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## Stereoselective synthesis of sterically constrained dipeptides. Part 2<sup>†</sup>

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### Abstract

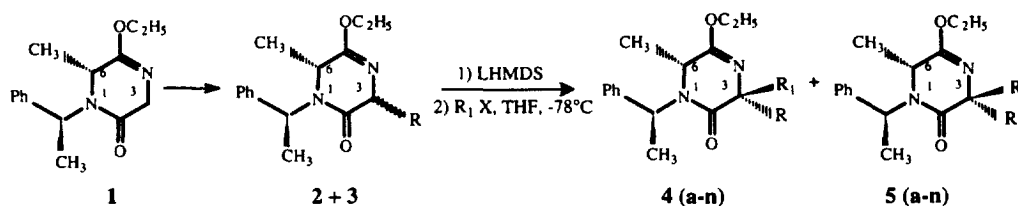
The alkylation of the diastereomeric mixture of lactims **2** and **3** occurs in total regioselectivity and good to high facial stereoselectivity (d.s. ranging from 82 to 97%). Cleavage of the lactim **4e** gives enantiomerically pure dipeptide **12**, sterically constrained at the  $\alpha$ -carbon. The absolute configuration of the new stereocentres has been assigned on the basis of <sup>1</sup>H-NMR data and NOE measurements. © 1998 Elsevier Science Ltd. All rights reserved.

In a previous paper we reported a new approach to the stereoselective synthesis of uncommon dipeptides monoalkylated at the  $\alpha$ -carbon.<sup>1</sup> Our current aim is the development of a new stereoselective synthesis to obtain conformationally constrained dipeptides C- $\alpha\alpha'$  dialkylated in good enantiomeric excess. This is because in recent years this class of compound has received considerable attention (particularly in the medical field) owing to its peptidomimetic properties for receptor ligands, i.e. agents that can imitate (agonists) or block (antagonists) the biological functions of bioactive peptides.<sup>2</sup> Therefore, in a continuation of our studies in this field, we accomplished an extension of the previously reported diastereoselective synthesis of dipeptides.<sup>1</sup> The procedure followed consists of a double alkylation of the chiral synthon (6*R*,1'*S*)-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **1** synthesized starting from the methansulfonate of naturally occurring (*S*)-ethyl lactate and following the same protocol reported for ( $\pm$ )-2-bromopropionate.<sup>1</sup>

In the previous paper<sup>1</sup> we described the conversion of lactim **1** into the *trans*-**2** and *cis*-**3** diastereomers which occurs with moderate to good *trans* stereoselectivity. We report herein the stereochemical results concerning the alkylation of the diastereomeric mixture of **2** and **3** (Scheme 1). The reaction was carried out with good to high diastereoselectivity and chemical yield, demonstrating a new synthetic route to enantiomerically pure uncommon C- $\alpha\alpha'$  dialkyl dipeptides. This second alkylation, totally regioselective at C-3, was performed directly on the diastereomeric mixture of the lactims **2** (*trans*) and **3** (*cis*) thereby avoiding their separation. The stereochemical outcome of such alkylations thus represents the most salient feature of this approach to the synthesis of C- $\alpha\alpha$ .

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<sup>†</sup> Ref. <sup>1</sup> is considered to be Part 1.

Scheme 1. R and R<sub>1</sub> are reported in Table 1Table 1  
Diastereoselectivity of the alkylation

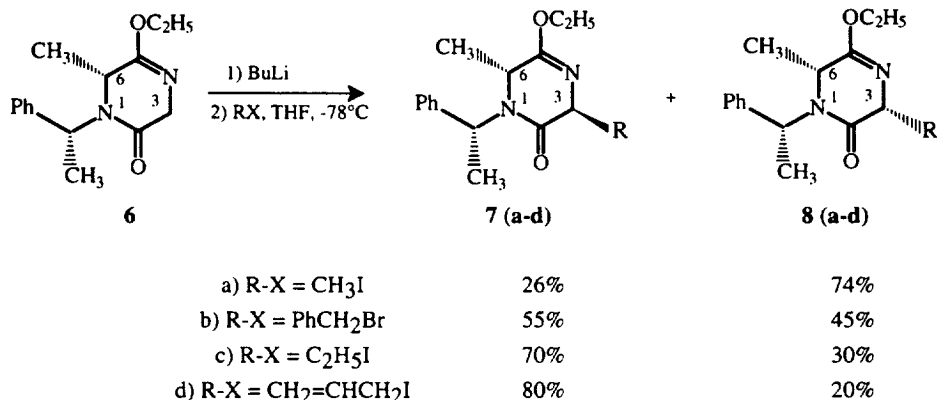
Entry		R	R <sub>1</sub>	Yield (a)			
				4	5	9	10
1	a	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	93	7	85	15
2	b	CH <sub>3</sub>	CH <sub>2</sub> =CHCH <sub>2</sub>	95	5	88	12
3	c	CH <sub>3</sub>	PhCH <sub>2</sub>	90	10	75	25
4	d	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	90	10	75	25
5	e	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> =CHCH <sub>2</sub>	97	3	97	3
6	f	C <sub>2</sub> H <sub>5</sub>	PhCH <sub>2</sub>	95	5	54	46
7	g	CH <sub>2</sub> =CHCH <sub>2</sub>	CH <sub>3</sub>	82	18	81	19
8	h	CH <sub>2</sub> =CHCH <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	98	2	85	15
9	i	CH <sub>2</sub> =CHCH <sub>2</sub>	PhCH <sub>2</sub>	98	2	86	14
10	l	PhCH <sub>2</sub>	CH <sub>3</sub>	83	17	75	25
11	m	PhCH <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	98	2	88	12
12	n	PhCH <sub>2</sub>	CH <sub>2</sub> =CHCH <sub>2</sub>	98	2	92	8

(a) The reported yields were calculated by <sup>1</sup>H-NMR.

The results summarized in Table 1 indicate that, regardless of the alkylating reagent used, the alkylation of the diastereomeric mixture (3*S*,6*R*)-2 and (3*R*,6*R*)-3 yields the isomer 4 in large predominance with respect to 5. It can therefore be asserted that the reaction occurs with a good 1,4-*trans* induction with respect to (C-6)-CH<sub>3</sub>.<sup>3</sup>

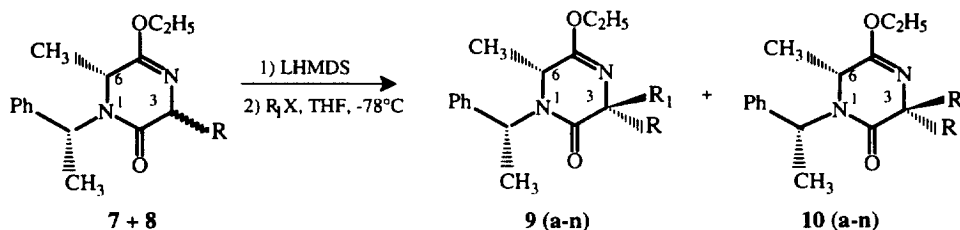
To investigate the influence of the chiral auxiliary configuration on the stereochemical outcome of the alkylation, the reaction was also performed on the lactim 6 in which the (N-1)-phenethyl group possessed the *R* instead of the *S* configuration. By comparing the stereochemical results, reported in Scheme 2, to

those previously obtained in the alkylation of **1**,<sup>1</sup> it is evident that the change of the auxiliary configuration produces an appreciable decrease of the diastereoselection comparable to that already observed<sup>1</sup> when the (*S*)-1-phenethyl group was substituted by the sterically similar achiral benzyl group.



Scheme 2.

These findings prompted us to also investigate the influence of the (*R*)-phenethyl group on the alkylation of the diastereomeric mixture of **7** and **8** (Scheme 3) in order to compare the stereochemical results with those observed for the (**2** and **3**) diastereomeric mixture.

Scheme 3. R and R<sub>1</sub> are reported in Table 1

The data collected in Table 1 reveal that, in this case as well, the second alkylation proceeds with a prevalent *trans* induction, although an overall slight decrease of the diastereoselectivity was registered, particularly for entry 6.

In summary, the data described in this paper and those previously reported,<sup>1</sup> allow us to make the following conclusions: (a) the first alkylation is evidence that the *trans* diastereoselection is prevalently, but not exclusively, influenced by the C-6 center; (b) both the first and the second alkylation reactions occur with better *trans* diastereoselection if the (*S*)-phenethyl group is employed and the (C-6) stereocentre has the *R* configuration, i.e. the stereocentres are of opposite configuration. Assuming that in the enolate ion the atoms N-1, C-2, C-3, N-4 and C-5 are substantially coplanar, while the C-6 is out of the plane and that the benzylic hydrogen preferentially lies *syn*-periplanar with respect to the carbonyl group (as can be seen from the NOE experiments illustrated in Figs 2 and 3), a reasonable explanation of the observed diastereoselection could be the result of differences in steric hindrance of the lithium enolate diastereotopic faces during the approach of the achiral electrophile (Fig. 1).

Actually, in the *syn*-periplanar conformer the phenyl ring could increase the steric hindrance on the *re* face (hindered as well by the (C-6)-CH<sub>3</sub>) thereby favouring the attack on the *si* face of the enolate anion (model **A** in Fig. 1). Conversely, in the model **B** enolate the phenyl ring produces steric interactions on the face opposite where the (C-6)-CH<sub>3</sub> lies, leading to a lower facial discrimination which is significant for entry 6 (Table 1).

Finally, in a model study, the lactim **4e** was debenzylated and easily converted into the corresponding dipeptide **12** (following the procedure previously reported for a similar substrate<sup>1</sup>) which was then functionalized as acetamido derivative **13** (Scheme 4).

In conclusion, we can assert that the above reported double alkylation of the chiral synthon **1** provides a good synthetic route to enantiomerically pure uncommon and conformationally constrained C- $\alpha\alpha'$  dialkylated dipeptides.

The configuration of the introduced stereocentre (C-3) was deduced on the basis of  $^1\text{H}$ -NMR spectroscopic data using the approach previously employed for similar molecules.<sup>1</sup> We previously reported<sup>1</sup> that the preferred geometry of the lactims **1**, **2** and **3** is the boat-like conformation in which the (C-6)-CH<sub>3</sub> preferentially lies in an axial-like arrangement. Thus, the relative configuration of the C-3 stereocentre both of **4** and **5** has been assigned on the basis of the NOE measurements and the shielding effects registered. In fact, for the derivatives **4** upon irradiation of (C-6)-CH<sub>3</sub> the NOE was exclusively observed on the (C-3)-R, while the lactims **5** displayed a significant NOE between (C-6)-CH<sub>3</sub> and (C-3)-R<sub>1</sub>. It is important to underline that neither in **4** nor in **5** were any NOEs registered between (C-6)-H and (C-3)-R or (C-3)-R<sub>1</sub>. For both the isomers, in addition to a meaningful NOE between (C-6)-H and the methyl of the chiral auxiliary,<sup>4</sup> a characteristic shielding effect of about 0.4 ppm, induced by the phenyl ring of the phenethyl group,<sup>1</sup> was observed on the (C-6)-CH<sub>3</sub>. These findings were evidence that for both the isomers, the preferred geometry is the boat-like conformation in which the (C-6)-CH<sub>3</sub> is axially arranged and the (*S*)-phenethyl group preferentially lies in the *syn* periplanar conformation. As examples, the NOEs recorded for **4b** and **5b** are schematized in Fig. 2.

Furthermore, the high field resonance (0.16 ppm) of the (C-6)-CH<sub>3</sub> doublet in the spectrum of the *cis* isomer **3** (when R=CH<sub>2</sub>Ph) is diagnostically very useful in assigning the relative configuration of C-3, in contrast to the value of 0.69 ppm registered for the corresponding *trans* isomer **2**.<sup>1</sup> In fact, this upfield shift is induced by the shielding effect of the phenyl ring of the (C-3)-CH<sub>2</sub>Ph group which lies in the axial-like position, thus adopting the preferential ‘aryl inside’ arrangement. As previously observed in analogous substrates,<sup>4,5</sup> such a conformation causes significant shielding of the axial-like (C-6)-CH<sub>3</sub> that we registered both in **4**(l,m,n) and **5**(c,f,i), this shielding of about 0.8 ppm providing clear evidence that both the (C-6)-CH<sub>3</sub> and (C-3)-CH<sub>2</sub>Ph are axially arranged (Fig. 3). The *trans* relationship between the

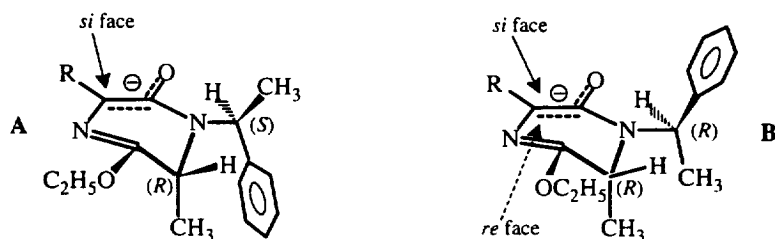
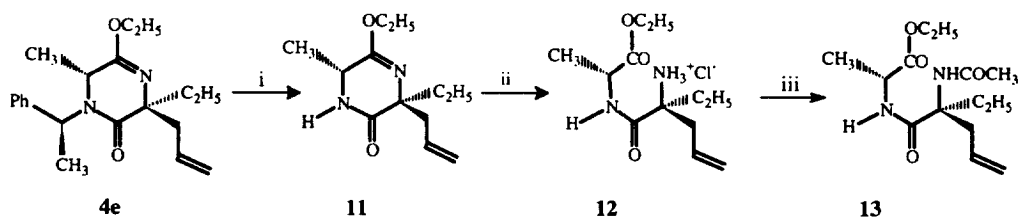


Fig. 1. Models proposed for the enolate anions: **A** (6*R*,1'*S*) and **B** (6*R*,1'*R*)



Scheme 4. (i) Na/NH<sub>3</sub>; (ii) 0.5 N HCl/acetone at 0°C; (iii) CH<sub>3</sub>COCl/Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> at 0°C

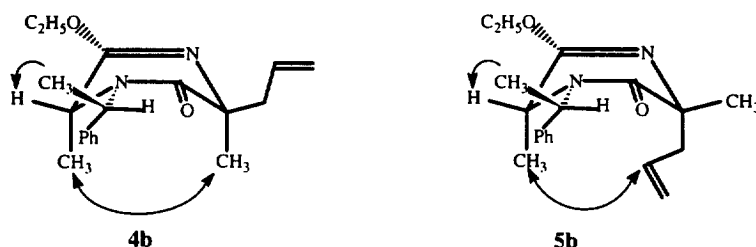


Fig. 2. Representative NOE registered for **4b** and **5b**

(C-3)-CH<sub>2</sub>Ph and the (C-6)-CH<sub>3</sub> in **4**(c,f,i) and **5**(l,m,n) was ascertained by both the absence of the above mentioned shielding effect and the significant NOE registered between the (C-6)-CH<sub>3</sub> and the alkyl group at C-3 (Fig. 3).

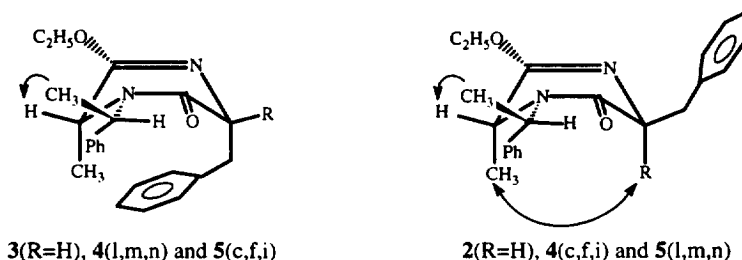


Fig. 3. Shielding induced by the (C-3)-CH<sub>2</sub>Ph on (C-6)-CH<sub>3</sub> and significant NOE registered on **4** and **5**

The relative configuration of the C-3 stereocentre of **7** and **8** was determined as described in the previous paper,<sup>1</sup> but considering that since in this case the chiral auxiliary possesses the *R*-configuration, the phenyl ring of the *R*-phenethyl group shields the (C-6)-H rather than the (C-6)-CH<sub>3</sub>.

Finally, the relative configuration of the C-3 stereocentre of **9** and **10** was assigned on the basis of <sup>1</sup>H-NMR data and NOE measurements as described above for **4** and **5**.

## 2. Experimental

<sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Gemini spectrometer at 300 MHz using CDCl<sub>3</sub> as solvent, unless otherwise stated. Chemical shifts are reported in ppm relative to the solvent. Optical rotation values were measured on a Perkin–Elmer 343 polarimeter. Chromatographic separations were performed with silica gel 60 (230–400 mesh). Dry THF was distilled from sodium benzophenone ketyl.

### 2.1. Alkylation of diastereomeric mixture 2 and 3: general procedure

3 ml of LHMDs (1M solution in THF) were dropped into a stirred solution of 3 mmol of diastereomeric mixture (2 and 3) in dry THF (30 ml), cooled at  $-78^{\circ}\text{C}$  under an inert atmosphere. After 1 h, 4.5 mmol of the appropriate alkyl halide were added and the reaction mixture was stirred for 3 h. The reaction mixture, slowly warmed up to r.t., was quenched with water and extracted with ethyl acetate. The organic extract was dried, evaporated under reduced pressure and the diastereomers were separated by silica gel chromatography (hexane:ethyl acetate as eluent).

### 2.2. (3S,6R,1'S)-5-Ethoxy-3-ethyl-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 4a or 5d

Iodoethane was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.7 (t, 3H,  $J=7.3$  Hz), 0.89 (d, 3H,  $J=6.8$  Hz), 1.26 (t, 3H,  $J=7.1$  Hz), 1.39 (s, 3H), 1.55 (m, 1H), 1.62 (d, 3H,  $J=7.1$  Hz), 2.18 (m, 1H), 4.05 (q, 1H,  $J=6.8$  Hz), 4.11 (m, 2H), 5.78 (q, 1H,  $J=7.1$  Hz), 7.32 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  8.8, 14, 16.3, 21.1, 28.6, 34.9, 50.4, 51.5, 60.9, 61.4, 127.26, 127.33, 128.2, 141.1, 159.7, 171.9. The pure 4a was isolated in 70% yield:  $[\alpha]_{\text{D}}=-195.5$  ( $c=2.9$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 71.49; H, 8.67; N, 9.26. Found: C, 71.72; H, 8.7; N, 9.23.

### 2.3. (3S,6R,1'S)-3-Allyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 4b or 5g

3-Iodopropene was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.87 (d, 3H,  $J=6.8$  Hz), 1.25 (t, 3H,  $J=7.1$  Hz), 1.4 (s, 3H), 1.59 (d, 3H,  $J=7.2$  Hz), 2.33 (dd, 1H,  $J=7.3$ , 13.1 Hz), 2.82 (dd, 1H,  $J=7.3$ , 13.1 Hz), 3.99 (q, 1H,  $J=6.8$  Hz), 4.07 (m, 2H), 5.02 (m, 2H), 5.63 (m, 1H), 5.75 (q, 1H,  $J=7.2$  Hz), 7.3 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  14, 16.3, 21.1, 28.2, 46.1, 50.3, 51.5, 61, 61.1, 117.5, 127.3, 127.4, 128.2, 134.4, 141, 159.4, 171.6. The pure 4b was isolated in 80% yield:  $[\alpha]_{\text{D}}=-168.9$  ( $c=3.5$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 72.58; H, 8.34; N, 8.91. Found: C, 72.45; H, 8.35; N, 8.95.

### 2.4. (3S,6R,1'S)-3-Benzyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 4c or 5l

Benzyl bromide was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.81 (d, 3H,  $J=6.8$  Hz), 1.25 (t, 3H,  $J=7.1$  Hz), 1.29 (d, 3H,  $J=7.1$  Hz), 1.54 (s, 3H), 2.83 (d, 1H,  $J=2.5$  Hz), 3.47 (d, 1H,  $J=12.5$  Hz), 3.65 (q, 1H,  $J=6.8$  Hz), 4.12 (m, 2H), 5.66 (q, 1H,  $J=7.1$  Hz), 7.22 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  14.1, 15.7, 21.1, 28.9, 47.5, 50, 51.2, 60.9, 62.3, 125.9, 127.1, 127.2, 128.2, 130.7, 137.9, 141.1, 158.9, 171.1. The pure 4c was isolated in 81% yield:  $[\alpha]_{\text{D}}=-107.9$  ( $c=3.6$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 72.79; H, 7.74; N, 7.69. Found: C, 76.02; H, 7.72; N, 7.67.

### 2.5. (3R,6R,1'S)-5-Ethoxy-3-ethyl-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 4d or 5a

Iodomethane was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.9 (t, 3H,  $J=7.5$  Hz), 1.01 (d, 3H,  $J=6.8$  Hz), 1.26 (t, 3H,  $J=7.1$  Hz), 1.41 (s, 3H), 1.65 (d, 3H,  $J=7.2$  Hz), 1.66 (m, 1H), 1.92 (m, 1H), 4.08 (m, 3H), 5.68 (q, 1H,  $J=7.2$  Hz), 7.31 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.1, 14.1, 16.1, 21.1, 28.2, 34.8, 51, 51.7, 61.1, 61.7, 127.1, 127.2, 128.3, 141.9, 158.4, 171. The pure 4d was isolated in 72% yield:  $[\alpha]_{\text{D}}=-149$  ( $c=0.4$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 71.49; H, 8.67; N, 9.26. Found: C, 71.61; H, 8.65; N, 9.22.

**2.6. (3S,6R,1'S)-3-Allyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4e** or **5h****

3-Iodopropene was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.85 (t, 3H,  $J=7.5$  Hz), 1.02 (d, 3H,  $J=6.8$  Hz), 1.27 (t, 3H,  $J=7$  Hz), 1.65 (d, 3H,  $J=7.2$  Hz), 1.63 (m, 1H), 2 (m, 1H), 2.3 (dd, 1H,  $J=7.2$ , 12.8 Hz), 2.73 (dd, 1H,  $J=7.2$ , 12.8 Hz), 4.1 (m, 3H), 4.95 (m, 2H), 5.51 (m, 1H), 5.6 (q, 1H,  $J=7.2$  Hz), 7.31 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.1, 14.1, 16.2, 21.1, 33.5, 45.5, 51.1, 52.1, 60.9, 65.1, 117.8, 127, 128.1, 133.8, 141.5, 158.6, 170.6. The pure **4e** was isolated in 92% yield:  $[\alpha]_{\text{D}}=-161.6$  ( $c=2.4$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 73.14; H, 8.59; N, 8.53. Found: C, 73.43; H, 8.57; N, 8.5.

**2.7. (3S,6R,1'S)-3-Benzyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4f** or **5m****

Benzyl bromide was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.84 (d, 3H,  $J=6.8$  Hz), 0.89 (t, 3H,  $J=7.5$  Hz), 1.22 (d, 3H,  $J=7.3$  Hz), 1.26 (t, 3H,  $J=7.1$  Hz), 1.75 (m, 1H), 2.24 (m, 1H), 2.79 (d, 1H,  $J=12.4$  Hz), 3.36 (d, 1H,  $J=12.4$  Hz), 3.55 (q, 1H,  $J=6.8$  Hz), 4.17 (m, 2H), 5.65 (q, 1H,  $J=7.3$  Hz), 7.25 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  9.4, 14.3, 15, 21.1, 34, 47.5, 49.9, 50.6, 60.8, 66.6, 126, 126.9, 127, 127.4, 128.1, 130.5, 137.5, 142.2, 158.6, 170. The pure **4f** was isolated in 90% yield:  $[\alpha]_{\text{D}}=-107.7$  ( $c=6.6$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.16; H, 7.99; N, 7.4. Found: C, 76.23; H, 8.02; N, 7.42.

**2.8. (3R,6R,1'S)-3-Allyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4g** or **5b****

Iodomethane was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  1.0 (d, 3H,  $J=6.8$  Hz), 1.25 (t, 3H,  $J=7$  Hz), 1.43 (s, 3H), 1.65 (d, 3H,  $J=7.2$  Hz), 2.38 (dd, 1H,  $J=7.4$ , 12.8 Hz), 2.64 (dd, 1H,  $J=7.4$ , 12.8 Hz), 4.1 (q, 2H,  $J=7$  Hz), 4.1 (q, 1H,  $J=6.8$  Hz), 5.1 (m, 2H), 5.7 (q, 1H,  $J=7.2$  Hz), 5.77 (m, 1H), 7.31 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  13.9, 15.9, 21.1, 28.4, 46.2, 50.8, 51.5, 60.9, 61.2, 118.2, 126.9, 127, 127.3, 128.1, 133.8, 141.5, 158.4, 171.5. The pure **4g** was isolated in 78% yield:  $[\alpha]_{\text{D}}=-134.2$  ( $c=0.96$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 72.58; H, 8.34; N, 8.91. Found: C, 72.65; H, 8.32; N, 8.88.

**2.9. (3R,6R,1'S)-3-Allyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4h** or **5e****

Iodomethane was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.64 (t, 3H,  $J=7.3$  Hz), 1.03 (d, 3H,  $J=6.8$  Hz), 1.28 (t, 3H,  $J=7.1$  Hz), 1.56 (m, 1H), 1.66 (d, 3H,  $J=7.2$  Hz), 2.11 (m, 1H), 2.36 (dd, 1H,  $J=7.1$ , 13.4 Hz), 2.67 (dd, 1H,  $J=7.1$ , 13.4 Hz), 4.3 (m, 3H), 5.1 (m, 2H), 5.62 (q, 1H,  $J=7.2$  Hz), 5.73 (m, 1H), 7.31 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  8.5, 14.2, 16.2, 21.5, 34.4, 45.7, 51.2, 52.1, 61.1, 65.1, 118.3, 127.2, 127.3, 128.1, 134.1, 141.7, 159.2, 170.5. The pure **4h** was isolated in 93% yield:  $[\alpha]_{\text{D}}=-168.6$  ( $c=3$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 73.14; H, 8.59; N, 8.53. Found: C, 73.03; H, 8.62; N, 8.55.

**2.10. (3S,6R,1'S)-3-Allyl-3-benzyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4i** or **5n****

Benzyl bromide was used as the alkylating reagent.  $^1\text{H-NMR}$   $\delta$  0.83 (d, 3H,  $J=6.8$  Hz), 1.24 (d, 3H,  $J=7.1$  Hz), 1.26 (t, 3H,  $J=7.1$  Hz), 2.5 (dd, 1H,  $J=6.9$ , 13.1 Hz), 2.82 (d, 1H,  $J=12.6$  Hz), 2.94 (dd, 1H,  $J=7.7$ , 13.1 Hz), 3.42 (d, 1H,  $J=12.6$  Hz), 3.55 (q, 1H,  $J=6.8$  Hz), 4.16 (m, 2H), 5.16 (m, 2H), 5.6 (q, 1H,

$J=7.1$  Hz), 5.75 (m, 1H), 7.24 (m, 10ArH);  $^{13}\text{C}$ -NMR  $\delta$  14.2, 15.1, 21.3, 45.6, 47.3, 50.1, 50.9, 60.9, 66, 118.5, 126.1, 126.9, 127.1, 127.5, 128, 128.7, 129, 130.5, 134, 137.3, 141.9, 158.7, 169.5. The pure **4i** was isolated in 92% yield:  $[\alpha]_{\text{D}}=-113$  ( $c=1.7$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.89; H, 7.74; N, 7.17. Found: C, 76.98; H, 7.77; N, 7.2.

**2.11. (3R,6R,1'S)-3-Benzyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4l** or **5c****

Iodomethane was used as the alkylating reagent.  $^1\text{H}$ -NMR  $\delta$  0.07 (d, 3H,  $J=6.8$  Hz), 1.28 (t, 3H,  $J=7.1$  Hz), 1.51 (s, 3H), 1.62 (d, 3H,  $J=7.2$  Hz), 2.82 (d, 1H,  $J=12.8$  Hz), 3.39 (d, 1H,  $J=12.8$  Hz), 3.88 (q, 1H,  $J=6.8$  Hz), 4.16 (q, 2H,  $J=7.1$  Hz), 5.19 (q, 1H,  $J=7.2$  Hz), 7.22 (m, 10ArH);  $^{13}\text{C}$ -NMR  $\delta$  14.1, 16.2, 19.2, 30.2, 47.1, 52, 53.2, 60.7, 62.9, 126.3, 126.7, 127.1, 127.3, 127.5, 127.8, 130.6, 137.3, 141.2, 157.9, 170.6. The pure **4l** was isolated in 79% yield:  $[\alpha]_{\text{D}}=-109.7$  ( $c=1.7$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 72.79; H, 7.74; N, 7.69. Found: C, 75.97; H, 7.77; N, 7.71.

**2.12. (3R,6R,1'S)-3-Benzyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4m** or **5f****

Iodoethane was used as the alkylating reagent.  $^1\text{H}$ -NMR  $\delta$  0.07 (d, 3H,  $J=6.8$  Hz), 0.6 (t, 3H,  $J=7.3$  Hz), 1.3 (t, 3H,  $J=7.2$  Hz), 1.65 (m, 1H), 1.62 (d, 3H,  $J=7.2$  Hz), 2.2 (m, 1H), 2.78 (d, 1H,  $J=12.7$  Hz), 3.35 (d, 1H,  $J=12.7$  Hz), 3.9 (q, 1H,  $J=6.8$  Hz), 4.2 (m, 2H), 5.12 (q, 1H,  $J=7.2$  Hz), 7.24 (m, 10ArH);  $^{13}\text{C}$ -NMR  $\delta$  8.3, 14.2, 16.1, 19.2, 35.6, 46.7, 52.2, 53.5, 60.7, 66.6, 126.3, 126.8, 127, 127.5, 127.6, 130.7, 137.4, 141.1, 158.8, 169.5. The pure **4m** was isolated in 92% yield:  $[\alpha]_{\text{D}}=-101.2$  ( $c=2.5$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.16; H, 7.99; N, 7.4. Found: C, 76.3; H, 7.97; N, 7.38.

**2.13. (3R,6R,1'S)-3-Allyl-3-benzyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **4n** or **5i****

3-Iodopropene was used as the alkylating reagent.  $^1\text{H}$ -NMR  $\delta$  0.05 (d, 3H,  $J=6.8$  Hz), 1.27 (t, 3H,  $J=7$  Hz), 1.6 (d, 3H,  $J=7.2$  Hz), 2.38 (dd, 1H,  $J=7.4$ , 12.8 Hz), 2.8 (d, 1H,  $J=12.6$  Hz), 2.85 (dd, 1H,  $J=7.4$ , 12.8 Hz), 3.4 (d, 1H,  $J=12.6$  Hz), 3.85 (q, 1H,  $J=6.8$  Hz), 4.17 (m, 2H), 4.85–5.05 (m, 2H), 5.1 (q, 1H,  $J=7.2$  Hz), 5.49 (m, 1H), 7.23 (m, 10ArH);  $^{13}\text{C}$ -NMR  $\delta$  14.1, 16, 19.2, 46.1, 46.7, 52, 53.4, 60.6, 66.1, 117.9, 126.3, 126.7, 126.9, 127.5, 130.6, 133.2, 137, 140.9, 158.5, 169. The pure **4n** was isolated in 93% yield:  $[\alpha]_{\text{D}}=-89.5$  ( $c=1.7$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.89; H, 7.74; N, 7.17. Found: C, 76.78; H, 7.72; N, 7.15.

**2.14. (6R,1'R)-5-Ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **6****

The product was prepared starting from the methanesulfonate of naturally occurring (*S*)-ethyl lactate and (*R*)-1-phenylethylamine by following the procedure employed for **1**.<sup>1</sup>  $^1\text{H}$ -NMR  $\delta$  1.18 (t, 3H,  $J=7$  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,  $J=7$  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);  $^{13}\text{C}$ -NMR  $\delta$  13.5, 17.4, 19.2, 49, 50.4, 51.1, 61.2, 126.8, 127.3, 128.2, 138.8, 163.5, 167.5.  $[\alpha]_{\text{D}}=-37.5$  ( $c=2.1$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$ : C, 69.2; H, 7.74; N, 10.76. Found: C, 69.45; H, 7.71; N, 10.8.



### 2.15. Alkylation of **6** to the diastereomeric mixture **7(a–d)** and **8(a–d)**.

The reaction was performed by following the procedure used for the alkylation of the compound **1**.<sup>1</sup>

### 2.16. (3S,6R,1'R)-5-Ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **7a**

After 4 h of reaction, the pure product was isolated in 23% yield. <sup>1</sup>H-NMR δ 1.18 (t, 3H, J=7.1 Hz), 1.37 (d, 3H, J=6.9 Hz), 1.58 (d, 3H, J=7.1 Hz), 1.62 (d, 3H, J=7.3 Hz), 3.65 (dq, 1H, J=1.1, 6.9 Hz), 4.05 (dq, 1H, J=1.1, 7.1 Hz), 4.1 (q, 2H, J=7.1 Hz), 5.85 (q, 1H, J=7.3 Hz), 7.3 (m, 5ArH); <sup>13</sup>C-NMR δ 14, 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. [α]<sub>D</sub>=−18.2 (c=0.9, CHCl<sub>3</sub>). Anal. Calcd for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.3; H, 8.11; N, 10.18.

### 2.17. (3S,6R,1'R)-3-Benzyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **7b**

After 12 h of reaction, the pure product was isolated in 52% yield. <sup>1</sup>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 Hz), 5.78 (q, 1H, J=7.2 Hz), 6.95 (m, 2ArH), 7.3 (m, 8ArH); <sup>13</sup>C-NMR δ 14, 17.7, 19.8, 39, 49.7, 51.7, 59.2, 61.4, 125.9, 127.1, 127.7, 128.4, 130.4, 138.9, 139.2, 162, 169.2. [α]<sub>D</sub>=−156.8 (c=1.5, CHCl<sub>3</sub>). Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: C, 75.4; H, 7.48; N, 7.99. Found: C, 75.6; H, 7.5; N, 8.01.

### 2.18. (3S,6R,1'R)-5-Ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **7c**

After 5 h of reaction, the pure product was isolated in 63% yield. <sup>1</sup>H-NMR δ 0.98 (t, 3H, J=7.2 Hz), 1.36 (d, 3H, J=6.9 Hz), 1.63 (d, 3H, J=7.2 Hz), 1.9 (t, 3H, J=7.2 Hz), 2.05 (m, 2H), 3.62 (dq, 1H, J=1.2, 6.9 Hz), 3.95 (m, 1H), 4.09 (m, 2H), 5.88 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); <sup>13</sup>C-NMR δ 9.2, 13.6, 17.5, 18.9, 25.6, 49.4, 51.2, 58, 61, 126.7, 127.1, 128.2, 139.3, 162.4, 169.6. [α]<sub>D</sub>=−32.1 (c=8.4, CHCl<sub>3</sub>). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.8; H, 8.39; N, 9.71. Found: C, 71.1; H, 8.37; N, 9.75.

### 2.19. (3S,6R)-3-Allyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **7d**

After 2 h of reaction the pure product was isolated in 76% yield. <sup>1</sup>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), 5.12 (m, 2H), 5.85 (q, 1H, J=7.3 Hz), 6 (m, 1H), 7.3 (m, 5ArH); <sup>13</sup>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. [α]<sub>D</sub>=−17.1 (c=3.7, CHCl<sub>3</sub>). Anal. Calcd for C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.16; H, 8.06; N, 9.3.

### 2.20. (3R,6R,1'R)-5-Ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **8a**

After 4 h of reaction, the pure product was isolated in 67% yield. <sup>1</sup>H-NMR δ 1.2 (t, 3H, J=7 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); <sup>13</sup>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. [α]<sub>D</sub>=20.3 (c=2.2, CHCl<sub>3</sub>). Anal. Calcd for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.23; H, 8.05; N, 10.17.

**2.21. (3R,6R,1'R)-3-Benzyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 8b**

After 12 h of reaction, the pure product was isolated in 43% yield.  $^1\text{H-NMR}$   $\delta$  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);  $^{13}\text{C-NMR}$   $\delta$  14.1, 17.6, 20.2, 40.3, 49.7, 52.5, 60.9, 61.1, 126.6, 127.7, 127.9, 128, 128.5, 130.5, 137.2, 138, 160.6, 168.1.  $[\alpha]_{\text{D}}=-5.5$  ( $c=1$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 75.4; H, 7.48; N, 7.99. Found: C, 75.3; H, 7.45; N, 7.97.

**2.22. (3R,6R,1'R)-5-Ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 8c**

After 5 h of reaction, the pure product was isolated in 27% yield.  $^1\text{H-NMR}$   $\delta$  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, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  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.  $[\alpha]_{\text{D}}=40.1$  ( $c=2.1$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$ : C, 70.8; H, 8.39; N, 9.71. Found: C, 70.6; H, 8.36; N, 9.68.

**2.23. (3R,6R,1'R)-3-Allyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 8d**

After 2 h of reaction, the pure product was isolated in 19% yield.  $^1\text{H-NMR}$   $\delta$  1.2 (t, 3H,  $J=7.1$  Hz), 1.39 (d, 3H,  $J=6.9$  Hz), 1.65 (d, 3H,  $J=7.1$  Hz), 2.6 (m, 2H), 3.55 (dq, 1H,  $J=1.2$ , 6.9 Hz), 4.02 (m, 2H), 4.28 (m, 1H), 5.13 (m, 2H), 5.8 (q, 1H,  $J=7.1$  Hz), 5.9 (m, 1H), 7.35 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  14, 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.  $[\alpha]_{\text{D}}=14.3$  ( $c=0.5$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2$ : C, 71.97; H, 8.05; N, 9.33. Found: C, 71.69; H, 8.08; N, 9.31.

**2.24. Alkylation of diastereomeric mixture 7 and 8**

The reaction was performed following the general procedure and the same alkylating reagents used for the alkylation of diastereomeric mixture (2 and 3) above described.

**2.25. (3S,6R,1'R)-5-Ethoxy-3,6-dimethyl-3-ethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9a or 10d**

$^1\text{H-NMR}$   $\delta$  0.78 (t, 3H,  $J=7.1$  Hz), 1.2 (t, 3H,  $J=7$  Hz), 1.38 (d, 3H,  $J=6.7$  Hz), 1.4 (s, 3H), 1.55 (m, 1H), 1.66 (d, 3H,  $J=7.2$  Hz), 2.2 (m, 1H), 3.58 (q, 1H,  $J=6.7$  Hz), 4.05 (q, 2H,  $J=7$  Hz), 5.76 (q, 1H,  $J=7.2$  Hz), 7.3 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.1, 14, 17.9, 22.1, 28.9, 34.9, 50, 52.5, 61, 61.5, 127.6, 128.6, 139.1, 159.7, 172. The pure **9a** was isolated in 81% yield:  $[\alpha]_{\text{D}}=15.9$  ( $c=0.8$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 71.49; H, 8.67; N, 9.26. Found: C, 71.68; H, 8.7; N, 9.23.

**2.26. (3S,6R,1'R)-3-Allyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9b or 10g**

$^1\text{H-NMR}$   $\delta$  1.2 (t, 3H,  $J=7.1$  Hz), 1.37 (d, 3H,  $J=6.8$  Hz), 1.42 (s, 3H), 1.65 (d, 3H,  $J=7.2$  Hz), 2.37 (dd, 1H,  $J=7.1$ , 13 Hz), 2.87 (dd, 1H,  $J=7.1$ , 13 Hz), 3.55 (q, 1H,  $J=6.8$  Hz), 4.3 (q, 2H,  $J=7.1$  Hz), 5.08 (m, 2H), 5.7 (m, 2H), 7.3 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  14, 17.9, 22.1, 28.5, 46.1, 50, 52.5, 61, 61.4, 117.6,

127.5, 127.6, 128.5, 134.6, 139, 159.4, 171.5. The pure **9b** was isolated in 66% yield:  $[\alpha]_D=43.8$  ( $c=0.8$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 72.58; H, 8.34; N, 8.91. Found: C, 72.85; H, 8.36; N, 8.95.

**2.27. (3S,6R,1'R)-3-Benzyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9c or 10l**

The product **9c** was obtained in 68% yield.  $^1\text{H-NMR}$   $\delta$  1.2 (t, 3H,  $J=7.1$  Hz), 1.27 (d, 3H,  $J=6.8$  Hz), 1.57 (s, 3H), 1.59 (d, 3H,  $J=6.8$  Hz), 2.87 (d, 1H,  $J=12.4$  Hz), 3.19 (q, 1H,  $J=7.1$  Hz), 3.49 (d, 1H,  $J=12.4$  Hz), 4.12 (m, 2H), 5.57 (q, 1H,  $J=7.1$  Hz), 6.65 (m, 2ArH), 7.3 (m, 8ArH);  $^{13}\text{C-NMR}$   $\delta$  14, 17.6, 22.1, 29, 47.5, 49.4, 51.8, 60.7, 62.6, 125.9, 127.1, 127.2, 127.4, 127.7, 127.8, 128.2, 128.3, 130.8, 137.9, 138.4, 159, 170.7.

**2.28. (3R,6R,1'R)-5-Ethoxy-3-ethyl-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9d or 10a**

$^1\text{H-NMR}$   $\delta$  0.87 (t, 3H,  $J=7.2$  Hz), 1.2 (t, 3H,  $J=7.2$  Hz), 1.37 (d, 3H,  $J=6.8$  Hz), 1.47 (s, 3H), 1.67 (d, 3H,  $J=7$  Hz), 1.67 (m, 1H), 1.95 (m, 1H), 3.61 (q, 1H,  $J=6.8$  Hz), 4.06 (m, 2H), 5.73 (q, 1H,  $J=7$  Hz), 7.33 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.2, 14.1, 18, 21.9, 28.7, 34.8, 50.4, 52.7, 60.9, 61.7, 127.6, 127.8, 128.6, 138.9, 158.3, 172.1. The pure **9d** was isolated in 60% yield:  $[\alpha]_D=21.4$  ( $c=0.6$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 71.49; H, 8.67; N, 9.26. Found: C, 71.28; H, 8.65; N, 9.22.

**2.29. (3S,6R,1'R)-3-Allyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9e or 10h**

The product **9e** was obtained in 78% yield.  $^1\text{H-NMR}$   $\delta$  0.83 (t, 3H,  $J=7.3$  Hz), 1.2 (t, 3H,  $J=7$  Hz), 1.33 (d, 3H,  $J=6.8$  Hz), 1.66 (d, 3H,  $J=7.1$  Hz), 1.63 (m, 1H), 2.05 (m, 1H), 2.35 (dd, 1H,  $J=6.7$ , 12.8 Hz), 2.8 (dd, 1H,  $J=7.7$ , 12.8 Hz), 3.56 (q, 1H,  $J=6.8$  Hz), 4.07 (m, 2H), 5.09 (m, 2H), 5.71 (m, 2H), 7.31 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.1, 14.1, 17.9, 21.9, 33.7, 45.7, 50.2, 52.8, 60.9, 65.5, 117.8, 127.5, 127.9, 128.5, 134.3, 138.5, 158.7, 170.1.

**2.30. (3S,6R,1'R)-3-Benzyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9f or 10m**

$^1\text{H-NMR}$   $\delta$  0.86 (t, 3H,  $J=7.4$  Hz), 1.17 (d, 3H,  $J=6.8$  Hz), 1.23 (t, 3H,  $J=7.2$  Hz), 1.56 (d, 3H,  $J=7.1$  Hz), 1.75 (m, 1H), 2.25 (m, 1H), 2.87 (d, 1H,  $J=12.4$  Hz), 3.08 (q, 1H,  $J=6.8$  Hz), 3.39 (d, 1H,  $J=12.4$  Hz), 4.14 (m, 2H), 5.5 (q, 1H,  $J=7.1$  Hz), 6.65 (m, 2ArH), 7.21 (m, 8ArH);  $^{13}\text{C-NMR}$   $\delta$  9.3, 14.2, 17.7, 21.7, 34.2, 47.5, 49.7, 52.1, 60.7, 66.9, 126, 127.2, 127.7, 128.2, 130.7, 137.9, 158.8, 169.3. The pure **9f** was isolated in 50% yield:  $[\alpha]_D=12.5$  ( $c=9.8$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.16; H, 7.99; N, 7.4. Found: C, 76.25; H, 8.02; N, 7.42.

**2.31. (3R,6R,1'R)-3-Allyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9g or 10b**

$^1\text{H-NMR}$   $\delta$  1.19 (t, 3H,  $J=7.1$  Hz), 1.35 (d, 3H,  $J=6.8$  Hz), 1.48 (s, 3H), 1.64 (d, 3H,  $J=7.2$  Hz), 2.36 (dd, 1H,  $J=7.5$ , 13.2 Hz), 2.65 (dd, 1H,  $J=7.5$ , 13.2 Hz), 3.58 (q, 1H,  $J=6.8$  Hz), 4.04 (m, 2H), 5.08 (m, 2H), 5.73 (m, 2H), 7.33 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  14, 17.9, 22, 28.9, 46.3, 50.4, 52.8, 61, 61.4, 118.4,

127.6, 127.8, 128.6, 134, 138.7, 158.5, 171.4. The pure **9g** was isolated in 68% yield:  $[\alpha]_D = -3.2$  ( $c=1.7$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 72.58; H, 8.34; N, 8.91. Found: C, 72.45; H, 8.32; N, 8.9.

**2.32. (3R,6R,1'R)-3-Allyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9h or 10e**

$^1\text{H-NMR}$   $\delta$  0.7 (t, 3H,  $J=7.3$  Hz), 1.21 (t, 3H,  $J=7$  Hz), 1.33 (d, 3H,  $J=6.8$  Hz), 1.6 (m, 1H), 1.65 (d, 3H,  $J=7.1$  Hz), 2.18 (m, 1H), 2.33 (dd, 1H,  $J=7.4$ , 13.1 Hz), 2.7 (dd, 1H,  $J=7.4$ , 13.1 Hz), 3.57 (q, 1H,  $J=6.8$  Hz), 4.05 (m, 2H), 5.1 (m, 2H), 5.71 (m, 2H), 7.32 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  8.7, 14, 17.8, 22.1, 34.2, 45.6, 50.2, 52.8, 60.8, 65.1, 118.2, 127.5, 127.7, 127.8, 128.5, 134, 138.5, 159, 170.1. The pure **9h** was isolated in 80% yield:  $[\alpha]_D = 2.3$  ( $c=1.1$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 73.14; H, 8.59; N, 8.53. Found: C, 73.25; H, 8.62; N, 8.5.

**2.33. (3S,6R,1'R)-3-Allyl-3-benzyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9i or 10n**

$^1\text{H-NMR}$   $\delta$  1.16 (d, 3H,  $J=6.9$  Hz), 1.22 (t, 3H,  $J=7$  Hz), 1.53 (d, 3H,  $J=7.1$  Hz), 2.48 (dd, 1H,  $J=7.5$ , 12.8 Hz), 2.88 (d, 1H,  $J=12.6$  Hz), 2.92 (dd, 1H,  $J=7.5$ , 12.8 Hz), 3.43 (d, 1H,  $J=12.6$  Hz), 4.17 (m, 2H), 5.12 (m, 2H), 5.46 (q, 1H,  $J=7.1$  Hz), 5.72 (m, 1H), 6.65 (m, 2ArH), 7.2 (m, 8ArH);  $^{13}\text{C-NMR}$   $\delta$  14.2, 17.6, 21.9, 45.7, 47.2, 49.6, 52.2, 60.8, 66.3, 118.6, 126.1, 127.2, 127.7, 128.2, 130.7, 133.9, 137.6, 137.9, 158.8, 168.8. The pure **9i** was isolated in 65% yield:  $[\alpha]_D = 56.2$  ( $c=2.2$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.89; H, 7.74; N, 7.17. Found: C, 76.65; H, 7.72; N, 7.2.

**2.34. (3R,6R,1'R)-3-Benzyl-5-ethoxy-3,6-dimethyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9l or 10c**

The product **9l** was obtained in 50% yield.  $^1\text{H-NMR}$   $\delta$  0.2 (d, 3H,  $J=6.8$  Hz), 1.21 (t, 3H,  $J=7.1$  Hz), 1.52 (d, 3H,  $J=7.1$  Hz), 1.62 (s, 3H), 2.84 (d, 1H,  $J=12.1$  Hz), 3.29 (q, 1H,  $J=6.8$  Hz), 3.42 (d, 1H,  $J=12.1$  Hz), 4.1 (m, 2H), 5.62 (q, 1H,  $J=7.1$  Hz), 7.3 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  14.2, 17.4, 19.9, 30.6, 47.6, 50.2, 52.7, 60.8, 62.9, 126.5, 127.3, 127.5, 127.6, 127.8, 128, 128.2, 128.3, 128.4, 130.8, 137.7, 138.3, 158.3, 170.8.

**2.35. (3R,6R,1'R)-3-Benzyl-5-ethoxy-3-ethyl-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9m or 10f**

The product **9m** was obtained in 84% yield.  $^1\text{H-NMR}$   $\delta$  0.18 (d, 3H,  $J=6.8$  Hz), 0.81 (t, 3H,  $J=7.4$  Hz), 1.22 (t, 3H,  $J=7.1$  Hz), 1.51 (d, 3H,  $J=7.1$  Hz), 1.7 (m, 1H), 2.33 (m, 1H), 2.78 (d, 1H,  $J=12.6$  Hz), 3.26 (q, 1H,  $J=6.8$  Hz), 3.4 (d, 1H,  $J=12.6$  Hz), 4.11 (q, 2H,  $J=7.1$  Hz), 5.64 (q, 1H,  $J=7.1$  Hz), 7.23 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  8.9, 14.3, 17.3, 20, 35.4, 47.1, 50.2, 52.7, 60.8, 66.8, 126.4, 127.5, 127.7, 128, 128.2, 128.5, 130.9, 137.6, 138.3, 159.1, 169.6.

**2.36. (3R,6R,1'R)-3-Allyl-3-benzyl-5-ethoxy-6-methyl-1-(1'-phenethyl)-3,6-dihydro-1H-pyrazine-2-one 9n or 10i**

$^1\text{H-NMR}$   $\delta$  0.19 (d, 3H,  $J=6.9$  Hz), 1.22 (t, 3H,  $J=7.3$  Hz), 1.5 (d, 3H,  $J=7.2$  Hz), 2.48 (dd, 1H,  $J=6.9$ , 12.8 Hz), 2.8 (d, 1H,  $J=12.5$  Hz), 3 (dd, 1H,  $J=7.7$ , 12.8 Hz), 3.23 (q, 1H,  $J=6.9$  Hz), 3.44 (d, 1H,  $J=12.5$

Hz), 4.01 (q, 2H,  $J=7.3$  Hz), 5.14 (m, 2H), 5.6 (q, 1H,  $J=7.2$  Hz), 5.71 (m, 1H), 7.23 (10ArH);  $^{13}\text{C}$ -NMR  $\delta$  14.2, 17.3, 20, 46.6, 46.7, 50.1, 52.7, 60.8, 66.6, 118.1, 126.5, 127.5, 127.8, 128.1, 128.2, 128.4, 130.9, 134, 137.4, 138.2, 158.9, 169. The pure **9n** was isolated in 87% yield:  $[\alpha]_{\text{D}}=9.5$  ( $c=2.7$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.89; H, 7.74; N, 7.17. Found: C, 76.76; H, 7.76; N, 7.15.

### 2.37. (3S,6R)-3-Allyl-5-ethoxy-3-ethyl-6-methyl-3,6-dihydro-1H-pyrazine-2-one **11**

To a stirred solution of Na (0.6 g, 26 mmol) dissolved in about 100 ml of liquid ammonia, cooled at  $-60^\circ\text{C}$ , was added **4e** (1.2 g, 3.7 mmol) in dry THF (25 ml) and ethanol (2.5 ml) under an inert atmosphere. After 5 minutes the reaction was quenched with 1.4 g of  $\text{NH}_4\text{Cl}$  and the cooling bath was removed allowing the complete removal of  $\text{NH}_3$ . Then, water was added and the solution extracted with ethyl acetate. After removal of the organic solvent the crude reaction product was purified by silica gel chromatography eluting with hexane:ethyl acetate. The pure product was isolated in 85% yield.  $^1\text{H}$ -NMR  $\delta$  0.78 (t, 3H,  $J=7.4$  Hz), 1.28 (t, 3H,  $J=7.1$  Hz), 1.38 (d, 3H,  $J=6.8$  Hz), 1.51–1.65 (m, 1H), 2.02 (m, 1H), 2.3 (dd, 1H,  $J=7.4$ , 13.1 Hz), 2.64 (dd, 1H,  $J=7.4$ , 13.1 Hz), 4.1 (m, 3H), 5.05 (m, 2H), 5.61 (m, 1H), 6.33 (bs, 1H);  $^{13}\text{C}$ -NMR  $\delta$  8.8, 14.4, 21.3, 32.8, 45.4, 48.7, 61, 64.7, 118.2, 133.4, 158.6, 172.7.  $[\alpha]_{\text{D}}=-25.5$  ( $c=5$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$ : C, 64.26; H, 8.99; N, 12.49. Found: C, 64.47; H, 9.02; N, 12.5.

### 2.38. (2R,5S)-5-Amino-3-aza-5-ethyl-2-methyl-4-oxo-ethyl-7-octenoate hydrochloride **12**

4.4 ml of 0.5 M HCl were dropped to **11** (0.5 gr, 2.2 mmol) dissolved in 50 ml of acetone and the solution was stirred at r.t. After about 3 h the acetone was evaporated and to the residue was added water then ethyl acetate. The product was recovered as an oil in practically quantitative yield by evaporation of the aqueous solution in vacuo.  $^1\text{H}$ -NMR  $\delta$  0.95 (t, 3H,  $J=7.4$  Hz), 1.26 (t, 3H,  $J=7.1$  Hz), 1.4 (d, 3H,  $J=7.3$  Hz), 1.72 (m, 1H), 1.96 (m, 1H), 2.37 (dd, 1H,  $J=8.8$ , 13.7 Hz), 2.76 (dd, 1H,  $J=6$ , 13.7 Hz), 4.17 (q, 2H,  $J=7.1$  Hz), 4.49 (dq, 1H,  $J=7.2$ , 7.3 Hz), 4.7 (bs, 3H), 5.18 (m, 2H), 5.77 (m, 1H), 7.8 (d, 1H,  $J=7.2$  Hz);  $^{13}\text{C}$ -NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8, 14.5, 17.3, 31.7, 43.4, 49.8, 62.4, 63.4, 121.2, 132.4, 173.8, 174.5.

### 2.39. (2R,5S)-5-Acetamido-3-aza-5-ethyl-2-methyl-4-oxo-ethyl-7-octenoate **13**

The dipeptide **12** was easily acetylated in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  with acetyl chloride in the presence of triethyl amine. After chromatographic elution with hexane:ethyl acetate, the pure product was obtained in 90% yield.  $^1\text{H}$ -NMR  $\delta$  0.8 (t, 3H,  $J=7.4$  Hz), 1.29 (t, 3H,  $J=7.1$  Hz), 1.41 (d, 3H,  $J=7.1$  Hz), 1.7 (m, 1H), 2 (s, 3H), 2.41 (dd, 1H,  $J=6.9$ , 14.3 Hz), 2.57 (m, 1H), 3.2 (dd, 1H,  $J=7.5$ , 14.3 Hz), 4.21 (m, 2H), 4.5 (dq, 1H,  $J=7.1$ , 6.4 Hz), 5.08 (m, 2H), 5.64 (m, 1H), 6.54 (d, 1H,  $J=6.4$  Hz), 6.62 (bs, 1H);  $^{13}\text{C}$ -NMR  $\delta$  7.8, 13.9, 17.9, 24, 28.1, 39.4, 48.3, 61.4, 64, 118.7, 132.3, 169.2, 172.1, 172.5.  $[\alpha]_{\text{D}}=7$  ( $c=3.3$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_4$ : C, 59.14; H, 8.51; N, 9.85. Found: C, 59.37; H, 8.5; N, 9.8.

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