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Diverse alkaloid-like structures from a common building block

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ABSTRACT

A wealth of unique enantiopure polycyclic alkaloid-like scaffolds can be prepared on a multigram scale in only a few steps from a common, commercially available intermediate. The attached nitromethyl group can then be used to construct highly diverse functionalized libraries suitable for screening against biological targets of interest.

1. Introduction

The diversity-oriented synthesis of natural product-like molecules for drug discovery is a topic of much current interest.[1] Especially sought after are non-planar ring systems, which can be readily constructed on scale and display varied substituents in diverse orientations in three-dimensional space. Recent analysis has shown that increasing the fraction of sp^3 hybridized carbons and chiral centers in a molecule leads to improved drug-like properties (aqueous solubility and oral bioavailability) and, potentially, better target selectivity.[2] It is also highly desirable to build in the capacity for advanced optimization by what has been termed a post-screening maturation process.[1d,e] It is challenging to achieve both these goals with a single synthetic platform.

Deprez-Poulain et al. have used commercially available chiral keto-carboxylic acid **1** to construct Meyers' bicyclic lactams[3] (Fig. 1). We felt that the defined stereochemistry and rich orthogonal functionality of **1** could be exploited to make new series of more complex polycyclic alkaloid-like molecules with different ring sizes and topologies using methodologies developed for acyl iminium cyclizations.[4] The versatile nitromethyl group could then be converted to an amine, alcohol, aldehyde or carboxylic acid functional group or heterocycle as part of the post-screening maturation process.[5] Our goal was to construct small libraries from these derivatives, which could be used for high-throughput screening. In particular, we hoped that these libraries would show activity against G-protein-coupled receptors, as is well documented for indole and tetrahydroisoquinoline alkaloids.[6] The relatively low molecular weight and novelty of these scaffolds were also seen as a benefit for new lead discovery.

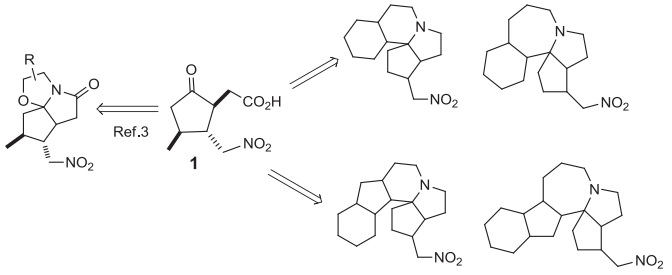

Fig. 1. Natural product-like scaffolds of increasing complexity from a common building block.

2. Results and discussion

2.1. Preparation of core structures

The polycyclic alkaloid-like molecules discussed in this paper are shown in Fig. 2. Each of these complex scaffolds was obtained in just two steps by coupling the appropriate amine to building block **1**, followed by acid catalyzed cyclization. Structural diversity was introduced in various ways. Thus the C ring could be six- or seven-membered depending on the length of the amine bearing side chain. Unfortunately, as precedented in the literature, we failed to synthesize molecules containing a five-membered C ring using acyl iminium chemistry.[4] The aromatic ring system could be either an electron rich benzene or an indole. Further studies to be reported later have shown that pyrroles, furans, thiophenes, benzothiophenes, and benzofurans

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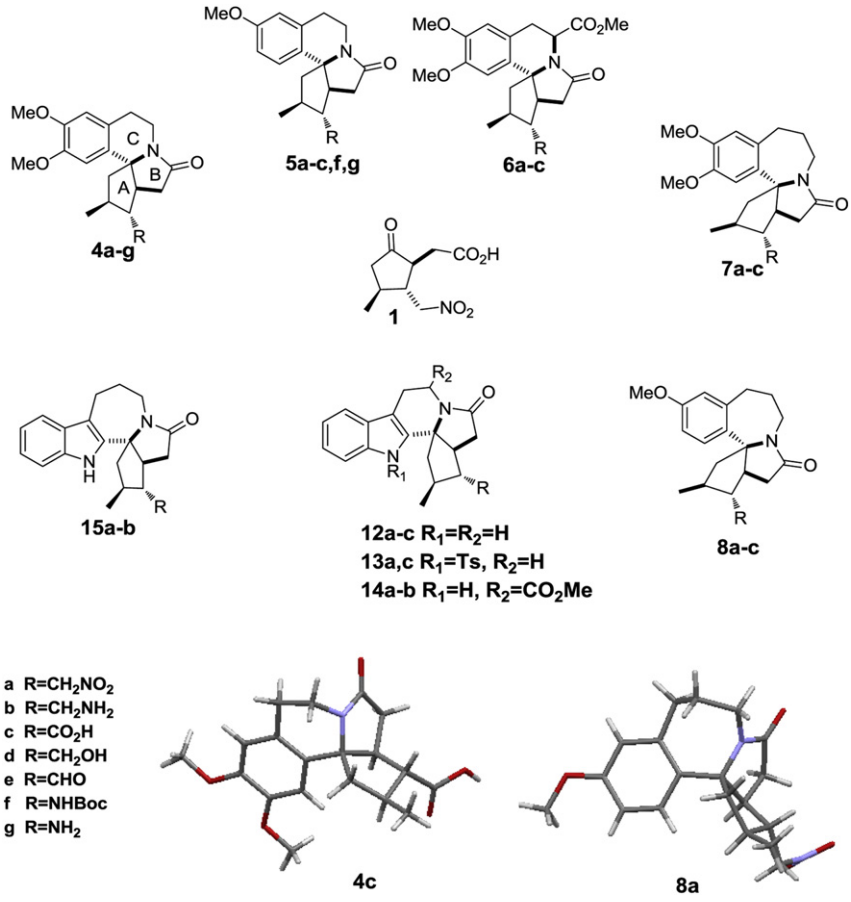


Fig. 2. Polycyclic alkaloid-like molecules from **1**.

all successfully participate in these cyclizations. Incorporation of an alkoxycarbonyl group into the C ring gave an additional point of diversification. All these molecules are azaspirocycles containing a quaternary carbon. This motif is found in naturally occurring alkaloids from many different families, although systems containing two fused five-membered rings are much less common than systems with five-membered rings fused to six- or seven-membered rings (Fig. 3).[7] Interestingly, Heathcock et al. used classical acyl iminium chemistry starting from 2-oxocyclopentane acetic acid to craft methyl homodaphniphyllate, which also contains a 6.5.5. azaspirocycle at its core.[8]

The synthesis of the 6.6.5.5 A-norerythrinan-like series is shown in more detail in Fig. 4. Until recently the only reported examples of this ring system contained an additional carbonyl group at C-4.[9,10] The homologous 6.6.5.6 erythrinan ring system characteristic of alkaloids such as (+)-erysotramidine **3**, however, is very well known and its representatives show sedative, hypotensive, muscle-relaxant, anticonvulsant, and CNS-depressant activities.[4b,d,11] The synthesis of the erythrinan ring system from 2-oxocyclohexane acetic acid has been reported.[4h]

Thus coupling of 3,4-dimethoxyphenethyl amine to building block **1** gave hemiketal **2**, which was initially isolated by column

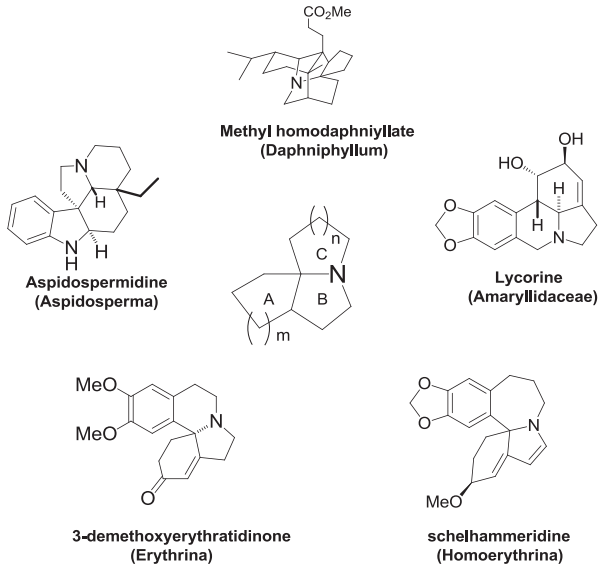


Fig. 3. Some naturally occurring azaspirocycles.

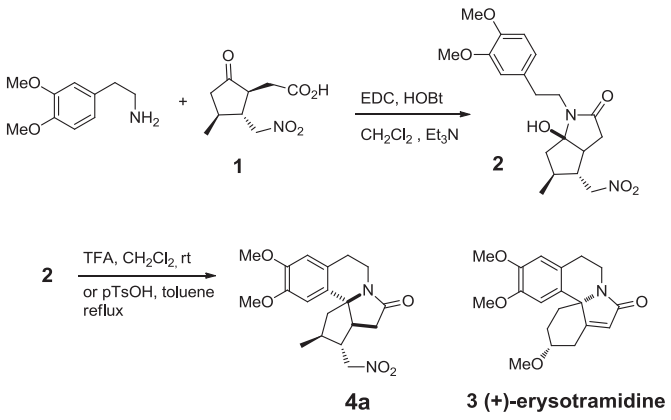


Fig. 4. Preparation of the A-norerythrinan ring system.

chromatography, then cyclized with *p*-toluenesulfonic acid in refluxing toluene. It was later determined that this intermediate could be cyclized directly without purification. Alternatively, the cyclization could be performed with 5% TFA in dichloromethane at rt. LCMS analysis of the crude product showed a single peak with the expected molecular weight and a single diastereomer, compound **4a**, was isolated by column chromatography.[12] The newly formed five-membered ring lactam was shown to be cis-fused by X-ray crystallographic analyses of compound **4a** (CCDC 896743) as well as its derivative compound **4c** (see inset to Fig. 2) The mono-methoxy analogue **5a** was similarly prepared from 3-methoxyphenethylamine.

Diversity could be introduced into the C ring by using L-3,4-dimethoxyphenylalanine methyl ester to give compound **6a**. The C-7 ester group provides an opportunity for post-synthetic modification. Ring C could also be expanded to a seven-membered ring by combining building block **1** and 3-(3,4-dimethoxyphenyl)propyl amine to give compound **7a**, which contains an uncommon 6.7.5.5 tetracyclic ring system. We found only a single example of the parent A-norschelhammerane ring system in the literature.[10] The homologous 6.7.5.6 homoerythrinan ring system is found in alkaloids such as schelhammeridine (Fig. 3) although little has been reported regarding biological activity.[13] The mono-methoxy analogue **8a** was similarly prepared. The crystal structure of this compound is also shown in Fig. 2. It should be emphasized at this point that all of the parent nitromethyl compounds shown in Fig. 2 were readily obtained on a multigram scale making further transformations practical.

2.2. Transformation of the nitromethyl group

Having demonstrated the versatility of building block **1** in preparing non-racemic tetracyclic alkaloid-like structures with different ring sizes and substitution patterns, we then explored the transformations of the nitromethyl group. As described above, this chemical handle serves as a highly versatile point of diversification. This versatility is illustrated for parent compound **4a** in Fig. 5. Thus the nitromethyl group of compound **4a** was readily reduced to amine **4b** by catalytic transfer hydrogenation.[3] The nitromethyl group of compound **4a** could also be readily oxidized to carboxylic acid **4c** using sodium nitrite in a mixture of DMF and acetic acid.[14] Acid **4c** could be reduced to alcohol **4d** and then re-oxidized to aldehyde **4e** with Dess–Martin periodinane.[15] Finally, acid **4c** was subjected to a recently described variant of the Curtius rearrangement to yield Boc protected amine **4f** (not shown), followed by conversion to free amine **4g**.[16] Small screening libraries of amides have been prepared by acylation of compounds **4b** and **4g**.

The newly generated aldehyde and carboxylic acid groups are particularly interesting from the standpoint of further diversification. Thus a focused screening library of amides was generated by coupling amines to compound **4c** (Fig. 5). Carboxylic acids can also be readily converted to heterocycles, which in some cases act as bio-isosteres. Thus carboxylic acid **4c** was converted to oxadiazole **4h** by condensation with benzoic hydrazide.[17] Aldehyde **4e** can potentially be transformed in many ways, the most obvious is reductive amination (Fig. 5). The nitromethyl group also serves as

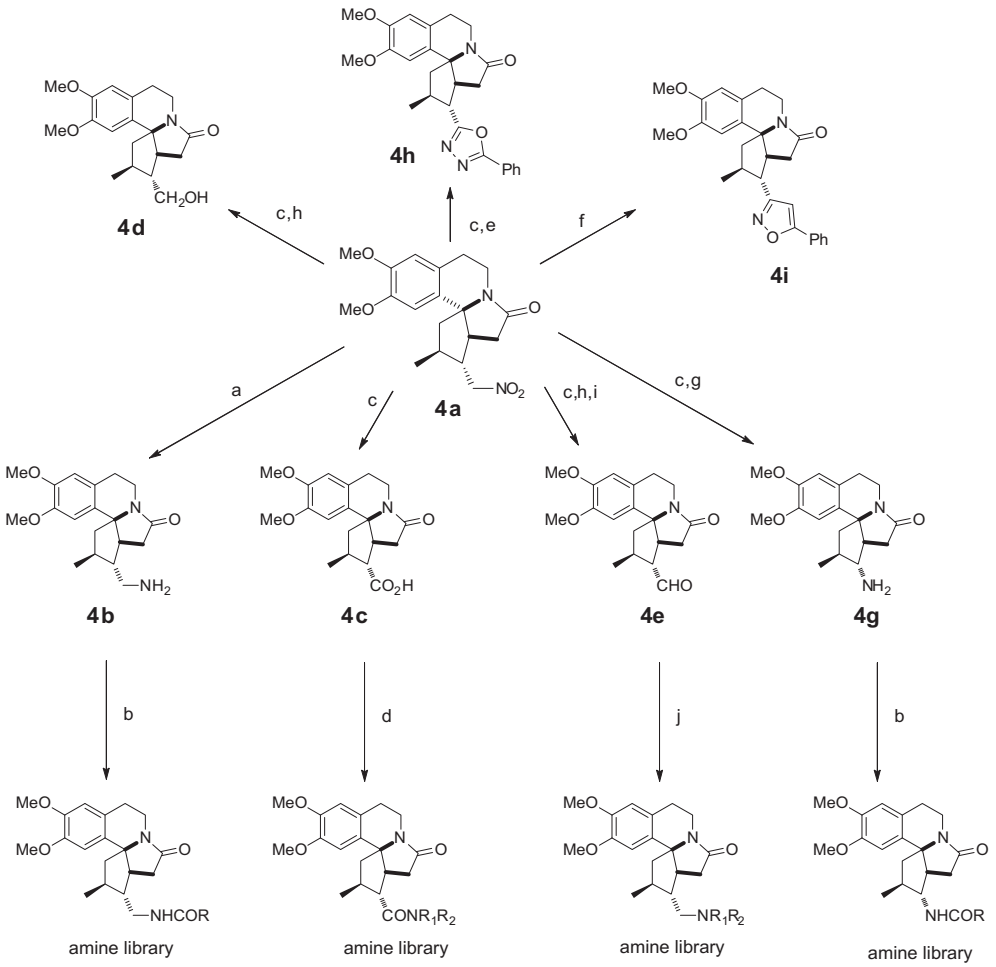


Fig. 5. Transformations of the nitromethyl group. (a) Ammonium formate, Pd/C, MeOH; (b) RCO_2H, HATU, DIEA, CH_2Cl_2; (c) $NaNO_2$, DMF, HOAc; (d) R_1R_2NH, HATU, DIEA, CH_2Cl_2; (e) $PhCONHNH_2$, PS–Ph_3P, CH_3CN, Cl_3CCN, μwave; (f) Boc_2O, DMAP, PhCCH; (g) Boc_2O, NaN_3, Bu_4NBr, $Zn(OTf)_2$, THF then TFA; (h) BH_3/THF; (i) Dess–Martin periodinane, CH_2Cl_2; (j) R_1R_2NH, $Na(OAc)_3BH$.

a nitrile oxide precursor, which can then undergo [3+2] cycloaddition reactions.[18] Thus the nitromethyl group of compound **4a** was converted in situ to a nitrile oxide and condensed with phenyl acetylene to give isoxazole **4i**.

The two basic transformations of the nitromethyl group, oxidation and reduction, have been successfully applied to most of the parent azaspirocycles shown in Fig. 2. For example, parent compound **6a** was converted to compound **6c**; containing two differentiated carboxylic acids, which could, in principle, be selectively modified.

2.3. Introduction of a phenol

Introduction of a free phenolic group to the D ring was also investigated. Not only would the phenol be expected to contribute to biological activity, but could also potentially be used for post-screening structural optimization. Preparation of 10-benzyloxy compound **9** proceeded uneventfully on a multigram scale (Fig. 6). Catalytic hydrogenation of methyl ester **9b** gave the free phenol **9c** cleanly. The X-ray crystallographic structure of compound **9c** is shown in Fig. 6. Reaction of compound **9c** with triflic anhydride gave triflate **9d**, which should be an interesting building block for palladium catalyzed cross-coupling chemistry.

More vigorous cyclization conditions, refluxing with 10% TFA, were required to obtain the 11-benzyloxy isomer, compound **10**, presumably due to the fact that the electron donating benzyloxy substituent is *meta* to the carbon undergoing cyclization. In this case the cyclic hemiketal (*Intermediate* ***A***) was isolated and characterized by NMR. Oxidation gave carboxylic acid **10a**.

2.4. Pentacyclic indoles

The fascinating structural diversity and medicinal importance of the indole alkaloids further inspired us to prepare scaffolds **12**, **14**, and **15** (Fig. 7). These pentacyclic natural product-like ring systems are not well known.[19] Coupling of tryptamine to building block **1** gave cyclic hemiketal **11**, which was purified by radial chromatography and characterized by ^{1}H NMR. We found, however, that compound **12a** could be prepared in good yield by treating the crude isolated EDC reaction product, either with *p*-toluenesulfonic acid (73%) or with TFA (86%).

The nitromethyl group of compound **12a** was readily reduced to amine **12b**, which again provided a good handle for derivatization. However, oxidation of compound **12a**, containing an unprotected indole NH, with nitrous acid failed to give sufficiently pure carboxylic acid **12c**. Therefore the sequence was repeated with *N*-1 tosyl tryptamine to give compound **13a**. Oxidation now proceeded smoothly to give *N*-tosyl protected acid **13b**. Several literature methods were evaluated to remove the tosyl group; the best turned out to be heating with excess Cs_2CO_3 in THF/methanol at 90 °C in a sealed tube to give deprotected acid **12c** in modest yield.[20] Coupling of scaffold **12c** to diverse amines should give an interesting screening collection. Use of L-tryptophan methyl ester gave facile access to ester substituted analogues **14a**,**b**.

Previously undescribed pentacycle **15a**, containing a seven-membered ring C, could likewise be prepared from 3-(3-aminopropyl)indole in 47% un-optimized yield (Fig. 7). Conversion of the nitromethyl to an aminomethyl group proceeded smoothly to give scaffold **15b**.

2.5. Focused library synthesis and screening

A variety of small focused libraries have been made from the azaspiro building blocks shown in Fig. 2. Fig. 8 illustrates a collection of amides that was made from scaffold **8c**. Primary and secondary amines as well as α-amino acid esters were smoothly coupled using the combination of HOAt and EDC to give amides

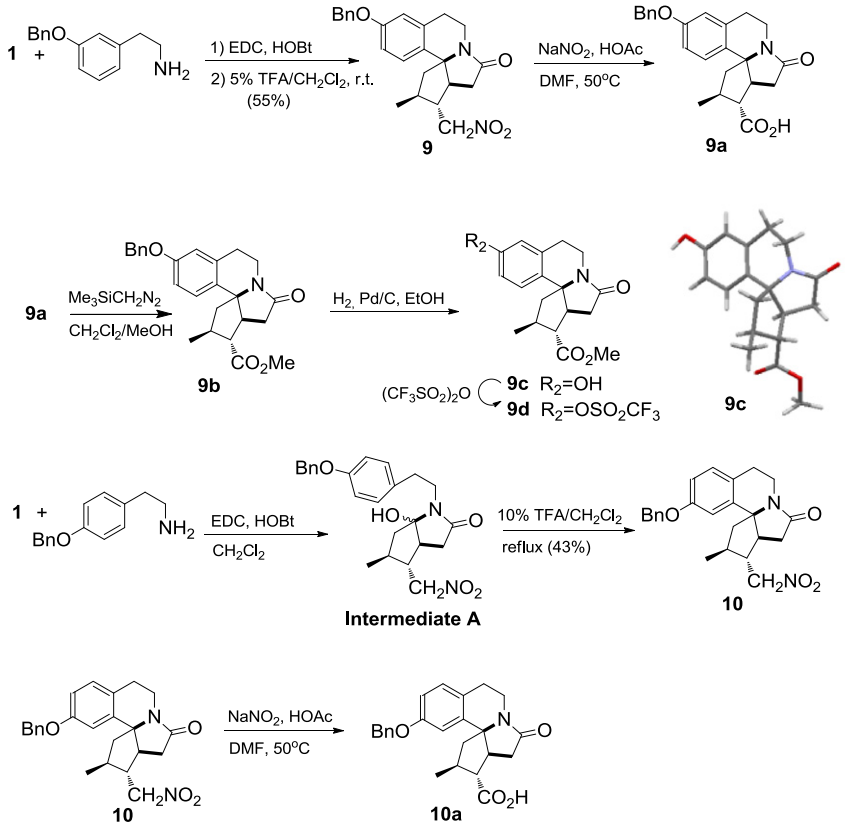


Fig. 6. Preparation of tetracyclic phenols.

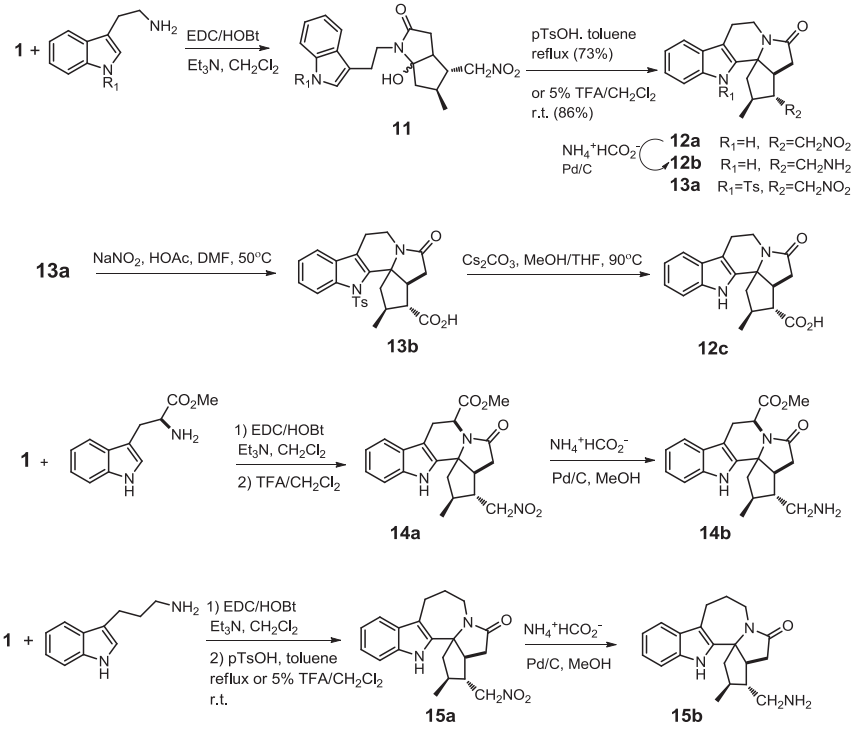


Fig. 7. Preparation of indole-alkaloid-like scaffolds.

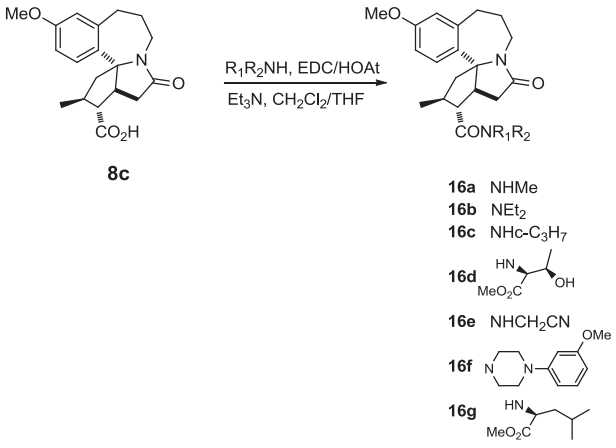


Fig. 8. Scaffold modification with diverse amines.

16a–**g** in 53–72% yield as white solids after RP-HPLC purification. These molecules, along with the building blocks described in this paper, have all been submitted to high-throughput screening against a variety of targets. Interestingly, several of the molecules described here have shown promising activity against TGR5, a G-protein-coupled receptor of current interest in the treatment of type 2 diabetes and metabolic syndrome.[21] These results, while preliminary, suggest that focused library synthesis based on natural product-like building blocks is a practical strategy for new lead drug discovery. In addition, the scaffolds presented in this paper appear to have good drug-like properties. The mean fraction of sp^3 hybridized carbons (Fsp^3) in the core scaffolds (excluding the amide derivatives **16a**–**g**) is 0.55, similar to that of approved drugs.[2] The mean Fsp^3 of compounds **16a**–**g** is 0.60. It may also be noted that the molecular weights of all but one of the compounds in the focused amide library (**16a**–**g**) are less than 500, and all the other Lipinski rule-of-five parameters are satisfied.[22] The calculated log *P* values for this small subset of compounds range from 1.61 (**16d**) to 3.13 (**16f**), which is within the value of 2–3 often suggested as optimal for an oral drug.[23]

3. Conclusion

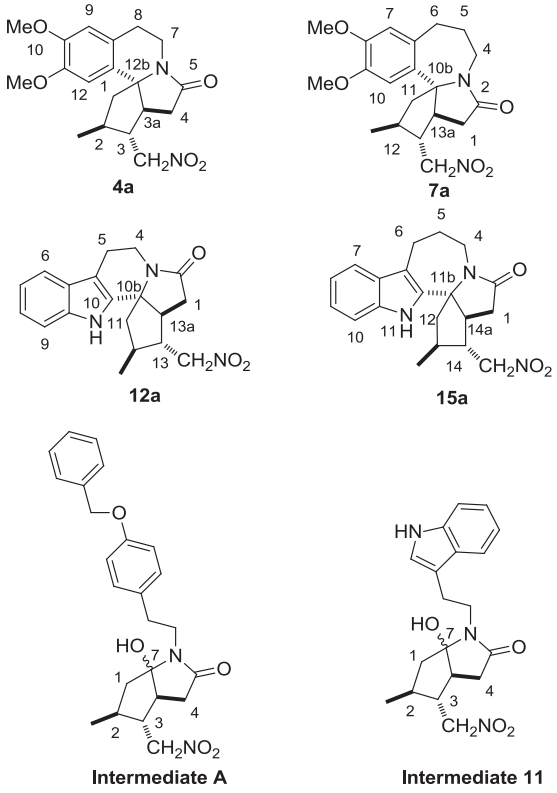
In summary, commercially available enantiopure building block **1** has been used to construct a diverse range of tetra and pentacylic natural product-like scaffolds containing four or five stereogenic centers in good overall yield on a multigram scale. The scaffolds can be designed to contain multiple functional groups. The nitromethyl handle is especially versatile and several of its transformations have been demonstrated. These derivatives can then serve as branch points for post-synthetic optimization of initial leads generated from screening. As previously mentioned, we have incorporated other heterocyles such as pyrrole, furan, and thiophene into these scaffolds and will report these in the future.

4. Experimental

4.1. General

NMR was performed on a Varian Mercury 300 MHz NMR. Chemical shifts were referenced to solvents. Assignments were based on chemical shifts and COSY experiments or DEPT experiments for ^{13}C and in some cases are tentative. Flash chromatography used J.T. Baker Silica Gel, 60–200 mesh. Radial chromatography was performed on a chromatotron (Harrison Research, Model 7924T). HPLC used a Waters 2695 Separation module equipped with a Micromass ZQ mass spectrometer operating in the electrospray mode. High resolution mass spectra were obtained on a Waters Acquity system using method A. HPLC methods: (A) Column: Kinetex C-18, 2.6 μm, 2.1×50 mm, flow rate 0.73 mL/min, gradient 95% H_2O containing 0.05% HCO_2H/5% CH_3CN to 100% CH_3CN in 3 min. (B) Phenomenex C-18 column, 3×100 mm, 5 μm. Flow rate 1.5 mL/min. Gradient containing 95% H_2O with 0.05% HCO_2H/5%

CH_3CN to 100% CH_3CN in 10 min. Purity was assessed by UV absorption at 254 nm or qualitatively by evaporative light scattering (ELSD). Preparative HPLC was performed on a Waters C-18 mass directed purification system. Microwave experiments were performed with a CEM Explorer microwave in closed vials with a constant temperature as indicated and a maximum power of 300 W. Optical rotations were performed on a Rudolph Autopol IV polarimeter. Chemical names and atom numbering for compounds **4c**, **6c**, **7a**, **12c**, and **15a** were provided by the Chemical Abstracts Service and the other compounds were named by analogy. The numbering for NMR assignments is shown in Scheme 1.



Scheme 1. Numbering for NMR assignments.

4.2. General procedures

1. *Amide bond formation*

The carboxylic acid (1.0 equiv) and the amine (1.0–1.1 equiv) were dissolved in CH_2Cl_2 (3–4 mL/mmol) and treated with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) (1.1 equiv), 1-hydroxybenzotriazole hydrate (HOBt) (1.1 equiv), and Et_3N (2.4 equiv or 3.4 equiv for amine hydrochlorides) and stirred at rt overnight. If the reaction was heterogeneous, DMF was added until homogeneity was obtained. The reaction mixture was washed with water, 10% aq HCl solution, and satd aq $NaHCO_3$ solution then dried over anhydrous sodium sulfate and concentrated under reduced pressure.

2. *Cyclization with TFA*

The crude amide was stirred with 5% TFA in CH_2Cl_2 (2 mL/mmol) at rt for the time indicated. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water and satd aq $NaHCO_3$ solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure.

3. *Reduction of the nitromethyl group to the amine*

The nitromethyl compound (1 equiv) was dissolved in methanol (20 mL/mmol) and treated with ammonium formate (0.8 equiv) and 10% Pd/C (wet, Degussa type E101 NE/W, Aldrich Cat. #330108, 0.65 g/mmol of nitromethyl compound). The mixture was heated at 80 °C until HPLC analysis showed complete consumption of starting material (approx. 5 h). The mixture was filtered hot over Celite and the cake was washed with hot MeOH. The filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of EtOAc and MeOH and washed with several small portions of satd aq NaCl solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the aminomethyl compound.

4. *Oxidation of the nitromethyl group to the carboxylic acid*

The nitromethyl compound (1 equiv) was dissolved in DMF (4–5 mL/mmol) and treated with $NaNO_2$ (7 equiv) and HOAc (20 equiv). The reaction mixture was heated at 50 °C for 7 h, then poured onto ice and carefully neutralized with solid $NaHCO_3$. The mixture was extracted with Et_2O (discarded) and then acidified with concd HCl. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was re-dissolved in EtOAc and extracted 10 times with satd aq NaCl solution (necessary to completely remove residual HOAc). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude carboxylic acid.

5. *Deprotection of the Boc group*

The Boc protected amine was dissolved in *p*-dioxane (1–1.5 mL/g) and treated with 4 M HCl in dioxane (5 mL/gm) at rt for 3.5 h. Dry Et_2O was added and the reaction mixture was filtered. The solid was washed with Et_2O and dried under vacuum to give the amine hydrochloride.

*4.2.1. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-nitromethyl,1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**4a**.* [1*S*-(1β,2α,3β)]-(+)-3-Methyl-2-(nitromethyl)-5-oxocyclopentane acetic acid (Aldrich, Cat. #647497) (**1**) (13.0 g, 60.4 mmol) and 3,4-dimethoxyphenethylamine (12.2 g, 67.3 mmol) were coupled using general procedure *1*. The crude product was cyclized according to general procedure *2* (5 h). Purification by flash column chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2 gave **4a**, 12.2 g (56%). HPLC (method A) t_R=1.63 min, (method B) t_R=5.92 min (93%); $[\alpha]_D^{22}$ +140 (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.55 (s, 1H), 6.52 (s, 1H), 4.60–4.68 (m, 2H, CH_2NO_2), 4.20–4.27 (m, 1H, H-7b), 3.86 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.07–3.13 (m, 1H, H-7a or H-8b), 2.95–3.02 (m, 1H, H-8b or H-7a), 2.87–2.91 (m, 1H, H-3a), 2.55–2.65 (m, 2H, H-8a and H-4b), 2.28–2.35 (m, 3H, H-4a, H-1b, and H-2), 2.01–2.07 (m, 1H, H-3), 1.74–1.81 (m, 1H, H-1a), 1.10 (d, *J*=5.9 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (CO), 148.1 (C), 148.0 (C), 133.6 (C), 125.1 (C), 111.7 (CH), 107.0 (CH), 76.5 (CH_2NO_2), 70.3 (C-12b), 56.2 (OMe), 55.9 (OMe), 52.9 (CH), 51.5 (CH_2), 47.2 (CH), 37.7 (CH), 36.2 (CH_2), 35.9 (CH_2), 27.0 (CH_2), 17.5 (2-CH_3); MS (ES): $C_{19}H_{24}N_2O_5$ calcd: 361.1764 $[M+H]^+$; found: 361.1773 $[M+H]^+$.

*4.2.2. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-aminomethyl,1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**4b**.* Compound **4a** (5.18 g, 14.4 mmol) was reduced to the amine according to general procedure *3*. The residue was dissolved in anhydrous MeOH and cooled on an ice bath. HCl (g) was bubbled in, followed by addition of dry Et_2O. Filtration and drying

under vacuum gave **4b** (HCl salt) as a white solid, 2.77 g (58%). HPLC (method B) t_R=2.13 min (95%). For analytical purposes the hydrochloride salt (2.60 g) was converted to the free base by partitioning between CH_2Cl_2 and satd aq K_2CO_3 solution. *Y*=2.20 g. HPLC (method B) t_R=2.13 min (100%), (method A) t_R=1.00 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.45 (s, 1H), 4.09–4.17 (m, 1H, H-7b), 3.76 (s, 3H, OMe), 3.73 (s, 3H, OMe), 2.93–3.07 (m, 1H), 2.79–2.95 (m, 3H), 2.66–2.70 (m, 1H), 2.54–2.66 (m, 2H), 2.16–2.28 (m, 2H), 2.00–2.06 (m, 1H), 1.57–1.66 (m, 1H), 1.35–1.40 (m, 1H), 0.94 (d, *J*=6.1Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6 (CO), 147.7 (2C), 135.0 (C), 125.0 (C), 111.5 (CH), 107.6 (CH), 70.7 (C-12b), 57.4 (CH), 56.1 (OMe), 55.8 (OMe), 52.0 (CH_2), 47.3 (CH), 42.6 (CH_2), 37.5 (CH_2), 36.9 (CH), 35.8 (CH_2), 27.1 (CH_2), 18.1 (2-CH_3); MS (ES): $C_{19}H_{26}N_2O_3$. calcd: 331.2022 $[M+H]^+$; found: 331.2016 $[M+H]^+$.

*4.2.3. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid,1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**4c**.* Compound **4a** (12.0 g, 33.3 mmol) was oxidized according to general procedure *4* to give carboxylic acid **4c** as an orange solid, 5.57 g (48%) sufficiently pure for further use. HPLC (method B) t_R=4.12 min (90%). An analytical sample was prepared by HPLC; t_R=1.55 (method A); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.55 (s, 1H), 4.21–4.28 (m, 1H, H-7b), 3.87 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.12–3.24 (m, 2H, H-7a and H-3a), 2.93–3.05 (m, 1H, H-8b), 2.58–2.70 (m, 3H, H-8a, H-4b, and H-2), 2.39–2.51 (m, 2H, H-3 and H-4a), 2.27–2.34 (dd, *J*=13.0, 7.0 Hz, 1H, H-1b), 1.80 (t, *J*=11.4 Hz, 1H, H-1a), 1.16 (d, *J*=6.4 Hz, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4 (CO), 172.6 (CO), 148.5 (C), 148.4 (C), 133.8 (C), 125.3 (C), 112.3 (CH), 108.3 (CH), 71.8 (C-12b), 59.4 (CH), 56.3 (OMe), 56.0 (OMe), 51.3 (CH_2), 48.1 (CH), 39.2 (CH), 37.1 (CH_2), 36.2 (CH_2), 27.0 (CH_2), 18.4 (2-CH_3); MS (ES): $C_{19}H_{23}NO_5$ calcd: 346.1654 $[M+H]^+$; found: 346.1662 $[M+H]^+$.

*4.2.4. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-hydroxymethyl,1,2,-3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,-12bR)-**4d**.* Compound **4c** (3.00 g, 8.69 mmol) was dissolved in dry THF (60 mL) and treated with 9.0 mL of 1 M borane/THF at rt for 1.5 h. The reaction mixture was treated with 10% aq HCl solution and then extracted three times with a mixture of EtOAc and MeOH. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with 5% MeOH in CH_2Cl_2 to give **4d**, 2.26 g (79%) as a white foam. HPLC (method B) t_R=4.11 min (95%). An analytical sample was prepared by HPLC; t_R=1.31 min (method A); $[\alpha]_D^{22}$ +132.6 (*c* 0.91 $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.79 (s, 1H), 6.61 (s, 1H), 3.74–3.98 (m, 1H, H-7b), 3.70 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.55–3.62 (m, 2H, CH_2OH), 3.00–3.15 (m, 1H, H-7a), 2.70–2.77 (m, 2H, H-8b and H-3a), 2.51–2.60 (m, 1H, H-8a), 2.33–2.43 (m, 1H, H-4b), 2.12–2.25 (m, 2H, H-4a and H-2), 2.02–2.16 (m, 1H, H-1b), 1.59–1.66 (t, *J*=12.1 Hz, 1H, H-1a), 1.35–1.42 (m, 1H, H-3), 0.95 (d, *J*=6.3 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.5 (CO), 148.1 (2C), 135.7 (C), 125.4 (C), 112.7 (CH), 108.7 (CH), 70.6 (C-12b), 60.8 (CH_2), 57.7 (CH), 56.3 (OMe), 56.1 (OMe), 52.5 (CH_2), 46.6 (CH), 39.4 (CH_2), 37.5 (CH_2), 36.0 (CH), 27.2 (CH_2), 18.8 (2-CH_3); MS (ES): $C_{19}H_{25}NO_4$ calcd: 332.1862 $[M+H]^+$; found: 332.1877 $[M+H]^+]^+$.

*4.2.5. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-formyl-1,2,3,3a,4,-5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**4e**.* Compound **4d** (0.43 g, 1.3 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and treated with $NaHCO_3$ (0.13 g, 1.2 equiv) and Dess–Martin periodinane (0.66 g, 1.2 equiv). After 3 h the reaction was quenched with 1 M aq sodium thiosulfate and satd aq $NaHCO_3$ solutions, then extracted twice with Et_2O. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by radial chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2 to give **4e** as a white foam, 0.19 g (44%). HPLC (method B) t_R=4.41 min (97%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H, CHO), 6.66 (s, 1H), 6.49 (s, 1H), 4.15–4.22 (m, 1H, H-7b), 3.82 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.10–3.20 (m, 1H), 3.04–3.08 (m, 1H), 2.88–2.98 (m, 1H), 2.49–2.66 (m, 4H), 2.22–2.28 (dd, *J*=17.7, 2.1 Hz, 1H), 2.13–2.20 (dd, *J*=13.4, 7.2 Hz, 1H), 1.78–1.87 (dd, *J*=13.4, 9.2 Hz, 1H), 1.14 (d, *J*=6.0 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, (CHO), 172.5 (CO), 148.3, 148.2, 133.4, 125.6, 111.8, 107.7, 72.3, 67.2, 56.4, 56.1, 50.6, 44.3, 37.5, 37.1, 36.3, 27.2, 19.4; MS (ES): $C_{19}H_{23}NO_4$ calcd: 330.1705 $[M+H]^+$; found: 330.1704 $[M+H]^+$.

*4.2.6. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-(N-tert-butoxycarbonyl)amino-1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**4f**.* Compound **4c** (3.05 g, 8.84 mmol) was dissolved in dry THF (100 mL) and treated with Bu_4NBr (0.60 g, 1.86 mmol), NaN_3 (2.20 g, 33.8 mmol), di-*tert*-butyldicarbonate (2.50 g, 11.4 mmol), and $Zn(OTf)_2$ (0.11 g, 0.30 mmol) and then heated at 45 °C for 23 h. The reaction mixture was cooled to rt and a solution of $NaNO_2$ (8.00 g, 119 mmol) in water (75 mL) was added. After stirring for 1 h the reaction mixture was extracted twice with EtOAc. The organic layers were washed twice with satd aq NH_4Cl solution, once with satd aq $NaHCO_3$ solution then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was passed over a pad of silica gel, eluting with 5% MeOH in CH_2Cl_2 to give **4f**, 2.50 g (68%), sufficiently pure for deprotection. An analytical sample was prepared by HPLC; t_R=1.81 min (method A); ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): δ 6.83 (s, 1H), 6.51 (s, 1H), 4.81 (m, 1H, NH), 4.17–4.24 (m, 1H, H-7b), 3.27–3.37 (m, 1H, H-3), 3.06–3.15 (m, 1H, H-7a), 2.88–3.04 (m, 1H, H-8b), 2.79 (br m, 1H, H-4b), 2.52–2.58 (m, 3H, H-3a, H-4a and H-8a), 2.29 (br m, 1H, H-2), 2.15–2.20 (m, 1H, H-1b), 1.65–1.75 (m, 1H, H-1a), 1.44 (s, 9H, *t*-Bu), 1.05 (d, *J*=6.4 Hz, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7 (CO), 155.5 (CO), 148.0 (2C), 134.3 (C), 125.1 (C), 111.6 (CH), 107.7 (CH), 79.4 ($C(CH_3)_3$), 69.0 (C-12b), 65.6 (CH), 56.2 (OMe), 55.8 (OMe), 49.3 (2C; 1CH, 1CH_2), 39.5 (CH), 35.7 (CH_2), 28.3 (4C overlap, $C(CH_3)_3$ and 1 CH_2), 27.0 (CH_2), 17.1 (2-CH_3); MS (ES): $C_{23}H_{32}N_2O_5$ calcd: 417.2390 $[M+H]^+$; found: 417.2373 $[M+H]^+$.

*4.2.7. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-amino-1,2,3,3a,4,5,-7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**4g**.* Compound **4f** (2.50 g, 6.0 mmol) was deprotected using general procedure **5** to give the HCl salt of **4g** as an off-white solid, 2.00 g (94%). HPLC (method A) t_R=0.93 min. For NMR analysis the free base was made by partitioning the HCl salt between CH_2Cl_2 and satd aq K_2CO_3 solution. HPLC (method B) t_R=1.78 min; $[\alpha]_D^{24}$ +182.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.50 (s, 1H), 4.06–4.23 (m, H-7a), 3.85 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.03–3.09 (m, 1H), 2.98–3.00 (m, 1H), 2.61–2.65 (m, 1H), 2.47–2.58 (m, 3H), 2.34–2.44 (m, 1H), 2.13–2.22 (m, H-1b), 1.96 (m, 1H, H-2), 1.88 (br s, 2H, NH_2), 1.66–1.74 (m, 1H, H-1a), 1.04 (d, *J*=6.1 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0 (CO), 147.4 (2C overlap), 134.2, 125.2, 111.6, 107.5, 69.6, 66.2, 56.2 (OMe), 55.9 (OMe), 52.5, 49.8, 43.1, 35.7 (2C overlap), 27.1, 17.0 (2-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.0 (CO), 148.2 (C), 148.1 (C) (these two aromatic carbons overlap at 147.4 ppm in $CDCl_3$), 133.8 (C), 125.0 (C), 112.5 (CH), 108.6 (CH), 69.5 (C-12b), 63.8 (CH), 56.8 (OMe), 55.9 (OMe), 49.6 (CH_2), 47.6 (CH), 8.0 (CH), 35.6 (CH_2), 35.2 (CH_2) (these two CH_2s overlap at 35.7 ppm in $CDCl_3$), 26.7 (CH_2), 16.9 (2-CH_3); MS (ES): $C_{18}H_{24}N_2O_3$ calcd: 317.1865 $[M+H]^+$; found: 317.1858 $[M+H]^+$.

*4.2.8. Compound **4h**.* Compound **4c** (100 mg, 0.29 mmol) was treated with benzoic hydrazide (1.1 equiv, 44 mg), polymer supported triphenylphosphine (570 mg, 3 equiv, Polymer Systems 1.52 mmol/g), and dry CH_3CN (3 mL). Then Cl_3CCN (60 μL, 2 equiv) was added followed by irradiation in the microwave at 150 °C for

20 min. The reaction mixture was filtered and the resin was washed with MeOH. The filtrate was concentrated under reduced pressure and the residue was purified by HPLC to give **4h** as an oil, 12 mg. HPLC (method A) t_R=1.75 min, (method B) t_R=5.57 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–8.08 (m, 2H, Ph), 7.45–7.57 (m, 3H, Ph), 6.86 (s, 1H), 6.56 (s, 1H), 4.25–4.33 (m, 1H), 3.90 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.32–3.40 (m, 1H), 3.15–3.24 (m, 1H), 2.96–3.09 (m, 2H), 2.75–2.86 (m, 1H, H-2), 2.46–2.72 (m, 3H), 2.39–2.46 (dd, J=13.2, 7.0 Hz, 1H, H-1b), 1.90–1.99 (t, J=11.4 Hz, 1H, H-1a), 1.22 (d, J=6.5 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (CO), 167.2, 165.2, 148.2, 148.1, 133.1, 131.9, 129.2, 128.8, 125.3, 123.7, 111.8, 107.2, 71.3 (C-12b), 56.2, 55.9, 51.4, 51.3, 49.3, 40.3, 36.7, 36.1, 27.0, 18.3 (2-CH_3); MS (ES): $C_{26}H_{27}N_3O_4$ calcd: 446.2080 $[M+H]^+$; found: 446.2063 $[M+H]^+$.

*4.2.9. Compound **4i**.* To a solution of phenyl acetylene (305 μL, 5 equiv), DMAP (15 mg), di-*tert*-butyldicarbonate (220 mg, 1 mmol, 1.8 equiv) in dry CH_3CN (5 mL) was added **4a** (200 mg, 0.56 mmol). The reaction mixture stirred at rt overnight whereupon it was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with satd aq NaCl solution, dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by radial chromatography on silica gel, eluting with 1–2% MeOH in CH_2Cl_2 to give **4i** as a white foam, 74 mg (30%). HPLC (method A) t_R=2.03 min, (method B) t_R=6.47 min (100%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75–7.81 (m, 2H, Ph), 7.44–7.51 (m, 3H, Ph), 6.84 (s, 1H), 6.55 (s, 1H), 6.46 (s, 1H), 4.25–4.31 (m, 1H, H-7b), 3.91 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.08–3.18 (m, 2H, H-7a and H-8b), 2.98–3.05 (m, 1H, H-3a), 2.77–2.81 (m, 1H, H-3), 2.56–2.68 (m, 3H, H-8a, H-2 and H-4b), 2.35–2.42 (m, 2H, H-4a and H-1b), 1.85–1.93 (t, J=12.8 Hz, 1H, H-1a), 1.12 (d, J=6.1 Hz, 3H, 2-CH_3). Assignments are tentative, based on the COSY spectrum; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6 (CO), 170.3, 164.6, 148.1, 133.8, 130.3, 129.0, 127.3, 125.8, 125.4, 111.7, 107.6, 105.0, 98.5, 71.0 (C-12b), 56.3, 55.9, 52.6, 51.6, 50.2, 41.0, 36.5, 36.0, 27.1, 18.0 (2-CH_3); MS (ES): $C_{27}H_{28}N_2O_4$ calcd: 445.2127 $[M+H]^+$; found: 445.2122 $[M+H]^+$.

*4.2.10. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-nitromethyl-1,2,3,3a,4,5,7,8-octahydro-10-methoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**5a**.* Compound **1** (30.6 g, 0.132 mol) and 3-methoxyphenethylamine (24.0 g, 0.158 mol) were coupled using general procedure *1*, then cyclized according to general procedure *2* (6.5 h). The crude product was purified by flash column chromatography on silica gel, eluting with 1–2% MeOH in CH_2Cl_2 to yield **5a**, 17.2 g (39%) as white foam. Additional impure material was also obtained. A smaller scale run on 5.0 g of **1** gave **5a** in 46% yield. HPLC (method B) t_R=5.45 min (91%). An analytical sample was prepared by HPLC; t_R=1.77 min (method A); $[\alpha]_D^{24}$ +128.7 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$): δ 7.05 (d, J=8.5 Hz, 1H, H-12), 6.75 (dd, J=8.5, 2.0 Hz, 1H, H-11), 6.60 (d, J=2.0 Hz, 1H, H-9), 4.62–4.72 (m, 2H, CH_2NO_2), 4.06–4.13 (m, 1H, H-7b), 3.72 (s, 3H, OMe), 3.16–3.25 (m, 1H, H-7a), 2.90–3.01 (m, 1H, H-8b), 2.79–2.85 (m, 1H, H-3a), 2.67–2.73 (m, 1H, H-8a), 2.50–2.60 (m, 1H, H-4b), 2.24–2.30 (m, 1H, H-4a), 2.10–2.22 (m, 3H, H-2, H-3 and H-1b), 1.74–1.81 (m, 1H, H-1a), 1.06 (d, J=4.7 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$): δ 173.2 (CO), 158.7 (C), 134.4 (C), 134.2 (C), 125.1 (CH), 114.0 (CH), 113.3 (CH), 77.4 (CH_2NO_2), 71.3 (C-12b), 55.2 (OMe), 52.8 (CH), 51.6 (CH_2), 48.0 (CH), 38.0 (CH), 36.6 (CH_2), 36.2 (CH_2), 27.8 (CH_2), 17.1 (2-CH_3); MS (ES): $C_{18}H_{22}N_2O_4$ calcd: 331.1658 $[M+H]^+$; found: 331.1656 $[M+H]^+$.

*4.2.11. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-aminomethyl-1,2,3,3a,4,5,7,8-octahydro-10-methoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**5b**.* Compound **5a** (5.17 g, 15.7 mmol) was reduced to the amine following general procedure *3*. The crude product was dissolved in anhydrous MeOH and cooled on an ice bath. HCl (g) was bubbled in, followed by addition of dry Et_2O. A gummy residue was obtained, so the solvent was removed under reduced pressure. Trituration with Et_2O gave the white solid HCl salt of **5b**. HPLC (method A) t_R=1.08 min. For NMR analysis the free base was made by partitioning the HCl salt between CH_2Cl_2 and satd aq K_2CO_3 solution to give **5b** as yellow oil, 1.82 g (39%). HPLC (method B) t_R=1.78 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, J=8.8 Hz, 1H, H-12), 6.51 (dd, J=8.8, 2.4 Hz, 1H, H-11), 6.32 (d, J=2.4 Hz, 1H, H-9), 3.89–3.96 (m, 1H, H-7b), 3.48 (s, 3H, OMe), 2.84–2.94 (m, 1H), 2.60–2.78 (m, 3H), 2.22–2.51 (m, 3H), 2.06–2.12 (m, 1H), 1.81–1.94 (m, 2H), 1.35–1.48 (m, 3H), 1.18 (m, 1H), 0.77 (d, J=5.8 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (CO), 157.9 (C), 135.2 (C), 134.1 (C), 125.1 (CH), 113.4 (CH), 112.7 (CH), 70.4 (C-12b), 57.0 (CH), 54.9 (OMe), 52.0 (CH_2), 47.3 (CH), 42.6 (CH_2), 37.2 (CH_2), 36.7 (CH), 35.5 (CH_2), 27.7 (CH_2), 17.9 (2-CH_3); MS (ES): $C_{18}H_{24}N_2O_2$ calcd: 301.1916 $[M+H]^+$; found: 301.1911 $[M+H]^+$.

*4.2.12. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid-1,2,3,3a,4,5,7,8-octahydro-10-methoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**5c**.* Compound **5a** (11.7 g, 35.4 mmol) was oxidized according to general procedure *4* to give carboxylic acid **5c** as an orange solid, 9.47 g (86%). An analytical sample was prepared by HPLC; t_R=1.46 min (method A), t_R=4.53 min (method B); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.20 (d, J=8.8 Hz, H-12), 6.82 (dd, J=8.8, 2.6 Hz, 1H, H-11), 6.65 (d, J=2.6 Hz, 1H, H-9), 3.89–3.97 (m, 1H, H-7b), 3.71 (s, 3H, OMe), 3.10–3.16 (m, 1H, H-7a), 2.96–3.04 (m, 1H, H-3a), 2.76–2.82 (m, 1H, H-8b), 2.62–2.72 (m, 1H, H-8a), 2.40–2.50 (m, 2H, H-2 and H-4b), 2.20–2.32 (m, 2H, H-3 and H-4a), 2.04–2.11 (dd, J=13.2, 7.0 Hz, 1H, H-1b), 1.79 (t, J=12.2 Hz, 1H, H-1a), 1.03 (d, J=6.2 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.1 (CO), 172.0 (CO), 158.6 (C), 135.3 (C), 135.2 (C), 125.7 (CH), 114.4 (CH), 113.6 (CH), 71.2 (C-12b), 59.7 (CH), 55.8 (OMe), 51.6 (CH_2), 48.2 (CH), 38.9 (CH), 37.1 (CH_2), 36.1 (CH_2), 27.8 (CH_2), 18.8 (2-CH_3); MS (ES): $C_{18}H_{21}NO_4$ calcd: 316.1549 $[M+H]^+$; found: 316.1532 $[M+H]^+$.

*4.2.13. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-(N-tert-butoxycarbonyl)amino-1,2,3,3a,4,5,7,8-octahydro-10-methoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**5f**.* Compound **5c** (3.00 g, 9.50 mmol) was dissolved in dry THF (100 mL) and treated with Bu_4NBr (0.58 g, 1.80 mmol), NaN_3 (2.20 g, 33.8 mmol), di-*tert*-butyldicarbonate (2.50 g, 11.4 mmol), and $Zn(OTf)_2$ (0.11 g, 0.30 mmol) and then heated at 45 °C for 18 h. The reaction mixture was cooled to rt and a solution of $NaNO_2$ (8.00 g, 119 mmol) in water (75 mL) was added. After stirring for 1 h the reaction mixture was diluted with EtOAc. After stirring for another 20 min, the reaction mixture was extracted twice with EtOAc. The organic layers were washed twice with satd aq NH_4Cl solution, twice with satd aq $NaHCO_3$ solution then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was passed over a pad of silica gel, eluting with 80:20 hexanes/EtOAc, then with 2% MeOH in CH_2Cl_2 to give **5f**, 2.82 g (77%), sufficiently pure for deprotection. An analytical sample was prepared by HPLC; t_R=1.94 min (method A), t_R=5.99 min (method B); ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): $\delta\delta$7.14 (d, J=8.5 Hz, 1H, H-12), 6.74 (d, J=8.5 Hz, 1H, H-11), 6.57 (s, 1H, H-9), 4.87 (d, J=7.9 Hz, 1H, NH), 4.13–4.21 (m, 1H, H-7b), 3.74 (s, 3H, OMe), 3.39–3.42 (m, 1H, H-3), 3.08–3.14 (m, 1H, H-7a), 2.95–3.02 (m, 1H, H-8b), 2.45–2.69 (m, 4H, H-8a, H-4b, H-4a, H-3a), 2.10–2.16 (m, 2H, H-2 and H-1b), 1.66–1.74 (m, 1H, H-1a), 1.45 (s, 9H, t-Bu), 1.04 (d, J=5.9 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (CO), 158.2 (C), 155.8 (CO), 134.7 (C), 134.4 (C), 125.1 (CH), 113.6 (CH), 113.1 (CH), 79.4 (C), 68.7 (C), 64.8 (CH), 55.2 (OMe), 50.0 (CH), 49.4 (CH_2), 40.1 (CH), 35.6 (CH_2), 28.4 (C(CH_3)$_3$), 27.81 (2CH_2 overlap), 16.9 (2-CH_3); MS (ES): $C_{22}H_{30}N_2O_4$ calcd: 387.2284 $[M+H]^+$; found: 387.2284 $[M+H]^+$.

*4.2.14. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-amino-1,2,3,3a,4,5,7,8-octahydro-10-methoxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**5g**.* Compound **5f** (2.40 g, 6.2 mmol) was deprotected using general procedure *5* to give the HCl salt of **5g** as a white solid, 1.92 g (96%).

HPLC (method A) t_R=1.09 min, (method B) t_R=2.04 min. For NMR analysis the free base was prepared by partitioning the HCl salt of **5g** between CH_2Cl_2 and satd aq K_2CO_3 solution. $[\alpha]_D^{24}$ +108.2 (*c* 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, *J*=8.8 Hz, 1H, H-12), 6.73 (d, *J*=8.3 Hz, 1H, H-11), 6.54 (s, 1H, H-9), 4.12–4.18 (m, 1H, H-7b), 3.72 (s, 3H, OMe), 2.90–3.10 (m, 2H), 2.33–2.62 (m, 5H), 2.09–2.16 (m, 1H), 1.92 (m, 1H), 1.62–1.70 (m, 1H, H-1a), 1.47 (br s, 2H, NH_2), 1.01 (d, *J*=6.1 Hz, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (CO), 158.0 (C), 134.8 (C), 134.2 (C), 125.2 (CH), 113.5 (CH), 113.0 (CH), 69.0 (C-12b), 66.5 (CH), 55.1 (OMe), 52.5 (CH), 50.0 (CH_2), 42.9 (CH), 35.7 (CH_2), 35.4 (CH_2), 27.7 (CH_2), 16.8 (2-CH_3); MS (ES): $C_{17}H_{22}N_2O_2$ calcd: 287.1760 $[M+H]^+$; found: 287.1767 $[M+H]^+$.

*4.2.15. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-nitromethyl-7-carboxylic acid 1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,7S,12bR)-methyl ester-**6a**.* Compound **1** (5.20 g, 22.6 mmol) and L-3,4-dimethoxyphenylalanine methyl ester (5.40 g, 22.6 mmol) were coupled using general procedure *1*, followed by cyclization according to general procedure *2* (6 h). The crude product was purified by flash column chromatography on silica gel, eluting with 1–2% MeOH in CH_2Cl_2 to yield **6a**, 6.41 g (68%) as pale yellow foam. An analytical sample was prepared by HPLC; t_R=1.72 min (method A), t_R=5.36 min (method B); $[\alpha]_D^{24}$ +12.7 (*c* 0.805, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.64 (s, 1H), 4.62–4.72 (m, 2H, CH_2NO_2), 4.41–4.48 (dd, *J*=11.3, 7.1 Hz, 1H, H-7), 3.88 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.18–3.25 (m, 2H, H-3a and H-8b), 2.90–3.00 (dd, *J*=18.1, 10.6 Hz, 1H, H-8a), 2.68–2.78 (dd, *J*=18.1, 10.6 Hz, 1H, H-4b), 2.39–2.47 (dd, *J*=18.1, 4.2 Hz, 1H, H-4a), 2.12–2.23 (m, 2H, H-1b and H-3), 1.94–1.99 (m, 2H, H-1a and H-2), 1.07 (d, *J*=6.0 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 60 °C): δ 173.2 (CO), 171.9 (CO), 149.0 (C), 148.5 (C), 135.3 (C), 124.7 (C), 113.0 (CH), 107.6 (CH), 76.8 (CH_2NO_2), 70.93 (C-12b), 56.8 (OMe), 56.5 (OMe), 53.5 (CH), 52.6 (CO_2Me), 52.1 (CH), 50.1 (CH_2), 44.4 (CH), 37.0 (CH_2), 36.9 (CH), 30.1 (CH_2), 16.9 (2-CH_3); MS (ES): $C_{21}H_{26}N_2O_7$ calcd: 419.1818 $[M+H]^+$; found: 419.1807 $[M+H]^+$.

*4.2.16. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-aminomethyl-7-carboxylic acid 1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,7S,12bR)-methyl ester-**6b**.* Compound **6a** (3.00 g, 7.2 mmol) was reduced to the amine following general procedure *3*. The crude product was dissolved in anhydrous MeOH and cooled on an ice bath. HCl (g) was bubbled in, followed by addition of dry Et_2O. A solid did not form, so the mixture was concentrated under reduced pressure to give a pinkish foam of the HCl salt of **6b**, 2.20 g (79%). HPLC (method A) t_R=1.09 min, (method B) t_R=2.49 min (85%). The compound was further purified by making the free base by partitioning between CH_2Cl_2 and satd aq K_2CO_3 solution, followed by flash chromatography on silica gel, eluting with 5–10% MeOH in CH_2Cl_2 and then with 10% 2 M NH_3 in MeOH/90% CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): δ 6.94 (s, 1H), 6.71 (s, 1H), 4.41–4.47 (m, 1H, H-7), 3.83 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.50–3.70 (br s, 2H, NH_2), 3.07–3.19 (m, 3H, H-3a, H-8b, and $CH_aH_bNH_2$), 2.91–3.01 (m, 2H, H-8a and $CH_aH_bNH_2$), 2.67–2.77 (dd, *J*=18.1, 10.7 Hz, 1H, H-4b), 2.46–2.54 (dd, *J*=18.1, 4.7 Hz, 1H, H-4a), 2.09–2.18 (m, 1H, H-1b), 1.80–1.91 (m, 2H, H-1a and H-2), 1.63–1.70 (m, 1H, H-3), 1.00 (d, *J*=5.9 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 173.7 (CO), 172.0 (CO), 147.9 (C), 147.7 (C), 136.0 (C), 124.2 (C), 111.7 (CH), 107.4 (CH), 71.0 (C-12b), 56.4 (2C overlap, OMe and CH– at 60 °C these resonances are separated: 56.6 and 56.5 ppm), 56.1 (OMe), 52.5 (CO_2Me), 52.0 (CH), 50.4 (CH_2), 44.4 (CH), 42.5 (CH_2), 37.9 (CH_2), 36.4 (CH), 30.0 (CH_2), 17.3 (2-CH_3); MS (ES): $C_{21}H_{28}N_2O_5$ calcd: 389.2076 $[M+H]^+$; found: 389.2060 $[M+H]^+$.

*4.2.17. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3,7-dicarboxylic acid 1,2,3,3a,4,5,7,8-octahydro-10,11-dimethoxy-2-methyl-5-oxo-(2S,3R,3aS,7S,12bR)-7-methyl ester-**6c**.* Compound **6a** (3.15 g, 7.54 mmol) was oxidized according to general procedure *4* to give carboxylic acid **6c** as a pale orange solid, 2.34 g (72%). An analytical sample was prepared by HPLC; t_R=1.42 min (method A), t_R=4.41 min (method B); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (s, 1H), 6.74 (s, 1H), 4.40–4.47 (dd, *J*=11.6, 6.9 Hz, 1H, H-7), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.46–3.51 (m, 1H, H-3a), 3.18–3.26 (dd, *J*=15.4, 6.9 Hz, 1H, H-8b), 2.91–3.00 (dd, *J*=15.1, 11.8 Hz, 1H, H-8a), 2.76–2.82 (dd, *J*=17.6, 10.8 Hz, 1H, H-4b), 2.50–2.60 (dd, *J*=17.9, 6.2 Hz, 1H, H-4a), 2.35–2.48 (m, 2H, H-2 and H-3), 2.20 (t, *J*=12.1 Hz, 1H, H-1b), 1.97–2.03 (m, 1H, H-1a), 1.16 (d, *J*=6.1 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1 (CO), 173.0 (CO), 171.9 (CO), 148.1 (C), 147.9 (C), 135.1 (C), 123.9 (C), 111.6 (CH), 107.5 (CH), 71.6 (C-12b), 59.2 (CH), 56.2 (OMe), 56.1 (OMe), 52.6 (CO_2Me), 52.0 (CH), 50.0 (CH_2), 45.3 (CH), 39.3 (CH), 37.8 (CH_2), 30.0 (CH_2), 17.9 (2-CH_3); MS (ES): $C_{21}H_{25}NO_7$ calcd: 404.1709 $[M+H]^+$; found: 404.1720 $[M+H]^+$.

*4.2.18. 4H-Cyclopenta[2,3]pyrrolo[2,1-a][2]benzazepine-2(1H)-one,5,6,11,12,13,13a-hexahydro-8,9-dimethoxy-12-methyl-13-(nitromethyl)-(10bR,12S,13R,13aS)-**7a**.* 3,4-Dimethoxycinnamonitrile (5.00 g) was dissolved in a mixture of EtOH (100 mL) and concd HCl (10 mL) and hydrogenated with 10% Pd/C (wet, Degussa Type E101, Aldrich) at 65 psi on a Parr shaker for 70 h. The reaction mixture was filtered over Celite and the filtrate was concentrated to remove most of the EtOH. The residue was extracted twice with Et_2O (discarded) and then cooled with ice and made strongly basic with 10 M aq NaOH solution. The basic aqueous layer was extracted with Et_2O and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 3-(3,4-dimethoxyphenyl)propylamine (5.07 g) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68–6.78 (m, 3H), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.70 (t, *J*=7.0 Hz, 2H), 2.58 (t, *J*=7.2 Hz, 2H), 1.70–1.75 (m, 2H), 1.17 (br s, 2H, NH_2).

Compound **1** (6.35 g, 29.5 mmol) and 3-(3,4-dimethoxyphenyl) propylamine (5.37 g, 27.5 mmol) were coupled using general procedure *1*. The crude product was cyclized according to general procedure *2* (7 h). Purification by flash column chromatography on silica gel, eluting with 1% MeOH in CH_2Cl_2 gave **7a**, 6.13 g (60%) as a pale orange foam. An analytical sample was prepared by HPLC; t_R=1.63 min (method A), t_R=5.20 min (83%) (method B); $[\alpha]_D^{24}$ +133.6 (*c* 0.855, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.50 (s, 1H), 4.57–4.59 (m, 2H, CH_2NO_2), 4.18–4.26 (m, 1H, H-4b), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.04–3.08 (m, 1H, H-4b), 2.85–2.91 (m, 1H), 2.70–2.75 (m, 1H), 2.52–2.61 (m, 2H), 2.29–2.38 (m, 2H), 2.07–2.22 (m, 2H), 1.90–1.98 (m, 2H), 1.77 (m, 1H), 1.13 (d, *J*=5.0 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (CO), 147.4 (C), 147.3 (C), 135.8 (C), 132.6 (C), 114.0 (CH), 110.1 (CH), 76.2 (CH_2NO_2), 75.5 (C-10b), 56.3 (OMe), 55.8 (OMe), 51.6 (CH), 50.8 (CH), 47.9 (CH_2), 38.6 (CH), 38.0 (CH_2), 33.9 (CH_2), 32.2 (CH_2), 26.5 (CH_2), 18.1 (12-CH_3); MS (ES): $C_{20}H_{26}N_2O_5$ calcd: 375.1920 $[M+H]^+$; found: 375.1927 $[M+H]^+$.

*4.2.19. 4H-Cyclopenta[2,3]pyrrolo[2,1-a][2]benzazepine-2(1H)-one,5,6,11,12,13,13a-hexahydro-8,9-dimethoxy-12-methyl-13-(aminomethyl)-(10bR,12S,13R,13aS)-**7b**.* Compound **7a** (1.90 g, 5.10 mmol) was reduced to the amine following general procedure *3*. The crude product was purified by flash chromatography on silica gel, eluting with 5–10% MeOH in CH_2Cl_2 to give **7b** as a yellow oil, 0.57g (33%). HPLC (method A) t_R=0.92 min, (method B) t_R=2.37 min; ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): δ 6.76 (s, 1H), 6.44 (s, 1H), 4.10–4.21 (m, 1H, H-4b), 3.77 (s, 3H, OMe), 3.74 (s, 3H, OMe), 2.95–3.04 (m, 1H, H-4a), 2.78–2.87 (m, 2H), 2.65–2.73 (m, 2H), 2.41–2.55 (m, 2H), 2.10–2.23 (m, 3H), 1.96–2.03 (m, 1H), 1.80–1.90 (m, 1H), 1.66–1.73 (m, 1H), 1.38 (br s, 2H, NH_2), 1.25–1.35 (m, 1H), 1.00 (d, *J*=6.3 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 60 °C): δ 173.8 (CO), 147.7 (C), 147.6 (C), 137.5 (C),

133.0 (C), 114.9 (CH), 111.8 (CH), 76.3 (C-10b), 56.7 (OMe), 56.1 (OMe), 55.2 (CH), 51.8 (CH_2), 48.6 (CH), 42.5 (CH_2), 38.3 (CH_2), 38.0 (CH), 35.2 (CH_2), 32.7 (CH_2), 26.8 (CH_2), 18.9 (12-CH_3); MS (ES): $C_{20}H_{28}N_2O_3$ calcd: 345.2178 $[M+H]^+$; found: 345.2182 $[M+H]^+$.

*4.2.20. 4H-Cyclopenta[2,3]pyrrolo[2,1-a][2]benzazepine-2(1H)-one,5,6,11,12,13,13a-hexahydro-8,9-dimethoxy-12-methyl-13-carboxylic acid-(10bR,12S,13R,13aS)-**7c**.* Compound **7a** (3.81 g, 10.2 mmol) was oxidized using general procedure *4* to give carboxylic acid **7c** as a pale yellow foam, 2.39 g (65%). HPLC (method A) t_R=1.68 min, (method B) t_R=4.29 min (90%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.08 (br s, CO_2H), 6.81 (s, 1H), 6.48 (s, 1H), 4.18–4.26 (m, 1H), 3.83 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.11–3.21 (m, 1H), 3.03–3.10 (m, 1H), 2.54–2.76 (m, 4H), 2.33–2.46 (m, 1H), 2.28–2.33 (m, 2H), 1.92–2.10 (m, 2H), 1.70–1.78 (m, 1H), 1.12 (d, J=6.4 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.2 (CO), 174.2 (CO), 147.2 (2C), 135.4 (C), 132.4 (C), 113.9 (CH), 110.2 (CH), 76.7 (C-10b), 57.5 (CH), 56.2 (OMe), 55.8 (OMe), 52.4 (CH), 47.6 (CH_2), 39.7 (CH), 38.5 (CH_2), 34.4 (CH_2), 32.3 (CH_2), 26.4 (CH_2), 18.7 (12-CH_3); MS (ES): $C_{20}H_{25}NO_5$ calcd: 360.1811 $[M+H]^+$; found: 360.1815 $[M+H]^+$.

*4.2.21. 4H-Cyclopenta[2,3]pyrrolo[2,1-a][2]benzazepine-2(1H)-one,5,6,11,12,13,13a-hexahydro-8-methoxy-12-methyl-13-(nitromethyl)-(10bR,12S,13R,13aS)-**8a**.* 3-Methoxybenzaldehyde (20.8 g, 0.153 mol) was treated with toluene (dry, 140 mL), pyridine (dry, 60 mL), ammonium acetate (0.59 g), and cyanoacetic acid (11.9 g, 0.140 mol) and then heated under reflux with a Dean–Stark trap for 71 h according to the procedure of Montgomery et.al.[24] The reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with 10% aq HCl solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with 2–5% EtOAc in hexanes to give 3-methoxycinnamonitrile, 14.65 g (60%). This material was dissolved in EtOH (75 mL) and concd HCl (15 mL) and hydrogenated with 10% Pd/C (2.00 g) at 70 psi on a Parr shaker for 67 h. The reaction mixture was filtered over Celite. The filtrate was extracted with EtOAc, and the EtOAc layer was concentrated under vacuum to give the hydrochloride salt of 3-(3-methoxyphenyl)propylamine as a waxy white solid, 17.3 g (93%). HPLC (method B) t_R=1.28 min $[M+H]^+$=166.30; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$): δ 7.14–7.19 (m, 1H), 6.70–6.77 (m, 3H), 4.51–4.58 (m, 2H), 3.75 (s, 3H, OMe), 2.85–2.91 (m, 2H), 2.63–2.68 (m, 2H), 1.95–2.01 (m, 2H).

Compound **1** (14.8 g, 68.8 mmol) and 3-(3-methoxyphenyl) propylamine hydrochloride (17.3 g, 85.6 mmol) were coupled using general procedure *1*. The crude product was stirred with 5% TFA in CH_2Cl_2 (200 mL) at rt for 3 h. Since the reaction had only gone 35% to completion (HPLC), an additional 10 mL of TFA was added, followed by heating at reflux for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed once with water and twice with sat aq $NaHCO_3$ solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with 1–5% MeOH in CH_2Cl_2 to yield **8a**, 11.06 g (46%) as a tan foam. HPLC (method B) t_R=5.75 min (84%). An analytical sample was prepared by HPLC; t_R=1.89 min (method A); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$): δ 6.92 (d, J=8.8 Hz, 1H, H-10), 6.50 (dd, J=8.8, 2.8 Hz, 1H, H-9), 6.34 (d, J=2.5 Hz, 1H, H-7), 4.34–4.41 (m, 2H, CH_2NO_2), 3.90–4.00 (m, 1H, H-4b), 3.51 (s, 3H, OMe), 2.87–2.94 (m, 1H, H-4a), 2.61–2.65 (m, 1H, H-6b), 2.33–2.48 (m, 2H, H-1a and H-1b), 2.24–2.33 (dd. J=17.5, 7.9 Hz, 1H, H-6a), 1.90–2.09 (m, 3H, H-12, H-11b and H-5b), 1.72–1.85 (m, 3H, H-5a, H-11a and H-13), 1.53–1.60 (m, 1H, H-13a), 0.86 (d, J=5.8 Hz, 3H, 12-CH_3). The assignments are tentative, based on the COSY spectrum; ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$): δ 173.7 (CO), 158.1 (C), 141.4 (C), 135.6 (C), 127.2 (CH), 116.4 (CH), 111.8 (CH), 76.8 (CH_2NO_2), 75.9 (C-10b), 55.0 (OMe), 51.2 (CH), 50.3 (CH), 47.3 (CH_2), 38.7 and 38.6 (CH and CH_2), 33.7 (CH_2), 33.1 (CH_2), 26.2 (CH_2), 17.5 (12-CH_3); MS (ES): $C_{19}H_{24}N_2O_4$ calcd: 345.1814 $[M+H]^+$; found: 345.1821 $[M+H]^+$.

*4.2.22. 4H-Cyclopenta[2,3]pyrrolo[2,1-a][2]benzazepine-2(1H)-one,5,6,11,12,13,13a-hexahydro-8-methoxy-12-methyl-13-aminomethyl-(10bR,12S,13R,13aS)-**8b**.* Compound **8a** (5.10 g, 14.8 mmol) was reduced according to general procedure *3* to give amine **8b**, 3.22 g (69%) as a pale yellow solid. HPLC (method A) t_R=1.15 min, (method B) t_R=2.64 min (84%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, J=8.8 Hz, 1H, H-10), 6.67 (dd, J=8.5, 2.5 Hz, 1H, H-9), 6.51 (d, J=2.6 Hz, 1H, H-7), 4.16–4.22 (m, 1H), 3.70 (s, 3H, OMe), 3.01–3.06 (m, 1H), 2.84–2.87 (m, 2H), 2.60–2.77 (m, 3H), 2.42–2.51 (m, 1H), 2.12–2.27 (m, 3H), 1.90–1.99 (m, 2H), 1.74 (m, 1H), 1.61 (br s, 2H, NH_2), 1.32 (m, 1H), 1.01 (d, J=5.9 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (CO), 158.3 (C), 142.1 (C), 137.7 (C), 128.2 (CH), 116.7 (CH), 112.2 (CH), 76.2 (C-10b), 55.7 (OMe), 55.0 (CH), 51.5 (CH), 48.5 (CH_2), 42.7 (CH_2), 38.9 (CH_2), 38.0 (CH), 35.4 (CH_2), 34.0 (CH_2), 27.1 (CH_2), 19.3 (12-CH_3); MS (ES): $C_{19}H_{26}N_2O_2$ calcd: 315.2072 $[M+H]^+$; found: 315.2079 $[M+H]^+$.

*4.2.23. 4H-Cyclopenta[2,3]pyrrolo[2,1-a][2]benzazepine-2(1H)-one,5,6,11,12,13,13a-hexahydro-8-methoxy-12-methyl-13-carboxylic acid-(10bR,12S,13R,13aS)-**8c**.* Compound **8a** (4.82 g, 14.0 mmol) was oxidized according to general method *4*. The crude carboxylic acid was purified by flash chromatography on silica gel eluting with 5% EtOAc in hexanes to give **8c** as a pale yellow foam, 2.60 g (56%). HPLC (method A) t_R=1.57 min, (method B) t_R=4.77 min (90%); ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C): δ 12.2 (br s, 1H, CO_2H), 7.27 (d, J=8.4 Hz, 1H, H-10), 6.77 (dd, J=8.6, 2.7 Hz, 1H, H-9), 6.22 (d, J=2.5 Hz, 1H, H-7), 4.02–4.10 (m, 1H), 3.70 (s, 3H, OMe), 3.02–3.10 (m, 2H), 2.63–2.69 (m, 2H), 2.47–2.57 (m, 1H), 2.34–2.43 (m, 1H), 2.10–2.20 (m, 4H), 1.79–1.84 (m, 1H), 1.68–1.73 (m, 1H), 1.04 (d, J=6.6 Hz, 3H, 12-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6, 60 °C): δ 175.3 (CO), 172.3 (CO), 158.3 (C), 142.2 (C), 137.1 (C), 127.9 (CH), 116.9 (CH), 112.4 (CH), 75.9 (C-10b), 57.9 (CH), 55.7 (OMe), 51.7 (CH), 47.3 (CH_2), 39.2 (CH), 38.6 (CH_2), 34.6 (CH_2), 33.5 (CH_2), 27.0 (CH_2), 19.0 (12-CH_3); MS (ES): $C_{19}H_{23}NO_4$ calcd: 330.1705 $[M+H]^+$; found: 330.1700 $[M+H]^+$.

*4.2.24. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-nitromethyl,1,2,3,-3a,4,5,7,8-octahydro-10-benzyloxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**9**.* A solution of 2-(3-hydroxyphenyl)ethylamine (5.15 g, 29.7 mmol) in THF (65 mL) was treated with Et_3N (9.30 mL, 2.2 equiv) and cooled on an ice-water bath. Di-*tert*-butyldicarbonate (6.80 g, 31.1 mmol) was added and the cooling bath was removed. After approx. 0.5 h THF (35 mL) and Et_3N (5.0 mL) were added to improve solubility. After stirring overnight, the reaction mixture was diluted with EtOAc, washed with water and satd aq NaCl solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in acetone (100 mL) and treated with benzyl bromide (3.90 mL, 33 mmol) and K_2CO_3 (4.50 g, 33 mmol). The reaction mixture was heated at 50 °C for 19 h. The solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and 2 M aq NaOH. The organic layer was washed with satd aq NaCl solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product, containing a small amount of residual benzyl bromide, was deprotected using general procedure *5* to give 2-(3-benzyloxyphenyl)ethylamine hydrochloride as a white solid, 5.49 g. HPLC (method A) t_R=2.85 min (94%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04 (br s, 3H, NH_3^+), 7.34–7.42 (m, 4H), 7.22 (t, J=7.7 Hz, 1H), 6.80–6.91 (m, 3H), 5.07 (s, 2H, PhCH_2O), 3.00 (m, 2H), 2.81–2.85 (m, 2H).

Compound **1** (4.49 g, 20.9 mmol) and 2-(3-benzyloxyphenyl) ethylamine hydrochloride (5.49 g, 20.9 mmol) were coupled using

general method *1*. The crude product was cyclized using general procedure *2* (4 h). Purification by flash column chromatography on silica gel, eluting with 1% MeOH in CH_2Cl_2 gave **9**, 4.69 g (55%) as a foam. HPLC (method B) t_R=6.86 min (88%). An analytical sample was prepared by HPLC; t_R=2.71 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.39 (m, 5H, Ph), 7.01 (d, *J*=8.8 Hz, 1H, H-12), 6.83 (dd, *J*=8.6, 2.5 Hz, 1H, H-11), 6.68 (d, *J*=2.8 Hz, 1H, H-9), 5.01 (s, 2H, Ph*CH*$_2$O), 4.50–4.69 (m, 2H, CH_2NO_2), 4.16–4.24 (m, 1H, H-7b), 3.10–3.20 (m, 1H, H-7a or H-8b), 2.95–3.06 (m, 1H, H-8b or H-7a), 2.76–2.80 (m, 1H, H-3a), 2.63–2.69 (m, 1H, H-8a), 2.52–2.62 (m, 1H, H-4b), 2.23–2.29 (m, 2H, H-4a and H-1b), 2.08–2.22 (m, 2H, H-2 and H-3), 1.73–1.82 (m, 1H, H-1a), 1.08 (d, *J*=5.5 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (CO), 157.8 (C), 137.0 (C), 134.8 (C), 134.7 (C), 128.9 (CH), 128.2 (CH), 127.7 (CH), 125.1 (CH), 115.2 (CH), 114.1 (CH), 77.5 (CH_2NO_2), 70.6 (C-12b), 70.2 (Ph*CH*$_2$O), 52.9 (CH), 51.8 (CH_2), 48.1 (CH), 38.2 (CH), 36.5 (CH_2), 36.1 (CH_2), 28.0 (CH_2), 17.7 (2-CH_3); MS (ES): $C_{24}H_{26}N_2O_4$ calcd: 407.1971 $[M+H]^+$; found: 407.1978 $[M+H]^+$.

*4.2.25. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid,1,2,3,3a,4,5,7,8-octahydro-10-benzyloxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**9a**.* Compound **9** (4.60 g, 11.3 mmol) was oxidized according to general procedure *4*. The crude acid was purified by flash chromatography on silica gel eluting with 5% MeOH in CH_2Cl_2 to give **9a** as a foam, 2.13 g (48%). HPLC (method B) t_R=6.02 min (75% by UV, >90% ELSD). An analytical sample was prepared by HPLC; t_R=2.32 min (method A); $[\alpha]_D^{24}$ +88.5 (*c* 0.61, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (br s, 1H, CO_2H), 7.33–7.40 (m, 5H, Ph), 7.25 (d, *J*=8.5 Hz, 1H, H-12), 6.85 (dd, *J*=8.5, 2.2 Hz, 1H, H-11), 6.68 (d, *J*=2.2 Hz, 1H, H-9), 5.02 (s, 2H, Ph*CH*$_2$O), 4.19–4.26 (m, 1H, H-7b), 3.14–3.20 (m, 2H, H-3a and H-7a), 2.99–3.08 (m, 1H, H-8b), 2.47–2.68 (m, 4H, H-8a, H-4b, H-4a, H-2), 2.34–2.42 (t, *J*=10.2 Hz, 1H, H-3), 2.22–2.29 (dd, *J*=12.8, 7.0 Hz, 1H, H-1b), 1.72–1.81 (t, *J*=12.5, 1H, H-1a), 1.13 (d, *J*=6.3 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3 (CO), 173.2 (CO), 157.9 (C), 137.0 (C), 134.6 (C), 134.5 (C), 128.8 (CH), 128.3 (CH), 127.7 (CH), 125.6 (CH), 115.1 (CH), 114.1 (CH), 71.8 (C-12b), 70.3 (Ph*CH*$_2$O), 59.7 (CH), 51.9 (CH_2), 48.3 (CH), 39.2 (CH), 37.1 (CH_2), 36.3 (CH_2), 28.1 (CH_2), 18.4 (2-CH_3); MS (ES): $C_{24}H_{25}NO_4$ calcd:392.1862 $[M+H]^+$; found: 392.1872 $[M+H]^+$.

*4.2.26. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid,1,2,3,3a,4,5,7,8-octahydro-10-benzyloxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-methyl ester **9b**.* Compound **9a** (1.46 g, 3.72 mmol) was dissolved in a 1:1 mixture of MeOH and CH_2Cl_2 (20 mL) and treated with excess 2 M TMS diazomethane in Et_2O. After 0.5 h the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with 1–2% MeOH in CH_2Cl_2 to give **9b** as a yellow oil, 1.29 g (85%). HPLC (method A) t_R=2.25 min, (method B) t_R=6.86 min (100%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.42 (m, 5H, Ph), 7.23 (d, *J*=8.8 Hz, 1H, H-12), 6.85 (dd, *J*=8.5, 2.6 Hz, 1H, H-11), 6.68 (d, *J*=2.6 Hz, 1H, H-9), 5.03 (s, 2H, Ph*CH*$_2$O), 4.16–4.24 (m, 1H, H-7b), 3.77 (s, 3H, CO_2Me), 3.10–3.17 (m, 2H, H-7b and H-3a), 2.95–3.06 (m, 1H, H-8b), 2.65–2.69 (m, 1H, H-8a), 2.51–2.63 (m, 2H, H-4b and H-2), 2.36–2.42 (m, 2H, H-4a and H-3), 2.20–2.27 (dd, *J*=13.1, 7.2 Hz, 1H, H-1b), 1.72–1.80 (t, *J*=12.2 Hz, 1H, H-1a), 1.08 (d, *J*=6.5 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (CO), 172.2 (CO), 157.5 (C), 136.9 (C), 134.4 (2 C), 128.5 (CH), 127.9 (CH), 127.3 (CH), 125.3 (CH), 114.8 (CH), 113.8 (CH), 71.1 (C-12b), 69.8 (Ph*CH*$_2$O), 59.2 (CH), 51.9 (CO_2Me), 51.5 (CH_2), 48.1 (CH), 39.0 (CH), 36.7 (CH_2), 35.8 (CH_2), 27.7 (CH_2), 18.2 (2-CH_3); MS (ES): $C_{25}H_{27}NO_4$ calcd: 406.2018 $[M+H]^+$; found: 406.2006 $[M+H]^+$.

*4.2.27. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid,1,2,3,3a,4,5,7,8-octahydro-10-hydroxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-methyl ester **9c**.* Compound **9b** (3.05 g, 7.53 mmol) was dissolved in EtOH (60 mL) and hydrogenated with 10% Pd/C (1.5 g) at 34 psi of H_2 in a Parr shaker for 7 h. The reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure to give **9c** as a tan solid, 2.06 g (87%). An analytical sample was purified by flash chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2. HPLC (method A) t_R=1.63 min, (method B) t_R=4.22 min (96%); $[\alpha]_D^{24}$ +124.4 (*c* 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (br s, 1H, OH), 7.13 (d, *J*=8.8 Hz, 1H, H-12), 6.74 (dd, *J*=8.5, 2.6 Hz, 1H, H-11), 6.56 (d, *J*=2.3 Hz, 1H, H-9), 4.12–4.20 (m, 1H, H-7b), 3.76 (s, 3H, CO_2Me), 3.08–3.18 (m, 2H, H-7a and H-3a), 2.89–3.00 (m, 1H, H-8b), 2.50–2.68 (m, 3H, H-4b, H-8a and H-2), 2.29–2.45 (m, 2H, H-4a and H-3), 2.19–2.26 (m, 1H, H-1b), 1.69–1.78 (t, *J*=12.5 Hz, 1H, H-1a), 1.06 (d, *J*=6.4 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (CO), 173.0 (CO), 155.7 (C), 134.2 (C), 133.0 (C), 125.3 (CH), 115.4 (CH), 114.5 (CH), 71.7 (C-12b), 59.3 (CH), 52.1 (CO_2Me), 51.5 (CH_2), 48.0 (CH), 39.0 (CH), 36.8 (CH_2), 36.2 (CH_2), 27.6 (CH_2), 18.1 (2-CH_3); MS (ES): $C_{18}H_{21}NO_4$ calcd: 316.1549 $[M+H]^+$; found: 316.1554 $[M+H]^+$.

*4.2.28. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid,1,2,3,3a,4,5,7,8-octahydro-10-(trifluoromethanesulfonyl)oxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-methyl ester **9d**.* Compound **9c** (1.14 g, 3.62 mmol) was dissolved in dry CH_2Cl_2 (20 mL), treated with Et_3N (1.20 mL, 8.60 mmol), and cooled on an ice-water bath. A solution of trifluoromethanesulfonic anhydride (0.73 mL, 4.30 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 1.5 h the reaction mixture was washed with satd aq $NaHCO_3$ and satd aq NaCl solutions, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 1:1 hexanes/EtOAc to give **9d** as a brown oil, 0.83 g (51%). HPLC (method A) t_R=2.03 min, (method B) t_R=6.43 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J*=8.5 Hz, 1H, H-12), 7.09 (dd, *J*=8.5, 2.5 Hz, 1H, H-11), 6.96 (d, *J*=2.5 Hz, 1H, H-9), 4.17–4.24 (m, 1H, H-7b), 3.74 (s, 3H, CO_2Me), 3.05–3.18 (m, 2H), 2.96–3.02 (m, 1H), 2.70–2.76 (m, 1H), 2.50–2.61 (m, 2H), 2.33–2.41 (m, 2H), 2.20–2.33 (m, 1H), 1.71–1.80 (t, *J*=12.5 Hz, 1H, H-1a), 1.07 (d, *J*=6.3 Hz, 3H, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (CO), 172.2 (CO), 148.2, 142.5, 136.2, 126.5, 121.9, 120.0, 117.8 (q, CF_3, $J_{C,F}$=320 Hz), 71.4, 59.6, 52.4, 51.6, 48.6, 39.6, 37.0, 35.7, 27.9, 18.5 (2-CH_3); MS (ES): $C_{19}H_{20}F_3NO_6S$ calcd: 448.1042 $[M+H]^+$; found: 448.1023 $[M+H]^+$.

*4.2.29. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-nitromethyl,1,2,3,-3a,4,5,7,8-octahydro-11-benzyloxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**10**.* A solution of tyramine (10.1 g, 73.6 mmol) in THF (100 mL) was treated with Et_3N (8.30 mL, 59.5 mmol) and cooled on an ice-water bath. Di-*tert*-butyldicarbonate (14.5 g, 66.4 mmol) was added and the cooling bath was removed. After stirring overnight, the reaction mixture was diluted with EtOAc, washed with water and satd aq NaCl solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in acetone (100 mL) and treated with benzyl bromide (8.00 mL, 67.2 mmol) and K_2CO_3 (9.10 g, 65.6 mmol). The reaction mixture was heated at 50 °C for 7.5 h. The solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and 2 M aq NaOH. The organic layer was washed with satd aq NaCl solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give *N*-(*tert*-butoxycarbonyl)-2-[4-(benzyloxy)phenyl]ethylamine as a white solid, 17.5 g (73%). HPLC (method B) t_R=7.71 min (>95% purity by ELSD) $[M]^-$=326.19 ($C_{20}H_{25}NO_3$=327); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.44 (m, 4H), 7.10 (d, *J*=8.5 Hz, 2H), 6.91 (d, *J*=8.5 Hz, 2H), 5.05 (s, 2H, Ph*CH*$_2$O), 3.33 (m, 2H), 2.70–2.75 (m, 2H), 1.43 (s, 9H, Boc).

The crude product above, 15.4 g, containing a small amount of residual benzyl bromide, was deprotected according to general procedure **5** to give 2-[4-(benzyloxy)phenyl]ethylamine hydrochloride as a white solid, 11.7 g. HPLC (method B) t_R=2.72 min (96%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.06 (br s, 3H, NH_3^+), 7.28–7.40 (m, 4H), 7.15 (d,

J=8.5 Hz, 2H), 6.94 (d, J=8.5 Hz, 2H), 5.06 (s, 2H, PhCH_2O), 2.93 (m, 2H), 2.77–2.83 (m, 2H).

The free base was made by partitioning the solid between Et_2O and 2 M aq NaOH solution. The organic layer was washed with satd aq NaCl solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 2-[4-(benzyloxy)phenyl] ethylamine as a white solid, 8.92 g.

*4.2.30. Intermediate **A**.* Compound **1** (9.07 g, 39.3 mmol) and 2-[(4-benzyloxyphenyl)]ethylamine (8.92 g, 39.3 mmol) were coupled using general procedure *1*. The crude product was purified by flash chromatography on silica gel to give *intermediate A*, 8.44 g (51%) as a pale yellow solid. HPLC (method B) t_R=6.47 min (90%) $[M-OH]^+$=407.28, $[M]^-$=423.21 ($C_{24}H_{28}N_2O_5$=424); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.29–7.40 (m, 5H), 7.11 (d, J=8.5 Hz, 2H), 6.92 (d, J=8.5 Hz, 2H), 5.93 (s, 1H, 7-OH, exchanges with D_2O), 5.04 (s, 2H, PhCH_2O), 4.69–4.73 (m, 1H, CH_bH$_a$NO$_2$), 4.52–4.59 (m, 1H, CH$_b$H$_a$NO$_2$), 3.20–3.33 (m, 2H), 2.73–2.88 (m, 2H), 2.44–2.54 (dd, J=17.2, 9.8 Hz, 1H), 2.13–2.21 (m, 1H), 1.98–2.08 (m, 2H), 1.75–1.93 (m, 2H), 1.81 (t, J=12.0 Hz, 1H), 0.85 (d, J=6.0 Hz, 3H, 2-CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.5 (CO), 157.3 (C), 137.7 (C), 132.1 (C), 130.1 (CH), 128.8 (CH), 128.2 (CH), 128.0 (CH), 115.2 (CH), 98.2 (C, assigned to C-7), 78.2 (CH$_2$NO$_2$), 69.6 (PhCH_2O), 52.1 (CH), 49.5 (CH), 47.1 (CH$_2$), 41.9 (CH$_2$), 36.5 (CH), 35.5 (CH$_2$), 33.9 (CH$_2$), 17.2 (2-CH$_3$). No peaks at >172 ppm corresponding to a ketone carbonyl were observed. When this reaction was repeated, the chromatographed *intermediate A* contained approx. 15% of what appeared to be an epimer at C-7 (as judged by the ratio of two broadened singlets at 5.63 ppm (15%) and 5.53 ppm (85%) assigned to the 7-OH-both peaks exchanged with D_2O). The 2-CH$_3$ also appeared as a pair of doublets at 0.61 ppm (72%) and 0.58 ppm (28%).

*Intermediate **A*** (1.00 g, 2.4 mmol) was stirred with 5% TFA in CH_2Cl_2 (25 mL) at rt for 4 h. By LCMS analysis, only unreacted **A** was present (t_R=6.49 min). TFA (1.25 mL) was added and the reaction mixture was heated to reflux for 5.5 h. LCMS analysis indicated 90% conversion to **10** (t_R=6.85 min). After refluxing overnight, the reaction mixture was diluted with CH_2Cl_2, washed with water and sat aq $NaHCO_3$ solution, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2 to yield **10**, 0.82 g (86%) as a yellow oil. HPLC (method B) t_R=6.85 min (95%). An analytical sample was prepared by HPLC; t_R=2.25 min (method A); ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD): δ 7.24–7.36 (m, 5H, Ph), 6.95 (d, J=8.5 Hz, 1H, H-9), 6.79 (dd, J=8.1, 2.5 Hz, 1H, H-10), 6.61 (d, J=2.4 Hz, 1H, H-12), 5.02 (s, 2H, PhCH_2O), 4.45–4.65 (m, 2H, CH$_2$NO$_2$), 4.06–4.13 (m, 1H, H-7b), 3.08–3.18 (m, 1H, H-7a), 2.78–2.95 (m, 1H, H-8b), 2.72–2.77 (m, 1H, H-3a), 2.58–2.66 (m, 1H, H-8a), 2.49–2.55 (m, 1H, H-4b), 2.19–2.27 (m, 2H, H-4a and H-1b), 1.95–2.08 (m, 2H, H-2 and H-3), 1.66–1.75 (t, J=12.0 Hz, 1H, H-1a), 1.01 (d, J=5.5 Hz, 3H, 2-CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (CO), 157.4 (C), 142.9 (C), 136.8 (C), 130.4 (CH), 128.7 (CH), 128.1(CH), 127.5 (CH), 125.3 (C), 113.5 (CH), 110.7 (CH), 76.6 (CH$_2$NO$_2$), 70.7 (C-12b), 70.3 (PhCH_2O), 52.8 (CH), 51.6 (CH$_2$), 47.9 (CH), 38.1(CH), 36.3 (CH$_2$), 36.1 (CH$_2$), 26.6 (CH$_2$), 17.4 (2-CH$_3$); MS (ES): $C_{24}H_{26}N_2O_4$ calcd: 407.1971 $[M+H]^+$; found: 407.1955 $[M+H]^+$.

When a new batch of *intermediate **A*** (7.24 g) was heated at reflux for 10.5 h in a mixture of CH_2Cl_2 (70 mL) and TFA (7 mL), followed by workup and silica gel chromatography, **10** was obtained as a pale yellow foam, 5.12 g (74%).

*4.2.31. Cyclopenta[2,3]pyrrolo[2,1-a]isoquinoline-3-carboxylic acid,1,2,3,3a,4,5,7,8-octahydro-11-benzyloxy-2-methyl-5-oxo-(2S,3R,3aS,12bR)-**10a**.* Compound **10** (5.12 g, 12.6 mmol) was oxidized according to general procedure *4*. The crude product was purified by flash chromatography on silica gel eluting with 3% MeOH in CH_2Cl_2 to give **10a** as a foam, 3.21 g (65%). HPLC (method A) t_R=1.92 min, (method B) t_R=5.79 min (100% purity by ELSD); $[\alpha]_D^{22}$ +134.7 (c 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.43 (m, 5H, Ph), 6.98 (d, J=8.5 Hz, 1H, H-9), 6.92 (d, 1H, J=2.3 Hz, 1H, H-12), 6.80 (dd, J=8.5, 2.6 Hz, 1H, H-10), 5.04 (s, 2H, PhCH_2O), 4.17–4.24 (m, 1H, H-7b), 3.10–3.21 (m, 2H), 2.94–3.02 (m, 1H), 2.44–2.68 (m, 4H), 2.31–2.39 (t, J=10.2 Hz, 1H), 2.19–2.26 (dd, J=13.0, 6.9 Hz, 1H), 1.69–1.78 (t, J=12.4 Hz, 1H, H-1a), 1.10 (d, J=6.5 Hz, 3H, 2-CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1 (CO), 172.7 (CO), 157.5, 142.9, 136.8, 130.1, 128.6, 128.0, 127.6, 125.1, 113.7, 110.7, 71.8, 70.1, 59.4, 51.6, 48.0, 39.0, 36.8, 36.3, 26.7, 18.1 (2-CH$_3$); MS (ES): $C_{24}H_{25}NO_4$ calcd: 392.1862 $[M+H]^+$; found: 392.1860 $[M+H]^+$.

*4.2.32. Intermediate **11**.* Compound **1** (6.57 g, 28.1 mmol) and tryptamine (5.40 g, 33.7 mmol) were coupled using general procedure *1* to give crude **11** as a solid. HPLC (method B) peak 1 t_R=5.11 min (84%) $[M-OH]^+$=340.2, $[M]^-$=356.13; peak 2 t_R=5.31 min (16%) $[M+H]^+$=358.19, $[M]^-$=356.13 ($C_{19}H_{23}N_3O_4$ FW=357). A portion of crude **11** was purified by radial chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2. Two bands were collected but only the more polar band gave sufficient material for analysis. HPLC (method B) t_R=5.06 min $[M-OH]^+$=340.24, $[M]^-$=356.13 (84%). From the predominant loss of H_2O in the positive ion ESMS and the NMR spectra, it was concluded that the major species present in crude **11** was the hemiketal as shown. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.80 (s, 1H, NH), 7.55 (d, J=7.7 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.15 (d, J=2.2 Hz, 1H, indole-2H), 7.05 (t, J=7.6 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 5.94 (s, 1H), 4.51–4.75 (m, 2H, CH$_2$NO$_2$), 3.30–3.86 (m, 2H), 2.91–3.00 (m, 2H), 2.48–2.56 (m, 1H), 2.15–2.19 (m, 1H), 2.03–2.10 (m, 1H), 1.92–2.00 (m, 1H), 1.85–1.91 (m, 1H), 1.70–1.84 (m, 1H), 1.27 (t, J=12.1 Hz, 1H), 0.83 (d, J=6.0 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.7 (CO), 136.9 (C), 127.9 (C), 123.3 (CH), 121.7 (CH), 119.0 (CH), 112.6 (CH), 112.1 (C), 98.5 (C, assigned to C-7), 78.6 (CH$_2$NO$_2$), 52.4 (CH), 49.9 (CH), 47.4 (CH$_2$), 36.8 (CH), 35.8 (CH$_2$), 25.2 (CH$_2$), 17.4 (2-CH$_3$). No resonances greater than 172 ppm corresponding to a ketone carbonyl were observed.

*4.2.33. 4H-Cyclopent[1,8a]indolizino[8,7-b] indole-13-nitromethyl,1,2,-5,10,11,12,13,13a-octahydro-12-methyl-2-oxo-(10bR,12S,13R,13aS)-**12a**.* Crude **11** (14 mmol) was cyclized using general method *2* (3.5 h). Purification by flash column chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2 gave **12a**, 4.10 g (86%) as a beige foam. HPLC (method B) t_R=5.92 min (91%) $[M+H]^+$=340.26. An analytical sample was obtained by re-purification of this material on silica gel, eluting 1–2% MeOH in CH_2Cl_2. HPLC (method A) t_R=1.91 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (br s, 1H, NH), 7.45 (d, J=7.6 Hz, 1H), 7.33 (d, J=7.9 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 4.58–4.71 (m, 2H, CH$_2$NO$_2$), 4.46–4.51 (m, 1H, H-4b), 3.08–3.14 (m, 1H, H-5b), 2.93–3.00 (m, 1H, H-4a), 2.83–2.91 (m, 1H, H-13a), 2.64–2.74 (m, 2H, H-1b and H-5a), 2.46–2.53 (dd, J=13.1, 6.9 Hz, 1H, H-11b), 2.32–2.39 (dd, J=17.7, 2.5 Hz, 1H, H-1a), 2.22–2.30 (m, 1H, H-12), 2.08–2.20 (m, 1H, H-13), 1.85–1.94 (m, 1H, H-11a), 1.13 (d, J=6.5 Hz, 3H, 12-CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (CO), 136.4 (two non-protonated carbons overlap), 126.7 (C), 122.3 (CH), 119.9 (CH), 118.3 (CH), 111.2 (CH), 107.6 (C), 76.8 (CH$_2$NO$_2$), 69.1 (C-10b), 52.8 (CH), 49.0 (CH$_2$), 45.3 (CH), 37.7 (CH), 36.8 (2 CH$_2$ overlap), 20.5 (CH$_2$), 17.5 (12-CH$_3$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.7 (CO), 138.1 (C), 136.6 (C), 126.8 (C), 121.7 (CH), 119.2 (CH), 118.3 (CH), 111.7 (CH), 106.2 (C), 78.5 (CH$_2$NO$_2$), 69.0 (C-10b), 52.6 (CH), 49.0 (CH$_2$), 45.8 (CH), 37.4 (CH), 36.6 (CH$_2$), 36.3 (CH$_2$), 20.5 (CH$_2$), 17.7 (12-CH$_3$). The two overlapping sets of resonances in the $CDCl_3$ spectrum at 136.4 and 36.8 ppm are resolved in the DMSO-d_6 spectrum; MS (ES): $C_{19}H_{21}N_3O_3$ calcd: 340.1661 $[M+H]^+$; found: 340.1651 $[M+H]^+$.

Alternatively, crude **11** (14 mmol) was cyclized by refluxing in toluene (150 mL) containing *p*-toluenesulfonic acid monohydrate

(500 mg) with a Dean–Stark trap. After 3.5 h the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed once with water and sat aq $NaHCO_3$ solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2 to yield **12a**, 3.48 g (73%) as a beige foam. HPLC (method B) t_R=5.92 min (93%) $[M+H]^+$=340.26.

*4.2.34. 4H-Cyclopent[1,8a]indolizino[8,7-b]indole-13-aminomethyl,1,-2,5,10,11,12,13,13a-octahydro-12-methyl-2-oxo-(10bR,12S,13R,13aS)-**12b**.* Compound **12a** (2.50 g, 7.37 mmol) was reduced using general procedure *3* to give amine **12b**, 2.09 g (93%) as a white foam. HPLC (method A) t_R=1.26 min, (method B) t_R=2.83 min (93%); $[\alpha]_D^{24}$ +124.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H, indole–NH), 7.44 (d, *J*=8.2 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 1H), 7.04–7.26 (m, 2H), 4.45–4.52 (m, 1H), 3.08–3.16 (m, 1H), 3.01 (m, 2H), 2.85–2.97 (m, 1H), 2.70–2.85 (m, 3H), 2.38–2.69 (m, 3H), 1.99 (br s, 2H), 1.72–1.82 (m, 1H), 1.60–1.62 (m, 1H), 1.10 (d, *J*=6.1 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (CO), 138.7 (C), 136.3 (C), 126.6 (C), 121.6 (C), 119.4 (CH), 118.2 (CH), 111.2 (CH), 105.9 (CH), 69.5 (C-10b), 55.9 (CH), 48.9 (CH_2), 44.6 (CH), 40.8 (CH_2), 39.2 (CH_2), 36.4 (CH_2), 35.7 (CH), 20.8 (CH_2), 18.5 (CH_3); MS (ES): $C_{19}H_{23}N_3O$ calcd: 310.1919 $[M+H]^+$; found: 310.1916 $[M+H]^+$.

*4.2.35. 4H-Cyclopent[1,8a]indolizino[8,7-b]indole-13-carboxylic acid,1,2,5,10,11,12,13,13a-octahydro-12-methyl-2-oxo-(10bR,12S,13R,13aS)-**12c**.* Compound **13b** (1.00 g, 2.09 mmol) in a mixture of THF/MeOH (1:3, 32 mL) with Cs_2CO_3 (4.07 g, 6 equiv) was heated at 90 °C in a sealed tube for 21 h. The reaction mixture was cooled to rt and then poured into ice-water. The mixture was extracted with Et_2O and then acidified with concd HCl. The aqueous layer was extracted twice with a mixture of EtOAc and MeOH, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 5% MeOH in CH_2Cl_2 to give **12c** as a tan foam, 0.24 g (36%). HPLC (method A) t_R=1.65 min, (method B) t_R=5.13 min (96%); ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): δ 8.80 (s, 1H, NH), 7.42 (d, *J*=7.9 Hz, 1H), 7.27 (d, *J*=7.9 Hz, 1H), 7.08–7.15 (m, 2H), 4.49–4.56 (m, 1H, H-4b), 3.13–3.19 (m, 2H, H-5b and H-13a), 2.89–2.95 (m, 1H, H-4a), 2.80–2.88 (m, 1H, H-1b), 2.68–2.80 (m, 2H, H-5a and H-12), 2.62–2.68 (m, 1H, H-1a), 2.45–2.60 (m, 2H, H-13 and H-11b), 1.90–1.98 (dd, *J*=13.5, 8.0 Hz, 1H, H-11a), 1.24 (d, *J*=6.5 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD): δ 177.2 (CO), 174.5 (CO), 136.8 (C), 136.4 (C), 126.6 (C), 121.9 (CH), 119.4 (CH), 118.0 (CH), 111.4 (CH), 100.7 (C), 71.1 (C-10b), 59.1 (CH), 48.0 (CH_2), 45.8 (CH), 38.9 (CH), 37.1 (2CH_2), 20.5 (CH_2), 18.2 (12-CH_3); MS (ES): $C_{19}H_{20}N_2O_3$ calcd: 325.1552 $[M+H]^+$; found: 325.1541 $[M+H]^+$.

*4.2.36. Compound **13a**.* Compound **1** (9.25 g, 43.0 mmol) and *N*-1-tosyl tryptamine[25] (10.7 g, 43.0 mmol) were coupled using general procedure *1*, then cyclized according to general procedure *2* (5 h). Purification by flash chromatography on silica gel, eluting with 1% MeOH in CH_2Cl_2 gave **13a** as a light yellow foam, 10.8 g (51%, 88% pure by HPLC). An analytical sample was prepared by radial chromatography on silica gel, eluting with 2% MeOH in CH_2Cl_2. HPLC (method A) t_R=2.26 min, (method B) t_R=7.24 min (97%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J*=8.0 Hz, 1H), 7.34–7.37 (m, 3H), 7.25–7.29 (m, 2H), 7.19 (d, *J*=8.5 Hz, 2H), 4.52–4.58 (m, 2H, CH_2NO_2), 4.30–4.35 (m, 1H, H-4b), 3.50–3.52 (m, 1H, H-13a), 3.09–3.14 (m, 1H, H-4a), 3.00–3.09 (m, 1H, H-5b), 2.75–2.83 (dd, *J*=14.0, 9.9 Hz, H-11b), 2.60–2.65 (m, 1H, H-5a), 2.50–2.60 (m, 1H, H-12), 2.34 (s, 3H, Ts–CH_3), 2.28–2.30 (m, 1H, H-13), 2.12–2.16 (m, 2H, H1a and H1b), 1.84–1.92 (dd, *J*=14.0, 7.7 Hz, H-11a), 1.09 (d, *J*=6.6 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9 (CO), 145.3 (C), 137.7 (C), 136.8 (C), 136.6 (C), 130.3 (CH), 129.0 (C), 126.0 (C), 125.8 (CH), 124.3 (CH), 121.1 (CH), 119.0 (CH), 115.5 (CH), 78.8 (CH_2NO_2), 73.9 (C-10b), 52.8 (CH), 47.2 (CH_2), 47.0 (CH), 37.5 (CH), 35.8 (CH_2), 35.0 (CH_2), 21.8 (Ts-CH_3), 21.1 (CH_2), 20.4 (12-CH_3); MS (ES): $C_{26}H_{27}N_3O_5S$ calcd: 494.1750 $[M+H]^+$; found: 494.1697 $[M+H]^+$.

*4.2.37. Compound **13b**.* Compound **13a** (2.89 g, 5.86 mmol) was oxidized using general procedure *4* to give carboxylic acid **13b** as an orange foam, 2.57 g (89%). HPLC (method B) t_R=6.34 min (95%). An analytical sample was prepared by HPLC; t_R=2.07 min (method A); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J*=7.6 Hz, 1H), 7.44 (d, *J*=8.2 Hz, 2H), 7.32–7.36 (m, 1H), 7.26–7.32 (m, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 4.29–4.33 (m, 1H, H-4b), 3.88–3.95 (m, 1H, H-13a), 3.00–3.14 (m, 3H, H-12, H-4a, H-5b), 2.73–2.82 (m, 1H, H-11b), 2.60–2.65 (m, 1H, H-5a), 2.48–2.52 (m, 1H, H-1b), 2.35–2.45 (m, 1H, H-13), 2.32 (s, 3H, Ts-CH_3), 2.10–2.19 (dd, *J*=17.6, 7.6 Hz, 1H, H-1a), 1.80–1.87 (dd, *J*=14.0, 8.8 Hz, 1H, H-11a), 1.17 (d, *J*=6.4 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8 (CO), 175.4 (CO), 144.9 (C), 137.5 (C), 136.7 (C), 136.3 (C), 130.0 (CH), 128.8 (CH), 125.7 (CH and C: in DMSO-d_6 these two carbons are observed at 126.37 and 126.22 ppm), 123.9 (CH), 120.7 (C), 118.7 (CH), 115.3 (CH), 73.5 (C-10b), 58.2 (CH), 47.0 (CH_2), 46.2 (CH), 36.9 (CH), 35.5 (CH_2), 34.7 (CH_2), 21.5 (Ts-CH_3), 21.0 (CH_2), 20.2 (12-CH_3); MS (ES): $C_{27}H_{26}N_2O_5S$ calcd: 479.1641 $[M+H]^+$; found: 479.1666 $[M+H]^+$.

*4.2.38. 4H-Cyclopent[1,8a]indolizino[8,7-b]indole-4-carboxylic acid,1,2,5,10,11,12,13,13a-octahydro-12-methyl-13-nitromethyl-2-oxo-methyl ester (10bR,12S,13R,13aS)-**14a**.* Compound **1** (4.30 g, 20.0 mmol) and L-tryptophan methyl ester hydrochloride (5.10 g, 20.0 mmol) were coupled using general procedure *1*. The crude product was treated cyclized using general procedure *2* (5 h). Purification by flash chromatography on silica gel, eluting with 0.5% MeOH in CH_2Cl_2 gave **14a** as a white foam, 2.85 g (36%, 98% HPLC purity). Another 400 mg of slightly impure material (92% HPLC purity) was also obtained. HPLC (method A) t_R=1.83 min, (method B) t_R=5.82 min (98%); $[\alpha]_D^{24}$ +99.5 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H, NH), 7.48 (d, *J*=7.6 Hz, 1H), 7.31 (m, 1H), 7.10–7.14 (m, 2H), 5.49 (d, *J*=7.9 Hz, 1H, H-4), 4.58–4.61 (m, 2H, CH_2NO_2), 3.71 (s, 3H, CO_2Me), 3.44 (d, *J*=16.1 Hz, H-5b), 3.13–3.16 (dd, *J*=15.9, 7.8 Hz, H-5a), 2.75–2.90 (m, 2H, H-13a and H-1b), 2.45–2.53 (dd, *J*=17.0, 3.8 Hz, H-1a), 2.05–2.30 (m, 4H, H-11a, H-11b, H-12, H-13), 1.12 (d, *J*=5.3 Hz, 3H, 12-CH_3); ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C): δ 10.57 (s, 1H, NH), 7.40 (d, *J*=7.9 Hz, 1H), 7.34 (d, *J*=7.9 Hz, 1H), 7.05–7.12 (m, 1H), 6.95–7.02 (m, 1H), 5.28 (dd, *J*=7.8, 1.4 Hz, 1H, H-4), 4.82–4.89 (m, 2H, CH_2NO_2), 3.63 (s, 3H, CO_2Me), 3.17–3.23 (dd, *J*=16.1, 1.5 Hz, 1H, H-5b), 2.82–2.90 (dd, *J*=16.1, 7.5 Hz, 1H, H-5a), 2.65–2.75 (m, 1H, H-13a), 2.55–2.64 (m, 1H, H-1b), 2.33–2.43 (dd, *J*=17.5, 4.6 Hz, 1H, H-1a), 2.23–2.33 (m, 2H, H-12 and H-13), 1.98–2.02 (dd, *J*=12.6, 5.5 Hz, 1H, H-11b), 1.88–1.93 (t, *J*=12.4, 1H, H-11a), 1.02 (d, *J*=5.9 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (CO), 171.2 (CO), 136.4 (C), 135.9 (C), 126.4 (C), 122.6 (CH), 120.1 (CH), 118.5 (CH), 111.2 (CH), 105.3 (C), 76.8 (CH_2NO_2), 68.6 (C-10b), 53.3 (CH), 52.4 (CO_2Me), 50.0 (CH), 49.0 (CH_2), 46.2 (CH), 38.1 (CH), 37.6 (CH_2), 21.6 (CH_2), 17.4 (12-CH_3); MS (ES): $C_{21}H_{23}N_3O_5$ calcd:398.1716 $[M+H]^+$; found: 398.1694 $[M+H]^+$.

*4.2.39. 4H-Cyclopent[1,8a]indolizino[8,7-b]indole-4-carboxylic acid,1,2,5,10,11,12,13,13a-octahydro-12-methyl-13-aminomethyl-2-oxo-methyl ester (10bR,12S,13R,13aS)-**14b**.* Compound **14a** (3.08 g, 7.75 mmol) was reduced using general procedure *3*. The crude amine was purified by flash chromatography on silica gel, eluting with 5–10% MeOH in CH_2Cl_2 to give **14b** as a white foam, 1.85 g (65%). HPLC (method A) t_R=1.12 min, (method B) t_R=5.13 min (97%); $[\alpha]_D^{24}$ +57.6 (*c* 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.19 (s, 1H, NH), 7.49 (m, 1H), 7.28 (m 1H), 7.08–7.13 (m, 2H), 5.36 (dd, *J*=8.4, 1.9 Hz, 1H, H-4), 3.72 (s, 3H, CO_2Me), 3.44–3.51 (dd, *J*=16.0, 1.8 Hz, H-5b), 3.06–3.14 (dd, *J*=16.0, 8.4 Hz, 1H, H-5a), 3.00 (br s, 2H, *C*H_2NH_2),

2.80–2.89 (dd, *J*=16.5, 10.6 Hz, H-1b), 2.63–2.69 (m, 1H, H-13a), 2.45–2.58 (m, 2H, H-1a, H-12), 2.17–2.23 (dd, *J*=12.5, 6.2 Hz, H-11b), 1.95–2.04 (t, *J*=12.6, 1H, H-11a), 1.74 (br s, 2H, NH_2, exchanges with D_2O), 1.61 (m, 1H, H-13), 1.09 (d, *J*=6.4 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0 (CO), 171.7 (CO), 138.5 (C), 136.4 (C), 126.4 (C), 121.6 (CH), 119.4 (CH), 118.4 (CH), 111.3 (CH), 103.4 (C), 68.6 (C-10b), 55.5 (CH), 52.4 (CO_2Me), 49.0 (CH), 48.6 (CH_2), 46.0 (CH), 40.4 (CH_2), 40.0 (CH_2), 35.4 (CH), 21.6 (CH_2), 18.6 (12-CH_3); MS (ES): $C_{21}H_{25}N_3O_3$ calcd: 368.1974 $[M+H]^+$; found: 368.1958 $[M+H]^+$.

*4.2.40. Cyclopenta[2′,3′]pyrrolo[1′,2′:1,2]azepino[3,4-b]indole-14-nitromethyl,1,2,5,10,11,12,13,13a-octahydro-13-methyl-2-oxo-, (10bR,12S,13R,13aS)-**15a**.* Compound **1** (4.00 g, 18.5 mmol) and 3-(3-aminopropyl)indole (3.22 g, 18.5 mmol)[26] were coupled according to general procedure *1*. The crude product was cyclized according to general procedure *2* (4 h). Purification by flash chromatography on silica gel, eluting with 2–5% MeOH in CH_2Cl_2 gave **15a** as a white foam, 3.06 g (47%). An analytical sample was prepared by HPLC; t_R=1.99 min (method A), t_R=6.06 min (method B); ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.45–7.48 (m, 1H), 7.25–7.28 (m, 1H), 7.09–7.14 (m, 2H), 4.58–4.62 (m, 2H, CH_2NO_2), 4.34–4.40 (m, 1H, H-4b), 3.13–3.18 (m, 1H, H-4a), 2.98–3.05 (m, 1H, H-14a), 2.80–2.88 (m, 2H, H-6a and H-6b), 2.60–2.70 (dd, *J*=17.6, 8.8 Hz, 1H, H-1b), 2.38–2.46 (dd, 1H, *J*=17.6, 7.6 Hz, H-12b), 2.25–2.29 (m, 2H, H-13, H-1a), 2.08–2.11 (m, 1H, H-5b), 1.91–2.08 (m, 3H, H-5a, H-12a, and H-14), 1.11 (d, *J*=6.0 Hz, 3H, 13-CH_3). Assignments are tentative, based on the COSY spectrum; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (CO), 137.9 (C), 135.7 (C), 128.4 (C), 122.4 (CH), 119.8 (CH), 118.5 (CH), 113.3 (C), 111.0 (CH), 76.7 (CH_2NO_2), 72.5 (C-11b), 51.4 (CH), 47.5 (CH), 47.0 (CH_2), 40.5 (CH_2), 37.9 (CH), 35.0 (CH_2), 27.6 (CH_2), 22.0 (CH_2), 17.9 (13-CH_3); MS (ES): $C_{20}H_{23}N_3O_4$ calcd: 354.1818 $[M+H]^+$; found: 354.1810 $[M+H]^+$.

*4.2.41. Cyclopenta[2′,3′]pyrrolo[1′,2′: 1,2]azepino[3,4-b]indole-14-aminomethyl,1,2,5,10,11,12,13,13a-octahydro-13-methyl-2-oxo-, (10bR,12S,13R,13aS) **15b**.* Compound **15a** (2.04 g, 5.78 mmol) was reduced using general method *3*. The crude amine was purified by flash chromatography on silica gel, eluting with 5% MeOH in CH_2Cl_2, then 10% 2 M NH_3 in MeOH/90% CH_2Cl_2 to give **15b** as a white foam, 0.52 g (28%). HPLC (method A) t_R=1.55 min, (method B) t_R=3.05 min (92%); $[\alpha]_D^{24}$ +45.6 (*c* 0.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 60 °C): δ 10.44 (br s, 1H, NH), 7.46 (m, 1H), 7.25–7.30 (m, 1H), 7.02–7.07 (m, 2H), 4.33–4.42 (m, H-4b), 3.22 (br s, 2H), 3.02–3.23 (m, 3H), 2.80–3.00 (m, 3H), 2.64–2.73 (m, 1H), 2.20–2.36 (m, 3H), 1.97–2.07 (m, 2H), 1.71–1.78 (m, 1H), 1.39–1.45 (m, 1H), 0.99 (d, *J*=6.1 Hz, 3H, 13-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 60 °C): δ 173.1 (CO), 139.8 (C), 135.3 (C), 128.3 (C), 121.4 (CH), 119.0 (CH), 118.1 (CH), 111.4 (CH), 110.8 (C), 73.0 (C-11b), 55.6 (CH), 48.2 (CH_2), 45.6 (CH), 41.5 (CH_2), 40.7 (CH_2), 37.2 (CH_2). 35.4 (CH), 27.8 (CH_2), 22.9 (CH2), 18.1 (13-CH_3); MS (ES): $C_{20}H_{25}N_3O$ calcd: 324.2076 $[M+H]^+$; found: 324.2086 $[M+H]^+$.

4.3. Compounds 16a–g. General procedure

Compound **8c** (800 mg, 2.43 mmol) was dissolved in a mixture of CH_2Cl_2 (15 mL) and THF (5 mL) and 1.30 mL (0.156 mmol) of this stock solution was aliquoted to seven glass vials. The appropriate amine (0.20 mmol) was added to each vial, followed by 1.0 mL of a stock solution prepared from 1-hydroxy-7-azabenzotriazole (1.22 g, 8.97 mmol), EDC (1.72 g, 8.97 mmol) and Et_3N (3.8 mL, 27.2 mmol) in dry CH_2Cl_2 (45 mL). The vials were shaken at rt for 48 h. The mixtures were diluted with CH_2Cl_2 and washed either with satd aq NaCl solution or 10% aq HCl solution as appropriate. After concentration under reduced pressure, the crude residues were purified by C-18 RP-HPLC to give **16a**–**g** in the yields indicated.

*4.3.1. Compound **16a**.* White solid, 39.9 mg, 75%. HPLC (method A) t_R=1.52 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J*=8.5 Hz, 1H, H-10), 6.80 (br s, 1H, NH), 6.72 (dd, *J*=8.5, 2.3 Hz, 1H, H-9), 6.56 (d, *J*=2.2 Hz, 1H, H-7), 4.22–4.27 (m, 1H, H-4b), 3.76 (s, 3H, OMe), 3.27–3.31 (m, 1H), 3.10–3.14 (m, 1H), 2.82 (d, *J*=4.7 Hz, NHCH_3), 2.70–2.80 (m, 3H), 2.45 (dd, *J*=17.0, 7.7 Hz, 1H), 2.12–2.29 (m, 2H), 1.92–2.02 (m, 3H), 1.75–1.85 (m, 1H), 1.04 (d, *J*=6.0 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5 (2 CO), 158.2, 141.7, 136.3, 128.0, 116.6, 111.7, 76.3 (C-10b), 60.0, 55.4, 51.9, 47.4, 39.6, 38.9, 34.4, 33.7, 26.6, 18.5 (12-CH_3); MS (ES): $C_{20}H_{26}N_2O_3$ calcd: 343.2022 $[M+H]^+$; found: 343.2032 $[M+H]^+$.

*4.3.2. Compound **16b**.* White solid, 44.6 mg, 74%. HPLC (method A) t_R=2.00 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.5 Hz, 1H, H-10), 6.71 (dd, *J*=8.7, 2.6 Hz, 1H, H-9), 6.56 (d, *J*=2.6 Hz, 1H, H-7), 4.22–4.40 (m, 1H, H-4b), 3.76 (s, 3H, OMe), 3.35–3.52 (m, 5H, 2 NCH_2CH_3 and 1H), 3.05–3.15 (m, 1H), 2.70–2.80 (m, 3H), 2.45–2.57 (m, 2H), 2.24–2.31 (dd, *J*=13.5, 7.7 Hz, 1H), 1.96–2.13 (m, 3H), 1.75–1.85 (m, 1H), 1.15–1.21 (m, 6H, 2 NCH_2CH_3), 1.03 (d, *J*=6.6 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (CO), 172.6 (CO), 158.1, 141.7, 136.5, 128.2, 116.4, 111.7, 76.2 (C-10b), 55.4, 53.7, 52.9, 47.6, 42.2, 41.1, 38.9, 34.4, 33.7, 26.7, 18.5, 15.6, 13.4; MS (ES): $C_{23}H_{32}N_2O_3$ calcd: 385.2491 $[M+H]^+$; found: 385.2493 $[M+H]^+$.

*4.3.3. Compound **16c**.* White solid, 42.7 mg, 74%. HPLC (method A) t_R=1.72 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J*=8.8 Hz, 1H, H-10), 6.92 (d, *J*=3.0 Hz, 1H, NH), 6.72 (dd, *J*=8.5, 2.7 Hz, 1H, H-9), 6.56 (d, *J*=2.7 Hz, 1H, H-7), 4.18–4.25 (m, 1H, H-4b), 3.76 (s, 3H, OMe), 3.27–3.33 (m, 1H), 3.05–3.10 (m, 1H), 2.72–2.82 (m, 4H), 2.41–2.50 (dd, *J*=17.0, 7.7 Hz, 1H), 2.21–2.29 (dd, *J*=13.6, 8.1 Hz, 1H), 2.13 (d, *J*=17.0 Hz, 1H), 1.88–1.98 (m, 3H), 1.75–1.85 (m, 1H), 1.03 (d, *J*=6.6 Hz, 3H, 12-CH_3), 0.74–0.78 (m, 2H, CH_2–cyclopropyl), 0.47–0.50 (m, 2H, CH_2–cyclopropyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (CO), 173.0 (CO), 157.8, 141.3, 135.9, 127.7, 116.3, 111.5, 76.1 (C-10b), 59.4, 55.3, 51.8, 47.3, 42.8, 39.4, 38.7, 34.2, 33.5, 26.5, 22.9, 18.4 (12-CH_3), 6.7 (2-cyclopropyl CH_2); MS (ES): $C_{22}H_{28}N_2O_3$ calcd: 369.2178 $[M+H]^+$; found: 369.2187 $[M+H]^+$.

*4.3.4. Compound **16d**.* White solid, 44.6 mg, 64%. HPLC (method A) t_R=1.72 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (s, 1H, NH), 7.33 (d, *J*=8.5 Hz, 1H, H-10), 6.72 (dd, *J*=8.6, 2.5 Hz, 1H, H-9), 6.55 (d, *J*=2.5 Hz, 1H, H-7), 4.65–4.69 (dd, *J*=9.0, 2.5 Hz, 1H, H-α), 4.24–4.34 (m, 2H, H-β and H-4b), 3.76 (s, 3H, OMe), 3.26–3.31 (m, 1H), 3.10–3.16 (m, 1H), 2.70–2.75 (m, 3H), 2.47–2.50 (dd, *J*=17.4, 7.4 Hz, 1H), 2.30–2.41 (m, 1H), 2.10–2.18 (t, *J*=10.8 Hz, 1H), 1.99–2.05 (m, 2H), 1.79–1.90 (m, 1H), 1.21 (d, *J*=6.3 Hz, 3H, CH(OH)CH_3), 1.11 (d, *J*=6.3 Hz, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (CO), 173.5 (CO), 171.6 (CO), 158.2, 141.6, 136.0, 128.0, 116.6, 111.9, 76.8 (C-10b), 68.1, 60.0, 58.1, 55.4, 52.7, 52.3, 47.7, 39.8, 39.0, 34.3, 33.5, 26.5, 20.5, 18.5 (12-CH_3); MS (ES): $C_{24}H_{32}N_2O_6$ calcd: 445.2339 $[M+H]^+$; found: 445.2357 $[M+H]^+$.

*4.3.5. Compound **16e**.* White solid, 31.3 mg, 55%. HPLC (method A) t_R=1.73 min; ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (br t, 1H, NH), 7.33 (d, *J*=8.8 Hz, 1H, H-10), 6.74 (dd, *J*=8.7, 2.7 Hz, 1H, H-9), 6.59 (d, *J*=2.5 Hz, 1H, H-7), 4.22–4.26 (m, 1H, H-4b), 4.15–4.20 (m, 2H, α-CH_2), 3.77 (s, 3H, OMe), 3.24–3.28 (m, 1H), 3.15–3.20 (m, 1H), 2.70–2.77 (m, 3H), 2.50–2.54 (dd, *J*=17.0, 7.7 Hz, 1H), 2.25–2.33 (m, 1H), 2.09–2.20 (m, 1H), 1.97–2.20 (m, 3H), 1.80–1.85 (m, 1H), 1.08 (d, *J*=6.3 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (CO), 173.5 (CO), 158.3, 141.6, 135.7, 127.9, 116.7, 116.5, 111.9, 76.7 (C-10b), 59.0, 55.5, 52.2, 47.4, 39.7, 39.0, 34.4, 33.6, 27.6, 26.6, 18.4 (12-CH_3); MS (ES): $C_{21}H_{25}N_3O_3$ calcd: 368.1974 $[M+H]^+$; found: 368.1997 $[M+H]^+$.

*4.3.6. Compound **16f**.* Oil, 54.5 mg, 69%. HPLC (method A) t_R=2.40 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J*=8.6 Hz, 1H, H-10), 7.14–7.18 (m, 1H), 6.74 (dd, *J*=8.5, 2.8 Hz, 1H, H-9), 6.57 (d,

J=2.8 Hz, H-7), 6.44–6.54 (m, 3H), 4.25–4.30 (m, 1H, H-4b), 3.79 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.70–4.00 (m, 4H), 3.46–3.52 (t, J=8.5 Hz, 1H), 3.11–3.20 (m, 6H), 2.65–2.75 (m, 3H), 2.46–2.57 (dd, J=17.0, 8.0 Hz, 1H), 2.27–2.34 (dd, J=13.6, 7.3 Hz, 1H), 1.98–2.08 (m, 3H), 1.80–1.85 (m, 1H), 1.05 (d, J=6.0 Hz, 3H, 12-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4 (CO), 172.1 (CO), 160.9, 158.2, 152.2, 141.8, 136.3, 130.2, 128.1, 116.5, 111.8, 109.5, 105.7, 103.4, 76.3 (C-10b), 55.5, 55.4, 53.4, 52.7, 50.4, 49.9, 47.6, 46.1, 42.5, 41.0, 38.9, 34.6, 33.7, 26.7, 18.7 (12-CH_3); MS (ES): $C_{30}H_{37}N_3O_4$ calcd: 504.2862 $[M+H]^+$; found: 504.2820 $[M+H]^+$.

4.3.7. Compound ***16g****.* White solid, 42.5 mg, 60%. HPLC (method A) t_R=2.24 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J=8.8 Hz, 1H, H-10), 6.71 (dd, J=8.8, 2.6 Hz, 1H, H-9), 6.57 (d, J=2.9 Hz, 1H, H-7), 6.49 (d, J=8.3 Hz, 1H, NH), 4.63–4.70 (m, 1H, H-α), 4.23–4.31 (m, 1H, H-4b), 3.76 (s, 3H), 3.74 (s, 3H), 3.28–3.35 (m, 1H), 3.06–3.15 (m, 1H), 2.67–2.77 (m, 3H), 2.45–2.54 (dd, J=17.0, 7.7 Hz, 1H), 2.23–2.30 (dd, J=13.6, 8.1 Hz, 1H), 2.09–2.19 (m, 1H), 1.51–1.70 (m, 3H), 1.95–2.06 (m, 3H), 1.80–1.84 (m, 1H), 1.10 (d, J=6.6 Hz, 3H, 12-CH_3), 0.93 (d, J=6.0 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (CO), 173.2 (CO), 172.9 (CO), 158.2, 141.8, 136.2, 127.9, 116.6, 111.7, 76.2 (C-10b), 59.8, 55.4, 52.5, 51.9, 51.1, 47.5, 41.5, 39.9, 38.8, 34.3, 33.7, 26.7, 25.2, 23.1, 21.9, 18.4 (12-CH_3); MS (ES): $C_{26}H_{36}N_2O_5$ calcd: 457.2702 $[M+H]^+$; found: 457.2693 $[M+H]^+$.

5. Crystal structure data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications 896741 (**4c**), 896742 (**8a**), 896743 (**4a**), and 896744 (**9c**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.UK).

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Supplementary data

^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.038.

References and notes

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