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Diastereodivergent synthesis of 2,5-diketopiperazine derivatives of β-carboline and isoquinoline from L-amino acids

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Abstract—Mild Pictet–Spengler-type condensation was applied to the synthesis of several tetrahydro-β-carboline and tetrahydroisoquinoline derivatives. L-Amino acids were promoters of 1,4-chirality transfer with up to 100% de. The stereochemistry of the final diketopiperazines strongly depended on the structure of the L-amino acids used: acyclic amino acids gave predominantly the (*R*)-configuration at the newly created stereogenic centre, whereas L-proline afforded the opposite configuration, as established by X-ray crystallography.

1. Introduction

One of the most challenging topics in modern organic chemistry is the synthesis of natural products. Despite the considerable exploration to date within this field, there is still a need for further development of alternative, preferably biomimetic and/or catalytic ways of preparation for the bioactive compounds.

Among the numerous families of natural products, isoquinoline and β-carboline alkaloids seem to attract the biggest attention due to their abundant presence in plant and even in the animal kingdom, along with their often important physiological activities.[1] Their bioactivity ranges from highly toxic, for example, strychnine to the antihypertensive, for example, ajmalicyne and the cytotoxic activity shown by vincoleucoblastine and vincristine used for cancer chemotherapy.[2] Several of them show phenanthridine inhibiting action towards HIV 1 and 2 reverse transcriptases.[2] The biodifferentiation of enantiomers together with clinical applications and regulatory pressure upon the pharmaceutical industry, constitute important reasons for the preparation of tetrahydroisoquinolines and of tetrahydro-β-carbolines in their enantiomerically pure forms. Apart from the Pictet–Spengler reaction,[3] which is probably the most popular in this field, several other methods such as stereoassisted Bischler–Napieralski[4] or Pommeranz–Fritsch[5] condensations, asymmetric nucleophilic and electrophilic introduction of a carbon unit at C-1[6] or reductions of dihydroderivatives employing chiral or achiral hydride reagents[7] have been utilized.[8] Some of these approaches have found their applications in the enantioselective creation of quaternary carbon centres, a challenging target to organic chemists. In the case of alkaloids based on isoquinoline or β-carboline skeletons, where the configuration at C-1 is closely related to the bioactivity, all the above mentioned methods have been extensively explored.

Herein the goal is the development of effective, diastereoselective preparations of some diketopiperazine derivatives of isoquinoline and indole-based systems. The 2,5-diketopiperazine (DKP) scaffold is interesting being a fundamental part of numerous natural products, often formed by the cyclization of dipeptides. These compounds exhibit a wide range of biological activities[9] and, due to their rigid structure imposed by diketopiperazine unit, can mimic a particular peptide conformation.[10] There are several examples of employing DKP's as building blocks[11] or chiral auxiliaries.[12] It has also been shown that the presence of diketopiperazine

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intermediates in a synthetic sequence can affect in unusual ways the reaction pathway and stereochemistry of products.[13] Lazaro et al. applied the DKP scaffold to constrain heterocycles that can act as inhibitors of platelet aggregation and of cell adhesion.[10]

The DKP ring is a substantial fragment of several members of the structurally unique and potentially biologically important family of fumitremorgins.[14] The derivative formed from 6-methoxy-L-tryptophan and L-proline causes severe tremorgenic reactions in mice on either oral or intraperitoneal administration.[15] Further research showed that fumitremorgin C reverses the multi-drug resistance in cells transfected with the breast cancer resistance protein.[16] Therefore, it is not surprising that several approaches focused on total syntheses of those mycotoxins have recently been completed.[17] The diketopiperazine skeleton could be used as a readily available building block,[18] created during the reaction sequence in the cyclization step.[19]

The DKP system constitutes the key motif in a variety of quinazolinone natural products such as fumiquinazolines and fiscalins.[20] An elegant and effective preparation of certain diketopiperazine system with an unusual use of photochemical method was presented recently by Snider and Busuyek.[21]

The DKP skeleton prepared from natural amino acids has also been used as an auxiliary in a general method for the stereoselective synthesis of substituted α-amino acids.[22] The application of amino acids as stereopromoters seems to be logical due to their widespread occurrence in living systems, accessibility in enantiomerically pure form and well established chemical behaviour. Moreover, amino acids could be utilized in many ways, such as building blocks of a final molecule, chiral ligands or parts of a catalyst applied in sub-molar amounts. Therefore, their application in the stereoselective preparation of isoquinoline and β-carboline skeletons usually gives effective results. A recently published successful combination of the Pictet–Spengler condensation of L-tryptophan with palladium catalyzed allenylation followed by carbonylation reactions allowed a straightforward access to novel and complex indolic heterocycles.[23] Another interesting approach to the synthesis of 1-substituted tetrahydroisoquinolines was realized by Kibayashi et al., who employed L-proline as a chiral adjuvant.[24]

Recently, we proposed a general method for the construction of isoquinoline and β-carboline systems, which utilizes natural amino acids as the source of chirality.[25] The obtained products are precursors of the so-called mammalian alkaloids, endogenous compounds that are supposed to play an important role in the pathogenesis of Parkinsonian disease and in the generation of toxic products under the influence of certain exogenous factors such as xenobiotics, alcohol, heroin or in an altered metabolism in infection.[26] The secondary metabolites thus formed were even considered to be responsible for mental illness such as schizophrenia, however this hypothesis obviously needs further confirmation.[27]

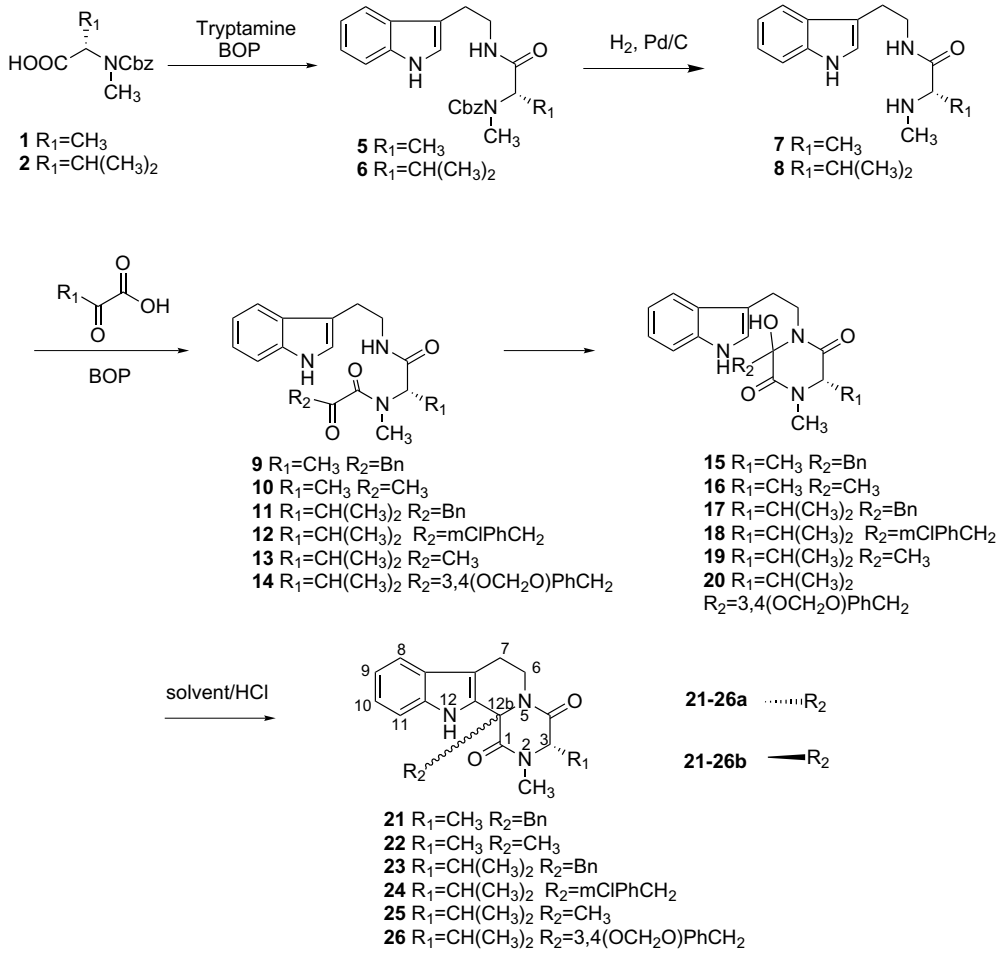
Herein, we describe in detail our results concerning the utilization of natural amino acids in the stereocontrolled construction of diketopiperazine derivatives of some isoquinoline and β-carboline derivatives.[25]

2. Results and discussion

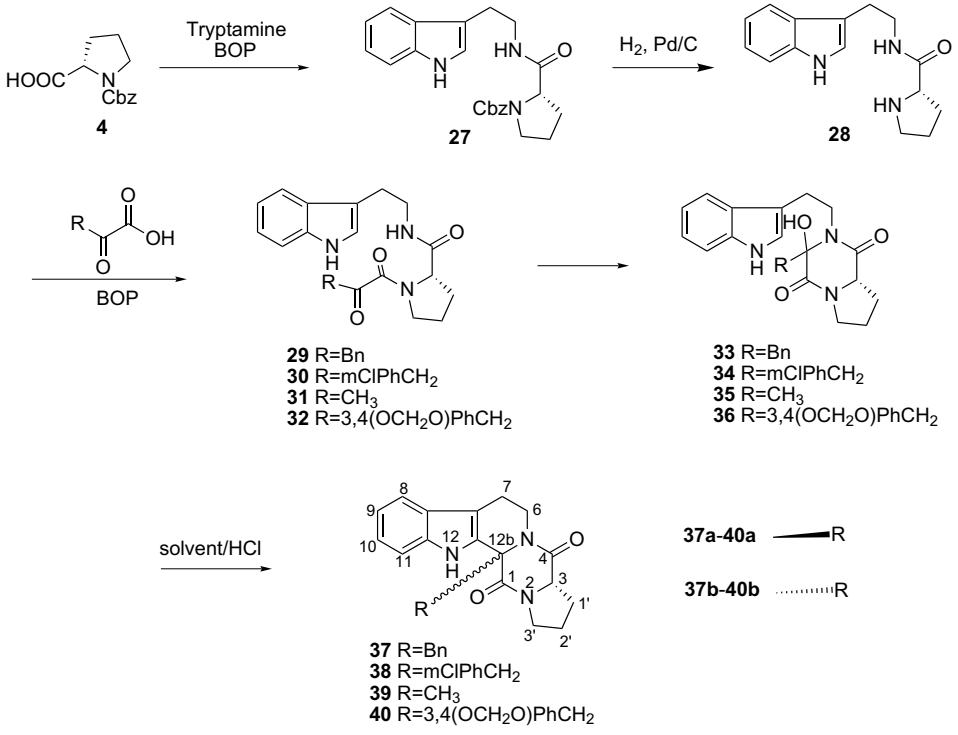
The approach presented is based on the idea that during biosynthesis reactive groups along a peptide chain influence the stereochemistry created in natural alkaloids.[28] Recently this hypothesis was strongly supported by the finding that the Pictet–Spengler reaction is responsible for the endogenous alkaloids formation in mammals from dopa-contained enkephalins and aldehydes.[29] We have also found that effective 1,4-chirality transfer could be realized under biomimetic conditions via Pictet–Spengler-like reactions involving the rigid diketopiperazine system.

N-Blocked-*N*-methyl L-alanine **1**, *N*-blocked-*N*-methyl L-valine **2**, *N*-blocked-*N*-methyl L-phenylalanine **3** or *N*-blocked L-proline **4** served as the sources of chirality in the reaction path outlined in Schemes 1–4. At the beginning of the synthetic sequence, compounds **1** and **2** were subjected to a BOP-mediated coupling with tryptamine and, after a palladium catalyzed deblocking of the nitrogen atom under hydrogenolytic conditions giving amides **7**, and **8**, respectively, with high chemical yield (Scheme 1). In the subsequent reaction with phenylpyruvic acid, again under BOP mediation, we obtained diketoamides **9**, and **11** with no observable racemization. Unfortunately, it was impossible to isolate and characterize either hydroxylactam **15** or **17** in this synthetic sequence. In the next step, the Pictet–Spengler cyclization was used to furnish a tetrahydro-β-carboline system. Initially, the use of methanolic hydrogen chloride gave poor diastereoselectivity (55:45), which presumably was caused by unfavourable hydrogen bonding with the solvent. Fortunately, the use of ethyl acetate proved to be beneficial to stereoselectivity even at room temperature. The tetrahydro-β-carboline derivatives **23a** and **23b** were formed in a 93:7 diastereomeric ratio, respectively, while the best result was obtained for compound **9** from which **21a** was obtained as a single diastereomer (established on the basis of ^{1}H NMR). Such an excellent stereoselectivity together with good chemical yields could be attributed to an intervention of *N*-acylimminium ions as intermediates in the cyclization process. They play a remarkable role in a stereoselective carbon–carbon bond formation in nitrogen heterocycles.[30] Furthermore, intramolecular reactions of cyclic *N*-acylimminium ions with π-nucleophiles proceed stereoselectively due to steric control provided by substituents already present in the ring[31] or along the chain connecting the π-nucleophiles with the nitrogen atom.[32] These make them useful and attractive as adjuvants in organic synthesis.[33]

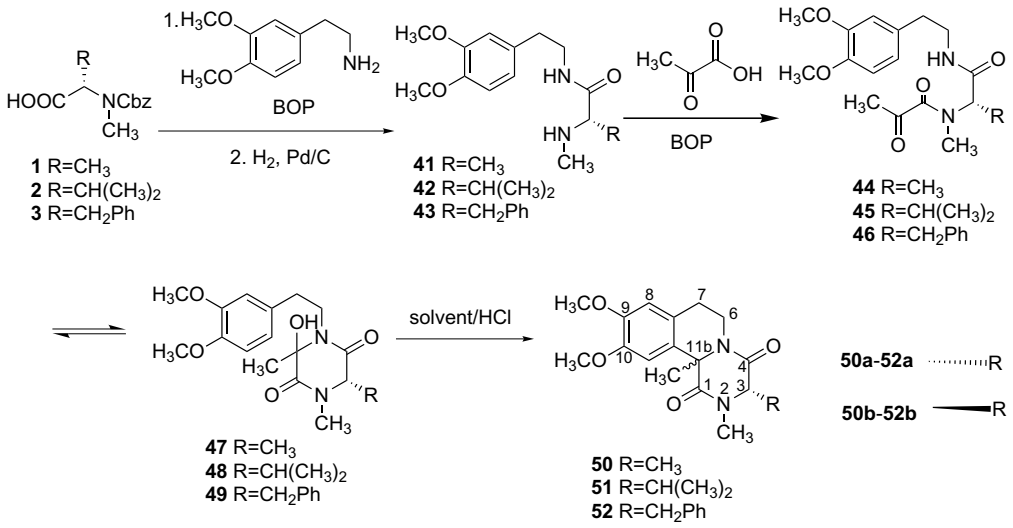
The X-ray analysis of the predominant diastereomer **23a**[25b] confirmed the same tendency as observed in the analogous isoquinoline series[25c] and proven (*R*)-configuration at the newly created stereogenic centre.



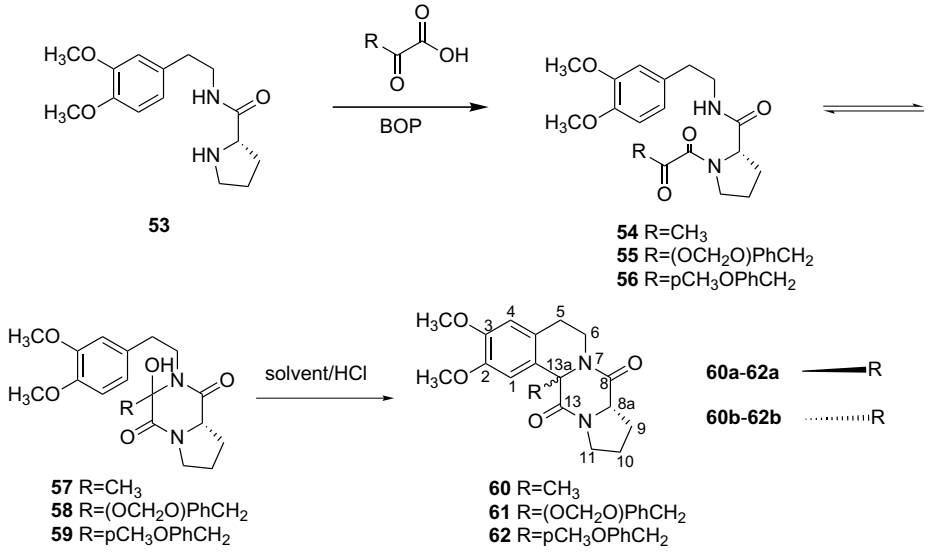
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

In order to check the universality of the method we decided to employ several derivatives of 2-oxopropanoic acid (pyruvic acid) in analogous synthetic sequences. The Pictet–Spengler cyclization of **12** gave compound **24** in a good chemical yield and an excellent diastereoselectivity (>99% as indicated by ^{1}H NMR of the crude reaction mixture). Even better results were obtained when pyruvic acid itself was used. Treatment of ketoamides **10** and **13** with hydrogen chloride in ethyl acetate afforded tetrahydro-β-carboline derivatives **22** and **25**, respectively, as single diastereomers (**22a** and **25a**, according to ^{1}H NMR spectroscopy).

Again, a final proof for the absolute stereochemistry came from X-ray crystallography taken on the monocrystal of compound **25a** (Fig. 1). It should be noted

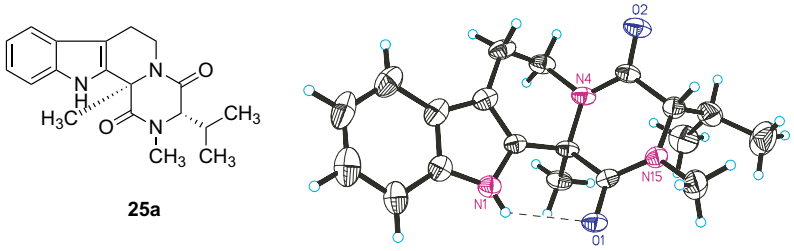


Figure 1. The chemical structure and the ORTEP diagram for compound **25a**.

here, that for unknown reasons compounds **11**, **12** and **14** were obtained only in quite low chemical yields due to an extensive decomposition of the mixture and formation of tar-like products.

In order to avoid a somewhat troublesome *N*-methylation procedure for *N*-blocked-*N*-methyl L-alanine **1** and *N*-blocked-*N*-methyl L-valine **2** we employed a similar synthetic path with *N*-nor-analogues of compounds **1** and **2**. Although the initial steps were extremely efficient and no racemization was observed, we were unable to promote formation of the desired cyclic derivatives. Presumably, the presence of a methyl group is crucial, as it prevents the enolization process that disabled the Pictet–Spengler reaction.

The high stereoselectivity observed in the predominant formation of diastereomer **26a** as well as **21a**–**25a** clearly follows our previous findings in the isoquinoline series.[25c] Furthermore, we observed the opposite diastereomeric preference in the case of β-carbolines when *N*-Cbz-L-proline **4** was used as the chiral adjuvant as it was the case for isoquinolines.

Amide **28** was conveniently prepared in two steps with 84% chemical yield. Subsequent coupling of **28** with phenylpyruvic acid gave a mixture of ketoamide **29** and hydroxylactam **33**, with the latter being the more stable tautomeric form. The results of optimization of the Pictet–Spengler cyclization made for the L-proline series are presented below in Table 1. Temperature variations had only a slight effect, whereas the solvent played the crucial role (Table 1).

Table 1. The solvent and temperature effect on the Pictet–Spengler reaction of **37**

Entry	Solvent	Temperature (°C)	**37a**:**37b**[a]
1	MeOH, HCl	5	55.5:44.5
2	THF, HCl	5	80:20
3	THF, HCl	25	83:17
4	THF, HCl	40	71:29
5	THF, HCl	66	78:22
6	AcOEt, HCl	25	93:7

[a] As established on the basis of ^{1}H NMR.

In order to check if kinetic or thermodynamic factors affect the cyclization process we treated the (3*S*,12b*R*) diastereomer **37b** with a strong acid (trifluoroacetic acid–TFA or HCl_{aq}). As compound **37b** appears to be thermodynamically less stable, we presumed that under an influence of the acid (TFA, room temperature; 10% HCl, reflux) it will be transformed into the more stable (3*S*,12b*S*) **37a**. Even after 10 days we observed no reaction. Therefore, it seems that the final β-carbolines and isoquinolines were formed in a nonreversible Pictet–Spengler reaction.

Despite many efforts, we were unable to obtain well-formed crystals of compound **37a** suitable for the X-ray analysis. In a search for a better crystallising derivative we decided to employ *m*-chlorophenylpyruvic acid in the synthesis. The diketopiperazine derivative **38** was obtained with 41% chemical yield and very high diastereoselectivity (98%, **38a**:**38b**). The X-ray diffraction measurements revealed the (*S*)-configuration at the C-1 quaternary carbon atom.[25b]

Two further sets of experiments with L-proline as the chirality source indicated the greater stability of selected hydroxylactams over the corresponding ketoamide forms. The amount of compound **36** after the coupling with 3-benzo[1,3]dioxyol-5-yl-pyruvic acid was undoubtedly bigger than its diketoamide analogue **32**, whereas the reaction with 2-oxopropanoic acid (pyruvic acid) gave only the cyclic tautomer **35**. Consequently, **35** and **32** together with **36** were transformed in the Pictet–Spengler cyclization into the desired β-carbolines **39** and **40**, respectively. The results of the X-ray analysis of the minor diastereomer of **39** (**39b**) correlated with our prior findings and confirmed (*S*)-configuration at the created stereogenic centre in the predominant diastereomer (Fig. 2). Here, as previously for **38a**, also two independent molecules are present in the asymmetric part of the crystal lattice. Interestingly, the crystal packing, in spite of the same crystal symmetry was dramatically different.

The cyclization of **35** suffered from low diastereoselectivity. The use of trifluoroacetic or formic acid as the promoters of cyclization process gave no observable improvement. Finally, the utilization of Lewis acid (BF_3) gave a reasonable diastereoselectivity (75%, see Table 2).

The generality of the presented approach was further demonstrated by the synthesis of two series of isoquinoline derivatives with pyruvic acid. In one of them, acyclic L-amino acids (Ala, Val and Phe) were used to give **41**, **42** and **43**, respectively.[25c]

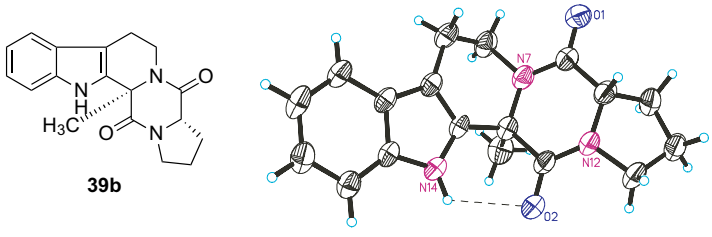


Figure 2. The chemical structure and the ORTEP diagram for compound **39b**.

Table 2. The solvent influence on diastereomeric ratio of **39a**:**39b**

Entry	Solvent, rt	**39a**:**39b**[a]	De	% Yield
1	Ethyl acetate, HCl	67:33	33	85
2	Dichloromethane, HCl	60:40	20	79
3	Acetone, HCl	60:40	20	64
4	Ether, HCl	67:33	33	81
5	THF, HCl	55.5:44.5	10	67
6	DMF, HCl	62:38	24	54
7	DMSO, HCl	60:40	20	48
8	TFA, neat	72:28	24	38
9	Formic acid, neat	62:38	24	41
10	5% $BF_3{\cdot}Et_2O$ in Et_2O	87.5:12.5	75	75

[a] Established on the basis of ^1H NMR spectroscopy.

The coupling with pyruvic acid under an influence of BOP gave ketoamides **45**, **46** and hydroxylactam **47**, respectively, in good chemical yields. Noteworthy, in the case of compound **47** both diastereomers **47a** and **47b** could be isolated and characterized spectroscopically and, after a careful experimentation, the X-ray structure for **47b** could also be solved (Fig. 3).

As could be expected, there was no observable difference in the behaviour of diastereomers **47a** and **47b** towards the acidic reagents. Both hydroxylactams smoothly formed **50a** and **50b** in the same ratios in a good yield upon the treatment with EtOAc/HCl at room temperature. The strong preference for the formation of the (*R*)-configuration at the quaternary carbon centre was also observed in the case of ketoamides **45** (>99% de of **51a**) and **46** (65% de of **52a**). The final proof for this observation came from the X-ray analysis for the minor diastereomer **52b** in which the chirality was generated by L-Phe (Fig. 4).

When L-Pro was used as the stereochemistry promoter, compounds **54**–**56** were obtained efficiently from the amide **53**[24] and the appropriate (aryl)pyruvic acids.

The application of hydrogen chloride in anhydrous ethyl acetate brought about the formation of hydroxylactam derivatives that underwent a mild Pictet–Spengler cyclization via *N*-acylimminium ion stage. The hydroxylactam **57a** was stable enough to allow its X-ray analysis (Fig. 5).

A diastereoselectivity of 56% was observed in the formation of the final diketopiperazine derivatives with isomer **60a** being predominant. The result of the X-ray structural analysis of **60b** is presented in Figure 6.

The versatility and efficiency of the above approach could be observed for other derivatives obtained from substituted arylpyruvic acids. Thus, the final diastereo-

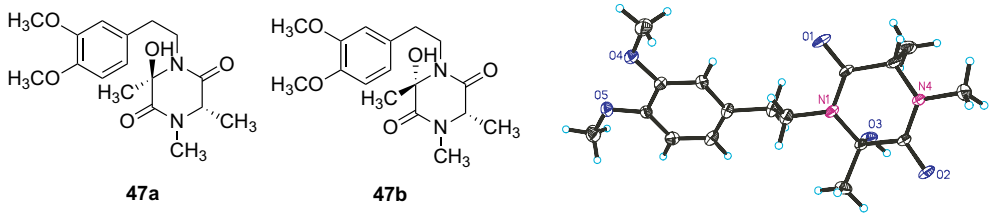


Figure 3. The structures of diastereomers **47a** and **47b** and ORTEP diagram for **47b**.

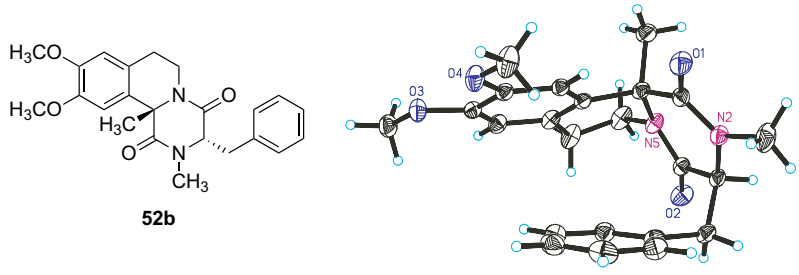


Figure 4. The structure and ORTEP diagram for compound **52b**.

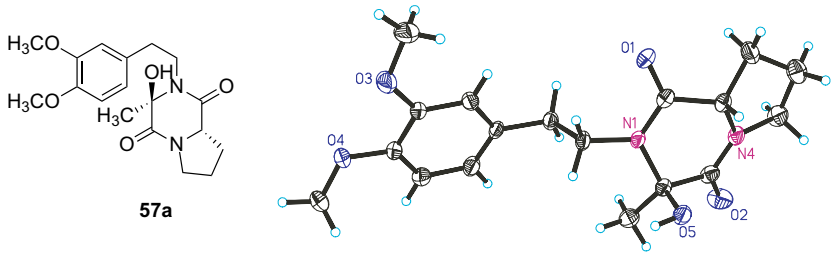


Figure 5. The structure and independent part of the unit cell for compound **57a**.

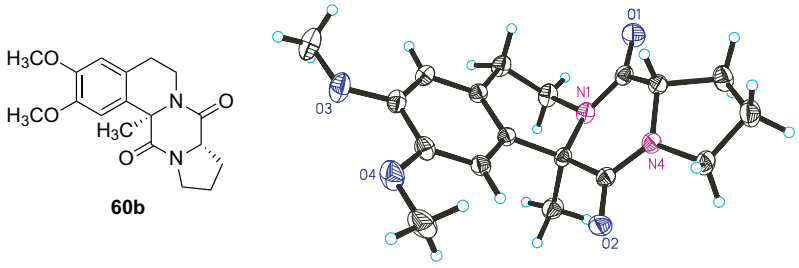


Figure 6. The structure and ORTEP diagram for compound **60b**.

mers **61** and **62** were obtained in 98% or better diastereoselectivities.

3. Conclusions

In summary, several tetrahydroisoquinoline and β-carboline derivatives bearing a quaternary carbon atom were prepared in a stereoselective way under the chiral influence of L-amino acids. The biomimetic type Pictet–Spengler condensation was accompanied by 1,4-chirality transfer which in several cases proceeded in surprisingly high efficiency approaching 100% de with good to excellent chemical yield. Selected intermediate hydroxylactams were isolated and subjected to X-ray analyses. The stereochemistry of the final diketopiperazines strongly depended on the structure of L-amino acids used: acyclic amino acids gave predominantly the (*R*)-configuration at the newly created stereogenic centre, whereas L-proline afforded the formation of the opposite configuration. This interesting feature allows the diastereodivergent creation of chirality within these reactions. Again, the X-ray analysis proved to be indispensable tool for the stereochemical assignments.

4. Experimental

4.1. General

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 and 200 MHz for ^{1}H NMR and at 125 and 50 MHz for ^{13}C NMR. Tetramethylsilane (TMS) or solvents were used as internal standards. Chemical shifts were reported in ppm. Mass spectra were collected on AMD 604 apparatus and Micromass LCT apparatus; high-resolution mass spectra were acquired using LSIMS (positive ion mode). Optical rotations were measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on Merck 60 silica gel glass plates and visualized using an UV hand lamp and iodine vapour. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 or under 400 mesh, Merck). Melting points were determined on a Boetius hot-plate microscope. The X-ray intensity data for **25a**, **39b**, **47b**, **52b**, **57a**, **60b** were measured at $T = 293$ K on Kuma KM4 diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods from SHELXS97[34] and refined using SHELXL97 software.[35]

4.2. Preparation of (2*S*)-{1-[2-(1*H*-indol-3-yl)-ethyl-carbamoyl]-ethyl}-methyl-carbamic acid benzyl ester 5

A sample of 5.00 g (21 mmol) of Cbz-*N*-methyl alanine **1** was dissolved in 100 mL of dry THF, cooled in ice bath and to the resultant mixture tryptamine (3.37 g, 21 mmol), triethylamine (3.75 g, 42 mmol) and BOP (10.25 g, 23 mmol) were introduced. Cooling and stirring were continued for 2 h and afterwards the reaction was left at room temperature overnight. After evaporation of the volatile components the crude mixture was dissolved in ethyl acetate (150 mL) and washed with brine (2 × 100 mL). The organic phase was dried with magnesium sulfate and the residue was purified with column chromatography on silica gel with 0.5% (v/v) methanol in dichloromethane as eluent to afford yellow oil of **5** (7.64 g, 95%); $[\alpha]_D^{23} = -33.3$ (*c* 1.05, $CHCl_3$); IR (film) 3320, 2930, 1680, 1660, 1450, 1300, 1150; ^{1}H NMR (severe broadening of selected signals was observed due to the presence of amide rotamers) ($CDCl_3$, 500 MHz): δ 7.99 (br s, 1H, NH, indole), 7.58 (d, $J = 8$ Hz, 1H, H-4$_{indole}$), 7.33 (m, 3H, H$_{arom}$), 7.32–7.21 (m, 3H, H$_{arom}$), 7.18 (t, $J = 7.5$ Hz, 1H, H-6$_{indole}$), 7.11 (t, $J = 7.5$ Hz, 1H, H-7$_{indole}$), 6.90 (s, 1H, H-2$_{indole}$), 6.13 (br s, 1H, N*H*CH$_2$CH$_2$), 5.08 (br s, 2H, C*H*$_2$Ph), 4.67 (br m, 1H, H-2), 3.55 (m, 2H, NHC*H*$_2$CH$_2$), 2.91 (br t, 2H, NHCH$_2$C*H*$_2$), 2.73 (s, 3H, NCH$_3$), 1.33 (d, $J = 7$ Hz, 3H, CH$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.97, 156.89, 136.36, 128.61, 128.24, 127.96, 127.17, 122.16, 122.04, 119.45, 118.63, 112.64, 111.24, 67.53, 54.39, 39.55, 29.46, 25.17, 13.64; ESI (+) *m/z* (%): 402 $[M+Na]^+$ (100).

4.3. Preparation of (2*S*)-{1-[2-(1*H*-indol-3-yl)-ethyl-carbamoyl]-2-methyl-propyl}-methyl-carbamic acid benzyl ester 6

Compound **2** (5.80 g, 21.88 mmol) was converted into **6** according to the procedure described for **5** as a yellow oil (8.68 g, 97%); $[\alpha]_D^{23} = -42$ (*c* 1.07, $CHCl_3$); IR (film): 3320, 2960, 2930, 1660, 1450; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (s, 1H, NH, indole), 7.57 (d, $J = 7.5$ Hz, 1H, H-4$_{indole}$), 7.38–7.27 (m, 5H, 5 × H$_{arom}$), 7.19–7.08 (m, 3H, 3 × H$_{indole}$), 6.89 (d, $J = 1.5$ Hz, 1H, H-2$_{indole}$), 6.13 (br t, 1H, N*H*CH$_2$CH$_2$), 5.11 and 5.08 (q_{AB}, $J = 12.5$ Hz, 2H, C*H*$_2$Ph), 4.00 (d, $J = 16.5$ Hz, 1H, H-2), 3.55 (m, 2H, NHC*H*$_2$CH$_2$), 2.90 (m, 2H, NHCH$_2$C*H*$_2$), 2.88 (s, 3H, NCH$_3$), 2.28 (m, 1H, C*H*(CH$_3$)$_2$), 0.90 and 0.85 (2d, $J = 7$ Hz, $J = 7.5$ Hz, 2 × 3H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ

170.10, 157.43, 136.70, 136.39, 128.58, 128.13, 127.65, 127.23, 122.25, 121.93, 119.37, 118.69, 112.65, 111.23, 67.40, 65.43, 39.36, 29.74, 26.10, 25.41, 19.67, 18.64; ESI (+) *m/z* (%): 430 $[M+Na]^+$ (100).

4.4. Preparation of (2*S*)-*N*-[2-(1*H*-indol-3-yl)-ethyl]-2-methylamino-propionamide 7

A mixture of **5** (5.40 g, 14.2 mmol) and concd HCl (4 mL) in absolute ethanol (100 mL) was hydrogenated over palladium on charcoal catalyst (10% Pd, 0.3 g) at 50 °C with vigorous stirring for 2 h. The mixture was than filtrated through Celite, evaporated and the residue was dissolved in chloroform, washed with saturated sodium bicarbonate solution and dried to afford yellow viscous oil of **7** (3.30 g, 95%); $[\alpha]_D^{23} = -4.2$ (*c* 1.03, $CHCl_3$); IR (KBr): 3300, 2950, 1650, 153; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.36 (br s, 1H, exchangeable with D_2O, NH, indole), 7.62 (d, $J = 8$ Hz, 1H, H-4_{indole}), 7.36 (m, 1H, H-7_{indole}), 7.24 (br s, 1H, exchangeable with D_2O, N*H*CH_2CH_2), 7.19 (m, 1H, H-6_{indole}), 7.12 (m, 1H, H-5_{indole}), 7.01 (d, $J = 2.5$ Hz, 1H, H-2_{indole}), 3.61 (m, 2H, NHC*H*$_2$$CH_2$), 2.98 (m, 2H, 2 × H-6), 2.98 (m, 1H, H-2), 2.27 (s, 3H, NCH_3), 1.34 (br s, 1H, exchangeable with D_2O, H-1), 1.24 (d, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): 174.88, 136.39, 127.37, 122.02, 121.99, 119.29, 118.74, 113.00, 111.23, 60.36, 39.14, 35.13, 25.47, 19.63; ESI (+) *m/z* (%): 246 $[M+H]^+$ (87), 268 $[M+Na]^+$ (50); ESI (−) *m/z* (%): 244 $[M-H]^-$ (100).

4.5. Preparation of (2*S*)-*N*-[2-(1*H*-indol-3-yl)ethyl]-3-methyl-2-(methylamino)butanamide 8

Compound **6** (8.60 g, 21.1 mmol) was subjected to the same procedure as described for the preparation of **7** to afford compound **8** as pink coloured product (5.20 g, 90%); $[\alpha]_D^{23} = -19.2$ (*c* 0.98, $CHCl_3$); IR (KBr): 3280, 2950, 1630, 750; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.61 (br s, 1H, exchangeable with D_2O, NH, indole), 7.62 (d, $J = 8$ Hz, 1H, H-4_{indole}), 7.35 (d, $J = 8.5$ Hz, 1H, H-7_{indole}), 7.27 (br t, 1H, exchangeable with D_2O, N*H*CH_2CH_2), 7.18 (td, $J = 7$ Hz, $J = 2$ Hz, 1H, H-6_{indole}), 7.10 (td, $J = 8.5$, $J = 1$ Hz, 1H, H-5_{indole}), 6.99 (d, $J = 2$ Hz, 1H, H-2_{indole}), 3.64 (m, 2H, NHC*H*$_2$$CH_2$), 2.98 (m, 2H, $NHCH_2CH_2$), 2.72 (d, $J = 5$ Hz, 1H, H-2), 2.24 (s, 3H, NCH_3), 2.05 (m, 1H, C*H*$(CH_3)_2$), 1.55 (very br s, 1H, exchangeable with D_2O, H-1), 0.94 and 0.87 (2d, $J = 7$ Hz, 2 × 3H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.53, 136.41, 127.30, 122.00, 121.86, 119.16, 118.65, 112.79, 111.24, 70.80, 39.07, 36.07, 31.27, 25.64, 19.58, 17.77; ESI (+) *m/z* (%): 274 $[M+H]^+$ (100), 296 $[M+Na]^+$ (40), 569 $[2M+Na]^+$ (10).

4.6. Preparation of (2*S*)-*N*-{1-[2-(1*H*-indol-3-yl)-ethyl-carbamoyl]-ethyl}-*N*-methyl-2-oxo-3-phenyl-propionamide 9

Phenylpyruvic acid (2.42 g, 14.7 mmol) was added to a solution of **7** (3.30 g, 13.4 mmol), triethylamine (2.38 g, 26.8 mmol) and BOP (6.52 g, 14.7 mmol) in dry THF (100 mL) and the mixture was stirred vigorously at 0 °C for 2 h. Stirring was continued at room temperature overnight. The solvent was evaporated and the residue was dissolved in dichloromethane (100 mL), washed with brine (2 × 60 mL) and dried. The product was purified with column chromatography on silica gel using cyclohexane–ethyl acetate 1:1 (v/v) to afford compound **7** (3.06 g, 57%) as an oil; $[\alpha]_D^{23} = -77.2$ (*c* 0.99, $CHCl_3$); IR (film): 3330, 2938, 1620, 1425; ^1H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II 4:3): δ 8.16 (br s, 1H, NH, indole) (I), 8.11 (br s, 1H, NH, indole) (II), 7.59 (t, $J = 8.5$ Hz, 2H, 2 × H-4_{indole}) (I), 7.36–7.35 (m, 2H, 2 × H-4_{indole}) (II), 7.31–7.25 (m, 6H, 6 × H_{arom}), 7.22–7.19 (m, 4H, 4 × H_{indole}), 7.18–7.15 (m, 2H, 2 × H_{arom}) (I), 7.14–7.10 (m, 2H, 2 × H_{arom}) (II), 7.01 (d, $J = 2.5$ Hz, 1H, H-2_{indole}) (II), 6.99 (d, $J = 2.5$ Hz, 1H, H-2_{indole}) (I), 6.30 (br s, 1H, N*H*CH_2CH_2) (I), 5.84 (br s, 1H, N*H*CH_2CH_2) (II), 4.91 (q, $J = 7$ Hz, 1H, H-2) (II), 4.24 and 3.89 (q_{AB}, $J = 14$ Hz, 2H, C*H*$_2$Ph) (I), 3.97 (s, 2H, C*H*$_2$Ph) (II), 3.61–3.54 (m, 1H, NHC*H*$_2$$CH_2$), 3.51–3.41 (m, 3H, NHC*H*$_2$$CH_2$), 3.79 (q, $J = 7$ Hz, 1H, H-2) (I), 2.94–2.90 (m, 4H, $NHCH_2CH_2$), 2.59 (s, 3H, NCH_3) (I), 2.48 (s, 3H, NCH_3) (II), 1.21 (d, $J = 7$ Hz, 3H, CH_3) (II), 0.82 (d, $J = 7$ Hz, 3H, CH_3) (I); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.32, 196.92, 169.31, 168.66, 167.15, 166.80, 136.41, 136.38, 131.04, 130.52, 129.94, 129.84, 129.34, 129.00, 127.99, 127.83, 127.17, 127.16, 122.25, 122.21, 122.15, 119.48, 119.45, 118.63, 112.53, 55.60, 51.73, 47.14, 47.01, 39.87, 39.66, 30.17, 27.43, 25.18, 25.17, 13.61, 12.79; ESI (+) *m/z* (%): 414 $[M+Na]^+$; ESI (−) *m/z* (%): 390 $[M-H]^-$.

4.7. Preparation of (2*S*)-*N*-{1-[2-(1*H*-indol-3-yl)-ethyl-carbamoyl]-ethyl}-*N*-methyl-2-oxo-propionamide 10

The reaction was performed in the same manner as for compound **9**. Amide **7** (600 mg, 2.45 mmol) was subjected to a coupling with pyruvic acid (215 mg, 2.45 mmol) diluted with dry THF (30 mL) in the presence of triethylamine (436 mg, 4.90 mmol) with the use of BOP (1.14 g, 2.69 mmol) to afford ketoamide **10** (556 mg, 72%); $[\alpha]_D^{23} = -57$ (*c* 1.04, $CHCl_3$); IR (film): 3350, 2930, 1630, 1450; ^1H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II 4:3): δ 8.20 (br s, 1H, NH, indole) (I), 8.17 (br s, 1H, NH, indole) (II), 7.59 (m, 2H, 2 × H-4_{indole}), 7.36 (s, 1H, H-7_{indole}) (II), 7.34 (s, 1H, H-7_{indole}) (I), 7.19 (m, 2H, 2 × H-5_{indole}), 7.14 (m, 2H, 2 × H-6_{indole}), 7.02 (d, $J = 2$ Hz, 1H, H-2_{indole}) (I), 7.01 (d, $J = 2$ Hz, 1H, H-2_{indole}) (II), 6.60 (br t, 1H, N*H*CH_2CH_2) (II), 6.08 (br t, 1H, N*H*CH_2CH_2) (I), 4.94 (q, $J = 7$ Hz, 1H, H-2) (II), 4.28 (q, $J = 7$ Hz, 1H, H-2) (I), 3.64 (m, 2H, NHC*H*$_2$$CH_2$), 3.59–3.49 (m, 2H, NHC*H*$_2$$CH_2$), 2.97 (m, 4H, $NHCH_2CH_2$), 2.83 (s, 3H, NCH_3) (I), 2.73 (s, 3H, NCH_3) (II), 2.43 (s, 3H, 3 × H-3′) (II), 2.30 (s, 3H, 3 × H-3′) (I), 1.35 (d, $J = 7$ Hz, 3H, CH_3) (I), 1.34 (d, $J = 7$ Hz, 3H, CH_3) (II); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.89, 198.11, 169.61, 168.88, 167.08, 166.69, 136.40, 127.21, 127.15, 122.24, 122.18, 119.48, 119.47, 118.61, 112.49, 112.48, 55.37, 51.84, 39.88, 39.61, 30.57, 25.14, 14.54, 14.14, 13.07; ESI (+) *m/z* (%): 338 $[M+Na]^+$ (100).

4.8. Preparation of (2*S*)-*N*-{1-[2-(1*H*-indol-3-yl)-ethyl]-3-methyl}-2-[methyl-(2-oxo-2-phenyl-propionyl)-amino]-butyramide 11

The same procedure as for **9** was applied for the formation of compound **11**. The BOP (6.23 g, 14.08 mmol)-mediated coupling of amide **8** (3.50 g, 12.8 mmol) with phenylpyruvic acid (2.30 g, 14.08 mmol) in the presence of triethylamine (2.27 g, 15.6 mmol) gave, after chromatographic purification (silica gel, 30% $CHCl_3$ in cyclohexane v/v), product **11** as an oil (846 mg, 16%); $[\alpha]_D^{23} = -52.3$ (*c* 1.01, $CHCl_3$); IR (film): 3350, 3000, 2950,1630; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II ~1:1): δ 8.13 (br s, 1H, NH, indole), 8.04 (br s, 1H NH, indole), 7.46 (d, $J = 2$ Hz, 1H, H-4$_{indole}$), 7.45 (d, $J = 2$ Hz, 1H, H-4$_{indole}$), 7.36–7.27 (m, 10H, $10 \times H_{arom}$), 7.22–7.15 (m, 6H, $6 \times H_{indole}$), 7.00 (d, $J = 2$ Hz, 1H, H-2$_{indole}$), 6.95 (d, $J = 2$ Hz, 1H, H-2$_{indole}$), 6.75 (br t, 1H, N*H*CH$_2$CH$_2$), 5.95 (br t, 1H, N*H*CH$_2$CH$_2$), 4.23 and 4.01 (q_{AB}, $J = 14.5$ Hz, 2H, C*H*$_2$Ph), 4.23 (d, $J = 11.5$ Hz, 1H, H-2), 4.03 and 3.92 (q_{AB}, $J = 15$ Hz, 2H, C*H*$_2$Ph), 3.57–3.46 (m, 4H, NHC*H*$_2$CH$_2$), 3.31 (d, $J = 11$ Hz, 1H, H-2), 2.92 (m, 4H, NHCH$_2$C*H*$_2$), 2.78 (s, 3H, NCH$_3$), 2.64 (s, 3H, NCH$_3$), 2.30–2.14 (m, 2H, C*H*(CH$_3$)$_2$), 0.87 and 0.59 (2d, $J = 6.5$ Hz, 6H, CH(C*H*$_3$)$_2$), 0.70 and 0.25 (2d, $J = 6.5$ Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.59, 197.02, 168.38, 167.94, 167.50, 166.27, 136.46, 134.11, 131.71, 131.04, 130.14, 129.90, 129.07, 124.89, 124.66, 122.52, 122.36, 122.18, 122.02, 119.62, 119.36, 118.76, 118.66, 112.66, 112.51, 111.22, 66.25, 62.68, 47.03, 46.99, 39.64, 39.41, 30.60, 29.74, 28.37, 28.16, 25.51, 25.35, 19.46, 18.15; ESI (+) *m*/*z* (%): 442 $[M+Na]^+$ (100).

4.9. Preparation of (2*S*)-2-{[3-(3-chloro-phenyl)-2-oxo-propionyl]-methyl-amino}-*N*-[2-(1*H*-indol-3-yl)-ethyl]-3-methyl-butyramide 12

Following the procedure described for the synthesis of **9**, compound **8** (340 mg, 1.24 mmol) underwent a reaction with *m*-chlorophenylpyruvic acid (270 mg, 1.36 mmol) upon addition of triethylamine (220 mg, 2.48 mmol) and BOP (600 mg, 1.36 mmol) in dry CH_2Cl_2 affording ketoamide **12** (50 mg, 9%); $[\alpha]_D^{23} = -39.4$ (*c* 0.97, $CHCl_3$); IR (film): 3330, 2970, 1640; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II ~1:1) δ: 8.10 (br s, 1H, NH, indole), 8.04 (br s, 1H, NH, indole), 7.60 (m, 1H, H-4$_{indole}$), 7.59 (m, 1H, H-4$_{indole}$), 7.37–7.16 (m, 8H, $8 \times H_{arom}$), 7.13–7.10 (m, 4H, $4 \times H_{arom}$), 7.07 (m, 1H, H_{arom}), 7.06 (m, 1H, H_{arom}), 7.01 (d, $J = 2$ Hz, 1H, H-2$_{indole}$), 6.96 (d, $J = 2$ Hz, 1H, H-2$_{indole}$), 6.72 (br t, 1H, N*H*CH$_2$CH$_2$), 5.99 (br t, 1H, N*H*CH$_2$CH$_2$), 4.24 (d, $J = 11$ Hz, 1H, H-2), 4.15 and 4.03 (q_{AB}, $J = 15$ Hz, 2H, C*H*$_2$Ph), 4.01 and 3.85 (q_{AB}, $J = 15$ Hz, 2H, C*H*$_2$Ph), 3.61–3.48 (m, 4H, NHC*H*$_2$CH$_2$), 3.34 (d, $J = 11$ Hz, 1H, H-2), 2.96 (t, $J = 7$ Hz, 2H, NHCH$_2$C*H*$_2$), 2.94 (t, $J = 6.5$ Hz, 2H, NHCH$_2$C*H*$_2$), 2.80 (s, 3H, NCH$_3$), 2.73 (s, 3H, NCH$_3$), 2.25 (m, 2H, C*H*(CH$_3$)$_2$), 0.89 and 0.64 (2d, $J = 6.5$ Hz, 6H, CH(C*H*$_3$)$_2$), 0.74 and 0.36 (2d, $J = 6.5$ Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.89, 196.25, 168.33, 167.79, 166.98, 165.83, 136.41, 136.38, 135.25, 134.83, 133.20, 133.19, 130.25, 130.16, 130.05, 129.99, 128.36, 128.25, 128.00, 127.96, 127.21, 127.15, 122.26, 122.20, 122.15, 122.12, 119.47, 119.45, 118.69, 118.65, 112.59, 112.49, 111.25, 111.18, 66.32, 62.78, 46.49, 46.20, 39.55, 39.34, 30.68, 30.17, 25.54, 25.37, 25.31, 25.27, 19.48, 19.41, 18.09, 17.86; ESI (+) *m*/*z* (%): 476 $[M+Na]^+$ (100); ESI (−) *m*/*z* (%): 452 $[M-H]^-$.

4.10. Preparation of (2*S*)-*N*-{1-[2-(1*H*-indol-3-yl)-ethyl-carbamoyl]-ethyl}-*N*-methyl-2-oxo-propionamide 13

Analogously to the previously mentioned procedure for the preparation of **9**, amide **8** (685 mg, 2.51 mmol) was coupled with pyruvic acid (220 mg, 2.51 mmol) diluted with dry THF (30 mL) to yield derivative **13** (620 mg, 72%) as a yellow oil; $[\alpha]_D^{23} = -84.1$ (*c* 1.01, $CHCl_3$); IR (KBr): 3320, 2970, 2930, 1640, 1450; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II ~1:1): δ 8.18 (br s, 1H, NH, indole), 8.12 (br s, 1H, NH, indole), 7.61 (d, $J = 8.5$ Hz, 1H, H-4$_{indole}$), 7.59 (d, $J = 8.5$ Hz, 1H, H-4$_{indole}$), 7.35 (d, $J = 8$ Hz, 1H, H-7$_{indole}$), 7.35 (d, $J = 8$ Hz, 1H, H-7$_{indole}$), 7.19 (t, $J = 8$ Hz, 1H, H-6$_{indole}$), 7.19 (t, $J = 8$ Hz, 1H, H-6$_{indole}$), 7.11 (t, $J = 8$ Hz, 1H, H-5$_{indole}$), 7.11 (t, $J = 8$ Hz, 1H, H-5$_{indole}$), 7.01 (d, $J = 2.5$ Hz, 1H, H-2$_{indole}$), 6.99 (d, $J = 2.5$ Hz, 1H, H-2$_{indole}$), 6.69 (br t, 1H, N*H*CH$_2$CH$_2$), 6.04 (br t, 1H, N*H*CH$_2$CH$_2$), 4.28 (d, $J = 11$ Hz, 1H, H-2), 3.66 (m, 2H, NHC*H*$_2$CH$_2$), 3.54 (m, 2H, NHC*H*$_2$CH$_2$), 3.46 (d, $J = 11$ Hz, 1H, H-2), 2.97 (m, 2H, NHCH$_2$C*H*$_2$), 2.97 (m, 2H, NHCH$_2$C*H*$_2$), 2.92 (s, 3H, NCH$_3$), 2.81 (s, 3H, NCH$_3$), 2.44 (s, 3H, CH$_3$), 2.35 (m, 1H, C*H*(CH$_3$)$_2$), 2.32 (s, 3H, CH$_3$), 0.93 (d, $J = 6.5$ Hz, 3H, CH(C*H*$_3$)$_2$), 0.86 (d, $J = 6.5$ Hz, 3H, CH(C*H*$_3$)$_2$), 0.85 (d, $J = 6.5$ Hz, 3H, CH(C*H*$_3$)$_2$), 0.77 (d, $J = 6.5$ Hz, 3H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.35, 198.21, 168.59, 167.78, 167.63, 166.75, 136.40, 127.16, 122.23, 122.20, 122.16, 122.09, 119.43, 119.41, 118.68, 118.62, 112.57, 112.43, 111.24, 111.19, 66.58, 62.69, 39.50, 39.30, 30.87, 29.70, 28.10, 27.59, 25.61, 25.52, 25.31, 19.55, 19.46, 18.73, 18.32; ESI (+) *m*/*z* (%): 366 $[M+Na]^+$ (100).

4.11. Preparation of (2*S*)-2[(3-benzo[1,3]dioxol-5-yl-2-oxo-propionyl)-methyl-amino]-*N*-[2-(1*H*-indol-3-yl)-ethyl]-3-methyl-butyramide 14

The procedure applied to the synthesis of **14** was the same as used in the preparation of **9**. Compound **8** (657 mg, 2.4 mmol) underwent a BOP-mediated (1.17 g, 2.6 mmol) coupling with 3-benzo[1,3]dioxol-5-yl-2-oxo-propionic acid (500 mg, 2.4 mmol) to give ketoamide **14** (130 mg, 12%); $[\alpha]_D^{23} = -36$ (*c* 1.02, MeOH); IR (film): 3350, 2960, 2920, 1640, 1590, 1250, 1050; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II 3:2): δ 8.17 (br s, 1H, NH, indole) (I), 8.11 (br s, 1H, NH, indole) (II), 7.60 (m, 1H, H-4$_{indole}$) (I), 7.59 (m, 1H, H-4$_{indole}$) (II), 7.36 (m, 2H, $2 \times$ H-7$_{indole}$), 7.19 (t, $J = 7$ Hz, 2H, $2 \times$ H-5$_{indole}$), 7.12 (m, 2H, $2 \times$ H-6$_{indole}$), 7.01 (s, 1H, H-2$_{indole}$) (I), 6.96 (s, 1H, H-2$_{indole}$) (II), 6.76 (d, $J = 7$ Hz, 1H, H_{arom}) (II), 6.72 (d, $J = 8$ Hz, 1H, H_{arom}) (I), 6.70 (d, $J = 1.5$ Hz, 1H, H_{arom}) (II), 6.68 (d, $J = 2$ Hz, 1H, H_{arom}) (I), 6.65 (dd, $J = 8$, $J = 1$ Hz, 1H, H_{arom})

(I), 6.62 (dd, $J = 7$ Hz, $J = 1.5$ Hz, 1H, H_{arom}) (II), 5.94 (m, 2H, OCH_2O) (II), 5.92 (br s, 2H, $NHCH_2CH_2$), 5.90 (s, 2H, OCH_2O) (I), 4.24 (d, $J = 11$ Hz, 1H, H-2) (II), 4.13 and 3.90 (q_{AB}, $J = 15$ Hz, 2H, $CH_2Ph(OCH_2)$) (II), 3.92 and 3.82 (q_{AB}, $J = 15$ Hz, 2H, $CH_2Ph(OCH_2)$) (I), 3.73 (m, 1H, $NHCH_2CH_2$) (II), 3.68 (m, 1H, $NHCH_2CH_2$) (I), 3.63–3.58 (m, 2H, $NHCH_2CH_2$), 3.33 (d, $J = 11$ Hz, 1H, H-2) (I), 2.95 (t, $J = 6.5$ Hz, 2H, $NHCH_2CH_2$) (I), 2.93 (t, $J = 6.5$ Hz, 2H, $NHCH_2CH_2$) (II), 2.78 (s, 3H, NCH_3) (I), 2.68 (s, 3H, NCH_3) (II), 2.25 (m, 2H, $CH(CH_3)_2$), 0.88 and 0.35 (2d, $J = 6.5$ Hz, $CH(CH_3)_2$) (II), 0.73 and 0.65 (2d, $J = 6.5$ Hz, $CH(CH_3)_2$) (I); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.84, 198.48, 168.38, 167.91, 167.51, 166.22, 148.24, 148.19, 147.35, 147.25, 136.42, 136.38, 130.91, 127.23, 127.14, 123.37, 123.15, 122.31, 122.15, 122.07, 119.42, 118.69, 118.64, 112.60, 112.47, 110.29, 110.11, 108.80, 108.71, 101.22, 66.25, 61.85, 46.67, 46.28, 39.58, 39.37, 31.64, 30.63, 25.49, 25.36, 25.30, 19.44, 19.25, 18.10, 17.72; ESI (+) m/z (%): 486 $[M+Na]^+$ (100).

4.12. Preparation of (3*S*,12b*R*) and (3*S*,12b*S*)-12b-benzyl-2,3-dimethyl-2,3,6,7,12,12b-hexahydro-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione, 21a and 21b

(a) Ketoamide **7** (50 mg, 0.1 mmol) was dissolved in dry THF (50 mL) saturated with HCl_{gas} and left at room temperature overnight. After evaporation of the solvent, the reaction mixture was taken up into a sodium bicarbonate solution (20 mL) and extracted with toluene (50 mL) and water (20 mL). The organic layer was then dried with $MgSO_4$ and evaporated leaving a mixture of **21a** and **21b** (33.2 mg, 70%, total yield; 91:9 ratio based on ^{1}H NMR spectroscopy). A column chromatography on Al_2O_3 using 10% ethyl acetate in cyclohexane (v/v) afforded the pure diastereomers **21a** and **21b**.

(b) Ketoamide **7** (50 mg, 0.01 mmol) was dissolved in dry THF (50 mL) saturated with HCl_{gas} and left at 5 °C for 10 days. The solvent was evaporated, the residue was dissolved in $CHCl_3$, washed with a sodium bicarbonate solution (20 mL), water (20 mL) and dried. After a chromatographic purification (Al_2O_3, 10% ethyl acetate in cyclohexane [v/v]) the compound **21a** was obtained (26 mg, 55%, the compound **21b** was undetectable with ^{1}H NMR spectra).

The major diastereomer (3*S*,12b*R*)-**21a**: $[\alpha]_D^{23} = -24.6$ (c 1.06, $CHCl_3$); IR (KBr): 3410, 3350, 2930, 1660, 1440; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.47 (s, 1H, H-12), 7.52 (d, $J = 8$ Hz, 1H, H-8), 7.39 (d, $J = 8$ Hz, 1H, H-9 or H-10), 7.33 (m, 2H, $2 \times H_{arom}$), 7.27 (m, 1H, H-9 or H-10), 7.21 (m, 1H, H-11), 7.17 (td, $J = 7$ Hz, $J = 1$ Hz, 1H, H_{arom}), 7.16 (m, 2H, $2 \times H_{arom}$), 5.18–5.14 (m, 1H, H-6), 3.74 and 3.39 (q_{AB}, $J = 12.5$ Hz, 2H, CH_2Ph), 3.73 (d, $J = 7$ Hz, 1H, H-3), 3.44 (td, $J = 13$ Hz $J = 5$ Hz, 1H, H-6), 3.03–2.97 (m, 1H, H-7), 2.88 (dd, $J = 15.5$ Hz, $J = 3.5$ Hz, 1H, H-7), 2.79 (s, 3H, NCH_3), 0.38 (d, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.61, 165.49, 136.04, 134.91, 132.38, 130.49, 128.83, 127.80, 126.30, 122.65, 119.65, 118.47, 111.52, 109.05, 65.17, 57.56, 45.60, 37.24, 32.03, 20.67, 17.51; ESI (+) m/z (%): 374 $[M+H]^+$ (4), 396 $[M+Na]^+$ (100).

4.13. Preparation of (3*S*,12b*R*)-2,3,12b-trimethyl-2,3,6,7,12,12b-hexahydro-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione 22a

Compound **10** (116 mg, 0.4 mmol) was dissolved in ethyl acetate (50 mL) saturated with hydrogen chloride and was left at room temperature overnight. The solvent was evaporated in vacuo and the residue was taken up into $CHCl_3$, washed with sodium bicarbonate solution (30 mL), water (30 mL), dried ($MgSO_4$) and chromatographed (silica gel, $CHCl_3$) to give **22a** as a single diastereomer (based on ^{1}H NMR) (61 mg, 56%); $[\alpha]_D^{23} = -35.2$ (c 0.99, $CHCl_3$); IR (KBr): 3400, 2930, 2830, 1660, 1450; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.39 (br s, 1H, H-12), 7.48 (d, $J = 8$ Hz, 1H, H-8), 7.36 (d, $J = 8.5$ Hz, 1H, H-11), 7.19 (td, $J = 7.5$ Hz, $J = 1.5$ Hz, 1H, H-9), 7.06 (td, $J = 6.5$ Hz, $J = 1$ Hz, 1H, H-10), 5.04 (m, 1H, H-3), 3.74–3.58 (m, 1H, H-6), 3.18 (m, 1H, H-6), 3.00 (s, 3H, NCH_3), 2.91 (m, 1H, H-7), 2.82–2.79 (m, 1H, H-7), 1.94 (s, 3H, $3 \times$ H-1′), 1.61 (d, $J = 6.5$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.60, 165.50, 136.35, 132.68, 126.18, 122.55, 119.59, 118.41, 111.51, 109.74, 59.92, 58.20, 37.25, 32.52, 26.91, 20.58, 19.16; ESI (+) m/z (%): 320 $[M+Na]^+$.

4.14. Preparation of (3*S*,12b*R*) and (3*S*,12b*S*)-12b-benzyl-3-isopropyl-2-methyl-2,3,6,7,12,12b-hexahydro-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione, 23a and 23b

Following the procedure described for the preparation of **22a**, ketoamide **11** (50 mg, 0.1 mmol) was converted into diastereomeric mixture of **23a** and **23b**. In toluene (50 mL) saturated with hydrogen chloride the diastereomeric ratio was 72:28 (38 mg, 79%), whereas when ethyl acetate (50 mL) was used the ratio improved to 97:3 (according to ^{1}H NMR spectroscopy) (40 mg, 84%).

The major diastereomer (3*S*,12b*R*)-**23a**: mp 220–227 °C; $[\alpha]_D^{23} = -53.2$ (c 0.97, $CHCl_3$); IR (KBr): 3410, 2910, 1660, 1400; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.27 (br s, 1H, H-12), 7.49 (d, $J = 8$ Hz, 1H, H_{arom}), 7.38 (d, $J = 8$ Hz, 1H, H_{arom}), 7.28–7.18 (m, 4H, $4 \times H_{arom}$), 7.15–7.08 (m, 3H, $3 \times H_{arom}$), 4.90 (dd, $J = 13$ Hz, $J = 5$ Hz, 1H, H-6), 3.81 and 3.48 (q_{AB}, $J = 14.5$ Hz, 2H, CH_2Ph), 3.49 (d, $J = 6.5$ Hz, 1H, H-3), 3.25 (td, $J = 12.5$ Hz, $J = 4.5$ Hz, 1H, H-6 or H-7), 3.03 (m, 1H, H-6 or H-7), 2.93 (s, 3H, NCH_3), 2.74 (dd, $J = 16$, $J = 4$ Hz, 1H, H-6 or H-7), 1.08 (octet, $J = 6.5$ Hz, 1H, $CH(CH_3)_2$), 0.79 and 0.50 (2d, $J = 7.0$ Hz, $J = 6.5$ Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.69, 165.34, 136.02, 135.38, 132.76, 130.55, 128.77, 127.63, 126.51, 122.72, 119.69, 118.58, 109.53, 68.22, 66.04, 45.54, 38.48, 35.90, 29.76, 20.68, 20.20, 18.47; ESI (+) m/z (%): 402 $[M+H]^+$ (27), 424 $[M+Na]^+$ (100).

4.15. Preparation of (3*S*,12b*R*)-12b-(3-chloro-benzyl)-3-isopropyl-2-methyl-2,3,6,7,12,12b-hexahydro-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione 24a

Compound **12** (38 mg, 0.08 mmol) underwent a Pictet–Spengler-type condensation in an ethyl acetate/hydrogen chloride solution (50 mL) in the manner described for **22a** to afford the diastereomer **24a** almost quantitatively.

The major diastereomer (3*S*,12b*R*): $[\alpha]_D^{23} = -41.8$ (*c* 0.96, $CHCl_3$); IR (film): 2960, 2930, 1650, 1400; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.20 (br s, 1H, H-12), 7.49 (d, $J = 7.5$ Hz, 1H, H-9), 7.38 (d, $J = 8$ Hz, 1H, H-10), 7.25–7.16 (m, 4H, $4 \times H_{arom}$), 7.11 (t, $J = 7.5$ Hz, 1H, H-11), 7.02 (d, $J = 7.5$ Hz, 1H, H-8), 4.92 (dd, $J = 13.5$ Hz, $J = 5$ Hz, 1H, H-6), 3.81 and 3.42 (q_{AB}, $J = 14.5$ Hz, 2H, CH_2PhCl), 3.51 (d, $J = 6$ Hz, 1H, H-3), 3.29 (td, $J = 12.5$ Hz, $J = 4$ Hz, 1H, H-7), 3.06 (m, 1H, H-6), 2.94 (s, 3H, NCH_3), 2.76 (dd, $J = 15.5$ Hz, $J = 4$ Hz, 1H, H-7), 1.15 (m, 1H, $CH(CH_3)_2$), 0.84 (d, $J = 7.0$ Hz, 3H, $CH(CH_3)_2$), 0.50 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.24, 165.26, 137.36, 135.91, 134.64, 132.46, 130.56, 129.93, 128.73, 127.77, 126.44, 122.81, 119.74, 118.55, 111.50, 109.46, 68.06, 65.84, 44.77, 38.50, 35.70, 33.26, 20.50, 19.98, 18.08; ESI (+) *m*/*z* (%): 458 $[M+Na]^+$ (8).

4.16. Preparation of (3*S*,12b*R*)-3-isopropyl-2,12b-dimethyl-2,3,6,7,12,12b-hexahydro-pyrazino[1′,2′:1,2]-pyrido[3,4-*b*]indole-1,4-dione 25a

The procedure described for **22a** was applied for the formation of **25a** (>99% according to ^{1}H NMR, 70% chemical yield) from ketoamide **13** (120 mg, 0.3 mmol); $[\alpha]_D^{23} = -93.9$ (*c* 1.03, $CHCl_3$); IR (film): 3400, 3000, 1650, 1410, 1300, 1200; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.24 (br s, 1H, H-12), 7.47 (dd, $J = 7.5$ Hz, $J = 1$ Hz, 1H, H-11), 7.35 (dt, $J = 13$ Hz, $J = 1$ Hz, 1H, H-8), 7.18 (m, 1H, H-9), 7.09 (m, 1H, H-10), 4.97 (ddd, $J = 13.0$ Hz, $J = 5.5$ Hz, $J = 1.0$ Hz, 1H, H-6), 3.87 (d, $J = 3.5$ Hz, 1H, H-3), 3.19 (td, $J = 13$ Hz, $J = 4.5$ Hz, 1H, H-7), 2.99 (s, 3H, NCH_3), 2.95 (m, 1H, H-6), 2.74 (ddd, $J = 15$ Hz, $J = 4$ Hz, $J = 1$ Hz, 1H, H-7), 2.33 (m, 1H, $CH(CH_3)_2$), 2.00 (s, 3H, $3 \times$ H-1′), 1.21 (d, $J = 7$ Hz, 3H, $CH(CH_3)_2$), 1.06 (d, $J = 7$ Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.97, 163.17, 135.97, 133.96, 126.33, 122.51, 119.56, 118.38, 108.80, 67.87, 60.30, 37.53, 34.40, 31.76, 28.56, 20.35, 19.80, 18.26; ESI (+) *m*/*z* (%): 326 $[M+H]^+$ (5), 348 $[M+Na]^+$ (100); X-ray data: $C_{19}H_{23}N_3O_2$, $M_r = 325.40$, monoclinic $P2_1$, $a = 7.1980(14)$, $b = 9.950(2)$, $c = 24.047(5)$ Å, $\beta = 94.82(3)°$, $V = 1716.2(6)$ Å^3, $Z = 4$, $\rho_x = 1.259$ g cm^{-3}, $F(000) = 696$; data collection: Kuma KM4CCD κ-axis diffractometer, 33 reflections with $11.4 > 2\theta > 23.7°$ were used in a least squares procedure to determine a crystal lattice, colourless crystal $0.2 \times 0.5 \times 0.7$ mm, 5683 intensities were measured, 5292 independent ($R_{int} = 0.0255$); 2218 with $I > 2\sigma(I)$; structure solution and refinement: direct methods,[34] refined using SHELXL,[35] least squares on F^2 (all reflections), $R = 0.0509$, $wR2 = 0.1478$ (observed). There are two independent molecules in asymmetric part of the unit cell differing only slightly in molecular geometry.

4.17. Preparation of (3*S*,12b*R*)-12b-benzo[1,3]dioxol-5-ylmethyl-3-isopropyl-2-methyl-2,3,6,7,12,12b-hexahydro-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione 26a

Analogously to the procedure applied to the synthesis of **22a** compound **14** (30 mg, 0.06 mmol) was transformed into the diketopiperazine derivative **26a** (>99% de) in an ethyl acetate/hydrogen chloride solution; $[\alpha]_D^{23} = -38.7$ (*c* 1.07, $CHCl_3$); IR (film): 3350, 2900, 1730, 1650, 1500, 1450, 1250; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.22 (br s, 1H, H-12), 7.48 (d, $J = 7.5$ Hz, 1H, H-11), 7.37 (d, $J = 8$ Hz, 1H, H-8), 7.21 (m, 1H, H-9), 7.11 (m, 1H, H-10), 6.71 (d, $J = 8.5$ Hz, 1H, H_{arom}), 6.62 (d, $J = 1.5$ Hz, 1H, H_{arom}), 6.59 (dd, $J = 8$ Hz, $J = 1.5$ Hz, 1H, H_{arom}), 5.91 (d, $J = 3$ Hz, 2H, OCH_2O), 4.91 (dd, $J = 13$ Hz, $J = 5.5$ Hz, 1H, H-6), 3.73 and 3.37 (q_{AB}, $J = 14.5$ Hz, 2H, $CH_2Ph(OCH_2O)$), 3.52 (d, $J = 6$ Hz, 1H, H-3), 3.23 (td, $J = 13$ Hz, $J = 4$ Hz, 1H, H-7), 3.03 (m, 1H, H-6), 2.94 (s, 3H, NCH_3), 2.73 (m, 1H, H-7), 1.37 (m, 1H, $CH(CH_3)_2$), 0.88 (d, $J = 7$ Hz, 3H, $CH(CH_3)_2$), 0.60 (d, $J = 7.5$ Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.58, 165.23, 147.87, 147.13, 135.93, 132.63, 128.94, 126.46, 123.75, 122.67, 119.65, 118.50, 111.47, 110.79, 109.43, 108.49, 100.99, 68.12, 66.02, 45.06, 38.39, 33.22, 20.53, 20.04, 18.44, 18.31; ESI (+) *m*/*z* (%): 468.2 $[M+Na]^+$ (35).

4.18. Preparation of (2*S*)-{1-[2-(1*H*-indol-3-yl)-ethylcarbamoyl]-ethyl}-methyl-carbamic acid benzyl ester 27

(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carboxylic acid **4** (6.92 g, 27.8 mmol) was converted into **27** (6.69 g, 79.2%) analogously to the procedure described for **5**; $[\alpha]_D^{23} = -48.6$ (*c* 1.02, $CHCl_3$); IR (film): 3450, 3200, 3000, 2500, 1700, 1450, 1200; ^{1}H NMR (a severe broadening of selected signals was observed due to amide rotamers) ($CDCl_3$, 500 MHz): δ 8.17 (br s, 1H, exchan- geable with D_2O, NH, indole), 7.55 (m, 1H, H-7_{indole}), 7.36–7.26 (m, 5H, $5 \times H_{arom}$), 7.18 (t, $J = 7.5$ Hz, 1H, H-6_{indole}), 7.10 (t, $J = 7.5$ Hz, 1H, H-5_{indole}), 6.95 (br s, 1H, H-4_{indole}), 6.74 (m, 1H, H-2_{indole}), 6.03 (br s, 1H, $NHCH_2CH_2$), 5.07 (br m, 2H, CH_2Ph), 4.27 (br d, $J = 12.5$ Hz, 1H, H-2), 3.51 (m, 2H, $NHCH_2CH_2$), 3.38 (s, 2H, NCH_2CH_2 CH_2), 2.90 (m, 2H, $NHCH_2$- CH_2), 2.27–2.07 (m, 2H, $NCH_2CH_2CH_2$), 1.83 (m, 2H, $NCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.67, 155.52, 136.43, 128.56, 128.18, 127.93, 127.27, 122.33, 121.97, 119.97, 118.58, 112.56, 111.22, 67.19, 60.91, 47.23, 39.59, 30.95, 25.10, 23.46; HR ESI: calcd for $C_{23}H_{25}N_3O_3Na$ 414.1794. Found 414.1797.

4.19. Preparation of (2*S*)-*N*-[2-(1*H*-indol-3-yl)ethyl]pyrrolidine-2-carboxamide 28

The compound **27** (5.20 g, 13.2 mmol) underwent a hydrogenolysis over palladium-on-charcoal catalyst (10% Pd, 0.3 g) following the procedure described for **7** to give **28** as dark-orange oil (2.85 g, 84%); $[\alpha]_D^{23} = -32.5$ (*c* 1.08, $CHCl_3$); IR (film): 3300, 2950, 1650, 1520, 1450, 1100; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.46 (br s, 1H, exchangeable with D_2O, NH, indole), 7.61 (d, $J = 7.5$ Hz, 1H, H-4_{indole}), 7.28 (br t, 1H, exchangeable with D_2O, $NHCH_2CH_2$), 7.16 (dt, $J = 8$ Hz, $J = 1$ Hz, 1H, H-5_{indole}), 7.11 (m, 1H, H-6_{indole}), 7.02 (d, $J = 2.5$ Hz, 1H, H-2_{indole}), 3.56 (q, $J = 6.5$ Hz, 2H, $NHCH_2CH_2CH_2$), 3.34 (m, 2H, $NHCH_2CH_2$), 2.97 (t, $J = 7$ Hz, 2H, $NHCH_2CH_2$), 2.45 (very br s, 1H, exchangeable with D_2O, $NHCH_2CH_2CH_2$), 2.01 (m, 1H, H-2), 1.88 (m, 2H, $NHCH_2CH_2CH_2$), 1.69 (td, $J = 7$ Hz, $J = 2$ Hz, 1H, $NHCH_2CH_2CH_2$), 1.64 (qt, $J = 7$ Hz, 1H,

$NHCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.03, 136.36, 127.54, 123.89, 121.97, 119.21, 118.70, 113.09, 111.22, 60.56, 47.20, 36.95, 30.74, 26.18, 25.45; ESI (+) *m/z* (%): 258 $[M+H]^+$ (100).

4.20. Preparation of (2*S*)-1-(2-oxo-3-phenyl-propionyl)-pyrrolidine-2-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-amide 29 and (8a*S*)-3-benzyl-3-hydroxy-2-[2-(1*H*-indol-3-yl)-ethyl]-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione 33

Following the preparation scheme applied for **9**, phenylpyruvic acid (1.54 g, 9.35 mmol) was added to a stirring solution of **28** (2.20 g, 8.5 mmol) in dry THF (150 mL), with triethylamine (1.51 g, 17 mmol) and BOP (4.16 g, 9.35 mmol). A purification with column chromatography (silica gel, cyclohexane–ethyl acetate 1:1 [v/v], increasing polarity) gave compound **29** (0.75 g, 22%) and **33** (0.81 g, 23%).

Analytical data for **29**: $[\alpha]_D^{23} = -37.9$ (*c* 1.06, $CHCl_3$); IR (KBr): 3310, 1640, 1450; ^1H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II 3:2): δ 8.07 (br s, 2H, exchangeable with D_2O, $2\times NH$, indole), 7.60 (d, $J = 7.5$ Hz, 1H, H-4_{indole}) (I), 7.55 (d, $J = 8$ Hz, 1H, H-4_{indole}) (II), 7.36–7.18 (m, 10H, $10\times H_{arom}$), 7.15–7.12 (m, 4H, $4\times H_{indole}$), 7.08 (m, 2H, $2\times$ H-7_{indole}), 7.02 (s, 1H, H-2_{indole}) (I), 6.88 (s, 1H, H-2_{indole}) (II), 6.52 (br t, 1H, $NHCH_2CH_2$) (I), 5.68 (br t, 1H, $NHCH_2CH_2$) (II), 4.44 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H, H-2) (I), 4.40 (t, $J = 6.5$ Hz, 1H, H-2) (II), 4.32 and 4.05 (q_{AB}, $J = 17$ Hz, 4H, CH_2Ph), 3.64–3.45 (m, 8H), 2.96 (m, 4H, $NHCH_2CH_2$), 2.53 (m, 2H, $NCH_2CH_2CH_2$), 2.23 (m, 2H, $NCH_2CH_2CH_2$), 2.00–1.63 (m, 4H, $NCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.46, 196.56, 171.25, 170.00, 164.05, 163.96, 136.22, 132.99, 131.87, 130.13, 129.82, 128.89, 128.56, 127.62, 127.57, 127.26, 122.49, 122.32, 122.06, 122.11, 119.49, 119.42, 118.66, 118.56, 112.74, 112.32, 111.28, 111.23, 61.16, 60.51, 47.26, 46.15, 45.45, 45.31, 39.82, 39.70, 29.48, 29.37, 25.08, 24.91, 22.70, 22.23; ESI (+) *m/z* (%): 404 $[M+H]^+$ (6), 426 $[M+Na]^+$ (100).

Analytical data for **33**: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.07 (br s, 1H, exchangeable with D_2O, NH, indole), 7.82 (d, $J = 8$ Hz, 1H, H-4_{indole}), 7.36–7.18 (m, 5H, $5\times H_{arom}$), 7.08 (m, 3H, $3\times H_{indole}$), 7.07 (s, 1H, H-2_{indole}), 4.10 (m, 1H, H-8a), 4.07 (br s, 1H, OH), 3.64–3.45 (m, 4H), 3.16 and 3.09 (q_{AB}, $J = 13.5$ Hz, 2H, CH_2Ph), 2.96 (m, 2H, NCH_2CH_2), 2.15 (m, 2H, $2\times$ H-8), 2.00–1.63 (m, 2H, $2\times$ H-7); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.34, 165.78, 136.34, 133.60, 130.37, 128.50, 127.78, 127.14, 122.18, 121.96, 119.45, 119.37, 113.59, 111.06, 86.63, 59.07, 47.86, 45.56, 43.30, 29.70, 25.73, 21.95.

4.21. Preparation of (2*S*)-1-[3-(3-chloro-phenyl)-(2-oxo-propionyl)-pyrrolidine-2-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-amide 30 and (8a*S*)-3-(3-chloro-benzyl)-3-hydroxy-2-[2-(1*H*-indol-3-yl)-ethyl]-hexahydro-pyrrolo-[1,2-*a*]pyrazine-1,4-dione 34

Amide **28** (600 mg, 2.3 mmol) was coupled with *m*-chlorophenylpyruvic acid (500 mg, 2.6 mmol) following the procedure described for **9** to give products **30** (140 mg, 13%) and **34** (120 mg, 12%).

Analytical data for **30**: $[\alpha]_D^{23} = -43.3$ (*c* 1.05, $CHCl_3$); IR (KBr): 3330, 2950, 1650, 1400; ^1H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II ~1:1): δ 8.09 (br s, 2H, $2\times NH$, indole), 7.78 (d, $J = 7.5$ Hz, 1H, H-4_{indole}), 7.56 (d, $J = 8$ Hz, 1H, H-4_{indole}), 7.37 (m, 1H, H-7_{indole}), 7.34 (m, 1H, H-7_{indole}), 7.25–7.17 (m, 6H, $6\times H_{arom}$), 7.14–7.09 (m, 2H, $2\times H_{arom}$), 6.96 (s, 1H, H-2_{indole}), 6.95 (s, 1H, H-2_{indole}), 6.51 (br t, 1H, $NHCH_2CH_2$), 5.52 (br t, $J = 2$ Hz, 1H, $NHCH_2CH_2$), 4.25 (m, 2H, $2\times$ H-2), 3.65 (m, 2H, $NCH_2CH_2CH_2$), 3.59 (m, 2H, $NHCH_2CH_2$), 3.45 (m, 2H, $NCH_2CH_2CH_2$), 3.12 (m, 1H, $NHCH_2CH_2$), 3.10 (d, $J = 4$ Hz, 2H, $NHCH_2CH_2$), 3.06 (d, $J = 4$ Hz, 4H, CH_2PhCl), 3.01 (m, 1H, $NHCH_2CH_2$), 2.97 (m, 1H, $NHCH_2CH_2$), 2.90 (m, 1H, $NHCH_2CH_2$), 2.08 (m, 2H, $NCH_2CH_2CH_2$), 1.97 (m, 2H, $NCH_2CH_2CH_2$), 1.80 (m, 4H, $NCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.88, 195.82, 171.27, 169.98, 163.76, 163.44, 136.37, 136.36, 135.33, 134.18, 134.15, 129.99, 129.89, 129.74, 129.65, 128.53, 128.41, 127.66, 127.60, 127.23, 127.15, 122.27, 122.18, 122.14, 122.08, 119.52, 119.44, 118.56, 112.79, 112.34, 111.31, 111.23, 61.02, 60.81, 48.10, 47.40, 44.94, 44.68, 39.84, 39.77, 29.70, 29.56, 25.68, 25.07, 22.69, 22.43; ESI (+) *m/z* (%): 438 $[M+H]^+$ (5), 460 $[M+Na]^+$ (100).

Analytical data for **34**: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.10 (br s, 1H, NH, indole), 7.56 (d, $J = 7.5$ Hz, 1H, H-4_{indole}), 7.36 (m, 1H, H-7_{indole}), 7.25–7.17 (m, 3H, $3\times H_{arom}$), 7.14–7.09 (m, 2H, $2\times H_{indole}$), 7.06 (m, 1H, H_{arom}), 6.91 (s, 1H, H-2_{indole}), 4.70 (br s, 1H, OH), 4.29 and 4.06 (q_{AB}, $J = 18$ Hz, 2H, CH_2PhCl), 4.02 (m, 1H, H-8a), 3.59 (m, 2H, NCH_2CH_2), 3.45 (m, 2H, $2\times$ H-6), 2.97 (m, 2H, NCH_2CH_2), 1.97 (m, 2H, H-8), 1.80 (m, 2H, $2\times$ H-7); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.12, 165.63, 136.21, 135.59, 134.27, 130.40, 130.22, 128.02, 127.88, 127.33, 122.46, 121.97, 119.36, 118.68, 113.45, 111.08, 86.11, 59.40, 45.40, 43.21, 36.82, 32.21, 27.38, 22.11.

4.22. Preparation of (8a*S*)-3-hydroxy-2-[2-(1*H*-indol-3-yl)-ethyl]-3-methyl-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione 35

The coupling of **28** (2.20 g, 0.8 mmol) with pyruvic acid (0.82 g, 9.4 mmol) proceeded analogously to the procedure described for **9** but afforded the product in a form of hydroxylactam **35** (2.4 g, 78%) as the predominant form; $[\alpha]_D^{23} = -50.9$ (*c* 1.03, $CHCl_3$); IR (film): 3300, 2930, 2870, 1660, 1450, 1200; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.06 (br s, 1H, exchangeable with D_2O, NH, indole), 7.76 (d, $J = 7.5$ Hz, 1H, H-4_{indole}), 7.34 (d, $J = 8$ Hz, 1H, H-7_{indole}), 7.18 (td, $J = 8$ Hz, $J = 7.5$ Hz, 1H, H-5_{indole}), 7.12 (t, $J = 7$ Hz, 1H. H-6_{indole}), 7.06 (s, 1H, H-2_{indole}), 4.70 (br s, 1H, exchangeable with D_2O, OH), 4.11 (m, 1H, H-8a), 3.97 (m, 1H, NCH_2CH_2), 3.67 (m, 1H, NCH_2CH_2), 3.57 (m, 2H, $2\times$ H-6), 3.12–3.00 (m, 2H, NCH_2CH_2), 2.46 (m, 1H, H-8), 2.07 (m, 1H, H-8), 1.96 (m, 2H, $2\times$ H-7), 1.52 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.44,

166.23, 136.15, 127.59, 121.98, 121.90, 119.31, 119.29, 113.50, 111.01, 83.05, 59.74, 46.16, 42.31, 29.42, 25.67, 25.11, 22.59; EI 70 eV *m/z* (%): 70 (14), 130 (38), 143 (100), 144 (19), 327 [M] (8); LSIMS (+) (%): 135 (54), 143 (17), 180 (100), 328 $[M+H]^+$ (8), 350 $[M+Na]^+$ (5); EI HR: calcd for $C_{18}H_{21}N_3O_3$ 327.15829. Found 327.15874.

4.23. Preparation of (2*S*)-1-(3-benzo[1,3]dioxol-5-yl-2-oxo-propionyl)-pyrrolidine-2-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-amide 32 and (8a*S*)-3-benzo[1,3]dioxol-5-ylmethyl-3-hydroxy-2-[2-(1*H*-indol-3-yl)-ethyl]-3-methyl-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione 36

Following the preparation of **9**, the product was obtained as a mixture of **32** (177 mg, 16%) and **36** (355 mg, 32%) from amide **28** (640 mg, 2.5 mmol) and 3-benzo[1,3]dioxyol-5-yl-pyruvic acid (520 mg, 2.5 mmol) in the presence of triethylamine (440 mg, 4.9 mmol) and BOP (1.20 g, 2.7 mmol).

Analytical data for **32**: $[\alpha]_D^{23} = -49.2$ (*c* 0.96, MeOH); IR (film): 3320, 2950, 1660, 1450, 1250, 1050; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II ~1:1): δ 8.15 (br s, 2H, 2 × NH, indole), 7.60 (d, J = 7.5 Hz, 1H, H-4$_{indole}$), 7.56 (d, J = 7.5 Hz, 1H, H-4$_{indole}$), 7.35 (m, 2H, 2 × H-7$_{indole}$), 7.18 (m, 2H, 2 × H-5$_{indole}$), 7.13 (m, 2H, 2 × H-6$_{indole}$), 7.05 (d, J = 1.5 Hz, 1H, H-2$_{indole}$), 7.03 (d, J = 2 Hz, 1H, H-2$_{indole}$), 6.70 (d, J = 1.5 Hz, 1H, H$_{arom}$), 6.68 (d, J = 2 Hz, 1H, H$_{arom}$), 6.73 (d, J = 7.5 Hz, 1H, H$_{arom}$), 6.65 (dd, J = 8 Hz, J = 2 Hz, 1H, H$_{arom}$), 6.61 (dd, J = 8 Hz, J = 2 Hz, 1H, H$_{arom}$), 6.54 (br t, 1H, N*H*CH$_2$CH$_2$), 5.92 (m, 2H, OCH$_2$O), 5.88 and 5.86 (q_{AB}, J = 1.5 Hz, 2H, OCH$_2$O), 5.71 (br t, J = 5.5 Hz, 1H, N*H*CH$_2$CH$_2$), 4.43 (m, 2H, 2 × H-2), 4.22 and 3.96 (q_{AB}, J = 17 Hz, 2H, C*H*$_2$ C*H*$_2$Ph(OCH$_2$O)), 3.98 and 3.88 (q_{AB}, J = 15 Hz, 2H, C*H*$_2$Ph(OCH$_2$O)), 3.72 (m, 2H), 3.63–3.55 (m, 2H), 3.63–3.55 (m, 4H), 2.95 (m, 2H), 2.87 (m, 2H), 2.05–1.90 (m, 4H), 1.56 (m, 2H, NCH$_2$C*H*$_2$CH$_2$), 1.36 (m, 2H, NCH$_2$C*H*$_2$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.59, 196.50, 171.25, 170.01, 163.98, 163.91, 148.01, 147.69, 147.02, 146.67, 136.37, 135.35, 127.31, 127.18, 127.11, 126.53, 123.22, 123.01, 122.43, 122.30, 122.19, 122.10, 121.94, 121.10, 118.68, 18.56, 112.76, 112.40, 111.30, 111.22, 110.44, 110.09, 108.33, 108.31, 101.16, 100.97, 61.81, 61.12, 47.93, 47.26, 45.01, 44.85, 39.84, 39.77, 32.05, 31.61, 25.10, 24.99, 22.28, 22.10; ESI (+) *m/z* (%): 470 $[M+Na]^+$ (82).

Analytical data for **36**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (br s, 1H, NH, indole), 7.80 (d, J = 7.5 Hz, 1H, H-4$_{indole}$), 7.35 (d, J = 8 Hz, 1H, H-7$_{indole}$), 7.18 (dt, J = 7,5 Hz, J = 1 Hz, 1H, H-5$_{indole}$), 7.13 (t, J = 7.5 Hz, 1H, H-6$_{indole}$), 7.05 (s, 1H, H-2$_{indole}$), 6.68 (d, J = 8 Hz, 1H, H$_{arom}$), 6.58 (d, J = 2 Hz, 1H, H$_{arom}$), 6.51 (dd, J = 8 Hz, J = 1.5 Hz, 1H, H$_{arom}$), 4.03 (m, 1H, H-8a), 3.64 (m, 1H), 3.45 (m, 2H, 2 × H-6), 3.10 (d, J = 4.5 Hz, 2H, C*H*$_2$Ph(OCH$_2$O)), 3.03 (m, 2H, NCH$_2$C*H*$_2$), 2.26 (m, 1H), 1.97 (m, 1H), 1.75 (m, 2H, 2 × H-7); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.28, 165.96, 147.68, 147.15, 136.23, 127.62, 127.12, 123.52, 122.09, 121.94, 119.41, 119.35, 113.53, 110.53, 108.32, 101.11, 86.42, 59.36, 45.63, 45.01, 43.01, 29.57, 25.73, 22.11.

4.24. Preparation of (3*S*,12b*S*) and (3*S*,12b*R*)-12b-benzyl-2,3,6,7,12,12b-hexahydropyrrolo-pyrazino[1′,2′:1,2]-pyrido[3,4-*b*]indole-1,4-dione, 37a and 37b

Compounds **29** and **33** (50 mg, 0.12 mmol) underwent a facile Pictet–Spengler-type condensation in AcOEt, THF or MeOH (50 mL each) saturated with hydrogen chloride affording diastereomeric mixture of **37a** and **37b** in different proportions depending on the solvent used: 93:7, 83:17, 55.5:44.5, respectively (25 mg, 53%). All the operations followed the procedure described for **22**. Diastereomers **37a** and **37b** were separated chromatographically (silica gel, ethyl acetate–cyclohexane 1:1 [v/v]).

The major diastereomer (3*S*,12b*S*)-**37a**: $[\alpha]_D^{23} = +68.6$ (*c* 0.97, $CHCl_3$); IR (film): 3410, 2930, 1650, 1450, 1300; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (s, 1H, H-12), 7.51 (d, J = 8 Hz, 1H, H-8), 7.40 (d, J = 8 Hz, 1H, H-11), 7.32 (m, 3H, 3 × H$_{arom}$), 7.19 (m, 3H, 3 × H$_{arom}$), 7.12 (td, J = 8 Hz, J = 1 Hz), 5.19 (ddd, J = 12 Hz, J = 5 Hz, J = 3 Hz, 1H, H-6), 3.62 and 3.39 (q_{AB}, J = 14 Hz, 2H, C*H*$_2$Ph), 3.53 (dt, J = 12 Hz, J = 8.5 Hz, 1H, H-3′), 3.31 (m, 2H), 2.89 (m, 2H), 2.19 (dd, J = 11 Hz, J = 6 Hz, 1H, H-3), 2.08 (dtd, J = 11.5 Hz, J = 5 Hz, J = 1.5 Hz, 1H, H-1′), 1.82 (m, 1H, H-1′), 1.66 (dq, J = 11.5 Hz, J = 8 Hz, 1H), 1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.08, 164.96, 136.64, 134.52, 132.22, 130.16, 128.60, 128.07, 126.16, 122.62, 119.63, 118.47, 111.65, 109.77, 66.43, 57.67, 45.47, 44.80, 36.89, 29.42, 20.79, 20.99; ESI (+) *m/z* (%): 386 $[M+H]^+$ (5), 408 $[M+Na]^+$ (100).

The minor diastereomer (3*S*,12b*R*)-**37b**: $[\alpha]_D^{23} = -79.5$ (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.40 (s, 1H, H-12), 7.52 (m, 1H, H-8), 7.39 (dd, J = 5.5 Hz, J = 1.5 Hz, 1H, H-11), 7.33 (m, 2H, 2 × H$_{arom}$), 7.28 (m, 1H, H-9), 7.22 (m, 1H, H-10), 7.15 (m, 2H, 2 × H$_{arom}$), 7.12 (m, 1H, H$_{arom}$), 5.25 (ddd, J = 13.5 Hz, J = 5.5 Hz, J = 1.2 Hz, 1H, H-6), 3.77 (dd, J = 12 Hz, J = 6 Hz, 1H, H-3), 3.69 and 3.42 (q_{AB}, J = 13.5 Hz, 2H, C*H*$_2$Ph), 3.48 (m, 1H), 3.14 (m, 1H), 2.98 (m, 1H), 2.92 (m, 1H), 1.91 (m, 1H), 1.58 (m, 3H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.42, 164.29, 136.03, 134.71, 131.66, 130.38, 128.57, 127.77, 126.35, 122.60, 119.69, 118.43, 111.50, 108.51, 65.85, 59.29, 46.33, 44.30, 36.43, 28.57, 21.02, 20.81.

4.25. Preparation of (3*S*,12b*S*) and (3*S*,12b*R*)-12b-(3-chloro-benzyl)-2,3,6,7,12,12b-hexahydropyrrolo-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione, 38a and 38b

Both ketoamide **30** and hydroxylactam **34** (50 mg, 0.11 mmol) were converted directly into **38** (19.6 mg, 41%) analogously to **22a**. Several different solvents were applied (toluene, THF, ethyl acetate, 50 mL each), and again ethyl acetate/hydrogen chloride solution was found optimal (>99% **38a**).

The major diastereomer (3*S*,12b*S*)-**38a**: mp 205–208 °C; $[\alpha]_D^{23} = +61.4$ (*c* 1.08, $CHCl_3$); IR (KBr): 3410, 2950, 1660, 1430; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.62 (s, 1H, H-12), 7.51 (d, $J = 7$ Hz, 1H, H-8), 7.41 (d, $J = 7.5$ Hz, 1H, H-11), 7.32 (m, 1H, H_{arom}), 7.24 (m, 3H, $3 \times H_{arom}$), 7.12 (m, 1H, H-9), 7.05 (m, 1H, H-10), 5.18 (ddd, $J = 13$ Hz, $J = 5$ Hz, $J = 2$ Hz, 1H, H-6), 3.61 and 3.37 (q_{AB}, $J = 14$ Hz, 2H, CH_2PhCl), 3.56 (m, 1H, H-3′), 3.30 (m, 2H), 2.90 (m, 2H, $2 \times$ H-7), 2.37 (dd, $J = 11$ Hz, $J = 6$ Hz, 1H, H-3), 2.15 (m, 1H, H-1′), 1.86 (m, 1H, H-1′), 1.65 (m, 2H, $2 \times$ H-2′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.71, 164.71, 136.66, 136.58, 134.52, 131.84, 130.66, 129.88, 128.41, 128.19, 126.13, 122.77, 119.73, 118.51, 111.69, 109.96, 66.25, 57.84, 45.04, 44.94, 36.97, 29.53, 21.03, 20.74; ESI (+) *m*/*z* (%): 442 $[M+Na]^+$ (100); LSIMS (+) (%): 136 (38), 294 (42), 420 $[M+H]^+$ (13), 442 $[M+Na]^+$ (9).

4.26. Preparation of (3*S*,12b*S*) and (3*S*,12b*R*)-12b-methyl-2,3,6,7,12,12b-hexahydropyrrolo-pyrazino-[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione, 39a and 39b

The same protocol as for **22a** was applied for **35** (50 mg, 0.15 mmol) to give a mixture of **39a** and **39b** (with the diastereomeric ratio given in Table 2).

The major diastereomer (3*S*,12b*S*)-**39a**: $[\alpha]_D^{23} = +147.2$ (*c* 0.97, $CHCl_3$); IR (film): 3360, 3020, 1650, 1430; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.40 (s, 1H, H-12), 7.48 (d, $J = 8$ Hz, 1H, H-8), 7.37 (d, $J = 7.5$ Hz, 1H, H-11), 7.18 (td, $J = 7.5$ Hz, $J = 1$ Hz, 1H, H-9), 7.09 (t, $J = 7.5$ Hz, 1H, H-10), 5.04 (ddd, $J = 13.5$ Hz, $J = 4$ Hz, $J = 2$ Hz, 1H, H-6), 4.14 (m, 1H), 3.62 (m, 2H), 3.12 (m, 1H, H-1′), 2.82 (m, 2H, $2 \times$ H-7), 2.51 (m, 1H, H-3), 2.04 (m, 2H), 1.94 (m, 1H), 1.86 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.49, 165.88, 136.88, 132.73, 126.13, 122.48, 119.56, 118.40, 111.60, 109.69, 61.31, 58.59, 45.82, 37.04, 29.88, 26.09, 21.80, 20.57; ESI (+) *m*/*z* (%): 310 $[M+H]^+$ (5), 332 $[M+Na]^+$ (30); ESI (−) *m*/*z* (%): 308 $[M-H]^-$ (8).

The minor diastereomer (3*S*,12b*R*)-**39b**: mp 196–198 °C; $[\alpha]_D^{23} = -168.5$ (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.06 (s, 1H, H-12), 7.47 (d, $J = 8.5$ Hz, 1H, H-8), 7.34 (d, $J = 8.5$ Hz, 1H, H-11), 7.19 (td, $J = 7.5$ Hz, $J = 1$ Hz, 1H, H-9), 7.10 (td, $J = 8$ Hz, $J = 1$ Hz, 1H, H-10), 5.06 (ddd, $J = 13.5$ Hz, $J = 7.5$ Hz, $J = 1.0$ Hz, 1H, H-6), 4.00 (m, 2H, H-3′), 3.37 (m, 1H, H-6), 3.28 (m, 1H, H-7), 2.94 (m, 1H, H-7), 2.77 (ddd, $J = 16$ Hz, $J = 4.5$ Hz, $J = 1$ Hz, 1H, H-3), 2.52 (m, 1H, H-1′), 2.06 (m, 1H, H-1′), 1.97 (s, 3H, CH_3), 1.90 (m, 2H, $2 \times$ H-2′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.84, 164.36, 135.84, 132.20, 126.46, 122.50, 119.67, 118.34, 111.40, 108.05, 61.46, 59.43, 44.96, 37.06, 30.17, 30.07, 21.34, 20.73; X-ray data: $C_{18}H_{19}N_3O_2$, $M_r = 309.36$, monoclinic $P2_1$, $a = 9.100(10)$, $b = 14.092(11)$, $c = 12.476(17)$ Å, $\beta = 103.04(10)°$, $V = 1559(3)$ Å^3, $Z = 4$, $\rho_x = 1.318$ g cm^{-3}, $F(000)=656$; data collection: Kuma KM4 κ-axis diffractometer, 32 reflections with $11.5 > 2\theta > 21.5°$ were used in a least squares procedure to determine a crystal lattice, colourless fragment of dimensions $0.2 \times 0.5 \times 0.7$ mm, cut from the larger crystal, 5647 intensities measured; 5432 independent ($R_{int} = 0.0223$); 2073 with $I > 2\sigma(I)$; structure solution and refinement: direct methods from SHELXS97[34] and then refined on F^2 by application of SHELXL97 software,[35] final *R* and *wR* were 0.0334 and 0.0925, respectively. There are two independent molecules in asymmetric part of the unit cell differing only slightly in molecular geometry.

4.27. Preparation of (3*S*,12b*S*) and (3*S*,12b*R*)-12b-benzo[1,3]dioxol-2,3,6,7,12,12b-hexahydropyrrolo-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indole-1,4-dione, 40a and 40b

The cyclization step of **32** and **36** (74 mg, 0.16 mmol) proceeded in ethyl acetate/hydrogen chloride solution following the procedure described for **22a** to give **40a** as a single diastereomer (36 mg, 49%), while when diethyl ether saturated with HCl_{gas} was applied, the ratio between **40a** and **40b** was estimated at the level of 80:20.

Data for (3*S*,12b*S*)-**40a**: $[\alpha]_D^{23} = +33.0$ (*c* 1.09, $CHCl_3$); IR (film): 3400, 2930, 1660, 1500, 1250, 1050; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.60 (s, 1H, H-12), 7.50 (d, $J = 8.0$ Hz, 1H, H-8), 7.40 (d, $J = 8$ Hz, 1H, H-11), 7.21 (td, $J = 8.5$ Hz, $J = 1$ Hz, 1H, H-9), 7.11 (m, 1H, H-10), 6.75 (d, $J = 8.5$ Hz, 1H, H_{arom}), 6.68 (d, $J = 2$ Hz, 1H, H_{arom}), 6.64 (dd, $J = 8$ Hz, $J = 2$ Hz, 1H, H_{arom}), 5.96 (s, 2H, OCH_2O), 5.17 (ddd, $J = 13.5$ Hz, $J = 5.5$ Hz, $J = 1.5$ Hz, 1H, H-6), 3.71 (m, 1H), 3.65 (m, 2H), 3.54 and 3.30 (q_{AB}, $J = 13.5$ Hz, 2H, CH_2Ph(OCH_2O)), 2.90 (m, 2H, $2 \times$ H-7), 2.60 (dd, $J = 6$ Hz, $J = 5.5$ Hz, 1H, H-3), 2.20 (m, 1H, H-1′), 1.90 (m, 1H, H-1′), 1.57 (m, 2H, $2 \times$ H-2′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.98, 165.07, 147.83, 147.39, 136.60, 132.15, 130.17, 126.15, 123.36, 122.63, 119.65, 118.47, 111.64, 110.27, 109.75, 108.44, 101.20, 66.46, 57.93, 45.12, 44.92, 36.88, 29.55, 21.08, 20.77; ESI (+) *m*/*z* (%): 452 $[M+Na]^+$ (100); ESI (−) *m*/*z*: 428 $[M-H]^-$.

4.28. Preparation of (6*S*)-4-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-hydroxy-1,3,6-trimethyl-piperazine-2,5-dione 47

The BOP-mediated (1.95 g, 4.6 mmol) coupling of amide **41** (1.07 g, 4.0 mmol) with pyruvic acid (390 mg, 4.4 mmol) proceeded analogously as described for **9** to give the mixture of diastereomeric hydroxylactams **47a** and **47b** (1.00 g, 74%, total yield). No contamination of other tautomeric forms was detected. Both diastereomers could be isolated with column chromatography on silica gel (ethyl acetate–cyclohexane 1:1 [v/v]).

Diastereomer (3*R*,6*S*)-**47a**: $[\alpha]_D^{23} = +2.6$ (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.81 (s, 3H, $3 \times H_{arom}$), 4.76 (very br s, 1H, OH), 4.01 (q, $J = 7$ Hz, 1H, H-6), 3.88 and 3.86 ($2 \times$ s, 2×3H, $2 \times OCH_3$), 3.85 (m, 1H, NCH_2CH_2), 3.43 (m, 1H, NCH_2CH_2), 3.05 (s, 3H, NCH_3), 2.95 (m, 1H, NCH_2CH_2), 2.84 (m, 1H, NCH_2CH_2), 1.58 (s, 3H, $3 \times$ H-1′), 1.54 (d, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.07, 165.68, 148.86, 147.54, 131.85, 120.84, 112.10, 111.21, 82.23, 58.45, 55.91, 55.87, 44.14, 35.18, 32.40, 28.21, 18.00.

Diastereomer (3*S*,6*S*)-**47b**: mp 165–170 °C; $[\alpha]_D^{23} = +18.5$ (*c* 0.97, $CHCl_3$); IR (film): 3330, 2940, 1660, 1500, 1250, 1100; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.81 (s, 3H, $3 \times H_{arom}$), 4.39 (s, 1H, exchangeable with D_2O, OH), 4.00 (q, $J = 7$ Hz, 1H, H-6), 3.88 and 3.86 ($2 \times$ s, 2×3H, $2 \times OCH_3$), 3.81 (m, 1H, NCH_2CH_2), 3.57 (m, 1H, NCH_2CH_2), 3.01 (s, 3H, NCH_3), 2.93 (m, 1H, NCH_2CH_2), 2.84 (m, 1H, NCH_2CH_2), 1.73 (s, 3H, $3 \times$H-1′), 1.61 (d, $J = 6.5$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.49, 166.32, 147.84, 146.54, 130.60, 119.69, 111.00, 110.17, 81.98, 56.26, 54.85, 54.81, 43.32, 33.99, 31.15, 24.87, 17.37; HR ESI: calcd for $C_{17}H_{24}N_2O_5Na$ 359.1583. Found 359.1567; X-ray data: $C_{17}H_{24}N_2O_5$, monoclinic P_1, $a = 10.79(3)$, $b = 7.006(17)$, $c = 11.79(4)$ Å, $\beta = 106.5(3)°$; data collection: Kuma KM4 κ-axis diffractometer, colourless crystal of dimensions $0.2 \times 0.35 \times 0.65$ mm, 2822 reflection measured (2691 independent, $R_{int} = 0.1496$), 1609 of them had intensities larger than 2σ; structure solution and refinement: direct methods[34] and then refined on F^2 by application of SHELXL97 software.[35] Although there were no trouble in either solving or refining the structure the respective *R* and *wR* factors were unacceptably high (0.1770 and 0.3609, respectively), probably due to low quality of the crystal and data collection (as suggested by high R_{int} value). Nevertheless there was no ambiguity in structure determination and hence we decided not to redetermine this structure.

4.29. Preparation of (2*S*)-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-methyl-2-[methyl-(2-oxo-propionyl)-amino]-butyramide 45

Amide **42** (1.02 g, 3.7 mmol) was converted into **45** (945 mg, 72%) following the operation scheme applied for **9**; $[\alpha]_D^{23} = -75.3$ (*c* 0.98, $CHCl_3$); IR (film): 3350, 2960, 1640, 1510, 1260, 1030; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II ~4:3): δ 6.79 (m, 2H, $2 \times H_{arom}$), 6.71 (m, 4H, $4 \times H_{arom}$), 6.06 (br t, 2H, $NHCH_2CH_2$), 4.28 (d, $J = 11$ Hz, 1H, H-2) (II), 3.87 and 3.86 ($2 \times$ s, 2×6H, $4 \times OCH_3$ I and II), 3.57 (m, 2H, NCH_2CH_2) (I), 3.49 (m, 2H, NCH_2CH_2) (I), 3.47 (d, $J = 10.5$ Hz, 1H, H-2) (I), 2.95 (s, 3H, NCH_3) (II), 2.82 (s, 3H, NCH_3) (I), 2.75 (m, 6H), 2.48 (s, 3H, $3 \times$H-3′) (II), 2.38 (s, 3H, $3 \times$H-3′) (I), 0.93 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)_2$) (II), 0.87 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)_2$) (I), 0.86 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)_2$) (II), 0.78 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)_2$) (II); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.54, 197.91, 168.70, 167.83, 167.56, 166.62, 149.01, 148.95, 147.71, 147.62, 130.99, 130.96, 120.72, 120.64, 111.76, 111.71, 111.31, 66.54, 62.81, 55.92, 55.91, 55.85, 55.80, 40.69, 40.49, 35.30, 35.27, 30.97, 28.15, 27.81, 27.61, 25.58, 25.55, 19.55, 19.47, 18.72, 18.35; ESI (+) *m*/*z* (%): 387 $[M+Na]^+$ (100).

4.30. Preparation of (2*S*)-*N*-{1-[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-2-phenyl-ethyl}-*N*-methyl-2-oxo-propionamide 46

According to the same procedure as described for **9**, a coupling of **43** (672 mg, 1.9 mmol) with pyruvic acid (172 mg, 1.9 mmol) diluted in dry THF (50 mL) gave **46** (845 mg, 92%) as a yellow oil; $[\alpha]_D^{23} = -72.5$ (*c* 1.06, $CHCl_3$); IR (film): 2950, 1730, 1640, 1510, 1260; ^{1}H NMR ($CDCl_3$, 500 MHz) (two conformers I and II, I:II 3:1): δ 7.32–7.20 (m, 8H, $4 \times H_{arom}$ I, $4 \times H_{arom}$ II), 7.05 (m, 2H, $2 \times H_{arom}$), 6.79 (m, 2H, $2 \times H_{arom}$), 6.72 (m, 2H, $2 \times H_{arom}$), 6.70 (d, $J = 2$ Hz, 1H, H_{arom}) (II), 6.62 (dd, $J = 8$ Hz, $J = 2$ Hz, 1H, H_{arom}) (II), 6.51 (br t, $J = 5$ Hz, 1H, $NHCH_2CH_2$) (I), 5.98 (br t, 1H, $NHCH_2CH_2$) (II), 5.14 (dd, $J = 9$ Hz, $J = 7$ Hz, 1H, H-2) (II), 4.29 (dd, $J = 11$ Hz, $J = 3.5$ Hz, 1H, H-2) (I), 3.87 and 3.86 ($2 \times$ s, 2×6H, $4 \times OCH_3$ I and II), 3.62 (m, 2H, $NHCH_2CH_2$) (II), 3.48 (m, 2H, $NHCH_2CH_2$) (I), 3.13 and 2.99 (q_{AB}, $J = 14.5$ Hz, 2H, CH_2Ph) (I), 3.12 and 2.96 (q_{AB}, $J = 14.5$ Hz, 2H, CH_2Ph) (II), 2.87 (s, 3H, NCH_3) (II), 2.81 (s, 3H, NCH_3) (I), 2.78 (m, 4H, $NHCH_2CH_2$), 2.20 (s, 3H, $3 \times$H-3′) (II), 1.74 (s, 3H, $3 \times$H-3′) (I); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.13 (I), 197.84 (II), 168.55 (II), 168.22 (I), 167.35 (II), 167.19 (I), 149.03 (I and II), 147.72 (I and II), 137.33 (I), 136.41 (II), 132.44 (I and II), 130.89 (I), 130.87 (II), 129.11 (I), 129.11 (I), 128.94 (I), 128.94 (I), 128.80 (II), 128.80 (II), 128.64 (II), 128.64 (II), 111.69 (I and II), 111.36 (I), 111.31 (II), 62.74 (I and II), 55.91 (I and II), 55.82 (I and II), 40.98 (I), 40.73 (II), 35.28 (I), 35.15 (II), 33.51 (II), 33.37 (I), 28.14 (I and II), 27.39 (II), 26.66 (I); ESI (+) *m*/*z* (%): 413 $[M+H]^+$ (56), 435 $[M+Na]^+$ (100).

4.31. Preparation of (3*S*,11b*R*) and (3*S*,11b*S*)-9,10-dimethoxy-2,3,11b-trimethyl-2,3,7,11b-tetrahydro-6*H*-pyrazino[2,1-*a*]isoquinoline-1,4-dione, 50a and 50b

Hydroxylactam **47** (150 mg, 0.4 mmol) underwent the Pictet–Spengler-type cyclization in ethyl acetate (50 mL), dichloromethane (50 mL) and methanol (50 mL) saturated with hydrogen chloride (gas) as described for **22a** affording the diketopiperazines **50a** and **50b** (114 mg, 80%, total yield) in the ratio 75:25, 71.5:28.5, 75:25, respectively, according to ^{1}H NMR spectroscopy.

The major diastereomer (3*S*,11b*R*)-**50a**: $[\alpha]_D^{23} = -128.2$ (*c* 1.02, $CHCl_3$); IR (film): 3400, 2940, 1660, 1510, 1450, 1260; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (s, 1H, H-11), 6.53 (s, 1H, H-8), 4.89 (m, 1H, H-6), 4.04 (q, $J = 7$ Hz, 1H, H-3), 3.94 and 3.85 ($2 \times$ s, 6H, $2 \times OCH_3$), 3.85 (m, 1H, H-6), 2.96 (s, 3H, NCH_3), 2.95 (m, 1H, H-7), 2.60 (m, 1H, H-7), 1.90 (s, 3H, $3 \times$H-1″), 1.56 (d, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.04, 166.06, 148.26, 146.94, 128.24, 127.23, 112.76, 110.73, 61.96, 58.03, 56.05, 55.81, 37.17, 33.15, 30.80, 28.93, 18.92; ESI (+) *m*/*z* (%): 341 $[M+Na]^+$ (80).

4.32. Preparation of (3*S*,11b*R*)-3-isopropyl-9,10-dimethoxy-2,11b-dimethyl-2,3,7,11b-tetrahydro-6*H*-pyrazino[2,1-*a*]isoquinoline-1,4-dione 51a

Dissolving **45** (145 mg, 0.4 mmol) in ethyl acetate/hydrogen chloride solution promoted the Pictet–Spengler

condensation analogously to the formation of **22a** and after purification with column chromatography (silica gel, chloroform), gave compound **51** (130 mg, 94%) as a single diastereomer (3*S*,11b*R*)-**51a**: $[\alpha]_D^{23} = -62.0$ (*c* 1.08, $CHCl_3$); IR (film): 2960, 2930, 1650, 1250; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (s, 1H, H-11), 6.53 (s, 1H, H-8), 4.80 (m, 1H, H-6), 3.91 and 3.85 (2 × s, 6H, 2 × OCH_3), 3.85 (m, 1H, H-6), 3.06 (m, 2H, 2 × H-7), 2.93 (s, 3H. NCH_3), 2.57 (d, J = 13 Hz, 1H, H-3), 2.32 (m, 1H, C*H*$(CH_3)_2$), 1.96 (s, 3H, 3 × H-1′) 1.19 (d, J = 7 Hz, 3H, CH(C*H*$_3$)$_2$), 1.01 (d, J = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.72, 163.42, 148.23, 147.06, 129.76, 126.77, 111.15, 111.10, 67.59, 62.53, 56.01, 55.79, 37.31, 34.80, 31.48, 30.46, 28.08, 19.74, 17.81; ESI (+) *m*/*z* (%): 347 $[M+H]^+$ (20), 369 $[M+Na]^+$ (100).

4.33. Preparation of (3*S*,11b*R*) and (3*S*,11b*S*)-3-benzyl-9,10-dimethoxy-2,11b-dimethyl-2,3,7,11b-tetrahydro-6*H*-pyrazino[2,1-*a*]isoquinoline-1,4-dione, 52a and 52b

Operating on the same scheme as described for **22a** the condensation of **46** (140 mg, 0.3 mmol) in CH_2Cl_2/HCl_{gas} (50 mL), AcOEt/HCl_{gas} (50 mL), MeOH/HCl_{gas} (50 mL) afforded a diastereomeric mixture of **52a** and **52b** (60 mg, 45%, total yield) in the ratio 83.3:16.7, 75:25, 83.3:16.7, respectively.

The major diastereomer (3*S*,11b*R*)-**52a**: oil; $[\alpha]_D^{23} = -50.1$ (*c* 1.04, $CHCl_3$); IR (film): 3000, 2940, 1650, 1520, 1450, 1250, 1100; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (s, 1H, H-11), 7.31 (m, 2H, 2 × H_{arom}), 7.15 (m, 2H, 2 × H_{arom}), 6.81 (m, 1H, H_{arom}), 6.47 (s, 1H, H-8), 4.81 (ddd, J = 12.5, J = 5.5 Hz, J = 1.5 Hz, 1H, H-3), 4.29 (m, 1H, H-6), 3.85 and 3.81 (2 × s, 6H, 2 × OCH_3), 3.36 and 3.23 (q_{AB}, J = 4.0 Hz, 2H, C*H*$_2$Ph), 3.05 (s, 3H, NCH_3), 2.98 (m, 1H, H-6), 2.81 (td, J = 12.5 Hz, J = 3.5 Hz, 1H, H-7), 2.53 (dd, J = 16 Hz, J = 2 Hz, 1H, H-7), 0.88 (s, 3H, 3 × H-1′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.41, 163.41, 148.07, 146.95, 135.01, 130.20, 129.28, 128.77, 127.53, 126.59, 111.28, 110.91, 63.28, 62.14, 55.87, 55.76, 37.23, 36.75, 33.78, 29.53, 28.51; ESI (+) *m*/*z* (%): 417 $[M+Na]^+$ (100).

The minor diastereomer (3*S*,11b*S*)-**52b** was obtained in a very tiny amount in a form of single monocrystal, which unfortunately was destroyed during the X-ray measurements: mp 224–226 °C; X-ray data: $C_{22}H_{26}N_2O_4$, orthorhombic unit cell with a = 8.473(3), b = 13.963(3), c = 16.480(5) Å, $\alpha = \beta = \gamma = 90°$, V = 1949.7(11) Å^3, Z = 4, ρ_x = 1.344 g cm^{-3}, $F(000)$ = 840, space group $P2_12_12_1$; data collection: Kuma KM4 κ-axis diffractometer, 42 reflections with $12.6 > 2\theta > 21.8°$ were used in a least squares procedure to determine a crystal lattice, colourless crystal 0.4 × 0.4 × 0.7 mm, Mo Kα radiation, 3549 intensities measured, 3475 independent (R_{int} = 0.0157); 2188 with $I > 2\sigma(I)$; structure solution and refinement: direct methods,[34] refined using SHELXL,[35] final R and wR 0.0376 and 0.1031, respectively. There was no observable hydrogen bonding in the structure.

4.34. Preparation of (2*S*)-1-(2-oxo-propionyl)-pyrrolidine-2-carboxylic acid [2-(3,4-dimethoxy-phenyl)-ethyl]-amide 54 and (8a*S*)-2-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-hydroxy-3-methyl-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione 57

The same operation scheme as for **9** was applied to the synthesis of **54** (20 mg, 4%) and **57** (diastereomeric mixture of **57a** and **57b**) (1.5 g, 80% yield).

Analytical data for **54**: $[\alpha]_D^{23} = +11.2$ (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.74 (m, 3H, 3 × H_{arom}), 6.60 (br t, 1H, N*H*CH_2CH_2), 4.59 (dd, J = 8 Hz, J = 5 Hz, 1H, H-2), 3.89 and 3.87 (2 × s, 6H, 2 × OCH_3), 3.67–3.42 (m, 4H), 2.76 (m, 2H, $NHCH_2CH_2$), 2.17 (m, 2H, $NCH_2CH_2CH_2$), 1.96 (m, 2H, $NCH_2CH_2CH_2$), 1.52 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.30, 163.60, 163.33, 148.81, 147.51, 131.79, 120.87, 112.13, 111.18, 61.18, 55.90, 55.90, 47.41, 40.94, 35.25, 27.06, 25.10, 22.64; ESI (+) *m*/*z* (%): 371 $[M+Na]^+$ (100).

Analytical data for the enolic form of **54**: IR (film): 3300, 2950, 1670, 1510, 1250, 750; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.11 (NHCO), 157.79 (NHCO), 149.00 (*C*–OCH_3), 147.86 (*C*–OCH_3), 137.91 (C_{arom}), 130.48 (C–OH), 120.79 (C_{arom}), 112.04 (C_{arom}), 111.38 (C_{arom}), 102.70 (C-3′), 58.84 (C-2), 55.95 (OCH_3), 55.92 (OCH_3), 45.52 (NH*C*H_2CH_2), 44.57 (N*C*$H_2CH_2CH_2$), 31.92 ($NHCH_2CH_2$), 29.35 ($NCH_2CH_2CH_2$), 21.84 ($NCH_2CH_2CH_2$).

Analytical data for diastereomer (8a*S*,3*R*)-**57a**: mp 150–155 °C; $[\alpha]_D^{23} = -87.9$ (*c* 0.96, $CHCl_3$); IR (KBr): 3490, 2950, 1660, 1640, 1520, 1250, 1150, 1030; ^{1}H NMR ($CDCl_3$, 500 MHz): 6.78 (m, 3H, 3 × H_{arom}), 4.35 (m, 1H, H-8a), 4.30 (br s, 1H, exchangeable with D_2O, OH), 3.88 and 3.86 (2 × s, 6H, 2 × OCH_3), 3.81 (m, 1H, N*C*H_2CH_2), 3.61–3.48 (m, 3H), 2.87 (m, 1H, NCH_2CH_2), 2.82 (m, 1H, NCH_2CH_2), 2.01 (m, 2H, 2 × H-8), 1.86 (m, 2H, 2 × H-7), 1.82 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.23, 165.16, 149.01, 147.74, 131.47, 120.67, 112.03, 111.30, 85.08, 58.64, 55.91, 55.91, 45.76, 44.44, 34.97, 29.18, 23.28, 22.33; X-ray data: $C_{18}H_{24}N_2O_5$, orthorhombic $P2_12_12_1$, a = 10.272(8), b = 14.404(12), c = 23.39(2) Å, $\alpha = \beta = \gamma = 90°$, V = 3460(5) Å^3, Z = 8, ρ_x = 1.338 g cm^{-3}, $F(000)$ = 1488; data collection: Kuma KM4 κ-axis diffractometer, 32 reflections with $12.5 > 2\theta > 23.3°$, colourless crystal 0.2 × 0.25 × 0.7 mm, Mo Kα radiation, 5849 intensities measured; 5811 independent (R_{int} = 0.0131), 1986 with $I > 2\sigma(I)$; structure solution and refinement: direct methods,[34] refined using SHELXL,[35] final R and wR 0.0395 and 0.1086, respectively. There are two independent molecules in the asymmetric unit with molecular geometric parameters differing only slightly. The planar fragments of the two molecules are inclined to each other by 19.7(2)°. Molecules A and B are interlinked by series of O–H···O hydrogen bonds. Additionally some C–H···O contacts are observed (Table 3).

Table 3. The hydrogen bonds distances (Å) and angles (°) for **57a**

D–H	H···A	D···A	<(DHA)	Bond
0.80(5)	1.98(5)	2.780(4)	173(5)	O5A–H5A···O1B[a]
0.78(5)	1.97(5)	2.744(4)	171(5)	O5B–H5B···O1A[a]
0.97	2.55	3.368(5)	142.2	C7A–H7A2···O1B[a]
0.97	2.56	3.413(5)	147.2	C7B–H7B2···O1A[a]

Symmetry operations to generate equivalent atoms:
[a] $-0.5 + x$, $1.5 - y$, $-z$.

Analytical data for diastereomer (8a*S*,3*S*)-**57b**: $[\alpha]_D^{23} = -60.6$ (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.79 (m, 3H, $3 \times H_{arom}$), 4.75 (s, 1H, OH), 4.13 (m, 1H, H-8a), 3.88 and 3.86 ($2 \times$ s, 6H, $2 \times OCH_3$), 3.87 (m, 1H, NCH_2CH_2), 3.68 (m, 1H, H-6), 3.59 (m, 1H, H-6), 3.45 (m, 1H, NCH_2CH_2), 2.83 (m, 2H, NCH_2CH_2), 2.48 (m, 1H, H-8), 2.08 (m, 2H), 1.95 (m, 1H), 1.52 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.42, 166.17, 148.79, 147.50, 131.80, 120.86, 112.12, 111.17, 83.08, 59.72, 55.90, 55.85, 46.20, 43.16, 35.66, 29.49, 25.09, 22.62.

4.35. Preparation of (2*S*)-1-(3-benzo[1,3]dioxol-5-yl-2-oxo-propionyl)-pyrrolidine-2-carboxylic acid [2-(3,4-dimethoxy-phenyl)-ethyl]-amide 55 and (8a*S*)-3-benzo-[1,3]dioxol-5-ylmethyl-2-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-hydroxy-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione 58

A conversion of amide **53** (372 mg, 1.3 mmol) into product **55** (126 mg, 21%) and **58** (379 mg, 62%) proceeded analogously to the formation of **9**.

Analytical data for **55**: ^1H NMR ($CDCl_3$, 500 MHz): δ 6.75 (m, 4H, $4 \times H_{arom}$), 6.67 (d, $J = 1$ Hz, 1H, H_{arom}), 6.50 (dd, $J = 8$ Hz, $J = 1$ Hz, 1H, H_{arom}), 5.89 (m, 2H, OCH_2O), 5.61 (br t, 1H, exchangeable with D_2O, 1H, $NHCH_2CH_2$), 4.98 and 4.23 (q_{AB}, $J = 16.0$ Hz, 2H, $CH_2Ph(OCH_2O)$), 4.46 (m, 1H, H-2), 3.89 and 3.85 ($2 \times$ s, 6H, $2 \times OCH_3$), 3.61 (t, $J = 7$ Hz, 1H, $NHCH_2CH_2$), 3.55–3.30 (m, 3H), 2.88 (m, 1H, $NHCH_2CH_2$), 2.75 (m, 1H, $NHCH_2CH_2$), 2.01 (m, 2H, $NCH_2CH_2CH_2$), 1.81 (m, 2H, $NCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.59, 171.22, 163.91, 149.04, 148.05, 147.63, 147.05, 131.28, 126.42, 123.19, 112.07, 111.31, 110.40, 110.04, 108.07, 101.18, 61.16, 55.87, 47.27, 44.92, 40.95, 35.18, 27.15, 22.27; ESI (+) *m*/*z* (%): 491 $[M+Na]^+$ (100).

Analytical data for **58**: $[\alpha]_D^{23} = -78.6$ (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.80 (s, 3H, $3 \times H_{arom}$), 6.71 (d, $J = 8$ Hz, 1H, H_{arom}), 6.59 (d, $J = 1$ Hz, 1H, H_{arom}), 6.53 (dd, $J = 8$ Hz, $J = 1$ Hz, 1H, H_{arom}), 5.94 (s, 2H, OCH_2O), 4.75 (br s, 1H, exchangeable with D_2O, OH), 4.12 (q, $J = 7.5$ Hz, 1H, H-8a), 3.89 and 3.86 ($2 \times$ s, 6H, $2 \times OCH_3$), 3.67 (m, 1H, NCH_2CH_2), 3.47 and 3.45 (q_{AB}, $J = 7$ Hz, 2H, $CH_2Ph(OCH_2O)$), 3.46 (m, 1H, H-6), 3.33 (td, $J = 11.0$ Hz, $J = 5.0$ Hz, 1H, NCH_2CH_2), 3.01 (m, 1H, H-6), 2.89 (m, 1H, NCH_2CH_2), 2.78 (m, 1H, NCH_2CH_2), 2.29 (m, 1H, H-8), 2.00 (m, 1H, H-8), 1.83 (m, 2H, $2 \times$ H-7); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.20, 165.89, 148.84, 147.71, 147.54, 147.19, 131.85, 127.03, 123.51, 120.91, 112.19, 111.20, 110.50, 108.34, 101.14, 86.34, 59.35, 55.84, 45.65, 45.03, 44.07, 36.68, 29.64, 22.13.

4.36. Preparation of (8a*S*)-2-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-hydroxy-3-(4-methoxy-benzyl)-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione 59

In the same preparation scheme as presented for **9** amide **53** underwent a reaction with (4′-methoxy)-phenylpyruvic acid (270 mg, 1.4 mmol) affording predominantly compound **59** (66 mg, 11%; only a slight amount of **56** was present in the crude reaction mixture and therefore it was impossible to isolate it for characterization); $[\alpha]_D^{23} = -61.1$ (*c* 0.96, $CHCl_3$); IR (film): 3400, 3000, 1650, 1520, 1250; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.99 (m, 2H, $2 \times H_{arom}$), 6.87–6.73 (m, 5H, $5 \times H_{arom}$), 4.61 (very br s, 1H, OH), 3.95 (m, 2H), 3.89 and 3.87 and 3.78 ($3 \times$ s, 9H, $3 \times OCH_3$), 3.65 (m, 1H, H-6), 3.39 (m, 2H), 3.10 and 3.03 (q_{AB}, $J = 14$ Hz, 2H, CH_2PhOCH_3), 2.91 (td, $J = 12.0$ Hz, $J = 5.5$ Hz, 1H, NCH_2CH_2), 2.81 (td, $J = 11.5$ Hz, $J = 5.5$ Hz, 1H, NCH_2CH_2), 2.20 (m, 1H, H-8), 1.96 (m, 1H, H-8), 1.75 (m, 2H, $2 \times$ H-7); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.26, 165.84, 159.22, 148.85, 147.53, 131.93, 131.36, 125.45, 120.90, 113.88, 112.18, 111.21, 86.64, 59.11, 55.88, 55.87, 55.26, 45.46, 44.66, 44.14, 35.69, 29.59, 21.94; ESI (+) *m*/*z* (%): 455 $[M+H]^+$ (38), 477 $[M+Na]^+$ (20); ESI (−) *m*/*z* (%): 453 $[M-H]^-$ (100).

4.37. Preparation of (8a*S*,13a*S*) and (8a*S*,13a*R*)-13a-methyl-2,3-dimethoxy-5,8a,9,10,11,13a-hexahydro-8*H*-pyrrolo[1′,2′:4,5]pyrazino[2,1-*a*]isoquinoline-8,13(6*H*)-dione, 60a and 60b

The compounds **54** and **57** (100 mg, 0.3 mmol) were converted into a diastereomeric mixture of diketopiperazines **60a** and **60b** (50 mg, 53%, dr of 78:22, 67:33, 75:25, respectively) under acidic conditions (ethyl acetate/HCl, dichloromethane/HCl, methanol/HCl, 50 mL each) accordingly to the procedure described for **22a**.

The major diastereomer (8a*S*,13a*S*)-**60a**: $[\alpha]_D^{23} = +106.9$ (*c* 1.06, $CHCl_3$); IR (film): 2990, 1650, 1500, 1250; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28 (s, 1H, H-1), 6.57 (s, 1H, H-4), 4.83 (m, 1H, H-8a), 3.87 (m, 1H, H-6), 3.86 and 3.84 ($2 \times$ s, 6H, $2 \times OCH_3$), 3.54 (m, 1H, H-6), 3.40 (m, 1H, H-11), 3.14 (m, 1H, H-11), 2.64 (dd, $J = 17$ Hz, $J = 5.5$ Hz, 2H, $2 \times$ H-5), 2.46 (m, 1H, H-9), 2.04 (m, 1H, H-9), 1.96 (m, 1H, H-10), 1.94 (s, 3H, CH_3), 1.86 (m, 1H, H-10); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.90, 165.63, 148.57, 147.42, 129.51, 125.24, 112.14, 107.94, 64.40, 58.71, 56.13, 56.02, 46.19, 37.29, 30.40, 29.91, 26.67, 21.78; ESI (+) *m*/*z* (%): 353 $[M+Na]^+$ (100).

The minor diastereomer (8a*S*,13a*R*)-**60b**: mp 194–195 °C; $[\alpha]_D^{23} = -86.6$ (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (s, 1H, H-1), 6.55 (s, 1H, H-4), 4.88 (m, 1H, H-8a), 4.22 (dd, $J = 9.5$ Hz, $J = 6.5$ Hz, 1H, H-6), 3.94 and 3.86 ($2 \times$ s, 6H, $2 \times OCH_3$), 3.61 (m, 1H, H-6), 2.86 (m, 2H, $2 \times$ H-11), 2.66 (m, 1H, H-5), 2.52 (m, 1H, H-5), 2.04 (m, 2H, $2 \times$ H-9), 1.93 (m, $2 \times$ H-10), 1.82

(s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.40, 166.57, 148.29, 146.70, 127.31, 126.55, 114.09, 110.41, 63.05, 58.74, 56.16, 55.83, 46.43, 36.87, 30.00, 29.09, 26.50, 22.14; X-ray data: $C_{18}H_{22}N_2O_4$, orthorhombic $P2_12_12_1$, a = 10.142(4), b = 12.484(3), c = 13.041(6) Å, $\alpha = \beta = \gamma = 90°$, V = 1651.2(10) Å^3, $Z = 4$, ρ_x = 1.329 g cm^{-3}, $F(000) = 704$; data collection: Kuma KM4 κ-axis diffractometer, 54 reflections with $12.0 > 2\theta > 26.3°$, colourless crystal of dimensions $0.6 \times 0.6 \times 0.4$ mm, 5488 intensities measured, 4848 independent (R_{int} = 0.0756), 3518 with $I > 2\sigma(I)$; structure solution and refinement: direct methods,[34] refined using SHELXL,[35] final R and wR 0.0376 and 0.1098, respectively. There was no observable hydrogen bonding in the structure.

4.38. Preparation of (8a*S*,13a*S*) and (8a*S*,13a*R*)-13a-([1,3]dioxol-benzyl)-2,3-dimethoxy-5,8a,9,10,11,13a-hexahydro-8*H*-pyrrolo[1′,2′:4,5]pyrazino[2,1-*a*]isoquinoline-8,13(6*H*)-dione 61a and 61b

The same as above Pictet–Spengler reaction was applied to compounds **55** and **58** (42 mg, 0.09 mmol) in order to obtain the diketopiperazines **61a** and **61b** (16 mg, 40%). Depending on the solvent used, the diastereomeric ratio was of 75:25 (50 mL of MeOH/HCl), 75:25 (50 mL of AcOEt/HCl) and 99.9:0.1 (5.0 mL of 5% $BF_3{\cdot}Et_2O$ in Et_2O).

The major diastereomer (8a*S*,13a*S*)-**61a**: $[\alpha]_D^{23} = +41.6$ (c 0.99, $CHCl_3$); IR (film): 3300, 3050, 2950, 1650, 1500, 1250, 1050; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.84 (s, 1H, H-1), 6.72 (d, J = 1.5 Hz, 1H, H_{arom}), 6.58 (dd, J = 8 Hz, J = 1.5 Hz, 1H, H_{arom}), 6.55 (s, 1H, H-4), 6.10 (d, J = 1.5 Hz, 1H, H_{arom}), 5.95 and 5.94 (q_{AB}, J = 1 Hz, 2H, OCH_2O), 4.96 (m, 1H, H-8a), 4.00 and 3.87 (2 × s, 6H, 2 × OCH_3), 3.84 (m, 1H, H-6), 3.71 (m, 1H, H-11), 3.57 (m, 1H, H-6), 3.48 and 3.27 (q_{AB}, J = 14.0 Hz, 2H, $CH_2Ph(OCH_2O)$), 3.38 (m, 1H, H-11), 2.74 (m, 2H, 2 × H-5), 2.23 (m, 1H, H-9), 1.89 (m, 1H, H-9), 1.67 (m, 2H, 2 × H-10); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.65, 165.40, 148.36, 147.73, 147.29, 146.73, 128.48, 128.07, 126.52, 123.74, 113.87, 110.69, 110.59, 108.32, 101.14, 68.10, 57.93, 56.18, 55.83, 46.48, 45.51, 36.97, 29.84, 29.28, 21.24; ESI (+) m/z (%): 473 $[M+Na]^+$ (100).

4.39. Preparation of (8a*S*,13a*S*)-13a-(4-methoxy-benzyl)-2,3-dimethoxy-5,8a,9,10,11,13a-hexahydro-8*H*-pyrrolo-[1′,2′:4,5]pyrazino[2,1-*a*]isoquinoline-8,13(6*H*)-dione 62a

The condensation step of **59** (53 mg, 0.12 mmol) proceeded analogously to the procedure applied for **22a**. Dissolving hydroxylactam **59** in 50 mL of AcOEt saturated with HCl afforded the isoquinoline derivative **62** (5.5 mg, 11%) as a single diastereomer **62a**; $[\alpha]_D^{23} = +75.6$ (c 0.97, $CHCl_3$); IR (film): 2900, 1650, 1520, 1250, 1040; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.87 (s, 1H, H-1), 7.04 (m, 2H, 2 × H_{arom}), 6.81 (m, 2H, 2 × H_{arom}), 6.56 (s, 1H, H-4), 4.98 (m, 1H, H-8a), 4.10 (m, 1H, H-6), 4.01 and 3.87 and 3.79 (3 × s, 9H, 3 × OCH_3), 3.56 (m, 1H, H-6), 3.53 and 3.29 (q_{AB}, J = 15.5 Hz, 2H, CH_2PhOCH_3), 2.85 (m, 2H, 2 × H-11), 2.62 (m, 1H, H-5), 2.47 (dd, J = 11 Hz, J = 6 Hz, 1H, H-5), 2.17 (m, 1H, H-9), 1.86 (m, 1H, H-9), 1.70 (m, 1H, H-10), 1.60 (m, 1H, H-10); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.77, 165.38, 159.35, 149.70, 148.30, 131.52, 128.01, 126.86, 126.69, 113.92, 113.82, 110.65, 68.19, 57.77, 56.18, 55.82, 55.29, 46.10, 45.42, 36.87, 29.78, 29.34, 21.13; ESI (+) m/z (%): 437 $[M+H]^+$ (100); ESI (+) (+NaOAc) m/z (%): 459 $[M+Na]^+$ (100).

CCDC-251687 **25a**, CCDC-251689 **39b**, CCDC-251690 **52b**, CCDC-251691 **57a** and CCDC-252557 **60b**, contain the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

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