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3,6-Dioxoperhydropyrrolo[1,2-*a*]pyrazines as Templates for Peptidomimetics

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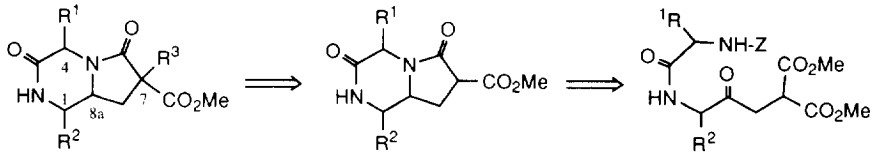
Abstract: The synthesis of 4,7-di- and 4,7,7-trisubstituted 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine-7-carboxylate derivatives is described. The approach used for the preparation of this heterocyclic template is based on the reductive amination of 4-ketodiesters derived from dipeptides.

With the aim of circumventing the known limitations of peptides as potential drugs; i.e. poor bioavailability and short duration of action, various strategies have been devised for finding small nonpeptide molecules, referred to as peptidomimetics, that could bind to peptide receptors.[1] A useful step along the path towards the rational design of these compounds has been the incorporation of conformational constraint into peptides by replacing dipeptide or tripeptide fragments with lactams.[2-5] A more recent approach is that involving the selection of a template, or scaffold, onto which the pharmacophore amino acid side chains required for binding to the receptor can be attached in an appropriate orientation. Thus, bicyclo[1.2.2]octane, β-D-glucose, cyclohexane and the steroid nucleus have been successfully used as templates in the synthesis of mimetics of enkephalins,[6] somatostatin,[7] TRH[8] and RGD,[9] respectively. Synthetic accessibility and ability to carry variable amino acid side chains must be considered when new templates are designed. Based on these considerations and on the reported possibility to obtain high receptor binding affinity with three conveniently oriented binding groups,[10] we focused our attention on compounds **1** in which three amino acid side chains are attached to the 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine template.

As it happens with the construction of the nitrogen bridged lactam system in 8-amino-3-oxoindolizidine-2-carboxylates from suitable protected ornithine derivatives,[11] it was expected that intramolecular reductive amination of analogous 4-ketodiesters derived from dipeptides and subsequent γ-lactamization provided ready access to the corresponding 1,4-disubstituted-3,6-dioxoperhydropyrrolo[1,2,-*a*]pyrazine-7-carboxylate onto which the third amino acid side chain could be appended (Scheme 1). Eventually, the 7-carboxylate group could be either removed or used for incorporation into higher peptides.



1

R^1, R^2, R^3 = amino acid side chains

Scheme 1

According to this approach, variable amino acid side chains could be mounted on the 3,6-dioxoperhydropyrrolo[1,2-a]pyrazine template in different spatial relationships, starting from different dipeptide derivatives. In the case of mimetics with two or three appended hydrophobic chains, this conformationally restricted template, replacing the tripeptide backbone, could prevent the hydrophobic collapse effect.[1e]

This paper deals with the synthesis of a series of compounds **1** as Xaa-Gly-Yaa mimetics (Xaa=Ala, Leu, Phe, Trp, Asp, Orn; Yaa=Gly, Phe).[12] The different aspects involved in the construction of the bicyclic bis-lactam system and the factors affecting the stereochemistry of the new chiral centers formed are discussed.

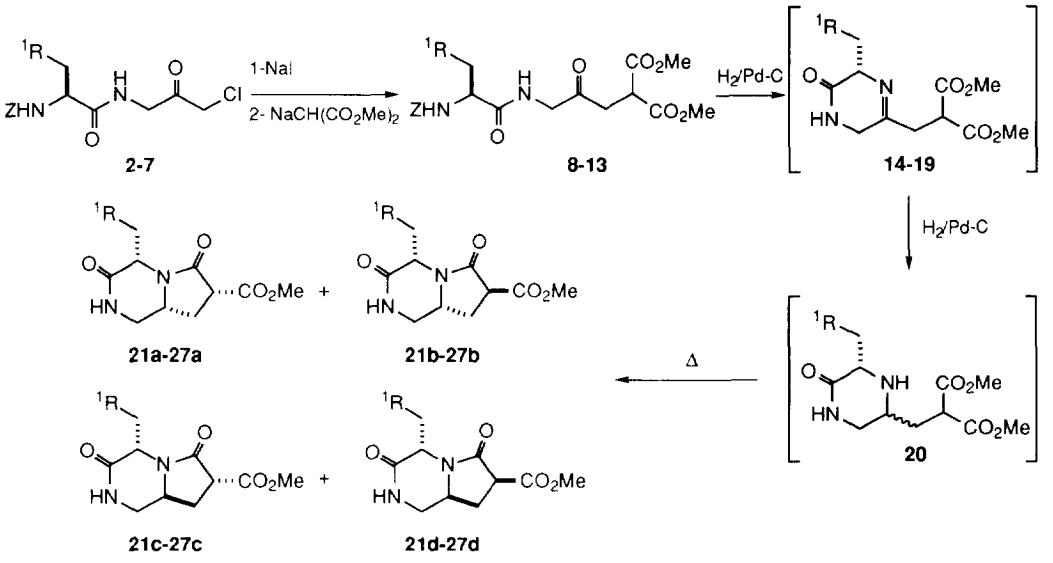
RESULTS AND DISCUSSION

Bearing in mind that catalytic hydrogenation of 4-ketodiesters derived from Boc-Orn(Z)-OH directly provide the 3-oxoindolizidine system,[11] we decided to explore this method for the elaboration of the structurally related 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine template. To this end, the starting 4-ketodiester analogues **8-13** were prepared by alkylation of dimethyl malonate with the Z-Xaa-Gly halomethyl ketones [Xaa=Ala (**2**), Leu (**3**), Phe (**4**), Trp (**5**), Asp(OBzl) (**6**), Orn(Boc) (**7**)], previously obtained from the corresponding dipeptides following a similar procedure to that reported for amino acid derivatives (Scheme 2).[13]

As indicated in Table 1, although catalytic hydrogenation of compounds **8-13** at 30 psi of pressure, using 10% Pd-C as catalyst, gave the corresponding bicyclic bis-lactams **21-25** and **27**, different reaction times and temperature were required to complete the process. Thus, dioxoperhydropyrrolopyrazines **21** and **25** were directly formed when ketodiesters **8** and **12** were hydrogenated for 2-3 days, whereas more prolonged reaction times were required for the reductive aminations of ketodiesters **9, 10, 11** and **13** as for the subsequent γ-lactamization of the resulting 2-oxopiperazine intermediates **20** [R^1=$CH(CH_3)_2$, Ph, In, $(CH_2)_2NHBoc$] to the bicyclic derivatives **22, 23, 24** and **27**, respectively, which were refluxed in toluene to complete this second cyclization. Since the reduction involved in the formation of the mentioned 2-oxopiperazines **20** was very slow, the corresponding intermediate imines **15, 16, 17** and **19** could be isolated when the catalytic hydrogenation was stopped after disappearance of the starting 4-ketodiesters **9, 10, 11** and **13**, respectively.

Concerning the stereochemical course of the reaction, it can be noted that diastereoisomers with *R* configuration at C_{8a} were always obtained as major compounds. This result can be rationalized by the hydrogenation of the imine intermediate in such a way that the hydrogen enters by the less hindered side of the molecule and, hence, by the opposite side to the R^1 substituent. As the 8a*R*/8a*S* ratio found for the Ala, Leu and Orn (Boc) derivatives **21, 22** and **27** is very similar, it seems that the size of the R^1 substituent does not have a significant influence on the stereochemical results. Therefore, the formation of the more stable 5*R*-2-oxopiperazine, with the substituents at C_3 and C_5 in pseudoequatorial disposition, could explain the predominance of the 8aR diastereomers. Additionally, the existence of stabilizing interactions between the tetrahydropyrazine ring and the R^1 aromatic moiety in the imine intermediates **16** and **17** could be responsible for the higher diastereomeric excess at C_{8a} in the Phe and Trp derivatives **23** and **24**.[14] The low stereoselectivity at C_{8a} found for the Asp derivative **25** (**ab/cd** 1.1:1), which was transformed into the diester analogue **26** for easy of isolation and characterization, could be attributed to the participation of a «chelation

mechanism» in the hydrogenation process, involving the formation of a six-membered cyclic complex through electrostatic interactions between the palladium catalyst and the carboxylic oxygen of the Asp residue and the imino group. Related five-membered substrate-catalyst complexes have been proposed to explain the stereochemical course in the catalytic hydrogenation of α-ketoamides and Schiff bases of α-ketoacids.[15,16]



Compd.	R^1	Compd.	R^1	Isomer	C_4,C_7,C_{8a}
2,8,14,21	H	**6,12**	CO_2Bzl	**a**	*S,R,R*
3,9,15,22	$CH(CH_3)_2$	**18,25**	CO_2H	**b**	*S,S,R*
4,10,16,23	Ph	**26**	CO_2Me	**c**	*S,R,S*
5,11,17,24	In	**7,13,19,27**	$(CH_2)_2NHBoc$	**d**	*S,S,S*

Scheme 2

As expected, γ-lactamization of compounds **20** provided mixtures of 7*R* and 7*S* diastereoisomers. The chromatographic separation of the resulting diastereomeric bis-lactams was very difficult, being only possible for the Ala derivatives **21**, in which isomers 7*R*,8a*R* **21a** and 7*S*,8a*S* **21d** were almost exclusively formed, and for the Asp derivatives **26b** and **26c** with 7*S*,8a*R* and 7*R*,8a*S* configuration, respectively. In addition to that, compounds **22ab, 22cd, 23ab, 24ab** and **26ad** could also be separated from the corresponding reaction mixtures.

The absolute configuration at C_{8a} and C_7 was assigned by means of NOE experiments. Thus, isomers with *R* configuration at C_{8a} showed a weak, but significant, NOE between H_4 and H_{8a} protons, indicating that these protons are located on the same side of the heterocyclic ring. Similarly, the observed weak NOE between H_7 and H_{8a} protons in some of the diastereoisomers, revealed a *cis*-relationship between these protons and, therefore, 8a*R*,7*R* or 8a*S*,7*S*, stereochemistry. The existence of minor compounds **23cd** and **27cd**,

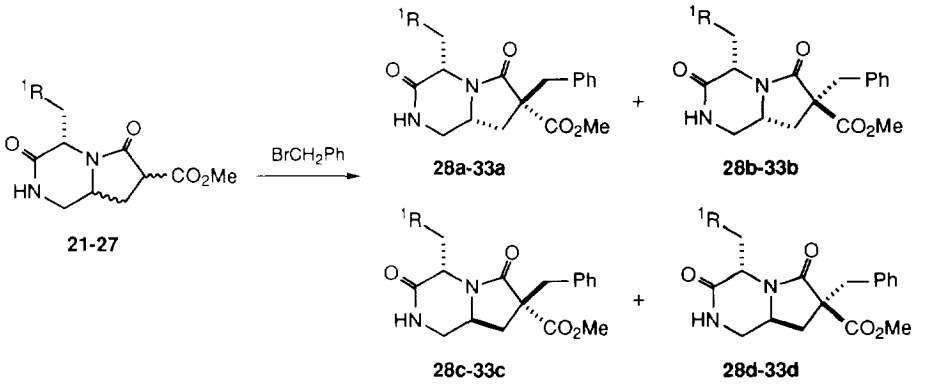
that could not be either separated or unequivocally identified, was shown from the characterization of their corresponding 7-benzyl derivatives, as will be discussed.

Table 1. Results of the hydrogenation reaction of 4-ketodiesters derived from Z-Xaa-Gly-OH

4-Ketodiester	Reaction time[a] (days)	Final Compd.	Yield[b] (%)	**ab/cd** ratio	8a*R*/8a*S* de
8	2	**21**	94	5.3:1	68
9	9	**22**	70	5.5:1	69
10	13	**23**	68	7.5:1[c]	76
11	13[d]	**24**	31[d]	7.0:1[c]	75
12	3	**25**[e]	56[f]	1.1:1	5
13	11	**27**	80	5.5:1[c]	69

[a] Time needed for complete disappearance of the imine intermediate. [b] Yield of isolated compounds. [c] Estimated by ^{1}H NMR (from the integrals of H_2 and H_4 protons). [d] Imine **17** (12%) was isolated after 13 days of hydrogenation and 2 days of reflux in toluene. [e] This compound was converted into **26** by treatment with diazomethane. [f] Total yield of the hydrogenation and treatment with diazomethane.

In order to test the possibility of replacing the C-terminal Gly residue in the Xaa-Gly-Gly mimetics **21-24**, **26** and **27** with other amino acid side chains, these compounds were alkylated with benzyl bromide, in the presence of sodium methoxide, to give the corresponding Xaa-Gly-Phe analogues **28-33** (Scheme 3).



Compd.	R^1	Compd.	R^1
21,28	H	**24,31**	In
22,29	$CH(CH_3)_2$	**26,32**	CO_2Me
23,30	Ph	**27,33**	$(CH_2)_2NHBoc$

Scheme 3

Table 2. Results of the alkylation of compounds **21-24, 26** and **27** with benzyl bromide

Starting Compd.	Final Compd.	Yield[a] (%)	**a/b** ratio	**c/d** ratio
21a	**28ab**	68	3.5:1	—
21d	**28d**[b]	69	—	0:1[b]
22ab	**29ab**	80	3:1[c]	—
22cd	**29cd**	69	—	1:1[c]
23abcd	**30abcd**	74	4:1[d]	1:3[d]
24ab	**31ab**	43	3.5:1	—
26ad	**32abcd**	35	3:1[c]	1:3[c]
26b	**32ab**	41	3:1[c]	—
27abcd	**33abcd**	62	4:1[c]	1:2[c]

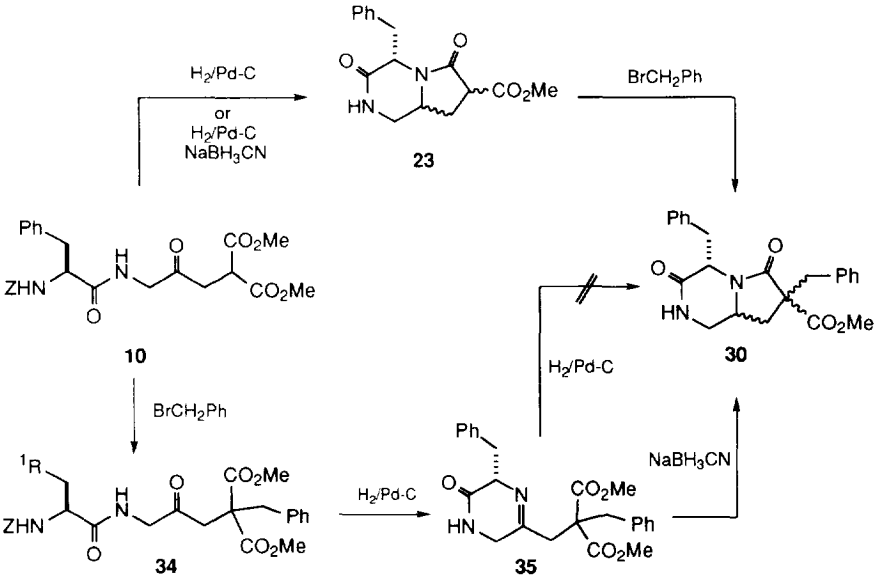
[a] From isolated compounds. [b] Traces of compound **28c** were detected in the ^{1}H NMR spectrum of **28d**. [c] Estimated by ^{1}H NMR (from the integrals of H_2 and H_4, and/or H_{8a} protons). [d] Measured by HPLC from the crude reaction mixture.

As shown in Table 2, alkylation of the 8a*R* derivatives preferentially led to the 7*R*-benzyl analogues with a degree of stereoselectivity which was independent on the nature of the R^1 substituent. This fact seems to indicate a preferential attack of the alkyl halide from the opposite side to the unshared lone pair on the lactam nitrogen .[17] A similar attack on the 8a*S* analogues involves a close proximity between the alkylating agent and the R^1 substituent and, therefore, the degree of stereoselectivity at C_7 would be dependent on the R^1 substituent size.[17]

The absolute configuration at C_7 of the 7-benzyl derivatives was established on the basis of the chemical shifts of the H_{8a} protons. Thus, the observed shielding for this proton in compounds having 8a*R*,7*R* configuration, when compared to the same proton in their parent bicyclic derivatives ($\Delta\delta$~1-1.5 ppm), indicated that the 7-benzyl group and the H_{8a} proton are in *cis* disposition (Table 5). A similar shielding effect of the 7-arylmethyl chain on the H_{8a} proton was found for those diastereoisomers having 8a*S*,7*S* configuration ($\Delta\delta$~0.4-1 ppm).

An alternative strategy for the preparation of the restricted Xaa-Gly-Phe analogues **28-33** would imply the use of 4-ketodiesters in which the Phe side chain has been previously introduced. To examine this strategy, we prepared the disubstituted malonate **34** by alkylation of the 4-ketodiester **10** with benzyl bromide (Scheme 4). Surprisingly, when compound **34** was hydrogenated under the same conditions as those used for the synthesis of **23**, neither the target bicyclic lactam **30** nor the corresponding 2-oxopiperazine intermediate was formed but imine **35** was isolated. However, reduction of imine **35** was achieved by treatment with $NaBH_3CN$ in MeOH for 20 h, leading to a mixture of mono- and bicyclic compounds, that was refluxed in toluene to complete the γ-lactamization process. The evaluation of the mixture of diastereoisomers **30** by HPLC revealed a decrease in the 8a*R*/8a*S* selectivity when compared to that obtained by the hydrogenation method of 4-ketodiester **10** (Table 3). In order to evaluate whether this change in the stereoselectivity is due to the $NaBH_3CN$ used as reducting agent or to the presence of the benzyl group at the malonate moiety of

compound **34**, this new strategy was applied to the reduction of the monosubstituted malonate analogue **10**. Thus, removal of Z group in **10** by catalytic hydrogenation followed by reduction of the resulting imine intermediate **16** with $NaBH_3CN$ and reflux in toluene afforded a 13:1 mixture of diastereoisomers **23ab** and **23cd**. Since this reduction led to a higher 8a*R* diastereomeric excess than the catalytic hydrogenation, the decrease selectivity obtained in the reduction of malonate **34** must be due to the presence of the additional benzyl substituent in the imine **35**. Support for this assumption comes from considering that the benzyl derivatives **16** and **35** are preferentially in a conformation in which the 3-arylmethyl side chain folds over the tetrahydropyrazine ring. Therefore, any additional interaction between this heterocyclic ring and the benzyl group at the malonic moiety in compound **35** must occur by the other face of the imine intermediate, thus blocking in some extent the attack of the hydride from this face. On the other hand, the preparation of diastereomers **30** from **34** resulted in lower stereoselectivities at C_7, but isomer 7*S*,8a*R* **30b** is now predominant over their 8a*R*7*R* epimer **30a**. Comparing the synthesis of derivatives **23** by the two alternate reducing methods it must be noted that reaction with $NaBH_3CN$ improves both the yield (from 68 to 78%) and the 8aR/8aS diastereoselectivity (Δde=11%), and substantially shortens the reaction time.



Scheme 4

In conclusion, the approach reported here, essentially based on the intramolecular reductive amination of 4-ketodiesters derived from dipeptides, allows one to elaborate 3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines as templates bearing variable amino acid side chains. The degree of stereocontrol at the new asymmetric center C_{8a} depends on the starting dipeptide and the reducing agent. It would be expected that a similar basis could be applied to construct a variety of new nitrogen-bridged bicyclic templates, with different rigidity and functionalities in the six-membered heterocyclic ring, starting from suitable dipeptide analogues in which the -CONH- bond has been replaced with the corresponding peptide bond surrogate.

Table 3. 4,7-Dibenzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazines. Influence of the synthetic method on the steroeselectivity.

Starting compound	Reduction method	Yield of **23** (%)[a]	8a*R*/8a*S* ratio[b] (de, %)	Yield of **30**[a,c]	**30a/30b** ratio[d]	**30c/30d** ratio[d]
10	H_2/Pd-C	68	7.5:1 (75)	77 (48)	4:1	1:3
10	$NaBH_3CN$	78	13:1 (86)	77 (60)	4:1	1:3
34	$NaBH_3CN$	—	3:1[d] (50)	60 (39)	1:1.7	1:2.4

[a] From isolated compounds. [b] Measured by ^1H NMR from the crude reaction mixtures (integrals of H_2 and H_4 protons). [c] Global yields from **10** are given in parenthesis. [d] Measured by HPLC from the crude reaction mixture **29a-d.**

EXPERIMENTAL PROCEDURES

^1H NMR spectra were recorded with a Varian EM 390, a Varian Gemini 200 or a Varian XL-300 spectrometers operating at 90, 200 or 300 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were registered on a Varian Gemini 200 (50 MHz). Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical TLC was performed on aluminun sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck). Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Analytical HPLC was carried out on a Waters apparatus (3.9 x 150 mm, Nova-Pack C_{18}, 4 μm) with CH_3CN(A)/H_2O (0.05% TFA) (B) system as eluent (Flow rate 1 mL/min) and UV (214 nm) detection. Z-Protected dipeptides were purchased from Bachem.

Synthesis of chloromethyl ketones derived from Z-Xaa-Gly-OH dipeptides

General procedure. To a solution of the Z-Xaa-Gly-OH dipeptide (18 mmol) in dry THF (40 mL) were successively added, at -20°C, *N*-methyl-morpholine (21 mmol) and isobutylchloroformate (21 mmol). After stirring for 15 min. at -20°C, an ethereal solution of diazomethane (from *N*-nitroso-*N*-methylurea, 6 g) was added. After 30 min. of reaction, a solution of 2N HCl/MeOH (15 mL, 30 mmol) was added and the stirring continued until N_2 evolution ceased. The solution was neutralized with Et_3N and the solvents were evaporated. The resulting residue was dissolved in EtOAc (150 mL), washed with H_2O and the organic layer was dried over Na_2SO_4. Evaporation and precipitation from Et_2O or purification on a silica gel column, using the solvent system specified in each case, afforded the following compounds:

***Z-Ala-Gly-CH$_2$Cl* (2).** Yield: 62%. Chromatographic solvent system: EtOAc/hexane (1:1). ^1H NMR (90 MHz, $CDCl_3$): δ 1.3 (d, 3H, β-CH_3 Ala), 4.0 (s, 2H, CH_2Cl), 4.2 (m, 3H, α-CH Ala and Gly), 5.0 (s, 2H, CH_2 Z), 5.4 (d, 1H, α-NH Ala), 6.8 (m, 1H, α-NH Gly), 7.1-7.2 (m, 5H, C_6H_5 Z). Anal. Calcd. for $C_{14}H_{17}ClN_2O_4$: C 53.77, H 5.48, Cl 11.34, N 8.96. Found: C 53.50, H 5.31, Cl 11.41, N 8.92.

***Z-Leu-Gly-CH$_2$Cl* (3).** Yield: 47%. Precipitated with Et_2O. ^1H NMR (90 MHz, $CDCl_3$): δ 0.7 (d, 6H, δ-CH_3 Leu), 1.3-1.6 (m, 3H, β-CH_2 and γ-CH Leu), 3.9 (m, 1H, α-CH Leu), 4.0 (s, 2H, CH_2Cl), 4.1 (m, 2H, α-CH_2 Gly), 4.9 (s, 2H, CH_2 Z), 5.3 (d, 1H, α-NH Leu), 6.8 (m, 1H, α-NH Gly), 7.1-7.2 (m, 5H, C_6H_5 Z). Anal. Calcd. for $C_{17}H_{23}ClN_2O_4$: C 57.54, H 6.53 Cl 9.99, N 7.89. Found: C 57.70, H 6.81, Cl 9.72, N 7.67.

***Z-Phe-Gly-CH$_2$Cl* (4).** Yield: 69%. Precipitated with Et_2O. ^1H NMR (90 MHz, $CDCl_3$): δ 3.0 (d, 2H, β-CH_2 Phe), 4.0 (s, 2H, CH_2Cl), 4.1 (d, 2H, α-CH_2 Gly), 4.4 (m, 1H, α-CH Phe), 5.0 (s, 2H, CH_2 Z), 5.4 (d,

1H, α-NH Phe), 6.6 (m, 1H, α-NH Gly), 7.0-7.3 (m, 10H, C_6H_5 Ph, Z). Anal. Calcd. for $C_{20}H_{21}ClN_2O_4$: C 61.78, H 5.44, Cl 9.12, N 7.20. Found: 61.53, H 5.79, Cl 9.02, N 7.60.

***Z-Trp-Gly-CH$_2$Cl* (5)**. Yield: 50%. Chromatographic solvent system: EtOAc/hexane (1:1). ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.2 (m, 2H, β-CH_2 Trp), 3.9 (s, 2H, CH_2Cl), 4.0 (d, 2H, α-CH_2 Gly), 4.5 (m, 1H, α-CH Trp), 5.1 (s, 2H, CH_2 Z), 5.5 (d, 1H, α-NH Trp), 6.4 (m, 1H, α-NH Gly), 7.0-7.6 (m, 10H, C_6H_5 Z, In), 8.2 (s, 1H, NH^1). Anal. Calcd. for $C_{22}H_{22}ClN_3O_4$: C 61.75, H 5.18, Cl 8.28, N 9.82. Found: C 61.87, H 5.24, Cl 7.95, N 9.58.

***Z-Asp(OBzl)-Gly-CH$_2$Cl* (6)**. Yield: 64%. Precipitated with Et_2O. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (dd, 1H, β-CH_2 Asp), 3.03 (dd, 1H, β-CH_2 Asp), 4.06 (s, 2H, CH_2Cl), 4.22 (d, 2H, α-CH_2 Gly), 4.62 (m, 1H, α-CH Asp), 5.09 (s, 4H, CH_2 Z, Bzl), 5.92 (d, 1H, α-NH Asp), 7.04 (br s, 1H, α-NH Gly), 7.20-7.30 (m, 10H, C_6H_5 Z, Bzl). Anal. Calcd. for $C_{22}H_{23}ClN_2O_6$: C 59.13, H 5.19, Cl 7.93, N 6.27. Found: C 59.26, H 4.83, Cl 7.94, N 6.31.

***Z-Orn(Boc)-Gly-CH$_2$Cl* (7)**. Yield: 49%. Precipitated with Et_2O. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.3 (s, 9H, CH_3 Boc), 1.3-1.8 (m, 4H, β- and γ-CH_2 Orn), 3.1 (m, 2H, δ-CH_2 Orn), 4.1 (s, 2H, CH_2Cl), 4.2 (d, 2H, α-CH_2 Gly), 4.3 (m, 1H, α-CH Orn), 4.9 (m, 1H, δ-NH Orn), 5.0 (s, 2H, CH_2 Z), 5.8 (d, 1H, α-NH Orn), 7.2 (m, 1H, α-NH Gly), 7.3-7.4 (m, 5H, C_6H_5 Z). Anal. Calcd. for $C_{21}H_{30}ClN_3O_6$: C 55.32, H 6.63, Cl 7.77, N 9.22. Found: C 55.15, H 6.54, Cl 7.52, N 8.98.

Synthesis of 4-ketodimethyl esters derived from Z-Xaa-Gly-OH dipeptides

General procedure. A mixture of the corresponding chloromethyl ketone (9 mmol) and sodium iodide (9 mmol) in 1,2-dimethoxyethane or THF (30 mL) was stirred at room temperature for 10 min and then added to a solution of freshly prepared sodium salt of dimethylmalonate (10 mmol) in 1,2-dimethoxyethane or THF (20 mL). Stirring was continued for 3-15 h, the solvent removed and the residue was stracted with EtOAc (100 mL) and washed with H_2O (75 mL). The organic layer was dried (Na_2SO_4) and evaporated leaving a residue which was purified on a silica gel column with EtOAc/hexane (1:1). The following compounds were obtained by this method:

***Methyl 5-[(N-Benzyloxycarbonyl)-L-alanyl]amino-2-methoxycarbonyl-4-oxopentanoate* (8)**. Yield: 77%. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.3 (d, 3H, β-CH_3 Ala), 3.0 (d, 2H, 3-H), 3.6 (s, 6H, CO_2CH_3), 3.8 (t, 1H, 2-H), 4.0 (d, 2H, 5-H), 4.2 (m, 1H, α-CH Ala), 5.0 (s, 2H, CH_2 Z), 5.4 (d, 1H, α-NH Ala), 6.8 (m, 1H, 5-NH), 7.2-7.3 (m, 5H, C_6H_5 Z). Anal. Calcd. for $C_{19}H_{24}N_2O_8$: C 55.88, H 5.92, N 6.86. Found: C 55.70, H 6.12, N 7.01.

***Methyl 5-[(N-Benzyloxycarbonyl)-L-leucyl]amino-2-methoxycarbonyl-4-oxopentanoate* (9)**. Yield: 48%. ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.8 (d, 6H, δ-CH_3 Leu), 1.4-1.7 (m, 3H, β-CH_2 and γ-CH Leu), 3.0 (d, 2H, 3-H), 3.7 (s, 6H, CO_2CH_3), 3.9 (t, 1H, 2-H), 4.1 (d, 2H, 5-H), 4.2 (m, 1H, α-CH Leu), 5.0 (s, 2H, CH_2 Z), 5.3 (d, 1H, α-NH Leu), 6.9 (m, 1H, 5-NH), 7.3 (m, 5H, C_6H_5 Z). Anal. Calcd. for $C_{22}H_{30}N_2O_8$: C 58.66, H 6.71, N 6.22. Found: C 58.71, H 7.08, N 6.04.

***Methyl 5-[(N-Benzyloxycarbonyl)-L-phenylalanyl]amino-2-methoxycarbonyl-4-oxopentanoate* (10)**. Yield: 69%. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.9 (m, 4H, 3-H and β-CH_2 Phe), 3.6 (s, 6H, CO_2CH_3), 3.8 (t, 1H, 2-H), 4.0 (d, 2H, 5-H), 4.3 (m, 1H, α-CH Phe), 5.0 (s, 2H, CH_2 Z), 5.4 (d, 1H, α-NH Phe), 6.6 (m, 1H, 5-NH), 7.0-7.2 (m, 10H, C_6H_5 Z, Ph). Anal. Calcd. for $C_{25}H_{28}N_2O_8$: C 61.97, H 5.82, N 5.78. Found: C 61.75, H 5.77, N 5.65.

Methyl 5-[(N-Benzyloxycarbonyl)-L-tryptophyl]amino-2-methoxycarbonyl-4-oxopentanoate **(1 1)**. Yield: 51%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.81 (d, 2H, 3-H), 3.08 (dd, 1H β-CH_2 Trp), 3.23 (dd, 1H, β-CH_2 Trp), 3.65 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 3.75 (t, 1H, 2-H), 3.90 (d, 2H, 5-H), 4.54 (m, 1H, α-CH Trp), 5.00 (s, 2H, CH_2 Z), 5.44 (d, 1H, α-NH Trp), 6.35 (br s, 1H, 5-NH), 6.92-7.29 (m, 10H, C_6H_5 Z, Indole), 7.51 (s, 1H, NH^i). Anal. Calcd. for $C_{27}H_{29}N_3O_8$: C 61.94, H 5.58, N 8.02. Found: C 61.68, H 5.52, N 8.39.

Methyl 5-[(N$^\alpha$-Benzyloxycarbonyl-N$^\delta$-terc-butoxycarbonyl)-L-ornithyl]amino-2-methoxycarbonyl-4-oxopentanoate **(12)**. Yield: 54%. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.1 (s, 9H, CH_3 Boc), 1.4-2.0 (m, 4H, β- and γ-CH_2 Orn), 3.0 (d, 2H, 3-H), 3.1 (m, 2H, δ-CH_2 Orn), 3.7 (s, 6H, CO_2CH_3), 3.9 (t, 1H, 2-H), 4.1 (d, 2H, 5-H), 4.4 (m, 1H, α-CH Orn), 4.8 (m, 1H, δ-NH Orn), 5.1 (s, 2H, CH_2 Z), 5.8 (d, 1H, α-NH Orn), 7.1 (m, 1H, 5-NH), 7.2-7.4 (m, 5H, C_6H_5 Z). Anal. Calcd. for $C_{26}H_{37}N_3O_{10}$: C 56.61, H 6.76, N 7.62. Found: C 56.64, H 7.05, N 7.60.

Methyl 5-[(N-Benzyloxycarbonyl-O-benzyl)-L-aspartyl]amino-2-methoxycarbonyl-4-oxopentanoate **(13)**. Yield: 52%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (dd 1H, β-CH_2 Asp), 3.01 (d, 2H, 3-H), 3.08 (m, 1H, β-CH_2 Asp), 3.72 (s, 6H, CO_2CH_3), 3.93 (t, 1H, 2-H), 4.12 (d, 2H, 5-H), 4.62 (m, 1H, α-CH Asp), 5.09 (s, 2H, CH_2 Bzl), 5.11 (s, 2H, CH_2 Z), 5.89 (d, 1H, α-NH Asp), 7.04 (br s, 1H, 5-NH), 7.28-7.35 (m, 10H, C_6H_5 Z, Bzl). Anal. Calcd. for $C_{27}H_{30}N_2O_{10}$: C 59.77, H 5.57, N 5.16. Found: C 59.45, H 5.39, N 5.52.

Methyl 2-Benzyl-5-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-2-methoxycarbonyl-4-oxo-pentanoate **(34)**. A stirred solution of compound **10** (0.6 g, 1.24 mmol) and HNa (0.049 g, 1.24 mmol) in dry THF (14 mL) was treated with benzyl bromide (0.22 mL, 1.86 mmol). Stirring was continued for 6 h at room temperature, the solvent was evaporated, the residue was extracted with EtOAc and washed with water. The organic extract was dried (Na_2SO_4) and evaporated to leave a residue wich was purified on a silica gel column using EtOAc/hexane (2:3) as eluent. Yield: 0.49 g (68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (s, 2H, 2-CH_2), 3.08 (m, 2H, β-CH_2 Phe), 3.37 (s, 2H, H-3), 3.75 (s, 6H, CO_2CH_3) 3.98 (m, 2H, 5-H), 4.45 (m, 1H, α-CH Phe), 5.07 (s, 2H, CH_2 Z), 5.29 (d, 1H, α-NH Phe), 6.45 (m, 1H, 5-NH), 6.93-7.37 (m, 10H, C_6H_5 Z, Ph). Anal. Calcd. for $C_{32}H_{34}N_2O_8$: C 66,89, H 5.96, N 4.87. Found: C 66.98, H 6.10, N 5.21.

Synthesis of 4-substituted 7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazines.

Method A. A solution of the corresponding 4-ketodiester (5 mmol) in MeOH (100 mL) was hydrogenated at 30°C and 40 psi of pressure for 2-13 days (Table 1), using 10% Pd-C as catalyst. After filtration of the catalyst, the solvent was evaporated and the resulting residue refluxed in toluene for 1-2 days. Then, the solvent was eliminated *in vacuo* and the residue purified on a silica gel column as specified .

Method B. Compound **10** (1 mmol) was dissolved in MeOH (20 mL) and hydrogenated overnight at room temperature and 40 psi of pressure in the presence of 10% Pd-C. The catalyst was filtered and to the filtrate were added $ZnCl_2$ (0.5 mmol) and $NaBH_3CN$ (3 mmol). After stirring overnight at room temperature, the solvent was evaporated to dryness. The residue was extracted with EtOAc (50 mL), succesively washed with 1N HCl, 10% $NaHCO_3$ and H_2O, and the organic layer was dried over Na_2SO_4. The resulting residue was dissolved in toluene (20 mL) and refluxed for 2 days. After evaporation of the solvent, the residue was purified as specified.

7-Methoxycarbonyl-4-methyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine **(21)**. Chromatographic solvent system: CH_2Cl_2/MeOH (20:1). Isomer (4*S*,7*R*,8a*R*) **21a**: Yield, 79% (Method A). Anal. Calcd. for

$C_{10}H_{14}N_2O_4$: C 53.09, H 6.24, N 12.38. Found: C 52.78, H 6.61, N 12.53. Isomer (4*S*,7*S*,8a*S*) **21d**: Yield, 15% (Method A). Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C 53.09, H 6.24, N 12.38. Found: C 52.86, H 6.49, N 12.04.

***4-Isobutyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (22).** Chromatographic solvent system: Gradient from 2 to 10% of MeOH in CH_2Cl_2. Isomers (4*S*,7*RS*,8a*R*) **22ab**: Yield, 59% (Method A). Anal Calcd. for $C_{13}H_{20}N_2O_4$: C 58.19, H 7.51, N 10.44. Found: C 57.89, H 7.40, N 10.21. Isomers (4*S*,7*RS*,8a*S*) **22cd**: Yield, 11% (Method A). Anal Calcd. for $C_{13}H_{20}N_2O_4$: C 58.19, H 7.51, N 10.44. Found: C 58.02, H 7.67, N 10.18.

***4-Benzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (23).** Chromatographic solvent system: CH_2Cl_2/MeOH (40:1). Obtained in 68 and 78% total yield using methods A and B, respectively. Small quantities (< 5%) of the diastereomeric pair **23ab** can be separately obtained from the first column fractions. **23abcd:** Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C 63.66, H 6.20, N 9.32. Found: C 63.56, H 6.00, N 9.26.

***7-Methoxycarbonyl-4-(indole-3-yl)methyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (24).** Chromatographic solvent system: CH_2Cl_2/MeOH (40:1). Total yield 32% (Method A). Imine **17** (11%) was isolated using this method. A 6% of the diastereomeric pair **23ab** was separately obtained. **24abcd**: Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C 63.33, H 5.61, N 12.31. Found: C 63.08, H 5.92, N 11.97.

***7-Methoxycarbonyl-4-(methoxycarbonyl)methyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (26).** Obtained by treatment of the corresponding 4-carboxymethyl derivative **25** (Method A) with diazomethane. Chromatographic solvent system: Gradient from 5 to 15% of MeOH in CH_2Cl_2. Isomers **26ad**: yield 41% (**a/d** ratio, 1.2:1, method A). Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C 50.70, H 5.67, N 9.85. Found: C 50.36, H 5.83, N 10.17. Isomer **26b**: yield 7% (Method A). Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C 50.70, H 5.67, N 9.85. Found: C 50.46, H 6.06, N 9.62. Isomer **26c**: yield 8 % (Method A). Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C 50.70, H 5.67, N 9.85. Found: C 51.02, H 5.87, N 9.54.

***4-[3-(tert-Butoxycarbonyl)amino]propyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (27).** Chromatographic solvent system: CH_2Cl_2/MeOH (30:1) Yield, 80% (Method A). **27abcd**: Anal. Calcd. for $C_{17}H_{27}N_3O_6$: C 55.27, H 7.37, N 11.37. Found: C 54.89, H 7.42, N 10.98.

Isolation of imine intermediates

A solution of the corresponding 4-ketodiester (1 mmol) in MeOH (20 mL) was hydrogenated at room temperature and 30 psi of pressure for 5 h, in the presence of 10% Pd-C. After filtration of the catalyst and evaporation to dryness, the resulting imine derivative was characterized by ^{1}H- and ^{13}C-NMR without further purification.

***5-(2,2-Dimethoxycarbonyl)ethyl-3(S)-isobutyl-2-oxo-1,2,3,6-tetrahydropyrazine* (15).** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, 3H, CH_3 ^{i}Bu), 0.96 (d, 3H, CH_3 ^{i}Bu), 1.42 (m, 1H, 3-CH_2), 1.74 (m, 1H, 3-CH_2), 1.83 (m, 1H, CH, ^{i}Bu), 2,87 (m, 2H, 5-CH_2), 3.74 (m, 4H, 6-H and CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 3.94-4.06 (m, 3H, 3-H, 6-H and CH Et), 7.38 (s, 1H, H-1). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21,16 and 22.49 (CH_3 ^{i}Bu), 24.49 (CH ^{i}Bu), 34.72 (5-CH_2), 42.47 (3-CH_2), 46.07 (C-6), 47.97 (CH Et), 52.53, 52.65 (OMe), 58.62 (C-3), 160.43 (C-5), 169.55, 169.70, 171.79 (CO).

***3(S)-Benzyl-5-(2,2-dimethoxycarbonyl)ethyl-2-oxo-1,2,3,6-tetrahydropyrazine* (16).** ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (m, 1H, 5-CH_2), 2.78 (m, 1H, 5-CH_2), 2.96 (dd, 1H, 6-H, J=17.8, 2.7), 3.12 (dd, 1H, 3-CH_2, J=13.4, 4.4) 3.23 (dd, 1H, 3-CH_2, J=13.4, 5.6), 3.64 (dd, 1H, 6-H, J=17.8, 2.9), 3.72 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 4.03 (dd, 1H, CH Et, J=7.3, 7.1), 4.44 (m, 1H, 3-H), 6.52 (d, 1H, 1-H, J=2.9), 7.08-

7.34 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.59 (5-CH_2), 38.79 (3-CH_2), 45.94 (CH Et), 47.65 (C-6), 52.58 (OCH_3), 61.62 (C-3), 126.59, 127.97, 129.99 and 136.69 (Ph), 161.73 (C-5), 169.43, 169.97 (CO).

Table 4. Significant ^1H NMR data of compounds **21-24**, **26** and **27** (300 MHz, $CDCl_3$)

	δ (ppm)											$J_{7,8}$ (Hz)	
Compd.	H-1		H-2	H-4	H-7	H-8		H-8a	CO_2Me	4-CH_2[a]			
21a	3.49	3.31	7.29	4.21	3.55	2.41	2.16	3.75	3.82	1.67		8.2	11.2
21d	3.48	3.21	6.23	4.57	3.55	2.68	1.96	4.11	3.80	1.47		5.4	9.9
22a	3.48	3.33	6.86	4.24	3.54	2.38	2.16	3.74	3.81	2.04	1.86	8.0	11.3
22b[b]	3.48	3.23	6.86	4.24	3.48	2.49	1.86	4.08	3.77	2.04	1.86	0.0	c
22c[d]	3.45	3.22	6.62	4.20	3.74	2.67	1.80	4.21	3.77	2.45	1.80	0.0	c
22d[d]	3.80	3.25	6.30	4.95	3.38	2.36	1.80	4.85	3.79	2.25	2.00	c	c
23a[b]	2.82	1.52	6.85	4.44	3.50	2.16	1.77	3.56	3.81	3.85	3.07	7.8	11.3
23b[b]	2.84	1.52	6.89	4.44	3.45	2.25	1.45	3.86	3.71	3.91	3.11	0.0	9.7
24a[b]	2.74	1.67	6.12	4.48	3.56	2.19	1.78	3.59	3.86	4.01	3.42	7.9	11.9
24b[b]	2.74	1.47	6.67	4.53	3.47	2.19	1.15	3.84	3.76	4.16	3.32	0.0	11.3
26a[e]	3.70	3.44	6.60	4.28	3.51	2.42	2.36	3.82	3.79, 3,67	3.85	3.19	8.7	10.4
26b	3.50	3.35	6.79	4.26	3.60	2.48	2.27	3.89	3.69, 3.61	3.78	3.13	0.0	8.0
26c	3.72	3.43	6.86	4.29	3.46	2.44	2.01	4.00	3.76, 3.66	3.87	3.13	0.0	8.9
26d[e]	3.70	3.40	6.60	4.28	3.49	2.53	1.94	4.10	3.77, 3.66	3.98	3.20	2.2	8.9
27a[f]	3.44	3.28	7.13	4.21	3.50	2.38	2.12	3.72	3.78	2.30	2.05	8.5	11.5
27b[f]	3.44	3.19	7.13	4.19	3.47	2.47	1.88	4.03	3.74	2.30	2.05	0.0	9.0

[a] CH_3 group for Ala derivatives **21a** and **21d**. [b] From the **a/b** mixture. [c] Not measured. [d] From the **cd** mixture. [e] From the **ad** mixture. [f] From the **abcd** mixture.

5(2,2-Dimethoxycarbonyl)ethyl-3(S)-(indole-3-yl)methyl-2-oxo-1,2,3,6-tetrahydropyrazine **(17).** ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (m, 1H, 5-CH_2), 2.62 (m, 1H, 5-CH_2), 2.74 (dd, 1H, 6-H, J=17.6, 2.5), 3.19 (dd, 1H, 3-CH_2, J=14.4, 4.4) 3.38 (dd, 1H, 6-H, J=17.6, 2.7), 3.40 (dd, 1H, 3-CH_2, J=14.4, 5.2), 3.69 (s, 3H, CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 4.02 (dd, 1H, CH, Et, J=7.8, 6.7) 4.41 (m, 1H, 3-H), 6.63 (d, 1H, 1-H, J=2.7), 6.88-7.57 (m, 5H, In), 8.45 (s, 1H, NH^i). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.53 (3-CH_2), 34.49 (5-CH_2), 45.78 (C-6), 47.44 (CH Et), 52.65, 52.71 (OCH_3), 61.50 (C-3), 110.16, 110.93, 119.02, 119.17, 121.64, 123.77, 127.79, 135.73 (Indole), 161.17 (C-5), 169.54, 169.77, 170.48 (CO).

3(S)-[3-(tert-Butoxycarbonyl)amino]propyl-5-(2,2-dimethoxycarbonyl)ethyl-2-oxo-1,2,3,6-tetrahydropyrazin**e (19).** ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H, CH_3 Boc), 1.53 (m, 2H, 2-CH_2 Pr), 1.72 (m, 1H, 3-CH_2), 1.89 (m, 1H, 3-CH_2), 2.86 (m, 2H, 5-CH_2), 3.10 (m, 2H, 3-CH_2 Pr), 3.71 (m, 1H, 6-H), 3.72 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.97-4.02 (m, 3H, 3-H, 6-H and CH Et), 4.74 (m, 1H, 3-NH Pr), 7.26 (d, 1H, 1-H, J=1.3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.54 (2-CH_2 Pr), 28.40 (CH_3 Boc), 30.48 (3-CH_2), 34.70

(5-CH_2), 40.18 (3-CH_2 Pr), 46.43 (C-6), 47.78 (CH Et), 52.64 (OCH_3), 59.70 (C-3), 79.01 (C Boc), 161.02 (C-5), 169.41, 170.29 (CO).

***3(S)-Benzyl-5-(2-benzyl-2,2-dimethoxycarbonyl)ethyl-2-oxo-1,2,3,6-tetrahydropyrazine* (35).** ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (dd, 1H, 5-CH_2, J=17.4, 1.4), 2.69 (dd, 1H, 5-CH_2, J=17.4, 1.7), 3.05 (ddd, 1H, 6-H, J=17.8, 2.8, 1.1), 3.17 (dd, 1H, 3-CH_2, J=13.6, 6.0), 3.29 (dd, 1H, 3-CH_2, J=13.6, 4.4) 3.43 (d, 1H, CH_2 Bzl, J=19.4), 3.52 (m, 1H, 6-H), 3.56 (d, 1H, CH_2 Bzl), 3,69 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.47 (m, 1H, 3-H), 6.73 (br s, 1H, 1-H), 6.84-7.32 (m, 10H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.20, 37.85, 38.70 (3-CH_2, 5-CH_2 and CH_2 Bzl), 46.37 (C-6), 52.63 (OCH_3), 56.80 (5-CH_2), 61.64 (C-3), 126.71, 127.08, 128.17, 128.39, 129.61, 129.94, 136.23, 136.76 (Ph), 161.44 (C-5), 169.83, 170.86, 170.92 (CO).

Synthesis of 4-substituted 7-benzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazines

Method A. To a solution of the corresponding 4,7-disubstituted pyrrolopyrazine (1.8 mmol) in 1,2-dimethoxyethane or THF (25 mL) was added, under Ar atmosphere, freshly prepared NaMeO (1.8 mmol). After 5 min. of stirring, benzyl bromide (2.7 mmol) was added and the stirring continued overnight. After evaporation of the solvent, the residue was extracted with EtOAc (100 mL) and washed with H_2O (2 x 50 mL) and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The resulting residue was purified on a silica gel column using the solvent system specified in each case.

Method B. Identical to that described in method B for the synthesis of 4,7-disubstituted analogues, but starting from the disubstituted malonate derivative **34**.

***7-Benzyl-4-methyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (28).** Chromatographic solvent system: CH_2Cl_2/MeOH (75:1). Isomer **28a**: Yield, 53% (From **21a**, method A). Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85. Found: C 64.77, H 6.47, N 9.01. Isomer **28b**: Yield, 15% (From **21a**, method A). Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85. Found: C 64.29, H 6.52, N 8.64. Isomer **28d**: Yield, 69% (From **21d**, method A). Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C 64.54, H 6.37, N 8.85. Found: C 64.51, H 6.40, N 8.97.

***7-Benzyl-4-isobutyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (29).** Chromatographic solvent system: CH_2Cl_2/MeOH (130:1). Isomer **29ab**: Yield, 80% (**a**/**b**=3:1, from **22ab**, method A). Anal. Calcd. for $C_{20}H_{26}N_2O_4$: C 67.02, H 7.31, N 7.81. Found: C 67.10, H 7.60, N 8.01. Isomer **29cd**: Yield, 69% (**c**/**d**=1:1, from **22cd**, method A). Anal. Calcd. for $C_{20}H_{26}N_2O_4$: C 67.02, H 7.31, N 7.81. Found: C 67.23, H 7.58, N 7.67.

***4,7-Dibenzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine* (30).** Chromatographic solvent system: Gradient from 50 to 90% of EtOAc in hexane. Isomer **30a**: Obtained in 53 and 17% yield from **23** and **34**, respectively, using methods A and B. HPLC; t_R=37.73 min (A/B, 22:78). Anal Calcd. for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.18, H 6.40, N 7.03. Isomer **30b**: Obtained in 12 and 28% yield from **23** and **34**, respectively, using methods A and B. HPLC; t_R=87.27 min (A/B, 22:78). Anal Calcd. for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.12, H 6.02, N 6.98. Isomer **30c**: Obtained in 2 and 5% yield from **23** and **34**, respectively, using methods A and B. HPLC; t_R=41,80 min (A/B, 22:78). Anal Calcd. for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 69.98, H 6.16, N 6.99. Isomer **30d**: Obtained in 7 and 10% yield from **23** and **34**, respectively, using methods A and B. HPLC; t_R=81.93 min (A/B, 22:78). Anal Calcd. for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.15, H 6.40, N 6.97.

Table 5. Significant ^1H NMR data of 4,7,7-trisubstituted perhydropyrrolo[1,2-*a*]pyrazines (300 MHz, $CDCl_3$)

Compd.	δ (ppm)									
	H-1		H-2	H-4	H-8		H-8a	4-CH_2[a]		
28a	3.16	3.07	6.99	3.92	2.22		2.32	1.65		
28b	3.27	2.65	7.01	4.19	2.39	1.61	3.84	1.55		
28d	3.21		6.74	4.38	2.36	2.27	3.09	1.11		
29a[b]	3.13		6.55	3.97	2.21		2.38	2.02		
29b[b]	3.26	2.93	5.77	4.51	2.56	1.65	3.85	1.65		
29c[c]	3.72	3.01	6.33	4.17	2.27	2.00	4.94	1.80		
29d[c]	3.43	3.20	6.87	4.89	2.62	1.78	4.17	1.84	1.21	
30a	2.57	1.54	6.40	4.21	1.98		2.09	3.99	3.04	
30b	2.83	1.48	6.40	4.53	2.30	1.48	3.75	3.77	3.06	
30c	2.75	1.65	6.25	4.68	2.48	1.50	2.88	3.41	3.24	
30d	3.25	2.90	6.27	4.70	2.15	1.95	2.48	3.33	3.06	
31a	2.45	1.63	5.75	4.18	1.98		2.15	4.03	3.34	
31b	2.68	1.46	5.96	4.44	2.21	1.27	3.68	3.90	3.31	
32a	3.35	3.07	6.49	3.93	2.20		2.38	3.11	3.04	
32b[b]	3.40	1.49	6.46	4.43	2.04	1.25	3.37	3.05		
32c[c]	3.07	2.12	6.10	3.91	2.50	1.60	4.20	3.05		
32d	3.30		6.25	4.44	2.35	2.12	3.68	3.04	2.75	
33a[b]	3.05		6.74	3.91	2.18		2.26	2.51	1.95	
33b[b]	3.22	2.70	6.86	4.18	2.50	1.95	3.77	2.28	1.90	
33c[c]	3.10	2.65	[d]	4.29	2.24	1.55	3.70	2.45	2.12	
33d[c]	3.36	3.05	[d]	4.04	2.05		3.00	2.45	2.02	

[a] CH_3 group for Ala derivatives **29**. [b] From the **ab** mixture. [c] From the **cd** mixture. [d] Included in the aromatic signals.

7-Benzyl-4-(indole-3-yl)methyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine **(31)**. Chromatographic solvent system: CH_2Cl_2/MeOH (60:1). Isomer **31a**: Yield, 34% (From **24ab**, method A). Anal. Calcd. for $C_{25}H_{25}N_3O_4$: C 69.59, H 5.84, N 9.74. Found: C 69.32, H 6.53, N 9.41. Isomer **31b**: Yield, 9% (From **24ab**, method A). Anal. Calcd. for $C_{25}H_{25}N_3O_4$: C 69.59, H 5.84, N 9.74. Found: C 69.21, H 5.97, N 9.39.

7-Benzyl-4-(methoxycarbonyl)methyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-a]pyrazine **(32)**. Chromatographic solvent system: CH_2Cl_2/MeOH (15:1). Isomer **32a**: Obtained in 10 and 25% yield from **26abcd** and **26ab**, respectively, method A. Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C 60.95, H 5.92, N 7.48. Found: C 60.73, H 5.85, N 7.16. Isomer **32ab**: Obtained in 8% (**a**/**b**, 1:1) and 16% (**a**/**b**, 1:1.7) yield from **26abcd** and **26ab**, respectively, method A. Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C 60.95, H 5.92, N 7.48. Found: C 61.03, H 6.28, N 7.21. Isomer **32cd**: Obtained in 10% (**c**/**d**, 1:1.5, method A). Anal. Calcd. for $C_{19}H_{22}N_2O_6$:

C 60.95, H 5.92, N 7.48. Found: C 60.66, H 5.90, N 7.67. Isomer **32d**: Obtained in 7% yield from **26abcd**, method A. Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C 60.95, H 5.92, N 7.48. Found: C 60.74, H 5.71, N 7.59.

Complex mixtures of mono- and dicarboxylic acid derivatives were also isolated from this reaction.

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