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Efficient stereoselective synthesis of enantiopure *cis*- and *trans*-1,2,4-trisubstituted piperidines

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Abstract—Enantiomerically pure (2*R*,4*S*)- and (2*R*,4*R*)-2-[(*S*)-1,2-dibenzyloxyethyl]-4-[2-(diphenylmethoxy)ethyl]-1-[(*S*)-1-phenylethyl]-piperidines *cis*-**1** and *trans*-**1** have been synthesised from *N*-[(*S*)-1-phenylethyl]-(*S*)-2,3-di-*O*-benzylglyceraldimine in six steps in 31% and 18% overall yields, respectively. The efficiency of the synthetic strategy developed for the synthesis of these compounds relies on: (a) the totally diastereoselective tandem Mannich–Michael reaction between Danishefsky's diene and the starting glyceraldimine, (b) the high yielding Wadsworth–Emmons reaction of the 4-piperidone intermediate and (c) the diastereodivergent reduction of the exocyclic C–C double bond at C_4 of the piperidine ring. These transformations led to 1,2,4-trisubstituted piperidines with two new stereogenic centres with excellent stereoselectivity.

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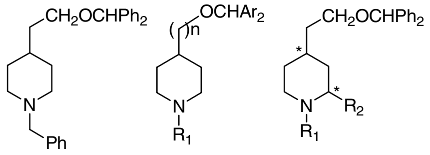
1. Introduction

Chiral polysubstituted piperidines represent one of the most common building blocks in natural products with biological activity[1–5] and have been identified as important therapeutic agents for the treatment of a range of diseases.[1–8] In recent years, thousands of piperidine compounds have been mentioned in clinical and preclinical studies directed towards the development of new drugs. As a consequence, the development of new and efficient stereoselective syntheses of not only the active compounds but also of chemically modified analogues is of major interest within medicinal chemistry. In this context, methods for the stereoselective synthesis of substituted piperidines have recently been reviewed.[9–13]

Biologically active piperidines which contain a 4-[2-(diarylmethoxy)ethyl] unit have shown a high affinity and selectivity for dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters[14–17] with 1-benzyl-4-[2-(diphenylmethoxy)ethyl]piperidine (compound **I** in Fig. 1) being one of the most potent and selective DAT inhibitors described to date.[18]



I **II** **III**

Figure 1. Structures of 1-benzyl-4-[2-(diphenylmethoxy)ethyl]piperidine **I** and related compounds.

Although structural analogues of compound **I** with different substituents at the 1- and 4-positions of the piperidine ring have been synthesised, to the best of our knowledge structural analogues of compound **I** with one substituent at C_2 (compounds **III** in Fig. 1) have not been previously synthesised. This new substitution pattern on the piperidine ring leads to compounds with two stereogenic centres on the ring, C_2 and C_4. As a result, four stereoisomers are possible for each newly synthesised compound and this significantly complicates the synthesis. On the other hand, trisubstituted piperidines incorporate a third site for structural diversity, in addition to stereochemical diversity, a situation that provides a powerful scaffold to further investigate the development of new drugs with activity on the central nervous system (CNS). For this reason, it should be interesting to develop new and efficient stereoselective processes to overcome the aforementioned synthetic difficulties.

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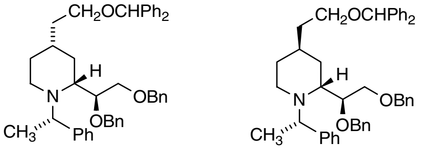
Herein we report in full detail on the asymmetric synthesis of two diastereoisomers of a 2-substituted 1-benzyl-4-[2-(diphenylmethoxy)ethyl]piperidine analogue from *N*-[(*S*)-1-phenylethyl]-(*S*)-2,3-di-*O*-benzylglyceraldimine, which is easily available on a multigram scale from inexpensive D-mannitol. These two analogues are (2*R*,4*S*)- and (2*R*,4*R*)-2-[(*S*)-1,2-dibenzyloxyethyl]-4-[2-(diphenylmethoxy)ethyl]-1-[(*S*)-1-phenylethyl]piperidine, *cis*-**1** and *trans*-**1**, respectively (Fig. 2), and they have both been obtained in enantiomerically pure form.



cis-**1** *trans*-**1**

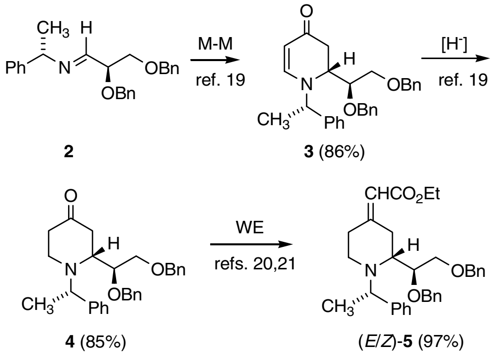
Figure 2. Structures of target compounds *cis*-**1** and *trans*-**1**.

2. Results and discussions

2.1. Synthesis

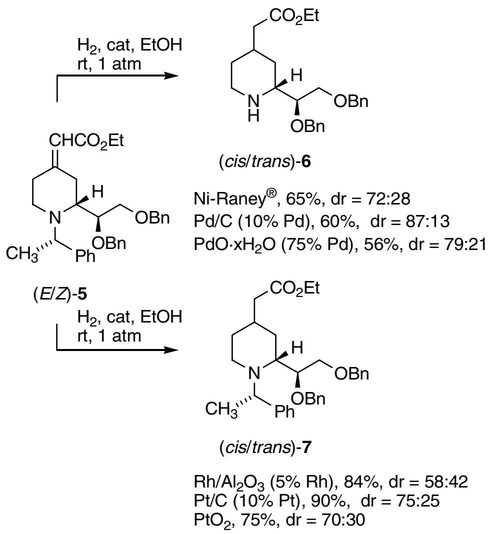
Target compounds *cis*-**1** and *trans*-**1** can be prepared from an imine derived from D-glyceraldehyde through a 2-substituted 4-alkoxycarbonylmethylidenepiperidine intermediate provided that the configuration at the 4-position of the piperidine ring could be controlled in a stereoselective reduction of the exocyclic double bond.

Compound **5**, an intermediate of this type, was prepared from imine **2** in a three-step procedure in 71% overall yield as a 97:3 mixture of alkenes of *E*- and *Z*-configuration according to our previously described procedures (Scheme 1).[19–21] The synthetic route consisted of: (a) a tandem Mannich–Michael reaction (M–M) between Danishefsky's diene and imine **2** in the presence of ZnI_2 to afford didehydropiperidone **3** with total diastereoselectivity; (b) a regioselective reduction of the enaminone C–C double bond with L-Selectride® to afford 4-piperidone **4**, a valuable and versatile building block for the synthesis of several biologically active compounds;[22–24] and (c) a Wadsworth–Emmons reaction (WE) of compound **4** with triethyl phosphonoacetate using LDA as the base.



Scheme 1. Synthesis of intermediate **5**.

The synthesis of compound *cis*-**1** required the reduction of the C–C double bond to take place opposite to the 1,2-dibenzyloxyethyl substituent. With this aim in mind, the heterogeneous catalytic hydrogenation of compound (*E*/*Z*)-**5** at room temperature and atmospheric pressure using absolute ethanol as solvent was investigated. In all cases, 2,4-disubstituted piperidines of *cis* configuration were obtained preferentially with good yields and *cis*/*trans* diastereoselectivities, as determined by ^1H NMR analyses of crude reaction mixtures, ranging from 58:42 to 87:13 after the starting material had been consumed. The structure of the resulting hydrogenation products was found to depend upon the catalyst (Scheme 2).



Scheme 2. Hydrogenation of the exocyclic double bond in compound **5**.

The use of Ni-Raney®, Pd/C or $PdO\cdot xH_2O$ as catalysts led to hydrogenation of the exocyclic C–C double bond with concomitant N-debenzylation. This gave secondary amine **6** as a mixture of *cis*- and *trans*-diastereoisomers and these proved very difficult to isolate and gave only a moderate yield after prolonged reaction times. When Rh/Al_2O_3 (5% Rh[†]), Pt/C (10% Pt[†]) or PtO_2 was used, the N-debenzylation process was not detected and piperidine **7** was obtained after shorter reaction times and in high yield as a *cis*/*trans* mixture of diastereoisomers, which were easily separated by column chromatography. The diastereomeric ratio depended on the catalyst and, of the different catalysts tested, Pt/C led to the best results in terms of yield and diastereoselectivity. These conditions gave 68% isolated yield of pure *cis*-**7** on a gram scale.

In an attempt to increase the *cis*-diastereoselectivity of the hydrogenation reaction, several homogeneous catalysts were tested. Upon using $[Ir(COD)(Py)(PCy_3)]PF_6$ (Crabtree catalyst)[25,26] or $Ru(PPh_3)_3Cl_2$ the hydrogenation did not proceed to any noticeable extent. However, the use of $Rh(PPh_3)_3Cl$ (Wilkinson catalyst)[27] gave compound **7** in

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[†] On using Rh/C (5% Rh) or Pt/C (3% Pt) as catalysts, compound **4** was recovered unaltered.

moderate yield (59%) and low *cis*/*trans* diastereoselectivity (58:42) when the hydrogenation was carried out at a hydrogen pressure of 20 atm.

The synthesis of *trans*-**1** required the reduction of the C–C double bond to take place from the same side as the 1,2-dibenzyloxyethyl substituent. For this purpose, several reducing agents were tested. The reduction of the double bond of α,β-unsaturated ethyl ester (*E*/*Z*)-**5** using Sm/I_2 or Mg in anhydrous ethanol or Al–$NiCl_2·6H_2O$–THF did not take place and only unreacted starting material was recovered. The use of $NaBH_4$–$NiCl_2·6H_2O$ led to a successful conjugate reduction and compound **7** was obtained in 86% yield, albeit with a low *cis*/*trans* diastereoselectivity (60:40) which favoured the compound with the *cis*-configuration. In an effort to increase the *trans*-selectivity, bulkier hydrides were used in this reaction. Compound **5** was inert towards Red-Al®-CuI and Superhydride®, while reaction with L-Selectride® at −78 °C led to a 1:1 mixture of *E*/Z-**8**, derived from 1,2-addition, and compound *trans*-**9**, derived from totally diastereoselective 1,4-addition and the subsequent reduction of the ester moiety (Scheme 3).

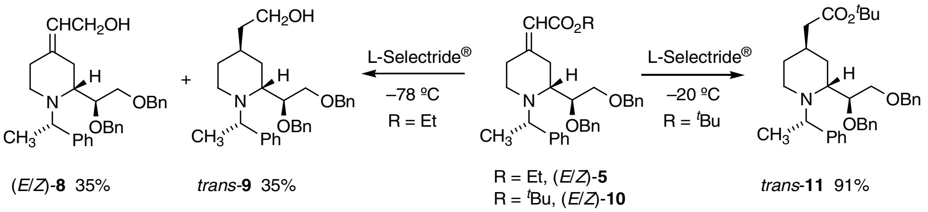
Pre-complexation of compound **5** with $BF_3·OEt_2$[28] was carried out prior to reduction with L-Selectride® in an attempt to avoid hydride attack on the carbonyl group. However, this approach led to the recovery of compound (*E*/*Z*)-**5**. Regioselective double bond reduction was finally achieved by using the related substrate *tert*-butyl ester (*E*/*Z*)-**10**, which was obtained according to our previously described procedure.[21] Reduction of compound (*E*/*Z*)-**10** with L-Selectride® led to the exclusive formation of compound **11** with a *trans*-configuration, although it was necessary to work at −20 °C to achieve total conversion. Under these conditions compound *trans*-**11** was obtained in 91% isolated yield on a gram scale.

Enantiomerically pure *cis*-**1** and *trans*-**1** were prepared from compounds *cis*-**7** and *trans*-**11**. Reduction of the ethyl and *tert*-butyl esters was achieved with $LiAlH_4$ to give primary alcohols *cis*-**9** (90%) and *trans*-**9** (60%). Whereas yields of coupling of benzhydryl bromide with the corresponding alkoxide, generated by treatment of the alcohol with sodium hydride, in the presence of tetra-*n*-butylammonium iodide were poor, acid-catalysed reaction of alcohols *cis*-**9** and *trans*-**9** with benzhydrol under azeotropic distillation conditions afforded the desired (2*R*,4*S*)- and (2*R*,4*R*)-2-[(*S*)-1,2-dibenzyloxyethyl]-4-[2-(diphenylmethoxy)ethyl]-1-[(*S*)-1-phenylethyl]piperidines in 71% and 46%, respectively (Scheme 4).

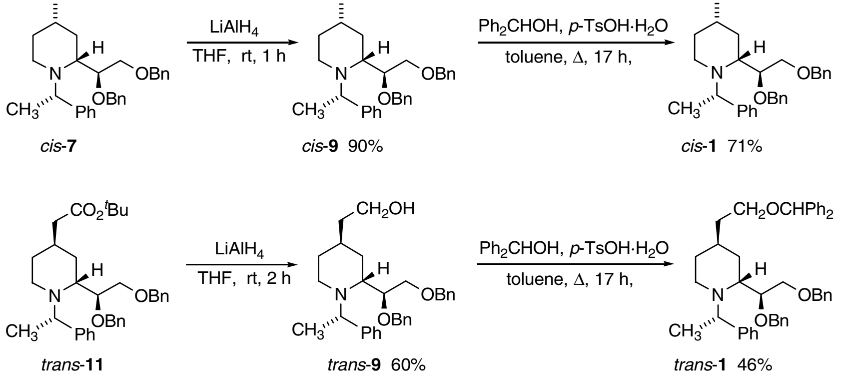
2.2. Stereochemical assignments

The *cis*- and *trans*-relative configurations of key compounds were determined on the basis of their NMR data and selective 1D gradient enhanced nuclear Overhauser enhancement spectroscopy (ge-1D NOESY) or homonuclear 2D-NOESY experiments (Fig. 3) after the complete unequivocal assignment of all signals in ^{1}H NMR spectra with the aid of 2D-NMR experiments (COSY, HSQC, HMBC).

For compounds *cis*-**6** and *cis*-**7**, a doublet of doublets of doublets, reduced to a quartet due to three identical *J* values of ca. 12 Hz was observed for proton H-3 at 0.92



Scheme 3. Reduction of exocyclic double bond in compounds **5** and **10**.



Scheme 4. Synthesis of target compounds *cis*-**1** and *trans*-**1**.

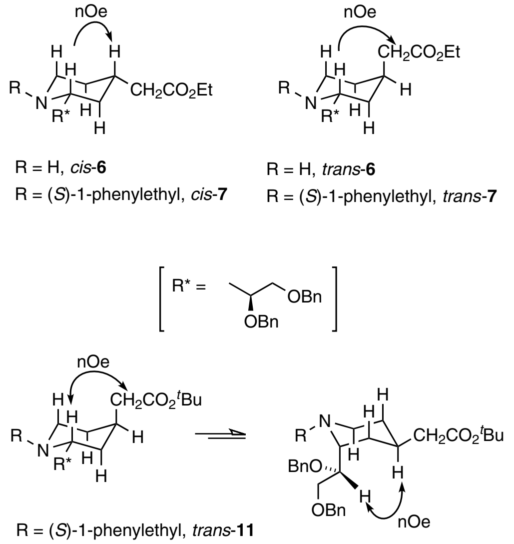


Figure 3. NOE analysis of key compounds.

and 0.86 ppm, respectively. This indicates a diaxial relationship between H-3 and both H-2 and H-4 only possible for a *cis* relationship between H-2 and H-4. This assignment was confirmed by NOE data as irradiation of H-2, at 2.68–2.75 ppm for *cis*-**6** and 2.69–2.75 ppm for *cis*-**7**, gave a significant enhancement of the H-4 proton, at 1.77–1.88 and 1.62–1.74 ppm, respectively.

For compound *cis*-**7**, an independent stereochemical assignment, which further confirmed these results, was possible by single crystal X-ray analysis.

The assignment of *trans* configuration for *trans*-**6** and *trans*-**7** follows by elimination and its also consistent with the nuclear Overhauser enhancements observed for these compounds, which were performed using C_6D_6 as solvent to overcome signal overlapping. Irradiation of H-2, at 3.07–3.13 ppm for *trans*-**6** and 3.45–3.55 ppm for *trans*-**7**, gave a significant enhancement of the protons of the methylene group bonded to C-4, at 2.25–2.32 and 2.15–2.20 ppm, respectively.

NOE cross-peaks observed by ^{1}H–^{1}H-NOESY between the methylene group of the *tert*-butoxycarbonylmethyl substituent at C-4 (2.05 ppm) and H-2 (3.35–3.42 ppm) and between the CH (3.94–4.01 ppm) group of substituent at C-2 and H-4 (2.13–2.26 ppm) indicated a *trans* configuration for compound *trans*-**11** obtained in the reduction of compound (*E*/*Z*)-**10** with L-Selectride®. In this case NOE experiments were performed using C_6D_6 as solvent to overcome signal overlapping.

3. Conclusions

In conclusion, an efficient diastereodivergent synthesis of enantiomerically pure *cis*- and *trans*-1,2-dialkyl-4-[2-(diphenylmethoxy)ethyl]piperidines (*cis*-**1** and *trans*-**1**), novel analogues of dopamine transporter inhibitors has been optimised, starting from the same chiral imine. Efficient control of the stereochemistry of the new stereogenic centre generated at C_4 in the synthetic strategy relies on highly diastereoselective reduction of the exocyclic C–C double bond of intermediates **5** and **10**, which in turn are obtained by a Wadsworth–Emmons reaction on the enantiopure 4-piperidone **4**. This synthesis highlights the utility of chiral 4-piperidone **4** as a versatile synthetic intermediate.

4. Experimental

4.1. General experimental procedures

Microanalyses were determined using a Perkin–Elmer 2400 CHNS elemental analyser. Melting points were determined in open capillaries using a Gallenkamp apparatus and are uncorrected. FT-IR spectra of oils were recorded as thin films on NaCl plates and FT-IR spectra of solids were recorded as KBr pellets, using a Thermo Nicolet Avatar 360 FT-IR spectrometer; $\nu_{\max}$ values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a Jasco P-1020 polarimeter at λ 589 nm and 25 °C in a cell with 10 cm path length, $[\alpha]_D$ values are given in 10^{-1} deg cm g^{-1} and concentrations are given in g/100 mL. NMR spectra were acquired on a Bruker AV-400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR at room temperature in $CDCl_3$ using a 5-mm probe. The chemical shifts (δ) are reported in parts per million and were referenced to the residual solvent peak. Coupling constants (*J*) are quoted in Hertz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; m, multiplet; br s, broad singlet; br d, broad doublet; br dd, broad doublet of doublets. Selective ge-1D NOESY experiments were performed with gradient pulses in the mixing time. Spectra were acquired at 300 K with optimised mixing times and 128 transients per spectrum using the Bruker standard selnogp pulse program. Special precautions such as degassing of the sample were not taken. NOESY spectra were acquired in the phase sensitive mode with gradient pulses in the mixing time as 2048 × 256 hipercomplex files with 8 transients for 256 time increments. A mixing time of 750 ms was used and processing was carried out using a sine-bell squared function shifted by $\pi/2$ and a states-TPPI method. High resolution mass spectra were recorded using a Bruker Daltronics MicroToF-Q electrospray instrument from methanolic solutions using the positive electrospray ionisation mode (ESI+). Single crystal X-ray diffraction studies were done on a Siemens P4 diffractometer.

All reagents for reactions were of analytical grade and used as obtained from commercial sources. Reactions were carried out using anhydrous solvents except when absolute ethanol was used as the solvent. Whenever possible, the reactions were monitored by thin layer chromatography (TLC). TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and ethanolic phosphomolybdic acid solution followed by heating. Column chromatography was performed using silica gel (Kiesegel 60, 230–400 mesh). (*E*/*Z*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylene-1-[(*S*)-1-phenylethyl]piperidine (*E*/*Z*)-**5** and (*E*/*Z*)-(*R*)-4-*tert*-

butoxycarbonylmethylene-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]piperidine (*E*/*Z*)-**10** were prepared as previously described in the literature.[20,21]

4.1.1. (2*R*,4*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylpiperidine *cis*-6.

An analytically pure sample of compound *cis*-**6** was isolated by silica gel column chromatography (first eluent: EtOAc/EtOH 2:1; second eluent: EtOH) from an 87:13 mixture of *cis*/*trans* diastereoisomers obtained in the hydrogenation of (*E*/*Z*)-**5** using Pd/C as catalyst. Oil; $[\alpha]_D = -7.2$ (*c* 1.14, $CHCl_3$); IR(neat) ν_{max} 3377, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (1H, ddd, *J* 11.9, 11.9, 11.9 Hz, H-3), 1.10 (1H, dddd, *J* = 12.2, 12.2, 12.2, 4.1 Hz, H-5), 1.18 (3H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.55–1.66 (2H, m, H-3, H-5), 1.77–1.88 (1H, m, H-4), 2.14 (2H, d, *J* = 7.0 Hz, CH_2CO_2Et), 2.52 (1H, br s, NH), 2.56 (1H, ddd, *J* = 12.2, 12.2, 2.4 Hz, H-6), 2.68–2.75 (1H, m, H-2), 3.05 (1H, br d, *J* = 12.2 Hz, H-6), 3.06–3.42 (1H, m, CHOBn), 3.52 (1H, dd, *J* = 10.5, 4.8 Hz, $CH(\mathit{H_a})OBn$), 3.64 (1H, dd, *J* = 10.5, 3.5 Hz, $CH(\mathit{H_b})OBn$), 4.06 (2H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 4.45 (1H, d, *J* = 12.2 Hz, $CH(\mathit{H_a})Ph$), 4.47 (1H, d, *J* = 11.2 Hz, $CH(\mathit{H_a})Ph$), 4.50 (1H, d, *J* = 12.2 Hz, $CH(\mathit{H_b})Ph$), 4.67 (1H, d, *J* = 11.2 Hz, $CH(\mathit{H_b})Ph$), 7.19–7.31 (10H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 ($CO_2CH_2\mathit{CH_3}$), 32.4 (C-5), 33.3 (C-4), 34.9 (C-3), 42.1 ($\mathit{CH_2}CO_2Et$), 46.0 (C-6), 57.5 (C-2), 60.5 ($CO_2\mathit{CH_2}CH_3$), 69.8 (CH_2OBn), 73.1 (CH_2Ph), 73.7 (CH_2Ph), 82.3 (CHOBn), 127.7 (Ph), 127.7 (Ph), 128.0 (Ph), 128.0 (Ph), 128.4 (Ph), 128.4 (Ph), 138.1 (C_{ipso} Ph), 138.5 (C_{ipso} Ph), 172.7 (C=O); HRMS (ESI+) calcd for $C_{25}H_{34}NO_4$ (MH^+): 412.2482. Found: 412.2480.

4.1.2. (2*R*,4*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethylpiperidine *trans*-6.

An analytically pure sample of compound *trans*-**6** was isolated by silica gel column chromatography (first eluent: EtOAc/EtOH 2:1; second eluent: EtOH) from an 87:13 mixture of *cis*/*trans* diastereoisomers obtained in the hydrogenation of (*E*/*Z*)-**5** using Pd/C as catalyst. Oil; $[\alpha]_D = -17.2$ (*c* 0.97, $CHCl_3$); IR-(neat) ν_{max} 3346, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.32 (1H, ddd, *J* = 13.0, 10.1, 5.1 Hz, H-5), 1.37–1.44 (1H, m, H-3), 1.52 (1H, ddd, *J* = 12.9, 8.5, 4.2 Hz, H-3), 1.63 (1H, ddd, *J* = 13.0, 10.8, 6.3 Hz, H-5), 2.15–2.22 (1H, m, H-4), 2.23 (1H, dd, *J* = 14.8, 6.5 Hz, $CH(\mathit{H_a})CO_2Et$), 2.28 (1H, dd, *J* = 14.8, 7.9 Hz, $CH(\mathit{H_b})CO_2Et$), 2.31 (1H, br s, NH), 2.66–2.69 (2H, m, H-6, H-6), 2.92 (1H, ddd, *J* = 8.1, 8.1, 3.5 Hz, H-2), 3.46–3.52 (2H, m, CHOBn, $CH(\mathit{H_a})OBn$), 3.63 (1H, dd, *J* = 9.1, 2.3 Hz, $CH(\mathit{H_b})OBn$), 4.03 (2H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 4.44 (1H, d, *J* = 11.3 Hz, $CH(\mathit{H_a})Ph$), 4.46 (1H, d, *J* = 12.5 Hz, $CH(\mathit{H_a})Ph$), 4.49 (1H, d, *J* = 12.5 Hz, $CH(\mathit{H_b})Ph$), 4.69 (1H, d, *J* = 11.3 Hz, $CH(\mathit{H_b})Ph$), 7.18–7.29 (10H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 ($CO_2CH_2\mathit{CH_3}$), 28.6 (C-4), 30.6 (C-5), 32.3 (C-3), 38.5 ($\mathit{CH_2}CO_2Et$), 40.8 (C-6), 52.5 (C-2), 60.3 ($CO_2\mathit{CH_2}CH_3$), 69.8 (CH_2OBn), 73.0 (CH_2Ph), 73.5 (CH_2Ph), 79.8 (CHOBn), 127.7 (Ph), 127.8 (Ph), 128.1 (Ph), 128.4 (Ph), 128.4 (Ph), 128.5 (Ph), 138.2 (C_{ipso} Ph), 138.4 (C_{ipso} Ph), 172.9 (C=O); HRMS (ESI+) calcd for $C_{25}H_{34}NO_4$ (MH^+): 412.2482. Found: 412.2494.

4.1.3. (2*R*,4*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethyl-1-[(*S*)-1-phenylethyl]piperidine *cis*-7.

To a 97:3 *E*/*Z* mixture of compound **5** (513 mg, 1.0 mmol) dissolved in absolute EtOH (16 mL) was added 10% Pt/C (126 mg) and the mixture was hydrogenated with H_2 at 1 atm with shaking at room temperature for 5 h. After completion of the reaction, the mixture was filtered through Celite® 545 and concentrated in vacuo to afford compound **7** as a 75:25 mixture of *cis* and *trans* diastereoisomers. Purification of the residue by silica gel column chromatography (first eluent: Et_2O/hexanes 1:1; second eluent: Et_2O/hexanes 4:1) allowed isolation of pure *cis*-**7** (350 mg, 68%) and pure *trans*-**7** (113 mg, 22%). Data for *cis*-**7**: Mp 69–71 °C; $[\alpha]_D = +10.3$ (*c* 0.52, $CHCl_3$); IR(KBr) ν_{max} 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.86 (1H, ddd, *J* = 12.4, 12.4, 12.4 Hz, H-3), 0.87 (1H, dddd, *J* = 12.2, 12.2, 12.2, 3.9 Hz, H-5), 1.13 (3H, d, *J* = 6.8 Hz, $\mathit{CH_3}CH$), 1.18 (3H, t, *J* = 7.0 Hz, $CO_2CH_2\mathit{CH_3}$), 1.44 (1H, br d, *J* = 12.2 Hz, H-5), 1.62–1.74 (1H, m, H-4), 2.00 (1H, ddd, *J* = 11.4, 11.4, 2.3 Hz, H-6), 2.02–2.06 (1H, m, H-3), 2.08 (1H, dd, *J* = 14.9, 5.8 Hz, $CH(\mathit{H_a})CO_2Et$), 2.17 (1H, dd, *J* = 14.9, 6.5 Hz, $CH(\mathit{H_b})CO_2Et$), 2.32 (1H, ddd, *J* = 11.4, 3.9, 3.9 Hz, H-6), 2.69–2.75 (1H, m, H-2), 3.63 (1H, dd, *J* = 10.6, 7.9 Hz, $CH(\mathit{H_a})OBn$), 4.01 (1H, br d, *J* = 10.6 Hz, $CH(\mathit{H_b})OBn$), 4.04–4.11 (4H, m, CHOBn, $CH_3\mathit{CH}$, $CO_2\mathit{CH_2}CH_3$), 4.46 (1H, d, *J* = 12.1 Hz, $CH(\mathit{H_a})Ph$), 4.57 (1H, d, *J* = 12.1 Hz, $CH(\mathit{H_b})Ph$), 4.68 (1H, d, *J* = 11.9 Hz, $CH(\mathit{H_a})Ph$), 4.78 (1H, d, *J* = 11.9 Hz, $CH(\mathit{H_b})Ph$), 7.13–7.38 (15H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 ($\mathit{CH_3}CH$), 14.3 ($CO_2CH_2\mathit{CH_3}$), 32.5 (C-5), 32.7 (C-3), 33.8 (C-4), 41.8 ($\mathit{CH_2}CO_2Et$), 44.8 (C-6), 53.7 ($CH_3\mathit{CH}$), 59.0 (C-2), 60.3 ($CO_2\mathit{CH_2}CH_3$), 71.2 (CH_2OBn), 73.0 (CH_2Ph), 73.6 (CH_2Ph), 77.8 (CHOBn), 126.3 (Ph), 127.5 (Ph), 127.5 (Ph), 127.6 (Ph), 127.6 (Ph), 127.8 (Ph), 127.9 (Ph), 128.3 (Ph), 128.4 (Ph), 138.6 (C_{ipso} Ph), 139.1 (C_{ipso} Ph), 143.9 (C_{ipso} Ph), 172.8 (C=O); HRMS (ESI+) calcd for $C_{33}H_{42}NO_4$ (MH^+): 516.3108. Found: 516.3127. Anal. Calcd for $C_{33}H_{41}NO_4$: C, 76.86; H, 8.01; N, 2.72. Found: C, 76.59; H, 7.91; N, 3.01.

4.1.4. (2*R*,4*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-ethoxycarbonylmethyl-1-[(*S*)-1-phenylethyl]piperidine *trans*-7.

Isolated by silica gel column chromatography (first eluent: Et_2O/hexanes 1:1; second eluent: Et_2O/hexanes 4:1) from a 75:25 mixture of *cis*/*trans* diastereoisomers obtained in the hydrogenation of (*E*/*Z*)-**5** using Pt/C (10% Pt) as a catalyst. Oil; $[\alpha]_D = -23.2$ (*c* 0.81, $CHCl_3$); IR(neat) ν_{max} 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.26 (3H, d, *J* = 5.5 Hz, $\mathit{CH_3}CH$), 1.21–1.23 (1H, m, H-5), 1.40–1.44 (1H, m, H-5), 1.49–1.55 (2H, m, H-3, H-3), 2.07–2.14 (1H, m, H-4), 2.12–2.16 (2H, m, CH_2CO_2Et), 2.54–2.62 (2H, m, H-6, H-6), 3.18–3.25 (1H, m, H-2), 3.56 (1H, dd, *J* = 10.7, 5.4 Hz, $CH(\mathit{H_a})OBn$), 3.71 (1H, dd, *J* = 10.7, 1.8 Hz, $CH(\mathit{H_b})OBn$), 3.98–4.03 (2H, m, CHOBn, $CH_3\mathit{CH}$), 4.06 (2H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 4.48 (2H, s, CH_2Ph), 4.62 (1H, d, *J* = 11.6 Hz, $CH(\mathit{H_a})Ph$), 4.75 (1H, d, *J* = 11.6 Hz, $CH(\mathit{H_b})Ph$), 7.11–7.39 (15H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 ($CO_2CH_2\mathit{CH_3}$), 19.6 (CH_3CH), 29.0 (C-4), 29.8 (C-5), 30.2 (C-3), 41.0 ($\mathit{CH_2}CO_2Et$), 42.6 (C-6), 54.2 (C-2), 59.5 ($\mathit{CH_3}CH$), 60.2

($CO_2\mathit{C}H_2CH_3$), 71.4 (CH_2OBn), 72.6 (CH_2Ph), 73.5 (CH_2Ph), 78.3 (CHOBn), 126.4 (Ph), 127.3 (Ph), 127.3 (Ph), 127.5 (Ph), 127.6 (Ph), 127.8 (Ph), 128.1 (Ph), 128.2 (Ph), 128.3 (Ph), 139.3 (C_{ipso} Ph), 139.5 (C_{ipso} Ph), 147.2 (C_{ipso} Ph), 171.0 (C=O); HRMS (ESI+) calcd for $C_{33}H_{42}NO_4$ (MH^+): 516.3108. Found: 516.3121.

4.1.5. (*E*)-(*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[2-(hydroxy)-ethylidene]-1-[(*S*)-1-phenylethyl]piperidine (*E*)-8. Data drawn from spectra of the 97:3 *E*/*Z* mixture of diastereoisomers obtained in the reduction of compound (*E*/*Z*)-**5** with L-Selectride®. IR(neat) ν_{max} 3364, 2846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, $J = 6.7$ Hz, $\mathit{CH_3}CH$), 1.83–1.92 (1H, m, H-5), 1.96 (1H, dd, $J = 13.4$, 8.2 Hz, H-3), 2.07–2.18 (1H, m, H-5), 2.18–2.26 (1H, m, H-6), 2.48 (1H, dd, $J = 13.4$, 4.2 Hz, H-3), 2.51 (1H, dd, $J = 10.7$, 4.8 Hz, H-6), 2.91–2.98 (1H, m, H-2), 3.61 (1H, dd, $J = 10.7$, 6.8 Hz, $CH(H_a)OBn$), 3.90 (1H, dd, $J =$ 10.7, 1.4 Hz, $CH(H_b)OBn$), 3.92–3.97 (1H, m, CHOBn), 4.02 (2H, dd, $J = 7.0$, 1.5 Hz, $\mathit{CH_2}OH$), 4.05 (1H, q, $J =$ 6.7 Hz, $CH_3\mathit{CH}$), 4.47 (1H, d, $J = 12.0$ Hz, $CH(H_a)Ph$), 4.54 (1H, d, $J = 12.0$ Hz, $CH(H_b)Ph$), 4.61 (1H, d, $J =$ 11.8 Hz, $CH(H_a)Ph$), 4.73 (1H, d, $J = 11.8$ Hz, $CH(H_b)Ph$), 5.31 (1H, br s, HC=C), 7.12–7.38 (15H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 ($\mathit{C}H_3CH$), 28.0 (C-5), 36.1 (C-3), 45.0 (C-6), 56.5 ($CH_3\mathit{C}H$), 58.5 (CH_2OH), 58.7 (C-2), 71.2 (CH_2OBn), 72.7 (CH_2Ph), 73.7 (CH_2Ph), 78.3 (CHOBn), 121.8 (H*C*=C), 126.5 (Ph), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.7 (Ph), 128.1 (Ph), 128.3 (Ph), 128.4 (Ph), 138.4 (C_{ipso} Ph), 139.2 (C_{ipso} Ph), 140.8 (C_{ipso} Ph), 144.8 (C-4); HRMS (ESI+) calcd for $C_{31}H_{38}NO_3$ (MH^+): 472.2846. Found: 472.2838.

4.1.6. (2*R*,4*R*)-4-*tert*-Butoxycarbonylmethyl-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]piperidine *trans*-11. To a 98:2 *E*/*Z* mixture of compound **10** (541 mg, 1.0 mmol) dissolved in anhydrous THF (22 mL) at −20 °C under argon was added dropwise a 1.0 M solution of L-Selectride® in THF (4.0 mL, 4.0 mmol) and the mixture was stirred for 24 h at −20 °C. Saturated aqueous NH_4Cl (30 mL) was added carefully with stirring at 0 °C. The reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuo to afford a crude product in which *cis*-**11** was not detected. The residue was purified by silica gel column chromatography (first eluent: Et_2O/hexanes 1:2; second eluent: Et_2O/hexanes 4:1) to give pure *trans*-**11** (494 mg, 91%). Oil; $[\alpha]_D = -25.2$ (*c* 0.86, $CHCl_3$); IR(neat) ν_{max} 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06–1.21 (2H, m, H-5, H-5), 1.24 (3H, d, $J = 6.6$ Hz, $\mathit{CH_3}CH$), 1.37 (9H, s, ^{t}Bu), 1.47–1.53 (2H, m, H-3, H-3), 2.00–2.08 (3H, m, $CH_2CO_2{}^tBu$, H-4), 2.50–2.55 (2H, m, H-6, H-6), 3.17–3.23 (1H, m, H-2), 3.55 (1H, dd, $J = 10.7$, 5.6 Hz, $CH(H_a)OBn$), 3.71 (1H, dd, $J = 10.7$, 2.4 Hz, $CH(H_b)OBn$), 3.97–4.02 (1H, m, CHOBn), 3.99 (1H, q, $J = 6.6$ Hz, $CH_3\mathit{CH}$), 4.47 (2H, br s, CH_2Ph), 4.60 (1H, d, $J = 11.7$ Hz, $CH(H_a)Ph$), 4.74 (1H, d, $J = 11.7$ Hz, $CH(H_b)Ph$), 7.08–7.38 (15H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 ($\mathit{C}H_3CH$), 28.4 ($CO_2C(\mathit{C}H_3)_3$), 29.3 (C-4), 30.0 (C-5), 31.6 (C-3), 42.2 ($\mathit{C}H_2CO_2{}^tBu$), 42.6 (C-6), 54.1 (C-2), 59.6 ($CH_3\mathit{C}H$), 71.6 (CH_2OBn), 72.7 (CH_2Ph), 73.4 (CH_2Ph), 78.3 (CHOBn), 80.1 ($CO_2\mathit{C}(CH_3)_3$), 126.4 (Ph), 127.3 (Ph), 127.3 (Ph), 127.5 (Ph), 127.6 (Ph), 127.8 (Ph), 128.1 (Ph), 128.2 (Ph), 128.4 (Ph), 138.6 (C_{ipso} Ph), 139.2 (C_{ipso} Ph), 147.2 (C_{ipso} Ph), 172.3 (C=O); HRMS (ESI+) calcd for $C_{35}H_{46}NO_4$ (MH^+): 544.3421. Found: 544.3432.

4.1.7. (2*R*,4*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[2-(hydroxy)-ethyl]-1-[(*S*)-1-phenylethyl]piperidine *cis*-9. To a solution of compound *cis*-**7** (515 mg, 1.0 mmol) in anhydrous THF (20 mL) at room temperature under argon was added dropwise a 1.0 M solution of $LiAlH_4$ in THF (1.2 mL, 1.2 mmol) and the mixture was stirred for 1 h at room temperature. Saturated aqueous NH_4Cl (30 mL) was added carefully with stirring at 0 °C. The resulting mixture was filtered through Celite® 545 and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuo to afford a crude product, which was purified by silica gel column chromatography (first eluent: Et_2O/hexanes 4:1; second eluent: EtOAc/EtOH 1:1) to give pure *cis*-**9** (426 mg, 90%). Oil; $[\alpha]_D = +1.4$ (*c* 0.86, $CHCl_3$); IR(neat) ν_{max} 3387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (1H, ddd, $J = 11.7$, 11.7, 11.7 Hz, H-3), 0.90 (1H, dddd, $J = 11.5$, 11.5, 11.5, 3.6 Hz, H-5), 1.13 (3H, d, $J = 6.8$ Hz, $\mathit{CH_3}CH$), 1.20–1.31 (1H, m, H-3), 1.32–1.48 (3H, m, H-5, $\mathit{CH_2}CH_2OH$), 1.95–2.05 (2H, m, H-6, H-4), 2.34 (1H, br d, $J = 11.3$ Hz, H-6), 2.70 (1H, br d, $J = 11.7$ Hz, H-2), 3.61 (2H, dd, $J = 6.8$, 6.8 Hz, $CH_2\mathit{CH_2}OH$), 3.66 (1H, dd, $J = 10.7$, 8.1 Hz, $CH(H_a)OBn$), 4.02 (1H, dd, $J = 10.7$, 6.6 Hz, $CH(H_b)OBn$), 4.06–4.12 (2H, m, CHOBn, $CH_3\mathit{CH}$), 4.47 (1H, d, $J = 12.2$ Hz, $CH(H_a)Ph$), 4.57 (1H, d, $J = 12.2$ Hz, $CH(H_b)Ph$), 4.67 (1H, d, $J = 12.0$ Hz, $CH(H_a)Ph$), 4.79 (1H, d, $J = 12.0$ Hz, $CH(H_b)Ph$), 7.13–7.39 (15H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 ($\mathit{C}H_3CH$), 32.5 (C-5), 33.0 (C-3), 33.1 (C-4), 39.7 ($\mathit{C}H_2CH_2OH$), 45.1 (C-6), 54.1 ($CH_3\mathit{C}H$), 59.2 (C-2), 60.6 ($CH_2\mathit{C}H_2OH$), 71.3 (CH_2OBn), 72.8 (CH_2Ph), 73.5 (CH_2Ph), 77.9 (CHOBn), 126.3 (Ph), 127.5 (Ph), 127.5 (Ph), 127.6 (Ph), 127.6 (Ph), 127.8 (Ph), 127.9 (Ph), 128.3 (Ph), 128.4 (Ph), 138.4 (C_{ipso} Ph), 139.0 (C_{ipso} Ph), 144.0 (C_{ipso} Ph); HRMS (ESI+) calcd for $C_{31}H_{40}NO_3$ (MH^+): 474.3003. Found: 474.3026.

4.1.8. (2*R*,4*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[(2-hydroxy)-ethyl]-1-[(*S*)-1-phenylethyl]piperidine *trans*-9. To a solution of compound *trans*-**11** (543 mg, 1.0 mmol) in anhydrous THF (20 mL) at room temperature under argon was added dropwise a 1.0 M solution of $LiAlH_4$ in THF (4.0 mL, 4.0 mmol) and the mixture was stirred for 2 h at room temperature. Saturated aqueous NH_4Cl (30 mL) was added carefully with stirring at 0 °C. The resulting mixture was filtered through Celite® 545 and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuo to afford a crude product, which was purified by silica gel column chromatography (first eluent: Et_2O/hexanes 4:1; second eluent: EtOAc/EtOH 1:1) to give pure *trans*-**9** (286 mg, 60%). Oil; $[\alpha]_D = -17.7$ (*c* 0.81, $CHCl_3$); IR(neat) ν_{max} 3366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06–1.20 (1H, m, H-5), 1.26 (3H, d, $J = 6.4$ Hz, $\mathit{CH_3}CH$), 1.30–1.43 (3H, m, H-5, $\mathit{CH_2}CH_2OH$), 1.41–1.51 (2H, m, H-3, H-3), 1.65–1.74 (1H, m, H-4), 2.54–2.63 (2H, m, H-6, H-6), 3.14–3.22 (1H, m, H-2), 3.51 (1H, dd, $J = 10.6$, 4.2 Hz, CH(H_a)OBn), 3.53 (2H, dd, $J = 6.6$, 6.6 Hz, CH_2CH_2OH), 3.63 (1H, dd, $J = 10.6$, 3.3 Hz, CH(H_b)OBn), 3.97–4.03 (2H, m, CHOBn, CH_3CH), 4.44 (1H, d, $J = 12.1$ Hz, CH(H_a)Ph), 4.48 (1H, d, $J = 12.1$ Hz, CH(H_b)Ph), 4.59 (1H, d, $J = 11.7$ Hz, CH(H_a)Ph), 4.71 (1H, d, $J = 11.7$ Hz, CH(H_b)Ph), 7.10–7.36 (15H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3CH), 28.0 (C-4), 30.6 (C-5), 31.5 (C-3), 39.1 (CH_2CH_2OH), 43.0 (C-6), 54.9 (C-2), 59.7 (CH_3CH), 60.7 (CH_2CH_2OH), 71.6 (CH_2OBn), 73.0 (CH_2Ph), 73.4 (CH_2Ph), 78.0 (CHOBn), 126.5 (Ph), 127.3 (Ph), 127.4 (Ph), 127.6 (Ph), 127.8 (Ph), 127.8 (Ph), 128.1 (Ph), 128.3 (Ph), 128.4 (Ph), 138.4 (C_{ipso} Ph), 139.3 (C_{ipso} Ph), 139.8 (C_{ipso} Ph); HRMS (ESI+) calcd for $C_{31}H_{40}NO_3$ (MH^+): 474.3003. Found: 474.3018.

4.1.9. (2*R*,4*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[2-(diphenylmethoxy)ethyl]-1-[(*S*)-1-phenylethyl]piperidine *cis*-1.

To a solution of compound *cis*-**9** (473 mg, 1.0 mmol) in anhydrous toluene (45 mL) under argon were added successively benzhydrol (473 mg, 3.2 mmol) and *p*-TsOH·H_2O (228 mg, 1.2 mmol) and the mixture was heated at reflux under azeotropic distillation conditions for 17 h. The reaction mixture was cooled to room temperature, neutralised with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuo to afford a crude product, which was purified by silica gel column chromatography (first eluent: Et_2O/hexanes 1:8; second eluent: Et_2O/hexanes 1:4) to give pure *cis*-**1** (545 mg, 71%). Oil; $[\alpha]_D = +8.8$ (*c* 1.05, $CHCl_3$); IR(neat) ν_{max} 1098, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69–0.85 (2H, m, H-3, H-5), 1.08 (3H, d, $J = 6.7$ Hz, CH_3CH), 1.26–1.37 (2H, m, H-4, H-5), 1.34–1.45 (1H, m, CH(H_a)CH_2OCHPh_2), 1.45–1.55 (1H, m, CH(H_b)CH_2OCHPh_2), 1.92 (1H, br dd, $J = 11.0$, 11.0 Hz, H-6), 1.99 (1H, br d, $J = 10.5$ Hz, H-3), 2.26 (1H, ddd, $J = 11.0$, 2.9, 2.9 Hz, H-6), 2.61–2.67 (1H, m, H-2), 3.34 (2H, t, $J = 6.6$ Hz, $CH_2CH_2OCHPh_2$), 3.59 (1H, dd, $J = 10.6$, 6.3 Hz, CH(H_a)OBn), 3.97 (1H, br d, $J = 10.6$ Hz, CH(H_b)OBn), 4.01–4.07 (2H, m, CHOBn, CH_3CH), 4.40 (1H, d, $J = 12.2$ Hz, CH(H_a)Ph), 4.52 (1H, d, $J = 12.2$ Hz, CH(H_b)Ph), 4.65 (1H, d, $J = 12.0$ Hz, CH(H_a)Ph), 4.73 (1H, d, $J = 12.0$ Hz, CH(H_b)Ph), 5.20 (1H, br s, $CHPh_2$), 7.06–7.34 (25H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (CH_3CH), 32.6 (C-5), 33.1 (C-3), 33.7 (C-4), 37.0 ($CH_2CH_2OCHPh_2$), 45.1 (C-6), 53.8 (CH_3CH), 59.2 (C-2), 66.9 ($CH_2CH_2OCHPh_2$), 71.4 (CH_2OBn), 72.8 (CH_2Ph), 73.6 (CH_2Ph), 78.0 (CHOBn), 83.8 ($CHPh_2$), 126.4 (Ph), 126.6 (Ph), 127.0 (Ph), 127.1 (Ph), 127.4 (Ph), 127.4 (Ph), 127.6 (Ph), 127.6 (Ph), 127.7 (Ph), 127.9 (Ph), 127.9 (Ph), 128.0 (Ph), 128.4 (Ph), 128.4 (Ph), 128.5 (Ph), 138.6 (C_{ipso} Ph), 139.2 (C_{ipso} Ph), 142.7 (C_{ipso} Ph), 142.7 (C_{ipso} Ph), 144.1 (C_{ipso} Ph); HRMS (ESI+) calcd for $C_{44}H_{50}NO_3$ (MH^+): 640.3785. Found: 640.3774.

4.1.10. (2*R*,4*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-[2-(diphenylmethoxy)ethyl]-1-[(*S*)-1-phenylethyl]-piperidine *trans*-1.

To a solution of compound *trans*-**9** (473 mg, 1.0 mmol) in anhydrous toluene (45 mL) under argon were added successively benzhydrol (590 mg, 3.2 mmol) and *p*-TsOH·H_2O (228 mg, 1.2 mmol) and the mixture was heated at reflux under azeotropic distillation conditions for 17 h. The reaction mixture was cooled to room temperature, neutralised with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuo to afford a crude product, which was purified by silica gel column chromatography (first eluent: Et_2O/hexanes 1:4; second eluent: Et_2O/hexanes 1:1) to give pure *trans*-**1** (294 mg, 46%). Oil; $[\alpha]_D = -18.1$ (*c* 0.35, $CHCl_3$); IR(neat) ν_{max} 1095, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.16 (1H, m, H-5), 1.24 (3H, d, $J = 7.3$ Hz, CH_3CH), 1.28–1.39 (1H, m, H-5), 1.42–1.60 (4H, m, H-3, H-4, $CH_2CH_2OCHPh_2$), 1.69–1.79 (1H, m, H-3), 2.47–2.59 (2H, m, H-6, H-6), 3.13–3.21 (1H, m, H-2), 3.38 (2H, t, $J = 6.6$ Hz, $CH_2CH_2OCHPh_2$), 3.49 (1H, dd, $J = 10.7$, 5.5 Hz, CH(H_a)OBn), 3.65 (1H, br d, $J = 10.7$ Hz, CH(H_b)OBn), 3.94–4.05 (2H, m, CHOBn, CH_3CH), 4.41 (2H, br s, CH_2Ph), 4.59 (1H, d, $J = 11.6$ Hz, CH(H_a)Ph), 4.72 (1H, d, $J = 11.6$ Hz, CH(H_b)Ph), 5.23 (1H, br s, $CHPh_2$), 7.09–7.37 (25H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.2 (CH_3CH), 28.5 (C-4), 30.3 (C-3), 31.8 (C-5), 35.9 ($CH_2CH_2OCHPh_2$), 42.7 (C-6), 54.3 (C-2), 59.3 (CH_3CH), 67.0 ($CH_2CH_2OCHPh_2$), 71.6 (CH_2OBn), 72.7 (CH_2Ph), 73.3 (CH_2Ph), 78.3 (CHOBn), 83.7 ($CHPh_2$), 126.3 (Ph), 126.9 (Ph), 126.9 (Ph), 127.3 (Ph), 127.3 (Ph), 127.4 (Ph), 127.5 (Ph), 127.7 (Ph), 128.0 (Ph), 128.2 (Ph), 128.3 (Ph), 128.3 (Ph), 128.4 (Ph), 138.4 (C_{ipso} Ph), 139.2 (C_{ipso} Ph), 139.2 (C_{ipso} Ph), 142.5 (C_{ipso} Ph), 147.1 (C_{ipso} Ph); HRMS (ESI+) calcd for $C_{44}H_{50}NO_3$ (MH^+): 640.3785. Found: 640.3782.

4.1.11. X-ray diffraction analysis of *cis*-7.

Single crystals of *cis*-**7** were obtained by slow evaporation from an absolute ethanol solution. The X-ray diffraction data were collected at room temperature using graphite-monochromated Mo Kα radiation ($\lambda = 0.7103$ Å). Structure was solved by direct methods using the SHELXS-97[29] program and refinement was performed using the SHELXL-97[30] program by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atoms were calculated at idealised positions, and during refinement they were allowed to ride on their carrying atom with an isotropic thermal factor fixed to 1.2 times the Ueq value of the carrier atom. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 649978. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Deposited data may be accessed by the journal and checked as part of the refereeing process.

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