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SYNTHESIS OF 4-SUBSTITUTED INDOLIZIDIN-9-ONE AMINO ACID DERIVATIVES

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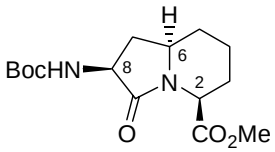
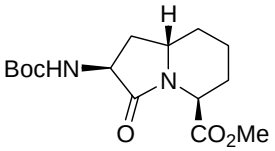
Abstract – Synthesis of 4-substituted indolizidin-9-one amino acid by cyclization of pipecolic acid derivatives has been described.

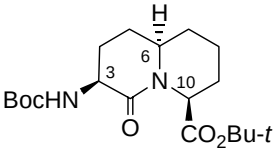
A great deal of work has been devoted to the synthesis of metabolically stable peptides analogues ("peptidomimetics"), due to their ability to mimic or block the biological effects of natural peptides.[1] For this purpose, the use of conformationally constrained structures in a peptide sequence, to rigidify its backbone and side geometries, is a way to elucidate conformation-activity relationships.[2] Azabicyclo-[*X.Y.0*]alkane amino acids are particularly attractive for this goal, especially for their ability to rigidify the three contiguous ψ, ω, ϕ dihedral angles within the peptide backbone,[3] and by the way, to operate as surrogates of peptide turn secondary structures.[4] The very close structural relationship of these compounds (such as **1a**[4g] or **2**[4d]) to indolizidine and quinolizidine alkaloids suggested us to apply the strategy developed in our laboratory on pipecolic acid derivatives.[5] Moreover the recent report on protected (2*S*,6*S*,8*S*)-indolizidin-9-one amino acid (*i.e* **(1b)**[6]) prompted us to disclose our results in this area (Figure 1).



(2*S*,6*R*,8*S*)-**1a**



(2*S*,6*S*,8*S*)-**1b**

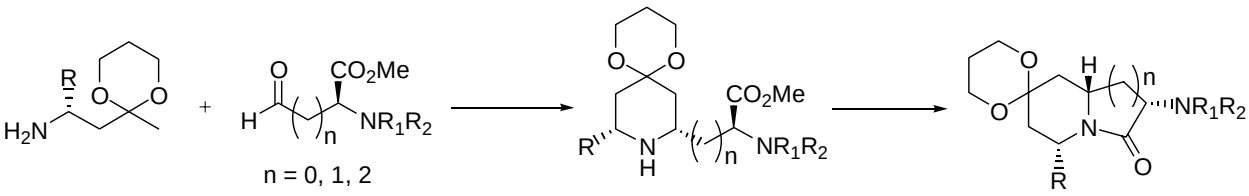


(3*S*,6*R*,10*S*)-**2**

Figure 1

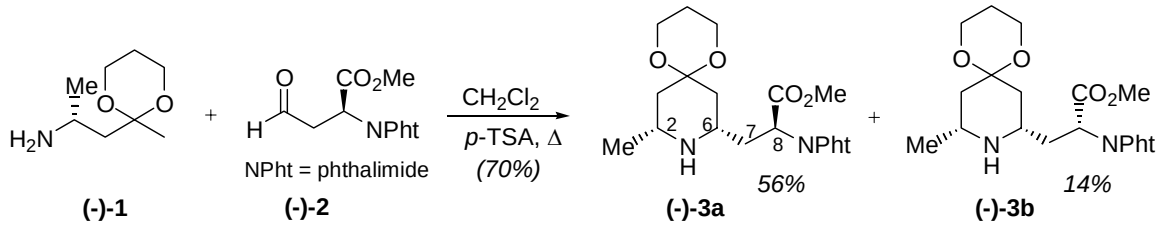
We have recently described an efficient route to various 2,6-disubstituted piperidines[7] which give exclusively the 2,6-*cis*-isomers through a stereoselective Mannich type reaction.[8] When this reaction was applied to ethyl glyoxylate, leading to 6-alkyl substituted pipecolic acid derivatives, *cis* and *trans* isomers were obtained (de = 80-85%).[5b] The extension of this approach between an aspartic or glutamic aldehyde and a chiral amine seems suitable for the diastereoselective synthesis of polysubstituted piperidines which

could be further engaged in a cyclization step to lead indolizidine and quinolizidine amino acid derivatives. (Scheme 1).



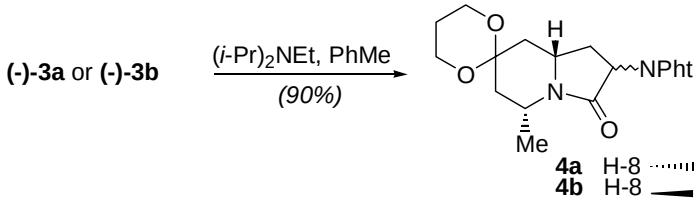
Scheme 1

In order to develop this synthetic pathway, we first orientated our studies to the use of chiral amine **(-)-(1)**[9] and aspartic aldehyde derivative **(-)-(2)**[10] which could be obtained in three steps from L-methionine. So, amine **(-)-(1)** and aldehyde **(-)-(2)** were engaged in the one-pot cyclization procedure and led exclusively to a mixture of piperidines **(-)-(3a)** and **(-)-(3b)** in a 70% overall yield. Structures and relative stereochemistry of **3a** and **3b** were established unambiguously from their spectral data and particularly from ^{1}H-NMR spectral measurements. In the two compounds 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), values which are in accordance with an axial position for H-2 and H-6 and therefore to a 2,6-*cis* relationship.[7] On the other hand, pronounced differences were observed on the amino ester residue since H-7 methylene group give separate multiplets in **3a** and only one multiplet for **3b**, and H-8 a doublet of doublet (J = 4.0 and 11.5 Hz for **3a**; J = 6.0 and 9.0 Hz for **3b**).[11] On this base, we could assume that the difference between **3a** and **3b** is only the configuration of C-8, due to the slight racemisation observed during the preparation of aldehyde **(2)**.[5b,10] (Scheme 2).



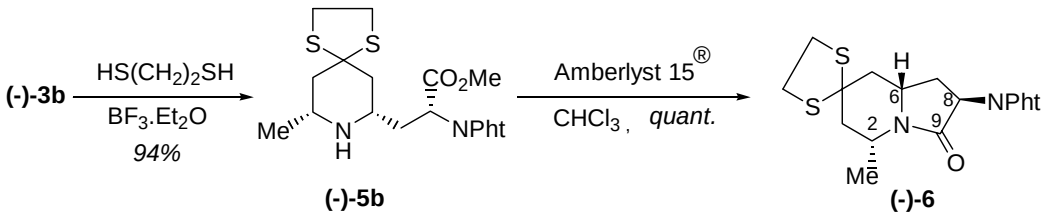
Scheme 2

Treatment of **(-)-3a** with Hünig base in toluene at reflux furnished after 48 h a 1/1 mixture of indolizidin-9-one[5] **(4a)** and **(4b)** in 90% yield whose analytical data showed that they were epimers at C-8. This result was rather surprising, since for similar structures and reactions conditions this racemisation was not observed.[4g] This effect has been attributed to the relative acidity of proton H-8, due mainly to the nitrogen protective group, in this case a phtalimide and also a too long reaction time.[12] Treatment of **(-)-3b** in the same conditions furnish the same ratio of **4a,b** (Scheme3).



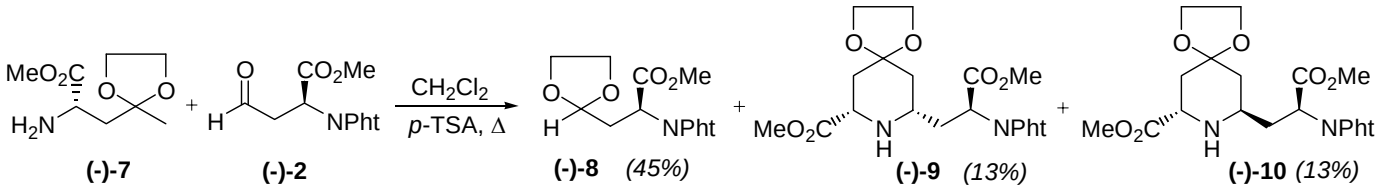
Scheme 3

We then decided to remove the acetal group by using our sequence thioacetalization/hydrogenolysis as previously described for piperidine derivatives.[13] Thus treatment of **(-)-3a** and **(-)-3b** respectively with ethanedithiol in presence of $BF_3.OEt_2$ furnished the dithiolane derivative **(-)-(5a)** and **(-)-(5b)** in good yield. Subsequent desulfurization with Raney nickel W2 on **(-)-5a** did not give the expected piperidine but led to a rapid degradation. On the other hand, using acidic conditions (Amberlyst15® resin, chloroform), **(-)-5b** was smoothly (8 days) but **quantitatively and stereoselectively** transformed in indolizidin-9-one **(-)-(6)** (Scheme 4).



Scheme 4

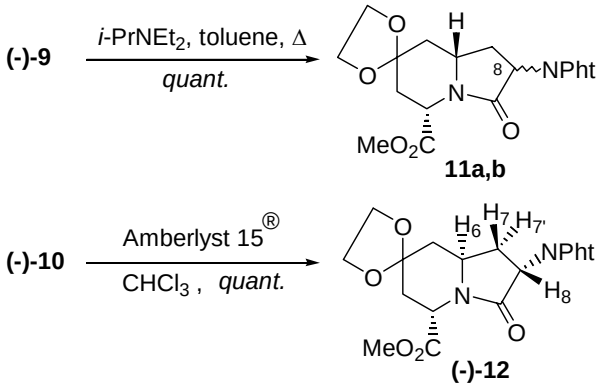
With these experimental conditions in hands, we try now to apply this methodology to the synthesis of indolizidin-9-one amino acid derivatives. Thus, reaction of aldehyde **(-)-(2)** with amine **(-)-(7)**[5b] in standard conditions led to a mixture of three compounds which were easily separated by flash chromatography (Scheme 5).



Scheme 5

Major compound isolated with a 45% yield was the protected aldehyde **(-)-(8)** which occurred from a transacetalization process between the two starting materials.[14] The two others compounds **(-)-(9)** and **(-)-(10)** were isolated each in a very disappointing 13% yield. The structures and relative stereochemistry of **(-)-9** and **(-)-10** were determined from ^{1}H-NMR spectral measurements and by comparison with relative structures prepared before.[5b] The values obtained for **(-)-9** are in accordance with an axial position for H-2

and H-6 [H-3ax and H-5ax respectively gives a triplet (J = 12.5 Hz)] leading to a 2,6-*cis*-disubstituted piperidine. The same measurements effected on **(-)-10** confirm the axial position of the carbomethoxy group : H-3ax gives a doublet of doublet (J = 6.0 and 13.5 Hz) while H-5ax is still a triplet (J = 12.5 Hz). These results are in agreement with those observed for cyclohexane analogues,[15] and thus confirm the presence of a 2,6-*trans* relationship. Here again, the use of an amine derived from an amino acid led to the formation of a mixture of 2,6-stereoisomers, confirming the role of the ester function in the stereochemical behavior of the piperidine framework.[5b] Cyclization reactions were conducted separately on each isomer. Exposure of **(-)-9** to basic conditions (*i*-Pr_2NEt, toluene, reflux) furnished the mixture of indolizidin-9-one **(11a,b)** of which stereochemistry was determined by comparison with compounds **(4a,b)** and with relative compounds early described.[4g] Reaction of **(-)-9** with Amberlyst15® after 8 days did not gave any indolizidin-9-one structure and starting material was recovered while on the same conditions, **(-)-10** give quantitatively the indolizidin-9-one derivative **(-)-(12)** of which relative stereochemistry was determined by NOE experiments (Scheme 6).



Scheme 6

We have described a rapid entry to azabicyclo[4.3.0]alkane amino acids, through the formation of stereoselective *cis*-or *trans*-4,6-substituted pipecolic acid derivatives. Application of this methodology has allowed the synthesis of indolizidin-9-one amino acid derivative **(-)-(6)** and **(-)-(12)** and can be now extended to the synthesis of more complex molecules, by changing the nature of starting amino acid (glutamic acid derivatives or higher homologues). Moreover, side chains could be introduced at early stage of the synthesis by variation around the structure of the aminoacetal counterpart.[16] Examination of the two possible ways of synthesis[5b] has shown the limits of the amino acid route, especially in terms of yield and stereoselectivity, therefore, the route using glyoxylate derivatives has to be privileged.

EXPERIMENTAL

Melting points were determined on a *Reichert* hot stage microscope and are uncorrected. IR spectra were recorded on a FTIR spectrophotometer. NMR spectra were recorded on a Bruker AC 400 spectrometer

operating at 400.13 MHz for ^{1}H-NMR spectrum and at 100.61 MHz for ^{13}C-NMR spectrum. Chemical shifts (δ) 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 g 100 mL^{-1}. EIMS spectra were obtained at 70 eV. FABMS and exact MS 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 P_2O_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 (Kiesegel 60 Merck 200-400 mesh).

(8*R*,10*R*,2'*S*)-8-[Methyl-2'-[*N*-phthalimidoamino]propionate]-10-methyl-1,5-dioxa-9-azaspiro[5.5]undecane (3a) and (8*R*,10*R*,2'*R*)-8-[Methyl-2'-[*N*-phthalimidoamino]propionate]-10-methyl-1,5-dioxa-9-azaspiro[5.5]undecane (3b)

To a stirred solution of aldehyde **(-)-(2)** (0.862 g, 3.30 mmol) in CH_2Cl_2 (20 mL) was added $MgSO_4$ (1 g, 8.31 mmol) followed by a solution of amine **(-)-(*R*)-(1)** (0.5 g, 3.14 mmol) in CH_2Cl_2 (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 $NaHCO_3$ (15 mL) was added and the protected piperidone was extracted with ethyl acetate (4×20 mL). The combined extracts were dried on $MgSO_4$ and evaporated. The residue, purified by column chromatography (eluent : ethyl acetate/methanol, 5/1), gave the corresponding protected 4-piperidones **(-)-(3a)** (0.710 g, 56%) and **(-)-(3b)** (0.175 g, 14%)

3a : oil. $[\alpha]_D^{20}$ = -51° (c 1.15, $CHCl_3$); IR (neat) ν : 2972, 2875, 1774, 1745, 1716 cm^{-1}. ^{1}H-NMR δ : 7.86 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.70 (dd, J = 5.5 Hz, J = 5.0 Hz, 2H), 5.03 (dd, J = 11.5 Hz, J = 4.0 Hz, H-8), 3.86-3.74 (m, 4H), 3.71 (s, 3H), 2.69 (qdd, J = 12.0 Hz, J = 7.0 Hz, J = 2.5 Hz, H-6), 2.60 (tt, J = 12.0 Hz, J = 7.0 Hz, J = 2.5 Hz, H-2), 2.37-2.29 (m, J = 15.0 Hz, J = 11.5 Hz, J = 3.5 Hz, H-7b), 2.24-2.15 (m, J = 15.0 Hz, J = 10.5 Hz, J = 4.0 Hz, H-7a), 2.21(td, J = 13.0 Hz, J = 2.5 Hz, H-5e), 2.09 (td, J = 13.5 Hz, J = 2.5 Hz, H-3e), 1.75 (br s, 1H), 1.66-1.63 (m, 2H), 1.18 (dd, J = 13.5 Hz, J = 12.5 Hz, H-3a), 1.05 (t, J = 7.0 Hz, 3H), 1.01 (dd, J = 13.0 Hz, J = 12.0 Hz, H-5a). ^{13}C-NMR δ : 169.7, 167.7, 134.3, 131.8,123.5, 97.3, 59.5, 59.2, 52.8, 49.1, 49.0, 47.8, 40.9, 40.6, 35.7, 25.5, 22.4. HRMS (EI) *m/z* : 402.17895 (calcd for $C_{21}H_{26}N_2O_6$: 402.17909). Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found : C, 61.80; H, 6.76; N, 7.01.

3b : oil. $[\alpha]_D^{20}$ = -47° (c 1.2, $CHCl_3$); IR (neat) ν : 2972, 2875, 1774, 1745, 1716 cm^{-1}. ^{1}H-NMR δ : 7.85 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.77 (dd, J = 5.5 Hz, J = 5.0 Hz, 2H), 4.98 (dd, J = 9.0 Hz, J = 6.5 Hz, H-

8), 4.91 (br s, 1H), 3.97-3.83 (m, 4H), 3.70 (s, 3H), 2.84 (qdd, J = 12.0 Hz, J = 6.5 Hz, J = 2.5 Hz, H-6), 2.76 (m, H-2), 2.65 (td, J = 13.0 Hz, J = 2.5 Hz, H-3e), 2.38 (m, 2H-7), 1.98 (td, J = 13.0 Hz, J = 2.5 Hz, H-5e), 1.78-1.57 (m, 2H), 1.22 (dd, J = 13.0 Hz, J = 12.5 Hz, H-5a), 1.15 (t, J = 13.0 Hz, H-3a), 0.97 (d, J = 6.5 Hz, 3H). ^{13}C-NMR δ : 175.3, 168.9, 167.7, 134.3, 131.9, 123.5, 96.6, 59.5, 59.3, 53.8, 52.1, 50.1, 49.7, 41.6, 39.3, 29.3, 25.5, 18.6. HRMS (EI) *m/z* : 402.17902 (calcd for $C_{21}H_{26}N_2O_6$: 402.17909).

2-Methyl-9-oxo-8-[*N*-phthalimidoamino]spiro-[4,2'-(1',3-dioxacyclohexyl)-1-azabicyclo-[4.3.0]nonane] (4a,b)

To a solution of **(-)-3a** (0.107 g, 0.265 mmol) in toluene (10 mL) was added diisopropylethylamine (Hünig base) (0.23 mL, 1.325 mmol), and the resulting mixture was stirred under reflux for 48 h. Evaporation of the solvent led to a residue which was purified by chromatography on silica (eluent : ethyl acetate/cyclohexane : 2/1) to give **4a,b** (0.088 g, 90%) in a 1/1 ratio. Repetitive chromatography allow the isolation of **4a** as a white solid : mp = 171-172°C (ethyl ether). IR (KBr) ν : 1716, 1424, 1394, 1210, 1146, 745 cm^{-1}. ^{1}H-NMR δ : 7.83 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.70 (dd, J = 5.5 Hz, J = 5.0 Hz, 2H), 4.90 (dd, J = 10.5 Hz, J = 7.0 Hz, H-8), 3.93 (m, 5H), 3.57 (ddd, J = 13.5 Hz, J = 7.0 Hz, J = 3.0 Hz, H-2), 2.46 (td, J = 13.0 Hz, J = 2.5 Hz, H-5e), 2.40 (m, J = 13.5 Hz, J = 9.0 Hz, J = 7.0 Hz, H-7a), 2.26 (td, J = 13.0 Hz, J = 3.0 Hz, H-3e), 2.06 (m, J = 13.5 Hz, J = 10.5 Hz, J = 4.5 Hz, H-7b), 1.75 (m, 2H), 1.70 (d, J = 7.0 Hz, 3H), 1.44 (dd, J = 13.5 Hz, J = 12.0 Hz, H-3a), 1.37 (t, J = 13.0 Hz, H-5a). ^{13}C-NMR δ : 169.1, 167.5, 134.3, 131.8, 123.4, 96.4 (C-4), 59.4, 59.3 (acetal), 53.7 (C-6), 50.2 (C-8), 49.5 (C-2), 41.5 (C-3), 39.1 (C-5), 29.2 (C-7), 25.3 (acetal), 18.5 (CH_3). HRMS (EI) *m/z* : 370.15280 (calcd for $C_{20}H_{22}N_2O_5$: 370.15287). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found : C, 64.70; H, 6.03; N, 7.52.

4b : ^{13}C-NMR δ : 169.1, 168.9, 167.5, 134.1, 131.8, 123.3, 96.2 (C-4), 59.4, 59.3 (acetal), 51.9 (C-6), 50.8 (C-8), 48.7 (C-2), 41.2 (C-3), 39.5 (C-5), 30.1 (C-7), 25.3 (acetal), 19.1 (CH_3).

(7*R*,9*R*,2'*S*)-7-[Methyl-2'-[*N*-phthalimidoamino]propionate]-9-methyl-1,4-dithia-8-azaspiro[5.4]decane (5a) and (7*R*,9*R*,2'*R*)-7-[Methyl-2'-[*N*-phthalimidoamino]propionate]-9-methyl-1,4-dithia-8-azaspiro[5.4]decane (5b)

To a stirred solution of **(-)-3a** (0.201 g, 0.5 mmol) in dichloromethane (10mL) was added drop wise at rt ethanedithiol (0.21 mL, 2.49 mmol) then $BF_3.Et_2O$ (0.31 mL, 2.49 mmol). After stirring overnight, 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 $MgSO_4$. Evaporation of the solvent followed by column chromatography (eluent : ethyl acetate) gave compound **(-)-(5a)** as a yellow oil (0.197 g, 94%): $[\alpha]_D^{20}$ = -22.6° (*c* 1.0, $CHCl_3$). IR (neat) ν : 2956, 2951, 1773, 1746, 1724,

1436 cm^{-1}. ^{1}H-NMR δ : 7.84 (dd, J = 5.0 Hz, J = 3.0 Hz, 2H), 7.71 (dd, J = 5.0 Hz, J = 3.0 Hz, 2H), 4.98 (dd, J = 11.0 Hz, J = 4.0 Hz, H-8), 3.66 (s, 3H), 3.16 (m, 4H), 2.61 (m, 2H, H-2 and H-6), 2.28 (m, 2H, H-7), 1.95 (m, 2H, H-3e and H-5e), 1.55 (m, 2H, H-3a and H-5a), 1.02 (d, J = 6.0 Hz, CH_3). ^{13}C-NMR δ : 169.5, 167.6, 134.2, 131.6, 123.5, 66.4, 52.7, 52.2, 51.3, 49.6, 48.8, 48.5, 39.0, 37.6, 34.9, 22.2. HRMS (EI) *m/z* : 420.1170 (calcd for $C_{20}H_{24}N_2O_4S_2$: 420.11775).

Following the same procedure, **(-)-3b** (0.150 g, 0.37 mmol) afforded after purification by chromatography (eluent : ethyl acetate) compound **(-)-(5b)** as a yellow viscous oil (0.148 g, 95%) : $[\alpha]_D^{20}$ = -31.0° (*c* 1.0, $CHCl_3$). IR (neat) ν : 2956, 2951, 1775, 1742, 1728 cm^{-1}. ^{1}H-NMR δ : 7.84 (dd, J = 5.0 Hz, J = 3.0 Hz, 2H), 7.71 (dd, J = 5.0 Hz, J = 3.0 Hz, 2H), 4.97 (dd, J = 7.5 Hz, J = 7.0 Hz, H-8), 3.72 (s, 3H), 3.22 (m, 4H), 2.77 (m, J = 13.0 Hz, J = 7.5 Hz, J = 2.5 Hz,1H, H-2), 2.68 (m, J = 12.0 Hz, J = 6.5 Hz, J = 2.0 Hz, 1H, H-6), 2.65 (br s, 1H), 2.30 (dd, J = 7.5 Hz, J = 7.0 Hz, 2H, H-7), 2.21 (dt, J = 13.0 Hz, J = 2.5 Hz, 1H, H-3e), 1.98 (dt, J = 12.5 Hz, J = 2.5 Hz, 1H, H-5e), 1.61 (t, J = 13.0 Hz, 1H, H-3a), 1.58 (t, J = 12.5 Hz, 1H, H-5a), 0.91 (d, J = 6.5 Hz, CH_3). ^{13}C-NMR δ : 169.5, 167.5, 134.2, 131.8, 123.4, 66.3, 53.4, 52.8, 51.7, 49.1, 47.4, 38.7, 37.7, 34.6, 21.7.

(2*R*,6*R*,8*R*)-2-Methyl-9-oxo-8-[*N*-phthalimidoamino]spiro-[4,2'-(1',3'-dithiacyclopentyl)-1-azabicyclo[4.3.0]nonane] (6)

To a stirred solution of **(-)-5b** (0.120g, 0.285mmol) in anhydrous $CHCl_3$ (5 mL) was added few grains of Amberlyst 15® resin. Stirring was maintained during eight days at rt, then the resulting suspension was filtered. The filtrate was washed with brine, and dried over $MgSO_4$. Evaporation of the solvent, followed by column chromatography gave quantitatively compound **(-)-(6)** (0.110g) as a white solid : mp = 195-196°C (ethyl ether). $[\alpha]_D^{20}$ = -54.0° (*c* 1.0, $CHCl_3$). IR (KBr) ν : 3467, 2928, 1774, 1714, 1394, 1313, 1127, 719 cm^{-1}. ^{1}H-NMR δ : 7.82 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.70 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 4.89 (dd, J = 10.5 Hz, J = 7.0 Hz, 1H, H-8), 3.90 (m, J = 12.5 Hz, J = 7.0 Hz, J = 4.0 Hz, J = 3.0 Hz, 1H, H-6), 3.56 (m, 1H, H-2), 3.36 (s, 4H), 2.43 (ddd, J = 13.0 Hz, J = 8.0 Hz, J = 7.0 Hz, 1H, H-7a), 2.22 (dt, J = 13.0 Hz, J = 3.0 Hz, 1H, H-5e), 2.03 (m, 2H, H-7b and H-3e), 1.90 (t, J = 12.0 Hz, 1H, H-3a), 1.87 (t, J = 13.0 Hz, 1H, H-5a), 1.68 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C-NMR δ : 169.2, 168.9, 167.6, 134.2, 131.9, 123.5, 65.4, 56.8, 53.3, 50.5, 50.1, 48.3, 39.3, 38.1, 29.3, 18.5. HRMS (EI) *m/z* : 388.0919 (calcd for $C_{19}H_{20}N_2O_3S_2$: 388.09154). Anal. Calcd for $C_{19}H_{20}N_2O_3S_2$: C, 58.74; H, 5.19; N, 7.21. Found : C, 58.85; H, 5.25; N, 7.15.

(*S*)-2[Methyl-(2'-amino)propionate]-1,3-dioxolane (8) ; (7*S*,9*R*)-7-Methoxycarbonyl-9-[methyl-(2'*S*)-[*N*-phthalimidoamino]propionate]-1,4-dioxo-8-aza-spiro[5.4]decane (9) and (7*S*,9*S*)-7-

Methoxycarbonyl-9-[methyl-(2'*S*)-[*N*-phthalimidoamino]propionate]-1,4-dioxo-8-aza-spiro[5.4]-decane (10)

Following the procedure employed in the synthesis of **3a** and **3b**, starting from amine **(-)-(7)** (0.300 g, 1.58 mmol) and aldehyde **(-)-(2)** (0.450 g, 1.74 mmol), compounds **(-)-(8)** (0.240 g, 45%), **(-)-(9)** (0.090 g, 13%) and **(-)-(10)** (0.090 g, 13%) were obtained after chromatography (eluent : cyclohexane/ethyl acetate 3/1 then ethyl acetate).

8 : colorless oil. $[\alpha]_D^{20}$ = -22.0° (*c* 0.94, $CHCl_3$). IR (neat) ν : 2960, 2890, 1772, 1748, 1718, 1690 cm^{-1}. ^{1}H-NMR δ : 7.86 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.73 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 5.18 (dd, J = 9.0 Hz, J = 5.0 Hz, 1H), 4.98 (t, J = 4.0 Hz, 1H), 3.81 (m, 4H), 3.74 (s, 3H), 2.66 (m, J = 11.5 Hz, J = 9.0 Hz, J = 5.0 Hz, J = 4.0 Hz, 2H). ^{13}C-NMR δ : 169.6,167.5, 134.5, 134.1, 131.9, 123.7, 123.5, 101.9, 65.0, 64.9, 52.9, 47.4, 32.0.

9 : viscous oil. $[\alpha]_D^{20}$ = -60.6° (*c* 0.7, $CHCl_3$). IR (neat) ν : 3019, 2952, 2880, 2837, 1777, 1753, 1737, 1713, 1705, 1468 cm^{-1}. ^{1}H-NMR δ : 7.86 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.74 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 5.13 (dd, J = 11.0 Hz, J = 4.0 Hz, 1H), 3.90, (m, 4H), 3.72 (s, 6H), 3.46 (dd, J = 12.5 Hz, J = 2.5 Hz, 1H, H-2), 2.66 (m, 1H, H-6), 2.32 (m, 2H, H-7), 2.00 (dt, J = 12.5 Hz, J = 2.5 Hz, 1H, H-3e), 1.85 (br s, 1H, NH), 1.63 (dt, J = 13.0 Hz, J = 2.0 Hz, 1H, H-5e), 1.52 (t, J = 12.5 Hz, 1H, H-3a), 1.40 (dd, J = 13.0 Hz, J = 12.0 Hz, 1H, H-5a). ^{13}C-NMR δ : 172.9, 169.7, 167.7, 134.3, 131.8, 123.7, 107.3, 64.5, 64.3, 56.4, 52.9, 52.1, 50.1, 48.9, 41.7, 38.2, 35.5. HRMS (EI) *m/z* : 431.4235 (calcd for $C_{21}H_{23}N_2O_8$: 431.4241).

10 : viscous oil. $[\alpha]_D^{20}$ = -64.8° (*c* 0.7, $CHCl_3$). IR (neat) ν : 3025, 2952, 2935, 2875, 1777, 1753, 1731 cm^{-1}. ^{1}H-NMR δ : 7.86 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 7.74 (dd, J = 5.5 Hz, J = 3.0 Hz, 2H), 5.15 (dd, J = 9.5 Hz, J = 4.5 Hz, 1H), 3.87 (m, 6H), 3.71 (s, 3H), 3.58 (s, 3H), 3.27 (m, 1H), 2.44 (m, 1H), 2.34 (m, 1H), 2.15 (ddd, J = 13.0 Hz, J = 4.0 Hz, J = 2.0 Hz, 1H, H-5e), 1.95 (br s, 1H, NH), 1.85 (dd, J = 13.0 Hz, J = 6.0 Hz, 1H, H-3a), 1.75 (dt, J = 13.0 Hz, J = 2.0 Hz, 1H, H-3e), 1.45 (dd, J = 13.0 Hz, J = 10.5 Hz, 1H, H-5a). ^{13}C-NMR δ : 174.1, 169.9, 167.6, 134.2, 131.9, 123.5, 106.8, 64.4, 64.0, 54.3, 52.9, 51.5, 49.5, 48.5, 39.7, 35.4, 35.2.

Methyl-9-oxo-8-[*N*-phthalimidoamino]spiro-[4,2'-(1',3'-dioxacyclopentyl)-1-azabicyclo-[4.3.0]nonane]-2-carboxylate (11a,b)

Following the procedure employed in the synthesis of **4a,b**, compound **(-)-(9)** (0.060 g, 0.14 mmol) was dissolved in toluene (5 mL). After addition of Hünig base (0.12 mL, 0.70 mmol), the resulting mixture

was heated at reflux for two days. Purification by chromatography (eluent : ethyl acetate) gave a 1/1 mixture of **11a,b** which could not be separated.

11a,b : viscous oil. ^{1}H-NMR δ : 7.78 (m, 2H), 7.74 (m, 2H), 5.25 (m, 1H), 5.05 (m, 1H), 4.95 (m, 1H), 4.05-3.85 (m, 8H), 3.74 (s, 3H), 3.55 (s, 3H), 3.45 (m, 1H), 2.80 (m, 1H), 2.70-2.60 (m 2H), 2.45-2.05 (m, 4H), 2.00-1.80 (m, 5H), 1.75 (br s, 2H), 1.60 (m, 1H), 1.55 (m, 1H), 1.40 (m, 1H), 1.25 (m, 1H).

(2*S*,6*S*,8*S*)-Methyl-9-oxo-8-[*N*-phthalimidoamino]spiro-[4,2'-(1',3'-dioxacyclopentyl)-1-azabicyclo-[4.3.0]nonane]-2-carboxylate (12)

Following the procedure employed in the preparation of **(-)-(6)**, starting from **(-)-(10)** (0.090 g, 0.21 mmol) compound **(-)-(12)** (0.083 g) was obtained quantitatively, after chromatography, as a white solid : mp = 181-182°C (ethyl ether). $[\alpha]_D^{20}$ = -79.0° (*c* 0.7, $CHCl_3$). IR (KBr) ν : 33023, 2948, 2900, 1729, 1721, 1698 cm^{-1}. ^{1}H-NMR δ : 7.83 (dd, J = 5.0 Hz, J = 3.0 Hz, 2H), 7.71 (dd, J = 5.0 Hz, J = 3.0 Hz, 2H), 5.02 (dd, J = 11.0 Hz, J = 7.5 Hz, 1H, H-8), 4.97 (d, J = 6.5 Hz, 1H, H-2), 4.45 (dddd, J = 12.5 Hz, J = 8.5 Hz, J = 4.0 Hz, J = 4.0 Hz, 1H, H-6), 4.08-3.85 (m, 4H), 3.80 (s, 3H), 2.55 (ddd, J = 14.0 Hz, J = 8.5 Hz, J = 7.5 Hz, 1H, H-7'), 2.47 (d, J = 14.0 Hz, 1H, H-3e), 2.18 (ddd, J = 14.0 Hz, J = 11.0 Hz, J = 4.0 Hz, 1H, H-7), 1.95 (dt, J = 12.5 Hz, J = 3.0 Hz, 1H, H-5e), 1.78 (dd, J = 14.0 Hz, J = 7.0 Hz, 1H, H-3a), 1.60 (t, J = 12.5 Hz, 1H, H-5a). ^{13}C-NMR δ : 170.2, 168.8, 167.2, 134.2, 131.9, 123.5, 106.4, 64.7, 64.5 (acetal), 52.5 (OCH_3), 51.0 (C-6), 50.6 (C-2), 48.4 (C-8), 41.5 (C-5), 34.5 (C-3), 29.1(C-7). HRMS (EI) *m/z* : 400.3876 (calcd for $C_{20}H_{20}N_2O_7$: 400.3881). Anal. Calcd for $C_{20}H_{20}N_2O_7$: C, 60.00; H, 5.03; N, 7.00. Found : C, 60.68; H, 5.15; N, 6.94.

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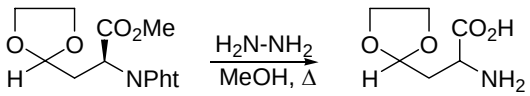

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