β-Hydroxypiperidinecarboxylates: additions to the chiral pool from bakers' yeast reductions of β-ketopiperidinecarboxylates

David W. Knight,[a]*† Neil Lewis,[a] Andrew C. Share[a] and David Haigh[b]

[a] *Chemistry Department, University Park, Nottingham, UK NG7 2RD*
[b] *SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*

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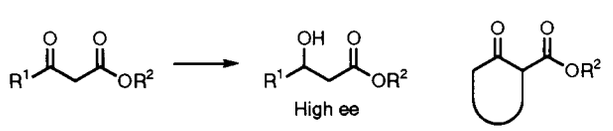
Reduction of the piperidine keto esters **16**–**19** using fermenting bakers' yeast provides high yields of the corresponding hydroxy esters **20**, **26**, **32** and **37** respectively, exclusively as the *cis*-diastereoisomers and with good levels (≥80%) of enantiomeric enrichment. The relative stereochemistries of the products were deduced from NMR data while the absolute configurations were determined by degradation to known piperidinemethanol derivatives or, in the case of hydroxy ester **37**, by homologation to (*R*)-3-quinuclidinol **41b**.

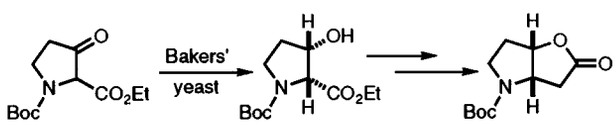
The impact of biological methods on organic synthesis has been extremely significant in recent times, particularly for the many contributions made to asymmetric synthesis. An attractive feature of much of this methodology is that the biological catalysts can be treated in a similar fashion to standard laboratory reagents, often needing no special handling or experience, beyond the normal requirements of cleanliness and reactant and solvent purity.[1] Notable examples are the many applications of lipases and of fermenting bakers' yeast. The latter is especially remarkable as, in many examples, this naturally complex living mixture of enzyme systems is capable of effecting highly enantioselective reductions, along with a variety of other useful transformations, without any effort having to be made to purify the organism although, in some cases, various additives have been found to have a beneficial effect.[2] Perhaps the most widely applied transformation using bakers' yeast is the reduction of β-keto esters **1** to the corresponding β-hydroxy esters **2**



1 **2** **3**

Scheme 1

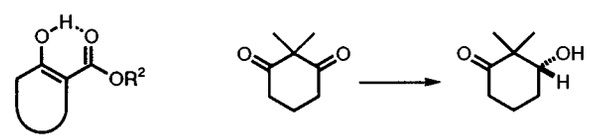
which often results in excellent chemical and optical yields. To a large extent, this methodology, at least with simple, saturated acetoacetate derivatives, has been superceded by the highly efficient Noyori hydrogenation methods using rhodium(I)–BINAP complexes as the catalysts.[3] However, for cyclic β-keto esters **3**, this latter method is not so useful as there is already an asymmetric (racemic) centre in the reduction substrate. In such cases, bakers' yeast has been shown to be particularly effective in delivering *cis*-β-hydroxy esters with good to excellent levels of enantiomeric enrichment;[2] examples include both 5- and 6-membered carbocycles[4] and some related sulfur-containing heterocycles[5] along with ethyl *N*-benzyl-3-oxopiperidine-4-carboxylate, the latter by using a large excess of fermenting yeast in the absence of added sugar.[6] We have reported that the 3-oxoproline derivative **4** is similarly reduced by fermenting bakers' yeast to the hydroxyproline **5** with 78% enantiomeric enrichment; amongst other uses, this initial product can be used to prepare the (−)-Geissman–Waiss lactone **6**,[7] useful as a precursor to many pyrrolizidine alkaloids.[8]



4 **5** **6**

Scheme 2

In view of the foregoing, we were intrigued by the possibility that piperidine-based β-keto esters could be similarly reduced to the corresponding disubstituted piperidines, which would be potentially useful additions to the chiral pool. Additionally, the completely deprotected derivatives of the anticipated initial hydroxy esters display significant activity on the functioning of the central γ-aminobutyric acid (GABA) neurotransmitter system and are therefore of interest in therapies for various psychiatric and neurological disorders.[9] 4-Hydroxypiperidine-3-carboxylic acid is a potent substrate-competitive inhibitor of the neuronal GABA uptake process[10] while the isomeric 3-hydroxy-4-carboxylic acid is a specific GABA receptor agonist.[11] In mechanistic terms, such reactions can occur in two ways, either by reduction of the carbon–carbon double bond in the enol forms **7** of the keto esters or by a kinetic resolution wherein one enantiomer of the β-keto ester is more rapidly reduced and the remaining enantiomer undergoes facile racemization. The latter mechanism seems the more likely, as simple carbonyls such as benzaldehyde can be successfully reduced by bakers' yeast,[1] as can 2,2-dimethylcyclohexane-1,3-dione **8**, which cannot exist in a conjugated enolic form, to give the hydroxy ketone **9**.[12] However, to our disappointment, various 4-keto-3-pyrrolidinecarboxylate derivatives, isomeric with the successful yeast substrate **4**, were not efficiently



7 **8** **9**

Scheme 3

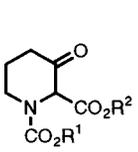
† *Present address*: Chemistry Department, Cardiff University, PO Box 912, Cardiff, UK CF1 3TB.

reduced by bakers' yeast.[13] With this uncertainty in mind, we proceeded to the preparation of examples of the three possible keto-piperidinecarboxylate isomers **10**–**12**, which we hoped would be suitable for yeast reduction; herein, we report in full on our work in this area, some of which has appeared in preliminary form.[14]

Results and discussion

The first route chosen to a 3-keto-2-carboxylate isomer **10** featured a rhodium-catalysed intramolecular carbenoid N–H insertion reaction using the α-diazo-β-keto ester **13**, as described by Rapoport.[15] However, in our hands, the approach work proved somewhat capricious, yields of the final piperidine-2-carboxylate were relatively poor and the desired product was difficult to separate from other products. We therefore turned to an alternative approach, also developed by the Rapoport group, which relies on a Dieckmann cyclisation to establish the piperidine ring.[16] Thus, *N*-alkylation of pyrrolidin-2-one by ethyl bromoacetate provided the homologous ester **14**, which was exhaustively hydrolysed to give the amino diacid hydrochloride **15a**. Subsequent esterification led to the diester **15b** and thence to the *N*-*tert*-butoxycarbonyl (Boc) derivative **15c**, following treatment with Boc anhydride.[17] Dieckmann cyclisation under aprotic conditions (KOBu^t–dry toluene)[16] led to the desired 3-keto-2-carboxylate **16**, along with the corresponding 4-carboxylate **19**. By analogy with similar cyclisations leading to the corresponding keto-prolines, these are the kinetic and thermodynamic products respectively.[18] Yields of the former were best when the reaction was worked up after only ten minutes and, fortunately, the two isomers were easily separated by column chromatography. The 4-keto-3-carboxylate **17** was obtained from the commercially available amine hydrochloride by reaction with Boc anhydride and triethylamine in dichloromethane. At the outset of the project, the alternatively esterified 4-carboxylate **18** was also commercially available and was used for some preliminary studies; however, subsequently, supplies were unavailable and we therefore had to prepare additional material using the Dieckmann method: esterification of the diacid **15a** using acidic ethanol provided the diethyl ester **15d** and thence the *N*-methoxycarbonyl derivative **15e**, after acylation by methyl chloroformate. Dieckmann cyclisation for a longer period delivered a slightly better yield of the 4-carboxylate **18**, relative to the foregoing preparation of keto ester **19**. Each β-keto ester existed very largely in its enol form in deuteriochloroform.

The yeast reductions were performed using the established method detailed by the Seebach group using commercial, dried bakers' yeast available from a local supermarket and sucrose.[19] As previously observed,[7] it was important to use tap rather than distilled water; presumably, trace elements present in the former aid the growth and metabolism of the yeast. If distilled water was used, the reductions tended to stop after around 50–60% conversion. We also found that it was advisable to use dried yeast from a 'high turnover' store, as older samples (>*ca*. two months), even when kept in unopened packets, also gave lower yields. Under optimum conditions, reduction of the 3-keto-2-carboxylate **16** routinely gave *ca*. 80% isolated yields of the hydroxy ester **20** which was isolated simply by filtration and extraction with dichloromethane, even though the filtration process had to be carried out twice and was rather slow. The samples were remarkably clean according to NMR analysis, which was fortunate as compound **20** proved to be somewhat unstable to chromatography. However, NMR analysis was complicated by the presence of rotamers; this proved to be a continuing problem throughout this project. Although some useful ^{1}H data could be obtained by heating the latter samples, ^{13}C spectra, obtained in d_6-DMSO at 350 K, proved more useful



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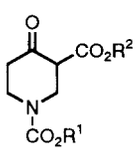

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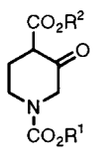

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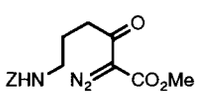

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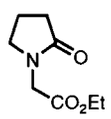

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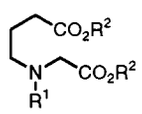
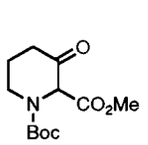


15a) $R^1 = R^2 = H$ (HCl);
b) $R^1 = H$; $R^2 = Me$ (HCl);
c) $R^1 = Boc$; $R^2 = Me$;
d) $R^1 = H$; $R^2 = Et$ (HCl);
e) $R^1 = CO_2Me$; $R^2 = Et$



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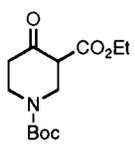

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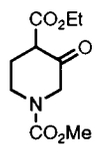

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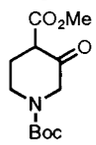

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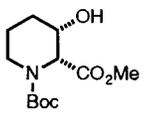

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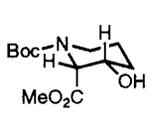
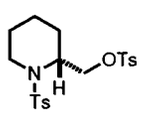


21 $J_{2,3} = 6.4$ Hz



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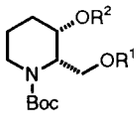
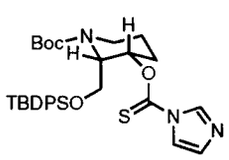
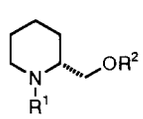


23a) $R^1 = R^2 = H$;
b) $R^1 = SiBu^tPh_2$; $R^2 = H$;
c) $R^1 = SiBu^tPh_2$; $R^2 = C(S)Im$



24 $J_{3ax,4ax} = 12.0$ Hz;
$J_{3ax,4(2)eq} = 6.0$ (5.6) Hz;
$J_{3ax,2(4)eq} = 5.6$ (6.0) Hz



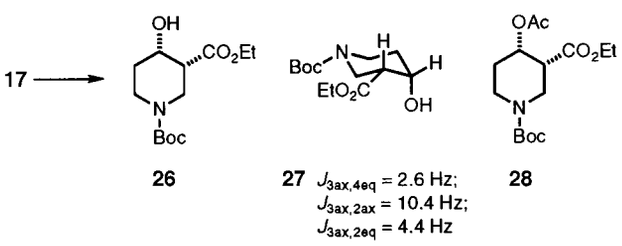
25a) $R^1 = Boc$; $R^2 = SiBu^tPh_2$;
b) $R^1 = Ts$; $R^2 = SiBu^tPh_2$;
c) $R^1 = Ts$; $R^2 = H$.

and gave convincing evidence of chemical and stereochemical purity. The hydroxy ester **20** produced from keto ester **16** was a single diastereoisomer according to ^{13}C data and showed $[\alpha]_D^{23}$ +47.9 (*c*, 3.8, CH_2Cl_2). We were able to measure $J_{2,3}$ by observing 2-H only; a value of 6.4 Hz seemed to rule out a diaxial relationship between 2-H and 3-H but this did not help significantly in determining the relative configuration of the ester and hydroxy groups. It has been established that 2-substituents in *N*-alkoxycarbonyl piperidines are usually positioned axially, rather than the more expected equatorial placement, in order to avoid unfavourable steric interaction with the *N*-substituent.[20] If this were the case, then both the *trans*- and *cis*-isomers **21** could give such a value; the value of 6.4 Hz only ruled out the *trans*-isomer, in which the 2-carboxylate was positioned equatorially, which was not expected. Unfortunately, we were unable to observe 3-H as an isolated resonance, either in the initial product or in the corresponding acetate. We therefore sought to partly establish the absolute stereochemistry of the reduction product **20** by degradation to the known bis-tosylate **22**, derived from (*R*)-(+)piperidine-2-methanol.[21] The latter was reported to show $[\alpha]_D^{18}$ +56.6 (*c*, 1.03, EtOH) and so appeared suitable for comparison purposes; we hoped to resolve the relative stereochemistry problem along the way.

The initial yeast reduction product **20** was smoothly reduced to the diol **23a** by lithium aluminium hydride in tetrahydrofuran; subsequent selective protection of the primary alcohol group provided a good overall yield of the monosilyl derivative **23b**. Barton–McCombie deoxygenation by conversion to the thiocarbamate **23c** followed by reduction using tributyltin hydride[22] gave a reasonable isolated yield of the piperidine-2-methanol derivative **25a**. A bonus in this sequence was the appearance in the ^1H NMR spectrum of the thiocarbamate **23c** of an essentially first-order resonance for 3-H at δ_H 5.53 as a ddd pattern with *J* 12.0, 6.0 and 5.6 Hz. This provided clear evidence for the *cis*-stereochemistry in conformation **24** (or its enantiomer). On the assumption[20] that the 2-substituent is positioned axially, then one large coupling constant suggests that 3-H must be axial (*i.e.* $J_{3,4}$ = 12.0 Hz), with the remaining two being smaller ax–eq couplings. Were this the *trans*-isomer, then 3-H should display either no large coupling constants (both groups axial[20]) or two large *trans*-diaxial values, if both substituents were positioned equatorially. Similarly, no large *J* values would be expected in the 3-H resonance of the *cis*-isomer, if the 2-substituent were positioned equatorially as this would also place 3-H in an equatorial position. Completion of the sequence involved selective removal of the *N*-Boc group using trifluoroacetic acid and tosylation of the resulting free amine gave the monotosylate **25b**, which was then desilylated to give the alcohol **25c**. Finally, this was tosylated to give the bis-tosylate **22** which displayed $[\alpha]_D^{23}$ +55.0 (*c*, 0.8, EtOH), indicating the (*R*)-absolute stereochemistry shown[21] and also an enantiomeric enrichment of 97%. Hence, we concluded that the initial yeast reduction product **20** had the (2*R*,3*S*) absolute configuration shown. As a check on the level of optical purity in the sample of the bis-tosylate **22**, we prepared a sample of the racemic material and examined its ^1H NMR spectra in the presence of increasing amounts of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III). We observed almost baseline separation of two broadened signals due to the resonances of a pair of protons on one of the tosyl aromatic rings. When a similar experiment was repeated with the yeast reduction product, only one line was observed. However, the lack of complete separation and line broadening precluded any firm conclusion beyond that the sample was of at least 90% enantiomeric enrichment.

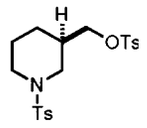
Interest in the synthesis of the various isomers of 3-hydroxypiperidine-2-carboxylic acid (3β-hydroxypipecolic acid) has increased recently, due both to its occurrence in some natural products as well as its potential for the elaboration of modified peptides and related structures. A separable mixture of both the *cis*- and *trans*-isomers, as single enantiomers, was originally prepared by the Rapoport group[23] and more recently by enecarbamate epoxidation, methanolysis and displacement with cyanide.[24] Various selective routes to the *trans*-isomer have also been reported,[25] together with two approaches to the *cis*-isomer.[26] Very recently, the Williams group[27] have reported an application of their asymmetric method for amino acid synthesis to the preparation of both the (2*R*,3*R*) and (2*S*,3*S*) (*trans*) isomers of this hydroxy acid, with a view to determining the absolute stereochemistry of such a residue which occurs in the natural antitumor antibiotic Tetrazomine. These were not identical to the natural material and neither was the (2*R*,3*S*)-isomer, prepared using the foregoing yeast reduction method, although comparative NMR data showed these to have the same *cis*-geometry. Further, the optical rotations of these samples {$[\alpha]_D^{20}$ −72.3 (*c*, 0.10, 1 M HCl) for the natural amino acid; $[\alpha]_D^{20}$ +82.1 (*c*, 0.12, 1 M HCl) for amino acid obtained by hydrolysis of yeast reduction product **20**}, were essentially equal but opposite in sign. Hence, the 3-hydroxypiperidine-2-carboxylic acid residue in the natural product has the (2*S*,3*R*) configuration, the only one which has yet to be synthesized selectively.

We next examined yeast reduction of the 4-keto-3-carboxylate **17** and were pleased to find that a hydroxy ester was



Scheme 4

produced in 74% yield as a crystalline solid, mp 58–60 °C, which showed $[\alpha]_D^{23}$ +25.6 (*c*, 3.4, CH_2Cl_2). Once again, a simple solvent extraction provided remarkably clean material which, according to ^{13}C NMR analysis, was a single diastereoisomer. In this case, the relative stereochemistry was deduced to be *cis* (*i.e.* **26** or its enantiomer) from ^1H NMR data, although rotameric broadening again necessitated running these spectra at above ambient temperature. The spectrum was fully assigned on the basis of COSY data. On the assumption that the larger ester group would occupy an equatorial position, 3-H was clearly in an axial position whereas 4-H was equatorial (see data associated with conformation **27**). All other coupling constant data were consistent with this assignment and argued against any of the other three possibilities (*i.e. cis* with an axial ester group or *trans* with both substituents equatorial or both axial). As a further check, we also prepared the corresponding acetate **28**; in its ^1H NMR spectrum, the 4-H was now shifted downfield and appeared as an apparent quartet with *J* = 3.2 Hz, again confirming that the 4-substituent was in an axial position.[28] We determined the absolute stereochemistry of the initial reduction product **26** in a similar fashion to that of the foregoing 3-hydroxy-2-carboxylate **20**, relying on a literature optical rotation value of +54 for the bis-tosylate **29** derived from (*R*)-piperidine-3-methanol.[29] Thus, the initial product **26** was reduced using lithium aluminium hydride and the resulting diol **30a** selectively protected as the monosilyl ether **30b**. Similar yields in the initial reduction step were also obtained using a combination of diisobutylaluminium hydride (DIBAL-H) and boron trifluoride–diethyl ether in THF at −78 °C.[30] Removal of the remaining free hydroxy group was effected by a recent modification[31] of the Barton–McCombie method, by conversion into the pentafluorophenyl thiocarbonate **30c** followed by tin hydride reduction, which gave a reasonable overall yield



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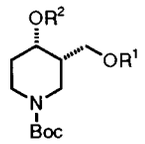
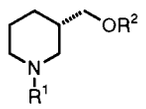




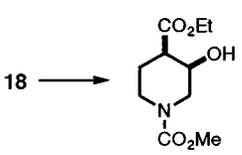
30 a) $R^1 = R^2 = H$;
b) $R^1 = SiBu^tPh_2$; $R^2 = H$;
c) $R^1 = SiBu^tPh_2$; $R^2 = C(S)OC_6F_5$

31a) R^1 = Boc; $R^2 = SiBu^tPh_2$;
b) R^1 = Ts; $R^2 = SiBu^tPh_2$;
c) R^1 = Ts; R^2 = H;
d) $R^1 = R^2$ = Ts.

of the piperidine-3-methanol derivative **31a**. Subsequent replacement of the Boc group by *p*-tolylsulfonyl gave the tosyl derivative **31b** which was then desilylated and the resulting alcohol **31c** tosylated to give the bis-tosylate **31d**. This proved to have a similar melting point to that recorded for the (*R*)-enantiomer[29] and an almost equal (−50.2) but opposite optical rotation in the same solvent. Hence, we assigned the (*S*)-stereochemistry to this final product **31d** and hence the (3*R*,4*S*) stereochemistry **26** to the initial yeast reduction product from keto ester **19**. The optical rotation values suggest an enantiomeric enrichment of 93%. Chiral shift reagent NMR experiments, using the same europium reagent as described for the foregoing 3-hydroxy-2-carboxylate, confirmed this as a minimum value.

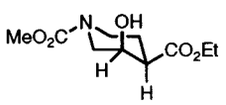
Our final series of experiments were conducted on the 3-ketopiperidine-4-carboxylates **18** and **19**. Once again, yeast reduction of the *N*-methoxycarbonyl derivative **18** led to an excellent isolated yield of a single diastereoisomer (according to ^{13}C NMR data) of a hydroxy ester, which was isolated in a clean state after simple solvent extraction and which showed $[a]_D^{21}$ −21.4 (*c*, 1.1, $CHCl_3$). Assuming that the ester group would be positioned equatorially in a reasonably well-behaved chair-like conformation, we were able to assign the *cis*-stereochemistry **32** to this product on the basis of coupling constant data. Although the resonance for the 3-H was masked, it was evident that 4-H was axial and that this and 2-H_{ax} were both adjacent to an equatorial proton, consistent with conformation **33**. In the ^1H NMR spectrum of the corresponding acetate **34**, the 3-H was now visible as a narrow multiplet, again only consistent with an equatorial positioning; all other data indicated a *cis*-geometry.[28] This was further indicated by a facile preparation of the homologue **36** of the Geissman–Waiss lactone **6**. Thus, reduction of the initial hydroxy ester using methanolic sodium borohydride gave the diol **35a** which was tosylated at the primary alcohol position and the resulting tosylate **35b** treated with sodium cyanide in dimethyl sulfoxide to give the nitrile **35c** in good yield. Acid hydrolysis at ambient temperature led to an excellent yield of the lactone **36** which could find use in the elaboration of further homologues. The robust nature of the *N*-protecting group in the initial reduction product **32**, in contrast to the corresponding *N*-Boc derivatives, also allowed us to determine its optical purity using chiral GC. Firstly, a sample of the keto ester **18** was reduced using sodium borohydride in methanol (0 °C, 0.5 h) to give a racemic mixture of the *cis* (*cf.* **32**) and *trans* hydroxy esters, in a ratio of *ca.* 4:1, according to ^1H NMR integration. This mixture was separated into four well-resolved peaks using a 25 m × 0.33 mm Chirval column, operating under a temperature programme of 150 °C to 175 °C at 1.0 °C per minute. The minor *trans*-isomers were eluted first (R_t 14.3 and 14.5 min), followed by the *cis*-isomers at R_t 15.2 and 15.5 min. The ratio of diastereoisomers was 24:76 *trans*:*cis*. Under identical conditions, the yeast reduction product **32** showed only two peaks (R_t 15.2 and 15.5 min) in a ratio of 89:11, indicating an enantiomeric excess of 78%.

However, the foregoing measurements and the preparation of lactone **36** did not allow us to assign the absolute stereochemistry to the major enantiomer of the yeast reduction product **32**. This was determined in a more constructive way than in the foregoing cases by homologation of the initial reduction product into a quinuclidine ring system.[32] Starting with the related *N*-Boc keto ester **19**, yeast reduction provided an excellent yield of pure hydroxy ester **37**, again as a single diastereoisomer which showed $[a]_D^{21}$ −32.7 (*c*, 1.0, $CHCl_3$). The *cis*-stereochemistry was assigned on the basis of closely similar coupling constant data to those displayed by the hydroxy ester **32**. The secondary alcohol function was protected as the methoxymethoxy (MOM) ether and the resulting derivative **38a** saponified to give the acid **38b**. Conversion into the corresponding acid chloride and treatment with diazomethane provided the diazo ketone **38c** which underwent Wolff rearrangement to give the homologated ester **39**. Dibal-H reduction led to the alcohol **40a** which was converted into the mesylate **40b**. Removal of the Boc protecting group using trifluoroacetic acid and cyclisation of the resulting material in hot ethanol[32] gave the polar quinuclidine **41a** which was deprotected to give 3-quinuclidinol **41b**, which showed spectral data identical to an authentic sample (Aldrich) of the racemate. The sample also showed $[a]_D^{25}$ −39.5 (*c*, 0.5, 1 M HCl), indicating the (*R*)-configuration shown and hence the (3*R*,4*R*) stereochemistry as shown for the initial yeast reduction products **17** and **18**. Comparisons with authentic samples and literature rotation data

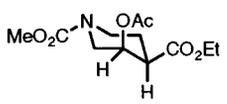


18

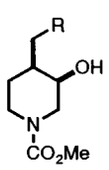
32



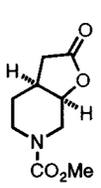
33 *J* H_{4ax} = 11.9, 4.0 and 2.4 Hz;
J H_{5ax} = 13.5, 11.9, 11.9 and 4.4 Hz;
J H_{2ax} = 13.0 (br d) Hz



34 *J* H_{4ax} = 12.0, 4.1 and 3.2 Hz;
J H_{3eq} = (app. br s) $\omega_{1/2}$ = 6.0 Hz;
J H_{2ax} = (br d) 12.0 Hz

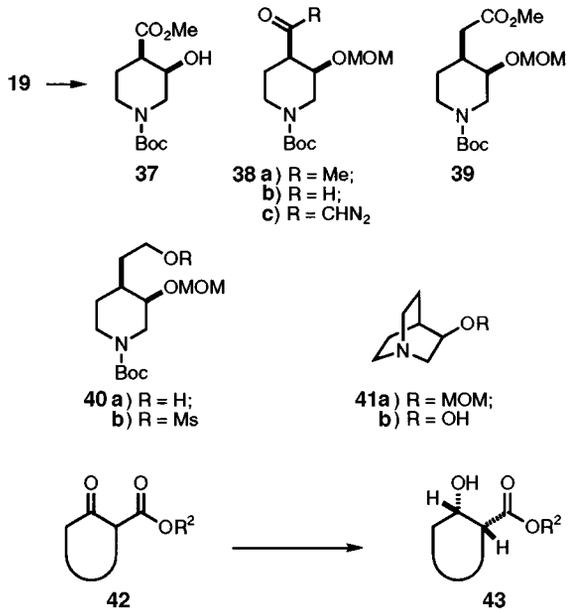


35a) R = OH;
b) R = OTs
c) R = CN



36

Scheme 5



Scheme 6

suggested an enantiomeric enrichment of 94%, although this is likely to be an upper limit for the initial reduction product **37**, in view of the chiral GC results for the *N*-methoxycarbonyl derivative **32**. Some enrichment could well have occurred during one or more of the chromatographic separations leading to the quinuclidinol **41b**.

Two groups[35,36] have reported modifications to our original method which gave the hydroxy proline **5** with 78% enantiomeric enrichment, by using an alternative *Dipodacus* yeast species,[35] or using bakers' yeast immobilized on calcium alginate.[36] In the present work, we briefly examined the latter method using keto esters **17** and **19** but chemical yields were very similar and, according to optical rotation data, this did not improve the enantiomeric excess of the products (**26** and **37**). However, the work-ups were significantly easier as the yeast residues were much more readily removed by filtration when immobilized.

In conclusion, these examples of yeast reductions have provided some potentially useful intermediates for piperidine synthesis with good optical purities. The absolute stereochemistries of the initial hydroxy esters **20**, **26**, **32** and **37** fall into the same pattern as previously found for yeast reductions of 'cyclic' β-keto esters.[4–7] This is that if the keto esters **42** are drawn with the ester group to the right, these will be reduced to give exclusively the *cis*-hydroxy ester diastereoisomers **43**, in which the major enantiomer has the two functional groups pointing downwards to the α-face.

Experimental

General details

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-10 polarimeter. Infrared spectra were recorded using a Perkin-Elmer 1600 series Fourier transform spectrometer using thin films between sodium chloride plates, unless otherwise stated. ^{1}H NMR spectra were determined using a Perkin-Elmer R32 operating at 90 MHz, a Bruker WM-250, a JEOL EX-270 or a Bruker AM-400 spectrometer, operating at the frequencies indicated [*i.e.* (90) refers to 90 MHz *etc.*]. ^{13}C NMR spectra were determined using any of the latter three instruments, operating at 62.5, 67.8 and 100.1 MHz respectively, as indicted after δ_C. Unless otherwise stated, all spectra were determined using dilute solutions in deuteriochloroform and tetramethylsilane as internal standard. *J* Values are expressed in Hertz. Mass spectra were measured using either an AEI MS902 or a VG 7070E instrument, both operating in the electron impact mode, unless otherwise stated; FAB spectra were obtained using the latter instrument or were obtained from the EPSRC Mass Spectrometry Service, Swansea University.

Unless otherwise stated, all reactions were carried out in anhydrous solvents which were obtained by the usual methods.[37] All organic solutions from work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. Solvents were removed by rotary evaporation. CC refers to column chromatography over Sorbsil silica gel using the eluents specified.

N-Ethoxycarbonylmethylpyrrolidin-2-one 14

Pyrrolidin-2-one (85 g, 1 mol) was added dropwise to a rapidly stirred suspension of molten sodium (23 g, 1 mol) in refluxing toluene (600 ml). After a further hour at reflux, ethyl bromoacetate (167 g, 1 mol) was added dropwise during 20 min and heating continued for an additional hour. The mixture was then cooled, filtered and the solvents evaporated. Distillation of the residue gave the pyrrolidine **14** (142 g, 83%), bp 127 °C at 0.1 mmHg (lit.,[38] bp 108–113 °C at 1–2 mmHg) as a colourless oil; ν_{max}/cm^{-1} 1740; δ_H (270) 1.28 (3H, t, *J* 7.3, CH_3), 2.02–2.12 (2H, m, 4-CH_2), 2.39 (2H, t, *J* 8.0, 3-CH_2), 3.50 (2H, br t, *J ca.* 7.0, 5-CH_2), 4.05 (2H, s, NCH_2CO) and 4.19 (2H, q, *J* 7.3, OCH_2); δ_C (68.5) 13.5 (CH_3), 17.3, 29.7, 43.4, 47.0, 60.5 (all CH_2), 168.0 and 174.9 (both CO); *m*/*z* 171 (M^+, 20%), 98 (100), 84 (19) and 70 (26) (Found: M^+, 171.0900. $C_8H_{13}NO_3$ requires *M*, 171.0895).

Dimethyl *N*-(*tert*-butoxycarbonyl)-3-azaheptane-1,7-dioate 15c

A solution of pyrrolidinone **14** (120 g) in aqueous 6 M hydrochloric acid (800 ml) was refluxed for 48 h then cooled and evaporated. The residue was dissolved in methanol (400 ml) and the solution again evaporated. Repetition of this process gave 3-azaheptane-1,7-dioic acid hydrochloride **15a** (126 g, 91%) as a colourless gum, δ_H (400; D_2O) 1.58–1.72 (2H, m, 5-CH_2), 2.21 (2H, t, *J* 7.2, 6-CH_2), 2.86 (2H, apparent t, *J* 7.8, 4-CH_2) and 3.67 (2H, s, 2-CH_2); δ_C (100; D_2O) 23.1, 33.0, 49.2, 49.8 (all CH_2), 171.2 and 179.1 (both CO).

Acetyl chloride (50 ml) was added to methanol (500 ml) and the solution stirred for 15 min then added to the foregoing diacid **15a** (88 g). The resulting solution was refluxed for 5 h then cooled and evaporated to leave dimethyl 3-azaheptane-1,7-dioate hydrochloride **15b** (94.3 g, 94%) as a colourless oil, ν_{max}/cm^{-1} 3360, 1741 and 1728; δ_H (400; CD_3OD) 2.01–2.16 (2H, m, 5-CH_2), 2.57 (2H, t, *J* 7.3, 6-CH_2), 3.15–3.25 (2H, m, 4-CH_2), 3.71 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.10 (2H, s, 2-CH_2) and 5.48 (1H, br s, NH); *m*/*z* 189 (M^+ − HCl, 3%), 130 (89), 98 (100), 70 (46) and 59 (17) (Found: M^+ − HCl, 189.0992. $C_8H_{15}NO_4$ requires *M*, 189.1001).

Di-*tert*-butyl dicarbonate (32 g, 146 mmol) in dichloromethane (20 ml) was added dropwise to a solution of the foregoing diester hydrochloride **15b** (30 g, 113 mmol) and triethylamine (14.8 g, 146 mmol) in dry dichloromethane (200 ml) at ambient temperature. The resulting solution was stirred overnight then diluted with dichloromethane (200 ml) and washed with 2 M aqueous citric acid (2 × 30 ml) and brine (30 ml) then dried and filtered through a bed of silica gel. Evaporation of the filtrate left the *N-Boc diester* **15c** (32.7 g, 85%) as a colourless oil, ν_{max}/cm^{-1} 1738, 1725 and 1668; δ_H (400) 1.23 (9H, s, Bu^t), 1.55–1.68 (2H, m, 5-CH_2), 2.15 (2H, t, *J* 7.3, 6-CH_2), 3.13 (2H, t, *J* 6.8, 4-CH_2), 3.46 (3H, s, OCH_3), 3.52 (3H, s, OCH_3) and 3.70 (2H, br s, 2-CH_2); δ_C (100) 23.4 (CH_2), 27.9 [$C(CH_3)_3$], 30.8, 39.9, 47.5 (all CH_2), 50.9, 51.3 (both CH_3), 79.8 [$C(CH_3)_3$], 155.7, 170.0 and 173.0 (all CO); *m*/*z* 188 (M^+ − Boc, 14%), 158 (8), 157 (8), 101 (16), 70 (15), 59 (15) and 57 (100) (Found: M^+ − Boc, 188.0884. $C_9H_{14}NO_4$ requires *M*, 188.0923) (Found:

C, 54.3; H, 8.1; N, 4.8. $C_{14}H_{23}NO_6$ requires C, 54.0; H, 8.0; N, 4.8%).

1-*tert*-Butyl 2-methyl 3-oxopiperidine-1,2-dicarboxylate 16 and 1-*tert*-butyl 4-methyl 3-oxopiperidine-1,4-dicarboxylate 19

Potassium *tert*-butoxide (9.7 g, 87 mmol) was added in portions during 10 min to an ice-cooled, stirred solution of the Boc diester **15c** (25 g, 87 mmol) in dry toluene (200 ml). After a further 10 min, the mixture was acidified to pH 3 using 2 M aqueous citric acid and the organic layer separated. The aqueous phase was extracted with dichloromethane (3 × 100 ml). The combined organic solutions were washed with brine (50 ml) then dried and evaporated. CC [CH_2Cl_2–EtOAc (9:1)] of the residue gave (i) the *3-oxo-4-carboxylate* **19** (10.4 g, 47%) as a colourless oil, R_F 0.9; ν_{max}/cm^{-1} 3361, 1690 and 1662; δ_H (270) 1.47 (9H, s, Bu^t), 2.32–2.40 (2H, m, 5-CH_2), 3.49 (2H, apparent t, *J* 6.0, 6-CH_2), 3.78 (3H, s, OCH_3), 4.03 (2H, s, 2-CH_2) and 12.00 (1H, s, OH); δ_C (68.5) 21.9 and 23.8 (CH_2), 28.0 and 28.1 [C(*C*H_3)$_3$], 39.9 and 41.2 (CH_2), 45.0 and 45.5 (CH_2), 51.5 (CH_3), 79.4 and 80.3 [*C*(CH_3)$_3$], 96.6 and 98.5 (C), 154.0 and 154.4 (*C*O_2Bu^t), 167.0 (C) and 173.0 (CO); *m/z* 156 (M^+ − Boc, 6%), 125 (13), 97 (8), 59 (10) and 57 (100) (Found: M^+ − Boc, 156.0634. $C_7H_{10}NO_3$ requires *M*, 156.0661) (Found: C, 56.2; H, 7.8; N, 5.4. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.5; N, 5.5%) and (ii) the *3-oxo-2-carboxylate* **16** (6.0 g, 27%) as a colourless oil, R_f 0.8; ν_{max}/cm^{-1} 3407, 1740 and 1698; δ_H (270) 1.44 (6H, br s, Bu^t), 1.49 (3H, br s, Bu^t), 1.81–1.95 (0.7H, m, 5-CH_2), 1.95–2.08 (1.3H, m, 5-CH_2), 2.41 (0.7H, t, *J* 7.2, 4-CH_2), 2.42–2.60 (1.3H, m, 4-CH_2), 3.28–3.45 (1H, m), 3.79 (3H, s, OCH_3), 3.86–4.10 (1H, m), 5.06 and 5.22 [total 1H, both br s, 2-H (keto)] and 11.12 (1H, br s, OH); δ_C (68.5) 22.3, 22.8, 26.5 (all CH_2), 27.9 [C(*C*H_3)$_3$], 37.8, 40.4, 41.5 (all CH_2), 53.1 (CH_3), 65.6 and 66.9 (both 2-CH), 80.5 and 81.2 [both *C*(CH_3)$_3$], 107.9, 154.2, 154.8, 155.0, 167.4, 169.4, 199.9 and 200.0 (all C); *m/z* 257 (M^+, 2%), 156 (10), 125 (18), 59 (11) and 57 (100) (Found: M^+, 257.1235. $C_{12}H_{19}NO_5$ requires *M*, 257.1263) (Found: C, 56.1; H, 7.6; N, 5.4%).

1-*tert*-Butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate 17

Di-*tert*-butyl dicarbonate (5.8 g, 26.5 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of ethyl 4-oxopiperidine-3-carboxylate hydrochloride (5.0 g, 24.1 mmol; Fluka) and triethylamine (2.68 g, 26.5 mmol) in dichloromethane (100 ml). The mixture was stirred overnight at ambient temperature then diluted with dichloromethane (200 ml). The resulting suspension was washed with 2 M hydrochloric acid (2 × 30 ml) and brine (30 ml) then dried and filtered through a pad of silica gel. Evaporation of the filtrates left the *4-oxopiperidine-3-carboxylate* **17** (5.1 g, 78%) which crystallized from hexane as a colourless solid, mp 62 °C; ν_{max}/cm^{-1} (KBr) 3424, 1691 and 1626; δ_H (400; 333 K) 1.31 (3H, t, *J* 7.0, CH_2CH_3), 1.48 [9H, s, C(*CH*$_3$)$_3$], 2.37 (2H, apparent br t, *J ca.* 5.8, 5-CH_2), 3.57 (2H, t, *J* 5.9, 6-CH_2), 4.03–4.10 (2H, br s, 2-CH_2), 4.24 (2H, q, *J* 7.0, OCH_2) and 12.07 (1H, s, OH); δ_C (68.5) 13.66 (OCH_2CH_3), 27.9 [C(*C*H_3)$_3$], 28.5, 38.9 (very br), 39.8 (br) (all CH_2), 60.1 (OCH_2), 79.6 [*C*(CH_3)$_3$], 95.5 (sl. br), 154.1, 169.5 (br) and 169.9 (all C); *m/z* 214 (M^+ − Bu^t, 40%), 198 (9), 170 (10), 142 (12), 98 (28) and 57 (100) (Found: M^+ − Bu^t, 214.0707. $C_9H_{12}NO_5$ requires *M*, 214.0715) (Found: C, 57.5; H, 8.0; N, 4.9. $C_{13}H_{21}NO_5$ requires C, 57.5; H, 7.8; N, 5.2%).

Diethyl *N*-(methoxycarbonyl)-3-azaheptane-1,7-dioate 15e

Esterification of the diacid **15a** (105 g) using ethanol (500 ml) in place of methanol, but otherwise the same conditions, gave diethyl 3-azaheptane-1,7-dioate hydrochloride **15d** (113 g, 84%) as a colourless oil, ν_{max}/cm^{-1} 3290, 1738 and 1735; δ_H (400; CD_3OD) 1.28 (3H, t, *J* 7.0, CH_3), 1.35 (3H, t, *J* 7.0, CH_3), 2.03–2.16 (2H, m, 5-CH_2), 2.55 (2H, br t, *J* 7.0, 6-CH_2), 3.22 (2H, t, *J* 6.5, 4-CH_2), 4.05 (2H, s, 2-CH_2), 4.16 (2H, q, *J* 7.0, OCH_2) and 4.32 (2H, q, *J* 7.0, OCH_2); δ_C (100; CD_3OD) 14.4, 14.5 (both CH_3), 22.3, 27.0, 31.9, 48.8 (all CH_2), 61.7, 63.5 (both OCH_2), 167.5 and 174.0 (both CO); *m/z* 217 (M^+ − HCl, 3%), 144 (100), 115 (14), 99 (22) and 84 (18).

Methyl chloroformate (8.2 g, 87 mmol) was added dropwise to a stirred solution of the foregoing diester hydrochloride **15d** (20 g, 78 mmol) and triethylamine (8.8 g, 87 mmol) in dry dichloromethane (200 ml), cooled in an ice bath. No additional coolant was added and the mixture was stirred overnight then diluted with dichloromethane (200 ml). The resulting suspension was washed with 2 M hydrochloric acid (2 × 30 ml) and brine (40 ml), then dried and filtered through a pad of silica gel. Evaporation of the filtrate gave the protected *diester* **15e** (15.2 g, 70%) as a colourless oil; ν_{max}/cm^{-1} 1736, 1732 and 1670; δ_H (400) 1.07 (3H, t, *J* 7.0, CH_3), 1.11 (3H, t, *J* 7.0, CH_3), 1.55–1.75 (2H, m, 5-CH_2), 2.08–2.28 (2H, t, *J* 7.0, 6-CH_2), 3.16 and 3.19 (total 2H, both t, *J* 7.0, 4-CH_2 rotamers), 3.46 and 3.51 (total 3H, both s, OCH_3 rotamers), 3.75 and 3.80 (total 2H, both s, 2-CH_2 rotamers), 3.93 (2H, q, *J* 7.0, OCH_2) and 3.95 (2H, q, *J* 7.0, OCH_2); δ_C (100) 13.1, 13.2 (both CH_3), 22.3 and 22.6 (5-CH_2), 30.1 and 30.2 (6-CH_2), 46.4 and 46.6 (4-CH_2), 47.9 and 48.1 (2-CH_2), 51.6 and 51.7 (OCH_3), 59.1 and 59.4 (OCH_2), 59.9 and 60.0 (OCH_2), 155.6 and 155.9 (*C*O_2Me), 167.7 and 168.7 (CO) and 171.9 (CO); *m/z* 275 (M^+, 9%), 230 (29), 216 (18), 188 (18), 128 (24) and 70 (100) (Found: M^+, 275.1350. $C_{12}H_{21}NO_6$ requires *M*, 275.1369).

4-Ethyl 1-methyl 3-oxopiperidine-1,4-dicarboxylate 18

Potassium *tert*-butoxide (4.0 g, 36.4 mmol) was added in portions during 10 min to a stirred solution of the foregoing *N*-methoxycarbonyl diester **15e** (10.0 g, 36.4 mmol) in dry toluene (150 ml). After 1 h, the mixture was acidified to pH 1 using 2 M hydrochloric acid and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 100 ml) and the combined organic solutions washed with brine (50 ml) then dried and evaporated. CC [CH_2Cl_2–EtOAc (9:1)] separated the *3-oxo-4-carboxylate* **18** (4.25 g, 51%) as a colourless oil, bp 170 °C (oven temperature) at 50 mmHg, R_f 0.9; ν_{max}/cm^{-1} 3350, 1701 and 1668; δ_H (400) 1.31 (3H, t, *J* 7.0, CH_2CH_3), 2.34 (2H, apparent br s, 5-CH_2), 3.54 (2H, apparent br s, 6-CH_2), 3.73 (3H, s, OCH_3), 4.06 (2H, s, 2-CH_2), 4.23 (2H, q, *J* 7.0, OCH_2) and 12.01 (1H, s, OH); δ_C (100) 13.31 (OCH_2CH_3), 21.5 (br), 40.2 (br), 44.1 (all CH_2), 51.7 (OCH_3), 59.6 (2-CH_2), 95.9 (C), 154.8 (*C*O_2Me), 166.6 (br, C) and 170.9 (C); *m/z* 229 (M^+, 76%), 184 (24), 168 (15), 156 (52), 140 (75), 59 (100) and 45 (54) (Found: M^+, 229.0952. $C_{10}H_{15}NO_5$ requires *M*, 229.0950).

(2*R*,3*S*)-1-(*tert*-Butyl) 2-methyl 3-hydroxypiperidine-1,2-dicarboxylate 20

The 3-oxopiperidine-2-carboxylate **16** (5.0 g, 19.5 mmol) was added to a fermenting, gently stirred suspension of dried bakers' yeast (30 g) and sucrose (50 g) in tap water (500 ml), maintained at 30–32 °C. After 24 h, the mixture was suction filtered and the filtrate re-filtered through Kieselguhr then extracted with dichloromethane (5 × 200 ml). The combined extracts were washed with brine (100 ml) then dried and evaporated to leave the *3-hydroxy-2-carboxylate* **20** (4.0 g, 79%) as a pale yellow oil, $[\alpha]_D^{23}$ +47.9 (*c*, 3.8, CH_2Cl_2); ν_{max}/cm^{-1} 3437, 1739 and 1695; δ_H (400; 297 K) 1.41–1.59 (1H, m), 1.43 [9H, s, C(*CH*$_3$)$_3$], 1.67–1.78 (1H, m), 1.91–2.00 (2H, m), 2.79 (1H, m, 6-H_{ax}), 3.70–3.82 (1H, m, 3-H), 3.74 (3H, s, OCH_3), 3.92 (1H, br d, *J ca.* 13.3, 6-H_{eq}) and 4.54 (1H, br, 2-H); δ_H (400; 350 K, d_6-DMSO) 1.38 [9H, s, C(*CH*$_3$)$_3$], 1.38–1.70 (4H, m), 3.09 (1H, ddd, *J* 12.8, 3.0 and 3.0, 6-H_{eq}), 3.62 (3H, s, OCH_3), 3.65–3.80 (2H, m) and 4.67 (1H, br d, *J* 6.4, 2-H); δ_C (100; 297 K) 23.4 and 24.0 (CH_2), 28.3 [C(*C*H_3)$_3$], 30.1 (CH_2), 40.0 and 41.4 (CH_2), 52.3 (OCH_3), 57.3 and 58.9 (CH), 68.9 (br, CH), 80.6 [*C*(CH_3)$_3$], 154.9 (br) and 172.4 (both CO); δ_C (100; 350 K, d_6-DMSO) 22.3

(CH_2), 27.8 (CH_2), 28.0 [C(CH_3)$_3$], 40.0 (br, CH_2), 51.0 (OCH_3), 58.9 (CH), 72.0 (CH), 79.4 [C(CH_3)$_3$], 154.5 and 170.9 (both CO); *m*/*z* 259 (M^+, 2%), 203 (18), 200 (11), 186 (5), 158 (18), 144 (90), 141 (14), 126 (17), 100 (98) and 57 (100) (Found: M^+, 259.1441. $C_{12}H_{21}NO_5$ requires *M*, 259.1420) (Found: C, 55.9; H, 8.7; N, 5.7. $C_{12}H_{21}NO_5$ requires C, 55.6; H, 8.2; N, 5.4%).

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-hydroxymethylpiperidine-1-carboxylate 23a

A solution of the hydroxy ester **20** (2.0 g, 7.7. mmol) in tetrahydrofuran (5 ml) was added to a stirred, ice-cold suspension of lithium aluminium hydride (1.17 g, 30.9 mmol) in tetrahydrofuran (50 ml). After 3 h, 2 M aqueous sodium hydroxide (1.2 ml) was added and after 5 min stirring, the resulting mixture was filtered. The solid residue was washed with dichloromethane (200 ml) and the combined organic solutions washed with water (20 ml) and brine (20 ml) then dried and evaporated to leave the *diol* **23a** (1.28 g, 72%) as a colourless oil, $[a]_D^{22}$ +19.5 (*c*, 1.6, CH_2Cl_2); ν_{max}/cm^{-1} 3425 and 1678; δ_H (400; 300 K) 1.39 [9H, s, C(CH_3)$_3$], 1.42–1.78 (4H, m), 2.25–2.38 (2H, br s, 2 × OH), 2.81 (1H, br t, *J* 13.5, 6-H_{ax}), 3.68–3.72 (1H, m, 6-H_{eq}), 3.70 (1H, dd, *J* 11.3 and 6.5, CH_AH$_B$OH), 3.87 (1H, dt, *J* 10.3 and 4.9, 3-H), 4.03 (1H, dd, *J* 11.3 and 6.4, CH$_A$$H_B$OH) and 4.25 (1H, td, *J ca*. 6.4 and 5.1, 2-H); δ_C (68.5) 23.7, 28.3 (both CH_2), 28.4 [C(CH_3)$_3$], 39.7 (br, CH_2), 56.0 (CH), 59.4 (CH_2), 69.5 (CH), 80.3 (C) and 155.7 (CO); *m*/*z* 158 (M^+ − OBu^t, 12%) and 57 (100) (Found: M^+ − 57, 158.0808. $C_7H_{12}NO_3$ requires *M*, 158.0817).

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-(*tert*-butyldiphenylsilyloxymethyl)piperidine-1-carboxylate 23b

tert-Butyldiphenylsilyl chloride (1.31 g, 4.76 mmol) was added to a solution of the piperidine diol **23a** (1.0 g, 4.3 mmol), triethylamine (0.48 g, 4.8 mmol) and 4-(dimethylamino)pyridine (DMAP) (26 mg) in dichloromethane (100 ml). The resulting solution was stirred at ambient temperature overnight then diluted with dichloromethane (200 ml) and the solution washed with water (50 ml) and brine (50 ml) then dried and evaporated. CC [CH_2Cl_2–EtOAc (9 : 1)] of the residue gave the *silyl ether* **23b** (1.59 g, 78%) as a colourless oil, R_F 0.65; $[a]_D^{22}$ +42.8 (*c*, 3.5, CH_2Cl_2); ν_{max}/cm^{-1} 3424 and 1668; δ_H (400; 300 K) 1.09 [9H, s, SiC(CH_3)$_3$], 1.44 [9H, s, C(CH_3)$_3$], 1.47–1.65 (3H, m), 1.88 [1H, br d, *J* 9.2, 4-(5-)-H_{eq}], 2.64 (1H, br t, *J* 13.3, 6-H_{ax}), 2.89 (1H, br s, OH), 3.84–3.90 (3H, m, 1′-CH_A, 3-H and 6-H_{eq}), 4.10 (1H, dd, *J* 10.4 and 7.2, 1′-CH$_A$$H_B$OSi), 4.58 (1H, td, *J ca*. 6.3 and 6.2, 2-H) and 7.38–7.72 (10H, m, 2 × Ph); δ_C (100) 19.1 (CSi), 24.0 (CH_2), 26.8 [SiC(CH_3)$_3$], 28.4 [C(CH_3)$_3$], 28.9, 38.9 (br, both CH_2), 54.9 (CH), 60.7 (CH_2), 69.9 (CH), 79.1 (C), 127.9, 129.9 (both CH), 132.6 and 132.8 (both C), 135.6 and 135.7 (both CH) and 154.9 (CO); *m*/*z* 396 (M^+ − OBu^t, 3%), 143 (4), 100 (100) and 57 (45) (Found: M^+ − 57, 396.1997. $C_{23}H_{30}NO_3Si$ requires *M*, 396.1995) (Found: C, 69.1; H, 8.6; N, 3.2. $C_{27}H_{39}NO_4Si$ requires C, 69.0; H, 8.4; N, 3.0%).

(2*R*)-*tert*-Butyl 2-(*tert*-butyldiphenylsilyloxymethyl)piperidine-1-carboxylate 25a

1,1′-Thiocarbonyldiimidazole (0.38 g, 2.1 mmol) was added to a stirred solution of the silyl ether **23b** (0.50 g, 1.1 mmol) in dichloromethane (20 ml) and the resulting solution refluxed for 24 h then cooled and evaporated. CC [CH_2Cl_2–EtOAc (9 : 1)] of the residue separated the *thiocarbamate* **23c** (0.57 g, 95%) as a colourless oil, R_F 0.3; δ_H (270) 1.02 [9H, s, SiC(CH_3)$_3$], 1.48 [9H, s, C(CH_3)$_3$], 1.62–2.05 (4H, m), 3.00 (1H, br t, *J* 13.5, 6-H_{ax}), 3.80–4.05 (3H, m, 1′-CH_2OSi and 6-H_{eq}), 4.75–4.82 (1H, m, 2-H), 5.53 (1H, ddd, *J* 12.0, 6.0 and 5.6, 3-H), 7.01 (1H, br s, Im-4-H), 7.26–7.66 (11H, m, 2 × Ph and Im-5-H) and 8.23 (1H, br s, Im-2-H); δ_C (68.5) 19.0 (CSi), 23.7, 25.1 (both CH_2), 26.7 [SiC(CH_3)$_3$], 28.4 [C(CH_3)$_3$], 39.0 (br, CH_2), 60.1 (CH), 60.2 (CH_2), 79.6 (CH), 80.3, 117.9 (both C), 127.8, 127.9, 129.9, 129.9 (all CH), 132.9 (C), 135.5, 135.6 (both CH) and 154.7 (CO).

A solution of the thiocarbamate **23c** (0.57 g, 1.0 mmol), tributyltin hydride (0.29 g, 1.0 mmol) and azoisobutyronitrile (6 mg) in toluene (10 ml) was refluxed for 2 h then cooled and evaporated. CC [CH_2Cl_2–EtOAc (9 : 1)] gave the *piperidine* **25a** (0.24 g, 53%) as a colourless oil, R_F 0.60; $[a]_D^{21}$ +21.7 (*c*, 1.4, CH_2Cl_2); ν_{max}/cm^{-1} 1693; δ_H (270) 0.91 [9H, s, SiC(CH_3)$_3$], 1.22–2.01 (6H, m), 1.29 [9H, s, C(CH_3)$_3$], 2.61 (1H, br t, *J* 13.5, 6-H_{ax}), 3.68 (2H, AB, J_{AB} 10.5, CH_2OSi), 3.95 (1H, br d, *J* 13.5, 6-H_{eq}), 4.36 (1H, br s, 2-H_{eq}) and 7.18–7.60 (10H, m, 2 × Ph); δ_C (68.5) 19.0 (CH_2), 19.1 (CSi), 24.8, 25.3 (both CH_2), 26.8 [SiC(CH_3)$_3$], 28.4 [C(CH_3)$_3$], 39.8 (br, CH_2), 51.6 (br, CH), 61.5 (CH_2), 79.1 (C), 127.6, 129.6 (both CH), 133.6 (C), 135.6 (CH) and 155.1 (CO); *m*/*z* 454 (M^+ + H, 4%), 397 (21), 352 (12) and 199 (100) (Found: M^+ + H, 454.2777. $C_{27}H_{40}NO_3Si$ requires *M*, 454.2777).

(2*R*)-*O*-(*tert*-Butyldiphenylsilyl)-1-(*p*-tolylsulfonyl)piperidine-2-methanol 25b

Trifluoroacetic acid (1.9 g, 16.6 mmol) was added to a stirred solution of the piperidine **25a** (0.25 g, 0.55 mmol) in dichloromethane (20 ml). The resulting solution was stirred at ambient temperature for 1 h then diluted with dichloromethane (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 × 20 ml) before drying and evaporating. The residue was dissolved in dichloromethane (5 ml) and the resulting solution added to a stirred solution of toluene-*p*-sulfonyl chloride (0.21 g, 1.1 mmol), triethylamine (0.23 g, 2.2 mmol) and DMAP (4 mg) in dichloromethane (5 ml). The mixture was stirred at ambient temperature overnight, diluted with dichloromethane (50 ml) and washed with water (10 ml) and brine (10 ml) then dried and evaporated. CC [CH_2Cl_2–EtOAc (9 : 1)] gave the *N-tosylate* **25b** (0.20 g, 70%) as a colourless oil, R_F 0.45; $[a]_D^{22}$ −20.1 (*c*, 1.0, CH_2Cl_2); ν_{max}/cm^{-1} 1343, 1161 and 1116; δ_H (270) 0.97 [9H, s, SiC(CH_3)$_3$], 1.16–1.48 (5H, m), 1.90 (1H, br d, *J* 11.0, H_{eq}), 2.30 (3H, s, CH_3Ar), 2.76 (1H, br t, *J* 11.4, 6-H_{ax}), 3.53–3.72 (3H, m, CH_2OSi and 6-H_{eq}), 4.09–4.20 (1H, m, 2-H_{eq}), 7.13 (2H, d, *J* 8.2, 2 × Ts-H) and 7.28–7.64 (12H, m, 2 × Ph and 2 × Ts-H); δ_C (68.5) 18.4 (CH_2), 19.1 (CSi), 21.4 (CH_3), 24.2, 24.4 (both CH_2), 26.8 [SiC(CH_3)$_3$], 41.8 (CH_2), 53.4 (CH), 61.1 (CH_2), 126.8, 127.7, 127.8, 129.5, 129.7, 129.8 (all CH), 133.2, 133.3 (both C), 135.5 (CH), 138.6 and 142.7 (both C); *m*/*z* 450 (M^+ − Bu^t, 69%), 294 (14), 239 (14), 238 (100) and 155 (13) (Found: M^+ − Bu^t, 450.1557. $C_{25}H_{28}NO_3SSi$ requires *M*, 450.1559).

(2*R*)-*N*,*O*-Bis(*p*-tolylsulfonyl)piperidine-2-methanol 22

Tetrabutylammonium fluoride (TBAF; 0.6 ml of a 1 M solution in tetrahydrofuran, 0.6 mmol) was added to a stirred solution of the foregoing piperidine **25b** (0.15 g, 0.2 mmol) in tetrahydrofuran (0.5 ml) which was then stirred overnight at ambient temperature and diluted with dichloromethane (100 ml). The resulting solution was washed with water (10 ml) and brine (10 ml) then dried and filtered through silica gel. Evaporation of the filtrates left the *alcohol* **25c** (54 mg, 68%) as a colourless oil, $[a]_D^{23}$ +17.3 (*c*, 1.5, CH_2Cl_2); ν_{max}/cm^{-1} 1354, 1184 and 1115; δ_H (400) 1.00–1.38 (5H, m), 1.52 (1H, br d, *J* 13.5, H_{eq}), 2.24 (3H, s, CH_3Ar), 2.90 (1H, br t, *J* 11.4, 6-H_{ax}), 3.46 (1H, dd, *J* 11.4 and 7.0, 6-H_{eq}), 3.61 (2H, m, CH_2OH), 3.87–3.95 (1H, m, 2-H_{eq}), 7.13 (2H, d, *J* 8.2, 2 × Ts-H) and 7.59 (2H, d, *J* 8.2, 2 × Ts-H); δ_C (100) 18.4 (CH_2), 21.0 (CH_3), 23.6, 24.0, 41.0 (all CH_2), 53.9 (CH), 59.8 (CH_2), 128.5, 129.3, (both CH), 138.0 and 142.9 (both C); *m*/*z* 238 (M^+ − CH_2OH, 100%), 84 (12) and 83 (8) (Found: M^+ − CH_2OH, 238.0863. $C_{12}H_{16}NO_2S$ requires *M*, 238.0902).

The foregoing alcohol **25c** (50 mg, 0.19 mmol) was added to a solution of triethylamine (21 mg, 0.2 mmol) and DMAP (2 mg) in dichloromethane (10 ml), followed by toluene-*p*-sulfonyl

chloride (39 mg, 0.2 mmol). The resulting mixture was stirred at ambient temperature overnight, diluted with dichloromethane (20 ml), washed with water (5 ml) and brine (5 ml) then dried and evaporated. CC [CH_2Cl_2–EtOAc (9:1)] separated the *bis-tosylate* **22** (55 mg, 75%) as a colourless oil (lit.,[21] oil), R_F 0.40; $[\alpha]_D^{23}$ +55.0 (*c*, 0.8, EtOH) {lit.,[21] $[\alpha]_D^{18}$ +56.6 (*c*, 1.03, EtOH) for (*R*)-**22**}; ν_{max}/cm^{-1} 1362, 1190, 1177 and 1160; δ_H (400) 1.20–1.53 (5H, m), 1.68 (1H, br d, *J* 12.4, H_{eq}), 2.40 (3H, s, CH_3Ar), 2.44 (3H, s, CH_3Ar), 2.81 (1H, br t, *J* 12.2, 6-H_{ax}), 3.69 (1H, br d, *J* 12.2, 6-H_{eq}), 4.01–4.12 (2H, m, CH_2OTs), 4.18–4.29 (1H, m, 2-H_{eq}), 7.26 (2H, d, *J* 8.2, 2 × Ts-H), 7.40 (2H, d, *J* 8.2, 2 × Ts-H), 7.66 (2H, d, *J* 8.2, 2 × Ts-H) and 7.73 (2H, d, *J* 8.2, 2 × Ts-H); δ_C (100) 18.2 (CH_2), 21.4, 21.5 (both CH_3), 24.0, 24.3, 41.3 (all CH_2), 50.4 (CH), 66.8 (CH_2), 126.7, 127.8, 129.7, 129.9 (all CH), 132.4, 137.7, 143.2 and 145.0 (all C); *m*/*z* 238 ($M^+ - CH_2OTs$, 100%) and 91 (43) (Found: $M^+ - CH_2OTs$, 238.0889. $C_{12}H_{16}NO_2S$ requires *M*, 238.0902) (Found: C, 57.0; H, 6.0; N, 3.5. $C_{20}H_{25}NO_5S_2$ requires C, 56.7; H, 6.0; N, 3.3.%).

A sample of racemic bis-tosylate was obtained from (±)-piperidine-2-methanol by the foregoing method, but using 2.2 equivalents of toluene-*p*-sulfonyl chloride, and showed identical spectroscopic and analytical data as the foregoing sample, with the exception of an optical rotation.

(3*R*,4*S*)-1-(*tert*-Butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate 26

The ethyl 4-oxopiperidine-3-carboxylate **17** (5.0 g, 18.5 mmol) was reduced by fermenting yeast in an identical fashion to that described above for the preparation of the corresponding 3-hydroxy-2-carboxylate **20** and gave the *4-hydroxy-3-carboxylate* **26** (3.73 g, 74%) as a colourless solid, mp 58–60 °C; $[\alpha]_D^{23}$ +25.6 (*c*, 3.4, CH_2Cl_2); ν_{max}/cm^{-1} 3414, 1732 and 1668; δ_H (400; 333 K) 1.21 (3H, t, *J* 7.1, OCH_2CH_3), 1.43 [9H, s, $C(CH_3)_3$], 1.55–1.62 (1H, m, 5-H_{ax}), 1.81 (1H, dddd, *J* 13.9, 4.5, 3.3 and 3.3, 5-H_{eq}), 2.51 (1H, ddd, *J* 10.4, 4.4 and 2.6, 3-H_{ax}), 3.19 (1H, ddd, *J* 14.0, 11.0 and 3.0, 6-H_{ax}), 3.34 (1H, dd, *J* 14.0 and 10.4, 2-H_{ax}), 3.59 (1H, ddd, *J* 14.0, 4.5 and 3.7, 6-H_{eq}), 3.86 (1H, dd, *J* 14.0 and 4.4, 2-H_{eq}), 4.12 (2H, q, *J* 7.1, OCH_2) and 4.15–4.25 (1H, m, 4-H); δ_C (100) 13.9, 28.1 (both CH_3), 31.3, 38.1 (br), 40.3 (br, all CH_2), 45.6 (CH), 60.7 (CH_2), 64.8 (sl. br, CH), 79.5, 154.5 and 172.5 (all C); *m*/*z* 273 (M^+, 2%), 216 (32), 200 (15), 172 (23), 154 (21), 126 (44), 100 (30), 82 (82) and 57 (100) (Found: M^+, 273.1600. $C_{13}H_{23}NO_5$ requires *M*, 273.1576) (Found: C, 57.0; H, 8.4; N, 5.1. $C_{13}H_{23}NO_5$ requires C, 57.1; H, 8.5; N, 5.1%).

(3*R*,4*S*)-1-*tert*-Butyl 3-ethyl 4-acetyloxypiperidine-1,3-dicarboxylate 28

To a stirred solution of the foregoing 4-hydroxypiperidine-3-carboxylate **26** (0.31 g, 1.1 mmol) in tetrahydrofuran (10 ml) was added acetic anhydride (0.55 ml, 5.7 mmol) and DMAP (5 mg). After 0.5 h at ambient temperature, the volatiles were evaporated and the residue dissolved in ether (10 ml). The resulting solution was washed with saturated aqueous sodium hydrogen carbonate (3 × 2 ml) then dried and evaporated. CC [40–60 petrol–ether (2:1)] separated the *acetate* **28** (0.26 g, 62%) as a colourless oil, R_F 0.4; ν_{max}/cm^{-1} 1740 and 1700; δ_H (400) 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.46 [9H, s, $C(CH_3)_3$], 1.73 (1H, br t, *J ca.* 12.8, 5-H_{ax}), 1.94 (1H, ddd, *J* 14.4, 3.2 and 3.0, 5-H_{eq}), 2.05 (3H, s, OAc), 2.85 (1H, ddd, *J* 11.1, 4.6 and 3.2, 3-H_{ax}), 3.05 (1H, apparent br t, *J ca.* 11.5, 6-H_{ax}), 3.30 (1H, apparent br t, *J ca.* 10.1, 2-H_{ax}), 3.70–4.00 (1H, m, 6-H_{eq}), 4.20–4.40 (1H, m, 2-H_{eq}), 4.17–4.24 (2H, m, OCH_2) and 5.48 (1H, apparent q, *J ca.* 3.2, 4-H); δ_C (100; 377 K, d_6-DMSO) 17.2 (CH_3), 23.8 (CH_3CO), 31.5 (CH_3), 31.7, 42.4, 44.4 (all CH_2), 47.0 (CH), 63.4 (CH_2), 71.5 (CH), 82.5, 157.4, 172.5 and 173.2 (all C); *m*/*z* 258 ($M^+ - Bu^t$, 8%), 214 (10), 199 (10), 170 (6), 155 (21), 126 (43), 110 (26), 82 (97) and 57 (100) (Found: $M^+ - Bu^t$, 258.0948. $C_{11}H_{16}NO_6$ requires *M*, 258.0978).

(3*S*,4*S*)-*tert*-Butyl 4-hydroxy-3-(*tert*-butyldiphenylsilyloxymethyl)piperidine-1-carboxylate 30b

A sample of the foregoing 4-hydroxy-3-carboxylate **26** (2.0 g, 7.3 mmol) was reduced using the same method ($LiAlH_4$) detailed above for the reduction of the 3-hydroxy-2-carboxylate **20** and gave the *diol* **30a** (1.22 g, 72%) as a thick, colourless oil, R_F 0.56; $[\alpha]_D^{27}$ +16.0 (*c*, 1.66, CH_2Cl_2); ν_{max}/cm^{-1} 3420 and 1670; δ_H (400) 1.45 [9H, s, $C(CH_3)_3$], 1.60–1.91 (3H, m), 3.40–3.52 (2H, m) and 3.70–4.18 (5H, m); δ_C (68.5) 25.6 (CH_2), 28.4 (CH_3), 32.0, 39.3 (br, both CH_2), 41.7 (CH), 62.5 (CH_2, sl. br), 67.4 (CH), 79.8 and 155.3 (both C); *m*/*z* 231 (M^+, 2%), 174 (12), 157 (13), 126 (13), 112 (6), 100 (10), 82 (16) and 57 (100) (Found: M^+, 231.1501. $C_{11}H_{21}NO_4$ requires *M*, 231.1471).

The diol **30a** (1.0 g, 4.3 mmol) was monosilylated using the same method as in the preparation of the silyl ether **23b** to give the *silyl ether* **30b** (1.60 g, 79%) as a colourless oil, R_F 0.7; $[\alpha]_D^{21}$ +10.6 (*c*, 2.0, CH_2Cl_2); ν_{max}/cm^{-1} 3422 and 1665; δ_H (270) 1.06 [9H, s, $SiC(CH_3)_3$], 1.43 [9H, s, $C(CH_3)_3$], 1.49–1.78 (3H, m), 3.20–3.35 (2H, m), 3.75–3.92 (4H, m), 4.21 (1H, br s, 4-H_{eq}), 7.26–7.48 (6H, m) and 7.62–7.71 (4H, m); δ_C (68.5; 333 K) 19.1 (C), 26.8, 28.4 (both CH_3), 32.3, 38.7 (both CH_2), 41.4 (CH), 41.5, 65.6 (both CH_2), 67.9 (CH), 79.4 (C), 127.9, 130.0 (both CH), 132.5 (C), 135.6 (CH) and 155.0 (C); *m*/*z* (NH_3 chemical ionization) 470 (M^+ + H, 45%), 414 (36), 370 (100), 336 (73), 312 (11), 278 (21) and 258 (14) (Found: M^+ + H, 470.2701. $C_{27}H_{40}NO_4Si$ requires *M*, 470.2726).

(3*S*)-*tert*-Butyl 3-(*tert*-butyldiphenylsilyloxymethyl)piperidine-1-carboxylate 31a

Pentafluorophenyl chlorothioformate (1.24 g, 4.7 mmol) was added to a stirred solution of the foregoing silyl ether **30b** (0.37 g, 0.79 mmol), pyridine (0.13 g, 1.6 mmol) and *N*-hydroxysuccinimide (18 mg) in benzene (20 ml). The mixture was refluxed for 5h then cooled and evaporated. CC [CH_2Cl_2–EtOAc (9:1)] of the residue gave the *thiocarbonate* **30c** (0.50 g, 91%) as a colourless oil, R_F 0.85; δ_H (270) 0.83 [9H, s, $SiC(CH_3)_3$], 1.41 [9H, s, $C(CH_3)_3$], 1.49–2.38 (3H, m), 2.55–3.23 (2H, m), 3.40–3.62 (2H, m), 3.72–4.04 (2H, m), 5.64 (1H, br s, 4-H_{eq}) and 7.24–7.65 (10H, m). The sample was carried through to the next step without delay.

The thiocarbonate **30c** (0.50 g, 0.72 mmol) was refluxed with tributyltin hydride (0.21 g, 0.72 mmol) and azoisobutyronitrile (6 mg) in benzene (20 ml) for 0.5 h. The cooled solution was evaporated; CC [CH_2Cl_2–EtOAc (9:1)] of the residue gave the *piperidine-3-methanol* **31a** (0.28 g, 58%) as a colourless oil, R_F 0.70; $[\alpha]_D^{25}$ +12.6 (*c*, 1.15, CH_2Cl_2); ν_{max}/cm^{-1} 1665; δ_H (400) 1.00–1.30 (2H, m), 1.11 [9H, s, $SiC(CH_3)_3$], 1.47 [9H, s, $C(CH_3)_3$], 1.45–1.60 (2H, m), 1.75 (1H, m), 2.50–2.62 (1H, m), 2.62–2.75 (1H, m), 3.49–3.56 (2H, m), 4.00 (1H, m), 4.20 (1H, m), 7.30–7.42 (6H, m) and 7.63–7.75 (4H, m); δ_C (100; 333 K) 19.0 and 19.3 (C), 24.7 (CH_2), 26.9 (CH_3), 27.2 (CH_2), 28.6 (CH_3), 38.7 (CH), 44.4 (sl. br), 47.5 (br), 66.4 (all CH_2), 79.8 (C), 127.7, 129.6, 129.7, (all CH), 133.7 (C), 134.9, 135.4, 135.6 (all CH) and 155.1 (C); *m*/*z* 454 (M^+ + H, 10%), 396 (7), 352 (35), 199 (100) and 198 (46) (Found: M^+ + H, 454.2778. $C_{27}H_{40}NO_3Si$ requires *M*, 454.2777).

(3*S*)-*N*-(*p*-Tolylsulfonyl)piperidine-3-methanol 31c

The foregoing *N*-Boc-piperidine **31a** (0.20 g) was deprotected at nitrogen using trifluoroacetic acid, as described above for the 2-isomer **25a**, to give the free amine which was immediately treated with toluene-*p*-sulfonyl chloride, as described above, to give (3*S*)-*O*-(*tert-butyldiphenylsilyl*)-*N*-(*p-tolylsulfonyl*)*piperidine-3-methanol* **31b** (0.17 g, 74%) as a colourless oil, R_F 0.60; $[\alpha]_D^{25}$ −22.3 (*c*, 1.1, $CHCl_3$); ν_{max}/cm^{-1} 1673, 1361 and 1114; δ_H (270) 1.03 [9H, s, $SiC(CH_3)_3$], 1.42–1.97 (4H, m), 2.12 (1H, br t, *J* 10.5), 2.26 (1H, td, *J* 11.7 and 3.5), 2.43 (3H, s, CH_3Ar), 3.41–3.78 (5H, m), 7.28–7.46 (8H, m) and 7.58–7.68 (6H, m); δ_C

(68.5) 14.0 (CH_3), 19.2 (C), 24.1, 25.6 (both CH_2), 26.3 (CH_3), 38.2 (CH), 46.7, 60.3, 66.0 (all CH_2), 127.6, 129.3 and 129.5 (all CH), 133.2 and 133.3 (both C), 134.3, 135.6 (both CH) and 143.3 (C); *m*/*z* 450 ($M^+ - Bu^t$, 1%), 199 (100), 78 (7) and 77 (12) (Found: $M^+ - Bu^t$, 450.1576. $C_{25}H_{28}NO_3SSi$ requires *M*, 450.1559).

The foregoing *N*-tosylate **31b** (0.10 g, 0.2 mmol) was deprotected at oxygen using TBAF, exactly as outlined in the preparation of the corresponding piperidine-2-methanol **25c**, and gave the *piperidine-3-methanol* **31c** (53 mg, 78%) as a colourless oil, $[\alpha]_D^{21}$ −16.5 (*c*, 3.0, $CHCl_3$); ν_{max}/cm^{-1} 3304, 1379 and 1149; δ_H (270) 0.99–1.10 (1H, m), 1.50–1.97 (3H, m), 2.24 (1H, br t, *J ca*. 11), 2.44 (3H, s, CH_3Ar), 2.29–2.53 (1H, m), 3.18–3.71 (5H, m), 7.30 (2H, d, *J* 8.3, 2 × Ar-H) and 7.62 (2H, m); δ_C (68.5) 21.4 (CH_3), 23.9, 26.1 (both CH_2), 38.0 (CH), 46.5, 49.0, 64.7 (all CH_2), 127.6, 129.5 (both CH), 133.0 and 143.4 (both C); *m*/*z* 269 (M^+, 1%), 115 (8), 114 (100), 91 (69), 84 (7) and 83 (6) (Found: C, 58.2; H, 7.2; N, 5.4. $C_{13}H_{19}NO_3S$ requires C, 58.0; H, 7.1; N, 5.2%).

(3*S*)-*N*,*O*-Bis(*p*-tolylsulfonyl)piperidine-3-methanol 31d

The foregoing alcohol (50 mg, 0.19 mmol) was converted into the bis-tosylate **31d** (46 mg, 63%), as described above for the corresponding 2-isomer **22**. The compound **31d** crystallized from methanol as a colourless solid, mp 88–89 °C [lit.,[29] mp 87–89 °C for the (*R*)-enantiomer], $[\alpha]_D^{25}$ −50.2 (*c*, 1.1, $CHCl_3$) {lit.,[29] $[\alpha]_D^{25}$ +54 (*c*, 1.0, $CHCl_3$) for the (*R*)-enantiomer}; ν_{max}/cm^{-1} 1359, 1342 and 1175; δ_H (400) 1.03–1.11 (1H, m), 1.49–1.65 (2H, m), 1.93–1.97 (1H, m), 2.22 (1H, apparent t, *J* 9.5), 2.31–2.41 (1H, m, partly obsc.), 2.39 (3H, s, CH_3Ar), 2.44 (3H, s, CH_3Ar), 2.48–2.55 (1H, m), 3.39–3.47 (2H, m), 3.83 (1H, dd, *J* 10.0 and 6.6, CH_AH_BOTs), 3.91 (1H, dd, *J* 10.0 and 6.0, CH_AH_BOTs), 7.25 (2H, d, *J* 8.3, 2 × Ar-H), 7.30 (2H, d, *J* 8.3, 2 × Ar-H), 7.55 (2H, d, *J* 8.3, 2 × Ar-H) and 7.72 (2H, d, *J* 8.3, 2 × Ar-H); δ_C (100) 21.5, 21.7 (both CH_3), 23.5, 25.7 (both CH_2), 35.1 (CH), 46.6, 48.3, 71.4 (all CH_2), 127.6, 127.9, 129.0, 129.7, (all CH), 132.6, 132.9, 143.6 and 145.0 (all C); *m*/*z* 269 ($M^+ - Ts + H$, 4%), 268 (27), 252 (4), 97 (7), 96 (100), 91 (50), 82 (6) and 69 (22) (Found: C, 56.8; H, 6.0; N, 3.2. $C_{20}H_{25}NO_5S_2$ requires C, 56.7; H, 6.0; N, 3.3%).

A sample of racemic bis-tosylate was obtained from (±)-piperidine-3-methanol by the same method, but using 2.2 equivalents of toluene-*p*-sulfonyl chloride; the product had mp 87–89 °C and did not show an optical rotation but was otherwise identical according to spectroscopic and analytical analysis.

(3*R*,4*R*)-4-Ethyl 1-methyl 3-hydroxypiperidine-1,4-dicarboxylate 32

The *N*-methoxycarbonyl-3-oxopiperidine-4-carboxylate **18** (5.0 g, 21.8 mmol) was reduced with fermenting yeast exactly as described for the 3-oxo-2-carboxylate **16** and gave the *3-hydroxy-4-carboxylate* **32** (4.49 g, 89%) as an oil, $[\alpha]_D^{21}$ −21.4 (*c*, 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3460, 1732 and 1690; δ_H (400) 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.76 (1H, br d, *J* 13.5, 5-H_{eq}), 2.07 (1H, dddd, *J* 13.5, 11.9, 11.9 and 4.4, 5-H_{ax}), 2.56 (1H, ddd, *J* 11.9, 4.0 and 2.4, 4-H_{ax}), 2.87 (1H, br dd, *J* 12.5 and 11.9, 6-H_{ax}), 3.00 (1H, br d, *J* 13.0, 2-H_{ax}), 3.70 (3H, s, OCH_3), 4.10–4.20 (3H, m) and 4.21 (2H, q, *J* 7.1, OCH_2); δ_C (68.5) 14.0 (CH_3), 22.2, 42.9 (both CH_2), 45.1 (CH), 48.9 (CH_2), 52.9 (CH_3), 60.8 (CH_2), 64.9 (CH; sl. br), 156.6 and 171.0 (sl. br) (both CO); *m*/*z* (FAB) 232 ($M^+ + H$, 100%), 214 (14), 200 (21), 186 (13) and 172 (6) (Found: $M^+ + H$, 232.1175. $C_{10}H_{18}NO_5$ requires *M*, 232.1185) (Found: C, 51.5; H, 8.1; N, 5.8. $C_{10}H_{17}NO_5$ requires C, 51.7; H, 7.8; N, 6.0%).

(3*R*,4*R*)-4-Ethyl 1-methyl 3-acetoxypiperidine-1,4-dicarboxylate 34

To a solution of the foregoing 3-hydroxypiperidine-4-carboxylate **32** (0.20 g, 0.87 mmol) in dry pyridine (1 ml) was added acetic anhydride (0.08 ml, 0.87 mmol) and the resulting solution stirred at ambient temperature overnight then diluted with ether (10 ml). The resulting solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 5 ml) and saturated aqueous copper(II) sulfate (2 × 5 ml) then dried and filtered through silica. Evaporation of the filtrates left the *acetate* **34** (0.13 g, 55%) as a colourless oil, ν_{max}/cm^{-1} 1739 and 1704; δ_H (400; 333 K) 1.15 (3H, t, *J* 7.2, OCH_2CH_3), 1.77 (1H, br d, *J ca*. 11.7, 5-H_{eq}), 1.80–2.05 (1H, m, 5-H_{ax}), 1.92 (3H, s, CH_3CO), 2.59 (1H, ddd, *J* 12.0, 4.1 and 3.2, 4-H_{ax}), 2.60–2.80 (1H, m, 6-H_{ax}), 2.92 (1H, br d, *J ca*. 12.0, 2-H_{ax}), 3.61 (3H, s, OCH_3), 3.95–4.35 (4H, m) and 5.10–5.25 (1H, app br s, $w_{\frac{1}{2}}$ 6.0, 3-H_{eq}); δ_C (68.5) 15.6 (CH_3), 22.1 (CH_3CO), 23.9, 44.5 (both CH_2), 45.5 (CH), 48.2 (CH_2), 54.1 (CH_3), 62.2 (CH_2), 68.8 (CH), 157.8, 171.4 and 172.5 (all C); *m*/*z* 228 (M^+ − OEt, 4%), 213 (19), 186 (18), 140 (100) and 43 (29) (Found: M^+ − OEt, 228.0832. $C_{10}H_{14}NO_5$ requires *M*, 228.0870).

(3*R*,4*S*)-Methyl 3-hydroxy-4-hydroxymethylpiperidine-1-carboxylate 35a

Sodium borohydride (4.84 g, 130 mmol) was added in portions during 10 min to a stirred solution of the hydroxy ester **32** (3.0 g, 13 mmol) in methanol (100 ml), maintained at 0 °C. The resulting solution was stirred overnight with no further addition of coolant then evaporated. The residue was dissolved in dichloromethane (300 ml) and water (20 ml). The separated organic solution was washed with brine (20 ml) then dried and evaporated. CC (EtOAc) gave the *diol* **35a** (1.70 g, 68%) as a colourless oil, R_F 0.20; ν_{max}/cm^{-1} 3430 and 1680; δ_H (270) 1.18–1.85 (3H, m), 2.62–3.06 (2H, m), 3.55–3.84 (2H, m), 3.61 (3H, s, OCH_3) and 3.90–4.20 (3H, m); δ_C (68.5) 22.2 (CH_2), 41.2 (CH), 43.7, 50.1 (both CH_2), 52.6 (CH_3), 64.4 (CH_2), 66.1 (CH) and 156.9 (C); *m*/*z* 189 (M^+, 10%), 171 (16), 153 (11), 151 (13), 141 (14), 140 (82), 130 (23), 115 (14), 102 (100), 88 (24), 83 (14), 71 (16) and 59 (20) (Found: M^+, 189.1045. $C_8H_{15}NO_4$ requires *M*, 189.1001) (Found: C, 50.5; H, 8.2; N, 7.5. $C_8H_{15}NO_4$ requires C, 50.8; H, 8.0; N, 7.4%).

(1*R*,5*S*)-Methoxycarbonyl-2-oxa-8-azabicyclo[3.4.0]nonan-2-one 36

The foregoing diol **35a** (1.0 g, 5.3 mmol) in dichloromethane (25 ml) was added to a stirred solution of toluene-*p*-sulfonyl chloride (1.11 g, 5.8 mmol) and triethylamine (0.59 g, 5.8 mmol) in dichloromethane (25 ml). The mixture was stirred at ambient temperature overnight then diluted with dichloromethane (100 ml) and the resulting suspension washed with water (20 ml), 2 M hydrochloric acid (30 ml) and brine (10 ml), then dried and evaporated. CC [CH_2Cl_2–EtOAc (1:1)] separated the *monotosylate* **35b** (1.52 g, 84%) as a colourless oil, R_F 0.60; ν_{max}/cm^{-1} 3425, 1678, 1190 and 1160; δ_H (400) 1.43 (1H, br d, *J* 13.3, 5-H_{eq}), 1.51 (1H, dddd, *J* 13.3, 12.8, 12.8 and 4.4, 5-H_{ax}) 1.94–2.00 (1H, m, 4-H_{ax}), 2.03 (1H, br s, OH), 2.45 (3H, s, Ts-CH_3), 2.73 (1H, br t, *J ca*.11.8, 6-H_{ax}), 2.87 (1H, br d, *J* 13.9, 2-H_{ax}), 3.68 (3H, s, OCH_3), 3.70–3.93 (2H, m), 4.07–4.19 (3H, m), 7.35 (2H, d, *J* 8.2, 2 × Ts-H) and 7.79 (2H, d, *J* 8.2, 2 × Ts-H); δ_C (68.5) 21.4 (CH_3), 21.8 (CH_2), 39.6 (CH), 43.2, 49.8 (both CH_2), 52.6 (CH_3), 63.9 (CH), 71.2 (CH_2), 127.7, 129.7 (both 2 × CH), 132.6, 144.7 and 156.7 (all C); *m*/*z* 284 ($M^+ - CO_2Me$, 3%), 231 (5), 188 (5), 172 (6), 170 (5), 156 (10), 154 (15), 153 (100), 142 (10), 140 (34), 130 (11), 114 (21), 112 (14), 102 (49), 91 (30) and 88 (12) (Found: $M^+ - CO_2Me$, 284.0955. $C_{13}H_{18}NO_4S$ requires *M*, 284.0957).

The foregoing tosylate **35b** (0.50 g, 1.5 mmol) was added to a stirred suspension of sodium cyanide (0.18 g, 3.6 mmol) in dimethyl sulfoxide (10 ml) and the mixture heated to 50 °C for 6 h, then cooled and a small sample (*ca*. 0.5 ml) removed, added to cold water (5 ml) and the product extracted into dichloro-

methane (2 × 5 ml). The combined extracts were washed with water (2 × 3 ml) then dried and evaporated to leave essentially pure nitrile **35c** which showed δ_H 1.54–1.77 (2H, m), 1.87–1.99 (1H, m), 2.39 (1H, dd, *J* 12.2 and 5.8, CH_AH$_B$CN), 2.53 (1H, dd, *J* 12.2 and 6.3, CH$_A$$H_B$CN), 2.80 (1H, br t, *J ca.*12.0, 6-H$_{ax}$), 2.93 (1H, br d, *J ca.* 13.5, 2-H$_{ax}$), 3.69 (3H, s, OCH$_3$), 3.90 (1H, br s, OH) and 4.04–4.35 (3H, m); δ_C 20.0, 25.0 (both CH$_2$), 37.3 (CH), 43.4, 49.8 (both CH$_2$), 52.7 (OMe), 65.3 (CH), 118.7 (CN) and 156.8 (CO). The sample was returned to the bulk of the DMSO solution which was then treated with concentrated hydrochloric acid (50 ml) and the resulting solution stirred at ambient temperature overnight then extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with water (20 ml) and brine (20 ml) then dried and evaporated. CC [CH$_2$Cl$_2$–EtOAc (1:1)] of the residue separated the *lactone* **36** (0.26 g, 88%) as a colourless oil, R_F 0.50; $[\alpha]_D^{23}$ −22.4 (*c*, 1.13, CHCl$_3$); ν_{max}/cm^{-1} 1780 and 1701; δ_H (400) 1.27–1.55 (1H, m, 6-H), 1.69–1.83 (1H, m, 6-H), 2.26 (1H, dd, *J* 17.8 and 2.0, 4-H$_a$), 2.44–2.58 (1H, m, 5-H), 2.67 (1H, dd, *J* 17.8 and 7.6, 4-H$_b$), 2.76–3.05 (1H, m, 7-H$_{ax}$), 3.25 (1H, br d, *J* 13.5, 9-H$_{ax}$), 3.65 (3H, s, OCH$_3$), 4.00–4.15 (1H, m, 7-H$_{eq}$), 4.20 (1H, br d, *J* 13.5, 9-H$_{eq}$) and 4.37 (1H br res, 1-H); δ_C (68.5) 26.5, 30.1 (both CH$_2$), 33.2 (CH), 41.6, 44.6 (both CH$_2$), 53.3 (CH$_3$), 76.4 (CH), 156.6 and 176.8 (both C); *m*/*z* 199 (M$^+$, 42%), 168 (12), 154 (22), 140 (100), 114 (49), 102 (39) and 59 (18) (Found: M$^+$, 199.0840. C$_9$H$_{13}$NO$_4$ requires *M*, 199.0845).

(3*R*,4*R*)-1-*tert*-Butyl 4-methyl 3-hydroxypiperidine-1,4-dicarboxylate 37

The *N*-*tert*-butoxycarbonyl-3-oxopiperidine-4-carboxylate **19** (5.0 g, 19.45 mmol) was reduced with fermenting yeast exactly as described for the 3-oxo-2-carboxylate **16** and gave the *3-hydroxy-4-carboxylate* **37** (4.08 g, 81%) as an oil, $[\alpha]_D^{25}$ −32.7 (*c*, 1.0, CHCl$_3$); ν_{max}/cm^{-1} 3450, 1735 and 1690; δ_H (270) 1.46 [9H, s, C(CH_3)$_3$], 1.73 (1H, br d, *J ca.* 13.5, 5-H$_{eq}$), 2.07 (1H, dddd, *J* 13.5, 11.5, 11.5 and 4.5, 5-H$_{ax}$), 2.56 (1H, ddd, *J* 10.6, 3.0 and 3.0, 4-H$_{ax}$), 2.83 (1H, ddd, *J ca.* 11.5, 11.5 and 3.6, 6-H$_{ax}$), 2.97 (1H, br d, *J* 13.2, 2-H$_{ax}$), 3.73 and 3.78 (3H, 2 × s, OCH$_3$) and 4.03–4.19 (3H, m); δ_C (68.5) 22.2 (CH$_2$), 28.3 (CH$_3$), 42.8 (CH$_2$), 45.2 (CH), 48.9 (CH$_2$), 51.8 (CH$_3$), 65.2 (CH), 79.8 (C), 155.5 and 172.0 (both C); *m*/*z* 200 (M$^+$ − CO$_2$Me, 7%), 158 (16), 144 (43), 141 (8), 126 (14), 100 (72) and 57 (100) (Found: M$^+$ − CO$_2$Me, 200.1269. C$_{10}$H$_{18}$NO$_3$ requires *M*, 200.1287) (Found: C, 55.6; H, 8.1; N, 5.6. C$_{12}$H$_{21}$NO$_5$ requires C, 55.6; H, 8.2; N, 5.4%).

(3*R*,4*R*)-*tert*-Butyl 4-acetyl-3-(methoxymethoxy)piperidine-1 carboxylate 38a

Chloromethyl methyl ether (6.22 g, 77.2 mmol) was added to an ice-cooled, stirred solution of the hydroxy ester **37** (4.0 g, 15.4 mmol) and diisopropylethylamine (5.0 g, 38.6 mmol) in dichloromethane (200 ml). The resulting mixture was stirred overnight without further cooling then washed with 2 M hydrochloric acid (2 × 40 ml) and brine (50 ml) then dried and evaporated. CC [EtOAc–CH$_2$Cl$_2$ (9:1)] gave the *MOM ether* **38a** (4.3 g, 92%) as a colourless oil, R_F 0.6, $[\alpha]_D^{25}$ +23.4 (*c*, 0.9, CHCl$_3$); ν_{max}/cm^{-1} 1734 and 1687; δ_H (270) 1.46 [9H, s, C(CH_3)$_3$], 1.74 (1H, br d, *J ca.* 13.5, 5-H$_{eq}$), 2.02 (1H, dddd, *J ca.* 13.5, 11.5, 11.5 and 4.0, 5-H$_{ax}$), 2.57 (1H, ddd, *J* 11.5, 3.0 and 3.0, 4-H$_{ax}$), 2.64–2.89 (1H, m, 6-H$_{ax}$), 2.97 (1H, br d, *J* 13.2, 2-H$_{ax}$), 3.33 (3H, s, CH_3OCH$_2$), 3.75 (3H, s, OCH$_3$), 4.02–4.48 (3H, m), 4.55 (1H, d, *J* 7.0, OCH_AH$_B$) and 4.76 (1H, d, *J* 7.0, OCH$_A$$H_B$); δ_C (68.5) 22.4 (sl. br, CH$_2$), 28.8 (CH$_3$), 42.6 and 42.9 (br, CH$_2$), 45.8 (CH), *ca.* 46.1 (br, CH$_2$), 52.1, 56.0 (both CH$_3$), 70.0 (sl. br; CH), 80.0 (C), 94.9 (sl. br; OCH$_2$O), 154.8 and 172.0 (both C); *m*/*z* 244 (M$^+$ − CO$_2$Me, 8%), 202 (7), 188 (29), 158 (41), 144 (22), 112 (16), 98 (14), 71 (22) and 57 (100) (Found: M$^+$ − CO$_2$Me, 244.1553. C$_{12}$H$_{22}$NO$_4$ requires *M*, 244.1549).

Methyl (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-(methoxymethoxy)-piperidine-4-acetate 39

The foregoing *O*-MOM-ester **38a** (1.00 g, 3.3 mmol) was added to a stirred solution of potassium hydroxide (0.92 g, 16.5 mmol) in water (10 ml). The resulting mixture was stirred at ambient temperature overnight, then washed with ether (2 × 3 ml) and acidified to pH 2 using 2 M citric acid. The liberated carboxylic acid was extracted into chloroform (3 × 30 ml). The combined extracts were dried and evaporated to leave the *acid* **38b** (0.94 g, 98%) as a thick, colourless oil, ν_{max}/cm^{-1} 3275 and 1691; δ_H (400) 1.45 [9H, s, C(CH_3)$_3$], 1.68–1.80 (1H, m, 5-H$_{eq}$), 2.03 (1H, dddd, *J ca.* 13.5, 11.5, 11.5 and 4.0, 5-H$_{ax}$), 2.63 (1H, br d, *J ca.* 12.5, 4-H$_{ax}$), 2.70–2.86 (1H, m, 6-H$_{ax}$), 2.87 (1H, br d, *J ca.* 14.0, 2-H$_{ax}$), 3.36 (3H, s, CH_3OCH$_2$), 3.92–4.49 (3H, m), 4.61 (1H, d, *J* 7.0, OCH_AH$_B$) and 4.78 (1H, d, *J* 7.0, OCH$_A$$H_B$); δ_C (68.5) 20.8 (CH$_2$), 28.2 (CH$_3$), 42.5 and 42.9 (br, CH$_2$), 45.1 (CH), *ca.* 46.2 (br, CH$_2$), 55.5 (CH$_3$), 69.2 (br, CH), 79.7 (C), 94.5 (br, OCH$_2$O), 155.0 and 176.9 (both C); *m*/*z* (FAB) 312 (M$^+$ + Na, 35%), 290 (M$^+$ + H, 66), 234 (73), 202 (100), 190 (22), 172 (43), 158 (20) and 128 (33) (Found: M$^+$ + H, 290.1614. C$_{13}$H$_{24}$NO$_6$ requires *M*, 290.1604).

Freshly distilled oxalyl chloride (1.1 ml, 8.6 mmol) was added to an ice-cold, stirred solution of the foregoing acid **38b** (0.50 g, 1.7 mmol) and dimethylformamide (10 µl) in ether (25 ml). The resulting mixture was stirred for 0.5 h at 0 °C then for 1.5 h without cooling and the volatiles evaporated. The residue was dissolved in ether (10 ml) and the resulting solution treated with an excess of ice-cold, ethereal diazomethane. After 16 h, the solvent was evaporated and the residue purified by CC [EtOAc–CH$_2$Cl$_2$ (9:1)] to give the *diazo ketone* **38c** (0.41 g, 75%) as a colourless oil, R_F 0.5; ν_{max}/cm^{-1} 2253, 1734 and 1686; δ_H (250) 1.45 [9H, s, C(CH_3)$_3$], 3.40 (3H, s, CH_3OCH$_2$), 4.68 (1H, d, *J* 7.0, OCH_AH$_B$), 4.72 (1H, d, *J* 7.0, OCH$_A$$H_B$) and 5.31 (1H, s, CHN$_2$).

Silver benzoate (14 mg) and triethylamine (0.05 ml) were added to a solution of the diazo ketone **38c** (0.41 g) in methanol (15 ml) and the mixture stirred overnight at ambient temperature then evaporated. CC [EtOAc–CH$_2$Cl$_2$ (9:1)] of the residue gave the homologated *ester* **39** (0.24 g, 62%) as a colourless oil, R_F 0.6, $[\alpha]_D^{25}$ +18.0 (*c*, 1.4, CHCl$_3$); ν_{max}/cm^{-1} 1740 and 1684; δ_H (400) 1.40–1.68 (2H, m), 1.45 [9H, s, C(CH_3)$_3$], 1.77–1.91 (1H, m), 2.05–2.60 (2H, m), 2.80 (1H, br t, *J* 11.9, 6-H$_{ax}$), 3.08–3.20 (1H, m, 2-H$_{ax}$), 3.55 (3H, s, CH_3OCH$_2$), 3.69 (3H, s, CO$_2$CH$_3$), 4.10–4.40 (3H, m), 4.57 (1H, d, *J* 7.0, OCH_AH$_B$) and 4.75 (1H, d, *J* 7.0, OCH$_A$$H_B$); δ_C (68.5) 25.8 (CH$_2$), 28.2 (CH$_3$), 30.9 (CH$_2$), 34.5 (CH), 41.0, 46.2 (both CH$_2$), 51.9, 55.4 (both CH$_3$), 69.7 (CH), 79.5 (C), 95.6 (CH$_2$), 154.8 and 172.0 (both C); *m*/*z* 216 (M$^+$ − CO$_2$Bu^t, 10%), 199 (43), 172 (16), 126 (40), 82 (45) and 57 (100) (Found: M$^+$ − CO$_2$Bu^t, 216.1238. C$_{10}$H$_{18}$NO$_4$ requires *M*, 216.1236).

(3*R*)-3-Hydroxy-1-azabicyclo[2.2.2]octane [(*R*)-quinuclidin-3-ol] 41b

Diisobutylaluminium hydride (1.7 ml of a 1.5 M solution in toluene, 2.52 mmol) was added dropwise to a stirred solution of the foregoing ester **39** (0.20 g, 0.63 mmol) in toluene (10 ml) maintained at −78 °C. After 6 h at this temperature, saturated aqueous potassium tartrate (2 ml) was added followed by dichloromethane (100 ml). The resulting suspension was warmed to ambient temperature, washed with water (2 × 5 ml) and brine (10 ml) then dried and evaporated. CC [EtOAc–CH$_2$Cl$_2$ (1:1)] of the residue gave the *alcohol* **40a** (0.10 g, 55%) as a colourless oil, R_F 0.6; ν_{max}/cm^{-1} 3270 and 1688; δ_H (250) 1.27–1.52 (1H, m, 5-H$_{eq}$), 1.42 [9H, s, C(CH_3)$_3$], 1.63 (1H, ddd, *J* 13.6, 11.2 and 7.3, 5-H$_{ax}$), 1.70–1.90 (3H, m), 2.60–2.85 (2H, m), 3.40 (3H, s, CH_3OCH$_2$), 3.54–3.71 (2H, m, CH_2OH), 3.85–3.92 (1H, m, 6-H$_{eq}$), 3.94–4.40 (2H, m), 4.61 (1H, d, *J* 7.0, OCH_AH$_B$) and 4.80 (1H, d, *J* 7.0, OCH$_A$$H_B$).

Methanesulfonyl chloride (0.7 g, 0.55 mmol) was added to a

stirred solution of the foregoing alcohol **40a** (80 mg, 0.28 mmol) and pyridine (50 μl) in dichloromethane (5 ml) maintained at 0 °C. After 3 h, the reaction mixture was diluted with dichloromethane (10 ml) and the suspension washed with water (2 × 5 ml) and brine (5 ml) then dried and evaporated to leave the *mesylate* **40b** (63 mg, 62%) as a colourless oil, ν_{max}/cm^{-1} 1690, 1112 and 1160; δ_H (250) 1.36–1.78 (3H, m), 1.46 [9H, s, $C(CH_3)_3$], 1.98–2.16 (2H, m), 2.49–2.87 (2H, m), 3.01 (3H, s, CH_3SO_2), 3.49 (3H, s, CH_3OCH_2), 3.81–3.86 (2H, m), 4.03–4.51 (3H, m), 4.57 (1H, d, *J* 7.0, OCH_AH_B) and 4.80 (1H, d, *J* 7.0, OCH_AH_B).

Trifluoroacetic acid (1.1 ml) was added to a stirred solution of the foregoing crude mesylate (192 mg, 0.51 mmol) in dichloromethane (15 ml). After 1 h, the solution was diluted with dichloromethane (20 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 × 10 ml) then dried and evaporated. The residue was dissolved in ethanol (10 ml) containing potassium carbonate (140 mg) and the mixture stirred and refluxed for 3 h, then cooled, filtered and evaporated. CC [MeOH–conc. NH_3 (19 : 1)] gave the *quinuclidine* **41a** (57 mg, 64%) as a colourless oil, R_F 0.4, $[a]_D^{25}$ −23.4 (*c*, 1.0, 1 M HCl); δ_H (250; CD_3OD) 1.86–1.97 (2H, m), 2.06–2.18 (1H, m), 2.21–2.26 (1H, m), 2.28–2.40 (1H, m), 3.14 (1H, ddd, *J* 13.0, 3.0 and 3.0), 3.29–3.49 (4H, m), 3.65 (3H, s, CH_2OCH_3), 3.71 (1H, ddd, *J* 13.0, 8.1 and 3.0), 4.24–4.29 (1H, m) and 4.54 (2H, s, OCH_2O); δ_C (100; CD_3OD) 18.3, 21.9 (both CH_2), 28.5 (CH), 51.9, 53.1 (both CH_2), 61.1 (CH_3), 61.6 (CH_2), 65.0 (CH) and 92.8 (CH_2).

Concentrated hydrochloric acid (2 ml) was added to the foregoing quinuclidine **41a** (50 mg) in ethanol (4 ml) and the resulting solution stirred and refluxed for 0.25 h then cooled and concentrated. CC [MeOH–conc. NH_3 (9 : 1)] separated the *quinuclidinol* **41b** (28 mg, 78%) as a colourless oil, R_F 0.15, which soon solidified to a solid, mp 217–219 °C (lit.,[33] mp 223–224 °C), which showed $[a]_D^{25}$ −39.5 (*c*, 0.5, 1 M HCl) {lit.,[33] $[a]_D^{25}$ +45.8 (*c*, 3.0, 1 M HCl) for the (*S*)-enantiomer}; ν_{max}/cm^{-1} 3450; δ_H (400) 1.12–1.47 (2H, m), 1.48–1.78 (2H, m), 1.79–2.00 (1H, m), 2.39–2.90 (5H, m), 2.90–3.09 (1H, m), 3.61–3.78 (1H, m) and 5.31 (1H, br s, OH); δ_C (100) 18.7, 24.5 (both CH_2), 28.1 (CH), 46.1, 47.1, 57.7 (all CH_2) and 66.7 (CH_2). The NMR data were identical to those recorded for racemic material (Aldrich).[34] Under the above conditions (*c*, 0.5, 1 M HCl), an authentic sample of the (*R*)-(−)-enantiomer **41b** (Acros; 99%+) showed $[a]_D^{23}$ −44.8.

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