Diastereoselective Synthesis of 1-Benzyltetrahydroisoquinoline Derivatives from Amino Acids by 1,4 Chirality Transfer[‡]

Anna Zawadzka,[a] Andrzej Leniewski,[a] Jan K. Maurin,[b,c] Krystyna Wojtasiewicz,[a] Aleksandra Siwicka,[a] Dariusz Blachut,[a] and Zbigniew Czarnocki*[a]

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L-Amino acids (L-Ala, L-Phe, L-Val, L-Pro) were used as a source of chirality in the diastereoselective synthesis of tetrahydroisoquinoline derivatives. The key step was the Pictet–Spengler condensation of ketoamides **4** and **10**, which proceeded under very mild conditions. L-Ala, L-Phe and L-Val gave rise the *R*-configuration at the newly formed stereogenic center. Surprisingly, L-Pro gave the opposite result. The stereochemistry of **6d** and **12a** were established on the basis of X-ray crystallographic data.

Introduction

Notable developments in the stereocontrolled synthesis of tetrahydroisoquinolines and related systems have been observed within the last two decades. Because of their wide distribution and significant biological activities, tetrahydroisoquinolines have received considerable attention.[1−3]

Because of appreciable stereodiscrimination of organic compounds in living systems, the physiological activity of tetrahydroisoquinolines depends on their stereochemistry, especially at the C-1 carbon atom. Tetrahydroisoquinolines that have a reactive substituent at this position are valuable substrates for the synthesis of many isoquinoline alkaloids.[4,5] The need for asymmetric induction at the C-1 carbon atom in the isoquinoline system was inspired, at least partially, by requirements of the pharmaceutical industry together with the parallel development of modern methodologies.

Several methods of stereoselective synthesis of these compounds, using chiral building blocks, auxiliaries or reagents, have been reported, mainly in the asymmetric Pictet−Spengler cyclization,[6−10] Bischler−Napieralski reactions,[11−13] as well as other[14−19] methods.

Recently, the main interest has been focused on the use of naturally occurring compounds in the stereoselective syntheses. Amino acids and their derivatives have been found to be efficient chiral inductors and therefore are used often in the synthesis of chiral, enantiomerically enriched heterocycles.[20−24]

Interesting applications of amino acids and their derivatives in the synthesis of tetrahydroisoquinoline and β-carboline alkaloids and related systems have recently appeared in the literature.

Itoh et al. used L-alanine derivatives as chiral auxiliaries in the asymmetric addition of nucleophiles to the C-1 position of isoquinolines.[25] They also reported the use of a chiral auxiliary derived from L-proline for the preparation of both enantiomers of 1-allyl-1,2,3,4-tetrahydro-β-carboline.[26]

Waldmann et al.[27] showed that readily available amino acid esters could be applied as efficient chiral auxiliary groups in the asymmetric Pictet−Spengler reactions that gave tetrahydro-β-carbolines with high diastereoselectivity. The chiral induction derived from several *N*-alkylated amino acid esters (L-alanine, L-valine, L-leucine and L-isoleucine) was elaborated under the conditions of Pictet−Spengler condensation. It was found that increasing the size of the amino acid side chain had a positive effect on the diastereoselectivity of the process.[27]

In our laboratory we have already used some amino acids as chiral inductors in the diastereoselective synthesis of 1-substituted tetrahydroisoquinoline derivatives.[28,29] Here we report our detailed results obtained when selected L-amino acids were applied as starting materials in the stereocontrolled synthesis of benzyltetrahydroisoquinoline derivatives.

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[a] Faculty of Chemistry, Warsaw University, Pasteur St. 1, 02-093, Warsaw, Poland
E-mail: czarnoz@chem.uw.edu.pl
[b] National Institute of Public Health, Chelmska 30/34, 00-750, Warsaw, Poland
[c] Institute of Atomic Energy, 05-400, Otwock-Swierk, Poland

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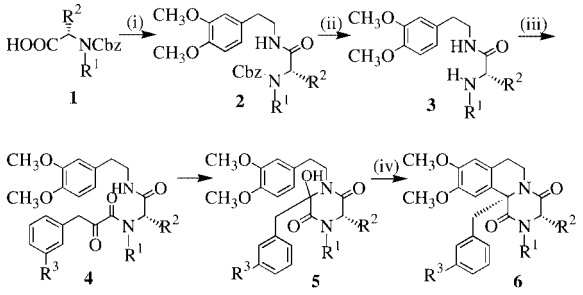
Results and Discussion

The work presented here was influenced by Lawton's concept[30] of the role of the peptide chain in the biosynthesis of isoquinoline alkaloids. Although the full details of this communication have never been published, the idea still seems to be a very attractive one since the role of the chirality induction by amino acids (peptides) is obvious and many modern synthetic approaches try to mimic biological conditions. Probably the most fruitful and effective methods are based on the chemistry of *N*-acyliminium ions, which were introduced by Speckamp[31] and have been widely applied in different areas of synthetic organic chemistry,[32] including stereocontolled transformations towards chiral, non-racemic tetrahydroisoquinolines and related systems.[33,34]

During the reinvestigation of this "achiral" approach,[30] we found that amide **3a** (Scheme 1) could be prepared efficiently from 2-(3,4-dimethoxyphenyl)ethylamine when blocked sarcosine **1a** was used as a starting compound in a BOP-mediated coupling.[35]



(i) 2-(3,4-dimethoxyphenyl)ethylamine, Et_3N, BOP; (ii) H_2, Pd/C; (iii) arylpyruvic acid, Et_3N, BOP; (iv) HCl, MeOH

	1-3a	1-3b	1-3c	1-3d	1-3e	1-3f	1-3g	1-3h	1-3i
R^1	CH_3	H	CH_3	CH_3	H	CH_3	CH_3	H	CH_3
R^2	H	CH_3	CH_3	CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_2Ph	CH_2Ph

	4-6a	4-6b	4-6c	4-6d	4-6e	4-6f	4-6g	4-6h	4-6i
R^1	CH_3	H	CH_3	CH_3	H	CH_3	CH_3	H	CH_3
R^2	H	CH_3	CH_3	CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_2Ph	CH_2Ph
R^3	H	H	H	Cl	H	H	Cl	H	H

Scheme 1

Treatment of **3a** with 1 equiv. of 2-oxo-3-phenylpropanoic acid, again in the presence of BOP reagent, gave directly the hydroxylactam derivative **5a** in 70% yield (yields for all products are given in Table 1). Despite prolonged efforts, we were unable to isolate ketoamide **4a** in this reaction sequence. Compound **5a** underwent a facile Pictet–Spengler-type condensation with methanolic hydrogen chloride at 0 °C, affording a diketopiperazine derivative **6a** almost quantitatively. In the chemistry of isoquinolines, such an easy cyclization of non-phenolic derivatives is quite rare and, thus, this reaction provides further evidence for the significant influence of the peptide-like moiety in this process.

Table 1. Chemical yields of all products obtained

	2	3	4	5	6	8	9	10	11	12
a	50%	100%	–	70%	100%	93%	78%	68%	6.2%	60%
b	95%	76%	54%	–	–	–	–	65%	–	51%
c	100%	69%	51%	11%	77%	–	–	–	–	–
d	–	–	48%	–	51%	–	–	–	–	–
e	100%	69%	65%	–	–	–	–	–	–	–
f	97%	85%	51%	–	89%	–	–	–	–	–
g	–	–	48%	–	57%	–	–	–	–	–
h	75%	97%	55%	–	–	–	–	–	–	–
i	95%	83.6%	55%	–	92%	–	–	–	–	–

These preliminary results prompted us to investigate the stereocontrolled Pictet–Spengler-type condensation and the chiral induction at the C-11b[36] carbon atoms in the formation of compounds **6c**, **6d**, **6f**, **6g** and **6i**.

Thus, the analogous reaction sequences were carried out using protected L-alanine **1b**, *N*-methyl-L-alanine **1c**, L-valine **1e**, *N*-methyl-L-valine **1f**, L-phenylalanine **1h** and *N*-methyl-L-phenylalanine **1i**. Condensation with 2-(3,4-dimethoxyphenyl)ethylamine and subsequent deblocking of the nitrogen atom under hydrogenolytic conditions (H_2, Pd/C), afforded amides **3b–i** in good chemical yields.

Treatment of the amides **3b–i** with arylpyruvic acids in the presence of BOP reagent[35] gave isolable ketoamides **4b–i**, which is in contrast to the earlier findings when sarcosine was employed.

The Pictet–Spengler condensation on amides **4b–i** gave interesting results. When L-Ala **1b**, L-Val **1e** and L-Phe **1h** were used as chiral inductors, no cyclization products of the appropriate ketoamides **4b**, **4e** and **4h** were formed, probably because the cyclization step is disfavored by a partial or complete enolization that precludes cyclization for either geometric or deactivation reasons.[37]

In the contrary, good results were obtained when *N*-methyl-L-alanine was used as a chiral inductor. Amide **3c**, coupled with phenylpyruvic acid, gave diketoamide **4c** in good yield. Subsequent treatment of **4c** with hydrogen chloride in dry methanol at 0 °C promoted the Pictet–Spengler cyclization and afforded **6c** as the mixture of diastereoisomers in an 87:13 ratio, which was indicated by the ^1H NMR spectroscopic analysis of the crude reaction mixture. Although both diastereoisomers of **6c** could be separated chromatographically, we were unable to obtain a single crystal suitable for an X-ray crystallography study. To establish the stereochemistry of the newly formed chiral center at C-11b, amide **3c** was reacted with *m*-chlorophenylpyruvic acid to form a product that might have better crystallization properties. The analogous reaction sequence yielded diastereoisomers (3*S*,11b*R*)-**6d** and (3*S*,11b*S*)-**6d** with surprisingly high selectivity (99.7:0.3, based on ^1H NMR spectroscopy). A single crystal of the dominant component was subjected to an X-ray crystallographic analysis, which indicated the *R* configuration at the C-11b carbon atom (Figure 1).

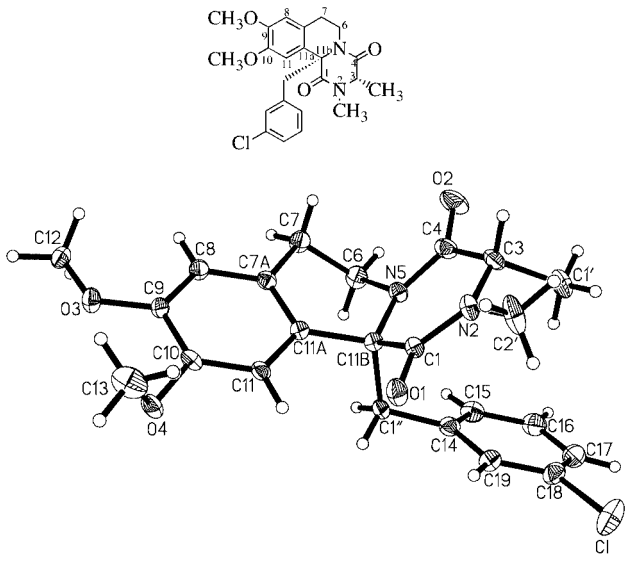


Figure 1. The structure and ORTEP diagram of compound (3*S*,11b*R*)-**6d**

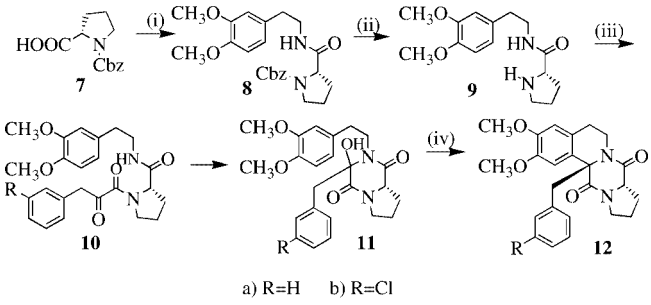
Similar results were obtained when *N*-methyl-L-valine was used as a chiral inductor. Amide **3f** was isolated in 85% yield with no observable racemization.[38] Subsequent coupling with arylpyruvic acids and the Pictet−Spengler cyclization at 0 °C afforded the final derivatives **6f** (89%) and **6g** (57%) as single diastereoisomers.

Finally, compound **4i** underwent efficient stereocontrolled Pictet−Spengler-type condensation with methanolic hydrogen chloride, giving two diastereoisomers of **6i** in a ratio of 89:11 in 92% chemical yield.

All the predominant diastereoisomers **6c**, **6d**, **6f**, **6g** and **6i** seem to bear the same sense of chirality as was proved to exist for **6d**. This conclusion can be drawn from the comparison of ^{1}H NMR spectra for each diastereoisomer. In the (3*S*,11b*R*) series, **6c**, **6d**, **6f**, **6g** and **6i** display more profound deshielding effects for H-11 than in the respective (3*S*,11b*S*) series.

Also, the sign of the optical rotation seems to follow the above suggestions for the same sense of chirality in all the major diastereoisomers, but obviously this feature is only indicative. Completely unexpected results were obtained when L-proline was used as a chiral synthon. In the analogous reaction sequence, amide **9a** was formed in 78% yield (Scheme 2).

Further coupling with phenylpyruvic acid and *m*-chlorophenylpyruvic acid gave **10a** and **10b**, respectively, as relatively unstable compounds. Their instability appeared to be due partially to facile condensation to the intermediate hydroxy compounds **11a** and **11b**, respectively, which, in turn underwent acid-catalyzed Pictet−Spengler condensation to yield the final diketopiperazines **12a** and **12b**, both as mixtures of diastereoisomers (ca. 95:5). The single-crystal X-ray crystallographic analysis of the major component of **12a** revealed, surprisingly, the *S* configuration at the newly formed chiral center at C-13a[39] (Figure 2).



a) R=H b) R=Cl

(i) 2-(3,4-dimethoxyphenyl)ethylamine, Et_3N, BOP; (ii) H_2, Pd/C; (iii) arylpyruvic acid, Et_3N, BOP; (iv) HCl, MeOH

Scheme 2

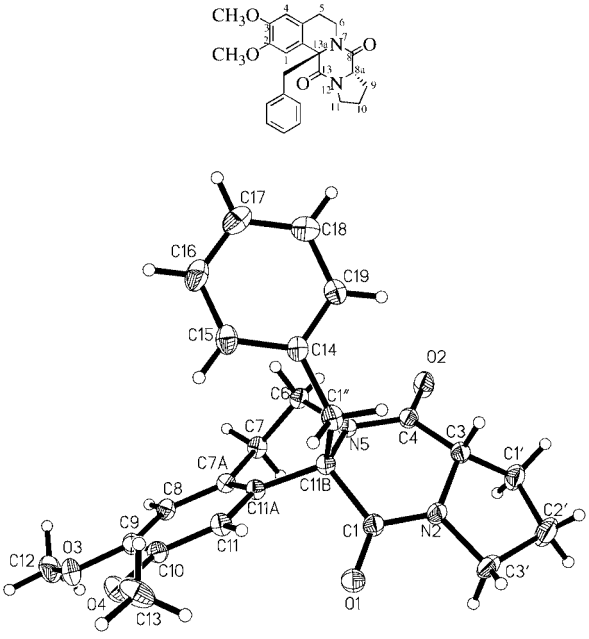
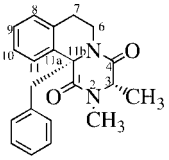


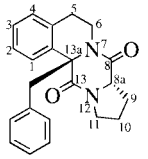
Figure 2. The structure and ORTEP diagram of compound (8a*S*,13a*S*)-**12a**.

The unexpected results for the condensation step (iv), in which the L-proline-derived sequence led to the prevalence of the *S* diastereoisomer whereas an opposite tendency was observed for all other products derived from L-amino acids, asked for some rationale. We thought that quantum mechanical methods might give us some useful hints in this regard. It appears reasonable to assume that the Pictet−Spengler cyclization occurs via *N*-acyliminium ions derived from structures **5** or **11** and is kinetically controlled by the energy differences of the appropriate transition states or intermediates.[40] Since their exact configuration and conformation could not be designated easily, we decided, with some discomfort, to concentrate first on the thermodynamic properties of the products. Thus, model compounds were studied using molecular mechanical, semi-empirical and finally ab initio methods. Sets of compounds (Figure 3) were built on the basis of the molecular structures of (3*S*,11b*R*)-**6d** and (8a*S*,13a*S*)-**12a** obtained from

the X-ray crystallography studies, but by replacing methoxyl groups and chlorine atom with hydrogen atoms to save on computation time.

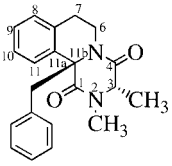


(3*S*, 11b*R*)-**6d'**

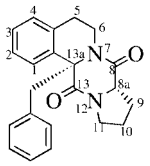


(8a*S*, 13a*S*)-**12a'**

Figure 3. Model compounds (3*S*,11b*R*)-**6d′** and (8a*S*,13a*S*)-**12a′**



(3*S*, 11b*S*)-**6d'**



(8a*S*, 13a*R*)-**12a'**

Figure 4. Model compounds (3*S*,11b*S*)-**6d′** and (8a*S*,13a*R*)-**12a′**

The conformational analysis using molecular mechanics was performed for two pairs of compounds, (3*S*,11b*R*)-**6d′**/(3*S*,11b*S*)-**6d′** and (8a*S*,13a*S*)-**12a′**/(8a*S*,13a*R*)-**12a′** (Figure 3 and 4), after initial semi-empirical optimization. Then, the final optimization of the structure of the lowest-energy conformer for either compound was performed using ab initio quantum chemical methods. The Hartree−Fock method was applied with the standard 6−31G** basis set.

For the model compounds (3*S*,11b*R*)-**6d′** and (3*S*,11b*S*)-**6d′**, the calculated total energies (−1066.73981696 and −1066.73245403 e.u.,[41] respectively) differed by only −4.62 kcal/mol, showing that compound (3*S*,11b*R*)-**6d′** is energetically more stable than its diastereoisomer (3*S*,11b*S*)-**6d′**. Contradictory results were obtained for the second model (proline-derived molecules), which now favored the compound (8a*S*,13a*S*)-**12a′** having the opposite configuration at the respective carbon atom. The difference in total energies for the diastereoisomers (8a*S*,13a*S*)-**12a′** and (8a*S*,13a*R*)-**12a′** (−1104.61822265 and −1104.61393160 e.u., respectively) is −2.69 kcal/mol. These variations in the stability of diastereoisomers were magnified by solute−solvent interactions. Under the influence of methanol, these preferences became of −5.80 and −5.62 kcal/mol for diastereoisomers **6d′**(3*S*,11b*S*) and **12a′**(8a*S*,13a*R*), respectively, which is in accordance with the experimental observations and might suggest possible thermodynamic control at the level of the transition state, which is apparently "product-like".

Atomic charge distributions and resultant dipole moments for all model molecules were also derived from the above calculations. Interestingly, diastereoisomers (3*S*,11b*R*)-**6d′** and (3*S*,11b*S*)-**6d′** differ significantly in their dipole moments (μ = 0.7637 and 2.0569 D, respectively), whereas there is virtually no difference for molecules (8a*S*,13a*S*)-**12a′** and (8a*S*,13a*R*)-**12a′** (μ = 1.4767 and 1.4532 D, respectively).

All the results shown above, including the unambiguous assignments of the stereochemistries of compounds **6d** and **12a**, clearly indicate that our first hypothesis[30] were incorrect with regard to the configuration at the C-11b carbon atoms in diketopiperazines derived from acyclic amino acids (Val, Phe). Therefore, direct extension of the stereochemical outcome of the process that utilizes substrates that may appear similar (e.g., a series of L-amino acids) can lead to a severe error in judgment. Nevertheless, we stress that the different chirality induction in the Pictet−Spengler reaction from acyclic L-amino acids and L-proline makes our approach "enantiodivergent-like" and, therefore, more attractive from the point of view of stereocontrolled synthesis.

Experimental Section

NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR spectroscopy. Tetramethylsilane (TMS) or solvents were used as internal standards. Chemical shifts are reported in ppm. Coupling constants (*J*) are reported in hertz and multiplicities are represented as s = singlet, d = doublet, t = triplet and q = quadruplet. Mass spectra were collected on an AMD 604 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 a UV hand lamp and iodine vapor. Column chromatography was carried out at atmospheric pressure using silica gel (230−400 or under 400 mesh, Merck). X-ray crystallographic intensity data for (3*S*,11b*R*)-**6d** and (8a*S*,13a*S*)-**12a** were measured at *T* = 293 K on a Kuma KM4 diffractometer with Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods from *SHELXS-97*[42]and refined by using the *SHELXL-97* software.[43]

Benzyl 2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-2-oxoethyl(methyl)carbamate (2a): 2-(3,4-Dimethoxyphenyl)ethylamine (2.76 g, 15.2 mmol) and triethylamine (3.38 mL, 30.45 mmol) were added to a solution of Cbz-sarcosine **1a** (3.4 g, 15.2 mmol) in dry THF (100 mL). BOP (7.42 g, 16.75 mmol) was introduced to the resultant mixture, stirring was continued for 2 h and then the mixture was left at room temperature overnight. After evaporation of the THF, the residue was dissolved in chloroform (100 mL), washed with saturated sodium chloride solution (2 × 20 mL) and water (20 mL). The organic phase was then dried ($MgSO_4$) and the solvent was evaporated to give a white crystalline product, which was then purified, by chromatography on silica gel. Elution with 2% (v/v) methanol in chloroform gave compound **2a** (2.85 g 50%): m.p. 108 °C. IR (KBr): $\tilde{\nu}$ = 3330, 2825−3075, 1690, 1675, 1520, 1260, 1240, 1160 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$); two stable rotamers are visible: δ = 7.39−7.28 (m, 5 H, H_{arom}), 6.79−6.62 (m, 3 H, H_{arom}), 6.20 and 5.97 (two br. s, 1 H, NH), 5.12 (br. s, 2 H, PhCH_2), 3.86 and 3.88 (two s, 3 H each, 2 × OCH_3), 3.82 (s, 2 H, CH_2CO), 3.48 (br. s, 2 H, NHCH_2CH_2), 2.92 (br. s, 3 H, NCH_3), 2.74 and 2.68 (two br. s, 1 H each, NHCH_2CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 156.9, 149.0, 147.7, 136.2, 131.1, 128.2, 128.5, 127.9, 120.6, 111.8, 111.3, 67.6, 55.9, 55.8, 53.4, 40.6, 35.5, 35.1 ppm. LSIMS (+) (*M* = 386.44 for $C_{21}H_{26}N_2O_5$): *m/z* (%) = 773 $[2M + H]^+$ (4), 409 $[M + Na]^+$ (23), 387 $[M + H]^+$ (70), 343 (33), 279 (6), 255 (6), 225 (9), 164 (97), 97 (31).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(methylamino)acetamide (3a):** Concd. HCl (3 mL) was added to a solution of compound **2a** (2.0 g, 5.18 mmol) in ethanol (200 mL). The resulting solution was then hydrogenated over palladium-on-charcoal catalyst (0.2 g) at 50 °C for 2 h with vigorous stirring. After completion of the reaction, the catalyst was removed by filtration through Celite. The solvent was evaporated and the residue was taken up into saturated sodium bicarbonate solution and extracted with chloroform. Drying ($MgSO_4$) and evaporation afforded compound **3a** as a yellow-orange oil in quantitative yield (1.3 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (br. s, 1 H, exchangeable with D_2O, N*H*CH_2CH_2), 6.84−6.72 (m, 3 H, H_{arom}), 3.88 and 3.87 (two s, 3 H each, 2 × OCH_3), 3.53 (app q, 2 H, *J* = 6.4 Hz, NHC*H*$_2$$CH_2$), 3.21 (s, 2 H, C*H*$_2$CO), 2.79 (t, *J* = 7.0 Hz, 2 H, NHCH_2C*H*$_2$), 2.35 (s, 3 H, NCH_3), 1.69 (s, 1 H, exchangeable with D_2O, N*H*CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 148.9, 147.6, 131.5, 120.6, 111.9, 111.3, 55.9, 55.8, 54.6, 40.2, 36.7, 35.4 ppm. *M* = 252.31 for $C_{13}H_{20}N_2O_3$.

3-Benzyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxy-1-methylpiperazine-2,5-dione (5a): Despite prolonged efforts, we were unable to isolate the ketoamide **4a**. Compound **3a** was directly converted into **5a**. Thus, compound **3a** (0.85 g, 3.38 mmol) was introduced to a stirred solution of phenylpyruvic acid (0.55 g, 3.38 mmol) in dry THF (20 mL) and then Et_3N (0.75 mL, 6.76 mmol) and BOP (1.65 g, 3.72 mmol) were added at room temperature. After 2 h of stirring, the mixture was left overnight. The solvent was evaporated in vacuo and the residue was dissolved in dichloromethane (10 mL) and washed with a solution of saturated sodium chloride and water. The organic phase was dried ($MgSO_4$) and the solvent was evaporated giving a yellow oil, which was purified by chromatography on silica gel using 2% (v/v) methanol in chloroform to give white crystals of **5a** (942 mg, 70%): m.p. 86−88 °C. IR (KBr): $\tilde{\nu}$ = 3200, 2830−3100, 1650, 1520, 1460 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29 (m, 3 H, H_{arom}), 7.02 (m, 2 H, H_{arom}), 6.85 (m, 3 H, H_{arom}), 4.06 (m, 1 H, NC$H_2$$CH_2$), 3.91 and 3.88 (two s, 3 H each, 2 × OCH_3), 3.47 (m, 1 H, NC$H_2$$CH_2$), 3.38 ($d_{AB}$, 1 H, *J* = 17.6 Hz, N($CH_3$)C*H*$_2$), 3.18 ($d_{AB}$, 1 H, *J* = 13.7 Hz, PhC*H*$_2$), 3.14 (d_{AB}, 1 H, *J* = 13.7 Hz, PhC*H*$_2$), 2.95 (m, 2 H, NCH_2C*H*$_2$), 2.80 (s, 3 H, NCH_3), 2.18 (d_{AB}, 1 H, *J* = 17.6 Hz, N(CH_3)C*H*$_2$), 1.9 (br. s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 162.7, 148.9, 147.6, 133.4, 131.8, 130.1, 128.6, 128.0, 120.9, 112.2, 111.3, 85.8, 55.9, 51.1, 46.2, 44.4, 35.4, 33.3 ppm. EI-MS (*M* = 398.45 for $C_{22}H_{26}N_2O_5$): *m*/*z* = (%) 398 [M]$^+$ (10), 307 (25), 289 (28), 261 (2), 164 (100).

11b-Benzyl-9,10-dimethoxy-2-methyl-7,11b-dihydro-2*H*-pyrazino-[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6a): Acetyl chloride (1 mL) was added to ice-cooled dry methanol (30 mL) and after 15 min compound **5a** (200 mg, 0.5 mmol) was added in one portion and the mixture was left for two weeks in a refrigerator at 0 °C. The solvent was evaporated in vacuo and the residue was dissolved in chloroform (50 mL). The organic phase was washed with sodium bicarbonate solution (20 mL), water (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel. Elution with 1% (v/v) methanol in chloroform gave a white crystalline compound **6a** in quantitative yield (190 mg): m.p. 187−192 °C. IR (KBr): $\tilde{\nu}$ = 3320, 2850−3100, 1670, 1650, 1525 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, H_{arom}-11), 7.32−7.11 (m, 5 H, H_{arom}), 6.58 (s, 1 H, H_{arom}-8), 5.07 (app dt, NC$H_2$$CH_2$), 4.01 and 3.88 (two s, 3 H each, 2 × OCH_3), 3.45 and 2.35 (d_{AB}, 2 H, *J* = 17.3 Hz, H-3), 3.60 and 3.30 (d_{AB}, 2 H, *J* = 13.7 Hz, PhC*H*$_2$), 3.06 (m, 2 H, NCH_2C*H*$_2$), 2.68 (m, 1 H, NC$H_2$$CH_2$), 2.70 (s, 3 H, NCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 163.0, 148.8, 147.1, 134.9, 130.4, 128.4, 127.9, 127.6, 127.3, 112.9, 110.9, 66.6, 56.1, 55.8, 50.8, 47.7, 36.6, 34.0, 29.2 ppm. LSIMS (+) (*M* = 380.44 for $C_{22}H_{24}N_2O_4$): *m*/*z* (%) = 403 [M + Na]$^+$ (37), 381 [M + H]$^+$ (19), 199 (12), 120 (7), 105 (22), 91 (21), 81 (12).

Benzyl (1*S*)-2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-1-methyl-2-oxoethylcarbamate (2b): compound **1b** (3 g, 13.45 mmol) was converted into carbamate **2b**, following the procedure described for the synthesis of **2a**, as a white crystalline product (4.93 g, 95%): m.p. 143−145 °C. $[\alpha]_D^{23}$ = −13.9 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 3100−2830, 1690, 1650, 1550, 1530, 1520, 1260 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38−7.30 (m, 5 H, H_{arom}), 6.78 (m, 1 H, H_{arom}), 6.70 (br. s, 2 H, H_{arom}), 6.10 (br. s, 1 H, N*H*CH_2CH_2), 5.30 (br. s, 1 H, N*H*$CHCH_3$), 5.08 (q_{AB}, 2 H, *J* = 12.0 Hz, PhC*H*$_2$), 4.16 (m, 1 H, H-1), 3.86 and 3.84 (two s, 3 H each, 2 × OCH_3), 3.48 (m, 2 H, NHC$H_2$$CH_2$), 2.74 (app t, 2 H, NHC$H_2$C*H*$_2$), 1.34 (d, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 155.9, 149.0, 147.7, 136.1, 131.1, 128.6, 128.3, 128.1, 120.6, 111.8, 111.3, 67.0, 55.9, 55.8, 50.6, 40.8, 35.2, 18.6 ppm. LSIMS (+) (*M* = 386.44 for $C_{21}H_{26}N_2O_5$): *m*/*z* (%) = 409 [M + Na]$^+$ (100), 387 [M + H]$^+$ (3), 223 (7).

(2*S*)-2-Amino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (3b): The procedure described for the synthesis of **3a** was applied to **2b** (4 g, 10.4 mmol) and gave **3b** (2.0 g, 76%) as a yellow crystalline product: m.p. 48−50 °C. $[\alpha]_D^{23}$ = +7.6 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3360, 3320, 3090−2840, 1650, 1630, 1520, 1260, 1220, 1140 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (br. s, 1 H, NH, exchangeable with D_2O), 6.75 (m, 1 H, H_{arom}), 6.69 (m, 2 H, H_{arom}), 3.82 and 3.80 (two s, 3 H each, 2 × OCH_3), 3.42 (m, 2 H, NHC$H_2$$CH_2$), 2.71 (app t, 2 H, NHC$H_2$C*H*$_2$), 2.59 (d, *J* = 9.5 Hz, 1 H, H-2), 1.92 (br. s, 2 H, exchangeable with D_2O, NH_2), 1.25 (d, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7, 148.9, 147.6, 131.6, 120.7, 111.9, 111.3, 55.9, 55.8, 50.7, 40.3, 35.3, 21.8 ppm. LSIMS (+) (*M* = 252.31 for $C_{13}H_{20}N_2O_3$): *m*/*z* (%) = 275 [M + Na]$^+$ (10), 253 [M + H]$^+$ (100), 180 (13).

***N*-((1*S*)-2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-1-methyl-2-oxoethyl)-2-oxo-3-phenylpropanamide (4b):** The procedure described for the synthesis of **5a** was applied to **3b** (0.5 g, 1.98 mmol) and provided **4b** (427 mg, 54%) as a white crystalline product: m.p. 146−150 °C. $[\alpha]_D^{23}$ = −19.7 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3310, 3100−2850, 1650, 1520 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (m, 1 H, H_{arom}), 7.34−7.20 (m, 4 H, H_{arom}), 6.82−6.66 (m, 3 H, H_{arom}), 6.08 (br. s, 1 H, N*H*CH_2CH_2), 4.33 (m, 1 H, H-1), 4.16 (q_{AB}, 2 H, *J* = 16.0 Hz, PhC*H*$_2$), 3.86 and 3.83 (two s, 3 H each, 2 × OCH_3), 3.48 (m, 2 H, NHC$H_2$$CH_2$), 2.74 (m, 2 H, NHC$H_2$C*H*$_2$), 1.96 (br. s, 1 H, exchangeable with D_2O, N*H*$CHCH_3$), 1.37 (d, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 170.9, 159.6, 149.0, 147.7, 132.4, 130.9, 129.8, 128.7, 127.3, 120.6, 111.9, 111.3, 55.9, 55.8, 49.0, 43.1, 40.8, 35.0, 18.0 ppm. LSIMS (+) (*M* = 398.45 for $C_{22}H_{26}N_2O_5$): *m*/*z* (%) = 421 [M + Na]$^+$ (61), 399 [M + H]$^+$ (20), 301 (12).

Benzyl (1*S*)-2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-1-methyl-2-oxoethyl(methyl)carbamate (2c): Following the procedure described for the synthesis of **2a**, compound **1c** (2 g, 8.44 mmol) was converted into **2c** (3.38 g, 100%), which was obtained as a white crystalline product: m.p. 85−87 °C. $[\alpha]_D^{23}$ = −51.3 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3350, 3090−2825, 1675, 1520, 1330, 1260, 1230, 1170 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 5 H, H_{arom}), 6.79−6.64 (m, 3 H, H_{arom}), 5.17 (q, *J* = 4.5 Hz, 1 H, H-1), 5.12 (q_{AB}, 2 H, *J* = 12.0 Hz, PhC*H*$_2$), 4.74 (br. s, 1 H, NH), 3.86 and 3.82 (two s, 3 H each, 2 × OCH_3), 3.46 (m, 2 H, NHC$H_2$$CH_2$),

2.77 (s, 3 H, NCH_3), 2.71 (m, 2 H, $NHCH_2CH_2$), 1.33 (d, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 157.4, 149.0, 147.7, 136.3, 131.2, 128.8, 128.6, 128.5, 120.6, 111.7, 111.3, 67.7, 55.9, 55.8, 55.8, 40.7, 35.2, 27.4, 19.0 ppm. M = 400.47 for $C_{22}H_{28}N_2O_5$.

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(methylamino)-propanamide (3c): The procedure described for the synthesis of **3a** was applied to **2c** (3.38 g, 8.44 mmol) to give **3c** (1.54 g, 69%) as a white crystalline product: m.p. 77−80 °C. $[\alpha]_D^{23}$ = −6.0 (c = 1.0, $CHCl_3$). IR (KBr): ṽ = 3300, 3100, 2980−2770, 1640, 1520, 1230, 1130 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.22 (br. t, 1 H, NH), 6.82−6.72 (m, 3 H, H_{arom}), 3.87 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.51 (m, 2 H, $NHCH_2CH_2$), 3.08 (q, J = 7.0 Hz, 1 H, H-2), 2.78 (app t, 2 H, $NHCH_2CH_2$), 2.30 (s, 3 H, NCH_3), 1.25 (d, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 148.9, 147.6, 131.5, 120.7, 111.9, 111.3, 60.4, 55.9, 55.8, 40.1, 35.4, 35.2, 19.7 ppm. M = 266.34 for $C_{14}H_{22}N_2O_3$.

***N*-[(1*S*)-2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-1-methyl-2-oxoethyl]-*N*-methyl-2-oxo-3-phenylpropanamide (4c):** The procedure described for the synthesis of **5a** was applied to **3c** (0.86 g, 3.2 mmol) to give **4c** (675 mg, 51%) as an oil: $[\alpha]_D^{23}$ = −96.4 (c = 1.0, $CHCl_3$). IR (film): ṽ = 3350, 3100−2850, 1650, 1520, 1450, 1270, 1230, 1050 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$), two stable conformers present (I:II, 4:3): δ = 7.20−7.40 (m, 10 H, H_{arom}), 6.80 (m, 2 H, H_{arom}), 6.70 (m, 4 H, H_{arom}), 6.37 (br. t, 1 H, NH) (I), 5.85 (br.t, 1 H, NH) (II), 4.27 and 4.04 (q_{AB}, 2 H, J = 14.5 Hz, $PhCH_2$) (I), 4.02 and 3.92 (q_{AB}, 2 H, J = 14.5 Hz, $PhCH_2$) (II), 3.82 (q, J = 6.5 Hz, 1 H, H-1) (I), 4.93 (q, J = 6.5 Hz, 1 H, H-1) (II), 3.86 and 3.85, 3.88 and 3.84 (four s, 3 H each, 4 × OCH_3), 3.30−3.56 (m, 4 H, $NHCH_2CH_2$), 2.71 (m, 4 H, $NHCH_2CH_2$), 2.63 (s, 3 H, NCH_3) (I), 2.51 (s, 3 H, NCH_3) (II), 0.83 (d, J = 7.0 Hz, 3 H, CH_3) (I), 1.22 (d, J = 7.0 Hz, 3 H, CH_3) (II) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.6, 196.7, 169.4, 168.7, 167.2, 166.7, 149.0, 149.0, 147.7, 147.7, 131.1, 131.1, 131.0, 130.5, 130.0, 130.0, 129.9, 129.9, 129.4, 129.4, 129.0, 129.0, 128.0, 127.8, 120.7, 120.6, 111.8, 111.7, 111.4, 111.3, 55.9, 55.9, 55.9, 55.8, 47.2, 47.0, 41.0, 40.9, 35.2, 35.2, 30.2, 27.4, 13.6, 12.8 ppm. LSIMS (+) (M = 412.48 for $C_{23}H_{28}N_2O_5$): m/z (%) = 435 $[M + Na]^+$ (100), 413 $[M + H]^+$ (2).

(6*S*)-3-Benzyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxy-1,6-dimethylpiperazine-2,5-dione (5c): The procedure described for the synthesis of **5a** was applied to **3c** (0.86 g, 3.2 mmol) to give **5c** (146 mg, 11%) as an unstable oil: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (m, 3 H, H_{arom}), 6.95 (m, 2 H, H_{arom}), 6.83 (m, 3 H, H_{arom}), 4.10 (m, 1 H, NCH_2CH_2), 3.91 and 3.87 (two s, 3 H each, 2 × OCH_3), 3.48 (m, 1 H, NCH_2CH_2), 3.17 (q_{AB}, 2 H, J = 13.5 Hz, $PhCH_2$), 2.85 (m, 2 H, NCH_2CH_2), 2.77 (s, 3 H, NCH_3), 2.30 (q, J = 6.5 Hz, 1 H, $N(CH_3)CHCH_3$), 1.71 (s, 1 H, OH), 1.34 (d, J = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1, 165.7, 148.9, 147.6, 133.6, 131.9, 130.1, 128.5, 127.9, 121.0, 112.2, 111.3, 86.0, 55.9, 55.9, 55.7, 46.4, 44.5, 35.3, 31.5, 18.2 ppm. M = 412.48 for $C_{23}H_{28}N_2O_5$.

(3*S*,11b*RS*)-11b-Benzyl-9,10-dimethoxy-2,3-dimethyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6c): Following the procedure described for the synthesis of **6a**, compound **4c** (970 mg, 2.3 mmol) was converted into a mixture of diastereoisomers **6c** (699 mg, 77%) as an oil with 87:13 diastereoisomeric ratio (based on the ^1H NMR spectrum of the crude reaction mixture). Column chromatography on Al_2O_3 using cyclohexane/ethyl acetate (7:3, v/v) allowed the isolation of (3*S*,11b*R*)-**6c**. Data for (3*S*,11b*R*)-**6c**: $[\alpha]_D^{23}$ = −135.1 (c = 1.0, $CHCl_3$). IR (KBr): 2830−3100, 1650, 1520, 1260 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.22 (s, 1 H, H_{arom}-11), 7.34−7.12 (m, 5 H, H_{arom}), 6.58 (s, 1 H, H_{arom}-8), 4.98 (ddd, 1 H, J_1 = 12.5, J_2 = 5.5, J_3 = 1.5 Hz, NCH_2CH_2), 3.98 and 3.87 (two s, 3 H each, 2 × OCH_3), 3.73 (q, J = 7.0 Hz, 1 H, H-3), 3.74 and 3.32 (q_{AB}, 2 H, J = 14 Hz, $PhCH_2$), 3.26 (td, 1 H, J_1 = 12.5, J_2 = 3.5 Hz, NCH_2CH_2), 3.08 (m, 1 H, NCH_2CH_2), 2.75 (s, 3 H, NCH_3), 2.67 (m, 1 H, NCH_2CH_2), 0.44 (d, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 165.9, 148.4, 147.2, 135.6, 130.6, 128.6, 128.5, 127.5, 127.2, 111.7, 111.2, 67.3, 57.3, 56.1, 55.8, 47.1, 37.2, 32.7, 28.7, 18.0 ppm. LSIMS (+) (M = 394.46 for $C_{23}H_{26}N_2O_4$): m/z (%) = 395 (28) $[M + H]^+$, 303 (42), 95 (40), 81 (41). HR LSIMS: $C_{23}H_{27}N_2O_4$ (calcd.: 395.19708, found 395.20085).

Minor Diastereoisomer (3*S*,11b*S*)-6c (selected data): ^1H NMR (500 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, H_{arom}-11), 6.59 (s, 1 H, H_{arom}-8), 2.74 (s, 3 H, NCH_3) ppm.

3-(3-Chlorophenyl)-*N*-[(1*S*)-2-{[2-(3,4-dimethoxyphenyl)ethyl]-amino}-1-methyl-2-oxoethyl]-*N*-methyl-2-oxopropanamide (4d): Compound **3c** (566 mg, 2.13 mmol) was introduced at room temperature to a stirred solution of *m*-chlorophenylpyruvic acid (465 mg, 2.34 mmol) in dry THF (20 mL), followed by the addition of Et_3N (0.47 mL, 4.26 mmol) and BOP reagent (1.035 g, 23.4 mmol). After 2 h of stirring, the mixture was left overnight. The solvent was then evaporated in vacuo and the residue was dissolved in dichloromethane (10 mL) and washed with saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and the solvent was evaporated giving a yellow oil that was purified by chromatography on silica gel using 2% (v/v) methanol in chloroform to give compound **4d** (501 mg, 48%) as an oil: $[\alpha]_D^{23}$ = −82.7 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$), two stable conformers present (I:II, 10:9): δ = 7.29 (m, 4 H, H_{arom}), 7.24 (m, 2 H, H_{arom}), 7.11 (m, 2 H, H_{arom}), 6.79 (m, 2 H, H_{arom}), 6.70 (m, 4 H, H_{arom}), 6.42 (br. t, J = 4.9 Hz, 1 H, NH) (I), 5.90 (br. t, J = 4.9 Hz, 1 H, NH) (II), 4.22 and 3.97 (q_{AB}, 2 H, J = 14.6 Hz, $PhCH_2$) (I), 4.00 (m, 2 H, $PhCH_2$) (II), 4.93 (d, J = 6.8 Hz, 1 H, H-1) (II), 3.45 (d, J = 6.8 Hz, 1 H, H-1) (I), 3.86 and 3.84, 3.88 and 3.86 (four s, 3 H each, 4 × OCH_3), 3.53 (m, 2 H, $NHCH_2CH_2$) (I), 3.39 (m, 2 H, $NHCH_2CH_2$) (II), 2.73 (m, 4 H, $NHCH_2CH_2$), 2.68 (s, 3 H, NCH_3) (I), 2.63 (s, 3 H, NCH_3) (II), 1.27 (d, J = 6.8 Hz, 3 H, CH_3) (II), 0.99 (d, J = 6.8 Hz, 3 H, CH_3) (I) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.0, 196.0, 169.4, 168.6, 166.7, 166.3, 149.0, 149.0, 147.7, 147.7, 135.0, 134.8, 133.4, 132.9, 131.0, 130.9, 130.5, 130.2, 129.9, 129.9, 128.2, 128.1, 128.1, 128.0, 120.6, 120.6, 111.8, 111.7, 111.3, 111.3, 55.9, 55.9, 55.8, 55.4, 51.9, 51.9, 46.4, 46.4, 35.2, 35.2, 30.4, 27.7, 13.9, 12.9 ppm. LSIMS (+) (M = 446.92 for $C_{23}H_{27}ClN_2O_5$): m/z (%) = 469 $[M + Na]^+$ (26), 447 $[M + H]^+$ (41), 395 (20), 266 (30), 95 (35), 81 (37).

(3*S*,11b*RS*)-11b-(3-Chlorobenzyl)-9,10-dimethoxy-2,3-dimethyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6d): Following the procedure described for the synthesis of **6a**, compound **4d** (670 mg, 1.5 mmol) was converted into a mixture of diastereoisomers **6d** (324 mg, 51%; 99.7:0.3 ratio based on ^1H NMR spectroscopy) in the form of a white crystalline product.

Major Diastereoisomer (3*S*,11b*R*)-6d: M.p. 186−190 °C. $[\alpha]_D^{23}$ = −120.6 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.18 (s, 1 H, H_{arom}-11), 7.23 (m, 3 H, H_{arom}), 7.02 (m, 1 H, H_{arom}), 6.58 (s, 1 H, H_{arom}-8), 4.96 (ddd, 1 H, J_1 = 12.5, J_2 = 5.0, J_3 = 1.5 Hz, NCH_2CH_2), 3.97 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.77 (q, J = 7.0 Hz, 1 H, H-3), 3.73 and 3.28 (two d_{AB}, 1 H each, J = 13.5 Hz, $PhCH_2$), 3.23 (td, 1 H, J_1 = 15.0, J_2 = 3.5 Hz,

NCH_2CH_2), 3.09 (m, 1 H, NCH_2CH_2), 2.79 (s, 3 H, NCH_3), 2.67 (dd, 1 H, J_1 = 16.0, J_2 = 2.0 Hz, NCH_2CH_2), 0.57 (d, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 165.9, 148.5, 147.2, 137.6, 134.5, 130.6, 129.8, 128.7, 128.2, 127.6, 127.2, 111.4, 111.2, 67.2, 57.2, 56.0, 55.9, 46.6, 37.3, 32.7, 28.5, 18.3 ppm. LSIMS (+) (M = 428.90 for $C_{23}H_{25}ClN_2O_4$): m/z (%) = 429 [M + H]$^+$(34), 303 (100), 273 (8), 190 (6), 107 (10), 91 (10), 81 (10).

Minor Diastereoisomer (3*S*,11b*S*)-6d (selected data): 8.03 (s, 1 H, H_{arom}-11), (5.86 (dd, 1 H, J_1 = 16, J_2 = 2 Hz, NCH_2CH_2) ppm.

Benzyl (1*S*)-1-({[2-(3,4-Dimethoxyphenyl)ethyl]amino}carbonyl)-2-methylpropylcarbamate (2e): Following the procedure described for the synthesis of **2a**, compound **1e** (2 g, 8 mmol) was converted into **2e** (3.3 g, 100%), which was obtained as a white crystalline product: m.p. 142−144 °C with decomposition. $[\alpha]_D^{23}$ = −8.4 (c = 1.0, $CHCl_3$). IR (KBr): ṽ =3300, 2950, 1700, 1650, 1500−1550, 1300 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37−7.29 (m, 5 H, H_{arom}), 6.78 (m, 1 H, H_{arom}), 6.70 (br. s, 2 H, H_{arom}), 6.09 (br. s, 1 H, NHCH$_2$CH$_2$), 5.40 [d, J = 9.0 Hz, 1 H, NHCHCH(CH$_3$)$_2$], 5.07 (q_{AB}, 2 H, J = 11.5 Hz, PhCH_2), 3.85 and 3.84 (two s, 3 H each, 2 × OCH_3), 3.90 (q, J = 6.5 Hz, 1 H, H-1), 3.55 (m, 1 H, NHCH_2CH$_2$), 3.45 (m, 1 H, NHCH_2CH$_2$), 2.24 (app t, 2 H, NHCH$_2$CH_2), 2.07 [m, 1 H, CH(CH$_3$)$_2$], 0.92 and 0.88 (two d, 3 H each, J = 7.0 Hz, 2 × CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 156.4, 149.0, 147.7, 136.2, 131.1, 128.5, 128.2, 128.0, 120.6, 111.8, 111.3, 67.0, 60.6, 55.9, 55.8, 40.7, 35.3, 31.0, 19.2, 17.8 ppm. LSIMS (+) (M = 414.49 for $C_{23}H_{30}N_2O_5$): m/z (%) = 437 [M + Na]$^+$ (27), 415 [M + Na]$^+$ (16), 371 (14), 164 (57), 91 (100).

(2*S*)-2-Amino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-3-methylbutanamide (3e): The procedure described for the synthesis of **3a** was applied to **2e** (7 g, 16.91 mmol) to give **3e** (3.25 g, 69%) as a white crystalline product: m.p. 51−55 °C. $[\alpha]_D^{23}$ = −22.4 (c = 1.0, $CHCl_3$). IR (KBr): ṽ = 3300−3400, 2900−3000, 1700, 1500, 1200, 1250, 1050 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (br. s, 1 H, NH, exchangeable with D_2O), 6.81 (m, 1 H, H_{arom}), 6.74 (m, 2 H, H_{arom}), 3.87 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.55 (m, 1 H, NHCH_2CH$_2$), 3.48 (m, 1 H, NHCH_2CH$_2$), 3.20 (d, J = 3.5 Hz, 1 H, H-2), 2.77 (m, 2 H, NHCH$_2$CH_2), 2.29 [m, 1 H, CH(CH$_3$)$_2$], 1.36 (br. s, 2 H, exchangeable with D_2O, NH_2), 0.97 and 0.78 (two d, 3 H each, J = 7.0 Hz, 2 × CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 148.9, 147.6, 131.6, 120.6, 111.9, 111.3, 60.2, 55.9, 55.8, 40.3, 35.5, 30.7, 19.7, 15.9 ppm. LSIMS (+) (M = 280.36 for $C_{15}H_{24}N_2O_3$): m/z (%) = 303 [M + Na]$^+$ (49), 281 [M]$^+$ (39), 176 (84), 97 (95).

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methyl-2-[(2-oxo-3-phenylpropanoyl)amino]butanamide (4e): The procedure described for the synthesis of **5a** was applied to **3e** (1 g, 3.57 mmol) to give **4e** (988 mg, 65%) as an oil: $[\alpha]_D^{23}$ = −13.5 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33−7.20 (m, 5 H, H_{arom}), 6.77 (m, 1 H, H_{arom}), 6.69 (m, 1 H, H_{arom}), 6.19 (app. t, 1 H, NHCH$_2$CH$_2$), 4.16 and 3.60 (q_{AB}, 2 H, J = 16.0 Hz, PhCH_2), 4.09 (m, 1 H, H-2), 3.84 and 3.83 (two s, 3 H each, 2 × OCH_3), 3.53 (m, 1 H, NHCH_2CH$_2$), 3.44 (m, 1 H, NHCH_2CH$_2$), 2.76 (br. s, 1 H, NHCHCH(CH$_3$)$_2$], 2.74 (m, 2 H, NHCH$_2$CH_2), 2.11 [m, 1 H, CH(CH$_3$)$_2$], 0.89 and 0.86 (two d, 3 H each, J = 7.0 Hz, 2 × CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.1, 169.9, 159.9, 149.0, 147.7, 132.5, 131.0, 129.8, 128.7, 127.2, 120.6, 111.8, 111.3, 56.0, 55.9, 55.8, 43.2, 40.8, 35.2, 31.0, 19.2, 18.0 ppm. M = 426.50 for $C_{24}H_{30}N_2O_5$.

Benzyl (1*S*)-1-({[2-(3,4-Dimethoxyphenyl)ethyl]amino}carbonyl)-2-methylpropyl(methyl)carbamate (2f): The procedure described for the synthesis of **2a** was applied to **1f** (2.24 g, 8.45 mmol) to give **2f** (3.5 g, 97%) as an oil: $[\alpha]_D^{23}$ = −61.6 (c = 1.0, $CHCl_3$). IR (film): ṽ = 3360, 3050−2825, 1680, 1670, 1520, 1260, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, H H_{arom}), 6.14 (br. t, 1 H, NH), 5.13 (s, 2 H, PhCH_2), 3.86 and 3.82 (two s, 3 H each, 2 × OCH_3), 3.98 (d, J = 10.5 Hz, 1 H, H-1), 3.47 (m, 2 H, NHCH_2CH$_2$), 2.87 (s, 3 H, NCH_3), 2.71 (t, J = 7.5 Hz, 2 H, NHCH$_2$CH_2), 2.27 [m, 1 H, CH(CH$_3$)$_2$], 0.91 and 0.85 (two d, 3 H each, J = 6.5 Hz, 2×CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 157.4, 149.0, 147.6, 136.5, 131.2, 128.5, 128.1, 127.5, 120.6, 111.8, 111.3, 67.4, 65.4, 55.9, 55.8, 40.4, 35.4, 29.8, 26.0, 19.6, 18.6 ppm. LSIMS (+) (M = 428.52 for $C_{24}H_{32}N_2O_5$): m/z (%) = 467 [M + K]$^+$ (1), 451 [M + Na]$^+$ (100), 429 [M + H]$^+$ (4), 301 (5).

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methyl-2-(methylamino)-butanamide (3f): The procedure described for the synthesis of **3a** was applied to **2f** (3.5 g, 8.19 mmol). Compound **3f** (2.04 g, 85%) was obtained as a white crystalline product: m.p. 52−54 °C. $[\alpha]_D^{23}$ = −20.4 (c = 1.0, $CHCl_3$). IR (KBr): ṽ = 3340, 3320, 3100−2810, 1620, 1520, 1270, 1050 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (br. t, 1 H, NHCH$_2$CH$_2$), 6.80 (d_{AB}, 1 H, J = 8.5 Hz, H_{arom}-5), 6.75 (d_{AB}, 1 H, J = 8.5 Hz, H_{arom}-6), 6.74 (d_{AB}, 1 H, J = 2.0 Hz, H_{arom}-2), 3.87 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.54 (m, 2 H, NHCH_2CH$_2$), 2.78 (m, 2 H, NHCH$_2$CH_2), 2.73 (d, J = 4.5 Hz, 1 H, H-2), 2.29 (s, 3 H, NCH_3), 2.06 [m, 1 H, CH(CH$_3$)$_2$], 0.96 and 0.84 (two d, 3 H each, J = 7.0 Hz, 2 × CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4, 148.9, 147.6, 131.6, 120.6, 111.9, 111.3, 70.8, 55.9, 55.8, 40.0, 36.2, 35.6, 31.3, 19.6, 17.7 ppm. LSIMS (+) (M = 294.39 for $C_{16}H_{26}N_2O_3$): m/z (%) = 295 [M + H]$^+$ (100).

(2S)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methyl-2-[methyl(2-oxo-3-phenylpropanoyl)amino]butanamide (4f): The procedure described for the synthesis of **5a** was applied to **3f** (1.67 g, 5.68 mmol) and provided **4f** (1.27 g, 51%) as an oil. Data for **4f**: $[\alpha]_D^{23}$ = −30.6 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$); two stable conformers present (I:II, 11:10): δ = 7.37−7.14 (m, 10 H, H_{arom}), 6.82−6.65 (m, 6 H, H_{arom}), 6.70 (m, 1 H, NH) (I), 5.94 (br. t, J = 5.5 Hz, 1 H, NH) (II), 4.25 and 4.06 (q_{AB}, 2 H, J = 15.0 Hz, PhCH_2) (I), 4.04 and 3.97 (q_{AB}, 2 H, J = 15.0 Hz, PhCH_2) (II), 4.22 (d, J = 10.5 Hz, 1 H, H-2) (II), 3.31 (d, J = 10.5 Hz, 1 H, H-2) (I), 3.88 (s, 3 H, OCH_3), 3.85 (s, 9 H, 3 × OCH_3), 3.52 (m, 2 H, NHCH_2CH$_2$) (I), 3.38 (m, 2 H, NHCH_2CH$_2$) (II), 2.79 (s, 3 H, NCH_3) (I), 2.72 (m, 4H NHCH$_2$CH_2), 2.65 (s, 3 H, NCH_3) (II), 2.22 [m, 2 H, CH(CH$_3$)$_2$], 0.88 and 0.61 (two d, 3 H each, J = 6.5 Hz, 2 × CH_3) (I), 0.71 and 0.27 (two d, 3 H each, J = 6.8 Hz, 2 × CH_3) (II) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.9, 196.7, 168.4, 167.9, 167.4, 166.2, 149.0, 148.9, 147.7, 147.6, 131.0, 131.0, 131.0, 131.0, 130.1, 129.9, 129.1, 129.0, 128.0, 127.8, 120.7, 120.7, 111.8, 111.7, 111.4, 111.3, 66.2, 62.7, 55.9, 55.9, 55.8, 55.8, 47.1, 46.8, 40.7, 40.6, 35.3, 35.3, 30.6, 28.2, 25.4, 25.3, 19.5, 19.5, 18.1, 17.6 ppm. LSIMS (+) (M = 440.53 for $C_{25}H_{32}N_2O_5$): m/z (%) = 441 [M + H]$^+$ (30), 260 (47), 164 (68), 91 (41), 86 (56).

(3*S*,11b*R*)-11b-Benzyl-3-isopropyl-9,10-dimethoxy-2-methyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione 6f: Following the procedure described for the synthesis of **6a**, compound **4f** (256 mg, 0.58 mmol) was converted into (3*S*,11b*R*)-**6f** (196 mg, 89%), which was obtained as an oil. Data for (3*S*,11b*R*)-**6f**: $[\alpha]_D^{23}$ = −48.4 (c = 1.0, $CHCl_3$). IR (KBr): ṽ = 3100−2820, 1670, 1650, 1510, 1250, 1220 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1 H, H_{arom}-11), 7.2 (m, 5 H, H_{arom}), 6.56 (s, 1 H, H_{arom}-8), 4.78 (ddd, 1 H, J_1 = 12.5, J_2 = 5.5, J_3 = 1.0 Hz, NCH_2CH$_2$), 3.94 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.61 (d, J = 4.0 Hz, 1 H, H-3), 3.85 and 3.37 (q_{AB}, 2 H, J = 14 Hz, PhCH_2), 3.30 (m, 1 H, NCH$_2$CH_2), 3.17 (m, 1 H, NCH$_2$CH_2), 2.86 (s, 3 H, NCH_3), 2.60

(m, 1 H, NCH_2CH$_2$), 1.67 [m, 1 H, CH(CH$_3$)$_2$], 0.83 and 0.21 (two d, 3 H each, J = 7.0 Hz, 2 × CH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 165.5, 148.5, 147.1, 135.9, 130.7, 129.4, 128.5, 127.3, 126.7, 111.4, 110.6, 68.0, 67.1, 56.0, 55.8, 46.3, 38.1, 31.7, 27.4, 20.0, 16.4 ppm. EI-MS (M = 422.52 for $C_{25}H_{30}N_2O_4$): m/z (%) = 422 [M$^+$](3), 331 (100), 303 (17), 260 (24), 245 (14). HR EI: calcd. for $C_{25}H_{30}N_2O_4$ 422.220; found 422.221.

(2*S*)-2-{[3-(3-Chlorophenyl)-2-oxopropanoyl](methyl)amino}-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-3-methylbutanamide 4g: The procedure described for the synthesis of **4d** was applied to **3f** (0.75 g, 2.5 mmol) to give **4g** (486 mg, 48%) as an oil: $[\alpha]_D^{23}$ = −75.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); two stable conformers present (I:II, 15:16): δ = 7.20−7.30 (m, 8 H, H$_{arom}$), 7.07−7.16 (m, 2 H, H$_{arom}$), 6.65−6.82 (m, 6 H, H$_{arom}$), 6.70 (m, 1 H, NH) (I), 5.96 (br. t, J = 5.9 Hz, 1 H, NH) (II), 4.19 and 4.07 (q$_{AB}$, 2 H, J = 15.6 Hz, PhCH_2) (II), 4.05 and 3.92 (q$_{AB}$, 2 H, J = 14.6 Hz, PhCH_2) (I), 4.23 (d, J = 10.7 Hz, 1 H, H-2) (II), 3.35 (d, J = 10.7 Hz, 1 H, H-2) (I), 3.87 (s, 3 H, OCH$_3$), 3.85 (s, 9 H, 3 × OCH$_3$), 3.54 (m, 2 H, NHCH_2CH$_2$) (II), 3.42 (m, 2 H, NHCH_2CH$_2$) (I), 2.74 (s, 3 H, NCH$_3$) (II), 2.81 (s, 3 H, NCH$_3$) (I), 2.73 (m, 2 H, NHCH$_2$CH_2) (II), 2.73 (m, 2 H, NHCH$_2$CH_2) (I), 2.25 [m, 1 H, CH(CH$_3$)$_2$] (II), 2.25 [m, 1 H, CH(CH$_3$)$_2$] (I), 0.89 and 0.75 (two d, 3 H each, J = 6.9 Hz, 2 × CH$_3$) (II), 0.66 and 0.38 (two d, 3 H each, J = 6.8 Hz, 2 × CH$_3$) (I) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.2, 195.9, 168.4, 167.8, 167.0, 165.8, 149.1, 149.0, 147.8, 147.7, 134.9, 134.8, 133.3, 133.2, 131.0, 131.0, 130.3, 130.2, 130.0, 130.0, 128.3, 128.1, 128.0, 128.0, 120.7, 120.7, 111.9, 111.7, 111.4, 111.4, 66.3, 62.9, 55.9, 55.9, 55.8, 55.7, 46.5, 46.3, 40.7, 40.6, 35.6, 35.3, 30.7, 28.3, 25.5, 25.4, 19.5, 19.4, 18.1, 17.9 ppm. LSIMS (+) (M = 474.98 for $C_{25}H_{31}ClN_2O_5$): m/z (%) = 497 [M + Na]$^+$ (22), 475 [M + H]$^+$ (39), 266 (14), 164 (39), 120 (18), 107 (27), 86 (33), 83 (29).

(3*S*,11b*R*)-11b-(3-Chlorobenzyl)-3-isopropyl-9,10-dimethoxy-2-methyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6g): Following the procedure described for the synthesis of **6a**, compound **4g** (76 mg, 0.16 mmol) was converted into (3*S*,11b*R*)-**6g** (42 mg, 57%), which was obtained as an oil.: $[\alpha]_D^{23}$ = −71.0 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300−3500, 1650, 1500, 1200 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 1 H, H$_{arom}$-11), 7.19 (m, 3 H, H$_{arom}$), 7.09 (m, 1 H, H$_{arom}$), 6.57 (s, 1 H, H$_{arom}$-8), 4.80 (dd, 1 H, J_1 = 12.5, J_2 = 5.5 Hz, NCH_2CH$_2$), 3.93 and 3.87 (two s, 3 H each, 2 × OCH$_3$), 3.64 (d, J = 3.5 Hz, 1 H, H-3), 3.85 and 3.31 (two d$_{AB}$, 1 H each, J = 14.0 Hz, PhCH_2), 3.33 (m, 1 H, NCH$_2$CH_2), 3.20 (td, 1 H, J_1 = 16.0, J_2 = 5.0 Hz, NCH$_2$CH_2), 2.87 (s, 3 H, NCH$_3$), 2.62 (dd, 1 H, J_1 = 16.0, J_2 = 3.0 Hz, NCH_2CH$_2$), 1.73 [m, 1 H, CH(CH$_3$)$_2$], 0.87 and 0.21 (two d, 3 H each, J = 7.0 Hz, 2 × CH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 165.5, 148.6, 147.2, 137.9, 134.3, 130.8, 129.7, 129.2, 129.0, 127.4, 126.5, 111.5, 110.2, 67.8, 67.0, 56.0, 55.8, 45.6, 38.1, 34.8, 31.6, 27.2, 19.8, 16.1 ppm. LSIMS (+) (M = 456.96 for $C_{25}H_{29}ClN_2O_4$): m/z (%) = 479 [M + Na]$^+$ (2), 457 [M + H]$^+$ (33), 331 (98), 120 (8), 107 (14), 89 (13). HR LSIMS: calcd. for $C_{25}H_{29}CLN_2O_4$ 457.189; found 457.191.

Benzyl (1*S*)-1-Benzyl-2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-2-oxoethylcarbamate (2h): Following the procedure described for the synthesis of **2a**, compound **1h** (7 g, 23.4 mmol) was converted into **2h** (8 g, 75%), which was obtained as a white crystalline product: m.p. 145−146 °C. $[\alpha]_D^{23}$ = +4.9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3320, 3110−2830, 1680, 1650, 1525, 1275, 1230, 1170 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36−7.13 (m, 10 H, H$_{arom}$), 6.73 (d, J = 8.0 Hz, 1 H, H$_{arom}$-5), 6.61 (d, J = 2.0 Hz, 1 H, H$_{arom}$-2), 6.54 (dd, 1 H, J = 8.0 Hz, H$_{arom}$-6), 5.81 (t, J = 5.5 Hz, 1 H, NHCH$_2$CH$_2$), 5.42 (d, J = 7.5 Hz, 1 H, NHCHCH$_2$Ph), 5.05 (q$_{AB}$, 2 H, J = 12.5 Hz, PhCH_2), 4.32 (q, J = 7.0 Hz, 1 H, H-1), 3.82 (s, 6 H, 2 × OCH$_3$), 3.37 (m, 2 H, NHCH_2CH$_2$), 3.04 (m, 2 H, CHCH_2Ph), 2.66−2.52 (m, 2 H, NHCH$_2$CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 155.8, 149.0, 147.7, 136.4, 136.1, 131.0, 129.3, 128.7, 128.5, 128.2, 128.0, 127.0, 120.5, 111.7, 111.2, 67.0, 56.5, 55.9, 55.8, 40.7, 38.8, 35.0 ppm. EI-MS (M = 462.54 for $C_{27}H_{30}N_2O_5$): m/z (%) = 462 [M]$^+$ (33), 354 (49), 220 (3), 210 (1), 164 (100), 151 (10), 91 (20).

(2S)-2-Amino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-3-phenylpropanamide (3h): The procedure described for the synthesis of **3a** was applied to **2h** (2 g, 4.3 mmol) to give **3h** (1.37 g, 97%) as a white crystalline product: m.p. 100−104 °C. $[\alpha]_D^{23}$ = −31.4 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3350, 3285, 3080−2840, 1640, 1520, 1470, 1270, 1230, 1140, 1025 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34−7.20 (m, 6 H, H$_{arom}$ and NH), 6.80 (d, J = 7.8 Hz, 1 H, H$_{arom}$-5), 6.71 (s, 1 H, H$_{arom}$-2), 6.69 (s, 1 H, H$_{arom}$-6), 3.86 (s, 6 H, 2 × OCH$_3$), 3.58 (dd, 1 H, J_1 = 13.7, J_2 = 4.1 Hz, CHCH_2Ph), 3.51 (m, 2 H, NHCH_2CH$_2$), 3.25 (dd, 1 H, J_1 = 9.3, J_2 = 4.1 Hz, CHCH_2Ph), 2.74 (app t, 2 H, NHCH$_2$CH_2), 2.69 (dd, 2 H, J_1 = 13.7, J_2 = 9.3 Hz, H-2), 1.38 (br. s, 2 H, exchangeable with D_2O, NH$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 148.9, 147.6, 137.9, 131.5, 129.3, 128.7, 126.8, 120.6, 111.8, 111.2, 55.9, 55.8, 56.4, 41.0, 40.4, 35.4 ppm. EI-MS (M = 328.41 for $C_{19}H_{24}N_2O_3$): m/z (%) = 328 [M]$^+$ (9), 237 (15), 220 (2), 209 (15), 192 (4), 180 (9), 164 (100), 151 (11), 126 (5), 120 (85), 103 (7), 91 (8), 77 (4).

***N*-[(1*S*)-1-Benzyl-2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-2-oxoethyl]-2-oxo-3-phenylpropanamide (4h):** The procedure described for the synthesis of **5a** was applied to **3h** (1.5 g, 4.6 mmol) and provided **4h** (1.2 g, 55%) as white crystals: m.p. 123−128 °C. $[\alpha]_D^{23}$ = −6.8 (c = 0.88, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3320, 3300, 3090−2825, 1675, 1520, 1250, 1225 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60−7.00 (m, 10 H, H$_{arom}$), 6.65 (d, J = 7.9 Hz, 1 H, H$_{arom}$-5), 6.52 (d, J = 1.8 Hz, 1 H, H$_{arom}$-2), 6.45 (dd, 1 H, J_1 = 8.2, J_2 = 1.8 Hz, H$_{arom}$-6), 5.57 (t, J = 5.3 Hz, 1 H, NHCH$_2$CH$_2$), 4.39 (m, 1 H, H-1), 4.07 (s, 2 H, PhCH_2), 3.77 (s, 6 H, 2 × OCH$_3$), 3.31 (m, 2 H, NHCH_2CH$_2$), 2.98 (m, 2 H, CHCH_2Ph), 2.62 (d, J = 10.1 Hz, 1 H, NHCHCH$_2$Ph), 2.51 (m, 2 H, NHCH$_2$CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.6, 169.0, 159.4, 149.0, 147.7, 136.1, 132.4, 130.7, 130.0, 129.2, 129.2, 128.7, 127.3, 127.2, 120.5, 111.6, 111.2, 55.7, 55.7, 54.8, 43.1, 40.6, 38.3, 34.9 ppm. EI-MS (M = 474.55 for $C_{28}H_{30}N_2O_5$): m/z (%) = 474 [M]$^+$ (39), 355 (4), 266 (2), 208 (2), 164 (100), 151 (6), 120 (8), 91 (10).

Benzyl (1*S*)-1-Benzyl-2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-2-oxoethyl(methyl)carbamate (2i): Following the procedure described for the synthesis of **2a**, compound **1i** (2 g, 6.39 mmol) was converted into **2i** (2.89 g, 95%), which was obtained as an oil: $[\alpha]_D^{23}$ = −39.3 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3350, 2830−3100, 1690, 1675, 1520, 1450 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40−7.10 (m, 10 H, H$_{arom}$), 6.73 (d$_{AB}$, 1 H, J = 8.0 Hz, H$_{arom}$-5), 6.66 (s, 1 H, H$_{arom}$-2), 6.61 (d$_{AB}$, 1 H, J = 8.0 Hz, H$_{arom}$-6), 6.08 (br. s, 1 H, NH), 5.06 (q$_{AB}$, 1 H, J = 12.4 Hz, PhCH_2), 4.92 (q$_{AB}$, 1 H, J = 11.6 Hz, PhCH_2), 4.86 (app t, 1 H, J = 7.8 Hz, H-1), 3.85 and 3.81 (two s, 3 H each, 2 × OCH$_3$), 3.44 (m, 2 H, NHCH_2CH$_2$), 3.33 (dd, 1 H, J_1 = 14.6, J_2 = 7.1 Hz, CHCH_2Ph), 2.95 (dd, 1 H, J_1 = 14.1, J_2 = 8.8 Hz, CHCH_2Ph), 2.76 (s, 3 H, NCH$_3$), 2.66 (m, 2 H, NHCH$_2$CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 157.0, 149.1, 147.6, 137.3, 136.4, 131.2, 129.0, 129.0, 128.5, 128.0, 127.6, 126.6, 120.6, 111.8, 111.3, 67.4, 60.3, 55.9, 55.8, 40.7, 35.2, 34.1, 30.4 ppm. LSIMS (+) (M = 476.56 for $C_{28}H_{32}N_2O_5$): m/z (%) = 499 [M + Na]$^+$ (6), 477 [M + H]$^+$ (56), 433 (16), 369 (6), 296 (10), 224 (24), 164 (100), 134 (36).

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(methylamino)-3-phenylpropanamide (3i): The procedure described for the synthesis of **3a** was applied to **2i** (2 g, 4.2 mmol) to give **3i** (1.2 g, 83.6%) as a white crystalline product: m.p. 75−82 °C. $[\alpha]_D^{23}$ = −36.7 (*c* = 0.76, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3350, 3320, 2800−3050, 1650, 1520 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33−7.18 (m, 6 H, H_{arom} and $NHCH_2CH_2$), 6.82−6.69 (m, 3 H, H_{arom}), 3.86 and 3.85 (two s, 3 H each, 2 × OCH_3), 3.51 (m, 2 H, $NHCH_2CH_2$), 3.17 (m, 2 H, $CHCH_2Ph$), 2.75 (t, *J* = 6.5 Hz, 2 H, $NHCH_2CH_2$), 2.64 (m, 1 H, H-2), 2.18 (s, 3 H, NCH_3), 1.47 (br. s, 1 H, exchangeable with D_2O, $NHCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.3, 149.0, 147.7, 137.6, 131.5, 129.1, 128.7, 126.9, 120.7, 111.9, 111.4, 66.1, 55.9, 55.9, 40.2, 39.3, 35.4, 35.4 ppm. LSIMS (+) (*M* = 342.43 for $C_{20}H_{26}N_2O_3$): *m*/*z* (%) = 685 $[2M + H]^+$ (8), 343 $[M + H]^+$ (66), 251 (18), 134 (100), 107 (8), 91 (14).

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[methyl(2-oxo-3-phenylpropanoyl)amino]-3-phenylpropanamide (4i): The procedure described for the synthesis of **5a** was applied to **3i** (1 g, 2.92 mmol) providing **4i** (788 mg, 55%) as an oil: $[\alpha]_D^{23}$ = −69.2 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3100−2850, 1675, 1520 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); two stable conformers present (I:II, 2:1): δ = 7.38−6.98 (m, 20 H, H_{arom}), 6.85−6.58 (m, 6 H, H_{arom}), 6.41 (br. t, 1 H, NH) (I), 5.83 (br. t, 1 H, NH) (II), 5.10 (t, *J* = 7.8 Hz, 1 H, H-2) (II), 4.19 (dd, 1 H, J_1 = 9.6, J_2 = 5.1 Hz, H-2) (I), 4.05 and 2.88 (q_{AB}, 2 H, *J* = 18.3 Hz, $PhCH_2$) (I), 3.92 and 3.81 (q_{AB}, 2 H, *J* = 14.4 Hz, $PhCH_2$) (II), 3.86 and 3.84 (two s, 3 H each, 2 × OCH_3), 3.80 (s, 6 H, 2 × OCH_3), 3.54 (m, 1 H, $NHCH_2CH_2$) (I), 3.39 (m, 1 H, $NHCH_2CH_2$) (I), 3.31 (m, 2 H, $NHCH_2CH_2$) (II), 3.14 (dd, 2 H, J_1 = 14.7, J_2 = 4.9 Hz, $CHCH_2Ph$) (I), 2.84 (m, 2 H, $CHCH_2Ph$) (II), 2.83 (s, 3 H, NCH_3) (I), 2.69 (m, 4 H, $NHCH_2CH_2$), 2.59 (s, 3 H, NCH_3) (II) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.5, 196.6, 168.3, 167.9, 167.4, 166.9, 149.0, 149.0, 147.7, 147.6, 137.4, 136.5, 131.6, 131.2, 130.9, 130.9, 129.8, 129.7, 129.1, 129.1, 128.9, 128.9, 128.7, 128.6, 127.7, 127.5, 127.2, 126.9, 120.7, 120.6, 111.7, 111.6, 111.3, 111.3, 55.9, 62.6, 57.3, 55.8, 55.8, 55.7, 46.8, 45.5, 41.0, 40.9, 35.2, 35.2, 33.7, 33.4, 30.9, 28.3 ppm. LSIMS (+) (*M* = 488.57 for $C_{29}H_{32}N_2O_5$): *m*/*z* (%) = 511[M + Na]$^+$ (36), 489 $[M + H]^+$ (10), 107 (14), 81 (22).

(3*S*,11b*RS*)-3,11b-Dibenzyl-9,10-dimethoxy-2-methyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6i): Following the procedure described for the synthesis of **6a**, compound **4i** (530 mg, 1.09 mmol) was converted into a mixture of diastereoisomers **6i** in 92% yield (471 mg), which was obtained as an oil. Column chromatography on Al_2O_3 using cyclohexane/ethyl acetate (20:3, v/v) and careful re-chromatography allowed the separation of **6i** into (3*S*,11b*R*)-**6i** and (3*S*,11b*S*)-**6i** (in an 89:11 ratio based on the ^1H NMR spectrum of the crude reaction mixture). Data for the predominant diastereoisomer (3*S*,11b*R*)-**6i**: $[\alpha]_D^{23}$ = −110.1 (*c* = 1.05, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3020, 2930, 2850, 1650, 1610, 1510, 1425, 1400, 1340, 1330 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, H_{arom}-11), 7.41−6.98 (m, 10 H, H_{arom}), 6.56 (s, 1 H, H_{arom}-8), 4.95 (ddd, 1 H, J_1 = 12.6, J_2 = 5.0, J_3 = 1.5 Hz, NCH_2CH_2), 3.96 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.96 (m, 1 H, H-3), 3.63 and 3.33 (d_{AB}, 2 H, *J* = 14 Hz, $PhCH_2$), 3.18 (m, 1 H, J_1 = 12.5, J_2 = 3.5 Hz, NCH_2CH_2), 3.07 (m, 1 H, NCH_2CH_2), 2.64 (m, 1 H, J_1 = 15.0, J_2 = 1.5 Hz, NCH_2CH_2), 2.50 (s, 3 H, NCH_3), 2.40 (m, 1 H, J_1 = 14.5, J_2 = 4.0 Hz, $CHCH_2Ph$), 1.90 (m, 1 H, $CHCH_2Ph$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 165.2, 148.4, 147.1, 138.5, 135.9, 130.9, 128.9, 128.8, 128.6, 128.3, 127.7, 127.4, 126.7, 111.9, 111.1, 67.5, 64.3, 56.1, 55.8, 47.1, 41.1, 37.6, 34.9, 28.6 ppm. LSIMS (+, 8 *k*V): *m*/*z* (%) = 471 $[M + H]^+$ (29), 379 (40), 365 (2), 329 (3), 279 (4), 176 (11).

Minor Diastereoisomer (3*S*,11b*S*)-6i: $[\alpha]_D^{23}$ = −47.1 (*c* = 1.28, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3025, 3000, 2930, 2870, 1660, 1520, 1450, 1270 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1 H, H_{arom}-11), 7.28−6.74 (m, 10 H, H_{arom}), 6.30 (s, 1 H, H_{arom}-8), 4.83 (ddd, 1 H, J_1 = 12.6, J_2 = 5.0, J_3 = 1.5 Hz, NCH_2CH_2), 3.94 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.88 (m, 1 H, H-3), 3.52 and 3.22 (d_{AB}, 2 H, *J* = 14 Hz, $PhCH_2$), 3.12 (m, 1 H, NCH_2CH_2), 3.09 (m, 1 H, NCH_2CH_2), 2.90 (m, 1 H, NCH_2CH_2), 2.84 (s, 3 H, NCH_3), 2.45 (m, 1 H, $CHCH_2Ph$), 1.92 (m, 1 H, $CHCH_2Ph$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 164.3, 148.9, 147.1, 135.3, 133.7, 129.8, 129.4, 128.1, 128.1, 127.9, 127.3, 126.9, 125.9, 111.2, 110.0, 66.2, 61.5, 56.0, 55.9, 48.1, 36.9, 36.5, 33.4, 28.1 ppm. LSIMS (+) (*M* = 470.56 for $C_{29}H_{30}N_2O_4$): *m*/*z* (%) = 471 $[M + H]^+$(24), 413 (3), 391 (6), 379 (21).

Benzyl (2*S*)-2-({[2-(3,4-Dimethoxyphenyl)ethyl]amino}carbonyl)-pyrrolidine-1-carboxylate (8a): Following the procedure described for the synthesis of **2a**, compound **7a** (6 g, 24.1 mmol) was converted into **8a** (9.22 g, 93%), which was obtained as a white solid: m.p. 103−105 °C. $[\alpha]_D^{23}$ = −54.7 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 1650, 1500, 1450, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 5 H, H_{arom}), 6.77 (d_{AB}, 1 H, *J* = 8.0 Hz, H_{arom}), 6.62−6.75 (m, 2 H, H_{arom}), 5.95 (br. s, 1 H, NH), 5.12 (br. q_{AB}, 2 H, *J* = 12.0 Hz, $PhCH_2$), 4.30 (br. s, 1 H, H-2), 3.86 and 3.83 (two s, 3 H each, 2 × OCH_3), 3.44 (m, 2 H, $NHCH_2CH_2$), 3.43 (m, 2 H, $NCHCH_2CH_2CH_2$), 2.52−2.28 (br. m, 2 H, $NHCH_2CH_2$), 2.32 (br. s, 1 H, $NCHCH_2CH_2CH_2$), 2.10 (br. s, 1 H, $NCHCH_2CH_2CH_2$), 1.88 (br. m, 2 H, $NCHCH_2CH_2CH_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 156.1, 149.1, 147.7, 136.4, 131.5, 128.6, 128.2, 127.9, 120.6, 112.0, 111.3, 67.3, 60.7, 55.9, 55.9, 47.4, 47.0, 35.2, 28.3, 24.5 ppm. EI-MS (*M* = 412.48 for $C_{23}H_{28}N_2O_5$): *m*/*z* (%) = 412 $[M]^+$ (2), 164 (100), 91 (64), 70 (6).

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]pyrrolidine-2-carboxamide (9a): The procedure described for the synthesis of **3a** was applied to **8a** (9.22 g, 22.3 mmol) to give **9a** (5.2 g, 78%) as a white crystalline product: m.p. 65−66.5 °C. $[\alpha]_D^{23}$ = −24.4 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 1650, 1500, 1200 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (br. s, 1 H, $NHCH_2CH_2$), 6.80 (d, *J* = 8.5 Hz, 1 H, H_{arom}), 6.73 (m, 2 H, H_{arom}), 3.87 and 3.86 (two s, 3 H each, 2 × OCH_3), 3.71 (m, 1 H, H-2), 3.51 (m, 1 H, $NHCH_2CH_2$), 3.44 (m, 1 H, $NHCH_2CH_2$), 2.96 (m, 1 H, $NHCHCH_2CH_2CH_2$), 2.80 (m, 1 H, $NHCHCH_2CH_2CH_2$), 2.76 (t, *J* = 7.0 Hz, 2 H, $NHCH_2CH_2$), 2.15 (br. s, 1 H, $NHCHCH_2CH_2CH_2$), 2.11 (m, 1 H, $NHCHCH_2CH_2CH_2$), 1.87 (m, 1 H, $NHCHCH_2CH_2CH_2$), 1.65 (m, 2 H, $NHCHCH_2CH_2CH_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1, 148.9, 147.6, 131.6, 120.7, 111.9, 111.3, 60.6, 55.9, 55.8, 47.2, 40.2, 35.4, 30.7, 26.1 ppm. EI-MS (*M* = 278.35 for $C_{15}H_{22}N_2O_3$): *m*/*z* (%) = 278 $[M^+]$(2), 209 (15), 164 (13), 70 (100).

(2*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-(2-oxo-3-phenylpropanoyl)pyrrolidine-2-carboxamide (10a): The procedure described for the synthesis of **5a** was applied to **9a** (1.2 g, 4.32 mmol) and provided **10a** (1.39 g, 68%) as an oil: $[\alpha]_D^{23}$ = −55.4 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300−3500, 1050−1200, 500 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); two stable conformers present and compound **11a** formed during measurement of the NMR spectrum: δ = 7.36−7.19 (m, H_{arom}), 7.08 (m, H_{arom}), 6.84−6.82 (m, H_{arom}), 6.54 (m), 5.67 (m), 4.66 (m), 4.44 (m), 4.41 (m), 4.33 (m), 4.08 (m), 3.95 (m), 3.89, 3.88, 3.86, 3.85, 3.84 and 3.81 (six s, 3 H each, 6 × OCH_3), 3.84 (m), 3.64 (m), 3.60 (m), 3.45 (m), 3.36 (m), 3.12 (m), 2.90 (m), 2.80 (m), 2.73 (m), 2.63 (m), 2.56 (m), 2.25 (m), 2.15 (m), 2.01 (m), 1.89 (m), 1.77 (m), 1.74 (m), 1.63 (m), 1.55 (m), 1.27 (m), 1.16 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5, 196.4, 171.2, 170.0, 166.3, 165.2, 164.1, 164.0, 149.1, 149.0, 148.9, 147.7,

147.7, 147.6, 133.6, 132.9, 132.0, 131.9, 131.3, 131.1, 130.4, 130.1, 129.8, 128.9, 128.6, 128.5, 127.8, 127.6, 127.2, 120.9, 120.7, 120.6, 112.3, 112.1, 112.0, 111.4, 111.4, 111.3, 86.6, 70.3, 61.2, 60.5, 59.1, 56.0, 55.9, 55.9, 55.9, 55.9, 55.9, 47.9, 47.2, 46.2, 45.6, 45.5, 45.4, 44.2, 43.5, 41.0, 40.9, 35.7, 35.6, 35.2, 35.1, 32.0, 30.2, 29.5, 27.2, 26.9, 25.5, 25.0, 24.1, 22.2, 22.0 ppm. EI-MS (M = 424.49 for $C_{24}H_{28}N_2O_5$): m/z (%) = 424 $[M]^+$ (6), 164 (100), 151 (9), 91 (20), 70 (23).

(8a*S*)-3-Benzyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxyhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (11a): The procedure described for the synthesis of **5a** was applied to **9a** (1.2 g, 4.32 mmol) providing **11a** (127 mg, 6.2%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (m, 2 H, H_{arom}), 7.59 (m, 1 H, H_{arom}), 7.45 (m, 2 H, H_{arom}), 6.80−6.70 (m, 3 H, H_{arom}), 5.39 (br. s, 1 H, OH), 4.18 (m, 1 H, H-8a), 3.88 (m, 2 H, PhCH_2), 3.85 and 3.84 (two s, 3 H each, 2 × OCH_3), 3.71 (m, 1 H, NCHCH_2CH_2CH_2), 3.52 (m, 1 H, NCH_2CH_2), 3.43 (m, 1 H, NCH_2CH_2), 2.74 (m, 2 H, NCH_2CH_2), 2.48 (m, 1 H, NCHCH_2CH_2CH_2), 2.12 (m, 1 H, NCHCH_2CH_2CH_2), 2.02 (m, 1 H, NCHCH_2CH_2CH_2), 1.88 (m, 2 H, NCHCH_2CH_2CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 163.1, 148.8, 147.5, 134.0, 133.4, 131.7, 130.2, 128.5, 120.8, 112.1, 111.2, 89.6, 60.8, 55.9, 55.8, 47.1, 44.3, 35.5, 35.0, 29.4, 22.8 ppm. M = 424.49 for $C_{24}H_{28}N_2O_5$.

(8a*S*,13a*RS*)-13a-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 (12a): Following the procedure described for the synthesis of **6a**, compound **10a** (530 mg, 1.25 mmol) was converted into a mixture of diastereoisomers **12a** (320 mg, 60%; 92:8 ratio based on GC-MS analysis of the crude reaction mixture). Preparative chromatography on Al_2O_3 by using ethyl acetate/methanol (20:3) allowed the separation of **12a** into (8a*S*,13a*S*)-**12a** and (8a*S*,13a*R*)-**12a**.

Major Diastereoisomer (8a*S*,13a*S*)-12a: M.p. 117−120 °C. $[\alpha]_D^{23}$ = +215.6 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3400−3550, 1650, 1550, 1450, 1350 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, H_{arom}-1), 7.28 (m, 3 H, H_{arom}), 7.14 (m, 2 H, H_{arom}), 6.56 (s, 1 H, H_{arom}-4), 4.99 (m, 1 H, NCH_2CH_2), 4.01 and 3.87 (two s, 3 H each, 2 × OCH_3), 3.56 and 3.36 (q_{AB}, 2 H, J = 13.5 Hz, PhCH_2), 3.55 (m, 1 H, NCH_2CH_2), 3.32 (m, 1 H, NCH_2CH_2), 2.86 (m, 2 H, NCHCH_2CH_2CH_2), 2.62 (m, 1 H, NCH_2CH_2), 2.34 (dd, 1 H, J_1 = 10.7, J_2 = 5.7 Hz, H-8a), 2.12 (m, 1 H, NCHCH_2CH_2CH_2), 1.83 (m, 1 H, NCHCH_2CH_2CH_2), 1.64 (m, 1 H, NCHCH_2CH_2CH_2), 1.57 (m, 1 H, NCHCH_2CH_2CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 165.3, 148.4, 146.8, 135.0, 130.5, 130.5, 128.4, 128.4, 128.1, 127.9, 126.8, 114.0, 110.8, 68.2, 57.7, 56.2, 55.9, 46.9, 45.4, 36.9, 29.7, 29.3, 21.1 ppm. EI-MS (M = 407.20 for $C_{24}H_{26}N_2O_4$): m/z (%) = 315 $[M - C_7H_7]^+$ (100), 287 (33), 190 (20), 175 (7), 91 (3). HR EI: calcd. for $C_{24}H_{27}N_2O_4$ 407.19708, found 407.19651.

Minor Diastereoisomer (8a*S*,13a*R*)-12a: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, H_{arom}-1), 7.28 (m, 3 H, H_{arom}), 7.14 (m, 2 H, H_{arom}), 6.61 (s, 1 H, H_{arom}-4), 5.07 (ddd, 1 H, J_1 = 12.8, J_2 = 5.7, J_3 = 0.7 Hz, NCH_2CH_2), 3.97 and 3.88 (two s, 3 H each, 2 × OCH_3), 3.74 and 3.34 (q_{AB}, 2 H, J = 13.8 Hz, PhCH_2), 3.77 (m, 1 H, NCHCH_2CH_2CH_2), 3.72 (m, 1 H, NCH_2CH_2), 3.57 (m, 1 H, NCH_2CH_2), 3.08 (m, 1 H, NCHCH_2CH_2CH_2), 2.73 (dd, 1 H, J_1 = 15.7, J_2 = 2.8 Hz, NCH_2CH_2), 2.12 (dd, 1 H, J_1 = 12.0, J_2 = 6.5 Hz, H-8a), 2.01 (m, 1 H, NCHCH_2CH_2CH_2), 1.86 (m, 1 H, NCHCH_2CH_2CH_2), 1.57 (m, 1 H, NCHCH_2CH_2CH_2), 0.39 (app q, 1 H, NCHCH_2CH_2CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0, 164.7, 148.4, 147.4, 135.5, 130.3, 130.3, 128.3, 128.3, 127.9, 127.4, 126.4, 111.4, 110.3, 68.4, 58.7, 56.0, 55.1, 47.6, 45.2, 34.5, 29.6, 28.6, 21.0 ppm. EI-MS (5 kHz, M = 407.20 for $C_{24}H_{26}N_2O_4$): m/z (%) = 315 $[M - C_7H_7]^+$ (100), 287 (33), 190 (20), 175 (7), 91 (3).

(2*S*)-1-[3-(3-Chlorophenyl)-2-oxopropanoyl]-*N*-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2-carboxamide (10b): The procedure described for the synthesis of **4d** was applied to **9a** (254 mg, 0.92 mmol) and provided **10b** (274 mg, 65%) as an oil: $[\alpha]_D^{23}$ = −37.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); two stable conformers present and a compound without a carbonyl group: δ = 8.07 (br. t, 1 H, NH), 7.30−7.19 (m, H_{arom}), 7.17−7.12 (m, H_{arom}), 6.90 (m, H_{arom}), 6.84−6.64 (m, H_{arom}), 6.56 (br. t, 1 H, NH), 5.62 (br. t, 1 H, NH), 4.52 (m), 4.48 (m), 4.30 (m), 4.05 (m), 3.89, 3.88, 3.87, 3.86, 3.84, and 3.83 (six s, 3 H each, 6 × OCH_3), 3.70−3.59 (m), 3.58−3.53 (m), 3.52−3.45 (m), 3.40−3.30 (m), 3.08 (m), 3.00−2.96 (m), 2.91−2.84 (m), 2.82−2.65 (m), 2.62−2.52 (m), 2.29 (m), 2.15 (m), 2.00 (m), 1.84 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.9, 195.7, 171.3, 171.2, 166.1, 165.6, 163.7, 163.1, 149.0, 149.0, 148.8, 147.7, 147.6, 147.6, 135.5, 135.3, 134.6, 134.3, 134.2, 133.4, 131.0, 130.4, 130.2, 129.9, 129.7, 129.6, 128.5, 128.4, 128.0, 127.9, 120.9, 120.7, 120.6, 112.2, 112.0, 112.0, 111.3, 111.3, 111.2, 61.1, 60.8, 60.4, 56.0, 55.9, 55.9, 55.9, 55.8, 55.7, 48.2, 47.5, 45.7, 45.4, 44.9, 44.7, 44.1, 40.9, 40.9, 35.6, 35.1, 35.0, 32.3, 29.6, 27.3, 22.4, 22.1, 21.1 ppm. LSIMS (+) (M = 458.93 for $C_{24}H_{27}ClN_2O_5$): m/z (%) = 459 $[M + H]^+$(15), 441 (14), 333 (11), 316 (14), 277 (12), 164 (90), 81 (32).

(8a*S*,13a*RS*)-13a-(3-Chlorobenzyl)-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 (12b): Following the procedure described for the synthesis of **6a**, compound **10b** (159 mg, 0.35 mmol) was converted into a mixture of diastereoisomers **12b** (80 mg, 51%; 93:7 ratio based on GC-MS analysis of the crude reaction mixture): $[\alpha]_D^{23}$ = +96.5 (c = 1.0, $CHCl_3$).

Major Diastereoisomer (8a*S*,13a*S*)-12b: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (s, 1 H, H_{arom}-1), 7.18−7.32 (m, 3 H, H_{arom}), 7.00 (m, 1 H, H_{arom}), 6.56 (s, 1 H, H_{arom}-4), 4.99 (m, 1 H, NCH_2CH_2), 4.00 and 3.87 (two s, 3 H each, 2 × OCH_3), 3.94 and 3.54 (q_{AB}, 2 H, J = 14.5 Hz, PhCH_2), 3.57 (m, 1 H, NCH_2CH_2), 3.39 (m, 1 H, NCH_2CH_2), 2.86 (m, 2 H, NCHCH_2CH_2CH_2), 2.62 (m, 1 H, NCH_2CH_2), 2.50 (dd, 1 H, J_1 = 11.0, J_2 = 6.0 Hz, H-8a), 2.18 (m, 1 H, NCHCH_2CH_2CH_2), 1.88 (m, 1 H, NCHCH_2CH_2CH_2), 1.67 (m, 2 H, NCHCH_2CH_2CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 165.0, 148.4, 146.8, 137.0, 134.4, 130.4, 129.7, 128.8, 128.1, 128.0, 126.3, 113.7, 110.7, 67.9, 57.8, 56.2, 55.8, 45.5, 46.4, 37.0, 29.8, 29.2, 21.1 ppm. EI-MS (M = 440.92 for $C_{24}H_{25}ClN_2O_4$): m/z (%) = 440 $[M - H]^+$ (0.002), 315 (100), 287 (38), 190 (19), 175 (7), 91 (3).

Minor Diastereoisomer (8a*S*,13a*R*)-12b (selected data): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 1 H, H_{arom}-1), 7.18−7.32 (m, 3 H, H_{arom}), 6.87 (m, 1 H, H_{arom}), 6.60 (s, 1 H, H_{arom}-4), 5.02 (m, 1 H, NCH_2CH_2), 3.89 and 3.88 (two s, 3 H each, 2 × OCH_3), 3.89 and 3.77 (q_{AB}, 2 H, J = 14.0 Hz, PhCH_2), 2.72 (m, 1 H, H-8a), 0.57 (app. q, 1 H, NHCHCH_2CH_2CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.4, 165.0, 148.5, 147.4, 137.5, 134.2, 130.1, 129.6, 128.5, 128.4, 128.1, 126.3, 111.4, 109.9, 68.2, 58.1, 56.0, 55.9, 47.0, 45.3, 36.6, 29.9, 28.4, 21.0 ppm. EI-MS: m/z (%) = 440 $[M - H]^+$ (0.6), 315 (20), 287 (9), 164 (100), 151 (12), 91 (3).

X-ray Data for (3*S*,11b*R*)-6d: $C_{23}H_{25}ClN_2O_4$, M_r = 428.90, orthorhombic $P2_12_12_1$, a = 7.2867(15), b = 10.430(2), c = 27.795(6) Å, α = β = γ = 90°, V = 2112.5(7) Å^3, Z = 4, ρ_x = 1.349 g·cm^{-3}, F(000) = 904, μ(Mo-K_α) = 0.213 mm^{-1}, T = 293 K. Data collection: Kuma KM4 κ-axis diffractometer, λ(Mo-K_α) = 0.71073 Å,

colorless crystals 0.2×0.25×0.45 mm, unit cell parameters by least-squares for 25 reflections with $15.6 < 2\theta < 18.2°$, 2978 data collected, 1335 with $I \geq 2\sigma(I)$. Structure solution and refinement: direct methods (*SHELXS-97*[42]), least-squares on F^2 (*SHELXL-97*[43]), final $R = 0.0501$ and $wR = 0.1562$ (observed reflections). Several weak CH−O hydrogen bonds were detected involving molecules related by translation along the *a* direction. Benzyl rings of the neighbouring molecules are in a stacking arrangement.

CCDC-166095 (**12a**) and -207277 (**6d**) contain the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/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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[36] The numbering mode for compounds **6** in Scheme 1 is shown in Figure 1 and is based on IUPAC rules.
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[38] The ratio of $S{:}R \geq 99.5{:}0.5$ was determined on a ChiraDex column (Merck).
[39] The numbering scheme of **12a** and **12b** is shown in Figure 2 and is based on IUPAC rules.
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