Concise total synthesis and structural revision of (+)-pestalazine B†

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A convergent synthesis of the proposed structure of (+)-pestalazine B has been achieved in 4 steps using the *N*-alkylation of an unprotected tryptophan diketopiperazine with a 3a-bromopyrrolidinoindoline as the key step. Although its structure was confirmed by X-ray analysis, the spectroscopic data did not match those of the natural product. The versatility of the methodology allowed the preparation of several diastereomers, and the database generated led to the proposal of an isomeric structure for the natural alkaloid where the D-leucine and D-phenylalanine residues exchanged positions, which was corroborated by total synthesis

Introduction

Pestalazines A and B (Fig. 1) are heterodimeric diketopiperazine alkaloids isolated from the pathogenic fungus *Pestalotiopsis theae* that contain two tryptophan units, one of them as a pyrrolidinoindoline fused to the diketopiperazine ring. In contrast to other dimeric structures, joined through the C3–C3′ bond, both natural products show an unsymmetrical connection (C3–C24 and C3–N30, respectively, for pestalazine A **1** and pestalazine B **2**, Fig. 1) between the indoline core and the indole unit.[1] Attracted by the striking architecture of **2** and the recent synthetic advances in the preparation of tryptophan-based dimeric alkaloids,[2,3] we undertook a program directed towards the total synthesis of the proposed structure of pestalazine B.

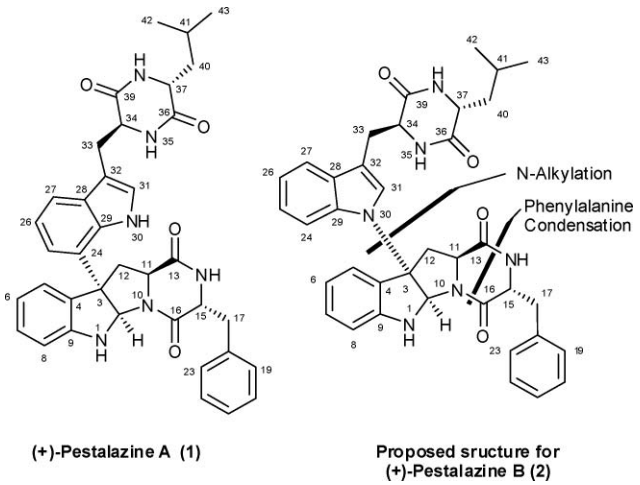

Fig. 1 Proposed structures of pestalazines A and B and main disconnections of pestalazine B.

According to our retrosynthetic analysis, **2** could be prepared in a quite concise and convergent manner on the basis of two disconnections; i) the final condensation of D-phenylalanine with the corresponding hexahydropyrrolo[2,3-*b*]indole to form the fused diketopiperazine ring, and ii) the *N*-alkylation of the tryptophan/leucine diketopiperazine subunit with 3a-bromo-2-methylcarboxylate-hexahydropyrrolo[2,3-*b*]indole. The expedient construction of C–N bonds between the latter compound and indole derivatives has been reported by Espejo and Rainier,[4] who have proposed that the ester enolate initially formed under basic conditions displaces the bromine atom to afford a transient cyclopropane that is then trapped by the indole nitrogen. Subsequent kinetic protonation results in the *endo* isomer of the substituted indoline.[5] Therefore, besides the formation of the key C–N bond, the required configuration at C11 of **2** is expected to be established in the same step.

Results and discussion

In order to assess the feasibility of the synthetic plan, diketopiperazine **3** and protected 3a-bromopyrrolidinoindoline **4** were prepared in multi-gram scale. Condensation between L-tryptophan methyl ester and *N*-Fmoc-D-leucine in the presence of EDC (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride) as coupling agent afforded the corresponding L-Trp-D-Leu dipeptide, which underwent the removal of the Fmoc group and the concomitant ring-closure under basic conditions (Et_2NH in MeOH) to give **3** (55% yield over the two steps). Diketopiperazine **3** has been previously isolated from the fungus *Penicillium brevicompactum* and shown to regulate plant growth.[6] 3a-Bromopyrrolidinoindoline **4** was synthesised in one step from bis-BOC-D-tryptophan methyl ester and NBS (*N*-bromosuccinimide) following our reported procedure.[3a]

Since the presence in **3** of three NH moieties could produce mixtures of regioisomers on its reaction with **4**, we first studied the reactivity of **3** towards silicon electrophiles to explore an eventual protection of the amide NH as silyl enol ethers. Interestingly, treatment of **3** with TIPSCl (2 equiv.) and Et_3N in CH_2Cl_2 afforded exclusively the indole *N*-silylated product. To extrapolate this finding to the alkylation with 3a-bromo-hexahydropyrroloindole **4**, we assayed the conditions reported by Espejo and Rainier,[4] by adding a 1 M solution of KO*t*Bu in THF to a suspension of **3** and **4** in CH_3CN. Despite the poor solubility of **3** in CH_3CN, the desired coupling product **5** was obtained in modest yields (25–30%).

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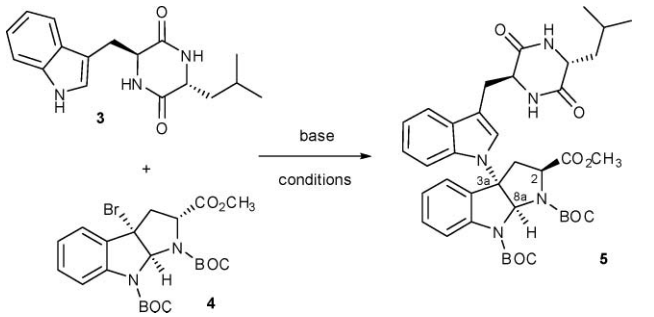
† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C-NMR spectra, CD spectra and X-ray details. CCDC reference numbers 767367. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00531b

Table 1 *N*-Alkylation of tryptophan derivative **3** with 3-*exo*-bromopyrrolidinoindoline **4**

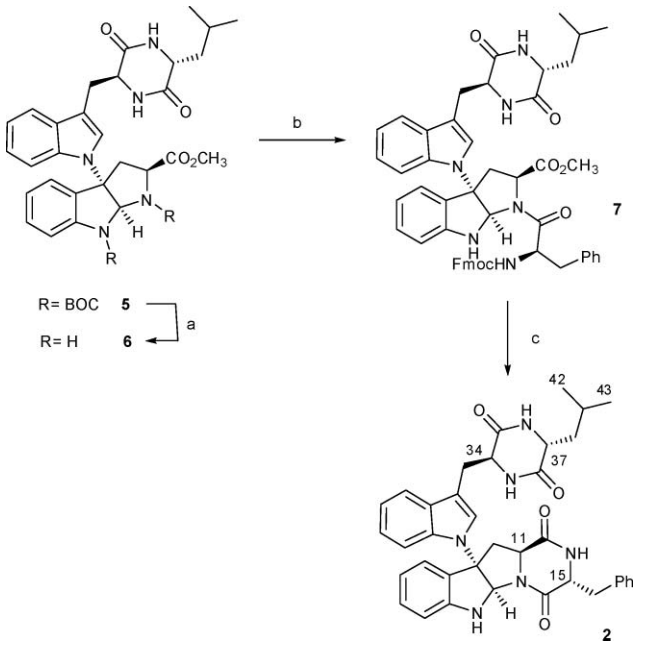


Entry	Base (equiv.)	Conditions	Yield of **5** (%)
1	KO*t*Bu (2.0)	CH_3CN, 12 °C	31
2	KO*t*Bu (2.0)	CH_3CN–THF (5 : 1), 10 °C	23
3	KO*t*Bu (2.5)	CH_3CN–DMF (5 : 1), 10 °C	18
4	NaH (2.0)	CH_3CN, 25 °C	25
5	NaH (2.0)	THF–DMF (1 : 1), 25 °C	15

Nevertheless, other regioisomers could not be identified, and the starting materials **3** and **4** were partially recovered. Although the solubility of **3** improved using THF and DMF as co-solvents, the yields dropped. Alternatively, the use of NaH either in acetonitrile or in a THF–DMF mixture did not afford better yields and more complex mixtures were observed. The expected inversion of configuration at C2 was confirmed in all cases by ^{1}H NMR, on the basis of the characteristic chemical shift of the *endo* methyl ester at δ ~3.2 ppm (Table 1).[7]

The rapid access to advanced intermediate **5**, despite the room for improvement in the yield of this step,[8] prompted us to complete the synthesis of the natural product. Hence, the BOC groups of **5** were removed using TMSI (trimethylsilyl iodide) to afford **6** (91% yield, Scheme 1), which was subsequently condensed with *N*-Fmoc-D-phenylalanine in the presence of HATU as coupling agent and Et_3N to give the tetrapeptide **7**.[3b] This was not characterised due to severe NMR line broadening, with rotameric effects arising from the carbamate protecting group and the peptide bond. The deprotection of the Fmoc group and the ring-closure to the diketopiperazine was effected in the same step upon addition of excess Et_2NH in MeOH to **7** (56% yield over the two steps). Much to our disappointment the ^{1}H and ^{13}C NMR spectra of **2** in acetone-d_6 (or acetone-d_6–DMSO-d_6 mixtures)[9] did not match those reported for the natural product (Scheme 1).[1] Recrystallisation of **2** from MeOH and hexane led to the formation of prism-shaped crystals. X-Ray analysis confirmed the stereochemistry of the final product and ruled out configurational scrambling of any of the four enolizable chiral centers along the sequence (Fig. 2). These results showed the need to revise the structure of pestalazine B.

Taking into account the versatility of this synthetic route that allows the preparation of diverse diastereomers of **2**, we tried to identify which stereogenic centers could be involved in the misassignment of the structure of pestalazine B. Since the *R* absolute configuration at C15 and C37 was secured by amino acid identification using Marfey's method,[10] and the relative configuration of the C2–C3–C11 triad was established by NOESY experiments, we initially directed our attention to the C34



Scheme 1 *Reagents and conditions*: (a) TMSI (2.2 equiv.), CH_3CN, 0 °C, 91%. (b) *N*-Fmoc-D-phenylalanine (1.1 equiv.), HATU (1.1 equiv.), Et_3N (2.2 equiv.), DMF, 0 to 25 °C. (c) Et_2NH (55 equiv.), MeOH, 25 °C, 56% combined.

stereocenter. This was assigned as *S* by the similarity of the CD (circular dichroism) spectra of **2** and pestalazine A (**1**), whereas the latter was correlated with that of (+)-asperazine,[11] a close analog of pestalazine A in which both diketopiperazine subunits are formed with phenylalanine residues. In the absence of other proofs for the absolute configuration at C34 in pestalazine B, we decided to prepare the C34 epimer of **2**.

Utilising the same sequence of steps, epimer **11** was assembled in a straightforward manner using the epimeric *cis*-diketopiperazine **8** (readily prepared using D-tryptophan methyl ester and *N*-Fmoc-D-leucine in an analogous manner to **3**) and 3a-bromopyrrolidinoindoline **4** (Scheme 2). Disappointingly the spectroscopic data of **11** did not match those of the natural product either. Incidentally, we found that *cis* diketopiperazine **8** and the intermediates containing fragment **8**, including the final product **11**, show a characteristic signal in the ^{1}H NMR spectrum between δ 0.0 and δ –0.5 ppm for one of the diastereotopic C40 protons (pestalazine numbering), which is attributed to the shielding effect of the indole ring.[12] The absence of this signal in the spectrum of pestalazine B is a good indication that it does not contain a *cis* diketopiperazine.

We then considered the opposite configuration of the indoline ring-fusion. We have recently revised the structure of the related dimeric diketopiperazine alkaloid (+)-asperdimin[3c] and showed that the indoline ring-fusion stereostructure cannot be safely determined based on the comparison of NMR data of analogous compounds.[3c] A reverse 2*S*, 3*R* and 11*R* configuration would still comply with the results of Marfey's analysis and the NOE signals observed for the natural product. Diastereoisomer **15** was therefore prepared from enantiomeric 3a-bromopyrrolidinoindoline **12**[3b] and diketopiperazine **3** using the same protocol (Scheme 2). Unfortunately, the NMR data of **15** also differed from those of the natural product. Furthermore, the specific optical rotation ($[\alpha]_D^{23}$

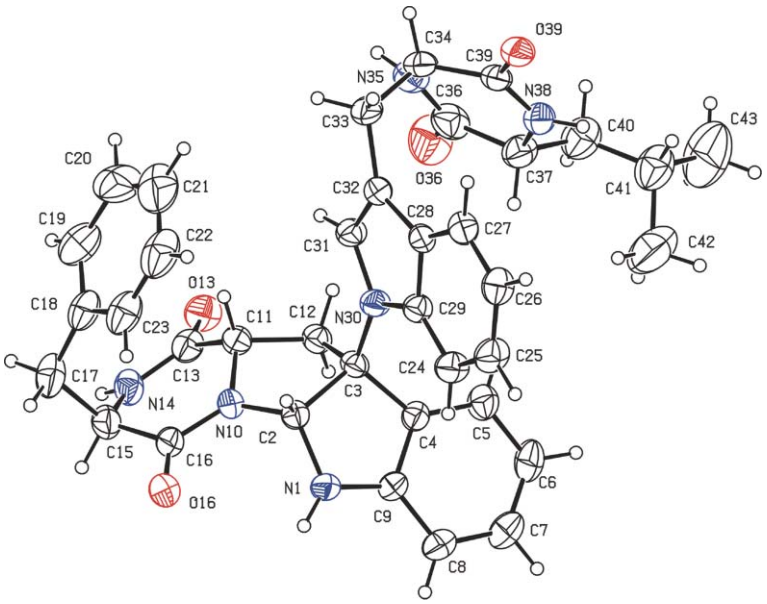


Fig. 2 ORTEP representation of synthetic **2**.

Table 2 Comparison of selected ^{1}H-NMR chemical shifts for natural pestalazine B and synthetic diastereoisomers of **2**

Ass.	600 MHz **pestalazine B** δ (ppm)	400 MHz **2** δ (ppm)	400 MHz **11** δ (ppm)	400 MHz **15** δ (ppm)	400 MHz **16** δ (ppm)
C15	3.47	4.21	4.12	4.76	4.53
C34	3.62	4.30	4.35	4.25	4.22
C42	0.95	0.76	0.60	0.68	0.78
C43	0.90	0.52	0.34	0.39	0.59

–77 (*c* 0.09, MeOH)) and CD spectrum[13] were very different to those reported for pestalazine B ($[\alpha]_D$ +199 (*c* 0.1, MeOH)).[1]

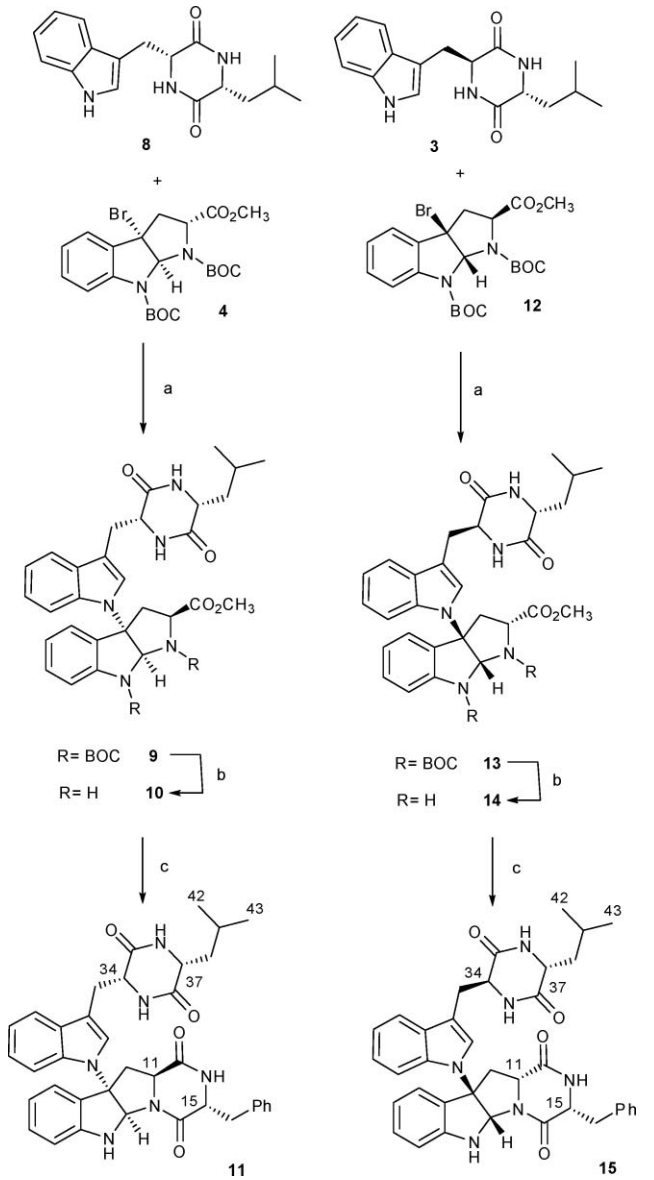
Thorough examination of the NMR data of the synthetic compounds **2**, **11** and **15** revealed contrasting differences in chemical shifts of key hydrogens when compared to the natural product. Remarkably the hydrogens attached to the stereogenic centres C15 and C34 are found to be deshielded in the synthetic series (Table 2). Moreover, the chemical shift of H34 is rather insensitive to changes not only in the relative configurations of the southern pyrrolidinoindoline unit stereocenters but also of C34. The chemical shift of H15 shows greater variation (δ 4.12–4.76 ppm) in the diastereomeric series (Table 2), but it was always found downfield relative to the natural product (δ = 3.47 ppm) even in the C15-epimer **16** (δ = 4.56 ppm), which was easily prepared by condensation of the advanced intermediate **6** with *N*-Fmoc-L-phenylalanine in two steps (Scheme 3). Conversely, the isobutyl methyl groups were found shielded in the synthetic series relative to the natural product (Table 2). Taken together, the spectroscopic analysis led us to propose for the natural product the structure of an isomer with the same relative and absolute configurations of **2** in which the residues of phenylalanine and leucine are interchanged. This proposal would be fully compatible with the spectroscopic data and the degradation analysis described for natural pestalazine B. A benzyl substituent at C37 with the *R* configuration could shield H34, whereas the pyrrolidinoindoline diketopiperazine subunit would affect the chemical shift of the isobutyl methyl groups differently to the diketopiperazine ring of the diastereomers of **2**.[14] Compound **21** was assembled from diketopiperazine **17**[15] and 3a-bromopyrrolidinoindoline **4** followed by the final construction of the fused diketopiperazine ring using a D-leucine derivative (Scheme 4). Much to our delight, the spectroscopic data (including optical rotation, $[\alpha]_D^{23}$ +194 (*c* 0.1, MeOH)) of **21** matched those of the natural product,[16] thus confirming the connectivity and absolute stereostructure of (+)-pestalazine B.

In summary, a convergent and versatile synthetic route aimed to the total synthesis of (+)-pestalazine B has led to its structural revision to isomer **21**. The rapid modular assembly of the two subunits with minimal use of protecting groups has provided a series of diastereomers that greatly facilitated the structural revision. The analysis of their spectroscopic data showed the inconsistencies with the natural product and suggested a structure with exchange of the phenylalanine and leucine residues on the diketopiperazine rings, which finally explained the spectroscopic discrepancies. The structural revision of (+)-pestalazine B is yet another example of the fundamental role of total synthesis in the validation of the proposed structures of natural products.[17]

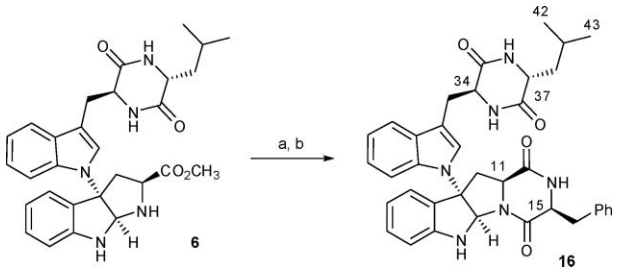
Experimental Section

(3*S*,6*R*)-3-((1*H*-Indol-3-yl)methyl)-6-isobutylpiperazine-2,5-dione (3)

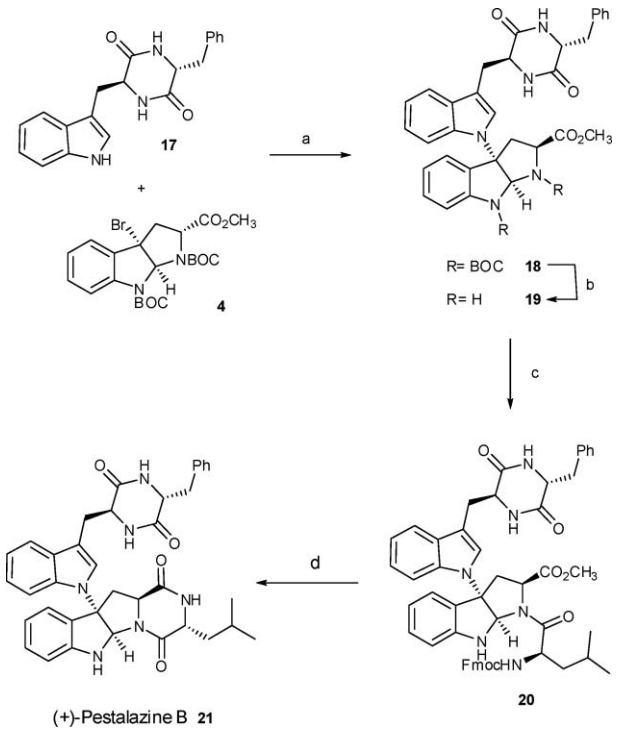
EDC (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride) (0.74 g, 3.87 mmol, 1.0 equiv) was added to a solution of L-tryptophan methyl ester (0.85 g, 3.87 mmol) and *N*-Fmoc-D-leucine (1.37 g, 3.87 mmol) in CH_2Cl_2 (24 mL) and the resulting solution was stirred overnight at 25 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2×). The organic layer was dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 90 : 10 CH_2Cl_2–MeOH) to afford the



Scheme 2 *Reagents and conditions*: (a) KO*t*Bu (2.0 equiv.), CH_3CN, 12 °C, **9**, 31%; **13**, 31%. (b) TMSI (2.2 equiv), CH_3CN, 0 °C, **10**, 84%; **14**, 91%. (c) 1). *N*-Fmoc-D-phenylalanine (1.1 equiv.), HATU (1.1 equiv.), Et_3N (2.2 equiv.), DMF, 0 to 25 °C. 2) Et_2NH (55 equiv.), MeOH, 25 °C, **11**, 66%; **15**, 55% combined.



Scheme 3 *Reagents and conditions*: (a) *N*-Fmoc-L-phenylalanine (1.1 equiv.), HATU (1.1 equiv.), Et_3N (2.2 equiv.), DMF, 0 to 25 °C. (b) Et_2NH (55 equiv.), MeOH, 25 °C, 56% combined.



Scheme 4 *Reagents and conditions*: (a) KO*t*Bu (2.0 equiv.), CH_3CN, 12 °C, 30%. (b) TMSI (2.2 equiv.), CH_3CN, 0 °C, 85%. (c) 1). *N*-Fmoc-D-leucine (1.1 equiv.), HATU (1.1 equiv.), Et_3N (2.2 equiv.), DMF, 0 to 25 °C. 2) Et_2NH (55 equiv.), MeOH, 25 °C, 57% combined.

corresponding dipeptide L-Trp-D-Leu (1.48 g, 70% yield) as a white solid. Et_2NH (5 mL, 48.33 mmol, 22 equiv.) was added to a solution of the dipeptide obtained above (1.23 g, 2.22 mmol) in MeOH (75 mL) and the mixture was stirred overnight at 25 °C. Acetonitrile (100 mL) was added to the suspension and the resulting precipitate was filtered and washed with acetonitrile. The white solid obtained was dried under vacuum, identified as the title compound **3** (0.52 g, 79% yield) and used in the next reaction without further purification. **M.p.** (CH_3CN): 105–107 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.61 (d, J = 8.0 Hz, 1H, ArH), 7.33 (d, J = 8.0 Hz, 1H, ArH), 7.1–7.0 (m, 2H, ArH), 7.06 (s, 1H, ArH), 7.00 (t, J = 7.1 Hz, 1H, ArH), 4.22 (t, J = 3.9 Hz, 1H), 3.46 (dd, J = 14.6, 4.5 Hz, 1H), 3.15 (dd, J = 14.6, 4.5 Hz, 1H), 2.63 (dd, J = 7.1, 4.7 Hz, 1H), 1.6–1.5 (m, 1H), 1.5–1.4 (m, 1H), 1.4–1.3 (m, 1H), 0.75 (d, J = 6.5 Hz, 3H), 0.62 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 171.7 (s, *C*O), 171.5 (s, *C*O), 138.1 (s), 128.9 (s), 126.2 (d), 122.7 (d), 120.3 (d), 119.9 (d), 112.3 (d), 109.2 (s), 57.6 (d) 53.4 (d), 41.9 (t), 31.1 (t), 25.2 (d), 23.3 (q, CH_3), 22.1 (q, CH_3) ppm. **IR** (NaCl) ν 3400–3050 (br, N–H), 2956 (w, C–H), 2926 (w, C–H), 2869 (w, C–H), 1666 (s, C=O), 1456 (s), 1318 (m), 1098 (w), 1010 (w), 740 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 332 ([M+K]$^+$, 77), 322 ([M+Na]$^+$, 99), 300 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{17}H_{22}N_3O_2$ ([M+1]$^+$), 300.1706; found, 300.1798. $[\alpha]_D^{24}$ +69 (*c* 0.16, MeOH).

(2*S*,3a*S*,8a*S*)-1,8-Di-*tert*-butyl-2-methyl-3a-(3-(((2*S*,5*R*)-5-isobutyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (5)

A solution of KO*t*Bu (400 µL, 1.0 M in THF, 0.40 mmol, 2.0 equiv) was added dropwise over a period of 15 min to a suspension

of the diketopiperazine **3** (60 mg, 0.20 mmol, 1.0 equiv) and the bromoindoline **4** (150 mg, 0.30 mmol, 1.5 equiv) in CH_3CN (15 mL) at 12 °C. The cooling bath was removed and stirring was continued for 1 h. A saturated $NaHCO_3$ aqueous solution (7 mL) was added and the mixture was extracted with CH_2Cl_2 (2×). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 95 : 5 CH_2Cl_2–MeOH) to give 45 mg of the title compound (32% yield) as a white solid. **M.p.** (MeOH): 99–100 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.8–7.6 (m, 2H, ArH), 7.38 (t, J = 7.8 Hz, 1H, ArH), 7.32 (d, J = 7.5 Hz, 1H, ArH), 7.2–7.0 (m, 5H, ArH), 6.69 (s, 1H), 4.93 (d, J = 8.7 Hz, 1H), 4.19 (t, J = 4.0 Hz, 1H), 3.55 (dd, J = 12.8, 9.2 Hz, 1H), 3.40 (dd, J = 14.7, 3.6 Hz, 1H), 3.23 (s, 3H, CO_2CH_3), 3.2–3.0 (m, 2H), 2.53 (dd, J = 7.3, 4.4 Hz, 1H), 1.57 (s, 9H), 1.48 (s, 9H), 1.5–1.3 (m, 3H), 0.74 (d, J = 6.4 Hz, 3H), 0.46 (d, J = 6.4 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 172.5 (s, CO_2CH_3), 171.6 (s, CO), 171.3 (s, CO), 153.8 (s, 2xOCON), 144.8 (s), 136.8 (s), 132.0 (d), 131.3 (s), 131.1 (s), 128.0 (d), 125.2 (d), 123.5 (d), 121.5 (d, 2x), 121.1 (d), 112.4 (d, 2x), 110.3 (s), 83.7 (d), 81.4 (s), 74.1 (s), 60.9 (d), 57.3 (d), 53.5 (d), 52.9 (q, CO_2CH_3), 41.9 (t, 2x), 30.8 (t), 28.8 (q, 3x), 28.7 (q, 3x), 25.0 (d), 23.4 (q), 21.9 (q) ppm. **IR** (NaCl) ν 3400–3050 (br, N–H), 2956 (m, C–H), 2931 (m, C–H), 2871 (w, C–H), 1720 (s, C=O), 1679 (s, C=O), 1456 (m), 1393 (s), 1158 (s), 1015 (m), 856 (m), 738 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 738 ([M+Na]$^+$, 9), 716 ([M+1]$^+$, 25) 616 ([M–CO_2tBu]$^+$, 90), 560 (100), 516 (93). **HRMS** (ESI$^+$) calcd for $C_{39}H_{50}N_5O_8$ ([M+1]$^+$), 716.3654; found, 716.3664. $[\alpha]_D^{21}$ +95 (*c* 0.1, MeOH).

(2*S*,3a*S*,8a*S*)-Methyl-3a-(3-(((2*S*,5*R*)-5-isobutyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (6)

Iodotrimethylsilane (33 µL, 0.23 mmol, 2.2 equiv) was added dropwise to a solution of the protected indoline **5** (75 mg, 0.11 mmol) in acetonitrile (2.5 mL) at 0 °C. The resulting yellow solution was stirred at 0 °C for 30 min. Polymer-bound benzyldiisopropylamine (210 mg, 50–90 mesh, Aldrich) and then wet MeOH (3 mL) were added. The cooling bath was removed and the suspension was stirred for 15 min. The resin was filtered and washed with acetonitrile (10 mL) and MeOH (10 mL), the solvents of the collected filtrate were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (90 : 10 CH_2Cl_2–MeOH) to afford 49 mg (91% yield) of the title compound as a white solid. **M.p.** (MeOH): 115–118 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.6–7.5 (m, 1H, ArH), 7.5–7.4 (m, 1H, ArH), 7.35 (s, 1H, ArH), 7.1–7.0 (m, 1H, ArH), 7.0–6.9 (m, 3H, ArH), 6.64 (d, J = 7.9 Hz, 1H, ArH), 6.61 (td, J = 7.4, 0.9 Hz, 1H, ArH), 5.45 (s, 1H), 4.3–4.2 (m, 1H), 4.18 (dd, J = 7.7, 3.0 Hz, 1H), 3.50 (dd, J = 14.5, 3.1 Hz, 1H), 3.4–3.3 (m, 1H), 3.34 (s, 3H, CO_2CH_3), 3.11 (dd, J = 10.8, 3.9 Hz, 1H), 3.07 (dd, J = 8.8, 3.9 Hz, 1H), 2.4–2.3 (m, 1H), 1.5–1.2 (m, 3H), 0.70 (d, J = 6.3 Hz, 3H), 0.31 (d, J = 6.3 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 175.0 (s, CO_2CH_3), 172.0 (s, CO), 171.7 (s, CO), 151.8 (s), 137.4 (s), 131.2 (d), 130.7 (s), 129.6 (s), 128.1 (d), 125.6 (d), 123.0 (d), 120.9 (d), 120.4 (d), 120.1 (d), 113.2 (d), 111.1 (d), 109.2 (s), 83.4 (d), 77.4 (s), 61.1 (d), 57.5 (d), 53.3 (d), 52.6 (q, CO_2CH_3), 43.0 (t), 41.4 (t), 31.1 (t), 24.9 (d), 23.4 (q), 21.6 (q) ppm. **IR** (NaCl) ν 3400–3050 (br, N–H), 2954 (w, C–H), 2871 (w, C–H), 1735 (m, C=O), 1673 (s, C=O), 1457 (m), 1317 (m), 743 (m) cm^{-1}. **MS** (ESI$^+$) m/z (%) 516 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{29}H_{34}N_5O_4$ ([M+1]$^+$), 516.2605; found, 516.2614. $[\alpha]_D^{24}$ +50 (*c* 0.14, MeOH).

Proposed structure of (+)-pestalazine B (2)

N-Fmoc-D-phenylalanine (17 mg, 0.04 mmol, 1.1 equiv) was added to a solution of diamine **6** (20 mg, 0.03 mmol, 1.0 equiv) in DMF (1.0 mL). The mixture was cooled down to 0 °C and Et_3N (13 µL, 0.08 mmol, 2.0 equiv) was added, followed by HATU (16 mg, 0.04 mmol, 1.1 equiv). The cooling bath was removed and the mixture was stirred for 16 h at 25 °C. The resulting mixture was diluted with EtOAc (10 mL) and washed with H_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (95 : 5 CH_2Cl_2–MeOH) to give 20 mg (60% yield) of the coupled tetrapeptide which was used directly in the next step. Et_2NH (125 µL, 1.21 mmol, 55 equiv) was added to a solution of the dipeptide obtained above (20 mg, 0.02 mmol) in MeOH (2 mL) and the mixture was stirred at 25 °C for 8 h (TLC monitoring). The solvents were removed under reduced pressure and the residue was purified by flash chromatography (silica gel, 95 : 5 CH_2Cl_2–MeOH) to give 13 mg of the title compound (93% yield) as a white solid. This solid was recrystallised from MeOH–hexane to afford colourless prism-shaped crystals. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.62 (d, J = 7.8 Hz, 1H, H27), 7.48 (d, J = 4.0 Hz, 1H, H14), 7.29 (s, 1H, H31), 7.22 (t, J = 7.3 Hz, 1H, H21), 7.14 (br s, 1H), 7.13 (t, J = 7.2 Hz, 1H, H7), 7.1–7.0 (m, 4H, H19/H20/H22/H23), 6.98 (t, J = 7.8 Hz, 1H, H26), 6.89 (t, J = 7.8 Hz, 1H, H25), 6.86 (d, J = 7.9 Hz, 1H, H5), 6.8–6.7 (m, 2H, H8/H38), 6.66 (d, J = 8.0 Hz, 1H, H24), 6.60 (t, J = 7.2 Hz, 1H, H6), 6.59 (d, J = 3.6 Hz, 1H, H1), 5.86 (d, J = 3.6 Hz, 1H, H2), 4.30 (dd, J = 4.8, 2.3 Hz, 1H, H34), 4.21 (dt, J = 5.7, 4.4 Hz, 1H, H15), 3.50 (dd, J = 14.5, 5.1 Hz, 1H, H33A), 3.4–3.2 (m, 3H, H11/H12A/H33B), 3.14 (dd, J = 13.6, 6.1 Hz, 1H, H17A), 2.99 (dd, J = 13.6, 6.1 Hz, 1H, H17B), 2.82 (m, 1H, H37), 2.19 (dd, J = 15.8, 13.3 Hz, 1H, H12B), 1.7–1.6 (m, 1H, H41), 1.6–1.5 (m, 1H, H40A), 1.4–1.3 (m, 1H, H40B), 0.76 (d, J = 6.5 Hz, 3H, H42), 0.52 (d, J = 6.5 Hz, 3H, H43) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 171.5 (s, C36), 169.7 (s, C39), 168.8 (s, C13), 167.7 (s, C16), 148.9 (s, C9), 137.0 (s, C18), 136.5 (s, C29), 130.8 (d, C19/C23), 130.7 (s, C28), 129.6 (s, C4), 129.4 (d, C20/C22), 128.0 (d, C7), 126.9 (d, C31), 123.8 (d, C21), 122.5 (d, 2x, C5/C25), 120.6 (s, C27), 120.5 (d, C26), 119.7 (d, C6), 112.8 (s, C24), 111.0 (d, C8), 109.8 (s, C32), 83.2 (d, C2), 74.1 (s, C3), 59.8 (d, C15), 56.8 (d, C11), 56.5 (d, C34), 53.2 (d, C37), 42.3 (t, C40), 41.2 (t, C12), 40.5 (t, C17), 30.4 (t, C33), 24.5 (d, C41), 23.4 (q, C42), 21.7 (q, C43) ppm. **IR** (NaCl) ν 3600–3100 (br, N–H), 2954 (m, C–H), 2924 (w, C–H), 2869 (w, C–H), 1673 (s, C=O), 1455 (m), 1317 (m), 1106 (m), 743 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 631 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{37}H_{39}N_6O_4$ ([M+1]$^+$), 631.3027; found, 631.3018. $[\alpha]_D^{24}$ +87 (*c* 0.1, MeOH).

(3*R*,6*R*)-3-((1*H*-Indol-3-yl)methyl)-6-isobutylpiperazine-2,5-dione (8)

According to the general procedure described for **3**, diketopiperazine **8** was prepared in 73% yield. **M.p.** (MeOH): 123–125 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.59 (d, J = 8.0 Hz, 1H, ArH),

7.31 (d, J = 8.0 Hz, 1H, ArH), 7.1–7.0 (m, 2H, ArH), 7.05 (s, 1H, ArH), 7.00 (t, J = 7.5 Hz, 1H, ArH), 4.26 (t, J = 4.0 Hz, 1H), 3.57 (dd, J = 9.9, 4.2 Hz, 1H), 3.48 (dd, J = 14.6, 3.5 Hz, 1H), 3.15 (dd, J = 14.6, 4.6 Hz, 1H), 1.2–1.0 (m, 1H), 0.66 (ddd, J = 13.8, 9.6, 4.2 Hz, 1H), 0.60 (d, J = 6.5 Hz, 3H), 0.49 (d, J = 6.5 Hz, 3H), –0.1– –0.2 (m, 1H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 170.7 (s, *C*O), 170.0 (s, *C*O), 138.0 (s), 129.4 (s), 126.0 (d), 122.6 (d), 120.3 (d), 120.2 (d), 112.5 (d), 109.6 (s), 57.6 (d) 54.3 (d), 45.2 (t), 30.8 (t), 24.7 (d), 23.4 (q, CH_3), 21.4 (q, CH_3) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2954 (w, C–H), 1664 (s, C═O), 1457 (s), 1325 (m), 1093 (w), 1011 (w), 840 (m), 741 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 332 ([M+K]$^+$, 100), 322 ([M+Na]$^+$, 38), 300 ([M+1]$^+$, 76). **HRMS** (ESI$^+$) calcd for $C_{17}H_{22}N_3O_2$ ([M+1]$^+$), 300.1706; found, 300.1705. $[\alpha]_D^{26}$ –2 (*c* 0.16, MeOH).

(2*S*,3a*S*,8a*S*)-1,8-Di-*tert*-butyl-2-Methyl 3a-(3-(((2*R*,5*R*)-5-isobutyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2H, 8aH)-tricarboxylate (9)

According to the general procedure described for **5**, substituted indoline **9** was prepared in 31% yield. **M.p.** (MeOH): 91–92 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.8–7.6 (m, 1H, ArH), 7.63 (d, J = 7.8 Hz, 1H, ArH), 7.5–7.3 (m, 2H, ArH), 7.25 (d, J = 7.9 Hz, 1H, ArH), 7.2–7.1 (m, 2H, ArH), 7.1–7.0 (m, 1H, ArH), 6.91 (br s, 1H, ArH), 6.75 (s, 1H), 4.94 (d, J = 9.0 Hz, 1H), 4.3–4.2 (m, 1H), 3.7–3.5 (m, 2H), 3.46 (dd, J = 14.7, 3.1 Hz, 1H), 3.23 (s, 3H, CO_2CH_3), 3.00 (d, J = 12.9 Hz, 1H), 2.93 (dd, J = 14.6, 5.1 Hz, 1H), 1.6–1.4 (m, 18H), 1.2–1.0 (m, 1H), 0.92 (ddd, J = 13.5, 10.0, 3.7 Hz, 1H), 0.61 (d, J = 6.5 Hz, 3H), 0.41 (d, J = 6.5 Hz, 3H), –0.2– –0.3 (m, 1H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 172.6 (s, CO_2CH_3), 171.0 (s, *C*O), 169.8 (s, *C*O), 153.8 (s, 2xO*C*ON), 145.0 (s), 136.2 (s), 132.2 (d), 131.8 (s), 131.1 (s), 128.5 (d, 2x), 125.2 (d), 123.5 (d), 121.5 (d, 2x), 112.6 (d, 2x), 109.9 (s), 83.6 (s), 81.0 (d), 74.0 (s), 61.0 (d), 56.9 (d), 54.4 (d), 52.9 (q, CO_2CH_3), 45.4 (t, 2x), 30.4 (t), 28.8 (q, 3x), 28.6 (q, 3x), 24.8 (d), 23.9 (q), 21.4 (q) ppm. **IR** (NaCl) ν 3400–3050 (br, N–H), 2956 (m, C–H), 2931 (m, C–H), 2870 (w, C–H), 1720 (s, C═O), 1679 (s, C═O), 1456 (s), 1393 (s), 1325 (m), 1158 (s), 1015 (m), 856 (m), 738 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 738 ([M+Na]$^+$, 100), 716 ([M+1]$^+$, 28) 616 ([M–CO_2tBu]$^+$, 17). **HRMS** (ESI$^+$) calcd for $C_{39}H_{49}N_5NaO_8$ ([M+Na]$^+$), 738.3473; found, 738.3486. $[\alpha]_D^{21}$ –13 (*c* 0.08, MeOH).

(2*S*,3a*S*,8a*S*)-Methyl-3a-(3-(((2*R*,5*R*)-5-isobutyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (10)

According to the general procedure described for **6**, diamine **10** was prepared in 84% yield. **M.p.** (MeOH): 130–133 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.58 (dd, J = 7.0, 1.7 Hz, 1H, ArH), 7.44 (d, J = 7.4 Hz, 1H, ArH), 7.21 (s, 1H, ArH), 7.1–6.9 (m, 4H, ArH), 6.7–6.6 (m, 2H, ArH), 5.43 (s, 1H, H8a), 4.3–4.2 (m, 2H), 3.61 (dd, J = 10.0, 3.9 Hz, 1H), 3.44 (m, 2H), 3.33 (s, 3H, CO_2CH_3), 3.02 (dd, J = 14.6, 4.8 Hz, 1H), 2.93 (dd, J = 12.9, 2.9 Hz, 1H), 1.2–1.1 (m, 1H), 0.82 (ddd, J = 13.6, 9.7, 4.1 Hz, 1H), 0.56 (d, J = 6.6 Hz, 3H), 0.38 (d, J = 6.6, Hz, 3H), –0.13 (ddd, J = 13.6, 10.0, 4.7 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 175.3 (s, CO_2CH_3), 170.9 (s, *C*O), 169.8 (s, *C*O), 152.0 (s), 136.7 (s), 131.5 (d), 131.4 (s), 128.9 (s), 128.3 (d), 126.6 (d), 122.8 (d), 120.9 (d, 2x), 119.9 (d), 113.4 (d), 111.5 (d), 109.0 (s), 83.3 (d, C8a), 77.4 (s, C3a), 61.4 (d), 57.1 (d), 54.3 (d), 52.7 (q, CO_2CH_3), 45.3 (t), 42.3 (t), 30.6 (t), 24.8 (d), 23.6 (q), 21.4 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2953 (m, C–H), 2922 (w, C–H), 2870 (w, C–H), 1734 (m), 1670 (s, C═O), 1608 (m), 1457 (s), 1319 (m), 1212 (m), 742 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 516 ([M+1]$^+$, 100), 217 (22). **HRMS** (ESI$^+$) calcd for $C_{29}H_{34}N_5O_4$ ([M+1]$^+$), 516.2605; found, 516.2623. $[\alpha]_D^{24}$ +105 (*c* 0.20, $CHCl_3$).

C34 Epimer of 2 (11)

According to the general procedure described for **2**, epimer **11** was prepared in 66% yield. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.71 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.38 (d, J = 4.3 Hz, 1H), 7.33 (dd, J = 7.8, 1.4 Hz, 2H), 7.3–7.1 (m, 4H), 7.09 (d, J = 1.9 Hz, 1H), 6.99 (t, J = 7.0 Hz, 1H), 6.93 (t, J = 7.0 Hz, 1H), 6.9–6.8 (m, 2H), 6.7–6.6 (m, 3H), 6.07 (d, J = 4.0 Hz, 1H), 4.76 (dd, J = 12.1, 5.7 Hz, 1H), 4.4–4.3 (m, 1H), 4.12 (dt, J = 11.4, 4.0 Hz, 1H), 3.7–3.5 (m, 4H), 3.23 (dd, J = 14.4, 5.4 Hz, 1H), 3.05 (dd, J = 13.6, 3.9 Hz, 1H) 2.38 (dd, J = 14.4, 12.2 Hz, 1H), 1.2–1.1 (m, 1H), 0.96 (ddd, J = 13.3, 11.0, 2.6 Hz, 1H), 0.60 (d, J = 6.5 Hz, 3H), 0.34 (d, J = 6.5 Hz, 3H), –0.49 (ddd, J = 13.3, 11.0, 2.6 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 170.2 (s), 169.0 (s), 167.9 (s), 167.9 (s), 148.9 (s), 138.2 (s), 136.2 (s), 131.3 (s), 130.8 (d, 2x), 130.8 (d), 129.6 (s), 129.3 (d, 3x), 127.6 (d), 127.2 (d), 123.5 (d), 122.4 (d), 120.9 (d), 120.7 (d), 119.8 (d), 113.1 (d), 111.1 (d), 109.6 (s), 84.1 (d), 74.3 (s), 60.1 (d), 57.5 (d), 56.5 (d), 54.0 (d), 44.1 (t), 41.6 (t), 39.9 (t), 30.7 (t), 24.1 (d), 23.9 (q), 21.0 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2956 (m, C–H), 2925 (m, C–H), 2870 (w, C–H), 1672 (s, C═O), 1456 (s), 1320 (m), 741 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 653 ([M+Na]$^+$, 98), 631 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{37}H_{39}N_6O_4$ ([M+1]$^+$), 631.3027; found, 631.3052. $[\alpha]_D^{20}$ +139 (*c* 0.16, MeOH).

(2*R*,3a*R*,8a*R*)-1,8-Di-*tert*-butyl-2-methyl-3a-(3-(((2*S*,5*R*)-5-isobutyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (13)

According to the general procedure described for **5**, substituted indoline **13** was prepared in 30% yield. **M.p.** (MeOH): 101–102 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.8–7.6 (m, 1H, ArH), 7.66 (d, J = 7.5 Hz, 1H, ArH) 7.5–7.4 (m, 2H, ArH), 7.3–7.1 (m, 4H, ArH), 6.93 (br s, 1H, ArH), 6.76 (s, 1H), 4.94 (d, J = 9.1 Hz, 1H), 4.20 (t, J = 3.7 Hz, 1H), 3.59 (dd, J = 12.6, 9.4 Hz, 1H), 3.45 (dd, J = 14.6, 3.2 Hz, 1H), 3.24 (s, 3H, CO_2CH_3), 3.1–2.9 (m, 2H), 2.51 (dd, J = 6.2, 5.0 Hz, 1H), 1.6–1.3 (m, 21H), 0.78 (d, J = 6.5 Hz, 3H), 0.64 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 172.6 (s, CO_2CH_3), 171.9 (s, *C*O), 171.2 (s, *C*O), 153.8 (s, 2x O*C*ON), 145.0 (s), 136.3 (s), 132.2 (d), 131.5 (s), 130.8 (s), 128.5 (d, 2x), 125.2 (d), 123.5 (d), 121.5 (d), 121.2 (d), 112.5 (d, 2x), 109.9 (s), 83.6 (s), 81.0 (d), 74.0 (s), 60.8 (d), 57.2 (d), 53.6 (d), 52.9 (q, CO_2CH_3), 42.0 (t, 2x), 30.7 (t), 28.8 (q, 3x), 28.6 (q, 3x), 25.2 (d), 23.3 (q), 22.3 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2976 (m, C–H), 2932 (m, C–H), 2871 (w, C–H), 1718 (s, C═O), 1680 (s, C═O), 1481 (s), 1394 (s), 1327 (m), 1157 (s), 1016 (m), 856 (m), 737 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 738 ([M+Na]$^+$, 83), 716 ([M+1]$^+$, 62), 480 (100). **HRMS** (ESI$^+$) calcd for $C_{39}H_{50}N_5O_8$ ([M+1]$^+$), 716.3654; found, 716.3664. $[\alpha]_D^{21}$ +61 (*c* 0.08, MeOH).

(2*R*,3a*R*,8a*R*)-Methyl-3a-(3-(((2*S*,5*R*)-5-isobutyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (14)

According to the general procedure described for **6**, diamine **14** was prepared in 91% yield. **M.p.** (MeOH): 117–118 °C. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.7–7.5 (m, 1H, ArH), 7.4–7.3 (m, 1H, ArH), 7.24 (s, 1H, ArH), 7.10 (td, J = 7.7, 1.2 Hz, 1H, ArH), 7.1–6.9 (m, 3H, ArH), 6.7–6.6 (m, 2H, ArH), 5.43 (s, 1H), 4.24 (dd, J = 7.8, 3.4 Hz, 1H), 4.21 (t, J = 3.4 Hz, 1H), 3.45 (dd, J = 14.5, 3.4 Hz, 1H), 3.4–3.3 (m, 1H), 3.37 (s, 3H, CO_2CH_3), 3.06 (dd, J = 14.6, 4.6 Hz, 1H), 2.94 (dd, J = 13.1, 3.4 Hz, 1H), 2.50 (dd, J = 6.4, 4.7 Hz, 1H), 1.7–1.2 (m, 3H), 0.73 (d, J = 6.5 Hz, 3H), 0.59 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 175.3 (s, CO_2CH_3), 171.8 (s, CO), 171.3 (s, CO), 151.8 (s), 136.9 (s), 131.4 (d), 131.1 (s), 129.2 (s), 128.2 (d), 126.2 (d), 122.9 (d), 121.0 (d), 120.6 (d), 119.9 (d), 113.3 (d), 111.5 (d), 109.0 (s), 83.8 (d), 77.6 (s), 61.4 (d), 57.5 (d), 53.5 (d), 52.7 (q, CO_2CH_3), 42.6 (t), 42.0 (t), 30.9 (t), 25.2 (d), 23.3 (q), 22.3 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2954 (m, C–H), 2870 (w, C–H), 1733 (m, C═O), 1674 (s, C═O), 1609 (m), 1458 (m), 1316 (m), 1211 (m), 742 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 516 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{29}H_{34}N_5O_4$ ([M+1]$^+$), 516.2605; found, 516.2614. $[\alpha]_D^{10}$ −24 (c 0.08, MeOH).

Diastereoisomer 15 of 2

According to the general procedure described for **2**, diastereoisomer **15** was prepared in 55% yield. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.66 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.4–7.3(m, 3H), 7.3–7.2 (m, 2H), 7.11 (s, 1H), 7.0–6.9 (m, 1H), 6.9–6.8 (m, 3H), 6.7–6.6 (m, 1H), 6.7–6.5 (m, 3H), 5.92 (d, J = 3.9 Hz, 1H), 4.97 (dd, J = 11.7, 6.2 Hz, 1H), 4.76 (dd, J = 7.5, 4.8 Hz, 1H), 4.3–4.2 (m, 1H), 3.6–3.5 (m, 2H), 3.41 (dd, J = 14.4, 4.7 Hz, 1H), 3.15 (dd, J = 14.4, 5.0 Hz, 1H), 3.00 (dd, J = 14.8, 7.6 Hz, 1H), 2.45 (dd, J = 14.8, 11.8 Hz, 1H), 2.13 (dd, J = 8.5, 4.2 Hz, 1H), 1.6–1.5 (m, 1H), 1.39 (ddd, J = 13.5, 9.0, 4.3 Hz, 1H), 1.27 (ddd, J = 13.5, 8.4, 5.7 Hz, 1H), 0.68 (d, J = 6.5 Hz, 3H), 0.39 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 171.0 (s), 170.5 (s), 169.6 (s), 168.7 (s), 148.9 (s), 138.5 (s), 136.7 (s), 130.8 (d), 130.7 (s), 130.3 (d, 2x), 129.5 (s), 129.4 (d, 2x), 127.8 (d), 127.5 (d), 123.5 (d), 122.6 (d), 120.8 (d), 120.7 (d), 119.8 (d), 113.2 (d), 111.3 (d), 109.9 (s), 83.6 (d), 75.2 (s), 58.7 (d), 57.0 (d), 56.9 (d), 52.7 (d), 41.4 (t), 40.2 (t), 35.7 (t), 30.8 (t), 24.3 (d), 23.4 (q), 21.2 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2956 (m, C–H), 2927 (m, C–H), 2870 (w, C–H), 1673 (s, C═O), 1456 (s), 1320 (m), 741 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 653 ([M+Na]$^+$, 37), 631 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{40}H_{37}N_6O_4$ ([M+1]$^+$), 631.3027; found, 631.3013. $[\alpha]_D^{23}$ −79 (c 0.09, MeOH).

C15-Epimer (16)

According to the general procedure described for **2**, diastereoisomer **16** was prepared in 56% yield. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.69 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.4–7.3 (m, 2H), 7.3–7.2 (m, 2H), 7.2–7.1 (m, 4H), 7.0–6.8 (m, 4H), 6.86 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H), 6.62 (d, J = 3.7 Hz, 1H), 6.06 (d, J = 3.4 Hz, 1H), 4.83 (dd, J = 11.6, 5.9 Hz, 1H), 4.53 (dd, J = 6.8, 5.2 Hz, 1H), 4.3–4.2 (m, 1H), 3.68 (dd, J = 14.6, 6.1 Hz, 1H), 3.41 (dd, J = 14.6, 4.5 Hz, 1H), 3.3–3.2 (m, 2H), 3.02 (dd, J = 14.6, 7.6 Hz, 1H), 2.41 (dd, J = 14.6, 11.2 Hz, 1H), 1.8–1.6 (m, 1H), 1.56 (ddd, J = 13.5, 8.8, 4.5 Hz, 1H), 1.7–1.6 (m 1H), 0.78 (d, J = 6.5 Hz, 3H), 0.59 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 169.9 (s), 169.8 (s), 169.6 (s), 168.2 (s), 148.9 (s), 138.1 (s), 136.5 (s), 130.9 (s), 130.8 (d), 130.5 (d, 2x), 129.8 (s), 129.4 (d, 2x), 127.6 (d), 126.8 (d), 123.7 (d), 122.5 (d), 120.7 (d), 120.4 (d), 119.8 (d), 113.0 (d), 111.1 (d), 110.1 (s), 83.1 (d), 74.9 (s), 58.6 (d), 57.2 (d), 56.7 (d), 53.3 (d), 42.4 (t), 40.6 (t), 36.2 (t), 30.4 (t), 24.7 (d), 23.4 (q), 21.9 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2956 (m, C–H), 2927 (m, C–H), 2870 (w, C–H), 1682 (s, C═O), 1456 (s), 1434 (s), 1319 (m), 740 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 631 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{40}H_{37}N_6O_4$ ([M+1]$^+$), 631.3027; found, 631.3035. $[\alpha]_D^{28}$ +167 (c 0.08, MeOH).

(3*S*,6*R*)-3-((1*H*-Indol-3-yl)methyl)-6-benzylpiperazine-2,5-dione (17)

According to the general procedure described for **3**, diketopiperazine **17** was prepared in 68% yield. **M.p.** 198–200 °C (CH_3CN). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.51 (d, J = 8.0 Hz, 1H, ArH), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.2–7.1 (m, 3H, ArH), 7.1–7.0 (m, 3H, ArH), 7.02 (s, 1H, ArH), 7.98 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H, ArH), 3.53 (td, J = 4.4, 1.0 Hz, 1H), 3.36 (td, J = 4.5, 1.0 Hz, 1H), 3.26 (dd, J = 14.7, 4.6 Hz, 1H), 3.1–3.0 (m, 2H), 2.79 (dd, J = 14.0, 4.7 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 170.8 (s), 169.9 (s), 138.1 (s), 136.7 (s), 131.3 (d, 2x), 129.5 (d, 2x), 128.9 (s), 128.3 (d), 126.0 (d), 122.7 (d), 120.2 (d), 119.9 (d), 112.3 (d), 109.2 (s), 56.6 (d) 56.5 (d), 39.5 (t), 30.5 (t) ppm. **IR** (NaCl) ν 3400–3050 (br, N–H), 2966 (w, C–H), 2881 (w, C–H), 1673 (s, C═O), 1456 (s), 1321 (m), 1090 (w), 1010 (w), 743 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 334 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{20}H_{20}N_3O_2$ ([M+1]$^+$), 334.1550; found, 334.1547. $[\alpha]_D^{24}$ −5 (c 0.12, MeOH). $[\alpha]_D^{24}$ −5 (c 0.12, MeOH).

(2*S*,3a*S*,8a*S*)-1,8-Di-*tert*-butyl-2-methyl-3a-(3-(((2*S*,5*R*)-5-benzyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate (18)

According to the general procedure described for **5**, substituted indoline **18** was prepared in 30% yield. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.8–7.6 (m, 1H, ArH), 7.53 (d, J = 7.6 Hz, 1H, ArH), 7.4–7.3 (m, 2H, ArH), 7.2–7.1 (m, 3H, ArH), 7.1–6.9 (m, 7H, ArH), 6.69 (s, 1H), 5.0–4.9 (m, 1H), 3.57 (dd, J = 12.9, 9.3 Hz, 1H), 3.5–3.4 (m, 1H), 3.23 (s, 3H, CO_2CH_3), 3.3–3.1 (m, 2H), 3.09 (d, J = 12.9 Hz, 1H), 2.99 (dd, J = 13.9, 4.6 Hz, 2H), 2.80 (dd, J = 13.9, 4.6 Hz, 1H), 1.55 (s, 9H), 1.49 (s, 9H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 172.6 (s), 170.6 (s), 169.9 (s), 153.8 (s), 144.9 (s), 136.8 (s), 136. 6 (s), 132.2 (d), 131.4 (s), 131.2 (d, 2x), 131.1 (s), 129.5 (d, 3x), 128.3 (d), 126.6 (d), 127.7 (d), 124.9 (d), 123.5 (d), 121.4 (d), 121.0 (d), 112.4 (d), 110.2 (s), 83.7 (s), 81.3 (d), 74.1 (s), 60.8 (d), 56.6 (d), 56.5 (d), 52.9 (q), 39.5 (t, 2x), 30.2 (t), 28.7 (q, 6x) ppm. **IR** (NaCl) ν 3400–3050 (br, N–H), 2977 (m, C–H), 2930 (m, C–H), 1716 (s, C═O), 1681 (s, C═O), 1455 (m), 1393 (s), 1157 (s), 1015 (m), 855 (m), 741 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 772 ([M+Na]$^+$, 43), 750 ([M+1]$^+$, 23), 650 ([M–CO_2tBu]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{42}H_{48}N_5O_8$ ([M+1]$^+$), 750.3497; found, 750.3499. $[\alpha]_D^{26}$ +30 (c 0.18, MeOH).

(2*S*,3a*S*,8a*S*)-Methyl-3a-(3-(((2*S*,5*R*)-5-benzyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (19)

According to the general procedure described for **6**, diamine **19** was prepared in 85% yield. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.49 (d, J = 7.4 Hz, 1H, ArH), 7.42 (d, J = 7.8 Hz, 1H, ArH), 7.29 (s, 1H, ArH), 7.2–7.1 (m, 3H, ArH), 7.1–6.9 (m, 6H, ArH), 6.7–6.6 (m, 2H, ArH), 5.45 (s, 1H, H8a), 4.17 (dd, J = 7.7, 3.0 Hz, 1H), 3.66 (t, J = 3.9 Hz, 1H), 3.5–3.3 (m, 2H), 3.44 (m, 2H), 3.34 (s, 3H, CO_2CH_3), 3.1–2.9 (m, 4H), 2.78 (dd, J = 14.0, 4.5 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, CD_3OD) δ 175.1 (s), 171.0 (s), 172.0 (s), 151.8 (s), 137.2 (s), 136.7 (s), 131.4 (d), 131.1 (d, 2x), 130.9 (s), 129.6 (s), 129.5 (d, 2x), 128.2 (d), 127.8 (d), 125.5 (d), 123.0 (d), 120.9 (d), 120.4 (d), 120.0 (d), 113.2 (d), 111.2 (d), 109.1 (s), 83.4 (d), 77.4 (s), 61.1 (d), 56.8 (d), 56.3 (d), 52.7 (q), 42.8 (t), 39.0 (t), 30.6 (t) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2950 (m, C–H), 2926 (w, C–H), 1736 (m, C═O), 1672 (s, C═O), 1607 (m), 1457 (m), 1319 (m), 1209 (m), 741 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 550 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{32}H_{32}N_5O_4$ ([M+1]$^+$), 550.2448; found, 550.2438. $[\alpha]_D^{24}$ +227 (c 0.10, MeOH).

(+)-Pestalazine B (21)

According to the general procedure described for **2**, isomer **21** was prepared in 57% yield. **^{1}H NMR** (600 MHz, $(CD_3)_2CO$) δ 7.81 (d, J = 4.3 Hz, 1H), 7.66 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.2–7.1 (m, 7H), 7.0–6.9 (m, 4H), 6.85 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.7–6.6 (m, 2H), 6.05 (d, J = 3.3 Hz, 1H), 4.84 (dd, J = 11.7, 6.0 Hz, 1H), 3.89 (dt, J = 9.6, 4.8 Hz, 1H), 3.69 (dd, J = 14.8, 6.0 Hz, 1H), 3.7–3.6 (m, 1H), 3.50 (br t, J = 4.7 Hz, 1H), 3.21 (app. d, J = 3.2 Hz, 2H), 3.06 (dd, J = 13.9, 5.4 Hz, 1H), 2.96 (dd, J = 13.9, 4.6 Hz, 1H), 2.46 (dd, J = 14.8, 11.7 Hz, 1H), 1.9–1.8 (m, 1H), 1.8–1.7 (m, 1H), 1.52 (ddd, J = 13.6, 8.5, 5.3 Hz, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 169.0 (s, 2x), 168.6 (s, 2x), 148.9 (s), 137.1 (s), 136.6 (s), 131.0 (d, 2x), 130.8 (s), 130.8 (d), 129.1 (d, 2x), 127.7 (d), 126.6 (d), 123.6 (d), 122.4 (d), 120.5 (d), 120.4 (d), 119.7 (d), 113.0 (s), 111.0 (d), 110.0 (s), 83.5 (d), 74.4 (s), 57.3 (d), 56.9 (d), 56.3 (d), 55.8 (d), 42.9 (t), 41.3 (t), 39.1 (t), 30.4 (t), 25.1 (d), 23.3 (q), 21.8 (q) ppm. **IR** (NaCl) ν 3500–3050 (br, N–H), 2956 (m, C–H), 2925 (m, C–H), 2870 (w, C–H), 1682 (s, C═O), 1457 (s), 1321 (m), 741 (s) cm^{-1}. **MS** (ESI$^+$) m/z (%) 631 ([M+1]$^+$, 100). **HRMS** (ESI$^+$) calcd for $C_{40}H_{37}N_6O_4$ ([M+1]$^+$), 631.3027; found, 631.3027. $[\alpha]_D^{28}$ +194 (c 0.1, MeOH).

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