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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of sterically constrained dipeptides. Part 2 †

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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 α-carbon. The absolute configuration of the new stereocentres has been assigned on the basis of ^{1}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 α-carbon.[1] Our current aim is the developement of a new stereoselective synthesis to obtain conformationally constrained dipeptides C-αα′ 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.[2] Therefore, in a continuation of our studies in this field, we accomplished an extension of the previously reported diastereoselective synthesis of dipeptides.[1] 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 (±)-2-bromopropionate.[1]

In the previous paper[1] 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-αα′ 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-αα.

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† Ref. [1] is considered to be Part 1.

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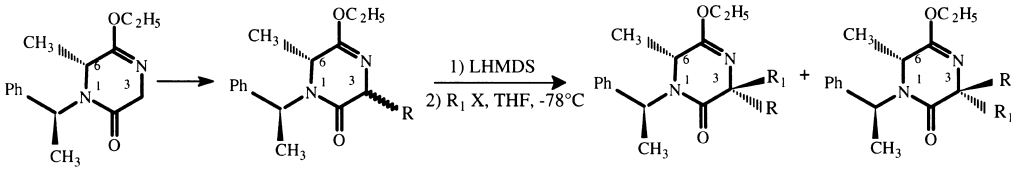


Scheme 1. R and R_1 are reported in Table 1

Table 1
Diastereoselectivity of the alkylation

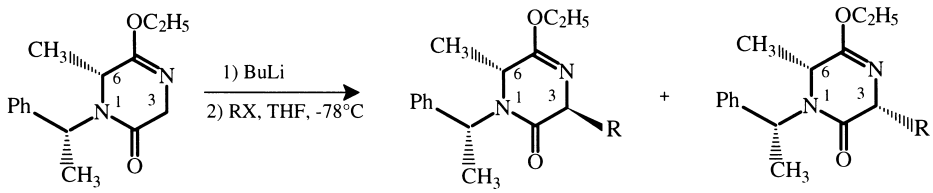
Entry		R	R_1	Yield (a) 4	5	9	10
1	a	CH_3	C_2H_5	93	7	85	15
2	b	CH_3	CH_2=$CHCH_2$	95	5	88	12
3	c	CH_3	$PhCH_2$	90	10	75	25
4	d	C_2H_5	CH_3	90	10	75	25
5	e	C_2H_5	CH_2=$CHCH_2$	97	3	97	3
6	f	C_2H_5	$PhCH_2$	95	5	54	46
7	g	CH_2=$CHCH_2$	CH_3	82	18	81	19
8	h	CH_2=$CHCH_2$	C_2H_5	98	2	85	15
9	i	CH_2=$CHCH_2$	$PhCH_2$	98	2	86	14
10	l	$PhCH_2$	CH_3	83	17	75	25
11	m	$PhCH_2$	C_2H_5	98	2	88	12
12	n	$PhCH_2$	CH_2=$CHCH_2$	98	2	92	8

(a) The reported yelds were calculated by ^{1}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_3.[3]

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**,[1] it is evident that the change of the auxiliary configuration produces an appreciable decrease of the diastereoselection comparable to that already observed[1] when the (*S*)-1-phenethyl group was substituted by the sterically similar achiral benzyl group.

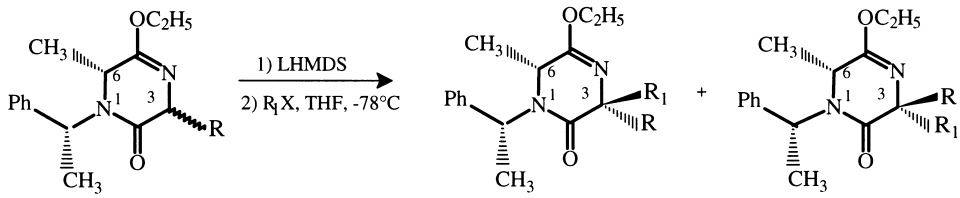


6 **7 (a-d)** **8 (a-d)**

a) R-X = CH_3I	26%	74%
b) R-X = $PhCH_2Br$	55%	45%
c) R-X = C_2H_5I	70%	30%
d) R-X = $CH_2{=}CHCH_2I$	80%	20%

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.



7 + 8 **9 (a-n)** **10 (a-n)**

Scheme 3. R and R_1 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,[1] 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_3) 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_3 lies, leading to a lower facial discrimination which is significant for entry 6 (Table 1).

Thus, it can be deduced that in both the first and second alkylations of the synthon **1** the best stereoselection is achieved when the two stereocentres have opposite configurations, since the *si* face is sterically less hindered than the *re* one (**A** enolate). In addition, as previously observed,[1] the alkylation of a synthon without the chiral auxiliary gives lower diastereoselection; however, the results are comparable to those observed when the two stereocentres have the same configuration (**B** enolate).

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[1]) 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.

1. Stereochemical assignments

The configuration of the introduced stereocentre (C-3) was deduced on the basis of ^{1}H-NMR spectroscopic data using the approach previously employed for similar molecules.[1] We previously reported[1] that the preferred geometry of the lactims **1**, **2** and **3** is the boat-like conformation in which the (C-6)-CH_3 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_3 the NOE was exclusively observed on the (C-3)-R, while the lactims **5** displayed a significant NOE between (C-6)-CH_3 and (C-3)-R_1. 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_1. For both the isomers, in addition to a meaningful NOE between (C-6)-H and the methyl of the chiral auxiliary,[4] a characteristic shielding effect of about 0.4 ppm, induced by the phenyl ring of the phenethyl group,[1] was observed on the (C-6)-CH_3. These findings were evidence that for both the isomers, the preferred geometry is the boat-like conformation in which the (C-6)-CH_3 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_3 doublet in the spectrum of the *cis* isomer **3** (when R=CH_2Ph) 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**.[1] In fact, this upfield shift is induced by the shielding effect of the phenyl ring of the (C-3)-CH_2Ph group which lies in the axial-like position, thus adopting the preferential 'aryl inside' arrangement. As previously observed in analogous substrates,[4,5] such a conformation causes significant shielding of the axial-like (C-6)-CH_3 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_3 and (C-3)-CH_2Ph are axially arranged (Fig. 3). The *trans* relationship between the

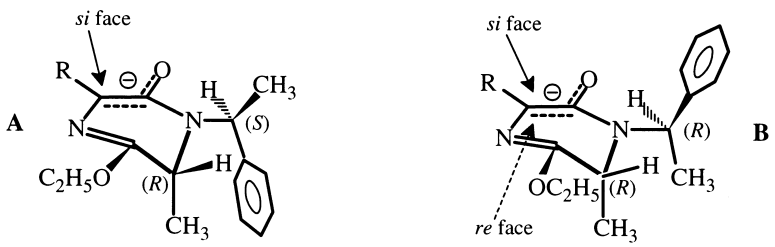
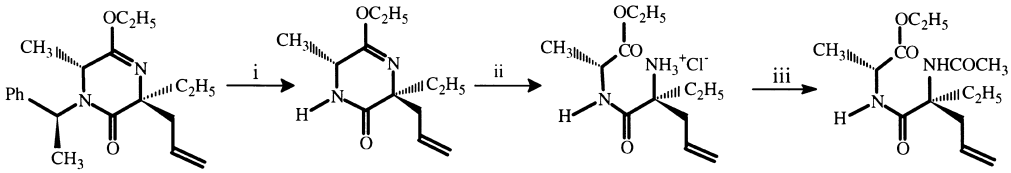


Fig. 1. Models proposed for the enolate anions: **A** (6*R*,1′*S*) and **B** (6*R*,1′*R*)



Scheme 4. (i) Na/NH_3; (ii) 0.5 N HCl/acetone at 0°C; (iii) CH_3COCl/Et_3N in CH_2Cl_2 at 0°C

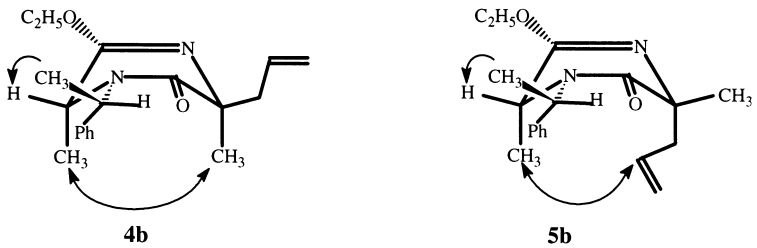


Fig. 2. Representative NOE registered for **4b** and **5b**

(C-3)-CH_2Ph and the (C-6)-CH_3 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_3 and the alkyl group at C-3 (Fig. 3).

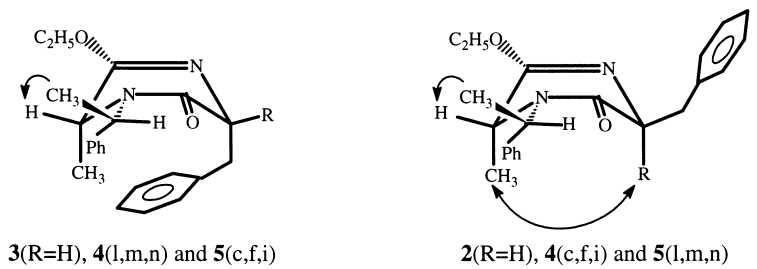


Fig. 3. Shielding induced by the (C-3)-CH_2Ph on (C-6)-CH_3 and significant NOE registered on **4** and **5**

The relative configuration of the C-3 stereocentre of **7** and **8** was determined as described in the previous paper,[1] 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_3.

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

2. Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$ 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°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 sperarated 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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D$=−195.5 (c=2.9, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.72; H, 8.7; N, 9.23.

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

3-Iodopropene was used as the alkylating reagent. ^{1}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D$=−168.9 (c=3.5, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}N_2O_2$: 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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D$=−107.9 (c=3.6, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_2$: 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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D$=−149 (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, 71.61; H, 8.65; N, 9.22.

*2.6. (3*S*,6*R*,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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-161.6$ (c=2.4, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.43; H, 8.57; N, 8.5.

*2.7. (3*S*,6*R*,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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-107.7$ (c=6.6, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.4. Found: C, 76.23; H, 8.02; N, 7.42.

*2.8. (3*R*,6*R*,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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-134.2$ (c=0.96, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.65; H, 8.32; N, 8.88.

*2.9. (3*R*,6*R*,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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-168.6$ (c=3, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.03; H, 8.62; N, 8.55.

*2.10. (3*S*,6*R*,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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-113$ (c=1.7, $CHCl_3$). Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.98; H, 7.77; N, 7.2.

*2.11. (3*R,*6*R,*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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-109.7$ (c=1.7, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 72.79; H, 7.74; N, 7.69. Found: C, 75.97; H, 7.77; N, 7.71.

*2.12. (3*R,*6*R,*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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-101.2$ (c=2.5, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.4. Found: C, 76.3; H, 7.97; N, 7.38.

*2.13. (3*R,*6*R,*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}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=-89.5$ (c=1.7, $CHCl_3$). Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.78; H, 7.72; N, 7.15.

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

The product was prepared starting from the methansulfonate of naturally occurring (*S*)-ethyl lactate and (*R*)-1-phenylethylamine by following the procedure employed for **1**.[1] ^{1}H-NMR δ 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}C-NMR δ 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. $[\alpha]_D=-37.5$ (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, 69.45; 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**.[1]

*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. ^{1}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); ^{13}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. $[\alpha]_D=-18.2$ (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, 8.11; 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. ^{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 Hz), 5.78 (q, 1H, J=7.2 Hz), 6.95 (m, 2ArH), 7.3 (m, 8ArH); ^{13}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. $[\alpha]_D=-156.8$ (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; 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. ^{1}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); ^{13}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. $[\alpha]_D=-32.1$ (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, 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. ^{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), 5.12 (m, 2H), 5.85 (q, 1H, J=7.3 Hz), 6 (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, 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. ^{1}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); ^{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, 70.23; H, 8.05; N, 10.17.

*2.21. (3*R,*6*R,*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}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, 128.5, 130.5, 137.2, 138, 160.6, 168.1. $[\alpha]_D=-5.5$ (c=1, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.4; H, 7.48; N, 7.99. Found: C, 75.3; H, 7.45; N, 7.97.

*2.22. (3*R,*6*R,*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}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, 5ArH); ^{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, 70.6; H, 8.36; N, 9.68.

*2.23. (3*R,*6*R,*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}H-NMR δ 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}C-NMR δ 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. $[\alpha]_D=14.3$ (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, 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. (3*S,*6*R,*1′*R*)-5-Ethoxy-3,6-dimethyl-3-ethyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one* ***9a*** *or* ***10d***

^{1}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D=15.9$ (c=0.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.68; H, 8.7; N, 9.23.

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

^{1}H-NMR δ 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}C-NMR δ 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, $CHCl_3$). 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, 8.95.

*2.27. (3*S*,6*R*,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}H-NMR δ 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}C-NMR δ 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. (3*R*,6*R*,1′*R*)-5-Ethoxy-3-ethyl-3,6-dimethyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one* ***9d*** *or* ***10a***

^{1}H-NMR δ 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}C-NMR δ 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, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.28; H, 8.65; N, 9.22.

*2.29. (3*S*,6*R*,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}H-NMR δ 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}C-NMR δ 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. (3*S*,6*R*,1′*R*)-3-Benzyl-5-ethoxy-3-ethyl-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one* ***9f*** *or* ***10m***

^{1}H-NMR δ 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}C-NMR δ 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, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.4. Found: C, 76.25; H, 8.02; N, 7.42.

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

^{1}H-NMR δ 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}C-NMR δ 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, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.45; H, 8.32; N, 8.9.

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

^{1}H-NMR δ 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}C-NMR δ 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, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.25; H, 8.62; N, 8.5.

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

^{1}H-NMR δ 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}C-NMR δ 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, $CHCl_3$). Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.65; H, 7.72; N, 7.2.

*2.34. (3*R,*6*R,*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}H-NMR δ 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}C-NMR δ 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. (3*R,*6*R,*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}H-NMR δ 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}C-NMR δ 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. (3*R,*6*R,*1′*R*)-3-Allyl-3-benzyl-5-ethoxy-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one* ***9n*** *or* ***10i***

^{1}H-NMR δ 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}C-NMR δ 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: $[\alpha]_D$=9.5 (c=2.7, $CHCl_3$). Anal. Calcd for $C_{25}H_{30}N_2O_2$: 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°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 NH_4Cl and the cooling bath was removed allowing the complete removal of 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}H-NMR δ 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}C-NMR δ 8.8, 14.4, 21.3, 32.8, 45.4, 48.7, 61, 64.7, 118.2, 133.4, 158.6, 172.7. $[\alpha]_D$=−25.5 (c=5, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}N_2O_2$: 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}H-NMR δ 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}C-NMR (CD_3OD) δ 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 CH_2Cl_2 at 0°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}H-NMR δ 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}C-NMR δ 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. $[\alpha]_D$=7 (c=3.3, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.14; H, 8.51; N, 9.85. Found: C, 59.37; H, 8.5; N, 9.8.

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3. In order to ascertain that the stereocentre C-6 remained unchanged during the alkylation reactions, we carried out debenzylation and heterocyclic ring cleavage of the lactims mixture (**4c** and **5c**) with 57% HI, as previously described [4]. Subsequent esterification by $SOCl_2/CH_3OH$ and chromatographic purification led to the pure (*R*)-alanine methyl ester. The obtained alanine methyl ester gave, as hydrochloride, $[\alpha]_D=-7.6$ (c=1.6, CH_3OH); the value reported in the literature is $[\alpha]_D=-8$ (c=1.6, CH_3OH) (*Beil*. **4**, 2485).
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