Bicyclo[3.3.1]nonanes as synthetic intermediates. Part 20.[1] Asymmetric synthesis of the indolizidine alkaloids monomorine I and indolizidine 223AB

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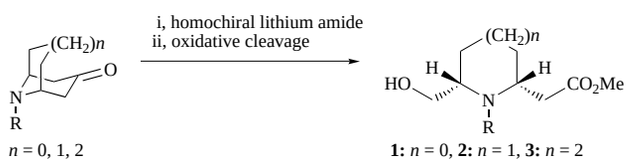
Total syntheses of the indolizidine alkaloids monomorine I and indolizidine 223AB have been achieved by starting from the chiral *cis*-2,5-disubstituted pyrrolidine or *cis*-2,6-disubstituted piperidine obtained from the asymmetric cleavage of 8-azabicyclo[3.2.1]octan-3-one or 9-azabicyclo[3.3.1]nonan-3-one at the 'fork head'.

Introduction

In the preceding paper,[1] we described the asymmetric cleavage of 8-azabicyclo[3.2.1]octan-3-one, 9-azabicyclo[3.3.1]nonan-3-one or 10-azabicyclo[4.3.1]decan-3-one at the 'fork head' by use of Koga's protocol[2] to give the *cis*-2,5-disubstituted pyrrolidine (−)-**1**, *cis*-2,6-disubstituted piperidine (−)-**2** or *cis*-2,7-disubstituted hexahydroazepine (−)-**3**. In order to illustrate their synthetic availability as chiral building blocks for alkaloid synthesis, we investigated the asymmetric synthesis of indolizidine alkaloids of significant biological activity. This paper describes a full account of the experiments investigated.[3]



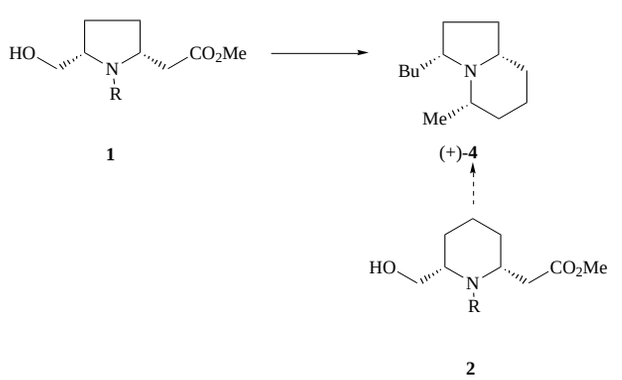
n = 0, 1, 2 **1:** *n* = 0, **2:** *n* = 1, **3:** *n* = 2

Scheme 1

Results and discussion

Asymmetric total synthesis of (+)-monomorine I

(+)-Monomorine I **4**, a trail pheromone of the pharaoh ant,[4] is a suitable target to test new synthetic strategies, having been synthesised earlier by several groups.[5] Although, this alkaloid could be synthesised *via* a 'chiral pyrrolidine' or 'chiral piperidine' route, we chose the former[5a] as shown in Scheme 2.



Scheme 2

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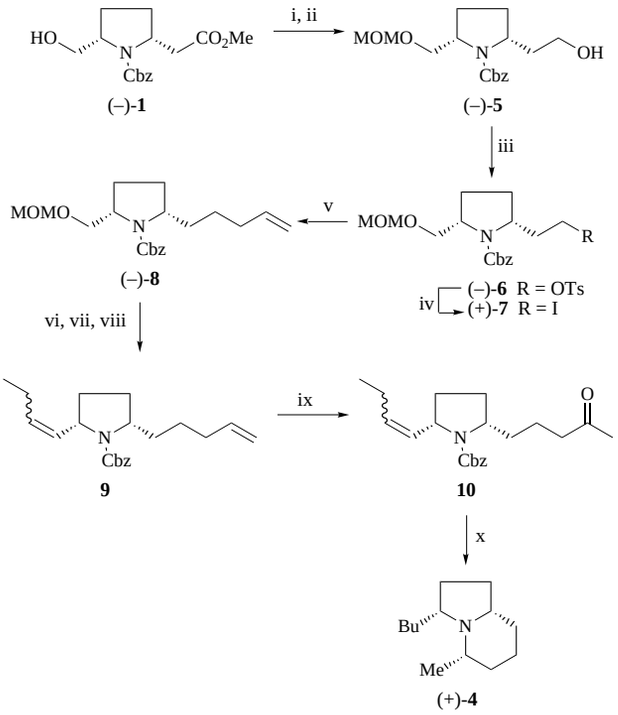
Protection of the hydroxy group in (−)-**1** with methoxymethyl chloride (MOMCl) followd by reduction with lithium triethylborohydride (Super-Hydride) afforded the alcohol (−)-**5** in 84% overall yield. Carbon-chain elongation of the 2-hydroxyethyl group of (−)-**5** was effected through Grignard cross coupling of the iodide (+)-**7**, prepared from (−)-**5** *via* its toluene-*p*-sulfonate (−)-**6**, with allylmagnesium chloride in the presence of copper(I) iodide (CuI) to give the olefin (−)-**8** in 49% overall yield. Deprotection of (−)-**8** with acid followed by Swern oxidation of the resulting alcohol and subsequent Wittig reaction afforded the diene **9** in 77% overall yield. The site-selective oxidation of **9** by the Wacker process proceeded smoothly to give the ketone **10** (84%). Finally, hydrogenation of **10** over 5% palladium-on-carbon furnished (+)-monomorine I **4** (70%), the ^{1}H NMR, ^{13}C NMR and mass spectral results for which were identical with those of an authentic specimen.[5a] The present result also established the absolute stereochemistry of the starting pyrrolidine synthon (−)-**1**.

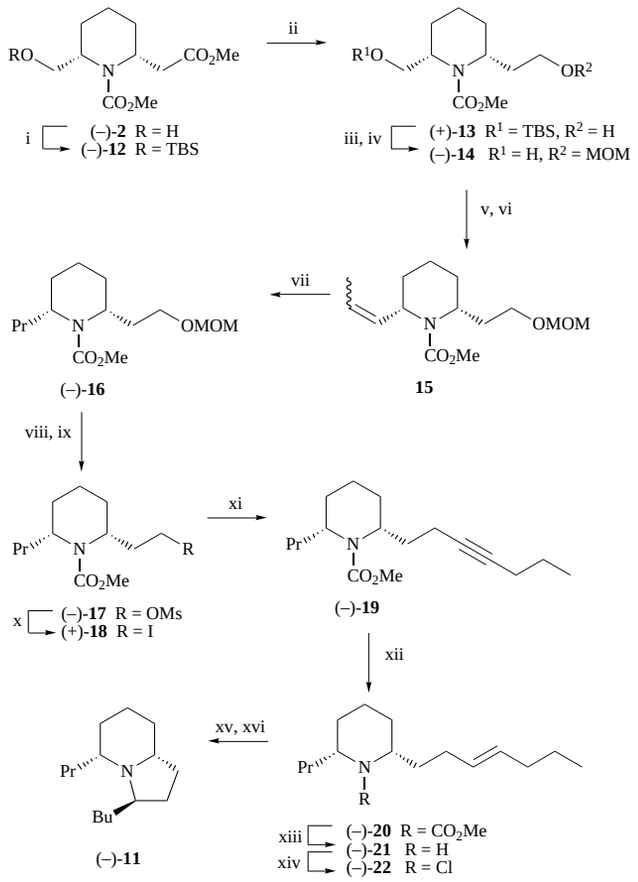
Enantiodivergent synthesis of indolizidine 223AB

A variety of biologically significant alkaloids have been isolated from neotropical dart-poison frogs (family *Dendrobatidae*).[6] In order to demonstrate the synthetic utility of (−)-**2**, we investigated the enantiodivergent synthesis of indolizidine 223AB **11**, a 3,5-disubstituted indolizidine class of *Dendrobatid* alkaloid, by starting from the common chiral synthon piperidine (−)-**2**.

Protection of the hydroxy group in (−)-**2** with *tert*-butyldimethylsilyl chloride (TBSCl) gave the ether (−)-**12** (90%), which was reduced with Super-Hydride to afford the alcohol (+)-**13** (95%). Protection of the hydroxy group in (+)-**13** with MOMCl followed by deprotection at the other α-substituent with tetrabutylammonium fluoride (TBAF) gave the alcohol (−)-**14** in 98% overall yield. The Swern oxidation of (−)-**14** and subsequent Wittig reaction of the resulting aldehyde afforded the olefin **15** in 74% overall yield. Hydrogenation of **15** over 5% palladium-on-carbon gave the piperidine (−)-**16** (86%). The piperidine (−)-**16** was converted into the iodide (+)-**18** *via* the methanesulfonate (−)-**17** in 68% overall yield. The reaction of (+)-**18** with lithium pent-1-yn-1-ide gave the alkyne (−)-**19** (98%). Reduction of (−)-**19** under Birch conditions afforded the *E*-olefin (−)-**20** as a single product in 94% yield. Deprotection of (−)-**20** with lithium propanethiolate[7] in hexamethylphosphoric triamide (HMPA) gave the amine (−)-**21** (83%). Finally, (−)-**21** was converted into the desired (−)-indolizidine 223AB **11** *via* the *N*-chloropiperidine (−)-**22** according to Broka's method.[8] The ^{1}H and ^{13}C NMR spectral results for synthetic (−)-**11** were identical with those of a natural sample.[6b]



Scheme 3 *Reagents and conditions:* i, MOMCl, Hünig's base, 0 °C ~ RT; ii, Super-Hydride, RT; iii, TsCl, pyridine, RT; iv, NaI, acetone, RT; v, allylmagnesium chloride, CuI, −78 ~ −35 °C; vi, conc. HCl, MeOH, 50 °C; vii, $(COCl)_2$, DMSO, Et_3N, −78 °C ~ RT; viii, $(Ph)_3P^+PrBr^-$, BuLi, 0 °C ~ RT; ix, $PdCl_2$, CuCl, O_2, DMF-H_2O, RT; x, H_2, 5% Pd–C



Scheme 4 *Reagents and conditions:* i, TBSCl, Et_3N, DMAP; ii, Super-Hydride, RT; iii, MOMCl, Hünig's base; iv, TBAF, THF, RT; v, $(COCl)_2$, DMSO, Et_3N, −78 °C ~ RT; vi, $(Ph)_3P^+EtBr^-$, BuLi, 0 °C ~ RT; vii, H_2, 5% Pd–C; viii, conc. HCl, MeOH, reflux; ix, MsCl, pyridine, RT; x, NaI, acetone, RT; xi, pent-1-yne, BuLi, RT; xii, Na, liq. NH_3, −33 °C; xiii, PrSH, BuLi, HMPA, RT; xiv, NCS; xv, CuCl, $CuCl_2$; xvi, Bu_3SnH, AIBN, reflux

Next, we examined a formal synthesis of (+)-**11** by starting from the same common synthon piperidine (−)-**2**. The Swern oxidation of (+)-**13**, obtained from (−)-**2** in two steps as above, and subsequent Wittig reaction of the resulting aldehyde provided the olefin (−)-**23** in 48% overall yield. Hydrogenation of (−)-**23** over 5% palladium-on-carbon and subsequent deprotection with TBAF afforded the alcohol (−)-**24** in 90% overall yield. The Swern oxidation of (−)-**24** and subsequent Wittig reaction of the resulting aldehyde gave the enol ether **25** in 62% overall yield as a 3:2 mixture of *E* and *Z* isomers. Acid hydrolysis of the mixture of *E* and *Z* enol ethers and subsequent reduction of the resulting aldehyde with sodium borohydride ($NaBH_4$) provided the homologated alcohol (−)-**26** in 68% overall yield. Finally, the alcohol (−)-**26** was converted into the iodide (−)-**18** *via* the methanesulfonate (+)-**17**. The IR, ^{1}H NMR and mass spectral results for synthetic (−)-**18** were identical with those of (+)-**18**.

Conclusion

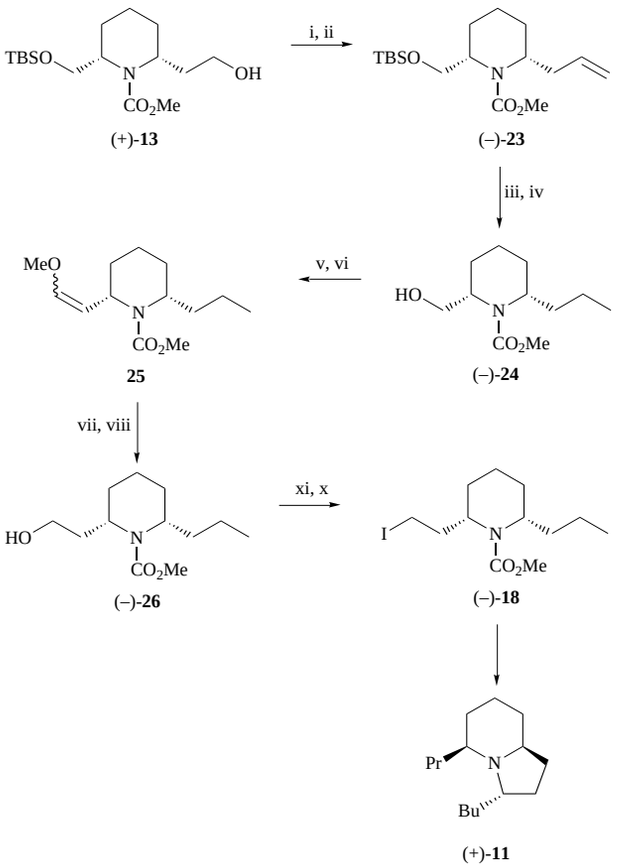
We have described the efficient total synthesis of (+)-monomorine I **4** and (−)-indolizidine 223AB **11** starting from *cis*-(2,5)-pyrrolidine (−)-**1** and *cis*-(2,6)-piperidine (−)-**2**, respectively, chiral synthons readily available from the asymmetric cleavage of nitrogen-bridged bicyclic systems.

Experimental

Optical rotations were measured with a JASCO DIP-140 polarimeter and are recorded as 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a JASCO A-102 grating spectrophotometer or Perkin-Elmer 1600 FT-IR spectrophotometer. ^{1}H NMR spectra were taken on a JEOL GX-270 spectrometer in deuteriochloroform unless otherwise stated. Chemical shifts are given in ppm (δ) downfield from internal tetramethylsilane. Resonance patterns in ^{1}H NMR spectra are shown as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Low- and high-resolution MS were obtained on a JEOL JMS D-200 instrument with a direct inlet system at 70 eV. Mps were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this University. Column chromatography was performed on silica gel [Fuji-Davison BW-200, Merck 60 (No 9385)]. The organic extracts were dried over $MgSO_4$ unless otherwise stated.

Benzyl (2*R*,5*S*)-(−)-2-(2-hydroxyethyl)-5-(methoxymethoxymethyl)pyrrolidine-1-carboxylate 5

To a stirred solution of (−)-**1**[1] in CH_2Cl_2 (2 cm^3) were added MOMCl (0.17 cm^3, 2.2 mmol) and diisopropylethylamine (Hünig's base) (0.48 cm^3, 2.76 mmol), and the resulting solution was stirred at room temperature for 8 h. The reaction mixture was then diluted with Et_2O (30 cm^3), and the organic layer was separated, washed with saturated brine (5 cm^3 × 2), dried and evapaorated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in THF (15 cm^3) was added Super-Hydride (4.1 cm^3, 4.17 mmol) at 0 °C, and the solution was stirred for 2 h at room temperature. The reaction was quenched by the addition of water (5 cm^3) to the reaction mixture after which the aqueous layer was separated and extracted with CH_2Cl_2 (10 cm^3 × 5). The organic extracts were combined, dried and evaporated to afford a colourless oil, which was purified by column chromatography on SiO_2 (10 g; hexane–acetone, 10:1) to give (−)-**5** [497 mg, 84% from (−)-**1**] as a colourless oil (Found: M^+, 323.1725. $C_{17}H_{25}NO_5$ requires *M*, 323.1731); ν_{max}(neat)/cm^{-1}: 3445 and 1689; δ_H 1.50–1.82 (2 H, br, CH_2CH$_2$OH), 1.83–2.14 (5 H, m,



Scheme 5 *Reagents and conditions:* i, $(COCl)_2$, DMSO, Et_3N, −78 °C ~ RT; ii, $(Ph)_3P^+MeI^-$, BuLi, 0 °C ~ RT; iii, H_2, 5% Pd–C; iv, TBAF, THF, RT; v, $(COCl)_2$, DMSO, Et_3N, −78 °C ~ RT; vi, $(Ph)_3P^+$-CH_2OMeCl^-, BuLi, 0 °C ~ RT; vii, conc. HCl, CH_2Cl_2, RT; viii, $NaBH_4$, MeOH, 0 °C ~ RT; ix, MsCl, pyridine, RT; x, NaI, acetone, RT

3- and 4-H and OH exchangeable with D $_2$O), 3.28 (3 H, s, OMe), 3.46–3.70 (4 H, m, CH_2OMOM and CH_2OH), 3.89–4.12 (2 H, br, 2- and 5-H), 4.54 (2 H, s, OCH_2O), 5.12 and 5.20 (each 1 H, each d, *J* 13, CH_2Ph) and 7.27–7.39 (5 H, m, ArH); $[\alpha]_D^{26}$ −34.9 (*c* 1.98, $CHCl_3$).

Benzyl (2*S*,5*R*)-(−)-2-(methoxymethoxymethyl)-5-(2-*p*-tolylsulfonyloxyethyl)pyrrolidine-1-carboxylate 6

To a stirred solution of (−)-**5** (416 mg, 0.872 mmol) in CH_2Cl_2 (5 cm^3) were added pyridine (0.42 cm^3, 3.49 mmol) and *p*-TsCl (820 mg, 2.61 mmol) at 0 °C, and the reaction mixture was stirred for 18 h at room temperature. The reaction was quenched by the addition of saturated brine (5 cm^3) to the mixture after which the aqueous layer was separated and extracted with Et_2O (50 cm^3 × 2). The organic extracts were combined, dried and evaporated to give an oil, which was purified by column chromatography on SiO_2 (30 g; hexane–acetone 10 : 1) to give (−)-**6** (430 mg, 70%) as a colourless oil (Found: M^+, 477.1835. $C_{24}H_{31}NO_7S$ requires *M*, 477.1819); ν_{max}(neat)/cm^{-1} 1698 and 1176; δ_H 1.60–1.82 (3 H, m), 1.86–2.04 (3 H, m), 2.45 (3 H, s, PhMe), 3.29 (3 H, s, OMe), 3.40–3.70 (2 H, m, CH_2O-MOM), 3.84–4.03 (2 H, m, 2- and 5-H), 4.09 (2 H, t, *J* 6.5, CH_2OTs), 4.55 (2 H, s, OCH_2O), 5.07 and 5.14 (each 1 H, each d, *J* 12, CH_2Ph), 7.31–7.39 (7 H, m, ArH) and 7.75 (2 H, br s, ArH); $[\alpha]_D^{26}$ −14.3 (*c* 1.28, $CHCl_3$).

Benzyl (2*R*,5*S*)-(+)-2-(2-iodoethyl)-5-(methoxymethoxymethyl)pyrrolidine-1-carboxylate 7

To a stirred solution of (−)-**6** (430 mg, 0.90 mmol) in acetone (5 cm^3) was added sodium iodide (1.35 g, 9.0 mmol) at 0 °C, and the resulting suspension was stirred at room temperature for 5 h. It was then concentrated by the removal of solvent, and the residue was diluted with CH_2Cl_2 (20 cm^3). The organic layer was washed with 10% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (5 cm^3 × 1) and saturated brine (5 cm^3 × 1), dried and evaporated to afford a pale yellow oil, which was purified by column chromatography on SiO_2 (7 g; hexane–acetone 50 : 1) to give (+)-**7** (390 mg, 99%) as a pale yellow oil (Found: M^+, 433.0798. $C_{17}H_{24}INO_4S$ requires *M*, 433.0752); ν_{max}(neat)/cm^{-1} 1700; δ_H 1.50–1.75 (2 H, m, CH_2CH_2I), 1.80–2.10 (4 H, m, 3- and 4-H), 2.95–3.20 (2 H, m, CH_2OMOM), 3.30 (3 H, s, OMe), 3.40–3.65 (2 H, br, CH_2I), 3.85–4.10 (2 H, m, 2- and 5-H), 4.55 (2 H, s, OCH_2O), 5.12 (2 H, s, CH_2Ph) and 7.21–7.39 (5 H, m, ArH); $[\alpha]_D^{26}$ +6.0 (*c* 1.27, $CHCl_3$).

Benzyl (2*S*,5*S*)-(−)-2-(methoxymethoxymethyl)-5-pent-4-enylpyrrolidine-1-carboxylate 8

To a stirred suspension of CuI (520 mg, 2.70 mmol) in THF (2 cm^3) was added allylmagnesium chloride (2.0 M; 2.70 cm^3, 5.40 mmol) at −78 °C; the reaction temperature was then gradually raised to −40 °C, and the stirring was continued for 10 min. The suspension was recooled at −78 °C, and (+)-**7** (390 mg, 0.90 mmol) in THF (3 cm^3) was added to the suspension; the stirring was then continued at −40 °C for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 cm^3) to the mixture after which the aqueous layer was extracted with CH_2Cl_2 (5 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (30 g; hexane–acetone 120 : 1) to afford (−)-**8** (218 mg, 70%) as a colourless oil (Found: M^+, 347.2106. $C_{20}H_{29}NO_4$ requires *M*, 347.2096); ν_{max}(neat)/cm^{-1} 1700; δ_H 1.20–1.50 (4 H, m, CH_2CH_2CH$_2$CH=CH$_2$), 1.85–1.97 (2 H, m, CH_2CH=CH$_2$), 2.00–2.19 (4 H, m, 3- and 4-H), 3.30 (3 H, s, OMe), 3.54–3.76 (2 H, m, CH_2OMOM), 3.85 (1 H, br, 2- or 5-H), 4.05 (1 H, br, 2- or 5-H), 4.56 (2 H, s, OCH_2O), 4.85–5.05 (2 H, m, CH=CH_2), 5.15 (2 H, s, CH_2Ph), 5.65–5.91 (1 H, m, C*H*=CH$_2$) and 7.30–7.45 (5 H, m, ArH); $[\alpha]_D^{26}$ −1.2 (*c* 1.22, $CHCl_3$).

Benzyl (2*S*,5*S*)-2-but-1-enyl-5-pent-4-enylpyrrolidine-1-carboxylate 9

To a stirred solution of (−)-**8** (218 mg, 0.63 mmol) in MeOH (1 cm^3) was added concentrated hydrochloric acid (0.1 cm^3), and the resulting mixture was stirred for 1 h at 60 °C. After cooling, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (2 cm^3) to quench the reaction, after which the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 1, 5 cm^3 × 3). The organic extracts were combined, dried and evaporated to give a colourless oil (190 mg), which was used directly in the next step. To a stirred solution of oxalyl chloride (0.08 cm^3, 0.942 mmol) in CH_2Cl_2 (5 cm^3) was added DMSO (0.13 cm^3, 1.05 mmol) at −78 °C, and the mixture was stirred for 5 min; the oil obtained above (190 mg) in CH_2Cl_2 (2 cm^3) was then added to the mixture, and the stirring was continued at −78 °C for 45 min. To the reaction mixture was added Et_3N (0.37 cm^3, 2.83 mmol) at −78 °C, and the reaction temperature was gradually increased to 0 °C. The reaction mixture was diluted with Et_2O (45 cm^3), and the organic layer was washed with water (5 cm^3 × 3), dried and evaporated to afford a pale yellow oil (179 mg), which was used directly in the next step. To the suspension of propyl(triphenyl)phosphonium bromide (600 mg, 1.56 mmol) in THF (5 cm^3) was added BuLi (10% w/v in hexane; 0.76 cm^3) at 0 °C, and the mixture was stirred for 30 min at room temperature. To the mixture was added the oil obtained above (179 mg) in THF (3 cm^3) at 0 °C, and the resulting suspension was stirred for 3 h at room temperature. The reaction was quenched by the addition of water (1 cm^3) to the mixture, after which the aqueous layer was extracted with Et_2O (10 cm^3 × 4). The organic extracts were combined, washed with saturated brine (5 cm^3 × 1), dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (10 g; hexane–acetone 80 : 1) to afford **9** [150 mg, 77% from (−)-**8**] as a pale yellow oil (Found: M^+, 327.2222. $C_{21}H_{29}NO_2$

requires *M*, 327.2197); ν_{max}(neat)/cm^{-1}: 1697; δ_H 0.70–1.11 (3 H, m, =CHCH$_2$C*H*$_3$), 1.20–1.55 (4 H, m, C*H*$_2$C*H*$_2$CH$_2$CH=CH$_2$), 1.75–2.43 (8 H, m, =CHC*H*$_2$CH$_3$, C*H*$_2$CH=CH$_3$, 3- and 4-H), 3.78–4.02 (1 H, m, 5-H), 4.56–4.68 (1 H, m, 2-H), 4.85–5.19 (4 H, m, CH=C*H*$_2$, CH$_2$Ph), 5.21–5.58 (2 H, m, C*H*=C*H*CH$_2$), 5.65–5.95 (1 H, m, C*H*=CH$_2$) and 7.24–7.43 (5 H, m, ArH).

Benzyl (2*S*,5*S*)-2-(but-1-enyl)-5-(4-oxopentyl)pyrrolidine-1-carboxylate 10

To a stirred solution of **9** (30 mg, 0.092 mmol) in DMF (1.5 cm^3) and water (0.5 cm^3) were added CuCl (10 mg, 0.092 mmol) and $PdCl_2$ (5 mg, 0.028 mmol), and the resulting suspension was stirred for 17 h at room temperature under an oxygen atmosphere. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 cm^3) to the mixture, after which the aqueous layer was extracted with Et_2O (10 cm^3 × 5). The organic extracts were combined, washed with saturated brine (5 cm^3 × 1), dried and evaporated to afford a pale yellow oil, which was purified by column chromatography in SiO_2 (3 g; hexane–acetone, 50:1) to give **10** (26.4 mg, 84%) as a colourless oil (Found: M^+, 343.2138. $C_{21}H_{29}NO_3$ requires *M*, 343.2145); ν_{max}(neat)/cm^{-1}: 1697; δ_H 0.71–1.08 (3 H, m, =CH$_2$CH$_2$C*H*$_3$), 1.46–1.82 (6 H, m), 1.85–2.07 (4 H, m), 2.10 (3 H, s, COCH$_3$), 2.30–2.55 (2 H, br, C*H*$_2$COCH$_3$), 3.78–3.97 (1 H, m, 5-H), 4.50–4.78 (1 H, m, 2-H), 5.11 (2 H, br, CH$_2$Ph), 5.18–5.50 (2 H, m, CH=CH) and 7.31–7.51 (5 H, m, ArH).

(+)-Monomorine I 4

To a stirred solution of the amine **10** (100 mg, 0.291 mmol) in MeOH (5 cm^3) was added 5% Pd–C (80 mg), and the resulting suspension was hydrogenated at 1 atm for 4 h. The catalyst was removed by filtration through a Celite plug and washed with CH_2Cl_2. The filtrate and washings were evaporated to afford a colourless oil, which was purified by column chromatography on Al_2O_3 (20 g; hexane–$CHCl_3$, 10:1) to give (+)-**4** {40 mg, 70%, $[\alpha]_D^{26}$ +30.0 (*c* 1.80, hexane)} as a colourless oil. Recrystallisation of the corresponding hydrochloride from diethyl ether–EtOH furnished enantiomerically pure (+)-**4** (21 mg), $[\alpha]_D^{26}$ +33.2 (*c* 0.98, hexane) {lit.,[5a] $[\alpha]_D^{22}$ +34.3 (*c* 1.02, hexane)}; ν_{max}(neat)/cm^{-1} 2957, 2859, 1655, 1553, 1478 and 1455; δ_H(400 MHz) 0.88 (3 H, t, *J* 6, CH$_2$C*H*$_3$), 1.13 (3 H, d, *J* 6, CH$_3$), 1.29 (6 H, m), 1.43 (4 H, m), 1.70 (6 H, m), 2.06 (1 H, br s), 2.20 (1 H, br s) and 2.46 (1 H, br s); δ_C(100 MHz) 14.17 (q), 22.87 (t), 22.93 (t), 24.94 (t), 29.41 (t), 29.78 (t), 30.35 (t), 30.95 (t), 35.88 (t), 39.74 (t), 60.29 (d), 62.93 (d) and 67.19 (d); *m*/*z* 195 (M^+), 194, 180, 139, 138 and 98.

Methyl (2*R*,6*S*)-(−)-6-(*tert*-butyldimethylsiloxymethyl)-1-methoxycarbonylpiperidin-2-ylethanoate 12

To a stired solution of (−)-**2**[1] (2.0 g, 8.19 mmol) in CH_2Cl_2 (30 cm^3) were added TBSCl (1.47 g, 12.3 mmol), DMAP (81 mg, 0.82 mmol) and Et_3N (2.7 cm^3, 24.6 mmol) at 0 °C, and the reaction mixture was stirred for 21 h at room temperature. The reaction was quenched by the addition of water (5 cm^3) to the mixture, after which the aqueous layer was extracted with Et_2O (20 cm^3 × 5). The organic extracts were combined, washed with saturated brine (10 cm^3 × 2), dried and evaporated to give an oil, which was purified by column chromatography on SiO_2 (50 g; hexane–acetone, 50:1) to afford (−)-**12** (2.68 g, 90%) as a colourless oil (Found: $M^+ - C_4H_9$, 302.1424. $C_{14}H_{24}NO_5Si$ requires $M - C_4H_9$, 302.1424); ν_{max}(neat)/cm^{-1} 1741 and 1701; δ_H 0.07 [6 H, s, Si(CH$_3$)$_2$], 0.89 [9 H, s, SiC(CH$_3$)$_3$], 1.41–1.69 (6 H, m, 3-~5-H), 3.48–3.60 (4 H, m, CH$_2$OTBS and C*H*$_2$CO$_2$Me), 3.66 (3 H, s, OCH$_3$), 3.69 (3 H, s, OCH$_3$), 4.16 (1 H, br, 6-H) and 4.60 (1 H, br, 2-H); $[\alpha]_D^{26}$ −24.4 (*c* 1.06, $CHCl_3$).

Methyl (2*S*,6*R*)-(+)-2-(*tert*-butyldimethylsiloxymethyl)-6-(2-hydroxyethyl)piperidine-1-carboxylate 13

To a stirred solution of (−)-**12** (2.83 g, 7.8 mmol) in THF (70 cm^3) was added Super-Hydride (15.6 cm^3, 15.6 mmol) at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of water (20 cm^3) to the mixture, after which the aqueous layer was separated and extracted with CH_2Cl_2 (20 cm^3 × 10). The organic extracts were combined, dried and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (90 g; hexane–acetone, 10:1) to afford (+)-**13** (2.7 g, 95%) as a colourless oil (Found: M^+, 331.2160. $C_{16}H_{33}NO_4Si$ requires *M*, 311.2182); ν_{max}(neat)/cm^{-1} 3461, 1733 and 1695; δ_H 0.06 [6 H, s, Si(CH$_3$)$_2$], 0.89 [9 H, s, SiC(CH$_3$)$_3$], 1.58–1.76 (8 H, m, 3-, 4-, 5-H and C*H*$_2$CH$_2$OH), 3.45–3.64 (4 H, m, CH$_2$OTBS and C*H*$_2$OH), 3.72 (3 H, s, OCH$_3$), 4.14–4.26 (1 H, br, 2- or 6-H), 4.36–4.56 (1 H, br, 2- or 6-H); $[\alpha]_D^{26}$ +6.6 (*c* 1.09, $CHCl_3$).

Methyl (2*S*,6*R*)-(−)-2-hydroxymethyl-6-[2-(methoxymethoxy)-ethyl]piperidine-1-carboxylate 14

To a stirred solution of (+)-**13** (1.50 g, 4.56 mmol) in CH_2Cl_2 (40 cm^3) were added MOMCl (0.35 cm^3, 5.47 mmol) and Hünig's base (0.79 cm^3, 6.84 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 10 h. The reaction mixture was then diluted with Et_2O (50 cm^3), and the organic layer was separated, washed with saturated brine (10 cm^3 × 2), dried and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in THF (40 cm^3) was added TBAF (1.0 M in THF; 4.4 cm^3, 4.4 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 cm^3) to the mixture, after which the aqueous layer was extracted with CH_2Cl_2 (15 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (45 g; hexane–acetone, 10:1) to afford (−)-**14** (1.04 g, 98% in 2 steps) as a colourless oil (Found: M^+, 261.1608. $C_{12}H_{23}NO_5$ requires *M*, 261.1575); ν_{max}(neat)/cm^{-1} 3446 and 1694; δ_H 1.54–1.79 (4 H, m), 1.82–2.14 (4 H, m), 3.32 (3 H, s, OCH$_3$), 3.46–3.60 (4 H, m, CH$_2$OMOM and C*H*$_2$OH), 3.71 (3 H, s, COOCH$_3$), 3.93–4.05 (1 H, m, 2- or 6-H), 4.07–4.20 (1 H, m, 2- or 6-H) and 4.48 (2 H, s, OCH$_2$O); $[\alpha]_D^{26}$ −9.6 (*c* 1.19, $CHCl_3$).

Methyl (2*R*,6*S*)-2-[2-(methoxymethoxy)ethyl]-6-prop-1-enylpiperidine-1-carboxylate 15

To a stirred solution of oxalyl chloride (0.27 cm^3, 3.10 mmol) in CH_2Cl_2 (10 cm^3) was added DMSO (0.44 cm^3, 6.20 mmol) at −78 °C, and the mixture was stirred for 5 min. To the mixture was added (−)-**14** (540 mg, 2.06 mmol) in CH_2Cl_2 (2 cm^3), and stirring was continued for 45 min at −78 °C. Triethylamine (1.30 cm^3, 9.31 mmol) was added at −78 °C to the mixture, the temperature of which was gradually increased to 0 °C. The reaction mixture was then diluted with Et_2O (50 cm^3), and the organic layer was separated, washed with water (5 cm^3 × 3), dried and evaporated to give a pale yellow oil (523 mg), which was used directly in the next step. To the suspension of ethyl(triphenyl)phosphonium bromide (1.92 g, 5.17 mmol) in THF (10 cm^3) was added BuLi (10% w/v in hexane; 2.80 cm^3) at 0 °C, and the mixture was stirred for 30 min at room temperature. To the mixture was added the crude aldehyde obtained above (523 mg) in THF (3 cm^3) at 0 °C, and the resulting suspension was stirred for 1 h at room temperature. The reaction was quenched by the addition of water (10 cm^3) to the mixture, after which the aqueous layer was separated and extracted with Et_2O (10 cm^3 × 6). The organic extracts were combined, washed with saturated brine (10 cm^3 × 1), dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (50 g; hexane–acetone, 40:1) to afford **15** [417 mg, 74% from (−)-**14**] as a colourless oil (Found: C, 61.35; H, 9.24; N, 5.24. $C_{14}H_{25}NO_4$ requires C, 61.69; H, 9.29; N, 5.16); ν_{max}(neat)/cm^{-1} 1698; δ_H 1.35–2.04 (11 H, br m, CH$_3$, 3-, 4-, 5-H and C*H*$_2$CH$_2$OMOM), 3.32 (3 H, s, OCH$_3$), 3.49 (2 H, apparent t, *J* 6, CH$_2$OMOM), 3.67 (3 H, s, CO$_2$CH$_3$), 4.25–4.38 (1 H, m,

2-H), 4.56 (2 H, s, OCH_2O), 5.02–5.11 (1 H, m, C_6-H) and 5.39–5.72 (2 H, m, CH=CH).

Methyl (2*R*,6*R*)-(−)-2-[2-(methoxymethoxy)ethyl]-6-propylpiperidine-1-carboxylate 16

To a stirred solution of **15** (360 mg, 1.32 mmol) in MeOH (12 cm^3) was added 5% Pd–C (250 mg), and the resulting suspension was hydrogenated at 1 atm for 4 h. The catalyst was removed by filtration through a Celite pad and washed with CH_2Cl_2. The combined organic layer and washings were evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (9 g; hexane–acetone, 10:1) to give (−)-**16** (310 mg, 86%) as a pale yellow oil (Found: C, 61.17; H, 9.77; N, 5.18. $C_{14}H_{27}NO_4$ requires C, 61.51; H, 9.96; N, 5.12); ν_{max}(neat)/cm^{-1} 1693; δ_H 0.92 (3 H, t, *J* 7, CH_3), 1.19–1.70 (10 H, br m), 1.77–1.97 (2 H, m), 3.35 (3 H, s, OCH_3), 3.53 (2 H, apparent t, *J* 7, CH_2OMOM), 3.68 (3 H, s, $COOCH_3$), 4.07–4.23 (1 H, m, 2- or 6-H), 4.24–4.37 (1 H, m, 2- or 6-H) and 4.62 (2 H, s, OCH_2O); $[\alpha]_D^{26}$ −0.15 (*c* 1.03, $CHCl_3$).

Methyl (2*R*,6*R*)-(−)-2-(2-methyllsulfonyloxyethyl)-6-propylpiperdine-1-carboxylate 17

To a stirred solution of (−)-**16** (632 mg, 2.31 mmol) in MeOH (4 cm^3) was added concentrated hydrochloric acid (0.4 cm^3), and the resulting solution was heated at 60 °C for 2 h. After cooling, the mixture was treated with saturated aqueous $NaHCO_3$ (4 cm^3) to quench the reaction, and the solvent was removed. The residue was extracted with CH_2Cl_2 (5 cm^3 × 5), and the organic extracts were combined and evaporated to give a colourless oil, which was used directly in the next step. To a stirred solution of the alcohol obtained above in CH_2Cl_2 (8 cm^3) were added MsCl (0.32 cm^3, 3.17 mmol) and pyridine (0.52 cm^3, 3.17 mmol), and the resulting solution was stirred for 3 h at room temperature. The mixture was diluted with Et_2O (30 cm^3), and the organic layer was separated, washed with saturated brine (5 cm^3), dried and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (10 g; hexane–acetone, 10:1) to give (−)-**17** (482 mg, 68% in 2 steps) as a colourless oil (Found: C, 50.58; H, 8.13; N, 4.73. $C_{13}H_{25}NO_5S$ requires C, 50.79; H, 8.20; N, 4.56); ν_{max}(neat)/cm^{-1} 1686 and 1355; δ_H 0.92 (3 H, t, *J* 7, CH_3), 1.19–1.70 (10 H, br, m), 1.88–2.15 (2 H, m), 3.03 (3 H, s, OSO_2CH_3), 3.68 (3 H, s, CO_2CH_3), 4.17–4.34 (4 H, m, 2- and 6-H and CH_2OMs); $[\alpha]_D^{26}$ −4.4 (*c* 0.77, $CHCl_3$).

Methyl (2*R*,6*R*)-(+)-2-(2-iodoethyl)-6-propylpiperidine-1-carboxylate 18

To a stirred solution of (−)-**17** (227 mg, 0.73 mmol) in acetone (6 cm^3) was added NaI (1.10 g, 7.30 mmol), and the resulting suspension was stirred at room temperature for 11 h. It was then filtered, and evaporated. The residue was extracted with CH_2Cl_2 (10 cm^3 × 3), and the organic extracts were combined, washed with 10% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (5 cm^3) and saturated brine (5 cm^3), dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (10 g; hexane–acetone, 30:1) to give (+)-**18** (223 mg, 89%) as a pale yellow oil (Found: M^+, 339.0680. $C_{12}H_{22}NO_2I$ requires *M*, 339.0695); ν_{max}(neat)/cm^{-1} 1692; δ_H 0.93 (3 H, t, *J* 7, CH_3), 1.28–1.68 (10 H, br m), 2.00–2.27 (2 H, m), 3.03–3.22 (2 H, m, CH_2I), 3.69 (3 H, s, CO_2CH_3), 4.10–4.29 (2 H, m, 2- and 6-H); $[\alpha]_D^{26}$ +19.7 (*c* 1.34, $CHCl_3$).

Methyl (2*R*,6*R*)-(−)-2-(hept-3-ynyl)-6-propylpiperidine-1-carboxylate 19

To a stirred solution of pent-1-yne (0.21 cm^3, 2.14 mmol) in THF (6 cm^3) was added BuLi (10% w/v in hexane; 1.00 cm^3) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. To the solution was then added (+)-**18** (485 mg, 1.43 mmol) in THF (1 cm^3) at 0 °C, and the resulting mixture was stirred for 19 h at room temperature. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (8 cm^3) to the mixture, after which the aqueous layer was separated and extracted with CH_2Cl_2 (5 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (15 g; hexane–acetone, 80:1) to give (−)-**19** (390 mg, 98%) as a pale yellow oil (Found: M^+, 279.2202. $C_{17}H_{29}NO_2$ requires *M*, 279.2206); ν_{max}(neat)/cm^{-1} 2345, 2335, 2175 and 1695; δ_H 0.91 (3 H, t, *J* 7, CH_3), 0.97 (3 H, t, *J* 7, CH_3), 1.10–1.85 (14 H, m), 2.09–2.25 (4 H, m, CH_2CCCH_2, 3.67 (3 H, s, $COOCH_3$), 4.16–4.21 (2 H, m, 2- and 6-H); $[\alpha]_D^{26}$ −7.6 (*c* 1.07, $CHCl_3$).

Methyl (2*R*,6*R*)-(−)-2-(hept-3-enyl)-6-propylperidine-1-carboxylate 20

To liquid NH_3 (5 cm^3) was added sodium (112 mg, 4.80 mmol) at −78 °C, and the resulting blue solution was stirred for 30 min at −50 °C. To the solution was added (−)-**19** (135 mg, 0.48 mmol) in THF (6 cm^3) at −50 °C, and the resulting mixture was then stirred for 40 min at −50 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the mixture after which it was diluted with CH_2Cl_2 (5 cm^3) and water (5 cm^3). The aqueous layer was then separated and extracted with CH_2Cl_2 (5 cm^3 × 8). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (15 g; hexane–acetone, 80:1) to give (−)-**20** (128 mg, 94%) as a pale yellow oil (Found: C, 72.52; H, 11.34; N, 5.20. $C_{17}H_{31}NO_2$ requires C, 72.55; H, 11.10; N, 4.98); ν_{max}(neat)/cm^{-1} 1696; δ_H 0.88 (3 H, t, *J* 7), 0.91 (3 H, t, *J* 7), 1.26–1.66 (14 H, m, 3-, 4-, 5-H), $CH_2CH_2CH_3$ and $CH_2CH_2CH{=}CHCH_2CH_2CH_3$), 1.92–1.98 (4 H, m, $CH_2CH{=}CHCH_2$), 3.67 (3 H, s, CO_2CH_3), 4.13 (2 H, br s, 2- and 6-H) and 5.38–5.42 (2 H, m, CH=CH); $[\alpha]_D^{26}$ −1.7 (*c* 1.01, $CHCl_3$).

(2*R*,6*R*)-(−)-2-(Hept-3-enyl)-6-propylpiperidine 21

To a stirred solution of PrSH (0.065 cm^3, 0.71 mmol) in HMPA (0.3 cm^3) was added BuLi (10% w/v in hexane; 0.46 cm^3) at 0 °C, and the resulting solution was stirred for 30 min at 0 °C. To the solution was added (−)-**20** (50 mg, 0.17 mmol) in THF (0.5 cm^3) at 0 °C, and the resulting mixture was stirred for 2 days at room temperature. The reaction was quenched by the addition of 10% aqueous hydrochloric acid to the mixture after which the aqueous layer was separated and washed with Et_2O (5 cm^3 × 3). The aqueous layer was adjusted to pH 10 with NH_4OH and extracted with Et_2O (5 cm^3 × 5). The organic extracts were combined, dried (K_2CO_3) and evaporated to give a pale yellow oil, which was purified by column chromatography on Al_2O_3 (20 g; benzene–acetone, 100:1) to give (−)-**21** (33 mg, 83%) as a pale yellow oil (Found: M^+, 223.2254. $C_{15}H_{29}N$ requires *M*, 223.2298); ν_{max}(neat)/cm^{-1} 994; δ_H 0.88–1.47 (17 H, m), 1.60 (1 H, br), 1.65 (1 H, m), 1.71–1.79 (4 H, m), 1.91–2.07 (2 H, m), 2.43–2.53 (2 H, m, 2- and 6-H), 5.38–5.42 (2 H, m, CH=CH); $[\alpha]_D^{26}$ −2.76 (*c* 0.49, $CHCl_3$).

(2*R*,6*R*)-(−)-1-Chloro-2-(hept-3-enyl)-6-propylpiperidine 22

To a stirred solution of (−)-**21** (230 mg, 1.03 mmol) in Et_2O (10 cm^3) was added *N*-chlorosuccinimide (145 mg, 1.08 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1.5 h. After this the mixture was evaporated, and the residue was purified by column chromatography on SiO_2 (20 g; hexane) to give (−)-**22** (236 mg, 89%) as a pale yellow oil (Found: M^+, 257.6752. $C_{15}H_{28}NCl$ requires *M*, 257.6747); ν_{max}(neat)/cm^{-1} 2360, 1458, 967 and 668; δ_H 0.87 (3 H, t, *J* 7, CH_3), 0.90 (3 H, t, *J* 7, CH_3), 1.25–1.42 (8 H, m), 1.64 (6 H, br), 1.91–2.05 (4 H, m, $CH_2CH{=}CHCH_2$), 2.75 (2 H, br s, 2- and 6-H) and 5.35–5.41 (2 H, m, CH=CH); $[\alpha]_D^{26}$ −4.2 (*c* 0.75, $CHCl_3$).

(−)-Indolizidine 223AB 11.

To a stirred solution of (−)-**22** (20 mg, 0.0761 mmol) in THF (0.8 cm^3) were added CuCl (0.8 mg, 0.007 61 mmol) and $CuCl_2$

(10.4 mg, 0.0761 mmol) in THF (0.4 cm^3), AcOH (0.2 cm^3) and water (0.2 cm^3) at −45 °C, and the resulting mixture was stirred for 40 min at −45 °C. The reaction was quenched by the addition of 5 M aqueous NaOH to the mixture, after which the aqueous layer was separated and extracted with CH_2Cl_2 (5 cm^3 × 8). The organic extracts were combined, dried (K_2CO_3) and evaporated to give a pale yellow oil, which was purified by column chromatography on Al_2O_3 (8 g; hexane–benzene, 5:1) to give the indolizidine (10.1 mg, 50%) as a pale yellow oil; δ_H 0.88 and 0.92 (each 3 H, each t, each *J* 7), 1.14–2.01 (18 H, m), 2.68–2.78 (1 H, m), 3.06–3.18 (1 H, m), 3.68–3.77 (1 H, m) and 4.33–4.44 (1 H, m).

To a stirred solution of Bu_3SnH (0.1 cm^3, 0.36 mmol) and AIBN (3 mg, 0.018 mmol) in benzene (1 cm^3) was added the indolizidine obtained above (19 mg, 0.073 mmol) in benzene (1 cm^3) under reflux during 30 min, and the resulting solution was refluxed for 40 min. After cooling, the mixture was concentrated by solvent removal, after which it was diluted with Et_2O (5 cm^3) and aq. KF (7 cm^3). The insoluble material was filtered off, and the organic layer was separated, dried (K_2CO_3) and evaporated to give a pale yellow oil. This was purified by column chromatography on Al_2O_3 (20 g; hexane–$CHCl_3$, 10:1) to give (−)-**11** (7.0 mg, 36%) as a pale yellow oil; $\nu_{max}(CHCl_3)$/cm^{-1} 2955, 2800 and 1465; δ_H 0.91 (6 H, m), 1.08 (4 H, m), 1.36 (9 H, m), 1.71 (7 H, m), 2.37 (2 H, br m) and 3.30 (1 H, m); δ_C 14.17, 14.45, 19.00, 22.98, 24.69, 24.98, 26.39, 29.15, 30.10, 30.99, 32.42, 35.92, 56.61, 58.51 and 59.01; $[\alpha]_D^{26}$ −91.4 (*c* 0.175, hexane) {lit.,[6c] $[\alpha]_D^{20}$ −101 (*c* 2.3, hexane)}.

Methyl (2*S*,6*R*)-(−)-2-(*tert*-butyldimethylsiloxymethyl)-6-prop-2-enylpiperidine-1-carboxylate 23

To a stirred solution of oxalyl chloride (0.30 cm^3, 3.47 mmol) in CH_2Cl_2 (22 cm^3) was added DMSO (0.49 cm^3, 6.94 mmol) at −78 °C, and the mixture was stirred for 10 min. To the mixture was added (+)-**13** (766 mg, 2.31 mmol) in CH_2Cl_2 (8 cm^3), and the stirring was continued for 30 min at −78 °C. To the reaction mixture was added Et_3N (1.45 cm^3, 10.40 mmol) at −78 °C, the temperature of which was gradually increased to 0 °C. The reaction mixture was then diluted with Et_2O (80 cm^3), after which the organic layer was separated, washed with water (8 cm^3 × 5), dried and evaporated to give a pale yellow oil (798 mg). This was used directly in the next step. To the suspension of methyl(triphenyl)phosphonium iodide (3.27 g, 8.10 mmol) in THF (22 cm^3) was added BuLi (10% w/v in hexane; 4.45 cm^3) at 0 °C, and the mixture was stirred for 30 min at room temperature. To the mixture was added the crude aldehyde obtained above (798 mg) in THF (8 cm^3) at 0 °C, and the resulting suspension was stirred for 14 h at room temperature. The reaction was quenched by the addition of water (10 cm^3) to the mixture, after which the aqueous layer was separated and extracted with Et_2O (20 cm^3 × 4). The organic extracts were combined, washed with saturated brine (10 cm^3 × 1), dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (23 g; hexane–acetone, 50:1) to afford (−)-**23** [348 mg, 48% from (+)-**13**] as a pale yellow oil (Found: $M^+ - C_4H_9$, 270.1518. $C_{14}H_{24}NO_5Si$ requires $M - C_4H_9$, 270.1524); ν_{max}(neat)/cm^{-1}: 3075, 2952 and 1700; δ_H 0.07 [6 H, s, $Si(CH_3)_2$], 0.89 [9 H, s, $SiC(CH_3)_3$], 1.40–1.70 (6 H, m, 3-, 4-, 5-H), 2.09–2.25 (2 H, m, CH_2CH=), 3.46–3.68 (2 H, m, CH_2OTBS), 3.72 (3 H, s, $COOCH_3$), 4.15 (2 H, br, 2- and 6-H), 4.99–5.04 (2 H, m, =CH_2) and 5.66–5.81 (1 H, m, CH=); $[\alpha]_D^{26}$ −4.9 (*c* 1.01, $CHCl_3$).

Methyl (2*S*,6*S*)-(−)-2-hydroxymethyl-6-propylpiperidine-1-carboxylate 24

To a stirred solution of (−)-**23** (97 mg, 0.30 mmol) in MeOH (5 cm^3) was added 5% Pd–C (60 mg), and the resulting suspension was hydrogenated at 1 atm for 6 h. The catalyst was removed by filtration through a Celite pad and washed with CH_2Cl_2. The combined organic layer and washings were evaporated to give a colourless oil, which was used directly in the next step. To a stirred solution of the oil obtained above in THF (5 cm^3) was added TBAF (1 M in THF, 0.32 mmol; 0.32 cm^3) at room temperature, and the resulting mixture was stirred for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 cm^3) to the mixture, after which the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (5 g; hexane–acetone, 20:1) to afford (−)-**24** [57 mg, 90% from (−)-**23**] as a colourless oil (Found: M^+, 215.1534. $C_{11}H_{21}NO_3$ requires *M*, 215.1521); ν_{max}(neat)/cm^{-1} 3440, 2954, 2871 and 1694; δ_H 0.92 (3 H, t, *J* 7, CH_3), 1.20–1.65 (10 H, m, 3-, 4-, 5-H and $CH_2CH_2CH_3$), 3.64 (2 H, apparent d, *J* 7.5, CH_2OH), 3.70 (3 H, s, CO_2CH_3), 4.15 (1 H, br, 2- or 6-H), 4.31 (1 H, br, 2- or 6-H); $[\alpha]_D^{26}$ −19.3 (*c* 0.50, $CHCl_3$).

Methyl (2*S*,6*S*)-(+)-2-(2-methoxyethenyl)-6-propylpiperidine-1-carboxylate 25

To a stirred solution of oxalyl chloride (0.057 cm^3, 0.66 mmol) in CH_2Cl_2 (3 cm^3) was added DMSO (0.093 cm^3, 1.31 mmol) at −78 °C, and the mixture was stirred for 10 min. To the mixture was added (−)-**24** (94 mg, 0.44 mmol) in CH_2Cl_2 (2 cm^3), and the stirring was continued for 30 min at −78 °C. To the reaction mixture was added Et_3N (0.27 cm^3, 1.97 mmol) at −78 °C, and the temperature was gradually increased to 0 °C. The reaction mixture was diluted with Et_2O (25 cm^3) and the organic layer was separated and washed with water (3 cm^3 × 5), dried and evaporated to give a pale yellow oil (107 mg) which was used directly in the next step. To the suspension of methoxymethyl(triphenyl)phosphonium chloride (375 mg, 1.09 mmol) in THF (3 cm^3) was added BuLi (10% w/v in hexane; 0.56 cm^3) at 0 °C, and the mixture was stirred for 30 min at room temperature. To the mixture was added the crude aldehyde obtained above (107 mg) in THF (2 cm^3) at 0 °C, and the resulting suspension was stirred for 17 h at room temperature. The reaction was quenched by the addition of water (2 cm^3) to the reaction mixture, after which the aqueous layer was separated and extracted with Et_2O (10 cm^3 × 3). The organic extracts were combined, washed with saturated brine (10 cm^3 × 1), dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (3 g; hexane–acetone, 200:1) to afford (+)-**25** [65.5 mg, 62% from (−)-**24**] as a pale yellow oil (3:2 mixture of *E* and *Z* isomers) (Found: M^+, 241.1534. $C_{13}H_{23}NO_3$ requires *M*, 241.1521); ν_{max}(neat)/cm^{-1}: 2936, 2869 and 1694; δ_H 0.87–0.93 (3 H, m, CH_3), 1.21–1.76 (10 H, br m, 3-, 4-, 5-H and $CH_2CH_2CH_3$), 3.50 (1.2 H, s, OCH_3), 3.59 (1.8 H, s, OCH_3), 3.67 (3 H, s, CO_2CH_3), 4.16 (1 H, m, 6-H), 4.55 (0.6 H, apparent dd, *J* 8 and 6.5, 2-H), 4.73 (0.4 H, br m, 2-H), 4.95 (0.4 H, apparent dd, *J* 12.5 and 9, =CH), 5.16 (0.6 H, br m, =CH), 5.82 [0.6 H, apparent d, *J* 6.5, =C(OMe)H], 6.56 [0.4 H, apparent d, *J* 12.5, =C(OMe)H]; $[\alpha]_D^{26}$ +9.2 (*c* 0.63, $CHCl_3$).

Methyl (2*S*,6*S*)-(−)-2-(2-hydroxyethyl)-6-propylpiperidine-1-carboxylate 26

To a stirred solution of (+)-(**25** (26 mg, 0.11 mmol) in CH_2Cl_2 (3 cm^3) was added concentrated hydrochloric acid (1 drop), and the mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 cm^3) to the mixture, after which the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 cm^3 × 5), and the organic layer and extracts were combined, dried and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the crude aldehyde obtained above in MeOH (1 cm^3) was added $NaBH_4$ (4.1 mg, 0.11 mmol) at 0 °C, and the resulting mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of 10% aqueous hydrochloric acid to the mixture and then the solvent was removed. The residue was extracted with CH_2Cl_2 (5 cm^3 × 5), and the organic extracts were com-

bined, dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (1 g; hexane–acetone, 40:1) to afford (−)-**26** [17 mg, 68% from (+)-**25**] as a pale yellow oil (Found: M^+, 229.1668. $C_{12}H_{23}NO_3$ requires *M*, 229.1676); ν_{max}(neat)/cm^{-1} 3446, 2937, 2870 and 1693; δ_H 0.91 (3 H, t, *J* 7, CH_3), 1.16–1.89 (12 H, br m, 3-, 4-, 5-H, $CH_2CH_2CH_3$ and CH_2CH_2OH), 3.44–3.69 (2 H, m, CH_2OH), 3.71 (3 H, s, CO_2CH_3), 4.14 (1 H, br, 2- or 6-H) and 4.41 (1 H, br, 2- or 6-H); $[\alpha]_D^{26}$ −7.4 (*c* 0.58, $CHCl_3$).

Methyl (2*S*,6*S*)-(−)-2-(2-iodoethyl)-6-propylpiperidine-1-carboxylate 18

To a stirred solution of (−)-**26** (22.6 mg, 0.097 mmol) in CH_2Cl_2 (1 cm^3) were added pyridine (0.048 cm^3, 0.592 mmol) and MsCl (0.029 cm^3, 0.30 mmol) at 0 °C, and the mixture was stirred for 1.5 h at room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 cm^3) to the mixture, after which the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 cm^3 × 5), and the combined organic layer and extracts were dried and evaporated to give a pale yellow oil. This was purified by column chromatography on SiO_2 (3 g; hexane–acetone, 10:1) to afford the methanesulfonate (22.4 mg, 74%) as a pale yellow oil (Found: M^+, 307.1425. $C_{13}H_{25}NO_5S$ requires *M*, 307.1451); ν_{max}(neat)/cm^{-1} 1686 and 1355; δ_H 0.92 (3 H, t, *J* 7, CH_3), 1.19–1.70 (10 H, br m), 1.88–2.15 (2 H, m), 3.03 (3 H, s, OSO_2CH_3), 3.68 (3 H, s, CO_2CH_3), 4.17–4.34 (4 H, m, 2-, 6-H and CH_2OMs); $[\alpha]_D^{26}$ +9.9 (*c* 1.07, $CHCl_3$).

To a stirred solution of the methanesulfonate obtained above (22.4 mg, 0.073 mmol) in acetone (1 cm^3) was added NaI (109 mg, 0.73 mmol), and the resulting suspension was stirred for 16 h at room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated. The residue was extracted with CH_2Cl_2 (5 cm^3 × 3), and the organic extracts were combined, washed with 10% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (3 cm^3) and saturated brine (3 cm^3), dried and evaporated to give a pale yellow oil. This was purified by column chromatography on SiO_2 (1 g; hexane–acetone, 100:1) to give (−)-**18** (21.7 mg, 87%) as a pale yellow oil (Found: M^+, 339.0688. $C_{12}H_{22}NO_2I$ requires *M*, 339.0695); ν_{max}(neat)/cm^{-1} 1692; δ_H 0.93 (3 H, t, *J* 7.1, CH_3), 1.28–1.68 (10 H, br m), 2.00–2.27 (2 H, m), 3.03–3.22 (2 H, m, CH_2I), 3.69 (3 H, s, CO_2CH_3) and 4.10–4.29 (2 H, m, 2- and 6-H); $[\alpha]_D^{26}$ −20.7 (*c* 0.93, $CHCl_3$). The spectral features of the product were identical with those of (+)-**18**.

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