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Enantioselective rearrangement of a *meso*-cyclohexene oxide using norephedrine-derived chiral bases

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Abstract

Using a chiral base from a norephedrine-derived diamine, the enantioselective rearrangement of a *meso*-cyclohexene oxide can be performed in 94% yield and with 94% enantioselectivity. The enantioselectivity is lower (86% ee) with the diastereoisomeric chiral base. In order to prepare the diastereoisomeric chiral base, a potentially useful way of converting norephedrine into norpseudoephedrine was developed. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Some time ago, we reported[1] that it was possible to rearrange *meso*-epoxide *trans*-**1** to allylic alcohol (1*S*,4*R*,5*S*)-**2** of 76% ee using a lithium amide derived from Singh's diamine (*R*)-**3**[2] (Scheme 1).[3,4] In an attempt to improve the enantioselectivity of this reaction, we turned to chiral diamines with a substituent adjacent to the pyrrolidinyl group such as (1*R*,2*S*)-**4** and (1*S*,2*S*)-**7** which are derived from norephedrine (1*R*,2*S*)-**5** and norpseudoephedrine (1*S*,2*S*)-**6**, respectively. In this paper, we describe in full[5] the synthesis of the novel diamines (1*R*,2*S*)-**4** and (1*S*,2*S*)-**7** and a comparison of the enantioselectivity obtained in the conversion of epoxide *trans*-**1** into allylic alcohols (1*S*,4*R*,5*S*)-**2** or (1*R*,4*S*,5*R*)-**2**.

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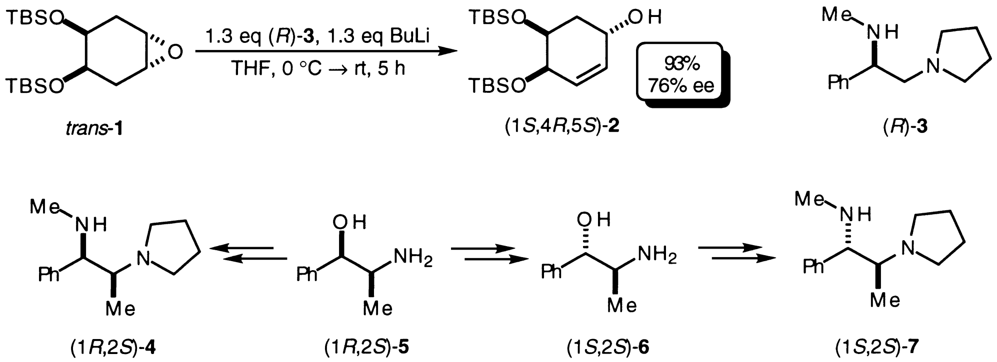
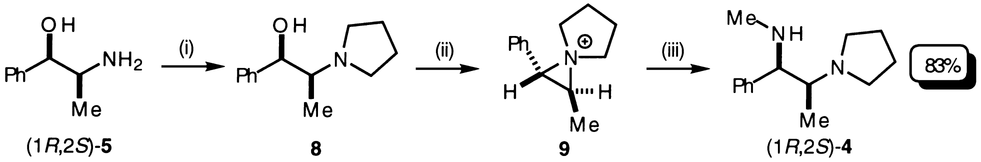


Scheme 1.

2. Results and discussion

2.1. Diamine synthesis

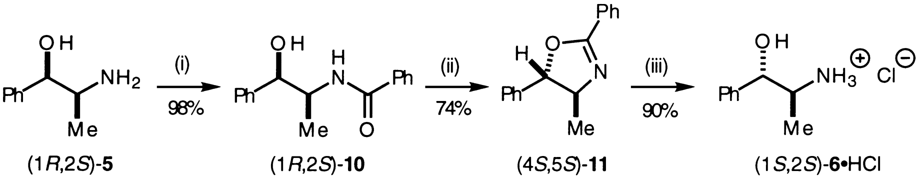
We anticipated that the preparation of diamine (1*R*,2*S*)-**4** would proceed via dialkylation of norephedrine (1*R*,2*S*)-**5** with 1,4-dibromobutane (to furnish the pyrrolidine ring) and subsequent double inversion of the benzylic stereogenic centre in aminoalcohol **8** as outlined in Scheme 2. This double inversion would occur via formation of an intermediate aziridinium ion **9**.[6,7] Thus, treatment of norephedrine (1*R*,2*S*)-**5** with 1,4-dibromobutane, tetra-*n*-butylammonium iodide and sodium carbonate in refluxing THF for 48 h gave known[8] aminoalcohol **8** which was used directly in the next step without isolation. Since aminoalcohol **8** was only sparingly soluble in Et_2O, subsequent mesylation and reaction with methylamine was performed in THF. These reactions proceeded as expected to give the novel diamine (1*R*,2*S*)-**4** in 83% overall yield from norephedrine (1*R*,2*S*)-**5** (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) 1,4-dibromobutane, 3 equiv. Na_2CO_3, 0.5 equiv. TBAI, THF, reflux, 40 h; (ii) 3 equiv. Et_3N, 1.2 equiv. MsCl, THF, 0°C, 30 min; (iii) 2 equiv. Et_3N, excess $MeNH_2$ (aq.), rt, 40 h

Diamine (1*R*,2*S*)-**4** was the only product from this reaction: there was no evidence (by ^1H NMR spectroscopy) for formation of the other diastereoisomer, which has also been synthesised (vide infra), or the other regioisomer. We assigned the indicated structure to diamine (1*R*,2*S*)-**4** on the basis of preferential opening of aziridinium ion **9** at the activated benzylic position as expected from the work of Dieter et al.[7] where related ephedrine-derived diamines were prepared. The formation of a single regioisomer is interesting since both potential sites of attack are secondary in nature. An alternative mechanism for this type of transformation which has recently been forwarded[9] can explain equally well the synthetic outcome in this reaction. The other enantiomer, (1*S*,2*R*)-**4**, has been prepared via the same route in 84% yield from (1*S*,2*R*)-**5**.

We had expected to prepare the diastereoisomeric diamine (1*S*,2*S*)-**7** using a similar approach starting from norpseudoephedrine (1*S*,2*S*)-**6** but were surprised to find that the required starting material was not commercially available. A number of synthetic approaches to enantiomerically enriched norpseudoephedrine **6** have been reported[10] including acid-mediated isomerisation of norephedrine **5**.[11] However, the approach we adopted involved converting norephedrine (1*R*,2*S*)-**5** into norpseudoephedrine (4*S*,5*S*)-**6** via an intramolecular Mitsunobu reaction (Scheme 3) and is related to a previously described method.[12]

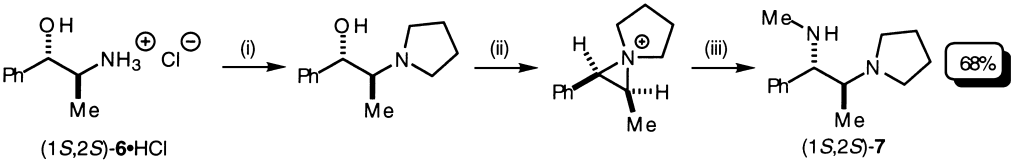


Scheme 3. *Reagents and conditions*: (i) 1 equiv. Et_3N, 1 equiv. PhCOCl, CH_2Cl_2, rt, 3 h; (ii) 1.3 equiv. DIAD, 1.3 equiv. PPh_3, THF, rt, 16 h; (iii) 1.1 M HCl (aq.), reflux, 30 h

First of all, norephedrine (1*R*,2*S*)-**5** was transformed into benzamide (1*R*,2*S*)-**10** in 98% yield under standard conditions as previously reported.[13] Then, intramolecular Mitsunobu cyclisation[14] of benzamide (1*R*,2*S*)-**10** was performed with triphenylphosphine and DIAD in THF and the reaction proceeded smoothly. Purification by flash chromatography afforded oxazoline (1*S*,2*S*)-**11** in 74% isolated yield as a single diastereoisomer (Scheme 3). Racemic **11** is a known[15–17] compound and our NMR spectroscopic data was in complete agreement with the published data.[16]

Finally, hydrolysis of oxazoline (4*S*,5*S*)-**11** was accomplished by refluxing for 30 h in 1.1 M hydrochloric acid using the procedure of Kniezo et al.[17] In this way, a 90% recrystallised yield of norpseudoephedrine (1*S*,2*S*)-**6**, isolated as its hydrochloride salt, was obtained (Scheme 3). The salt exhibited mp 176–179°C (lit.[11] 179–181°C), $[\alpha]_D$ +38 (*c* 1.0 in H_2O) {lit.[11] +42.7 (*c* 4.9 in H_2O)} and had distinctly different ^1H and ^{13}C NMR spectra to the hydrochloride salt prepared from commercially available norephedrine (1*R*,2*S*)-**5**. The sign of the specific rotation confirmed that we had produced norpseudoephedrine (1*S*,2*S*)-**6** and the magnitude of the specific rotation demonstrated the anticipated stereospecificity of the Mitsunobu reaction.

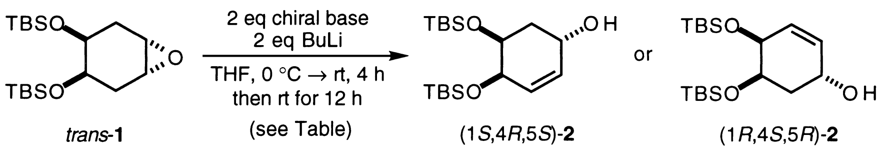
Our synthesised hydrochloride salt of norpseudoephedrine (1*S*,2*S*)-**6** was then converted into the required diamine (1*S*,2*S*)-**7** in 68% overall yield in an analogous fashion to that described previously for norephedrine (1*R*,2*S*)-**5** (Scheme 4). The only difference was that an extra equivalent of sodium carbonate was required to generate the free amine in the dialkylation step. Diamine (1*S*,2*S*)-**7** was obtained as a single diastereoisomer [different by ^1H and ^{13}C NMR spectroscopy to diamine (1*R*,2*S*)-**4**] and a single regioisomer, and its formation was rationalised by comparison with Dieter's work.[7]



Scheme 4. *Reagents and conditions*: (i) 1,4-dibromobutane, 4 equiv. Na_2CO_3, 0.5 equiv. TBAI, THF, reflux, 40 h; (ii) 3 equiv. Et_3N, 1.2 equiv. MsCl, THF, 0°C, 30 min; (iii) 2 equiv. Et_3N, excess $MeNH_2$ (aq.), rt, 40 h

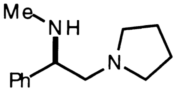
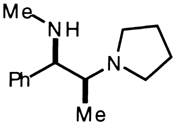
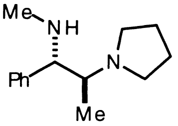
2.2. Enantioselective epoxide rearrangement reactions

With two new diamines in hand [(1*R*,2*S*)-**4** and (1*S*,2*S*)-**7**], we have investigated the effect of an extra substituent adjacent to the pyrrolidinyl group on the enantioselectivity for the rearrangment of epoxide *trans*-**1** to allylic alcohol (1*S*,4*R*,5*S*)-**2** and (1*R*,4*S*,5*R*)-**2** (Scheme 5). We were particularly interested in discovering which of the two chiral centres was the more important for determining the sense and degree of asymmetric induction. The full results, including a comparison with Singh's diamine (*R*)-**3**, are presented in Table 1.



Scheme 5.

Table 1

Entry	Diamine		Product	Yield (%)	$[\alpha]_D$[a]	ee (%)[b]
1		(*R*)-**3**	(1*S*,4*R*,5*S*)-**2**	71	–85.2 (1.0)	76
2		(1*R*,2*S*)-**4**	(1*S*,4*R*,5*S*)-**2**	94	–106.3 (1.2)	94
3		(1*S*,2*S*)-**7**	(1*R*,4*S*,5*R*)-**2**	97	+95.1 (0.9)	86

[a] $[\alpha]_D$ determined in $CHCl_3$ (concentration in brackets); [b] ee determined by formation of Mosher's esters

The epoxide rearrangement reactions were run using two equivalents of chiral base (generated from the diamine and *n*-butyllithium at 0°C) in THF and generated the allylic alcohol product in high yields. The enantiomeric excesses were determined by preparation of Mosher's esters,[1,18] and the sense of asymmetric induction was determined by the sign of the specific rotation in comparison with allylic alcohol (1*S*,4*R*,5*S*)-**2** of known stereochemistry.[1]

There are several points to note from the results presented in Table 1. Both of the new chiral bases (entries 2 and 3) gave higher enantioselectivity than the parent diamine (*R*)-**3** (entry 1). The norephedrine-derived diamine (1*R*,2*S*)-**4** (entry 2) gave slightly higher enantioselectivity than diamine (1*S*,2*S*)-**7** derived from norpseudoephedrine (entry 3). This is a particularly important result as this diamine is more readily synthesised. Finally, since diamines (1*R*,2*S*)-**4** (entry 2) and (1*S*,2*S*)-**7** (entry 3) generate enantiomeric allylic alcohols, then the benzylic stereogenic centre α to the NHMe group must be controlling the sense of the asymmetric induction in these reactions.

3. Conclusion

The enantioselective rearrangement of *meso* epoxide *trans*-**1** to allylic alcohol (1*S*,4*R*,5*S*)-**2** can now be achieved in 94% yield and with 94% enantioselectivity using a chiral base from a norephedrine-derived diamine (1*R*,2*S*)-**4**. It has also been shown that lower enantioselectivity is obtained with the diastereoisomeric chiral base [(1*S*,2*S*)-**7**] or the chiral base lacking the methyl group [(*R*)-**3**]. As part of this study, a potentially useful synthesis of the hydrochloride salt of norpseudoephedrine (1*S*,2*S*)-**6** has been developed.

4. Experimental

4.1. General

General methods have been described previously.[1,6] For the Kugelrohr distillation, the temperatures quoted correspond to the oven temperature. For ^{1}H NMR spectra recorded in $(CD_3)_2SO$, chemical shifts are quoted in parts per million with reference to the solvent signal at 2.52 ppm; for ^{13}C NMR spectra recorded in $(CD_3)_2SO$, chemical shifts are quoted in parts per million with reference to the solvent signal at 39.8 ppm.

4.2. *(1*R*,2*S*)-*N*-Methyl-1-phenyl-2-(1-pyrrolidinyl)-1-propanamine* **4**

Sodium carbonate (21.2 g, 200.0 mmol), tetra-*n*-butylammonium iodide (12.2 g, 33.0 mmol) and then 1,4-dibromobutane (7.9 cm^3, 66.1 mmol) were added successively to a stirred solution of norpseudoephedrine (1*R*,2*S*)-**5** (10.0 g, 66.2 mmol) in THF (250 cm^3) at room temperature under nitrogen. The resulting suspension was heated at reflux for 40 h. After cooling to room temperature, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (100 cm^3), washed with water (3×50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Under nitrogen, this crude product was dissolved in THF (180 cm^3), triethylamine (23.0 cm^3, 165.0 mmol) was added and the solution was cooled to 0°C. Then, methanesulfonyl chloride (6.2 cm^3, 80.1 mmol) was added dropwise and, after 30 min, triethylamine (14.0 cm^3, 100.0 mmol) was added. After warming to room temperature, methylamine (68 cm^3 of a 40% aqueous solution, 875.7 mmol) was added and the resulting two phase reaction mixture was vigorously stirred for 40 h. The layers were separated and the light brown aqueous layer was extracted with Et_2O (2×100 cm^3). The combined organic extracts were washed with 5% sodium hydrogencarbonate solution (50 cm^3) and water (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by Kugelrohr distillation to give diamine (1*R*,2*S*)-**4** (12.0 g, 83%) as a colourless oil, $[\alpha]_D$ −22.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3323, 2966, 2789, 1452, 1381, 750 and 704; δ_H (270 MHz; $CDCl_3$) 7.36–7.15 (5H, m, Ph), 3.83 (1H, d, *J* 3.2, PhCHN), 2.64–2.59 (4H, m, NCH_2), 2.32 (3H, s, NMe), 2.26 (1H, dq, *J* 3.2 and 6.6, CHN), 1.81–1.76 (4H, m, CH_2), 1.26 (1H, br s, NH) and 0.85 (3H, d, *J* 6.6, Me); δ_C (67.9 MHz; $CDCl_3$) 141.8 (*ipso*-Ph), 127.9, 127.8, 126.4 (Ph), 66.9 (CHN), 66.2 (CHN), 52.3 (NCH_2), 35.4 (NHMe), 23.4 (CH_2) and 12.9 (Me); *m/z* (CI, NH_3) 219 [45%, $(M+H)^+$], 188 (30, M−NHMe) and 98 (100) [found: $(M+H)^+$, 219.1855. $C_{14}H_{22}N_2$ requires *M*+H, 219.1861].

4.3. *(1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)benzamide* **10**

A solution of freshly distilled benzoyl chloride (1.54 cm^3, 13.2 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise to a stirred solution of norephedrine (1*R*,2*S*)-**5** (2.0 g, 13.2 mmol) and triethylamine (1.84 cm^3, 13.2 mmol) in CH_2Cl_2 (10 cm^3) at 0°C under nitrogen. The resulting mixture was stirred at room temperature for 3 h and then water (10 cm^3) was added. The layers were separated and the organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave known[13] benzamide (1*R*,2*S*)-**10** (3.3 g, 98%) as a white solid, mp 160–163°C (EtOAc) (lit.[13] 164°C); R_f (EtOAc) 0.5; $[\alpha]_D$ +33 (*c* 1.0 in MeOH); ν_{max} (Nujol)/cm^{-1} 3286, 1637 and 1547; δ_H (270 MHz; $(CD_3)_2SO$) 7.80–7.77 (2H, m, Ph), 7.54–7.18 (8H, m, Ph), 5.40 (1H, br s, NH), 4.74 (1H, d, *J* 5.6, CHO), 4.26–4.13 (1H, m, CHN), 3.30

(1H, br s, OH) and 1.13 (3H, d, *J* 6.8, Me); δ_C (67.9 MHz; $(CD_3)_2SO$) 165.4 (C=O), 147.0 (*ipso*-Ph), 130.2, 127.9, 127.6, 127.0, 126.5, 126.1 (Ph), 74.4 (CHO), 50.6 (CHN) and 14.6 (Me).

4.4. (4S,5S)-4-Methyl-2,5-diphenyl-4,5-dihydro-1,3-oxazole **11**

Triphenylphosphine (2.5 g, 9.4 mmol) and then diisopropylazodicarboxylate (1.85 cm^3, 9.4 mmol) were added sequentially to a stirred solution of benzamide (1*R*,2*S*)-**10** (2.0 g, 7.5 mmol) in THF (50 cm^3) at 0°C under nitrogen. After warming to room temperature, the resulting mixture was stirred at room temperature for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude dark product. Purification by flash column chromatography on silica using petrol:EtOAc (5:1) as eluent gave oxazole (4*S*,5*S*)-**11** (1.4 g, 74%) as a colourless oil, R_f (petrol:EtOAc, 5:1) 0.3; $[\alpha]_D$ +71 (*c* 1.15 in $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 2969 and 1648; δ_H (270 MHz; $CDCl_3$) 8.07–8.02 (2H, m, Ph), 7.54–7.30 (8H, m, Ph), 5.11 (1H, d, *J* 7.8, CHO), 4.22 (1H, qd, *J* 6.5 and 7.7, CHN) and 1.50 (3H, d, *J* 6.5, Me); δ_C (67.9 MHz; $CDCl_3$) 162.7 (C=N), 140.5 (*ipso*-Ph), 131.4, 128.8, 128.3 (Ph), 127.7 (*ipso*-Ph), 125.6 (Ph), 88.2 (CHO), 71.0 (CHN) and 21.4 (Me); *m/z* (CI, NH_3) 238 [100%, $(M+H)^+$] [found: $(M+H)^+$, 238.1228. $C_{16}H_{15}NO$ requires *M*+H, 238.1232].

4.5. (1S,2S)-2-Amino-1-phenyl-1-propanol (norpseudoephedrine) **6**·HCl

A solution of oxazole (1*S*,2*S*)-**11** (400 mg, 1.7 mmol) in 1.1 M hydrochloric acid (12.7 cm^3) was heated under reflux for 30 h. After cooling to room temperature, charcoal was added. The solid product was collected by filtration and washed with EtOH (20 cm^3). Azeotroping with EtOH (3×20 cm^3) gave the crude product as a white solid. Recrystallisation from EtOAc gave known[11] norpseudoephedrine (1*S*,2*S*)-**6**·HCl (284 mg, 90%) as a colourless crystalline solid, mp 176–179°C (lit.[11] 179–181°C); $[\alpha]_D$ +38 (*c* 1.0 in H_2O) {lit.[11] $[\alpha]_D$ +42.7 (*c* 4.9 in H_2O)}; ν_{max} ($CDCl_3$)/cm^{-1} 3369; δ_H (270 MHz; $(CD_3)_2SO$) 8.19 (3H, s, NH_3), 7.39–7.36 (5H, m, Ph), 6.16 (1H, br s, OH), 4.51 (1H, d, *J* 8.7, CHO), 3.31–3.18 (1H, br m, CHN) and 0.99 (3H, d, *J* 6.6, Me); δ_C (67.9 MHz; $(CD_3)_2SO$) 141.2 (*ipso*-Ph), 128.2, 127.8, 126.9 (Ph), 74.3 (CHO), 52.3 (CHN) and 14.8 (Me).

4.6. (1R,2S)-2-Amino-1-phenyl-1-propanol (norephedrine) **5**·HCl

Norephedrine (1*R*,2*S*)-**5**·HCl was prepared from norephedrine (1*R*,2*S*)-**5**, acetyl chloride and EtOH and was characterised by NMR spectroscopy: δ_H (270 MHz; $(CD_3)_2SO$) 8.19 (3H, s, NH_3), 6.65–6.50 (5H, m, Ph), 4.20 (1H, d, *J* 3.6, CHO), 3.95 (4H, s, NH_3 and OH), 2.75 (1H, dq, *J* 3.6 and 6.8) and 0.33 (3H, d, *J* 6.8, Me); δ_C (67.9 MHz; $(CD_3)_2SO$) 131.9 (*ipso*-Ph), 120.0, 119.5, 117.7 (Ph), 63.9 (CHO), 44.3 (CHN) and 2.8 (Me).

4.7. (1S,2S)-N-Methyl-1-phenyl-2-(1-pyrrolidinyl)-1-propanamine **7**

Sodium carbonate (1.24 g, 11.7 mmol), tetra-*n*-butylammonium iodide (541 mg, 1.5 mmol) and then 1,4-dibromobutane (0.35 cm^3, 2.9 mmol) were added successively to a stirred solution of norpseudoephedrine (1*S*,2*S*)-**6**·HCl (538 mg, 2.9 mmol) in THF (20 cm^3) at room temperature under nitrogen. The resulting suspension was heated at reflux for 40 h. After cooling to room temperature, the solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in Et_2O (30 cm^3), washed with water (3×30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Under nitrogen, this crude product was dissolved in THF (20 cm^3), triethylamine

(0.65 cm^3, 4.7 mmol) was added and the solution was cooled to 0°C. Then, methanesulfonyl chloride (0.27 cm^3, 3.5 mmol) was added dropwise and, after 30 min, triethylamine (0.86 cm^3, 5.9 mmol) was added. After warming to room temperature, methylamine (4.5 cm^3 of a 40% aqueous solution, 81.4 mmol) was added and the resulting two phase reaction mixture was vigorously stirred for 40 h. The layers were separated and the light brown aqueous layer was extracted with Et_2O (2×30 cm^3). The combined organic extracts were washed with 5% sodium hydrogencarbonate solution (30 cm^3) and water (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by Kugelrohr distillation to give diamine (1*S*,2*S*)-**7** (435 mg, 68%) as a colourless oil, bp 150–160°C/0.3 mmHg; $[\alpha]_D$ +68 (*c* 1.0 in $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 3290; δ_H (270 MHz; $CDCl_3$) 7.34–7.20 (5H, m, Ph), 3.19 (1H, d, *J* 9.9, PhCHN), 2.96 (1H, qd, *J* 6.6 and 9.9, CHN), 2.85 (1H, br s, NH), 2.63–2.58 (4H, m, NCH_2), 2.22 (3H, s, NMe), 1.77–1.73 (4H, m, CH_2) and 0.63 (3H, d, *J* 6.6, Me); δ_C (67.9 MHz; $CDCl_3$) 142.9 (*ipso*-Ph), 128.4, 128.0, 127.1 (Ph), 70.3 (PhCHN), 59.3 (CHN), 46.9 (NCH_2), 34.8 (NHMe), 23.8 (CH_2) and 8.2 (Me); *m/z* (CI, NH_3) 219 [70%, $(M+H)^+$] 188 (10, M−NHMe) and 98 (100) [found: $(M+H)^+$, 219.1859. $C_{14}H_{22}N_2$ requires *M*+H, 219.1861].

4.8. (1S,4R,5S)-4,5-Bis(tert-butyldimethylsilyloxy)cyclohex-2-enol **2**

n-Butyllithium (0.76 cm^3 of a 1.6 M solution in hexanes, 1.12 mmol) was added dropwise to a stirred solution of diamine (*R*)-**3** (228 mg, 1.12 mmol) in THF (2 cm^3) at 0°C under nitrogen. After 30 min at 0°C, a solution of the epoxide *trans*-**1** (200 mg, 0.56 mmol) in THF (3 cm^3) was added dropwise by means of a cannula and the resulting solution was allowed to warm to room temperature over 4 h. After stirring at room temperature for a further 12 h, saturated ammonium chloride solution (5 cm^3) and Et_2O (20 cm^3) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3×20 cm^3) and the combined organic extracts were washed with saturated ammonium chloride solution (20 cm^3), 5% sodium hydrogencarbonate solution (20 cm^3), 2% hydrochloric acid solution (20 cm^3), saturated brine solution (20 cm^3) and water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol:Et_2O (3:1) as eluent gave known[1] allylic alcohol (1*S*,4*R*,5*S*)-**2** (142 mg, 71%, 76% ee) as a white solid, $[\alpha]_D$ −85.2 (*c* 1.0 in $CHCl_3$).

4.9. (1S,4R,5S)-4,5-Bis(tert-butyldimethylsilyloxy)cyclohex-2-enol **2**

Using the procedure described above, *n*-butyllithium (0.55 cm^3 of a 1.6 M solution in hexanes, 0.88 mmol), diamine (1*R*,2*S*)-**4** (190 mg, 0.87 mmol) and epoxide *trans*-**1** (156 mg, 1.44 mmol) in THF (5 cm^3) gave the crude product. Purification by flash column chromatography on silica with petrol:Et_2O (3:1) as eluent gave known[1] allylic alcohol (1*S*,4*R*,5*S*)-**2** (147 mg, 94%, 94% ee) as a white solid, $[\alpha]_D$ −106.3 (*c* 1.2 in $CHCl_3$).

4.10. (1R,4S,5R)-4,5-Bis(tert-butyldimethylsilyloxy)cyclohex-2-enol **2**

Using the procedure described above, *n*-butyllithium (0.52 cm^3 of a 1.6 M solution in hexanes, 0.83 mmol), diamine (1*S*,2*S*)-**7** (183 mg, 0.84 mmol) and epoxide *trans*-**1** (150 mg, 0.42 mmol) in THF (5 cm^3) gave the crude product. Purification by flash column chromatography on silica with petrol:Et_2O (7:3) as eluent gave known[1] allylic alcohol (1*R*,4*S*,5*R*)-**2** (145 mg, 97%, 86% ee) as a white solid, $[\alpha]_D$ +95.1 (*c* 0.9 in $CHCl_3$).

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References

1. O'Brien, P.; Poumellec, P. *Tetrahedron Lett*. **1996**, *37*, 8057–8058; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2435–2441.
2. Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem*. **1996**, *61*, 6108–6113.
3. For reviews, see: O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439–1457; Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384.
4. For recent examples, see: Asami, M.; Ogawa, M.; Inoue, S. *Tetrahedron Lett*. **1999**, *40*, 1563–1564; Södergen, M. J.; Andersson, P. G. *J. Am. Chem. Soc*. **1998**, *120*, 10760–10761.
5. For a preliminary communication of some of this work, see: de Sousa, S. E.; O'Brien, P.; Steffens, H. C. *Tetrahedron Lett*. **1999**, *40*, in press.
6. O'Brien, P.; Poumellec, P. *Tetrahedron Lett*. **1996**, *37*, 5619–5622; de Sousa, S. E.; O'Brien, P. *Tetrahedron Lett*. **1997**, *38*, 4885–4888; de Sousa, S. E.; O'Brien, P.; Poumellec, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2613–2618; de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483–1492.
7. Dieter, R. K.; Lagu, B.; Dieter, J. W.; Deo, N.; Pennington, W. T. *Synlett* **1990**, 109–110; Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem*. **1992**, *57*, 1663–1671.
8. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem*. **1991**, *56*, 4264–4268.
9. Anderson, S. R.; Ayers, J. T.; De Vries, K. M.; Ito, F.; Mendenhall, D.; Vanderplas, B. C. *Tetrahedron: Asymmetry* **1999**, *10*, 2655–2663.
10. Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc*. **1981**, *103*, 6157–6163; Lamant, M.; Guignard, A. *Helv. Chim. Acta* **1987**, *70*, 1279–1285; Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc*. **1992**, *114*, 5900–5902; Bonar-Law, R. P.; Davis, A. P.; Dorgan, B. J.; Reetz, M. T.; Wehrsig, A. *Tetrahedron Lett*. **1990**, *31*, 6725–6728; Kreutz, O. C.; Moran, P. J. S.; Rodrigues, J. A. R. *Tetrahedron: Asymmetry* **1997**, *8*, 2649–2653; Koga, K.; Yamada, S.-i. *Chem. Pharm. Bull*. **1972**, *20*, 539–542; Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc*. **1986**, *108*, 8265–8266; Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem*. **1990**, *43*, 2045–2062; Boerner, A.; Krause, H. *Tetrahedron Lett*. **1989**, *30*, 929–930; Boerner, A.; Krause, H. *J. Prakt. Chem*. **1990**, *332*, 307–312.
11. Grunewald, G. L.; Ye, Q. *J. Med. Chem*. **1988**, *31*, 1984–1986; Fodor, G.; Bruckner, V.; Kiss, J.; Ohegyi, G. *J. Org. Chem*. **1949**, *14*, 337–345.
12. Brauch, F.; Dralle, H.; Blanka, H. J. Ger. Patent 3408 850, 1984; *Chem. Abstr*. **1985**, *102*, 24270; Herrmann, R. In *Stereoselective Synthesis*, *Houben-Weyl*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; 1996; Vol. 9, pp. 5780–5785.
13. Tlahuext, H.; Contreras, R. *Tetrahedron: Asymmetry* **1992**, *6*, 727–730.
14. For related examples, see: Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375–1376; Okuda, M.; Tomioka, K. *Tetrahedron Lett*. **1994**, *35*, 4585–4586; Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett*. **1990**, *31*, 5253–5256.
15. Fitton, A. O.; Frost, J. R. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1153–1154; Ardabilchi, N.; Fitton, A. O.; Frost, J. R.; Oppong-Boachie, F. K.; Hadi, A. B. A.; Sharif, A. B. M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 539–543.
16. Oussaid, B.; Berlan, J.; Soufiaoui, M.; Garrigues, B. *Synth. Commun*. **1995**, *25*, 659–665.
17. Kniezo, L.; Kristian, P.; Budesinsky, M.; Havrilova, K. *Collect. Czech. Chem. Commun*. **1981**, *46*, 717–728.
18. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543–2549.