

**STEREOSELECTIVE SYNTHESIS OF C-6 SUBSTITUTED PIPECOLIC ACID DERIVATIVES. FORMAL SYNTHESIS OF (+)-INDOLIZIDINE 167B AND (+)-INDOLIZIDINE 209D**

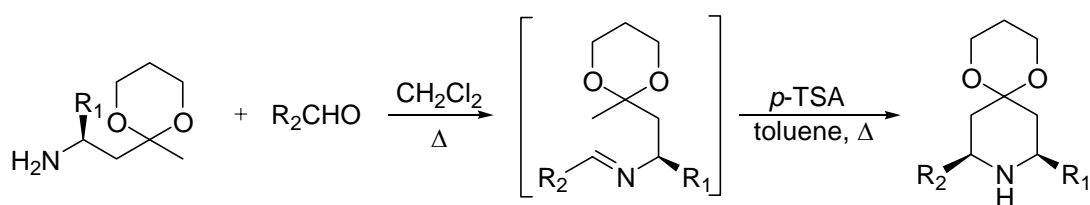
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**Abstract** – C-6 Substituted pipercolic acid derivatives were synthesized through two different pathways. The synthetic potential of each route was demonstrated by the formal synthesis of indolizidine *Dendrobates* alkaloids

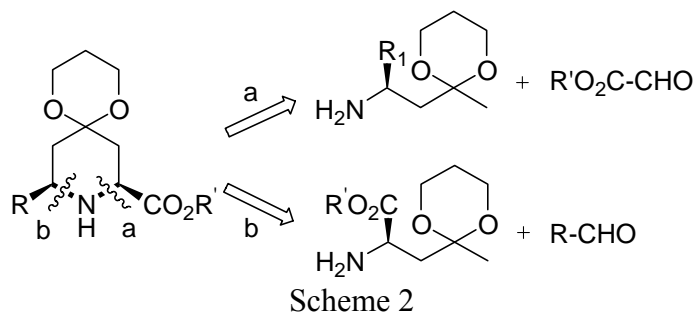
Pipecolic acid (piperidine-2-carboxylic acid) and in particular its C-4 oxygenated derivatives are naturally occurring nonproteinogenic amino acids found in a variety of biologically active compounds. For example, pipecolate residues are used in the elaboration of rigid analogues of NMDA receptor agonists<sup>1</sup> and antagonists,<sup>2</sup> or for the synthesis of inhibitors of HIV protease.<sup>3</sup> Moreover, substituted pipecolic acid derivatives have been used extensively as starting materials for the synthesis of natural and/or biologically active alkaloids containing the piperidine framework<sup>4</sup> For all these valuable reasons, the elaboration of various alkylpipecolic acid derivatives<sup>5</sup> has received considerable attention.<sup>6</sup>

We have recently described an efficient stereoselective route to various 2,6-disubstituted piperidines.<sup>7</sup> This approach, based on the use of achiral aldehydes in a Mannich-type reaction<sup>8</sup> with an  $\alpha$ -chiral amine, gives the 2,6-*cis*-isomers exclusively (Scheme 1).



The diastereoselectivity of this reaction can be explained by the preferred position of the asymmetric center in the transition state.<sup>7</sup> We wished to extend this methodology to the stereoselective synthesis of C-6 alkyl substituted pipecolic acid derivatives.<sup>9</sup> Two different strategies could be envisaged towards this goal : the first (pathway a) involves the condensation of an  $\alpha$ -chiral alkylamine with alkyl glyoxylate; the

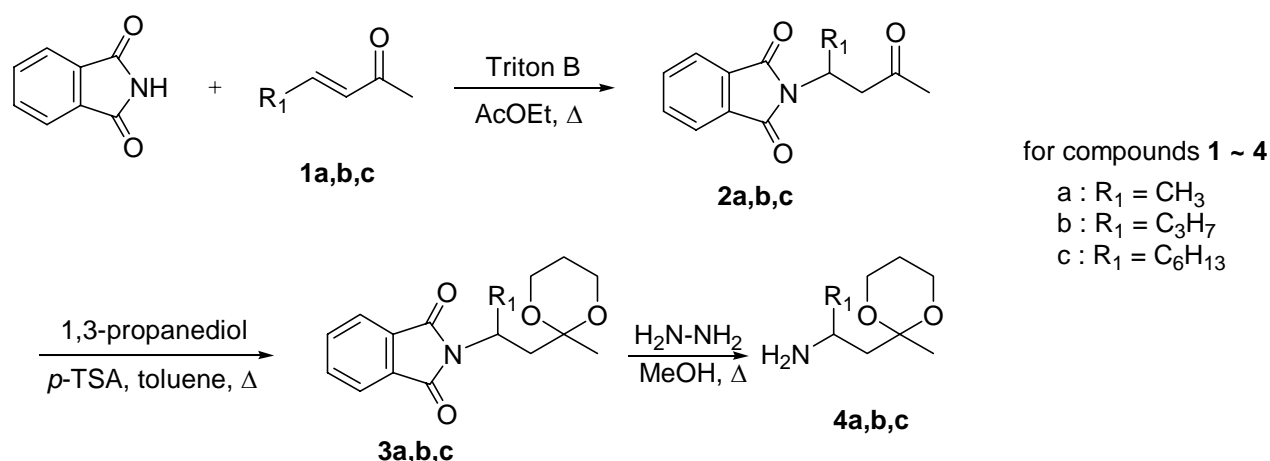
second (pathway b) involves an  $\alpha$ -chiral carboxyl amine, derived from a chiral amino acid, and an achiral aldehyde (Scheme 2).



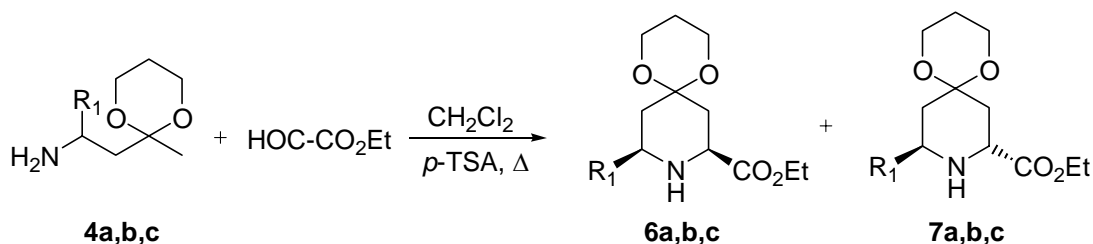
## DISCUSSION

### Pathway a analysis

Amines (**4a-c**) were easily prepared in good overall yield following the conventional three steps procedure<sup>10</sup> summarized in Scheme 3. Amine (+)-(**4a**)<sup>11</sup> was obtained in multigram scale by resolution with tartaric acid. The same procedure applied to amine (**4b**) was not so successful, since no crystallization occurred with tartaric acid. Changing the resolving agent to (2*R*,3*R*)-(-)-di-*O*-benzoyl tartaric acid induced precipitation of the salt and furnish (+)-**4b** whose purity could not exceed 90% (determined on the basis of the corresponding MTPA ester<sup>12</sup> by NMR spectrometry). Concerning resolution of amine (**4c**), all attempts with tartaric or substituted tartaric acid were unsuccessful.

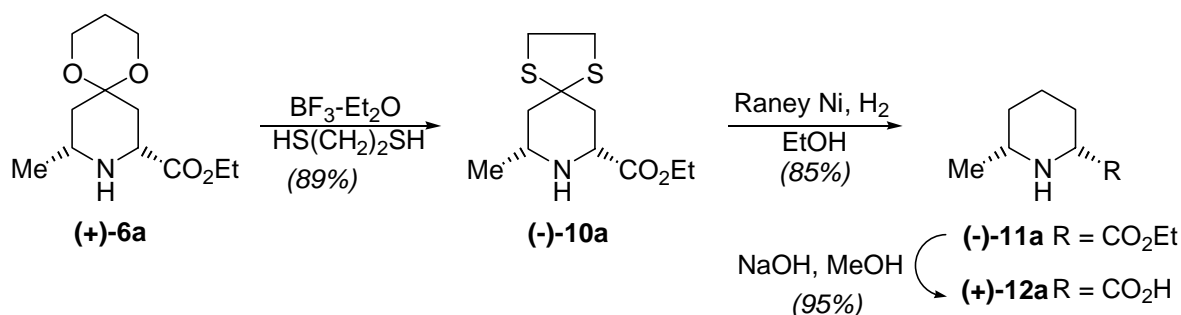


Amines (**4a-c**) were then engaged in the one-pot cyclisation procedure with freshly prepared ethyl glyoxylate (**5**).<sup>13</sup> The expected piperidines were isolated as a mixture of diastereoisomers (**6a-c**) and (**7a-c**) (de = 80-85%) which could be easily separated by flash chromatography (Scheme 4).



Scheme 4

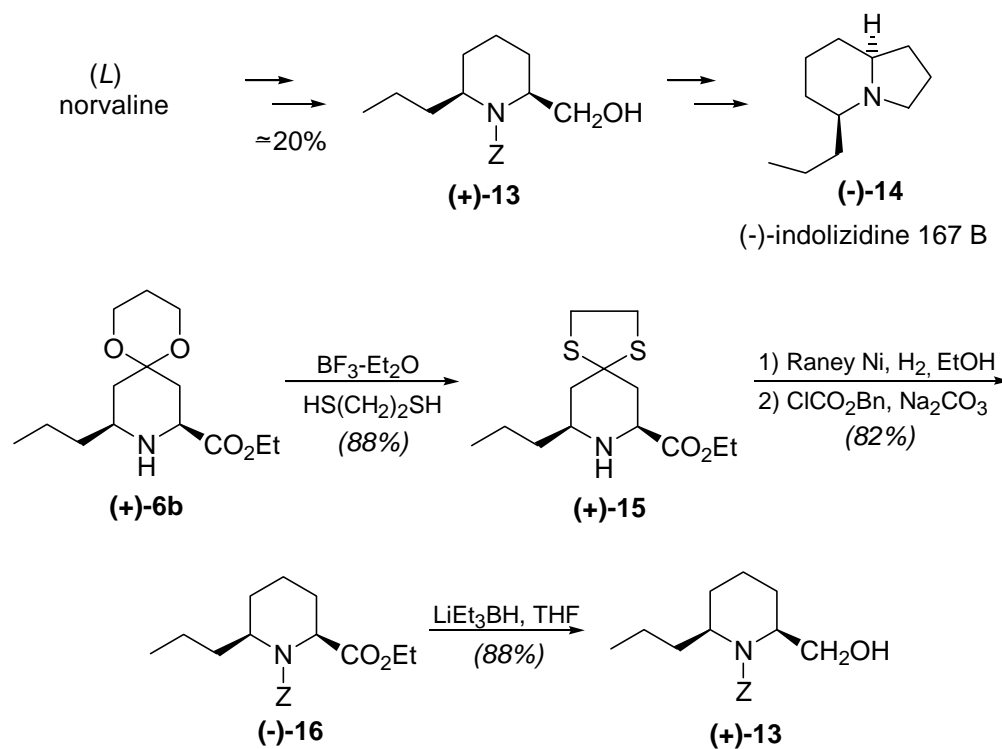
The relative configurations of compounds (+)-**(6a)** and (-)-**(7a)** (overall yield 83%) were established unambiguously from their spectral data and particularly from  $^1\text{H-NMR}$  spectral measurements. In compound (+)-**(6a)**, H-3ax (H-5ax respectively) gives a triplet ( $J = 12.5$  Hz) resulting of coupling with H-3eq and H-2 (H-5eq and H-6 respectively). These values are in accordance with an axial position for H-2 and H-6. On the other hand, the same measurements on compound (-)-**(7a)** gave for H-3ax a doublet of doublets ( $J = 13.5$  and  $6.5$  Hz) showing an equatorial position for H-2 while H-5ax still appeared as a triplet ( $J = 13.0$  Hz). These data confirm the axial position of the carboethoxy group, a result in agreement with those observed for the cyclohexane analogues.<sup>14</sup> Similar results were obtained from amine (+)-**(4b)** (overall yield 64%) and **(4c)** (70%). Treatment of compound (+)-**(6a)** with an excess of ethane dithiol in the presence of  $\text{BF}_3\text{-OEt}_2$  gave in 89% yield the dithiolane derivative (-)-**(10a)** which was quantitatively converted into the 6-methyl-ethyl pipercolate derivative (-)-**(11a)** by hydrogenolysis using W2 Raney nickel<sup>15</sup> in refluxing methanol. Subsequent saponification of the ester function furnished the 6-methyl pipercolic acid (+)-**(12a)** whose specific rotation,  $[\alpha]_{20}^D = +11.8^\circ$  ( $c$  1.1, HCl), was in excellent agreement with that previously described for its enantiomer.<sup>6d</sup> (Scheme 5).



Scheme 5

This value confirmed the stereochemistry and enantiomeric purity of compound (+)-**(6a)** and proved, that the entire procedure induced no racemisation. Thus, enantioselective preparation of more complex piperidine alkaloids could be envisaged. In order to demonstrate this, we decided to apply the methodology to the preparation of naturally occurring indolizidine alkaloids. (-)-Indolizidine 167B (-)-**(14)**<sup>16</sup> is an alkaloid obtained from the skin secretions of neotropical frogs of the genera *Dendrobates*. Among the various syntheses of this alkaloid,<sup>17</sup> two of them<sup>17a,c</sup> are quite similar with regards to the

starting material, the structure of the intermediate piperidinol and the annelation procedure. In the stereoselective synthesis of Momose and co-workers<sup>17c</sup> (-)-indolizidine 167 B (**14**) was obtained from *L*-norvaline through the sequence depicted in Scheme 6.



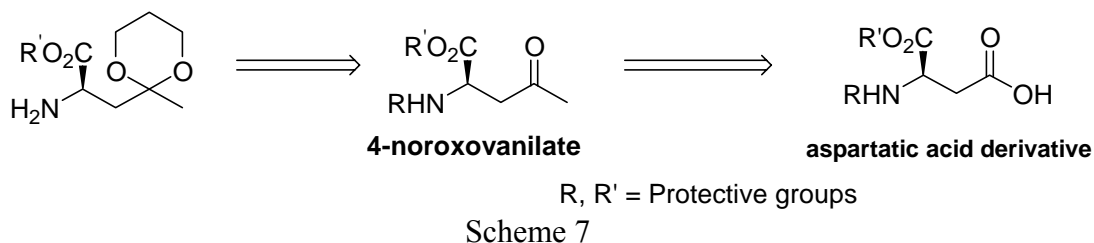
Scheme 6

The corner stone of this procedure is the obtention of amino alcohol (+)-**13** (20% from *L*-norvaline) which was obtained from a mixture of diastereomers separated by chromatography. In an effort to circumvent the first steps of this synthesis, we examined a more efficient access to compound (+)-**13**, starting from pipercolate (+)-**6b**. Transacetalation with ethane dithiol furnished in 88% yield the dithioderivative (+)-**15** which was subsequently reduced with W2 Raney nickel and *N*-protected with benzyl chloroformate to afford the pipercolate (-)-**16** in 82% yield for the two steps. Super-Hydride<sup>®</sup> reduction<sup>18</sup> of the ester function gave the desired piperidinol (+)-**13** (38% from amine (+)-**4b**) which showed spectral data (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR, MS) identical with those reported, except for the optical rotation which is slightly lower than those described ( $[\alpha]_{20}^{\text{D}} = +7.7^\circ$  (*c* 1.19, MeOH); lit.,<sup>17c</sup>  $[\alpha]_{20}^{\text{D}} = +9.3^\circ$  (*c* 1.28, MeOH) and due to the optical purity of amine (+)-**4b**, precursor of pipercolate (+)-**6b**) (Scheme 6).

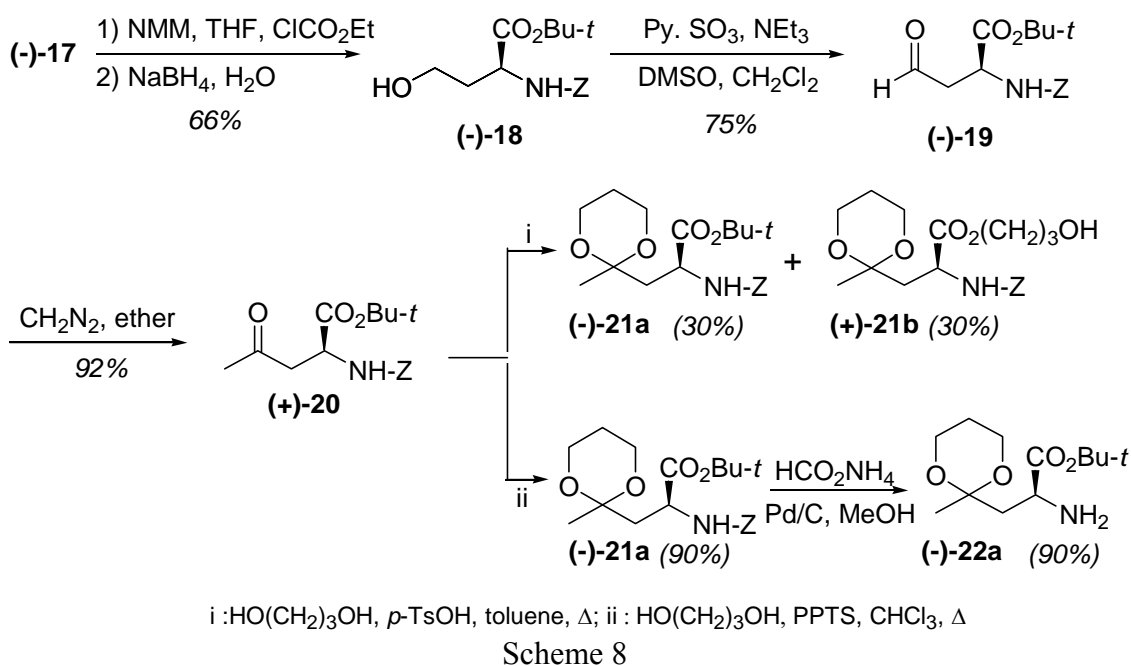
#### Pathway b analysis.

In this case, according to Scheme 2, the starting materials were an aldehyde and an  $\alpha$ -chiral carboxy amine. In the latter, the initial source of chirality could be the amino acid chiral pool. Retrosynthetic

analysis suggested that it could be obtained from 4-noroxovanilate, itself derived from aspartic acid derivative. (Scheme 7)

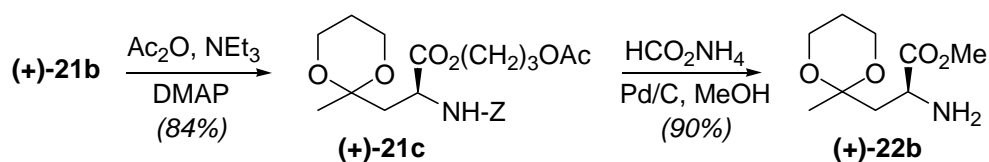


4-noroxovaline could be obtained from glycine,<sup>19</sup> serine,<sup>20</sup> or aspartic acid.<sup>21</sup> As the precursor, we chose aspartic acid since its use represented the simplest route in terms of modification of the side chain. The target molecule (-)-(22a) was prepared as described in Scheme 8 starting from *Z*-*L*-aspartic acid 1-*tert*-butyl ester (-)-(17).<sup>22</sup>

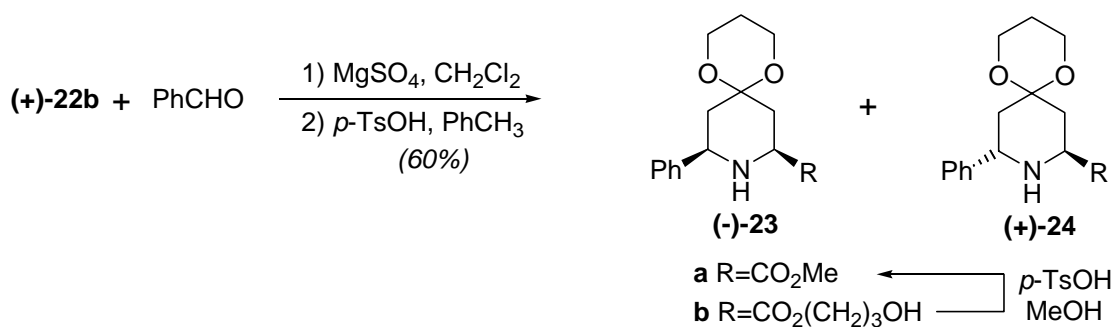


Reduction of the acid to the aldehyde was achieved in two steps : activation as a mixed anhydride then reduction with sodium borohydride to furnish primary alcohol (-)-(18). Subsequent oxidation using the Parikh-Doering procedure<sup>23</sup> gave the rather unstable aldehyde (-)-(19) whose treatment with an ethereal solution of diazomethane gave the desired methyl ketone (+)-(20) which showed spectral data identical with those reported.<sup>21f</sup> Further protection of the carbonyl function was performed in mild conditions (pyridinium *para*-toluenesulfonate (PPTS), CHCl<sub>3</sub>) since those traditionally used (*para*-toluenesulfonic acid (*p*-TSA), toluene) gave a mixture of desired compound (-)-(21a) and compound (+)-(21b) resulting from a transesterification reaction with 1,3- propanediol. Finally, hydrogenolysis of the benzyl carbamate with ammonium formate and palladium led to the free amine (-)-(22a) ([α]<sub>20</sub><sup>D</sup> = -3.8° (*c* 0.58, CHCl<sub>3</sub>))

which was obtained with a 18% overall yield from aspartic acid (Scheme 8). With target compound (-)-**(22a)** in hand, we attempted the condensation reaction with benzaldehyde. Unfortunately, we obtained a complex mixture from which no identifiable product could be isolated. As previously observed for the synthesis of (-)-**(22a)**, it seemed that *p*-TSA led predominantly to hydrolysis of the *tert*-butyl group. Attempts to modify the reactions conditions, by replacing *p*-TSA with PPTS or a Lewis acid were unsuccessful. In order to see if these hypothesis was correct, we decide to replace the *tert*-butyl ester by a methyl ester. Compound (+)-**(21b)** was first acetylated with acetic anhydride to give (+)-**(21c)**, then *N*-deprotected by hydrogenolysis to furnish in good overall yield the amine (+)-**(22b)** in which the ester function was, once again, transesterified by methanol (Scheme 9).

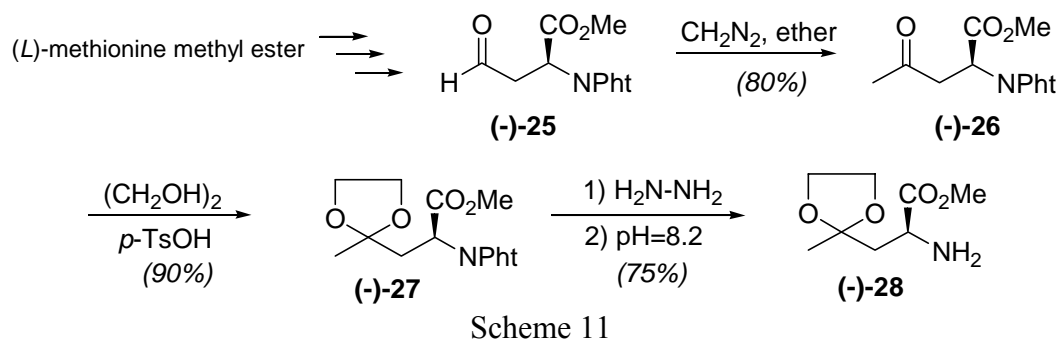


Treatment of amine (+)-**(22b)** with benzaldehyde in standard conditions, then produced in 61% yield, a mixture of four compounds (**(23a,b)** and **(24a,b)**) which were characterized as 2,6-*cis*- and 2,6-*trans*-piperidines (Scheme 10).

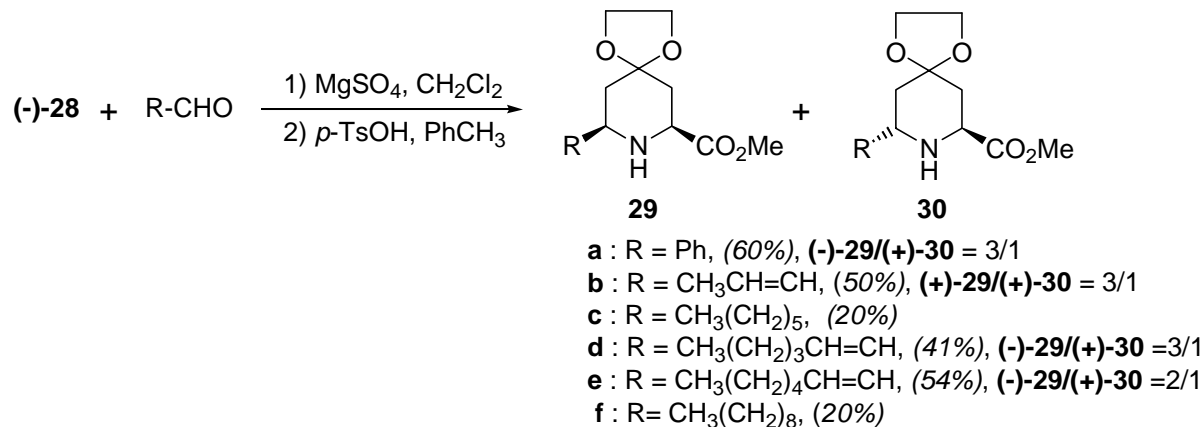


The structures and relative stereochemistry of **(23a,b)** and **(24a,b)** were determined as previously described, especially from <sup>1</sup>H-NMR spectral measurements. This result showed the feasibility of the reaction without a *tert*-butyl ester and the importance of changing the protective group of the carbonyl function. We thus decided to prepare amine (**(28)**), in which the dioxane protective group was replaced by a dioxolane. Since homologation of aldehyde (-)-**(19)** to methyl ketone (+)-**(20)** had proved efficient, we focused our efforts to the preparation of aldehyde (**(25)**)<sup>24</sup> by a process which could be conducted on a large scale. For this purpose we used a very recent report which described the synthesis of (-)-**(25)** starting from (*L*)-methionine methyl ester.<sup>25</sup> Thus, aldehyde (-)-**(25)** (ee = 92%) was treated with ethereal diazomethane solution to furnish methyl ketone (-)-**(26)**<sup>21d</sup> in a 80% yield. Protection of the carbonyl function was

achieved in classical conditions with ethylene glycol to give (-)-**27** which was subsequently submitted to hydrazonolysis, conducted under pH control in order to avoid saponification of the ester function, which led to amine (-)-**(28)** (Scheme 11).

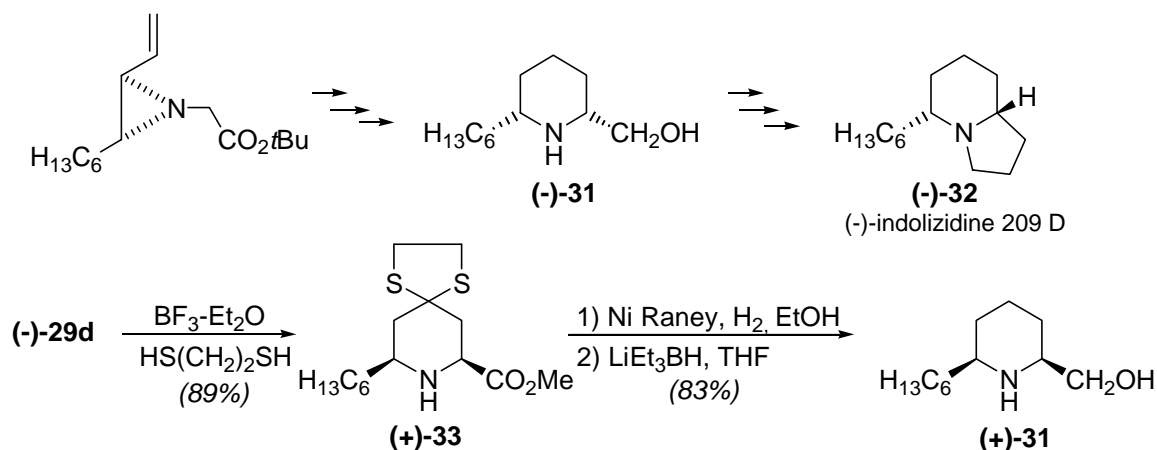


The optical purity of amine (-)-**(28)** was determined by derivatisation with either (*R*)-(+)- or (*S*)-(-)- $\alpha$ -methylbenzyl isocyanate<sup>26</sup> and was found to be 73% ee which confirmed a slight racemisation over the all process. Nevertheless, amine (-)-**(28)** was reacted with a variety of aldehydes in order to produce piperidines. Results are summarized in Scheme 12.



Scheme 12

These reactions involving various aldehydes were disappointing in terms of yield and stereoselectivity and could not be improved by changing reaction parameters (time, temperature, acid...). On the other hand, this approach could be an alternative route for the preparation of *trans*-6-pipecolic acid derivatives. As in pathway a we used this approach to prepare **31**, a valuable intermediate described by Somfai and co-worker in the synthesis of (-)-indolizidine 209D (-)-**(32)**,<sup>27</sup> another alkaloid isolated from neotropical frogs (*Dendrobatidae* family) (Scheme 13).



Scheme 13

Compound **(-)-29d** was transformed into dithiolane derivative **(+)-33**. Further hydrogenolysis with W2 Raney nickel gave a piperidine in which the double bond of the side chain was also reduced (Scheme 13). Finally, reduction of the ester function led to piperidinol **(+)-31** whose spectral data were identical with those previously described except for optical purity ( $[\alpha]_{20}^D = +2.9^\circ$  ( $c$  0.73,  $\text{CHCl}_3$ ); lit.,<sup>27</sup> $[\alpha]_{20}^D = -3.95^\circ$  ( $c$  0.73,  $\text{CHCl}_3$ ), but was in line with the optical purity of our starting amine **(-)-28**).

In conclusion, the procedure described herein offer a simple and convenient stereoselective process for the synthesis of C-6 substituted piperidic acid derivatives from readily available materials. Synthetic efficiency was demonstrated through the synthesis of pivotal intermediates of indolizidine alkaloids of *Dendrobatidae* family. Moreover, since polysubstituted amines of type **4** could be now available,<sup>28</sup> other substitutions on the piperidine ring are now envisaged.

## EXPERIMENTAL

Melting points were determined on a *Reichert* hot stage microscope and are uncorrected. Infrared spectra were recorded on a FTIR spectrometer. NMR spectra were recorded on a Bruker AC 400 spectrometer operating at 400.13 MHz for  $^1\text{H-NMR}$  and at 100.61 MHz for  $^{13}\text{C-NMR}$  solutions. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) and the coupling constants (J) are given in Hertz. Optical rotations were measured at 589 nm, at 25°C with concentrations expressed in  $\text{g } 100 \text{ mL}^{-1}$ . EIMS were obtained at 70 eV. FABMS and exact mass spectra were obtained from the *Centre Régional de Mesures Physiques*, Université de Rennes. THF and ether were distilled from benzophenone ketyl. Chloroform and dichloromethane were distilled from  $\text{P}_2\text{O}_5$ . Reactions were monitored by TLC, using precoated silica gel plates. Products were visualized using UV light (254 nm) and phosphomolybdic acid/ethanol. Column chromatography was performed using silica gel (Kieselgel 60 Merck 200-400 mesh). Compounds **(1a)** and



(**1b**) were used as purchased. Compounds (**1c**),<sup>29</sup>(**2a**),<sup>11</sup> (**3a**),<sup>11</sup> and (**4a**)<sup>11</sup> were prepared according to the procedure described earlier.

#### ***N*-4-Oxoheptan-2-ylphthalimide (**2b**)**

To a stirred solution of commercial hept-3-en-2-one (**1b**) (5.0 g, 44.6 mmol) in ethyl acetate (75 mL) was added phthalimide (5.24 g, 35.7 mmol) and a 40% solution of Triton<sup>®</sup> B in methanol (1 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the phthalimide. The mixture was then allowed to cool to room temperature. Evaporation of the solvent followed by recrystallisation from ethanol afforded compound (**2b**) (8.7 g, 94%) as a white solid: mp = 51°C. IR (neat)  $\nu$  : 2958, 1773, 1702  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR  $\delta$  : 7.82-7.75 (m, 2H), 7.70-7.65 (m, 2H), 4.75-4.66 (m, 1H), 3.35-3.27 (dd,  $J = 17.5$  Hz,  $J = 8.5$  Hz, 1H), 2.99-2.91 (dd,  $J = 17.5$  Hz,  $J = 6.0$  Hz, 1H), 2.13 (s, 3H), 2.05-1.95 (m, 1H), 1.68-1.58 (m, 1H), 1.35-1.20 (m, 2H), 1.27 (s, 3H), 0.90 (t,  $J = 7.5$  Hz, 3H). <sup>13</sup>C-NMR  $\delta$  = 205.9, 168.4, 133.9, 131.8, 123.2, 46.7, 45.7, 34.6, 30.2, 19.5, 13.6. Anal. Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub> : C, 69.48; H, 6.61; N, 5.40. Found : C, 69.62; H, 6.65; N, 5.42.

#### ***N*-4-Oxodecan-2-ylphthalimide (**2c**)**

The same protocol is applied, starting from 3-decen-2-one (**1c**)<sup>29</sup> (1.7 g, 11 mmol). Compound (**2c**) (1.99 g, 60%) is obtained as a yellow oil : IR (neat)  $\nu$  : 2952, 2853, 1773, 1709  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR  $\delta$  : 7.78-7.70 (m, 2H), 7.65-7.50 (m, 2H), 4.53 (m, 1H), 3.15 (m, 1H), 2.82 (m, 1H), 1.95 (s, 3H), 1.80 (m, 1H), 1.50 (m, 1H), 1.15-0.95 (m, 8H), 0.62 (t,  $J = 7$  Hz, 3H). <sup>13</sup>C-NMR  $\delta$ : 205.9, 168.4, 133.9, 131.7, 123.1, 46.9, 45.6, 32.5, 31.5, 30.1, 28.7, 26.3, 22.5, 13.9. Anal. Calcd for C<sub>18</sub>H<sub>23</sub>NO<sub>3</sub> : C, 71.73; H, 7.69; N, 4.65. Found : C, 71.28; H, 7.58; N, 4.68.

#### **(2-Methyl-1,3-dioxan-2-yl)-2-phthalimidopentane (**3b**)**

In a round bottomed flask, fitted with a Dean-Stark apparatus, was added, to a solution of **2b** (1.68 g, 6.5 mmol) in toluene (2 mL), freshly distilled propane-1,3-diol (1mL, 0.25 mol) and 20 mg of APTS. The mixture was refluxed for 5 h, then cooled to rt and treated with a saturated NaHCO<sub>3</sub> solution. The two layers were separated, and the aqueous phase was extracted several times with dichloromethane. The combined organic layers were washed with a brine solution and then dried on MgSO<sub>4</sub>. After evaporation of the solvent, the residue was purified by alumina chromatography (eluent : cyclohexane/ethyl acetate, 9/1) and furnished **3b** (1.73 g, 84%) as a white solid : mp = 74-76°C. IR (neat)  $\nu$  : 2966, 2874, 1769, 1705  $\text{cm}^{-1}$ . <sup>1</sup>H-NMR  $\delta$  : 7.82-7.75 (m, 2H), 7.70-7.65 (m, 2H), 4.68-4.58 (m, 1H), 3.84-3.69 (m, 2H), 3.47-3.40 (m, 3H), 2.75-2.67 (m, 1H), 2.15-2.02 (m, 1H), 1.80-1.68 (m, 2H), 1.65-1.56 (m, 1H), 1.39 (s, 3H), 1.31-1.22 (m, 2H), 0.90 (t,  $J = 7.5$  Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 168.9, 133.5, 132.2, 122.8, 98.5, 59.8, 46.5, 41.4,

35.4, 19.9, 19.6, 13.7. Anal. Calcd for C<sub>18</sub>H<sub>23</sub>NO<sub>4</sub> : C, 68.12; H, 7.30; N, 4.41. Found : C, 68.05; H, 7.28; N, 4.45.

### **(2-Methyl-1,3-dioxan-2-yl)-2-phthalimidooctane (3c)**

The same method was used as those described above, starting from **2c** (1.95 g, 6.5 mmol), compound **(3c)** (1.94 g, 78%) was obtained, after chromatography (eluent : cyclohexane/ethyl acetate, 2/1), as an oil : IR (neat)  $\nu$  : 2928, 2857, 1773, 1769 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 7.82-7.75(m, 2H), 7.70-7.65 (m, 2H), 4.68-4.62 (m, 1H), 3.85-3.71 (m, 2H), 3.50-3.43 (m, 3H), 2.80-2.70 (m, 1H), 2.15-2.10 (m, 1H), 1.80-1.60 (m, 2H), 1.40 (s, 3H), 1.35-1.15 (m, 9H), 0.85 (t, J = 7.5 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 168.9, 133.5, 132.2, 122.8, 98.4, 59.8, 59.7, 46.9, 41.4, 33.4, 31.6, 28.8, 26.2, 22.5, 24.9, 19.9, 14.0. Anal. Calcd for C<sub>21</sub>H<sub>29</sub>NO<sub>4</sub> : C, 70.17; H, 8.13; N, 3.90. Found : C, 70.41; H, 8.21; N, 3.93.

### **2-(2-Aminopentyl)-2-methyl-1,3-dioxane (4b)**

To a solution of **3b** (7.82 g, 25 mmol) in methanol (15 mL), was added 90% hydrazine monohydrate (27 mL, 0.5 mol). The mixture was refluxed overnight. After cooling the reaction mixture to rt, a 2.6N KOH solution (11 mL ) was added. The aqueous layer was extracted three times with dichloromethane (3×25 mL). The combined organic layers were washed with a saturated brine solution and dried on MgSO<sub>4</sub>. After evaporation of the solvent under reduce pressure (without heating), **4b** ( 4.58 g, 98%) was obtained as a yellow oil and was used further without purification : IR (neat)  $\nu$  : 3379, 2956, 2870, 1587cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 3.94-3.75 (m, 4H), 3.10-3.03 (m, 1H), 1.85-1.74 (m, 1H), 1.70-1.65 (m, 1H), 1.63-1.50 (m, 3H), 1.49-1.41 (m, 1H), 1.38-1.20 (m, 7H), 0.85 (t, J = 7.5 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 99.5, 59.5, 46.9, 46.5, 41.1, 25.5, 20.5, 19.1, 14.1. HRMS (EI)  $m/z$  : 172.1342 (M-CH<sub>3</sub> calcd for C<sub>9</sub>H<sub>18</sub>NO<sub>2</sub> : 172.1337).

### **(S)-2-(2-Aminopentyl)-2-methyl-1,3-dioxane (4b)**

Racemic amine **(4b)** (0.567 g, 3 mmol) was added to a solution of (-)-(2*R*,3*R*)-di-*O*-benzoyltartaric acid monohydrate (1.17 g, 3 mmol) in methanol (2 mL). The resulting solution was left to crystallize for 3 days. The crop of crystals was then recrystallized four times in methanol to afford the monotartrate (mp : 174-175°C), which was treated with an excess of 1M NaOH. The free amine was extracted with dichloromethane (4×5 mL). The combined organic extracts were dried on MgSO<sub>4</sub>, and evaporated to give amine **(4b)** (0.244 g, 43%);  $[\alpha]_{20}^D = + 11.7^\circ$  (*c* 1.07, CHCl<sub>3</sub>).

### **2-(2-Aminoethyl)-2-methyl-1,3-dioxane (4c)**

The same method was used as those described above, starting from **3c** (1.7g, 4.7 mmol), compound **(4c)** (1.05 g, 98%) was obtained as a pale yellow oil : IR (neat)  $\nu$  : 3376, 2940, 2860, 1581 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  :

3.95-3.75 (m, 4H), 3.04 (m, 1H), 1.82-1.73 (m, 1H), 1.71-1.62 (m, 3H), 1.59-1.53 (m, 1H), 1.35 (s, 3H), 1.32-1.15 (m, 10 H), 0.82 (t, J = 7.0 Hz, 3H). <sup>13</sup>C-NMR δ : 99.5, 59.7, 59.5, 47.1, 46.7, 38.5, 31.8, 29.3, 25.9, 22.5, 25.5, 20.3, 14.0. HRMS (EI) *m/z* : 229.2047 ( calcd for C<sub>13</sub>H<sub>27</sub>NO<sub>2</sub>: 229.2042).

**(8*R*,10*R*)-8-Ethoxycarbonyl-10-methyl-1,5-dioxa-9-azaspiro[5.5]undecane (6a) and (8*S*,10*R*)-8-ethoxycarbonyl-10-methyl-1,5-dioxa-9-azaspiro[5.5]undecane (7a)**

To a stirred solution of ethyl glyoxylate (0.353 g, 3.45 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added MgSO<sub>4</sub> (1 g) followed by a solution of amine (-)-(**R**)-(**4a**) (0.5 g, 3.14 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the amine (3-4 h), then cooled to rt and transferred *via* a cannula to a solution of dry *p*-TSA (1.18 g, 6.28 mmol) in toluene (25 mL). The resulting mixture was heated at 70°C for 3 h. After being cooled to rt, saturated aqueous NaHCO<sub>3</sub> (15 mL) was added and the protected piperidone was extracted with ethyl acetate (4×20 mL). The combined extracts were dried on MgSO<sub>4</sub> and evaporated. The residue, purified by column chromatography (eluent : ethyl acetate/methanol, 5/1), gave the corresponding protected 4-piperidones (**6a**) (0.572 g, 75%) and (**7a**) (0.064 g, 8%) .

**6a** : [α]<sub>20</sub><sup>D</sup> = -14.8° (c 1, CHCl<sub>3</sub>); IR (neat) ν : 2962, 2932, 2868, 2837, 2813, 1739 cm<sup>-1</sup>. <sup>1</sup>H-NMR δ : 4.15 (q, J = 7.0 Hz, 2H) 3.90 (m, 4H), 3.50 (dd, J = 12.0 Hz, J = 3.0 Hz, 1H), 2.85 (m, 1H), 2.62 (dt, J = 13.5 Hz, J = 3.0 Hz, 1H), 2.12 (dt, J = 13.5 Hz, J = 3.0 Hz, 1H), 1.80 (br s, 1H), 1.66-1.62 (m, 2H), 1.26 (t, J = 12.5 Hz, 1H), 1.02 (t, J = 12.5 Hz, 1H), 1.17 (t, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H). <sup>13</sup>C-NMR δ: 172.8, 96.9, 60.9, 59.2, 55.4, 47.4, 41.6, 35.3, 25.5, 22.1, 14.1. HRMS (EI) *m/z* : 243.1468 (calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> : 243.1470). Anal. Calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> : C, 59.24; H, 8.70; N, 5.76. Found : C, 59.61; H, 8.74; N, 5.85.

**7a** : [α]<sub>20</sub><sup>D</sup> = + 25.4° (c 1.28, CHCl<sub>3</sub>); IR (neat) ν : 2963, 2928 ,2870, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR δ : 4.21-4.12 (q, J = 7.0 Hz, 2H), 3.93-3.71 (m, 5H), 3.23 (m, 1H), 2.99 (dt, J = 13.5 Hz, J = 3.0 Hz, 1H), 1.94 (dt, J = 13.0 Hz, J = 3.0 Hz, 1H), 2.70 (br s, 1H), 1.79-1.53 (m, 2H), 1.71 (dd, J = 13.5 Hz, J = 6.5 Hz, 1H), 1.24 (t, J = 13.0 Hz, 1H), 1.27 (t, J = 7.0, 3H), 1.10 (d, J = 6.5 Hz, 3H). <sup>13</sup>C-NMR δ : 173.9, 96.4, 60.8, 59.6, 59.4, 54.4, 44.0, 42.8, 31.2, 25.4, 22.4, 14.2. HRMS (EI) *m/z* : 243.1468 (calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> : 243.1470). Anal. Calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> : C, 59.24; H, 8.70; N, 5.76. Found : C, 59.48; H, 8.68; N, 5.72.

**(8*S*,10*S*)-8-Ethoxycarbonyl-10-propyl-1,5-dioxa-9-azaspiro[5.5]undecane (6b) and (8*S*,10*R*)-8-ethoxycarbonyl-10-propyl-1,5-dioxa-9-azaspiro[5.5]undecane (7b)**

The same method was used as those described above, starting from amine (+)-(**S**)(**4b**) (0.296 g, 1.58

mmol). Compounds **(6b)** (0.257 g, 60%) and **(7b)** (0.017 g, 4%) were obtained after chromatography (eluent :ethyl acetate/methanol, 5/1).

**6b** :  $[\alpha]_{20}^D = +7.6^\circ$  (*c* 1, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 2990, 2932, 2871, 1736 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 4.15 (q, *J* = 7.2 Hz, 2H), 3.89 (m, 4H), 3.48 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1H), 2.72 (m, 1H), 2.64 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.15 (dt, *J* = 12.5 Hz, *J* = 2.5 Hz, 1H), 1.86 (br s, 1H), 1.74-1.66 (m, 2H), 1.35 (m, 1H), 1.05 (t, *J* = 12.5 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 1H), 1.35 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.9, 96.9, 60.9, 59.2, 55.3, 51.6, 40.0, 38.6, 35.5, 25.4, 18.9, 14.1, 13.9. HRMS (EI) *m/z* : 271.1780 (calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: 271,1783). Anal. Calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub> : C, 61.97; H, 9.29; N, 5.16. Found : C, 62.21; H, 9.42; N, 5.27.

**7b** :  $[\alpha]_{20}^D = -21.8^\circ$  (*c* 0.85, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 2950, 2924, 2861, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 4.23–4.13 (q, *J* = 7.0 Hz, 2H), 3.92-3.73 (m, 5H), 3.13 (br s, 1H), 3.12 (m, 1H), 3.06 (dt, *J* = 13.5 Hz, *J* = 2.5 Hz, 1H), 1.97 (dt, *J* = 13.0 Hz, *J* = 2.5 Hz), 1.84-1.53 (m, 2H), 1.74 (dd, *J* = 13.5 Hz, *J* = 6.5 Hz, 1H), 1.37 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 13.0 Hz, 1H), 0.95 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 173.8, 96.5, 60.9, 59.7, 59.6, 54.2, 48.1, 41.5, 38.6, 31.1, 25.5, 18.8, 14.2, 14.1. HRMS (EI) *m/z* : 271.1780 (calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: 271,1783).

### **8-Ethoxycarbonyl-10-hexyl-1,5-dioxa-9-azaspiro[5.5]undecane (6c) and 8-ethoxycarbonyl-10-hexyl-1,5-dioxa-9-azaspiro[5.5]undecane (7c)**

The same method was used as those described above, starting from amine **(4c)** (0.3 g, 1.30 mmol). Compounds **(6c)** (0.260 g, 64%) and **(7c)** (0.024 g, 6%) were obtained after chromatography (eluent : ethyl acetate).

**6c** : IR (neat)  $\nu$  : 2961, 2924, 2856, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 4.23-4.18 (q, *J* = 7.2 Hz, 2H), 3.94-3.87 (m, 4H), 3.53 (dd, *J* = 12.5 Hz, *J* = 3.0 Hz, 1H), 2.75 (m, 1H), 2.68 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.18 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.80 (br s, 1H), 1.77-1.68 (m, 2H), 1.43 (t, *J* = 13.5, 1H), 1.32-1.27 (m, 5H), 1.11 (t, *J* = 12.5 Hz, 1H), 0.86 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.9, 96.9, 60.9, 59.1, 57.3, 55.4, 52.1, 40.1, 36.5, 35.6, 31.7, 29.4, 25.8, 25.3, 22.5, 14.1, 14.0. HRMS (EI) *m/z* : 313.4410 (calcd for C<sub>17</sub>H<sub>31</sub>NO<sub>4</sub>: 313.4405). Anal. Calcd for C<sub>17</sub>H<sub>31</sub>NO<sub>4</sub> : C, 65.14; H, 9.97; N, 4.47. Found : C, 65.21; H, 9.91; N, 4.51.

**7c** : IR (neat)  $\nu$  : 2956, 2929, 2851, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 4.20-4.10 (q, *J* = 7.0 Hz, 2H), 3.93-3.68 (m, 5H), 3.05 (m, 1H), 3.02 (dt, *J* = 13.5 Hz, *J* = 3.0 Hz, 1H), 1.95 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.36 (br s, 1H), 1.81-1.51 (m, 2H), 1.70 (dd, *J* = 13.5 Hz, *J* = 6.5 Hz, 1H), 1.32-1.29 (m, 5H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 173.9, 96.5, 60.8, 59.6, 59.5, 54.4, 48.4, 41.6, 36.5, 31.6, 31.3, 29.3, 25.6, 25.4, 22.6, 14.2, 14.1. HRMS (EI) *m/z* : 313.4410 (calcd for C<sub>17</sub>H<sub>31</sub>NO<sub>4</sub>: 313.4405).

### **(7*R*,9*R*)-7-Ethoxycarbonyl-9-methyl-1,4-dithia-8-azaspiro[5.4]decane (10a)**

To a stirred solution of protected piperidone (**6a**) (0.140 g, 0.575 mmol) in dichloromethane (10 mL) was added drop wise at rt ethane dithiol (0.24 mL, 2.87 mmol) then BF<sub>3</sub>.Et<sub>2</sub>O (0.36 mL, 2.87 mmol). After 20 h of stirring, an excess of 2 M aqueous NaOH was added and the resulting mixture was extracted with dichloromethane (4×20 mL). The combined organic extracts were washed with brine and dried over MgSO<sub>4</sub>. Evaporation of the solvent, followed by column chromatography (eluent : cyclohexane/ethyl acetate, 2/1), gave protected piperidone (**10a**) as a yellow oil (0.135 g, 90%):  $[\alpha]_D^{20} = -3.4^\circ$  (*c* 0.565, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 2964, 2927, 1739 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 4.15 (q, *J* = 7.0 Hz, 2H), 3.58 (dd, *J* = 11.5 Hz, *J* = 2.5 Hz, 1H), 3.29 (s, 4H), 2.81 (m, *J* = 6.0 Hz, *J* = 2.5 Hz, 1H), 2.38 (dt, *J* = 13.0 Hz, *J* = 2.5 Hz, 1H), 2.03 (dt, *J* = 13.0 Hz, *J* = 2.5 Hz, 1H), 1.87 (t, *J* = 13.0 Hz, 1H), 1.83 (br s, 1H), 1.64 (t, *J* = 13.0 Hz, 1H), 1.23 (t, *J* = 7.0 Hz, 3H) 1.11 (d, *J* = 6.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.3, 66.2, 61.1, 58.1, 51.0, 49.3, 44.9, 39.1, 37.9, 22.1, 14.2. HRMS (EI) *m/z* : 261.0872 (calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub>S<sub>2</sub>: 261.0857). Anal. Calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub>S<sub>2</sub> : C, 50.54; H, 7.33; N, 5.36. Found : C, 50.71; H, 7.41; N, 5.40.

### **(2*R*,6*R*)-Ethyl 6-methyl-2-piperidinecarboxylate (11a)**

To a stirred solution of protected piperidone (**10a**) (0.150 g, 0.57 mmol) in absolute ethanol (5 mL) was added freshly prepared W2 Raney nickel (0.5 g). The resulting suspension was heated at reflux for 30 mn then cooled to rt. The suspension was then filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1M aqueous NaOH and the piperidine was extracted with dichloromethane (4×10 mL). The combined organic extracts were washed with brine and dried over MgSO<sub>4</sub>. Evaporation of the solvent, followed by column chromatography (eluent : ethyl acetate) gave piperidine (**11a**) as a colorless oil (0.083 g, 85%):  $[\alpha]_D^{20} = -11.6^\circ$  (*c* 1.015, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 2961, 2932, 2838, 2795, 1743 cm<sup>-1</sup>. <sup>1</sup>H- NMR  $\delta$  : 4.16 (q, *J* = 6.0 Hz, 2H), 3.32 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1H), 2.63 (m, 1H), 2.25 (br s, 1H), 1.96 (dd, *J* = 13.5 Hz, *J* = 2.0 Hz, 1H), 1.84 (dt, *J* = 13.0 Hz, *J* = 3.5 Hz, 1H), 1.58 (dd, *J* = 13.0 Hz, *J* = 2.0 Hz, 1H), 1.43-1.32 (m, 3H), 1.24 (t, *J* = 7.0 Hz, 1H), 1.08 (d, *J* = 6.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.3, 60.8, 59.1, 51.9, 33.7, 28.9, 24.5, 22.7, 14.2. HRMS (EI) *m/z* : 98.0964 (calcd for C<sub>6</sub>H<sub>12</sub>N (M-CO<sub>2</sub>Et) : 98.0969). Anal. Calcd for C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub> : C, 63.13; H, 10.01; N, 8.18. Found : C, 63.27; H, 10.12; N, 8.15.

### **(2*R*,6*R*)-6-Methylpipercolic acid (12a)**

To a stirred solution of piperidine (**11a**) (0.076 g, 0.44 mmol) in methanol (1.5 mL) was added drop wise 1N NaOH (0.49 mL, 0.49 mmol). After four days of stirring at rt, the methanol was evaporated and the resulting mixture was acidified with 1N HCl. The sodium salts were eliminated by filtration on Dowex<sup>®</sup>

50W X 8 ion exchange resin, then the resin was washed with water, followed by an 2% aqueous  $\text{NH}_4\text{OH}$  solution to gave **12a** (0.060 g, 95%) as a white solid. To a solution of **12a** in diethyl ether was added a saturated solution of hydrogen chloride in ether (4 mL). After filtration, the crude **12a.HCl** was recrystallized from absolute ethanol to afford **12a.HCl** as white needles: mp > 215°C.  $[\alpha]_{20}^{\text{D}} = +11.8^\circ$  (c 1.1, 0.1N HCl) [lit.,<sup>6d</sup>  $[\alpha]_{20}^{\text{D}} = -11.7^\circ$  (c 1.1, 0.1N HCl)] for its enantiomer]. Spectral data are identical with those reported.

#### **(7S,9S)-7-Ethoxycarbonyl-9-propyl-1,4-ditha-8-azaspiro[5.4]decane (15)**

Following the dithioacetalation procedure, protected piperidone (**6b**) (0.17 g, 0.627 mmol) afforded the dithio derivative (**15**) as a pale yellow oil (0.165 g, 92%) :  $[\alpha]_{\text{D}}^{20} = +5.5^\circ$  (c 0.98,  $\text{CHCl}_3$ ). IR (neat)  $\nu$ : 2957, 2926, 2871, 1737  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$   $\delta$ : 4.14 (q, J = 7.0 Hz, 2H), 3.56 (dd, J = 11.5 Hz, J = 2.5 Hz, 1H), 3.29 (s, 4H), 2.67 (m, 1H), 2.38 (dt, J = 13.0 Hz, J = 2.5 Hz, 1H), 2.05 (dt, J = 13.0 Hz, J = 2.0 Hz, 1H), 1.88 (t, J = 11.5 Hz, 1H), 1.86 (br s, 1H), 1.63 (t, J = 13.0 Hz, 1H), 1.37 (m, 4H), 1.23 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H).  $^{13}\text{C-NMR}$   $\delta$ : 172.3, 66.3, 61.0, 58.1, 55.2, 47.7, 45.5, 39.1, 38.6, 37.9, 18.9, 14.2, 14.1. Anal. Calcd for  $\text{C}_{13}\text{H}_{23}\text{NO}_2\text{S}_2$ : C, 53.94; H, 8.01; N, 4.84. Found: C, 53.71; H, 7.93; N, 4.86.

#### **(2S,6S)-Ethyl N-benzyloxycarbonyl-6-propyl-2-piperidinecarboxylate (16)**

Following the hydrogenolysis procedure, protected piperidine (**15**) (0.1 g, 0.36 mmol) afforded an oil which was taken with dichloromethane (12 mL). To this solution was added an aqueous solution of 0.4 M  $\text{Na}_2\text{CO}_3$  (1.8 mL, 0.72 mmol) and the resulting mixture was kept at 0°C. Benzyl chloroformate was added rapidly dropwise (78  $\mu\text{L}$ , 0.54 mmol). The slurry was kept under stirring at room temperature for 10 h. After that, it was transferred in a separating funnel, the aqueous phase was extracted twice with dichloromethane. The combined extracts were dried and evaporated. The residue was purified by chromatography (eluent: cyclohexane/ethyl acetate, 7/1) gave compound (**16**) (0.096 g, 82%) as a colorless oil :  $[\alpha]_{20}^{\text{D}} = -44.9^\circ$  (c 0.965,  $\text{CHCl}_3$ ). IR (neat)  $\nu$ : 2957, 2871, 1731, 1698  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$   $\delta$ : 7.33 (m, 5H), 5.14 (m, 2H), 4.83 (m, 1H), 4.25 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.31 (m, 2H), 1.58 (m, 6H), 1.38 (m, 2H), 1.34 (m, 2H), 1.27 (t, J = 7.0 Hz, 1H), 0.89 (t, J = 7.0 Hz, 3H).  $^{13}\text{C-NMR}$   $\delta$ : 172.7, 156.4, 136.9, 129.4, 128.8, 128.6, 128.4, 67.3, 61.1, 52.5, 51.2, 34.5, 27.5, 25.8, 19.9, 15.8, 14.0. HRMS (EI)  $m/z$ : 333.1933 (calcd for  $\text{C}_{19}\text{H}_{27}\text{NO}_4$ : 333.1940). Anal. Calcd for  $\text{C}_{19}\text{H}_{27}\text{NO}_4$ : C, 68.44; H, 8.16; N, 4.20. Found: C, 68.60; H, 8.22; N, 4.17.

#### **(2S,6S)-N-Benzyloxycarbonyl-6-propyl-2-hydroxymethylpiperidine (13)**

To a stirred solution of compound (**16**) (0.092 g, 0.285 mmol) in anhydrous THF was added drop wise Super-Hydride<sup>®</sup> (1M solution in THF, 0.71 mL, 0.71 mmol) at 0°C. Stirring was maintained for 2 h, then

methanol (1 mL) was added. The solvents were evaporated, the residue was taken with dichloromethane and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated to give an oil which was purified by chromatography (eluent : cyclohexane/ethyl acetate, 2/1) to afford **13** as a pale yellow oil (0.073 g, 88%) :  $[\alpha]_{20}^D = +7.7^\circ$  (*c* 1.19, MeOH) [ lit.,<sup>17c</sup>  $[\alpha]_{20}^D = +9.3^\circ$  (*c* 1.285, MeOH)]. IR (neat)  $\nu$  : 3400, 2995, 2871, 1667 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 7.35 (m, 5H), 5.14 (m, 2H), 4.34 (m, 1H), 4.18 (m, 1H), 3.64 (m, 2H), 1.78 (m, 1H), 1.57 (m, 4H), 1.47 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 156.2, 136.8, 128.5, 128.0, 127.9, 67.3, 65.1, 52.3, 50.5, 37.0, 27.3, 25.0, 20.4, 14.5, 14.1. HRMS (EI) *m/z* : 260.1654 [calcd for C<sub>16</sub>H<sub>22</sub>NO<sub>2</sub> (M-CH<sub>2</sub>OH) : 260.1650]. Anal. Calcd for C<sub>17</sub>H<sub>25</sub>NO<sub>3</sub> : C, 70.07; H, 8.65; N, 4.81. Found : C, 70.51; H, 8.72; N, 4.89.

#### **(2S)-tert-Butyl 2-[N-benzyloxycarbonylamino]-4-oxopentanoate (20)**

To a solution of compound (**19**) (2.45 g, 7.98 mmol) in dichloromethane (100 mL) was added an ethereal solution of diazomethane (large excess) at rt. The resulting mixture was kept, under stirring, for 20 h (fading of the yellow color). An aqueous solution of 0.1 N HCl (20 mL) was added. The aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine and dried over MgSO<sub>4</sub>. After evaporation of the solvent, the oil such obtained was purified by chromatography (eluent : cyclohexane/ethyl acetate, 3/1) to afford **20** (2.3 g, 92%) as a colorless oil :  $[\alpha]_{20}^D = +19.4^\circ$  (*c* 0.95, CHCl<sub>3</sub>) [ lit.,<sup>21f</sup>  $[\alpha]_{20}^D = +20^\circ$  (*c* 1, CHCl<sub>3</sub>)]. IR (neat)  $\nu$  : 3432, 3019, 1740, 1718, 1670 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 7.35 (m, 5H), 5.80 (d, *J* = 8.0 Hz, 1H), 5.10 (s, 2H), 4.44 (td, *J* = 8 Hz, *J* = 4 Hz, 1H), 3.10 (dd, *J* = 16 Hz, *J* = 4 Hz, 1H), 2.90 (dd, *J* = 16 Hz, *J* = 4 Hz, 1H), 2.12 (s, 3H), 1.45 (s, 9H). <sup>13</sup>C-NMR  $\delta$  : 206.3, 169.8, 156.0, 136.2, 128.4, 128.0, 127.9, 66.8, 50.4, 45.3, 29.8, 27.7. HRMS (EI) *m/z* : 265.0948 [calcd for C<sub>13</sub>H<sub>15</sub>NO<sub>5</sub> (M-C<sub>4</sub>H<sub>8</sub>): 265.0950].

#### **(S)-2-Methyl-2[tert-butyl-2'-[N-(benzyloxycarbonyl)aminopropionate]-1,3-dioxane (21a)**

In a round bottomed flask, fitted with a Soxhlet apparatus (filled with molecular sieves), was added in chloroform (20 mL) methyl ketone (**20**) (0.5 g, 1.55 mmol) then 1,3-propanediol (0.25 mL, 3.1 mmol) and PPTS (catalytic). The resulting mixture was heated to reflux for 24 h. After cooling to rt, a saturated solution of NaHCO<sub>3</sub> (10 mL) was added. After transfer in a separating funnel, the aqueous phase was extracted with ethyl acetate (2×15 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub> and evaporated. The residue was purified by chromatography (eluent : cyclohexane/ethyl acetate, 3/1) to gave compound (**21a**) (0.618 g, 90%) as a colorless oil:  $[\alpha]_{20}^D = -5.4^\circ$  (*c* 0.845, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3412, 3340, 2971, 2866, 1722, 1668 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 7.33 (m, 5H), 6.10 (br s, 1H), 5.15 (s,

2H), 4.32 (dd,  $J = 12.0$  Hz,  $J = 7.0$  Hz, 1H), 3.94-3.77 (m, 4H), 2.11 (m, 2H), 1.93-1.36 (m, 2H), 1.45 (br s, 15H).  $^{13}\text{C-NMR}$   $\delta$  : 171.2, 156.0, 136.7, 128.4, 128.1, 127.9, 99.0, 66.6, 59.8, 59.6, 51.6, 41.4, 27.9, 25.1, 19.3. HRMS (EI)  $m/z$  : 364.1769 [calcd for  $\text{C}_{19}\text{H}_{26}\text{NO}_6$  (M- $\text{CH}_3$ ): 364.1760]. Anal. Calcd for  $\text{C}_{20}\text{H}_{29}\text{NO}_6$  : C, 63.31; H, 7.70; N, 3.69. Found : C, 63.48; H, 7.80; N, 3.72.

**(S)-2-Methyl-2-[propanoyl-2'-[N-(benzyloxycarbonyl)aminopropionate]-1,3-dioxane (21b)**

Following the same procedure as above, starting from **20** (2.2 g, 6.86 mmol) and 1,3-propanediol (1.24 mL, 17.15 mmol), but changing chloroform for toluene and PPTS for APTS, after 4 h at reflux, **21b** (0.85 g, 30%) was obtained as a colorless oil :  $[\alpha]_{20}^{\text{D}} = +4.7^\circ$  ( $c$  1.12,  $\text{CHCl}_3$ ). IR (neat)  $\nu$  : 3603, 3350, 2957, 2886, 1694,  $1682\text{cm}^{-1}$ .  $^1\text{H-NMR}$   $\delta$  : 7.35 (m, 5H), 6.28 (br s, 1H), 5.12 (s, 2H), 4.43 (m, 1H), 4.23 (m, 2H), 3.90-3.70 (m, 4H), 3.68 (m, 2H), 2.69 (br s, 1H), 2.10, (m, 2H), 1.92 (m, 1H), 1.85 (m, 2H), 1.42 (s, 3H), 1.31 (m, 1H).  $^{13}\text{C-NMR}$   $\delta$  : 172.5, 156.1, 136.5, 128.4, 128.0, 127.8, 99.1, 66.7, 62.2, 60.5, 59.8, 58.8, 51.5, 41.5, 31.2, 24.8, 19.2.

**21a** (0.772 g, 30%) was also obtained which spectral data were identical with those previously obtained

**(S)-2-Methyl-2-[3-acetoxypropyl-2'-[N-(benzyloxycarbonyl) amino]propionate]-1,3-dioxane (21c)**

To a solution of **21b** (0.392 g, 1.03 mmol) in dichloromethane (10 mL) at  $0^\circ\text{C}$  were added successively triethylamine (0.17 mL, 1.24 mmol) and acetic anhydride (97  $\mu\text{L}$ , 1.24 mmol) and a catalytic amount of DMAP (0.012 g). Stirring was continued for 1 h then was treated with a cold solution of saturated  $\text{NaHCO}_3$ . The two layers were separated and the aqueous phase was extracted several times with dichloromethane. The combined organic layers were washed with brine, then dried over  $\text{MgSO}_4$  and evaporated. The residue obtained was purified by chromatography (eluent : cyclohexane/ethyl acetate, 1/1) to afford **21c** (0.365 g, 84%) as a colorless oil :  $[\alpha]_{20}^{\text{D}} = +10.8^\circ$  ( $c$  0.71,  $\text{CHCl}_3$ ). IR (neat)  $\nu$  : 3449, 3040, 2961, 1785, 1722,  $1670\text{cm}^{-1}$ .  $^1\text{H-NMR}$   $\delta$  : 7.35 (m, 5H), 6.25 (br s, 1H), 5.11 (s, 2H), 4.44 (dd,  $J = 11.5$  Hz,  $J = 6.5$  Hz, 1H), 4.19-4.12 (m, 4H), 3.93-3.74 (m, 4H), 2.20 (dd,  $J = 14.5$  Hz,  $J = 6.5$  Hz, 1H), 2.08 (dd,  $J = 14.5$  Hz,  $J = 6.5$  Hz, 1H), 2.05 (s, 3H), 1.95 (q,  $J = 6.0$  Hz, 3H), 1.43 (s, 3H), 1.33 (m, 1H).  $^{13}\text{C-NMR}$   $\delta$  : 172.2, 170.0, 156.1, 136.6, 128.6, 128.4, 128.3, 128.2, 128.1, 99.1, 66.8, 61.2, 60.9, 59.9, 59.8, 50.7, 41.6, 27.8, 25.0, 20.9, 19.1. HRMS (EI)  $m/z$  : 423.1904 [calcd for  $\text{C}_{21}\text{H}_{29}\text{NO}_8$  : 423.1893]. Anal. Calcd for  $\text{C}_{21}\text{H}_{29}\text{NO}_8$  : C, 59.56; H, 6.90; N, 3.31. Found : C, 59.78; H, 7.02; N, 3.39.

**(S)-2-Methyl-2[tert-butyl-(2'-amino)propionate]-1,3-dioxane (22a)**

To a stirred solution of **21a** (0.5 g in anhydrous methanol (15 mL), was added Pd/C 10% (0.050 g) and ammonium formate (0.473 g, 7.5 mmol). The mixture was heated to reflux under argon for 45 min, then,



after cooling to rt, the solution was filtered off, washed with water, the organic layer was dried over MgSO<sub>4</sub> and evaporated to afford after purification by chromatography (eluent : ethyl acetate) amine (**22a**) (0.35 g, 93%) as an oil :  $[\alpha]_{20}^D = -3.8^\circ$  (*c* 0.58, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3330, 2977, 2872, 1743 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 6.40 (br s, 2H), 3.95-3.82 (m, 5H), 2.20 (dd, *J* = 15.0 Hz, *J* = 5.0 Hz, 1H), 2.05 (dd, *J* = 15.0 Hz, *J* = 6.5 Hz, 1H), 1.94 (m, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 1.35 (m, 1H). <sup>13</sup>C-NMR  $\delta$  : 170.9, 98.9, 59.8, 59.7, 50.5, 41.8, 27.8, 25.0, 19.3, 19.0. Anal. Calcd for C<sub>12</sub>H<sub>23</sub>NO<sub>4</sub> : C, 58.75; H, 9.45; N, 5.71. Found : C, 58.68; H, 9.40; N, 5.73.

### **(S)-2-Methyl-2[methyl-(2'-amino)propionate]-1, 3-dioxane (22b)**

Following the procedure employed for the synthesis of **22a**, starting from **21c** (0.366 g, 0.86 mmol) in anhydrous methanol (8 mL), 10% Pd/C (0.080 g) and ammonium formate (0.272 g, 4.3 mmol), **22b** was obtained as a pale yellow oil (0.217 g, 90%) :  $[\alpha]_{20}^D = -33.2^\circ$  (*c* 0.8, CHCl<sub>3</sub>). <sup>1</sup>H-NMR  $\delta$  : 6.10 (br s, 2H), 4.30 (m, 1H), 3.95-3.86 (m, 4H), 3.72 (s, 3H), 2.33 (dd, *J* = 15.0 Hz, *J* = 5.0 Hz, 1H), 2.22 (dd, *J* = 15.0 Hz, *J* = 7.0 Hz, 1H), 1.98 (m, 1H), 1.47 (s, 3H), 1.41 (m, 1H). <sup>13</sup>C-NMR  $\delta$  : 170.5, 98.8, 60.2, 60.0, 52.5, 49.8, 40.7, 24.7, 18.8. Anal. Calcd for C<sub>9</sub>H<sub>17</sub>NO<sub>4</sub> : C, 53.19; H, 8.43; N, 6.89. Found : C, 53.34; H, 8.61; N, 7.01.

### **(8R,10R)-8-Methoxycarbonyl-10-phenyl-1,5-dioxa-9-azaspiro[5.5]undecane (23a) and (8S,10R)-8-methoxycarbonyl-10-phenyl-1,5-dioxa-9-azaspiro[5.5]undecane (24a)**

To a stirred solution of benzaldehyde (0.059 g, 0.55 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added MgSO<sub>4</sub> (1 g) followed by a solution of amine (**22b**) (0.1 g, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the amine (3-4 h), then cooled to rt and transferred *via* a cannula to a solution of dry toluene-*p*-TSA (1.10 mmol) in toluene (25 mL). The resulting mixture was heated at 70°C for 3 h. After being cooled to rt, saturated aqueous NaHCO<sub>3</sub> (15 mL) was added and the protected piperidone was extracted with ethyl acetate (4×15 mL). The combined extracts were dried over MgSO<sub>4</sub>, and evaporated. The residue, purified by column chromatography (eluent : cyclohexane/ethyl acetate, 2/1), gave the corresponding protected 4-piperidones (**23a,b**) (0.060 g, 41%) and (**24a,b**) (0.025 g, 17%) .

**23a**: <sup>1</sup>H-NMR  $\delta$  : 7.39-7.27 (m, 5H), 3.96 (m, 4H), 3.88 (m, 1H), 3.74 (s, 3H), 3.71 (m, 1H), 2.75 (m, 1H), 2.35 (m, 1H), 2.15 (br s, 1H), 1.76 (m, 2H), 1.57 (m, 2H).

**23b**: <sup>1</sup>H-NMR  $\delta$  : 4.24-4.14 (m, 4H), 2.68 (m, 1H), 2.41 (m, 1H), 1.99 (m, 2H).

**24a:**  $^1\text{H-NMR } \delta$  : 7.43-7.26 (m, 5H), 4.23-3.87 (m, 6H), 3.76 (s, 3H), 3.12 (m, 1H), 3.38 (br s, 1H), 2.17 (m, 1H), 2.05 (m, 1H), 1.84 (m, 2H), 1.64 (m, 1H).

**24b:**  $^1\text{H-NMR } \delta$  : 4.23-3.87 (m, 4H), 2.93 (m, 1H), 2.30 (m, 1H), 1.91 (m, 2H).

**(2S)-Methyl 2-[N-phthalimidoamino]-4-oxopentanoate (26)**

Following the procedure employed for the synthesis of **20**, starting from aldehyde (**25**) (8.2 g, 31.4 mmol), methyl ketone (**26**) was obtained after column chromatography (eluent : cyclohexane/ethyl acetate, 2/1), as a colorless oil (7 g, 80%) which spectral data were identical with those previously described, except for the optical rotation :  $[\alpha]_{20}^{\text{D}} = -53^\circ$  (*c* 1.2,  $\text{CHCl}_3$ ) [ lit.,<sup>21d</sup>  $[\alpha]_{20}^{\text{D}} = -57.1^\circ$  (*c* 1.203,  $\text{CHCl}_3$ )].

**(S)-2-Methyl-2[methyl-2'-[N-(phthalimido)amino]propionate]-1,3-dioxolane (27)**

Following the same procedure used for the synthesis of **3b**, starting with compound (**26**) (0.472 g, 1.72 mmol), ethylene glycol (0.19 mL, 3.44 mmol) in toluene (20 mL), compound (**27**) was obtained after chromatography (eluent : cyclohexane/ethyl acetate, 2/1), as a colorless oil (0.494 g, 90%) :  $[\alpha]_{20}^{\text{D}} = -16.7^\circ$  (*c* 1,  $\text{CHCl}_3$ ). IR (neat)  $\nu$  : 2984, 2950, 2894, 1778, 1770, 1754, 1746, 1731, 1713, 1698  $\text{cm}^{-1}$ .  $^1\text{H-NMR } \delta$  : 7.85 (dd, *J* = 5.5 Hz, *J* = 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5 Hz, *J* = 5.0 Hz, 2H), 5.15 (dd, *J* = 10.5 Hz, *J* = 2.5 Hz, 1H), 3.92-3.78 (m, 4H), 3.72 (s, 3H), 2.74 (dd, *J* = 15.0 Hz, *J* = 10.5 Hz, 1H), 2.62 (dd, *J* = 15.5 Hz, *J* = 2.5 Hz, 1H), 1.30 (s, 3H).  $^{13}\text{C-NMR } \delta$  : 169.9, 167.6, 134.3, 134.0, 132.0, 123.6, 123.4, 108.5, 64.6, 64.3, 52.9, 47.8, 35.9, 23.7. HRMS (EI) *m/z* : 304.0818 [calcd for  $\text{C}_{15}\text{H}_{14}\text{NO}_6$  (M.  $\text{CH}_3$ ) : 304.0821]. Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_6$  : C, 60.18; H, 5.37; N, 4.39. Found : C, 60.29; H, 5.43; N, 4.42.

**(S)-2-Methyl-2[methyl-(2'-amino)propionate]-1,3-dioxolane (28)**

Following the procedure employed in the synthesis of amines (**4**), starting from compound (**27**) (0.4 g, 1.31 mmol), amine (**28**) was obtained as an oil (0.187 g, 75%) :  $[\alpha]_{20}^{\text{D}} = -28.8^\circ$  (*c* 0.77,  $\text{CHCl}_3$ ). IR (neat)  $\nu$  : 3410, 1720  $\text{cm}^{-1}$ .  $^1\text{H-NMR } \delta$  : 3.93 (s, 4H), 3.69 (s, 3H), 3.64 (t, *J* = 7.0 Hz, *J* = 5.0 Hz, 1H), 2.22 (dd, *J* = 14.5 Hz, *J* = 5.0 Hz, 1H), 1.94 (dd, *J* = 14.5 Hz, *J* = 7.0 Hz, 1H), 1.83 (br s, 2H), 1.30 (s, 3H).  $^{13}\text{C-NMR } \delta$  : 170.5, 108.3, 64.6, 64.3, 52.5, 49.8, 40.7, 18.8. Anal. Calcd for  $\text{C}_8\text{H}_{15}\text{NO}_4$  : C, 50.78; H, 7.99; N, 7.40. Found : C, 51.03; H, 8.09; N, 7.45.

**(7S,9S)-7-Methoxycarbonyl-9-phenyl-1,4-dioxo-8-azaspiro[5.4]decane (29a) and (7S,9R)-7-methoxycarbonyl-9-phenyl-1,4-dioxo-8-azaspiro[5.4]decane (30a)**

Following the procedure employed in the synthesis of **6a** and **7a**, starting from amine (**28**) (0.13 g, 0.69

mmol) and benzaldehyde (0.087 g, 0.82 mmol), compound (**29a**) (0.086 g, 45%) and compound (**30a**) (0.029 g, 15%) were obtained after chromatography (eluent : cyclohexane/ethyl acetate, 1/1).

**29a** : yellow oil.  $[\alpha]_{20}^D = -5.2^\circ$  (*c* 0.56, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3310, 2977, 2956, 2852, 1743 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 7.39 (dd, *J* = 7.0 Hz, *J* = 3.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (m, 1H), 4.05-3.87 (m, 5H), 3.76 (d, *J* = 3.0 Hz, 1H), 3.72 (s, 3H), 2.18 (br s, 1H), 2.15 (m, 1H), 1.89-1.71 (m, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.6, 142.9, 128.4, 127.4, 126.7, 107.4, 64.4, 64.3, 58.2, 56.7, 51.9, 43.0, 37.7. HRMS (EI) *m/z* : 277.1303 [calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub> : 277.1314]. Anal. Calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub> : C, 64.97; H, 6.91; N, 5.05. Found : C, 65.12; H, 6.98; N, 5.01.

**30a** : yellow oil.  $[\alpha]_{20}^D = +30^\circ$  (*c* 1.12, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3305, 2945, 2882, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 7.43-7.25 (m, 5H), 4.34 (dd, *J* = 11.0 Hz, *J* = 4.0 Hz, 1H), 4.06-3.86 (m, 5H), 3.77 (s, 3H), 2.45 (dt, *J* = 13.5 Hz, *J* = 2.5 Hz, 1H), 2.24 (br s, 1H), 2.03 (dd, *J* = 13.5 Hz, *J* = 6.5 Hz, 1H), 1.84 (t, *J* = 12.5 Hz, 1H), 1.79 (dd, *J* = 12.5 Hz, *J* = 2.5 Hz, 1H). <sup>13</sup>C-NMR  $\delta$  : 174.0, 143.9, 128.5, 127.5, 126.9, 107.2, 64.5, 64.2, 55.3, 54.9, 51.8, 42.9, 34.4.

**(7S,9S)-7-Methoxycarbonyl-9-(prop-1-enyl)-1,4-dioxo-8-azaspiro[5.4]decane (29b) and (7S,9R)-7-methoxycarbonyl-9-(prop-1-enyl)-1,4-dioxo-8-azaspiro[5.4]decane (30b)**

Following the same procedure, crotonaldehyde (173  $\mu$ L, 2.1 mmol) and amine (**28**) (0.264 g, 1.39 mmol) afforded after purification by chromatography (eluent : cyclohexane/ethyl acetate, 1/1), the piperidines (**29b**) (0.129 g, 37%) and (**30b**) (0.037 g, 13%).

**29b** : yellow oil.  $[\alpha]_{20}^D = +5.1^\circ$  (*c* 1.1, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3310, 2955, 2884, 1741 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 5.67 (dt, *J* = 13.0 Hz, *J* = 6.5 Hz, 1H), 5.46 (ddd, *J* = 15.0 Hz, *J* = 7.5 Hz, *J* = 2.0 Hz, 1H), 3.96 (s, 4H), 3.72 (s, 3H), 3.63 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1H), 3.33 (m, 1H), 2.06 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.95 (br s, 1H), 1.70 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.68 (d, *J* = 6.5 Hz, 3H), 1.61 (t, *J* = 12.5 Hz, 1H), 1.47 (t, *J* = 12.5 Hz, 1H). <sup>13</sup>C-NMR  $\delta$  : 172.9, 132.9, 126.6, 107.4, 64.5, 64.4, 56.4, 55.8, 52.1, 41.4, 37.7, 17.8. HRMS (EI) *m/z* : 241.1313 [calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub> : 241.1314]. Anal. Calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub> : C, 59.73; H, 7.94; N, 5.81. Found : C, 59.98; H, 7.98; N, 5.77.

**30b** : yellow oil.  $[\alpha]_{20}^D = +20.3^\circ$  (*c* 1, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3305, 2953, 2886, 1737 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 5.64 (m, 1H), 5.38 (ddd, *J* = 15.0 Hz, *J* = 7.5 Hz, *J* = 2.0 Hz, 1H), 3.96-3.89 (m, 4H), 3.89-3.75 (m, 2H), 3.70 (s, 3H), 2.75 (br s, 1H), 2.28 (dt, *J* = 13.5 Hz, *J* = 2.5 Hz, 1H), 1.86 (ddd, *J* = 13.5 Hz, *J* = 6.5 Hz, *J* = 1.5 Hz, 1H), 1.64 (d, *J* = 6.5 Hz, 3H), 1.62 (dt, *J* = 13.5 Hz, *J* = 3.0 Hz, 1H), 1.52 (t, *J* = 13.5 Hz, 1H). <sup>13</sup>C-NMR  $\delta$  : 174.4, 133.3, 126.6, 106.8, 64.6, 64.3, 54.5, 52.8, 51.7, 41.5, 34.2, 17.8.

**(7*S*,9*S*)-7-Methoxycarbonyl-9-hexyl-1,4-dioxo-8-azaspiro[5.4]decane (29c) and (7*S*,9*R*)-7-methoxycarbonyl-9-hexyl-1,4-dioxo-8-azaspiro[5.4]decane (30c)**

Following the same procedure, heptanal (230  $\mu$ L, 1.65 mmol) and amine (**28**) (0.284 g, 1.50 mmol) afforded after purification by chromatography (eluent : cyclohexane/ethyl acetate, 1/1), the piperidines (**29c**) and (**30c**) (overall yield 20%).

**29c** : yellow oil.  $[\alpha]_{20}^D = +2.2^\circ$  (*c* 0.78, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3310, 2966, 2919, 2856, 1743 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 3.97 (s, 4H), 3.70 (s, 3H), 3.58 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1H), 2.76 (m, 1H), 2.06 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.87 (br s, 1H), 1.71 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.56 (t, *J* = 12.5 Hz, 1H), 1.26 (m, 11H), 0.86 (t, *J* = 7.0 Hz, 3H).

**30c** : yellow oil.  $[\alpha]_{20}^D = -7.3^\circ$  (*c* 0.8, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3307, 2961, 2919, 2856, 1722 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 3.98-3.74 (m, 5H), 3.71 (s, 3H), 3.16 (m, 1H), 2.76 (br s, 1H), 2.35 (dt, *J* = 13.5 Hz, *J* = 3.0 Hz, 1H), 1.89 (dd, *J* = 13.5 Hz, *J* = 6.5 Hz, 1H), 1.67 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.42 (t, *J* = 13.0 Hz, 1H), 1.28 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H).

**(7*S*,9*S*)-7-Methoxycarbonyl-9-(hex-1-enyl)-1,4-dioxo-8-azaspiro[5.4]decane (29d) and (7*S*,9*R*)-7-methoxycarbonyl-9-(hex-1-enyl)-1,4-dioxo-8-azaspiro[5.4]decane (30d)**

Following the same procedure, 2-heptenal (218  $\mu$ L, 1.65 mmol) and amine (**28**) (0.284 g, 1.50 mmol) afforded after purification by chromatography (eluent : cyclohexane/ethyl acetate, 1/1), the piperidines (**29d**) (0.181 g, 31%) and (**30d**) (0.080 g, 10%).

**29d** : yellow oil.  $[\alpha]_{20}^D = -2.5^\circ$  (*c* 1.02, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3308, 2950, 2924, 2866, 1738 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 5.63 (dd, *J* = 15.0 Hz, *J* = 6.5 Hz, 1H), 5.41 (ddd, *J* = 15.0 Hz, *J* = 7.0 Hz, *J* = 1.5 Hz, 1H), 3.96 (s, 4H), 3.70 (s, 3H), 3.62 (dd, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 3.31 (m, 1H), 2.04 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.00 (q, *J* = 7.0 Hz, 2H), 1.90 (br s, 1H), 1.69 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.59 (t, *J* = 12.5 Hz, 1H), 1.45 (t, *J* = 12.5 Hz, 1H), 0.87 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.9, 132.0, 131.6, 107.5, 64.5, 64.4, 56.5, 55.9, 52.1, 41.6, 37.7, 31.9, 31.3, 22.2, 13.9. HRMS (EI) *m/z* : 283.1783 [calcd for C<sub>15</sub>H<sub>25</sub>NO<sub>4</sub> : 287.1784]. Anal Calcd for C<sub>15</sub>H<sub>25</sub>NO<sub>4</sub> : C, 63.58; H, 8.89; N, 4.94. Found : C, 63.89; H, 9.01; N, 4.92.

**30d** : yellow oil.  $[\alpha]_{20}^D = +10.4^\circ$  (*c* 1.075, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3304, 2950, 2919, 2866, 1738 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 5.61 (dt, *J* = 15.0 Hz, *J* = 7.0 Hz, 1H), 5.33 (dd, *J* = 15.0 Hz, *J* = 8.0 Hz, 1H), 4.10-3.85 (m, 4H), 3.83-3.71 (m, 2H), 3.65 (s, 3H), 2.45 (br s, 1H), 2.33 (dt, *J* = 13.5 Hz, *J* = 2.5 Hz, 1H), 1.95 (q, *J* = 7.0 Hz, 2H), 1.84 (dd, *J* = 13.5 Hz, *J* = 6.0 Hz, 1H), 1.61 (dt, *J* = 12.5 Hz, *J* = 3.0 Hz, 1H), 1.51 (t, *J* =

12.5 Hz, 1H), 1.40-1.20 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). <sup>13</sup>C-NMR δ : 174.5, 132.1, 131.9, 106.9, 64.3, 64.0, 54.5, 52.7, 51.7, 41.1, 34.2, 31.9, 31.2, 22.1, 13.8.

**(7S,9S)-7-Methoxycarbonyl-9-(non-1-enyl)-1,4-dioxo-8-azaspiro[5.4]decane (29e) and (7S,9R)-7-methoxycarbonyl-9-(non-1-enyl)-1,4-dioxo-8-azaspiro[5.4]decane (30e)**

Following the same procedure, 2-decenal (125 μL, 0.68 mmol) and amine (**28**) (0.117 g, 0.62 mmol) afforded after purification by chromatography (eluent : ethyl acetate), the piperidines (**29e**) (0.076 g, 36%) and (**30e**) (0.036 g, 18%).

**29e** : pale yellow oil.  $[\alpha]_{20}^D = -1.5^\circ$  (c 0.975, CHCl<sub>3</sub>). IR (neat) ν : 3305, 2956, 2924, 2851, 2840, 2840, 1738 cm<sup>-1</sup>. <sup>1</sup>H-NMR δ : 5.60 (dt, J = 15.0 Hz, J = 6.5 Hz, 1H), 5.38 (dd, J = 15.0 Hz, J = 7.0 Hz, 1H), 3.96 (s, 4H), 3.67 (s, 3H), 3.59 (dd, J = 12.0 Hz, J = 3.0 Hz, 1H), 3.28 (m, 1H), 2.04 (dt, J = 13.0 Hz, J = 2.5 Hz, 1H), 1.95 (q, J = 7.0 Hz, 2H), 1.85 (br s, 1H), 1.69 (dt, J = 13.0 Hz, J = 3.0 Hz, 1H), 1.59 (t, J = 12.5 Hz, 1H), 1.45 (t, J = 12.5 Hz, 1H), 1.37-1.16 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H). <sup>13</sup>C-NMR δ : 172.9, 132.2, 131.4, 107.4, 64.5, 64.4, 56.4, 55.9, 52.1, 41.5, 37.7, 32.3, 31.8, 29.2, 22.7, 14.1. HRMS (EI) m/z : 325.2260 [calcd for C<sub>18</sub>H<sub>31</sub>NO<sub>4</sub> : 325.2253]. Anal. Calcd for C<sub>18</sub>H<sub>31</sub>NO<sub>4</sub> : C, 66.43; H, 9.60; N, 4.30. Found : C, 66.62; H, 9.72; N, 4.34.

**30e** : pale yellow oil.  $[\alpha]_{20}^D = +8.7^\circ$  (c 0.95, CHCl<sub>3</sub>). IR (neat) ν : 3304, 2961, 2929, 2851, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR δ : 5.65 (dt, J = 14.5 Hz, J = 7.0 Hz, 1H), 5.38 (dd, J = 15.0 Hz, J = 7.0 Hz, 1H), 3.98-3.92 (m, 4H), 3.87-3.76 (m, 2H), 3.70 (s, 3H), 2.68 (br s, 1H), 2.33 (dt, J = 13.5 Hz, J = 2.5 Hz, 1H), 2.00 (q, J = 7.0 Hz, 2H), 1.90 (dd, J = 13.5 Hz, J = 6.0 Hz, 1H), 1.65 (dt, J = 13.0 Hz, J = 3.0 Hz, 1H), 1.58 (t, J = 12.0 Hz, 1H), 1.40-1.05 (m, 6H), 0.85 (t, J = 7.0 Hz, 3H). <sup>13</sup>C-NMR δ : 174.3, 132.5, 131.7, 106.9, 64.5, 64.2, 54.7, 52.9, 51.9, 41.0, 34.2, 32.3, 31.9, 29.7, 22.7, 14.1.

**(7S,9S)-7-Methoxycarbonyl-9-nonyl-1,4-dioxo-8-azaspiro[5.4]decane (29f) and (7S,9R)-7-methoxycarbonyl-9-nonyl-1,4-dioxo-8-azaspiro[5.4]decane (30f)**

Following the same procedure, 2-decanal (128 μL, 0.68 mmol) and amine (**28**) (0.117 g, 0.62 mmol) afforded after purification by chromatography (eluent : ethyl acetate), the piperidines (**29f**) and (**30f**) (overall yield : 20%)

**29f** : colorless oil.  $[\alpha]_{20}^D = -9.5^\circ$  (c 0.63, CHCl<sub>3</sub>). IR (neat) ν : 3312, 2970, 2919, 2850, 1745 cm<sup>-1</sup>. <sup>1</sup>H-NMR δ : 4.02 (br s, 4H), 3.75 (s, 3H), 3.61 (dd, J = 12.0 Hz, J = 3.0 Hz, 1H), 2.77 (m, 1H), 2.07 (dt, J = 13.0 Hz, J = 3.0 Hz, 1H), 1.77 (br s, 1H), 1.71 (dt, J = 13.0 Hz, J = 3.0 Hz, 1H), 1.58 (t, J = 12.5 Hz, 1H), 1.26 (m, 17H), 0.89 (t, J = 7.0 Hz, 3H).

**30f** : colorless oil.  $[\alpha]_{20}^D = +2.5^\circ$  (*c* 0.61, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3305, 2960, 2922, 2853, 1725 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 4.10-3.89 (m, 5H), 3.83 (s, 3H), 3.18 (m, 1H), 2.65 (br s, 1H), 2.63 (dt, *J* = 13.5 Hz, *J* = 3.0 Hz, 1H), 2.15 (dd, *J* = 13.5 Hz, *J* = 6.5 Hz, 1H), 1.93 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.44 (t, *J* = 13.0 Hz, 1H), 1.30 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3H).

**(7S,9S)-7-Methoxycarbonyl-9-(hex-1-enyl)-1,4-dithia-8-azaspiro[5.4]decane (33)**

Following the dithioacetalation procedure, protected piperidone (**29d**) (0.20 g, 0.696 mmol) afforded the dithio derivative (**33**) as a pale yellow oil (0.198 g, 89%):  $[\alpha]_{20}^D = +2.7^\circ$  (*c* 1.05, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3320, 2951, 2923, 2855, 1741 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 5.64 (dt, *J* = 15.0 Hz, *J* = 6.5 Hz, 1H), 5.39 (ddd, *J* = 15.5 Hz, *J* = 7.0 Hz, *J* = 1.5 Hz, 1H), 3.71 (s, 3H), 3.63 (dd, *J* = 11.5 Hz, *J* = 3.0 Hz, 1H), 3.31 (s, 4H), 3.24 (m, 1H), 2.40 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 2.07 (dt, *J* = 13.0 Hz, *J* = 3.0 Hz, 1H), 1.98 (q, *J* = 7.0 Hz, 2H), 1.97-1.93 (m, 4H), 1.81 (t, *J* = 12.5 Hz, 1H), 1.29 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 172.6, 132.3, 131.3, 65.9, 57.9, 52.1, 47.5, 44.7, 39.2, 37.9, 31.9, 31.3, 22.1, 13.9.

**(2S,6S) 2-Hydroxymethyl -6-hexylpiperidine (31)**

Following the hydrogenolysis procedure, protected piperidine (**33**) (0.1 g, 0.32 mmol) afforded an oil which was taken with anhydrous THF (12 mL). To the stirred resulting solution was added dropwise Super-Hydride<sup>®</sup> (1M solution in THF, 0.71 mL, 0.71 mmol) at 0°C. Stirring was maintained for 2 h, then methanol (1 mL) was added. The solvents were evaporated, the residue was taken with dichloromethane and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated to give an oil which was purified by chromatography (eluent : ethyl acetate) to afford **31** as a white solid (0.053 g, 83%) : mp=62-63°C.  $[\alpha]_{20}^D = +2.9^\circ$  (*c* 0.73, CDCl<sub>3</sub>) [lit.,<sup>27</sup>  $[\alpha]_{20}^D = -3.95^\circ$  (*c* 0.73, CDCl<sub>3</sub>)]. IR (neat)  $\nu$  : 3432, 3310, 2931, 2857, 1681 cm<sup>-1</sup>. <sup>1</sup>H-NMR  $\delta$  : 3.58 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1H), 3.53 (br s, 2H), 3.41 (dd, *J* = 11.0 Hz, *J* = 8.0 Hz, 1H), 2.70 (m, 1H), 2.50 (m, 1H), 1.79 (m, 1H), 1.68 (m, 1H), 1.52 (m, 1H), 1.41-1.28 (m, 12H), 1.05 (m, 2H), 0.83 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C-NMR  $\delta$  : 65.9, 58.3, 56.7, 37.0, 32.1, 31.8, 29.5, 28.1, 25.9, 24.2, 22.6, 14.1. HRMS (EI) *m/z* : 198.1860 [calcd for C<sub>12</sub>H<sub>24</sub>NO (M-H): 198.1858]; HRMS (FAB) *m/z* : 200.2013 [calcd for C<sub>12</sub>H<sub>26</sub>NO (MH<sup>+</sup>): 200.2014]. Anal. Calcd for C<sub>12</sub>H<sub>25</sub>NO : C, 72.31; H, 12.64; N, 7.03. Found : C, 72.49; H, 12.73; N, 7.06.

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