Bicyclo[3.3.1]nonanes as synthetic intermediates. Part 21.[1] Enantiodivergent synthesis of the *cis,cis* 2,6-disubstituted piperidin-3-ol chiral building block for alkaloid synthesis

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Enantiodivergent synthesis of the enantio-pure *cis,cis* 3-protected 2,6-disubstituted piperidin-3-ol 1 has been achieved *via* a biochemical method, and the absolute stereochemistry of (+)-1 has been established by its conversion into the known piperidine (−)-17. The utility of 1 as a chiral building block for alkaloid synthesis is demonstrated by the total synthesis of (−)-cassine and (+)-spectaline.

Introduction

The construction of versatile chiral building blocks provides us with powerful tools for the efficient syntheses of biologically active natural products. A large number of methods leading to the syntheses of the piperidine,[2,3] decahydroquinoline,[3] indolizidine,[3,4a,b] and quinolizidine[3,4b] systems have already been developed. For instance, a piperidin-3-ol bearing appendages with versatile functionality at the 2- and 6-positions would serve as a building block for efficient syntheses of piperidin-3-ols found in natural products,[5] and several methods for their stereoselective construction have been reported. These methods involve strategies starting with photooxygenation of a pyridine ring system,[6] intramolecular cyclisation reaction of a 2-hydroxy-5-ketoamine,[7] oxidative cleavage of a 2-azabicyclo[2.2.2]octan-5-one ring system[8] and an aza-annulation reaction of an enamino ester with acrylic anhydride.[9] Other methods which have been investigated for this chiral construction involve an aza-Achmatowicz rearrangement of a furan derivative,[10] an intramolecular double Michael reaction[11] or palladium-catalysed cyclisation[12] of an *N*-protected amino-olefin, radical cyclisation of a 2,3-dihydrooxazolone derivative[13] and a 1,3-dipolar cycloaddition of a nitrone to a dipolarophile.[14] However, no example of the asymmetric synthesis of piperidin-3-ols starting with desymmetrisation of prochiral substrates has appeared to date. Our previous report on the chiral synthesis of 2,6-disubstituted piperidines, starting with the asymmetric enolisation of a σ-symmetric nitrogen-bridged bicyclic ketone, demonstrated the asymmetric differentiation of a rigid piperidone system with a chiral base. Alternatively, a *meso* glycol such as 9-azabicyclo[3.3.1]nonane-2,4-diol, if readily available, could be differentiated with a chemo-enzymatic method to result in analogous desymmetrisation of the σ-symmetric bicyclo system. It was of interest to determine whether the ring differentiation of a conjoined twin piperidine system such as 9-azabicyclo[3.3.1]nonane-2,8-diol by chemo-enzymatic differentiation of the ring-crossed *meso* glycol system could be effected in a highly enantiotoposelective fashion. To this end, we examined a strategy for the asymmetric construction of a piperidin-3-ol **1** *via* an enantiodivergent process starting with a lipase-mediated enantiotoposelective reaction of an azabicyclic *meso* glycol system **2** (R^1 = H or Ac), followed by chemical transformation of the chiral adduct into both enantiomers of **1** in an optically pure state, as depicted in Fig. 1.

Herein we describe a full account of the experimental details of the chiral construction of both enantiomers of **1** and examine their application to the synthesis of piperidin-3-ol alkaloids.[15]

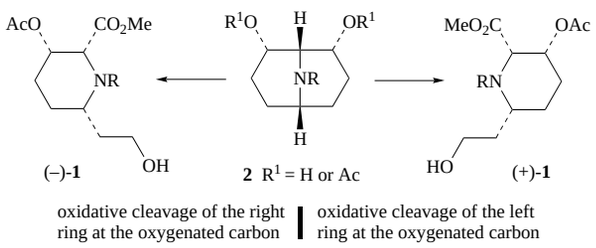


Fig. 1

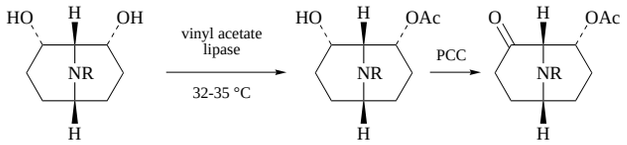
Results and discussion

First, we examined the preparation of the starting material **2** (R^1 = H or Ac); a substrate for the lipase-mediated enantiotoposelective reaction. The dealkylative carbamoylation of the bicyclic amine **3**[16] with $ClCO_2Me$ afforded the desired urethane **4** in 95% yield. Allylic oxidation of **4** with SeO_2 gave the alcohol **5** in 77% yield, which was converted by oxidation with pyridinium chlorochromate (PCC) into the enone **6** in 90% yield. Hydrogenation of **6** over 5% Pd–C gave the ketone **7** in 98% yield, reduction of which with $NaBH_4$ and subsequent hydrolysis of the resulting monoacetate afforded the *meso* glycol **2** (R^1 = H) in 77% yield from **7**. Acetylation without hydrolysis of the above monoacetate provided the *meso* acetate **2** (R^1 = Ac) in 74% yield from **7** (Scheme 1). With **2** (R^1 = H or Ac) in hand, we examined the lipase-mediated ring differentiation reaction, and the results are summarised in Tables 1 and 2.

As shown in Tables 1 and 2, the use of lipase CE gave the best results in both differentiation reactions. Recrystallisation, from Pr^i_2O, of the enantiomeric ketone **7** derived from oxidation of the enantiomeric monoacetate with PCC furnished an enantiomerically pure sample of (+)- or (−)-**7** in 74 or 65% yield, respectively, from **2** (R^1 = H or Ac). The treatment of (+)-**7** with $HC(OMe)_3$ in the presence of catalytic amounts of *conc*. H_2SO_4 and 4 Å molecular sieves gave the enol ether (+)-**8** in 86% yield. Ozonolysis of (+)-**8** afforded the desired piperidine (+)-**1** in 98% yield. Similarly, (−)-**7** was converted into the enantiomer (−)-**1** as depicted in Scheme 2.

In order to establish the absolute stereochemistry of (+)-**1**, we next examined the transformation of (+)-**1** into the known piperidine (−)-**17**.[17] Protection of the hydroxy group in (+)-**1** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) gave the silyl ether (+)-**9** in 94% yield. Hydrolysis of (+)-**9** and subsequent reaction of the resulting alcohol with methoxymethyl chloride (MOMCl) in the presence of the Hünig base

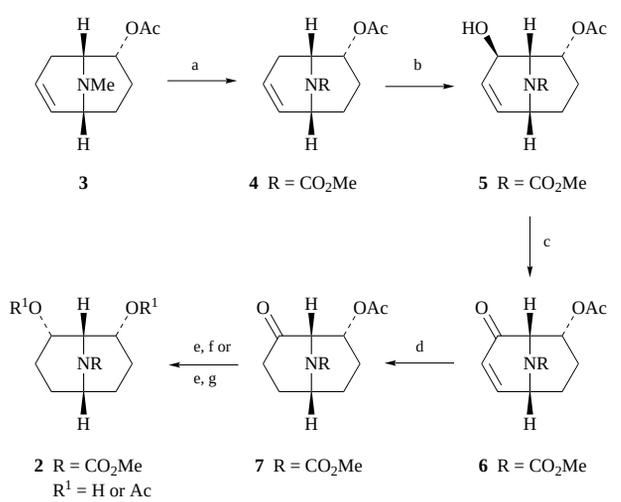
Table 1[a]



(+)-**7** R = CO_2Me

Lipase[b]	Solvent	*t*/h	Yield (%)[c]	(%ee)[d]
CE	C_6H_6	98	38 (99)	32
CE	Pr^i_2O	109	85 (99)	90 (>99)
AY	Pr^i_2O	87	33 (99)	56
CCL	Pr^i_2O	91	15 (94)	54

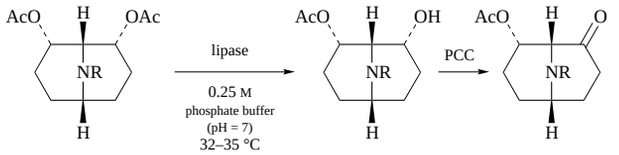
[a] All runs were conducted with the substrate (0.23 mmol), lipase (100 mg) and vinyl acetate (2 equiv.) in the organic solvent (10 cm^3); see Experimental section. [b] Lipase CE (from *Humicola lanuginosa*) and AY (from *Candida rugosa*) were supplied by the Amano Pharmaceutical Co., Ltd. and CCL (from *Candida cylindracea*) was purchased from the Sigma Chemical Co., Ltd. [c] Yields for the isolated monoacetate. Yields in parentheses are those based on the conversion rate. [d] Optical yields were determined by HPLC analyses by using a column packed with Chiralpak AD (EtOH–hexane, 1:9) after oxidation of the monoacetate with PCC. Optical yield in parentheses is based on a sample after single recrystallisation from Pr^i_2O.



Scheme 1 *Reagents and conditions:* a, $ClCO_2Me$, $CHCl_3$, reflux (95%); b, SeO_2, dioxane–H_2O = 10:1 (77%); c, PCC, AcONa (90%); d, H_2, 5% Pd–C (95%); e, $NaBH_4$, MeOH; f, 10% aq. Na_2CO_3 (77% over 2 steps); g, Ac_2O, pyridine (74% over 2 steps)

afforded the piperidine (+)-**10** in 88% yield in two steps. Reduction of (+)-**10** with Super-Hydride afforded the alcohol (−)-**11** in 87% yield. The PCC oxidation of (−)-**11** followed by treatment of the resulting aldehyde with ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ afforded the dithioacetal (+)-**12** in 68% yield. Desulfurisation of (+)-**12** with Raney nickel (W-4) gave the piperidine **13** in 95% yield. Removal of the TBDPS group in **13** with tetrabutylammonium fluoride (TBAF) afforded the alcohol (+)-**14** in 85% yield, and its oxidation with pyridinium dichromate (PDC) in *N*,*N*-dimethylformamide (DMF), followed by esterification with CH_2N_2, provided the methyl ester (+)-**15** in 66% yield. Removal of the MOM group in (+)-**15** with acid followed by mesylation and subsequent elimination at the resulting methanesulfonate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the olefin **16** in 48% overall yield. Finally, hydrogenation of **16** over 5% Pd–C in MeOH furnished the known piperidine (−)-**17**, which had a value of $[\alpha]_D^{26}$ −40.0 (lit.,[17] $[\alpha]_D^{26}$ −38.9). Thus, the absolute stereochemistry of (+)-**1** was determined to be (2*S*,3*R*,6*R*) (Scheme 3).

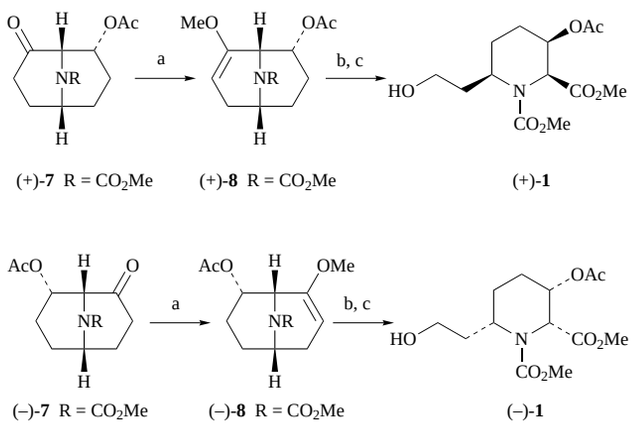
Table 2[a]



(–)-**7** R = CO_2Me

Lipase[b]	*t*/h	Yield (%)[c]	(%ee)[d]
CE	23	84 (99)	80 (>99)
AY	35	42 (76)	78
CCL	66	23 (70)	58
PPL	84	14 (45)	48
PLE	48	39 (76)	75

[a] All runs were conducted with the substrate (0.17 mmol), lipase (100 mg) and phosphate buffer in the solvent (6 cm^3); see Experimental section. [b] PLE (pig liver esterase) was supplied by the Amano Pharmaceutical Co., Ltd. and PPL (porcine pancreas lipase) was purchased from the Sigma Chemical Co., Ltd. [c] Yields for the isolated monoacetate. Yields in parentheses are those based on the conversion rate. [d] Determined for (−)-**7** as in the transesterification of **2**. Optical yield in parentheses is based on a sample after recrystallisation twice from Pr^i_2O.

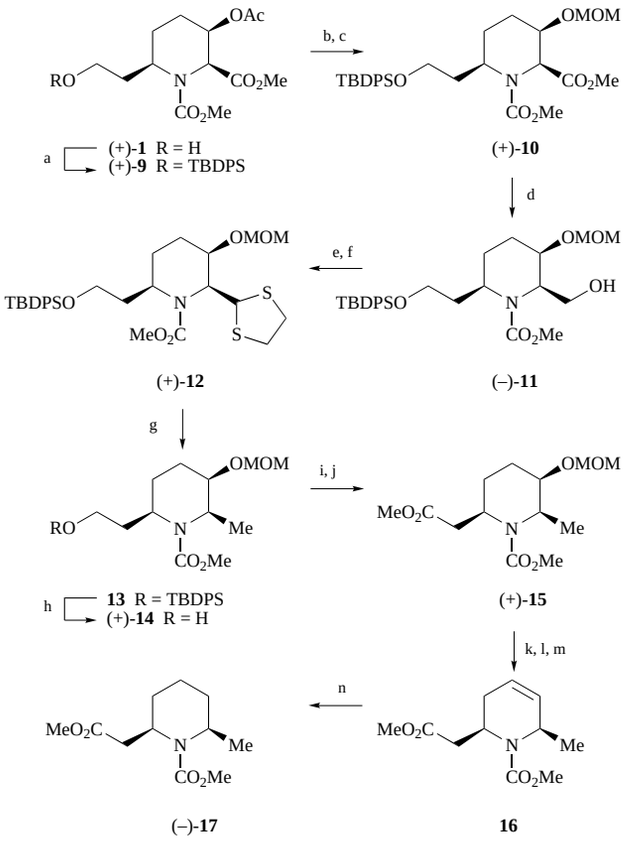


Scheme 2 *Reagents and conditions:* a, $HC(OMe)_3$, cat. H_2SO_4 (86%); b, O_3, CH_2Cl_2–MeOH (10:1), −78 °C; c, $NaBH_4$, −78 ~ 0 °C (98% over 2 steps)

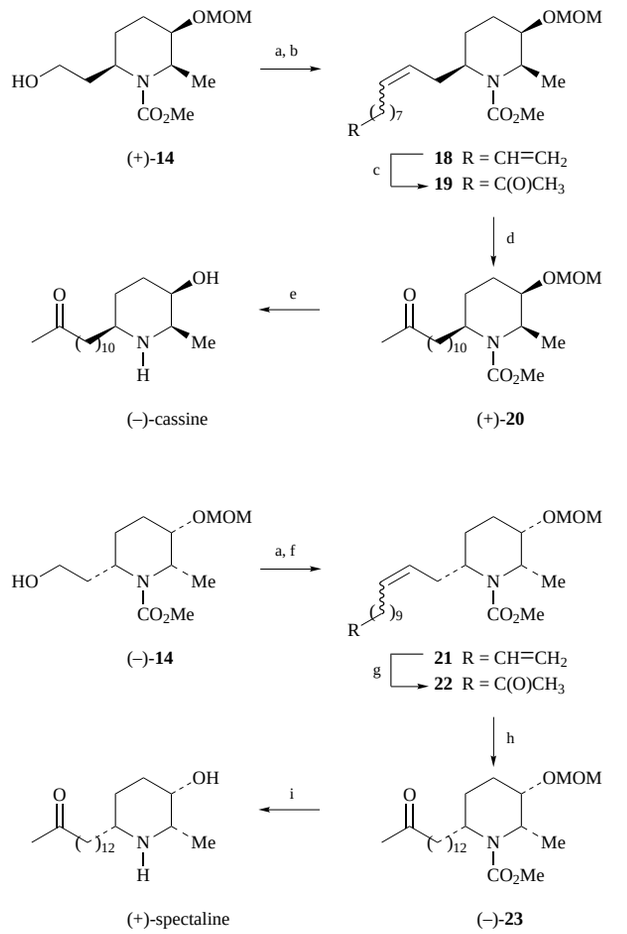
With the chiral building block (+)-**1** of established absolute stereochemistry, we next examined the chiral synthesis of the piperidin-3-ol alkaloids (−)-cassine and (+)-spectaline. The alcohol (+)-**14** was converted into the diene **18** in 86% yield *via* Swern oxidation and subsequent Wittig reaction. The Wacker oxidation of **18** afforded the ketone **19** in 70% yield. Catalytic hydrogenation of **19** over 5% Pd–C gave the saturated ketone (+)-**20** and its treatment with trimethylsilyl iodide (Me_3SiI) in hot $CHCl_3$ furnished (−)-cassine {$[\alpha]_D^{26}$ −0.7 (*c* 0.59, EtOH); lit.,[18] $[\alpha]_D^{25}$ −0.6 (*c* 8.0, EtOH)} in 65% yield (Scheme 4). The synthetic sample of (−)-cassine was in good accordance with the natural product in its physical properties[18a] and possessed spectral properties (^1H and ^{13}C NMR) identical with those of the synthetic racemate.[18c] Similarly, (+)-spectaline {$[\alpha]_D^{26}$ +9.0 (*c* 1.3, $CHCl_3$); lit.,[19] $[\alpha]_D^{25}$ +8.0 (*c* 0.27, $CHCl_3$); lit.,[5c] $[\alpha]_D^{25}$ −8.2 (*c* 0.32, $CHCl_3$)} was synthesised from the alcohol (−)-**14**. The spectral data for the synthetic (+)-spectaline was in good accordance with those for (±)-spectaline.[18c]

Conclusions

We have achieved the enantiodivergent synthesis of a *cis*,*cis* 3-protected 2,6-disubstituted piperidin-3-ol **1** using a hybrid process (biochemical method), and have demonstrated its utility as a chiral building block in the first total synthesis of (−)-cassine and (+)-spectaline.



Scheme 3 *Reagents and conditions:* a, TBDPSCl, Et_3N, DMAP (94%); b, K_2CO_3, MeOH; c, MOMCl, Hünig base (88% over 2 steps); d, Super-Hydride (87%); e, PCC, AcONa; f, ethanedithiol, $BF_3{\cdot}Et_2O$ (68% over 2 steps); g, Raney Ni (W-4) (95%); h, TBAF (85%); i, PDC, DMF; j, CH_2N_2 (66% over 2 steps); k, conc. HCl, MeOH; l, MsCl, pyridine; m, DBU, toluene (48% over 3 steps); n, H_2 5% Pd–C (80%)



Scheme 4 *Reagents and conditions:* a, Swern oxidn.; b, CH_2=CH-$(CH_2)_8P^+Ph_3Br^-$, Bu^nLi, THF, 0 °C–room temp. (86% in 2 steps); c, O_2, $PdCl_2$, CuCl, DMF–H_2O (70%); d, H_2, 5% Pd–C, MeOH (92%); e, TMSI, $CHCl_3$, reflux (65%); f, CH_2=$CH(CH_2)_{10}P^+Ph_3Br^-$, Bu^nLi, THF, 0 °C ~ room temp. (77% over 2 steps); g, O_2, $PdCl_2$, CuCl, DMF–H_2O (75%); h, H_2, 5% Pd–C, MeOH (97%); i, TMSI, $CHCl_3$, reflux (70%)

Experimental

Melting points were determined with a Yanaco micro melting point apparatus and were uncorrected. Microanalyses were performed by the Microanalysis Center of Toyama Medical and Pharmaceutical University. Infrared spectra (IR) were measured with a Perkin-Elmer 1600 series FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were performed at 270 or 67.5 MHz on a JEOL GX270 instrument with tetramethylsilane as an internal standard. Resonance patterns in ^{1}H NMR spectra are shown as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and app. = apparent. Carbon signals were assigned by a DEPT pulse sequence and are shown as u = methyl or methine, d = methylene and s = quaternary carbons. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed on silica gel [Fuji-Davison BW-200 or Merck 60 (No 9385)].

Methyl 6-acetoxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate 4

To a stirred solution of 6-acetoxy-9-methyl-9-azabicyclo-[3.3.1]non-2-ene **3**[16] (13.93 g, 71.4 mmol) in $CHCl_3$ (200 cm^3) was added $ClCO_2Me$ (11.0 cm^3, 142.8 mmol), and the mixture was refluxed for 1 h. After cooling, the reaction mixture was washed with 10% aqueous HCl (15 cm^3 × 3) and then with H_2O (15 cm^3 × 5), and the organic layer was dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (180 g, hexane–acetone, 10:1 ~ 5:1) to afford **4** (16.2 g, 95%) as a pale yellow oil (Found: M^+, 239.1149. $C_{12}H_{17}NO_4$ requires *M*, 239.1156); ν_{max}(neat)/cm^{-1} 3033, 2953, 1735, 1703, 1654, 1450, 1412, 1368, 1351, 1338, 1325, 1310, 1290, 1241, 1197, 1115, 1089, 1037, 951 and 766; δ_H 1.57–1.92 (4H, br m, 7- and 8-H_2), 2.06 (3H, s, COMe), 2.15–2.50 (2H, br m, =CCH_2), 3.70 (3H, s, CO_2Me), 4.41–4.54 (1.5H, br m, AcOC*H* and 1- or 5-H), 4.65 (0.5H, br, 1- or 5-H), 4.83–4.87 (1H, br m, 1- or 5-H), 5.67–5.72 (1H, br m, =CH) and 5.91–5.93 (1H, br m, =CH); *m/z* 240 (M^+ + 1), 239 (M^+) and 59 (100%).

Methyl 6-acetoxy-4-hydroxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate 5

To a stirred solution of **4** (2.3 g, 9.74 mmol) in dioxane (50 cm^3) and H_2O (5 cm^3) was added SeO_2 (2.7 g, 24.35 mmol), and the resulting suspension was refluxed for 14 h. After cooling, the insoluble material was removed by filtration and the filtrate was evaporated to give a pale yellow viscous oil, which was taken up in hot $CHCl_3$ (100 cm^3). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ (5 cm^3 × 2), dried over $MgSO_4$ and evaporated to give a pale yellow viscous oil, which was purified by column chromatography on SiO_2 (40 g, hexane–acetone, 15:1 ~ 5:1) to afford **5** (1.9 g, 77%) as a pale yellow viscous oil (Found: M^+, 255.1147. $C_{12}H_{17}NO_5$ requires *M*, 255.1187); ν_{max}(neat)/cm^{-1} 3427, 2955, 1732, 1687, 1651, 1455, 1416, 1353, 1329, 1290, 1236, 1204, 1096 and 1039; δ_H 1.50–1.90 (4H, br m, 7- and 8-H_2), 2.08 (3H, s, COMe), 3.35–3.60 (1H, br, OH), 3.70 (3H, s, CO_2Me), 4.10–4.22 (1H, br, HOC*H*), 4.50–4.68 (2H, br m, 1- and 5-H), 4.82 (1H, dt, *J* 11.5 and 5.5, AcOC*H*), 5.87–5.89 (1H, br, =CH) and 6.12 (1H, app. dd, *J* 10 and 4, =CH); δ_C 20.67 (u), 21.32 (d), 25.77 and 26.17 (each d, due to rotamers), 45.81 and 46.56 (each u, due to rotamers), 52.38 (u), 55.94 and 56.55 (each u, due to rotamers), 61.75 (u),

68.43 and 68.65 (each u, due to rotamers), 128.19 and 128.72 (each u, due to rotamers), 129.08 and 129.58 (each u, due to rotamers), 154.81 and 154.98 (each s, due to rotamers) and 169.54 (s); *m/z* 256 ($M^+ + 1$), 255 (M^+) and 118 (100%).

Methyl 6-acetoxy-4-oxo-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate 6

To a stirred suspension of PCC (810 mg, 3.76 mmol) in CH_2Cl_2 (20 cm^3) was added a solution of **5** (643 mg, 2.52 mmol) in CH_2Cl_2 (15 cm^3) at 0 °C and the resulting suspension was stirred for 3 h at room temperature. After removal of the insoluble material by filtration, the filtrate was evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (20 g, hexane–acetone, 15:1 ~ 5:1) to afford **6** (575 mg, 90%) as a cyrstalline solid, mp 115–117 °C (Found: C, 56.88; H, 6.02; N, 5.56. $C_{12}H_{15}NO_5$ requires C, 56.91; H, 5.97; N, 5.53%); ν_{max}(KBr)/cm^{-1} 2962, 2884, 1748, 1697, 1682s, 1619, 1449, 1414, 1376, 1361, 1332, 1286, 1245, 1227, 1200, 1138, 1108, 1062, 1042 and 972; δ_H 1.71–2.18 (4H, br m, 7- and 8-H_2), 2.07 (3H, s, COMe), 3.73 (3H, br s, CO_2Me), 4.83 (2H, br, 1- and 5-H), 4.98 (1H, br, AcOC*H*), 6.31 (1H, d, *J* 10, 2-H) and 7.01 (1 H, br, 3-H); δ_C 20.62 and 20.67 (each u, due to rotamers), 21.68 (d), 24.21 and 24.63 (each d, due to rotamers), 47.27 and 47.94 (each u, due to rotamers), 52.81 and 52.90 (each u, due to rotamers), 58.20 and 58.67 (each u, due to rotamers), 66.98 (u), 130.69 (u), 147.16 and 147.25 (each u, due to rotamers), 154.13 (s), 169.78 (s) and 192.19 (s); *m/z* 254 ($M^+ + 1$), 253 (M^+) and 53 (100%).

Methyl 2-acetoxy-8-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate 7

To a solution of **6** (1.34 g, 5.3 mmol) in MeOH (30 cm^3) was added 5% Pd–C (50 mg), and the resulting suspension was hydrogenated at 1 atm for 6 h. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated to give essentially pure **7** (1.32 g, 98%) as a colourless solid, which was used in the next step without further purification. Recrystallisation of the crude ketone from Pr^i_2O–benzene gave an analytically pure sample, mp 125–127 °C (Found: C, 56.47; H, 6.71; N, 5.40. $C_{12}H_{17}NO_5$ requires C, 56.46; H, 6.71; N, 5.49%); ν_{max}(KBr)/cm^{-1} 2962, 2937, 2908, 2884, 1737, 1716, 1687, 1476, 1451, 1423, 1404, 1380, 1367, 1330, 1308, 1287, 1272, 1246, 1229, 1193, 1114, 1090, 1071, 1040 and 992; δ_H 1.67–2.13 (5H, br m, 3-, 4-H_2 and 6-H), 2.08 (3H, s, COMe), 2.30–2.63 (3H, br m, 6-H and 7-H_2), 3.73 (3H, br s, CO_2Me), 4.45–4.62 (1H, br, 1- or 5-H) and 4.76–4.91 (2H, br m, AcOC*H* and 1- or 5-H); δ_C 20.93 (u), 24.50 (d), 25.61 and 25.66 (each d, due to rotamers), 28.90 and 28.97 (each d, due to rotamers), 37.28 (d), 43.91 (u), 53.06 (u), 60.37 and 60.40 (each u, due to rotamers), 68.87 (u), 155.01 (s), 170.06 and 170.10 (each s, due to rotamers) and 205.94 (s); *m/z* 256 ($M^+ + 1$), 255 (M^+) and 54 (100%).

Methyl 2,8-dihydroxy-9-azabicyclo[3.3.1]nonane-9-carboxylate 2 (R^1 = H)

To a stirred solution of **7** (1 g, 3.92 mmol) in MeOH (10 cm^3) was added $NaBH_4$ (100 mg, 2.63 mmol) at 0 °C, and the resulting mixture was stirred for 10 min at room temperature. To the mixture was added 10% aqueous Na_2CO_3 (5 cm^3) at 0 °C, and the mixture was stirred for 30 min at room temperature. The solvent was removed and the residue was taken up in hot $CHCl_3$ (10 cm^3 × 6). The combined $CHCl_3$ layers were dried over $MgSO_4$ and evaporated to give a colourless viscous oil, which was purified by column chromatography on SiO_2 (20 g, $CHCl_3$–EtOH, 1:0 ~ 30:1) to afford **2** (R^1 = H, 653 mg, 77% from **7**) as a colourless solid. Recrystallisation of the solid from benzene gave an analytically pure sample as colourless needles, mp 134–135 °C (Found: C, 55.83; H, 7.75; N, 6.41. $C_{10}H_{17}NO_4$ requires C, 55.80; H, 7.96; N, 6.51%); ν_{max}(KBr)/cm^{-1} 3263, 2996, 2956, 2908, 2860, 2839, 1698, 1490, 1452, 1422, 1404, 1378, 1356, 1329, 1302, 1277, 1250, 1207, 1165, 1124, 1100, 1074, 1058, 1019 and 950; δ_H($CDCl_3$) 1.79–1.98 (4H, m, 3- and 4-H_2), 2.03–2.29 (4H, m, 6- and 7-H_2), 3.70 (3H, s, CO_2Me), 4.05–4.20 (3H, br m, 1-H_2 and OH), 4.44 and 4.54 (1H, each app. t, *J* 5.5, 5-H) and 4.81 and 4.94 (2H, app. d, *J* 6, 2- and 8-H); δ_H([$^2H_6$]DMSO, 25 °C) 1.67–1.74 (4H, m, 3- and 4-H_2), 1.84–2.02 (4H, m, 6- and 7-H_2), 3.59 and 3.61 (3H, each s, CO_2Me), 3.83 (2H, septet, *J* 6, 5-H and OH), 3.99 and 4.02 (1H, each app. t, *J* 4, 1-H), 4.19 and 4.26 (1H, each *ca.* t, *J* 5, OH) and 5.29 (2H, dd, *J* 9.5 and 6.5, 2- and 8-H); δ_H([$^2H_6$]DMSO, 120 °C) 1.66–1.80 (4H, m, 3- and 4-H_2), 1.86–2.02 (4H, m, 6- and 7-H_2), 3.61 (3H, s, CO_2Me), 3.86 (2H, br, OH), 4.02 (1H, br, 5-H), 4.26 (1H, app. t, *J* 6, 1-H) and 4.91 (2H, br, 2- and 8-H); δ_C([$^2H_6$]DMSO, 25 °C) 28.06 and 28.54 (each d, due to rotamers), 30.53 (d), 44.19 and 44.92 (each u, due to rotamers), 51.52 (u), 52.21, 52.25 and 52.34 (each u, due to rotamers), 70.24 and 70.31 (each u, due to rotamers) and 154.19 and 154.41 (each s, due to rotamers); δ_C([$^2H_6$]DMSO, 120 °C) 27.74 (d), 29.95 (d), 44.30 (u), 51.36 (u), 51.84 (u), 70.04 (u) and 153.94 (s); *m/z* 216 ($M^+ + 1$), 215 (M^+) and 169 (100%).

Methyl 2,8-diacetoxy-9-azabicyclo[3.3.1]nonane-9-carboxylate 2 (R^1 = Ac)

To a stirred solution of **7** (2.45 g, 10.5 mmol) in CH_2Cl_2 (20 cm^3) and MeOH (2 cm^3) was added $NaBH_4$ (200 mg, 5.2 mmol) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and then at room temperature for 5 min. The reaction was quenched with 10% AcOH, and the solvent was removed. The residue was taken up in hot $CHCl_3$ (15 cm^3 × 5), and the combined $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to give a colourless viscous oil. To a stirred solution of the oil obtained above in pyridine (3 cm^3) was added Ac_2O (2 cm^3) and the mixture was stirred for 18 h at room temperature. The solvent was removed, and the residue was purified by column chromatography on SiO_2 (35 g, hexane–acetone, 15:1–10:1) to afford **2** (R^1 = Ac, 2.32 g, 74% from **7**) as a colourless solid. Recrystallisation of the solid from Pr^i_2O–benzene gave an analytically pure sample as a colourless solid, mp 127–129 °C (Found: C, 56.11; H, 7.06; N, 4.66. $C_{14}H_{21}NO_6$ requires C, 56.17; H, 7.07; N, 4.68%); ν_{max}(KBr)/cm^{-1} 2996, 2962, 2873, 1738, 1691, 1449, 1411, 1378, 1332, 1290, 1259, 1229, 1192, 1048 and 1031; δ_H 1.73–2.31 (8H, br m, 3-, 4-, 6- and 7-H_2), 2.07 (6H, s, COMe × 2), 3.72 (3H, s, CO_2Me), 4.18 and 4.31 (1H, each br, 5-H), 4.67 and 4.77 (1H, each br app. t, *J* 5, 1-H) and 5.03 (2H, dt, *J* 16 and 5.5, 2- and 8-H); δ_C 21.11 (u), 22.46 and 22.84 (each d, due to rotamers), 25.84 (d), 46.79 and 47.43 (each u, due to rotamers), 52.85 (u), 70.35 and 70.64 (each u, due to rotamers), 155.00 (s) and 169.83 and 170.04 (each s, due to rotamers); *m/z* 300 ($M^+ + 1$), 299 (M^+) and 196 (100%).

General procedure for the lipase-mediated transesterification of the diol 2 (R^1 = H)

To a stirred solution of **2** (R^1 = H, 50 mg, 0.23 mmol) in the appropriate solvent (10 cm^3) were added a lipase preparation (100 mg) and vinyl acetate (0.1 cm^3, 1 mmol), and the resulting suspension was stirred at 32–35 °C. The suspension was filtered through a Celite pad and the lipase preparation remaining on the pad was washed with CH_2Cl_2. The filtrate and washings were combined and evaporated to give an oil, which was fractionated by column chromatography on SiO_2 (10 g, hexane–acetone, 8:1–4:1) to afford a monoacetate.

To a stirred suspension of PCC (2 equiv.) in CH_2Cl_2 (3 cm^3) was added the monoacetate in CH_2Cl_2 (2 cm^3) at 0 °C, and the resulting suspension was stirred for 12 h at room temperature. Following oxidation, the enantiomeric excess (ee) of the monoacetate was determined by HPLC analysis using a column packed with Chiralcel AD (EtOH–hexane, 1:9). Direct column chromatography of the reaction mixture on SiO_2 (10 g, hexane–acetone, 8:1) afforded (+)-**7** (98%) as a colourless solid, which was recrystallised from Pr^i_2O to give an enantiomerically pure

sample [74% from **2** (R^1 = H)], mp 96–97 °C (Found: C, 56.44; H, 6.81; N, 5.54. $C_{12}H_{17}NO_5$ requires C, 56.46; H, 6.71; N, 5.49%); $[\alpha]_D^{25}$ +116.5 (*c* 1.07, $CHCl_3$). The spectral properties (^{1}H, ^{13}C NMR) were identical with those of the racemate.

General procedure for the lipase-mediated hydrolysis of the diacetate 2 (R^1 = Ac)

To a stirred suspension of **2** (R^1 = Ac, 50 mg, 0.17 mmol) in a phosphate buffer (pH 7, 6 cm^3) was added a lipase preparation (100 mg), and the resulting suspension was stirred at 32–35 °C. After extraction of the aqueous layer with CH_2Cl_2 (10 cm^3 × 8), the organic extracts were combined, dried over $MgSO_4$ and evaporated to give an oil, which was fractionated by column chromatography on SiO_2 (10 g, hexane–acetone, 8:1–4:1) to afford the monoacetate. The ee of the monoacetate was determined by the same procedure as that for the product from the transesterification of the diol **2** (R^1 = H). The enantiomerically pure (−)-**7** was obtained in 65% yield from **2** (R^1 = Ac) by recrystallisation twice from Pr^i_2O to afford a colourless solid, mp 96–97 °C (Found: C, 56.69; H, 6.72; N, 5.73. $C_{12}H_{17}NO_5$ requires C, 56.46; H, 6.71; N, 5.49%); $[\alpha]_D^{25}$ −116.1 (*c* 1.09, $CHCl_3$). The spectral properties (^{1}H, ^{13}C NMR) were identical with those of the racemate.

Methyl (+)-8-acetoxy-2-methoxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate (+)-8

To a stirred solution of (+)-**7** (680 mg, 2.67 mmol) in CH_2Cl_2 (20 cm^3) were added $HC(OMe)_3$ (5.3 cm^3, 95.4 mmol), 5 Å mol. sieves and conc. H_2SO_4 (cat.) at 0 °C, and the resulting suspension was stirred for 12 h at room temperature. The reaction was quenched with sat. aqueous $NaHCO_3$ (20 cm^3), and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 3). The organic extracts were combined, washed with H_2O (5 cm^3 × 1), dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (30 g, hexane–acetone, 40:1–10:1) to afford (+)-**8** (617 mg, 86%) as a colourless solid, mp 100–101 °C (Found: C, 57.79; H, 7.17; N, 5.23; M^+, 269.1232. $C_{13}H_{19}NO_5$ requires C, 57.98; H, 7.11; N, 5.20%; *M*, 269.1262); ν_{max}(neat)/cm^{-1} 2953, 2845, 1741, 1703, 1673, 1452, 1415, 1379, 1362, 1346, 1326, 1299, 1282, 1235, 1174, 1153, 1111, 1091, 1067, 1038, 1019 and 976; δ_H 1.64–2.06 (5H, m, 6-, 7-H_2 and one of 4-H_2), 2.02 (3H, s, COMe), 2.50–2.73 (1H, br m, one of 4-H_2), 3.52 (3H, s, OMe), 3.71 (3H, s, CO_2Me), 4.32–4.44 (1H, br m, 5-H) and 4.75–4.81 (3H, br m, 1-, 3- and 8-H); δ_C 21.01 (u), 22.75 (d), 27.70 (d), 30.65 (d), 44.24 (u), 51.01 (u), 52.78 (u), 54.27 (u), 70.64 (u), 94.60 (u), 152.06 (s), 154.98 (s) and 170.45 (s); *m/z* 270 (M^+ + 1) and 69 (M^+, 100%); $[\alpha]_D^{26}$ +109.0 (*c* 1.16, $CHCl_3$).

In a similar manner, the enantiomer (−)-**8** was obtained from (−)-**7** in 86% yield; $[\alpha]_D^{26}$ −108.8 (*c* 0.91, $CHCl_3$).

Dimethyl (+)-3-acetoxy-6-(2-hydroxyethyl)piperidine-1,2-dicarboxylate (+)-1

Through a stirred solution of (+)-**8** (280 mg, 1.04 mmol) in CH_2Cl_2 (10 cm^3) and MeOH (1 cm^3) was bubbled ozone at −78 °C for 30 min, and then $NaBH_4$ (80 mg, 2.08 mmol) was added to the reaction mixture at −78 °C. The resulting suspension was stirred for 1 h at 0 °C, and the reaction was quenched with 10% aqueous AcOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 3). The organic layer and extracts were combined, dried over $MgSO_4$ and evaporated to give a colourless oil which was purified by column chromatography on SiO_2 (15 g, hexane–acetone, 6:1) to afford (+)-**1** (309 mg, 98%) as a colourless oil (Found: M^+, 303.1326. $C_{13}H_{21}NO_7$ requires *M*, 303.1318); ν_{max}(neat)/cm^{-1} 3500, 2956, 1748, 1694, 1560, 1508, 1446, 1405, 1363, 1331, 1238, 1171, 1117, 1086, 1053 and 994; δ_H 1.62–2.10 (6H, br m, 4-, 5-H_2 and $HOCH_2CH_2$), 2.06 (3H, s, COMe), 3.40–3.60 (2H, m, $HOCH_2$), 3.72 and 3.73 (each 3H, each br s, CO_2Me) and 4.88–5.17 (3H, br m, 2-, 3- and 6-H); δ_C 20.83 (u), 21.16 (d), 26.69 (d), 36.66 (d), 46.39 (br, u), 51.99 (u), 53.56 (u), 54.91 (u), 59.00 (d), 68.78 (u), 157.39 (s), 169.94 (s) and 170.01 and 170.06 (each s, due to rotamers); *m/z* 304 (M^+ + 1), 303 (M^+) and 226 (100%); $[\alpha]_D^{26}$ +19.0 (*c* 1.52, $CHCl_3$).

In a similar manner, the enantiomer (−)-**1** was obtained from (−)-**8** in 98% yield; $[\alpha]_D^{26}$ −18.6 (*c* 1.76, $CHCl_3$).

Dimethyl (+)-3-acetoxy-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-piperidine-1,2-dicarboxylate (+)-9

To a stirred solution of (+)-**1** (300 mg, 1.00 mmol) in CH_2Cl_2 (3 cm^3) were added Et_3N (0.40 cm^3, 2.60 mmol), Bu^tPh_2SiCl (0.35 cm^3, 1.30 mmol) and 4-dimethylaminopyridine (DMAP) (12 mg, 0.10 mmol) at 0 °C, and the resulting mixture was stirred for 15 h at room temperature. The reaction mixture was diluted with Et_2O (150 cm^3) and the organic layer was washed with H_2O (5 cm^3 × 2), dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (20 g, hexane–acetone, 30:1 ~ 15:1) to afford (+)-**9** (501 mg, 94%) as a colourless oil (Found: $M^+ - C_4H_9$, 484.1829. $C_{25}H_{30}NO_7Si$ requires $M - C_4H_9$, 484.1867); ν_{max}(neat)/cm^{-1} 3071, 3048, 2998, 2954, 2857, 1960, 1890, 1747, 1704, 1589, 1472, 1444, 1428, 1404, 1362, 1320, 1293, 1236, 1195, 1173, 1111, 1050 and 998; δ_H 1.05 [9H, s, $C(Me)_3$], 1.60–2.10 (6H, m, 4-, 5-H_2 and $SiOCH_2CH_2$), 2.05 (3H, s, COMe), 3.68 (6H, s, CO_2Me × 2), 3.50–3.76 (2H, br, $SiOCH_2$), 4.30–4.43 (1H, br, 6-H), 4.86–4.98 (1H, br m, 2-H), 5.07 (1H, br, 3-H), 7.28–7.45 (6H, m, Ph-H) and 7.52–7.70 (4H, m, Ph-H); δ_C 19.18 (s), 20.92 (u), 20.99 (d), 25.05 (d), 26.79 (u), 35.65 (d), 47.97 and 48.00 (each u, due to rotamers), 51.86 (u), 53.04 (u), 54.87 (u), 61.68 and 61.71 (each d, due to rotamers), 69.07 (u), 127.63 (u), 129.58 (u), 133.76 (s), 135.53 (u), 156.44 (s), 169.94 (s) and 170.06 (s); *m/z* 484 (M^+ − 57) and 424 (100%); $[\alpha]_D^{26}$ +4.19 (*c* 1.52, $CHCl_3$).

In a similar manner, the enantiomer (−)-**9** was obtained from (−)-**1** in 93% yield; $[\alpha]_D^{26}$ −4.2 (*c* 1.80, $CHCl_3$).

Dimethyl (+)-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-3-(methoxymethoxy)piperidine-1,2-dicarboxylate (+)-10

To a stirred solution of (+)-**9** (663 mg, 1.23 mmol) in MeOH (5 cm^3) was added K_2CO_3 (102 mg, 0.74 mmol) at 0 °C, and the resulting suspension was stirred for 50 min at room temperature. The reaction mixture was neutralised with 10% aqueous acetic acid and concentrated. The residue was taken up in hot $CHCl_3$ (10 cm^3 × 5). The organic extracts were combined, dried over $MgSO_4$ and evaporated to give a colourless oil, which was used directly in the next step without further purification. To a stirred solution of the oil obtained above in $CHCl_3$ (10 cm^3) were added MOMCl (0.2 cm^3, 2.45 mmol) and $EtPr^i_2N$ (0.65 cm^3, 3.68 mmol) at 0 °C, and the resulting mixture was refluxed for 2 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 (150 cm^3), and the organic layer was washed with H_2O (5 cm^3 × 2), dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (30 g, hexane–acetone, 40:1–30:1) to afford (+)-**10** [584 mg, 88% from (+)-**9**] as a colourless oil (Found: $M^+ - C_4H_9$, 486.1963. $C_{25}H_{32}NO_7Si$ requires $M - C_4H_9$, 486.1978); ν_{max}(neat)/cm^{-1} 3071, 2953, 2892, 2857, 1747, 1704, 1589, 1444, 1361, 1320, 1297, 1248, 1213, 1194, 1170, 1110, 1041, 1007 and 938; δ_H 1.05 [9H, s, $C(Me)_3$], 1.60–2.15 (6H, br m, 4-, 5-H_2 and $SiOCH_2CH_2$), 3.37 (3H, s, OMe), 3.60–3.74 (2H, br, $SiOCH_2$), 3.68 and 3.69 (each 3H, each s, CO_2Me × 2), 3.80–3.90 (1H, m, 6-H), 4.33–4.42 (1H, br m, MOMOCH), 4.64 and 4.72 (each 1H, ABq, *J* 7, OCH_2O), 5.00 (1H, br, 2-H), 7.30–7.45 (6H, m, Ph-H) and 7.67 (4H, app. d, *J* 7, Ph-H); δ_C 19.18 (s), 21.87 (d), 25.18 (d), 26.78 (u), 35.72 (d), 47.86 (u), 51.70 (u), 52.94 (u), 55.63 (u), 55.99 (u), 61.67 (d), 72.39 (u), 95.20 (d), 127.58 (u), 129.54 (u), 133.80 (s), 135.52 (u), 156.44 (s), 156.84 (s) and 171.01 (s); *m/z* 486 (M^+ − 57) and 488 (100%); $[\alpha]_D^{26}$ +20.3 (*c* 1.94, $CHCl_3$).

In a similar manner, the enantiomer (−)-**10** was obtained from (−)-**9** in 88% yield; $[\alpha]_D^{26}$ −20.3 (*c* 1.82, $CHCl_3$).

Methyl (−)-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-2-hydroxymethyl-3-(methoxymethoxy)piperidine-1-carboxylate (−)-11

To a stirred solution of (+)-**10** (569 mg, 1.05 mmol) in THF (10 cm^3) was added Super-Hydride (1 M solution in THF, 2.6 cm^3) at 0 °C, and the reaction mixture was stirred for 0.5 h at room temperature. To the reaction mixture was added CH_2Cl_2 (150 cm^3), and the organic layer was washed with H_2O (10 cm^3 × 1), dried over $MgSO_4$ and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (15 g, hexane–acetone, 30:1–10:1) to afford (−)-**11** (470 mg, 87%) as a colourless oil (Found: $M^+ - C_4H_9$, 458.2000. $C_{24}H_{32}NO_6Si$ requires $M - C_4H_9$, 458.2001); ν_{max}(neat)/cm^{-1} 3463, 3071, 3049, 2952, 2891, 2858, 1831, 1694, 1589, 1446, 1428, 1409, 1361, 1321, 1221, 1191, 1150, 1109, 1043, 739, 704 and 688; δ_H 1.05 [9H, s, $C(Me)_3$], 1.50–1.83 (6H, br, 4-, 5-H_2 and $SiOCH_2CH_2$), 2.62 (1H, br, OH), 3.39 (3H, s, OMe), 3.40–3.58 (1H, br m, 6-H), 3.59–3.63 (2H, br m, $SiOCH_2$), 3.67 (3H, s, CO_2Me), 3.79–3.87 (0.5H, br m, 2-H due to rotamers), 3.97–4.07 (0.5H, br m, 2-H due to rotamers), 4.26–4.37 (1H, br m, MOMOC*H*), 4.54–4.71 (1H, br, 3-H), 4.68 (2H, s, OCH_2O), 7.32–7.46 (6H, m, Ph-H) and 7.66 (4H, app. d, *J* 6.5, Ph-H); δ_C 19.13 (s), 21.25 (d), 25.90 (d), 26.79 (u), 36.69 (d), 47.33 (u), 52.84 (u), 54.60 (u), 55.71 (u), 61.85 (d), 62.66 (d), 74.93 (u), 95.01 (d), 127.65 (u), 129.64 (u), 133.63 (s), 135.53 (u) and 157.95 (s); *m/z* 458 ($M^+ - 57$) and 366 (100%); $[\alpha]_D^{26}$ −7.2 (*c* 1.77, $CHCl_3$).

In a similar manner, the enantiomer (+)-**11** was obtained from (−)-**10** in 85% yield; $[\alpha]_D^{26}$ +7.1 (*c* 2.26, $CHCl_3$).

Methyl (+)-6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-2-(1,3-dithiolan-2-yl)-3-(methoxymethoxy)piperidine-1-carboxylate (+)-12

To a stirred suspension of PCC (170 mg, 0.78 mmol) and AcONa (130 mg, 1.55 mmol) in CH_2Cl_2 (3 cm^3) was added (−)-**11** (200 mg, 0.388 mmol) in CH_2Cl_2 (2 cm^3), and the resulting suspension was stirred for 3 h at room temperature. Direct column chromatography of the reaction mixture on SiO_2 (10 g, hexane–acetone, 30:1–20:1) gave the aldehyde (185 mg, 93%) as a colourless paste, which was immediately used in the next step. To a stirred solution of the aldehyde obtained above (185 mg, 0.36 mmol) in CH_2Cl_2 (10 cm^3) were added 3 Å molecular sieves, ethane-1,2-dithiol (0.044 cm^3, 0.525 mmol) and $BF_3{\cdot}Et_2O$ (0.044 cm^3, 0.36 mmol) at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. The reaction was quenched with sat. aqueous $NaHCO_3$ (3 cm^3) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 3), and the organic layer and extracts were combined, dried over $MgSO_4$ and evaporated to give a pale green oil, which was purified by column chromatography on SiO_2 (10 g, hexane–acetone, 40:1–20:1) to afford (+)-**12** (144 mg, 68%) as a colourless paste (Found: $M^+ - C_4H_9$, 532.1664. $C_{26}H_{34}NO_5S_2Si$ requires $M - C_4H_9$, 532.1647); ν_{max}(neat)/cm^{-1} 2931, 1700, 1442, 1400, 1304, 1152, 1109, 1040, 931, 824, 738 and 703; δ_H 1.06 [9H, s, $C(Me)_3$], 1.52–1.74 (5H, br, 4-, 5-H_2 and one of $SiOCH_2CH_2$), 2.02–2.20 (1H, br, one of $SiOCH_2CH_2$), 3.01–3.32 (4H, br m, SCH_2CH_2S), 3.40 (3H, s, OMe), 3.69 (3H, s, CO_2Me), 3.60–3.78 (2H, br, $SiOCH_2$), 3.80–3.91 (1H, m, 6-H), 4.34–4.47 (1H, br, 2-H), 4.62 (1H, d, *J* 7, SCHS), 4.68–4.82 (3H, br m, OCH_2O and MOMOC*H*), 7.32–7.46 (6H, m, Ph-H) and 7.61–7.72 (4H, m, Ph-H); δ_C 19.15 (s), 21.95 (d), 25.71 (d), 26.78 (u), 36.31 (d), 37.65 (d), 39.59 (d), 47.21 (u), 52.88 (u), 53.83 (u), 55.73 (u), 58.61 (u), 61.49 (d), 73.17 (u), 95.08 (d), 127.80 (u), 129.57 (u), 133.70 (s), 135.54 (u) and 157.41 (s); *m/z* 532 ($M^+ - 57$) and 140 (100%); $[\alpha]_D^{26}$ +39.8 (*c* 1.78, $CHCl_3$).

In a similar manner, the enantiomer (−)-**12** was obtained from (+)-**11** in 68% yield; $[\alpha]_D^{26}$ −39.8 (*c* 2.05, $CHCl_3$).

Methyl 6-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate 13

To a stirred solution of (+)-**12** (144 mg, 0.244 mmol) in EtOH (2 cm^3) was added freshly prepared Raney nickel (W-4), and the resulting suspension was refluxed for 2 h. After cooling, the catalyst was removed by filtration, and the filtrate was evaporated to give **13** (116 mg, 95%) as an essentially pure colourless paste, which was used directly in the next step; ν_{max}(neat)/cm^{-1} 2950, 1699, 1443, 1307, 1148, 1111, 1044, 919 and 824; δ_H 1.05 [9H, s, $C(Me)_3$], 1.15 (3H, d, *J* 7, 2-Me), 1.53–1.90 (6H, br m, 4-, 5-H_2 and $SiOCH_2CH_2$), 3.37 (3H, s, OMe), 3.64 (3H, s, CO_2Me), 3.54–3.73 (3H, br, $SiOCH_2$ and 6-H), 4.20–4.29 (1H, br, 2-H), 4.41–4.54 (1H, br, MOMOC*H*), 4.66 (2H, br s, OCH_2O), 7.31–7.43 (6H, m, Ph-H) and 7.59–7.72 (4H, m, Ph-H); *m/z* 442 ($M^+ - 57$), 135 (100%) [Calc. for $C_{24}H_{32}NO_5Si$ ($M^+ - C_4H_9$), 442.2049. Found: ($M - C_4H_9$), 442.2060].

Methyl (+)-6-(2-hydroxyethyl)-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate (+)-14

To a stirred solution of **13** (116 mg, 0.232 mmol) in THF (3 cm^3) was added Bu^n_4NF (1 M solution in THF, 0.25 cm^3, 0.25 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. aqueous NH_4Cl (1 cm^3). The aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 4), and the organic extracts were combined, dried over $MgSO_4$ and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (5 g, hexane–acetone, 15:1–10:1) to afford (+)-**14** (42 mg, 85%) as a colourless oil (Found: M^+, 261.1599. $C_{12}H_{23}NO_5$ requires *M*, 261.1576); ν_{max}(neat)/cm^{-1} 3447, 2949, 1670, 1448, 1406, 1353, 1314, 1147, 1087 and 1041; δ_H 1.14 (3H, d, *J* 7, 2-Me), 1.55–1.97 (6H, br m, 4-, 5-H_2 and $HOCH_2CH_2$), 3.39 (3H, s, OMe), 3.41–3.52 (1H, br, OH), 3.53–3.80 (3H, br m, 6-H and $HOCH_2$), 3.74 (3H, s, OMe), 4.26–4.33 (1H, br, 2-H), 4.46–4.55 (1H, br, MOMOC*H*) and 4.69 (2H, s, OCH_2O); δ_C 14.45 (u), 20.77 (d), 28.09 (d), 37.65 (d), 46.14 (u), 49.25 (u), 53.13 (u), 55.55 (u), 58.97 (d), 74.54 (u), 95.05 (d) and 157.50 (s); *m/z* 262 ($M^+ + 1$), 261 (M^+), 246 ($M^+ - 15$) and 84 (100%); $[\alpha]_D^{26}$ +30.5 (*c* 1.00, $CHCl_3$).

In a similar manner, the enantiomer (−)-**14** was obtained from the enantiomer of **13** in 88% yield; $[\alpha]_D^{26}$ −30.7 (*c* 0.71, $CHCl_3$).

Methyl (+)-1-methoxycarbonyl-5-(methoxymethoxy)-6-methylpiperidine-2-ethanoate (+)-15

To a stirred solution of (+)-**15** (42 mg, 0.197 mmol) in *N*,*N*-dimethylformamide (1 cm^3) was added PDC (445 mg, 1.182 mmol), and the resulting suspension was stirred for 18 h at room temperature. To the reaction mixture were added H_2O (5 cm^3) and 10% aqueous HCl (0.5 cm^3), and the aqueous layer was extracted with Et_2O (10 cm^3 × 5). The organic extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil. To a solution of the oil obtained above in Et_2O (10 cm^3) was added an ethereal solution of CH_2N_2 at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. The solvent was removed to give a pale yellow oil, which was purified by column chromatography on SiO_2 (5 g, hexane–acetone, 10:1) to afford (+)-**15** (38 mg, 66%) as a colourless oil (Found: M^+, 289.1511. $C_{13}H_{23}NO_6$ requires *M*, 289.1524); ν_{max}(neat)/cm^{-1} 2989, 2951, 2824, 1738, 1698, 1444, 1319, 1300, 1081 and 1043; δ_H 1.16 (3H, d, *J* 7, 6-Me), 1.70–1.81 (4H, br, 3- and 4-H_2), 2.51 (1 H, dd, *J* 15 and 4.5, one of MeO_2CCH_2), 2.65 (1H, dd, *J* 15 and 10, one of MeO_2CCH_2), 3.38 (3H, s, OMe), 3.68 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 4.43–4.52 (2H, m, 2- and 6-H), 4.54–4.63 (1H, br, MOMOC*H*) and 4.67 (2H, s, $MeOCH_2O$); δ_C 14.35 (u), 20.27 (d), 26.71 (d), 38.77 (d), 46.48 (u), 49.11 (u), 51.64 (u), 52.75 (u), 55.47 (u), 74.15 (u), 94.91 (d), 156.05 (s) and 171.62 (s); *m/z* 290 ($M^+ + 1$), 289 (M^+) and 154 (100%); $[\alpha]_D^{26}$ +2.81 (*c* 0.88, $CHCl_3$).

Methyl 1-methoxycarbonyl-6-methyl-1,2,3,6-tetrahydropyridine-2-ethanoate 16

To a stirred solution of (+)-**15** (38 mg, 0.130 mmol) in MeOH (1 cm^3) was added conc. aqueous HCl (1 drop) at 0 °C, and the reaction mixture was refluxed for 1 h. After cooling, the mixture was neutralised with sat. aqueous $NaHCO_3$ and the volatiles were removed. The residue was extracted with CH_2Cl_2 (10 cm^3 × 3), and the organic extracts were combined, dried over $MgSO_4$ and evaporated to afford the alcohol, which was essentially pure and used directly in the next step. To a stirred solution of the alcohol obtained above in CH_2Cl_2 (0.5 cm^3) were added CH_3SO_2Cl (0.03 cm^3, 0.39 mmol) and pyridine (0.053 cm^3, 0.65 mmol) at 0 °C, and the mixture was stirred for 14 h at room temperature. The mixture was diluted with CH_2Cl_2 (50 cm^3) and the organic layer was washed with H_2O (5 cm^3 × 1), dried over $MgSO_4$ and evaporated to give the methanesulfonate as a colourless oil, which was used in the next step without further purification. To a stirred solution of the methanesulfonate obtained above in toluene (0.5 cm^3) was added DBU (0.2 cm^3, 1.3 mmol), and the reaction mixture was refluxed for 36 h. After cooling, the mixture was diluted with benzene (50 cm^3), and the organic layer was washed with H_2O (1 cm^3 × 2), 10% aqueous HCl (1 cm^3 × 1) and H_2O (1 cm^3 × 2), dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (5 g, hexane–acetone, 50 : 1–40 : 1) to afford **16** [14.2 mg, 48% from (+)-**15**] as a colourless oil (Found: M^+, 227.1173. $C_{11}H_{17}NO_4$ requires *M*, 227.1157); δ_H 1.25 (3H, d, *J* 7, 6-Me), 2.04 (1H, app. dd, *J* 17.5 and 6, 3-H), 2.40 (1H, app. br d, *J* 17.5, 3-H), 2.52 (1H, dd, *J* 15.5 and 7, one of MeO_2CCH_2), 2.63 (1H, dd, *J* 15.5 and 9, one of MeO_2CCH_2), 3.68 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 4.32–4.44 (1H, br, 2-H), 4.84–4.97 (1H, br, 6-H) and 5.58–5.75 (2H, br m, OCH_2O); *m/z* 228 ($M^+ + 1$) and 227 (M^+).

Methyl (−)-1-methoxycarbonyl-6-methylpiperidine-2-ethanoate (−)-17

To a stirred solution of **16** (14 mg, 0.0624 mmol) in MeOH (0.5 cm^3) was added 5% Pd–C (10 mg), and the suspension was stirred for 5 h at room temperature under a hydrogen atmosphere. After filtration of the suspension through a Celite pad, the catalyst on the pad was washed with CH_2Cl_2 (5 cm^3 × 5). The filtrate and washings were combined and evaporated to give an oil, which was purified by column chromatography on SiO_2 (1 g, hexane–acetone, 60 : 1) to afford (−)-**17** (11 mg, 80%) as a colourless oil. The spectral data (^{1}H NMR, IR and mass) of the synthetic sample of (−)-**17** were completely identical with those for the authentic specimen;[17] $[\alpha]_D^{26}$ −40.0 (*c* 0.50, $CHCl_3$) {lit.,[17] $[\alpha]_D^{26}$ −38.9 (*c* 0.50, $CHCl_3$)}.

Methyl 6-(dodeca-2,11-dienyl)-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate 18

To a stirred solution of $(COCl)_2$ (0.072 cm^3, 0.85 mmol) in CH_2Cl_2 (3 cm^3) was added dimethyl sulfoxide (DMSO) (0.12 cm^3, 1.69 mmol) at −78 °C, and the mixture was stirred for 5 min. To the mixture was added a solution of (+)-**14** (100 mg, 0.38 mmol) in CH_2Cl_2 (3 cm^3) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.36 cm^3, 2.60 mmol) was added to the mixture at −78 °C, and the resulting mixture was warmed to 0 °C for 1 h and then diluted with H_2O (20 cm^3) and Et_2O (50 cm^3). The aqueous layer was extracted with Et_2O (10 cm^3 × 4), and the organic extracts were combined, dried over $MgSO_4$ and evaporated to give the aldehyde, a pale yellow oil, which was used directly in the next step. To a stirred suspension of $CH_2{=}CH(CH_2)_7P^+Ph_3Br^-$ (400 mg, 0.84 mmol) in THF (5 cm^3) was added Bu^{n}Li (10% in hexane, 0.46 cm^3, 0.72 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the orange solution was added a solution of the aldehyde obtained above in THF (5 cm^3) at 0 °C, and the suspension was stirred at room temperature for 2 h. The reaction was quenched with H_2O (5 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 4). The organic extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (10 g, hexane–acetone, 70 : 1–60 : 1) to afford **18** [126 mg, 86% from (+)-**14**] as a pale yellow oil (Found: M^+, 381.2898. $C_{22}H_{39}NO_4$ requires *M*, 381.2877); ν_{max}(neat)/cm^{-1} 3075, 2927, 2854, 1699, 1654, 1640, 1443, 1401, 1376, 1350, 1319, 1281, 1245, 1218, 1189, 1146, 1108, 1078, 1043, 1022, 990, 917 and 774; δ_H 1.17 (3H, d, *J* 7, 2-Me), 1.20–1.42 (10H, br, C_6-sidechain-CH_2), 1.48–1.79 (4H, br m, 4- and 5-H_2), 1.94–2.07 (4H, br m, =CHCH_2 × 2), 2.10–2.25 (1H, br m, one of 6-CH_2), 2.33–2.47 (1H, br m, one of 6-CH_2), 3.37 (3H, s, OMe), 3.60–3.71 [4H, br m, including δ 3.69 (3H, s), 6-H and CO_2Me], 4.01–4.12 (1H, br, 2-H), 4.42–4.53 (1H, br, MOMOC*H*), 4.66 (2H, s, OCH_2O), 4.88–5.03 (2H, m, CH_2=CH), 5.24–5.34 (1H, br m, C*H*=CH), 5.39–5.50 (1H, br m, C*H*=CH) and 5.80 (1H, ddt, *J* 17, 10 and 6.5, CH_2=C*H*); *m/z* 382 ($M^+ + 1$), 381 (M^+), 320 ($M^+ - 61$) and 217 (100%).

Methyl 3-(methoxymethoxy)-2-methyl-6-(11-oxododec-2-enyl)-piperidine-1-carboxylate 19

To a stirred solution of **18** (25 mg, 0.066 mmol) in DMF (0.6 cm^3) and H_2O (0.2 cm^3) were added CuCl (8 mg, 0.079 mmol) and $PdCl_2$ (2.5 mg, 0.013 mmol) at room temperature, and the resulting suspension was stirred at room temperature for 11 h under an oxygen atmosphere. The reaction was quenched with sat. aqueous $NaHCO_3$ (5 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 4). The organic extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (5 g, hexane–acetone, 20 : 1) to afford **19** (18.3 mg, 70%) as a colourless oil (Found: M^+, 397.2801. $C_{22}H_{39}NO_5$ requires *M*, 397.2826); ν_{max}(neat)/cm^{-1} 2926, 2854, 1699, 1654, 1560, 1543, 1508, 1443, 1404, 1351, 1319, 1146, 1107, 1080 and 1042; δ_H 1.18 (3H, d, *J* 7, 2-Me), 1.22–1.40 (8H, br s, C_6-sidechain-CH_2), 1.50–1.77 (6H, br m, C_6-sidechain-CH_2, 4- and 5-H_2), 1.97–2.26 [6H, br m, including δ 2.13 (3H, s), =CHCH_2, one of C(O)-CH=CHCH_2 and C(O)Me], 2.41 [3H, app. t, *J* 7.5, 6-CH_2 and one of $C(O)CH_2$], 3.38 (3H, s, OMe), 3.62–3.73 [4H, br m, including δ 3.70 (3H, s, 6-H and CO_2Me)], 4.03–4.14 (1H, br, 2-H), 4.40–4.54 (1H, br, MOMOC*H*), 4.67 (2H, s, OCH_2O), 5.22–5.34 (1H, br m, C*H*=CH) and 5.39–5.49 (1H, br m, C*H*=CH); *m/z* 398 ($M^+ + 1$), 397 (M^+) and 217 (100%).

Methyl (+)-3-(methoxymethoxy)-2-methyl-6-(11-oxododecyl)-piperidine-1-carboxylate (+)-20

To a stirred solution of **19** (76 mg, 0.19 mmol) in MeOH (3 cm^3) was added 5% Pd–C (15 mg), and the suspension was stirred at room temperature for 7 h under a hydrogen atmosphere. The catalyst was removed by filtration through a Celite pad, and the catalyst was washed with CH_2Cl_2 (10 cm^3 × 5). The filtrate and washings were combined and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (10 g, hexane–acetone, 20 : 1) to afford (+)-**20** (70 mg, 92%) as a colourless oil (Found: M^+, 399.3001. $C_{22}H_{41}NO_5$ requires *M*, 399.2985); ν_{max}(neat)/cm^{-1} 2925, 2853, 1698, 1560, 1444, 1406, 1352, 1308, 1246, 1145, 1094 and 1043; δ_H 1.14 (3H, d, *J* 7, 2-Me), 1.15–1.27 (15H, br s, C_6-sidechain-CH_2), 1.38–1.70 (7H, br m, C_6-sidechain-CH_2, 4- and 5-H_2), 2.12 [3H, s, C(O)Me], 2.40 [2H, app. t, *J* 7, $C(O)CH_2$], 3.37 (3H, s, OMe), 3.55–3.68 [4H, br m, including δ 3.68 (3H, s), 6-H and CO_2Me], 3.95–4.08 (1H, br, 2-H), 4.36–4.48 (1H, br, MOMOC*H*) and 4.66 (2H, s, OCH_2O); δ_C 14.24 and 14.28 (each u, due to rotamers), 20.54 (d), 23.74 (d), 26.29 (d), 26.36 (d), 27.28 (d), 29.05 (d), 29.26 (d), 29.30 (d), 29.41 (d), 29.67 (d), 29.73 (u), 34.67 (d), 43.67 (d), 49.07 (u), 49.95 (u), 52.36 and 52.39 (each u, due to rotamers), 55.32 and 55.37 (each u, due to rotamers), 74.61 (u), 94.78 (d), 156.39 (s) and 209.11 (s); *m/z* 400 ($M^+ + 1$), 399 (M^+) and 154 (100%); $[\alpha]_D^{26}$ +22.2 (*c* 0.57, $CHCl_3$).

(−)-Cassine

To a stirred solution of (+)-**20** (60 mg, 0.15 mmol) in $CHCl_3$ (5 cm^3) was added Me_3SiI (0.1 cm^3, 0.66 mmol) at 0 °C, and the reaction mixture was refluxed for 24 h. After cooling, the reaction was quenched with 10% $Na_2S_2O_3$ in sat. aqueous $NaHCO_3$ (10 cm^3) and the aqueous layer was extracted with $CHCl_3$ (10 cm^3 × 5). The organic layer and extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was purified by column chromatography on Al_2O_3 (20 g, $CHCl_3$–EtOH, 100:1) to afford (−)-cassine (28 mg, 65%) as a colourless solid, mp 55–57 °C (lit.,[18a] mp 57–58.5 °C) (Found: M^+, 297.2644. $C_{18}H_{35}NO_2$ requires *M*, 297.2666); $\nu_{max}(CCl_4)/cm^{-1}$ 3550, 3520, 2950, 2870, 1722, 1515, 1440, 1385, 1357, 1320, 1164 and 968; δ_H 1.10 (3H, d, *J* 6.5, 2-Me), 1.16–1.40 (16H, br s, C_6-sidechain-CH_2), 1.45–1.64 (5H, br m, one of C_6-sidechain-CH_2, 4- and 5-H_2), 1.90 (1H, dm, *J* 14, one of C_6-sidechain-CH_2), 2.13 [3H, s, C(O)Me], 2.41 [2H, t, *J* 7, C(O)CH_2], 2.47–2.60 (1H, br, 6-H), 2.75 (1H, qd, *J* 6.5 and 1.5, 2-H) and 3.54 (1H, br s, 3-H); δ_C 18.62 (u), 23.84 (d), 25.77 (d), 26.03 (d), 29.14 (d), 29.34 (d), 29.40 (d), 29.47 (d), 29.51 (d), 29.76 (u), 32.03 (d), 36.90 (d), 43.78 (d), 55.81 (u), 57.22 (u), 67.97 (u) and 209.31 (s); *m/z* 298 ($M^+ + 1$), 297 (M^+), 240 ($M^+ - 57$) and 69 (100%); $[\alpha]_D^{26}$ −0.7 (*c* 0.59, EtOH) {lit.,[18a] $[\alpha]_D^{25}$ −0.6 (*c* 8.0, EtOH)}.

Methyl 3-(methoxymethoxy)-2-methyl-6-(tetradeca-2,13-dienyl)piperidine-1-carboxylate 21

To a stirred solution of $(COCl)_2$ (0.072 cm^3, 0.85 mmol) in CH_2Cl_2 (3 cm^3) was added DMSO (0.12 cm^3, 1.69 mmol) at −78 °C, and the mixture was stirred for 5 min. To the mixture was added a solution of (−)-**14** (100 mg, 0.38 mmol) in CH_2Cl_2 (3 cm^3) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.36 cm^3, 2.60 mmol) was then added at −78 °C, and the resulting mixture was warmed to 0 °C for 1 h, and then diluted with H_2O (20 cm^3) and Et_2O (50 cm^3). The organic layer was separated and the aqueous layer was extracted with Et_2O (10 cm^3 × 4). The organic layer and extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred suspension of $CH_2{=}CH(CH_2)_9P^+Ph_3Br^-$ (487 mg, 0.96 mmol) in THF (5 cm^3) was added Bu^{n}Li (10% in hexane, 0.54 cm^3, 0.84 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the orange solution was added a solution of the crude aldehyde obtained above in THF (5 cm^3) at 0 °C, and the suspension was stirred at room temperature for 2 h. The reaction was quenched with H_2O (5 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 4). The organic layer and extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (10 g, hexane–acetone, 70:1–60:1) to afford **21** (120 mg, 77%) as a pale yellow oil (Found: M^+, 409.3204. $C_{24}H_{43}NO_4$ requires *M*, 409.3192); ν_{max}(neat)/cm^{-1} 3070, 2926, 2853, 1700, 1654, 1640, 1443, 1401, 1319, 1147, 1108, 1079 and 1043; δ_H 1.18 (3H, d, *J* 7, 2-Me), 1.20–1.43 (14H, br, C_6-sidechain-CH_2), 1.50–1.81 (4H, br m, 4- and 5-H_2), 1.92–2.09 (4H, br m, =CHCH_2 × 2), 2.10–2.26 (1H, br m, one of 6-CH_2), 2.36–2.52 (1H, br m, one of 6-CH_2), 3.38 (3H, s, OMe), 3.61–3.73 [4H, br m, including δ 3.70 (3H, s), 6-H and CO_2Me], 4.01–4.12 (1H, br, 2-H), 4.42–4.55 (1H, br, MOMOC*H*), 4.67 (2H, s, OCH_2O), 4.90–5.05 (2H, m, CH_2=CH), 5.24–5.34 (1H, br m, C*H*=CH), 5.40–5.51 (1H, br m, C*H*=CH) and 5.81 (1H, ddt, *J* 17, 10 and 6.5, CH_2=C*H*); *m/z* 410 ($M^+ + 1$), 409 (M^+), 348 ($M^+ - 61$) and 55 (100%).

Methyl 3-(methoxymethoxy)-2-methyl-6-(13-oxotetradec-2-enyl)piperidine-1-carboxylate 22

To a stirred solution of **21** (110 mg, 0.27 mmol) in DMF (3 cm^3) and H_2O (1 cm^3) were added CuCl (32 mg, 0.32 mmol) and $PdCl_2$ (10 mg, 0.05 mmol) at room temperature and the resulting suspension was stirred at room temperature for 16 h under an oxygen atmosphere. The reaction was quenched with sat. aqueous $NaHCO_3$ (10 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 4). The combined CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (10 g, hexane–acetone, 20:1) to afford **22** (90 mg, 75%) as a colourless oil (Found: M^+, 425.3093. $C_{24}H_{43}NO_5$ requires *M*, 425.3140); ν_{max}(neat)/cm^{-1} 2926, 2854, 1699, 1654, 1560, 1543, 1508, 1443, 1404, 1351, 1319, 1146, 1107, 1080 and 1042; δ_H 1.18 (3H, d, *J* 7, 2-Me), 1.22–1.40 (15H, br s, C_6-sidechain-CH_2, 4- and 5-H), 1.66–1.79 (3H, br m, C_6-sidechain-CH_2), 1.97–2.09 (2H, br m, =CHCH_2), 2.11–2.26 [4H, br m, including δ 2.13 (3H, s), one of 6-CH_2 and C(O)Me], 2.41 [3H, app. t, *J* 7.5, one of 6-CH_2 and C(O)CH_2], 3.38 (3H, s, OMe), 3.62–3.77 [4H, br m, including δ 3.70 (3H, s), 6-H and CO_2Me], 4.03–4.14 (1H, br, 2-H), 4.45–4.54 (1H, br, MOMOC*H*), 4.67 (2H, s, OCH_2O), 5.27–5.36 (1H, br m, C*H*=CH) and 5.40–5.51 (1H, br m, C*H*=CH); *m/z* 426 ($M^+ + 1$), 425 (M^+) and 154 (100%).

Methyl (−)-6-(13-oxotetradecyl)-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate (−)-23

To a stirred solution of **22** (80 mg, 0.19 mmol) in MeOH (3 cm^3) was added 5% Pd–C (10 mg) and the suspension was stirred at room temperature for 7 h under a hydrogen atmosphere. The catalyst was removed by filtration through a Celite pad, and the catalyst was washed with CH_2Cl_2 (10 cm^3 × 5). The filtrate and washings were combined and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (10 g, hexane–acetone, 20:1) to afford (−)-**23** (78 mg, 97%) as a colourless oil (Found: M^+, 427.3291. $C_{24}H_{45}NO_5$ requires *M*, 427.3295); ν_{max}(neat)/cm^{-1} 2925, 2853, 1698, 1560, 1444, 1406, 1352, 1308, 1246, 1145, 1094 and 1043; δ_H 1.12 (3H, d, *J* 7, 2-Me), 1.15–1.31 (19H, br s, C_6-sidechain-CH_2), 1.40–1.74 (7H, br m, C_6-sidechain-CH_2, 4- and 5-H_2), 2.09 [3H, s, C(O)Me], 2.38 [2H, app. t, *J* 7, C(O)CH_2], 3.34 (3H, s, OMe), 3.55–3.68 [4H, br m, including δ 3.65 (3H, s), 6-H and CO_2Me], 3.97–4.10 (1H, br, 2-H), 4.39–4.51 (1H, br, MOMOC*H*) and 4.63 (2H, s, OCH_2O); δ_C 14.27 (u), 20.54 (d), 23.75 (d), 26.27 (d), 27.31 (d), 29.06 (d), 29.15 (d), 29.28 (d), 29.34 (d), 29.47 (d), 29.73 (u), 34.67 (d), 43.70 (d), 49.05 (u), 49.95 (u), 52.40 (u), 55.36 (u), 74.59 (u), 94.77 (d), 156.42 (s) and 209.25 (s); *m/z* 428 ($M^+ + 1$), 427 (M^+) and 102 (100%); $[\alpha]_D^{26}$ −19.4 (*c* 3.87, $CHCl_3$).

(+)-Spectaline

To a stirred solution of (−)-**23** (70 mg, 0.16 mmol) in $CHCl_3$ (5 cm^3) was added Me_3SiI (0.1 cm^3, 0.66 mmol) at 0 °C, and the reaction mixture was refluxed for 23 h. After cooling, the reaction was quenched with 10% $Na_2S_2O_3$ in sat. aqueous $NaHCO_3$ (10 cm^3) and the aqueous layer was extracted with $CHCl_3$ (10 cm^3 × 5). The organic layer and extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was purified by column chromatography on Al_2O_3 (20 g, $CHCl_3$–EtOH, 100:1) to afford (+)-spectaline (38 mg, 70%) as a colourless solid, mp 59–61 °C, lit.,[7] mp 118 °C for the (−)-enantiomer (Found: M^+, 325.2991. $C_{20}H_{39}NO_2$ requires *M*, 325.2979); ν_{max}(KBr)/cm^{-1} 3323, 2918, 2850, 1709, 1524, 1466, 1436, 1372, 1261, 1225, 1210, 1164, 1078, 1009 and 995; δ_H 1.08 (3H, d, *J* 6.5, 2-Me), 1.20–1.35 (21H, br, C_6-sidechain-CH_2), 1.42–1.58 (4H, br m, 4- and 5-H_2), 1.85–1.90 (1 H, br m, OH), 2.12 [3H, s, C(O)Me], 2.40 [2H, t, *J* 7.5 C(O)CH_2], 2.49–2.54 (1H, m, 6-H), 2.73 (1H, qd, *J* 7 and 1, 2-H) and 3.52 (1H, br s, 3-H); δ_C 18.73 (u), 23.81 (d), 25.78 (d), 26.19 (d), 28.38 (d), 29.13 (d), 29.36 (d), 29.42 (d), 29.49 (d), 29.54 (d), 29.57 (d), 29.61 (d), 29.75 (d), 29.77 (d), 29.83 (u), 32.05 (d), 37.05 (d), 43.79 (d), 55.72 (u), 57.15 (u), 68.01 (u) and 209.47 (s); *m/z* 326 ($M^+ + 1$), 325 (M^+) and 115 (100%); $[\alpha]_D^{26}$ +9.0 (*c* 1.3, $CHCl_3$) {lit.,[19] $[\alpha]_D^{25}$ +8.0 (*c* 0.27, $CHCl_3$); lit.,[5c] $[\alpha]_D^{25}$ −8.2 (*c* 0.32, $CHCl_3$) for the (−)-enantiomer}.

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