A simple synthesis of (+)- and (−)-alkaloid 241D and C-4 epimers

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An enantioselective preparation of both enantiomers of alkaloid 241D **1** and its C-4 epimer is reported. This simple and concise synthesis, seven steps from pent-3-en-2-one, involves a highly diastereoselective Mannich-type cyclisation as the key step.

Introduction

Alkaloid (+)-241D **1** is one of the rare simple piperidines found in amphibians.[1] It has been isolated as a major alkaloid from *Dendrobates speciosus* and occurs as a trace alkaloid in *Dendrobates pumilio*.[2]

Synthetic racemic alkaloid 241D **1** and the parent 4-piperidone **2**[3] (Fig. 1) were found to be potent inhibitors of binding of [^{3}H]perhydrohistrionicotoxin to nicotinic receptor channels of electroplax membranes.[3] It has also been found that racemic **1** blocks the action of acetylcholine by a noncompetitive blockade of the nicotinic receptor channel complex.[4] Compounds **(±)-1** and **(±)-2** exhibit activities comparable with agents widely used as noncompetitive blockers and as radioligands for nicotinic receptor channels.[3] In regard to the potent biological activities observed, it is of interest to isolate both enantiomers of **1** and **2**, in pure form, in order to evaluate the effect of each compound.

As far as we know, only one asymmetric synthesis of alkaloid (+)-241D **1** has been reported.[5] This synthesis requires fifteen steps from chelidamic acid and involves the enzymatic desymmetrization of a *meso* piperidine as the key step.

Part of our research program concerns the stereoselective construction of polysubstituted piperidines and we have recently proposed[6] an efficient route to homochiral 2,6-*cis*-disubstituted piperidines from various aldehydes and enantiopure amine **(+)-** and **(−)-3**, *via* an intramolecular Mannich-type reaction (Scheme 1).

We thought that this methodology seemed particularly suitable for the asymmetric elaboration of natural products such as alkaloid 241D **1** since, in our case, a 2,6-*cis*-disubstitution is almost exclusively obtained.

Results and discussion

Enantiopure amines **(−)-3** and **(+)-3** were previously synthesized in seven steps using a chemoenzymatic pathway.[7] We, however, have found that both enantiomers could be very easily isolated, on a multigram scale, by simple resolution of racemic amine **3** (prepared following a conventional high yield procedure from pent-3-en-2-one) using tartaric acid (Scheme 2).

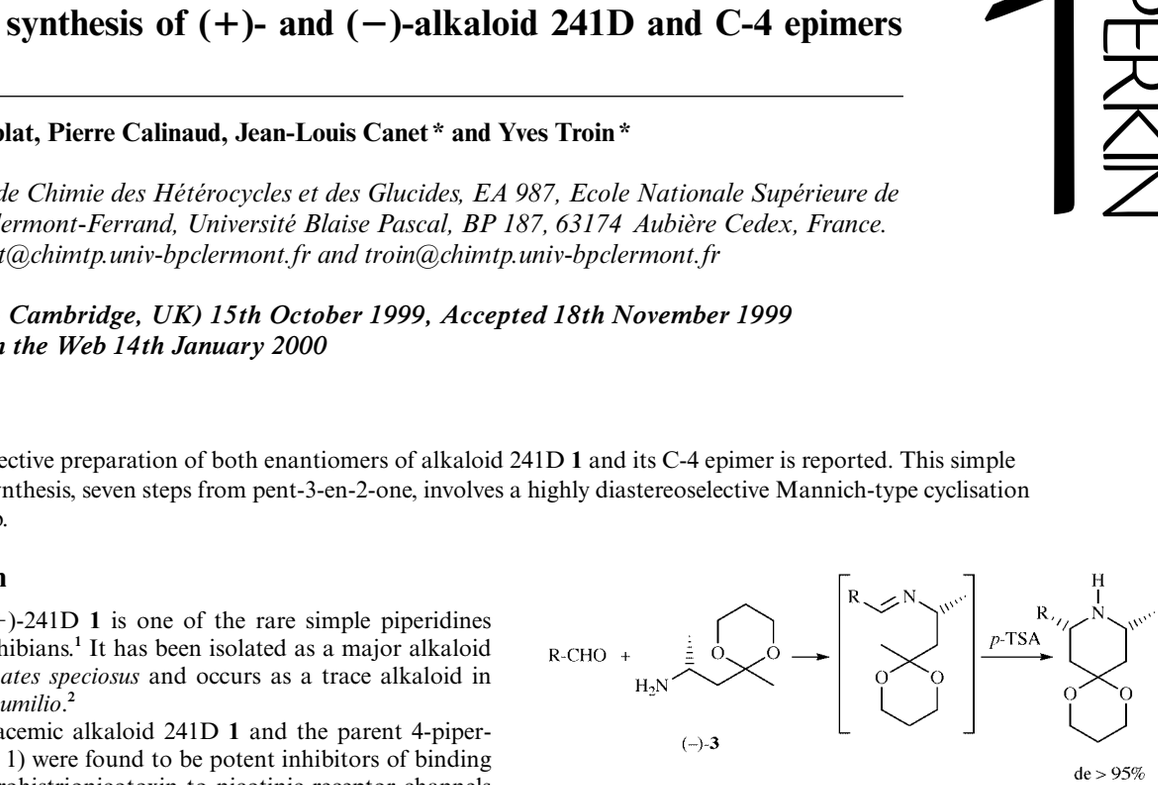
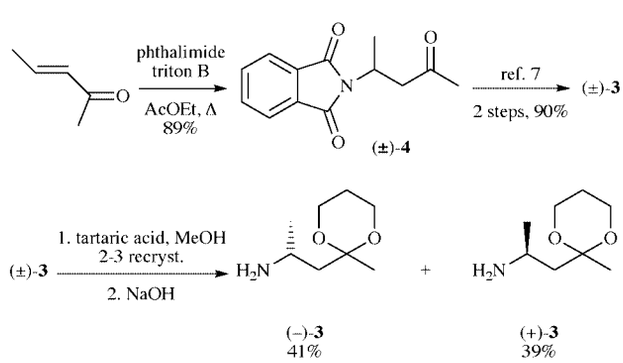


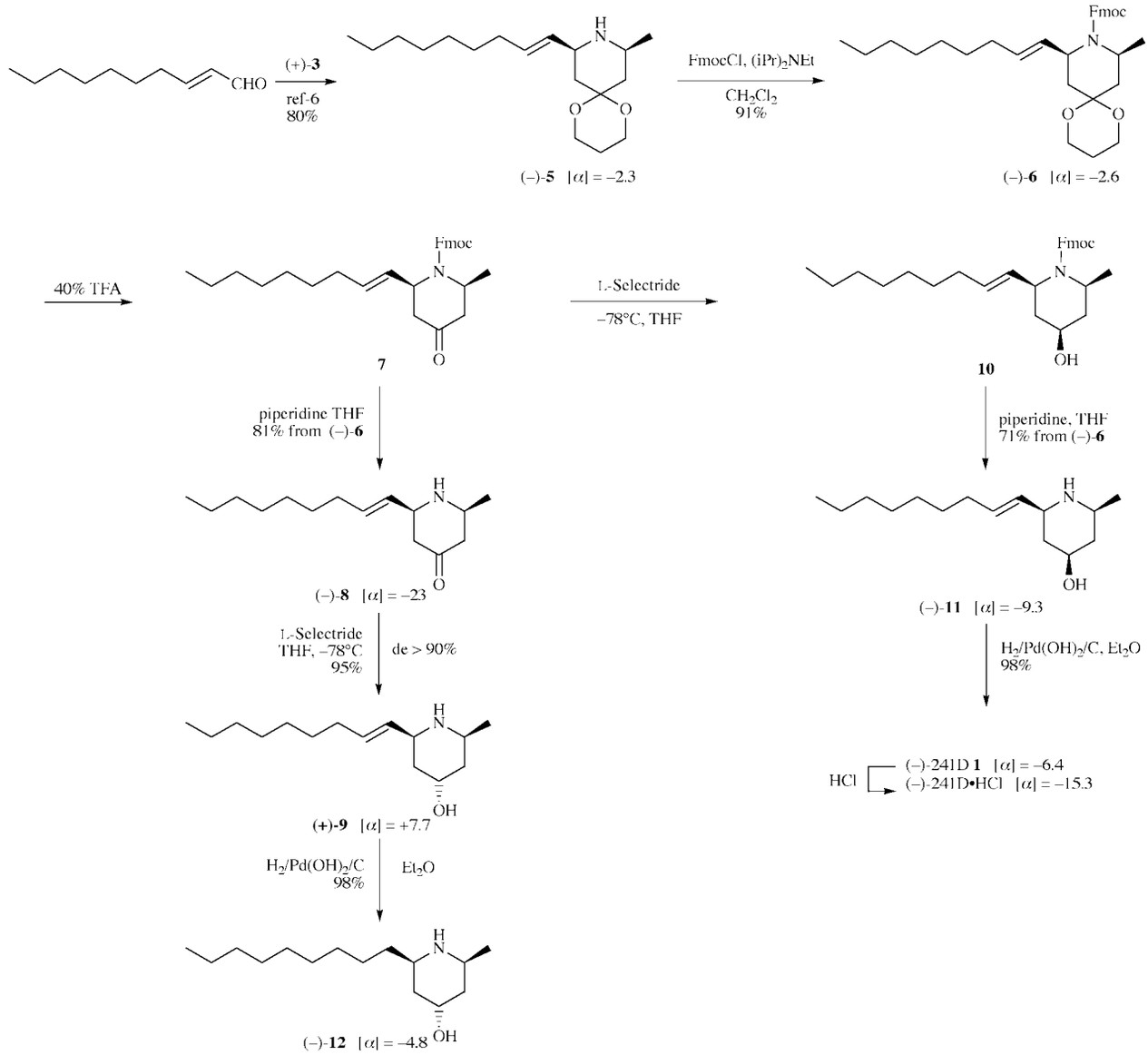
Fig. 1

Scheme 1



Scheme 2

As we have previously described the stereospecific synthesis of piperidine **(−)-5**, presenting a nonen-1-yl chain at the C-2 position, starting from amine **(+)-3**,[6] we decided to prepare alkaloid (−)-241D **1** from this readily available compound. Our first goal was the stereoselective transformation of the acetal group of **(−)-5** into the desired alcohol function. Unfortunately, and as observed previously,[8] ketone function deprotection using classical conditions failed to give the corresponding 4-piperidone efficiently (<30%). Thus, compound **(−)-5** was converted into its *N*-Fmoc derivative **(−)-6**[9] by treatment with FmocCl in the presence of Hünig's base (91% yield). Cleavage of the dioxane appendage was then achieved using a 40% aqueous trifluoroacetic acid solution and furnished the unstable piperidone **7**, which was directly N-deprotected using a piperidine solution in THF, to give the expected piperidone **(−)-8** (81% yield from **(−)-6**). Subsequent L-Selectride® reduction, a reagent known to give equatorial attack on cyclic ketones, gave,



Scheme 3

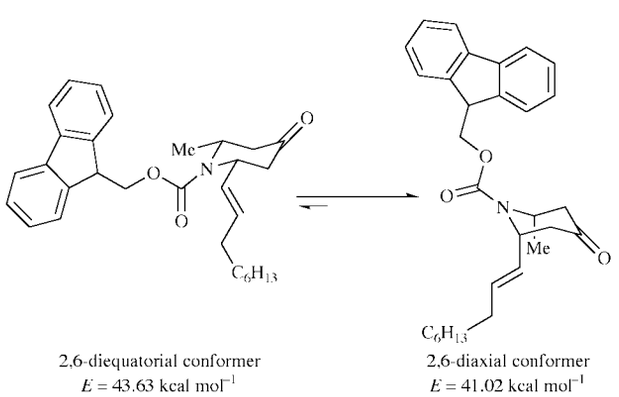


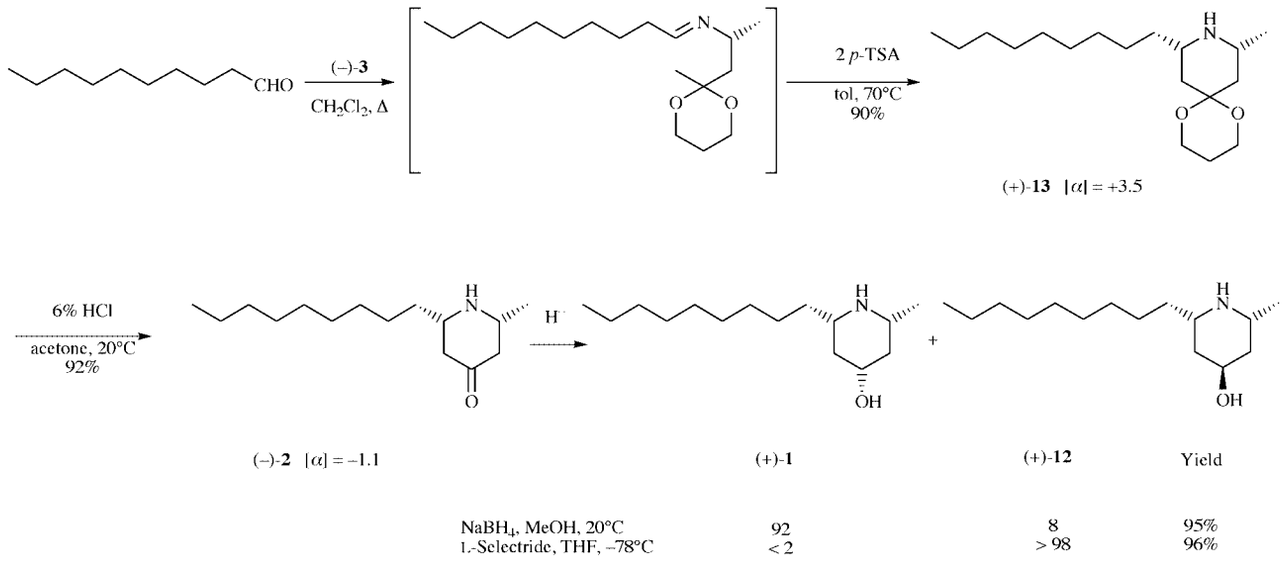
Fig. 2 Conformational analysis of compound **7**.

in 95% yield, the axial piperidinol **(+)-9** selectively (de > 95% from NMR spectra).

On the other hand, inverting the N-deprotection–reduction sequence (using the same conditions) afforded the equatorial piperidinol **(−)-11** as the sole product (71% yield from **(−)-6**). The stereochemical behaviour of the *N*-Fmoc piperidone **7** reduction could be explained by the fact that a carbamate group induces the inversion of the ring conformation in order to minimize A[1,3] strain.[10] This fact was demonstrated with 2-substituted-4-piperidones.[8] Confirmation that this phenomenon also occurred with the 2,6-*cis*-disubstituted piperidone **7** has been obtained by conformational analysis using the Batchmin program within the MM2 force field of the Macromodel package (Fig. 2).[11]

A significant difference in energy (2.61 kcal mol^{-1}) in favour of the diaxial conformer was found, justifying the almost exclusive obtention of the *cis*,*cis*-2,4,6-trisubstituted piperidinol **10** by L-Selectride® reduction of **7**. Finally, hydrogenation of piperidinols **(−)-11** and **(+)-9** in diethyl ether in the presence of Pearlman's catalyst gave respectively the non-natural (−)-241D **1** and its C-4 epimer **(−)-12**, quantitatively (Scheme 3). Optical rotation of (−)-241D **1** (−6.5, *c* 1.32 in methanol) was in good agreement with the values observed by Chênevert and Dickman[5] for its enantiomer (6.5, *c* 2.0 in methanol).

In order to improve the preparation of alkaloid 241D **1**, a saturated aldehyde was used in the cyclisation step. Thus, reaction of *n*-decanal with amine **(−)-3** in refluxing dichloromethane in the presence of magnesium sulfate as drying agent led quantitatively (TLC monitoring), in 3 hours, to the corresponding imine which was directly treated, for 4 hours, with 2 equivalents of dry toluene-*p*-sulfonic acid at 70 °C in toluene. Under these conditions, 2,6-*cis*-dialkylpiperidine **(+)-13** was obtained in 90% yield (de 95%, the 2,6-*trans*-isomer was not



Scheme 4

detected from NMR spectra). Surprisingly (*vide supra*), keto-deprotection of **(+)-13** was cleanly achieved, this time, with 6% hydrochloric acid in acetone at room temperature and gave the desired piperidone **(−)-2** in 92% yield (Scheme 4). Finally, sodium borohydride reduction of **(−)-2** gave selectively (95%, de 83%) the natural (+)-isomer of alkaloid 241D **1** while the use of L-Selectride® in THF at low temperature yielded its C-4 epimer **(+)-12**, exclusively, in 96% yield (Scheme 4). Optical rotation of (+)-241D **1** (6.4, *c* 1.03 in methanol) was in agreement with those reported.[5]

As both enantiomers of amine **3** are readily available, (−)-241D **1** and **(−)-11** were prepared in 3 steps (70% overall yield) from **(+)-3** by the same pathway.

Conclusion

We have described herein a simple and efficient enantioselective synthesis of both enantiomers of alkaloid 241D and their C-4 epimers. Our competitive strategy, seven steps from commercially available pent-3-en-2-one (*vs.* fifteen steps from chelidamic acid) will be applied to the total synthesis of other alkaloids exhibiting important biological interest.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz respectively; chemical shifts are reported in ppm relative to $SiMe_4$. *J* Values are given in Hz. Infrared spectra were recorded on a FTIR spectrometer. Electron impact (EI) mass spectra were obtained at 70 eV. Fast atom bombardment (FAB) mass spectra were obtained from the *Centre Régional de Mesures Physiques*, Université de Rennes. Optical rotations were measured at 589 nm. Column chromatography was carried out on silica gel (70–230 mesh). Solvents were dried and freshly distilled following the usual procedures. Product solutions were dried over Na_2SO_4 prior to evaporation of the solvents under reduced pressure on a rotary evaporator. Specific optical rotations are given in units of 10^{-1} deg cm^2 g^{-1}.

(±)-4-*N*-4-Oxopentan-2-ylphthalimide 4

To a stirred solution of commercial pent-3-en-2-one containing *ca.* 30% mesityl oxide (10 g, 108 mmol) in ethyl acetate (70 mL) was added phthalimide (12 g, 75 mmol) and a 40% solution of benzyltrimethylammonium hydroxide in methanol (3 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the phthalimide (3 h). The mixture was then allowed to cool to room temperature. Evaporation of the solvent followed by a recrystallisation in ethanol afforded the ketone **4** (14.6 g, 84%) as a white solid. Mp = 61 °C. Spectral data are identical with those reported.[7]

(±)-4-2-(2-Aminopropyl)-2-methyl-1,3-dioxane 3

The racemic amine was prepared in 90% yield from the ketone **(±)-4** as described.[7] Spectral data are identical with those reported.[7]

Resolution of amine 3

(−)-(*R*)-2-(2-Aminopropyl)-2-methyl-1,3-dioxane 3. The amine **(−)-3** was completely resolved with (+)-tartaric acid. Racemic amine **3** (10 g, 62.9 mmol) was added to a solution of 9.4 g of (+)-tartaric acid in methanol (40 mL). The resulting solution was left to crystallize for 3 days. This crop of crystals was then recrystallized three times in methanol and afforded the monotartrate [mp = 150 °C; $[a]_D^{25}$ 3.3 (*c* 1.00, H_2O)] which was treated with an excess of 1 M NaOH. The free amine was extracted with dichloromethane (4 × 30 mL). The combined organic extracts were dried, filtered and evaporated to give the amine **(−)-3** (4.1 g, 41%) as a colourless liquid; $[a]_D^{25}$ −20.1 (*c* 2.39, $CHCl_3$).

(+)-(*S*)-2-(2-Aminopropyl)-2-methyl-1,3-dioxane 3. Following the same procedure, amine **(+)-3** was prepared in 39% yield from the racemic amine and (−)-tartaric acid [$[a]_D^{25}$ +19.8 (*c* 1.96, $CHCl_3$)].

Enantiomeric purity of amines **(+)-** and **(−)-3** was easily verified by ^{1}H NMR, using (+)-mandelic acid as chiral solvating agent.[7,12]

Procedure for intramolecular Mannich-type cyclisation

To a stirred solution of aldehyde (2.24 mmol) in CH_2Cl_2 (20 mL) was added $MgSO_4$ (1 g) followed by a solution of amine **(−)-** or **(+)-3** (2.20 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 room temperature and transferred *via* a cannula to a solution of dry toluene-*p*-sulfonic acid (4.40 mmol) in toluene (25 mL). The resulting mixture was heated at 70 °C for 3 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ (15 mL) was added and the protected piperidone was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried, filtered and evaporated. The residue, purified by column chromatography, gave the corresponding protected 4-piperidone.

(−)-(8*S*,10*S*)-10-Methyl-8-(non-1-enyl)-1,5-dioxa-9-aza-spiro[5.5]undecane 5. Following the cyclisation procedure, dec-2-en-1-al (339 mg, 2.24 mmol) and amine **(+)-3** (350 mg, 2.20 mmol) afforded the protected piperidone **(−)-5** as a pale yellow oil (519 mg, 80%). R_f 0.33 (ethyl acetate–methanol, 5:1); $[\alpha]_D^{25}$ −2.3 (*c* 0.97, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3314, 1146, 1099, 1009, 963; δ_H($CDCl_3$) 5.63 (1H, m), 5.45 (1H, dd, *J* 15.5 and 7.0), 3.93 (4H, m), 3.29 (1H, m, H-8), 2.93 (1H, m, H-10), 2.26 (1H, dt, *J* 13.5 and 3.0, H-7eq), 2.18 (1H, dt, *J* 13.5 and 3.0, H-11eq), 1.99 (2H, m), 1.72 (2H, m), 1.60 (1H, br s, N–H), 1.45–1.00 (12H, m), 1.10 (3H, d, *J* 7.0), 0.85 (3H, t, *J* 7.0); δ_C($CDCl_3$) 132.2, 131.2, 97.2, 59.0, 54.9, 49.8, 41.0, 38.9, 32.1, 31.7, 29.0, 28.9, 25.5, 22.5, 22.2, 14.0; *m*/*z* (EI) 295 ($M^{+\bullet}$, 20), 235 (100), 194 (100), 179 (30), 101 (75); Found (FAB) 296.2595, $C_{18}H_{33}NO_2$ + H^+ requires 296.2590.

(−)-(8*S*,10*S*)-*N*-(Fluoren-9-ylmethoxycarbonyl)-10-methyl-8-(non-1-enyl)-1,5-dioxa-9-azaspiro[5.5]undecane 6. To a stirred solution of protected piperidone **(−)-5** (500 mg, 1.69 mmol) in CH_2Cl_2 (15 mL) was added diisopropylethylamine (356 µl, 2.03 mmol) and fluoren-9-ylmethyl chloroformate (527 mg, 2.03 mmol). The resulting mixture was stirred at room temperature for 20 min. Water (5 mL) was added and the N-protected piperidine was extracted with dichloromethane (4 × 25 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent, followed by column chromatography (ethyl acetate–cyclohexane, 1:3) afforded piperidone **(−)-6** (797 mg, 91%) as a yellow oil. R_f 0.40 (ethyl acetate–cyclohexane, 1:3); $[\alpha]_D^{25}$ −2.8 (*c* 1.42, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1686, 1450, 1412, 1101, 736; δ_H($CDCl_3$) 7.80–7.25 (8H, m), 5.70 (1H, dd, *J* 15.5 and 7.0), 5.47 (1H, m), 4.78 (1H, m, H-8), 4.47 (2H, d, *J* 7.0), 4.38 (1H, m, H-10), 4.27 (1H, t, *J* 6), 3.91 (4H, m), 2.28 (1H, dt, *J* 13.4 and 3.1), 2.10 (1H, m), 1.98 (2H, m), 1.93–1.65 (4H, m), 1.53–1.20 (13H, m), 0.90 (3H, t, *J* 7); δ_C($CDCl_3$) 155.4, 144.2, 141.3, 131.3, 127.7, 126.9, 124.8, 119.9, 96.5, 67.0, 65.1, 59.4, 52.4, 47.4, 45.5, 36.6, 35.7, 32.2, 31.8, 29.1, 25.3, 22.5, 21.8, 14.1; *m*/*z* (EI) 514 ($M^{+\bullet}$, 1.4), 177 (100); Found (FAB) 518.3272, $C_{18}H_{33}NO_2$ + H^+ requires 518.3270.

(2*S*,6*S*)-*N*-(Fluoren-9-ylmethoxycarbonyl)-6-methyl-2-(non-1-enyl)piperidin-4-one 7. To a stirred solution of protected piperidone **(−)-6** (400 mg, 0.77 mmol) in dichloromethane (15 mL) was added a 40% trifluoroacetic acid solution in water (2 mL). After 3 h of stirring, excess of 1 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. Evaporation of the solvent followed by column chromatography (ethyl acetate–cyclohexane, 1:3) gave piperidone **7**. This compound, which degrades readily, was directly engaged in the next step.

Procedure for *N*-(fluoren-9-ylmethoxycarbonyl) deprotection of piperidines

To a stirred solution of N-protected piperidine (1 mmol) in diethyl ether (15 mL) was added piperidine (20 equiv.). After 1 h of stirring, evaporation of the solvent, followed by column chromatography (ethyl acetate–cyclohexane 1:3) afforded N-deprotected piperidine.

(−)-(2*S*,6*S*)-6-Methyl-2-(non-1-enyl)piperidin-4-one 8. Following the N-deprotection procedure, starting from **7**, piperidone **(−)-8** (149 mg, 81% from **(−)-6**) was obtained as a pale yellow oil. R_f 0.48 (ethyl acetate–methanol, 5:1); $[\alpha]_D^{25}$ −23.0 (*c* 0.47, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3314, 2855, 1717, 1458, 1303; δ_H($CDCl_3$) 5.55 (1H, m), 5.36 (1H, m), 3.32 (1H, m, H-2), 2.94 (1H, m, H-6), 2.24 (2H, m), 2.14 (1H, t, *J* 9.8), 1.90 (4H, m), 1.37–1.07 (13H, m), 0.82 (3H, t, *J* 7); δ_C($CDCl_3$) 208.7, 132.4, 130.9, 58.6, 51.7, 49.6, 47.9, 32.1, 31.7, 29.0, 22.5, 22.4, 14.0; Found (FAB) 238.2172, $C_{18}H_{33}NO_2$ + H^+ requires 238.2171.

Procedure for the L-Selectride® reduction of 4-piperidones

To a cold (−78 °C) stirred solution of 4-piperidone (0.3 mmol) in THF (10 mL) was added dropwise L-Selectride® (330 µL of a 1 M solution in THF). After 10 min of stirring at −78 °C, methanol (1 mL) was added and the resulting solution was allowed to warm to room temperature. Water (5 mL) was added and the piperidinol was extracted with dichloromethane (4 × 25 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvents under reduced pressure followed by column chromatography yielded the pure corresponding 4-piperidinol.

(+)-(2*S*,4*S*,6*S*)-6-Methyl-2-(non-1-enyl)piperidin-4-ol 9. Following the L-Selectride® reduction procedure, starting from piperidone **(−)-8** (130 mg, 0.5 mmol), piperidinol **(+)-9** (128 mg, 95%), was obtained exclusively as a white solid. Mp = 89–91 °C, R_f 0.09 (ethyl acetate–methanol, 5:1); $[\alpha]_D^{25}$ +7.7 (*c* 1.05, MeOH); ν_{max} (neat)/cm^{-1} 3265, 2925, 1460, 1378, 1109, 969, 733; δ_H($CDCl_3$) 5.62 (1H, m), 5.42 (1H, m), 4.18 (1H, m, H-4), 3.55 (1H, m, H-2), 3.22 (1H, m, H-6), 2.23 (2H, br s, N-H and O-H), 2.00 (2H, m), 1.70 (2H, m), 1.47 (1H, dt, *J* 15.4 and 3), 1.41–1.20 (11H, m), 0.88 (3H, t, *J* 7); δ_C($CDCl_3$) 132.1, 131.7, 64.7, 53.1, 45.8, 40.1, 38.7, 32.2, 31.7, 29.0, 22.5, 22.1, 14.0; Found (FAB) 240.2327, $C_{18}H_{33}NO_2$ + H^+ requires 240.2329.

Procedure for hydrogenation of piperidinol (+)-9 and (−)-11

To a stirred solution of unsaturated piperidinol (1 mmol) in diethyl ether (5 mL), was added 50 mg of 20% $Pd(OH)_2$/C catalyst. The resulting mixture was stirred at room temperature for 24 h, under hydrogen. The solution was filtered on Celite® and concentrated under reduced pressure. The residue was dissolved in 1 M aqueous NaOH and the piperidine was extracted with dichloromethane (4 × 10 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent followed by column chromatography (ethyl acetate–methanol 3:1) gave the corresponding saturated piperidinol.

(−)-(2*R*,4*S*,6*S*)-6-Methyl-2-nonylpiperidin-4-ol 12. From piperidinol **(+)-9**. Following the hydrogenation procedure, starting from piperidone **(+)-9** (230 mg, 0.96 mmol), piperidinol **(−)-12** (227 mg, 98%), was obtained as a white solid. Mp = 68 °C, R_f 0.45 (ethyl acetate–methanol, 1:1); $[\alpha]_D^{25}$ −4.5 (*c* 0.87 MeOH); ν_{max} (KBr)/cm^{-1} 3250, 1467, 1109, 858; δ_H($CDCl_3$) 4.15 (1H, m, H-4), 3.10 (1H, m), 2.95 (1H, m), 2.30 (2H, br s, N-H and O-H), 1.20 (2H, m), 1.40–1.15 (16H, m), 1.05 (3H, d, *J* 8), 0.85 (3H, t, *J* 7); δ_C($CDCl_3$) 65.2, 50.7, 46.1, 41.0, 39.0, 36.8, 31.8, 29.8, 29.6, 29.5, 29.3, 25.9, 22.6, 22.4, 14.1; *m*/*z* (EI) 242 ($M^{+\bullet}$, 85), 114 (100), 70 (36), 41 (35), 29 (25); Found (FAB) 241.2410, $C_{15}H_{31}NO$ + H^+ requires 241.2406.

From piperidone (+)-2. Following the L-Selectride® reduction procedure, starting from piperidone **(+)-2** (350 mg, 1.46 mmol), piperidinol **(−)-12** (339 mg, 96%) was obtained as a white solid. Mp = 68 °C, $[\alpha]_D^{25}$ −4.5 (*c* 0.95 MeOH). Data identical with those reported above.

(+)-(2*S*,4*R*,6*R*)-6-Methyl-2-nonylpiperidin-4-ol 12. Following the same procedure, **(+)-12** was prepared in 95% yield from **(−)-2**, $[\alpha]_D^{25}$ +4.5 (*c* 1.02, MeOH). Spectral data identical with those reported above for its enantiomer.

(2*S*,4*R*,6*S*)-*N*-(Fluoren-9-ylmethoxycarbonyl)-6-methyl-2-(non-1-enyl)piperidin-4-ol 10. Following the L-Selectride® reduction procedure, starting from the piperidone **7** (400 mg, 0.5 mmol), the piperidinol **10** (385 mg, 96%) was obtained. This unstable compound was directly engaged in the next step.

(−)-(2*S*,4*R*,6*S*)-6-Methyl-2-(non-1-enyl)piperidin-4-ol 11. Following the N-deprotection procedure, starting from piper-

idone **10**, piperidone **(−)-11** was obtained as a white solid (131 mg, 71% from **(−)-6**). Mp = 86 °C, R_f 0.22 (ethyl acetate–methanol, 5:1); $[a]_D^{25}$ −9.3 (*c* 1.02, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3263, 3165, 1485, 1368, 1115, 1038, 966, 896, 848, 624; $\delta_H(CDCl_3)$ 5.55 (1H, m), 5.39 (1H, m), 3.62 (1H, m, H-4), 3.07 (1H, m, H-2), 2.67 (1H, m, H-6), 2.16 (2H, br s, N-H and O-H), 2.00–1.85 (5H, m), 1.36–0.95 (14H, m), 0.87 (3H, t, *J* 7); $\delta_C(CDCl_3)$ 132.1, 131.4, 68.7, 57.2, 50.1, 43.2, 41.5, 32.3, 31.8, 29.2, 22.6, 22.3, 14.1; Found (FAB) 240.2327, $C_{18}H_{33}NO_2 + H^+$ requires 240.2329.

(−)-(2*R*,4*R*,6*S*)-4-Hydroxy-6-methyl-2-nonylpiperidine [241D] 1. From piperidinol **(−)-11**. Following the hydrogenation procedure, starting from piperidone **(−)-11** (120 mg, 0.50 mmol), alkaloid 241D **(−)-1** (119 mg, 98%) was obtained as a white solid. Mp = 107 °C (lit.[5] mp = 108–109 °C for its enantiomer), R_f 0.38 (ethyl acetate–methanol, 1:1); $[a]_D$ −6.4 (*c* 1.03, MeOH) [lit.[5] $[a]_D^{25}$ 6.5 (*c* 2.00, MeOH) for its enantiomer]. Spectral data are identical with those reported for its enantiomer.[5]

From piperidone (+)-2. To a stirred solution of piperidone **(+)-2** (200 mg, 0.84 mmol) in methanol (5 mL) was added at room temperature sodium borohydride (1.46 mmol). The resulting mixture was stirred for 10 min before addition of saturated aqueous NH_4Cl (5 mL). The piperidinol was extracted with dichloromethane (4 × 20 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvents, followed by column chromatography (ethyl acetate–methanol, 5:1) gave separated piperidinols **(−)-1** (213 mg, 85%) and **(−)-12** (16 mg, 9%). 241D **(−)-1**: mp = 107 °C (lit.[5] mp = 108–109 °C), $[a]_D^{25}$ −6.5 (*c* 1.32, MeOH) [lit.[5] $[a]_D^{25}$ 6.5 (*c* 2.00, MeOH) for its enantiomer]. Spectral data are identical with those reported.[5]

(+)-(2*S*,4*S*,6*R*)-4-Hydroxy-6-methyl-2-nonylpiperidine [241D] 1. Following the same procedure, **(+)-1** was prepared in 85% yield from **(−)-2**. Mp = 108 °C (lit.[5] mp = 108–109 °C), $[a]_D^{25}$ +6.6 (*c* 1.24, MeOH) [lit.[5] $[a]_D^{25}$ +6.5 (*c* 2.00, MeOH)].

(−)-(2*R*,4*R*,6*S*)-4-Hydroxy-6-methyl-2-nonylpiperidine hydrochloride [241D-HCl] 1·HCl. To a solution of **(−)-1** (119 mg, 0.49 mmol) in diethyl ether (3 mL) was added a saturated solution of hydrogen chloride in diethyl ether (4 mL). After filtration, the crude **(−)-1·HCl** was recrystallized from absolute EtOH–AcOEt 1:3 to afford **(−)-1·HCl** as white needles. Mp = 230 °C (lit.[5] mp = 228 °C for its enantiomer), $[a]_D^{25}$ −15.3 (*c* 1.09, MeOH) [lit.[5] $[a]_D^{25}$ +15.8 (*c* 1.30, MeOH) for its enantiomer]. Spectral data are identical with those reported.[5]

(+)-(2*S*,4*S*,6*R*)-4-Hydroxy-6-methyl-4-nonylpiperidine hydrochloride [241D·HCl] 1·HCl. Following the same procedure, **(+)-1·HCl** was prepared from **(+)-1**. Mp = 229 °C (lit.[5] mp = 228 °C), $[a]_D^{25}$ +15.5 (*c* 1.14, MeOH) [lit.[5] $[a]_D^{25}$ +15.8 (*c* 1.30, MeOH)].

(+)-(8*S*,10*R*)-10-Methyl-8-nonyl-1,5-dioxa-9-azaspiro[5.5]-undecane 13. Following the cyclisation procedure, decanal (343 mg, 2.20 mmol) and amine **(−)-3** (350 mg, 2.20 mmol) afforded the protected piperidone **(+)-13** as a pale yellow oil (852 mg, 90%). R_f 0.38 (ethyl acetate–methanol, 5:1); $[a]_D^{25}$ +3.5 (*c* 0.99, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3314, 1143, 1097; $\delta_H(CDCl_3)$ 3.94 (2H, t, *J* 6.5), 3.89 (2H, t, *J* 6.5), 2.90 (1H, m, H-10), 2.74 (1H, m, H-8), 2.25 (2H, m, H-7eq and H-11eq), 2.05 (1H, br s, NH), 1.73 (2H, m), 1.49–1.20 (17H, m), 1.15–1.04 (1H, m), 1.09 (3H, d, *J* 7.0), 0.89 (3H, t, *J* 7.0); $\delta_C(CDCl_3)$ 97.4, 59.1, 52.6, 48.0, 40.9, 39.1, 36.4, 31.9, 29.7, 29.5, 26.3, 25.9, 25.6, 22.6, 22.1, 14.1; Found (FAB) 297.2667, $C_{18}H_{33}NO_2 + H^+$ requires 297.2868.

(−)-(8*R*,10*S*)-10-Methyl-8-nonyl-1,5-dioxa-9-azaspiro[5.5]-undecane 13. Following the same procedure, **(−)-13** was prepared in 92% yield from **(+)-3.** $[a]_D^{25}$ −3.5 (*c* 1.16, $CHCl_3$).

(−)-(2*S*,6*R*)-6-Methyl-2-nonylpiperidin-4-one 2. To a stirred solution of protected piperidone **(+)-13** (800 mg, 2.71 mmol) in acetone (15 mL) was added 6% hydrochloric acid (10 mL). The resulting mixture was stirred at room temperature for 10 days. The organic solvent was eliminated under reduced pressure and the residue was diluted with excess of 1 M aqueous NaOH. The piperidone was then extracted with dichloromethane (4 × 20 mL). The combined organic extracts were washed with brine and dried. Evaporation of the solvent, followed by column chromatography (ethyl acetate) afforded piperidone **(−)-2** (741 mg, 92%) as a white solid. Mp = 29–30 °C, R_f 0.43 (ethyl acetate–methanol, 5:1); $[a]_D$ −1.1 (*c* 1.56, $CHCl_3$). Spectral data are identical with those reported for **(±)-2**.[3]

(+)-(2*R*,6*S*)-6-Methyl-2-nonylpiperidin-4-one 2. Following the same procedure, **(+)-2** was prepared in 89% yield from **(−)-13**. $[a]_D^{25}$ +1.0 (*c* 1.23, $CHCl_3$). Spectral data identical with those reported above.

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