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Synthesis of 1-indolyl substituted β-carboline natural products and discovery of antimalarial and cytotoxic activities

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ABSTRACT

A series of 1-indolyl substituted β-carbolines including the natural products hyrtiosulawesine, pityriacitrin and pityriacitrin B were prepared via Pictet–Spengler condensation—oxidation strategy from the corresponding indolyl-acetaldehydes and substituted tryptamines. Efforts to prepare the C-1 methylene-linked β-carboline analogues for structure–activity relationship studies were unsuccessful. Biological evaluation revealed two analogues (**5** and **41**) to exhibit weak inhibition of phospholipase A_2 (IC_{50} 171 and 131 μM, respectively), two to act as antioxidants (**3** and **43**), and 12 analogues with activity towards a chloroquine-resistant strain (FcB1) of *Plasmodium falciparum* (IC_{50} 1.0–23 μM). Testing against a panel of 60 human tumour cell lines revealed a general lack of cytotoxic effect for most of the compounds with the exception of β-carboline **42** exhibiting modest antileukaemic activity towards the HL-60(TB) cell line (LC_{50} 4.2 μM). In addition, two novel structures (**30** and **32**) resulting from aldol condensation followed by Pictet–Spengler cyclisation displayed cytotoxicity with pronounced subpanel specificities towards colon cancer (COLO 205 and HCC-2998) cell lines.

1. Introduction

Alkaloids containing the β-carboline skeleton are ubiquitous in Nature having been found in animals, plants, marine organisms and even in humans.[1,2] In addition to the three different oxidation states: 1,2,3,4-tetrahydro-β-carboline, 3,4-dihydro-β-carboline and β-carboline, this class of compounds can also be substituted at any of the nine positions along the tricyclic core structure giving rise to a large structural diversity. Substitution at the C-1 position of a β-carboline structure is the most common, as C-1 is the only atom in the β-carboline ring system that does not belong to tryptophan, the amino acid precursor for the biosynthesis of this class of compounds.[3]

A relatively rare subset of β-carboline alkaloids contain a 1-acyl-linked heterocycle (Fig. 1). For example, hyrtiomanzamine (**1**),[4] dragmacidonamine B (**2**)[5] and hyrtiosulawesine (**3**)[6] were isolated from marine sponges while pityriacitrin (**4**) was isolated from extracts of the marine bacterium *Paracoccus* sp.[7] Both **4** and pityriacitrin B (**5**) were isolated from the yeast *Malassezia furfur*.[8,9]

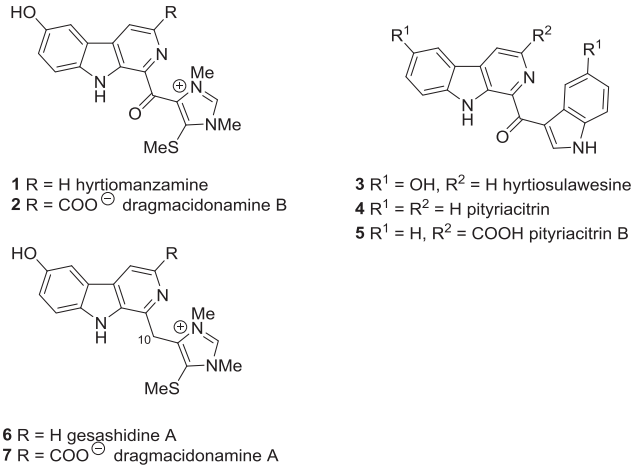

Fig. 1. Structures of hyrtiomanzamine (**1**), dragmacidonamine B (**2**), pityriacitrin (**4**), pityriacitrin B (**5**), hyrtiosulawesine (**3**), gesashidine A (**6**) and dragmacidonamine A (**7**).

Closely related deoxy analogues gesashidine A (**6**)[10] and dragmacidonamine A (**7**)[5] are representative of an even more selective group of β-carboline alkaloids that contain a methylene-linked

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heterocycle positioned at C-1. One could speculate that the 1-acyl group arises from a subsequent oxidation step at the methylene group in a possible biosynthetic pathway.

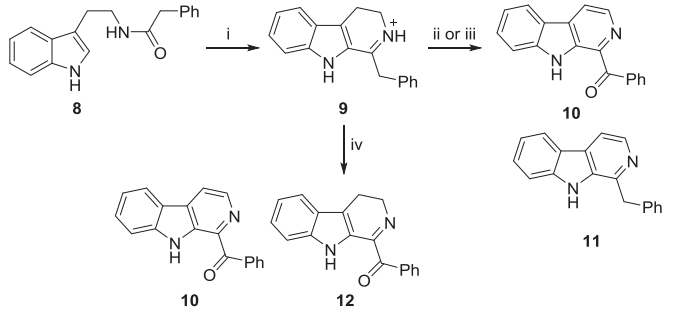
The marine β-carboline alkaloid hyrtiosulawesine has been previously reported as a PLA_2 inhibitor[11] and so represents an interesting anti-inflammatory lead compound. It was envisaged that the 1-acyl natural product as well as a series of analogues, including deoxy derivatives, could be synthesised and evaluated for structure–activity relationships. Alkaloids belonging to the β-carboline family typically exhibit wide ranging biological activities including effects on the central nervous system (e.g., harmine and harman),[2] cytotoxicity towards cancer cell lines (e.g., eudistomidins, shishijimicins)[12,13] and antimalarial (opacalines, manzamines)[14,15] properties. As the antimalarial and antitumour effects of β-carboline alkaloids are well documented, all analogues were also evaluated against *Plasmodium falciparum* and human tumour cell lines.

During the course of the present study, Zhang et al. reported syntheses of **3**–**5** using a Pictet–Spengler reaction between tryptamine or tryptophan and substituted indole-3-glyoxals to construct the C-8′ keto-β-carboline skeleton.[16,17] They also reported cytotoxicity data towards three human tumour cell lines. Herein we report our alternative route for the syntheses of 1-acylindole-β-carbolines pityriacitrin (**4**), pityriacitrin B (**5**), hyrtiosulawesine (**3**) and investigation of the structure–activity relationships (SAR) of these and model compounds against PLA_2, malaria, human tumour cell line cytotoxicity and as anti-oxidants.

2. Results and discussion

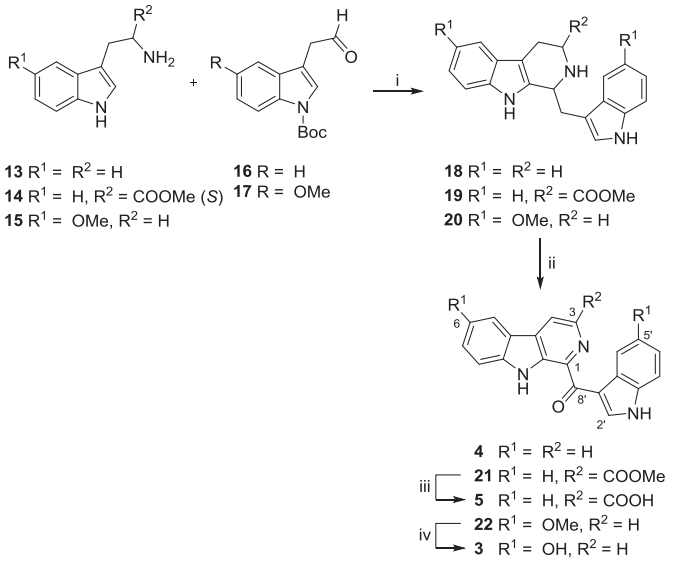
2.1. Chemistry

We explored the use of the two most prevalently used methods to construct the β-carboline scaffold, namely the Bischler–Napieralski and Pictet–Spengler condensation reactions.[18–20] As a model for the former reaction, amide **8**,[21] prepared by PyBOP-mediated coupling of tryptamine with phenylacetic acid, was subjected to reaction with $POCl_3$ in toluene to afford 3,4-dihydro-β-carboline **9** in 83% yield (Scheme 1). Oxidation of **9** with DDQ gave product mixtures of the 1-acyl product **10** and deoxy product **11** with variable yields in different solvents (CH_2Cl_2 and THF), while oxidation with $KMnO_4$ gave **10** (27%) and 1-benzyl-3,4-dihydro-β-carboline (**12**) (17%). Extension of this model reaction to the corresponding indole analogue *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(1*H*-indol-3-yl)acetamide[22] was unfortunately unsuccessful, with the amide not undergoing $POCl_3$-mediated ring closure.



Scheme 1. Reagents and conditions: (i) $POCl_3$, toluene, 120 °C, 30 min, 83%; (ii) DDQ, CH_2Cl_2, N_2, rt, 70 min, 1%, 26% (over two steps); (iii) DDQ, THF, N_2, rt, 15 min, 5%, 10% (over two steps); (iv) $KMnO_4$, DMF, 0 °C, 1 h, rt, 30 min, 27%, 17% (over two steps).

Switching to the Pictet–Spengler condensation, reaction of tryptamine (**13**) with *N*-Boc-indole-3-acetaldehyde (**16**) under acidic conditions (5% HOAc)[23] afforded 1,2,3,4-tetrahydro-β-carboline **18** in 37% yield (Scheme 2). With **18** in hand, a variety of



13 R^1 = R^2 = H
14 R^1 = H, R^2 = COOMe (*S*)
15 R^1 = OMe, R^2 = H

16 R = H
17 R = OMe

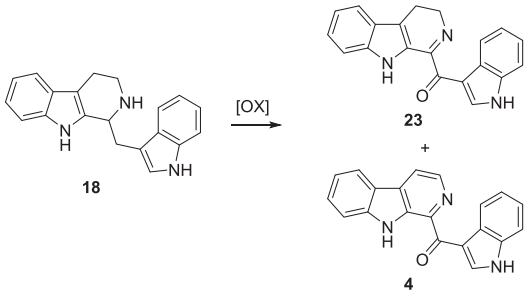
18 R^1 = R^2 = H
19 R^1 = H, R^2 = COOMe
20 R^1 = OMe, R^2 = H

4 R^1 = R^2 = H
21 R^1 = H, R^2 = COOMe
5 R^1 = H, R^2 = COOH
22 R^1 = OMe, R^2 = H
3 R^1 = OH, R^2 = H

Scheme 2. Synthesis of pityriacitrin (**4**), pityriacitrin B (**5**) and hyrtiosulawesine (**3**). Reagents and conditions: (i) 5 or 10% HOAc/H_2O, reflux, 1.5–5 h, 37–77%; (ii) DDQ, CH_2Cl_2/H_2O, rt, 30–90 min, 11–37%; (iii) LiOH, THF/H_2O (3:1), reflux, 12 h, 83%; (iv) BBr_3, CH_2Cl_2, N_2, −78 °C, 40 min, rt, 3 h, 87%.

conditions were trialed in an effort to achieve one of our SAR objectives, the conversion to the pyridine ring oxidation state without concomitant oxidation of the doubly benzylic methylene group. This selective oxidation has precedence, with Diker et al. reporting the use of 10% palladium on carbon in xylenes.[24] As shown in Table 1, we could not repeat the literature oxidation (entry 1), and furthermore no reagent or condition was found that could achieve the selective oxidation, either returning unreacted starting material or affording the oxidised products **23** and pityriacitrin (**4**). The spectroscopic data observed for **4** were in complete agreement with the literature.[9,17]

Table 1
Oxidation conditions examined

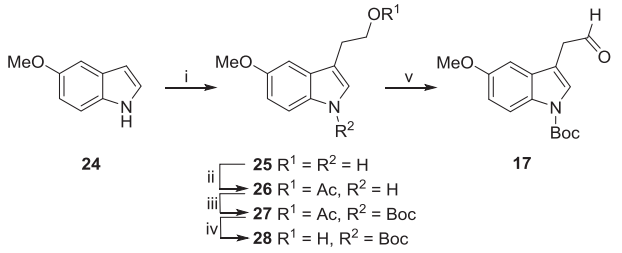


Entry	Reagent and conditions	Results
1	5% Pd/C (19% wt of THBC), xylenes, reflux, 4 h	No reaction
2	DDQ (4.0 equiv), CH_2Cl_2 (anhydrous), rt, 15 min	Unidentified decomposition products
3	IBX (2.5 equiv), DMSO, rt, 5 h	**23** (trace) and **4** (trace)
4	$KMnO_4$ (1.4 equiv), DMF, 0 °C–rt	**23** (28%) and **4** (trace)
5	MnO_2 (3.5 equiv), CH_2Cl_2, rt, 24 h	No reaction
6	S_8 (4.0 equiv), DMSO, reflux, 24 h	**4** (7%)

Similarly, L-tryptophan methyl ester (**14**) and **16** were heated to reflux in MeOH before subjection to acidic conditions, which gave 1,2,3,4-tetrahydro-β-carboline **19** in 44% yield. Subsequent oxidation using DDQ in CH_2Cl_2 afforded β-carboline **21** (11%) and

hydrolysis with LiOH in THF/H_2O gave pityriacitrin B (**5**) in 83% yield. The spectroscopic data observed for **21** again agreed with literature values.[8,17]

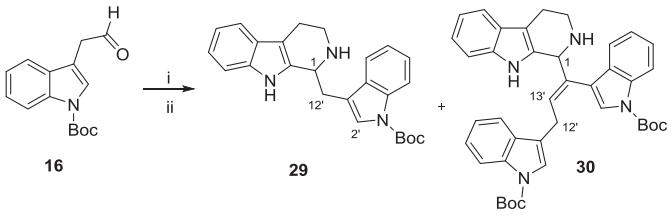
Synthesis of the third target 1-acylindole β-carboline natural product, hyrtiosulawesine (**3**) required *tert*-butoxycarbonyl-5-methoxyindole-3-acetaldehyde (**17**), which was prepared from 5-methoxyindole (Scheme 3). Reaction of 5-methoxyindole (**24**) with oxalyl chloride in anhydrous ether at 0 °C for 1 h followed by stirring at rt for 1 h gave 5-methoxyindole-3-glyoxyloyl chloride, which was immediately reduced with lithium aluminium hydride in THF to afford indole-ethyl-alcohol **25** in 76% yield over two steps. A sequence of acetylation (to give **26**), *tert*-butoxycarbonyl protection (to give **27**) and ester hydrolysis afforded alcohol **28**, which smoothly underwent oxidation with IBX in DMSO to afford aldehyde **17**.



Scheme 3. Preparation of *tert*-butoxycarbonyl-5-methoxyindole-3-acetaldehyde (**17**). Reagents and conditions: (i) (a) oxalyl chloride, diethyl ether, N_2, 0 °C, 1 h, rt, 1 h, 87%; (b) LAH, THF, N_2, reflux, 5 h, 87%, (ii) acetic anhydride, pyridine, N_2, rt, 16 h, 83%; (iii) di-*tert*-butyl dicarbonate, DMAP, CH_2Cl_2, N_2, rt, 19 h, quant.; (iv) 1 M K_2CO_3, MeOH/H_2O (1:1), rt, 16 h, 84%; (v) IBX, DMSO, N_2, rt, 2 h, 81%.

Pictet–Spengler coupling of commercially available 5-methoxytryptamine (**15**) with aldehyde **17** afforded the corresponding 1,2,3,4-tetrahydro-β-carboline **20** in 77% yield. Subsequent steps of oxidation (DDQ in CH_2Cl_2/H_2O) to give **22** (37%) and demethylation, using BBr_3 in CH_2Cl_2, afforded hyrtiosulawesine (**3**, 87% yield).[16]

Changing the solvent used in the Pictet–Spengler reaction between tryptamine and *N*-Boc-indole-3-acetaldehyde (**16**) to toluene, followed by CH_2Cl_2/TFA cyclisation, afforded two products **29** (6%) and **30** (15%) (Scheme 4), while use of CH_2Cl_2 as the solvent led to the same two products in higher yields of 46% and 39%, respectively (see Experimental). HRESIMS analysis of the major reaction product established a molecular formula of $C_{25}H_{28}N_3O_2$, $[M+H]^+$ consistent with the presence of a 1,2,3,4-tetrahydro-β-carboline skeleton linked via a methylene group to a Boc-protected indole. Detailed analysis of the 1D and 2D NMR data confirmed the structure of **29**. HRESIMS analysis of the second product of the reaction (**30**) identified a pseudomolecular ion at *m*/*z* 643.3256 (requires $C_{40}H_{43}N_4O_4$ $[M+H]^+$) suggesting the presence of a 1,2,3,4-tetrahydro-β-carboline group and two *N*-protected *tert*-butyloxycarbonyl indole moieties. Inspection of NMR data confirmed the presence of these three moieties, in addition to a fourth ^{1}H-spin system comprised of a tri-substituted olefin [δ_H 6.16 (1H, t, *J*=7.2 Hz, H-13′), δ_C 131.7 (C-13′)] coupled to an adjacent methylene [δ_H 3.49–3.38 (2H, m, H_2-12′), δ_C 26.0 (C-12′)]. HMBC data established connectivity between these fragments, while NOESY correlations observed between H-13′ (δ_H 6.16) and H-1 (δ_H 4.96) and NH-9 (δ_H 7.70) established the olefin geometry as *E*.



Scheme 4. Pictet–Spengler reaction of *N*-Boc-indole-3-acetaldehyde (**16**) and tryptamine. Reagents and conditions: (i) tryptamine, toluene, N_2, reflux, 3 h; (ii) CH_2Cl_2, TFA, N_2, rt, 12 h, 46%, 39%.

The unusual structure of **30** prompted further investigation. Reaction of tryptamine with phenylacetaldehyde in toluene, followed by stirring in CH_2Cl_2/TFA afforded 1-benzyl-1,2,3,4-tetrahydro-β-carboline[25] (**31**, 14%) and a diphenyl analogue of **30** (i.e., **32**) as the major product (22%) (Fig. 2). Similarity in ^{1}H and ^{13}C chemical shifts observed for **32** and **30**, in addition to scalar and dipolar couplings observed in 2D data secured the structure of **32**.

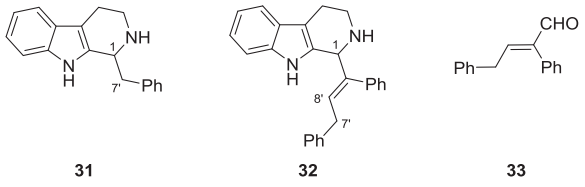
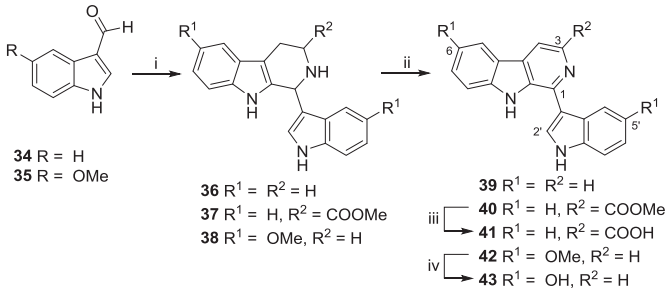


Fig. 2. Structures of **31**, **32** and **33**.

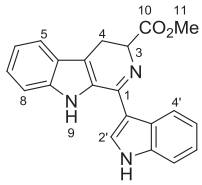
In an effort to optimise the yield of formation of **32**, (*E*)-2,4-diphenylbut-2-enal (**33**)[26] was prepared and reacted with tryptamine using the standard reaction conditions, affording **32** in 30% yield. The formation of **30** and **32** is somewhat at odds with a previous report that reaction of tryptamine with propionaldehyde in CH_2Cl_2/TFA affords no ring closure and a product derived from homo-aldol condensation and imine formation.[27] A proposed route to the formation of **32**, via an enamine-mediated aldol condensation, is presented in Scheme S1.

To complete the SAR study, a series of decarbonylated analogues modelled on the ascidian metabolite eudistomin U (**39**)[28,29] were also synthesised via a Pictet–Spengler reaction between the appropriate tryptamine or tryptophan and either indole-3-carboxaldehyde (**34**) or the 5-methoxy analogue **35** (Scheme 5). It was found that harsher reaction conditions were essential to drive these particular reactions, with initial imine formation requiring heating at reflux in toluene or MeOH, before solvent removal and addition of CH_2Cl_2/TFA to achieve ring closure. In this manner, the reaction of tryptamine with indole-3-carboxaldehyde afforded 1,2,3,4-tetrahydro-β-carboline **36** (36%) and subsequent oxidation with DDQ in THF gave eudistomin U (**39**, 40%) as previously reported by Massiot et al.[29] Application of similar methodology using L-tryptophan methyl ester or 5-methoxytryptamine as the amine component with either **34** or **35** afforded 1,2,3,4-tetrahydro-β-carboline **37** and **38**, and upon subjecting to oxidation gave ester **40** and methylether **42**. This was followed by deprotection steps to



Scheme 5. Synthesis of eudistomin U (**39**) and analogues. Reagents and conditions: (i) **13**, **14** or **15**, toluene or MeOH reflux, 1–72 h, then CH_2Cl_2, TFA, rt, 16–24 h, 36–76%; (ii) DDQ, THF or CH_2Cl_2, rt, 50 min–24 h, 24–40%; (iii) LiOH, THF/H_2O (3:1), reflux, 13 h, 96%; (iv) BBr_3, CH_2Cl_2, N_2, −78 °C, 2 h, then rt, 2 h, 31%.

obtain acid **41** and phenol **43** (Scheme 5). In the case of DDQ oxidation of 1,2,3,4-tetrahydro-β-carboline **37**, a 3,4-dihydro-β-carboline reaction intermediate (**44**) was also isolated from the product mixture (Fig. 3).



44

Fig. 3. Structure of 3,4-dihydro-β-carboline reaction intermediate (**44**).

2.2. Biological activities

Most of the compounds were assayed for anti-phospholipase A_2 activity, for antimalarial activity against a chloroquine-resistant strain of *P. falciparum*, for cytotoxicity against a panel of human cancer cell lines at the NCI and for antioxidant activity (Table 2).

Table 2
Biological results of compounds tested for anti-phospholipase A_2 activity, for antimalarial activity against a chloroquine-resistant strain of *Plasmodium falciparum*, for cytotoxicity against human tumour cell line (COLO 205) at the NCI and for antioxidant activity

Compound number	PLA_2 IC_{50} (μM)[a]	*Pf* (FcB1) IC_{50} (μM)[b]	COLO 205[c] Mean cell growth (%)	$ORAC_{FL}$[d]
3	>1166	1.3±0.2	79.2	6.2±1.4
4	>1286	>32*	88.6	
5	171±6	>28*	93.4	
10	>1471	>37*	86.5	
11	>1550	32.2±1.6	91.6	
18	320±30	9.6±1.6	96.3	
19	>1114	17.2±0.6	95.0	
21	>1084	23.3±0.7	97.8	
22	>1078	1.0±0.4	97.6	
29	>998	8.5±3.1	76.7	
30	>622	>16*	32.3	
32	nt[e]	nt	53.2	
36	958±41	5.1±0.4	87.8	
37	>930	13.6±8.4	98.6	
38	494±35	8.0±1.8	85.3	
39	>1413	14.4±4.9	67.9	
40	>1173	>29*	73.1	
41	131±9	>31*	97.1	
42	>657	4.7±1.3	26.2	
43	929±10	11.0±1.4	96.4	5.7±0.9
44	239±10	>29*	65.6	

[a] *Apis mellifera* bee venom PLA_2 IC_{50} values are presented as the mean±SEM (n=2). Manoalide was used as a positive control (IC_{50} 0.5±0.05 μM).[30]

[b] *Plasmodium falciparum* IC_{50} values are presented as the mean±SEM (n=4), except for values marked with an asterisk for which n = 2. Chloroquine was the positive control (IC_{50}=61.8±6.2 nM).[30]

[c] Details of the testing of compounds for antitumour activity at the NCI/NIH are available online.[32]

[d] The ORAC assay was only carried for compounds with a positive result in the qualitative DPPH assay. Vitamin C was used as a positive control ($ORAC_{FL}$ value 0.48±0.19).[33]

[e] nt: not tested.

2.2.1. Anti-phospholipase A_2 activity. Hyrtiosulawesine (**3**) has previously been reported to inhibit *Crotalus adamentus* (snake) venom PLA_2 with IC_{50} 14 μM.[11] In the present study,[30] no activity was observed for the natural product against bee venom (*Apis mellifera*) enzyme (Table 2, entry 1). Most of the remaining test compounds were also inactive, with the two most active compounds, carboxylic acids pityriacitrin B (**5**) and eudistomin U analogue **41** being considered weak inhibitors (IC_{50} 171 μM and 131 μM, respectively).

2.2.2. Antimalarial activity. Using previously reported protocols,[31] the library was evaluated for antimalarial activity against a chloroquine-resistant strain (FcB1) of *P. falciparum* (Table 2). In the case of fully oxidised β-carbolines, hyrtiosulawesine (**3**) was found to be moderately active (IC_{50} 1.3 μM) with the methylated synthetic precursor **22** (IC_{50} 1.0 μM) and the corresponding decarbonyl eudistomin U analogues **42** (IC_{50} 4.7 μM) and **43** (IC_{50} 11.0 μM) also exhibiting activity. The data indicates that more enhanced activity is observed for C-5 and C-6′ hydroxylated or methoxylated analogues (cf. pityriacitrin (**4**), IC_{50} >32 μM), and that C-3 substitution, as in **21** (IC_{50} 23.3 μM), **5** (IC_{50} >28 μM), **40** (IC_{50} >29 μM) and **41** (IC_{50} >31 μM), is detrimental to antimalarial activity. The bioassay results observed for 1,2,3,4-tetrahydro-β-carboline analogues suggest a different structure–antimalarial relationship. Amongst precursors to pityriacitrin, pityriacitrin B, hyrtiosulawesine and eudistomin U tested, the 1,2,3,4-tetrahydro-β-carboline analogues (**18**, **19**, **29** and **36**) all exhibited either comparable or enhanced antimalarial activity versus the corresponding fully aromatic β-carboline structure.

2.2.3. Cytotoxic activity. The library of analogues was also evaluated for cytotoxicity by the NCI in their in vitro disease-oriented primary antitumour screen (Table 2). The preliminary one-dose (10 μM) testing regimen at the NCI[32] identified that most of the compounds were relatively inactive, with mean cell growth close to +100%. Three analogues, β-carboline **42** and 1,2,3,4-tetrahydro-β-carbolines **30** and **32** were identified as exhibiting some measure of cytotoxic activity, with subpanel specificities towards leukaemia and ovarian cancer (for **42**) and colon cancer (COLO 205 and HCC-2998) cell lines for both **30** and **32** (see Supplementary data). Although less active, **29** exhibited similar colon cancer subpanel specificity to that observed for **30** (data not shown). Further 5-dose testing of **42** and **30** established modest antileukaemic activity of **42** towards the HL-60(TB) cell line (LC_{50} 4.2 μM), while **30** exhibited relatively specific antiproliferative activity towards the COLO 205 cell line with LC_{50} 2.7 μM. The selective anti-colon tumour cell line activity observed for **30** and **32** is particularly exciting, warranting further research.

2.2.4. Antioxidant activity. Evaluation of the compounds in a qualitative DPPH TLC assay[33] identified two, hyrtiosulawesine (**3**) and **43** with antioxidant properties. Their antioxidant activity were subsequently measured in a quantitative ORAC assay[33] against ascorbic acid. The relative ORAC values were expressed as Trolox equivalents with both compounds displaying around 6-fold more potent antioxidant activity than Trolox (ORAC value of 6.23 and 5.66, respectively). In the same assay, both compounds displayed significant activity over vitamin C (positive control, ORAC value of 0.48). The antioxidant activity displayed here could be attributed to the presence of the phenolic hydroxyl group; in contrast, the carbonyl group does not seem to be essential for antioxidant activity.

2.2.5. Conclusions. In summary, we have reported the use of the Pictet–Spengler reaction between substituted tryptamines and indole-3-acetaldehyde derivatives to gain entry to the bioactive 1-acylindole natural products pityriacitrin, pityriacitrin B and hyrtiosulawesine. We were unfortunately unable to realise one of our original aims of specific oxidation of the C-8′-methylene-1,2,3,4-tetrahydro-β-carboline intermediates to enable evaluation of the influence of the oxo group on observed bioactivity. While poor activity was observed towards the phospholipase A_2 target enzyme, pronounced activity was observed towards a drug resistant strain of *P. falciparum*, identifying *O*-methyl or methoxylated

analogues of the marine natural products hyrtiosulawesine and eudistomin U as new leads for antimalarial drug development. Although β-carboline alkaloids are well known to exhibit DNA intercalation properties and hence whole cell cytotoxicity, the library of analogues were typically only weakly cytotoxic towards a panel of human tumour cell lines. The discovery however of selective cytotoxicity for 1,2,3,4-β-carbolines **30** and **32** against COLO 205 and HCC-2998 colon tumour cell lines is particularly encouraging and will be the focus of future studies.

3. Experimental

3.1. General experimental procedures

Details of instrumental methods and general experimental procedures[34] have been reported previously. NMR chemical shifts were calibrated to residual solvent signals (DMSO-d_6: δ_H 2.50, δ_C 39.52; CD_3OD: δ_H 3.31, δ_C 49.00; CD_3CN: δ_H 1.94, δ_C 1.32, 118.26; $CDCl_3$: δ_H 7.26, δ_C 77.16)[35] and structural assignments were aided by COSY, edited-HSQC and HMBC (optimised for $^xJ_{CH}$=8.33 Hz) experiments.

tert-Butyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (**16**),[36] L-tryptophan methyl ester·HCl (**14**),[37] eudistomin U (**39**),[29] 5-methoxy-1*H*-indole-3-carboxaldehyde (**35**)[38] and 1-(1*H*-indol-3-yl)-1,2,3,4-tetrahydro-β-carboline (**36**),[29] were prepared by literature methods.

*3.1.1. Hyrtiosulawesine (**3**).*[6,16] A solution of 6,5′-dimethyl hyrtiosulawesine (**22**) (4 mg, 0.01 mmol) in CH_2Cl_2 (3 mL) cooled to −78 °C and was added BBr_3 (305 μL, 3.23 mmol) under N_2. The reaction was allowed to stir at −78 °C for 40 min then warmed to rt with stirring under N_2 continued for 3 h. MeOH (4 mL) was added to quench the remaining BBr_3. Solvent was removed under pressure to give a crude material, which was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (5×30 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (40% EtOAc/*n*-hexanes) to afford **3** as a yellow solid (4.0 mg, 87% yield). Mp 300 °C (lit.[16] 362–363 °C); R_f (50% EtOAc/*n*-hexanes) 0.26; IR ν_{max} (ATR) 3402, 3201, 1603, 1493, 1132, 739 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 8.88 (1H, s, H-2′), 8.42 (1H, d, *J*=5.0 Hz, H-3), 8.14 (1H, d, *J*=5.0 Hz, H-4), 8.02 (1H, d, *J*=2.4 Hz, H-4′), 7.57 (1H, d, *J*=2.4 Hz, H-5), 7.54 (1H, d, *J*=8.8 Hz, H-8), 7.32 (1H, d, *J*=8.8 Hz, H-7′), 7.14 (1H, dd, *J*=8.8, 2.4 Hz, H-7), 6.82 (1H, dd, *J*=8.8, 2.4 Hz, H-6′); ^{13}C NMR (CD_3OD, 100 MHz) δ 189.9 (C-8′), 154.4 (C-5′), 152.6 (C-6), 140.3 (C-1), 139.1 (C-2′), 137.5 (C-9a), 137.4 (C-8a), 137.3 (C-3), 132.5 (C-4a), 132.3 (C-7′a), 129.8 (C-3′a), 122.6 (C-4b), 119.8 (C-7), 118.5 (C-4), 116.0 (C-3′), 113.9 (C-8), 113.8 (C-6′), 113.3 (C-7′), 108.0 (C-4′), 106.8 (C-5); (+)-HRESIMS *m*/*z* 344.1037 $[M+H]^+$ (calcd for $C_{20}H_{14}N_3O_3$, 344.1030). The spectroscopic data were consistent with literature values.[6,16]

*3.1.2. Pityriacitrin (**4**).*[9,17] To a solution of 1-(3-methyl-1*H*-indole)-1,2,3,4-tetrahydro-β-carboline (**18**) (35 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was added H_2O (100 μL). DDQ (132 mg, 0.58 mmol) was added to the reaction mixture with vigorous stirring. The reaction was allowed to stir under N_2 for 45 min. The reaction mixture was poured over 1 M KOH solution (50 mL) and extracted with CH_2Cl_2 (40 mL). The organic fraction was washed once more with 1 M KOH solution (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude reaction product was purified by silica gel column chromatography (CH_2Cl_2) to afford **4** as a bright yellow solid (5.5 mg, 15% yield). Mp 241–242 °C (lit.[9] 227–230 °C); R_f (CH_2Cl_2) 0.18; IR ν_{max} (ATR) 3418, 3226, 2923, 1598, 1510, 1492, 1468 cm^{-1}; ^1H NMR (CD_3CN, 400 MHz) δ 10.97 (1H, br s, NH-9), 10.09 (1H, br d, *J*=3.1 Hz, NH-1′), 9.40 (1H, d, *J*=3.1 Hz, H-2′), 8.62–8.60 (1H, m, H-4′), 8.58 (1H, d, *J*=4.8 Hz, H-3), 8.28-8.25 (2H, m, H-4 and H-5), 7.78 (1H, d, *J*=7.8 Hz, H-8), 7.62 (1H, ddd, *J*=7.8, 7.8, 1.0 Hz, H-7), 7.60–7.56 (1H, m, H-7′), 7.36–7.29 (3H, m, H-6, H-5′ and H-6′); ^{13}C NMR (CD_3CN, 100 MHz) δ 189.4 (C-8′), 142.4 (C-8a), 139.4 (C-1), 138.7 (C-2′), 138.4 (C-3), 137.0 (C-9a), 136.9 (C-7′a), 132.1 (C-4a), 129.9 (C-7), 128.4 (C-3′a), 124.2 (C-6′), 123.3 (C-5′), 123.1 (C-4′), 122.6 (C-5), 121.7 (C-4b), 121.2 (C-6), 118.8 (C-4), 115.8 (C-3′), 113.4 (C-8), 112.9 (C-7′); (+)-HRESIMS *m*/*z* 312.1135 $[M+H]^+$ (calcd for $C_{20}H_{14}N_3O$, 312.1131). The spectroscopic data were consistent with literature values.[9,17]

*3.1.3. Pityriacitrin B (**5**).*[8,17] Pityriacitrin B methyl ester (**21**) (5.0 mg, 0.001 mmol) was dissolved in THF (1.5 mL). LiOH (6.0 mg, 0.012 mmol) was dissolved into H_2O (0.5 mL) and added to the reaction mixture. The reaction mixture was heated to reflux under N_2 for 12 h. The pH of the cooled reaction mixture was adjusted with 1 M HCl solution until yellow solids appeared. The yellow solids were filtered and washed with H_2O (2.5 mL), MeOH (0.5 mL) and ether (2.5 mL) successively in 0.5 mL portions. The yellow solids were dried under vacuum to yield pityriacitrin B (**5**) (4.0 mg, 83% yield). Mp 285 °C (lit.[8] >300 °C); R_f (5% MeOH/CH_2Cl_2) 0.30; IR ν_{max} (ATR) 3226, 2923, 1702, 1596, 733 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 9.64 (1H, s, H-2′), 9.02 (1H, s, H-4), 8.63 (1H, m, H-4′), 8.30 (1H, d, *J*=7.8 Hz, H-5), 7.76 (1H, d, *J*=7.8 Hz, H-8), 7.62 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.52–7.49 (1H, m, H-7′), 7.36 (1H, dd, *J*=7.8, 7.8 Hz, H-6), 7.28–7.26 (2H, m, H-5′ and H-6′); ^{13}C NMR (CD_3OD, 100 MHz) δ 189.3 (C-8′), 171.4 (C-10), 143.5 (C-1 or C-3), 143.3 (C-8a), 140.4 (C-1 or C-3), 140.2 (C-2′), 138.9 (C-7′a), 137.7 (C-9a), 133.1 (C-4a), 130.2 (C-7), 128.9 (C-3′a), 124.2 (C-6′), 123.4 (C-4′), 123.2 (C-5′), 122.7 (C-5), 122.4 (C-4b), 121.8 (C-6), 120.0 (C-4), 116.2 (C-3′), 113.7 (C-8), 112.8 (C-7′); (+)-HRESIMS *m*/*z* 356.1007 $[M+H]^+$ (calcd for $C_{21}H_{14}N_3O_3$, 356.1030). The spectroscopic data were consistent with literature values.[8]

^1H NMR (DMSO-d_6, 400 MHz) δ 12.38 (1H, br s, NH-9), 12.26 (1H, br s, NH-1′), 9.75 (1H, d, *J*=2.9 Hz, H-2), 9.14 (1H, s, H-4), 8.62–8.59 (1H, m, H-4′), 8.46 (1H, d, *J*=7.8 Hz, H-5), 7.90 (1H, d, *J*=7.8 Hz, H-8), 7.64 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.58–7.55 (1H, m, H-7′), 7.36 (1H, dd, *J*=7.8, 7.8 Hz, H-6), 7.33–7.27 (2H, m, H-5′ and H-6′); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 186.4 (C-8′), 166.9 (C-10), 142.1 (C-8a), 138.5 (C-2′), 137.1 (C-1 or C-3), 136.1 (C-1 or C-3), 135.9 (C-9a or C-7′a), 135.8 (C-9a or C-7′a), 131.3 (C-4a), 129.1 (C-7), 127.3 (C-3′a), 123.0 (C-6′), 122.2 (C-5), 122.1 (C-5′), 121.7 (C-4′), 120.7 (C-6), 120.5 (C-4b), 119.8 (C-4), 114.2 (C-3′), 113.4 (C-8), 112.3 (C-7′). The spectroscopic data were consistent with literature values.[17]

*3.1.4. 1-Benzyl-3,4-dihydro-β-carboline (**9**).* To a suspension of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-phenylacetamide (**8**) (50 mg, 0.18 mmol) stirring in toluene (10 mL) was added $POCl_3$ (167 μL, 1.80 mmol). The reaction mixture was heated to reflux at 120 °C under N_2 for 30 min. After cooling to rt, the reaction mixture was poured over ice. The mixture was poured over saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (100 mL). The CH_2Cl_2 fraction was washed with H_2O (2×100 mL), dried ($MgSO_4$) and concentrated to afford **9** as the hydrochloride salt[39] (orange oil, 44 mg, 83% yield).

R_f (10% MeOH/CH_2Cl_2) 0.55; IR ν_{max} (ATR) 3027, 2827, 1628, 1555, 1275, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 11.67 (1H, br s, NH-9), 11.51 (1H, br s, NH-2), 7.60 (1H, d, *J*=8.0 Hz, H-5), 7.51 (1H, d, *J*=8.2 Hz, H-8), 7.46 (2H, d, *J*=7.3 Hz, H-2′ and H-6′), 7.38 (1H, ddd, *J*=8.0, 8.0, 0.7 Hz, H-6), 7.25–7.21 (2H, m, H-3′ and H-5′), 7.18–7.11 (2H, m, H-7 and H-4′), 4.37 (2H, s, H_2-7′), 3.86 (2H, ddd, *J*=8.7, 8.7, 2.8 Hz, H_2-3), 3.09 (2H, t, *J*=8.7 Hz, H_2-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3 (C-1), 142.4 (C-8a), 132.4 (C-1′), 129.8 (C-7), 129.6 (C-3′ and C-5′), 129.5 (C-2′ and C-6′), 128.3 (C-4′), 125.6 (C-4a), 125.4 (C-9a), 124.5 (C-4b), 122.3 (C-6), 121.5 (C-5), 114.4 (C-8), 42.7

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(C-3), 38.2 (C-7′), 19.5 (C-4); (+)-HRESIMS *m/z* 261.1392 $[M+H]^+$ (calcd for $C_{18}H_{17}N_2$, 261.1386).

*3.1.5. 1-Phenylmethanone-β-carboline (**10**),[40] 1-benzyl-β-carboline (**11**) and 1-benzyl-3,4-dihydro-β-carboline (**12**).* To a suspension of **8** (26 mg, 0.09 mmol) stirring in toluene (10 mL) was added $POCl_3$ (87 μL, 0.93 mmol). The reaction mixture was heated to reflux at 120 °C under N_2 for 30 min. After cooling to rt, the reaction mixture was poured over ice. The mixture was poured over saturated $NaHCO_3$ solution (50 mL), extracted with CH_2Cl_2 (2×50 mL), dried ($MgSO_4$) and concentrated to obtain **9**, which was dissolved into CH_2Cl_2 (10 mL). DDQ (85 mg, 0.37 mmol) was added to the reaction mixture, which was allowed to stir at rt under N_2 for 70 min. The reaction was poured into 1 M KOH solution (50 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated to obtain a brown crude material, which was immediately purified by silica gel column chromatography (CH_2Cl_2–1% MeOH/CH_2Cl_2) to afford **10** as a yellow solid (1.0 mg, 4% yield over two steps) and **11** as an orange-brown oil (6.3 mg, 26% yield over two steps).

An alternative, higher yielding route to **10** is as follows: To a solution of **9**, prepared from **8** (88 mg, 0.32 mmol) as previously described, in DMF (2 mL) was added $KMnO_4$ (105 mg, 0.66 mmol) and the reaction stirred at 0 °C for 1 h. The reaction mixture was allowed warm to rt over 30 min. The resulting mixture was diluted with water (30 mL) and extracted with DCM (3×50 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated to obtain a crude material, which was immediately purified by silica gel column chromatography (CH_2Cl_2) to afford **10** as a yellow solid (23 mg, 27% yield over two steps) and 1-benzyl-3,4-dihydro-β-carboline (**12**) as a yellow oil (12 mg, 14% yield over two steps).

Compound **10**: mp 132–133 °C (lit.[40] 135–138 °C); R_f (CH_2Cl_2) 0.71; IR ν_{max} (ATR) 3430, 3056, 1640, 1619 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.07 (1H, br s, NH-9), 8.53 (1H, d, *J*=5.0 Hz, H-3), 8.45 (1H, d, *J*=5.0 Hz, H-4), 8.33 (1H, dd, *J*=7.5, 0.8 Hz, H-5), 8.21–8.18 (2H, m, H-2′ and H-6′), 7.83 (1H, d, *J*=8.0 Hz, H-8), 7.69–7.55 (4H, m, H-7, H-3′, H-4′ and H-5′), 7.32 (1H, ddd, *J*=7.5, 7.5, 0.9 Hz, H-6); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 193.9 (C-7′), 141.7 (C-8a), 137.5 (C-1′), 137.2 (C-3), 136.3 (C-1), 135.8 (C-9a), 132.2 (C-4′), 131.0 (C-4a), 130.8 (C-2′ and C-6′), 129.0 (C-7), 127.9 (C-3′ and C-5′), 121.8 (C-5), 120.2 (C-6), 120.1 (C-4b), 118.9 (C-4), 113.0 (C-8); (+)-HRESIMS *m/z* 273.1008 $[M+H]^+$ (calcd for $C_{18}H_{13}N_2O$, 273.1022). The spectroscopic data were consistent with literature values.[40]

Compound **11**: R_f (5% MeOH/CH_2Cl_2) 0.74; IR ν_{max} (ATR) 3061, 1626, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.43 (1H, d, *J*=5.4 Hz, H-3), 8.09 (1H, d, *J*=7.9 Hz, H-5), 7.87 (1H, d, *J*=5.4 Hz, H-4), 7.48 (1H, ddd, *J*=8.3, 8.3, 0.7 Hz, H-7), 7.38–7.23 (7H, m, H-6, H-8, H-2′, H-3′, H-4′, H-5′ and H-6′), 4.55 (2H, s, H_2-7′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6 (C-1), 140.6 (C-8a), 138.1 (C-3), 137.9 (C-1′), 134.6 (C-9a), 129.9 (C-4a), 129.1 (C-3′ and C-5′), 129.0 (C-2′ and C-6′), 128.8 (C-7), 127.1 (C-4′), 121.9 (C-4b), 121.7 (C-5), 120.5 (C-6), 113.7 (C-4), 111.9 (C-8), 41.3 (C-7′); (+)-HRESIMS *m/z* 259.1235 $[M+H]^+$ (calcd for $C_{18}H_{15}N_2$, 259.1230).

Compound **12**: R_f (50% *n*-hexanes/CH_2Cl_2) 0.45; IR ν_{max} (ATR) 3439, 3056, 2926, 2831, 1655, 1538, 1189, 1173, 954, 878, 741, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.42 (1H, br s, NH-9), 8.19–8.17 (2H, m, H-2′ and H-6′), 7.63–7.58 (2H, m, H-5 and H-4′), 7.51–7.47 (2H, m, H-3′ and H-5′), 7.42 (1H, ddd, *J*=7.4, 0.8, 0.8 Hz, H-8), 7.31 (1H, ddd, *J*=7.4, 7.4, 1.0 Hz, H-7), 7.16 (1H, ddd, *J*=7.4, 7.4, 0.8 Hz, H-6), 4.20–4.15 (2H, m, H_2-3), 3.05–3.01 (2H, m, H_2-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.5 (C-7′), 156.0 (C-1), 137.1 (C-8a), 135.5 (C-1′), 133.6 (C-4′), 131.2 (C-2′ and C-6′), 128.4 (C-3′ and C-5′), 126.8 (C-9a), 125.3 (C-7), 124.9 (C-4b), 120.5 (C-6), 120.1 (C-5), 118.2 (C-4a), 112.4 (C-8), 49.4 (C-3), 19.2 (C-4); (+)-HRESIMS *m/z* 275.1182 $[M+H]^+$ (calcd for $C_{18}H_{15}N_2O$, 275.1179).

*3.1.6. tert-Butyl-5-methoxy-3-(2-oxoethyl)-1H-indole-1-carboxylate (**17**).* IBX (384 mg, 1.37 mmol) was dissolved in DMSO (1.0 mL) with stirring at rt under N_2 for 50 min. *tert*-Butyl 3-(2-hydroxyethyl)-5-methoxy-1*H*-indole-1-carboxylate (**28**) (200 mg, 0.69 mmol) in DMSO (1.6 mL) was added to the reaction mixture and allowed to stir for 2 h at rt under N_2. H_2O (10 mL) was added to the reaction, and the solids were removed by filtration and washed with CH_2Cl_2 (50 mL). The filtrate was transferred into a separating funnel and washed with H_2O (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude material was purified by silica gel column chromatography (CH_2Cl_2) to afford **17** as an unstable pale yellow oil (153 mg, 81% yield). R_f (CH_2Cl_2) 0.60; IR ν_{max} (ATR) 2978, 1722, 1376, 1076, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.77 (1H, s, H-9), 8.03 (1H, br d, *J*=7.3 Hz, H-7), 7.55 (1H, s, H-2), 6.96 (1H, d, *J*=7.3 Hz, H-6), 6.88 (1H, s, H-4), 3.85 (3H, s, OMe-14), 3.73 (2H, s, H_2-8), 1.66 (9H, s, $3H_3$-13); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5 (C-9), 156.1 (C-5), 149.5 (C-10), 131.0 (C-3a), 130.2 (C-7a), 125.4 (C-2), 116.2 (C-7), 113.5 (C-6), 110.7 (C-3), 101.4 (C-4), 83.7 (C-12), 55.7 (C-14), 40.1 (C-8), 28.2 (C-13).

*3.1.7. 1-(3-Methyl-1H-indole)-1,2,3,4-tetrahydro-β-carboline (**18**).[23]* *tert*-Butyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (**16**) (83 mg, 0.32 mmol) was weighed into a round bottom flask as a neat oil. Tryptamine (**13**) (31 mg, 0.19 mmol) and tryptamine·HCl (38 mg, 0.19 mmol) were weighed into a separate vial. 5% HOAc solution (20 mL) was added to the tryptamine mixture. This mixture was transferred to the round bottom flask as a suspension and set to reflux at 100 °C under N_2 for 2 h with vigorous stirring. The reaction mixture was allowed to cool to rt, then to 0 °C with stirring for another 30 min. Water (30 mL) was added to the reaction mixture, and extracted with EtOAc (3×50 mL). The organic solvent fractions were combined, dried ($MgSO_4$) and solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (6–10% MeOH/CH_2Cl_2) to afford **18** as a brown-orange oil (36 mg, 37% yield). R_f (10% MeOH/CH_2Cl_2) 0.44; IR ν_{max} (ATR) 3399, 2915, 1730, 1560, 1452, 1151, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (1H, br s, NH-1′), 7.94 (1H, br s, NH-9), 7.62 (1H, d, *J*=7.6 Hz, H-4′), 7.45 (1H, d, *J*=7.6 Hz, H-5), 7.36 (1H, d, *J*=8.4 Hz, H-7′), 7.22–7.17 (2H, m, H-8 and H-6′), 7.12–7.05 (3H, m, H-6, H-7 and H-5′), 6.96 (1H, s, H-2′), 4.58 (1H, t, *J*=6.8 Hz, H-1), 3.37–3.23 (3H, m, H_2-3A and H_2-8′), 3.05–2.98 (1H, m, H_2-3B), 2.84–2.70 (2H, m, H_2-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.5 (C-7′a), 135.8 (C-8a), 134.8 (C-9a), 127.4 (C-3a), 127.1 (C-4b), 123.3 (C-2′), 122.6 (C-6′), 121.8 (C-7), 119.9 (C-5′), 119.5 (C-6), 119.0 (C-4′), 118.3 (C-5), 111.6 (C-7′), 111.4 (C-3′), 111.0 (C-8), 108.9 (C-4a), 52.8 (C-1), 42.2 (C-3), 30.7 (C-8′), 21.8 (C-4); (+)-HRESIMS *m/z* 302.1637 $[M+H]^+$ (calcd for $C_{20}H_{20}N_3$, 302.1652). The spectroscopic data were consistent with literature values.[23]

*3.1.8. 1-(1H-Indol-3-yl)methyl-3-methylcarboxylate-1,2,3,4-tetrahydro-β-carboline (**19**).* L-Tryptophan methyl ester·HCl (**14**) (57 mg, 0.22 mmol) and *tert*-butyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (**16**) (58 mg, 0.22 mmol) were dissolved in anhydrous MeOH (4 mL) and allowed to stir under N_2 at rt for 3 h. MeOH was removed before redissolving the crude material into AcOH/H_2O (1:10) (11 mL) and set to stir under N_2 at 50 °C for 1.5 h. The reaction mixture was then heated to reflux for 4 h. After cooling to rt, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3×50 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (2% MeOH/CH_2Cl_2) to afford **19** [a mixture of diastereomers (1:0.9)] as a yellow oil (35 mg, 44% yield). R_f (5% MeOH/CH_2Cl_2) 0.28; IR ν_{max} (ATR) 3403, 2918, 1728, 1455, 738 cm^{-1}; Major diastereomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (1H, br s, NH-1′), 7.75 (1H, br s, NH-9), 7.65 (1H, d, *J*=8.0 Hz, H-5), 7.51–7.46 (1H, m, H-6′), 7.39 (1H, d, *J*=3.5 Hz,

H_2-8), 7.26–7.21 (1H, m, H-7), 7.18–7.06 (4H, m, H-6, H-4′, H-5′ and H-7′), 7.06 (1H, d, *J*=2.4 Hz, H-2′), 4.61 (1H, tt, *J*=6.7, 2.0 Hz, H-1), 3.83–3.80 (1H, m, H-3), 3.79 (3H, s, OMe-11), 3.32–3.21 (2H, m, H_2-8′), 3.19–3.12 (1H, m, H_2-4A), 2.86 (1H, ddd, *J*=15.0, 11.4, 2.5 Hz, H_2-4B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7 (C-10), 136.6 (C-8a), 135.9 (C-7′a), 135.4 (C-9a), 127.3 (C-3′a), 127.0 (C-4b), 123.1 (C-2′), 122.7 (C-7), 121.9 (C-4′), 119.9 (C-6), 119.7 (C-5′), 119.0 (C-5), 118.2 (C-6′), 111.8 (C-3′), 111.6 (C-8), 111.0 (C-7′), 108.3 (C-4a), 56.7 (C-3), 53.0 (C-1), 52.4 (C-11), 31.5 (C-8′), 26.1 (C-4); Minor diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (1H, br s, NH-1′), 7.63 (1H, d, *J*=8.0 Hz, H-5), 7.51–7.46 (2H, m, NH-9 and H-6′), 7.41 (1H, d, *J*=3.5 Hz, H-8), 7.26–7.21 (1H, m, H-7), 7.18–7.06 (4H, m, H-6, H-4′, H-5′ and H-7′), 6.99 (1H, d, *J*=2.3 Hz, H-2′), 4.69 (1H, t, *J*=7.1 Hz, H-1), 4.07 (1H, dd, *J*=7.2, 7.2 Hz, H-3), 3.72 (3H, s, OMe-11), 3.32–3.21 (2H, m, H_2-8′), 3.19–3.12 (1H, m, H_2-4A), 3.03 (1H, ddd, *J*=15.3, 7.2, 1.3 Hz, H_2-4B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2 (C-10), 136.5 (C-8a), 135.8 (C-7′a), 135.4 (C-9a), 127.4 (C-3′a), 127.0 (C-4b), 123.0 (C-2′), 122.6 (C-7), 121.8 (C-4′), 119.9 (C-6), 119.5 (C-5′), 119.0 (C-5), 118.2 (C-6′), 112.3 (C-3′), 111.5 (C-8), 110.9 (C-7′), 107.2 (C-4a), 52.9 (C-3), 52.3 (C-11), 50.8 (C-1), 32.2 (C-8′), 25.1 (C-4); (+)-HRESIMS *m*/*z* 360.1694 $[M+H]^+$ (calcd for $C_{22}H_{22}N_3O_2$, 360.1707).

*3.1.9. 1-(5-Methoxy-1H-indol-3-yl)methyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (**20**).* Aldehyde (**17**) (49 mg, 0.17 mmol) and 5-methoxytryptamine hydrochloride (46 mg, 0.20 mmol) were weighed into a round bottom flask. Acetic acid (0.5 mL) and H_2O (10 mL) was added and the reaction was purged with N_2. The reaction mixture was set to reflux with vigorous stirring for 5 h. Reaction mixture was allowed to cool to rt, and then to 0 °C with stirring for another 30 min. The reaction mixture was slowly added to a saturated solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3×30 mL). The organic solvent fractions were combined, dried ($MgSO_4$) and solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (4–10% MeOH/CH_2Cl_2) to afford **20** as an orange-brown oil (47 mg, 77% yield). R_f (10% MeOH/CH_2Cl_2) 0.48; IR ν_{max} (ATR) 3402, 1624, 1483, 1212 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (1H, br s, NH-1′), 7.60 (1H, br s, NH-9), 7.28 (1H, d, *J*=8.8 Hz, H-7′), 7.08 (1H, d, *J*=8.8 Hz, H-8), 7.01 (1H, d, *J*=2.4 Hz, H-4′), 6.99 (1H, d, *J*=2.2 Hz, H-2′), 6.93 (1H, d, *J*=2.4 Hz, H-5), 6.89 (1H, dd, *J*=8.8, 2.4 Hz, H-6′), 6.77 (1H, dd, *J*=8.8, 2.4 Hz, H-7), 4.49 (1H, t, *J*=6.8 Hz, H-1), 3.84 (3H, s, OMe-10), 3.77 (3H, s, OMe-8′), 3.37 (1H, dt, *J*=12.4, 4.3 Hz, H_2-3A), 3.27–3.16 (2H, m, H_2-9′), 3.08–3.01 (1H, m, H_2-3B), 2.78–2.66 (2H, m, H_2-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4 (C-5′), 154.2 (C-6), 137.1 (C-9a), 131.6 (C-7′a), 130.8 (C-8a), 127.9 (C-3′a or C-4b), 127.8 (C-3′a or C-4b), 123.8 (C-2′), 113.0 (C-6′), 112.3 (C-7′), 111.9 (C-3′), 111.5 (C-8), 111.4 (C-7), 109.3 (C-4a), 100.7 (C-4′), 100.5 (C-5), 56.1 (C-10), 56.0 (C-8′), 52.9 (C-1), 42.9 (C-3), 31.4 (C-9′), 22.8 (C-4); (+)-HRESIMS *m*/*z* 362.1860 $[M+H]^+$ (calcd for $C_{22}H_{24}N_3O_2$, 362.1863).

*3.1.10. Pityriacitrin B methyl ester (**21**).*[17] To a solution of 1-(1*H*-indol-3-yl)methyl-3-methylcarboxylate-1,2,3,4-tetrahydro-β-carboline (**19**) (17 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) with vigorous stirring was added H_2O (50 μL). DDQ (43 mg, 0.19 mmol) was added and the reaction mixture and allowed to stir under N_2 for 30 min. The reaction mixture was poured over 1 M KOH solution (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried ($MgSO_4$), concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2) to afford **21** as a yellow solid (2.0 mg, 11% yield). Mp 259–260 °C (lit.[17] 251–252 °C); R_f (2% MeOH/CH_2Cl_2) 0.68; IR ν_{max} (ATR) 3356, 3336, 1704, 1422, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.43 (1H, br s, NH-9), 12.25 (1H, br s, NH-1′), 9.66 (1H, d, *J*=2.0 Hz, H-2′), 9.15 (1H, s, H-4), 8.62–8.58 (1H, m, H-4′), 8.48 (1H, d, *J*=7.9 Hz, H-5), 7.90 (1H, d, *J*=7.9 Hz, H-8), 7.65 (1H, ddd, *J*=7.9, 7.9, 1.0 Hz, H-7), 7.61–7.56 (1H, m, H-7′), 7.36 (1H, dd, *J*=7.9, 7.9 Hz, H-6), 7.33–7.27 (2H, m, H-5′ and H-6′), 4.03 (3H, s, OMe-11); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 186.3 (C-8′), 165.6 (C-10), 142.1 (C-8a), 138.4 (C-2′), 137.3 (C-1), 136.0 (C-9a), 135.9 (C-7′a), 134.8 (C-3), 131.3 (C-4a), 129.2 (C-7), 127.3 (C-3′a), 123.0 (C-6′), 122.2 (C-5′), 122.1 (C-5), 121.7 (C-4′), 120.8 (C-6), 120.5 (C-4b), 119.9 (C-4), 114.1 (C-3′), 113.5 (C-8), 112.3 (C-7′), 52.4 (C-11); (+)-HRESIMS *m*/*z* 370.1187 $[M+H]^+$ (calcd for $C_{22}H_{16}N_3O_3$, 370.1186). The spectroscopic data were consistent with literature values.[17]

*3.1.11. 6,5′-Dimethyl hyrtiosulawesine (**22**).*[16] To a solution of 1-(5-methoxy-1*H*-indol-3-yl)methyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (**20**) (29 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) was added H_2O (50 μL). DDQ (91 mg, 0.40 mmol) was added to the reaction mixture with vigorous stirring. The reaction was allowed to stir under N_2 for 1.5 h. The reaction mixture was poured into 1 M KOH (50 mL) and extracted with additional CH_2Cl_2 (30 mL). The organic fraction was washed with 1 M KOH solution (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude reaction product was purified by silica gel column chromatography (CH_2Cl_2) to afford **22** as a bright yellow solid (11.0 mg, 37% yield). Mp 220–221 °C (lit.[16] 220–221 °C); R_f (2% MeOH/CH_2Cl_2) 0.45; IR ν_{max} (ATR) 3568, 3424, 3157, 1603, 1491 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.99 (1H, s, NH-1′), 11.86 (1H, s, NH-9), 9.24 (1H, d, *J*=3.2 Hz, H-2′), 8.52 (1H, d, *J*=4.8 Hz, H-3), 8.37 (1H, d, *J*=4.8 Hz, H-4), 8.11 (1H, d, *J*=2.3 Hz, H-4′), 7.85 (1H, d, *J*=2.2 Hz, H-5), 7.75 (1H, d, *J*=8.8 Hz, H-8), 7.46 (1H, d, *J*=8.7 Hz, H-7′), 7.23 (1H, dd, *J*=8.8, 2.2 Hz, H-7), 6.91 (1H, dd, *J*=8.7, 2.3 Hz, H-6′), 3.88 (3H, s, OMe-10), 3.86 (3H, s, OMe-8′); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 187.3 (C-9′), 155.7 (C-5′), 153.8 (C-6), 138.5 (C-1), 137.9 (C-2′), 136.5 (C-8a), 136.3 (C-3), 135.5 (C-9a), 130.7 (C-4a and C-7′a), 128.1 (C-3′a), 120.4 (C-4b), 118.6 (C-7), 118.0 (C-4), 114.2 (C-3′), 113.9 (C-8), 113.0 (C-7′), 112.8 (C-6′), 103.5 (C-5), 103.4 (C-4′), 55.7 (C-10), 55.3 (C-8′); (+)-HRESIMS *m*/*z* 372.1341 $[M+H]^+$ (calcd for $C_{22}H_{18}N_3O_3$, 372.1343). The spectroscopic data were consistent with literature values.[16]

*3.1.12. 1-(3-Methanone-1H-indole)-3,4-dihydro-β-carboline (**23**).* To a solution of 1,2,3,4-tetrahydro-β-carboline **18** (24 mg, 0.08 mmol) in DMF (1 mL), which was cooled to 0 °C, was added $KMnO_4$ (18 mg, 0.11 mmol). The reaction mixture was stirred at this temperature for 1 h, and warmed to rt in another 2 h. The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (2×20 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (CH_2Cl_2–5% EtOAc/CH_2Cl_2) to afford **23** as a bright yellow solid (7.0 mg, 28%) and **4** in trace amounts.

Mp 203–204 °C; R_f (10% MeOH/CH_2Cl_2) 0.81; IR ν_{max} (ATR) 3458, 3044, 2924, 2830, 1626, 1609, 1581, 1497, 1442, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.16 (1H, br s, NH-1′), 11.21 (1H, br s, NH-9), 8.53 (1H, s, H-2′), 8.41–8.38 (1H, m, H-4′), 7.59 (1H, d, *J*=7.8 Hz, H-5), 7.57–7.55 (1H, m, H-7′), 7.53 (1H, d, *J*=7.8 Hz, H-8), 7.31–7.26 (2H, m, H-5′ and H-6′), 7.20 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.05 (1H, dd, *J*=7.8, 7.8 Hz, H-6), 4.04 (2H, t, *J*=8.6 Hz, H_2-3), 2.94 (2H, t, *J*=8.6 Hz, H_2-4); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 186.6 (C-8′), 157.5 (C-1), 138.3 (C-2′), 137.2 (C-8a), 136.5 (C-7′a), 126.3 (C-9a and C-3′a), 124.3 (C-4b), 123.9 (C-7), 123.2 (C-6′), 122.3 (C-5′), 121.4 (C-4′), 119.4 (C-5 and C-6), 116.3 (C-4a), 113.3 (C-3′), 113.1 (C-8), 112.5 (C-7′), 48.2 (C-3), 18.6 (C-4); HRESIMS *m*/*z* 314.1293 $[M+H]^+$ (calcd for $C_{20}H_{16}N_3O$, 314.1288).

*3.1.13. 2-(5-Methoxy-1H-indol-3-yl)ethanol (**25**).* To a solution of 5-methoxyindole (**24**) (1.00 g, 6.79 mmol) in ether (20 mL) at 0 °C was added oxalyl chloride (690 μL, 8.15 mmol) in a dropwise manner over 5 min. The reaction mixture was allowed to stir at 0 °C for 1 h and then allowed to warm to rt in another 1 h with stirring. The orange precipitate was filtered and washed with cold diethyl ether (100 mL). The product was dried in vacuo to yield a fine orange

powder (1.40 g, 87% yield), which was used in the next step without further purification.

To lithium aluminium hydride (997 mg, 26.28 mmol) in a round bottom flask under N_2 cooled to 0 °C was slowly added THF (30 mL) with gentle stirring. 2-(5-Methoxy-1*H*-indol-3-yl)-2-oxoacetyl chloride (1.39 g, 5.84 mmol) in THF (30 mL) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was then heated to reflux for 5 h. The reaction mixture was cooled to 0 °C before slow addition of EtOAc to quench any remaining lithium aluminium hydride. When fizzing had ceased, a solution of sodium potassium tartrate tetrahydrate (9.00 g, 31.90 mmol) in H_2O (100 mL) was added to the reaction mixture. EtOAc (100 mL) was added to extract the organic material and the mixture was allowed to stir slowly at rt until a clear layer (EtOAc) appeared on top. The EtOAc layer was washed with H_2O (3×100 mL), dried ($MgSO_4$) and concentrated in vacuo to give a green oil. The crude reaction product was purified by silica gel column chromatography (30% EtOAc/*n*-hexanes) to afford **25** as a pale yellow oil (970 mg, 87% yield). R_f (50% EtOAc/*n*-hexanes) 0.37; IR ν_{max} (ATR) 3406, 3330, 2937, 1484, 1211, 1027, 793 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (1H, br s, NH-1), 7.21 (1H, d, *J*=8.8 Hz, H-7), 7.04 (1H, d, *J*=2.4 Hz, H-4), 6.99 (1H, d, *J*=2.4 Hz, H-2), 6.86 (1H, dd, *J*=8.8, 2.4 Hz, H-6), 3.88 (2H, td, *J*=6.1, 5.1 Hz, H_2-9), 3.84 (3H, s, OMe-10), 2.98 (2H, t, *J*=6.1 Hz, H_2-8), 1.77 (1H, br t, *J*=5.1 Hz, OH-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.1 (C-5), 131.7 (C-7a), 127.9 (C-3a), 123.5 (C-2), 112.4 (C-6), 112.1 (C-7), 112.0 (C-3), 100.8 (C-4), 62.7 (C-9), 56.1 (C-10), 28.8 (C-8); (+)-HRESIMS *m*/*z* 192.1019 $[M+H]^+$ (calcd for $C_{11}H_{14}NO_2$, 192.1019). The ^1H NMR data were in agreement with literature values.[41]

*3.1.14. 2-(5-Methoxy-1H-indol-3-yl)ethyl acetate (**26**).* To a solution of 2-(5-methoxy-1*H*-indol-3-yl)ethanol (**25**) (970 mg, 5.07 mmol) dissolved in pyridine (10 mL) was added acetic anhydride (956 μL, 10.14 mmol) in a dropwise manner. The reaction mixture was purged with N_2 and allowed to stir at rt overnight (16 h). The reaction mixture was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic fraction was washed with H_2O (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo. The remaining pyridine was removed under vacuum to give a pale green crude oil. The product was purified by silica gel column chromatography (20% EtOAc/*n*-hexanes) to afford **26** as white crystals (980 mg, 83% yield). Mp 60 °C; R_f (50% EtOAc/*n*-hexanes) 0.36; IR ν_{max} (ATR) 3361, 3002, 1724, 1488 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05 (1H, br s, NH-1), 7.21 (1H, d, *J*=8.8 Hz, H-7), 7.07 (1H, d, *J*=2.4 Hz, H-4), 6.98 (1H, d, *J*=2.4 Hz, H-2), 6.85 (1H, dd, *J*=8.8, 2.4 Hz, H-6), 4.34 (2H, t, *J*=7.2 Hz, H_2-9), 3.86 (3H, s, OMe-13), 3.05 (2H, td, *J*=7.2, 0.8 Hz, H_2-8), 2.05 (3H, s, H_3-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3 (C-11), 154.1 (C-5), 131.5 (C-7a), 127.9 (C-3a), 123.0 (C-2), 112.4 (C-6), 112.0 (C-7), 111.7 (C-3), 100.7 (C-4), 64.7 (C-9), 56.0 (C-13), 24.9 (C-8), 21.2 (C-12); (+)-HRESIMS *m*/*z* 234.1120 $[M+H]^+$ (calcd for $C_{13}H_{16}NO_3$, 234.1125).

*3.1.15. tert-Butyl 3-(2-acetoxyethyl)-5-methoxy-1H-indole-1-carboxylate (**27**).* 2-(5-Methoxy-1*H*-indol-3-yl)ethyl acetate (**26**) (918 mg, 3.94 mmol), di-*tert*-butyl dicarbonate (1.29 g, 5.90 mmol) and DMAP (48 mg, 0.39 mmol) were dissolved in CH_2Cl_2 (30 mL) and allowed to stir at rt under N_2 overnight (19 h). The reaction mixture was poured over H_2O (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated in vacuo to give the crude material as a clear orange oil. The product was purified by silica gel column chromatography (CH_2Cl_2) to give **27** as a colourless oil (1.43 g, quantitative yield). R_f (CH_2Cl_2) 0.68; IR ν_{max} (ATR) 2958, 1733, 1716, 1367, 1247, 1160, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (1H, br d, *J*=7.0 Hz, H-7), 7.41 (1H, br s, H-2), 7.01 (1H, d, *J*=2.5 Hz, H-4), 6.93 (1H, dd, *J*=7.0, 2.5 Hz, H-6), 4.34 (2H, t, *J*=7.2 Hz, H_2-9), 3.87 (3H, s, OMe-17), 2.99 (2H, td, *J*=7.2, 0.8 Hz, H_2-8), 2.06 (3H, s, H_3-12), 1.66 (9H, s, $3H_3$-16); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (C-11), 156.0 (C-5), 149.8 (C-13), 131.4 (C-3a), 130.2 (C-7a), 124.1 (C-2), 116.6 (C-3), 116.1 (C-7), 113.1 (C-6), 101.8 (C-4), 83.5 (C-15), 63.8 (C-9), 55.8 (C-17), 28.3 (C-16), 24.7 (C-8), 21.1 (C-12); (+)-HRESIMS *m*/*z* 356.1471 $[M+Na]^+$ (calcd for $C_{18}H_{23}NNaO_5$, 356.1468).

*3.1.16. tert-Butyl 3-(2-hydroxyethyl)-5-methoxy-1H-indole-1-carboxylate (**28**).* To a solution of *tert*-butyl 3-(2-acetoxyethyl)-5-methoxy-1*H*-indole-1-carboxylate (**27**) (1.40 g, 4.19 mmol) dissolved in MeOH (40 mL) was added K_2CO_3 (11.58 g, 83.80 mmol) in H_2O (40 mL). The concentration of K_2CO_3 in solution was approximately 1.0 M. The reaction mixture was allowed to stir at rt overnight (16 h). MeOH was removed under reduced pressure and the remaining H_2O fraction was extracted CH_2Cl_2 (3×100 mL). The CH_2Cl_2 fractions were combined, dried ($MgSO_4$) and concentrated in vacuo to give **28** as a colourless oil (1.02 g, 84% yield). R_f (CH_2Cl_2) 0.10; IR ν_{max} (ATR) 3557, 2920, 1699, 1480, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.01 (1H, br d, *J*=7.8 Hz, H-7), 7.44 (1H, br s, H-2), 6.98 (1H, d, *J*=2.6 Hz, H-4), 6.93 (1H, dd, *J*=7.8, 2.6 Hz, H-6), 3.92 (2H, td, *J*=6.3, 6.0 Hz, H_2-9), 3.86 (3H, s, OMe-14), 2.93 (2H, td, *J*=6.3, 0.8 Hz, H_2-8), 1.65 (9H, s, H_3-13), 1.56 (1H, t, *J*=6.0 Hz, OH-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0 (C-5), 149.8 (C-10), 131.4 (C-3a), 130.5 (C-7a), 124.4 (C-2), 116.9 (C-3), 116.2 (C-7), 113.1 (C-6), 102.0 (C-4), 83.5 (C-12), 62.1 (C-9), 55.9 (C-14), 28.6 (C-8), 28.4 (C-13); (+)-HRESIMS *m*/*z* 292.1537 $[M+H]^+$ (calcd for $C_{16}H_{22}NO_4$, 292.1543).

*3.1.17. 1-(1H-tert-Butyloxycarbonyl-indol-3-yl)methyl-1,2,3,4-tetrahydro-β-carboline (**29**)and 1-(1,3-bis(1H-tert-butyloxycarbonyl-indol-3-yl)prop-1-ene)-1,2,3,4-tetrahydro-β-carboline (**30**).* *tert*-Butyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (**16**) (130 mg, 0.50 mmol) and tryptamine (120 mg, 0.75 mmol) were stirred in toluene (20 mL) and heated to reflux for 3 h. Toluene was removed and the residue was dissolved in CH_2Cl_2 (30 mL). TFA (186 μL, 2.51 mmol) was added and the resulting mixture was allowed to stir at rt overnight (13 h). TEA (486 μL, 3.51 mmol) was slowly added to the reaction. The reaction mixture was poured into H_2O (100 mL) and extracted with additional CH_2Cl_2 (60 mL). The organic fraction was washed once more with H_2O (100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by silica gel column chromatography eluting in 2% MeOH/CH_2Cl_2. The first product **30** was recrystallised from MeOH as a white solid (48 mg, 15% yield). The mother liquor was concentrated and purified by silica gel column chromatography (2% MeOH/CH_2Cl_2), which gave a second product **29** as a yellow-orange oil (11 mg, 6% yield).

Alternatively, using the same procedure but substituting CH_2Cl_2 as the solvent, the reaction of *tert*-butyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (**16**) (70 mg, 0.27 mmol) and tryptamine (48 mg, 0.30 mmol) afforded **29** as a yellow-orange oil (50 mg, 46% yield) and **30** as a white solid (34 mg, 39% yield).

Compound **29**: R_f (10% MeOH/CH_2Cl_2) 0.54; IR ν_{max} (ATR) 2931, 1728, 1451, 1368, 1152, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, br d, *J*=7.6 Hz, H-7′), 7.86 (1H, br s, NH-9), 7.56 (1H, d, *J*=7.8 Hz, H-4′), 7.50–7.47 (2H, m, H-5 and H-2′), 7.35 (1H, ddd, *J*=7.6, 7.6, 1.1 Hz, H-6′), 7.26–7.22 (2H, m, H-8 and H-5′), 7.14–7.06 (2H, m, H-6 and H-7), 4.49–4.46 (1H, m, H-1), 3.33 (1H, dt, *J*=12.0, 4.4 Hz, H_2-3A), 3.23 (1H, dd, *J*=14.4, 6.0 Hz, H_2-12′A), 3.09–2.99 (2H, m, H_2-3B and H_2-12′B), 2.84–2.70 (2H, m, H_2-4), 1.64 (9H, s, H_3-11′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.7 (C-8′), 135.7 (C-7′a and C-9a), 135.5 (C-8a), 130.4 (C-3′a), 127.4 (C-4b), 124.9 (C-6′), 124.1 (C-2′), 122.8 (C-5′), 121.7 (C-7), 119.5 (C-6), 119.1 (C-4′), 118.3 (C-5), 116.9 (C-3′), 115.6 (C-7′), 110.9 (C-8), 109.5 (C-4a), 83.9 (C-10′), 52.4 (C-1), 42.6 (C-3), 31.1 (C-12′), 28.3 (C-11′), 22.6 (C-4); (+)-HRESIMS *m*/*z* 402.2165 $[M+H]^+$ (calcd for $C_{25}H_{28}N_3O_2$, 402.2176).

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Compound **30**: mp 194–195 °C; R_f (10% MeOH/CH_2Cl_2) 0.68; IR ν_{max} (ATR) 3152, 2984, 1740, 1721, 1453, 1366, 1152, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18–8.13 (2H, m, H-7′ and H-21′), 7.70 (1H, br s, NH-9), 7.47 (2H, d, J=7.4 Hz, H-5 and H-18′), 7.37–7.31 (4H, m, H-4′, H-6′, H-16′ and H-20′), 7.26–7.19 (3H, m, H-8, H-5′ and H-19′), 7.13 (1H, ddd, J=7.3, 7.3, 1.3 Hz, H-7), 7.08 (1H, ddd, J=7.3, 7.3, 1.1 Hz, H-6), 6.88 (1H, br s, H-2′), 6.16 (1H, t, J=7.2 Hz, H-13′), 4.96 (1H, s, H-1), 3.49–3.38 (2H, m, H_2-12′), 3.28 (1H, dt, J=12.7, 4.1 Hz, H_2-3A), 3.03–2.97 (1H, m, H_2-3B), 2.72–2.61 (2H, m, H_2-4), 1.67 (9H, s, $3H_3$-11′), 1.47 (9H, s, H_3-25′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.9 (C-8′ or C-22′), 149.5 (C-8′ or C-22′), 135.8 (C-7′a), 135.7 (C-8a), 135.3 (C-21′a), 133.5 (C-9a), 133.3 (C-14′), 131.7 (C-13′), 130.4 (C-3′a and C-17′a), 127.8 (C-4b), 124.8 (C-20′), 124.6 (C-4′), 124.2 (C-2′), 123.1 (C-19′), 122.8 (C-16′), 122.5 (C-5′), 121.9 (C-7), 120.3 (C-18′), 119.5 (C-6), 119.3 (C-3′), 119.0 (C-6′), 118.3 (C-5), 116.6 (C-17′), 115.6 (C-7′), 115.5 (C-21′), 111.1 (C-8), 111.0 (C-4a), 83.8 (C-24′), 83.7 (C-10′), 60.8 (C-1), 42.5 (C-3), 28.4 (C-11′), 28.1 (C-25′), 26.0 (C-12′), 22.6 (C-4); (+)-HRESIMS m/z 643.3256 $[M+H]^+$ (calcd for $C_{40}H_{43}N_4O_4$, 643.3279).

*3.1.18. 1H-1-Benzyl-1,2,3,4-tetrahydro-β-carboline (**31**)[25] and (E)-1-(1,3-diphenylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**32**).* To a solution of phenylacetaldehyde (0.30 mL, 2.56 mmol) in dry toluene (51.3 mL) was added tryptamine (370 mg, 2.31 mmol) and tryptamine·HCl (454 mg, 2.31 mmol). The mixture was then heated to reflux under a nitrogen atmosphere for 3 h. Toluene was removed in vacuo and the crude material was re-dissolved in dry CH_2Cl_2 (50 mL) and TFA (0.95 mL, 12.82 mmol). This was stirred overnight under a nitrogen atmosphere at ambient temperature. The reaction was quenched with Et_3N (5.49 mL, 18.0 mmol) and the mixture was diluted to 100 mL with CH_2Cl_2. The organic layer was washed with H_2O (2×100 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by silica gel column chromatography (MeOH/CH_2Cl_2) gave **31** as a yellow oil (94 mg, 14%) and **32** as a yellow oil (206 mg, 22%).

Compound **31**: R_f (10% MeOH/CH_2Cl_2) 0.58; IR (ATR) ν_{max} 2941, 1671, 1447, 1187, 1129, 742, 720, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (1H, s, NH-9), 7.43 (1H, d, J=7.6 Hz, H-5), 7.33–7.30 (3H, m, H-3′, H-4′ and H-5′), 7.25–7.22 (2H, m, H-2′ and 6′), 7.18–7.15 (1H, m, H-8), 7.15–7.11 (1H, m, H-7), 7.10–7.06 (1H, m, H-6), 4.64 (1H, t, J=7.6 Hz, H-1), 3.36 (1H, dt, J=12.6, 5.0 Hz, H_2-3A), 3.28 (1H, dd, J=13.6, 6.3 Hz, H_2-7′A), 3.16–3.09 (2H, m, H_2-3B and H_2-7′B), 2.93–2.85 (1H, m, H_2-4A), 2.82–2.75 (1H, m, H_2-4B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.5 (C-1′), 135.9 (C-8a), 132.0 (C-9a), 129.6 (C-3′ and C-5′), 129.2 (C-2′ and C-6′), 127.6 (C-4′), 126.6 (C-5a), 122.4 (C-7), 119.8 (C-6), 118.4 (C-5), 111.2 (C-8), 108.4 (C-4a), 53.8 (C-1), 41.7 (C-3) 40.2 (C-7′), 20.6 (C-4); (+)-HRESIMS $[M+H]^+$ 263.1542 (calcd for $C_{18}H_{19}N_2$, 263.1543). The ^1H NMR data were consistent with literature values.[25]

Compound **32**: R_f (10% MeOH/CH_2Cl_2) 0.66; IR (ATR) ν_{max} 2921, 1493, 1446, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (1H, br s, NH-9), 7.48 (1H, d, J=7.5 Hz, H-5), 7.31–7.26 (6H, m, H-8, H-3′, H-5′, H-11′, H-13′, H-15′), 7.22–7.18 (1H, m, H-4′), 7.16–7.15 (1H, m, H-7), 7.12–7.11 (2H, m, H-2′ and H-6′), 7.11–7.09 (1H, m, H-6), 7.08–7.05 (2H, m, H-12′ and H-14′), 5.95 (1H, t, J=7.6 Hz, H-8′), 4.92 (1H, s, H-1), 3.37–3.35 (2H, m, H_2-7′), 3.28–3.23 (1H, m, H_2-3A), 3.03–2.96 (1H, m, H_2-3B), 2.68–2.64 (2H, m, H_2-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.5 (C-10′), 140.8 (C-1′), 137.7 (C-9′), 135.8 (C-8a), 133.9 (C-9a), 130.1 (C-8′), 129.1 (C-2′ and C-6′), 128.7 (C-3′ and C-5′), 128.6 (C-12′ and C-14′), 128.4 (C-11′ and C-15′), 127.8 (C-4b), 127.7 (C-4′), 126.3 (C-13′), 121.8 (C-7), 119.5 (C-6), 118.3 (C-5), 111.0 (C-8), 110.6 (C-4a), 60.2 (C-1), 42.3 (C-3), 35.2 (C-7′), 22.6 (C-4); (+)-HRESIMS $[M+H]^+$ 365.1999 (calcd for $C_{26}H_{25}N_2$, 365.2012).

Alternative route to **32**: To a solution of (*E*)-3-benzyl-2-phenylpropenal (**33**) (177 mg, 0.80 mmol) in dry toluene (15.9 mL) was added tryptamine (115 mg, 0.72 mmol) and tryptamine·HCl (142 mg, 0.72 mmol). The mixture was heated at 130 °C under a nitrogen atmosphere for 3 h. The toluene was then removed in vacuo and the crude material was re-dissolved in dry CH_2Cl_2 (10 mL) and TFA (0.296 mL, 3.98 mmol). This mixture was stirred overnight under a nitrogen atmosphere at ambient temperature. The reaction was then quenched with NEt_3 (0.77 mL, 5.57 mmol) and the mixture was diluted to 100 mL with CH_2Cl_2. The organic layer was washed with water (2×100 mL), dried over $MgSO_4$ and the solvent removed in vacuo. Purification by silica gel column chromatography (MeOH/CH_2Cl_2) gave the product **32** as a yellow oil (87 mg, 30%). The product exhibited identical spectroscopic data to those observed earlier.

*3.1.19. (E)-3-Benzyl-2-phenyl-propenal (**33**).* Phenylacetaldehyde (0.3 mL, 2.56 mmol) and ammonium acetate (198 mg, 2.56 mmol) were refluxed in a solution of AcOH (1 mL), H_2O (5 mL) and EtOAc (1 mL) overnight under a nitrogen atmosphere. The solution was washed with EtOAc (2×30 mL) and the organic layer dried ($MgSO_4$) and the solvent removed in vacuo. Purification by silica gel column chromatography (CH_2Cl_2) gave the product as a yellow oil (248 mg, 44%). R_f (CH_2Cl_2) 0.94; IR (ATR) ν_{max} 3059, 3027, 1688, 1494, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.65 (1H, s, H-10), 7.46–7.42 (2H, m, H-13 and H-15), 7.39–7.38 (1H, m, H-14), 7.34–7.32 (2H, m, H-3 and H-5), 7.29–7.27 (2H, m, H-12 and H-16), 7.24–7.22 (1H, m, H-4), 7.17–7.15 (2H, m, H-2 and H-6), 6.86 (1H, t, J=7.7 Hz, H-8), 3.69 (2H, d, J=7.7 Hz, H_2-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.6 (C-10), 153.5 (C-8), 144.2 (C-9), 138.2 (C-1), 132.3 (C-11), 129.6 (C-12 and C-16), 129.0 (C-2 and C-6), 128.6 (C-13 and C-15), 128.5 (C-3 and C-5), 128.3 (C-14), 126.9 (C-4), 35.9 (C-7); (+)-HRESIMS $[M+Na]^+$ 245.0934 (calcd for $C_{16}H_{14}ONa$, 245.0937). The ^1H NMR data agreed with literature values.[26]

*3.1.20. 1-(1H-Indol-3-yl)-3-methylcarboxylate-1,2,3,4-tetrahydro-β-carboline (**37**).* L-Tryptophan methyl ester·HCl (**14**) (100 mg, 0.39 mmol) and indole-3-carboxaldehyde (57 mg, 0.39 mmol) were dissolved in MeOH (10 mL) and heated to reflux under N_2 for 72 h. MeOH was removed and the crude material suspended in CH_2Cl_2 (10 mL) with stirring under N_2. TFA (1 mL) was added to the reaction mixture and it was allowed to stir under N_2 at rt for 23 h. The reaction mixture was diluted with EtOAc (20 mL) and carefully added to saturated $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with EtOAc (3×100 mL), the organic solvent layers combined, dried ($MgSO_4$) and concentrated in vacuo. The crude reaction product was purified by silica gel column chromatography (1% MeOH/CH_2Cl_2) to afford [as a mixture of stereoisomers (1:0.7)] **37** as a yellow-orange oil (63 mg, 47% yield). R_f (5% MeOH/CH_2Cl_2) 0.45; IR ν_{max} (ATR) 3395, 3056, 1725, 1454, 1243, 739 cm^{-1}; Major stereoisomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (1H, br s, NH-1′), 7.69 (1H, br s, NH-9), 7.59–7.53 (1H, m, H-5), 7.31–7.27 (2H, m, H-4′ and H-7′), 7.19–7.01 (5H, m, H-6, H-7, H-8, H-2′ and H-6′), 6.99–6.94 (1H, m, H-5′), 5.51 (1H, s, H-1), 4.01 (1H, dd, J=11.1, 4.3 Hz, H-3), 3.77 (3H, s, OMe-11), 3.24–3.22 (1H, m, H_2-4A), 3.15–2.99 (1H, m, H_2-4B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (C-10), 136.6 (C-7′a), 136.0 (C-8a), 135.4 (C-9a), 127.4 (C-4b), 126.1 (C-3′a), 124.1 (C-2′), 122.6 (C-6′), 121.8 (C-7), 120.3 (C-5′), 119.6 (C-6), 119.4 (C-4′), 118.2 (C-5), 115.0 (C-3′), 111.6 (C-7′), 111.2 (C-8), 108.0 (C-4a), 57.3 (C-3), 52.3 (C-11), 50.9 (C-1), 26.0 (C-4); Minor stereoisomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (1H, br s, NH-1′), 7.72 (1H, br s, NH-9), 7.59–7.53 (1H, m, H-5), 7.48 (1H, d, J=8.0 Hz, H-4′), 7.31–7.27 (1H, m, H-7′), 7.19–7.01 (5H, m, H-6, H-7, H-8, H-5′ and H-6′), 6.74 (1H, d, J=2.4 Hz, H-2′), 5.71 (1H, s, H-1), 3.95 (1H, dd, J=7.5, 5.2 Hz, H-3), 3.67 (3H, s, OMe-11), 3.29–3.27 (1H, m, H_2-4A), 3.15–2.99 (1H, m, H_2-4B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3 (C-10), 136.7 (C-7′a), 136.1 (C-8a), 134.1 (C-9a), 127.2 (C-4b), 126.3 (C-3′a), 123.9 (C-2′), 122.6 (C-6′), 121.8 (C-7), 120.3 (C-5′), 119.5 (C-6), 119.1 (C-4′), 118.3 (C-5), 116.8 (C-3′), 111.5 (C-7′), 111.1 (C-8), 107.9 (C-4a),

53.0 (C-3), 52.2 (C-11), 47.5 (C-1), 24.9 (C-4); (+)-HRESIMS *m*/*z* 346.1546 $[M+H]^+$ (calcd for $C_{21}H_{20}N_3O_2$, 346.1550).

*3.1.21. 1-(5-Methoxy-1H-indol-3-yl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline (**38**).* 5-Methoxy-1*H*-indole-3-carbaldehyde (**35**) (155 mg, 0.88 mmol) and 5-methoxytryptamine·HCl (200 mg, 0.88 mmol) were heated at reflux in MeOH (10 mL) overnight (24 h) under N_2. The MeOH was then removed under reduced pressure to give a pale yellow oil. The crude material was suspended in CH_2Cl_2 (10 mL), TFA (1 mL) added and the solution stirred at rt under N_2 overnight (19 h). The reaction mixture was diluted with EtOAc (10 mL) and added slowly to a saturated solution of $NaHCO_3$ (50 mL). EtOAc (30 mL) was added to extract the product. The aqueous layer was extracted with EtOAc (2×50 mL). The organic layers were combined, dried ($MgSO_4$) and solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to afford **38** as a yellow-orange solid (224 mg, 73% yield). Mp 145–146 °C; R_f (5% MeOH/CH_2Cl_2) 0.44; IR ν_{max} (ATR) 2832, 1673, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.91 (1H, br s, NH-1′), 8.00 (1H, s, NH-9), 7.06 (1H, d, *J*=8.8 Hz, H-7′), 6.98 (1H, d, *J*=8.8 Hz, H-8), 6.93 (1H, d, *J*=2.4 Hz, H-5), 6.78 (1H, s, H-2′), 6.75 (1H, dd, *J*=8.8, 2.4 Hz, H-7), 6.69 (1H, dd, *J*=8.8, 2.2 Hz, H-6′), 6.47 (1H, d, *J*=2.2 Hz, H-4′), 5.34 (1H, s, H-1), 3.83 (3H, s, OMe-10), 3.44 (3H, s, OMe-8′), 3.23 (1H, dt, *J*=12.4, 4.5 Hz, H_2-3A), 3.09–3.02 (1H, m, H_2-3B), 2.91–2.83 (1H, m, H_2-4A), 2.78–2.74 (1H, m, H_2-4B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2 (C-6 and C-5′), 133.3 (C-9a), 131.5 (C-7′a), 131.2 (C-8a), 127.4 (C-4b), 126.4 (C-3′a), 125.9 (C-2′), 112.7 (C-6′), 112.5 (C-7′), 112.2 (C-3′), 111.9 (C-7 and C-8), 108.5 (C-4a), 100.6 (C-5), 100.4 (C-4′), 56.1 (C-10), 55.6 (C-8′), 50.1 (C-1), 42.4 (C-3), 21.1 (C-4); (+)-HRESIMS *m*/*z* 348.1703 $[M+H]^+$ (calcd for $C_{21}H_{22}N_3O_2$, 348.1707).

*3.1.22. 1-(1H-Indol-3-yl)-3-methylcarboxylate-β-carboline (**40**)[42] and 1-(1H-indol-3-yl)-3-methylcarboxylate-3,4-dihydro-β-carboline (**44**).* The stereoisomeric mixture of 1-(1*H*-indol-3-yl)-3-methylcarboxylate-1,2,3,4-tetrahydro-β-carboline (**37**) (30 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (10 mL), and DDQ (79 mg, 0.35 mmol) added. The reaction mixture was purged with N_2 and allowed to stir at rt for 50 min. The reaction mixture was poured into 1 M KOH solution (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic solvent fractions were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (2–10% MeOH/CH_2Cl_2) to afford **40** as an orange solid (7.0 mg, 24% yield) and **44** as a bright yellow oil (12 mg, 40% yield).

Compound **40**: mp 259–260 °C (lit.[42] 202 °C); R_f (5% MeOH/CH_2Cl_2) 0.40; IR ν_{max} (ATR) 3432, 3177, 2921, 1716, 1430, 735 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.80 (1H, br s, NH-1′), 11.69 (1H, br s, NH-9), 8.90 (1H, d, *J*=7.6 Hz, H-4′), 8.77 (1H, s, H-4), 8.46 (1H, s, H-2′), 8.39 (1H, d, *J*=7.8 Hz, H-5), 7.77 (1H, d, *J*=7.8 Hz, H-8), 7.60 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.54 (1H, d, *J*=7.6 Hz, H-7′), 7.33 (1H, dd, *J*=7.8, 7.8 Hz, H-6), 7.25 (1H, dd, *J*=7.6, 7.6 Hz, H-6′), 7.19 (1H, dd, *J*=7.6, 7.6 Hz, H-5′), 3.99 (3H, s, OMe-11); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.3 (C-10), 141.1 (C-8a), 140.0 (C-3), 136.5 (C-7′a), 136.2 (C-1), 133.2 (C-9a), 128.2 (C-4a and C-7), 126.5 (C-2′), 126.3 (C-3′a), 122.9 (C-4′), 122.3 (C-6′), 121.7 (C-5), 121.5 (C-4b), 120.3 (C-6), 120.2 (C-5′), 114.3 (C-4), 112.8 (C-8), 112.7 (C-3′), 111.5 (C-7′), 52.0 (C-11); (+)-HRESIMS *m*/*z* 342.1230 $[M+H]^+$ (calcd for $C_{21}H_{16}N_3O_2$, 342.1237). The spectroscopic data were consistent with literature values.[42]

Compound **44**: R_f (10% MeOH/CH_2Cl_2) 0.74; IR ν_{max} (ATR) 3386, 3179, 3059, 2952, 1727, 1435, 742 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.91 (1H, br s, NH-1′), 11.43 (1H, br s, NH-9), 8.37 (1H, d, *J*=7.8 Hz, H-4′), 8.14 (1H, s, H-2′), 7.69 (1H, d, *J*=7.8 Hz, H-5), 7.52 (2H, d, *J*=7.8 Hz, H-8 and H-7′), 7.27 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.24 (1H, dd, *J*=7.8, 7.8 Hz, H-6′), 7.17 (1H, dd, *J*=7.8, 7.8 Hz, H-5′), 7.11 (1H, dd, *J*=7.8, 7.8 Hz, H-6), 4.64 (1H, dd, *J*=12.1, 6.9 Hz, H-3), 3.75 (3H, s, H_3-11), 3.27 (1H, dd, *J*=16.2, 6.9 Hz, H_2-4A), 3.09 (1H, dd, *J*=16.2, 12.1 Hz, H_2-4B); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.3 (C-10), 154.7 (C-1), 137.7 (C-8a), 136.7 (C-7′a), 130.5 (C-2′), 127.8 (C-9a), 125.8 (C-3′a), 125.0 (C-4b), 124.3 (C-7), 122.7 (C-6′), 122.3 (C-4′), 120.7 (C-5′), 120.0 (C-6), 119.7 (C-5), 115.7 (C-4a), 113.0 (C-8), 111.9 (C-7′), 111.4 (C-3′), 59.5 (C-3), 52.1 (C-11), 21.9 (C-4); (+)-HRESIMS *m*/*z* 344.1386 $[M+H]^+$ (calcd for $C_{21}H_{18}N_3O_2$, 344.1394).

*3.1.23. Eudistomin U 3-carboxylic acid (**41**).*[42] To a solution of 1-(1*H*-indol-3-yl)-3-methylcarboxylate-β-carboline (**40**) (13 mg, 0.04 mmol) in THF/H_2O (3:1) (4 mL) was added LiOH (16 mg, 0.38 mmol). The reaction mixture was heated to reflux under N_2 for 13 h. The pH of the cooled reaction mixture was adjusted with 1 M HCl solution (a drop) and a yellow precipitate formed. The yellow solid was filtered, washed successively with H_2O (5 mL), MeOH (3 mL) and ether (5 mL) in 1 mL portions, then dried in vacuo to afford **41** as a yellow solid (12 mg, 96% yield). Mp 299 °C (lit.[42] 230 °C decomp.); R_f (10% MeOH/CH_2Cl_2) 0.52; IR ν_{max} (ATR) 3273, 2919, 1583, 1366, 733 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.87 (1H, br s, NH-1′), 11.70 (1H, br s, NH-9), 8.74–8.72 (2H, m, H-4 and H-4′), 8.45 (1H, s, H-2′), 8.36 (1H, d, *J*=7.8 Hz, H-5), 7.77 (1H, d, *J*=7.8 Hz, H-8), 7.58 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.54 (1H, d, *J*=7.5 Hz, H-7′), 7.31 (1H, dd, *J*=7.8, 7.8 Hz, H-6), 7.23 (1H, dd, *J*=7.5, 7.5 Hz, H-6′), 7.16 (1H, dd, *J*=7.5, 7.5 Hz, H-5′); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.7 (C-10), 141.3 (C-8a), 139.5 (C-3), 138.2 (C-1), 136.6 (C-7′a), 133.3 (C-9a), 128.5 (C-4a), 128.1 (C-7), 126.6 (C-2′), 126.2 (C-3′a), 122.6 (C-4′), 122.2 (C-6′), 121.6 (C-5), 121.5 (C-4b), 120.2 (C-6), 120.1 (C-5′), 113.9 (C-4), 112.9 (C-8), 112.7 (C-3′), 111.6 (C-7′); (+)-HRESIMS *m*/*z* 328.1081 $[M+H]^+$ (calcd for $C_{20}H_{14}N_3O_2$, 328.1081). The spectroscopic data were consistent with literature values.[42]

*3.1.24. 5′,6-Dimethoxy eudistomin U (**42**).* To a solution of 1-(5-methoxy-1*H*-indol-3-yl)-6-methoxy-1,2,3,4-tetrahydro-β-carboline (**38**) (8.0 mg, 0.02 mmol) in THF (1 mL) was added DDQ (26 mg, 0.12 mmol). The reaction mixture was allowed to stir at rt under N_2 for 3 h. The reaction mixture was poured into 1 M KOH solution (50 mL) and extracted with CH_2Cl_2 (2×25 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed in vacuo. The crude reaction product was purified by silica gel flash column chromatography (2% MeOH/CH_2Cl_2) to afford **42** as an orange oil (2.0 mg, 25% yield). R_f (5% MeOH/CH_2Cl_2) 0.53; IR ν_{max} (ATR) 2925, 1491, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.27 (1H, br s, NH-1′), 8.51 (1H, d, *J*=5.3 Hz, H-3), 8.46 (1H, br s, NH-9), 7.83 (1H, d, *J*=5.3 Hz, H-4), 7.58 (1H, d, *J*=2.4 Hz, H-5), 7.50 (1H, s, H-2′), 7.48 (1H, d, *J*=2.3 Hz, H-4′), 7.37 (1H, d, *J*=8.8 Hz, H-8), 7.25 (1H, d, *J*=8.0 Hz, H-7′), 7.18 (1H, dd, *J*=8.8, 2.4 Hz, H-7), 6.89 (1H, dd, *J*=8.0, 2.3 Hz, H-6′), 3.95 (3H, s, OMe-10), 3.77 (3H, s, OMe-8′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9 (C-5′), 154.3 (C-6), 139.7 (C-1), 138.3 (C-3), 135.2 (C-8a), 134.3 (C-9a), 131.7 (C-7′a), 129.0 (C-4a), 126.3 (C-3′a), 125.1 (C-2′), 122.4 (C-4b), 118.3 (C-7), 114.3 (C-3′), 113.2 (C-6′), 112.5 (C-8 and C-7′), 112.4 (C-4), 103.5 (C-5), 102.2 (C-4′), 56.0 (C-10), 55.9 (C-8′); (+)-HRESIMS *m*/*z* 344.1379 $[M+H]^+$ (calcd for $C_{21}H_{18}N_3O_2$, 344.1394).

*3.1.25. 5′,6-Dihydroxy eudistomin U (**43**).* To a solution of 5′,6-dimethoxy eudistomin U (**42**) (7.0 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) cooled to −78 °C was added BBr_3 (58 μL, 0.61 mmol). The reaction mixture was allowed to stir under N_2 at −78 °C for 2 h and then at rt for another 2 h. The reaction mixture was quenched by slow addition of water (40 mL) at 0 °C and extracted with EtOAc (5×30 mL). The organic solvent fractions were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The crude reaction product was purified by silica gel column chromatography (EtOAc) to afford **43** as a bright yellow solid (2.0 mg, 31% yield). Mp 252 °C; R_f (6% MeOH/EtOAc) 0.33; IR ν_{max} (ATR) 3215, 1195, 801 cm^{-1}; ^1H

NMR (CD_3OD, 400 MHz) δ 8.26 (1H, d, J=5.6 Hz, H-3), 7.98 (1H, d, J=5.6 Hz, H-4), 7.90 (1H, s, H-2′), 7.56 (1H, d, J=2.3 Hz, H-5), 7.48 (1H, d, J=8.8 Hz, H-8), 7.37 (1H, d, J=8.7 Hz, H-7′), 7.31 (1H, d, J=2.3 Hz, H-4′), 7.14 (1H, dd, J=8.8, 2.3 Hz, H-7), 6.83 (1H, dd, J=8.7, 2.3 Hz, H-6′); ^{13}C NMR (CD_3OD, 100 MHz) δ 152.8 (C-5′), 152.7 (C-6), 140.4 (C-1), 137.9 (C-8a), 135.4 (C-9a), 135.2 (C-3), 133.2 (C-7′a), 131.1 (C-4a), 127.9 (C-3′a), 127.8 (C-2′), 123.2 (C-4b), 120.3 (C-7), 114.1 (C-8), 113.8 (C-6′), 113.7 (C-4), 113.4 (C-7′), 111.7 (C-3′), 106.5 (C-5), 105.4 (C-4′); (+)-HRESIMS m/z 316.1074 $[M+H]^+$ (calcd for $C_{19}H_{14}N_3O_2$, 316.1081).

3.2. Biological assays

Details of all biological assays have been described in literature.[30–33]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.05.068. These data include MOL files and InChiKeys of the most important compounds described in this article.

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