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Stereocontrolled synthesis of unnatural cyclic dipeptides containing an L-valine unit

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Abstract—Stereoselective synthesis of unusual nonproteinogenic dipeptides **7a**,**b**,**d**,**e** and **h** and **13b** and **i**, containing an L-valine unit and a cyclic unnatural α-amino acid, has been accomplished starting from the L-valine derived chiral synthon **1**. The absolute configurations of the new stereocentres were assigned on the basis of ^{1}H NMR spectra.

1. Introduction

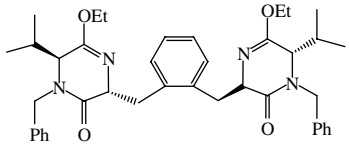
In continuation of our studies directed towards producing uncommon peptides[1–5] we undertook the asymmetric synthesis of new conformationally constrained pseudodipeptides **7a**,**b**,**d**,**e** and **h** and **13b** and **i** containing the L-valine and a cyclic nonproteinogenic α-amino acid.

Our interest in this field is twofold, firstly because some natural products containing a cyclic system fused to the diketopiperazine ring exhibit biological activity and secondly because the nonproteinogenic dipeptides could be useful as components for preparing higher peptides or act as starting materials in organic synthesis.

The strategy followed to accomplish the asymmetric synthesis of these compounds is based on the experience previously acquired on the stereoselective approach to similar substrates.[1–4] In fact, we have made use of chiral synthon **1**, a monolactim ether easily obtained starting from L-valine, although our synthetic method differentiates from that followed by Schollkopf. Actually, in an asymmetric synthesis of nonproteinogenic dipeptides, Schollkopf used the bislactim ether as a chiral synthon.[6] Also Davies et al.,[7] in an interesting investigation to assign the correct structure of some diketopiperazines derived from D-proline, described the synthetic approach starting from Schollkopf's auxiliary.

2. Synthesis and stereochemical assignments

Herein we have followed a strategy based on the use of mono-lactim ether **1**, a chiral synthon easily synthesized starting from the L-valine.[1–4] Deprotonation of **1** with LHMDS at −78 °C, followed by the alkylation with the appropriate dihaloderivative (3-chloro-2-chloromethylpropene, 1-chloro-4-iodobutane or α,α′-dibromo-*o*-xylene), generally afforded diastereomers **2a**,**d** and **g** with a 1,4-*trans* selectivity with at least a 98:2 ratio with respect to the isopropyl group, as already observed[1–4] (Scheme 1). The alkylated products were generally obtained in good yield except for intermediate **2g**, which was recovered in about 55% yield because it competitively reacts with the enolate of **1** to give the following product already described:[3]



Intermediate **2a** was easily converted into the bicyclic derivative **3a** by refluxing in acetone, in the presence of NaI, while **2d** and **2g** were cyclized by heating in DMF at 120 or 90 °C, respectively. Bicyclic compounds **3** were then converted into **4**, with over 98% 1,4-*trans* induction by alkylating with methyl iodide or allyl bromide. The removal of the benzyl group from bicyclic compounds **3a** and **d** and **4b**,**c**,**e**,**f**,**h** and **i** through a

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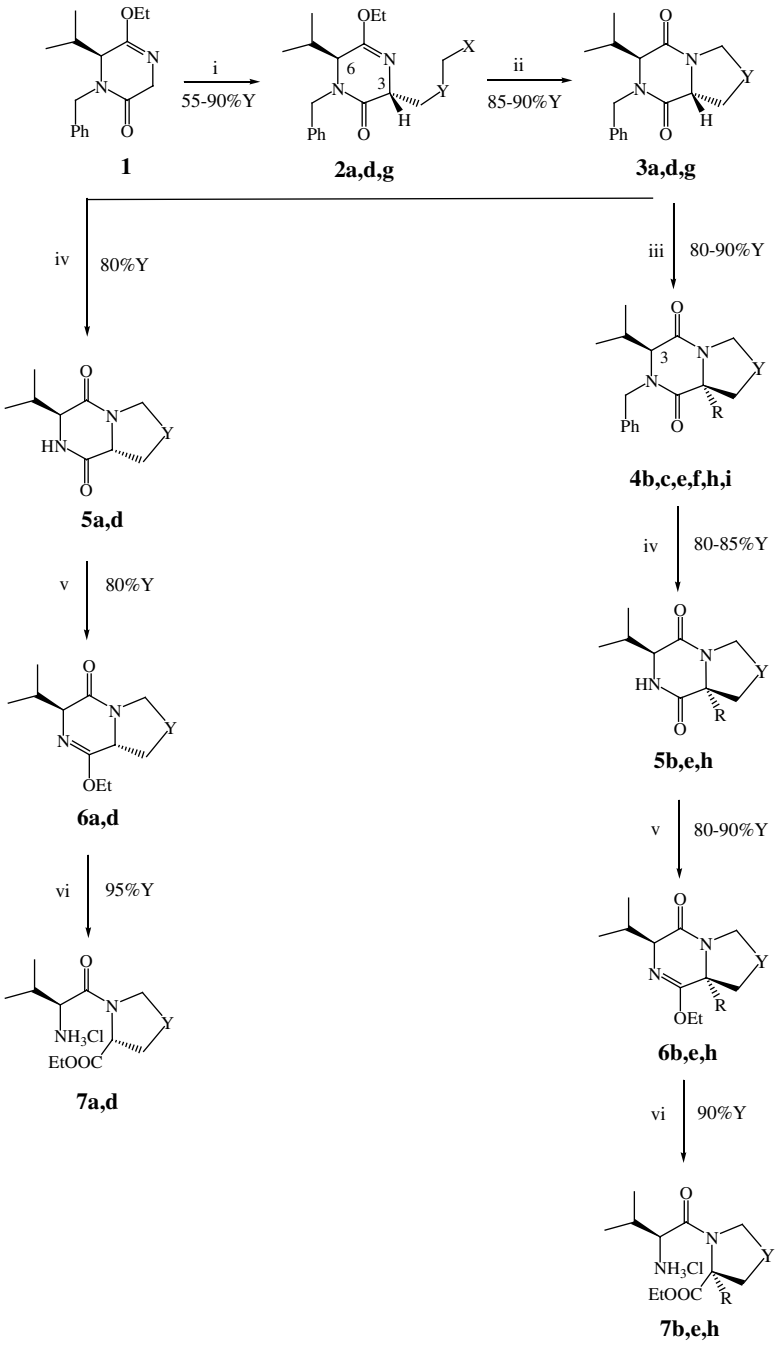
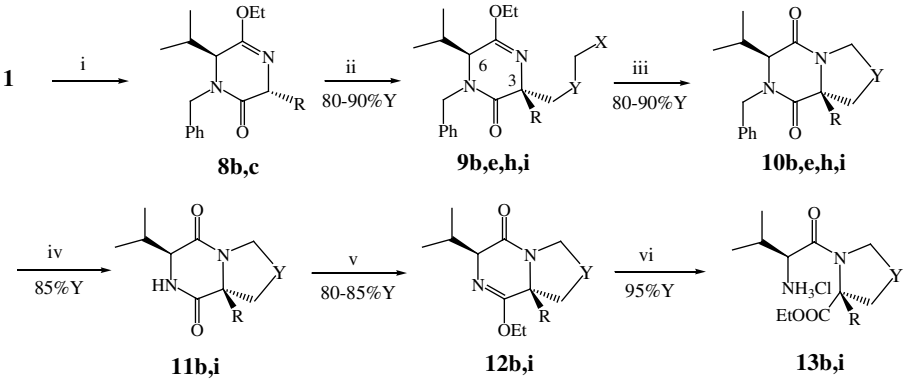


	a	b	c	d	e	f	g	h	i
Y	>C=CH_2	>C=CH_2	>C=CH_2	CH_2CH_2	CH_2CH_2	CH_2CH_2	*o*-C_6H_4	*o*-C_6H_4	*o*-C_6H_4
R	H	-CH_3	CH_2=$CHCH_2$	H	-CH_3	CH_2=$CHCH_2$	H	-CH_3	CH_2=$CHCH_2$

Scheme 1. Reagents and conditions: (i) 1 M LHMDS/THF, X–Y–X; (ii) heating in DMF, or refluxing in acetone/NaI; (iii) 1 M LHMDS/THF, R–X; (iv) Li/NH_3; (v) Et_3OBF_4/CH_2Cl_2; (vi) 0.5 M HCl at rt.

modified Birch reaction,[2] furnished the intermediates **5**, which were converted into monolactims **6** following the procedure already employed.[8,9] Finally, the unusual dipeptides **7a**,**b**,**d**,**e** and **h**, incorporating the L-valine, were quantitatively obtained by hydrolysis under mild acid conditions.

The synthesis of diastereomeric pseudodipeptides **13b** and **i** with an opposite configuration at the C-2 stereocentre of the pyrrolidine or piperidine ring, with respect to **7a**,**b**,**d**,**e** and **h**, was accomplished on the basis of the stereocontrolled *trans*-induction well tested in the alkylation reaction of the chiral synthon **1**.[1–4,8] Thus, non-



	a	b	c	d	e	f	g	h	i
Y	>C=CH$_2$	>C=CH$_2$	>C=CH$_2$	CH$_2$CH$_2$	CH$_2$CH$_2$	CH$_2$CH$_2$	*o*-C$_6$H$_4$	*o*-C$_6$H$_4$	*o*-C$_6$H$_4$
R	H	-CH$_3$	CH$_2$=CHCH$_2$	H	-CH$_3$	CH$_2$=CHCH$_2$	H	-CH$_3$	CH$_2$=CHCH$_2$

Scheme 2. Reagents and conditions: (i) 1 M LHMDS/THF, R–X; (ii) 1 M LHMDS/THF, X–Y–X; (iii) heating in DMF or refluxing in acetone/NaI; (iv) Li/NH$_3$; (v) Et$_3$OBF$_4$/CH$_2$Cl$_2$; (vi) 0.5 M HCl at rt.

proteinogenic dipeptides **13** were obtained simply by changing the sequence of the alkylation at C-3 of the chiral mono-lactim ether **1**. In fact, as reported in Scheme 2, chiral synthon **1** was alkylated firstly with methyl iodide or allyl bromide and then successively with the appropriate dihalo derivative (3-chloro-2-chloromethylpropene, 1-chloro-4-iodobutane or α,α′-dibromo-*o*-xylene). The alkylation of **1** with both methyl iodide and allyl bromide gave the *trans* diastereomers **8b** and **c**, as already described,[2] with a diastereoselectivity of ca. 75/25 and 85/15, respectively. However, in this case the extent of the diastereoselection is not relevant because the subsequent alkylation is performed on the diastereomeric mixture.

The absolute configuration of the new stereocentres in substrates **2** and **9** was ascertained by measuring the NOE between (C-6)-H and the substituents at the C-3, the stereochemistry of C-6 being worthy of note. In the case of substrate **4**, the NOE was measured between (C-3)-H and the substituents at C-6 or C-11a.

3. Conclusion

In conclusion, we have succeeded in synthesizing new conformationally constrained nonproteinogenic dipeptides incorporating L-valine and unnatural α-amino acids containing the pyrrolidine or piperidine ring. The approach, accomplished in six steps starting from the monolactim ether **1** easily obtained from L-valine, allowed us to obtain pseudodipeptides, which differ in the configuration of one stereogenic centre, that is, epimers. We believe that our synthetic pathway represents a useful complementary strategy to dipeptides and might also provide a new and simple access to more complex and unusual peptides incorporating conformationally constrained unnatural dipeptides, which are currently under study.

4. Experimental

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to $CDCl_3$ with the coupling constants (*J*) given in Hz. Optical rotation values were measured at 25 °C on a Perkin–Elmer 343 polarimeter. Melting points are uncorrected. The products isolated in not sufficiently pure form for elemental analysis were submitted to HPLC-MS analysis on a Hewlett-Packard Model 1100 liquid chromatograph-single-quadrupole mass-selective detector system, with an Atmospheric Pressure Chemical Ionisation–ElectroSpray interface, using a Zorbax Eclipse XDB-C 8 column.

Dry THF was distilled from sodium benzophenone ketyl. Chromatographic separations were performed with silica gel 60 (230–400 mesh).

4.2. Alkylation of 1

To a solution of **1** (2.74 g, 10 mmol) in dry THF (30 mL) cooled at −78 °C were added 10 mmol of LHMDS (1 M solution in THF). After about 1 h under stirring, the appropriate alkylating reagent (11 mmol) dissolved in 10 mL of dry THF was added dropwise and the reaction monitored by TLC. When the reaction was complete, water and ethyl acetate were then added, the organic extract dried over Na_2SO_4 and then evaporated to dryness in vacuo. The crude reaction product was purified by the

silica gel chromatography eluting with hexane/ethyl acetate.

4.3. (3*R*,6*S*)-1-Benzyl-5-ethoxy-3-(2-chloromethyl-allyl)-6-isopropyl-3,6-dihydro-1*H*-pyrazin-2-one, 2a

3-Chloro-2-chloromethylpropene was used as the alkylating reagent and the pure product was obtained as an oil in 90% yield. ^{1}H NMR δ: 0.95 (d, 3H, J = 7); 1.07 (d, 3H, J = 7); 1.27 (t, 3H, J = 7); 2.18–2.30 (m, 1H); 2.69 (dd, 1H, J = 8.1, 14.1); 3.08 (dd, 1H, J = 4.2, 14.1); 3.71 (dd, 1H, J = 1.8, 4.2); 3.95 (d, 1H, J = 15); 4.03–4.28 (m, 5H); 5.17 (d, 1H, J = 0.9); 5.28 (d, 1H, J = 0.9); 5.48 (d, 1H, J = 15); 7.19–7.40 (m, 5ArH). ^{13}C NMR δ: 13.8, 17.3, 19.7, 31.3, 36.3, 41.2, 48.9, 57.9, 61.0, 61.7, 116.4, 127.3, 127.5, 128.4, 135.9, 142.9, 159.1, 169.3. $[\alpha]_D$ = +53.6 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}ClN_2O_2$: C, 66.19; H, 7.5; N, 7.72. Found: C, 66.31; H, 7.48; N, 7.7.

4.4. (3*R*,6*S*)-1-Benzyl-5-ethoxy-3-(4-chlorobutyl)-6-isopropyl-3,6-dihydro-1*H*-pyrazin-2-one, 2d

1-Chloro-4-iodobutane was used as the alkylating reagent and the pure product was obtained as an oil in 75% yield. ^{1}H NMR δ: 0.92 (d, 3H, J = 7); 1.04 (d, 3H, J = 7); 1.25 (t, 3H, J = 7); 1.5 (m, 2H); 1.8–2.17 (m, 4H); 2.18–2.35 (m, 1H); 3.21 (t, 2H, J = 7); 3.69 (dd, 1H, J = 1.8, 4); 3.9 (d, 1H, J = 15); 4.02–4.22 (m, 3H); 5.48 (d, 1H, J = 15); 7.16–7.4 (m, 5ArH). ^{13}C NMR δ: 7.2, 14.1, 17.5, 19.9, 26.2, 31.5, 32.5, 33.4, 47.2, 57.5, 61.1, 61.8, 127.5, 127.8, 128.7, 136.2, 159.1, 170.3. $[\alpha]_D$ = +33.4 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}ClN_2O_2$: C, 65.83; H, 8.01; N, 7.68. Found: C, 66.1; H, 7.98; N, 7.7.

4.5. (3*R*,6*S*)-1-Benzyl-5-ethoxy-3-(2-bromomethyl-benzyl)-6-isopropyl-3,6-dihydro-1*H*-pyrazin-2-one, 2g

α,α′-Dibromo-*o*-xylene was used as the alkylating reagent and the pure product was obtained as an oil in 55% yield. ^{1}H NMR δ: 0.9 (d, 3H, J = 7); 1.02 (d, 3H, J = 7); 1.21 (t, 3H, J = 7); 2.19 (m, 1H); 3.37 (dd, 1H, J = 7.2, 13.8); 3.57 (dd, 1H, J = 1.6, 4.2); 3.64 (dd, 1H, J = 4.4, 13.8); 3.88 (d, 1H, J = 15); 3.9–4.2 (m, 2H); 4.4 (m, 1H); 4.84 (s, 2H); 5.48 (d, 1H, J = 15); 7.01 (m, 2ArH); 7.2–7.44 (m, 7ArH). ^{13}C NMR δ: 14.0, 17.4, 19.8, 31.4, 33.0, 35.0, 47.1, 59.1, 61, 61.7, 126.5, 127.3, 127.5, 128.2, 128.5, 130.1, 131.5, 135.8, 137.1, 138.1, 159.2, 169.4. $[\alpha]_D$ = −50.5 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{24}H_{29}BrN_2O_2$: C, 63.02; H, 6.39; N, 6.12. Found: C, 63.11; H, 6.38; N, 6.1.

4.6. (3*S*,6*R*)-4-Benzyl-3-isopropyl-8-methylene-1,4-diazabicyclo[4,3,0]nonane-2,5-dione, 3a

A solution of intermediate **2a** (7.24 g, 20 mmol) and NaI (6 g, 40 mmol), dissolved in 50 mL of acetone, was refluxed for about 18 h. The organic solvent was evaporated, water added to the residue and the reaction product extracted with ethyl acetate. The organic phase, after drying over Na_2SO_4, was evaporated in vacuo to dryness and the residue purified by the silica gel chromatography eluting with hexane/ethyl acetate. The product was obtained pure as an oil in 90% yield. ^{1}H NMR δ: 1.02 (d, 1H, J = 7); 1.12 (d, 1H, J = 7); 2.17–2.36 (m, 1H); 2.74–2.92 (m, 1H); 3.04 (ddd, 1H, J = 1.6, 7.4, 15.8); 3.72 (d, 1H, J = 5.6); 3.93 (m, 1H); 3.95 (d, 1H, J = 15); 5.30–5.54 (m, 2H); 5.09 (d, 1H, J = 1.6); 5.17 (d, 1H, J = 1.6); 5.4 (d, 1H, J = 15); 7.17–7.39 (m, 5ArH). ^{13}C NMR δ: 18.1, 19.9, 31.9, 36.8, 48.3, 49.9, 58.5, 66.6, 109.2, 127.9, 128.9, 135.7, 140.6, 164.1, 167.3. $[\alpha]_D$ = +23.1 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.5; H, 7.4; N, 9.36.

4.7. (3*S*,6*R*)-4-Benzyl-3-isopropyl-1,4-diazabicyclo-[4,4,0]decane-2,5-dione, 3d

A solution of intermediate **2d** (9.12 g, 20 mmol) dissolved in 20 mL of DMF, was heated at 120 °C for about 3 h. The organic solvent was evaporated, water added to the residue and the reaction product extracted with ethyl acetate. After drying over Na_2SO_4, the organic phase was evaporated in vacuo to dryness and the residue purified by the silica gel chromatography eluting with hexane/ethyl acetate. The product was obtained pure as a wax in 85% yield. ^{1}H NMR δ: 0.94 (d, 3H, J = 7); 1.11 (d, 3H, J = 7); 1.4–1.82 (m, 4H); 2.04 (m, 1H); 2.32 (m, 1H); 2.53 (m, 2H); 3.76 (d, 1H, J = 3); 3.9 (d, 1H, J = 15); 3.92 (m, 1H); 4.7 (m, 1H); 7.18–7.4 (m, 5ArH). ^{13}C NMR δ: 16.4, 19.2, 23.3, 23.5, 30.9, 31.8, 40.9, 46.8, 56.9, 62.8, 127.1, 127.3, 128.2, 135.3, 163.6, 166.2. $[\alpha]_D$ = −11.8 (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.11; H, 8.02; N, 9.29.

4.8. (3*S*,11a*R*)-2-Benzyl-3-isopropyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione, 3g

Intermediate **2g** (9.16 g, 20 mmol) dissolved in 20 mL of DMF was heated at 90 °C for about 3 h and the reaction mixture worked up as above reported for **3d**. The pure product was isolated as a solid in 85% yield after purification by the silica gel chromatography eluting with hexane/ethyl acetate. ^{1}H NMR δ: 0.99 (d, 3H, J = 7); 1.14 (d, 3H, J = 7); 2.3 (m, 1H); 2.99 (dd, 1H, J = 11.8, 15.4); 3.63 (dd, 1H, J = 3.6, 15.4); 3.81 (d, 1H, J = 5.2); 3.99 (d, 1H, J = 15); 4.22 (dd, 1H, J = 3.6, 11.8); 4.75 (q_{AB}, 2H, J = 17.2); 5.5 (d, 1H, J = 15); 7.17–7.42 (m, 5ArH). ^{13}C NMR δ: 17.7, 19.8, 31.9, 33.3, 44.6, 48.2, 54.3, 64.7, 126.9, 127.0, 127.7, 127.8, 128.6, 131.3, 133.4, 135.5, 165.1, 166.3. Mp 118–120 °C. $[\alpha]_D$ = +91.4 (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.55; H, 6.96; N, 8.07.

4.9. (3*S*,6*S*)-4-Benzyl-3-isopropyl-6-methyl-8-methylene-1,4-diazabicyclo[4,3,0]nonane-2,5-dione, 4b

To a solution of **3a** (6 g, 20 mmol) in dry THF (60 mL) cooled at −78 °C was added 20 mL (20 mmol) of LHMDS (1 M solution in THF). After about 1 h under stirring, iodomethane (1.4 mL, 20 mmol) was dropped and the reaction monitored by TLC. When the reaction was complete, water and ethyl acetate were then added.

The organic extract was dried over Na_2SO_4 and then evaporated to dryness in vacuo. The crude reaction product was purified by the silica gel chromatography eluting with hexane/ethyl acetate and the pure product isolated as an oil in about 90% yield. ^{1}H NMR δ: 0.87 (d, 3H, $J = 7$); 1.16 (d, 3H, $J = 7$); 1.5 (s, 3H); 2.4 (m, 1H); 2.85 (m, 2H); 3.79 (d, 1H, $J = 2.6$); 3.97 (d, 1H, $J = 15$); 4 (m, 1H); 4.47 (m, 1H); 5.19 (m, 2H); 5.55 (d, 1H, $J = 15$); 7.18–7.4 (m, 5ArH). ^{13}C NMR δ: 15.5, 19.8, 26.7 30.2, 43.4, 46.5, 48.4, 63.4, 63.8, 109.9, 127.8, 127.9, 128.7, 135.6, 140.6, 163.0, 169.9. $[\alpha]_D = +133.2$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.89; H, 7.77; N, 8.98.

4.10. (3*S*,6*S*)-6-Allyl-4-benzyl-3-isopropyl-8-methylene-1,4-diazabicyclo[4,3,0]nonane-2,5-dione, 4c

Compound **4c** was obtained by alkylating **3a** with allyl bromide and following the procedure used for **4b**. The pure product was isolated as an oil in about 85% yield. ^{1}H NMR δ: 0.81 (d, 3H, $J = 7$); 1.13 (d, 3H, $J = 7$); 2.38 (m, 1H); 2.39 (dd, 1H, $J = 7.4$, 14.4); 2.65 (dd, 1H, $J = 7.4$, 13.6); 2.85 (m, 2H); 3.8 (d, 1H, $J = 2.6$); 3.88–4.01 (m, 1H); 4.04 (d, 1H, $J = 15$); 5.04–5.24 (m, 4H); 5.39 (d, 1H, $J = 15$); 5.51 (m, 1H); 7.22–7.43 (m, 5ArH). ^{13}C NMR δ: 14.8, 19.4, 29.7, 42.2, 42.8, 46.6, 47.9, 63.4, 66.3, 109.4, 120.1, 127.4, 128.1, 128.4, 130.5, 134.8, 140.2, 163.0, 167.4. $[\alpha]_D = -82.4$ (c 1.2, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.77; H, 7.71; N, 8.26.

4.11. (3*S*,6*S*)-4-Benzyl-3-isopropyl-6-methyl-1,4-diazabicyclo[4,4,0]decane-2,5-dione, 4e

Compound **4e** was obtained by alkylating **3d** with iodomethane and following the procedure used for **4b**. The pure product was isolated as an oil in about 80% yield. ^{1}H NMR δ: 0.85 (d, 3H, $J = 7$); 1.04 (d, 3H, $J = 7$); 1.23 (m, 1H); 1.52 (s, 3H); 1.58–1.80 (m, 4H); 2.1–2.36 (m, 2H); 2.57–2.8 (m, 2H); 3.68 (d, 1H, $J = 2.6$); 3.85 (d, 1H, $J = 15$); 4.5 (m, 1H); 5.36 (d, 1H, $J = 15$); 7.08–7.3 (m, 5ArH). ^{13}C NMR δ: 16.6, 19.2, 19.7, 23.4, 24.9, 30.5, 33.8, 36.9, 46.7, 59.6, 62.5, 127.7, 128.4, 135.5, 162.1, 170.0. $[\alpha]_D = -54.9$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.8; H, 8.3; N, 8.89.

4.12. (3*S*,6*S*)-6-Allyl-4-benzyl-3-isopropyl-1,4-diazabicyclo[4,4,0]decan-2,5-dione, 4f

Compound **4f** was obtained by alkylating **3d** with allyl bromide and following the procedure used for **4b**. The pure product was isolated as an oil in about 85% yield. ^{1}H NMR δ: 0.92 (d, 3H, $J = 7$); 1.12 (d, 3H, $J = 7$); 1.2 (m, 1H); 1.8 (m, 4H); 2.31 (m, 2H); 2.64 (m, 2H); 3.03 (dd, 1H, $J = 7$, 14.4); 3.78 (d, 1H, $J = 3$); 3.97 (d, 1H, $J = 15$); 4.57 (m, 1H); 5.06 (m, 2H); 5.06 (m, 2H); 7.2–7.4 (m, 5ArH). ^{13}C NMR δ: 16.3, 19.4, 19.9, 24.6, 30.2, 33.9, 36.8, 38.0, 47.0, 62.3, 62.8, 119.9, 127.6, 128.4, 128.7, 130.6, 135.0, 163.1, 168.3. $[\alpha]_D = -51.6$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.83; H, 8.31; N, 8.26.

4.13. (3*S*,11a*S*)-2-Benzyl-3-isopropyl-11a-methyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione, 4h

Compound **4h** was obtained by alkylating **3g** with iodomethane and following the procedure used for **4b**. The pure product was isolated as a solid in about 85% yield. ^{1}H NMR δ: 0.9 (d, 3H, $J = 7$); 1.13 (d, 3H, $J = 7$); 1.6 (s, 3H); 2.36 (m, 1H); 3.3 (q_{AB}, 2H, $J = 16.4$); 3.89 (d, 1H, $J = 3$); 3.99 (d, 1H, $J = 14.8$); 4.25 (d, 1H, $J = 18$); 5.38 (d, 1H, $J = 18$); 5.56 (d, 1H, $J = 14.8$); 7.10–7.44 (m, 9ArH). ^{13}C NMR δ: 16.8, 19.9, 24.7, 30.8, 38.9, 41.4, 47.1, 58.9, 63.2, 126.1, 126.7, 126.9, 128.0, 128.1, 128.9, 129.6, 130.5, 130.9, 162.9, 169.4. $[\alpha]_D = -118.3$ (c 0.7, $CHCl_3$). Mp 161–163 °C. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.45; H, 7.22; N, 7.7.

4.14. (3*S*,11a*S*)-11a-Allyl-2-benzyl-3-isopropyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione, 4i

Compound **4i** was obtained by alkylating **3g** with allyl bromide and following the procedure used for **4b**. The pure product was isolated as an oil in about 80% yield. ^{1}H NMR δ: 0.87 (d, 3H, $J = 7$); 1.11 (d, 3H, $J = 7$); 2.36 (m, 1H); 2.59 (dd, 1H, $J = 7$, 14.4); 2.73 (dd, 1H, $J = 7.4$, 14.4); 3.22 (br s, 2H); 3.89 (d, 1H, $J = 2.8$); 4.01 (d, 1H, $J = 14.2$); 4.17 (d, 1H, $J = 18$); 5.05 (m, 2H); 5.35 (d, 1H, $J = 18$); 5.48 (m, 2H); 7.17–7.42 (m, 9ArH). ^{13}C NMR δ: 16.4, 19.9, 30.4, 38.8, 40.2, 41.5, 47.2, 62.1, 62.8, 120.2, 126.2, 126.8, 126.9, 128.1, 128.7, 129.0, 129.5, 130.6, 130.9, 135.1, 163.8, 167.8. $[\alpha]_D = -103.4$ (c 1, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.45; H, 7.23; N, 7.2.

4.15. (3*S*,6*R*)-3-Isopropyl-8-methylene-1,4-diazabicyclo-[4,3,0]nonane-2,5-dione, 5a

A solution of intermediate **3a** (1.5 g, 5 mmol) in dry THF/*tert*-butanol 9:1 (20 mL) was added to liquid ammonia (ca. 50 mL) cooled at −50 °C. Then, Li (0.07 g, 10 mmol), in small pieces, was added to the reaction mixture under stirring. The addition of Li was controlled by monitoring with TLC in the presence of the starting material and stopped as soon as the reaction mixture became blue. The reaction was then rapidly quenched by the addition of NH_4Cl (1 g) and the cooling bath removed allowing the complete removal of NH_3. After addition of water, the aqueous solution was extracted with ethyl acetate and the organic solution evaporated to dryness under vacuum. The pure product was recovered as a solid in 80% yield after silica gel chromatography by eluting with hexane/ethyl acetate. ^{1}H NMR δ: 1.01 (d, 3H, $J = 7$); 1.07 (d, 3H, $J = 7$); 2.3 (m, 1H); 2.8 (m, 1H); 3.01 (m, 1H); 3.82 (dd, 1H, $J = 4.6$, 4.6); 3.99 (m, 1H); 4.29 (dd, 1H, $J = 7$, 11); 4.48 (m, 1H); 5.16 (m, 2H); 6.27 (br s, 1H). ^{13}C NMR δ: 17.3, 18.9, 33.4, 36.2, 50.0, 57.9, 63.0, 109.3, 140.1, 165.0,

169.1. $[\alpha]_D = +135$ (*c* 0.4, $CHCl_3$). Mp 156–157 °C. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.3; H, 7.77; N, 13.5.

4.16. (3*S*,6*S*)-3-Isopropyl-6-methyl-8-methylene-1,4-diazabicyclo[4,3,0]nonane-2,5-dione, 5b

Compound **5b** was obtained starting from **4b** and following the procedure previously described for **5a**. The product was recovered as a wax in 80% yield. ^{1}H NMR δ: 0.9 (d, 3H, $J = 7$); 1.09 (d, 3H, $J = 7$); 1.45 (s, 3H); 2.65 (m, 1H); 2.96 (m, 1H); 3.97 (m, 1H); 4.04 (m, 1H); 4.38 (m, 1H); 5.17 (m, 2H); 6.11 (br s, 1H). ^{13}C NMR δ: 15.8, 19.0, 23.6, 28.9, 43.0, 48.9, 59.9, 110.2, 140.2, 164.3, 172.4. HPLC-MS: 223.3 (M^++1), 245.3 (M^++Na). The product was not isolated in sufficiently pure form to measure the specific rotation.

4.17. (3*S*,6*R*)-3-Isopropyl-1,4-diazabicyclo[4,4,0]decane-2,5-dione, 5d

The pure product was isolated as a wax in 80% yield starting from **3d** and following the procedure used for **5a**. ^{1}H NMR δ: 0.89 (d, 3H, $J = 7$); 1.05 (d, 3H, $J = 7$); 1.41–1.63 (m, 3H); 1.76 (m, 1H); 2.05 (m, 1H); 2.37–2.61 (m, 3H); 3.87 (m, 1H); 3.95 (m, 1H); 4.75 (m, 1H); 6.19 (br s, 1H). ^{13}C NMR δ: 15.7, 18.6, 24.2, 24.4, 31.1, 32.8, 42.4, 58.1, 59.9, 164.4, 168.5. HPLC-MS: 211.3 $[M+1]^+$, 233.3 $[M+Na]^+$. The product was not isolated in sufficiently pure form to measure the specific rotation.

4.18. (3*S*,6*S*)-3-Isopropyl-6-methyl-1,4-diazabicyclo-[4,4,0]decane-2,5-dione, 5e

Compound **5e** was obtained starting from **4e** and following the procedure previously described for **5a**. The pure product was recovered as an oil in 85% yield. ^{1}H NMR δ: 0.77 (d, 3H, $J = 7$); 0.96 (d, 3H, $J = 7$); 1.18–1.8 (m, 5H); 1.46 (s, 3H); 2.1 (m, 1H); 2.47 (m, 1H); 2.59–2.8 (m, 1H); 3.83 (br s, 1H); 4.53 (m, 1H); 7.67 (br s, 1H). ^{13}C NMR δ: 15.5, 18.3, 19.1, 32.3, 24.6, 31.5, 34.2, 37.3, 58.8, 58.9, 164.6, 172.2. $[\alpha]_D = -65$ (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.03; H, 9.02; N, 12.53.

4.19. (3*S*,11a*S*)-3-Isopropyl-11a-methyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione, 5h

Compound **5h** was obtained starting from **4h** and following the procedure previously described for **5a**. The pure product was recovered as a solid in 80% yield. ^{1}H NMR δ: 0.89 (d, 3H, $J = 7$); 1.09 (d, 3H, $J = 7$); 1.52 (s, 3H); 2.59 (m, 1H); 3.21 (q_{AB}, 2H, $J = 16$); 4.06 (br s, 1H); 4.36 (d, 1H, $J = 18$); 5.35 (d, 1H, $J = 18$); 6.61 (br s, 1H); 7.15–7.4 (m, 4ArH). ^{13}C NMR δ: 15.7, 18.7, 20.0, 31.7, 39.2, 42.3, 58.4, 59.7, 126.0, 126.9, 127.0, 129.4, 130.6, 130.8, 164.8, 171.3. $[\alpha]_D = -164.4$ (*c* 0.9, $CHCl_3$). Mp 184–186 °C. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.4; N, 10.29. Found: C, 70.74; H, 7.38; N, 10.25.

4.20. (3*S*,6*S*)-3-Isopropyl-5-ethoxy-8-methylene-1,4-diazabicyclo[4,3,0]-4-nonen-2-one, 6a

Intermediate **5a** (2.08 g, 10 mmol) was treated with Et_3OBF_4 (2.47 g, 13 mmol) dissolved in dry CH_2Cl_2 (15 mL) and the procedure already described was followed.[8,9] After the chromatographic elution with hexane/ethyl acetate, the product was recovered as an oil in 80% yield. ^{1}H NMR δ: 088 (d, 3H, $J = 7$); 1.06 (d, 3H, $J = 7$); 1.31 (t, 3H, $J = 7$); 2.27 (m, 1H); 2.58 (m, 1H); 2.87 (dd, 1H, $J = 6.6, 15.4$); 3.85 (m, 1H); 4.04–4.27 (m, 4H); 4.52 (m, 1H); 5.11 (m, 2H). ^{13}C NMR δ: 13.2, 16.8, 18.4, 32.7, 36.2, 48.0, 55.4, 60.5, 65.7, 107.7, 140.5, 158.3, 167.1. HPLC-MS: 237.3 $[M+1]^+$, 258.3 $[M+Na]^+$. The product was not isolated in sufficiently pure form to measure the specific rotation.

4.21. (3*S*,6*S*)-3-Isopropyl-6-methyl-5-ethoxy-8-methylene-1,4-diazabicyclo[4,3,0]-4-nonen-2-one, 6b

Compound **6b** was obtained starting from **5b** and following the procedure described for **6a**. After the chromatographic elution with hexane/ethyl acetate, the pure product was recovered as an oil in 85% yield. ^{1}H NMR δ: 071 (d, 3H, $J = 7$); 1.1 (d, 3H, $J = 7$); 1.27 (t, 3H, $J = 7$); 2.48–2.79 (m, 3H), 3.79 (d, 1H, $J = 2.6$); 3.9 (m, 1H); 4.18 (m, 2H); 4.37 (m, 1H); 5.11 (m, 2H). ^{13}C NMR δ: 13.8, 16.0, 19.7, 22.8, 28.9, 43.0, 47.4, 60.9, 61.6, 62.8, 109.1, 141.2, 162.3, 167.5. HPLC-MS: 251.3 $[M+1]^+$, 273.3 $[M+Na]^+$. The product was not isolated in sufficiently pure form to measure the specific rotation.

4.22. (3*S*,6*R*)-3-Isopropyl-5-ethoxy-1,4-diazabicyclo-[4,4,0]-4-decen-2-one, 6d

Compound **6d** was obtained as an oil in 80% yield starting from **5d** and following the procedure used for **6a**. ^{1}H NMR δ: 0.71 (d, 3H, $J = 7$); 1.11 (d, 3H, $J = 7$); 1.31 (t, 3H, $J = 7$); 1.37–1.76 (m, 4H); 1.95 (m, 1H); 2.25 (m, 1H); 2.33–2.6 (m, 2H); 3.82 (m, 1H); 3.97 (dd, 1H, $J = 2.4, 3$); 4.05–4.25 (m, 2H); 4.78 (m, 1H). ^{13}C NMR δ: 13.8, 15.8, 19.2, 23.7, 24.3, 30.6, 31.9, 41.2, 55.5, 60.4, 62.4, 157.4, 167.3. $[\alpha]_D = -53.3$ (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.3; N, 11.75. Found: C, 65.23; H, 9.33; N, 11.8.

4.23. (3*S*,6*S*)-3-Isopropyl-6-methyl-5-ethoxy-1,4-diazabicyclo[4,4,0]-4-decen-2-one, 6e

Compound **6e** was obtained starting from **5e** and following the procedure described for **6a**. After chromatographic elution with hexane/ethyl acetate, the pure product was recovered as an oil in 80% yield. ^{1}H NMR δ: 0.7 (d, 3H, $J = 7$); 1.09 (d, 3H, $J = 7$); 1,26 (t, 3H, $J = 7$); 1.2–1.8 (m, 5H); 1.48 (s, 3H); 1.97–2.14 (m, 1H); 2.56 (m, 1H); 2.71 (m, 1H); 3.89 (dd, 1H, $J = 1.2, 3.4$); 3.98–4.28 (m, 2H); 4.65 (m, 1H). ^{13}C NMR δ: 14.1, 16.3, 19.4, 19.7, 21.1, 25.2, 31.8, 34.7, 36.3, 57.0, 60.6, 62.2, 161.1, 168.1. $[\alpha]_D = -71.4$ (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.1. Found: C, 66.75; H, 9.55; N, 11.07.

4.24. (3*S*,11a*S*)-1-Ethoxy-3-isopropyl-11a-methyl-3,6,11,11a-tetrahydro-pyrazino[1,2-*b*]isoquinolin-4-one, 6h

Compound **6h** was obtained starting from **5h** and following the procedure described for **6a**. After chromatographic elution with hexane/ethyl acetate, the pure product was recovered as an oil in 90% yield. ^{1}H NMR δ: 0.7 (d, 3H, $J = 7$); 1.13 (d, 3H, $J = 7$); 1.36 (t, 3H, $J = 7$); 1.43 (s, 3H); 2.58 (m, 1H); 3.11 (q_{AB}, 2H, $J = 16.2$); 4.04 (d, 1H, $J = 2.8$); 4.10–4.39 (m, 3H); 5.43 (d, 1H, $J = 18$); 7.1–7.3 (m, 4ArH). ^{13}C NMR δ: 14.2, 16.3, 19.6, 22.3, 31.9, 39.4, 40.7, 56.0, 61.0, 62.8, 126.1, 126.6, 129.2, 130.8, 131.0, 160.2, 168.3. $[\alpha]_D = -162.8$ (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, 71.7; H, 8.07; N, 9.35.

4.25. (2*R*,2′*S*)-1-(2′-Amino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-carboxylic acid ethyl ester hydrochloride, 7a

To a solution of **6a** (1.18 g, 5 mmol) in ethanol (40 mL), 0.5 M HCl (20 mL) was added and the reaction mixture stirred at room temperature for about 12 h monitoring by TLC. The hydroalcoholic solution was evaporated in vacuo to dryness and the intermediate hydrochloride isolated as a wax in 95% yield. ^{1}H NMR (CD_3OD) δ: 1.06 (d, 3H, $J = 7$); 1.14 (d, 3H, $J = 7$); 1.29 (t, 3H, $J = 7$); 2.3 (m, 1H); 2.66 (m, 1H); 3.09 (m, 1H); 4.12–4.26 (m, 3H); 4.38 (m, 2H); 4.68 (dd, 1H, $J = 2.6, 10$); 5.15 (m, 2H). ^{13}C NMR (CD_3OD) δ: 14.4, 17.3, 19.2, 30.6, 36.1, 52.3, 57.8, 60.4, 62.6, 109.6, 143.2, 168.9, 172.9. IR ($CHCl_3$, cm^{-1}): 1660 ($\nu_{NC=O}$), 1732 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). HPLC-MS: 291.8 $[M+1]^+$, 313.8 $[M+Na]^+$. The product was not isolated in sufficiently pure form to measure the specific rotation.

4.26. (2*S*,2′*S*)-1-(2′-Amino-3′-methyl-butyryl)-4-methylene-pyrrolidine-2-methyl-2-carboxylic acid ethyl ester hydrochloride, 7b

Compound **7b** was obtained starting from **6b** and following the procedure used for **7a**. The product was isolated as a wax in 95% yield. ^{1}H NMR (CD_3OD) δ: 1.09 (d, 3H, $J = 7$); 1.18 (d, 3H, $J = 7$); 1.27 (t, 3H, $J = 7$); 1.53 (s, 3H); 2.27 (m, 1H); 2.58 (d, 1H, $J = 15$); 2.94 (m, 1H); 3.99 (d, 1H, $J = 5.6$); 4.18 (m, 2H); 4.4 (m, 2H); 5.18 (m, 2H). ^{13}C NMR (CD_3OD) δ: 14.7, 17.7, 19.4, 21.2, 31.1, 45.9, 53.1, 58.2, 62.9, 68.3, 110.2, 143.0, 168.6, 174.1. $[\alpha]_D = -12.2$ (c 0.4, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1659 ($\nu_{NC=O}$), 1735 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). Anal. Calcd for $C_{14}H_{25}ClN_2O_3$: C, 55.16; H, 8.27; N, 9.19. Found: C, 55.35; H, 8.24; N, 9.17.

4.27. (2*R*,2′*S*)-1-(2′-Amino-3′-methyl-butyryl)-piperidine-2-carboxylic acid ethyl ester hydrochloride, 7d

Compound **7d** was obtained as a solid in 95% yield starting from **6d** and following the procedure used for **7a**. ^{1}H NMR (CD_3OD) δ: 1.03 (d, 3H, $J = 7$); 1.16 (d, 3H, $J = 7$); 1.31 (t, 3H, $J = 7$); 1.49 (m, 2H); 1.77 (m, 3H), 2.1–2.4 (m, 2H); 3.42 (m, 1H); 3.85 (m, 1H); 4.24 (q, 2H, $J = 7$); 4.4 (d, 1H, $J = 4.4$); 5.21 (m, 1H). ^{13}C NMR (CD_3OD) δ: 14.9, 17.3, 19.6, 22.0, 26.3, 28.0, 31.3, 45.3, 54.6, 56.8, 62.9, 170.2, 172.2. $[\alpha]_D = +94.5$ (c 1, $CHCl_3$). Mp 151–152 °C. IR ($CHCl_3$, cm^{-1}): 1653 ($\nu_{NC=O}$), 1729 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). Anal. Calcd for $C_{13}H_{25}ClN_2O_3$: C, 53.33; H, 8.61; N, 9.57. Found: C, 53.5; H, 8.58; N, 9.55.

4.28. (2*S*,2′*S*)-1-(2′-Amino-3′-methyl-butyryl)-piperidine-2-methyl-2-carboxylic acid ethyl ester hydrochloride, 7e

Compound **7e** was obtained starting from **6e** and following the procedure used for **7a**. The pure product was isolated as an oil in 95% yield. ^{1}H NMR δ: 1.08 (d, 3H, $J = 7$); 1.16 (d, 3H, $J = 7$); 1.26 (t, 3H, $J = 7$); 1.5 (s, 3H); 1.58–1.97 (m, 6H); 2.23 (m, 1H); 3.33 (m, 1H); 3.8 (m, 1H); 3.98–4.27 (m, 2H); 4.29 (d, 1H, $J = 5$). ^{13}C NMR δ: 14.4, 17.2, 18.3, 18.8, 19.0, 24.5, 31.3, 35.2, 43.5, 56.8, 62.0, 62.2, 170.1, 175.4. $[\alpha]_D = +70.6$ (c 0.7, HCl 1 M). IR ($CHCl_3$, cm^{-1}): 1652 ($\nu_{NC=O}$), 1728 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). Anal. Calcd for $C_{14}H_{27}ClN_2O_3$: C, 54.8; H, 8.87; N, 9.13. Found: C, 54.7; H, 8.9; N, 9.16.

4.29. (3*S*,2′*S*)-2-(2′-Amino-3′-methyl-butyryl)-3-methyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid ethyl ester hydrochloride, 7h

Compound **7h** was obtained starting from **6h** and following the procedure used for **7a**. The pure product was isolated as a wax in 95% yield. ^{1}H NMR δ: 1.12 (t, 3H, $J = 7$); 1.13 (d, 3H, $J = 7$); 1.26 (d, 3H, $J = 7$); 1.35 (s, 3H); 2.4 (m, 1H); 2.98 (q_{AB}, 2H, $J = 15$); 3.94–4.37 (m, 2H); 4.62 (m, 1H); 4.73 (q_{AB}, 2H, $J = 14.6$); 7.06–7.43 (m, 4ArH); 8.47 (br s, 3H). ^{13}C NMR δ: 13.9, 17.1, 19.2, 20.9, 29.4, 40.2, 46.4, 56.2, 61.1, 62.0, 126.3, 127.0, 127.2, 127.9, 133.2, 133.9, 167.4. $[\alpha]_D = -26.4$ (c 1.2, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1655 ($\nu_{NC=O}$), 1730 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). Anal. Calcd for $C_{18}H_{27}ClN_2O_3$: C, 60.92; H, 7.67; N, 7.89. Found: C, 61.15; H, 7.65; N, 7.87.

4.30. (3*R*,6*S*)-1-Benzyl-5-ethoxy-6-isopropyl-3-methyl-3,6-dihydro-1*H*-pyrazin-2-one, 8b

Synthesis and spectroscopic data are reported in Ref. 2.

4.31. (3*R*,6*S*)-3-Allyl-1-benzyl-5-ethoxy-6-isopropyl-3,6-dihydro-1*H*-pyrazin-2-one, 8c

Synthesis and spectroscopic data are reported in Ref. 2.

4.32. (3*R*,6*R*)-1-Benzyl-5-ethoxy-3-methyl-6-isopropyl-3-methyl-3,6-dihydro-1*H*-pyrazin-2-one, 9b

Synthesis and spectroscopic data are reported in Ref. 2.

4.33. (3*R*,6*S*)-1-Benzyl-5-ethoxy-3-(4-chlorobutyl)-6-isopropyl-3-methyl-3,6-dihydro-1*H*-pyrazin-2-one, 9e

Compound **9e** was obtained starting from **8b** and following the procedure employed to synthesize **2**.

1-Chloro-4-iodobuatane was used as the alkylating reagent and the pure product was obtained as an oil in 80% yield. ^{1}H NMR δ: 0.95 (d, 3H, J = 7); 1.07 (d, 3H, J = 7); 1.16 (m, 1H); 1.26 (t, 3H, J = 7.4); 1.47 (s, 3H); 1.56 (m, 1H); 1.75 (m, 2H); 2.07 (m, 1H); 2.23 (m, 1H); 3.13 (t, 2H, J = 7); 3.78 (d, 1H, J = 2.6); 3.89 (d, 1H, J = 15); 4.1 (m, 2H); 5.53 (d, 1H, J = 15); 7.2–7.42 (m, 5ArH). ^{13}C NMR δ: 7.0, 14.0, 17.1, 20.3, 28.7, 29.5, 33.2, 42.0, 46.3, 60.2, 60.5, 60.9, 127.4, 128.3, 128.5, 135.8, 155.8, 172.0. $[\alpha]_D = -11.9$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{31}ClN_2O_2$: C, 66.56; H, 8.25; N, 7.39. Found: C, 66.33; H, 8.22; N, 7.42.

4.34. (3*R*,6*S*)-1-Benzyl-5-ethoxy-3-(2-bromomethyl-benzyl)-6-isopropyl-3-methyl-3,6-dihydro-1*H*-pyrazin-2-one, 9h

Compound **9h** was obtained starting from **8b** and following the procedure employed to synthesize **2**. α,α′-Dibromo-*o*-xylene was used as alkylating reagent and the pure product was obtained as an oil in 90% yield. ^{1}H NMR δ: 0.87 (d, 3H, J = 7); 0.94 (d, 3H, J = 7); 1.27 (t, 3H, J = 7); 1.68 (s, 3H); 2.1 (m, 1H); 3.09 (d, 1H, J = 13.6); 3.34 (d, 1H, J = 2.4); 3.64 (d, 1H, J = 13.6); 3.75 (d, 1H, J = 15); 3.9–4.4 (m, 2H); 4.83 (s, 2H); 5.43 (d, 1H, J = 15); 6.58 (m, 2ArH); 7.08–7.18 (m, 7ArH). ^{13}C NMR δ: 14.0, 16.8, 20.0, 28.9, 29.8, 33.1, 43.6, 45.6, 59.8, 60.3, 62.0, 126.5, 127.0, 127.6, 127.9, 128.9, 130.2, 131.5, 134.7, 136.5, 137.3, 155.9, 170.9. $[\alpha]_D = +12.2$ (c 1.1, $CHCl_3$). Anal. Calcd for $C_{25}H_{31}BrN_2O_2$: C, 63.69; H, 6.63; N, 5.94. Found: C, 63.75; H, 6.61; N, 5.93.

4.35. (3*R*,6*S*)-3-Allyl-1-benzyl-5-ethoxy-3-(2-bromomethyl-benzyl)-6-isopropyl-3,6-dihydro-1*H*-pyrazin-2-one, 9i

Compound **9i** was obtained starting from **8c** and following the procedure employed to synthesize **2**. α,α′-Dibromo-*o*-xylene was used as the alkylating reagent and the product was obtained as an oil in 80% yield. ^{1}H NMR δ: 0.87 (d, 3H, J = 7); 0.96 (d, 3H, J = 7); 1.29 (t, 3H, J = 7.2); 2.08 (m, 1H); 2.77 (dd, 1H, J = 6.9, 13.8); 2.87 (dd, 1H, J = 7.8, 13.8); 3.21 (d, 1H, J = 13.5); 3.32 (d, 1H, J = 2.7); 3.58 (d, 1H, J = 13.8); 3.92 (d, 1H, J = 15); 4.02 (m, 1H); 4.29 (m, 1H); 4.82 (br s, 2H); 5.27 (m, 3H); 6.11 (m, 1H); 6.7 (m, 2ArH); 7.16–7.4 (m, 7ArH). ^{13}C NMR δ: 14.1, 16.8, 20.4, 29.1, 33.1, 41.1, 46.6, 46.7, 60.2, 60.6, 64.7, 118.4, 126.7, 127.1, 127.8, 128.1, 128.3, 130.4, 131.6, 133.5, 135.1, 136.6, 137.6, 156.5, 170.4. HPLC-MS: 497.2 and 499.2 $[M+1]^+$, 519.2 and 521.2 $[M+Na]^+$. The product was not isolated in sufficiently pure form to measure the specific rotation.

4.36. (3*S*,6*R*)-4-Benzyl-3-isopropyl-6-methyl-8-methylene-1,4-diazabicyclo[4,3,0]nonane-2,5-dione, 10b

Compound **10b** was obtained starting from **9b** and following the procedure used to prepare **3a**. The pure product was obtained as an oil in 90% yield. ^{1}H NMR δ: 1.07 (d, 3H, J = 6.9); 1.18 (d, 3H, J = 6.9); 1.58 (s, 3H); 2.25 (m, 1H); 2.75 (br s, 2H); 3.72 (d, 1H, J = 6.2); 3.92 (m, 1H); 3.94 (d, 1H, J = 14.8); 4.61 (m, 1H); 5.13–5.23 (m, 2H); 5.48 (d, 1H, J = 14.8); 7.16–7.42 (m, 5ArH). ^{13}C NMR δ: 18.6, 20.0, 24.5, 31.5, 45.6, 47.9, 48.4, 63.8, 65.6, 109.2, 127.3, 128.4, 135.5, 140.1, 163.1, 169.3. $[\alpha]_D = -16.9$ (c 1.6, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.35; H, 7.72; N, 8.96.

4.37. (3*S*,6*R*)-4-Benzyl-3-isopropyl-6-methyl-1,4-diazabicyclo[4,4,0]decane-2,5-dione, 10e

Compound **10e** was obtained starting from **9e** and following the procedure used to prepare **3d**. The pure product was obtained as an oil in 80% yield. ^{1}H NMR δ: 0.95 (d, 3H, J = 7); 1.12 (d, 3H, J = 7); 1.22–1.85 (m, 5H); 1.65 (s, 3H); 2.17–2.36 (m, 2H); 2.7 (m, 1H); 3.78 (d, 1H, J = 3.2); 3.9 (d, 1H, J = 15); 4.66 (m, 1H); 5.44 (d, 1H, J = 15); 7.18–7.42 (m, 5ArH). ^{13}C NMR δ: 17.7, 20.1, 21.1, 24.4, 31.0, 37.1, 37.5, 47.4, 59.7, 63.2, 127.6, 127.8, 128.7, 135.7, 162.8, 170.5. $[\alpha]_D = -44.2$ (c 0.9, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.32; H, 8.35; N, 8.92.

4.38. (3*S*,11a*R*)-2-Benzyl-3-isopropyl-11a-methyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione, 10h

Compound **10h** was obtained starting from **9h** and following the procedure used to prepare **3g**. The pure product was obtained as an oil in 80% yield. ^{1}H NMR δ: 1.05 (d, 3H, J = 7); 1.22 (d, 3H, J = 7); 1.61 (s, 3H); 2.37 (m, 1H); 3.1 (d, 1H, J = 15.9); 3.37 (d, 1H, J = 15.9); 3.89 (d, 1H, J = 3.3); 3.99 (d, 1H, J = 15); 4.25 (d, 1H, J = 18); 5.54 (d, 1H, J = 18); 5.58 (d, 1H, J = 15); 7.17–7.42 (m, 9ArH). ^{13}C NMR δ: 17.9, 20.2, 22.7, 31.4, 41.7, 47.6, 58.7, 63.5, 125.8, 126.8, 126.9, 128.0, 128.9, 129.4, 130.3, 131.2, 135.6, 163.5, 169.8. $[\alpha]_D = +29.6$ (c 0.8, $CHCl_3$). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.91; H, 7.26; N, 7.75.

4.39. (3*S*,11a*R*)-2-Benzyl-3-isopropyl-11a-allyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione, 10i

Compound **10i** was obtained starting from **9i** and following the procedure used to prepare **3g**. The pure product was obtained as a solid in 85% yield. ^{1}H NMR δ: 1.06 (d, 3H, J = 7); 1.21 (d, 3H, J = 7); 2.35 (m, 1H); 2.56 (dd, 1H, J = 7.4, 14.2); 2.81 (dd, 1H, J = 7.6, 14.2); 3.04 (d, 1H, J = 16); 3.36 (d, 1H, J = 16); 3.84 (d, 1H, J = 3.6); 4.06 (d, 1H, J = 15); 4.2 (d, 1H, J = 18); 5.09 (m, 2H); 5.51 (d, 1H, J = 15); 5.57 (d, 1H, J = 18); 5.9 (m, 1H); 7.15–7.43 (m, 9ArH). ^{13}C NMR δ: 18.4, 20.7, 31.6, 39.4, 40.3, 41.5, 48.1, 61.9, 63.6, 119.4, 125.8, 126.9, 127.0, 127.8, 127.9, 128.9, 129.3, 130.8, 131.1, 132.4, 135.8, 164.4, 168.1. $[\alpha]_D = +16.4$ (c 0.9, $CHCl_3$). Mp 107–109 °C. Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.01; H, 7.28; N, 7.23.

4.40. (3*S*,6*R*)-3-Isopropyl-6-methyl-8-methylene-1,4-diazabicyclo[4,3,0]nonan-2,5-dione, 11b

Compound **11b** was obtained starting from **10b** and following the procedure used for **5b**. The pure product was isolated as a solid in 85% yield ^{1}H NMR δ: 1.03 (d, 3H, $J = 7$); 1.1 (d, 3H, $J = 7$); 1.53 (s, 3H); 2.25 (m, 1H); 2.62–2.91 (m, 2H); 3.81 (dd, 1H, $J = 3.2, 5.8$); 3.95 (m, 1H); 4.6 (m, 1H); 5.22 (m, 2H); 6.3 (br s, 1H). ^{13}C NMR δ: 18.1, 19.3, 25.6, 32.9, 44.4, 49.0, 62.6, 63.8, 109.8, 140.0, 164.1, 171.8, 184.4. $[\alpha]_D = +100.9$ (*c* 0.8, $CHCl_3$). Mp 148–150 °C. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.6. Found: C, 64.61; H, 8.18; N, 12.63.

4.41. (3*S*,11a*R*)-1-Ethoxy-3-isopropyl-11a-allyl-3,6,11,11a-tetrahydro-pyrazino[1,2-*b*]isoquinolin-4-one, 11i

Compound **11i** was obtained starting from **10i** and following the procedure used for **5h**. The pure product was isolated as a solid in 85% yield. ^{1}H NMR δ: 0.97 (d, 3H, $J = 7$); 1.11 (d, 3H, $J = 7$); 2.58 (dd, 1H, $J = 7.8, 14.4$); 2.65 (m, 1H); 2.82 (dd, 1H, $J = 6.9, 14.4$); 3.22 (br s, 2H); 4.04 (m, 1H); 4.17 (d, 1H, $J = 18$); 5.16 (m, 2H); 5.7 (d, 1H, $J = 18$); 5.73 (m, 1H); 6.7 (br s, 1H); 7.13–7.33 (m, 4ArH). ^{13}C NMR δ: 17.0, 19.0, 31.3, 38.6, 39.2, 41.1, 59.9, 62.1, 120.0, 126.0, 126.9, 127.0, 129.4, 130.6, 130.9, 131.8, 164.3, 169.3. $[\alpha]_D = +84.7$ (*c* 0.4, $CHCl_3$). Mp 60–62 °C. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.32; H, 7.45; N, 9.43.

4.42. (3*S*,6*R*)-3-Isopropyl-6-methyl-5-ethoxy-8-methylene-1,4-diazabicyclo[4,3,0]-4-nonen-2-one, 12b

Compound **12b** was obtained starting from **11b** and following the procedure used for **6b**. The pure product was isolated as an oil in 80% yield. ^{1}H NMR δ: 0.94 (d, 3H, $J = 7$); 1.12 (d, 3H, $J = 7$); 1.31 (t, 3H, $J = 7$); 1.41 (s, 3H); 2.2 (m, 1H); 2.50–2.55 (m, 2H); 3.84 (m, 1H); 3.97 (d, 1H, $J = 5.6$); 4.05–4.35 (m, 2H); 4.64 (m, 1H); 5.15 (m, 2H). ^{13}C NMR δ: 14.1, 18.7, 20.0, 25.1, 33.0, 44.5, 47.9, 61.1, 62.0, 66.4, 109.2, 141.3, 161.2, 168.2. $[\alpha]_D = +104.9$ (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.34; H, 8.83; N, 11.15.

4.43. (3*S*,11a*R*)-1-Ethoxy-3-isopropyl-11a-allyl-3,6,11,11a-tetrahydro-pyrazino[1,2-*b*]isoquinolin-4-one, 12i

Compound **12i** was obtained starting from **11i** and following the procedure used for **6h**. The pure product was isolated as an oil in 85% yield. ^{1}H NMR δ: 0.78 (d, 3H, $J = 7$); 1.15 (d, 3H, $J = 7$); 1.35 (t, 3H, $J = 7$); 2.58 (m, 3H); 3.1 (s, 2H); 3.97 (d, 1H, $J = 3.4$); 4.06 (d, 1H, $J = 18$); 4.10–4.38 (m, 2H); 5.06 (m, 2H); 5.63 (m, 1H); 5.68 (d, 1H, $J = 18$); 7.03–7.25 (m, 4ArH). ^{13}C NMR δ: 14.2, 17.4, 19.9, 31.0, 37.6, 39.1, 39.6, 59.4, 60.8, 62.5, 119.2, 126.0, 126.5, 129.1, 130.7, 131.2, 132.3, 158.1, 167.8. $[\alpha]_D = +121.5$ (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.35; H, 8.06; N, 8.61.

4.44. (2*R*,2′*S*)-1-(2′-Amino-3′-methyl-butyryl)-4-methylene-pyrrolidin-2-methyl-2-carboxylic acid ethyl ester hydrochloride, 13b

Compound **13b** was obtained starting from **12b** and following the procedure used for **7b**. The pure product was isolated as a wax in 95% yield. ^{1}H NMR δ: 1.09 (d, 3H, $J = 7$); 1.17 (d, 3H, $J = 7$); 1.23 (t, 3H, $J = 7$); 1.53 (s, 3H); 2.3 (m, 1H); 2.53 (d, 1H, $J = 15.2$); 2.88 (d, 1H, $J = 15.2$); 4.21 (m, 4H); 4.66 (d, 1H, $J = 13.6$); 5.07 (d, 2H, $J = 15.2$); 8.45 (br s, 3H). ^{13}C NMR δ: 14.1, 17.3, 18.8, 21.3, 29.8, 44.5, 52.4, 56.5, 61.7, 66.6, 109.0, 140.9, 166.9, 172.7. $[\alpha]_D = +47.5$ (*c* 0.7, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1660 ($\nu_{NC=O}$), 1735 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). Anal. Calcd for $C_{14}H_{25}ClN_2O_3$: C, 55.16; H, 8.27; N, 9.19. Found: C, 54.91; H, 8.29; N, 9.23.

4.45. (3*R*,2′*S*)-2-(2′-Amino-3′-methyl-butyryl)-3-allyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid ethyl ester hydrochloride, 13i

Compound **13i** was obtained starting from **12i** and following the procedure used for **7h**. The pure product was isolated as a wax in 95% yield. ^{1}H NMR δ: 0.96 (t, 3H, $J = 7$); 1.1 (d, 3H, $J = 7$); 129 (d, 3H, $J = 7$); 2.37 (m, 1H); 2.83 (m, 2H); 3.09 (q_{AB}, 2H, $J = 15.4$); 4 (m, 2H); 4.63 (q_{AB}, 2H, $J = 15$); 4.79 (m, 1H); 5.03 (m, 2H); 5.72 (m, 1H); 7.01–7.43 (m, 4ArH). ^{13}C NMR δ: 13.9, 16.7, 19.3, 30.0, 36.9, 38.4, 47.6, 56.1, 61.3, 63.9, 119.5, 125.9, 127.4, 128.1, 132.7, 133.2, 133.8, 167.7, 172.6. $[\alpha]_D = +21.4$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1653 ($\nu_{NC=O}$ and $\nu_{C=C}$) 1729 (ν_{COOEt}), 2800–3000 (broad, νNH_3^+). Anal. Calcd for $C_{20}H_{29}ClN_2O_3$: C, 63.06; H, 7.67; N, 9.31. Found: C, 63.22; H, 7.65; N, 9.25.

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