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DIASTEREOSELECTIVE SYNTHESIS OF 1-AZA-SPIRO[5.5]UNDECANE SKELETON

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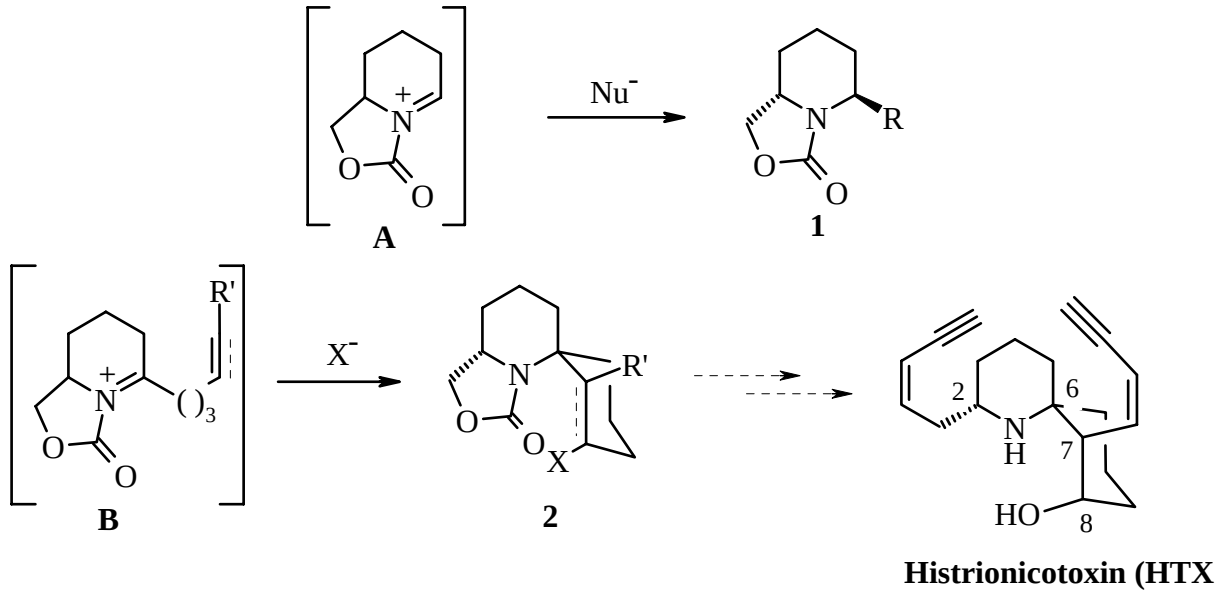
Abstract – The synthesis of various bicyclic enamines (**5**), bearing a side chain with a multiple C-C bond or a furan ring, was performed from racemic pipecolic acid through sulfone (**1c**). Cyclization of these derivatives (**5**), *via* the corresponding *in situ* generated *N*-acyliminium ions, was studied in various acidic conditions to afford, in some cases, spiro intermediates (**2**) which possess the backbone of the histrionicotoxin family of alkaloids.

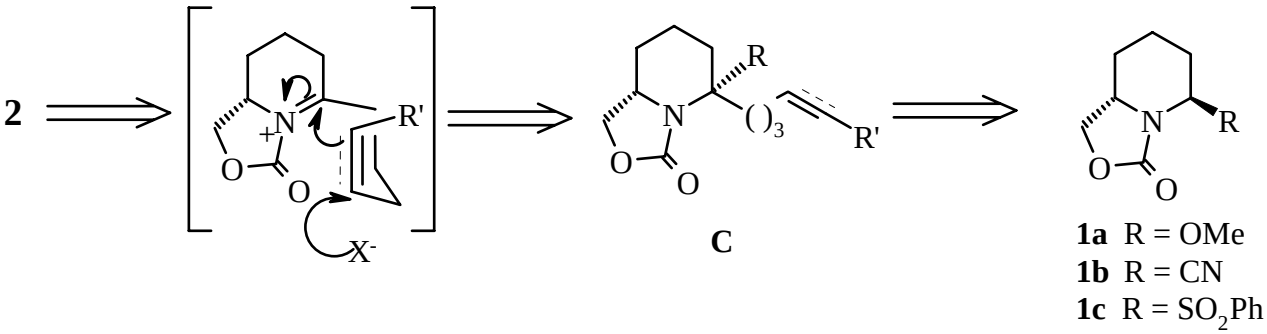
We have recently demonstrated that bicyclic *N*-acyliminium ion (**A)** (Scheme 1) reacted with various π-type nucleophiles to exclusively afford *trans*-disubstituted 2,6-piperidines.[1] This methodology was successfully applied to the total synthesis of tricyclic alkaloid (-)-porantheridine.[2] Based on these results, we next envisioned the stereoselective preparation of trisubstituted piperidines (**2**) containing a spirocyclohexane moiety, *via* an intramolecular nucleophilic addition on a bicyclic iminium ion of type (**B)** (Scheme 1). Herein, we wish to report some promising preliminary results concerning a stereoselective approach towards the 1-aza-spiro[5.5]undecane skeleton. Such azaspirocyclic substructures constitute actually the main core of histrionicotoxins (**HTX**), a family of alkaloids isolated from the skin secretions of the Colombian frog *Dendrobates histrionicus.*[3]

As summarized in Scheme 2, our strategy relies on an intramolecular nucleophilic addition of an unsaturated C-C bond on a tetrasubstituted bicyclic iminium ion. The generation of the required iminium ion was envisioned from derivatives (**1**), *via* tetrasubstituted intermediates of type (**C)**. The R group of compound (**1**) must fulfill two requirements, *i.e.* to be nucleofugal enough to generate the iminium ion, and to be an efficient electron withdrawing group to allow the introduction of the alkyl chain. To this end,



Scheme 1

cyano and arylsulfone derivatives (**1b**) and (**1c**) were considered. However, preliminary experiments from cyano-substituted model 1-carbomethoxy-2-cyano-2-(pent-4-enyl)piperidine showed that the *N*-acyliminium ion formation does not occur. This is probably due to the presence of the *N*-acyl moiety, which renders the cyano group less labile and prevents the formation of the iminium ion.

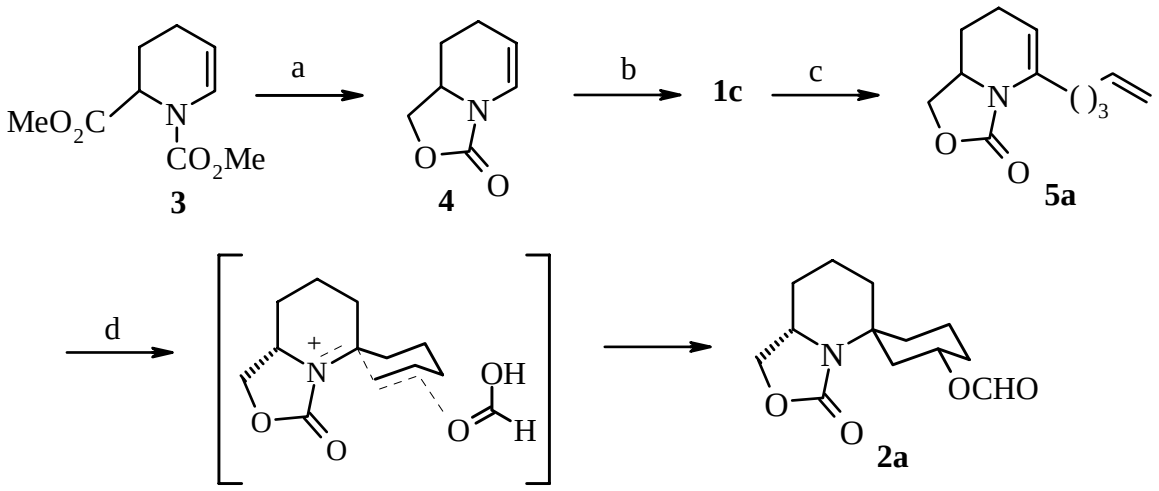


Scheme 2

We next examined the reactivity of phenylsulfone (**1c**). By analogy with the formation of α-phenylsulfonyl formamides,[4] we intended to prepare the required substrate by reaction of benzenesulfinic acid with aminoether (**1a**),[1] in the presence of calcium chloride. Under these conditions, only an inexploitable mixture was obtained. However**,** the desired sulfone (**1c**) was obtained in good yield by adding benzenesulfinic acid (2 equivalents) on bicyclic enamine (**4**) (Scheme 3), which was first synthesized by reductive cyclization of monocyclic enamine (**3**).[5]

With the required substrate in hand, the alkylation step was next examined under various conditions (RX,

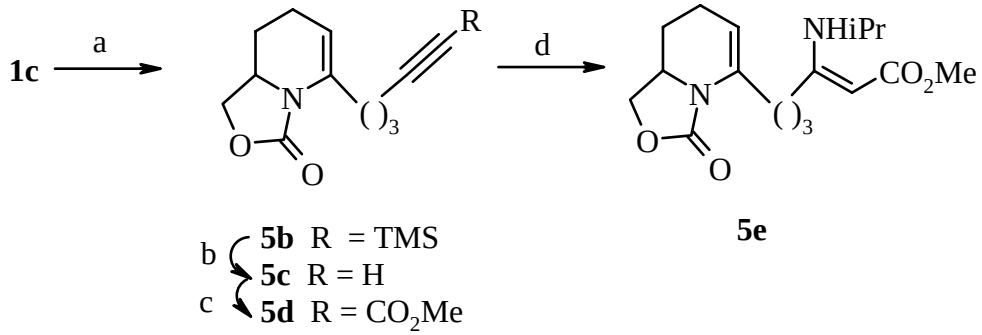
LDA/HMPA or *sec*-BuLi/TMEDA). We first investigated the introduction of a 4-pentenyl chain (Scheme 3). Whatever the conditions, the alkylated sulfone was never isolated. Instead, the expected compound resulting from the alkylation step underwent spontaneous elimination of sulfenic acid, to lead to the corresponding α-substituted enamine (**5a**)**,** which was isolated in 77% yield upon optimized conditions *i.e.* LDA (2.2 eq.)/HMPA (8 eq.). However, this result did not prevent the iminium ion generation. Indeed, stirring of enamine (**5a**) in formic acid at room temperature[6,7] led selectively to the expected spiro-piperidine containing formate (**2a**) in 65% yield (Scheme 3). The isolated crystalline compound (**2a**) proved to be a single isomer whose structure was established by X-Ray crystallography analysis. The observed relative stereochemistry was consistent with an approach of the C-C double bond proceeding as anticipated based on previous results.[1] Moreover, trapping of the resulting transient carbenium ion was also a stereoselective process which noteworthy led to a relative stereochemistry at C-8 identical to that found in histrionicotoxin alkaloids (Scheme 1).



Scheme 3 (a) $NaBH_4$, MeOH-DME, 90°C, 56%; (b) $PhSO_2H$, CH_2Cl_2, 88%; (c) LDA, HMPA, THF, 5-bromo-pent-1-ene, 77%; (d) HCO_2H, 65%

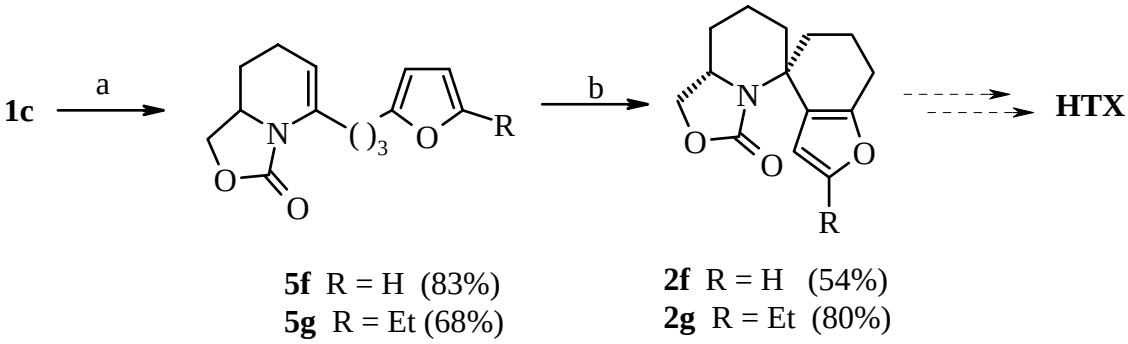
In order to access to more functionalized structures (in positions C-7 and C-8), we next examined the cyclization of enamines (**5e**), bearing a β-enamino ester moiety as the nucleophile. Compound (**5e)** was prepared from sulfone (**1c**) in four steps *via* ynoate (**5d**) (Scheme 4). When treated in the presence of protic acids (*p*-TSA, TFA, AcOH), compound (**5e**) only afforded a 2,6-diketo ester, resulting from the hydrolysis of both enamine functions of the substrate. Attempts of cyclization from less nucleophilic alkynes (**5b, c, d**) were equally unsuccessful.

Finally, taking the results of Tanis *et al.*[8] into account, we considered the cyclization of furan derivatives



Scheme 4 (a) LDA, HMPA, THF, 5-iodo-1-trimethylsilylpent-1-yne, 84%; (b) K_2CO_3, MeOH, 86%; (c) *n*-BuLi, MeOCOCl, 79%; (d) K_2CO_3, *iso*-$PrNH_2$, 65%.

(**5f**) and (**5g**), obtained from sulfone (**1c**) according to the previously optimized conditions used for the preparation of **5a** (Scheme 5). Various acidic conditions were then examined from substrate (**5f**). Whereas acetic acid was ineffective, the use of anhydrous *p*-TSA in CH_2Cl_2 or HCO_2H in hexane gave the expected cyclization product (**2f**) in low yields (< 25%). The best yield (54 %) was obtained by using diluted TFA (0.1 M in CH_2Cl_2). On the other hand, when reacted in the same conditions, substrate (**5g**) which possesses a 5-ethylfuran-2-ylpropyl chain, led to the corresponding spiro compound (**2g**) in a much better yield (80 %), probably owing to the presence of a more nucleophilic aromatic ring. The expected relative stereochemistry of crystalline compound (**2f**) was once again secured by X-Ray structure analysis (Figure 1). On the basis of the ^{13}C-NMR data comparison of **2f** and **2g**, we assume the same relative stereochemistry for both compounds.

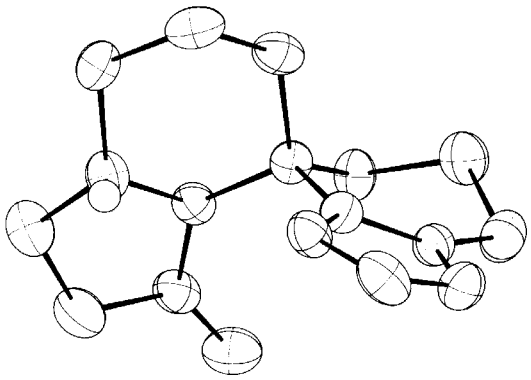


Scheme 5 (a) LDA, HMPA, THF, 2-(3-bromopropyl)furan (R = H) or 2-(3-bromopropyl)-5-ethylfuran (R = Et); (b) TFA, CH_2Cl_2.

In this study, we first developed access to disubstituted bicyclic enamines (**5**), some of which proved to be efficient precursors of aza-1-bicyclo[5.5]undecane frameworks, *via* the corresponding bicyclic iminium ions (**B)**. The successful cyclisations thus observed occurred with a total control of the incoming stereogenic center(s), based on radiocrystallographic analysis data. Noteworthy, the quaternary center

arising from this cyclisation stems, as anticipated, from an intramolecular approach of the nucleophilic moiety *anti* to the oxazolidinone ring. Moreover, azaspiranic compounds (**2**) (in particular **2g**), which possess the required relative stereochemistry of centers C-2 and C-6, are suitable precursors for the elaboration of HTX family of alkaloids. Judicious functional transformations on the furan ring would allow stereo-controlled introduction of the required C-7 and C-8 substituants.

Figure 1 Crystal structure of **2f**.



EXPERIMENTAL

General : The general experimental procedures were carried out as previously described.[9]

(8aS*)-1,7,8,8a-Tetrahydrooxazolo[3,4-*a*]pyridin-3-one (4) : To a solution of enamine (3)[5] (2.8 g, 14 mmol) in a mixture of MeOH (6 mL) and DME (28 mL) was added portionwise $NaBH_4$ (2.7 g, 71 mmol). The reaction mixture was stirred at 90°C for 6 h, then cooled to rt and concentrated *in vacuo.* EtOAc (50 mL) was added to the obtained residue and a 10 % aqueous citric acid was added until a limpid solution was obtained. The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (EtOAc/cyclohexane, 1:1) yielded 1.1 g (56 %) of bicyclic enamine (**4**) as a white solid; mp 39-40°C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1740 cm^{-1}. ^1H NMR : δ = 6.51 (dd, *J* = 8.1 and 2 Hz, 1H), 5.0-4.9 (m, 1H), 4.6-4.4 (m, 1H), 4.03 (dd, *J* = 14.3 and 7.1 Hz, 1H), 3.95-3.85 (m, 1H), 2.1-1.9 (m, 3H), 1.7-1.45 (m, 1H). ^{13}C NMR : δ = 152.0, 121.4, 107.6, 69.1, 52.6, 26.2, 21.1.

(5S*, 8aR*)- 5-Benzenesulfonylhexahydrooxazolo[3,4-*a*]pyridin-3-one (**1c**) : To a stirred solution of enamine (**4**) (2.54 g, 18.3 mmol) in CH_2Cl_2 (50 mL) was added freshly prepared benzenesulfinic acid (5.15 g, 36.3 mmol). After stirring at rt for 3 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (3 × 30 mL), then brine (30 mL). The organic layer was dried over Na_2SO_4,

concentrated *in vacuo* and column chromatographed (EtOAc/cyclohexane, 7:3) to yield 4.54 g (88%) of compound (**1c**)[10] as a white solid; mp 133-134°C (EtOAc). IR ($CHBr_3$) : ν_{max} = 1150, 1750 cm^{-1}. ^1H NMR : δ = 7.95-7.85 (m, 2H), 7.7-7.5 (m, 3H), 4.92 (d, *J* = 6.7 Hz, 1H), 4.49 (dd, *J* = 8.0 and 8.1 Hz, 1H), 4.45-4.3 (m, 1H), 3.92 (dd, *J* = 5.8 and 8.1 Hz, 1H), 2.75-2.65 (m, 1H), 2.25-2.1 (m, 1H), 2.0-1.7 (m, 3H), 1.4-1.3 (m, 1H). ^{13}C NMR : δ = 155.8, 137.0, 134.4, 129.4, 128.7, 69.1, 69.0, 50.5, 29.9, 21.6, 18.7. Anal.Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found : C, 55.36; H, 5.46; N, 4.97.

(±)-5-Pent-4-enyl-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-3-one (**5a**) : To a stirred cooled solution of LDA (2.4 mmol) in THF (5 mL) at –78°C, was added dropwise a solution of sulfone (**1c**) (300 mg, 1.07 mmol) in THF (10 mL) and HMPA (1.5 mL, 8.6 mmol). The reaction mixture was stirred for 1 h before the slow addition of 5-bromopent-1-ene (486 mg, 3.26 mmol) in THF (1 mL). Stirring was continued at –78°C for 45 min, then at rt for one night. A saturated aqueous NH_4Cl solution (20 mL) was then added and the mixture was concentrated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (EtOAc/cyclohexane, 1:1) yielded 170 mg (77 %) of compound (**5a**) as an oil. IR (neat) : ν_{max} = 1645, 1665, 1760 cm^{-1}. ^1H NMR : δ = 5.82 (ddt, *J* = 17, 10.3 and 6.7 Hz, 1H), 5.05-4.8 (m, 3H), 4.5 (t, *J* = 7.2 Hz, 1H), 3.95 (t, *J* = 7.2 Hz, 1H), 3.95-3.8 (m, 1H), 2.95-2.75 (m, 1H), 2.4-2.25 (m, 1H), 2.2-1.9 (m, 4H), 1.8-1.5 (m, 4H). ^{13}C NMR : δ = 154.1, 138.8, 136.2, 114.6, 107.5, 67.5, 54.3, 33.2, 31.4, 27.5, 27.3, 22.2. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found : C, 69.50; H, 8.34; N, 6.68.

(±)-5-(5-Trimethylsilanylpent-4-ynyl)-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-3-one (5b) : Sulfone (**1c**) (2.4 g, 8.5 mmol) and 5-iodo-1-trimethylsilylpent-1-yne (6.8 g, 25.6 mmol) were allowed to react following a procedure similar to the one described for compound (**5a**), to give 2 g (84%) of enamine (**5b**) as a yellow oil. IR (neat) : ν_{max} = 1750, 2180 cm^{-1}. ^1H NMR : δ = 4.9-4.8 (m, 1H), 4.87 (t, *J* = 7.3 Hz, 1H), 4.0-3.75 (m, 2H), 3.0-2.8 (m, 1H), 2.5-2.3 (m, 1H), 2.3-1.9 (m, 5H), 1.85-1.5 (m, 3H), 0.12 (s, 9H). ^{13}C NMR : δ =154.0, 135.2, 108.1, 107.3, 84.7, 67.5, 54.2, 31.0, 27.4, 27.0, 22.2, 19.1, 0.2. Anal. Calcd for $C_{15}H_{23}NO_2Si$: C, 64.94; H, 8.36; N, 5.05. Found : C, 65.04; H, 8.31; N, 4.76.

(±)-5-Pent-4-ynyl-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-3-one (5c) : A mixture of compound (**5b**) (2 g, 7.1 mmol) and potassium carbonate (5.4 g, 39.1 mmol) in methanol (90 mL) was stirred at rt for 16 h. The solvent was evaporated *in vacuo* and water (10 mL) was added to the resulting residue. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography

(EtOAc/cyclohexane, 1:1) yielded 1.26 g (86 %) of compound (**5c**) as a solid : mp 62-63°C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1750 cm^{-1}. ^1H NMR : δ = 4.95-4.85 (m, 1H), 4.5 (t, *J* = 7.8 Hz, 1H), 4.0-3.8 (m, 2H), 3.05-2.85 (m, 1H), 2.55-2.35 (m, 1H), 2.3-2.05 (m, 4H), 2.05-1.9 (m, 2H), 1.85-1.55 (m, 3H). ^{13}C NMR : δ = 153.9, 134.8, 108.0, 84.2, 68.4, 67.3, 54.0, 30.7, 27.1, 26.6, 22.0, 17.5. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N 6.82. Found : C, 70.36; H, 7.32; N 6.66.

(±)-6-(3-Oxo-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-5-yl)hex-2-ynoic acid methyl ester (5d) : To a solution of alkyne (**5c**) (1.26 g, 6.15 mmol) in THF (20 mL) at – 78°C was added dropwise 2.5 M solution of *n*-BuLi (2.8 mL, 7 mmol). Stirring was continued for 30 min before the addition of methyl chloroformiate (4.75 mL, 61 mmol). The reaction mixture was stirred at rt for 45 min prior to the addition of brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the organic layer was dried over Na_2SO_4, concentrated *in vacuo* and column chromatographed (EtOAc/Cyclohexane , 1:1) to give 1.28 g (79 %) of compound (**5d**) as a yellow solid: mp 56.5-57.5 °C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1705, 1740 cm^{-1}. ^1H NMR : δ = 4.75-4.6 (m, 1H), 4.4-4.25 (m, 1H), 3.85-3.65 (m, 2H), 3.52 (s, 3H), 2.8-2.65 (m, 1H), 2.3-2.1 (m, 3H), 2.05-1.75 (m, 3H), 1.65-1.3 (m, 3H). ^{13}C NMR : δ = 153.4, 153.3, 133.8, 108.1, 88.9, 72.5, 67.0, 53.5, 51.9, 30.5, 26.5, 25.3, 21.6, 17.1. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found C, 63.51; H, 6.59; N, 5.18.

(±)-3-Isopropylamino-6-(3-oxo-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-5-yl)hex-2-enoic acid methyl ester (5e) : A mixture of compound (**5d)** (200 mg, 0.76 mmol) and potassium carbonate (320 mg, 2.3 mmol) in isopropylamine (5 mL, 58 mmol) and water (0.5 mL) was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo*. Water (20 mL) was added to obtained residue and extraction was performed with CH_2Cl_2 (3 × 20 mL). Drying over Na_2SO_4, concentration *in vacuo* and column chromatography (EtOAc/cyclohexane , 1:1) yielded 160 mg (65 %) of the expected compound (**5e**) as an oil. IR (neat) : ν_{max} = 1750 cm^{-1}. ^1H NMR : δ = 8.4 (s, 1H), 4.8 (m, 1H), 4.41 (t, *J* = 7.8 Hz, 1H), 4.34 (s, 1H), 3.95-3.75 (m, 2H), 3.65-3.7 (m, 1H), 3.53 (s, 3H), 2.9-2.75 (m, 1H), 2.4-2.25 (m, 1H), 2.25-2.05 (m, 4H), 2.0-1.9 (m, 1H), 1.75-1.50 (m, 3H), 1.13 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR : δ =171.0, 164.7, 153.9, 135.2, 107.7, 80.1, 67.4, 54.1, 49.7, 43.9, 31.5, 27.1, 24.2, 22.0.

(±)-5-(3-Furan-2-ylpropyl)-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-3-one (**5f**) : Sulfone (**1**c) (5.5 g, 20 mmol) and 2-(3-bromopropyl)furan (11 g, 58 mmol) were allowed to react following a procedure similar to the one described for compound (**5a**) to afford 4 g (83%) of enamine (**5f**) as a white solid; mp 51-52°C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1750 cm^{-1}. ^1H NMR : δ = 7.27 (dd, *J* = 0.9 and 1.9 Hz, 1H), 6.26 (dd, *J* = 1.9 and 3.1 Hz, 1H), 6.0 (dd, *J* = 0.9 and 3.1 Hz, 1H), 4.95-4.8 (m, 1H), 4.5 (dd, *J*

= 8.0 and 8.0 Hz, 1H), 4.05-3.75 (m, 2H), 3.05-2.8 (m, 1H), 2.65 (t , *J* = 7.8 Hz, 2H), 2.45-2.25 (m, 1H), 2.2-1.5 (series of m, 6H). ^{13}C NMR : δ =156.0, 154.0, 140.6, 135.5, 110.0, 107.8, 104.7, 67.4, 54.1, 31.3, 27.3, 27.2, 26.2, 22.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found : C, 67.98; H, 7.04; N, 5.38.

(±)-5-(3-(5-Ethylfuran-2-ylpropyl)-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridin-3-one (**5g**) : Sulfone (**1c**) (3 g, 10.7 mmol) and 2-(3-bromopropyl)-5-ethylfuran (6.95 g, 32 mmol) were allowed to react following a procedure similar to the one described for compound (**5a**), to yield 2 g (68 %) of enamine (**5g**) as an oil. IR (neat) : ν_{max} = 1755 cm^{-1}. ^{1}H NMR : δ = 5.88 (d, *J* = 3 Hz, 1H), 5.84 (d, *J* = 3 Hz, 1H), 4.86 (m, 1H), 4.5 (t, *J* = 8.3 Hz, 1H), 4.05-3.8 (m, 2H), 3.0-2.85 (m, 1H), 2.75-2.5 (m, 4H), 2.45-2.3 (m, 1H), 2.25-1.55 (series of m, 6H), 1.21 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR : δ = 155.6, 153.8 (2C), 135.4, 107.6, 104.9, 103.9, 67.2, 54.0, 31.2, 27.1 (2C), 26.1, 21.9, 21.1, 12.0. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found : C, 69.70; H, 7.71; N, 5.11.

Spiro[(5R*, 8aS*)-hexahydrooxazolo[3,4-*a*]pyridin-3-one-5:1'-(3'S*)-formyloxycyclohexane] (**2a**) : A solution of compound (**5a**) (270 mg, 1.3 mmol) in formic acid (10 mL) was stirred for 24 h at rt. The mixture was concentrated at reduced pressure and CH_2Cl_2 (30 mL) was added to the obtained residue. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 30 mL), then brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatography (EtOAc/cyclohexane, 6:4) yielded 215 mg (65 %) of compound (**2a**) as a white crystalline solid; mp 93-94°C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1180, 1730 cm^{-1}. ^{1}H NMR : δ = 7.88 (s, 1H), 5.0-4.75 (m, 1H), 4.27 (t, *J* = 6.7 Hz, 1H), 3.9-3.65 (m, 2H), 3.11 (td, *J* = 7.2 and 20.7 Hz, 1H), 2.33 (m, 1H), 2.15-1.15 (series of m, 12H). ^{13}C NMR : δ =160.7, 156.5, 69.8, 67.2, 57.4, 53.4, 34.1, 33.4, 32.6, 31.0, 29.2, 19.3, 19.0. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found : C, 61.67; H, 7.70; N, 5.47. Crystal data : $C_{13}H_{19}NO_4$ (253.3); monoclinic, space group $P2_1$; a = 8.540(4), b = 10.678(4), c = 12.705(7) Å, β = 92.68 (4)°, V = 1293(1) Å^3; Z = 4 ; D = 1.30 g cm^{-3} ; F(000) = 544.17 ; μ(Mo-Kα) = 0.9 cm^{-1}.

Spiro[(5R*, 8aS*)-hexahydrooxazolo[3,4-*a*]pyridin-3-one-5: 4'-4'-5',6',7'-tetrahydobenzofuran (**2f**) : To a solution of compound (**5f**) (97 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise trifluoroacetic acid (115 μL, 1.5 mmol). After stirring for 30 min, 4 N aqueous NaOH solution (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and chromatographed (EtOAc/cyclohexane, 1:1) yielding 52 mg (54 %) of compound (**2f**) as a white crystalline solid; mp 125-126°C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1745 cm^{-1}. ^{1}H NMR : δ = 7.24 (d, *J* = 1.8 Hz, 1H), 6.4 (d, *J* = 1.8 Hz, 1H), 4.32 (t, *J* = 8.0 Hz, 1H), 4.25-

4.0 (m, 1H), 3.75 (t, *J* = 8.0 Hz, 1H), 3.25-3.05 (m, 1H), 2.8-2.45 (m, 2H), 2.2-1.2 (series of m, 9H). ^{13}C NMR : δ = 155.9, 151.8, 140.4, 120.5, 108.7, 67.8, 55.4, 54.5, 38.0, 33.4, 28.8, 22.9, 20.1, 19.0. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found : C, 68.00; H, 7.09; N, 5.54. Crystal data : $C_{14}H_{17}NO_3$ (247.3) orthorhombic, space group $P2_12_12_1$; a = 7.825(2), b = 8.278(4), c = 18.767(6) Å, V = 1215.7(8) Å^3 ; Z = 4 ; D = 1.35 g cm^{-3}; F(000) = 528.15 ; μ(Mo-Kα) = 0.9 cm^{-1}.

Spiro[2-ethyl-4'-5'-6'-7'-tetrahydrobenzofuran-4':(5R*, 8aS*)-5-hexahydrooxazolo[3,4-*a*]pyridin-3-one] (**2g**) : Compound (**5g**) (1 g, 3.65 mmol) and trifluoroacetic acid (1.1 mL, 13.9 mmol) were allowed to react for 90 min according to a procedure similar to the one described for compound (**2f**), yielding 0.8 g (80 %) of compound (**2g**) as a white crystalline solid; mp 108 °C (EtOAc/cyclohexane). IR ($CHBr_3$) : ν_{max} = 1750 cm^{-1}. ^{1}H NMR : δ = 5.84 (s, 1H), 4.23 (t, *J* = 7.0 Hz, 1H), 3.85-3.55 (m, 2H), 2.7-2.35 (m, 4H), 2.05-1.45 (m, 9H), 1.40-1.05 (m, 4H). ^{13}C NMR : δ = 155.6, 154.8, 148.5, 120.9, 102.1, 67.0, 54.0, 53.1, 36.4, 28.8, 28.6, 22.4, 21.0, 19.5, 19.2, 11.6. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found : C, 69.84; H, 7.76; N, 5.02.

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