Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2221–2229

TETRAHEDRON: *ASYMMETRY*

A simple and efficient enantioselective synthesis of piperidine alkaloids dihydropinidine and isosolenopsins A, B and C

Stéphane Ciblat,[a] Pascale Besse,[b] Vassiliki Papastergiou,[a,†] Henri Veschambre,[b] Jean-Louis Canet[a,*] and Yves Troin[a,*]

[a]*Laboratoire de Chimie des Hétérocycles et des Glucides, EA 987, Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, Université Blaise Pascal, BP187, 63174 Aubière Cedex, France*
[b]*Laboratoire de Synthèse, Electrosynthèse et Etude de Systèmes à Intérêt Biologique, UMR 6504 du CNRS, Université Blaise Pascal, 63177 Aubière Cedex, France*

Received 6 April 2000; accepted 2 May 2000

Abstract

A diastereospecific intramolecular Mannich-type reaction, involving enantiopure amine **4** and achiral aldehydes, is employed as the key step of an efficient total enantioselective synthesis of five piperidine alkaloids.

1. Introduction

Due to the wide diversity of potent biological activities associated with piperidine-containing alkaloids and synthetic analogs, the enantioselective preparation of such compounds is the object of considerable efforts.[1]

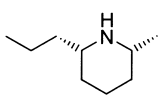
Among the numerous naturally occurring piperidines, simple 2-methyl-6-alkylpiperidines constitute an important class of alkaloids. Representative examples are dihydropinidine **1**, a defense alkaloid of the Mexican bean beetle *Epilachna varivestis* (Coccinellidae)[2] and solenopsins **2**–**3**, venom alkaloids of fire ants.[3] Ants of the genus *Solenopsis* (Myrmicinae) secrete a venom characterized by a predominance of (2*R*,6*R*)-*trans* and (2*R*,6*S*)-*cis*-2-methyl-6-alkylpiperidines named,[3a] respectively, solenopsins **2** and isosolenopsins **3** (Fig. 1). It has been shown that both **2** and **3** alkaloids were responsible for the pronounced hemolytic, necrotoxic, phytotoxic, antibiotic, insecticidal and antifungal activities of the fire ants' venom.[3c,d]

Moreover, these piperidine alkaloids exhibit physiological activities: solenopsin A **2b** and isosolenopsin A **3b** were found to block the neuromuscular transmissions while isosolenopsin C

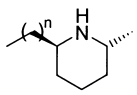
* Corresponding authors. Fax: 33 4 73 40 70 08; e-mail: canet@chimtp.univ-bpclermont.fr, troin@chimtp.univ-bpclermont.fr

† Aristote University of Thessalonniki, Greece; ERASMUS student.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00162-2

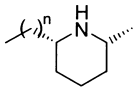


dihydropinidine **1**



solenopsins **2**

2a n = 8
2b n = 10, solenopsin A
2c n = 12, solenopsin B
2d n = 14, solenopsin C



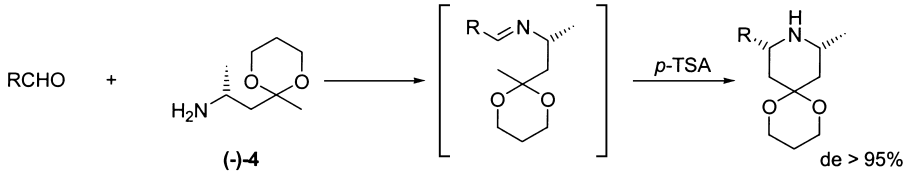
isosolenopsins **3**

3a n = 8
3b n = 10, isosolenopsin A
3c n = 12, isosolenopsin B
3d n = 14, isosolenopsin C

Figure 1.

3d, at low concentration, reduces the mitochondrial respiration and uncouples[5] oxidative phosphorylation through the inhibition of Na^+ and K^+ ATPases.[3c,d] Probably considered as target-molecules for the validation of different enantioselective routes to 2,6-*cis*- and 2,6-*trans*-disubstituted piperidine skeletons, dihydropinidine[4] **1** and solenopsins (particularly A **2b** and B **2c**) have been the object of considerable synthetic efforts.[4] In contrast, enantioselective preparation of isosolenopsins **3** remains poorly developed. Effectively, although three asymmetric syntheses of isosolenopsin A **3b** have been described[3a,5,6] (in two cases,[3a,5] **3b** was isolated as the minor diastereomer together with **2b**), to our knowledge, isosolenopsins **3a**, **3c**, and **3d** have never been prepared in an optically active form.

Part of our research interest concerns the enantioselective construction of polysubstituted piperidines. In this field we have recently described an efficient enantioselective access to 2,6-disubstituted piperidines.[7] As our approach, involving various aldehydes and homochiral amine (+)- or (–)-**4** in a Mannich-type reaction, furnished the 2,6-*cis*-isomer quasi exclusively (Scheme 1), it seemed particularly suitable for the enantioselective synthesis of alkaloids such as **1** and **3**, on which we focused our attention.

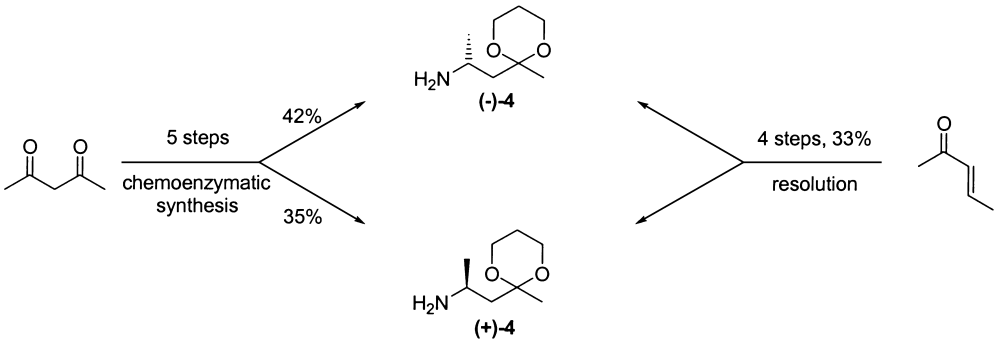


Scheme 1.

2. Results and discussion

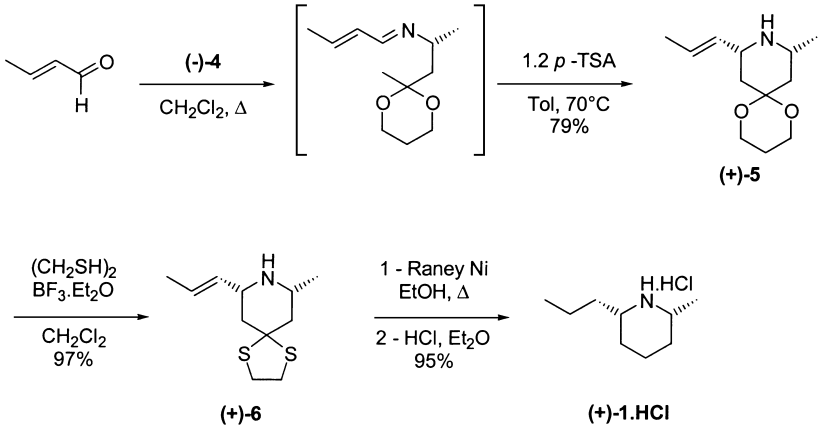
The limitation of our strategy, associated with the length of previous[8] enantioselective preparation of amines (+)- and (–)-**4** (seven steps, 13.5% overall yield) has been solved since we could propose new approaches. These compounds are now prepared on a multigram scale, using either a new and efficient chemoenzymatic pathway[9] (five steps from 2,4-pentanedione, 37–44% overall yield) or by resolution of (±)-**4** with tartaric acid[10] (four steps from pentenone, 33% yield), as summerized in Scheme 2.

Thus, reaction of crotonaldehyde with amine (–)-**4** in dichloromethane at reflux, in the presence of magnesium sulphate, gave quantitatively in 5 h (TLC monitoring) the corresponding imine



Scheme 2.

(Scheme 3). This unstable compound was directly treated with 1.2 equivalents of dry *para*-toluenesulphonic acid at 70°C in toluene for 12 h to yield, as expected,[7] 2,6-*cis*-disubstituted piperidine (+)-**5** as sole diastereomer (79%, de >95%, the 2,6-*trans*-isomer was not detected from NMR spectra).

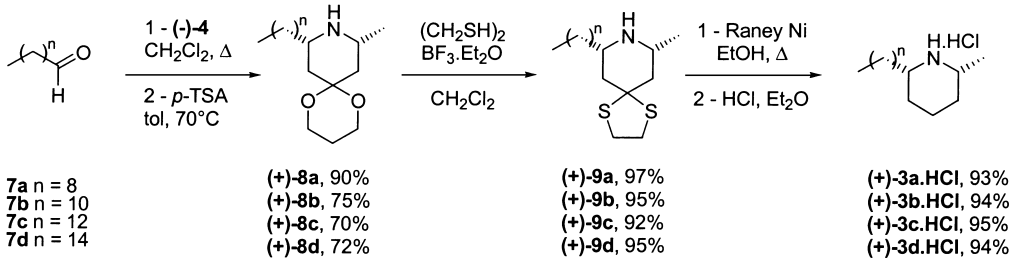


Scheme 3.

Subsequent treatment of piperidine (+)-**5** with an excess of ethanedithiol in dichloromethane in the presence of $BF_3{\cdot}Et_2O$ afforded quantitatively the dithiolane derivative (+)-**6**. Hydrogenolysis of (+)-**6** was completely and cleanly achieved in 30 min in the presence of freshly prepared W_2 Raney-nickel[11] in refluxing ethanol and furnished dihydropinidine (+)-**1**, which was isolated and characterized as its hydrochloride (95% from (+)-**6**).

The specific rotation of our synthetic (+)-dihydropinidine hydrochloride **1·HCl** ($[\alpha]_D^{25}=+14.1$, *c* 0.98 in ethanol) was in fair agreement with those reported (lit.[4] $[\alpha]_D^{25}=11.6$ to 14.2 in EtOH). As both enantiomers of amine **4** are readily available, we could prepare enantiomeric (–)-dihydropinidine hydrochloride **1·HCl** ($[\alpha]_D^{25}=-14.2$, *c* 0.45 in ethanol) in three steps from amine (+)-**4** using the same pathway (lit.[4] $[\alpha]_D^{25}=-9.1$ to –12.7 in EtOH).

These results show that no racemization occurred during this sequence. Since, to our knowledge, specific rotations of compounds **3a**, **c**, and **d** have never been reported, we decided to apply this sequence to the first total enantioselective synthesis of these alkaloids (Scheme 4).



Scheme 4.

Commercially available aldehydes **7** involved in the cyclization step with amine (–)-**4** gave (+)-2,6-*cis*-dialkylpiperidines **8**, exclusively (2,6-*trans*-isomers were not detected from NMR spectra), in 70–90% yield. Finally, treatment of piperidines (+)-**8** with ethanedithiol followed by hydrogenolysis, as described above, led to dithioderivatives (+)-**9** (92–97%) then to natural (+)-(2*R*,6*S*)-isomers of isosolenopsins **3** (93–95%).

The specific rotation of (+)-isosolenopsin A hydrochloride **3b·HCl** ($[\alpha]_D^{25} = +10.0$, *c* 1.17 in $CHCl_3$) was in good agreement with the literature data (lit.[3a5,6] $[\alpha]_D^{25} = +10.1$ to 10.6 in $CHCl_3$).

3. Conclusion

We have described herein a simple and competitive preparation of both enantiomers of dihydropinidine **1** together with the first asymmetric synthesis of natural isomers of three isosolenopsins. All these compounds were prepared in seven or eight steps from pentenone or pentanedione, respectively. Extension of this strategy to the stereoselective synthesis of highly substituted piperidinic systems from differently and more substituted chiral amines is in progress and will be published in due course.

4. Experimental

Melting points are uncorrected. ^1H 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 hertz. Infrared spectra were recorded on a FTIR spectrometer. 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 were 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.

4.1. Intramolecular Mannich-type cyclization. General procedure

To a stirred solution of aldehyde (2.20 mmol) in CH_2Cl_2 (20 mL) was added $MgSO_4$ (ca. 1 g) followed by a solution of amine (–)- or (+)-**4** (2 mmol) in CH_2Cl_2 (5 mL). The resulting solution was heated at reflux until complete disappearance (TLC monitoring) of the amine (5 h), then

cooled to room temperature and transferred via a cannula to a solution of dry *para*-toluenesulphonic acid (2.40 mmol) in toluene (25 mL). The resulting mixture was heated at 70°C for 12 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.

4.2. (+)-(8R,10R)-9-Aza-10-methyl-8-prop-1′-enyl-1,5-dioxaspiro[5.5]undecane **5**

Following the cyclization procedure, crotonaldehyde (169 μL, 2.07 mmol) and amine (–)-**4** (300 mg, 1.89 mmol) afforded the protected piperidone (+)-**5** as a pale yellow oil (315 mg, 79%). R_f 0.3 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$ = +10.3 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3319, 2962, 2865, 1718, 1439, 1377, 1313, 1248, 1146, 1096; δ_H ($CDCl_3$) 5.62 (1H, m), 5.45 (1H, m), 3.90–3.80 (4H, m), 3.28 (1H, m, H-8), 2.92 (1H, m, H-10), 2.27 (1H, dt, *J* = 13.5 and 2.5, H-7eq), 2.19 (1H, dt, *J* = 13.5 and 2.5, H-11eq), 1.75–1.65 (2H, m), 1.65 (3H, dd, *J* = 6 and 1.2), 1.60–1.50 (1H, br s, NH), 1.35–1.10 (2H, m), 1.10 (3H, d, *J* = 7); δ_C($CDCl_3$) 133.7, 125.8, 97.4, 59.1, 54.9, 47.7, 41.4, 38.7, 25.7, 22.6, 17.7; found (FAB) 212.1653, $C_{12}H_{21}NO_2$+H^+ requires 212.1651.

4.3. (–)-(8S,10S)-9-Aza-10-methyl-8-prop-1′-enyl-1,5-dioxaspiro[5.5]undecane **5**

Following the same procedure, (–)-**5** was prepared in 80% yield from (+)-**4**; $[\alpha]_D^{25}$ = –10.4 (*c* 1.0, $CHCl_3$). Spectral data are identical with those reported above for its enantiomer.

4.4. Dithioacetalation. General procedure

To a stirred solution of protected piperidone (2 mmol) in dichloromethane (20 mL) was added dropwise, at room temperature, ethanedithiol (10 mmol) then a 48% solution of $BF_3{\cdot}Et_2O$ in diethylether (10 mmol). After 1 h of stirring, an excess of 1 M aqueous NaOH was added and the resulting mixture was extracted with dichloromethane (4×20 mL). The combined organic extracts were dried, filtered and evaporated. The residue, purified by column chromatography, gave the corresponding dithiolane derivative.

4.5. (+)-(7R,9R)-8-Aza-9-methyl-7-prop-1′-enyl-1,4-dithiaspiro[5.4]undecane **6**

Following the thioacetalation procedure, protected piperidone (+)-**5** (300 mg, 1.42 mmol) afforded the dithiaspiropiperidine (+)-**6** as a pale yellow oil (316 mg, 97%). R_f 0.65 (ethyl acetate: methanol, 1:1); $[\alpha]_D^{25}$ = +21.9 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3297, 2924, 2822, 1432, 1376, 1314, 1276, 1103, 968, 733; δ_H ($CDCl_3$) 5.65 (1H, m), 5.30 (1H, m), 3.30 (4H, s), 3.77 (1H, m, H-9), 2.07 (2H, m, H-6eq and H-10eq), 1.81–1.68 (2H, m, H-6ax and H-10ax), 1.63 (4H, H-13 and NH), 1.09 (3H, t, *J* = 7.0); δ_C ($CDCl_3$) 132.8, 126.0, 66.1, 61.0, 57.9, 50.9, 49.4, 38.8, 37.5, 22.0, 17.6; found (FAB) 230.1037, $C_{11}H_{19}NS_2$+H^+ requires 230.1037.

4.6. (–)-(7S,9S)-8-Aza-9-methyl-7-prop-1′-enyl-1,4-dithiaspiro[5.4]undecane **6**

Following the same procedure, (–)-**6** was prepared in 97% yield from (+)-**5**; $[\alpha]_D^{25}$ = –21.7 (*c* 1.0, $CHCl_3$). Spectral data are identical with those reported above for its enantiomer.

4.7. Hydrogenolysis of dithiaspiropiperidines. General procedure

To a stirred solution of protected piperidone (2 mmol) in absolute ethanol (20 mL) was added freshly prepared W2 Raney-nickel[11] (500 mg). The resulting suspension was heated at reflux for 30 min, cooled to room temperature before filtration then concentration of the filtrate under reduced pressure. The residue was dissolved in 1 M NaOH and the piperidine was extracted with dichloromethane (4×20 mL). The combined organic extracts were dried, filtered and evaporated. To the residue, dissolved in diethyl ether (3 mL), was added a saturated ether solution of hydrogen choride (4 mL). Filtration, followed by recrystallization from absolute EtOH:AcOEt, 1:3, afforded the title compounds as white needles.

4.8. (+)-(2R,6S)-2-Methyl-6-propylpiperidine hydrochloride [(+)-dihydropinidine-HCl] **1·HCl**

Following the hydrogenolysis procedure, protected piperidone (+)-**6** (200 mg, 0.87 mmol) afforded the piperidine (+)-**1** as a pale yellow oil (115 mg, 95%). R_f 0.1 (ethyl acetate:methanol, 1:1). Recrystallization of the hydrochloride from absolute EtOH:AcOEt, 1:3 afforded dihydropinidine hydrochloride **1·HCl** as white needles; mp = 242–243°C (lit.[4] mp = 242–246°C), $[\alpha]_D^{25}$ = +14.1 (*c* 1.0, EtOH) (lit.[4] $[\alpha]_D^{25}$ = +11.6 to 14.2, *c* 1.14, EtOH); spectral data were identical with those reported.[4]

4.9. (–)-(2S,6R)-2-Methyl-6-propyl-piperidine hydrochloride [(-)-dihydropinidine-HCl] **1**

Following the same procedure, (–)-**1** was prepared in 96% yield from (–)-**6**; mp = 242–243°C; $[\alpha]_D^{25}$ = –14.2 (*c* 0.5, EtOH) (lit.[4] $[\alpha]_D^{25}$ = –9.1 to –12.7 in EtOH); spectral data were identical with those reported.[4]

4.10. (+)-(8S,10R)-9-Aza-10-methyl-8-n-nonyl-1,5-dioxaspiro[5.5]undecane **8a**

Following the cyclization procedure, decanal (324 mg, 2.07 mmol) and amine (–)-**4** (300 mg, 1.89 mmol) afforded the protected piperidone (+)-**8a** as a pale yellow oil (504 mg, 90%). R_f 0.42 (ethyl acetate:methanol, 5:1); $[\alpha]_D^{25}$ = +3.5 (*c* 0.99, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3314, 1143, 1097; δ_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); δ_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, $C_{18}H_{35}NO_2$+H^+ requires 297.2868.

4.11. (+)-(8S,10R)-9-Aza-10-methyl-8-n-undecyl-1,5-dioxaspiro[5.5]undecane **8b**

Following the cyclization procedure, dodecanal (382 mg, 2.07 mmol) and amine (–)-**4** (300 mg, 1.89 mmol) afforded the protected piperidone (+)-**8b** as a pale yellow oil (460 mg, 75%). R_f 0.42 (ethyl acetate:methanol, 1:1); $[\alpha]_D^{25}$ = +1.4 (*c* 1.4, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3314, 2925, 2854, 1466, 1380, 1321, 1144, 1097, 1012, 986; δ_H ($CDCl_3$) 3.94 (2H, t, *J* = 6.5), 3.86 (2H, t, *J* = 6.5), 2.87 (1H, m, H-10), 2.74 (1H, m, H-8), 2.25 (2H, m, H-7eq and H-11eq), 1.73 (2H, m), 1.49–1.20 (22H, m), 1.20–1.02 (4H, m), 0.83 (3H, t, *J* = 7.0); δ_C ($CDCl_3$) 179.5, 128.8, 125.9, 97.4, 59.2, 52.6, 48.0, 40.9, 39.0, 36.4, 31.9, 29.7, 29.6, 29.4, 26.0, 25.6, 22.7, 22.1, 14.1; found (FAB) 326.3058, $C_{20}H_{39}NO_2$+H^+ requires 326.3059.

*4.12. (+)-(8S,10R)-9-Aza-10-methyl-8-*n*-tridecyl-1,5-dioxaspiro[5.5]undecane* ***8c***

Following the cyclization procedure, tetradecanal (440 mg, 2.07 mmol) and amine (–)-**4** (300 mg, 1.89 mmol) afforded the protected piperidone (+)-**8c** as a pale yellow oil (466 mg, 70%). R_f 0.42 (ethyl acetate:methanol, 1:1); $[\alpha]_D^{25}=+1.8$ (*c* 1.4, $CHCl_3$); δ_H ($CDCl_3$) 3.90 (2H, t, $J=6.5$), 3.79 (2H, t, $J=6.5$), 2.80 (1H, m, H-10), 2.71 (1H, m, H-8), 2.21 (2H, m, H-7eq and H-11eq), 1.71 (2H, m), 1.49–1.22 (26H, m), 1.18–1.00 (4H, m), 0.80 (3H, t, $J=7.0$); δ_C ($CDCl_3$) 148.2, 128.8, 125.8, 97.6, 59.2, 59.1, 52.6, 48.0, 47.7, 41.1, 39.4, 36.7, 31.9, 29.8, 29.7, 29.6, 29.4, 26.2, 25.7, 22.4, 21.7, 14.1; found (FAB) 354.3372, $C_{22}H_{43}NO_2$+H^+ requires 354.3374.

*4.13. (+)-(8S,10R)-9-Aza-10-methyl-8-*n*-pentadecyl-1,5-dioxaspiro[5.5]undecane* ***8d***

Following the cyclization procedure, hexadecanal (498 mg, 2.07 mmol) and amine (–)-**4** (300 mg, 1.89 mmol) afforded the protected piperidone (+)-**8d** as a white solid (518 mg, 72%). R_f 0.38 (ethyl acetate:methanol, 1:1); mp = 28–29°C; $[\alpha]_D^{25}=+0.5$ (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2919, 2850, 1464, 1383, 1324, 1135, 1091, 992, 759; δ_H ($CDCl_3$) 3.83 (2H, t, $J=6.5$), 3.75 (2H, t, $J=6.5$), 2.77 (1H, m, H-10), 2.65 (1H, m, H-8), 2.14 (2H, m, H-7eq and H-11eq), 1.62 (2H, m), 1.33–1.12 (30H, m), 1.00–0.90 (4H, m), 0.77 (3H, t, $J=7.0$); δ_C ($CDCl_3$) 178.9, 128.5, 125.4, 97.3, 58.9, 58.8, 52.3, 47.7, 41.0, 39.2, 36.6, 31.7, 29.6, 29.5, 29.4, 29.2, 25.8, 25.5, 22.5, 22.2, 13.9; found (FAB) 382.3678, $C_{24}H_{47}NO_2$+H^+ requires 382.3685.

*4.14. (+)-(7S,9R)-8-Aza-9-methyl-7-*n*-nonyl-1,4-dithiaspiro[5.4]decane* ***9a***

Following the dithioacetalation procedure, protected piperidone (+)-**8a** (300 mg, 1.01 mmol) afforded the dithioderivative (+)-**9a** as a pale yellow oil (309 mg, 97%). R_f 0.58 (ethyl acetate: methanol, 5:1); $[\alpha]_D^{25}=+23.9$ (*c* 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3308, 2924, 2853, 2325, 2342, 1460, 1320, 1151, 1102; δ_H ($CDCl_3$) 3.25 (4H, s), 2.81 (1H, m, H-9), 2.69 (1H, m, H-7), 2.05 (2H, m, H-6eq and H-10eq), 1.62 (2H, m, H-6ax and H-10ax), 1.50 (1H, br s, NH), 1.40–1.16 (16H, m), 1.07 (3H, d, $J=6.5$), 0.84 (3H, t, $J=7.0$); δ_C($CDCl_3$) 66.8, 59.7, 56.0, 51.3, 50.5, 48.2, 39.1, 37.7, 36.7, 31.8, 29.5, 25.8, 22.6, 22.3, 14.1; found (FAB) 316.2138, $C_{17}H_{33}NS_2$+H^+ requires 316.2133.

*4.15. (+)-(7S,9R)-8-Aza-9-methyl-7-*n*-undecyl-1,4-dithiaspiro[5.4]decane* ***9b***

Following the dithioacetalation procedure, protected piperidone (+)-**8b** (400 mg, 1.23 mmol) afforded the dithioderivative (+)-**9b** as a pale yellow oil (395 mg, 94%). R_f 0.47 (ethyl acetate: methanol, 5:1); $[\alpha]_D^{25}=+7.36$ (*c* 1.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3326, 2924, 2853, 1707, 1468, 1146, 1099, 776, 650; δ_H ($CDCl_3$) 3.29 (4H, s), 2.92 (1H, m, H-9), 2.76 (1H, m, H-7), 2.08 (2H, m, H-6eq and H-10eq), 1.72 (2H, m, H-6ax and H-10ax), 1.47–1.18 (21H, m), 1.12 (3H, d, $J=6.5$), 0.87 (3H, t, $J=7.0$); δ_C ($CDCl_3$) 66.6, 56.2, 52.3, 50.1, 48.0, 39.1, 37.8, 36.2, 31.9, 29.7, 29.6, 29.4, 25.8, 22.7, 21.9, 14.2; found (FAB) 344.2449, $C_{19}H_{37}NS_2$+H^+ requires 344.2446.

*4.16. (+)-(7S,9R)-8-Aza-9-methyl-7-*n*-tridecyl-1,4-dithiaspiro[5.4]decane* ***9c***

Following the dithioacetalation procedure, protected piperidone (+)-**8c** (400 mg, 1.13 mmol) afforded the dithioderivative (+)-**9c** as a pale yellow oil (387 mg, 92%). R_f 0.46 (ethyl acetate: methanol, 1:1); $[\alpha]_D^{25}=+7.8$ (*c* 2.0, $CHCl_3$); δ_H($CDCl_3$) 3.27 (4H, s), 2.82 (1H, m, H-9), 2.70 (1H,

m, H-7), 2.06 (2H, m, H-6eq and H-10eq), 1.62 (2H, m, H-6ax and H-10ax), 1.46 (1H, br s, NH), 1.41–1.18 (24H, m), 1.09 (3H, d, $J=6.5$), 0.87 (3H, t, $J=7.0$); δ_C ($CDCl_3$) 66.9, 56.1, 51.4, 50.6, 48.6, 39.1, 37.7, 36.8, 31.9, 29.8, 29.7, 29.6, 29.4, 25.9, 22.7, 22.4, 14.2; found (FAB) 372.2759, $C_{21}H_{41}NS_2+H^+$ requires 372.2758.

4.17. (+)-(7S,9R)-8-Aza-9-methyl-7-n-pentadecyl-1,4-dithiaspiro[5.4]decane **9d**

Following the thioacetalation procedure, protected piperidone (+)-**8d** (400 mg, 1.05 mmol) afforded the thioacetal protected piperidone (+)-**9d** as a white solid (398 mg, 95%). R_f 0.29 (ethyl acetate:cyclohexane, 1:3); mp = 37–38°C; $[\alpha]_D^{25}=+6.9$ (*c* 1.7, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3321, 2918, 2850, 1471, 1320, 1106, 746, 718; δ_H ($CDCl_3$) 3.30 (4H, s), 2.88 (1H, m, H-9), 2.73 (1H, m, H-7), 2.10 (2H, m, H-6eq and H-10eq), 1.65 (2H, m, H-6ax and H-10ax), 1.55 (1H, br s, NH), 1.42–1.22 (28H, m), 1.12 (3H, d, $J=6.5$), 0.89 (3H, t, $J=7.0$); δ_C ($CDCl_3$) 66.7, 55.9, 51.3, 50.4, 48.4, 39.0, 37.6, 36.6, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.7, 22.6, 22.2, 14.0; found (FAB) 400.3078, $C_{23}H_{45}NS_2+H^+$ requires 400.3072.

4.18. (+)-(2S,6R)-2-Methyl-6-n-nonylpiperidine hydrochloride [(+)-isosolenopsin·HCl] **3a·HCl**

Following the hydrogenolysis procedure, dithiopiperidone (+)-**9a** (200 mg, 0.63 mmol) afforded the piperidine (+)-**3a** as a pale yellow oil (133 mg, 93%). R_f 0.07 (ethyl acetate:methanol, 1:1); Recrystallization of the hydrochloride from absolute EtOH:AcOEt 1:3 afforded the isosolenopsin **3a·HCl** as white needles; mp = 174–175°C; $[\alpha]_D^{25}=+11.1$ (*c* 0.92, $CHCl_3$); spectral data are identical with those reported for racemic material.[12]

4.19. (+)-(2S,6R)-2-Methyl-6-n-undecylpiperidine hydrochloride [(+)-isosolenopsin A·HCl] **3b·HCl**

Following the hydrogenolysis procedure, dithiopiperidone (+)-**9b** (300 mg, 0.89 mmol) afforded the piperidine (+)-**3b** as a pale yellow oil (208 mg, 95%). R_f 0.08 (ethyl acetate:methanol, 1:1); Recrystallization of the hydrochloride from absolute EtOH:AcOEt, 1:3, afforded isosolenopsin A hydrochloride **3b·HCl** as white needles; mp = 150–151°C (lit.[12] mp = 152–153°C for racemic material[12]); $[\alpha]_D^{25}=+10.0$ (*c* 1.17, $CHCl_3$) (lit.[3a] $[\alpha]_D^{25}=+10.6$ (*c* 0.3, $CHCl_3$)); spectral data are identical with those reported.[3a5,6]

4.20. (+)-(2S,6R)-2-Methyl-6-n-tridecylpiperidine hydrochloride [(+)-isosolenopsin B·HCl] **3c·HCl**

Following the hydrogenolysis procedure, dithiopiperidone (+)-**9c** (300 mg, 0.81 mmol) afforded the piperidine (+)-**3c** as a pale yellow oil (216 mg, 95%). R_f 0.08 (ethyl acetate:methanol, 1:1); Recrystallization of the hydrochloride from absolute EtOH:AcOEt, 1:3, afforded isosolenopsin B hydrochloride **3c·HCl** as white needles; mp = 145–146°C; $[\alpha]_D^{25}=+8.5$ (*c* 1.0, $CHCl_3$); spectral data are identical with those reported for racemic isosolenopsin B hydrochloride.[12]

4.21. (+)-(2S,6R)-2-Methyl-6-n-pentadecylpiperidine hydrochloride [(+)-isosolenopsin C·HCl] **3d·HCl**

Following the hydrogenolysis procedure, dithiopiperidone (+)-**9d** (300 mg, 0.75 mmol) afforded the piperidine (+)-**3d** as a pale yellow oil (218 mg, 94%). R_f 0.07 (ethyl acetate:methanol, 1:1);

Recrystallization of the hydrochloride from absolute EtOH:AcOEt, 1:3, afforded isosolenopsin C hydrochloride **3d·HCl** as white needles; mp = 140–141°C; $[\alpha]_D^{25} = +8.2$ (*c* 1.0, $CHCl_3$); spectral data are identical with those reported for racemic isosolenopsin C hydrochloride.[12]

References

1. (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553–2581. (b) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 633–640. (c) Schneider, M. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp. 155–299.
2. Attygale, A. B.; Xu, S. C.; McCormick, K. D.; Meinwald, J.; Blankespoor, C. L.; Eismer, T. *Tetrahedron* **1993**, *49*, 9333–9340.
3. For leading references, see: (a) Leclerq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Van der Meer, R.; Braeckman, J. C. *Tetrahedron* **1994**, *50*, 8465–8478. (b) Braeckman, J. C.; Daloze, D. In *Studies in Natural Products Chemistry*, Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1990; Vol 6, pp. 421–466. (c) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi A. Ed.; Academic Press: New York; 1987; Vol. 31, pp. 193–317. (d) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949–1958.
4. For previous enantioselective synthesis of (+)- and (–)-dihydropinidine, see: (a) Yamauchi, T.; Fujikura, H.; Higashiyama, K.; Takahashi, H.; Ohmiya, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2791–2794. (b) Yamauchi, T.; Takahashi, H.; Higashiyama, K. *Chem. Pharm. Bull.* **1998**, *46*, 384–389. (c) Davis, F. A.; Szewczyk, I. M. *Tetrahedron Lett.* **1998**, *39*, 5951–5954. (d) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6703. (e) Muraoka, O.; Zheng, B.-Z.; Okumura, K.; Tabata, E.; Tanabe, G.; Kubo, M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 113–120. (f) Bubnov, Y.; Klimkina, E. V.; Ignatenko, A. V.; Gridnev, I. D. *Tetrahedron Lett.* **1997**, *38*, 4361–4364. (g) Momose, T.; Toshima, M.; Toyooka, N.; Hirai, Y.; Eugster, C. H. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1307–1314. (h) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151–1160. (i) Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332–3341. (j) Amat, M.; Llor, N.; Hidalgo, J.; Hernandez, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977–980. (k) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399–5400. (l) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S. *Tetrahedron Lett.* **1995**, *36*, 417–421. (m) Comins, D. L.; Chung, G.; Foley, M. A. *Heterocycles* **1994**, *37*, 1121–1140. (n) Lu, Z.-H.; Zhou, W.-S. *J. Chem. Soc. Perkin Trans. 1* **1993**, 593–596. (o) Takahata, H.; Bandoh, H.; Hanayama, M.; Momose, T. *Tetrahedron: Asymmetry* **1992**, *3*, 607–608. (p) Higashiyama, K.; Nakahata, K.; Takahashi, H. *Heterocycles* **1992**, *33*, 17–20. (q) Theodorakis, E.; Royer, J.; Husson, H.-P. *Synth. Commun.* **1991**, *21*, 521–529. (r) Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.* **1990**, 1319–1322. (s) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754–7755. (t) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569.
5. Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1991**, *34*, 2911–2914.
6. Poewono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955–13970.
7. Ciblat, S.; Besse, P.; Canet, J. L.; Troin, Y.; Veschambre, H.; Gelas, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2225–2235.
8. Besse, P.; Ciblat, S.; Canet, J. L.; Troin, Y.; Veschambre, H. *Tetrahedron: Asymmetry* **1999**, *10*, 2213–2224.
9. Besse, P.; Ciblat, S.; Canet, J.-L.; Troin, Y.; Veschambre, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2211–2219.
10. Ciblat, S.; Calinaud, P.; Canet, J. L.; Troin, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 353–358.
11. Augustine, R. L. In *Catalytic Hydrogenation*; M. Dekler Inc., Ed.: New York, 1965; p. 23.
12. Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597–598.