Enantioselective Syntheses and Absolute Configuration of the Ladybird Defence Alkaloids (+)-Calvine and (+)-2-Epicalvine

Pascal Laurent,[a] Jean-Claude Braekman,*[a] and Désiré Daloze*[a]

Keywords: Alkaloids / Asymmetric synthesis / Electrochemistry / CN(*R*,*S*) method / Piperidines / Insects

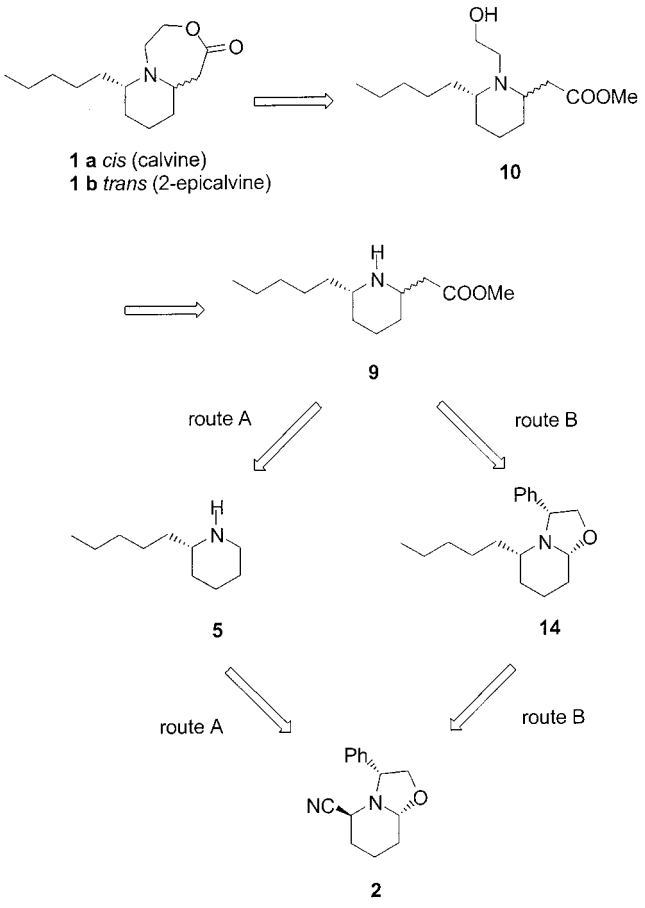
Enantiomerically pure (+)-calvine (**1a**) and (+)-2-epicalvine (**1b**), two piperidine alkaloids isolated from ladybird beetles of the genus *Calvia* (Coccinellidae), were synthesized by two different strategies starting from (–)-2,3,6,7,8,8a-hexahydro-3-phenyl-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile (**2**). The key steps of these syntheses are the stereocontrolled formation of an asymmetric centre α to the nitrogen atom of **2** and the subsequent introduction of the methoxycarbonylmethyl substituent at the α′-position. Comparison of the optical rotations of the synthetic benzoates (**12a**) and (**12b**) with those of the corresponding benzoates derived from the natural compounds has revealed the absolute configuration of (+)-calvine to be (2*S*,6*S*) and that of (+)-2-epicalvine to be (2*R*,6*S*).

Introduction

Alkaloids, once thought unique to the richness and diversity of secondary metabolism of plants, have now been found in a number of arthropods[1] such as, for example, coccinellid beetles. When disturbed or molested, these insects release small droplets of yellow "blood" at their knee joints. This well-described process, known as "reflex bleeding", serves as an efficient protection against certain predators,[2] and has been attributed to the presence of deterrent alkaloids in their hemolymph.[3] The study of more than 30 species of ladybird has led to the isolation and structure determination of about 45 alkaloids of many different structural families.[4,5]

Recently, the alkaloids of two coccinellid beetles belonging to the genus *Calvia* have been investigated.[6] The major alkaloid from these two species is the piperidinic *cis* lactone (+)-**1a**, which was named calvine. The corresponding *trans* lactone (+)-**1b** (2-epicalvine) is also present as a minor constituent (about 10%) in both species. The structure of these alkaloids has been determined on the basis of their spectral properties and confirmed by a total synthesis of racemic **1a** and **1b**.[6] In this paper, we wish to report two different enantioselective syntheses of (+)-calvine [(+)-**1a**] and (+)-2-epicalvine [(+)-**1b**], which allowed us to assign the absolute configuration (2*S*,6*S*) to natural (+)-calvine and (2*R*,6*S*) to natural (+)-2-epicalvine.

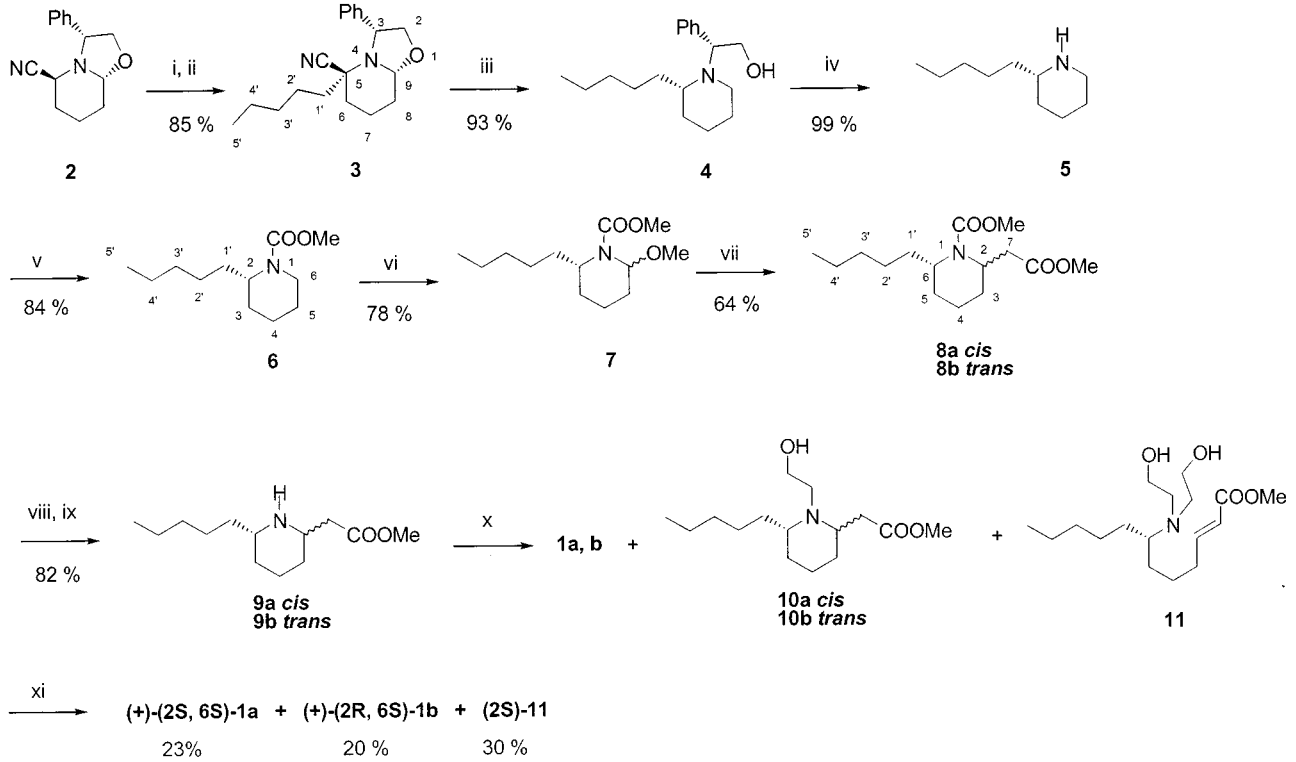
Our first approach used a combination of electrochemical[7,8] and CN(*R,S*)[9,10] methods, while the second was based exclusively on the latter technique. The two strategies are shown retrosynthetically in Scheme 1. Both start from (−)-2,3,6,7,8,8a-hexahydro-3-phenyl-5*H*-[1,3]oxazolo[3,2-*a*]-pyridine-5-carbonitrile (**2**). The key steps are: i) the regio- and stereoselective introduction of an *n*-pentyl chain at C-5 of **2**; ii) the introduction of a methoxycarbonylmethyl group at C-6 of the piperidine ring, either through anodic oxidation followed by nucleophilic substitution[11] (route A), or by using the CN(*R,S*) methodology[12] (route B); iii) the hydroxyethylation of the nitrogen atom of **9**, followed by lactonization.[6]



Scheme 1. Synthetic strategies for (+)-calvine (**1a**) and (+)-2-epicalvine (**1b**)

[a] Laboratory of Bio-organic Chemistry, Department of Organic Chemistry, University of Brussels, CP 160/07,
Av. F. D. Roosevelt 50, 1050 Brussels, Belgium
Fax: (internat.) +32(0)2/650-27-98
E-mail: ddaloze@ulb.ac.be; braekman@ulb.ac.be

  1434−193X/00/0611−2057 $ 17.50+.50/0



Scheme 2. Synthesis of (+)-(2*S*,6*S*)-**1a** and (+)-(2*R*,6*S*)-**1b**; reagents: i. LDA, HMPA, THF, −78 °C; ii. *n*-$C_5H_{11}Br$; iii. $NaBH_4$, EtOH, reflux; iv. H_2, Pd/C, MeOH; v. ClCOOMe, K_2CO_3, H_2O; vi. MeOH, Et_4NOTs, 8F/mol; vii. $TiCl_4$, 1-methoxy-1-trimethylsilyloxyethene, CH_2Cl_2; viii. TMSI, CH_2Cl_2, reflux; ix. MeOH; x. ethylene oxide, MeOH, 50 °C; xi. Amberlyst A15, 4 Å molecular sieves, CH_3CN, 50 °C

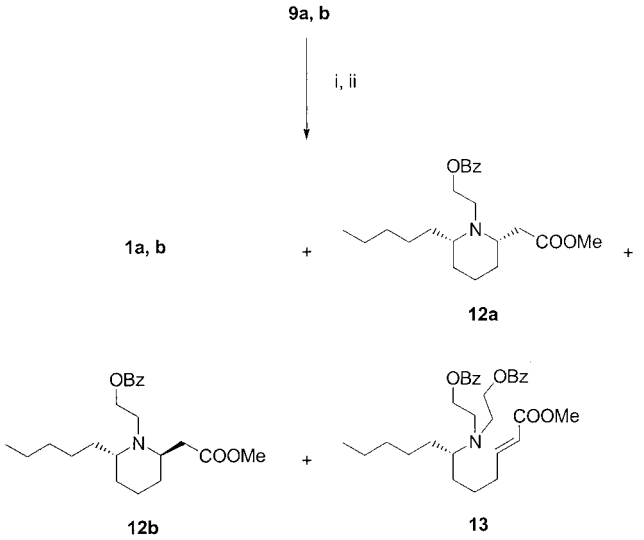
Results and Discussion

Alkylation of the anion of **2** with *n*-pentyl bromide led to the formation of a single product [(5*S*)-**3**], isolated in 85% yield after flash chromatography through silica gel (Scheme 2). Treatment of (5*S*)-**3** with $NaBH_4$ in refluxing ethanol effected both the removal of the cyano group and the opening of the oxazoline ring, affording (2*S*)-**4** as a single compound in 93% yield. The observed stereoselectivity is interpreted in terms of an elimination-addition mechanism in which the hydride ion approaches a preferred iminium conformer from an axial direction, under complete stereoelectronic control.[13] The chiral appendage of (2*S*)-**4** was then removed under catalytic hydrogenolysis conditions (H_2, 10% Pd/C, MeOH) to afford piperidine (2*S*)-**5** in nearly quantitative yield. Protection of the secondary amine of (2*S*)-**5** with methyl chloroformate led to the carbamate (2*S*)-**6** in 84% yield and > 99% *ee*. The enantiomeric excess was measured by chiral GC-MS analysis and comparison with a racemic sample of **6**. The final steps of this synthesis are identical to those of our synthesis of racemic calvine.[6]

An anodic oxidation carried out on (2*S*)-**6** regioselectively furnished the 2-methoxylated compound (6*S*)-**7** as a *cis*/*trans* mixture in 78% yield. Nucleophilic substitution of the methoxy function of (6*S*)-**7** by 1-methoxy-1-trimethylsilyloxyethene[14] led to an 87:13 mixture of the carbamate esters (2*S*,6*S*)-**8a** and (2*R*,6*S*)-**8b** in 64% yield (74% *de*). Deprotection of the carbamate (6*S*)-**8** by reaction with trimethylsilyl iodide (TMSI) gave the diastereomers (2*S*,6*S*)-**9a** and (2*R*,6*S*)-**9b**, which could be separated by flash column chromatography through silica gel. The *cis* configuration was assigned to the major stereomer by comparison of its ^1H NMR spectroscopic data and GC retention time with those of racemic **9a**.[6] Hydroxyethylation of the mixture of (2*S*,6*S*)-**9a** and (2*R*,6*S*)-**9b** was achieved by treatment with an excess of ethylene oxide in methanol. As we previously observed,[6] this procedure led to the formation of a mixture of lactones **1a** and **1b**, methyl esters **10a** and **10b**, and by-product **11**. This crude reaction mixture was not separated, but subjected directly to the lactonization reaction in the presence of Amberlyst A15 and 4 Å molecular sieves in acetonitrile.[6] This yielded a mixture of (+)-(2*S*,6*S*)-calvine [**1a** (23%)], (+)-(2*R*,6*S*)-2-epicalvine [**1b** (20%)] and by-product (2*S*)-**11** (30%), which were separated by silica gel flash chromatography. Synthetic (+)-**1a** {$[\alpha]_D^{20}$ = +18 (*c* = 0.66, CH_2Cl_2)}, and (+)-**1b** {$[\alpha]_D^{20}$ = +8 (*c* = 0.58, CH_2Cl_2)}, exhibited spectral data (^1H NMR and MS) and capillary GC retention times identical to those of the corresponding natural and synthetic racemic compounds.[6]

In order to determine the absolute configuration of natural calvine and 2-epicalvine, the mixture arising from another hydroxyethylation reaction of (2*S*,6*S*)-**9a** and (2*R*,6*S*)-**9b** was benzoylated with benzoic anhydride in the presence of 4-dimethylaminopyridine (DMAP) in toluene (Scheme 3).

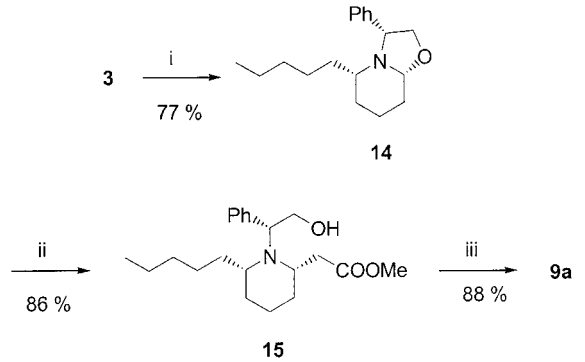
This reaction afforded, after chromatography through silica gel, benzoates (2*S*,6*S*)-**12a** {$[\alpha]_D^{20}$ = +18 (*c* = 0.17, CH_2Cl_2)} and (2*R*,6*S*)-**12b** {$[\alpha]_D^{20}$ = +8 (*c* = 0.40, CH_2Cl_2)} in 33% yield, accompanied by 21% of (+)-**1a** and (+)-**1b**, and 28% of benzoylated by-product (2*S*)-**13**. Comparison



Scheme 3. Synthesis of benzoates **12a** and **12b**; reagents: i. ethylene oxide, MeOH, 50 °C; ii. benzoic anhydride, DMAP, toluene

of the optical rotations of the synthetic benzoates with those of the *cis* and *trans* benzoates derived from the natural compounds {$[\alpha]_D^{20} = +16$ ($c = 0.11$, CH_2Cl_2) and $[\alpha]_D^{20} = +6$ ($c = 0.38$, CH_2Cl_2), respectively} allowed us to determine the absolute configuration of natural calvine as (2*S*,6*S*) and that of natural 2-epicalvine as (2*R*,6*S*).

Next, we compared this synthetic route with an alternative one based only on the CN(*R,S*) method[9,10] (route B). To this end, compound (5*S*)-**3** was subjected to a stereoselective decyanation[15] by sodium in liquid ammonia. This procedure afforded the 2,3,6,7,8,8a-hexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine (5*S*)-**14** in 77% yield (Scheme 4).



Scheme 4. Synthesis of piperidine **9a** by the CN(*R,S*) method; reagents: i. Na, NH_3, THF; ii. $BF_3.OEt_2$, 1-methoxy-1-trimethylsilyloxyethene, CH_3CN/Et_2O, −78 °C; iii. H_2, Pd/C, MeOH

When (5*S*)-**14** was reacted with 1-methoxy-1-trimethylsilyloxyethene[14] in the presence of $BF_3{\cdot}OEt_2$ at −78 °C,[12] compound (2*S*,6*S*)-**15** was obtained as a single isomer in 86% yield. The preferred formation of the *cis* isomer is ascribed to A[1,2] strain in the intermediate iminium species.[16] Hydrogenolysis of the chiral appendage of (2*S*,6*S*)-**15** afforded (2*S*,6*S*)-**9a** in 88% yield after flash chromatography through silica gel. This compound was identical in all respects (including optical rotation) with (2*S*,6*S*)-**9a** obtained by route A.

Conclusion

We have synthesized enantiomerically pure (+)-calvine (**1a**) and (+)-2-epicalvine (**1b**) by two different, albeit closely related, methods. The first approach (route A), using a combination of electrochemical and CN(*R,S*) methods, required eight steps and furnished (+)-**1a** and (+)-**1b** in yields of 6% and 5.5%, respectively (combined yield: 11.5%). The other synthesis (route B), based exclusively on the CN(*R,S*) methodology, required five steps and afforded the two target compounds in yields of 11% and 10% respectively (combined yield: 21%). While the enantiomeric purities obtained by the two routes are identical (>99%), the CN(*R,S*) method yielded exclusively the *cis* 2,6-disubstituted piperidine **15**, whereas the other route produced an 83:17 *cis*/*trans* mixture of carbamates **8a** and **8b**. In the case of the *Calvia* alkaloids, however, the epimerization at C-2, which is known to occur during the transformation of *cis*-**9a** and *trans*-**9b** into **1**,[6] led to the two epimers (+)-**1a** and (+)-**1b** whichever route was employed. Finally, these syntheses allowed us to assign the absolute configuration (2*S*,6*S*) to (+)-calvine and (2*R*,6*S*) to (+)-2-epicalvine. With the synthetic samples of the two alkaloids in hand, it will now be possible to assess their biological properties.

Experimental Section

General Remarks: EI-MS and EI-HRMS were performed with a Fisons VG Micromass Autospec instrument (70 eV), and GC/EI-MS analyses with a Fisons VG Micromass Autospec apparatus coupled to a gas chromatograph equipped with a capillary column (carrier gas He). In all cases, peak intensities are expressed as % relative to the base peak. The ^1H NMR spectra were recorded in $CDCl_3$ at 250 MHz with a Bruker WM 250 spectrometer and are reported in ppm from internal TMS on the δ scale. Data are reported as follows: chemical shift [multiplicity (s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, t: triplet, q: quadruplet, dd: double doublet, td: double triplet, m: multiplet, ms: superimposed multiplet), coupling constants in Hertz, integration, assignment]. The IR spectra were recorded with a Bruker IFS 25 instrument as a film on a NaCl disk and the UV/Vis spectra with a Philips PU 8700 spectrophotometer in 1 cm cells. GC analyses were performed with a Varian 3400 apparatus equipped with capillary columns (column 1: 25 m × 0.32 mm fused-silica column coated with OV1; column 2: 30 m × 0.53 mm fused-silica column coated with OV1701; column 3: 25m × 0.32 mm fused-silica column coated with CP-Chirasil-Dex CB), carrier gas N_2. Thin layer chromatography analyses (TLC) were performed on 0.25 mm Polygram silica gel SILG/UV_{254} precoated plates (Macherey−Nagel). Column chromatographies were performed over silica gel (MN Kieselgel 60 0.04−0.063 mm) using the flash technique. Melting points are uncorrected. Optical rotations were recorded at 589 nm (sodium D line) in a 1 dm cell at 20 °C on a Perkin−Elmer 141 polarimeter.

(−)-(5*S*)-2,3,6,7,8,8a-Hexahydro-5-pentyl-3-phenyl-5*H*-[1,3]-oxazolo[3,2-*a*]pyridine-5-carbonitrile (3): To a stirred solution of LDA [prepared at −78 °C from diisopropylamine (553 mg, 5.48 mmol) and 2.5 M *n*BuLi in hexane (2.2 mL, 5.50 mmol)] in THF (1.8 mL) and HMPA (1.9 mL, 10.9 mmol) was added dropwise a solution of commercial **2** (Acros, 500 mg, 2.19 mmol) in

THF (3.8 mL) at −78 °C. After 20 min, *n*-pentyl bromide (0.42 mL, 3.39 mmol) was added. After stirring for 2 h at −78 °C, the mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a residue which was purified by flash chromatography through silica gel (hexane/Et_2O 9:1) to afford **3** (557 mg, 1.87 mmol, 85%) as a pale yellow oil.

3: $[\alpha]_D^{20} = -153$ ($c = 0.51$, $CHCl_3$). − EIMS: *m/z* (%) = 298 [$M^{+\cdot}$] (4), 271 (15), 228 (38), 227 (25), 215 (35), 214 (37), 200 (52), 158 (10), 108 (11), 107 (14), 105 (18), 104 (100), 103 (24), 91 (34), 78 (13), 77 (16), 55 (20). − IR (film): $\tilde{\nu}$ = 2958, 2874, 2210, 1463, 1413, 1379, 1346, 1287, 1237, 1203, 1103, 1002, 885, 760, 701 cm^{-1}. − ^1H NMR: δ = 0.73 (t, $J = 7.0$, 3 H, 5′-H_3), 1.0−1.30 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.80 (ms, 6 H, 6-H_2, 7-H_2, 8-H_2), 3.75 (dd, $J = 8.4$, 4.8, 1 H, 3-H), 4.0 (dd, $J = 8.8$, 4.4, 1 H, 9-H), 4.2 (m, 2 H, 2-H_2), 7.20−7.40 (ms, 5 H, Ar-H). − UV (MeOH): λ_{max} (ε) = 220 nm (1600), 254 nm (190), 260 nm (220), 266 nm (160).

(−)-(2*S*)-2-Pentyl-1-(1-phenyl-2-hydroxyethyl)piperidine (4): To a suspension of $NaBH_4$ (158 mg, 4.16 mmol) in ethanol (5.2 mL) was added a solution of **3** (102 mg, 0.34 mmol) in ethanol (0.6 mL). The mixture was refluxed for 2 h and then cooled to room temperature. Water (ca. 3 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a residue which was purified by flash chromatography through silica gel (CH_2Cl_2 /MeOH 98:2) to afford **4** (88 mg, 0.32 mmol, 93%) as a yellow oil.

4: $[\alpha]_D^{20} = -11$ ($c = 0.50$, $CHCl_3$). − EIMS: *m/z* (%) = 275 (1, $M^{+\cdot}$), 245 (61), 244 (100), 205 (14), 204 (84), 172 (8), 121 (17), 106 (10), 104 (13), 103 (23), 91 (33), 84 (84), 77 (10), 56 (12), 55 (25). − IR (film): $\tilde{\nu}$ = 3418, 3062, 3021, 2937, 2853, 1496, 1471, 1446, 1379, 1195, 1128, 1053, 760, 735, 701 cm^{-1}. − ^1H NMR: δ = 0.87 (t, $J = 7.0$, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.60 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.48 (m, 2 H, 2-H, 6ax-H), 2.89 (m, 1 H, 6e-H), 3.69 (dd, $J = 10.6$, 5.9, 1 H, 8-H), 3.76 (dd, $J = 10.6$, 6.2, 1 H, 8-H), 3.85 (dd, $J = 12.1$, 5.8, 1 H, 7-H), 7.28−7.36 (ms, 5 H, Ar-H). − UV (MeOH): λ_{max} (ε) = 209 nm (1340).

(+)-(2*S*)-2-Pentylpiperidine (5): Compound **4** (654 mg, 2.38 mmol) in methanol (20 mL) was hydrogenolyzed in the presence of 10% Pd/C at atmospheric pressure and room temperature for 48 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash chromatography through silica gel (CH_2Cl_2/MeOH 9:1) gave **5** (366 mg, 2.36 mmol, 99%) as a white solid.

5: $[\alpha]_D^{20} = +10$ ($c = 0.52$, $CHCl_3$), $[\alpha]_D^{20} = +8$ ($c = 0.56$, EtOH). − M.p. 144−146 °C. − EIMS: *m/z* (%) = 155 [$M^{+\cdot}$] (3), 154 (5), 126 (3), 112 (5), 98 (5), 97 (6), 85 (14), 84 (100), 83 (5), 82 (5), 71 (6), 70 (5), 69 (9), 68 (5), 67 (5), 57 (11), 56 (19), 55 (15). − IR (film): $\tilde{\nu}$ = 3356, 2937, 2874, 2790, 2748, 1446, 1379, 1329, 1119, 1095, 1044, 868, 735 cm^{-1}. − ^1H NMR: δ = 0.88 (t, $J = 6.6$, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.59 (m, 1 H, 2-H), 2.68 (td, $J = 11.7$, 3.3, 1 H, 6ax-H), 3.0 (br. s, 1 H, N−H), 3.18 (bd, $J = 12.1$, 1 H, 6e-H).

(+)-Methyl (6*S*)-2-Pentylpiperidine-1-carboxylate (6): To a solution of **5** (100 mg, 0.65 mmol) in water (6 mL) was added a solution of K_2CO_3 (894 mg, 6.48 mmol) in water (6 mL). Methyl chloroformate (0.3 mL, 3.88 mmol) was then added dropwise at 0 °C. After stirring for 18 h at room temperature, the mixture was extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a residue which was purified by flash chromatography through silica gel (hexane/AcOEt 9:1) to afford **6** (116 mg, 0.55 mmol, 84%) as a colourless oil.

6: GC (column 1: injector temperature 150 °C, temperature program 100 °C then to 270 °C at 10 °C/min, detector temperature 280 °C): R_t = 7.8 min, (column 3: injector temperature 200 °C, temperature program 80 °C then to 180 °C at 3 °C/min then to 200 °C at 15 °C/min, detector temperature 210 °C): R_t (*S*)-**6** = 17.3 min; [racemic sample: R_t (*S*) = 17.3 min; R_t (*R*) = 18.1 min] − $[\alpha]_D^{20} = +30$ ($c = 0.52$, $CHCl_3$). − EIMS: *m/z* (%) = 213 [$M^{+\cdot}$], 198, 182, 170, 154, 142 (100), 70, 55. − ^1H NMR: δ = 0.88 (t, J = 6.8, 3 H, 5′-H_3), 1.20−1.50 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.50−1.70 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.81 (td, $J = 13.5$, 2.6, 1 H, 6ax-H), 3.68 (s, 3 H, OCH_3), 3.98 (bd, $J = 10.2$ Hz, 1 H, 6e-H), 4.22 (m, 1 H, 2-H).

Methyl (6*S*)-2-Methoxy-6-pentylpiperidine-1-carboxylate (7): A solution of **6** (483 mg, 2.27 mmol) and Et_4NOTs (48 mg, 0.16 mmol) as support electrolyte in methanol (36 mL) was placed in an electrolysis cell equipped with 4 carbon electrodes. A constant current (28 mA) was passed through the solution. After 8 F/mol had been consumed, a few drops of diluted ammonia were added and the solvent was evaporated under reduced pressure. The residue was diluted in 5% aqueous ammonia and the aqueous phase was then extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a residue which was purified by flash chromatography through silica gel (hexane/AcOEt 9:1) to afford **7** (*cis*/*trans* mixture, 428 mg, 1.76 mmol, 78%) as a colourless oil.

7: EIMS: *m/z* (%) = 243 [$M^{+\cdot}$], 228 (2), 212 (22), 172 (53),143 (17), 142 (100), 140 (13).

Methyl (6*S*)-2-[(Methoxycarbonyl)methyl]-6-pentylpiperidine-1-carboxylate (8a and 8b): To a solution of **7** (100 mg, 0.41 mmol) in CH_2Cl_2 (1.9 mL) was slowly added $TiCl_4$ (125 μL, 1.14 mmol) at −78 °C under an argon atmosphere. After stirring for 15 min at −78 °C, a solution of 1-methoxy-1-trimethylsilyloxyethene,[14] (430 mg, 2.95 mmol) in CH_2Cl_2 (2 mL) was added, and the stirring maintained for 3 h at −78 °C. The solution was then allowed to warm to room temperature and stirred for about 12 h. After addition of 5 mL of cold water, the solution was basified to pH 9 with ammonia and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a residue which was purified by flash chromatography through silica gel (hexane/AcOEt 8:2) to afford **8** (*cis*/*trans* mixture 87:13, 75 mg, 0.26 mmol, 64%) as a yellow oil.

8: GC (column 1: injector temperature 150 °C, temperature program 100 °C then to 270 °C at 10 °C/min, detector temperature 280 °C): R_t *trans* = 11.7 min, R_t *cis* = 12.1 min. − EIMS: *m/z* (%) = 285 [$M^{+\cdot}$], 254 (2), 226 (11), 214 (41), 212 (12), 182 (24), 141 (10), 140 (100), 82 (10), 55 (11). − ^1H NMR: (**8a**) δ = 0.89 (t, J = 6.6, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.45−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.52 (dd, $J = 15$, 5.1, 1 H, 7-H), 2.63 (dd, $J = 15$, 9.9, 1 H, 7-H), 3.68 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 4.12 (br. s, 1 H, 6-H), 4.65 (br. s, 1 H, 2-H). − ^1H NMR: (**8b**) δ = 0.89 (t, $J = 6.6$, 3H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.45−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.57 (bd, $J = 15.5$, 1 H, 7-H), 2.88 (dd, $J = 15.4$, 5.8, 1 H, 7-H),

3.66 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.80 (br. s, 1 H, 6-H), 3.93 (br. s, 1 H, 2-H).

(6*S*)-2-[(Methoxycarbonyl)methyl]-6-pentylpiperidine (9a and 9b): To a solution of **8a** and **8b** (100 mg, 0.35 mmol) in CH_2Cl_2 (4.5 mL) was added TMSI (0.2 mL, 1.40 mmol) under a nitrogen atmosphere. The mixture was refluxed for 2 h. After cooling, addition of methanol (1.2 mL) and stirring for 10 min at room temperature, the solution was concentrated to dryness under reduced pressure. The solid residue was distributed between water/1% NH_4OH and CH_2Cl_2. The water layer was extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to dryness. TLC of the solid residue (CH_2Cl_2/MeOH/NH_4OH 95:5:1) indicated the presence of two compounds which were purified and separated by flash chromatography through silica gel (CH_2Cl_2, then CH_2Cl_2/MeOH/NH_4OH 97:3:1 to 90:10:1). Compounds **9a** (56 mg, 0.25 mmol) and **9b** (10 mg, 0.04 mmol) were isolated in an 86:14 ratio and in 82% global yield as colourless gums.

9a: GC (column 1: injector temperature 150 °C, temperature program 100 °C then to 300 °C at 10 °C/min, detector temperature 310 °C): R_t = 8.2 min. − $[\alpha]_D^{20}$ = +23 (c = 0.52, $CHCl_3$). − EI-HRMS: m/z (%) = 227.1873 (1, $C_{13}H_{25}NO_2$) [calcd. for $C_{13}H_{25}NO_2$ 227.1885], 226.1811 (1, $C_{13}H_{24}NO_2$) [calcd. for $C_{13}H_{24}NO_2$ 226.1807], 212.1652 (1, $C_{12}H_{22}NO_2$) [calcd. for $C_{12}H_{22}NO_2$ 212.1650], 198.1490 (1, $C_{11}H_{20}NO_2$) [calcd. for $C_{11}H_{20}NO_2$ 198.1494], 184.1339 (1, $C_{10}H_{18}NO_2$) calcd. for $C_{10}H_{18}NO_2$ 184.1338], 170.1178 (1, $C_9H_{16}NO_2$) [calcd. for $C_9H_{16}NO_2$ 170.1181], 169.1102 (1, $C_9H_{15}NO_2$) [calcd. for $C_9H_{15}NO_2$ 169.1103], 168.1755 (1), 156.1022 (100, $C_8H_{14}NO_2$) [calcd. for $C_8H_{14}NO_2$ 156.1024], 142.0864 (1, $C_7H_{12}NO_2$) [calcd. for $C_7H_{12}NO_2$ 142.0868], 128.0713 (2, $C_6H_{10}NO_2$) [calcd. for $C_6H_{10}NO_2$ 128.0712], 124.0762 (18, C_7H_{10} NO) [calcd. for C_7H_{10} NO 124.0762]. − ^{1}H NMR: δ = 0.88 (t, J = 6.6, 3 H, 5′-H_3), 1.20−1.50 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.55−1.85 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.24 (br. s, 1 H, N−H), 2.46 (d, J = 6.2, 2 H, 7-H_2), 2.55 (m, 1 H, 6-H), 2.98 (m, 1 H, 2-H), 3.68 (s, 3 H, OCH_3).

9b: GC (column 1: injector temperature 150 °C, temperature program 100 °C then to 300 °C at 10 °C/min, detector temperature 310 °C): R_t = 8.6 min. − $[\alpha]_D^{20}$ = +5 (c = 0.53, $CHCl_3$). − ^{1}H NMR: δ = 0.89 (t, J = 6.6, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.70 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.53 (dd, J = 16.1, 6.2, 1 H, 7-H), 2.88 (dd, J = 16.4, 7.7, 1 H, 7-H), 3.08 (m, 1 H, 6-H), 3.54 (m, 1 H, 2-H), 3.70 (s, 3 H, OCH_3), 4.31 (br. s, 1 H, N−H).

(+)-Calvine (1a) and (+)-2-Epicalvine (1b): A solution of **9a** and **9b** (100 mg, 0.44 mmol) in methanol (4 mL) was added to ethylene oxide (1 mL) at −78 °C in a sealed tube under a nitrogen atmosphere. The solution was heated at 50 °C for 22 h and then cooled to room temperature. Removal of the solvent under reduced pressure and of the excess of ethylene oxide at atmospheric pressure gave a solid residue containing **1a, 1b**, **10a, 10b**, and **11**. This residue was dissolved in CH_3CN (8 mL) and maintained at 50 °C for 2 h in the presence of Amberlyst A15 and 4 Å molecular sieves. After cooling, the mixture was basified with diluted ammonia and extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a mixture of **1a**, **1b**, and **11**. The *cis* and *trans* lactones were purified and separated by flash chromatography through silica gel (hexane/THF/NH_4OH 75:25:5) to afford **1a** (24 mg, 0.1 mmol, 23%) and **1b** (21 mg, 0.09 mmol, 20%) as yellow oils.

1a: GC (column 2: injector temperature 180 °C, temperature program 10 min at 180 °C then to 250 °C at 10 °C/min, detector temperature 260 °C): R_t = 19 min. − $[\alpha]_D^{20}$ = +18 (c = 0.66, CH_2Cl_2). − EI-HRMS: m/z (%) = 240.1966 (7, $C_{14}H_{26}NO_2$) [calcd. for $C_{14}H_{26}NO_2$ 240.1694], 169.1059 (14), 168.1019 (100, $C_9H_{14}NO_2$) [calcd. for $C_9H_{14}NO_2$ 168.1024], 126.0916 (16, $C_7H_{12}NO$) [calcd. for $C_7H_{12}NO$ 126.0919]. − ^{1}H NMR: δ = 0.89 (t, J = 6.9, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.20−2.90 (m, 5 H, 2-H, 6-H, 7-H, 9-H_2), 3.30 (ms, 1 H, 7-H), 4.28 (m, 2 H, 10-H_2).

1b: GC (column 2: injector temperature 180 °C, temperature program 10 min at 180 °C then to 250 °C at 10 °C/min, detector temperature 260 °C): R_t = 19.5 min. − $[\alpha]_D^{20}$ = +8 (c = 0.58, CH_2Cl_2). − EI-HRMS: m/z (%) = 239.1884 (2, $C_{14}H_{25}NO_2$) [calcd. for $C_{14}H_{25}NO_2$ 239.1885], 169.1062 (11), 168.1024 (100, $C_9H_{14}NO_2$) [calcd. for $C_9H_{14}NO_2$ 168.1024], 126.0920 (10, $C_7H_{12}NO$) [calcd. for $C_7H_{12}NO$ 126.0919]. − ^{1}H NMR: δ = 0.88 (t, J = 6.6, 3H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.50−2.90 (m, 3 H, 6-H, 7-H_2), 2.90−3.10 (m, 2 H, 9-H_2), 3.32 (ms, 1 H, 2-H), 3.88 (m, 1 H, 10-H), 3.98 (m, 1 H, 10-H).

11: Identical R_f in TLC and R_t in capillary GC to those of the corresponding racemic compound.[6]

Benzoates 12a and 12b: The solid residue of a hydroxyethylation reaction (101 mg of **9**, 0.44 mmol) was dissolved in dry toluene (4 mL). DMAP (55 mg, 0.45 mmol) and benzoic anhydride (0.136 mg, 0.06 mmol) were added to the solution and the mixture was stirred at room temperature for 24 h. After addition of an aqueous solution of 1 M NaOH (8 mL) at 0 °C, the mixture was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure followed by filtration through silica gel (hexane/acetone 9:1) to remove the excess of DMAP gave a mixture containing **1a**, **1b**, **12a**, **12b** and **13**. The *cis* and *trans* benzoates were purified and separated by flash chromatography through silica gel (hexane/THF/NH_4OH 92.5:7.5:1) to afford **12a** and **12b** (55 mg, 0.15 mmol, 36%) as colourless gums.

12a: GC (column 2: injector temperature 200 °C, temperature program 10 min at 200 °C then to 260 °C at 10 °C/min, detector temperature 280 °C): R_t = 27.9 min. − $[\alpha]_D^{20}$ = +18 (c = 0.16, CH_2Cl_2). − EI-HRMS: m/z (%) = 375.2401 (1, $C_{22}H_{33}NO_4$) [calcd. for $C_{22}H_{33}NO_4$ 375.2410], 374.2339 (1, $C_{22}H_{32}NO_4$) [calcd. for $C_{22}H_{32}NO_4$ 374.2331], 344.2226 (1, $C_{21}H_{30}NO_3$) [calcd. for $C_{21}H_{30}NO_3$ 344.2226], 305.1581 (19), 304.1551 (100, $C_{17}H_{22}NO_4$) [calcd. for $C_{17}H_{22}NO_4$ 304.1549], 302.2124 (21, $C_{19}H_{28}NO_2$) [calcd. for $C_{19}H_{28}NO_2$ 302.2120], 240.1961 (32, $C_{14}H_{26}NO_2$) [calcd. for $C_{14}H_{26}NO_2$ 240.1963], 149.0600 (36, $C_9H_9O_2$) [calcd. for $C_9H_9O_2$ 149.0602], 105.0340 (28, C_7H_5O) [calcd. for C_7H_5O 105.0340]. − ^{1}H NMR: δ = 0.88 (t, J = 6.6, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.36 (dd, J = 14.6, 9.5, 1 H, 7-H), 2.57 (ms, 1 H, 2-H), 2.76 (dd, J = 15, 4.8, 1 H, 7-H), 2.85 (ms, 2 H, 8-H_2), 3.13 (ms, 1 H, 6-H), 3.67 (s, 3 H, OCH_3), 4.26 (t, J = 7.1, 2 H, 9-H_2), 7.43 (t, J = 7.5, 2 H, Ar-H), 7.56 (t, J = 7.7, 1 H, Ar-H), 8.04 (d, J = 7.3, 2 H, Ar-H).

12b: GC (column 2: injector temperature 200 °C, temperature program 10 min at 200 °C then to 260 °C at 10 °C/min, detector temperature 280 °C): R_t = 27.6 min. − $[\alpha]_D^{20}$ = +8 (c = 0.40, CH_2Cl_2). − EI-HRMS: m/z (%) = 375.2396 (1, $C_{22}H_{33}NO_4$) [calcd. for $C_{22}H_{33}NO_4$ 375.2410], 374.2330 (1, $C_{22}H_{32}NO_4$) [calcd. for $C_{22}H_{32}NO_4$ 374.2331], 344.2231 (1, $C_{21}H_{30}NO_3$) [calcd. for $C_{21}H_{30}NO_3$ 344.2226], 305.1580 (11), 304.1562 (100, $C_{17}H_{22}NO_4$)

[calcd. for $C_{17}H_{22}NO_4$ 304.1549], 302.2122 (22, $C_{19}H_{28}NO_2$) [calcd. for $C_{19}H_{28}NO_2$ 302.2120], 241.2000 (11), 240.1960 (70, $C_{14}H_{26}NO_2$) [calcd. for $C_{14}H_{26}NO_2$ 240.1963], 149.0598 (27, $C_9H_9O_2$) [calcd. for $C_9H_9O_2$ 149.0602], 105.0336 (28, C_7H_5O) [calcd. for C_7H_5O 105.0340]. − ^{1}H NMR: δ = 0.86 (t, *J* = 6.6, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.80 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.41 (dd, *J* = 14.6, 7.7, 1 H, 7-H), 2.71 (dd, *J* = 14.6, 7.7, 1 H, 7-H), 2.75 (m, 1 H, 2-H), 2.78 (dt, *J* = 13.9, 6.2, 1 H, 8-H), 2.93 (dt, *J* = 13.9, 7.3, 1 H, 8-H), 3.43 (ms, 1 H, 6-H), 3.63 (s, 3 H, OCH_3), 4.28 (t, *J* = 6.6, 2 H, 9-H_2), 7.43 (t, *J* = 7.3, 2 H, Ar-H), 7.55 (t, *J* = 7.3, 1 H, Ar-H), 8.04 (d, *J* = 7.3, 2 H, Ar-H).

13: EI-HRMS: *m*/*z* (%) = 523.2940 (4, $C_{31}H_{41}NO_6$) [calcd. for $C_{31}H_{41}NO_6$ 523.2934], 492.2751 (6, $C_{30}H_{38}NO_5$) [calcd. for $C_{30}H_{38}NO_5$ 429.2750], 453.2104 (29, $C_{26}H_{31}NO_6$) [calcd. for $C_{26}H_{31}NO_6$ 453.2151], 452.2071 (96, $C_{26}H_{30}NO_6$) [calcd. for $C_{26}H_{30}NO_6$ 452.2073], 397.2203 (21, $C_{24}H_{31}NO_4$) [calcd. for $C_{24}H_{31}NO_4$ 397.2253], 396.2169 (82, $C_{24}H_{30}NO_4$) [calcd. for $C_{24}H_{30}NO_4$ 396.2175], 389.2527 (19, $C_{23}H_{35}NO_4$) [calcd. for $C_{23}H_{35}NO_4$ 389.2566], 388.2488 (70, $C_{23}H_{34}NO_4$) [calcd. for $C_{23}H_{34}NO_4$ 388.2488], 178.0864 (12, $C_{10}H_{12}NO_2$) [calcd. for $C_{10}H_{12}NO_2$ 178.0868], 149.0598 (79, $C_9H_9O_2$) [calcd. for $C_9H_9O_2$ 149.0602], 105.0320 (100). − ^{1}H NMR: δ = 0.83 (t, *J* = 6.4, 3 H, 5′-H_3), 1.15−1.45 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.45−1.75 (ms, 4 H, 3-H_2, 4-H_2), 2.11 (dd, *J* = 13.9, 7.7, 2 H, 5-H_2), 2.51 (m, 1 H, 2-H), 2.92 (t, *J* = 5.8, 5.5, 4 H, 8-H_4), 3.71 (s, 3 H, OCH_3), 4.34 (t, *J* = 6.0, 4 H, 9-H_4), 5.77 (bd, *J* = 15.7, 1 H, 7-H), 6.86 (dt, *J* = 15.4, 6.9, 1 H, 6-H), 7.39 (t, *J* = 7.3, 4 H, Ar-H), 7.53 (t, *J* = 7.3, 2 H, Ar-H), 8.01 (d, *J* = 7.3, 4 H, Ar-H).

(−)-(5*S*)-5-Pentyl-3-phenyloctahydropyrido[2,1-*b*]oxazole (14): To liquid ammonia (10 mL), condensed under an argon atmosphere at −78 °C, was added sodium metal (69 mg, 2.98 mmol). After 30 min, a solution of **3** (105 mg, 0.35 mmol) in THF (2 mL) was added at −78 °C to the deep blue solution. After stirring for 1 h, the reaction was quenched by the addition of methanol (1 mL). The mixture was then warmed to room temperature to evaporate the excess of ammonia. After addition of a saturated aqueous NH_4Cl solution and extraction with CH_2Cl_2, the combined extracts were filtered through a WA filter paper and concentrated to give a crude mixture. After flash chromatography through silica gel (hexane/Et_2O 95:5), **14** (74 mg, 0.27 mmol, 77%) was obtained as a colourless oil.

14: $[\alpha]_D^{20}$ = −8 (*c* = 0.50, $CHCl_3$). − EIMS: *m*/*z* (%) = 274 (14), 273 [$M^{+\bullet}$] (6), 204 (20), 203 (31), 202 (100), 148 (12), 120 (13), 117 (12), 104 (33), 92 (14), 91 (23), 82 (34), 55 (32). − IR (film): $\tilde{\nu}$ = 3083, 3021, 2958, 2874, 1463, 1413, 1346, 1186, 1103, 1002, 902, 810, 760, 701 cm^{-1}. − ^{1}H NMR: δ = 0.85 (t, *J* = 7.0, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.50−1.70 (ms, 6 H, 6-H_2, 7-H_2, 8-H_2), 2.30 (m, 1 H, 5-H), 3.73 (m, 1 H, 2-H), 4.35 (dd, *J* = 15, 7.7, 1 H, 2-H), 4.40 (dd, *J* = 7.7, 4.1, 1 H, 3-H), 4.50 (m, 1 H, 9-H), 7.20−7.45 (ms, 5 H, Ar-H). − UV (MeOH): λ_{max} (ε) = 221 nm (1290), 254 nm (160), 260 nm (180), 266 nm (160).

(+)-(2*S*,6*S*)-2-[(Methoxycarbonyl)methyl]-6-pentyl-1-(1-phenyl-2-hydroxyethyl)piperidine (15): A solution of **14** (102 mg, 0.38 mmol) in an anhydrous 1:1 mixture of CH_3CN and ether (4 mL) was treated at 0 °C under argon with $BF_3{\cdot}OEt_2$ (150 μL, 1.2 mmol). After 15 min, the solution was cooled to −78 °C and 1-methoxy-1-trimethylsilyloxyethene[14] (129 mg, 0.88 mmol) was added. The resulting solution was then allowed to warm to 0 °C for about 2 h. The reaction mixture was treated with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were filtered through a WA filter paper and the solvent evaporated in vacuo to give a residue which was purified by flash chromatography through silica gel (hexane/Et_2O 5:5) to afford **15** (112 mg, 0.32 mmol, 86%) as a colourless oil.

15: $[\alpha]_D^{20}$ = +36 (*c* = 0.42, $CHCl_3$). − EIMS: *m*/*z* (%) = 347 [$M^{+\cdot}$], 318 (23), 317 (40), 316 (100), 277 (12), 276 (48), 274 (22), 240 (15), 156 (52), 154 (18), 124 (16), 121 (16), 106 (18), 104 (13), 103 (23), 91 (25), 82 (27), 77 (11), 55 (23). − IR (film): $\tilde{\nu}$ = 3460, 3083, 3021, 2958, 2874, 1739, 1454, 1413, 1354, 1287, 1203, 1170, 1053, 1028, 760, 701 cm^{-1}. − ^{1}H NMR: δ = 0.90 (t, *J* = 7.0, 3 H, 5′-H_3), 1.20−1.40 (ms, 8 H, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2), 1.40−1.60 (ms, 6 H, 3-H_2, 4-H_2, 5-H_2), 2.35 (dd, *J* = 15, 7.3, 1 H, 7-H), 2.48 (m, 1 H, 6-H), 2.68 (dd, *J* = 15, 6.7, 1 H, 7-H), 2.88 (m, 1 H, 2-H), 3.48 (dd, *J* = 14, 7.0, 1 H, 8-H), 3.66 (s, 3-H, OCH_3), 3.88 (m, 2 H, 9-H_2), 7.25−7.35 (ms, 5 H, Ar-H). − UV (MeOH): λ_{max} (ε) = 207 nm (8030).

(+)-(2*S*,6*S*)-2-[(Methoxycarbonyl)methyl]-6-pentylpiperidine (9a): Compound **15** (133 mg, 0.38 mmol) in methanol (5 mL) was hydrogenated in the presence of 10% Pd/C at atmospheric pressure and room temperature for 48 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash chromatography through silica gel (CH_2Cl_2, then CH_2Cl_2/MeOH/NH_4OH 97:3:1 to 90:10:1) gave (2*S*,6*S*)-**9a** (76 mg, 0.34 mmol, 88%) as a colourless gum.

(+)-(2*S*,6*S*)-9a: $[\alpha]_D^{20}$ = +22 (c = 0.56, $CHCl_3$).

Acknowledgments

We thank Drs. M. Luhmer and M. Plehiers for the NMR spectra, Mr. C. Moulard for the mass spectra and Dr. S. Heilporn for the GC-MS analyses. We also acknowledge Dr. C. Hootelé and Miss V. Plasman for helpful discussions, and an anonymous referee for bringing ref.[12] to our attention. P. L. gratefully acknowledges financial support from the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A).

[1] B. Tursch, J. C. Braekman, D. Daloze, *Experientia* **1976**, *32*, 401−407.
[2] G. M. Happ, T. Eisner, *Science* **1961**, *134*, 329−331.
[3] J. M. Pasteels, C. Deroe, B. Tursch, J. C. Braekman, D. Daloze, C. Hootelé, *J. Insect Physiol.* **1973**, *19*, 1771−1784.
[4] D. Daloze, J. C. Braekman, J. M. Pasteels, *Chemoecology* **1995**, *5/6*, 173−183.
[5] G. A. King, J. Meinwald, *Chem. Rev.* **1996**, *96*, 1105−1122.
[6] J. C. Braekman, A. Charlier, D. Daloze, S. Heilporn, J. M. Pasteels, V. Plasman, S. F. Wang, *Eur. J. Org. Chem.* **1999**, 1749−1755.
[7] T. Shono, *Tetrahedron* **1984**, *40*, 811−850.
[8] F. Driessens, C. Hootelé, *Can. J. Chem.* **1991**, *69*, 211−217.
[9] Thus named because it achieves chemo- and stereoselective reactions at either C-5 (α-amino nitrile) or C-9 (α-amino ether) of **2**. For valuable examples of this strategy, see ref.[10]
[10] H. P. Husson, J. Royer, *Chem. Soc. Rev.* **1999**, *6*, 383−394.
[11] A. Durant, C. Hootelé, *Can. J. Chem.* **1997**, *70*, 2722−2725.
[12] J. F. Berrien, M. A. Billion, H. P. Husson, J. Royer, *J. Org. Chem.* **1995**, *60*, 2922−2924.
[13] L. Guerrier, J. Royer, D. S. Grierson, H. P. Husson, *J. Am. Chem. Soc.* **1983**, *105*, 7754−7755.
[14] C. Ainsworth, Y. Kuo, *J. Organomet. Chem.* **1972**, *46*, 73−87.
[15] S. Arseniyadis, P. Q. Huang, D. Piveteau, H. P. Husson, *Tetrahedron* **1988**, *44*, 2457−2470.
[16] Y. C. Hwang, M. Chu, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 3885−3890.

Received October 29, 1999
[O99603]