Diastereoselective Alkylation of a Proline-Derived Bicyclic Lactim Ether

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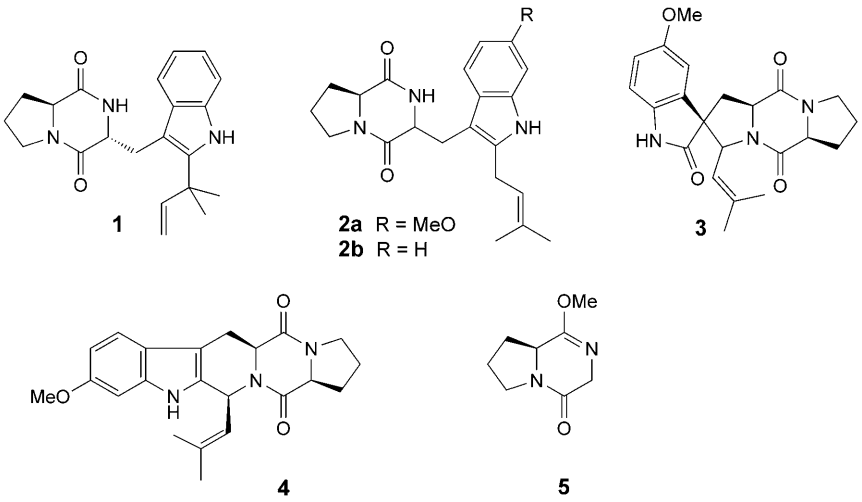
Dedicated to Professor *Dieter Hoppe* on the occasion of his 65th birthday

N-Boc-protected L-proline (**6**) was converted into the bicyclic lactim ether (8a*S*)-6,7,8,8a-tetrahydro-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (**5**) in four steps (*Scheme 1*). Deprotonation with LDA or LHMDS and subsequent alkylation resulted in the diastereoisomeric products *cis*- and *trans*-**9**. The diastereoselectivity was mainly dependent on the electrophile. Whereas small alkyl halides gave preferably *cis*-**9**, sterically more-demanding alkyl halides resulted in *cis*/*trans* mixtures. Electrophiles bearing a π-system favored the *trans*-products **9**. Some isolated *cis*- and *trans*-lactim ethers **9** were converted to the corresponding diketopiperazines *cis*- and *trans*-**10** by acid hydrolysis. The structures and configurations of several compounds were confirmed by NMR and NOE experiments, as well as by X-ray crystallography (*Figs. 1–4*).

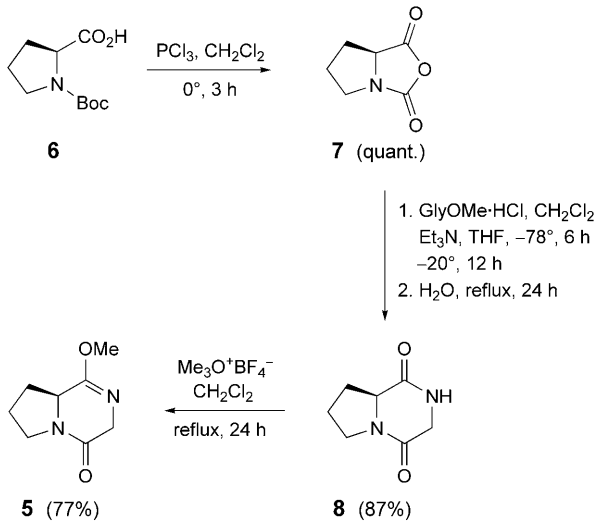
Introduction. – In contrast to the well-known '*Schöllkopf* bislactim-ether method' for the synthesis of α-amino acids [1–3], the alkylation of monolactim ethers has been rarely reported in the literature [4–6]. Recently, we have published the preparation of tricyclic diketopiperazines with an annulated tetrahydroisoquinoline moiety *via* diastereoselective alkylation of the corresponding monolactim ethers and subsequent hydrolysis [7].

Several secondary metabolites of microorganisms with interesting biological properties such as deoxybrevianamide E (**1**) [8], tryprostatins A and B (**2a**,**b**) [9], spirotryprostatin A (**3**) [10], and fumitremorgin C (**4**) [11] contain a proline-derived diketopiperazine as part of their molecular skeleton. Furthermore, this type of compound has been found in the bitter flavor of roasted coffee [12]. The diketopiperazine structural motif in these natural products was prepared in most cases by cyclocondensation [8–11][13][14]. However, we were interested to synthesize related proline-based diketopiperazines *via* alkylation of the bicyclic lactim ether **5**, followed by acidic hydrolysis. The results of our investigation are reported in this paper.

Results and Discussion. – The synthesis of the lactim ether **5** is outlined in *Scheme 1*. *N*-Boc-protected L-proline (**6**) was converted quantitatively into the anhydride **7** [7][15], which was reacted with glycine methyl ester hydrochloride in the presence of Et_3N, and subsequently exposed to boiling H_2O to afford the bicyclic diketopiperazine **8** in 87% yield over both steps [16]. Alternatively, compound **8** is accessible in 46% yield according to the method by *Viallefont* and co-workers [17]. Upon treatment of **8** with *Meerwein*'s salt, the desired lactim ether **5** was obtained in 77% yield (67% total yield over four steps).



Scheme 1



An X-ray crystal-structure analysis of the diketopiperazine **8** revealed the presence of H-bridges in the solid state (*Fig. 1*). The bond length of N(1)–H was found to be 2.8 Å, with a bridge angle N(1)–H···O(2) of 175.18°.

Next, the alkylation of **5** with different electrophiles was investigated (*Scheme 2*, *Table 1*). Since lithium diisopropylamide (LDA) and lithium hexamethyldisilazane (LHMDS) were previously found to be most promising with regard to yield and diastereoselectivity [7], both bases were tested in the deprotonation step. Treatment of the lactim ether **5** with LDA, followed by addition of MeI and aqueous workup after 16 h, gave the crude product **9a** in an excellent diastereoisomeric ratio of *cis*/*trans* 98 : 2 (96% diastereoisomeric excess). The mixture was separated by flash chromatography,

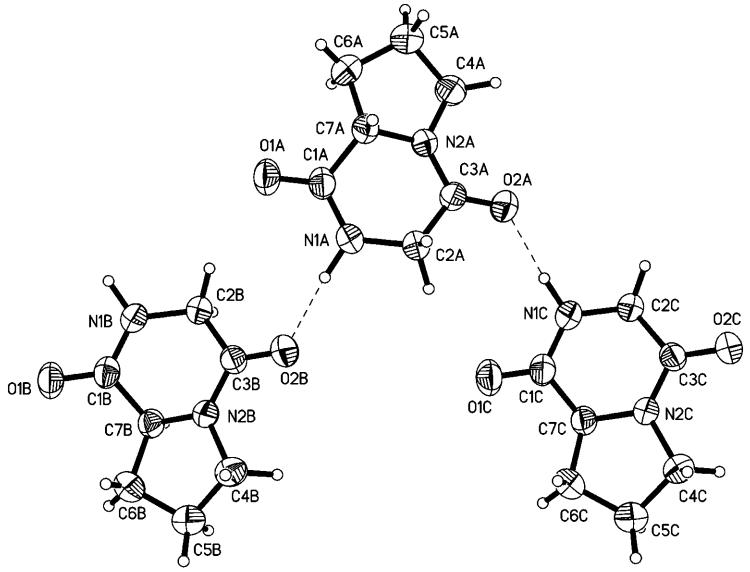


Fig. 1. *X-Ray crystal structure of* **8** (ORTEP representation)

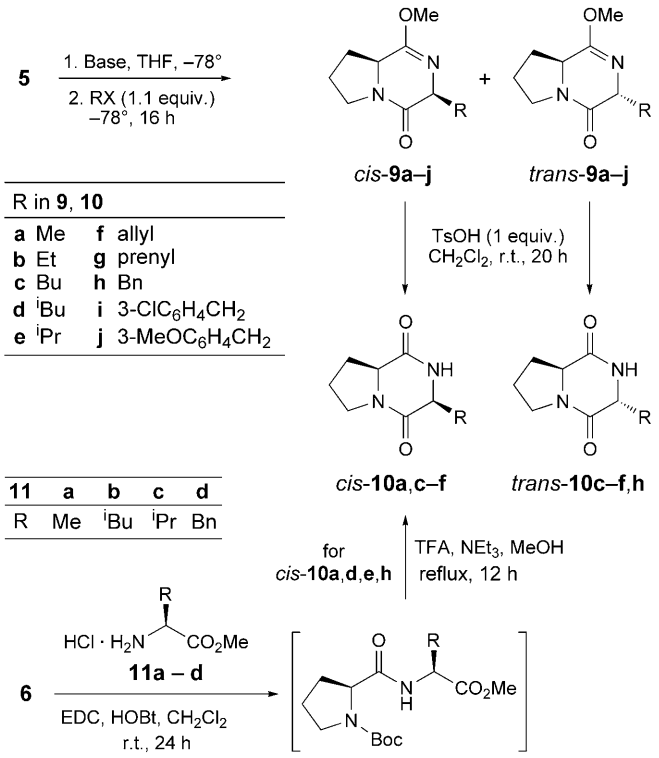
which afforded the major diastereoisomer *cis*-**9a** in 94% yield (*Table 1*, *Entry 1*). Similar results were obtained with LHMDS (*Entry 2*). The alkylation of **5** with EtI also favored the formation of the corresponding *cis*-**9b** (*Entry 3*). However, for electrophiles with either longer alkyl chains or bulkier alkyl groups, the diastereoselectivity decreased remarkably (*Entries 4–12*). While BuI gave an equimolar mixture of *cis*- and *trans*-**9c** (*Entries 4* and *5*), the i-Bu (**9d**) and i-Pr (**9e**) congeners were obtained in *cis*/*trans* ratios of 29 : 71 and 68 : 32, respectively (*Entries 6* and *10*, resp.).

The situation changed remarkably, when electrophiles with additional π-systems were applied (*Entries 13–21*). In these cases, a pronounced preference of the *trans*-products (**9f**–**9j**) was observed. The best selectivity (*cis*/*trans* < 1 : 99) was obtained for the benzylated product **9h** prepared with LHMDS as base (*Entry 19*). It should be noted that, in some cases, the yields of the isolated products **9** considerably decreased due to difficulties in chromatographic purification of the diastereoisomers. Furthermore, the *trans*-diastereoisomers of both the prenyl- and 3-chlorobenzyl-substituted lactim ethers **9g** and **9i** turned out to be more prone to hydrolysis than their *cis*-congeners. Upon prolonged chromatographic purification, the diketopiperazines *trans*-**10g** and *trans*-**10i** were isolated rather than the corresponding *trans*-configured lactim ethers. In contrast, the *cis*-lactim ethers *cis*-**9g** and *cis*-**9i** were readily obtained.

Finally, selected pure *cis*- and *trans*-lactim ethers **9** were treated with 1 equiv. of TsOH at room temperature in CH_2Cl_2 to afford the corresponding diketopiperazines *cis*-**10** and *trans*-**10** in good yields (*Scheme 2*, *Table 2*).

To confirm the preliminary stereochemical assignment of the lactim ethers **9** and of the corresponding diketopiperazines **10**, based on NMR and NOE experiments, *cis*-**10a**,**d**,**e**,**h** derived from methyl L-alaninate (**11a**), L-leucinate (**11b**), L-valinate (**11c**), and L-phenylalaninate (**11d**), were prepared, as outlined in *Scheme 2*. Following a pro-

Scheme 2



cedure by *de Costa et al.* [16], the L-proline derivative **6** was condensed with the amino acid esters **11** in the presence of *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxy-1*H*-benzotriazole (HOBt) to afford intermediate dipeptides, which were immediately cyclized to the *cis*-diketopiperazines *cis*-**10**.

The NMR data and optical-rotation values, together with an X-ray crystal structure analysis (*Fig. 2*) of the methyl-substituted diketopiperazine *cis*-**10a** derived from L-alanine, confirmed the *cis* assignment. Further support came from the X-ray crystal structures of the isobutyl-substituted diketopiperazines *cis*-**10d** and *trans*-**10d** (*Fig. 3*), isolated *via* the alkylation route after chromatographic separation, as well as of the prenyl-substituted diketopiperazine *trans*-**10g** (*Fig. 4*), obtained *via* hydrolysis on silica gel.

Compounds **8** (*Fig. 1*) and **10** (*Figs. 2–4*) crystallized in chiral space groups as pure enantiomers. In all cases, the determination of the absolute configuration by X-ray analysis[1]) was not possible due to the lack of atoms with evident anomalous scattering

[1]) Crystallographic data for the structures have been deposited with the *Cambridge Crystallographic Data Centre*, as CCDC-250728 (**8**), CCDC-605739 (*cis*-**10a**), CCDC-258427 (*cis*-**10d**), CCDC-605738 (*trans*-**10d**), and CCDC-605740 (*trans*-**10g**). Copies of the data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 1. *Alkylation of the Lactim Ether* **5** *to Compounds* **9** *under Various Conditions* (see *Scheme 2*)

Entry	R	X	Base	Product	Conv. [%][a])	Yield [%][b])	*cis*/*trans*[a])
1	Me	I	LDA	**9a**	100	94	98:2
2	Me	I	LHMDS	**9a**	80	75	95:5
3	Et	I	LDA	**9b**	70	60	96:4
4	Bu	I	LDA	**9c**	81	33[c])	50:50
5	Bu	I	LHMDS	**9c**	80	–	50:50
6	i-Bu	I	LDA	**9d**	96	–	29:71
7	i-Bu	Br	LDA	**9d**	65	48	30:70
8	i-Bu	Br	LHMDS	**9d**	56	–	40:60
9	i-Pr	Br	LDA	**9e**	86	67	60:40
10	i-Pr	I	LDA	**9e**	67	–	68:32
11	i-Pr	I	LHMDS	**9e**	39	–	50:50
12	i-Pr	Br	LHMDS	**9e**	85	–	50:50
13	Allyl	Br	LDA	**9f**	99	–	33:67
14	Allyl	I	LDA	**9f**	90	35[c])	33:67
15	Allyl	I	LHMDS	**9f**	35	–	12:88
16	Allyl	Br	LHMDS	**9f**	51	–	30:70
17	Prenyl	Br	LDA	**9g**	69	7[d])	15:85
18	Bn	Br	LDA	**9h**	77	71	4:96
19	Bn	Br	LHMDS	**9h**	61	–	<1:99
20	3-$ClC_6H_4CH_2$	Br	LDA	**9i**	68	6[d])	12:88
21	3-$MeOC_6H_4CH_2$	Br	LDA	**9j**	76	66	12:88

[a]) Determined by capillary GC of the crude products. [b]) Isolated yield. [c]) Low yield mainly due to losses during difficult chromatographic purification. [d]) Yield of minor *cis*-diastereoisomer; the *trans*-isomer was hydrolyzed to the corresponding diketopiperazine **10** during chromatography (see *Exper. Part*).

Table 2. *Hydrolysis of the Separated Lactim Ethers* cis- *and* trans-**9** *to the Diketopiperazines* cis- *and* trans-**10** (see *Scheme 2*)

Entry	Reactant	R	Product	Yield [%]
1	*cis*-**9a**	Me	*cis*-**10a**	81
2	*cis*-**9c**	Bu	*cis*-**10c**	81
3	*trans*-**9c**	Bu	*trans*-**10c**	quant.
4	*cis*-**9d**	i-Bu	*cis*-**10d**	quant.
5	*trans*-**9d**	i-Bu	*trans*-**10d**	quant.
6	*trans*-**9e**	i-Pr	*trans*-**10e**	94
7	*cis*-**9e**	i-Pr	*cis*-**10e**	quant.
8	*cis*-**9f**	Allyl	*cis*-**10f**	70
9	*trans*-**9f**	Allyl	*trans*-**10f**	60
10	*trans*-**9h**	Bn	*trans*-**10h**	83

parts (see crystal structure of **10d**, *Fig. 3*, *a*). Nevertheless, the X-ray data unambiguously confirmed the *cis*/*trans*-conformation of the diastereoisomers **10**. In the solid state, these compounds are stabilized by strong intermolecular H-bridges between the NH donor and the carbonyl O-functions. This H-bridge is nearly linear, with the exception of *cis*-**10d**, where the N–H···O bridge angle is 145°.

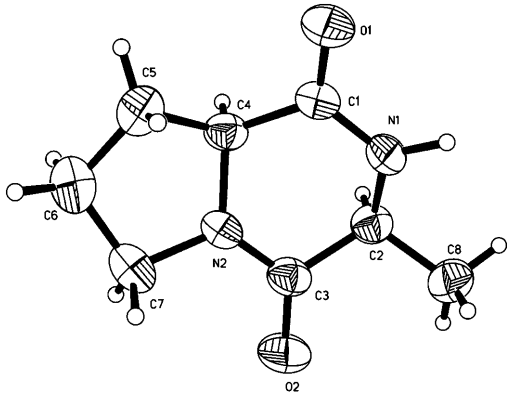


Fig. 2. *X-Ray crystal structure of* cis-**10a** (ORTEP representation)

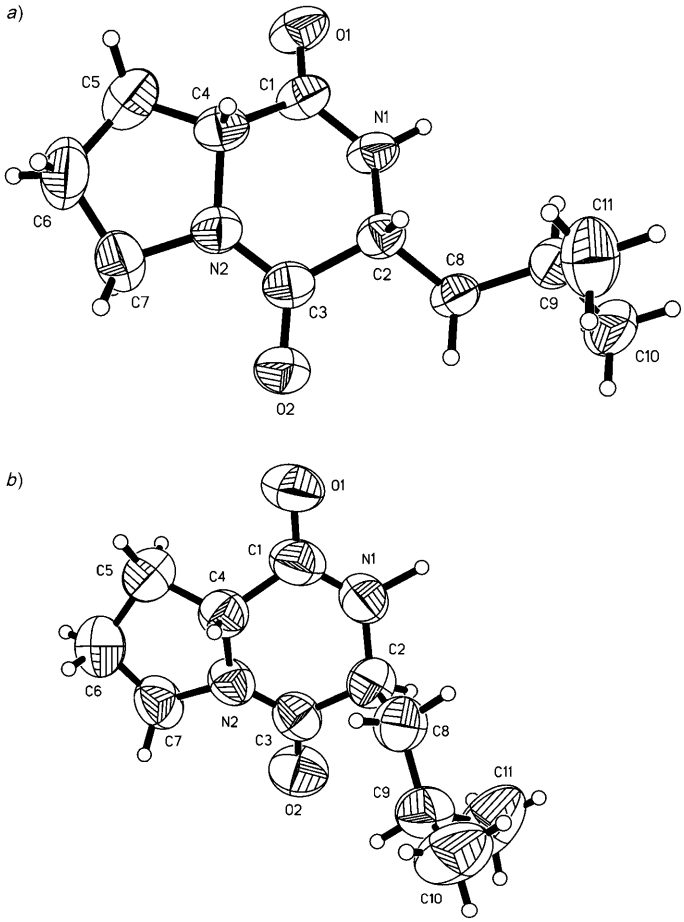


Fig. 3. *X-Ray crystal structures of* a) cis-**10d** *and* b) trans-**10d** (ORTEP representations)

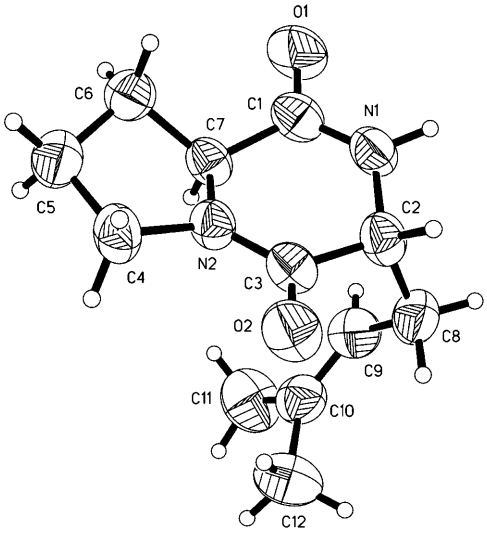


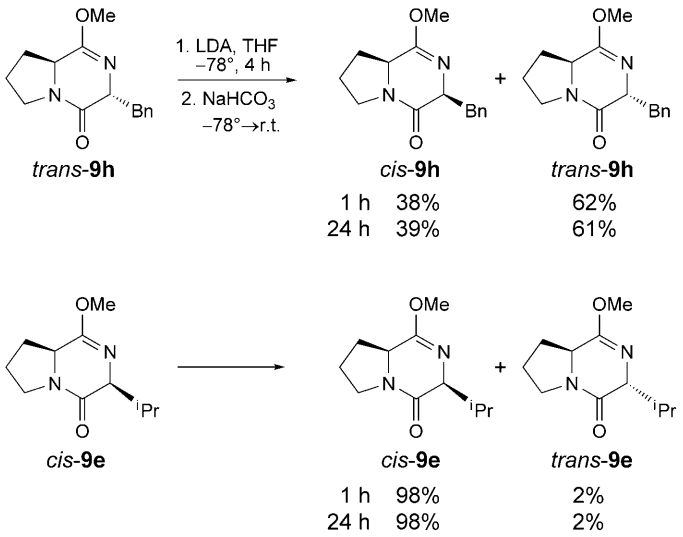
Fig. 4. *X-Ray crystal structure of* trans-**10g** (ORTEP representation)

A comparison of the NMR and optical-rotation data of the L-phenylalanine-derived *cis*-**10h** ($[\alpha]_D^{25} = -165$ ($c = 1.0$, CH_2Cl_2)) and *trans*-**10h** ($[\alpha]_D^{25} = -14$ ($c = 1.0$, CH_2Cl_2)), prepared *via* the benzylated lactim ether **9h**, indicated correct assignment of the diastereoisomers. At this point, it should be mentioned that the hydrolysis of **9** to **10** did not affect the center of chirality at C(3). The isolated *cis*- and *trans*-lactim ethers **9** gave, in each case, a single diketopiperazine **10** with the same configuration at C(3) and C(8), when treated with TsOH.

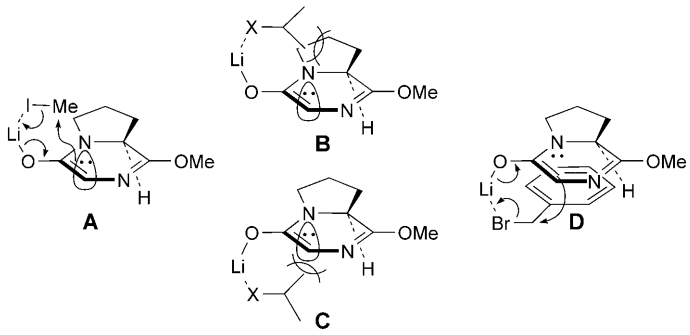
To check whether the observed diastereoselectivity in the alkylation step is due to epimerization, the isolated Bn- and i-Pr-substituted lactim ethers *cis*-**9e** and *trans*-**9h** were treated with LDA in THF at $-78°$ for 4 h, followed by quenching with aqueous $NaHCO_3$ (*Scheme 3*). At given time intervals, aliquots were taken from the reaction mixture and directly analyzed by capillary GC (for **9h**) or by HPLC (for **9e**). In the case of *trans*-**9h**, a significant amount of the *cis*-congener was detected after 1 h (*cis*/*trans* 38 : 62), remaining nearly constant after 24 h. Thus, the excellent *trans*-selectivity found in the alkylation step is probably due to kinetic control. In contrast, the i-Pr compound *cis*-**9e** epimerized only to a small extent, resulting in a *cis*/*trans* ratio of 98 : 2 after 24 h (*Scheme 3*).

From the results of the above alkylation reactions, the following mechanistic rationale may be deduced. Assuming a Li-mediated attack of the electrophile, the four different geometries **A**–**D** are conceivable. Small electrophiles such as MeI or EtI preferably approach from the top (*Si*-face) of the carbanion (**A**), because attack from the bottom face interferes with the lone pair at N(5). In the case of the bulkier i-Pr and i-Bn electrophiles, two competing geometries are possible, which, however, suffer either from steric hindrance between the alkyl moiety of the electrophile and the pyrrolidine ring (**B**), or from lone pair repulsion between the leaving halogen and N(5) (**C**), in accord with poor selectivities. For benzyl, allyl, and prenyl halides, which bear a π-sys-

Scheme 3



tem, a favorable π–π interaction between the electrophile and the carbanion is possible in arrangement **D** [18].



Conclusions. – L-Proline provides a useful template for the diastereoselective alkylation of the bicyclic lactim ether **5** to afford products **9**, which can be conveniently converted to the corresponding diketopiperazines *cis*- and *trans*-**10**. This synthetic route should allow a novel access to diketopiperazine alkaloids, and is currently under investigation.

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Experimental Part

General. Flash chromatography (FC): *Merck* silica gel *60* (0.040–0.60 mm), eluting with petroleum ether (PE; b.p. 40–60°)/AcOEt mixtures. Gas chromatography (GC): *HP 6890* apparatus, with an *Agilent HP-5* column (30 m) and H_2 as carrier gas. IR Spectra: in cm^{-1}. NMR Spectra: *Bruker ARX-300* and *ARX-500*; δ in ppm, J in Hz. ^{13}C-NMR Multiplicities were determined by DEPT experiments. Mass Spectra (MS): in m/z (rel. %).

*(7a*S*)-Tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-1,3-dione* (**7**) [15]. To a suspension of *N*-Boc-L-proline (**6**; 10.9 g, 0.05 mol) in anh. CH_2Cl_2 (50 ml) was added dropwise PCl_3 (8.20 g, 5.21 ml, 0.06 mol) at 0°, and the resulting mixture was stirred for 3 h at this temp. The solvent was removed under vacuum, and the residue was washed with hexane (5×20 ml) and dried under high vacuum in a desiccator over P_2O_5 to afford **7** (7.06 g) quantitatively. The product was used without further purification. Colorless solid. M.p. 50–52°. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.90–2.34 (*m*, CH_2(4), CH_2(5)); 3.28–3.36 (*m*, H_a–C(6)); 3.72–3.81 (*m*, H_b–C(6)); 4.33 (*t*, J=8.4, H–C(3)). ^{13}C-NMR (75 MHz, DMSO): 23.1 (C(5)); 27.9 (C(4)); 45.1 (C(6)); 58.6 (C(3a)); 154.9 (C (1)); 170.4 (C(3)).

*(8a*S*)-Hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione* (**8**) [7]. At −78°, compound **7** (7.28 g, 0.051 mol) was slowly added over 1–1.5 h to a cooled soln. of glycine methyl ester hydrochloride (8.8 g, 0.070 mol) and Et_3N (14.4 g, 0.142 mol) in CH_2Cl_2 (50 ml). After stirring for a further 6 h at −78°, the mixture was filtered over *Celite*, and the filtrate was washed with CH_2Cl_2 (50 ml). The solvent was evaporated, and the remaining yellowish oil was dissolved in H_2O and heated at reflux for 24 h. The solvent was distilled off, and the precipitate was purified by recrystallization from i-PrOH to afford **8** (6.8 g) in 87% yield. Colorless crystals. M.p. 216–217°. $[\alpha]_D^{20} = -171$ (c=2.0, $CHCl_3$). IR (neat): 3161*m*, 2876*m*, 1674*s*, 1639v*s*, 1453*s*, 1293*s*, 1110*m*, 1103*m*, 778v*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.76–1.92 (*m*, H_b–C(7)); 1.92–2.07 (*m*, H_a–C(7), H_b–C(8)); 2.26–2.36 (*m*, H_a–C(8)); 3.45–3.62 (*m*, CH_2(6)); 3.88 (*dd*, J=4.4, 16.4, H_b–C(3)); 4.08 (*d*, J=15.6, H–C(8a), H_a–C(3)); 6.89 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.8 (C(7)); 28.8 (C(8)); 45.7 (C(6)); 47.0 (C(3)); 58.9 (C(8a)); 163.9 (C(4)); 170.4 (C(1)). Anal. calc. for $C_7H_{10}N_2O_2$ (154.17): C 54.54, H 6.54, N 18.17; found: C 54.42, H 6.53, N 18.09.

*(8a*S*)-6,7,8,8a-Tetrahydro-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**5**). A ground mixture of **8** (1.35 g, 8.75 mmol) and trimethyloxonium tetrafluoroborate (1.55g, 0.0105 mol) was suspended in anh. CH_2Cl_2 (50 ml) and refluxed for 12 h. Then, further $Me_3O^+BF_4^-$ was added (0.809 g, 5.46 mmol), and the suspension was stirred for a further 12 h. Under vigorous stirring, the mixture was slowly poured into an ice-cold sat. $NaHCO_3$ soln. (pH>8), the layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3×20 ml). The combined org. layers were dried (Na_2SO_4) and evaporated to afford **5** (1.13 g) in 77% yield. Colorless oil. $[\alpha]_D^{20} = -138$ (c=1.0, CH_2Cl_2). IR (neat): 3455*w*, 2947*m*, 2847*m*, 1640v*s*, 1436*s*, 1315*s*, 1255*s*, 1019*s*, 748*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.76–1.93 (*m*, H_a–C(8), H_a–C(7)); 2.02–2.08 (*m*, H_b–C(7)); 2.30–2.34 (*m*, H_b–C(8)); 3.40–3.50 (*m*, H_a–(6)); 3.65–3.70 (*m*, H_b–C(6)); 3.74 (*s*, MeO); 4.02–4.06 (*m*, H–C(8a)); 4.08 (*dd*, J=4.4, 19.5, H_a–C(3)); 4.20 (*d*, J=17.9, H_b–C(3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.3 (C(7)); 29.4 (C(8)); 44.3 (C(3)); 52.7 (C(6)); 53.3 (MeO); 56.6 (C(8a)); 161.9 (C(4)); 166.4 (C(1)). HR-MS: 168.0902 (M^+, $C_8H_{12}N_2O_2^+$; calc. 168.0899).

General Procedure (*GP 1*) *for the Alkylation of the Lactim Ether* **5**. A soln. of **5** (100 mg, 0.594 mmol) in THF (2 ml) was added dropwise to a cooled soln. of the respective base (0.630 mmol) in THF (3 ml) at −78°. LDA or LHMDS in THF were freshly prepared from BuLi and (i-Pr)$_2$NH or hexamethyldisilazane, resp. After stirring for 4 h at −78°, the respective freshly distilled alkyl halide (0.653 mmol) was added, and the mixture was stirred for a further 16 h. Then, it was warmed to r.t., and hydrolyzed with sat. aq. $NaHCO_3$ soln. (20 ml). The layers were separated, and the aq. one was extracted with CH_2Cl_2 (3×20 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. The residue was purified by FC (neutral Al_2O_3), and analyzed by GC (determination of diastereoisomer ratios): temp. program: gradient from 80–180° at 8° min^{-1}, then 180–220° at 1° min^{-1}, then 220–300° at 16° min^{-1}.

*(3*S*,8a*S*)-6,7,8,8a-Tetrahydro-1-methoxy-3-methylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (*cis*-**9a**). Prepared according to *GP 1* with LDA, purified by FC (AcOEt/PE 3:2). Yield: 102 mg (94%). Pale-yellow oil. TLC (AcOEt/PE 4:1): R_f 0.58. $[\alpha]_D^{25} = -48.7$ (c=1.0, CH_2Cl_2). GC (*PS086*; gradient: 3 min at 100°, 100–175° at 2.5° min^{-1}, 175–300° at 20° min^{-1}): t_R 1.29 min (*cis*-**9a**), 1.85 min (*trans*-**9a**). IR (neat): 3246*m*, 2978*m*, 2948*m*, 2883*w*, 2198*w*, 1969*w*, 1637v*s*, 1436*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.38 (*d*, J=7.3, Me);

1.70–1.94 (*m*, H_a–C(7), H_a–C(8)); 2.00–2.08 (*m*, H_b–C(7)); 2.26–2.34 (*m*, H_b–C(8)); 3.40–4.48 (*m*, H_a–C(6)); 3.63–3.70 (*m*, H_b–C(6)); 3.74 (*s*, MeO); 3.99–4.05 (*m*, H–C(8a)); 4.22 (*dd*, *J* = 1.5, 7.2, H–C(3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.2 (Me); 22.5 (C(7)), 29.9 (C(8)); 44.8 (C(6)); 53.6 (MeO); 56.4 (C(8a)); 58.5 (C(3)); 161.1 (C(4)); 170.1 (C(1)). CI-MS (CH_4): 183 (100, $[M+H]^+$), 167 (2), 155 (11). HR-MS: 182.0155 (M^+, $C_9H_{14}N_2O_2^+$; calc. 182.0155).

*(3*S*,8a*S*)-3-Ethyl-6,7,8,8a-tetrahydro-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (*cis*-**9b**). Prepared according to *GP 1* with LDA, purified by FC (Et_2O/MeOH 8:1; R_f 0.58). Yield: 70 mg (60%). Pale-yellow oil. GC: t_R 11.67 min. $[\alpha]_D^{25} = -54$ (*c* = 1.0, CH_2Cl_2). IR (neat): 2996*m*, 1683v*s*, 1655v*s*, 1438*s*, 1321*m*, 1253*s*, 1130*w*, 1033*w*, 1004*w*, 808*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.96 (*t*, *J* = 7.4, Me); 1.68–1.87 (*m*, H_a–C(8), H_a–C(7), CH_2(1′)); 1.98–2.04 (*m*, H_b–C(7)); 2.28 (*quint.*, *J* = 5.9, H_b–C(8)); 3.34–3.45 (*m*, H_a–C(6)); 3.65–3.71 (*m*, H_b–C(6)); 3.73 (*s*, MeO); 3.98 (*ddd*, *J* = 6.1, 7.3, 11.2, H–C(8a)); 4.12 (*dt*, *J* = 5.9, 5.4, H–C(3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 9.6 (C(2′)); 22.1 (C(1′)); 27.8 (C(7)); 29.7 (C(8)); 44.5 (C(6)); 53.3 (MeO); 56.5 (C(3)); 63.5 (C(8a)); 161.0 (C(4)); 169.4 (C(1)). EI-MS: 196 (6, M^+), 181 (16, $[M-Me]^+$), 168 (100, $[M-Et]^+$), 153 (40), 139 (26), 126 (42), 112 (62), 96 (12), 83 (14), 70 (38), 60 (20). HR-MS: 196.1195 (M^+, $C_{10}H_{16}N_2O_2^+$; calc. 196.1212).

*3-Butyl-6,7,8,8a-tetrahydro-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**9c**). Prepared according to *GP 1* with LDA. Purified by FC (AcOEt), which gave, in a first fraction (R_f 0.49), 22 mg (16.5%) of *cis*-**9c**, and, in a second fraction (R_f 0.31), 23 mg (17%) of *trans*-**9c**.

*Data of (3*R*,8a*S*)-Isomer* (*trans*-**9c**). Pale-yellow oil. GC: t_R 14.54 min. $[\alpha]_D^{20} = -61.3$ (*c* = 1.0, CH_2Cl_2). IR (neat): 3232*w*, 2953*m*, 2871*w*, 1675v*s*, 1651v*s*, 1436*s*, 1323*w*, 1253*w*, 1013*w*, 742*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*t*, *J* = 6.6, Me(4′)); 1.26–1.45 (*m*, CH_2(2′), CH_2(3′)); 1.61–1.91 (*m*, CH_2(7), H_a–C(8)); 1.98–2.07 (*m*, CH_2(1′)); 2.25–2.33 (*m*, H_b–C(8)); 3.39–3.47 (*m*, H_a–C(6)); 3.64–3.71 (*m*, H_b–C(6)); 3.74 (*s*, MeO); 3.97–4.03 (*m*, H_a–C(8)); 4.13–4.18 (*m*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0 (C(4′)); 22.1 (C(3′)); 22.6 (C(7)); 27.7 (C(2′)); 29.7 (C(8)); 34.4 (C(1′)); 44.6 (C(6)); 53.3 (MeO); 56.4 (C(8a)); 62.5 (C(3)); 160.9 (C(4)); 169.6 (C(1)). HR-MS: 224.1525 (M^+, $C_{12}H_{20}N_2O_2^+$; calc. 224.1525).

*Data of (3*S*,8a*S*)-Isomer* (*cis*-**9c**). Colorless solid. M.p. 46–48°. GC: t_R 14.48 min. $[\alpha]_D^{25} = -62.6$ (*c* = 1.0, CH_2Cl_2). IR (neat): 2951*m*, 2859*w*, 1653v*s*, 1431*s*, 1313*m*, 1255*w*, 1037*m*, 763*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*t*, *J* = 6.7, Me); 1.30–1.44 (*m*, CH_2(2′), CH_2(3′)); 1.72–1.94 (*m*, CH_2(7), H_a–C(8)); 1.94–2.10 (*m*, CH_2(1′)); 2.20–2.34 (*m*, H_b–C(8)); 3.39–3.49 (*m*, H_a–C(6)); 3.57–3.69 (*m*, H_b–C(6)); 3.72 (*s*, MeO); 3.84–3.90 (*m*, H_a–C(8)); 3.98–4.05 (*m*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0 (C(4′)); 20.0 (C(3′)); 22.6 (C(7)); 27.5 (C(2′)); 29.1 (C(8)); 31.8 (C(1′)); 44.1 (C(6)); 53.3 (MeO); 55.4 (C(8a)); 59.1 (C(3)); 165.8 (C(4)); 172.9 (C(1)). HR-MS: 224.1525 (M^+, $C_{12}H_{20}N_2O_2^+$; calc. 224.1525).

*6,7,8,8a-Tetrahydro-1-methoxy-3-(2-methylpropyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**9d**). Prepared according to *GP 1* with LDA. Purified by FC (AcOEt), which gave, in a first fraction, 29 mg (22%) of *cis*-**9d**, and, in a second fraction, 35 mg (26%) of *trans*-**9d**.

*Data of (3*S*,8a*S*)-Isomer* (*cis*-**9d**). Pale-yellow oil. TLC (AcOEt/PE 1:1): R_f 0.35. GC: t_R 13.71 min. $[\alpha]_D^{25} = -59.7$ (*c* = 1.0, CH_2Cl_2). IR (neat): 2952*s*, 2869*m*, 1660v*s*, 1434*s*, 1333*m*, 1259*s*, 1038*m*, 798*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.86 (*d*, *J* = 6.4, Me); 0.90 (*d*, *J* = 6.5, Me); 1.46–1.55 (*m*, H–C(2′)); 1.72–1.80 (*m*, H_2C(1′)); 1.83–1.88 (*m*, H_a–C(7)); 1.91–2.02 (*m*, H_b–C(7), H_a–C(8)); 2.15–2.22 (*m*, H_b–C(8)); 3.33–3.40 (*m*, H_a–C(6)); 3.47–3.57 (*m*, H_b–C(6)); 3.65 (*s*, MeO); 3.80 (*dt*, *J* = 4.1, 9.9, H–C(8a)); 3.92–3.99 (*m*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.6 (C(3′)); 21.7 (C(4′)); 22.5 (C(7)); 23.8 (C(2′)); 28.0 (C(8)); 39.9 (C(1′)); 43.4 (C(6)); 52.2 (MeO); 55.8 (C(8a)); 57.1 (C(3)); 160.2 (C(4)); 168.5 (C(1)). HR-MS: 224.1525 (M^+, $C_{12}H_{20}N_2O_2^+$; calc. 224.1525).

*Data of (3*R*,8a*S*)-Isomer* (*trans*-**9d**). Yellow oil. TLC (AcOEt/PE 1:1): R_f 0.23. GC: t_R 13.88 min. $[\alpha]_D^{25} = -56.5$ (*c* = 1.0, CH_2Cl_2). IR (neat): 2951*m*, 1679v*s*, 1654v*s*, 1435*s*, 1316*m*, 1252*s*, 1004*m*, 730*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.97 (*d*, *J* = 3.4, Me); 0.98 (*d*, *J* = 3.4, Me); 1.40–1.46 (*m*, H–C(2′)); 1.54–1.59 (*m*, H_a–C(1′)); 1.71–1.80 (*m*, H_b–C(1′)); 1.81–1.91 (*m*, CH_2(7)); 1.99–2.05 (*m*, H_a–C(8)); 2.27–2.32 (*m*, H_b–C(8)); 3.04–3.45 (*m*, H_a–C(6)); 3.63–3.69 (*m*, H_b–C(6)); 3.73 (*s*, MeO); 4.00 (*dd*, *J* = 5.8, 9.7, H–C(8a)); 4.17–4.20 (*m*, H–C(3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.1 (C(3′), C(4′)); 23.0 (C(7)); 24.7 (C(2′)); 29.5 (C(8)); 43.3 (C(1′)); 44.5 (C(6)); 53.2 (MeO); 56.1 (C(8a)); 60.8 (C(3)); 160.9 (C(4)); 169.9 (C(1)). HR-MS: 224.1524 (M^+, $C_{12}H_{20}N_2O_2^+$; calc. 224.1525).

*6,7,8,8a-Tetrahydro-1-methoxy-3-(1-methylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**9e**). Prepared according to *GP 1* with LDA. Purified by FC (AcOEt), which gave, in a first fraction, 54 mg (43%) of *cis*-**9e**, and, in a second fraction, 30 mg (24%) of *trans*-**9e**.

*Data of (3*S*,8a*S*)-Isomer* (*cis*-**9e**). Yellow oil. TLC (AcOEt/PE 2:1): R_f 0.47. GC: t_R 13.70 min. $[\alpha]_D^{25} = -61.6$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3233*w*, 2958*m*, 2872*w*, 1635v*s*, 1435*s*, 1328*w*, 1239*w*, 997*w*, 772*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.73 (*d*, $J = 6.6$, Me); 1.12 (*d*, $J = 6.8$, Me); 1.82–1.96 (*m*, H_a–C(7), H_a–C(8)); 1.99–2.07 (*m*, H_b–C(7)); 2.25–2.31 (*m*, H_b–C(8)); 2.60 (*ddd*, $J = 13.5$, 6.7, 2.8, H–C(1′)); 3.39–3.44 (*m*, H_a–C(6)); 3.62–3.68 (*m*, H_b–C(6)); 3.74 (*s*, MeO); 3.79–3.81 (*m*, H–C(8a)); 3.95–4.01 (*m*, H–C(3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.6 (C(3′)); 19.4 (C(2′)); 22.5 (C(7)); 29.4 (C(8)); 33.6 (C(1′)); 44.0 (C(6)); 53.0 (MeO); 56.6 (C(8a)); 64.5 (C(3)); 160.6 (C(4)); 168.5 (C(1)). EI-MS: 210 (10, M^+), 168 (100, $[M - C_3H_7]^+$), 140 (20), 112 (25), 70 (30). HR-MS: 210.1368 (M^+, $C_{11}H_{18}N_2O_2^+$; calc. 210.1368).

*Data of (3*R*,8a*S*)-Isomer* (*trans*-**9e**). Yellow oil. TLC (AcOEt/PE 2:1): R_f 0.35. GC: t_R 13.86 min. $[\alpha]_D^{25} = -22.6$ ($c = 0.5$, CH_2Cl_2). IR (neat): 3232*w*, 2961*m*, 2873*w*, 1646v*s*, 1440*s*, 1327*w*, 1251*w*, 1021*w*, 780*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.89 (*d*, $J = 6.8$, Me); 1.00 (*d*, $J = 6.7$, Me); 1.80–1.96 (*m*, CH_2(7)); 2.00–2.06 (*m*, H_a–C(8)); 2.26–2.31 (*m*, H_b–C(8)); 2.38–2.42 (*m*, H–C(1′)); 3.40–3.45 (*m*, H_a–C(6)); 3.49–3.54 (*m*, H_b–C(6)); 3.75 (*s*, MeO); 3.79 (*d*, $J = 3.0$, H–C(8a)); 4.03 (*dd*, $J = 1.8$, 4.8, H–C(3)). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.2 (C(2′)); 18.9 (C(3′)); 21.5 (C(7)); 28.9 (C(8)); 33.1 (C(1′)); 45.0 (C(6)); 53.2 (MeO); 57.6 (C(8a)); 58.3 (C(3)); 160.7 (C(4)); 169.0 (C(1)). EI-MS: 210 (10, M^+), 168 (100, $[M - C_3H_7]^+$), 154 (35), 140 (25), 112 (30), 70 (50). HR-MS: 210.1368 (M^+, $C_{11}H_{18}N_2O_2^+$; calc. 210.1368).

*6,7,8,8a-Tetrahydro-1-methoxy-3-(prop-2-en-1-yl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**9f**). Prepared according to *GP 1* with LDA. Purified by FC (AcOEt/PE 5:1), which gave, in a first fraction, 7 mg (6%) of *cis*-**9f**, and, in a second fraction, 33 mg (29%) of *trans*-**9f**.

*Data of (3*S*,8a*S*)-Isomer* (*cis*-**9f**). Colorless oil. TLC (AcOEt/PE 1:1): R_f 0.56. GC: t_R 14.83 min. $[\alpha]_D^{20} = -15$ ($c = 0.5$, THF). IR (neat): 3231*m*, 2949*m*, 1638v*s*, 1432*s*, 1305*m*, 1177*w*, 996*w*, 917*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.73–1.92 (*m*, H_a–C(7), H_a–C(8)); 1.97–2.06 (*m*, H_b–C(7)); 2.23–2.30 (*m*, H_b–C(8)); 2.55–2.65 (*m*, H_a–C(1′)); 2.75–2.85 (*m*, H_b–C(1′)); 3.38–3.49 (*m*, H_a–C(6)); 3.58–3.67 (*m*, H_b–C(6)); 3.73 (*s*, MeO); 3.95–4.04 (*m*, H–C(8a), H–C(3)); 5.03–5.18 (*m*, CH_2(3′)); 5.85–5.99 (*m*, H–C(2′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.6 (C(7)); 29.2 (C(8)); 36.6 (C(1′)); 44.2 (C(6)); 53.3 (MeO); 56.9 (C(8a)); 60.0 (C(3)); 116.9 (C(3′)); 135.5 (C(2′)); 161.3 (C(4)); 168.2 (C(1)). EI-MS: 208 (100, M^+), 193 (46, $[M - CH_3]^+$), 167 (25, $[M - C_3H_7]^+$), 151 (12), 139 (60), 112 (35), 70 (40). HR-MS: 208.1211 (M^+, $C_{11}H_{16}N_2O_2^+$; calc. 208.1212).

*Data of (3*R*,8a*S*)-Isomer* (*trans*-**9f**). Yellow oil. TLC (AcOEt/PE 1:1): R_f 0.34. GC: t_R 15.08 min. $[\alpha]_D^{25} = -17.4$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3233*m*, 2947*m*, 2886*w*, 1637v*s*, 1433*s*, 1212*m*, 996*m*, 915*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.67–1.92 (*m*, H_a–C(7), H_a–C(8)); 1.97–2.09 (*m*, H_b–C(7)); 2.21–2.31 (*m*, H_b–C(8)); 2.51–2.65 (*m*, CH_2(1′)); 3.38–3.46 (*m*, H_a–C(6)), 3.57–3.69 (*m*, H_b–C(6)); 3.74 (*s*, MeO); 3.94–4.03 (*m*, H–C(8a)); 4.20–4.27 (*m*, H–C(3)); 5.02–5.18 (*m*, CH_2(3′)); 5.71–5.98 (*m*, H–C(2′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.0 (C(7)); 29.0 (C(8)); 36.2 (C(1′)); 43.4 (C(6)); 53.3 (MeO); 57.1 (C(8a)); 61.8 (C(3)); 116.3 (C(3′)); 135.4 (C(2′)); 161.8 (C(4)); 168.5 (C(1)). EI-MS: 208 (100, M^+), 207 (15, $[M - 1]^+$), 193 (12, $[M - CH_3]^+$), 167 (35, $[M - C_3H_7]^+$), 139 (60), 112 (20). HR-MS: 208.1211 (M^+, $C_{11}H_{16}N_2O_2^+$; calc. 208.1212).

*6,7,8,8a-Tetrahydro-1-methoxy-3-(3-methylbut-2-enyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**9g**). Prepared according to *GP 1* with LDA. Purified by FC (Et_2O/MeOH 8:1), which gave, in a first fraction, 10 mg (7%) of *cis*-**9g**, and, in a second fraction, a colorless solid, which turned out to be the diketopiperazine derivative of the second diastereoisomer (for anal. data, see the diketopiperazine section).

*Data of (3*S*,8a*S*)-Isomer* (*cis*-**9g**). Yellow oil. TLC (Et_2O/MeOH 8:1): R_f 0.44. GC: t_R 15.82 min. $[\alpha]_D^{25} = -19$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3246*m*, 2970*m*, 1664v*s*, 1444*s*, 1305*w*, 1180*w*, 1117*w*, 801*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.57 (*s*, Me); 1.66 (*s*, Me); 1.68–1.72 (*m*, H_a–C(8)); 1.76–1.86 (*m*, H_a–C(7)); 1.94–2.02 (*m*, H_b–C(7)); 2.24 (*q*, $J = 6.0$, H_b–C(8)); 2.49 (*t*, $J = 6.8$, CH_2(1′)); 3.37–3.41 (*m*, H_a–C(6)); 3.63–3.68 (*m*, H_b–C(6)); 3.71 (*s*, MeO); 3.88 (*dd*, $J = 5.9$, 11.3, H_a–C(8)); 4.03 (*dt*, $J = 1.5$, 5.5, H–C(3)); 5.08–5.11 (*m*, H–C(2′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.9 (C(3′)); 22.0 (C(7)); 26.0

(C(4′)); 29.7 (C(8)); 32.8 (C(1′)); 44.4 (C(6)); 53.3 (MeO); 56.7 (C(8a)); 62.5 (C(3)); 118.6 (C(2′)); 135.7 (C(3′)); 161.3 (C(4)); 169.2 (C(1)). EI-MS: 236 (22, M^+), 168 (28, $[M-C_5H_9]^+$), 70 (35). HR-MS: 236.1525 (M^+, $C_{13}H_{20}N_2O_2^+$; calc. 236.1525).

*(3*R*,8a*S*)-6,7,8,8a-Tetrahydro-1-methoxy-3-(phenylmethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (*trans*-**9h**). Prepared according to *GP 1* with LDA, and purified by FC (AcOEt/PE 1:20; R_f 0.3), which gave 109 mg (71%) of the title compound. Yellow oil. $[\alpha]_D^{20} = -31.1$ ($c = 1.0$, CH_2Cl_2). GC: 24.97 min (*trans*-**9h**)[2]). IR (neat): 3438*w*, 3027*w*, 2945*m*, 1679*s*, 1639*s*, 1437*m*, 1318*m*, 1253*m*, 1027*m*, 700*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.68–1.82 (*m*, H_a–C(7), H_a–C(8)); 1.86–2.02 (*m*, H_b–C(7)); 2.18–2.36 (*m*, H_b–C(8)); 2.97 (*dd*, $J = 4.6$, 13.3, $CH_2(1')$); 3.10–3.22 (*m*, H_a–C(6)); 3.47–3.57 (*m*, H_b–C(6)); 3.67 (*s*, MeO); 3.90–3.97 (*m*, H–C(8a)); 4.05 (*dd*, $J = 1.6$, 17.5, H–C(3)); 7.01–7.04 (*m*, 2 arom. H); 7.13–7.15 (*m*, 3 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.4 (C(7)); 29.0 (C(8)); 39.6 (C(1′)); 43.6 (C(6)); 53.1 (MeO); 55.6 (C(8a)); 62.8 (C(3)); 126.1, 126.6, 127.7, 128.0, 130.1, 136.4 (arom. C); 160.9 (C(4)); 167.0 (C(1)). EI-MS: 258 (30, M^+), 167 (35, $[M-C_6H_5CH_2]^+$), 139 (20), 57 (100), 43 (70), 29 (30), 18 (50). HR-MS: 258.1369 (M^+, $C_{15}H_{18}N_2O_2^+$; calc. 258.1368).

*(3*S*,8a*S*)-3-[(3-Chlorophenyl)methyl]-6,7,8,8a-tetrahydro-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (*cis*-**9i**). Prepared according to *GP 1* with LDA. Purified by FC (AcOEt), which gave, in a first fraction (R_f 0.31), 10.5 mg (6%) of *cis*-**9i**, and, in a second fraction (R_f 0.09), a colorless solid, which proved to be the diketopiperazine derivative of the second diastereoisomer (for anal. data, see the diketopiperazine section).

Data of cis-**9i**. Yellow oil. TLC (AcOEt): R_f 0.31. GC: t_R 27.17 min. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21–1.32 (*m*, H_a–C(8)); 1.74–1.81 (*m*, H_a–C(7)); 1.86–1.93 (*m*, H_b–C(7)); 2.08–2.14 (*m*, H_b–C(8)); 3.17 (*dd*, $J = 6.9$, 13.4, H_a–C(1′)); 3.30 (*dd*, $J = 4.3$, 13.4, H_b–C(1′)); 3.33–3.38 (*m*, H_a–C(6)); 3.58–3.64 (*dt*, $J = 8.6$, 17.1, H_b–C(6)); 3.72 (*s*, MeO); 3.87–3.91 (*m*, H–C(8a)); 4.19–4.22 (*quint.*, $J = 4.0$, H–C(3)); 7.15–7.17 (*m*, 3 arom. H); 7.31 (*s*, arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.4 (C(8)); 29.0 (C(7)); 38.2 (C(1′)); 44.2 (C(6)); 53.3 (MeO); 56.9 (C(3)); 60.9 (C(8a)); 126.2, 128.5, 128.9, 130.4, 133.4, 140.9 (arom. C); 160.9 (C(4)); 167.7 (C(1)). EI-MS: 294 (32), 292 (98, M^+), 167 (100), 139 (60), 112 (28), 70 (30), 43 (28), 28 (12). HR-MS: 292.0979 (M^+, $C_{15}H_{17}ClN_2O_2^+$; calc. 292.0979).

*6,7,8,8a-Tetrahydro-1-methoxy-3-[(3-methoxyphenyl)methyl]pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one* (**9j**). Prepared with LDA, and purified by FC (AcOEt) to afford, in a first fraction (R_f 0.44), 13.4 mg (8%) of *cis*-**9j**, and, in a second fraction (R_f 0.32), 99 mg (58%) of *trans*-**9j**.

*Data of (3*S*,8a*S*)-Isomer* (*cis*-**9j**). Pale yellow oil. GC: t_R 29.17 min. $[\alpha]_D^{25} = -58.4$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3229*m*, 2947*m*, 1655v*s*, 1600*m*, 1488*m*, 1434v*s*, 1294*w*, 1259v*s*, 1153*s*, 1109*w*, 1040*s*, 870*m*, 776v*s*, 730v*s*, 697v*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.13–1.27 (*m*, H_a–C(7)); 1.66–1.90 (*m*, H_b–C(7), H_a–C(8)); 2.02–2.11 (*m*, H_b–C(8)); 3.17 (*dd*, $J = 7.0$, 13.4, H_a–C(6)); 3.28–3.36 (*m*, $CH_2(1')$); 3.58–3.69 (*m*, H_b–C(6)); 3.72 (*s*, MeO); 3.77 (*s*, MeO); 3.82–3.89 (*m*, H–C(8a)); 4.20–4.25 (*m*, H–C(3)); 6.70–6.74 (*m*, 1 arom. H); 6.84–6.87 (*m*, 2 arom. H); 7.11–7.17 (*m*, 1 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.3 (C(8)), 28.9 (C(7)); 38.7 (C(1′)); 44.1 (C(6)); 53.1 (MeO); 55.1 (MeO); 56.8 (C(3)); 61.2 (C(8a)); 111.9, 115.5, 122.6, 128.6, 140.4, 159.1 (arom. C); 160.5 (C(4)); 167.9 (C(1)). CI-MS: 329 (1, $[M+C_3H_5]^+$), 317 (10, $[M+C_2H_5]^+$), 289 (100, $[M+H]^+$), 167 (15, $[M-MeOC_6H_4CH_2]^+$), 139 (15). HR-MS: 288.1458 (M^+, $C_{16}H_{20}N_2O_3^+$; calc. 288.1474).

*Data of (3*R*,8a*S*)-Isomer* (*trans*-**9j**). GC: t_R 32.20 min. $[\alpha]_D^{20} = -21.9$ ($c = 1.0$, CH_2Cl_2). IR (neat): 2949*m*, 1650v*s*, 1600*m*, 1487*w*, 1436v*s*, 1320*w*, 1256v*s*, 1152*s*, 1039*s*, 868*w*, 776*m*, 729v*s*, 697v*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.44–1.67 (*m*, $CH_2(7)$); 1.83–1.92 (*m*, H_a–C(8)); 1.98 (*dd*, $J = 5.1$, 11.4, H_b–C(8)); 3.03 (*dd*, $J = 4.6$, 13.2, H_a–C(6)); 3.19–3.26 (*m*, $CH_2(1')$); 3.57–3.67 (*m*, H_b–C(6)); 3.74 (*s*, MeO); 3.78 (*s*, MeO, H–C(8a)); 4.50 (*dt*, $J = 1.9$, 4.7, H–C(3)); 6.65–6.71 (*m*, 2 arom. H); 6.76 (*ddd*, $J = 0.8$, 2.6, 8.2, 1 arom. H); 7.12 (*t*, $J = 7.8$, 1 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.6 (C(8)); 29.3 (C(7)); 40.0 (C(1′)); 43.8 (C(6)); 53.3 (MeO); 55.2 (MeO); 55.9 (C(3)); 62.9 (C(8a)); 112.9, 115.1, 122.6, 128.9, 138.1, 159.3 (arom. C); 162.0 (C(4)); 167.9 (C(1)). EI-MS: 288 (68, M^+), 167 (100, $[M-MeOC_6H_4CH_2]$), 139 (18), 83 (12). HR-MS: 288.1458 (M^+, $C_{16}H_{20}N_2O_3^+$; calc. 288.1474).

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[2]) GC Retention time for *cis*-**9h**: t_R 23.94 min.

General Procedure (*GP 2*) *for the Hydrolysis of* cis- *and* trans-**9**. A soln. of *cis*- or *trans*-**9** (1 mmol) in CH_2Cl_2 (10 ml) was treated with 4-methylbenzenesulfonic acid ($TsOH \cdot H_2O$; 190 mg, 1 mmol), and the mixture was stirred at r.t. for 20 h. Then, a sat. aq. $NaHCO_3$ soln. (20 ml) was added, and the mixture was extracted with CH_2Cl_2 (5 × 100 ml). The combined org. layers were dried ($MgSO_4$) and evaporated, and the residue was purified by FC (SiO_2; AcOEt) to afford the *cis*- or *trans*-diketopiperazines **10**.

*(3*S*,8a*S*)-Hexahydro-3-methylpyrrolo[1,2-*a*]pyrazine-1,4-dione* (*cis*-**10a**) [19]. Prepared according to *GP 2*. Yield: 136 mg (81%). Yellow oil. TLC (Et_2O/MeOH 4:1): R_f 0.31. $[\alpha]_D^{25} = -84$ ($c = 0.5$, EtOH). IR (neat): 3245*m*, 2929*m*, 1645v*s*, 1444*s*, 1260*w*, 1080*w*, 796*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.49 (*d*, $J = 7.1$, Me); 1.85–2.10 (*m*, CH_2(7), H_a–C(8)); 2.37–2.45 (*m*, H_b–C(8)); 3.48–3.78 (*m*, CH_2C(6)); 3.97 (*dd*, $J = 4.2, 7.1$, H–C(3)); 4.00 (*dd*, $J = 6.4, 9.7$, H–C(8a)); 6.41 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.0 (C(1′)); 22.2 (C(7)); 28.2 (C(8)); 45.6 (C(6)); 51.2 (C(3)); 59.3 (C(8a)); 166.6 (C(1)); 169.3 (C(4)). HR-MS: 168.0899 (M^+, $C_8H_{12}N_2O_2^+$; calc. 168.0899).

cis-*3-Butylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione* (*cis*-**10c**). Prepared according to *GP 2*. Yield: 170 mg (81%). Colorless solid. M.p. 90–92°. TLC (Et_2O/MeOH 8:1): R_f 0.63. $[\alpha]_D^{25} = -58$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3228*m*, 2956*m*, 2870*m*, 1686v*s*, 1420*s*, 1297*w*, 1154*w*, 997*w*, 675*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.93 (*t*, $J = 7.0$, Me(4′)); 1.33–1.48 (*m*, CH_2(2′), CH_2(3′)); 1.72–1.81 (*m*, H_a–C(1′)); 1.87–1.96 (*m*, H_b–C(1′)); 1.99–2.13 (*m*, CH_2(7), H_a–C(8)); 2.32–2.37 (*m*, H_b–C(8)); 3.51–3.56 (*m*, H_a–C(6)); 3.59–3.64 (*m*, H_b–C(6)); 4.01–4.03 (*m*, H–C(8a)); 4.10 (*t*, $J = 7.5$, H–C(3)); 7.25 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.9 (C(4′)); 22.5(C(3′)); 22.6 (C(7)); 27.3 (C(2′)); 28.2 (C(8)); 29.6 (C(1′)); 45.3(C(6)); 55.4 (C(8a)); 59.0 (C(3)); 165.9 (C(1)); 170.7 (C(4)). HR-MS: 210.1368 (M^+, $C_{11}H_{18}N_2O_2^+$; calc. 210.1368).

trans-*3-Butylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione* (*trans*-**10c**). Prepared according to *GP 2*. Yield: 210 mg (quant.). Pale-yellow oil. TLC (Et_2O/MeOH 8:1): R_f 0.59. $[\alpha]_D^{25} = -58$ ($c = 1.0$, CH_2Cl_2). IR (neat): 3228*m*, 2956*m*, 2870*m*, 1686v*s*, 1420*s*, 1297*w*, 1154*w*, 997*w*, 675*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (*t*, $J = 7.0$, Me(4′)); 1.27–1.47 (*m*, CH_2(2′), CH_2(3′)); 1.65–2.06 (*m*, CH_2(1′), CH_2(7), H_a–C(8)); 2.34–2.44 (*m*, H_b–C(8)); 3.47–3.54 (*m*, H_a–C(6)); 3.60–3.69 (*m*, H_b–C(6)); 3.88 (*quint.*, $J = 4.8$, H–C(3)); 4.06 (*dd*, $J = 6.4, 9.1$, H–C(8a)); 7.13 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.8 (C(4′)); 22.1 (C(3′)); 22.2 (C(7)); 27.4 (C(2′)); 29.0 (C(8)); 34.0 (C(1′)); 45.5 (C(6)); 58.0 (C(8a)); 58.1 (C(3)); 166.1 (C(1)); 169.5 (C(4)). HR-MS: 210.1368 (M^+, $C_{11}H_{18}N_2O_2^+$; calc. 210.1368).

cis-*Hexahydro-3-(2-methylpropyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*cis*-**10d**). Prepared according to *GP 2*. Yield: 210 mg (quant.). Colorless crystals. M.p. 165°. TLC (Et_2O/MeOH 8:1): R_f 0.67. $[\alpha]_D^{25} = -137.5$ ($c = 0.4$, CH_2Cl_2). IR (neat): 3221*m*, 2956*m*, 2871*m*, 1659v*s*, 1125*s*, 1302*w*, 1157*w*, 919*w*, 730*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.95 (*d*, $J = 6.5$, Me); 1.00 (*d*, $J = 6.5$, Me); 1.53 (*ddd*, $J = 5.0, 9.4, 14.4$, H_a–C(1′)); 1.71–1.82 (*m*, H–C(2′)); 1.87–1.95 (*m*, H_a–C(7)); 1.99–2.08 (*m*, H_b–C(7), H_b–C(1′)); 2.10–2.16 (*m*, H_a–C(8)); 2.33–2.36 (*m*, H_b–C(8)); 3.51–3.62 (*m*, CH_2(6)); 4.01 (*dd*, $J = 3.4, 9.3$, H–C(8a)); 4.12 (*t*, $J = 8.3$, H–C(3)); 6.45 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.3 (C(3′)); 22.8 (C(7)); 23.3 (C(4′)); 24.6 (C(2′)); 28.1 (C(8)); 38.6 (C(1′)); 45.5 (C(6)); 53.4 (C(8a)); 59.0 (C(3)); 166.3 (C(1)); 170.4 (C(4)). Anal. calc. for $C_{11}H_{18}N_2O_2$ (210.27): C 62.83, H 8.63, N 13.32; found: C 62.71, H 8.58, N 13.29. X-Ray data: $C_{11}H_{18}N_2O_2$, M_r 210.3, orthorhombic, space group $P2_12_12_1$; $a = 6.3429(4)$, $b = 9.466(3)$, $c = 19.5950(16)$ Å; $\alpha = \beta = \gamma = 90°$; $V = 1176.5(4)$ Å^3, $Z = 4$; $D_c = 1.187$ g cm^{-3}; crystal size $0.50 \times 0.25 \times 0.05$ mm; 1592 reflections for $\theta = 4.51–67.88°$, 1434 unique reflections; 1434 reflection data ($I > 2\sigma(I)$), 141 parameters; $R = 0.0758$, $Rw = 0.2069$; residual electron density between 0.256 and −0.269 e Å^{-3}.

trans-*Hexahydro-3-(2-methylpropyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*trans*-**10d**). Prepared according to *GP 2*. Yield: 210 mg (quant.). Colorless crystals. M.p. 150–152°. TLC (Et_2O/MeOH 8:1): R_f 0.65. $[\alpha]_D^{25} = -93$ ($c = 0.4$, CH_2Cl_2). IR (neat): 3230*m*, 2955*m*, 2360*m*, 1649v*s*, 1433*s*, 1300*m*, 1144*w*, 918*w*, 729*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (*d*, $J = 6.5$, Me); 1.00 (*d*, $J = 6.5$, Me); 1.62–1.68 (*m*, H_a–C(1′)); 1.70–1.96 (*m*, H–C(2′), CH_2(7)); 1.97–2.07 (*m*, H_b–C(1′), H_a–C(8)); 2.36–2.43 (*m*, H_b–C(8)); 3.48–3.56 (*m*, H_a–C(6)); 3.60–3.70 (*m*, H_b–C(6)); 3.89–3.96 (*m*, H–C(3)); 4.06–4.11 (*m*, H–C(8a)); 6.50 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.4 (C(4′)); 22.2 (C(7)); 23.0 (C(3′)); 24.5 (C(2′)); 29.0 (C(8)); 42.6 (C(1′)); 45.6 (C(6)); 56.4 (C(8a)); 58.0 (C(3)); 166.3 (C(1)); 169.4 (C(4)). Anal. calc. for $C_{11}H_{18}N_2O_2$ (210.27): C 62.83, H 8.63, N 13.32; found: C 62.62, H 8.54, N 13.18. X-Ray data: $C_{11}H_{18}N_2O_2$, M_r 210.3, orthorhombic, space group $P2_12_12_1$; $a = 6.303(2)$, $b = 8.0267(14)$,

$c=23.146(4)$ Å; $\alpha=\beta=\gamma=90°$; $V=1171.0(5)$ Å^3, $Z=4$; $D_c=1.193$ g cm^{-3}; crystal size $0.65\times0.2\times0.05$ mm, 1103 reflections in the range $\theta=3.82-62.50°$, 1103 unique reflections; 1103 reflection data ($I>2\sigma(I)$), 141 parameters; $R=0.0775$, $Rw=0.2084$; residual electron density between 0.217 and -0.218 e Å^{-3}.

cis-*Hexahydro-3-(1-methylethyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*cis*-**10e**) [20]. Prepared according to *GP 2*. Yield: 195 mg (quant.). Colorless solid. M.p. 185–187°. TLC (CH_2Cl_2/MeOH 90:9): R_f 0.6. $[\alpha]_D^{25}=-146.6$ ($c=0.45$, CH_2Cl_2). IR (neat): 3393*s*, 2255*w*, 2128*w*, 1657*m*, 1050*s*, 1023v*s*, 1003v*s*, 823*m*, 761*m*. ^{1}H-NMR (500 MHz, (D_6)DMSO): 0.85 (*d*, $J=6.9$, Me); 1.01 (*d*, $J=7.2$, Me); 1.75–1.89 (*m*, CH_2(7), H_a–C(8)); 2.10–2.15 (*m*, H_b–C(8)); 2.34 (*dqq*, $J=7.2$, 6.9, 2.5, H–C(1′)); 3.31–3.43 (*m*, CH_2(6)); 3.90–3.92 (br. *s*, H–C(3)); 4.10–4.13 (*m*, H–C(8a)); 7.97 (br. *s*, NH). ^{13}C-NMR (125 MHz, (D_6)DMSO): 16.1 (C(2′)); 19.3 (C(3′)); 22.4 (C(7)); 28.4 (C(8)); 28.5 (C(1′)); 45.2 (C(6)); 58.8 (C(8a)); 60.4 (C(3)); 164.9 (C(1)); 170.1 (C(4)). HR-MS: 194.1212 (M^+, $C_{10}H_{16}N_2O_2^+$; calc. 194.1212).

trans-*Hexahydro-3-(1-methylethyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*trans*-**10e**). Prepared according to *GP 2*. Yield: 184 mg (94%). Colorless solid. M.p. 150°. TLC (CH_2Cl_2/MeOH 90:9): R_f 0.56. $[\alpha]_D^{25}=-20$ ($c=0.45$, CH_2Cl_2). IR (neat): 3216*m*, 2962*m*, 1674*s*, 1648v*s*, 1447*s*, 1270*m*, 777*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.88 (*d*, $J=6.7$, Me); 0.90 (*d*, $J=6.8$, Me); 1.69–1.80 (*m*, H_a–C(7), H_a–C(8)); 1.83–1.88 (*m*, H_b–C(7)); 2.00 (*dqq*, $J=6.8$, 6.8, 6.7, H–C(1′)); 2.12–2.16 (*m*, H_b–C(8)); 3.30–3.35 (*m*, H_a–C(6)); 3.38 (*dd*, $J=4.2$, 6.3, H–C(3)); 3.42–3.49 (*m*, H_b–C(6)); 4.09 (*dd*, $J=6.7$, 9.7, H–C(8a)); 8.45 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.2 (C(2′)); 19.0 (C(3′)); 21.5 (C(7)); 28.9 (C(8)); 32.4 (C(1′)); 45.1 (C(6)); 57.6 (C(8a)); 62.6 (C(3)); 165.0 (C(1)); 169.0 (C(4)). HR-MS: 194.1212 (M^+, $C_{10}H_{16}N_2O_2^+$; calc. 194.1212).

cis-*Hexahydro-3-(prop-2-enyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*cis*-**10f**). Prepared according to *GP 2*. Yield: 136 mg (70%). Yellow oil. TLC (Et_2O/MeOH 8:1): R_f 0.36. $[\alpha]_D^{25}=-89$ ($c=0.1$, CH_2Cl_2). IR (neat): 3202*m*, 2981*w*, 2880*w*, 1664v*s*, 1420*s*, 1336*m*, 1241*w*, 996*w*, 916*m*, 678*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.86–1.97 (*m*, H_a–C(7)); 1.98–2.17 (*m*, H_b–C(7), H_a–C(8)); 2.31–2.47 (*m*, H_b–C(8), H_a–C(1′)); 2.83–2.97 (*m*, H_b–C(1′)); 3.51–3.67 (*m*, CH_2(6)); 4.06 (*dd*, $J=3.8$, 9.3, H–C(3)); 4.13 (*t*, $J=7.4$, H–C(8a)); 5.21–5.27 (*m*, CH_2(3′)); 5.73–5.87 (*m*, H–C(2′)); 6.20 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.6 (C(7)); 28.1 (C(8)); 34.7 (C(1′)); 45.3 (C(6)); 53.8 (C(3)); 59.1 (C(8a)); 120.0 (C(3′)); 133.0 (C(2′)); 165.0 (C(4)); 169.6 (C(1)). HR-MS: 194.1056 (M^+, $C_{10}H_{14}N_2O_2^+$; calc. 194.1055).

trans-*Hexahydro-3-(prop-2-enyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*trans*-**10f**) [21]. Prepared according to *GP 2*. Yield: 116 g (60%). Yellow oil. TLC (Et_2O/MeOH 8:1): R_f 0.34. $[\alpha]_D^{25}=-86$ ($c=0.1$, CH_2Cl_2). IR (neat): 3220*m*, 2981*w*, 2881*w*, 1663v*s*, 1416*s*, 1305*m*, 1002*m*, 921*m*, 708*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.87–1.97 (*m*, H_a–C(7)); 2.01–2.14 (*m*, H_b–C(7), H_a–C(8)); 2.34–2.46 (*m*, H_b–C(8), H_a–C(1′)); 2.89–2.94 (*m*, H_b–C(1′)); 3.53–3.64 (*m*, CH_2(6)); 4.06 (*dd*, $J=3.2$, 8.8, H_a–C(3)); 4.13 (*t*, $J=7.6$, H–C(8a)); 5.22–5.26 (*m*, CH_2(3′)); 5.76–5.84 (*m*, CH(2′)); 6.33 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.5 (C(7)); 28.1 (C(8)); 34.6 (C(1′)); 45.3 (C(6)); 53.8 (C(3)); 59.0 (C(8a)); 119.9 (C(3′)); 133.0 (C(2′)); 165.0 (C(4)); 169.7 (C(1)). HR-MS: 194.1056 (M^+, $C_{10}H_{14}N_2O_2^+$; calc. 194.1055).

*(3*R*,8a*S*)-Hexahydro-3-(phenylmethyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*trans*-**10h**). Prepared according to *GP 2*. Yield: 203 mg (83%). Colorless oil. $[\alpha]_D^{25}=-14$ ($c=1.0$, CH_2Cl_2). IR (neat): 3245*m*, 2928*m*, 1661v*s*, 1453*s*, 1307*w*, 1184*w*, 1107*w*, 703*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.64–1.74 (*m*, H_a–C(7), H_a–C(8)); 1.76–1.86 (*m*, H_b–C(7)); 1.90–1.98 (*m*, H_b–C(8)); 2.01–2.09 (*m*, H_a–C(1′)); 2.20 (*q*, $J=5.9$, H_b–C(1′)); 3.00 (*q*, $J=6.4$, H–C(8a)); 3.10 (*dd*, $J=6.7$, 14.6, H–C(3)); 3.38–3.43 (*m*, H_a–C(6)); 3.60–3.68 (*m*, H_b–C(6)); 6.04 (br. *s*, NH); 7.20 (*d*, $J=5.8$, 2 arom. H); 7.26 (*s*, 1 arom. H); 7.30 (*t*, $J=7.5$, 2 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.7 (C(7)); 29.0 (C(8)); 40.7 (C(1′)); 45.2 (C(6)); 57.8 (C(3)); 59.2 (C(8a)); 127.5, 128.9, 134.3 (arom. C); 162.5 (C(1)); 169.0 (C(4)). HR-MS: 244.1211 (M^+, $C_{14}H_{16}N_2O_2^+$; calc. 244.1212).

trans-*Hexahydro-3-(3-methylbut-2-enyl)pyrrolo[1,2-*a*]pyrazine-1,4-dione* (*trans*-**10g**). Obtained during FC of the diastereoisomeric mixture **9g** on SiO_2. TLC (Et_2O/MeOH 8:1): R_f 0.28. GC: t_R 19.80 min. $[\alpha]_D^{25}=-2.7$ ($c=1.0$, CH_2Cl_2). IR (neat): 3235*m*, 2927*m*, 1666v*s*, 1447*s*, 1304*w*, 1263*w*, 731*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.64 (*s*, Me); 1.73 (*s*, Me); 1.84–2.09 (*m*, CH_2(7), H_a–C(8)); 2.37–2.44 (*m*, H_b–C(8)); 2.52 (*t*, $J=6.9$, CH_2(1′)); 3.49–3.56 (*m*, H_a–C(6)); 3.64–3.74 (*m*, H_b–C(6)); 3.93 (*td*, $J=3.9$, 6.1, H–C(3)); 4.05 (*dd*, $J=6.6$, 9.6, H–C(8a)); 5.15 (*m*, H–C(2′)); 6.42 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.9 (Me); 22.0 (C(7)); 26.0 (Me); 29.3 (C(8)); 33.0 (C(1′)); 45.5 (C(6)); 58.1 (C(3));

58.4 (C(8a)); 117.5 (C(3′)); 137.6 (C(2′)); 165.7 (C(1)); 169.3 (C(4)). EI-MS: 223 (45, M^+), 154 (100, $[M-C_5H_9]^+$), 125 (16), 70 (100). HR-MS: 222.1352 (M^+, $C_{12}H_{18}N_2O_2^+$; calc. 222.1368). X-Ray data: $C_{12}H_{18}N_2O_2$, M_r 222.3; orthorhombic, space group $P2_12_12_1$; $a=6.4274(8)$, $b=7.8705(9)$, $c=24.0198(19)$ Å; $\alpha=\beta=\gamma=90°$; $V=1215.1(2)$ Å^3, $Z=4$; $D_c=1.215$ g cm^{-3}; crystal size $0.5\times0.3\times0.3$ mm, 2377 reflections in the range $\theta=3.68-67.99°$, 1992 unique reflections; 1992 reflection data ($I>2\sigma(I)$), 150 parameters; $R=0.0821$, $Rw=0.1872$; residual electron density between 0.267 and -0.238 e Å^{-3}.

3-[(3-Chlorophenyl)methyl]hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (*trans*-**10i**). Obtained during FC of the diastereoisomeric mixture **9g** on SiO_2. M.p. 135–137°. TLC (AcOEt): R_f 0.09. GC: t_R 29.95 min. $[\alpha]_D^{25}=-20.6$ ($c=1.0$, CH_2Cl_2). IR (neat): 3226*m*, 2954*m*, 1646v*s*, 1439v*s*, 1305*s*, 1089*m*, 919*m*, 727*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.69–1.85 (*m*, H_a–C(7), H_b–C(8)); 1.94–2.00 (*m*, H_b–C(7)); 2.19–2.24 (*m*, H_a–C(8)); 3.05–3.09 (*m*, CH_2(1′)); 3.12 (*dd*, $J=6.4$, 13.6, H–C(8a)); 3.41–3.46 (*m*, H_a–C(6)); 3.64 (*dt*, $J=8.7$, 12.0, H_b–C(6)); 4.22–4.25 (*m*, H–C(3)); 7.12 (*dt*, $J=1.1$, 6.9, 1 arom. H)); 7.25 (*d*, $J=6.7$, 2 arom. H); 7.27–7.29 (*m*, 1 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.7 (C(7)); 29.0 (C(8)); 40.1 (C(1′)); 45.2 (C(6)); 57.8 (C(3)); 58.7 (C(8a)); 127.6, 128.1, 129.9, 130.0, 134.5, 137.6 (arom. C); 164.6 (C(4)); 169.4 (C(1)). Anal. calc. for $C_{16}H_{17}ClN_2O_2$ (292.10): C 60.33, H 5.42, Cl 12.72, N 10.05; found: C 60.17, H 5.45, Cl 12.81, N 10.01.

Preparation of cis-**10a**,**d**,**e**,**h** *from* **6** *and* L-*Amino Acid Esters* **11**. These compounds were prepared according to the procedure described in [16].

Data of cis-**10a**. M.p. 173–175°. TLC (Et_2O/MeOH 8:1): R_f 0.27. GC: $t_R=7.82$ min. $[\alpha]_D^{25}=-89$ ($c=0.5$, EtOH). IR (neat): 3228*m*, 1661v*s*, 1429*m*, 1302*w*, 1202*w*, 1159*w*, 1127*w*, 658*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.48 (*d*, $J=6.8$, Me); 1.86–1.95 (*m*, H_a–C(7)); 1.99–2.06 (*m*, H_b–C(7)); 2.07–2.15 (*m*, H_a–C(8)); 2.31–2.37 (*m*, H_b–C(8)); 3.52–3.56 (*m*, H_a–C(6)); 3.58–3.63 (*m*, H_b–C(6)); 4.10–4.15 (*m*, H_a–C(3), H–C(8a)); 7.27 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.9 (C(1′)); 22.8 (C(7)); 28.2 (C(8)); 45.4 (C(6)); 51.2 (C(3)); 59.3 (C(8a)); 166.6 (C(1)); 170.7 (C(4)). EI-MS: 169 (10, $[M+1]^+$), 168 (62, M^+), 125 (30), 112 (10), 97 (50), 70 (100), 55 (12). X-Ray data: $C_8H_{12}N_2O_2$, M_r 168.2; monoclinic, space group $P2_1$; $a=7.2825(13)$, $b=6.5604(13)$, $c=9.2844(13)$ Å; $\alpha=\gamma=90°$, $\beta=111.399(11)°$; $V=412.99(12)$ Å^3, $Z=2$; $D_c=1.353$ g cm^{-3}; crystal size $0.50\times0.25\times0.15$ mm, 858 reflections in the range $\theta=2.36-24.99°$, 795 unique reflections; 795 reflection data ($I>2\sigma(I)$), 158 parameters; $R=0.0352$, $Rw=0.0719$; residual electron density between 0.131 and -0.128 e Å^{-3}.

Data of cis-**10d**. M.p. 157–159°. TLC (Et_2O/MeOH 8:1): R_f 0.45. $[\alpha]_D^{25}=-120$ ($c=0.4$, CH_2Cl_2). IR (neat): 3262*m*, 2952*m*, 2871*w*, 1669v*s*, 1634v*s*, 1432*s*, 1301*m*, 1180*w*, 1157*w*, 916*m*, 710*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.95 (*d*, $J=6.5$, Me); 1.00 (*d*, $J=6.6$, Me); 1.51 (*ddd*, $J=4.9$, 9.5, 14.3, H_a–C(1′)); 1.73–1.81 (*m*, H–C(2′)); 1.85–1.93 (*m*, H_a–C(7)); 1.97–2.06 (*m*, H_b–C(7), H_b–C(1′)); 2.09–2.15 (*m*, H_a–C(8)); 2.23–2.36 (*m*, H_b–C(8)); 3.45–3.61 (*m*, CH_2(6)); 4.00 (*dd*, $J=3.4$, 9.4, H–C(8a)); 4.10 (*t*, $J=8.0$, H–C(3)); 6.42 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.3 (C(4′)); 22.8 (C(3′)); 24.6 (C(2′)); 28.1 (C(8)); 38.6 (C(1′)); 45.5 (C(6)); 53.4 (C(8a)); 58.9 (C(3)); 166.3 (C(1)); 170.5 (C(4)).

Data of cis-**10e**. M.p. 181–183°. TLC (Et_2O/MeOH 4:1): R_f 0.28. GC: $t_R=8.51$ min. $[\alpha]_D^{25}=-152$ ($c=0.45$, CH_2Cl_2). IR (neat): 3210*m*, 2962*m*, 1672v*s*, 1428*s*, 1298*m*, 1180*w*, 1121*w*, 916*m*, 735*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.91 (*d*, $J=6.6$, Me); 1.07 (*d*, $J=7.6$, Me); 1.86–1.96 (*m*, H_a–C(7)); 2.01–2.10 (*m*, H_b–C(7), H_a–C(8)); 2.36–2.41 (*m*, H_b–C(8)); 2.64 (*sept.*, $J=6.9$, H–C(1′)); 3.52–3.57 (*m*, H_a–C(6)); 3.62–3.67 (*m*, H_b–C(6)); 3.94 (*s*, H–C(3)); 4.08 (*t*, $J=7.3$, H–C(8a)); 5.96 (br. *s*, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.1 (C(2′)); 19.3 (C(3′)); 22.4 (C(7)); 28.3 (C(1′)); 28.5 (C(8)); 45.2 (C(6)); 58.8 (C(3)); 60.4 (C(8a)); 164.9 (C(1)); 167.0 (C(4)). EI-MS: 196 (5, M^+), 154 (100, $[M-C_3H_7]^+$), 125 (35), 110 (10), 98 (12), 72 (32), 70 (98).

Data of cis-**10h**. TLC (Et_2O/MeOH 4:1): R_f 0.45. GC: t_R 11.67 min. $[\alpha]_D^{25}=-165$ ($c=1.0$, CH_2Cl_2). IR (neat): 3228*m*, 2881*m*, 1660v*s*, 1453*s*, 1421*s*, 1310*w*, 1204*w*, 1115*w*, 920*w*, 731*m*, 702*m*, 593*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.86–2.04 (*m*, H_a–C(8), CH_2(7)); 2.29–2.34 (*m*, H_b–C(8)); 2.82 (*dd*, $J=10.2$, 14.5, H_a–C(1′)); 3.53–3.67 (*m*, H_b–C(1′), CH_2(6)); 4.07 (*t*, $J=7.9$, H–C(3)); 4.29 (*dd*, $J=3.2$, 10.1, H–C(8a)); 6.00 (br. *s*, NH); 7.23 (*d*, $J=6.8$, 2 H); 7.28 (*dd*, $J=8.5$, 14.8, 1 H); 7.34 (*t*, $J=7.1$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.5 (C(7)); 28.3 (C(8)); 36.8 (C(1′)); 45.4 (C(6)); 56.2 (C(3)); 59.1 (C(8a)); 127.5 (C); 129.2 (2 C); 136.0 (C); 165.1 (C(1)); 169.4 (C(4)). EI-MS: 245 (12, $[M+1]^+$), 244 (50, M^+), 153 (10, $[M-C_6H_5CH_2]^+$), 125 (100), 104 (12), 91 (70), 70 (60), 64.9 (20). Anal. calc. for $C_{14}H_{16}N_2O_2$ (244.12): C 68.83, H 6.60, N 11.47; found: C 68.30, H 6.55, N 11.43.

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