-situ from the acetal **26**. The attempted synthesis of indolizidinone **27** from the reaction of imine **24** with the stable, commercially available diphenylcyclopropenone was also unsuccessful, indicating that the formation, stability or reactivity of the imine **24** was the main issue.

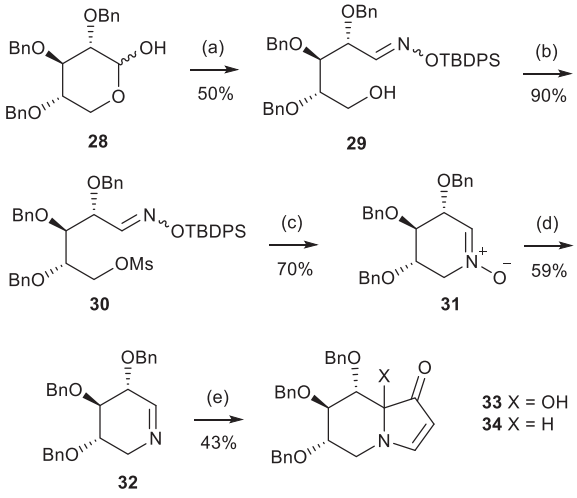
Based upon our observation that imine **24** was insufficiently stable, we explored the use of the alternative imine **32** (Scheme 4). We reasoned that we could generate the imine, although unknown, in one step from the known [30,31] stable nitrone **31** rather than



Scheme 2. An Approach to Australine and Hyacinthacine [21].



Scheme 3. Attempted Synthesis of Castanospermine – Route 1. Reagents and Conditions: (a) PPh_3, THF or $CHCl_3$, 15 min at RT, then reflux, 5 h; (b) diphenylcyclopropenone (see text); (c) acetone, H^+, - 10 °C – RT, overnight.



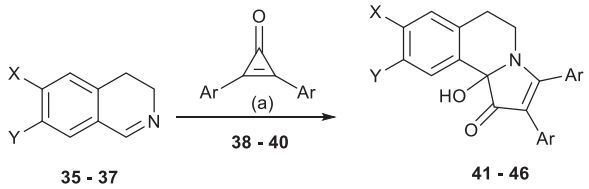
Scheme 4. Attempted Synthesis of Castanospermine: Route 2.

from the two step Staudinger aza-Wittig process used in Scheme 3. The nitrone **31** would be deoxygenated using tri-(*n*-butyl)phosphine in a process developed by Milet, Py and Toy [32] for 5-membered ring cyclic nitrones. We also anticipated that the benzyl protecting groups would allow reaction conditions that are more compatible with in-situ cyclopropenone generation from the cyclopropene acetal **26** than was the case with the acetal-protected precursor **24** used in Scheme 3. As shown in Scheme 4, the ring-opened aldehyde form of the readily available [30] tribenzyl protected sugar **28** was trapped with TBDPS-protected hydroxylamine to give the aldimine **29** [30]. Mesylation [30] of the primary alcohol and cyclisation [31] of the intermediate **30** gave the nitrone **31** [31]. Attempts to perform this chemistry directly with unprotected hydroxylamine were unsuccessful due to the emergence of competing processes upon attempted mesylation. Reaction of the nitrone **31** with tri-(*n*-butyl)phosphine [32] resulted in consumption of the nitrone to give a new product, which we assume to be the cyclic imine **32**, although it was insufficiently stable to allow characterisation. However, we were pleased to see that the imine was sufficiently stable to undergo reaction with freshly generated cyclopropenone to give the 8*a*-hydroxy substituted indolizidine **33** in 43% yield. The key evidence for the formation of the 8*a*-hydroxy compound **33** (rather than non-oxidized alternative compound **34**) was the presence of a quaternary carbon at 92.44 ppm in the ^{13}C NMR spectrum (and the absence of the expected CH), a clear OH in the ^1H NMR and infra-red spectra, and an additional oxygen atom in the high resolution mass spectrum. Compound **33** was isolated as a single major diastereoisomer (~95% purity), but we were not able to determine the stereochemistry at the bridgehead. We attribute the formation of compound **33** to the aerial oxidation of the desired product **34**, a process that, as discussed above, we have observed before in our work with pyrrolizidines related to the clazamycin, jenamidine, and legonmycin natural products. All attempts to isolate compound **34** or react it in-situ in the absence of oxygen were unsuccessful. We also attempted to reduce compound **33** into useful analogues of castanospermine, but were unsuccessful. Whilst this halted our attempts to access the natural product castanospermine, we note that this result offers further evidence of the facile nature of this type of bridgehead oxidation (see later for a mechanistic discussion).

Reagents and Conditions: (a) $TBDPSONH_2$, toluene, PPTS, reflux, 3 h; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C – RT, 3h; (c) THF, 4 Å MS, TBAF, 30 min, reflux; (d) THF, P^nBu_3, 65 °C, 48 h; (e) cyclopropenone, MeCN, - 10 °C – RT, overnight.

Having previously explored the reactivity of simple and complex 3,4-dihydro-2*H*-pyrroles and simple 2,3,4,5-tetrahydropyridines (see Introduction) and now a more complex 2,3,4,5-tetrahydropyridine, and having observed bridgehead oxidation in all cases, we next looked at dihydroisoquinolines. Our objective here was to study a potential route to the pyrroloisoquinoline core present in natural products such as crispine (structure **7** in Fig. 1). The known dihydroisoquinoline **35** (X = Y= H), shown in Table 1, was synthesized by the bromination (NBS) and then dehydrobromination of tetrahydroisoquinoline [33]. Compound **35** was nitrated (KNO_3) to give the corresponding nitro compound **36** (X = H, Y = NO_2) [33]. The dimethoxy compound **37** (X = Y = OMe) was synthesized using a known [34] Pictet-Spengler reaction on the corresponding arylethylamine and was selected for its similarity to crispine **7**. The reactivity of these three dihydroisoquinolines towards diphenylcyclopropenone **38** and the readily available [35,36] di-(4-methoxyphenyl) and di-(4-fluorophenyl)cyclopropenone **39** and **40** was explored (Table 1). The nitro-compound **36** was unreactive, but the dihydroisoquinolines **35** and **37** reacted with diarylcyclopropenones **38**–**40** to give adducts **41**–**46** which could be isolated in 34–69% yields (Table 1) in reasonable purity

Table 1
The synthesis of pyrroloisoquinolines. .



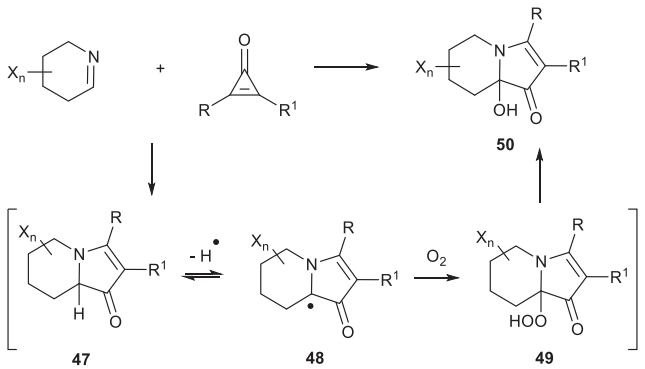
Product	X	Y	Ar	% Yield
41	H	H	Ph	59
42	H	H	4-$MeOC_6H_4$	52
43	H	H	4-FC_6H_4	36
44	OMe	OMe	Ph	65
45	OMe	OMe	4-$MeOC_6H_4$	69
46	OMe	OMe	4-FC_6H_4	34

Reagents and Conditions: (a) MeCN or $CHCl_3$, RT, 3–24 h.

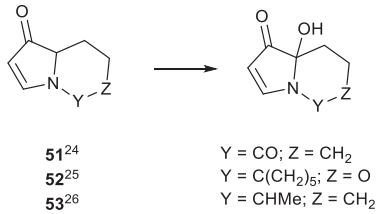
from complex reaction mixtures. Compounds **42** and **43** in particular contained small amounts (<10% and <5%, respectively) of an unidentified isomeric impurity which may be the lactam regioisomeric product or (see later) a ring-opened lactam. In each case the bridgehead OH species was the only product isolated. This was evidenced in the ^{13}C NMR spectra of the products by a quaternary carbon signal at 85–86 ppm for the bridgehead C–OH, and the absence of the expected C–H signal. Infra-red spectroscopy showed the OH signal, and high resolution mass spectrometry confirmed the additional oxygen atom. This offers further evidence that this bridgehead oxidation is quite general, occurring with each of the cyclic aldimines with which we have worked. In the case of compound **41**, our observation is in contrast to the product that Eicher reported, which had no bridgehead OH, as discussed above [27].

A mechanistic explanation for the formation of the bridgehead-OH systems is proposed in Scheme 5. The first step is the expected [21,22] and well-explored formal [3 + 2]-cycloaddition between the imine and the cyclopropenone to form intermediate **47**. We next propose the ready formation of a stabilized [26] captodative free radical species **48** that allows addition of oxygen in order to generate the hydroperoxide **49** which undergoes facile O–O bond cleavage to give the final isolated alcohol **50**. The exclusion of oxygen from our reaction media did not permit the isolation or observation of species **47**, with reaction work-up always resulting in the isolation of the oxidized products **50**. It has been noted by the research groups of Grošelj [23] and McNab [24–26] that the oxidation of 3-hydroxy pyrroles, or their tautomeric 1*H*-pyrrol-3(2*H*)-ones is a facile process. McNab obtained strong evidence [26] (ESR) that these oxidations do indeed proceed via a captodative radical such as that shown in Scheme 5. The compounds studied by McNab's group, **51**–**53**, are shown in Scheme 6, and were produced via flash vacuum pyrolysis of Meldrum's acid derivatives, a very different route to that detailed in our work, and all underwent the same oxidation. These observations present clear evidence that these bridgehead-H systems undergo facile aerial oxidation, and that this could therefore apply to the oxidation of natural products in the jenamidine, clazamycin and legonmycin classes.

The mechanistic rationale in Scheme 5 and the literature precedent in Scheme 6 mean that this oxidative process is limited to cyclic aldimines due to the inability of the corresponding cyclic ketimines to allow the formation of the intermediate bridgehead radical **48**. This is confirmed by the earlier work of Eicher, who showed that dihydroisoquinoline based cyclic ketimines **54a-d** reacted with diphenylcyclopropenone to give pyrroloisoquinolines **55a-d** (see Table 2) [27]. We did not repeat Eicher's work, but extended it by reacting the electron rich dihydroisoquinoline based cyclic ketimines **56a-d** (Table 2) with cyclopropenones **38**–**40** in

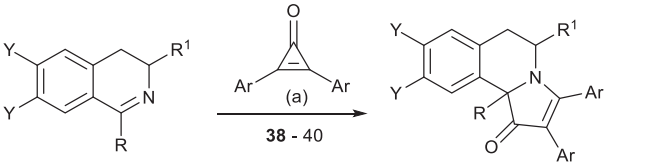


Scheme 5. Proposed Mechanism for Bridgehead Oxidation.



Scheme 6. Literature Precedent for Bridgehead Oxidation.

Table 2
Pyrroloisoquinolines from cyclic ketimines. .



54a - 54d; Y = H (Eicher's work)

55a - 55d; Y = H (Eicher's work)

56a - 56h; Y = OMe

57ai/ii - 57d; Y = OMe (our work)
57ai, 57e - 57h; Y = OMe (Cui's work)

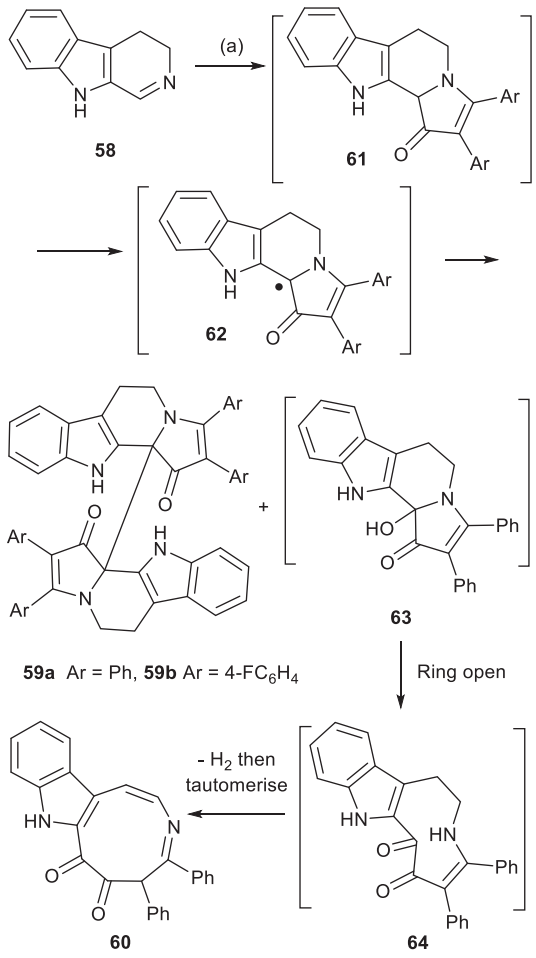
Cyclic imine	R	R [1]	Pro-duct	Ar	% Yield
54a	Me	H	**55a**	Ph	[a]
54b	iPr	H	**55b**	Ph	[a]
54c	Bn	H	**55c**	Ph	[a]
54d	Ph	H	**55d**	Ph	[a]
56a	Me	H	**57ai**	Ph	57[b,c]
56a	Me	H	**57aii**	*4*-MeOC$_6$H$_4$	53[b]
56b	CHF_2	H	**57b**	Ph	41[b]
56c	CH_2F	H	**57c**	*4*-FC$_6$H$_4$	27[b]
56d	Me	Me	**57d**	Ph	78[b]
56e	Ph	H	**57e**	Ph	[d]
56f	Et	H	**57f**	Ph	[d]
56g	$(CH_2)_2Ph$	H	**57g**	Ph	[d]
56h	*4*-ClC$_6$H$_4$	H	**57h**	Ph	[d]

[a] Compounds **55a-55d** were reported by Eicher [27] and were not synthesized as part of our work (see text).
[b] These five compounds were synthesized as part of our work.
[c] Compound **57ai** was also reported by Cui (63% yield) during the course of our work [40].
[d] Compounds **57e**-**57h** were recently reported by Cui [40] and were not synthesized as part of our work (see text).

acetonitrile or chloroform as solvent and obtained the expected pyrroloisoquinolines **57ai/ii-d** (Table 2). The dihydroisoquinoline **56a** [37] was prepared by a standard Bischler-Napieralski reaction, whereas the fluorinated analogues **56b** and **56c** [37] required the use of Movassaghi and Hill's [38] modified procedure using trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine. The dihydroisoquinoline **56d** was prepared from the reaction of methyl eugenol with acetonitrile [39], and gave the product **57d** as a 2:5 mixture of diastereoisomers. We did not determine which was the major diastereoisomer. During the preparation of this manuscript, the group of Cui [40] reported the synthesis of pyrroloisoquinoline **57ai** in 63% yield from the reaction of imine **56a** with diphenylcyclopropenone in DCE as solvent, and also reported the formation of pyrroloisoquinolines **57e-h** in high yields from the reaction of electron rich dihydroisoquinolines **56e-h** and diphenylcyclopropenone, also shown in Table 2 [40]. The reactions and literature observations shown in Table 2 confirm that cyclic ketimines react in the expected manner with cyclopropenones to give fused pyrrolidinones with no competing

oxidations. We have shown previously that cyclic imidates and thioimidates [21,35] also react to give the expected products, a process was recently exploited by Nahkla and Wood [41] who used an imidate-cyclopropenone addition process as a key step in their synthesis of aspergilline A.

We next used a known Bischler-Napieralski reaction of tryptamine to produce the dihydropyrido[3,4-*b*]indole **58** [42] (Scheme 7), hence targeting the indolizinoindole nucleus after reaction with cyclopropenones. The indolizinoindole nucleus is an attractive target and is present in natural products such as harmicine **8** (Fig. 1). The reaction of compound **58** with diphenylcyclopropenone resulted in a pure product precipitating from the solution, which was found to be the unexpected dimeric species **59a** (Scheme 7) formed in 27% yield. The structure of dimer **59a** was inferred by HRMS, and confirmed by X-ray crystallographic analysis (Fig. 2) [43]. Chromatographic purification of the remaining complex mixture gave a further 6% of compound **59a** together with a 13% yield of a second product, tentatively identified as the azoninoindole **60** on the basis of spectroscopic analysis. Compound **60** was formed as an inseparable mixture in ~95% purity with minor amounts (~5%) of other tautomers. Compound **58** reacted in a similar fashion with *bis*(4-fluorophenyl)cyclopropenone **40** to give the dimeric species **59b**, which again precipitated out from the solution in pure form (19% yield). The formation of the dimers **59a**/**b** is consistent with the pathway suggested in Scheme 5, above, whereby an initial reaction to give the pyrrolidinone **61** (Scheme 7)



Scheme 7. Reactivity of Dihydropyrido[3,4-b]indole **58** Reagents and Conditions: (a) **38** or **40**, MeCN, RT, 16 h.

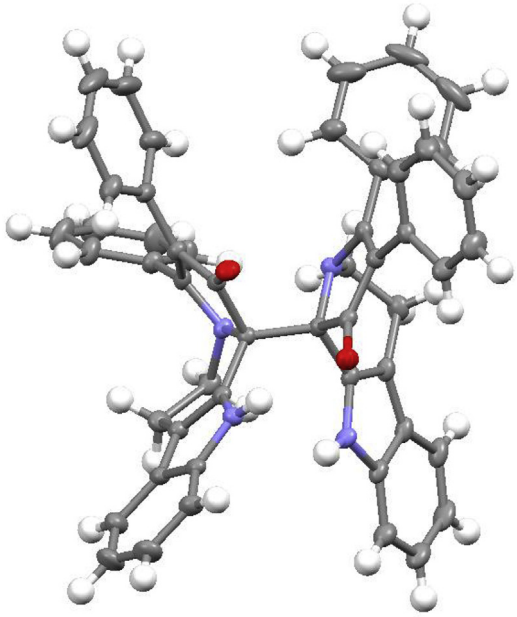
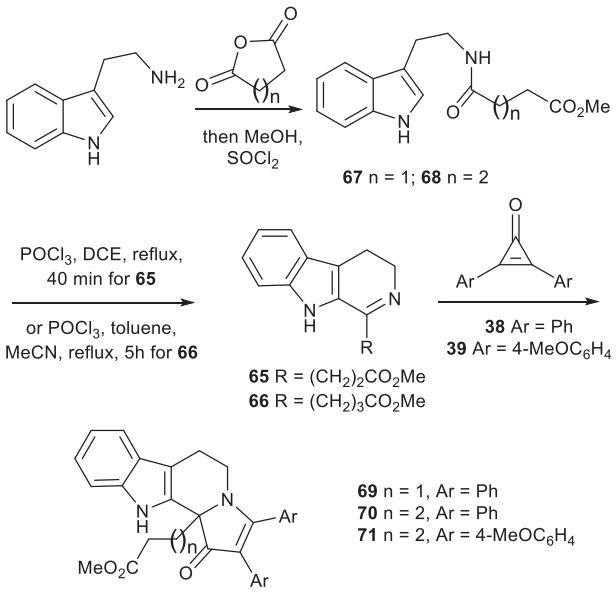


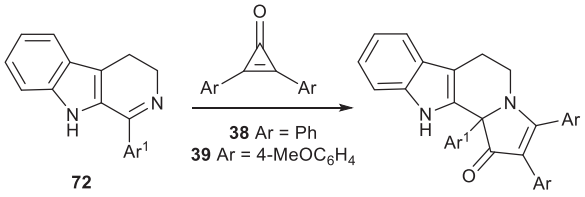
Fig. 2. X-ray structure of compound **59a**.

is followed by the formation of the stabilized captodative radical **62**. Dimerization would then give species **59a** and **59b**. The dimerization of captodative radicals is precedented [26], and it is interesting that radical **62** was able to dimerize, whereas such a process was not observed with the non-indole species that are discussed above (Scheme 5) and in our previous studies [22]. It is possible that the formation of the dimer is driven by the stabilization offered by the hydrogen bonding seen in the crystal structure of dimer **59a**, or that the different stabilization options that are present in radical **62** direct the reaction down a different pathway. The product tentatively identified as compound **60** had data that showed it had gained an extra oxygen atom and had lost two hydrogen atoms (HRMS). It also clearly showed two carbonyl groups and a non-aromatic/non-vinylic CH in the ^{13}C NMR data, and lacked any evidence of the bridgehead C—OH characteristic of the (now expected) bridgehead-hydroxy compound **63**. We propose that the radical **62** picks up oxygen to give the hydroxy intermediate **63**, consistent with previous observations, but that the aminol functionality undergoes ring opening to give the azoninoindole nucleus **64**, which after loss of hydrogen and tautomerism could form the proposed final azoninoindole **60**.

In order to understand more about how other dihydropyrido[3,4-*b*]indoles might react, we also explored the use of a cyclic ketimine system, choosing in this case the substituted dihydropyrido[3,4-*b*]indole (dihydro-β-carboline) systems **65** and **66**, as shown in Scheme 8. Precursors **65** and **66** were easily synthesized [44] by reacting tryptamine with either succinic anhydride or glutaric anhydride in the presence of methanol to give the esters **67** and **68** (Scheme 8) which then underwent Bischler-Napieralski ring closure to give the desired dihydropyrido[3,4-*b*]indoles **65** and **66** [44]. Reaction with diarylcyclopropenones then gave the expected indolizinoindoles **69**, **70** and **71** in 74–81% yield, showing that the cyclic ketimines **65** and **66** behaved perfectly as reaction partners, being unable to form a free-radical at the bridgehead and hence unable to undergo bridgehead oxidation to the hydroxy compound, dimerization or radical extrusion of hydrogen. We had hoped that the side-chain ester present in products **69**–**71** would allow the formation of an additional ring to give pentacyclic systems, but have so far found this to be unachievable. It is of note that, whilst



Scheme 8. The Synthesis of Indolizinoindoles.



Scheme 9. Cui's Recently Reported Synthesis of Indolizinoindoles [40].

we were preparing this manuscript, Cui reported that aryl substituted dihydro-β-carbolines **72** (cyclic ketimines) react with cyclopropenones **38** and **39** to give the expected indolizinoindoles in excellent yields, shown in Scheme 9[40]

3. Conclusions

During an attempted synthesis of castanospermine, using the addition of a cyclopropenone to a cyclic aldimine as the key step, we observed the installation of an additional OH at the carbon bridgehead of a precursor bicyclic indolizidinone system. We have previously observed the same phenomenon whilst attempting the synthesis of other indolizidines and pyrrolizidines using the equivalent key step. Dihydroisoquinolines that were unsubstituted at the imine carbon behaved in the same manner to give pyrroloisoquinolines with a hydroxy group on the carbon bridgehead, whereas dihydroisoquinolines that were substituted at the imine carbon gave the expected pyrroloisoquinolines. Dihydropyrido[3,4-b]indoles that were unsubstituted on the imine carbon reacted with cyclopropenones to give a dimeric indolizinoindole, whereas dihydropyrido[3,4-b]indoles which were substituted at the imine carbon reacted with cyclopropenones to give the expected indolizinoindoles.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

4. Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131570.

5. Experimental

Reagents, solvents and anhydrous solvents were purchased from Fischer Scientific, Acros Organics, Sigma-Aldrich, VWR, Manchester Organics, Fluorochem and Alfa-Aesar, and were used as supplied. Methyl eugenol was a gift from Citrefine International Limited. Reactions were monitored on Merck TLC silica gel 60 F_{254} aluminium sheets. Visualisation of spots was accomplished using a UV lamp (254 or 365 nm). Column chromatography was performed on silica gel (Aldrich, technical grade, pore size 60 Å, 40–63 μm particle size). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Ascend 400 (400 MHz – ^{1}H, and 100 MHz–^{13}C), Bruker Fourier 300 (300 MHz – ^{1}H, and 75 MHz–^{13}C), Bruker Avance 500 (500 MHz – ^{1}H, and 125 MHz–^{13}C) or Bruker Avance 600 (600 MHz – ^{1}H, and 150 MHz–^{13}C) spectrometers using $CDCl_3$, $(CD_3)_2SO$, $(CD_3)_2CO$, CD_3OD or D_2O as solvent and as internal standard. The chemical shifts (δ) are expressed in parts per million (ppm). Mass spectra were recorded on Agilent 6210 TOF MS (Dual ESI source), Agilent 6530 Q-TOF MS (Jet Stream ESI source), Agilent 1290 HPLC + 6530 Q-TOF (Dual AJSESI source + ve) or Agilent 7890A-5975C (EI-GCMS) and spectra were recorded in positive mode. FT-IR spectra were recorded on a Thermo Nicolet 380 FT-IR Spectrometer with Diamond ATR (neat sample). Melting points were recorded using a Stuart SMP10 melting point apparatus. Compounds **29** [30], **30** [30], **35** [33], **37** [34], and **65**–**67** [44], were synthesized by modified literature methods, procedures for which can be found in the supplementary information, together with NMR spectra of previously unreported compounds.

*5.1. Generation of (3aR,7S,7aR)-7-(benzyloxy)-2,2-dimethyl-3a,6,7,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridine (**24**)*

In an oven dried three neck RBF, the azido aldehyde **23** [28] (140 mg, 0.459 mmol) was dissolved in dry THF (10 mL) under an atmosphere of nitrogen. Activated powdered 4 Å molecular sieves (100 mg) were added and the mixture was stirred at room temperature for 15 min PPh_3 (121 mg, 0.461 mmol) in dry THF (2 mL) was added via syringe and the mixture was stirred until TLC showed complete loss of the azide (15 min). Attempts to isolate the intermediate iminophosphorane were unsuccessful. The reaction vessel was transferred into an oil bath, and the mixture was stirred at 55 °C for 5 h, at which point analysis by IR spectroscopy indicated that the aldehyde had disappeared. Attempts to purify the product resulted in its decomposition (see main text).

*5.2. Synthesis of (3R,4S,5S)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine 1- oxide (**31**) [31]*

To the mesylate (**30**) [29] (2.30 g, 3.06 mmol) dissolved in THF (30 mL), was added 4 Å molecular sieves (2 g), followed by TBAF (3.36 mL, 1 M solution in THF, 3.36 mmol). The mixture was heated at reflux for 30 min, concentrated under vacuum, and purified by chromatography over silica (MeOH/EtOAc, 5:95), to afford the

nitrone (**31**) (900 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.26 (15H, m, 3 × C_6H_5), 6.88 (1H, br, s, C*H*=N), 4.66–4.50 (7H, m, C*H* + 3 × CH_2), 4.38–4.37 (1H, m, C*H*), 4.06–4.00 (2H, m, 2 × C*H*), 3.76 (1H, dd, J = 8.5, 2.7 Hz, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7 (*C*H=N), 137.2 (qC), 137.1 (qC), 132.8 (qC), 128.63 (*C*H), 128.58 (*C*H), 128.4 (*C*H), 128.19 (*C*H), 128.16 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 82.8 (*C*H), 80.4 (*C*H), 77.5 (*C*H), 73.5 (CH_2), 71.9 (CH_2), 71.7 (CH_2), 66.1 (CH_2). Consistent with the literature data for this compound [31].

5.3. Synthesis of (6R,7S,8R)-6,7,8-tris(benzyloxy)-8a-hydroxy-6,7,8,8a-tetrahydroindolizin-1(5H)-one (**33**)

To a solution of nitrone (**31**) (350 mg, 0.838 mmol) in dry THF (20 mL) was added *n*-tributylphosphine (419 μl, 1.696 mmol), and the solution was stirred at 65 °C for 48 h. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography on silica with 1% MeOH in ethyl acetate to afford the imine (**32**) (198 mg, 59% yield) as an unstable oily mass, which was used immediately. A small sample (25 mg) was removed for analysis, but degraded. To a solution of the imine (**32**) (173 mg, 0.431 mmol) in acetonitrile (15 mL), cooled to −10 °C, was added cyclopropenone (70 mg, 1.295 mmol) generated in-situ from the acetal [29,35], in acetone (5 mL), dropwise over a period of 10 min. The solution was allowed to warm to room temperature over 3 h and then stirred overnight at room temperature. The reaction mass was concentrated by rotary evaporation under vacuum and the crude residue was purified using silica column chromatography to give the product (87 mg, 43% yield, ~95% single diastereoisomer) as a pale yellow oil. R_f 0.3 (ethyl acetate/petroleum ether, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (1H, d, J = 3.7 Hz, NC*H*=CH), 7.39–7.18 (15H, m, 3 × C_6H_5), 5.23 (1H, d, J = 3.7 Hz, NCH=C*H*C=O), 4.98 (1H, d, J = 11.7 Hz, C*H*H), 4.67 (1H, d, J = 11.7 Hz, C*H*H), 4.62 (1H, d, J = 11.7 Hz, C*H*H), 4.49–4.57 (4H, m, 4 × C*H*), 4.19 (1H, dd, J = 6.8 and 5.8 Hz, C*H*), 4.0 (1H, bs, *OH*), 3.82 (1H, d, J = 6.8 Hz, C*H*), 3.59 (1H, dd, J = 9.4 and 4.9 Hz, C*H*), 3.54 (1H, dd, J = 9.4 and 7.2 Hz, C*H*), 3.46 (1H, ddd, J = 9.4, 5.8 and 4.9 Hz, C*H*). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 202.2 (qC, C=O), 169.2 (*C*H=CH), 137.6 (qC), 137.5 (qC), 137.0 (qC), 128.6 (*C*H), 128.5 (*C*H), 128.41 (*C*H), 128.40 (*C*H), 128.1 (*C*H), 127.92 (*C*H), 127.85 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 102.5 (CH=*C*H), 92.4 (q*C*-OH), 87.4 (*C*H), 82.3 (*C*H), 73.6 (CH_2), 73.3 (CH_2), 72.8 (CH_2), 71.9 (CH_2), 63.1 (*C*H). IR (neat, cm^{-1}) υ_{max}: 3377 (br, OH), 3064, 3031, 2927, 2871, 1693 (C=O), 1538, 1454, 1114, 735. HRMS: [M + Na^+] for $C_{29}H_{29}NNaO_5$ calculated 494.1937, found 494.1948..

5.4. Synthesis of 10b-hydroxy-2,3-diphenyl-5,6-dihydropyrrolo [2,1-a]isoquinolin-1-one (**41**)

To a stirred solution of 3,4-dihydroisoquinoline [33] (0.030 g, 0.230 mmol) in MeCN (5 mL), was added diphenylcyclopropenone (0.050 g, 0.242 mmol) at room temperature under an air atmosphere. The reaction mixture was stirred at room temperature for 3 h and then solvents were removed by rotary evaporation. The crude product was purified by flash silica chromatography to afford the title compound as an orange yellow solid (0.051 g, 59% yield), m.p. 169–170 °C. R_f 0.42 (ethyl acetate/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (1H, d, J = 7.8 Hz, Ar), 7.53–7.34 (5H, m, Ar), 7.30 (2H, dd, J = 7.5 and 7.5 Hz, Ar), 7.07–7.03 (4H, m, Ar), 6.98 (2H, dd, J = 7.6 and 1.5 Hz, Ar), 3.88 (2H, bs and ddd, J = 13.8, 5.2 and 1.7 Hz, CH*H* and O*H*), 3.62 (1H, ddd, J = 12.2, 12.2 and 3.7 Hz, CH*H*), 2.72–2.63 (1H, m, CH*H*), 2.57 (1H, bd, J = 14.8 Hz, CH*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.2 (C=O), 174.2 (qC), 134.0 (qC), 133.3 (qC), 130.8 (*C*H), 130.6 (qC), 130.4 (qC), 129.2 (*C*H), 128.8 (*C*H), 128.60 (*C*H), 128.56 (*C*H), 128.3 (*C*H), 127.9 (*C*H), 127.5 (*C*H), 126.0 (*C*H), 113.4 (qC), 85.7 (qC), 40.7 (CH_2), 29.3 (CH_2); IR (neat, cm^{-1}) υ_{max}: 3256, 1657, 1601, 1542, 1427, 1350, 1121, 1074, 973, 791, 767, 720, 527; HRMS: [M^+] for $C_{24}H_{19}NO_2$ calculated 353.1416, found 353.1420.

5.5. Synthesis of 10b-hydroxy-2,3-bis(dimethoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**42**)

To a stirred solution of 3,4-dihydroisoquinoline [33] (0.024 g, 0.182 mmol) in $CDCl_3$ (5 mL), was added 2,3-*bis*(4-methoxyphenyl) cycloprop-2-en-1-one [35,36] (0.050 g, 0.186 mmol) at room temperature under an air atmosphere. The reaction mixture was stirred at room temperature for 3 h and then solvents were removed by rotary evaporation. The crude product was purified by flash silica chromatography to afford the title compound in ~90% purity as an orange yellow solid (0.040 g, 52% yield), m.p. 86–87 °C. R_f 0.37 (ethyl acetate/petroleum ether, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (1H, d, J = 8.0 Hz, Ar), 7.39–7.26 (5H, m, Ar), 7.07 (1H, d, J = 7.2 Hz, Ar), 6.96–6.91 (3H, m, Ar), 6.67 (2H, d, J = 8.7 Hz, Ar), 3.97–3.55 (3H, m, CH_2 & O*H*), 3.86 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 2.68–2.43 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.3 (C=O), 173.5 (qC), 161.4 (qC), 157.7 (qC), 134.0 (qC), 133.6 (qC), 130.5 (*C*H), 130.1 (*C*H), 128.7 (*C*H), 128.4 (*C*H), 128.1 (*C*H), 127.4 (*C*H), 123.4 (qC), 122.4 (qC), 114.5 (*C*H), 113.4 (*C*H), 112.9 (qC), 85.8 (qC), 55.4 (OCH_3), 55.1 (OCH_3), 40.9 (CH_2), 28.1 (CH_2); IR (neat, cm^{-1}) υ_{max}: 3341, 1668, 1604, 1518, 1456, 1289, 1243, 1173, 1110, 1024, 832, 747, 581, 531; HRMS: [M^+] for $C_{26}H_{23}NO_4$ calculated 413.1627, found 413.1627.

5.6. Synthesis of 10b-hydroxy-2,3-bis(difluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**43**)

To a solution of 3,4-dihydroisoquinoline [33] (0.027 g, 0.206 mmol) in acetonitile (10 mL) was added 2,3-bis(4-fluorophenyl)cycloprop-2-en-1-one [36] (0.050 g, 0.205 mmol). The solution was stirred at room temperature for 48 h. The acetonitrile was removed under vacuum and the crude product was purified via silica column chromatography to afford the title compound in ~95% purity as a bright yellow solid (0.028 g, 36% yield), m.p. 134–139 °C. R_f 0.28 (ethyl acetate/petroleum ether, 3:7); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.11 (1H, d, J = 7.9 Hz, Ar), 7.39–7.08 (7H, m, Ar), 6.92–6.90 (2H, m, Ar), 6.82–6.79 (2H, m, Ar), 4.52–3.80 (1H, bs, O*H*), 3.83 (1H, ddd, J = 2.1, 5.0, 13.9 Hz, CH*H*), 3.63 (1H, ddd, J = 4.3, 11.7, 13.9 Hz, C*H*H), 2.64–2.59 (m, 2H, m, CH_2); ^{19}F (376 MHz, $CDCl_3$) δ: −107.9 (m, ArF), −115.8 (m, ArF); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 198.1 (C=O), 172.8 (qC), 164.0 (d, J = 251 Hz, qC–F), 161.2 (d, J = 244 Hz, qC–F), 133.9 (qC), 133.2 (qC), 130.4 (d, J = 7.8 Hz, C*H*m-F) 128.6 (d, J = 8.7 Hz, C*H*m-F), 128.3 (*C*H), 127.6 (*C*H), 126.5 (d, J = 3.3 Hz, qC*p*-F), 126.1 (d, J = 3.5 Hz, qC*p*-F), 116.7 (d, J = 21.8 Hz, C*H*o-CF), 115.0 (d, J = 21.2 Hz, C*H*o-CF), 112.7 (qC), 85.8 (qC), 40.7 (CH_2), 29.3 (CH_2); IR (neat, cm^{-1}) υ_{max}: 3284, 2920, 1657, 1551, 1495, 1346, 1230, 1155, 1072, 974, 831, 752, 569, 522; HRMS: [M + H^+] for $C_{24}H_{18}NO_2F_2$ calculated 390.1304, found 390.1301.

5.7. Synthesis of 8,9-dimethoxy-10b-hydroxy-2,3-diphenyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**44**)

To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline [34] (0.09 g, 0.48 mmol) in chloroform (5 mL), was added diphenylcyclopropenone (0.10 g, 0.48 mmol) at room temperature under an air atmosphere. The reaction mixture was stirred for 3 h and then the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography affording the title compound as an orange yellow solid (0.13 g, 65% yield), m.p. 154–156 °C. R_f 0.30 (ethyl acetate/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (1H, s, Ar), 7.51–7.46 (5H, m, Ar), 7.12–7.01 (3H, m, Ar), 7.00 (2H, d, J = 7.5 Hz, Ar), 6.54 (1H, s, Ar), 4.00 (3H, s, OCH_3),

3.86 (3H, s, OC*H*$_3$), 3.89–3.81 (1H, m, CH*H*), 3.60 (2H, m, CH*H* & OH), 2.65–2.57 (1H, m, CH*H*), 2.47 (1H, bd, J = 14.0 Hz, CH*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.1 (C=O), 173.8 (qC), 149.4 (qC), 148.5 (qC), 130.69 (*C*H), 130.66 (qC), 130.5 (qC), 129.8 (*C*H), 129.2 (*C*H), 128.8 (*C*H), 127.9 (*C*H), 126.6 (qC), 126.0 (*C*H), 124.9 (qC), 113.2 (qC), 110.3 (*C*H), 110.3 (*C*H), 85.4 (qC), 56.2 (*C*H$_3$), 55.9 (*C*H$_3$), 40.7 (*C*H$_2$), 28.9 (*C*H$_2$); IR (neat, cm^{-1}) υ_{max}: 3250.1, 2921.1, 2852.2, 1643.7, 1446.6, 1360.1, 1257.0, 1223.2, 1124.7, 1037.7; HRMS: [M$^+$] for $C_{26}H_{23}NO_4$ calculated 413.1627, found 413.1617.

5.8. Synthesis of 8,9-dimethoxy-10b-hydroxy-2,3-bis(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**45**)

To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline [33] (0.15 g, 0.78 mmol) in chloroform (5 mL), was added 2,3-*bis*(4-methoxyphenyl)cycloprop-2-en-1-one [35,36] (0.21 g, 0.78 mmol) at room temperature under an air atmosphere. The reaction mixture was stirred at room temperature for 3 h and then solvents were removed by rotary evaporation. The crude product was purified by silica chromatography to afford the title compound as an orange yellow solid (0.16 g, 69% yield), m.p. 142–143 °C. R$_f$ 0.25 (ethyl acetate/hexane, 2:1); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.49 (1H, s, Ar), 7.29 (2H, bd, J = 8.5 Hz, Ar), 7.06 (2H, d, J = 7.7 Hz, Ar), 6.84 (2H, d, J = 8.0 Hz, Ar), 6.68 (2H, d, J = 8.5 Hz, Ar), 6.65 (1H, s, Ar), 3.81 (3H, s, C*H*$_3$), 3.78 (3H, s, C*H*$_3$), 3.71 (3H, s, C*H*$_3$), 3.64 (3H, s, C*H*$_3$), 3.50–3.29* (3H, m, O*H* and C*H*$_2$), 2.40–2.20* (2H, m, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7 (C=O), 172.6 (qC), 161.1 (CH), 157.4 (qC), 149.1 (qC), 147.9 (qC), 130.6 (qC), 129.9 (*C*H), 127.2 (qC), 126.6 (qC), 124.4 (qC), 122.9 (qC), 115.1 (*C*H), 113.6 (*C*H), 111.9 (*C*H), 111.4 (qC), 111.2 (*C*H), 85.5 (qC), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 55.8 (O*C*H$_3$), 55.3 (O*C*H$_3$), 40.5* (CH$_2$), 28.8 (CH$_2$); IR (neat, cm^{-1}) υ_{max}: 3318, 1644, 1604, 1517, 2492, 1337, 1248, 1172, 1113, 1014, 1001, 828, 725, 583, 561, 540, 528; HRMS: [M$^+$] for $C_{28}H_{27}NO_6$ calculated 473.1838, found 473.1837. (* signal overlaps with DMSO/H_2O signal from solvent).

5.9. Synthesis of 8,9-dimethoxy-10b-hydroxy-2,3-bis(4-fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**46**)

To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline [34] (0.096 g, 0.499 mmol) in chloroform (5 mL), was added 2,3-*bis*(4-fluorophenyl)cycloprop-2-en-1-one [36] (0.121 g, 0.497 mmol) at room temperature under an air atmosphere. The reaction mixture was stirred at room temperature for 3 h and then solvents were removed by rotary evaporation. The crude product was purified by silica chromatography to afford the title compound as a pale green oil (0.075 g, 34% yield). R$_f$ 0.3 (CH_2Cl_2/MeOH, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.63 (1H, s, Ar), 7.41 (2H, bs, Ar), 7.19 (2H, bs, Ar), 6.95–6.97 (2H, m, Ar), 6.84–6.87 (2H, m, Ar), 6.56 (1H, s, Ar), 4.00 (3H, s, OC*H*$_3$), 3.85–3.98 (2H, s, O*H* + C*H*H), 3.88 (3H, s, OC*H*$_3$), 3.60–3.66 (1H, m, CH*H*), 2.57–2.61 (1H, m, CH*H*), 2.50–2.53 (1H, m, C*H*H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 198.0 (C=O), 172.4 (qC), 163.0 (d, J = 251.1 Hz, q*C*–F), 161.2 (d, J = 244.3 Hz, q*C*–F), 149.5 (qC), 148.6 (qC), 130.4 (2C, d, J = 7.8 Hz, 2 × C*H*m-F), 126.49 (qC), 126.45 (bs, q*Cp*-F), 126.2 (d, J = 3.4 Hz, q*Cp*-F), 124.8 (qC), 116.7 (d, J = 21.8 Hz, C*H*o-F), 115.0 (d, J = 21.2 Hz, C*H*o-F), 112.6 (qC), 110.3 (2C, 2 × *C*H), 85.5 (q*C*OH), 56.2 (O*C*H$_3$), 55.9 (O*C*H$_3$), 40.8 (*C*H$_2$), 21.8 (*C*H$_2$); IR (neat, cm^{-1}) υ_{max}: 3460.4, 2928.0, 2853.3, 2117.0, 1677.6, 1513.9, 1265.8, 1226.0, 1154.9, 1132.2; HRMS: [M + H$^+$] for $C_{26}H_{22}F_2NO_4$ calculated 450.1518, found 450.1509.

5.10. Synthesis of 8,9-Dimethoxy-10b-methyl-2,3-diphenyl-5,6-dihydropyrrolo [2,1-a]isoquinolin-1-one (**57ai**)

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline [37] (0.0377 g, 0.1836 mmol) diphenylcyclopropenone (0.0250 g, 0.1212 mmol) were dissolved in acetonitrile (5 mL). The flask heated at 82 °C for 1 h, while continuously stirring. After heating, the solvent was removed *in vacuo*. The crude product was purified by silica column chromatography to give the product as a pale yellow solid (0.0296 g, 57% yield), m.p. 235–237 °C. R$_f$ 0.3 (ethyl acetate/hexane, 4:6); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (1H, s, Ar), 7.49–7.28 (5H, m, Ph), 7.10–7.06 (4H, m, Ph), 7.04–7.01 (1H, m, Ph), 6.52 (1H, s, Ar), 4.00 (3H, s, OMe), 3.92 (1H, dd, J = 10.2, 3.5 Hz, C*H*H), 3.84 (3H, s, OMe), 3.46 (1H, ddd, J = 10.2, 10.2, 2.7 Hz, C*H*H), 2.74–2.56 (1H, m, C*H*H), 2.49 (1H, dd, J = 11.9, 1.7 Hz, C*H*H), 1.76 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.5 (C=O), 172.3 (qC), 148.2 (qC), 147.9 (qC), 131.7 (qC), 130.9 (qC), 130.2 (CH), 129.1 (CH), 128.7 (CH), 128.4 (qC), 128.2 (CH), 127.7 (CH), 125.3 (CH), 124.3 (qC), 113.4 (qC), 110.6 (CH), 109.6 (CH), 67.9 (qC), 56.2 (OCH$_3$), 55.9 (OCH$_3$), 40.7 (CH$_2$), 29.8 (CH$_2$), 26.4 (CH$_3$). IR (neat, cm^{-1}) υ_{max}: 2937.2, 2835.0, 2360.6, 2339.3, 1656.6, 1602.6, 1544.8, 1504.3, 1432.9, 1404.0, 1344.2, 1324.9, 1259.4, 1230.4, 1207.3, 1124.4, 1080.0, 999.0, 773.4, 732.90, 690.4, 640.3, 551.6. HRMS: [M + H$^+$] for $C_{27}H_{26}NO_3$, calculated 412.1917, found 412.1913.

5.11. Synthesis of 8,9-Dimethoxy-10b-methyl-2,3-bis(4-dimethoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**57aii**)

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline [37] (0.029 g, 0.141 mmol) and 2,3-*bis*(4-methoxyphenyl)cycloprop-2-en-1-one [35,36] (0.025 g, 0.094 mmol) were dissolved in a mixture of acetonitrile (2.5 mL) and chloroform (7.5 mL). The solution was heated at reflux for 96 h, with continuous stirring. The solvent was removed and the crude product was purified via silica column chromatography to give the product as a bright yellow solid (0.024 g, 53% yield), m.p. 235–237 °C. R$_f$ 0.3 (ethyl acetate/hexane, 11:9); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (s, 1H, Ar), 7.37–7.36 (2H, m, Ar), 7.01 (2H, d, J = 8.6 Hz, Ar), 6.96 (2H, d, J = 7.6 Hz, Ar), 6.68 (2H, d, J = 8.6 Hz, Ar), 6.50 (1H, s, Ar), 4.00 (3H, s, OMe), 3.95 (1H, overlapping m, C*H*H), 3.86 (3H, s, OMe), 3.82 (3H, s, OMe), 3.72 (3H, s, OMe), 3.47–3.40 (1H, m, C*H*H), 2.61 (1H, m, C*H*H), 2.46 (1H, d, J = 14.4 Hz, C*H*H), 1.74 (3H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.6 (C=O), 171.7 (qC), 160.9 (qC), 157.2 (qC), 148.1 (qC), 147.8 (qC), 129.7 (2 × CH), 128.4 (qC), 124.5 (qC), 124.4 (qC), 122.9 (qC), 114.5 (CH), 113.2 (CH), 113.1 (qC), 110.5 (CH), 109.7 (CH), 67.8 (qC), 56.1 (OCH$_3$), 55.8 (OCH$_3$), 55.4 (OCH$_3$), 55.1 (OCH$_3$), 40.8 (CH$_2$), 29.7 (CH$_2$), 26.3 (CH$_3$); IR (neat, cm^{-1}) υ_{max}: 2929.5, 2833.1, 1652.8, 1515.9, 1459.9, 1404.0, 1342.3, 1299.9, 1247.8, 1174.5, 1022.1, 919.9, 829.3, 582.4, 549.6; HRMS: [M + H$^+$] for $C_{29}H_{30}NO_5$, calculated 472.2126, found 472.2119.

5.12. Synthesis of 10b-(Difluoromethyl)-8,9-dimethoxy-2,3-diphenyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**57b**)

1-(Difluoromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline [37] (0.035 g, 0.145 mmol) and diphenylcyclopropenone (0.025 g, 0.127 mmol) were dissolved in a mixture acetonitrile (5 mL) and chloroform (4 mL). The reaction mixture was heated at reflux, with continuous stirring, for 48 h. The mixture was cooled, the solvent was removed by rotary evaporation and the crude material was purified by silica column chromatography. The product was obtained as a yellow solid (0.023 g, 41% yield), m.p. 234–238 °C. R$_f$ 0.33 (ethyl acetate/hexane, 4:6); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (1H, s, Ar), 7.52–7.30 (5H, m, Ph), 7.16–7.03 (5H, m, Ph), 6.62 (1H, s, Ar), 6.35 (1H, t, J = 54 Hz, C*H*F$_2$), 4.03 (3H, s, OMe), 3.90–4.01 (1H, m, C*H*H), 3.88 (3H, s, OMe), 3.75–3.63 (1H, m, C*H*H), 2.73–2.53 (2H, m, C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.0 (C=O), 176.3 (qC), 148.9 (qC), 148.4 (qC), 130.8 (qC), 130.7 (*C*H), 130.2 (qC), 129.2 (*C*H), 128.8

(bs, qC), 128.5 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 126.3 (qC), 125.9 (*C*H), 117.0 (t, J = 245 Hz, CHF_2), 115.6 (qC), 111.2 (*C*H), 108.5 (*C*H), 70.0 (t, J = 18.5 Hz, q$CCHF_2$), 56.2 (OCH_3), 55.9 (OCH_3), 42.4 (CH_2), 29.0 (CH_2); IR (neat, cm^{-1}) υ_{max}: 2920, 2850, 1666, 1520, 1319, 1261, 1065, 1007, 876, 800, 735, 696, 542; HRMS: [M + H^+] for $C_{29}H_{24}F_2NO_3$, calculated 448.1725, found 448.1716.

5.13. Synthesis of 10b-(Fluoromethyl)-8,9-dimethoxy-2,3-bis(4-fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**57c**)

1-(Fluoromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline [37] (0.113 g, 0.506 mmol) and *bis*(4-difluorophenyl)cyclopropenone [36] (0.121 g, 0.495 mmol) were dissolved in chloroform (5 mL). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed by rotary evaporation and the crude material was purified by silica column chromatography. The product was obtained as a light brown oil (0.063 g, 27% yield). R_f 0.28 (ethyl acetate/hexane, 5:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (1H, s, Ar), 7.55–7.26 (2H, bm, Ph), 7.19–7.15 (2H, m, Ph), 7.01–6.98 (2H, m, Ar), 6.84–6.80 (2H, m, Ar), 6.58 (1H, s, Ar), 6.35 (2H, d, J = 47.5 Hz, CH_2F), 4.00 (3H, s, OMe), 3.97–3.87 (1H, m, *CH*H), 3.85 (3H, s, OMe), 3.65–3.58 (1H, m, *CH*H), 2.67–2.60 (1H, m, C*H*H), 2.55 (1H, dd, J = 16.0, 2.6, C*H*H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.2 (C=O), 173.3 (qC), 163.9 (d, J = 250.5 Hz, qC–F), 161.0 (d, J = 244.0 Hz, qC–F), 148.7 (qC), 148.39 (qC), 130.1 (d, J = 7.8 Hz, 2 × *C*H-*m*F), 127.0 (d, J = 3.1 Hz, qC-*p*F), 126.2 (d, J = 3.5 Hz, qC-*p*F), 125.9 (qC), 121.8 (d, J = 4.7 Hz, qC-CCF), 116.7 (d, J = 21.8 Hz, C*H*o-F), 114.8 (d, J = 21.2 Hz, C*H*o-F), 114.4 (qC), 111.1 (*C*H), 108.9 (*C*H), 86.8 (d, J = 181.3 Hz, CH_2F), 70.7 (d, J = 18.3 Hz, qCCH_2F), 56.2 (OCH_3), 55.9 (OCH_3), 41.8 (CH_2), 29.3 (CH_2); IR (neat, cm^{-1}) υ_{max}: 2924.5, 2852.9, 1662.2, 1602.8, 1513.8, 1262.7, 1225.6, 1155.9, 1022.2.; HRMS: [M + Na^+] for $C_{27}H_{22}F_3NNaO_3$ calculated 488.1453, found 488.1438.

5.14. Synthesis of 8,9-Dimethoxy-5,10b-dimethyl-2,3-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one (**57d**)

6,7-Dimethoxy-1,3-dimethyl-3,4-dihydroisoquinoline [39] (0.0424 g, 0.1933 mmol) and diphenylcyclopropenone (0.0250 g, 0.1212 mmol) were dissolved in acetonitrile (5 mL). The solution was stirred vigorously at 82 °C for 4.5 h. After heating, excess solvent was removed *in vacuo*. The crude material was purified via column chromatography with standard silica eluted with 42% ethyl acetate in hexane. The solvent was removed under pressure and vacuum, yielding a yellow solid (0.0423 g, 78%), m.p. 189–193 °C. R_f 0.33 (ethyl acetate/hexane, 42:58); ^{1}H NMR (300 MHz, $CDCl_3$), ~2:5 mixture of diastereoisomers, δ: 7.91–7.40 and 7.13–7.01 (11H, m, Ar*H* + 2Ph, mixture of diastereoisomers), 6.64 and 6.51 (1H, 2 × s, Ar*H*), 4.30–4.22 (1H, m, C*H*Me), 4.01 and 3.99 (3H, 2 × s, OMe), 3.86 and 3.84 (3H, 2 × s, OMe), 3.20 and 2.80 (1H, 2 × dd, J = 15.4, 3.9 Hz and 15.6, 6.0 Hz, C*H*H), 2.62 and 2.39 (dd and d, J = 15.4, 5.7 Hz and 15.6 Hz, CH*H*), 1.83 and 1.35 (3H, 2 × s, Me), 1.37 and 0.69 (3H, 2 × d, J = 7.2 and 6.6 Hz, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.8/199.2 (C=O), 173.3/172.2 (qC), 148.2/148.1 (qC), 147.9/147.8 (qC), 132.6/131.9 (qC), 131.8/131.7 (qC), 130.2/129.9 (qC), 129.2 (*C*H) 128.9/128.7 (*C*H), 128.5/128.4 (*C*H), 128.1/127.7 (*C*H), 126.8 (qC), 125.5/125.3 (*C*H), 122.3 (qC), 115.5/114.1 (qC), 111.5/111.2 (*C*H), 109.7/108.3 (*C*H), 68.7/67.4 (qC), 56.1/55.91 (OCH_3), 55.86 (OCH_3), 50.9/48.7 (*C*H), 36.6/35.2 (CH_2), 29.5/28.7 (CH_3), 20.2/20.0 (CH_3); IR (neat, cm^{-1}) υ_{max}: 2929, 2831, 1655, 1603, 1516, 1464, 1423, 1352, 1317, 1261, 1211, 1140, 1082, 1041, 997, 930, 854, 748, 731, 690, 538; HRMS: [M + H^+] for $C_{28}H_{28}NO_3$, calculated 426.2074, found 426.2068.

5.15. Synthesis of 2,2′,3,3′-tetraphenyl-6,6′,11,11′-tetrahydro-[11b,11b′-bis(indolozino[8,7-b]indole)]-1,1′-one (**59a**) and 4,5-diphenyl-5,8-dihydroazonino[5,4-b]indole-6,7-dione (**60**)

To a stirred solution of dihydropyrido[3,4-*b*]indole (**58**) [42] (0.086 g, 0.505 mmol) in acetonitrile (5 mL) was added diphenylcyclopropenone (0.086 g, 0.417 mmol) in one portion. The bright yellow solution was stirred at room temperature and monitored by TLC. After 4 h, a precipitate was formed, and the mixture was filtered. The precipitate (0.043 g, 27%) was found to be the *bis*(indolizino[8,7-b]indolone **59a**. The solution was concentrated by rotary evaporation and purified by column chromatography on silica to give an additional amount of the dimeric species (0.010 g, 6%). Also recovered from the mixture was a second product (0.021 g, 13%) tentatively identified as the azoninoindole **60**, and isolated in ~95% purity.

Bis(indolizino[8,7-b]indolone **59a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.22 (2H, bs, NH), 7.53–7.40 (10H, m, Ar), 7.30–7.24 (4H, m, Ar), 7.20–7.08 (14H, m, Ar), 3.98 (2H, app d, J = 8.6 Hz, NC*H*H), 3.49 (2H, bm, NCH*H*), 2.74 (2H, app d, J = 14.4 Hz, C*H*H), 2.64–2.55 (2H, m, CH*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.1 (qC), 174.5 (qC), 136.8 (qC), 130.9 (qC), 130.9 (qC), 130.4 (*C*H), 129.1 (2 × *C*H), 127.9 (2 × *C*H), 126.4 (qC), 126.1 (*C*H), 125.989 (qC), 122.8 (*C*H), 119.6 (*C*H), 118.5 (*C*H), 116.5 (qC), 112.3 (*C*H), 110.6 (qC), 72.7 (qC), 43.5 (CH_2), 22.0 (CH_2). IR (neat, cm^{-1}) υ_{max}: 3359, 1679, 1660, 1606, 1558, 1456, 1446, 1412, 1337, 1312, 1299, 1256, 1224, 1165, 1104, 1042, 1028, 797, 781, 693, 649, 610, 519; HRMS: [M + Na^+] for $C_{52}H_{38}N_4NaO_2$ calculated 773.2893, found 773.2884. X-ray crystallographic studies [39] confirmed the structural assignment.

Azoninoindole **60**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.21 (1H, s, N*H*), 8.43 (1H, d, J = 5.0 Hz, Ar*H*), 8.14–8.10 (4H, m, 3 × Ar*H* + *CH*=CH), 7.60–7.30 (12H, m, 2 × Ph + CH=C*H* + *CH*Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.4 (C=O), 195.1 (C=O), 141.1 (qC), 138.3 (*C*H), 136.4 (qC), 136.1 (qC), 134.3 (qC), 133.2 (qC), 133.1 (*C*H), 131.8 (qC), 130.3 (*C*H), 129.4 (*C*H), 129.2 (*C*H), 128.8 (*C*H), 128.7 (*C*H), 127.9 (*C*H), 121.9 (*C*H), 120.9 (*C*H), 120.6 (qC), 119.3 (*C*H), 112.0 (*C*H), 61.4 (*C*H); IR (neat, cm^{-1}) υ_{max}: 3304, 2954, 2919, 2851, 1729, 1462, 1377, 1270, 1120, 1071, 1093, 741, 703; HRMS: [M^+] for $C_{26}H_{18}N_2O_2$ calculated390.1368, found 390.1375.

5.16. Synthesis of methyl 3-(1-oxo-2,3-diphenyl-6,11-dihydro-1H-indolizino[8,7-b]indol-11b(5H)-yl)propanoate (**69**)

To a stirred solution of methyl 3-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)propanoate **65** [44] (0.06 g; 0.24 mmol) in acetonitrile (5 mL), was added diphenylcyclopropenone (0.05 g; 0.24 mmol) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 24 h and the solvents were removed by rotary evaporation under reduced pressure. The crude product was purified by flash silica chromatography affording the title compound as an orange yellow solid (0.09 g, 81% yield), m.p. 182–183 °C. R_f 0.35 (ethyl acetate/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.27 (1H, s, N*H*), 7.57–7.53 (2H, m, Ar), 7.47 (2H, d, J = 7.8 Hz, Ar), 7.43 (2H, d, J = 8.3 Hz, Ar), 7.24–7.09 (8H, m, Ar), 4.08 (1H, dd, 5.4 and 13.9 Hz, C*H*H), 3.63 (3H, s, CH_3), 3.59–3.55 (1H, m, C*H*H), 2.89–2.81 (1H, m, C*H*H), 2.75 (1H, dd, J = 15.5 and 4.0 Hz, C*H*H), 2.71–2.56 (3H, m, C*H*H + CH_2), 2.53–2.45 (1H, m, C*H*H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7 (C=O), 175.8 (C=O), 173.3 (qC), 136.8 (qC), 131.3 (qC), 131.0 (qC), 130.7 (qC), 130.5 (*C*H), 129.2 (*C*H), 128.6 (2*C*H), 127.9 (*C*H), 126.4 (*C*H), 125.9 (*C*H), 122.4 (*C*H), 119.7 (*C*H), 118.3 (*C*H), 115.7 (qC), 111.9 (qC), 107.1 (qC), 69.6 (qC), 51.8 (CH_3), 41.7 (CH_2), 31.9 (CH_2), 28.8 (CH_2), 22.4 (CH_2); IR (neat, cm^{-1}) υ_{max}: 3269, 2928, 2839, 1744, 1639, 1601, 1536, 1469, 1428, 1351, 1171, 1060, 859, 736, 694, 511; HRMS: [M^+] for $C_{30}H_{26}N_2O_3$ calculated 462.1943, found 462.1939.

5.17. Synthesis of methyl 4-(1-oxo-2,3-diphenyl-6,11-dihydro-1H-indolizino[8,7-b]indol-11b(5H)-yl)butanoate (**70**)

To a stirred solution of methyl 4-(4,9-dihydro-3H-pyrido[3,4-b] indol-1-yl)butanoate **66** [44] (0.12 g, 0.44 mmol) in acetonitrile (5 mL), was added diphenylcyclopropenone (0.09 g, 0.44 mmol) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 24 h and the solvents were removed by rotary evaporation. The crude product was purified by flash silica chromatography affording the title compound as an orange yellow solid (0.17 g, 80% yield), m.p. 180–181 °C. R_f 0.32 (ethyl acetate/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, bs, N*H*), 7.52–7.48 (4H, m, Ar), 7.42 (1H, d, J = 7.8 Hz, Ar), 7.40 (1H, d, J = 8.1 Hz, Ar), 7.20 (1H, t, J = 7.5 Hz, Ar), 7.14–7.03 (7H, m, Ar), 4.11 (1H, dd, J = 13.9 and 5.6 Hz, CH_2), 3.70 (3H, s, CH_3), 3.59–3.53 (1H, m, CH_2), 2.72 (1H, dd, J = 15.4 and 4.1 Hz, CH_2), 2.60–2.54 (1H, m, CH_2), 2.53–2.30 (3H, m, CH_2), 2.25–2.17 (1H, m, CH_2), 1.78–1.67 (2H, 2 × m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.9 (C=O), 175.4 (C=O), 173.6 (qC), 136.7 (qC), 131.8 (qC), 131.1 (qC), 130.7 (qC), 130.4 (*C*H), 129.1 (*C*H) 128.4 (*C*H), 127.8 (2*C*H), 126.5 (qC), 125.7 (*C*H), 122.4 (*C*H), 119.7 (*C*H), 118.3 (*C*H), 115.0 (qC), 111.7 (*C*H), 106.9 (qC), 70.0 (qC), 51.6 (*C*H$_3$), 41.6 (*C*H$_2$), 36.7 (*C*H$_2$), 33.7 (*C*H$_2$), 22.4 (*C*H$_2$), 19.2 (*C*H$_2$); IR (neat, cm^{-1}) υ_{max}: 3246, 1731, 1644, 1538, 1422, 1351, 1315, 1254, 1083, 988, 908, 769, 696, 511; HRMS: [M$^+$] for $C_{31}H_{28}N_2O_3$ calculated 476.2089, found 476.2100.

5.18. Synthesis of methyl 4-(2,3-bis(4-methoxyphenyl)-1-oxo-6,11-dihydro-1H-indolizino[8,7-b]indol-11b(5H)-yl)butanoate (**71**)

To a stirred solution of methyl 4-(4,9-dihydro-3H-pyrido[3,4-b] indol-1-yl)butanoate **66** [44] (0.15 g; 0.55 mmol) in acetonitrile (5 mL), was added 2,3-*bis*(4-methoxyphenyl) cycloprop-2-en-1-one (0.15 g; 0.55 mmol) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 24 h and then solvents were removed rotary evaporation under reduced pressure. The crude product was purified by flash silica chromatography affording the title compound as an orange yellow solid (0.22 g, 74%), m.p. 188–189 °C. R_f 0.72 (ethyl acetate/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.09 (N*H*), 7.42 (1H, d, J = 7.8 Hz, Ar), 7.38 (1H, d, J = 8.2 Hz, Ar), 7.32–7.25 (3H, m, Ar), 7.18 (1H, t, J = 7.4 Hz, Ar), 7.09 (1H, t, J = 7.4 Hz, Ar), 7.03–6.98 (3H, m, Ar), 6.70 (2H, d, J = 8.8 Hz, Ar), 4.16 (1H, dd, J = 13.9 Hz, 5.4 Hz, CH_2), 3.70 (3H, s, CH$_3$), 3.57 (3H, s, CH_3), 3.55 (3H, s, CH$_3$), 3.54–3.35 (1H, m, CH_2), 2.69 (1H, dd, J = 15.4 Hz, 3.9 Hz, CH_2), 2.58–2.31 (4H, m, CH_2), 2.22–2.15 (1H, m, CH_2), 1.82–1.79 (1H, m, CH_2), 1.74–1.71 (1H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.0 (C=O), 174.9 (C=O), 173.7 (qC), 161.1 (qC), 157.6 (qC), 136.7 (qC), 132.0 (qC), 130.3 (qC), 129.7 (*C*H), 129.1 (qC), 126.5 (qC), 123.8 (qC), 122.7 (qC), 122.2 (*C*H), 119.6 (*C*H), 118.2 (*C*H), 114.5 (*C*H), 113.4 (*C*H), 111.7 (*C*H), 106.8 (*C*H), 69.9 (qC), 55.4 (*C*H$_3$), 55.1 (*C*H$_3$), 51.6 (*C*H$_3$), 41.8 (*C*H$_2$), 36.6 (*C*H$_2$), 33.7 (*C*H$_2$), 22.3 (*C*H$_2$), 19.3 (*C*H$_2$); IR (neat, cm^{-1}) υ_{max}: 3270, 2929, 2839, 1742, 1635, 1606, 1577, 1519, 1462, 1437, 1344, 1295, 1243, 1171, 1023, 829, 759, 580; HRMS: [M$^+$] for $C_{33}H_{32}N_2O_5$ calculated 536.2311, found 536.2308.

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