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Stereoselective synthesis of dipeptides — I

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Abstract: The alkylation of **7** occurs in moderate to good *trans* stereoselection (d.e.40–98%), while a poorer d.e. (10–90%) is observed for **8**. On the contrary, in both substrates the alkylation with CH_3I produces a greater amount of the *cis* isomer (d.e.48%). Cleavage of the lactims **9(a,e)** gives enantiomerically pure dipeptides **14(a,e)**. The absolute configuration of the introduced stereogenic centres has been assigned on the basis of the ^{1}H-NMR data in connection with the conformational analysis. © 1997 Elsevier Science Ltd. All rights reserved.

In previous papers we have described the stereoselective alkylation[1] and aldol condensation[2] of piperazine-2,5-dione derivatives and recently we have accomplished a new approach for the preparation of a wide variety of natural and unnatural α-aminoacids in good chemical yield and enantiomeric purity[3]. In a continuation of our studies, we have directed our interest to the stereoselective synthesis of uncommon peptides because these compounds have recently received considerable attention[4]: bioactive peptides can indeed influence several physiological processes such as neurotransmitters, neuromodulators and hormones. In recent years efforts have been made to develop and to synthesize various peptidomimetics, i.e. compounds that act as substitutes for peptides in their interaction with receptors, for their relevant biochemical and pharmacological properties. In the last two decades many biologically active peptides have been discovered and studied and an increasing number of modified peptides have been synthetized for medical and pharmacological purposes.

We therefore wish to report here a new synthetic strategy to natural and unnatural dipeptides which allows a moderate to good stereoselectivity. The procedure we followed consists in the alkylation of new chiral synthones, such as (6*R*)-**7** and (6*S*)-1-((*S*)-phenethyl)-5-ethoxy-6-methyl-3,6-dihydro-1H-pirazin-2-one **8**, synthesized as later reported in Scheme 1. So, the stereochemical outcome of the alkylation reaction represents the most salient feature of this new approach to the synthesis of dipeptides.

The diastereomeric mixture of aminoesters **1** and **2**, obtained from (1*S*)-phenethyl amine and (±)-ethyl-2-bromo propionate, was easily separated by silica gel chromatography and subsequent acylation with chloropropionyl chloride gave **3** and **4**, respectively. The cyclization to piperazine-2,5-dione derivatives **5** and **6** was then easily achieved with NH_3 in ethanol at r.t. in quantitative yield. The chiral lactims **7** and **8** were obtained by treating the diketopiperazine derivatives **5** and **6**, respectively, with Et_3OBF_4, as previously reported for similar compounds[1]. All the steps of the synthesis occurred in good yield and both diastereomeric synthones **7** and **8** were recovered in high diastereomeric excess.

In order to explain the conversion of **3** or **4** into **5** or **6**, respectively, an informative study was made by submitting to ammonolysis both the possible precursors **3a** (prepared by ammonolysis of **1** and subsequent acylation with chloroacetylchloride) and **3b** (obtained by acid hydrolysis of lactime **7**) (Scheme 2). Treatment of **3b** with NH_3 in ethanol gave **5** in quantitative yield, while **3a** gave a mixture of products where **5** was recovered in low yield (about 20%) (Scheme 2). Thus we may assert that the formation of **5** proceeds through the cyclization of **3b** rather than of **3a**. Furthermore, it is interesting to underline that the treatment of **3a** with NH_3 in ethanol confirmed the unusual amidic ammonolysis assisted by the neighbouring unsubstituted amide group already observed by us on a

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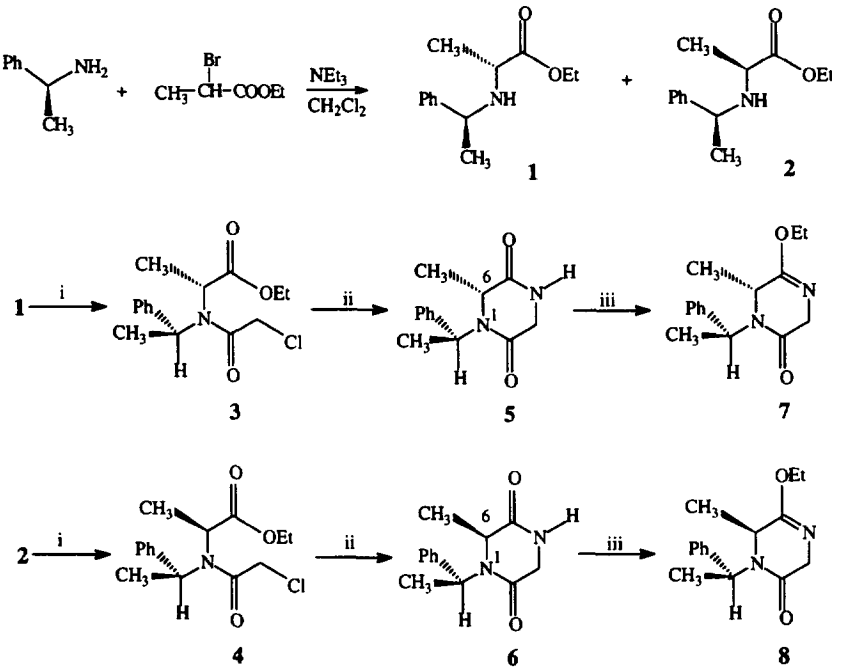
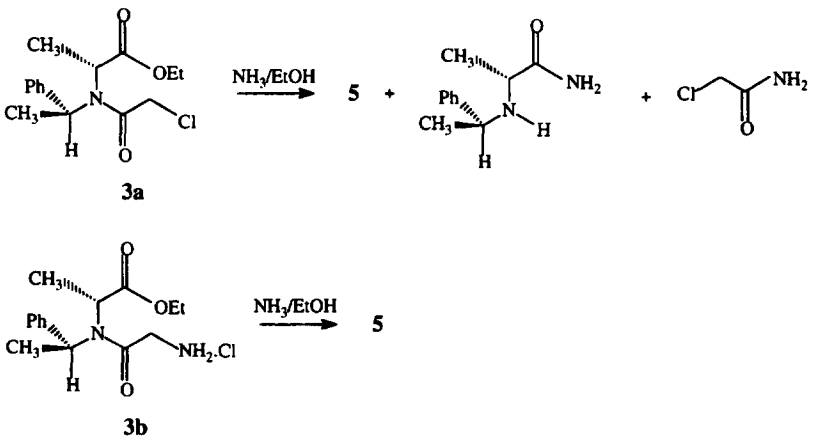


Scheme 1. Synthesis of synthones **7** and **8**: i) $ClCH_2COCl$; ii) NH_3/EtOH; iii) Et_3OBF_4.

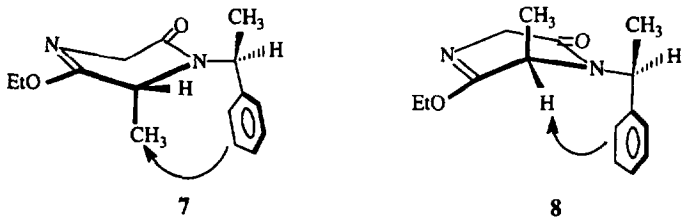
similar substrate[5] where the kinetics were investigated[6]. In fact, the amide **3a** preferentially undergoes cleavage to chloroacetamide and a 2-amino-propionamide derivative, induced by the ammonia, rather than cyclization to **5**.



Scheme 2.

The absolute configuration of the stereogenic centre C-6 both of **7** and **8** has been determined on the basis of the approach already used for piperazine-2,5-dione[1,2] and morpholine-2,5-dione[3] derivatives. As previously shown, the ^{1}H-NMR chemical shifts of substituents at C-6 are highly dependent on their absolute configuration owing to the phenyl shielding brought about by the adjacent chiral (*S*)-1-phenethyl amine moiety.

Molecular mechanics calculations[7], performed on both **7** and **8**, have shown that the preferred geometry of the heterocyclic ring is the boat conformation: the atoms N-1,C-2,N-4 and C-5 are almost



7 8

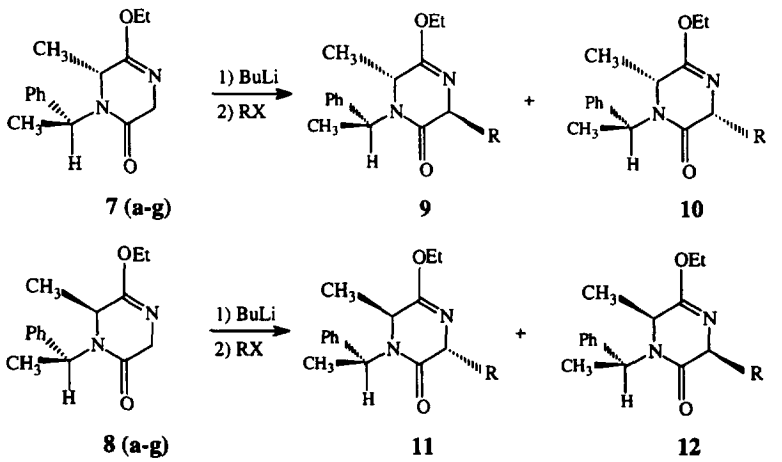
Figure 1. Different shielding suffered by (C-6)-CH_3 and (C-6)-H in **7** and **8**. The (C-6)-H in (6*S*)-**8** is significantly shielded by the Ph, resonating at downfield compared to (6*R*)-**7**; the converse is true for the (C-6)-CH_3.

coplanar, while C-3 and C-6 are out of the plane, analogously to that already observed for similar molecules[1–3]. Furthermore, both in **7** and **8** the (C-6)-CH_3 mainly prefers the axial rather than the equatorial position, this last conformation being less stable by about 3 Kcal/mole. In this regard, from the calculated geometries appreciable torsional strains can be observed in the conformer with (C-6)-CH_3 in an equatorial arrangement: the methyl and ethoxy groups are actually quasi-eclipsed (the dihedral angle CH_3-(C-6)-(C-5)-O being $\simeq 10°$) and the dihedral angle CH_3-(C-6)-(N-1)-C* is also relatively small (about 25°).

The conformational analysis[7], accomplished by a step to step rotation around the C*-(N-1) bond, showed that the phenethyl side chain can exist in two low energy conformers, with the benzylic hydrogen syn- or antiperiplanar to the adjacent carbonyl group, according to what was previously observed for similar derivatives[1–3]. However, it is only the rotamer with the benzylic hydrogen syn-periplanar (even though only present to a small extent) which can anisotropically influence the chemical shift of the substituents at C-6 (see Figure 1).

The analysis of ^{1}H-NMR spectra indeed reveals that the (C-6)-CH_3 is more shielded in (6*R*)-**7** (0.75 ppm) than in (6*S*)-**8** (1.4 ppm), whereas the (C-6)-H resonates at higher field in (6*S*)-**8** (3.5 ppm) than in (6*R*)-**7** (3.85 ppm) (see Figure 1). However the absolute configuration of C-6, assigned as described above, was confirmed by synthesising both **7** and **8** starting from the mesylates of (*R*)- and (*S*)-ethyl lactate, respectively, following the procedure summarized in Scheme 6 for the compound **15**.

When one equivalent of alkylating reagent is added to Lithium enolate of pure isomer (6*R*)-**7(a–g)** or (6*S*)-**8(a–g)**, cooled to −78°C, a practically total conversion into the products **9** and **10** or **11** and **12**, respectively, was obtained (Scheme 3). The stereochemical results of the alkylation reaction are reported in Table 1.



7 (a-g) **9** **10**

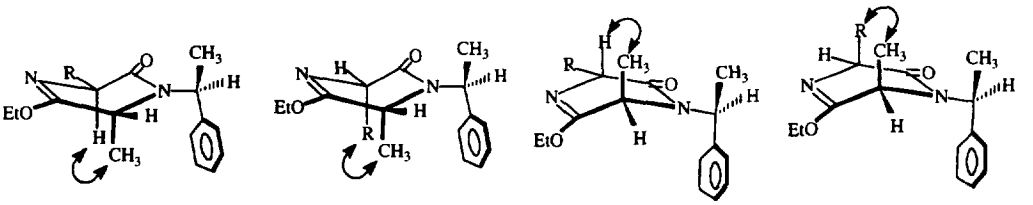
8 (a-g) **11** **12**

Scheme 3. R= a) $(CH_3)_2C{=}CHCH_2$; b) $(CH_3)_2CH$; c) $CH_2{=}CHCH_2$; d) C_2H_5; e) $PhCH_2$; f) n-C_3H_7; g) CH_3.

Table 1. Diastereoselective alkylation of **7**, **8** and **15**

Alkylating reagent			Yield% (a)					
n°	R	X	**9**	**10**	**11**	**12**	**16**	**17**
1	a	Br	≥98	-	78	22	91	9
2	b	I	≥98	-	≥98	-	81	19
3	c	I	92	8	80	20	84	16
4	d	I	85	15	70	30	71	29
5	e	Br	85	15	55	45	≥98	-
6	f	I	70	30	50	50	62	38
7	g	I	27	73	26	74	26	74

(a) calculated by ^{1}H-NMR.



9 **10** **11** **12**

Figure 2. nOe registered on **9**, **10**, **11** and **12** derivatives.

The relative configuration of the introduced stereogenic centre C-3 of **9–12** (**a–g**) has been determined on the basis of the nOe measurements registered between the axial substituents at C-3 and C-6 positions. On the *trans* derivatives **9** and **11** significant nOe was observed between the (C-6)-CH_3 and the (C-3)-H, while on the *cis* isomers **10** and **12** consistent nOe was registered between the (C-6)-CH_3 and the alkyl group at C-3 (see Figure 2).

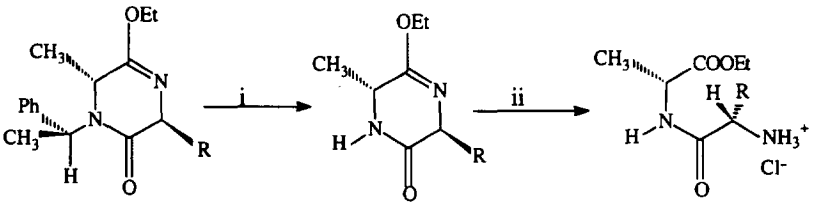
Thus, nOe experiments and molecular mechanics calculations[7] are according to that already observed for piperazine-2,5-dione derivatives[1,2], i.e. in the *cis* isomers **10** and **12** the substituents at C-3 and C-6 preferentially lie in the diaxial arrangement[8]. Also for the *trans* isomers **9** and **11** energy calculations are in agreement with the nOe observed: in fact, the conformer with (C-6)-CH_3 in axial position and the alkyl substituent at C-3 in equatorial is thermodynamically favoured[9].

It is interesting to note that both the isomers *trans* (3*R*,6*S*)-**11** (**c–g**) and the *cis* (3*S*,6*S*)-**12** (**c–g**) undergo isomerization in alkaline solution (LiOH/EtOH at 100°C or EtONa/EtOH at r.t.) to an approximately 1:1 mixture of *trans*- (3*R*,6*S*) and *cis*-(3*S*,6*S*) isomers, showing that the partial inversion of configuration exclusively occurs at the stereogenic centre C-3 which possesses the more acid proton (the negative charge of the corresponding anion can actually be delocalized on both the C=O and the N=C groups).

In a model study, we converted both **9a** and **9e** into the corresponding dipeptides **14** (**a**,**e**) through a Birch reaction (Na/NH_3) followed by acid hydrolysis in very mild conditions (Scheme 4).

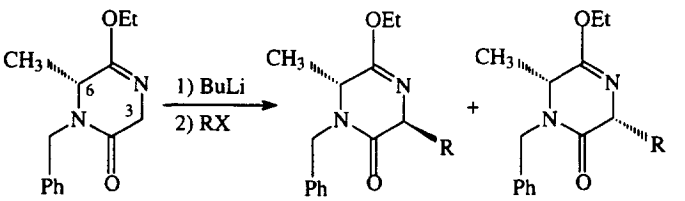
Finally, in order to explore the role played by the chiral (*S*)-1-phenethyl group on the stereochemical outcome of the alkylation, we also performed the reaction on the substrate **15** (see Scheme 5), prepared starting from the methansulfonate of (*S*)-ethyl lactate as summarized in Scheme 6, in which the chiral auxiliary was substituted by the achiral sterically similar group CH_2Ph.

The results reported in Table 1 show that the alkylation of **15** preferentially afforded the *trans* isomer in all cases investigated (except the entry 7) with a diastereoselection comparable to that observed for both the **7** and **8** (except the entries 2 and 5). In addition, the stereochemical result is essentially



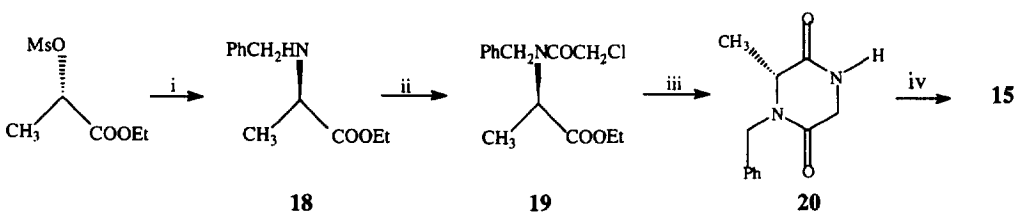
9 (a,e) **13(a,e)** **14(a,e)**

Scheme 4. i) Na/NH_3; ii) 0.5N HCl.



15 **16** **17**

Scheme 5. R= a) $(CH_3)_2C{=}CHCH_2$; b) $(CH_3)_2CH$; c) $CH_2{=}CHCH_2$; d) C_2H_5; e) $PhCH_2$; f) $n\text{-}C_3H_7$; g) CH_3.



18 **19** **20**

Scheme 6. i) $PhCH_2NH_2/Et_3N$; ii) $ClCH_2COCl/Et_3N$; iii) $NH_3/EtOH$; iv) Et_3OBF_4/CH_2Cl_2.

according to the asymmetric induction observed by Schollkopf[10] on the *trans* alkylation of similar substrates, i.e. bis-lactim ether derivatives. From the results obtained it is possible to argue that the diastereofacial bias in the alkylation both of **7** and **8** appears prevalently influenced by the C-6 center rather than by the (*S*)-methylbenzyl group. However, because at present we are not able to rationalize the observed results (indeed, the lithium enolates of **7** and **8** are substantially planar and the difference in energy between the *syn* and the antiperiplanar conformers appears very small, analogously to that previously observed for morpholine-2,5-dione derivatives[3]), further attempts are necessary in order to understand the stereochemical outcome of this asymmetric alkylation.

In conclusion, the reported strategy provides a new and versatile approach to the asymmetric synthesis of a wide variety of dipeptides with a moderate to good stereoselection, starting from easily accessible chiral synthones. Therefore further investigations are in progress in order to use this protocol for the synthesis of sterically hindered dipeptides biologically active.

Experimental

^1H- and ^{13}C-NMR spectra were recorded at room temperature on a Gemini spectrometer at 300 Mhz using $CDCl_3$ as solvent, unless otherwise stated. Optical rotation values were measured at room temperature on a Perkin Elmer 343 polarimeter. Chromatographic separations were performed with silica gel 60 (230–400 mesh). Melting points were determined in open capillaries and are uncorrected.

(2R,S)-(4S)-3-Aza-2-methyl-4-phenyl-ethylpentanoate 1,2

To a solution of 32.2 ml of (*S*)-1-phenethylamine (250 mmol) and 41.5 ml of triethylamine (300 mmol) in CH_2Cl_2 (150 ml) stirred at 0°C, were dropped 32.6 ml (250 mmol) of (*R,S*)-ethyl-2-bromopropionate in CH_2Cl_2 (25 ml). The reaction was then warmed up to room temperature and the mixture was stirred for 24 h at r.t. After addition of 2M HCl (25 ml) the reaction product was extracted with dichloromethane. The organic extract was dried, evaporated in vacuo and the residue was submitted to silica gel chromatographic separation of diastereomers **1** and **2**, eluting with hexane/ethyl acetate.

(2*R*)-1. The product was isolated pure as an oil; ^{1}H-NMR δ 1.22 (t, 3H, J=7.2 Hz), 1.3 (d, 3H, J=6.9 Hz), 1.38 (d, 3H, J=6.6 Hz), 3.35 (q, 1H, J=6.9 Hz), 3.81 (q, 1H, J=6.6 Hz), 4.08 (m, 2H), 7.3 (m, 5ArH); ^{13}C-NMR δ 14.1, 18.8, 23.1, 54.0, 55.7, 60.5, 126.6, 127, 128.3, 145, 175.5. $[\alpha]_D$ −16.3 (c=1.25, $CHCl_3$). Anal. Calcd. for $C_{13}H_{19}NO_2$: C;70.56, H;8.65, N;6.33. Found: C;70.8, H;8.68, N;6.3.

(2*S*)-2. It was obtained as an oil; ^{1}H-NMR δ 1.23 (d, 3H, J=7.1 Hz), 1.27 (t, 3H, J=7.2 Hz), 1.35 (d, 3H, J=6.6 Hz), 1.85 (m,1H), 3.1 (q, 1H, J=7.1Hz), 3.75 (q, 1H, J=6.6 Hz), 4.2 (q, 2H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 14.2, 19.7, 25.2, 54.1, 56.5, 60.1, 126.7, 126.9, 128.3, 144.9, 176.3. $[\alpha]_D$ −125.9 (c=1.59, $CHCl_3$). Anal. Calcd. for $C_{13}H_{19}NO_2$: C;70.56, H;8.65, N;6.33. Found: C;70.75, H;8.66, N;6.31.

(2R,4S)-3-Aza-3-chloroacetyl-2-methyl-4-phenyl-ethylpentanoate 3

To 8.85 g of **1** (40 mmol) dissolved in 50% water–acetone (120 ml) at O°C, $Na_2CO_3.10H_2O$ (12 g) was added. Then chloroacetyl chloride (4 ml, 50 mmol) in 10 ml of acetone was dropped under stirring. After 3 h, the solvent was removed in vacuo and the residue was acidified with 6M HCl. After extraction with ethyl acetate and removal of the solvent, the product was recovered pure (m.p. 78–80°C) in 90% yield after silica gel chromatography elution with hexane/ethyl acetate. ^{1}H-NMR δ 1.04 (d, 3H, J=6.8 Hz), 1.26 (t, 3H, J=7.2 Hz), 1.74 (d, 3H, J=7.0 Hz), 3.52 (q, 1H, J=6.8 Hz), 4.15 (q, 2H, J=7.2 Hz), 4.23 (s, 2H), 5.25 (q, 1H, J=7.0 Hz), 7.4 (m, 5ArH); ^{13}C-NMR δ 14.0, 14.4, 17.1, 41.4, 52.7, 56.2, 61.1, 127.7, 128.3, 128.7, 138.3, 165.3, 171.0. $[\alpha]_D$ −3.1 (c=3.26, $CHCl_3$). Anal. Calcd. for $C_{15}H_{20}ClNO_3$: C;60.5, H;6.77, Cl;11.91. Found: C;60.7, H;6.8, Cl;11.95.

(2S,4S)-3-Aza-3-chloroacetyl-2-methyl-4-phenyl-ethylpentanoate 4

The product was obtained starting from intermediate **2** following the procedure previously reported for the diastereomer **3**. ^{1}H-NMR δ 1.1 (t, 3H, J=7.1 Hz), 1.54 (d, 3H, J=6.9 Hz), 1.73 (d, 3H, J=7.0 Hz), 3.54 (q, 1H, J=6.9 Hz), 3.96 (q, 2H, J=7.1 Hz), 4.21 (qAB, 2H, J=12.2 Hz), 5.25 (q, 1H, J=7.0 Hz), 7.3–7.5 (m, 5ArH); ^{13}C NMR δ 13.7, 15.7, 18.5, 41.4, 52.2, 56.2, 60.7, 127.8, 128.0, 128.2, 138.0, 165.1, 170.1. $[\alpha]_D$ −102.7 (c=4.2, $CHCl_3$). Anal. Calcd. for $C_{15}H_{20}ClNO_3$: C;60.5, H;6.77, Cl;11.91. Found: C;60.75, H;6.8, Cl;11.85.

(6R,1'S)-1-(1'-Phenethyl)-6-methyl-piperazine-2,5-dione 5

The ester **3** (3 g, 10 mmol) was dissolved in 30 ml of 7M ammonia solution in ethanol. The flask was stopped and the reaction stirred at r.t. for 24 h. The reaction product, filtered off after evaporation of ammonia, was obtained as a solid (m.p. 145–8°C). ^{1}H-NMR (DMSO): δ 0.75 (d, 3H, J=7.0 Hz), 1.52 (d,3H, J=7.1Hz), 3.6 (dd, 1H, J=4.6, 17.2 Hz), 3.85 (dq, 1H, J=1, 7.0 Hz), 4.06 (d, 1H, J=17.2 Hz), 5.61 (q, 1H, J=7.1 Hz), 7.4 (m, 5ArH), 8.14 (dd, 1H, J=1, 4.6 Hz); ^{13}C-NMR (DMSO): δ 16.1, 17.7, 44.5, 51.1, 53.0, 127.68, 127.71, 128.4, 140.2, 164.8, 169.3. $[\alpha]_D$ −297.7 (c=2.5, $CHCl_3$). Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C;67.22, H;6.94, N;12.06. Found: C;67.0, H;6.9, N;12.1.

(6S,1'S)-1-(1'-Phenethyl)-6-methyl-piperazine-2,5-dione 6

The product was obtained as a solid (m.p. 228–230°C) starting from **4** and following the procedure previously reported for the diastereomer **5**. ^{1}H-NMR (DMSO): δ 1.41 (d, 3H, J=7.0 Hz), 1.57 (d, 3H, J=7.2 Hz), 3.50 (dq, 1H, J=1, 7.0 Hz), 3.66 (dd, 1H, J=4.6, 17.2 Hz), 4.15 (d, 1H, J=17.2 Hz),

5.67 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH), 8.15 (dd, 1H, J=1, 4.6 Hz); ^{13}C NMR (DMSO): δ 17.3, 18.9, 44.5, 51.1, 52.8, 126.9, 127.5, 128.6, 140.2, 165.2, 169.4. $[\alpha]_D$ 37.8 (c=2.13, $CHCl_3$). Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C;67.22, H;6.94, N;12.06. Found: C;67.5, H;6.95, N;12.0.

(6R,1'S)-1-(1'-Phenethyl)-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one 7

5.8 g of **5** (25 mmol) was dissolved in dry CH_2Cl_2 (60 ml) and added to triethyl-oxonium tetrafluoroborate prepared from BF_3 etherate (20 ml) and epichlorohydrin (10 ml)[11]. The reaction mixture was stirred at r.t. under inert atmosphere and after about 12 h a phosphate buffer solution at pH=7 (200 ml) was added. The organic layer was separated and the aqueous solution extracted with dichloromethane. The combinated extracts were evaporated under vacuum and submitted to chromatographic separation by silica gel eluting with hexane/ethyl acetate. The lactim **7** was recovered as a solid (m.p. 208–210°C) in 80% yield. ^{1}H-NMR δ 0.7 (d, 3H, J=6.9 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.56 (d, 3H, J=7.2 Hz), 3.93 (dq, 1H, J=1.2, 6.9 Hz), 4.04 (dd, 1H, J=1.2, 19.5 Hz), 4.08 (q, 2H, J=7.1 Hz), 4.23 (d, 1H, J=19.5 Hz), 5.95 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 14.0, 15.7, 18.2, 49.1, 50.5, 50.8, 61.7, 127.8, 128.4, 139.9, 164, 167.6. $[\alpha]_D$ −288.4 (c=2.71, $CHCl_3$). Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C;69.2, H;7.74, N;10.76. Found: C;69.0, H;7.7, N;10.8.

(6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one 8

The product was obtained as a solid (m.p. 52–4°C) starting from intermediate **6** and following the procedure previously reported for the diastereomer **7**. ^{1}H-NMR δ 1.18 (t, 3H, J=7.0 Hz), 1.38 (d, 3H, J=6.9 Hz), 1.64 (d, 3H, J=7.2 Hz), 3.61 (dq, 1H, J=1, 6.9 Hz), 4.03 (q, 2H, J=7.0 Hz), 4.09 (dd, 1H, J=1, 19.7 Hz), 4.27 (d, 1H, J=19.7 Hz), 5.87 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 13.5, 17.4, 19.2, 49.0, 50.4, 51.1, 61.2, 126.8, 127.3, 128.2, 138.8, 163.5, 167.5. $[\alpha]_D$ 37.5 (c=2.1, $CHCl_3$). Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C;69.2, H;7.74, N;10.76. Found: C;69.5, H;7.75, N;10.72.

Alkylation of 7, 8 and 15: general procedure

5 ml of LHMDS (1M solution in THF) (5 mmol) were slowly dropped to a stirred solution of 5 mmol of **7** (or **8** or **15**) in dry THF (50 ml), cooled at −78°C under an inert atmosphere. After 1 h, the alkylating reagent (10 mmol) was added and the reaction mixture stirred for about 3 h. The cooling bath was then removed allowing the reaction mixture to warm up to r.t. About 10 ml of 1M HCl was added and the mixture extracted with ethyl acetate. The organic extract was dried, evaporated in vacuo and the residue submitted to silica gel chromatographic separation of diastereomers by eluting with hexane/ethyl acetate.

(3S,6R,1'S)-1-(1'-Phenethyl)-5-ethoxy-3-(3-methyl-2-butenyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***9a***

^{1}H NMR δ 0.73 (d, 3H, J=6.9 Hz), 1.26 (t, 3H, J=7.1 Hz), 1.54 (d, 3H, J=7.1 Hz), 1.68 (s, 3H), 1.71 (s, 3H), 2.57 (m, 1H), 2.79 (m, 1H), 3.92 (m, 2H), 4.11 (m, 2H), 5.26 (m, 1H), 5.88 (q, 1H, J=6.9 Hz), 7.4 (m, 5ArH); ^{13}C NMR δ 14.0, 16.0, 17.9, 18.0, 25.8, 31.6, 49.9, 51.1, 58.1, 61.6, 120.9, 127.6, 127.8, 128.4, 133.3, 140.4, 162.8, 169.7. $[\alpha]_D$ −211.2 (c=11.4, $CHCl_3$). Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C;73.14, H;8.59, N;8.53. Found: C;72.95, H;8.3, N;8.5.

(3S,6R,1'S)-1-(1'-Phenethyl)-5-ethoxy-3-isopropyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***9b***

^{1}H-NMR δ 0.73 (d, 3H, J=6.9 Hz), 0.76 (d, 3H, J=6.8 Hz), 1.10 (d, 3H, J=6.8 Hz), 1.28 (t, 3H, J=7.1 Hz), 1.55 (d, 3H, J=7.2 Hz), 2.70 (m, 1H), 3.76 (dd, 1H, J=1.4, 2.8 Hz), 3.93 (dq, 1H, J=1.4, 6.9 Hz), 4.13 (m, 2H), 5.90 (q, 1H, J=7.2 Hz), 7.4 (m, 5ArH); ^{13}C-NMR δ 14.1, 16.2, 16.3, 18.3, 19.9, 29.8, 49.5, 50.9, 61.3, 62.1, 127.5, 127.7, 128.3, 140.5, 162.4, 169.4. $[\alpha]_D$ −268.4 (c=2.1, $CHCl_3$). Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C;71.49, H;8.67, N;9.26. Found: C;71.7, H;8.7, N;9.23.

(3S,6R,1'S)-1-(1'-Phenethyl)-3-allyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***9c***

^{1}H-NMR δ 0.72 (d, 3H, J=6.8 Hz), 1.27 (t, 3H, J=7.2 Hz), 1.54 (d, 3H, J=7.2 Hz), 2.5–2.9 (m, 2H), 3.9 (m, 2H), 4.1 (m, 2H), 5.1 (m, 2H), 5.9 (q, 1H, J=7.2 Hz), 6.0 (m, 1H), 7.4 (m, 5ArH); ^{13}C-

NMR δ 14.0, 16.0, 17.8, 37.1, 49.7, 50.9, 57.7, 61.7, 116.7, 127.7, 127.8, 128.4, 135.6, 140.2, 163.0, 169.4. $[\alpha]_D$ −264.1 (c=1.7, $CHCl_3$). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C;71.97, H;8.05, N;9.33. Found: C;71.75, H;8.0, N;9.36.

(3R,6R,1′S)-1-(1′-Phenethyl)-3-allyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***10c***

^{1}H-NMR δ 0.91 (d, 3H, J=6.9 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.63 (d, 3H, J=7.2 Hz), 2.4–2.7 (m, 2H), 4.0 (dq, 1H, J=1, 6.9 Hz), 4.08 (m, 2H), 4.25 (ddd, 1H, J=1, 5.5, 7.6 Hz), 5.1 (m, 2H), 5.8 (q, 1H, J=7.2 Hz), 5.9 (m, 1H), 7.4 (m, 5ArH); ^{13}C-NMR δ 0.9, 14.0, 15.7, 40.0, 49.8, 51.2, 60.4, 61.4, 117.6, 127.4, 128.3, 134.3, 140.9, 161.2, 169.0. $[\alpha]_D$ −132.8 (c=2.4, $CHCl_3$). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C;71.97, H;8.05, N;9.33. Found: C;72.15, H;8.08, N;9.3.

(3S,6R,1′S)-1-(1′-Phenethyl)-5-ethoxy-3-ethyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***9d***

^{1}H-NMR δ 0.73 (d,3H,J=6.8Hz), 0.97 (t,3H,J=7.4Hz), 1.29 (t,3H,J=7.1Hz), 1.54 (d,3H,J=7.1Hz), 2.0 (m,2H), 3.89 (m,1H), 3.95 (dq,1H,J=1.1, 6.8Hz), 4.2 (q,2H,J=7.1Hz), 5.9 (q,1H,J=7.1Hz), 7.4 (m,5ArH); ^{13}C-NMR δ 9.3, 13.7, 15.7, 17.4, 25.4, 49.4, 50.5, 58.0, 61.2, 127.3, 127.4, 128.0, 140.0, 162.6, 169.3. $[\alpha]_D$ −248.5 (c=6.8, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C;70.8, H;8.39, N;9.71. Found: C;70.6, H;8.38, N;9.75.

(3R,6R,1′S)-1-(1′-Phenethyl)-5-ethoxy-3-ethyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***10d***

^{1}H-NMR δ 0.88 (d,3H,J=6.9Hz), 1.1 (t,3H,J=7.4Hz), 1.31 (t,3H,J=7.1Hz), 1.62 (d,3H,J=7.2Hz), 1.75 (m,1H), 2.0 (m,1H), 4.07 (q,1H,J=6.9Hz), 4.17 (m,1H), 4.26 (m,2H), 5.86 (q,1H,J=7.2Hz), 7.35 (m,5H); ^{13}C-NMR δ 10.9, 14.0, 15.7, 21.2, 29.3, 49.7, 51, 61.4, 61.8, 127.5, 127.6, 128.4, 140.9, 161.2, 170. $[\alpha]_D$ −132.6 (c=1.8, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C;70.8, H;8.39, N;9.71. Found: C;70.55, H;8.36, N;9.75.

(3S,6R,1′S)-1-(1′-Phenethyl)-3-benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***9e***

^{1}H-NMR δ 0.69 (d, 3H, J=6.9 Hz), 1.24 (t, 3H, J=7.0 Hz), 1,46 (d, 3H, J=7.2 Hz), 3.12 (dd, 1H, J=7.8, 13.4 Hz), 3.45 (dd, 1H, J=4.1, 13.4 Hz), 3.81 (dq, 1H, J=1.3, 6.9 Hz), 4.1 (m, 3H), 5.87 (q, 1H, J=7.2 Hz), 7.4 (m, 10ArH); ^{13}C-NMR δ 14.0, 15.8, 18.0, 38.8, 49.7, 51.0, 59.1, 61.6, 125.8, 127.6, 127.7, 128.3, 130.2, 139.2, 140.3, 162.4, 169.2. $[\alpha]_D$ −209.1 (c=3.1, $CHCl_3$). Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C;75.4, H;7.48, N;7.99. Found: C;75.6, H;7.5, N;7.97.

(3R,6R,1′S)-1-(1′-Phenethyl)-3-benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***10e***

^{1}H-NMR δ 0.16 (d, 3H, J=6.9 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.62 (d, 3H, J=7.2 Hz), 3.13 (dd, 1H, J=4.6, 13.2 Hz),3.35 (dd, 1H, J=5.6, 13.2 Hz), 3.86 (dq, 1H, J=1.6, 6.9 Hz), 4.1 (m, 2H), 4.96 (ddd, 1H, J=1.6, 4.6, 5.6 Hz), 5.42 (q, 1H, J=7.2 Hz),7.4 (m, 10 H); ^{13}C-NMR δ 14.2, 16.0, 19.7, 40.2, 50.9, 52.7, 61.3, 126.6, 127.3, 127.4, 128.0, 128.1, 130.4, 137.3, 140.9, 160.7, 168.3.

(3S,6R,1′S)-1-(1′-Phenethyl)-5-ethoxy-6-methyl-3-propyl-3,6-dihydro-1H-pyrazine-2-one ***9f***

^{1}H-NMR δ 0.72 (d, 3H, J=6.9 Hz), 0.97 (t, 3H, J=7.3 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.45 (m, 2H), 1.54 (d, 3H, J=7.1 Hz), 1.83 (m, 1H), 2.05 (m, 1H), 3.88 (ddd, 1H, J=1.2, 4.4, 7.3 Hz), 3.93 (dq, 1H, J=1.2, 6.9 Hz), 4.12 (m, 2H), 5.92 (q, 1H, J=7.1 Hz), 7.4 (m, 5ArH); ^{13}C-NMR δ 14.1, 16.0, 17.7, 18.7, 34.8, 49.6, 50.8, 57.3, 61.6, 127.7, 127.8, 128.4, 140.3, 162.9, 170.0. $[\alpha]_D$ −237 (c=1.9, $CHCl_3$). Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C;71.49, H;8.67, N;9.26. Found: C;71.6, H;8.7, N;9.23.

(3R,6R,1′S)-1-(1′-Phenethyl)-5-ethoxy-6-methyl-3-propyl-3,6-dihydro-1H-pyrazine-2-one ***10f***

^{1}H-NMR δ 0.85 (d, 3H, J=6.9 Hz), 0.95 (t, 3H, J=7.2 Hz), 1.25 (t, 3H, J=7.1 Hz), 1.5–1.8 (m, 3H), 1.58 (d, 3H, J=7.1 Hz), 1.85 (m, 1H), 3.95 (dq, 1H, J=1, 6.9 Hz), 4.05 (m, 3H), 5.8 (q, 1H, J=7.1 Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 14.1, 16.2, 16.3, 18.3, 19.9, 29.9, 49.5, 51.0, 61.3, 62.1, 127.6, 127.7, 128.3, 140.5, 162.4, 169.5.

(3S,6R,1′S)-1-(1′-Phenethyl)-5-ethoxy-3,6-dimethyl-3,6-dihydro-1H-pyrazine-2-one ***9g***

^{1}H-NMR δ 0.70 (d, 3H, J=6.9 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.52 (d, 3H, J=7.2 Hz), 1.55 (d, 3H, J=7.2 Hz), 3.9 (dq, 1H, J=1.2, 6.9 Hz), 4.0 (dq, 1H, J=1.2, 7.2 Hz), 4.1 (m, 2H), 5.94 (q, 1H, J=7.2 Hz), 7.4 (m, 5H); ^{13}C-NMR δ 14.0, 15.8, 17.2, 19.2, 49.8, 50.7, 53.6, 61.8, 127.7, 127.9, 128.4, 140.1, 163.5, 170.4. $[\alpha]_D$ −256 (c=1.4, $CHCl_3$). Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C;70.04, H;8.08, N;10.21. Found: C;69.8, H;8.05, N;10.25.

(3R,6R,1′S)-1-(1′-Phenethyl)-5-ethoxy-3,6-dimethyl-3,6-dihydro-1H-pyrazine-2-one ***10g***

^{1}H-NMR δ 0.83 (d,3H,J=6.8Hz), 1.27 (t,3H,J=7.2Hz), 1.47 (d,3H,J=7.3Hz), 1.60 (d,3H,J=7.2Hz), 3.98 (dq,1H,J=1, 6.8Hz), 4.09 (dq,2H,J=1.2, 7.2Hz), 4.25 (dq,1H,J=1, 7.3Hz), 5.87 (q,1H,J=7.2Hz), 7.4 (m,5ArH); ^{13}C-NMR δ 13.9, 15.6, 21.2, 21.4, 49.4, 50.8, 56.3, 61.3, 127.4, 127.7, 128.3, 140.5, 161.6, 170.5. $[\alpha]_D$ −184.7 (c=3.7, $CHCl_3$). Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C;70.04, H;8.08, N;10.21. Found: C;70.24, H;8.1, N;10.18.

(3R,6S,1′S)-1-(1′-Phenethyl)-5-ethoxy-3-(3-methyl-2-butenyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***11a***

^{1}H-NMR δ 1.18 (t, 3H, J=7.1 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.63 (d, 3H, J=7.2 Hz), 1.7 (s, 3H), 1.74 (s, 3H), 2.7 (m, 3H), 3.6 (dq, 1H, J=1.2, 6.9 Hz), 4.05 (m, 2H), 5.25 (m, 1H), 5.85 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 13.8, 17.7, 18.0, 19.4, 25.8, 31.8, 49.7, 51.5, 58.0, 61.2, 120.6, 126.9, 127.3, 128.4, 133.3, 139.4, 162.2, 169.7. $[\alpha]_D$ −5.1 (c=8.4, $CHCl_3$). Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C;73.14, H;8.59, N;8.53. Found: C;73.34, H;8.61, N;8.5.

(3S,6S,1′S)-1-(1′-Phenethyl)-5-ethoxy-3-(3-methyl-2-butenyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***12a***

^{1}H-NMR δ 1.2 (t, 3H, J=7.2 Hz), 1.35 (d, 3H, J=6.8 Hz), 1.625 (s, 3H), 1.63 (d, 3H, J=7.2 Hz), 1,72 (s, 3H), 2.55 (m, 2H), 3.54 (dq, 1H, J=1.3, 6.9 Hz), 4.0 (m, 2H), 4.27 (ddd, 1H, J=1.3, 5.5, 6.1 Hz), 5.15 (m, 1H), 5.75 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 13.9, 17.8, 21.7, 25.8, 33.6, 49.7, 52.4, 60.5, 61.1, 119.8, 127.6, 127.7, 128.5, 134.5, 138.4, 160.6, 169.1. $[\alpha]_D$ −16.0 (c=4.8, $CHCl_3$). Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C;73.14, H;8.59, N;8.53. Found: C;73.45, H;8.62, N;8.51.

(3R,6S,1′S)-1-(1′-Phenethyl)-5-ethoxy-3-isopropyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***11b***

^{1}H-NMR δ 0.8 (d, 3H, J=6.8 Hz), 1.13 (d, 3H, J=6.8 Hz), 1.2 (t, 3H, J=7.0 Hz), 1.35 (d, 3H, J=6.9 Hz), 1.64 (d, 3H, J=7.1 Hz), 3.59 (dq, 1H, J=1.3, 6.9 Hz), 3.83 (dd, 1H, J=1.3, 2.7 Hz), 4.1 (m, 2H), 5.85 (q, 1H, J=7.1 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 14.0, 16.4, 17.8, 19.8, 19.9, 29.9, 49.5, 51.7, 61.1, 62.2, 127.1, 127.4, 128.5, 139.6, 162.2, 169.7. $[\alpha]_D$ 40.3 (c=2.2, $CHCl_3$). Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C;71.49, H;8.67, N;9.26. Found: C;71.25, H;8.64, N;9.3.

(3R,6S,1′S)-1-(1′-Phenethyl)-3-allyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***11c***

^{1}H-NMR δ 0.8 (t, 3H, J=7.2 Hz), 1.36 (d, 3H, J=6.9 Hz), 1.63 (d, 3H, J=7.3 Hz), 2.75 (m,2H), 3.61 (dq, 1H, J=1.3, 6.9 Hz), 4.05 (m, 3H), 5–5.25 (m, 2H), 5.85 (q, 1H, J=7.3 Hz), 6.0 (m, 1H), 7.3 (m, 5ArH); ^{13}C-NMR δ 13.9, 17.7, 19.3, 37.2, 49.8, 51.6, 57.7, 61.4, 116.8, 127.1, 127.4, 128.5, 135.4, 139.4, 162.7, 169.5. $[\alpha]_D$ 17.1 (c=3.7, $CHCl_3$). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C;71.97, H;8.05, N;9.33. Found: C;71.75, H;8.04, N;9.3.

(3S,6S,1′S)-1-(1′-Phenethyl)-3-allyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***12c***

^{1}H-NMR δ 1.2 (t,3H,J=7.1Hz), 1.39 (d,3H,J=6.9Hz), 1.65 (d,3H,J=7.1Hz), 2.6 (m,2H), 3.55 (dq,1H,J=1.2, 6.9Hz), 3.9–4.15 (m,2H), 4.28 (m,1H), 5.13 (m,2H), 5.8 (q,1H,J=7.1Hz), 5.9 (m,1H), 7.35 (m,5ArH); ^{13}C-NMR δ 14.0, 18.1, 22.3, 40.1, 49.7, 52.4, 60.2, 61.4, 117.8, 127.8, 128.7, 134.3, 138.5, 161.6, 169.0. $[\alpha]_D$ −14.3 (c=0.5, $CHCl_3$). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C;71.97, H;8.05, N;9.33. Found: C;72.25, H;8.07, N;9.29.

(3R,6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-3-ethyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***11d***

^{1}H-NMR δ 0.98 (t,3H,J=7.2Hz), 1.36 (d,3H,J=6.9Hz), 1.63 (d,3H,J=7.2Hz), 1.9 (t,3H,J=7.2Hz), 2.05 (m,2H), 3.62 (dq, 1H,J=1.2, 6.9Hz), 3.95 (m,1H), 4.09 (m,2H), 5.88 (q,1H,J=7.2Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 9.2, 13.6, 17.5, 18.9, 25.6, 49.4, 51.2, 58.0, 61.0, 126.7, 127.1, 128.2, 139.3, 162.4, 169.6. $[\alpha]_D$ 32.1 (c=8.4, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C;70.8, H;8.39, N;9.71. Found: C;70.55, H;8.37, N;9.75.

(3S,6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-3-ethyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***12d***

^{1}H-NMR δ 1.05 (t, 3H, J=7.4 Hz), 1.19 (t, 3H, J=7.2 Hz), 1.38 (d, 3H, J=6.9 Hz),1.63 (d, 3H, J=7.2 Hz), 1.7 (m, 1H), 1.95 (m, 1H), 3.56 (q, 1H, J=6.9 Hz), 4.04 (m, 3H), 5.82 (q, 1H, J=7.2 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 10.7, 13.9, 17.9, 22.1, 29.3, 49.4, 52.1, 61.2, 61.5, 127.6, 128.6, 138.6, 160.9, 169.8. $[\alpha]_D$ −40.1 (c=2.1, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C;70.8, H;8.39, N;9.71. Found: C;70.92, H;8.4, N;9.7.

(3R,6S,1'S)-1-(1'-Phenethyl)-3-benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***11e***

^{1}H-NMR δ 1.17 (t, 3H, J=7.1 Hz), 1.29 (d, 3H, J=6.9 Hz), 1.61 (d, 3H, J=7.2 Hz), 3.26 (dd, 1H, J=7, 13.3 Hz), 3.42 (dd, 1H, J=4.2, 13.3 Hz), 3.44 (dq, 1H, J=1.4, 6.9 Hz), 4.05 (m, 2H), 4.27 (ddd, 1H, J=1.4, 4.2, 7.0 Hz), 5.78 (q, 1H, J=7.2 Hz), 6.95 (m, 2ArH), 7.3 (m, 8ArH); ^{13}C-NMR δ 14.0, 17.7, 19.8, 39.0, 49.7, 51.7, 59.2, 61.4, 125.9, 127.1, 127.7, 128.4, 130.4, 138.9, 139.2, 162.0, 169.2. $[\alpha]_D$ 156.8 (c=1.5, $CHCl_3$). Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C;75.4, H;7.48, N;7.99. Found: C;75.6, H7.5, N;7.95.

(3S,6S,1'S)-1-(1'-Phenethyl)-3-benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***12e***

^{1}H-NMR δ 0.35 (d, 3H, J=6.9 Hz), 1.2 (t, 3H, J=7.1 Hz), 1.52 (d, 3H, J=7.2 Hz), 3.11 (dd, 1H, J=4.5, 13.1 Hz), 3.3 (dq, 1H, J=6.9, 13.1 Hz), 3.43 (dd, 1H, J=5.2, 13.1 Hz), 4.05 (m, 2H), 4.53 (ddd, 1H, J=1.8, 4.5, 5.2 Hz), 5.75 (q, 1H, J=7.2 Hz), 7.3 (m, 10ArH); ^{13}C-NMR δ 14.1, 17.6, 20.2, 40.3, 49.7, 52.5, 60.9, 61.1, 126.6, 127.7, 127.9, 128.0, 128.5, 130.5, 137.2, 138.0, 160.6, 168.1. $[\alpha]_D$ 5.5 (c=1.0, $CHCl_3$). Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C;75.4, H;7.48, N;7.99. Found: C;75.25, H7.45, N;8.0.

(3R,6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-6-methyl-3-propyl-3,6-dihydro-1H-pyrazine-2-one ***11f***

^{1}H-NMR δ 0.98 (t, 3H, J=7.2 Hz), 1.18 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=6.9 Hz), 1.5 (m, 2H), 1.63 (d, 3H, J=7.2 Hz), 1.9 (m, 1H), 2.05 (m, 1H), 3.61 (dq, 1H, J=1.3, 6.9 Hz), 3.95 (ddd, 1H, J=1.2, 4.5, 7.1 Hz), 4.05 (m, 2H), 5.85 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C-NMR δ 14.0, 14.1, 17.8, 18.6, 19.2, 35.1, 49.8, 51.7, 57.4, 61.4, 127.1, 127.5, 128.6, 139.7, 162.6, 170.3. $[\alpha]_D$ 19.6 (c=0.4, $CHCl_3$). Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C;71.49, H;8.67, N;9.26. Found: C;71.8, H;8.7, N;9.23.

(3S,6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-6-methyl-3-propyl-3,6-dihydro-1H-pyrazine-2-one ***12f***

^{1}H-NMR δ 0.98 (t,3H,J=7.2Hz), 1.2 (t,3H,J=7.1Hz), 1.4 (d,3H,J=6.8Hz), 1.5–1.7 (m,3H), 1.65 (d,3H,J=7.2Hz), 1.9 (m, 1H), 3.55 (dq,1H,J=1.2, 6.8Hz), 3.9–4.2 (m,3H), 6.85 (q,1H,J=7.2Hz), 7.35 (m,5ArH); ^{13}C-NMR δ 13.96, 14.01, 18.0, 19.6, 22.2, 38.6, 49.4, 52.1, 60.3, 61.3, 127.1, 127.7, 128.7, 138.8, 161.1, 170.2. $[\alpha]_D$ −20.8 (c=1.0, $CHCl_3$). Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C;71.49, H;8.67, N;9.26. Found: C;71.55, H;8.72, N;9.28.

(3R,6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-3,6-dimethyl-3,6-dihydro-1H-pyrazine-2-one ***11g***

^{1}H-NMR δ 1.18 (t,3H,J=7.1Hz), 1.37 (d,3H,J=6.9Hz), 1.58 (d,3H,J=7.1Hz), 1.62 (d,3H,J=7.3Hz), 3.65 (dq,1H,J=1.1, 6.9 Hz), 4.05 (dq,1H,J=1.1, 7.1Hz), 4.1 (q,2H,J=7.1Hz), 5.85 (q,1H,J=7.3Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 14.0, 17.8, 18.7, 19.5, 50.1, 51.6, 53.7, 61.6, 127.1, 127.6, 128.6, 139.7, 163.3, 171.0. $[\alpha]_D$ 18.2 (c=0.9, $CHCl_3$).Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C;70.04, H;8.08, N;10.21. Found: C;70.3, H;8.1, N;10.15.

(3S,6S,1'S)-1-(1'-Phenethyl)-5-ethoxy-3,6-dimethyl-3,6-dihydro-1H-pyrazine-2-one ***12g***

^{1}H-NMR δ 1.2 (t, 3H, J=7.0 Hz), 1.42 (d, 3H, J=6.8 Hz),1.49 (d, 3H, J=7.3 Hz), 1.65 (d, 3H, J=7.2 Hz), 3.57 (dq, 1H, J=0.8, 6.8 Hz), 4.07 (m, 2H), 4.28 (dq, 1H, J=0.8, 7.3 Hz), 5.85 (q, 1H, J=7.2 Hz), 7.4 (m, 5ArH); ^{13}C-NMR δ 13.8, 17.8, 21.7, 22.3, 49.3, 51.9, 56.2, 61.2, 127.4, 127.6, 128.5, 138.6, 161.5, 170.6. $[\alpha]_D$ −20.3 (c=2.2, $CHCl_3$). Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C;70.04, H;8.08, N;10.21. Found: C;70.25, H;8.11, N;10.25.

(3S,6R)-5-Ethoxy-3-(3-methyl-2-butenyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***13a***

To a stirred solution of Na (0.19 g, 8.4 mmol) dissolved in 100 ml of liquid ammonia, cooled at −60°C, was added **9a** (0.4 g, 1.2 mmol) in dry THF (10 ml) and ethanol (1 ml) under inert atmosphere. After 5 minutes the reaction was quenched with 0.5 g of NH_4Cl and the cooling bath was removed allowing the complete removal of ammonia. To the residue was added water and the solution was extracted with ethyl acetate. After removal of the organic solvent the reaction product was purified by silica gel chromatography eluting with hexane/ethyl acetate. ^{1}H-NMR δ 1.28 (t, 3H, J=7.1 Hz), 1.39 (d, 3H, J=6.9 Hz), 1.62 (s, 3H), 1.69 (s, 3H), 2.59 (dd, 2H, J=5.8, 6.8 Hz), 4.02 (dq, 1H, J=1.8, 6.9 Hz), 4.15 (m, 3H), 5.1 (m, 1H), 6.8 (m, 1H); ^{13}C-NMR δ 13.8, 17.7, 19.7, 25.7, 32.5, 48.0, 58.7, 60.9, 118.6, 134.7, 159.8, 172.1. $[\alpha]_D$ −32.0 (c=2.8, $CHCl_3$). Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C;64.26, H;8.99, N;12.49. Found: C;64.5, H;9.1, N;12.4.

(3S,6R)-3-Benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***13e***

The product was obtained starting from **9e** and following the procedure previously reported for **13a.** ^{1}H-NMR δ 1.22 (d, 3H, J=6.9 Hz), 1.28 (t, 3H, J=7.1 Hz), 3.10 (dq, 1H, J=2.1, 6.9 Hz), 3.13 (dd, 1H, J=4.7, 13.3 Hz), 3.27 (dd, 1H, J=5.1, 13.3 Hz), 4.15 (m, 2H), 4.43 (ddd, 1H, J=2.1, 4.7, 5.1 Hz), 5.95 (m, 1H), 7.2 (m,5ArH); ^{13}C-NMR δ 14.1, 19.5, 39.7, 47.7, 59.7, 61.2, 126.4, 127.7, 130.0, 136.8, 160.4, 171.4. $[\alpha]_D$ 23.3 (c=2.4, $CHCl_3$). Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C;68.27, H;7.37, N;11.37. Found: C;68.5, H;7.4, N;11.4.

(2R,5S)-2-Methyl-5-amino-3-aza-4-oxo-8-methyl-ethyl 7-nonenoate hydrochloride ***14a***

To the lactim **13a** (0.24 gr, 1 mmol) in 5 ml of acetone was added 3 ml of 0.5M HCl and the solution stirred at r.t. After about 3 h the acetone was evaporated and to the residue was added water, then extracted with ethyl acetate. After evaporation of the aqueous solution under vacuum, the product was recovered as an oil. ^{1}H-NMR δ 1.27 (t, 3H, J=7.1 Hz), 1.42 (d, 3H, J=7.1 Hz), 1.66 (s, 3H), 1.71 (s, 3H), 2.75 (m, 2H), 4.2 (q, 2H, J=7.1 Hz), 4.5 (m, 2H), 5.15 (m, 1H), 8.1 (m, 3H), 8.5 (m, 1H); ^{13}C-NMR δ 14.0, 17.6, 18.1, 25.8, 30.1, 48.4, 52.8, 61.7, 116.3, 137.6, 168.5, 173.0. $[\alpha]_D$ 28.9 (c=3.1, $CHCl_3$). Anal. Calcd. for $C_{12}H_{23}ClN_2O_3$: C;51.7, H;8.32, Cl;12.72. Found: C;51.9, H;8.35, Cl;12.7.

(2R,5S)-2-Methyl-5-amino-3-aza-4-oxo-6-phenyl-ethyl hexanoate hydrochloride ***14e***

The product was obtained from **13e** following the procedure previously reported for **14a.** ^{1}H-NMR (D_2O): δ 1.10 (d, 3H, J=6.9 Hz), 1.15 (t,3H, J=7.1 Hz), 3.1 (m, 2H), 4.15 (m, 4H), 7.3 (m, 5ArH); ^{13}C-NMR (D_2O): δ 12.7, 15.3, 36.4, 48.2, 53.9, 62.2, 127.5, 128.5, 128.9, 133.2, 168.2, 173.6.

Because the product is poor soluble for optical rotation measurement, it was converted into the corresponding acetamido derivative by treatment with acetyl chloride in CH_2Cl_2 at 0°C for 1 h in the presence of Et_3N.

The (2*R*,5*S*)-2-methyl-5-acetamido-3-aza-4-oxo-6-phenyl-ethyl hexanoate was then obtained pure after silica gel chromatography eluting with hexane/ethyl acetate: ^{1}H-NMR δ 1.20 (d, 3H, J=7.2 Hz), 1.24 (t, 3H, J=7.1 Hz), 1.95 (s, 3H), 2.97 (dd, 1H, J=8.3, 15.4 Hz), 3.13 (dd, 1H, J=6.1, 15.4 Hz), 4.13 (q, 2H, J=7.1 Hz), 4.43 (dq, 1H, J=7.2, 7.2 Hz), 4.68 (ddd, 1H, J=6.1, 7.1, 8.3 Hz), 6.25 (m, 2H), 7.25 (m, 5H); ^{13}C NMR δ 14.1, 18.0, 23.2, 38.7, 48.0, 54.5, 61.5, 127.0, 128.6, 129.3, 136.5, 169.9, 170.2, 172.4. $[\alpha]_D$ −7 (c=1.07, $CHCl_3$). Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C;62.73, H;7.24, N;9.14. Found: C;62.55, H;7.2, N;9.1.

(2R)-2-Benzylamino-ethyl propionate ***18***

Methansulfonate of (*S*)-ethyl lactate (9.85 g, 50 mmol), Et_3N (7.7 ml, 55 mmol) and benzylamine (6 ml, 55 mmol) were dissolved in 50 ml of benzene/DMF (2:1) and the reaction mixture was stirred at 80°C. After 24 h was added water, the aqueous solution was extracted with ethyl acetate, was made alkaline and then extracted with ethyl acetate. The organic solution was evaporated in vacuo and the residue was purified by silica gel chromatography eluting with hexane/ethyl acetate. The pure reaction product was isolated in 90% yield. ^{1}H-NMR δ 1.28 (t, 3H, J=7.0 Hz), 1.31 (d, 3H, J=7.0 Hz), 1.90 (s, 1H), 3.36 (q, 1H, J=7.0 Hz), 3.73 (q_{AB}, 2H, J=12.8 Hz), 4.18 (q, 2H, J=7.0 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 14.0, 18.8, 51.6, 55.6, 60.2, 126.7, 127.9, 128.0, 139.5, 175.3. $[\alpha]_D$ 31.9 (c=7.6, $CHCl_3$). Anal. Calcd. for $C_{12}H_{17}NO_2$: C;69.54, H;8.27, N;6.76. Found: C;69.8, H;8.3, N;6.73.

(2R)-2-(Benzylchloroacetamido)-ethyl propionate ***19***

To a stirred solution of **18** (8.3 g, 40 mmol) and Et_3N (7 ml, 50 mmol) in 50 ml of CH_2Cl_2 cooled at 0°C, chloroacetylchloride (3.2 ml, 40 mmol) was added dropwise. After about 1 h the reaction was stopped by adding 10 ml of 1N HCl and the organic layer was then evaporated under vacuum. The product was obtained pure in 90% yield after silica gel chromatography eluting with hexane/ethyl acetate. ^{1}H-NMR δ 1.27 (t, 3H, J=7.2 Hz), 1.41 (d, 3H, J=7.1 Hz), 4.03 (q_{AB}, 2H, J=12.6 Hz), 4.16 (q, 2H, J=7.2 Hz), 4.59 (d, 1H, J=17.6 Hz), 4.61 (q, 1H, J=7.1 Hz),4.73 (d, 1H, J=17.6 Hz), 7.35 (m, 5H); ^{13}C-NMR δ 14.0, 14.4, 41.3, 50.7, 55.0, 61.3, 126.4, 127.0, 127.9, 128.9, 130.1, 167.4, 170.9. $[\alpha]_D$ 44.0 (c=5.7, $CHCl_3$). Anal. Calcd. for $C_{14}H_{18}ClNO_3$: C;59.26, H;6.39, Cl;12.49. Found: C;59.5, H;6.42, Cl;12.52.

(6R)-1-N-Benzyl-6-methyl-piperazine-2,5-dione ***20***

10.8 g of **19** (40 mmol) were dissolved in 15 ml of 7M ammonia solution in ethanol. The flask was stopped and the reaction stirred at r.t. for about 24 h. The reaction product was recovered pure after evaporation of ammonia and cristallization from H_2O/EtOH. ^{1}H-NMR (DMSO) δ 1.33 (d, 3H, J=7.0 Hz), 3.69 (q, 1H, J=7.0 Hz), 3.73 (dd, 1H, J=4.0, 17.4 Hz), 4.12 (d, 1H, J=17.4 Hz), 4.18 (d, 1H, J=15.0 Hz), 4.94 (d, 1H, J=15.0 Hz), 7.35 (m, 5H), 8.20 (m, 1H); ^{13}C-NMR (DMSO) δ 16.9, 44.1, 46.3, 55.5, 127.4, 127.7, 128.6, 137.1, 164.8, 168.7. $[\alpha]_D$ 37.1 (c=2.9, $CHCl_3$). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C;59.26, H;6.39, N;12.49. Found: C;59.5, H;6.42, N;12.52.

(6R)-1-N-Benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***15***

The piperazine-2,5-dione **20** was converted into the lactime **15** in 80% yield following the procedure used for **7** and **8**. ^{1}H-NMR δ 1.24 (t, 3H, J=7.0 Hz), 1.36 (d, 3H, J=6.9 Hz), 3.8 (ddq, 1H, J=1.2, 1.2, 6.9 Hz), 4.0 (d, 1H, J=15.0 Hz), 4.07 (q, 2H, J=7.0 Hz), 4.13 (dd, 1H, J=1.2, 20.4 Hz), 4.29 (dd, 1H, J=1.2, 20.4 Hz), 5.3 (d, 1H, J=15.0 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 13.8, 17.2, 45.9, 49.9, 51.3, 61.4, 127.5, 127.9, 128.5, 135.8, 161.7, 167.0. $[\alpha]_D$ −22.5 (c=2.9, $CHCl_3$). Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C;68.27, H;7.37, N;11.37. Found: C;68.5, H;7.4, N;11.32.

(3S,6R)-1-N-Benzyl-5-ethoxy-3-(3-methyl-2-butenyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16a***

^{1}H-NMR δ 1.24 (t, 3H, J=6.9 Hz), 1.37 (d, 1H, J=6.8 Hz), 1.68 (s, 3H), 1.71 (s, 3H), 3.7 (m, 2H), 3.77 (dq, 1H, J=1.6, 6.8 Hz), 3.93 (d, 1H, J=15.0 Hz), 4-.42 (m, 3H), 5.16 (ddd, 1H, J=1, 7.2, 7.3 Hz), 5.46 (d, 1H, J=15.0 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 14.0, 17.4, 18.1, 25.9, 32.5, 45.7, 51.3, 57.9, 61.1, 119.7, 127.4, 127.8, 128.5, 134.1, 136.1, 159.9, 169.1. $[\alpha]_D$ 12.8 (c=4.7, $CHCl_3$). Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C;72.58, H;8.34, N;8.91. Found: C;72.85, H;8.36, N;8.88.

(3S,6R)-1-N-Benzyl-5-ethoxy-3-isopropyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16b***

^{1}H-NMR δ 0.76 (d, 3H, J=6.7 Hz), 1.12 (d, 3H, J=7.0 Hz), 1.24 (t, 3H, J=7.0 Hz), 1.37 (d, 3H, J=6.7 Hz), 2.70 (m, 1H), 3.78 (dq, 1H, J=2, 7.0 Hz), 3.92 (dd, 1H, J=2, 2.8 Hz), 3.93 (d, 1H, J=15.0 Hz), 4.13 (m, 2H), 5.44 (d, 1H, J=15.0 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 14.0, 16.2, 17.4, 19.7, 30.7,

45.8, 51.1, 60.9, 62.0, 127.4, 127.9, 128.5, 136.3, 160.1, 169.2. $[\alpha]_D$ −5.6 (c=3.1, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C;70.8, H;8.39, N;9.71. Found: C;70.52, H;8.4, N;9.88.

(3R,6R)-1-N-Benzyl-5-ethoxy-3-isopropyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***17b***

^{1}H-NMR δ 0.86 (d, 3H, J=6.8 Hz), 1.12 (d, 3H, J=6.9 Hz), 1.24 (t, 3H, J=7.0 Hz),1.42 (d, 3H, J=6.9 Hz), 2.35 (m, 1H), 3.81 (dq, 1H, J=2.1, 6.9 Hz), 3.95 (d, 1H, J=15.0 Hz), 3.8–4.25 (m,3H), 5.4 (d, 1H, J=15.0 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 14.1, 17.9, 18.9, 19.9, 32.7, 46.0, 51.0, 61.1, 64.4, 127.7, 128.3, 128.7, 136.3, 159.1, 169.0.

(3S,6R)-1-N-Benzyl-3-allyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16c***

^{1}H-NMR δ 1.23 (t,3H, J=7.1Hz), 1.36 (d,3H,J=6.8Hz), 2.75 (m,2H), 3.77 (dq,1H, J=1.9, 6.8Hz), 3.97 (d,1H,J=15.0Hz), 4.1 (m,3H), 5.08 (dd,1H,J=2.2, 10.2Hz), 5.17 (dd,1H,J=2.2, 17.2Hz), 5.75–5.95 (m,1H), 7.3 (m,5H); ^{13}C-NMR δ 13.8, 17.2, 29.4, 37.8, 51.4, 57.4, 61.1, 117.3, 127.3, 127.8, 128.4, 134.5, 135.9, 160.2, 168.6. $[\alpha]_D$ 0.4 (c=4.7, $CHCl_3$). Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C;71.3, H;7.74, N;9.78. Found: C;71., H;7.7, N;9.82.

(3R,6R)-1-N-Benzyl-3-allyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***17c***

^{1}H-NMR δ 1.24 (t, 3H, J=7.1 Hz), 1.40 (d, 3H, J=6.9 Hz), 2.5–2.7 (m, 2H), 3.79 (dq, 1H, J=1.6, 6.9 Hz), 4.0 (d, 1H, J=15.1 Hz), 3.9–4.2 (m, 2H), 4.3 (m, 1H), 5.0–5.2 (m, 2H), 5.32 (d, 1H, J=15.1 Hz), 7.3 (m, 5H).

(3S,6R)-1-N-Benzyl-3-ethyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16d***

^{1}H-NMR δ 0.93 (t,3H, J=7.3 Hz), 1.24 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=6.9 Hz), 2.05 (m, 2H), 3.79 (dq, 1H, J=1.9, 6.9 Hz), 3.96 (d, 1H, J=14.9 Hz), 4–4.2 (m, 3H), 5.38 (d, 1H, J=14.9 Hz), 7.25 (m, 5H); ^{13}C-NMR δ 9.1, 14.0, 17.2, 26.6, 46.0, 51.6, 58.2, 61.2, 127.5, 127.9, 128.6, 136.3, 160.4, 169.4. $[\alpha]_D$ −16.7 (c=2.4, $CHCl_3$). Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C;70.04, H;8.08, N;10.21. Found: C;70.23, H;8.1, N;10.2

(3R,6R)-1-N-Benzyl-3-ethyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***17d***

^{1}H-NMR δ 1.04 (t, 3H, J=7.4 Hz), 1.24 (t, 3H, J=7.0 Hz), 1.41 (d, 3H, J=6.9 Hz), 1.7–2.1 (m,2H), 3.79 (dq, 1H, J=1.6, 6.9 Hz), 4.0 (d, 1H, J=15.0Hz), 4–4.2 (m, 3H), 5.34 (d,1H,J=15.0 Hz), 7.3 (m,5H).

(3S,6R)-1-N-Benzyl-3-benzyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16e***

^{1}H-NMR δ 1.24 (t, 3H, J=7.1 Hz), 1.30 (d, 3H, J=6.9 Hz), 3.35 (m, 2H), 3.51 (dq, 1H, J=1.8, 6.9 Hz),3.90 (d, 1H, J=15.1 Hz),4.13 (q, 2H, J=7.1 Hz), 4.41 (ddd, 1H, J=1.8, 5.0, 5.0 Hz), 5.33 (d, 1H, J=15.1 Hz), 6.9 (m, 3H), 7.3 (m, 7H); ^{13}C-NMR δ 13.8, 17.2, 31.2, 45.5, 51.0, 58.6, 60.9, 125.8, 127.0, 127.3, 127.4, 128.2,130.2, 135.4, 137.8, 159.7, 168.1. $[\alpha]_D$ 4.9 (c=4.6, $CHCl_3$). Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C;74.97, H;7.19, N;8.33. Found: C;74.13, H;7.21, N;8.3.

(3S,6R)-1-N-Benzyl-3-propyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16f***

^{1}H-NMR δ 0.96 (t, 3H, J=7.0 Hz), 1.24 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=6.8 Hz), 1.4 (m, 2H), 1.8–2.1 (m, 2H), 3.79 (dq, 1H, J=1.8, 6.8 Hz), 3.97 (d, 1H, J=15.1 Hz), 3.95–4.15 (m, 3H), 5.37 (d, 1H, J=15.1 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 14.0, 17.2, 18.3, 35.9, 46.1, 51.2, 57.3, 61.2, 127.5, 127.9, 128.6, 136.3, 160.2, 169.7. $[\alpha]_D$ 2.5° (c=2.7, $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C;70.8, H;8.39, N;9.71. Found: C;70.33, H;8.41, N;9.68.

(3R,6R)-1-N-Benzyl-3-propyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***17f***

^{1}H-NMR δ 0.97 (t, 3H, J=7.2 Hz), 1.23 (t, 3H, J=7.1 Hz), 1.41 (d, 3H, J=6.9 Hz), 1.5 (m, 2H), 1.65 (m, 1H), 1.9 (m, 1H), 3.79 (dq, 1H, J=1.5, 6.9 Hz), 3.95 (d, 1H, J=15.1 Hz), 4.0–4.25 (m, 3H), 5.33 (d, 1H, J=15.1 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 13.9, 14.1, 19.0, 19.4, 38.5, 46.1, 51.2, 59.6, 61.3, 127.7, 128.2, 128.7, 136,2, 159.9, 169.9.

(3S,6R)-1-N-Benzyl-3-methyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***16g***

^{1}H-NMR δ 1.24 (dt, 3H, J=1.5, 6.8 Hz), 1.35 (dd, 3H, J=1.3, 6.9 Hz), 1.57 (dd, 3H, J=1.6, 7.1 Hz), 3.83 (m, 1H), 4.04 (d, 1H, J=15.1), 4.11 (m, 3H), 5.27 (d, 1H, J=15.1 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 14.0, 16.9, 20.5, 46.4, 52.1, 53.6, 61.4, 127.6, 128.0, 128.7, 136.3, 160.7, 170.4. $[\alpha]_D$ −12.5 (c=2.7, $CHCl_3$). Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C;69.2, H;7.74, N;10.76. Found: C;69.3, H;7.75, N;10.73.

(3R,6R)-1-N-Benzyl-3-methyl-5-ethoxy-6-methyl-3,6-dihydro-1H-pyrazine-2-one ***17g***

^{1}H-NMR δ 1.24 (t, 3H, J=6.9 Hz), 1.41 (d, 3H, J=6.9 Hz),1.50 (d, 3H, J=7.3 Hz), 3.78 (dq, 1H, J=1, 6.9 Hz), 3.97 (d, 1H, J=15.0 Hz), 4.09 (m, 2H), 4.28 (dq, 1H, J=1, 7.0 Hz), 5.34 (d, 1H, J=15.0 Hz), 7.3 (m, 5H); ^{13}C-NMR δ 13.9, 18.9, 22.0, 45.9, 51.1, 55.5, 61.2, 127.5, 128.0, 128.6, 135.9, 160.3, 170.3. $[\alpha]_D$ 26.1 (c=3.2, $CHCl_3$). Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C;69.2, H;7.74, N;10.76. Found: C;69.5, H;7.77, N;10.72.

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References

1. (a) Orena, M.; Porzi, G.; Sandri, S., *J. Org. Chem.* **1992**, *57*, 6532; (b) Orena, M.; Porzi, G.; Sandri, S., *J. Chem. Research (S)*, **1993**, 318; (c) Porzi, G.; Sandri, S., *Tetrahedron: Asymmetry* **1994**, *5(3)*, 453 and references therein.
2. (a) D'Arrigo, M. C.; Rossetti, M.; Porzi, G.; Sandri, S., *J. Chem. Research (S)*, **1995**, 162; (b) D'Arrigo, M. C.; Porzi, G.; Sandri, S., *J. Chem. Research (S)*, **1995**, 430.
3. Porzi, G,; Sandri, S.; *Tetrahedron: Asymmetry* **1996**, *7(1)*, 189.
4. (a) Giannis, A.; Kolter, T.; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244; (b) Gante, J.; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699.
5. Madau, A.; Porzi, G.; Sandri, S.; *Tetrahedron: Asymmetry* **1996**, *7(3)*, 825.
6. Arcelli, A.; Porzi, G.; Sandri, S.; *Tetrahedron* **1996**, *25(11)*, 4141.
7. Molecular mechanics optimizations were performed by the MM+ Force Field method (HyperChem programme, 1994) by using the 'steepest descendent algorithm' with an RMS gradient 0.01 Kcal.
8. Energy calculations showed that both the *cis* isomers **10g** and **12g** are 1.6 and 2.1 Kcal/mole, respectively, more stable in the diaxial than in the diequatorial arrangement.
9. From conformational analysis performed on *trans* isomers **9d**, **11d** and **9g**, **11g**, it resulted that (C-6)-CH_3 rather than (C-3)-CH_3 or (C-3)-C_2H_5 lies in the axial position. In fact, this conformation is c.a. 2.7 Kcal/mole more stable for **9d** and **11d** and 3.3 Kcal/mole for **9g** and **11g**.
10. Schollkopf, U., Neubauer, H. J., *Synthesis* **1982**, 861 and references therein.
11. Meerwein, H., *Organic Synthesis* **1966**, *46*, 113.

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