Bicyclo[3.3.1]nonanes as synthetic intermediates. Part 19.[1] Asymmetric cleavage of ω-azabicyclo[3.*n*.1]alkan-3-ones at the 'fork head'

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Asymmetric cleavage of ω-azabicyclo[3.*n*.1]alkan-3-ones was achieved by asymmetric deprotonation at the 'fork head' ketone system with Koga's chiral base and subsequent ozonolysis of the resulting chiral silyl enol ether to give the *cis*-α,α′-disubstituted piperidine, pyrrolidine and hexahydroazepine, respectively, in high enantiomeric excess.

Introduction

There have been isolated, from natural sources, a number of piperidines[2] bearing carbonaceous substituents at both the α and α′ positions in a *cis* mode and also pyrrolizidines or indolizidines[3] where the relative stereochemistry at the bridgehead and either of the other two α-nitrogenous positions, *i.e.* C-3 and C-5, is of a *cis* configuration.

Of the potential strategies available to construct these ring systems, cyclisation to form α,α′-disubstituted pyrrolidine systems by intramolecular attack of nitrogenous species upon an olefinic linkage is known to afford products with a *trans* disposition;[4] further, the construction of the indolizidine skeleton starting with a piperidine compound which undergoes cyclisation between the ring nitrogen and the ring substituent at the α position is known to afford a mixture of stereoisomers where the bridgehead hydrogen and the substituent at C-3 are in both *cis* and *trans* configurations, although products with the former stereochemistry predominate.[5]

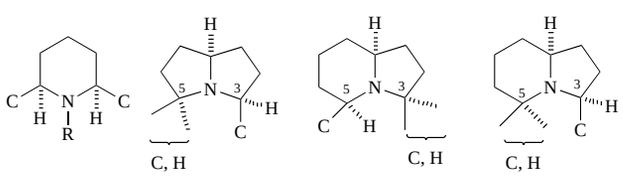

Fig. 1

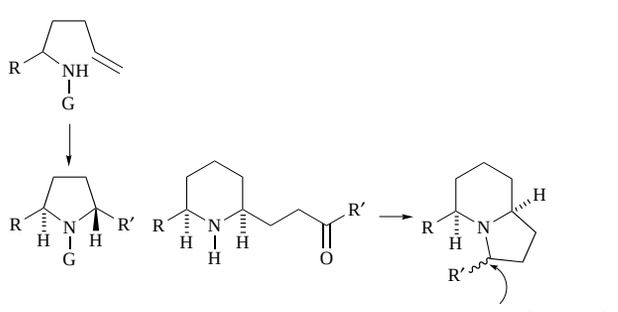

Fig. 2

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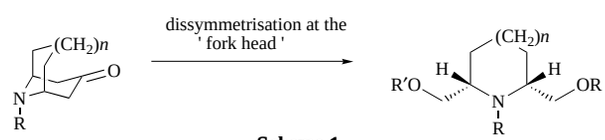
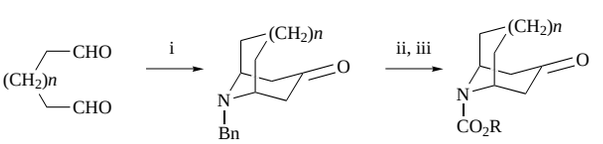
Nevertheless, several methods have been developed for the stereoselective construction of these molecules.[6] As part of our effort aimed at the use of the nitrogen-bridged bicyclic system for the stereoselective construction of nitrogen heterocycles, we examined the α-ketonic cleavage of the piperidone system embodied in the σ-symmetric rigid twin-ring system, ω-azabicyclo[3.*n*.1]alkan-3-one. Here the α- and α′-nitrogenous carbon linkages are forced to form a *cis* configuration, and we found that asymmetric enolisation of the 'fork head' ketone by Koga's protocol[7] and subsequent ozonolysis of the resulting chiral enol ether afforded *cis*-α,α′-disubstituted nitrogen heterocycles in high enantiomeric excess. This paper describes a full account of our experimental work.[8]



Scheme 1

Results and discussion

The starting materials, the azabicyclic ketones **1**–**3**, were prepared in 50–78% yields *via* the *N*-benzyl derivatives **4**–**6**, prepared by a known procedure;[9,10] asymmetric enolisation of the ketones **1**–**3** according to Koga's protocol was then examined.



n = 0,1,2

4 *n* = 1 (78%)
5 *n* = 0 (78%)
6 *n* = 2 (50%)

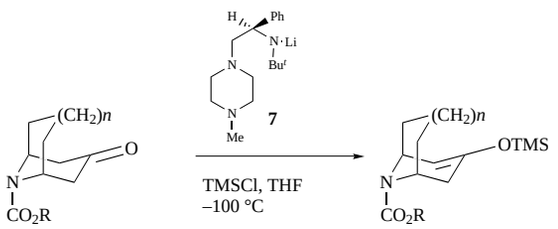
1 *n* = 1, R = Me (91%)
2 *n* = 0, R = Bn (91%)
3 *n* = 2, R = Bn (90%)

Scheme 2 *Reagents and conditions:* i, benzylamine·HCl, acetonedicarboxylic acid; ii, H_2, 5% Pd–C, AcOH, 60 °C; iii, $ClCO_2Me$ or $ClCO_2Bn$, aq. K_2CO_3–CH_2Cl_2

Asymmetric enolisation of the azabicyclic 'fork head' ketones 1–3

First, we examined the asymmetric deprotonation of methyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate **1** with Koga's

chiral lithium amide **7** in the presence of chlorotrimethylsilane (TMSCl) at −100 °C to give the desired silyl enol ether **8** in 94% yield. Similarly, asymmetric enolisation of benzyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate **2** and benzyl 3-oxo-10-azabicyclo[4.3.1]decane-10-carboxylate **3** by the same procedure gave the silyl enol ethers **9** (89%) and **10** (75%).



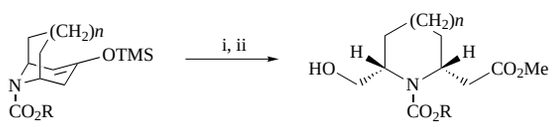
1 *n* = 1, R = Me
2 *n* = 0, R = Bn
3 *n* = 2, R = Bn

8 *n* = 1 (94%)
9 *n* = 0 (89%)
10 *n* = 2 (75%)

Scheme 3

Transformation of the chiral enol ethers 8–10 into the α,α′-bifunctionalised *cis*-disubstituted piperidine 11, pyrrolidine 12 and hexahydroazepine 13 and determination of their enantiomeric excesses (ee)

Ozonisation of the chiral enol ethers **8**–**10** and subsequent esterification of the products with diazomethane gave the α,α′-bifunctionalised *cis*-disubstituted piperidine **11** (60%), pyrrolidine **12** (60%) and hexahydroazepine **13** (75%). The ee values for these, 93, 90 and 90% respectively, were determined by high-performance liquid chromatography (HPLC) analysis[11] using a chiral column.



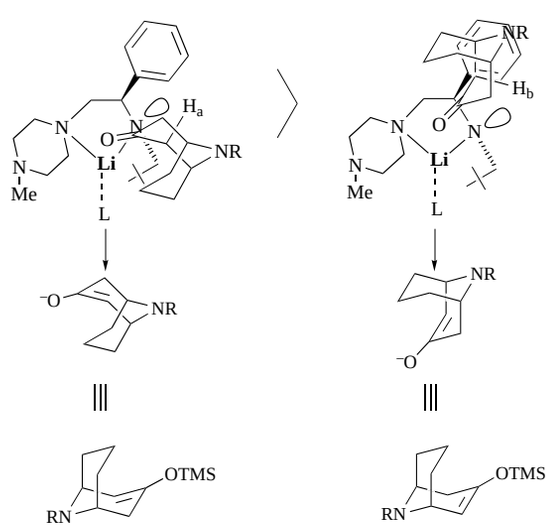
8 *n* = 1, R = Me
9 *n* = 0, R = Bn
10 *n* = 2, R = Bn

11 *n* = 1, R = Me (60%)
12 *n* = 0, R = Bn (60%)
13 *n* = 2, R = Bn (75%)

Scheme 4 *Reagents and conditions:* i, O_3, CH_2Cl_2:MeOH = 10:1, −78 °C, then $NaBH_4$; ii, CH_2N_2, Et_2O

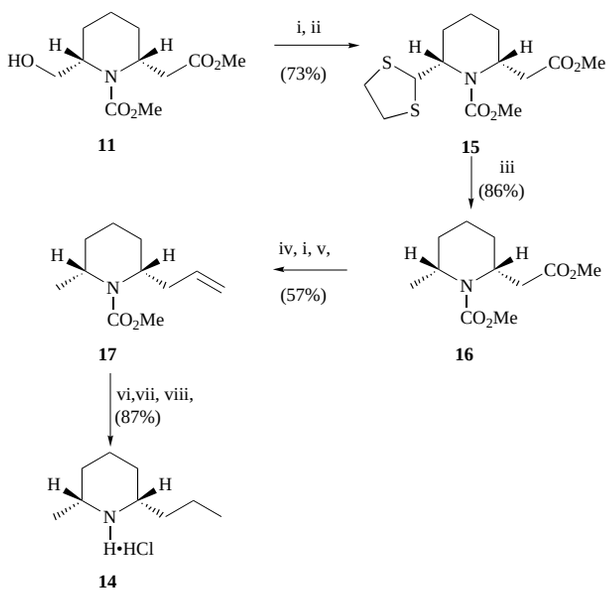
Determination of the absolute configuration of the piperidine 11

The action of Koga's chiral base on the ketones **1**–**3** resulted in the enantioselective abstraction of the axial hydrogen H_a leading to the ethers **8**–**10**; this behaviour was tentatively predictable by assuming the involvement of the transition state model proposed by Koga. The prediction was confirmed by chemical transformation of the products into compounds of known absolute configuration.



Scheme 5

Determination of the absolute configuration of **11** (2*R*,6*S*) was established by conversion of the compound into (+)-dihydropinidine **14**, the dihydro derivative of (−)-pinidine.[12] The piperidine **11** was converted into the thioacetal **15** (73%). Desulfurisation of **15** with Raney Ni (W-4) gave an α-methylpiperidine **16** (86%). Reduction of the ester group in **16** with lithium triethylborohydride (Super-Hydride) followed by a Swern oxidation and subsequent Wittig olefination of the resulting aldehyde afforded the olefin **17** (57%). The catalytic hydrogenation of **17** over 5% Pd–C and subsequent decarbamoylation with iodotrimethylsilane (TMSI)[13] furnished **14** (87%). Synthetic (+)-dihydropinidine hydrochloride had a value of $[\alpha]_D^{26}$ +11.6 (*c* 0.15, EtOH), similar to that {$[\alpha]_D^{25}$ +12.7 (*c* 1.07, EtOH}[14] reported for an authentic specimen derived from natural (−)-pinidine and the spectral properties (^{1}H NMR and mass) of **14** were identical with those of (±)-dihydropinidine hydrochloride.[15]

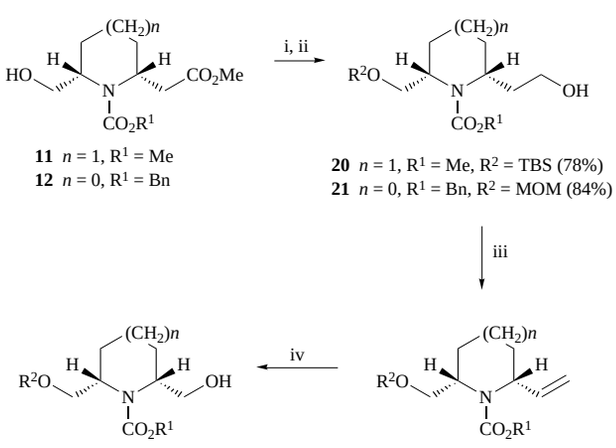


11
15
16
17
14

Scheme 6 *Reagents and conditions:* i, Swern oxidn.; ii, ethanedithiol, BF_3·Et_2O; iii, Raney Ni (W-4); iv, Super-Hydride; v, $Ph_3P{=}CH_2$; vi, H_2, 5% Pd–C; vii, TMSI; viii, HCl/MeOH

Synthesis of the enantiodivergent synthons 18 and 19

Finally, we examined the transformation of **11** or **12** into the enantiodivergent synthon **18** or **19**. Protection of the hydroxy group in **11** or **12** with *tert*-butylchlorodimethylsilane (TBSCl) or methoxymethyl chloride (MOMCl) and subsequent reduc-



11 *n* = 1, R^1 = Me
12 *n* = 0, R^1 = Bn

20 *n* = 1, R^1 = Me, R^2 = TBS (78%)
21 *n* = 0, R^1 = Bn, R^2 = MOM (84%)

18 *n* = 1, R^1 = Me, R^2 = TBS (94%)
19 *n* = 0, R^1 = Bn, R^2 = MOM (60%)

22 *n* = 1, R^1 = Me, R^2 = TBS (71%)
23 *n* = 0, R^1 = Bn, R^2 = MOM (70%)

Scheme 7 *Reagents and conditions:* i, TBSCl, Et_3N, DMAP or MOMCl, Pr^i_2NEt; ii, Super-Hydride; iii, *o*-$NO_2PhSeCN$, Bu_3P then H_2O_2; iv, O_3, −78 °C then $NaBH_4$

tion with Super-Hydride gave the alcohol **20** (78%) or **21** (84%). Dehydration of **20** or **21** was effected by treatment with *o*-nitrophenyl selenocyanate followed by oxidation with H_2O_2 [16] to afford the olefin **22** (71%) or **23** (70%). The olefin **22** or **23** was ozonised, and treatment of the resulting ozonide with sodium borohydride ($NaBH_4$) produced the desired σ-symmetry-fashioned piperidine **18** (94%) or pyrrolidine **19** (60%).

Conclusion

The piperidine **18** or pyrrolidine **19** have potential as chiral building blocks for the enantiodivergent synthesis of alkaloids possessing the *cis*-2,6-disubstituted piperidine or *cis*-2,5-disubstituted pyrrolidine skeleton. Thus, the ω-azabicyclo-[3.*n*.1]alkan-3-ones proved to be very suitable substrates for the asymmetric deprotonation with Koga's chiral base, and the *cis*-α,α′-disubstituted piperidine **11** or pyrrolidine **12** obtained from the ozonolysis of the silyl enol ether **8** or **9** could be one of the most important chiral building blocks for alkaloid syntheses. The enantioselective synthesis of alkaloids starting with **11** or **18** and with **12** or **19** will be published in due course.

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 and *J* values are given in Hz. 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.

9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one 4 [9]

Acetonedicarboxylic acid (30.8 g, 0.211 mol) was added to a solution of pentanedial (25% solution; 84.5 g, 0.211 mol) and benzylamine hydrochloride (36.3 g, 0.253 mol) in water (90 cm^3) at 0 °C, after which 10% aqueous AcONa (70 cm^3) was added to the reaction mixture. The mixture was stirred for 1 h at room temperature and then for 4 h at 50 °C. After this the reaction mixture was adjusted to pH 2 with 10% aqueous HCl and then washed with Et_2O (50 cm^3 × 3); it was then adjusted to pH 6 with $NaHCO_3$ and extracted with CH_2Cl_2 (50 cm^3 × 7). The organic extracts were dried and evaporated to give a pale orange paste, which was taken up in hot Et_2O (30 cm^3 × 10). The organic extracts were evaporated and the residue was purified by distillation under reduced pressure (bp 115–120 °C, 0.005 mmHg, lit.,[9] bp 165–169 °C, 0.2 mmHg) to afford **4** (38.5 g, 78%) as a colourless solid; ν_{max}(KBr)/cm^{-1} 1689; δ_H 1.49–1.59 (6 H, m, ring CH_2), 2.26 (2 H, d, *J* 19, $COCH_{2eq}$), 2.76 (2 H, dd, *J* 19 and 8, $COCH_{2ax}$), 3.28–3.49 (2 H, br, NCH), 3.91 (2 H, s, NCH_2Ar) and 7.22–7.46 (5 H, m, ArH).

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one 5 [10]

Acetonedicarboxylic acid (17.6 g, 0.121 mol) was added to a solution of butanedial (0.121 mol; prepared from 2,5-dimethoxytetrahydrofuran and 10% HCl) and benzylamine hydrochloride (20.8 g, 0.145 mol) in water (100 cm^3) at 0 °C, after which 10% aqueous AcONa (54 cm^3) was added to the reaction mixture. The mixture was stirred for 1 h at room temperature, and then for 2 h at 50 °C. After this the reaction mixture was adjusted to pH 2 with 10% aqueous HCl and washed with Et_2O (20 cm^3 × 6); the aqueous layer was then adjusted to pH 6 with $NaHCO_3$ and extracted with CH_2Cl_2 (20 cm^3 × 10). The organic extracts were dried and evaporated to give a pale orange paste, which was taken up in hot Et_2O (20 cm^3 × 10). The organic extracts were evaporated, and the residue was purified by distillation under reduced pressure [bp 175–180 °C, 0.8 mmHg (lit.,[10] bp 120 °C, 0.2 mmHg)] to afford **5** (20.3 g, 78%) as a colourless paste; ν_{max}(neat)/cm^{-1} 1697; δ 1.60–1.82 (2 H, m, ring CH_2), 1.85–2.33 (4 H, m, ring CH_2 and $COCH_{2eq}$), 2.48–2.97 (2 H, m, $COCH_{2ax}$), 3.38–3.65 (2 H, br, NCH), 3.85 (2 H, s, NCH_2Ar) and 7.10–7.56 (5 H, m, ArH).

10-Benzyl-10-azabicyclo[4.3.1]decan-3-one 6

Acetonedicarboxylic acid (8.1 g, 66.3 mmol) was added to a solution of hexanedial (6.3 g, 55.2 mmol; prepared from the ozonolysis of cyclohexene) and benzylamine hydrochloride (9.5 g, 55.2 mmol) in water (25 cm^3) at 0 °C; 10% aqueous AcONa (40 cm^3) was then added to the reaction mixture. After this it was stirred for 1 h at room temperature, and then for 4 h at 50 °C. The reaction mixture was then adjusted to pH 2 with 10% aqueous HCl and washed with Et_2O (50 cm^3 × 3); the aqueous layer was then adjusted to pH 6 with $NaHCO_3$ and extracted with CH_2Cl_2 (30 cm^3 × 7). The organic extracts were dried and evaporated to give a pale orange paste, which was taken up in hot Et_2O (15 cm^3 × 10). The organic extracts were evaporated and the residue was purified by distillation under reduced pressure (bp 190–193 °C, 0.8 mmHg) to afford **6** (6.7 g, 50%) as a colourless paste (Found: M$^+$, 243.1602. $C_{19}H_{21}NO$ requires *M*, 243.1622); ν_{max}(neat)/cm^{-1} 1686; δ_H 1.41–1.52 (4 H, m, ring CH_2), 1.74–1.91 (4 H, m, ring CH_2), 2.17 (2 H, d, *J* 13, $COCH_{2eq}$), 2.70 (2 H, dd, *J* 13 and 6.5, $COCH_{2ax}$), 3.46 (2 H, m, NCH), 3.95 (2 H, s, NCH_2Ar) and 7.22–7.42 (5 H, m, ArH).

Methyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate 1

To a stirred solution of **4** (8.0 g, 34.9 mmol) in acetic acid (40 cm^3) was added 5% Pd–C (1.0 g), and the resulting suspension was stirred for 2 days at 60 °C under a hydrogen atmosphere. After filtration of the reaction mixture through a Celite pad, 10% aqueous HCl (42 cm^3) was added to the filtrate, and the resulting mixture was evaporated to afford the amine hydrochloride (6.1 g). To a solution of the amine hydrochloride (6.1 g) obtained above in CH_2Cl_2 (100 cm^3)–H_2O (100 cm^3) were added 10% aqueous K_2CO_3 (100 cm^3) and $ClCO_2Me$ (4.5 cm^3, 65.8 mmol) at 0 °C; the reaction mixture was then stirred for 40 h at room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (20 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a pale yellow viscous oil, which was purified by column chromatography on SiO_2 (60 g, hexane–acetone, 10:1) to afford **1** (6.19 g, 91% from **4**) as a colourless solid. An analytical sample was prepared by recrystallisation (cyclohexane). Colourless crystals, mp 66–67 °C (Found: C, 60.78; H, 7.59. $C_{10}H_{15}NO_3$ requires C, 60.89; H, 7.67%); ν_{max}(KBr)/cm^{-1} 1702; δ_H 1.48–1.74 (6 H, m, ring CH_2), 2.38 (2 H, d, *J* 8, $COCH_{2eq}$), 2.52–2.69 (2 H, m, $COCH_{2ax}$), 3.74 (3 H, s, OCH_3), 4.66 (1 H, br s, NCH) and 4.77 (1 H, br s, NCH). The benzyl urethane corresponding to compound **1** was also prepared from the parent amine hydrochloride according to the same procedure using $ClCO_2Bn$ instead of $ClCO_2Me$ in 96% yield as a colourless paste (Found: M$^+$, 273.1359. $C_{16}H_{19}NO_3$ requires *M*, 273.1365); ν_{max}($CHCl_3$)/cm^{-1} 1705 and 1690; δ_H 1.51–1.87 (6 H, m, ring CH_2), 2.37 and 2.40 (2 H, each d, *J* 16.5, $COCH_{2eq}$ due to rotamers), 2.58 and 2.66 (2 H, each dd, *J* 16.5 and 7, $COCH_{2ax}$, due to rotamers), 4.73 and 4.80 (2 H, each br s), 5.19 (2 H, s) and 7.22 (5 H, br s).

Benzyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate 2

To a stirred solution of **5** (20.3 g, 94.6 mmol) in acetic acid (120 cm^3) was added 5% Pd–C (2.0 g), and the resulting suspension was stirred for 3 days at 60 °C under a hydrogen atmosphere. After filtration of the reaction mixture through a Celite pad, 10% aqueous HCl (100 cm^3) was added to the filtrate, and the resulting mixture was evaporated to afford the amine hydrochloride (15.2 g). To a solution of the amine hydrochloride (1.2 g) obtained above in CH_2Cl_2 (30 cm^3)–H_2O (30 cm^3) were added 10% aqueous K_2CO_3 (30 cm^3) and $ClCO_2Bn$ (2.2 cm^3, 15.4 mmol) at 0 °C; the reaction mixture was then stirred for 8 h at room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (20 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a pale yellow viscous oil, which was purified by column chromatography on SiO_2 (20 g; hexane–acetone, 10:1) to afford **2** (1.7 g, 91% from **5**) as a colourless paste. An analytical sample was prepared by distillation under reduced pressure (bp 145–150 °C, 0.6 mmHg (Found: M^+, 259.1211. $C_{15}H_{17}NO_3$ requires *M*, 259.1207); ν_{max}(neat)/cm^{-1} 1698; δ_H 1.62–1.75 (2 H, m, ring CH_2), 2.05–2.19 (2 H, m, ring CH_2), 2.35 (2 H, d, *J* 17, $COCH_{2eq}$), 2.48–2.84 (2 H, br, $COCH_{2ax}$), 4.58 (2 H, s, NCH), 5.19 (2 H, s, OCH_2Ar) and 7.32–7.40 (5 H, m, ArH).

Benzyl 3-oxo-10-azabicyclo[4.3.1]decane-10-carboxylate 3

To a stirred solution of **6** (1.97 g, 8.17 mmol) in acetic acid (20 cm^3) was added 5% Pd–C (0.4 g), and the resulting suspension was stirred for 3 days at 60 °C under a hydrogen atmosphere. After filtration of the reaction mixture through a Celite pad, 10% aqueous HCl (42 cm^3) was added to the filtrate, and the resulting mixture was evaporated to afford the amine hydrochloride (1.45 g). To a solution of the amine hydrochloride (530 mg) obtained above in CH_2Cl_2 (12 cm^3)–H_2O (12 cm^3) were added 10% aqueous K_2CO_3 (12 cm^3) and $ClCO_2Bn$ (0.95 cm^3, 5.6 mmol) at 0 °C, and the reaction mixture was stirred for 21 h at room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 5). The organic extracts were combined, dried and evaporated to give a pale yellow viscous oil, which was purified by column chromatography on SiO_2 (30 g; hexane–acetone, 10:1) to afford **3** (722 mg, 90% from **5**) as a colourless paste. An analytical sample was prepared by distillation under reduced pressure (bp 170–174 °C, 0.4 mmHg) (Found: M^+, 287.1519. $C_{17}H_{21}NO_3$ requires *M*, 287.1520); ν_{max}(neat)/cm^{-1} 1690; δ_H 1.36–1.61 (6 H, m, ring CH_2), 1.91–2.20 (2 H, m, ring CH_2), 2.26–2.41 (2 H, m, $COCH_{2eq}$), 2.57–2.75 (2 H, m, $COCH_{2ax}$), 4.80–4.89 (1 H, m, NCH), 4.90–5.05 (1 H, m, NCH), 5.16 (2 H, d, *J* 6, OCH_2Ar) and 7.26–7.37 (5 H, m, ArH).

Methyl (1*S*,5*R*)-(−)-3-trimethylsiloxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate 8

To a stirred solution of the amine **7**[7] (3.2 g, 11.0 mmol) in THF (50 cm^3) was added BuLi (10% w/v in hexane; 7.1 cm^3) and HMPA (3.8 cm^3, 22.1 mmol) at −100 °C; the resulting mixture was warmed to room temperature for 1 h and then recooled to −100 °C. To the cooled mixture were added Me_3SiCl (2.8 cm^3, 22.1 mmol) and then **1** (1.45 g, 7.36 mmol) in THF (10 cm^3) at −100 °C, and the reaction mixture was stirred for 2 h at −100 °C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 cm^3) to the mixture, after which the aqueous layer was separated and extracted with Et_2O (15 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, 50:1) to afford **8** (1.8 g, 94%) as a colourless oil (Found: M^+, 269.1452. $C_{13}H_{23}NO_3Si$ requires *M*, 269.1447); ν_{max}(neat)/cm^{-1} 1700 and 1669; δ_H 0.18 (9 H, s, $SiMe_3$), 1.33–1.97 [7 H, m, ring CH_2 and $=C(OSiMe_3)CH_2$], 2.40–2.63 [1 H, br, $=C(OSiMe_3)CH_2$], 3.68 (3 H, s, CO_2Me) and 4.40–4.89 (3 H, m, =CH and NCH); $[\alpha]_D^{26}$ −16.8 (*c* 1.35, $CHCl_3$).

Benzyl (1*S*,5*R*)-(−)-3-trimethylsiloxy-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate 9

To a stirred solution of the amine **7**[7] (1.85 g, 6.4 mmol) in THF (50 cm^3) were added BuLi (10% w/v in hexane; 4.0 cm^3) and HMPA (2.2 cm^3, 12.6 mmol) at −100 °C, and the resulting mixture was warmed to room temperature for 1 h; it was then recooled to −100 °C. To the cooled mixture were added Me_3SiCl (1.6 cm^3, 12.6 mmol) and then **2** (1.1 g, 4.24 mmol) in THF (10 cm^3) at −100 °C, and the reaction mixture was stirred for 2 h at −100 °C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 cm^3) to the mixture, after which the aqueous layer was separated and extracted with Et_2O (15 cm^3 × 5). The combined organic extracts were dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (30 g; hexane–acetone, 50:1) to afford **9** (1.25 g, 89%) as a colourless oil (Found: M^+, 331.1596. $C_{18}H_{25}NO_3Si$ requires *M*, 331.1602); ν_{max}(neat)/cm^{-1} 1705 and 1650; δ_H 0.06 (9 H, s, $SiMe_3$), 1.58–1.88 (4 H, m, ring CH_2), 2.34 [1 H, br d, *J* 5.5, $=C(OSiMe_3)CH_2$], 2.40 [1 H, br d, *J* 5.5, $=C(OSiMe_3)CH_2$], 4.69–4.83 (3 H, m, =CH and NCH), 5.22 (2 H, s, OCH_2Ar), 7.29–7.43 (5 H, m, ArH); $[\alpha]_D^{26}$ −22.1 (*c* 1.38, $CHCl_3$).

Benzyl (1*S*,5*R*)-3-trimethylsiloxy-10-azabicyclo[4.3.1]dec-2-ene-10-carboxylate 10

To a stirred solution of the amine **7**[7] (300 mg, 1.04 mmol) in THF (10 cm^3) were added BuLi (10% w/v in hexane; 0.7 cm^3) and HMPA (0.37 cm^3, 2.09 mmol) at −100 °C, and the resulting mixture was warmed to room temperature for 1 h; it was then recooled to −100 °C. To the cooled mixture were added Me_3SiCl (0.27 cm^3, 2.09 mmol) and then **3** (200 mg, 0.69 mmol) in THF (3 cm^3) at −100 °C; the reaction mixture was then stirred for 2 h at −100 °C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 cm^3) to the mixture, after which the aqueous layer was separated and extracted with Et_2O (10 cm^3 × 3). The combined organic extracts were dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (5 g, hexane–acetone, 50:1) to afford **10** (189 mg, 75%) as a colourless oil (Found: M^+, 359.1065. $C_{20}H_{29}NO_3Si$ requires *M*, 359.1055); ν_{max}(neat)/cm^{-1} 1700 and 1676; δ_H 0.20 (9 H, s, $SiMe_3$), 0.99–1.87 (8 H, m, ring CH_2), 2.25–2.48 [2 H, m, $=C(OSiMe_3)CH_2$], 4.67–4.74 (3 H, m, =CH and NCH), 5.18 (2 H, br s, OCH_2Ar) and 7.26–7.35 (5 H, m, ArH).

Methyl (2*R*,6*S*)-(−)-6-hydroxymethyl-1-methoxycarbonylpiperidin-2-ylethanoate 11

Ozone was bubbled through a stirred solution of **8** (3.67 g, 13.6 mmol) in CH_2Cl_2–MeOH (10:1; 33 cm^3) at −78 °C for 20 min, after which the excess of O_3 was eliminated by passage of a flow of argon through the solution; $NaBH_4$ (1.04 g, 27.2 mmol) was then added to it at −78 °C. After this the reaction mixture was warmed to room temperature and stirred for 2 h. It was then treated with 10% aqueous HCl (5 cm^3), and the aqueous layer was saturated with NaCl. The aqueous layer was separated and extracted with $CHCl_3$ (10 cm^3 × 5), and the organic layer and extracts were combined, dried and evaporated to give a viscous oil, which was used directly in the next step. To a stirred solution of the viscous oil in Et_2O (150 cm^3) was added CH_2N_2 in Et_2O, at 0 °C, and the mixture was stirred at room temperature for 3 h. The excess of CH_2N_2 was destroyed with AcOH, and the mixture was evaporated to give a viscous oil, which was purified by column chromatography on SiO_2 (120 g; hexane–Et_2O, 1:2) to afford **11** (2.33 g, 60%) as a viscous oil (Found: M^+, 245.2357. $C_{11}H_{19}NO_5$ requires *M*, 245.2375); ν_{max}(neat)/cm^{-1} 3449, 1736 and 1692; δ_H 1.61–2.53 (6 H, m, ring CH_2), 2.50 [1 H, dd, *J* 17 and 14, C(*H*)HCO_2Me], 2.61 [1 H, dd, *J* 17 and 14, C(*H*)HCO_2Me], 3.63 (2 H, t, *J* 7, CH_2OH), 3.69 (3 H, s, CH_2CO_2Me), 3.71 (3 H, s, NCO_2Me), 4.34–4.45 (1 H, m, NCH) and 4.64–4.75 (1 H, br m, NCH); $[\alpha]_D^{26}$ −4.4 (*c* 1.05, $CHCl_3$).

Methyl (2*R*,5*S*)-(−)-1-benzyloxycarbonyl-5-hydroxymethylpyrrolidin-2-ylethanoate 12

Ozone was bubbled through a stirred solution of **9** (1.20 g, 3.62 mmol) in CH_2Cl_2–MeOH (10:1; 16.5 cm^3) at −78 °C for 20 min, after which the excess of O_3 was eliminated by passage of a flow of argon through the solution; $NaBH_4$ (276 mg, 7.24 mmol) was then added to it at −78 °C. The reaction mixture was then warmed to room temperature and stirred for 2 h. After this the mixture was treated with 10% aqueous HCl (5 cm^3), and the aqueous layer was saturated with NaCl. The aqueous layer was separated and extracted with $CHCl_3$ (10 cm^3 × 5), and the organic layer and extracts were combined, dried and evaporated to give a viscous oil, which was used directly in the next step. To a stirred solution of the viscous oil obtained above in Et_2O (40 cm^3) was added CH_2N_2 in Et_2O at 0 °C, and the mixture was stirred at room temperature for 3 h. The excess of CH_2N_2 was destroyed with AcOH, and the mixture was evaporated to give a viscous oil, which was purified by column chromatography on SiO_2 (60 g; hexane–Et_2O, 1:2) to afford **12** (663 mg, 60%) as a viscous oil (Found: M^+, 307.1459. $C_{16}H_{21}NO_5$ requires *M*, 307.1419); ν_{max}(neat)/cm^{-1} 3450, 1737 and 1698; δ_H 1.72–2.00 (4 H, m, ring CH_2), 2.40 [1 H, br, C(*H*)HCO_2Me], 2.70 [1 H, br, C(*H*)HCO_2Me], 3.55 (3 H, s, CO_2Me), 3.87–4.05 (2 H, m, CH_2OH), 4.07–4.22 (1 H, br m, NCH), 4.24–4.42 (1 H, br m, NCH), 5.12 and 5.16 (each 1 H, each d, *J* 17, OCH_2Ar) and 7.40 (5 H, br s, ArH); $[\alpha]_D^{26}$ −12.3 (*c* 1.24, $CHCl_3$).

Methyl (2*R*,7*S*)-(−)-1-benzyloxycarbonyl-7-hydroxymethylhexahydroazepin-2-ylethanoate 13

Ozone was bubbled through a stirred solution of **10** (120 mg, 0.334 mmol) in CH_2Cl_2–MeOH (10:1; 2.2 cm^3) at −78 °C for 20 min, after which the excess of O_3 was eliminated by passage of a flow of argon through the solution. $NaBH_4$ (25 mg, 0.67 mmol) was added to the mixture at −78 °C, after which it was warmed to room temperature and stirred for 2 h. The mixture was then treated with 10% aqueous HCl (2 cm^3) and the aqueous layer was saturated with NaCl. The aqueous layer was separated and extracted with $CHCl_3$ (5 cm^3 × 5), and the organic layer and extracts were combined, dried and evaporated to give a viscous oil, which was used directly in the next step. To a stirred solution of the viscous oil obtained above in Et_2O (5 cm^3) was added CH_2N_2 in Et_2O at 0 °C, and the mixture was stirred at room temperature for 3 h. The excess $CH_2N_2$was destroyed with AcOH, and the mixture was evaporated to give a viscous oil, which was purified by column chromatography on SiO_2 (3 g; hexane–Et_2O, 1:2) to afford **11** (84.1 mg, 75%) as a viscous oil (Found: M^+, 335.1752. $C_{18}H_{25}NO_5$ requires *M*, 335.1732); ν_{max}(neat)/cm^{-1} 3442, 1737 and 1690; δ_H 1.34–1.89 (8 H, m, ring CH_2), 2.52 [1 H, dd, *J* 10 and 5.5, C(*H*)HCO_2Me], 2.87 [1 H, br, C(*H*)HCO_2Me), 3.65–3.80 (2 H, m, CH_2OH), 3.81–3.95 (1 H, m, NCH), 4.14–4.43 (1 H, m, NCH), 5.10 and 5.14 (each 1 H, each d, *J* 5, OCH_2Ar) and 7.27–7.35 (5 H, m, ArH); $[\alpha]_D^{26}$ −19.8 (*c* 2.75, $CHCl_3$).

Methyl (2*R*,6*S*)-(+)-6-(1,3-dithiolan-2-yl)-1-methoxycarbonylpiperidin-2-ylethanoate 15

To a stirred solution of $(COCl)_2$ (0.068 cm^3, 0.78 mmol) in CH_2Cl_2 (8 cm^3) was added DMSO (0.11 cm^3, 1.56 mmol) at −78 °C, and the resulting mixture was stirred for 10 min; compound **11** (127 mg, 0.52 mmol) in CH_2Cl_2 (2 cm^3) was then added to the mixture. After being stirred for 45 min, the mixture was treated with Et_3N (0.34 cm^3, 2.33 mmol), added at −78 °C; the temperature was then allowed gradually to rise to 0 °C. After this Et_2O (15 cm^3) and water (5 cm^3) were added to the reaction mixture, and the organic layer was separated and washed with water (5 cm^3 × 2), dried and evaporated to give a colourless oil. This was used directly in the next step. To a stirred solution of the aldehyde obtained above in CH_2Cl_2 (5 cm^3) were added ethanedithiol (0.051 cm^3, 0.61 mmol) and $BF_3{\cdot}Et_2O$ (0.074 cm^3, 0.61 mmol) at 0 °C, and the resulting mixture was stirred for 12 h at room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 cm^3) to the mixture; the aqueous layer was then separated and extracted with CH_2Cl_2 (5 cm^3 × 3). The organic layer and extracts were combined, dried and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (10 g; hexane–acetone, 15:1) to afford **15** (120 mg, 73% from **11**) as a colourless oil (Found: C, 48.61; H, 6.52. $C_{13}H_{21}NO_4S_2$ requires C, 48.88; H, 6.63%); ν_{max}(neat)/cm^{-1} 1738 and 1694; δ_H 1.50–2.00 (6 H, m, ring CH_2), 2.58 [1 H, dd, *J* 15.5 and 11.5, C(*H*)HCO_2Me], 2.72 [1 H, dd, *J* 15.5 and 14, C(*H*)HCO_2Me], 3.10–3.38 (4 H, m, SCH_2CH_2S), 3.69 (3 H, s, CH_2CO_2*Me*), 3.72 (3 H, s, NCO_2Me), 4.42 (1 H, br, NCH), 4.59 (1 H, d, *J* 11, SCHS) and 4.68 (1 H, br, NCH); $[\alpha]_D^{26}$ +3.3 (*c* 0.42, $CHCl_3$).

Methyl (2*R*,6*R*)-(−)-6-methyl-1-methoxycarbonylpiperidin-2-ylethanoate 16

To a stirred solution of **15** (700 mg, 2.19 mmol) in EtOH (5 cm^3) was added Raney Ni (W-4, 300 mg), and the resulting suspension was refluxed for 1 h. After cooling, the mixture was filtered through a Celite pad to remove the catalyst, and the filtrate was evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (20 g; hexane–acetone, 50:1) to afford **16** (433 mg, 86%) as a colourless oil (Found: M^+, 229.1283. $C_{11}H_{19}NO_4$ requires *M*, 229.1313); ν_{max}(neat)/cm^{-1} 1739 and 1698; δ_H 1.17 (3 H, d, *J* 7, Me), 1.46–1.72 (6 H, m, ring CH_2), 2.53 [1 H, dd, *J* 15 and 5, C(*H*)HCO_2Me], 2.65 [1 H, dd, *J* 15 and 10, C(*H*)HCO_2Me], 3.67 (3 H, s, CH_2CO_2*Me*), 3.69 (3 H, s, NCO_2Me), 4.32 (1 H, br, NCH) and 4.61 (1 H, br, NCH); $[\alpha]_D^{26}$ −37.8 (*c* 0.95, $CHCl_3$).

Methyl (2*R*,6*R*)-2-methyl-6-(prop-2-enyl)piperidine-1-carboxylate 17

To a stirred solution of **16** (332 mg, 1.45 mmol) in THF (5 cm^3) was added Super-Hydride (1 M in THF; 3.19 cm^3, 3.19 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. It was then diluted with water (5 cm^3) and CH_2Cl_2 (10 cm^3), and the aqueous layer was separated and extracted with CH_2Cl_2 (5 cm^3 × 5). The organic layer and extracts were combined, dried and evaporated to give a colourless oil, which was used directly in the next step. To a stirred solution of $(COCl)_2$ (0.044 cm^3, 0.524 mmol) in CH_2Cl_2 (4 cm^3) was added DMSO (0.074 cm^3, 1.05 mmol) at −78 °C and the mixture was stirred for 10 min. To the resulting mixture was added the alcohol (70 mg) obtained above in CH_2Cl_2 (2 cm^3) at −78 °C, and the mixture was stirred for 45 min. To the mixture was added Et_3N (0.22 cm^3, 1.57 mmol) at −78 °C, and the reaction temperature was raised to 0 °C. The mixture was then diluted with water (5 cm^3) and Et_2O (15 cm^3). The organic layer was separated, washed with water (5 cm^3 × 2), dried and evaporated to give a colourless oil, which was used directly in the next step. To a stirred suspension of methyl(triphenyl)phosphonium iodide (355 mg, 0.88 mmol) in THF (4 cm^3) was added BuLi (10% w/v in hexane; 0.54 cm^3) at 0 °C, and the resulting orange-coloured solution was stirred at room temperature for 30 min. To the mixture was added the aldehyde (70 mg) obtained above in THF (2 cm^3) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of water (4 cm^3) to the mixture, and the aqueous layer was separated and extracted with Et_2O (10 cm^3 × 3). The organic layer and extracts were combined, dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (6 g; hexane–acetone, 100:1) to afford **17** (39 mg, 57% from **16**) as a colourless oil (Found: M^+, 197.1420. $C_{11}H_{19}NO_2$ requires *M*, 197.1415); ν_{max}(neat)/cm^{-1} 1701; δ_H 1.18 (3 H, d, *J* 7, Me), 1.42–1.76 (6 H, m, ring CH_2), 2.32 (2 H, dd, *J* 7, CH_2CH=CH_2), 3.69 (3 H, s, NCO_2Me), 4.32 (1 H, br, NCH), 4.61 (1 H, br, NCH), 5.00–5.07 (2 H, m, CH=CH_2) and 5.66–5.84 (1 H, m, C*H*=CH_2).

(+)-Dihydropinidine hydrochloride 14

To a stirred solution of **17** (39 mg) in MeOH (0.8 cm^3) was added 5% Pd–C (10 mg), and the resulting suspension was stirred for 9 h under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was evaporated to give a colourless oil, which was used directly in the next step. To a stirred solution of the oil (10 mg) obtained above in $CHCl_3$ (0.4 cm^3) was added Me_3SiI (0.08 cm^3, 0.06 mmol), and the mixture was stirred at room temperature for 3 h; it was then evaporated to give a pale yellow paste. To the paste was added a saturated solution of HCl in MeOH, and the mixture was evaporated. The residue was washed with Et_2O and then with EtOAc to afford **14** (7.7 mg, 87%) as a colourless solid. The IR and ^1H NMR spectral data were identical with those of an authentic sample;[15] $[\alpha]_D^{26}$ +11.6 (*c* 0.15, EtOH) {lit.,[14] $[\alpha]_D^{25}$ +12.7 (*c*, 1.07 EtOH)}.

Methyl (2*S*,6*R*)-(+)-2-(*tert*-butyldimethylsiloxymethyl)-6-(2-hydroxyethyl)piperidine-1-carboxylate 20

To a stirred solution of **11** (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 at room temperature for 21 h. It was then diluted with Et_2O (100 cm^3) and water (5 cm^3). The organic layer was separated, 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 the silyl ether (2.68 g, 90%) as a colourless oil (Found: $M^+ - C_4H_9$, 302.1424. $C_{12}H_{24}NO_4Si$ requires $M - C_4H_9$, 302.1424); ν_{max}(neat)/cm^{-1} 1741 and 1701; δ_H 0.07 (6 H, s, $SiMe_2$), 0.89 (9 H, s, $SiBu^t$), 1.41–1.69 (6 H, m, ring CH_2), 3.48–3.60 (4 H, m, CH_2OH and CH_2OTBS), 3.66 (3 H, s, CH_2CO_2Me), 3.69 (3 H, s, NCO_2Me), 4.16 (1 H, br, NCH) and 4.60 (1 H, br, NCH); $[\alpha]_D^{26}$ −24.4 (*c* 1.06, $CHCl_3$).

To a stirred solution of the silyl ether (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 the addition of water (20 cm^3) to the mixture, and the aqueous layer was separated and extracted with CH_2Cl_2 (20 cm^3 × 5). The organic layer and 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 **20** (2.7 g, 95%) as a colourless oil (Found: M^+, 331.2160. $C_{16}H_{33}NO_4Si$ requires *M*, 331.2182); ν_{max}(neat)/cm^{-1} 3461, 1733 and 1695; δ_H 0.06 (6 H, s, $SiMe_2$), 0.89 (9 H, s, $SiBu^t$), 1.58–1.76 (8 H, m, ring CH_2 and CH_2CH_2OH), 3.45–3.64 (4 H, m, CH_2OH and CH_2OTBS), 3.72 (3 H, s, NCO_2Me), 4.14–4.26 (1 H, br, NCH) and 4.36–4.56 (1 H, br, NCH); $[\alpha]_D^{26}$ +6.6 (*c* 1.09, $CHCl_3$).

Methyl (2*S*,6*R*)-2-(*tert*-butyldimethylsiloxymethyl)-6-ethenylpiperidine-1-carboxylate 22

To a stirred solution of **20** (76 mg, 0.23 mmol) in THF (6 cm^3) were added *o*-nitrophenyl selenocyanate (65 mg, 0.28 mmol) and Bu_3P (0.07 cm^3, 0.28 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. After evaporation of the mixture, the residue was purified by column chromatography on SiO_2 (4 g; hexane–acetone, 50:1) to afford the selenide (111 mg, 93%) as a yellow oil; ν_{max}(neat)/cm^{-1} 1701; δ_H 0.06 (6 H, s, $SiMe_2$), 0.85 (9 H, s, $SiBu^t$), 1.63–1.76 (3 H, m, ring CH_2), 1.82–2.05 (3 H, m, ring CH_2), 2.91 (2 H, t, *J* 8, CH_2Se), 3.55 (2 H, d, *J* 7, CH_2OTBS), 3.71 (3 H, s, NCO_2Me) and 4.19–4.40 (2 H, br, NCH).

To a stirred solution of the selenide (60 mg, 0.12 mmol) in THF (2 cm^3) was added 31% H_2O_2 (0.13 cm^3, 0.12 mmol) at 0 °C, and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 cm^3), and the organic layer was separated and washed with saturated aqueous $NaHCO_3$ (5 cm^3) and saturated brine (5 cm^3), dried and evaporated to give a pale yellow oil. This was purified by column chromatography on SiO_2 (2 g; hexane–acetone, 50:1) to afford **22** (27.7 mg, 76%) as a pale yellow oil (Found: M^+, 313.2066. $C_{16}H_{31}NO_4Si$ requires *M*, 313.2071); ν_{max}(neat)/cm^{-1} 1698; δ_H 0.06 (6 H, s, $SiMe_2$), 0.85 (9 H, s, $SiBu^t$), 1.38–1.56 (3 H, m, ring CH_2), 1.82–1.99 (3 H, m, ring CH_2), 3.43–3.56 (2 H, m, CH_2OTBS), 3.70 (3 H, s, NCO_2Me), 4.14–4.25 (1 H, br, NCH), 4.72 (1 H, m, NCH), 5.04–5.17 (2 H, m, $C{=}CH_2$) and 5.79 (1 H, ddd, *J* 17, 10 and 5, $CH{=}CH_2$).

Methyl (2*S*,6*R*)-(+)-2-(*tert*-butyldimethylsiloxymethyl)-6-(hydroxymethyl)piperidine-1-carboxylate 18

Ozone was bubbled through a stirred solution of **22** (10 mg, 0.032 mmol) in CH_2Cl_2–MeOH (7.7 cm^3, 10:1) at −78 °C for 20 min, after which the excess of O_3 was eliminated by passage of a flow of argon through the solution. Sodium borohydride (2.4 mg, 0.064 mmol) was added to the mixture at −78 °C, which was then warmed to room temperature and stirred for 1 h. After evaporation of the mixture, the residue was purified by column chromatography on SiO_2 (1 g; hexane–acetone, 30:1) to afford **18** (9.5 mg, 94%) as a colourless oil (Found: M^+, 317.2015. $C_{15}H_{31}NO_4Si$ requires *M*, 317.2020); ν_{max}(neat)/cm^{-1} 3452 and 1670; δ_H 0.06 (6 H, s, $SiMe_2$), 0.85 (9 H, s, $SiBu^t$), 1.39–1.81 (6 H, m, ring CH_2), 3.53–3.65 (4 H, m, CH_2OTBS and CH_2OH), 3.75 (3 H, s, NCO_2Me) and 4.21–4.45 (2 H, br, NCH); $[\alpha]_D^{26}$ +6.7 (*c* 0.25, $CHCl_3$).

Benzyl (2*R*,5*S*)-(−)-2-(2-hydroxyethyl)-5-(methoxymethoxymethyl)pyrrolidine-1-carboxylate 21

To a stirred solution of **12** (563 mg, 1.83 mmol) in CH_2Cl_2 (2 cm^3) were added Pr^i_2EtN (0.48 cm^3, 2.75 mmol) and MOMCl (0.17 cm^3, 2.2 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. After this, the reaction mixture was diluted with Et_2O (30 cm^3) and water (5 cm^3). The organic layer was separated, washed with saturated brine (5 cm^3), dried and evaporated to give a pale yellow oil, which was used directly in the next step. To a solution of the oil (598 mg) obtained above in THF (15 cm^3) was added Super-Hydride (4.1 cm^3, 4.1 mmol) at 0 °C, and the resulting mixture was stirred for 2 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 separated and extracted with CH_2Cl_2 (10 cm^3 × 5). The organic layer and extracts were combined, dried and evaporated to give a colourless oil, which was purified by column chromatography on SiO_2 (10 g; hexane–acetone, 10:1) to afford **21** (538 mg, 91%) 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 1694; δ_H 1.50–1.82 (2 H, m, ring CH_2), 1.83–2.14 (4 H, m, ring CH_2 and CH_2CH_2OH), 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 m, NCH), 4.54 (2 H, s, OCH_2O), 5.15 and 5.17 (each 1 H, each d, *J* 13, CH_2Ar) and 7.27–7.39 (5 H, m, ArH); $[\alpha]_D^{26}$ −34.9 (*c* 1.98, $CHCl_3$).

Benzyl (2*R*,5*S*)-2-ethenyl-5-(methoxymethoxymethyl)-pyrrolidine-1-carboxylate 23

To a stirred solution of **21** (50 mg, 0.155 mmol) in THF (5 cm^3) were added *o*-nitrophenyl selenocyanate (42.2 mg, 0.186 mmol) and Bu_3P (0.05 cm^3, 0.186 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. It was then evaporated to give a crude selenide. To the crude selenide in THF (5 cm^3) was added 31% H_2O_2 (0.15 cm^3) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. It was treated with saturated aqueous $NaHCO_3$ (5 cm^3) and diluted with CH_2Cl_2 (10 cm^3). The organic layer was separated, dried and evaporated to give a pale yellow oil, which was purified by column chromatography on SiO_2 (3 g; hexane–acetone, 20:1) to afford **23** (33.2 mg, 70%) as a pale yellow oil (Found: M^+, 305.1620. $C_{17}H_{23}NO_4$ requires *M*, 305.1626); ν_{max}(neat)/cm^{-1} 1698; δ_H 1.35–1.61 (2 H, m, ring CH_2), 1.76–1.95 (2 H, m, ring CH_2), 3.29 (3 H, s, OMe), 3.44–3.65 (2 H, m, CH_2OMOM), 3.73–3.99 (2 H, br m, NCH), 4.51 (2 H, s, OCH_2O), 5.00–5.12 (2

H, m, C=CH_2), 5.16 and 5.18 (each 1 H, each d, *J* 12, CH_2Ar), 5.76 (1 H, ddd, *J* 17, 10 and 5, C*H*=CH_2) and 7.21–7.45 (5 H, m, ArH).

Benzyl (2*R*,5*S*)-(−)-2-(hydroxymethyl)-5-(methoxymethoxymethyl)pyrrolidine-1-carboxylate 19

Ozone was bubbled through a solution of **23** (24 mg, 0.079 mmol) in CH_2Cl_2–MeOH (10:1; 11 cm^3) at −78 °C for 20 min, after which the excess of O_3 was eliminated by passage of a flow of argon through the solution. Sodium borohydride (6.1 mg, 0.157 mmol) was added at −78 °C to the reaction mixture, after which it was warmed to room temperature and stirred for 1 h. After evaporation of the mixture, the residue was purified by column chromatography on SiO_2 (1 g; hexane–acetone, 10:1) to afford **19** (16.7 mg, 68%) as a colourless oil (Found: M^+, 309.1546. $C_{16}H_{23}NO_5$ requires *M*, 309.1575); ν_{max}(neat)/cm^{-1} 3452 and 1670; δ_H 1.90–2.08 (4 H, m, ring CH_2), 3.29 (3 H, s, OMe), 3.45–3.65 (3 H, br m, NCH and C*H*$_2$OH), 3.75–3.98 (1 H, m, NCH), 3.99–4.18 (2 H, m, CH_2OMOM), 4.50 (2 H, s, OCH_2O), 5.14 and 5.15 (each 1 H, each d, *J* 12, CH_2Ar) and 7.29–7.40 (5 H, m, ArH); $[\alpha]_D^{26}$ −8.3 (*c* 0.78, $CHCl_3$).

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