Pergamon

*Tetrahedron*, Vol. 52, No. 44, pp. 13991-14004, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00842-3

# Bicyclic Lactams as Templates for Peptidomimetics. Studies on Stereoselective Synthetic Routes to 6-Oxoperhydropyrrolo[1,2-*a*]pyrazines

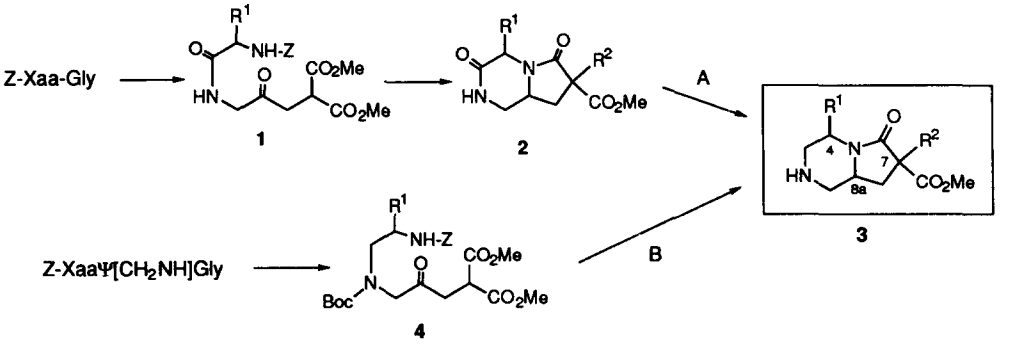
**Mercedes Martín-Martínez, Rosario Herranz, Mª Teresa García-López and Rosario González-Muñiz***

Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain.

***Abstract:*** The synthesis of 4,7,7-trisubstituted 6-oxoperhydropyrrolo[1,2-a]pyrazines, as spacer templates for peptidomimetics, from the corresponding 3,6-dioxo analogues is described using different reduction methods. An alternative approach, based on the intramolecular reductive amination of 4-ketodiesters derived from Ψ[$CH_2NH$] pseudodipeptides and subsequent γ-lactamization, was also used for the stereoselective preparation of these templates. 

In a recent paper we described the preparation of 4,7,7-trisubstituted 3,6-dioxoperhydropyrrolo-[1,2-*a*]pyrazines **2**, as conformationally restricted Xaa-Gly-Yaa tripeptide mimetics.[1] These mimetics, in which the attached 7-carboxylate substituent could serve to extend the peptide chain at *C*-terminus, do not possess an appropriate amino group to be incorporated as spacer templates into higher peptides. To overcome this limitation we focused our attention on the related 6-oxoperhydropyrrolo[1,2-*a*]pyrazines **3**, with a secondary amino function in position 2 for *N*-terminal extension.

As it is shown in Scheme 1, two alternative strategies were envisaged for the preparation of compounds **3**. These strategies involve the regioselective reduction of the δ-lactam carbonyl group of the previously obtained 3,6-dioxo derivatives **2** (Route A), and the elaboration of the 6-oxoperhydropyrrolo[1,2-*a*]pyrazine skeleton from the suitably protected 4-ketodiesters **4**, derived from the reduced peptide bond pseudodipeptides Z-XaaΨ[$CH_2NH$]Gly. As it happens with the construction of the nitrogen bridged lactam system in compounds **2** from 4-ketodiesters derived from Z-Xaa-Gly dipeptides,[1] it was expected that intramolecular reductive amination of the analogous 4-ketodiesters **4** and subsequent γ-lactamization would provide ready access to the target 6-oxoperhydropyrrolo[1,2-*a*]pyrazines.

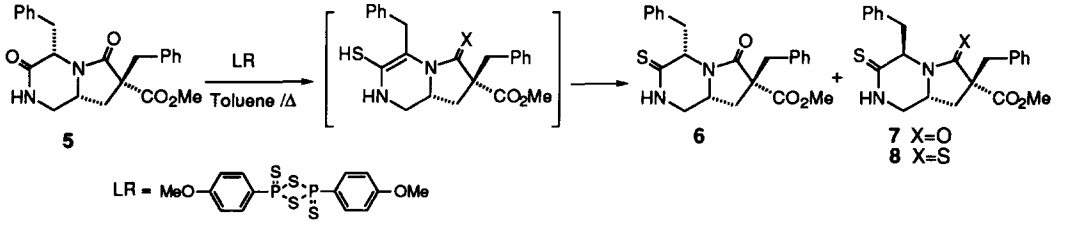



*Scheme 1*

This paper deals with the synthesis of compounds **3** by application of the above mentioned synthetic routes. The results obtained by using different reduction methods, in route A, and the different aspects involved in the construction of the bicyclic lactam system by route B are discussed. The stereoselectivity found in the formation of the new asymmetric centers C-7 and C-8a, by application of the latter route, will be compared to those obtained in the preparation of compounds **2** from dipeptide derivatives.[1]

## RESULTS AND DISCUSSION

To explore the synthetic route A, the (4*S*,7*R*,8a*R*)-4,7-dibenzyl-7-methoxycarbonyl-3,6-dioxo-perhydropyrrolo[1,2-*a*]pyrazine (**5**) was selected as starting compound.[1] Taking into account that the reduction of thioamides is, in general, easier than that of corresponding amides,[2] the preparation of thioamide derivatives from **5** was firstly investigated. Thus, treatment of compound **5** with one equivalent of the Lawesson's reagent in refluxing toluene resulted in a 1:2.6 mixture of the epimeric 3-thio derivatives **6** and **7**, while a similar reaction using two equivalents of this reagent and prolonged reaction time afforded the 3,6-dithio analogue **8**, resulting from the complete epimerization at C-4 (Scheme 2). Although the Lawesson's reagent has been used for the preparation of linear peptide thioamides with retention of the configuration at the different chiral centers,[3,4] the observed epimerization could be due to the formation of thioimide-like intermediates, that finally gave the thermodynamically more stable perhydropyrrolo[1,2-*a*]pyrazines **7** and **8**.[1]

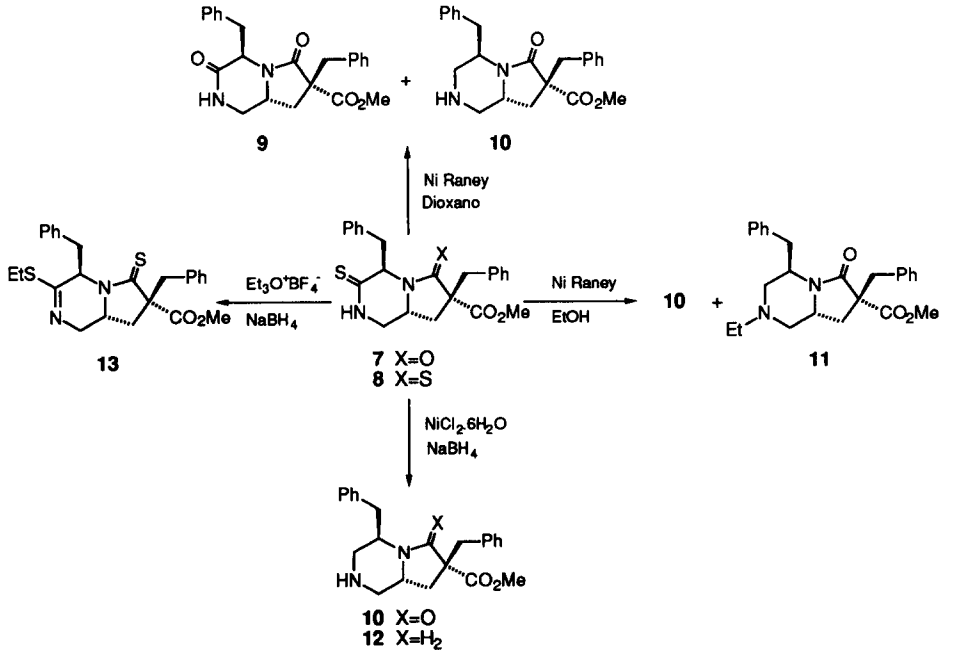



***Scheme 2***

The coupled $^{13}C$ NMR spectra of monothioamides **6** and **7** indicated that, in both compounds, the incorporation of sulphur took place exclusively in position 3. Significant differences were observed in the $^{1}H$ NMR spectra of these diastereoisomers, being the chemical shifts of the axially situated H-1 proton and the aromatic resonances the most marked (Table 1). Thus, in derivative **7** the H-1ax proton appeared at 1.7 and 2 ppm higher field than in compounds **5** and **6**, respectively, while the aromatic signals were considerably shielded when compared to the same signals in **5** and **6**. Both facts indicated that in compound **7** the benzyl substituents are located in the same face of the bicyclic ring. Additionally, the observed lower field shift of H-2 ($\Delta\delta \approx 2$ ppm) and H-4 ($\Delta\delta \approx 0.5$ ppm) protons, and of C=S ($\Delta\delta \approx 29$ ppm), C-4 ($\Delta\delta \approx 4.5$-6 ppm), C-1 and 4-$CH_2$ ($\Delta\delta \approx 3$ ppm) carbons in the $^{1}H$ and $^{13}C$ NMR spectra of compound **6** when compared to its corresponding 3,6-dioxo analogue **5** were in good agreement with the reported values for related thioamide derivatives.[3,4] Similar differences were found for the 4*R* derivative **7** when compared to the dioxo analogue **9**,

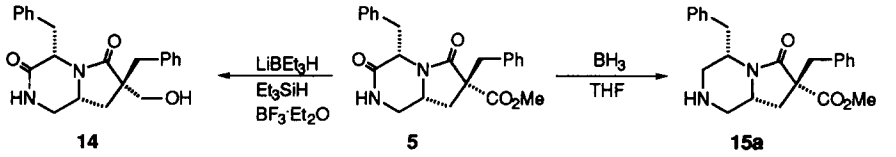
obtained as described later. The presence of the thiocarbonyl group in the five-membered ring of compound **8** induced a lower field shift in the C-7 (9 ppm) and the 7-$CH_2$ (2.5 ppm) carbons when compared to the dioxo derivative **9**, and in the H-4 proton (0.4 ppm) and C-4 carbon (3 ppm) when compared to the 3-monothioamide **7**.

In order to examine the desulphuration of the thioamides **6-8** three different reduction methods were used: a) Ni Raney;[5-8] b) Nickel boride,[9-11] and c) formation of *S*-alkyl thioimides and subsequent reduction with $NaBH_4$[12] (Scheme 3). Taking into account that the solvent is a crucial factor in the reductions using Ni Raney, we studied this reaction in two different solvents, dioxane and EtOH. In the first one, the 4*R*-benzyl thioamide **7** was mainly transformed into the 3,6-dioxo derivative **9**, while only an 8% of the reduced analogue **10** was obtained. However, the change from dioxane to EtOH allowed us to improve the yield of the expected compound **10** in 25%, although the *N*-ethyl derivative **11** was always formed as byproduct. This side reaction, due to the condensation of amine **10** with the acetaldehyde generated in the reaction medium,[6] was dependent on the amount of Ni Raney. In fact, the use of a large excess of this reducing agent afforded compound **11** as the only reaction product. Amine **10** was also prepared in moderate yield (35%) by reaction of thioamide **7** with Ni boride, generated *in situ* by treatment of $NiCl_2.6H_2O$ with $NaBH_4$.[9-11] A similar reaction of the 3,6-dithio derivative **8** gave the completely desulphurized analogue **12** (40%). However, all attempts to reduce the 4*S*-benzyl thioamide **6** by this method were unsuccessful, affording complex mixtures of reaction products, from which the corresponding 3,6-dioxoderivative **5** and its epimer **9** were isolated in low yields. Finally, the reaction of dithioamide **8** with $Et_3O^+BF_4^-$ gave *S*-ethyl intermediate **13** which remained unaltered after treatment with $NaBH_4$.[12]




*Scheme 3*

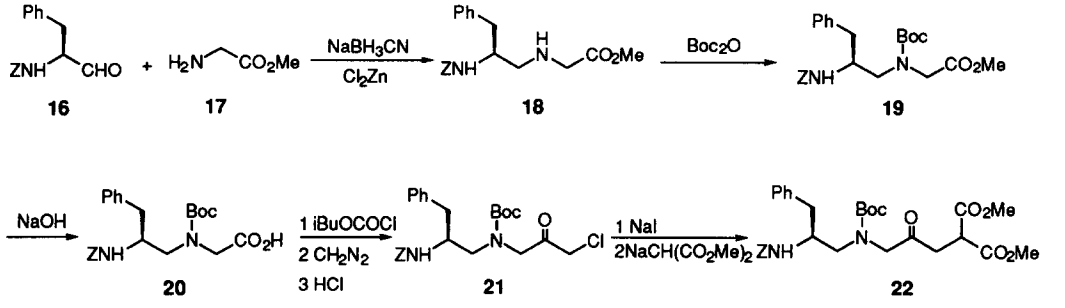
Although the $LiBEt_3H/Et_3SiH/BF_3.Et_2O$ system has been successfully used for the selective reduction of lactams in the presence of carboxylic esters,[13,14] its application to compound **5** exclusively gave the 7-hydroxymethyl derivative **14** (68%). The direct reduction of the δ-lactam carbonyl group of compound **5** was finally accomplished by treatment with diborane,[15,16] to give the desired amine derivative **15a** in which all the asymmetric centers remained unaltered (Scheme 4).




**14** **5** **15a**

*Scheme 4*

In order to examine the construction of the 6-oxoperhydropyrrolo[1,2-*a*]pyrazine system from pseudodipeptide derivatives, having a $CH_2NH$ group as peptide bond surrogate, the 4-ketodiester **22** was prepared as depicted in Scheme 5. Thus, reaction of the aminoaldehyde **16** with H-Gly-OMe, followed by reduction of the resulting imine intermediate with $NaBH_3CN$,[17] afforded Z-PheΨ[$CH_2NH$]Gly-OMe (**18**). In order to avoid side reactions due to the secondary amino group in compound **18**, it was protected with a *tert*-butyloxycarbonyl group to give derivative **19** that was, subsequently, saponified to the corresponding carboxylic acid **20**. Finally, the 4-ketodiester **22** was prepared by alkylation of dimethyl malonate with the chloromethyl ketone **21**, previously obtained from **20**, following a similar procedure to that reported for dipeptide derivatives.[1]



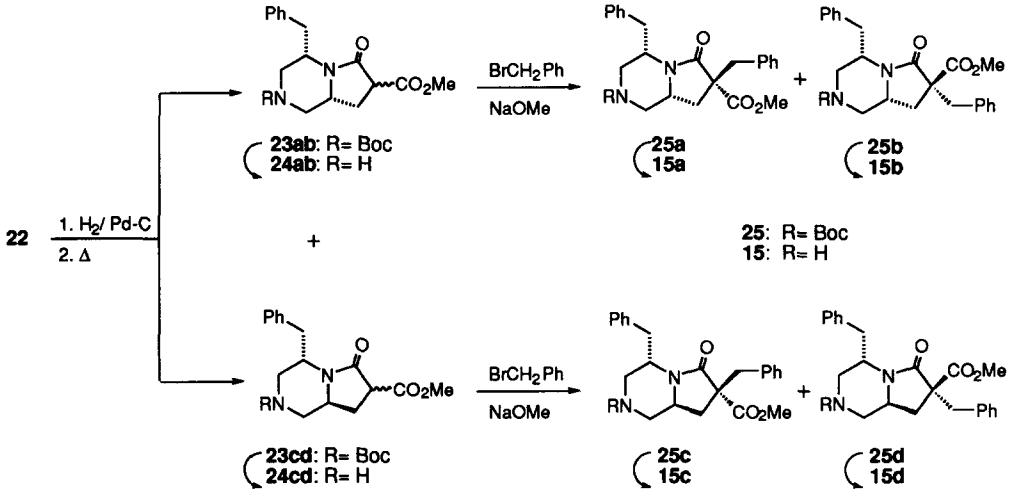

**16** **17** **18** **19**

**20** **21** **22**

*Scheme 5*

Catalytic hydrogenation of compound **22** at 30 psi of pressure, using Pd-C as catalyst, followed by reflux in toluene to complete the γ-lactamization process, afforded the expected 6-oxoperhydropyrrolo[1,2-*a*]pyrazines **23** as a 4.3:1 mixture of the diastereoisomeric pairs **23ab** and **23cd**, that were chromatographically separated (Scheme 6). Alkylation of the 8a*R* diastereoisomers **23ab** with benzyl bromide in the presence of sodium methoxide gave a 7:1 mixture of derivatives **25a** and **25b**, while a similar reaction of **23cd** afforded the 7-benzyl derivatives **25c** and **25d** in a 1:1.4 ratio.

The $^1H$ NMR spectra of bicyclic derivatives **23** and **25**, as those of linear compounds **19-22**, showed two sets of signals due to the existence of an equilibrium between the *cis* and *trans* rotamers around the CON linkage of the Boc group. Therefore, to facilitate the structural assignment of these bicyclic compounds, they were deprotected by treatment with TFA. The absolute configuration at C-7 and C-8a of the resulting 7-benzyl derivatives **15** was established on the basis of the chemical shifts of the H-1, H-3, H-4 and H-8a protons, as well as by NOE experiments. Thus, the observed shielding for H-4 (0.85 ppm) and H-8a (1.57 ppm) protons in compound **15a**, when compared to the same protons in **24a**, indicated that the 7-benzyl group and these protons are in *cis* disposition. Since the configuration at C-4 is fixed by that of the starting pseudodipeptide, the diastereoisomer **15a** has 4*S*,7*R*,8a*R* configuration. Moreover, this compound is identical to that obtained by reduction with diborane of bis-lactam **5**. A similar shielding effect of the 7-arylmethyl chain on the 8a proton was found for isomer **15d** ($\Delta\delta$ = 1.33 ppm), having 7*S*,8a*S* configuration. This isomer and their enantiomer **10** showed a significant NOE between the 4-$CH_2$ and H-8a protons indicating that these protons are located on the same face of the heterocyclic ring. The fact that this NOE was also present in compound **15c** allowed us to discriminate between diastereoisomers **15b** and **15c**.




***Scheme 6***

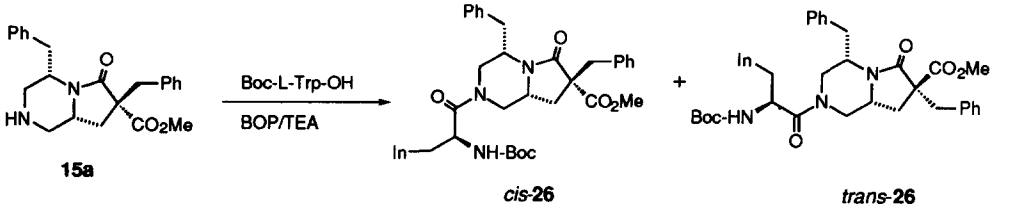
Concerning the stereochemical course of the reductive amination of 4-ketodiester **22** leading to the hexahydropyrazine ring of derivatives **23**, it can be noted that, although the 8a*R* diastereoisomers **23ab** were the major compounds, the 8a*R*/8a*S* diastereoisomeric excess (62%) was lower than that obtained in the case of the corresponding 4-ketodiester derived from Z-Phe-Gly (de = 76%).[1] In this case, it was demonstrated by $^1H$ NMR that the imine formed as intermediate, which could be isolated, is preferentially in a folded conformation in which the aromatic ring of the benzyl moiety folds over the oxotetrahydropyrazine ring. This conformation allows the existence of stabilizing interactions which hinder the entrance of the hydrogen by the same face of the benzyl group. Lower percentages of this folded conformation in the corresponding tetrahydropyrazine intermediate formed from intramolecular amination of **22** could be responsible for the decrease in the

stereoselectivity found in the synthesis of **23**. Support for this assumption comes from the 4-$CH_2$-H-4 coupling constant values of the 6-oxo derivatives **15** suggesting that the folded conformation is not predominant in these compounds. Contrastingly, in the 3,6-dioxo analogues **5** and **9** these coupling constant values were in good agreement with a preference for such a folded conformations (Table 1). Based on these considerations, it can be concluded that this type of folded conformations are stabilized by $\pi$-$\pi$ interactions between the carbonyl group of the pyrazine ring and the phenyl group of the 4-benzyl substituent.

Similarly to the alkylation leading to the incorporation of the 7-benzyl ($R^2$) substituent into the 3,6-dioxo-4,7,7-trisubstituted pyrrolopyrazines **2**,[1] the attack of the benzyl halide on the 6-oxo analogues **23**, to give the corresponding 7-benzyl derivatives **25**, preferentially occurs from the opposite side to the unshared lone pair on the lactam nitrogen.[18] However, the 7R/7S diastereoisomeric excess found in the alkylation of the 8aR diastereoisomers **23ab** was higher than that observed in the synthesis of the 3,6-dioxo analogue **5** and its 7*S*-epimer. In contrast, alkylation of the 8aS isomers **23cd** resulted in lower stereoselectivity at C-7 than in the case of the corresponding 3,6-dioxo derivatives.[1] The particular conformations of the 6-oxo- and 3,6-dioxoperhydropyrrolopyrazine rings and the different degree of mobility of the respective 4-benzyl groups could explain the differences in the stereoselectivity of the alkylation reaction between these two series of related compounds.

Comparing the synthesis of derivative **15a** by the two alternative methods, it must be noted that the regioselective reduction of compound **5** with diborane resulted in better global yield (10%, from commercial Z-Phe-Gly-OH) than the elaboration of the bicyclic ring from the reduced pseudopeptide (4.5%, from **20**). Moreover, this second synthetic route needs five additional steps of reaction for the preparation of the starting pseudodipeptide Z-Phe$\Psi$[$CH_2$N(Boc)]Gly (**20**).

In order to illustrate the utility of the secondary amino group in the 6-oxopyrrolopyrazine system for coupling reactions, compound **15a** was reacted with Boc-L-Trp-OH, in the presence of BOP as coupling reagent, to give the tryptophyl derivative **26** in 72% yield (Scheme 7). As it was observed for peptide derivatives containing alkylated peptide bonds,[19] the $^1$H NMR spectra of compound **26** showed the presence of the *cis/trans* isomerism around the CON bond of the secondary amide. The assignment of the signals corresponding to the *cis* and *trans* forms was based on the observation of a strong NOE cross peak between the H-1ec and the Trp α-CH protons for the *cis* rotamer. The percentage of *cis/trans* rotamers, calculated from the relative intensities of the Trp α-CH-signals in the spectra registered at 30°C, was 1.2:1 in $CDCl_3$ and 2:1 in DMSO-$d_6$. A stabilizing stacking between the indole ring of the Trp residue and the phenyl ring of the 4-benzyl moiety, occurring when the amide bond is *trans*, could be responsible for the slightly enhanced proportion of this conformer in the less polar solvent.




*Scheme 7*

In conclusion, the approaches reported here allow us to elaborate the 6-oxoperhydropyrrolo[1,2-a]-pyrazine system in stereoselective way. These new nitrogen-bridged bicyclic templates bear an appropriate amino function for N-terminal extension, while the elongation of the peptide chain at C-terminus could be performed through the 7-carboxylate group, following the procedure described for related 3-oxoindolizidine derivatives.[20]

## EXPERIMENTAL PROCEDURES

$^1$H NMR spectra were recorded with a Varian Gemini 200, a Varian XL-300 or a Varian Unity 500 spectrometers operating at 200, 300 or 500 MHz, respectively, using TMS as internal standard. $^{13}$C NMR spectra were registered on a Varian Gemini 200 (50 MHz). The $^{13}$C NMR assignations were performed by means of heteronuclear H-C correlations (HETCOR). Optical rotations were measured on a Perkin Elmer 141 polarimeter. Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 $F_{254}$ (Merck).Compounds were detected with UV light or ninhydrine spray. Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Z-Phe-H (**16**) was synthesized as described.[21]

### Synthesis of 3-thio- and 3,6-dithioxoperhydropyrrolo[1,2-a]pyrazines

*Method A.*– A solution of compound **5** (300 mg, 0.76 mmol) and Lawesson's reagent (310 mg, 0.76 mmol) in toluene (20 mL) was refluxed for 1h. After evaporation of the solvent, the resulting residue was purified on a silica gel column using a gradient from 10 to 25% of EtOAc in hexane.

*Method B.*– Identical to method A, but using 1.56 mmol of Lawesson's reagent and refluxing for 1 day.

**(4*S*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonyl-6-oxo-3-thioxoperhydropyrrolo[1,2-*a*]-pyrazine (6).–** Yield: 23% (Method A).White solid, m.p.: 164-166°C (EtOAc-hexane). Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C 67.62, H 5.92, N 6.86, S 7.85. Found: C 67.52, H 5.67, N 6.56, S 7.55.

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonyl-6-oxo-3-thioxoperhydropyrrolo[1,2-*a*]-pyrazine (7).**– Yield: 60% (Method A). Syrup. Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C 67.62, H 5.92, N 6.86, S 7.85. Found: C 67.28, H 5.71, N 7.00, S 7.70.

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonyl-3,6-dithioxoperhydropyrrolo[1,2-*a*]pyrazine (8).–** Yield: 79% (Method B). Foam. Anal. Calcd. for $C_{23}H_{24}N_2O_2S_2$: C 65.06, H 5.70, N 6.60, S 15.10. Found: C 65.41, H 5.54, N 6.38, S 14.95.

The NMR data of these compounds are recorded in Table 1.

### Reduction of 3-thio- and 3,6-dithioxoperhydropyrrolo[1,2-a]pyrazines

*Method A: Reduction with Ni-Raney/Dioxane.*– A solution of the 3-thio derivative **7** (50 mg, 0.12 mmol) in dioxane (4 mL) was treated with Ni-Raney (4x300 mg). After 7 h of reflux, the reaction mixture was filtered through celite, and the solvent evaporated to dryness. The resulting residue was purified on a silica gel column using a gradient from 10 to 70% of EtOAc in hexane, to give the following compounds:

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine (9).–** Yield: 30%. Syrup. $[\alpha]_D$: –27.1° (c= 0.3, $CHCl_3$). Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.10, H 6.53, N 6.97.

**Table 1.**– Significant NMR data of compounds **5-12**, **15** and **24**

| Compd. | $^1$H NMR[a] ($CDCl_3$, δ ppm) | | | | | | | | | | $^{13}$H NMR[b] ($CDCl_3$, δ ppm) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-1ax | H-1ec | H-2 | H-3ax | H-3ec | H-4 | 4-$CH_2$[c] | 4-$CH_2$[c] | H-8a | Ar | C-4 | C-7 | C-8a | C-3 | C-6 |
| **5**[1] | 1.54 | 2.57 | 6.40 | – | – | 4.21 | 3.04 (2.9) | 3.99 (4.9) | 2.09 | 7.13-7.23 | 58.06 | 58.23 | 51.75 | 169.92[d] | 171.48[d] |
| **6**[e] | 1.31 | 2.66 | 8.57 | – | – | 4.77 | 3.31 (2.9) | 4.05 (5.0) | 2.09 | 7.10-7.25 | 64.30 | 57.64 | 50.73 | 199.31 | 170.72 |
| **7** | 3.30 | 3.05 | 8.24 | – | – | 5.13 | 3.02 (6.0) | 3.80 (3.7) | 2.52 | 6.72-7.39 | 60.07 | 56.30 | 47.37 | 198.68 | 169.11 |
| **8**[e] | 3.50 | 3.04 | 9.04 | – | – | 5.68 | 3.20 (5.8) | 3.86 (3.1) | 2.70 | 6.68-7.28 | 65.05 | 66.34 | 56.72 | 197.65[d] | 198.39[d] |
| **9** | 3.25 | 2.90 | 6.27 | – | – | 4.70 | 3.06 (5.4) | 3.33 (3.4) | 2.48 | 6.58-7.36 | 55.27 | 56.67 | 49.20 | 169.82[d] | 170.20[d] |
| **11** | 1.70 | 2.84 | – | 1.70 | 2.60 | 4.18 | 2.52 (4.7) | 2.68 (11.0) | 2.96 | 7.18-7.32 | 50.50 | 56.82 | 50.50 | 60.49 | 170.07 |
| **12**[f] | 2.48 | 2.94 | – | 2.71 | 2.61 | 2.94 | 2.73 (9.6) | 2.94 | 2.94 | 6.95-7.24 | 57.06 | 52.80 | 54.25 | 46.43 | 58.23 |
| **15a**[f] | 2.37 | 2.86 | – | 2.40 | 2.64 | 3.12 | 2.92 (10.2) | 4.13 (4.5) | 2.30 | 7.13-7.24 | 59.88 | 57.35 | 56.09 | 49.50 | 171.98 |
| **15b**[f] | 1.69 | 2.92 | – | 2.19 | 2.71 | 3.52 | 2.82 (10.7) | 4.29 (4.4) | 3.52 | 7.12-7.31 | 58.85 | 57.38 | 55.53 | 49.10 | 171.36 |
| **15c**[f] | 1.52 | 2.96 | – | 2.12 | 2.79 | 4.26 | 2.36 | 2.96 | 3.69 | 7.08-7.26 | 50.28 | 56.66 | 50.28 | 46.13 | 169.68 |
| **15d**[f] **(10)** | 2.37 | 3.07 | – | 2.75 | 2.53 | 4.23 | 2.58 (5.1) | 2.69 (11.0) | 2.94 | 7.16-7.31 | 50.14 | 57.45 | 50.01 | 44.86 | 170.42 |
| **24a**[g] | 2.88 | 3.32 | – | 3.01 | 3.01 | 3.97 | 2.68 | 3.97 | 3.87 | 7.12-7.27 | – | – | – | – | – |
| **24b**[g] | 2.60 | 3.32 | – | 3.01 | 3.01 | 3.97 | 2.68 | 3.97 | 3.87 | 7.12-7.27 | – | – | – | – | – |
| **24c**[h] | 2.82 | 3.57 | – | 2.99 | 3.25 | 4.55 | 2.99 | 2.99 | 4.12 | 7.23-7.27 | – | – | – | – | – |
| **24d**[h] | 2.99 | 3.57 | – | 2.99 | 3.25 | 4.55 | 2.99 | 2.99 | 4.27 | 7.23-7.27 | – | – | – | – | – |

[a] Registered at 300 MHz unless otherwise indicated. [b] Registered at 50 MHz. [c] The $H_4$-4-$CH_2$ coupling constant values are indicated in parenthesis. [d] Signals that may be interchanged. [e] Registered at 200 MHz. [f] Registered at 500 MHz. [g] From the **24ab** mixture. [h] From the **24cd** mixture.

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (10).–** Yield: 8% . Syrup. $[\alpha]_D$= +120° (c= 0.5, $CHCl_3$). Anal. Calcd. for $C_{23}H_{26}N_2O_3$: C 72.99, H 6.92, N 7.40. Found: C 73.21, H 6.72, N 7.33.

Significant NMR data of these compounds are recorded in Table 1.

*Method B: Reduction with Ni-Raney/EtOH.–* A solution of compound **7** (100 mg, 0.24 mmol) in EtOH (8 mL) was treated with Ni-Raney (3x600 mg) and refluxed for 6.5 h. The reaction mixture was filtered through celite and the solvent evaporated to dryness. The resulting residue was dissolved in $CH_2Cl_2$, dried over $Na_2SO_4$ and evaporated. The residue was purified on a silica gel column using a gradient from 20 to 25% of EtOAc in hexane.

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-2-ethyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]-pyrazine (11).–** Yield: 68%. Foam. $^1H$ NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, $CH_3$, Et, J=7.3), 1.70 (m, 2H, H-1, H-3), 2.16 (dd, 1H, H-8, J=13.3, 7.8), 2.23 (m, 1H, H-8), 2.26 (dd, 1H, $CH_2$, Et, J=13.3, 7.3), 2.38 (dd, 1H, $CH_2$, Et, J=13.3, 7.3), 2.52 (dd, 1H, 4-$CH_2$, J=13.0, 4.7), 2.60 (d, 1H, H-3, J=11.7), 2.68 (dd, 1H, 4-$CH_2$, J=13.0, 11.0), 2.84 (m, 1H, H-1), 2.96 (m, 1H, H-8a), 3.08 (d, 1H, 7-$CH_2$, J=13.7), 3.28 (d, 1H, 7-$CH_2$, J=13.7), 3.80 (s, 3H, $CO_2Me$), 4.18 (m, 1H, H-4), 7.18-7.32 (m, 10H, Ph). $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 11.99 ($CH_3$, Et), 31.66 (C-8), 35.37 (4-$CH_2$), 39.52 (7-$CH_2$), 50.17 and 50.50 (C-4 y C-8a), 51.72 and 51.98 (C-1, $CH_2$-Et), 52.84 (OMe), 56.82 (C-7), 60.49 (C-3), 126.39, 127.12, 128.43, 129.51, 130.26, 135.97 and 138.42 (Ph), 170.07 and 172.65 (CO). Anal. Calcd. for $C_{25}H_{30}N_2O_3$: C 73.86, H 7.44, N 6.89. Found: C 73.51, H 7.75, N 7.12.

When this reaction was performed with 300 mg of Ni-Raney (7 h) a mixture of compounds **10** (33%) and **11** (31%) was obtained.

*Method C: Reduction with $NiCl_2/NaBH_4$.– General procedure:* A solution of the corresponding thio derivative (0.17 mmol) and $NiCl_2{\cdot}6H_2O$ (1.41 mmol) in MeOH/THF (1:1, 4 mL) was treated, at 0 °C, with $NaBH_4$ (8.49 mmol).After stirring at r.t. for 30 min, the reaction mixture was filtered though celite and the solvents evaporated to dryness. The resulting residue was dissolved in $CH_2Cl_2$, washed with $NaHCO_3$, saturated solution of EDTA and $H_2O$. The organic layer was dried over $MgSO_4$ and evaporated to give a residue which was purified on a silica gel column using the solvent system indicated in each case.

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonylperhydropyrrolo[1,2-*a*]pyrazine (12).–** Eluent: Gradient from 1 to 5% of MeOH in $CH_2Cl_2$. Yield: 40% (From **8**). Syrup. Anal. Calcd. for $C_{23}H_{28}N_2O_2$: C 75.79, H 7.74, N 7.69. Found: C 75.50, H 7.63, N 7.46.

Significant NMR data of this compound is indicated in Table 1.

When this reaction was performed with compound **7** the amino derivative **10** (35%) was obtained, while from reaction of compound **6** only the 3,6-dioxo derivatives **5** (12%) and **9** (5%) were isolated.

*Method D: Reduction with $Et_3O^+BF_4^-/NaBH_4$.–* A solution of compound **8** (75 mg, 0,17 mmol) in $CH_2Cl_2$ (4 mL) was treated, at 0 °C, with 1M $Et3O^+BF_4^-$ (420 mL, 0.42 mmol), under Ar atmosphere. After 20 h of stirring at r.t. the solvent was evaporated to dryness, the residue was dissolved in MeOH (3 mL) and treated with NaBH4 (53.3 mg, 1.4 mmol). After 2 days of reaction at r.t. a saturated solution of $NaHCO_3$ (3 mL) was added and the resulting mixture was extracted with EtOAc (3x30 mL). The organic layers were dried over $Na_2SO_4$ and evaporated. The resulting residue was purified on a silica gel column using a gradient from 10 to 15% of EtOAc in hexane, to give compound **13** (31 mg, 38%).

**(4*R*,7*R*,8a*R*)-4,7-Dibenzyl-2-ethylthio-7-methoxycarbonyl-6-thioxo-$\Delta^{2,3}$-hexahydropyrrolo-[1,2-*a*]pyrazine (13).–** $^1$H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, 3H, $CH_3$, Et, J=7.4), 2.03 (dd, 1H, H-8, J=13.9, 4.2), 2.24 (dd, 1H, H-8, J=13.9, 9.1), 2.56 (m, 1H, H-8a), 2.98 (dd, 1H, $CH_2$, Et, J=14.8, 7.4), 2.99 (dd, 1H, $CH_2$, Et, J=14.8, 7.4), 3.21 (dd, 1H, 4-$CH_2$, J=14.1, 5.9), 3.33 (dd, 1H, 4-$CH_2$, J=14.1, 2.9), 4.48 (m, 3H, H-1, 7-$CH_2$), 3.69 (dd, 1H, H-1, J=16.3, 4.6), 3.75 (s, 3H, $CO_2Me$), 5.29 (m, 1H, H-4), 6,69-7,37 (m, 10H, Ph). $^{13}$C NMR (50 MHz, $CDCl_3$): δ 14.14 ($CH_3$, Et), 23.69 (C-8), 30.88 (4-$CH_2$), 35.71 (7-$CH_2$), 41.70 (C-1), 53.10 (OMe), 55.20 ($CH_2$, Et), 56.97 y 60.37 (C-4 y C-8a), 66.31 (C-7), 127.13, 128.14, 128.33, 128.46, 129.76, 131.14, 135.71 and 136.36 (Ph), 163.39 (C-3), 171.65 (CO), 197.54 (C-6). Anal. Calcd. for $C_{25}H_{28}N_2O_2S_2$: C 66.34, H 6.23, N 6.29, S 14.17. Found: C 66.09, H 6.32, N 6.01, S 14.29.

**Reduction of 3,6-dioxoperhydropyrrolo[1,2-a]pyrazines**

*Method A: Reduction with $LiBEt_3H/Et_3SiH/BF_3{\cdot}Et_2O$.–* A solution of the bicyclic lactam **5** (235 mg, 0.6 mmol) in dry THF (5 mL), cooled to –78 °C and under Ar atmosphere, was treated with an 1M solution of $LiBEt_3H$ in THF (1.44 mL, 1.44 mmol). After stirring at r.t. for 45 min, a saturated solution of $NaHCO_3$ (1.5 mL) was added. Then, $H_2O_2$ (0.2 mL) was added at 0 °C and the reaction stirred at that temperature for 20 min. After evaporation of the solvents, the residue was extracted with $CH_2Cl_2$, the solution dried over $Na_2SO_4$ and evaporated to dryness. The residue was dissolved in $CH_2Cl_2$ (10 mL), treated with $Et_3SiH$ (2 x 0.19 mL, 2.4 mmol) and cooled to –78 °C. Then, $BF_3{\cdot}Et_2O$ (2 x 0.15 mL, 2.4 mmol) was added and the reaction mixture stirred for 1.5 h at the indicated temperature. The solution was treated with $NaHCO_3$ (2 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The residue was purified on a silica gel column using a gradient from 20 to 70% of EtOAc in hexane.

**(4*S*,7*R*,8a*R*)-4,7-Dibenzyl-7-(hydroxy)methyl-3,6-dioxoperhydropyrrolo[1,2-*a*]pyrazine (14).–** Yield: 68%. Foam. $^1$H NMR (200 MHz, $CDCl_3$): δ 1.27 (dd, 1H, H-8, J=12.5, 9.8), 1.49 (t, 1H, H-1, J=11.4), 1.79 (dd, 1H, H-8, J=12.5, 6.2), 2.31 (m, 1H, H-8a), 2.58 (d, 1H, 7-$CH_2$, Ph, J=13.2), 2.61 (m, 1H, H-1), 3.05 (dd, 1H, 4-$CH_2$, J=13.4, 2.7), 3.07 (d, 1H, 7-$CH_2$, Ph, J=13.2), 3.53 (m, 2H, 7-*$CH_2$*-O*H* ), 3.74 (dd, 1H, 7-*$CH_2$*-OH, J=10.7, 8.1), 3.94 (dd, 1H, 4-$CH_2$, J=13.4, 5.1), 4.21 (dd, 1H, H-4, J=2.7, 5.1), 6.82 (d, 1H, H-2, J=5.8), 7.07-7.20 (m, 10H, Ph). $^{13}$C NMR (50 MHz, $CDCl_3$): δ 29.46 (C-8), 35.10 (4-$CH_2$), 39.15 (7-$CH_2$, Ph), 44.34 (C-1), 51.91 (C-8a), 52.21 (C-7), 58.07 (C-4), 67.13 (7-*$CH_2$*-OH), 127.17, 127.19, 127.99, 128.43, 129.59, 130.24, 135.52 and 136.40 (Ph), 170.22 and 177.34 (CO). Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C 72.51, H 6.64, N 7.69. Found: C 72.22, H 6.90, N 7.42.

*Method B: Reduction with $BH_3{\cdot}THF$.–* To a 1M solution of $BH_3$ in THF (3.47 mL, 3.47 mmol), cooled to 0 °C and under Ar atmosphere, was added dropwise a solution of lactam **5** (124 mg, 0.32 mmol) in dry THF (2 mL). The solution was refluxed for 2 h, cooled to r.t. and, then, a solution of HCl/MeOH (2 mL) was added and the reflux continued for 1 h. After evaporation of the solvent, $H_2O$ was added and the solution acidified to pH 9 with $NaHCO_3$. The reaction mixture was extracted with EtOAc, dried over $Na_2SO_4$ and evaporated. The residue was purified on a silica gel column using $CH_2Cl_2$/MeOH (99:1) as eluent, to give compound **15a** (68 mg, 57%) as a syrup.

**(4*S*,7*R*,8a*R*)-4,7-Dibenzyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (15a).–** Anal. Calcd. for $C_{23}H_{26}N_2O_3$: C 72.99, H 6.92, N 7.40. Found: C 73.12, H 6.54, N 7.62.
$^1$H and $^{13}$C NMR data of this compound are recorded in Table 1.

**Synthesis of 6-oxoperhydropyrrolo[1,2-a]pyrazines from Z-PheΨ[$CH_2NH$]Gly-OH pseudopeptides**

**Z-PheΨ[$CH_2NH$]Gly-OMe (18).–** A solution of Z-Phe-H [21] (5.54 g, 19.5 mmol) in MeOH (60 mL) was treated with H-Gly-OMe·HCl (9.82 g, 78.2 mmol) and TEA (10.9 mL, 78.2 mmol), in the presence of molecular sieve 4 Å. After stirring at r.t. for 15 min., a solution of $NaBH_3CN$ (1.23 g, 19.5 mmol) and $ZnCl_2$ (1.33 g, 9.7 mmol) in MeOH (40 mL) was added. After 2.5 h of stirring the obtained suspension was filtered and the solvent evaporated to dryness. The resulting residue was extracted with EtOAc and washed with $H_2O$, 0.5 N HCl, saturated solution of $NaHCO_3$ and $H_2O$. The organic layer was dried over $Na_2SO_4$ and evaporated. The residue was purified on a silica gel column using a gradient from 20 to 50% of EtOAc in hexane, to give the title compound (4 g, 58%) as a syrup. $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.69 (m, 1H, Ψ[$CH_2$-*NH*]), 2.64 (m, 2H, β-Phe), 2.77 (dd, 1H, Ψ[*$CH_2$*-NH], J=13.6, 7.5), 2.90 (dd, 1H, Ψ[*$CH_2$*-NH], J=13.6, 5.6), 3.36 (m, 2H, α-Gly), 3.69 (s, 3H, $CO_2Me$), 3.93 (m, 1H, α-Phe), 5.07 (m, 2H, $CH_2$, Z), 5.16 (m, 1H, NH, Z), 7.15-7.32 (m, 10H, Ph). Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C 67.40, H 6.79, N 7.86. Found: C 67.01, H 7.05, N 8.05.

**Z-PheΨ[$CH_2$N(Boc)]Gly-OMe (19).–** A solution of compound **18** (4 g, 11.4 mmol) in dry $CH_2Cl_2$ (75 mL) was treated with TEA (1.59 mL, 11.4 mmol), DMAP (0.14 g, 1.14 mmol) and di-*tert*-butyldicarbonate (5 g, 22.9 mmol). After 1 day of stirring at r.t., the solvent was evaporated and the crude product was purified on a silica gel column using a gradient from 9 to 14% of EtOAc in hexane, to give derivative **19** (3.86 g, 74%) as a syrup. $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H, $CH_3$, Boc), 2.84 (m, 2H, β-Phe), 3.27 (m, 1H, Ψ[$CH_2$-N]), 3.42 (m, 1H, Ψ[$CH_2$-N]), 3.66 (s, 3H, $CO_2Me$), 3.82 (m, 3H, α-Gly and α-Phe), 5.04 (s, 2H, $CH_2$, Z), 5.41 (d, 1H, NH, Z, J=7.5), 7.20-7.30 (m, 10H, Ph). Anal. Calcd. for $C_{25}H_{32}N_2O_6$: C 65.77, H 7.06, N 6.14. Found: C 65.81, H 7.31, N 6.22.

**Z-PheΨ[$CH_2$N(Boc)]Gly-OH (20).–** A solution of compound **19** (3.3 g, 7.2 mmol) in MeOH (50 mL) was treated with 2N NaOH (5.4 mL, 10.8 mmol). After 20 h of reaction at r.t., the solvents were evaporated to dryness. The resulting residue was dissolved in $H_2O$, washed with EtOAc, acidified to pH 3 with 1N HCl and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$ and evaporated to give compound **20** (2.72 g, 85%), that was used in the following reaction step without further purification.

**Z-PheΨ[$CH_2$N(Boc)]Gly-$CH_2$-Cl (21).–** A solution of compound **20** (2.7 g, 6.1 mmol) in dry THF (10 mL), at –20 °C, was successively treated with N-methylmorpholine (0.87 mL, 7.9 mmol) and isobutylchloroformate (1.04 mL, 7.9 mmol). After stirring for 15 min. at –20 °C, an ethereal solution of diazomethane (from N-nitroso-N-methylurea, 4 g) was added. After 30 min. of reaction, a solution of 2N HCl/MeOH (5 mL, 10 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 crude product was dissolved in EtOAc (50 mL), washed with $H_2O$ and the organic layer was dried over $Na_2SO_4$. Evaporation and purification on a silica gel column, using a gradient from 10 to 20% of EtOAc in hexane as eluent, afforded the title compound (1.3 g, 44 %) as a syrup. $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 9H, $CH_3$, Boc), 2.80 (m, 2H, β-Phe), 3.34 (m, 1H, Ψ[$CH_2$-N]), 3.67 (m, 2H, $CH_2Cl$), 3.78-4.14 (m, 4H, α-Phe, α-Gly, Ψ[$CH_2$-N]), 5.01 (m, 3H, $CH_2$-Z, NH-Z), 7.19-7.30 (m, 10H, Ph). Anal. Calcd. for $C_{25}H_{31}ClN_2O_5$: C 63.22, H 6.58, Cl 7.46, N 5.90. Found: C 63.54, H 6.31, Cl 7.62, N 5.81.

**Methyl 5-[*N*-*tert*-Butoxycarbonyl-[2'(*S*)-(benzyloxycarbonyl)amino-3'-phenyl]propyl]-amino-2-methoxycarbonyl-4-oxopentanoate (22).–** A mixture of compound **21** (1.3 g, 2.7 mmol) and sodium iodide (0.6 g, 2.7 mmol) in THF (15 mL) was stirred at r.t. for 10 min. and then added to a solution of freshly prepared sodium salt of dimethylmalonate (3.3 mmol) in THF (15 mL). Stirring was continued for 3 h, the solvent removed and the residue was extracted with EtOAc and washed with $H_2O$. The organic layer was dried over $Na_2SO_4$ and evaporated leaving a residue which was purified on a silica gel column, using a gradient from 10 to 25% of EtOAc in hexane, to give the title compound (0.79 g, 52%) as a syrup. $^1H$ NMR (300 MHz, DMSO-$d_6$, 90°C): δ 1.32 (s, 9H, $CH_3$,Boc), 2.70 (m, 3H, Ψ[$CH_2$-N], 3-$CH_2$), 2.95 (m, 2H, $CH_2$, Ph), 3.10 (m, 1H, Ψ[$CH_2$-N], 3.64 (s, 6H, $CO_2Me$), 3.78 (m, 1H, α-$CO_2Me$), 3.92 (m, 1H, H-2'), 4.21 (m, 2H, 5-$CH_2$), 7.15-7.32 (m, 10H, Ph). Anal. Calcd. for $C_{30}H_{38}N_2O_9$: C 63.14, H 6.71, N 4.91. Found: C 63.46, H 6.90, N 5.17.

**4-Benzyl-2-*tert*-butoxycarbonyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (23).–** A solution of the 4-ketodiester **22** (0.6 g, 1.4 mmol) in MeOH (30 mL) was hydrogenated at r.t. and 30 psi. of pressure for 29 h. After filtration of the catalyst and evaporation, the resulting residue was dissolved in toluene (30 mL), refluxed for 3 days and evaporated. Purification on a silica gel column using a gradient from 10 to 70% of EtOAc in hexane afforded the following diasteroisomeric mixtures:

*Isomers* (4*S*,7*R*,8a*R*) and (4*S*,7*S*,8a*R*): **23ab.** Yield: 42% . Anal. Calcd. for $C_{21}H_{28}N_2O_5$: C 64.93, H 7.26, N 7.21. Found: C 65.15, H 7.02, N 7.32.

*Isomers* (4*S*,7*R*,8a*S*) and (4*S*,7*S*,8a*S*): **23cd.** Yield: 9% . Anal. Calcd. for $C_{21}H_{28}N_2O_5$: C 64.93, H 7.26, N 7.21. Found: C 64.81, H 7.13, N 7.40.

**4-Benzyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (24).–** A solution of the corresponding N-Boc protected 6-oxopyrrolopyrazine (0.05 mmol) in $CH_2Cl_2$ (1 mL) was treated with TFA (0.5 mL) and stirred at r.t. for 1 h. After neutralization with $NaHCO_3$, the organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated to dryness.

*Isomers* (4*S*,7*R*,8a*R*) and (4*S*,7*S*,8a*R*): **24ab**. Yield: 98% (From **23ab**).

*Isomers* (4*S*,7*R*,8a*S*) and (4*S*,7*S*,8a*S*): **24cd.** Yield: 96% (From **23cd**).

Significant $^1H$ RMN data of these diastereoisomeric mixtures are recorded in Table 1.

**4,7-Dibenzyl-2-*tert*-butoxycarbonyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (25).–** To a solution of the corresponding diastereomeric pair **23** (0.39g, 1 mmol) in THF (10 mL) was added, under Ar atmosphere, freshly prepared NaMeO (0.083 g, 1.5 mmol). After 5 min. of stirring, benzyl bromide (0.21 mL, 1.7 mmol) was added and the stirring continued for 1 h. After evaporation of the solvent, the residue was extracted with EtOAc and washed with $H_2O$ 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 a gradient from 10 to 20% of EtOAc in hexane.

*Isomer* (4*S*,7*R*,8a*R*): **25a**. Yield: 42 % (From **23ab**).Syrup. Anal. Calcd. for $C_{28}H_{34}N_2O_5$: C 70.27, H 7.16, N 5.85. Found: C 70.41, H 7.23, N 5.72.

*Isomer* (4*S*,7*S*,8a*R*) : **25b**. Yield: 6 % (From **23ab**). Syrup. Anal. Calcd. for $C_{28}H_{34}N_2O_5$: C 70.27, H 7.16, N 5.85. Found: C 69.98, H 7.32, N 5.92.

*Isomer* (4*S*,7*R*,8a*S*): **25c**. Yield: 15 % (From **23cd**). Syrup. Anal. Calcd. for $C_{28}H_{34}N_2O_5$: C 70.27, H 7.16, N 5.85. Found: C 70.52, H 7.11, N 5.66.
*Isomer* (4*S*,7*S*,8a*S*): **25d**. Yield: 21 % (From **23cd**). Syrup. Anal. Calcd. for $C_{28}H_{34}N_2O_5$: C 70.27, H 7.16, N 5.85. Found: C 70.18, H 7.48, N 5.51.

**4,7-Dibenzyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (15).–** Removal of Boc group from compounds **25** was performed as indicated for the preparation of compounds **24**.
*Isomer* (4*S*,7*R*,8a*R*): **15a**. Yield: 95% (From **25a**).Syrup.
*Isomer* (4*S*,7*S*,8a*R*) : **15b**. Yield: 97% (From **25b**). Syrup.
*Isomer* (4*S*,7*R*,8a*S*): **15c**. Yield: 94% (From **25c**). Syrup.
*Isomer* (4*S*,7*S*,8a*S*) : **15d**. Yield: 98% (From **25d**). Syrup. $[\alpha]_D$= –118,3 (c= 0.4, $CHCl_3$).
The $^1H$ y $^{13}C$ RMN data of all these compounds are recorded in Table 1.

**(4*S*,7*R*,8a*R*)-4,7-Dibenzyl-2-(N$^{\alpha}$-*tert*-butoxycarbonyl)-L-tryptophyl-7-methoxycarbonyl-6-oxoperhydropyrrolo[1,2-*a*]pyrazine (26).–** A solution of compound **15a** (30 mg, 0.79 mmol) and Boc-L-Trp-OH (27 mg, 0.87 mmol) in $CH_2Cl_2$ (3 mL) was treated with BOP (39 mg, 0.87 mmol) and TEA (0.12 mL, 0.87 mmol).After stirring overnight at r.t., $CH_2Cl_2$ (20 mL) and $H_2O$ (20 mL) was added and the organic layer separated and dried over $Na_2SO_4$. The solvent was evaporated and the resulting residue was purified on a silica gel column using a gradient from 10 to 35% of EtOAc in hexane. Compound **26** (38 mg, 72%) was obtained as a syrup. $^1H$ NMR (500 MHz, $CDCl_3$, 30°C):
*Cis* Rotamer: δ 1.42 (s, 9H, $CH_3$, Boc), 1.55 (dd, 1H, H-8, J= 12.9, 8.7), 1.70 (dd, 1H, H-3, J= 13.1, 10.2), 2.00 (dd, 1H, H-8, J= 12.9, 6.4), 2.13 (dd, 1H, H-1, J= 11.7, 11.1), 2.26 (m, 1H, H-8a), 2.62 (m, 1H, 4-$CH_2$), 2.95 (dd, 1H, H-3, J= 13.1, 3.9), 2.96 (d, 1H, 7-$CH_2$, J= 13.7), 3.15 (m, 2H, β-$CH_2$, Trp), 3.36 (d, 1H, 7-$CH_2$), 3.43 (m, 1H, H-4), 3.57 (dd, 1H, H-1, J= 11.1, 3.6), 3.80 (m, 4H, 4-$CH_2$ and OMe), 4.97 (m, 1H, α-CH, Trp), 5.32 (d, 1H, α-NH, Trp, J= 9.3), 7.04-7.73 (m, 10H, Ar), 8.11 (s, 1H, NH$^i$).
*Trans* Rotamer: δ 1.48 (s, 9H, $CH_3$, Boc), 1.90 (m, 1H, H-8a), 2.00 (dd, 1H, H-3, J= 14.3, 3.9), 2.05 (m, 2H, H-8), 2.41 (dd, 1H, 4-$CH_2$, J= 13.4, 9.7), 2.63 (dd, 1H, H-1, J= 12.7, 12.5), 2.94 (m, 1H, β-$CH_2$, Trp), 2.96 (dd, 1H, H-3, J= 14.3, 9.5), 3.09 (d, 1H, 7-$CH_2$, J= 13.7), 3.15 (m, 2H, H–4 and β-$CH_2$, Trp), 3.18 (d, 1H, 7-$CH_2$), 3.26 (dd, 1H, 4-$CH_2$, J= 13.4, 3.8), 3.65 (dd, 1H, H-1, J= 12.7, 3.4), 3.78 (s, 3H, OMe), 4.55 (m, 1H, α-CH, Trp), 5.58 (d, 1H, α-NH, Trp, J= 8.3), 6.81-7.38 (m, 10H, Ar), 7.98 (s, 1H, NH$^i$).

**Acknowledgements.–** We thank the Comisión Interministerial de Ciencia y Tecnología (SAF 94 0705), Ministerio de Educación y Ciencia (UE 95-0021) and Comunidad de Madrid (AE 00004/95) for financial support.

## REFERENCES

1. Martín-Martínez, M.; García-López, M.T.; Herranz, R.; González-Muñiz, R. *Tetrahedron* **1995**, *51*, 10361-10374.
2. Cava, M.P.; Levinson, M.J. *Tetrahedron* **1985**, *41*, 5061-5087.

3. Klausen, K.; Thorsen, M.; Lawesson, S.O. *Tetrahedron* **1981**, *37*, 3635-3639.
4. Jensen, O.E.; Lawesson, S.O.; Bardi, R.; Piazzesi, A.M.; Toniolo, C. *Tetrahedron* **1985**, *41*, 5595-5606.
5. Guziec, F.S.; Wasmund, L.M. *Tetrahedron Lett.* **1990**, *31*, 23-26.
6. Kornfeld, E.C. *J. Org. Chem.* **1951**, *16*, 131-138.
7. Watanabe, K.A.; Friedman, H.A.; Cushley, R.J.; Fox, J.J. *J. Org. Chem.* **1966**, *31*, 2942-2945.
8. Giri, V.S.; Ali, E.; Pakrashi, S.C. *J. Heterocyclic Chem.* **1980**, *17*, 1133-1134.
9. Dikshit, D.K.; Panday, S.K. *J. Org. Chem.* **1992**, *57*, 1920-1924.
10. Ede, N.J.; Rae, J.D.; Hearn, M.T.W. *Aust. J. Chem.* **1991**, *44*, 891-894.
11. Ede, N.J.; Rae, J.D.; Hearn, M.T.W. *Int. J. Peptide Protein Res.* **1994**, *44*, 568-581.
12. Chung, J.Y.L.; Wasicak, J.T.; Nadzan, A.M. *Synthetic Commun.* **1992**, *22*, 1039-1048.
13. Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1-12.
14. Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M.C.; García-Ruano, J.L. *Tetrahedron Lett.* **1994**, *35*, 2052-2056.
15. Brown, H.C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912-916.
16. Lane, C.F. *Chemical Rev.* **1976**, *76*, 773-799.
17. Bravo, A.; Gómez-Monterrey, I; González-Muñiz, R.; García-López, M.T. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3117-3120.
18. Meyers, A.I.; Wallace, R.H. *J. Org. Chem.* **1989**, *54*, 2509-2510.
19. Goudreau, N.; Weng, J.H.; Roques, B.P. *Biopolymers* **1994**, *34*, 155-169.
20. García-López, M.T.; Alkorta, I.; Domínguez, M.J.; González-Muñiz, R.; Herranz, R.; Johansen, N.L.; Madsen, K.; Thogersen, H.; Suzdak, P. *Lett. Peptide Sci.* **1995**, *1*, 269-276.
21. Hamada, Y.; Shiori, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921-1924.

(*Received in UK* 23 *July* 1996; *revised* 13 *September* 1996; *accepted* 19 *September* 1996)