Enantioselective deprotonation of 4-*tert*-butylcyclohexanone by conformationally constrained chiral lithium amide bases

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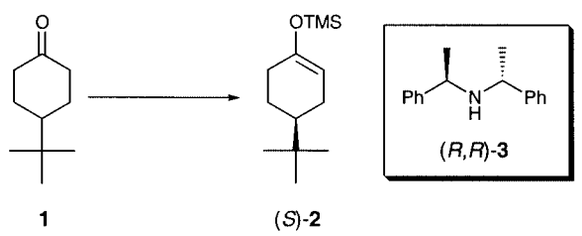
Conformationally rigid chiral lithium amides based on a tetrahydroisoquinoline motif have been prepared bearing a range of substituents at C1 and C3. These bases were tested in the asymmetric deprotonation reaction of 4-*tert*-butylcyclohexanone. Although the 1-substituted tetrahydroisoquinolines gave low enantioselectivity, the chiral bases containing a nitrogen heterocycle at C3 were found to induce high enantioselectivity (81% ee) in the presence of HMPA.

Introduction

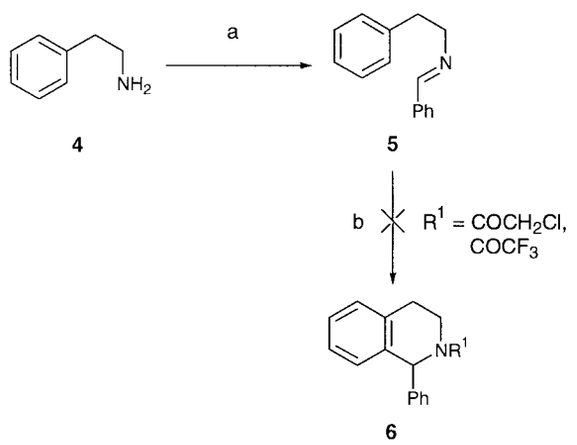
Enantioselective deprotonation of conformationally locked cyclic ketones *e.g.* 4-*tert*-butylcyclohexanone (**1**), using chiral lithium amide bases represents a powerful strategy in asymmetric synthesis (Scheme 1).[1] All the chiral bases developed to



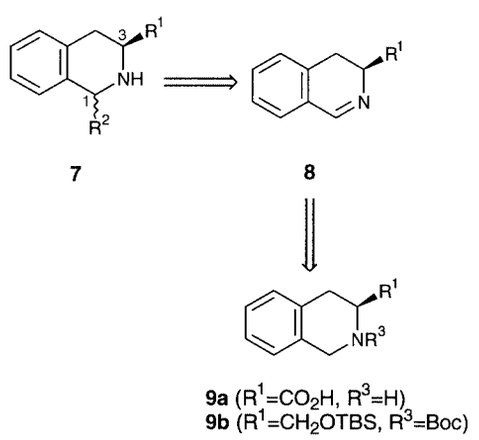
Scheme 1 *Reagents and conditions*: (*R*,*R*)-**3**, ^{n}BuLi, TMSCl, THF, −90 °C, 88% ee, 66%.

date, *e.g.* **3**, have chirality attached to a nitrogen *via* conformationally mobile bonds. Although good enantioselectivity has been achieved, we questioned whether it might be possible to raise this further using conformationally more rigid amide bases.

1,3-Disubstituted tetrahydroisoquinolines seemed ideal bases as (i) they contained two centres of chirality adjacent to a nitrogen analogous to base **3**[2,3] popularised by Simpkins; (ii) they were conformationally less flexible than Simpkins' base **3** and (iii) it would be possible to incorporate additional heteroatoms α to nitrogen which, according to Koga *et al.*,[4] can enhance the enantioselectivity observed. In this paper we describe the synthesis of a variety of substituted tetrahydroisoquinolines and their application in enantioselective desymmetrisation of prochiral ketones.



Scheme 2 *Reagents and conditions*: (a) PhCHO, Na_2SO_4, 1,2-DCE, 68%; (b) RCOCl, KI, 1,2-DCE, rt.



Scheme 3

Results

Synthesis of chiral bases

An ideal route to 1,3-disubstituted tetrahydroisoquinolines seemed to be *via* a Pictet–Spengler reaction of a phenylalanine derivative (Scheme 2). Although most reports of such reactions use electron rich aromatic rings,[5] there were a few examples where non-activated systems had been employed, and so the same conditions were used.[6] However, we were unable to obtain any cyclised material under any conditions.

We therefore adopted an alternative strategy in which the intact tetrahydroisoquinoline was used from the outset, as the amino acid **9a** is commercially available (Scheme 3). During the course of our work Laschat and co-workers[7] reported an alternative route to 1,3-disubstituted tetrahydroisoquinolines *via* a diastereoselective alkylation reaction of **9b**.

The synthesis began with a Lewis acid mediated borane reduction of **10** to afford amino alcohol **11**,[8] with no observed loss of stereochemical integrity (Scheme 4). This was followed

Table 1 Preparation of 1,3-disubstituted tetrahydroisoquinolines **14–18**

R	Yield (%)	*cis*:*trans*
Me	86	2.1:1
Ph	82	1:1.4
1-Np	94	1:1.6
Mesityl	65	1:4.9
2-Me-1-Np	82	0:1

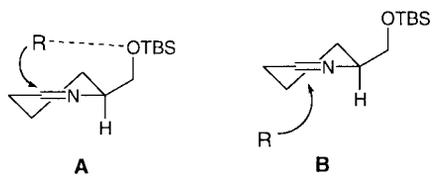
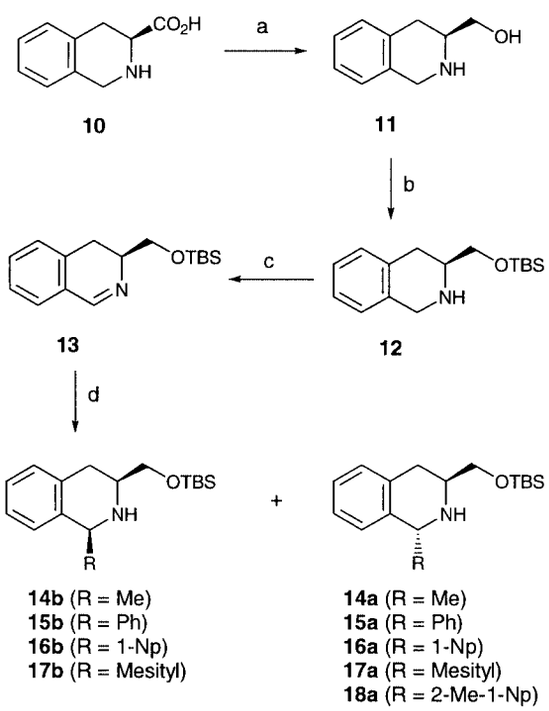


Fig. 1



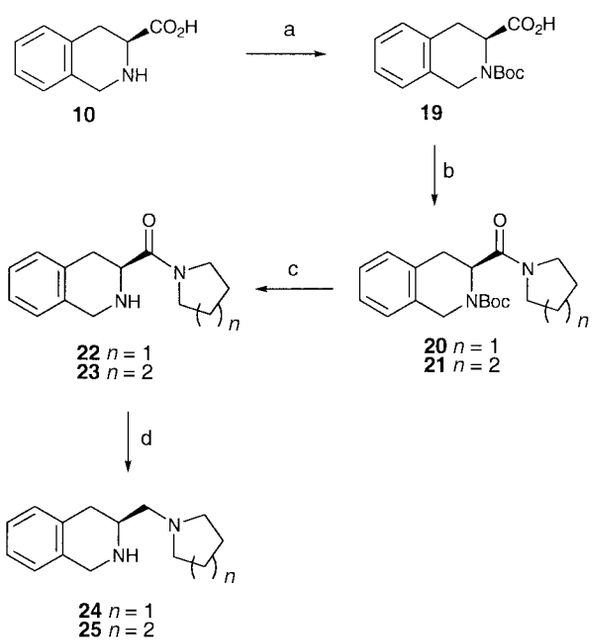
Scheme 4 *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$, $BH_3{\cdot}SMe_2$, THF, 96%; (b) TBSCl, imidazole, DMF, 100%; (c) (i) NCS, Et_2O, (ii) KOH, MeOH, 91% from **12**; (d) RLi, Et_2O, −78 °C.

by protection of the hydroxy group in **11** with *tert*-butyldimethylsilylchloride (TBSCl), which proceeded in quantitative yield. Silyl ether **12** was then treated with *N*-chlorosuccinimide (NCS), to form the *N*-chloro amine, followed by subsequent base mediated dehydrohalogenation affording the required imine **13**, in high yield.[9] Finally, we treated imine **13** with a variety of organolithium reagents,[10] and obtained a range of 1,3-disubstituted tetrahydroisoquinolines with varying degrees of diastereoselectivity (Table 1).[11]

A trend in the diastereoselectivity of the organolithium additions was apparent: small alkyllithiums gave predominantly the *cis* diastereoisomer whilst large alkyllithiums gave predominantly the *trans* isomer. This diastereoselectivity can be accounted for by considering the conformation of imine **13** (Fig. 1). Small alkyllithium reagents can complex with the silyl ether and are therefore delivered from the same face (*e.g.* MeLi, entry 1) furnishing the *cis* isomer. In contrast hindered reagents cannot complex with the bulky silyl ether and attack the imine from the less sterically hindered face (*e.g.* mesityllithium and 2-methyl-1-naphthyllithium, entries 4 and 5), giving the *trans* diastereomer. Organolithium reagents of intermediate steric size furnished adducts with low stereoselectivity (*e.g.* phenyllithium, entry 2).

The relative stereochemistry of the adducts was determined by NOE studies. The *cis* isomers showed a strong nOe between the C1 and C3 protons whereas this was absent in the *trans* isomers. Interestingly, adducts **17a** and **17b** derived from mesityllithium showed diastereotopic methyl signals indicating restricted rotation about the aryl–alkyl bond.[12] This was further in evidence in adduct **18a** which clearly existed as a mixture of diastereoisomers. Attempts to determine the barrier to rotation in **18a** by variable temperature NMR [−30 to 100 °C; $(CDCl_2)_2$] were inconclusive: at elevated temperatures line broadening and coalescence was achieved but broad signals were observed throughout. The fact that coalescence was achieved at 100 °C indicates that the barrier to rotation is relatively low and that the atropisomers were interconverting even at room temperature. Because of the low barrier to rotation it was not possible to separate the diastereoisomers.

The 3-amino substituted tetrahydroisoquinolines were prepared as shown in Scheme 5. The synthesis again commenced



Scheme 5 *Reagents and conditions*: (a) $(Boc)_2O$, NaOH, H_2O, ^{t}BuOH; (b) R_2NH, DCC, HOBT, $CuCl_2$, DMF; (c) TFA, Et_3SiH, DCM, [(65%, **22**), (57%, **23**)]; (d) LAH, THF, [(72%, **24**), (67%, **25**)].

from the commercially available amino acid **10**, with nitrogen protection achieved using Schotten–Baumann conditions.[13] Treatment of the unpurified carboxylic acid **19** with pyrrolidine ($n = 1$) or piperidine ($n = 2$) yielded *N*-Boc amides **20** and **21**, which were again used without further purification. The crude amides **22** and **23** were subsequently deprotected and following reduction of the amide moiety afforded chiral amines **24** and **25**. A similar route has been used by Asami in the synthesis of analogous amines derived from proline.[14]

Enantioselective deprotonation of 4-*tert*-butylcyclohexanone

We decided to test our novel chiral amines on 4-*tert*-butylcyclohexanone (**1**), in the presence of TMSCl (conditions that usually give high enantioselectivity, referred to as internal quench[2c,15]), to enable us to compare the levels of enantioselectivity achieved with those in the literature. Initially we tested the 1,3-disubstituted tetrahydroisoquinolines, and the results are summarised in Scheme 6 and Table 2.[16]

No clear trend emerged from this study except that the nature and stereochemistry of the C1 substituent influenced the asymmetric induction observed (as expected). Only in the case

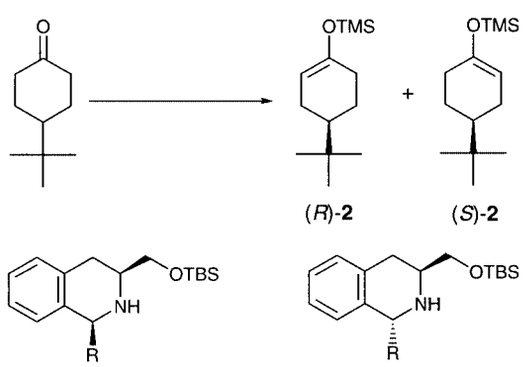
Table 2 Enantioselective deprotonation of ketone **1** utilising 1,3-disubstituted tetrahydroisoquinolines **14**–**18**

Chiral Amine	Yield (%)	ee (%) (*R*/*S*)
14a	81	22 (*S*)
14b	92	10 (*S*)
15a	41	24 (*S*)
15b	53	59 (*S*)
16a	66	47 (*R*)
16b	43	57 (*S*)
17a	52	42 (*S*)
17b	64	31 (*S*)
18a	49	2 (*S*)

Table 3 Enantioselective deprotonation of ketone **1** utilising 3-amino substituted tetrahydroisoquinolines **24** and **25**

Conditions[a]	Temp/°C	Yield (%)	ee (%) (*R*/*S*)
24, IQ	−78	52	0
24, EQ	−78	82	54 (*S*)
24, IQ	−100	78	9 (*R*)
24, EQ	−100	98	38 (*S*)
25, IQ	−78	60	6 (*R*)
25, EQ	−78	96	70 (*S*)
25, IQ	−100	38	12 (*S*)
25, EQ	−100	89	81 (*S*)

[a] IQ = Internal Quench; EQ = External Quench + HMPA (1 eq.).



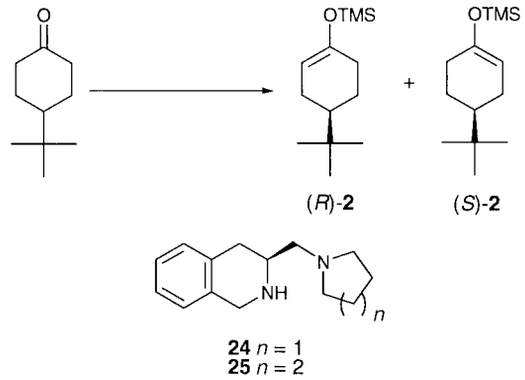
Scheme 6 *Reagents and conditions*: chiral amine, ^{n}BuLi, TMSCl, THF.

of the 1-naphthyl substituent (amines **16a** and **16b**) did this centre dominate the stereochemical outcome of the deprotonation reaction. The very low selectivity observed with **18a** could have been because it was present as a mixture of atropisomers.

We also investigated 3-amino substituted tetrahydroisoquinolines as chiral bases, as Koga had reported dramatic increases in enantioselectivity with chiral diamines when 1 equivalent of HMPA was added. Thus, the amines were tested under two sets of reaction conditions: (i) internal quench (ii) external quench and HMPA. The reactions were conducted at −78 and −100 °C, and the results are summarised in Scheme 7 and Table 3. Indeed we observed a dramatic increase in enantioselectivity in each case when we employed HMPA as an additive, in keeping with Koga's observations. Of the two amino groups, the piperidinyl group was superior to the pyrrolidinyl group and gave useful levels of enantioselectivity although not as high as those reported by Simpkins and Koga.

Conclusion

Reducing the conformational flexibility of the chiral bases has not led to an increase in enantioselectivity over the conformationally mobile bases of Simpkins and Koga. This suggests that such bases adopt and react through single conformations. Indeed recent molecular modelling has shown that the lithium amide dimer of the C_2 symmetric base **3** has one conformation in which the groups intercalate and pack like a jigsaw so that there is little opportunity for bond rotation (see Acknowledgements). If this is also the reactive conformer this could explain the high enantioselectivity achieved. The bases that we have synthesised may not fit together as well as the C_2 symmetric base, thus leading to a number of amide species, which could react with different selectivity.



Scheme 7 *Reagents and conditions*: chiral amine, ^{n}BuLi, TMSCl, THF.

Experimental

Optical rotations ($[\alpha]_D^{22}$) were measured using a Perkin-Elmer 141 Polarimeter and are recorded as 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 157G grating spectrophotometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker ACF-250 and a Bruker WH-400 (400 MHz) spectrometer supported by an Aspect 2000 data system. Chemical shifts are given in ppm (δ) and measured relative to the residual signal of chloroform and J values are given in Hz. Resonance patterns in NMR spectra are shown as s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. Low- and high-resolution MS were obtained on a Kratos MS 25 or MS 80 instrument supported by a DS 55 data system. Mps were determined with a Kofler Hot Stage Micro Melting Point Apparatus and are uncorrected. Elemental analyses were performed using a Perkin-Elmer 2400 Elemental Analyser CHN. Column chromatography was performed on silica gel (Kieselgel 60 F254 and on C560, 40–63 micron). Compound **13** was prepared according to literature procedures.[9]

(*S*)-1,2,3,4-Tetrahydroisoquinoline-3-methanol 11 [17,18]

To a solution of **10** (1.77 g, 10 mmol) in THF (15 mL), under a nitrogen atmosphere, was added $BF_3{\cdot}OEt_2$ (1.38 g, 10 mmol) dropwise to the slurry over a 5 minute period. The mixture was heated at reflux for 2 hours, resulting in a colourless, homogeneous solution. The $BH_3{\cdot}SMe_2$ (1.15 mL, 11.5 mmol) was added carefully to the vigorously refluxing solution over a 10 minute period. This solution was heated at reflux for an additional 6 hours after the addition was complete, then allowed to cool to ambient temperature. The excess borane was quenched by the slow addition of a 1 : 1 THF–water solution (2 mL) followed by a 5 M aq. NaOH solution (7.5 mL). The resulting two phase mixture was heated at reflux for 12 hours and subsequently cooled to room temperature. The filtrate was then concentrated *in vacuo* and the resulting slurry extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to furnish the crude product. Crystallisation of the crude material from EtOAc afforded pure **11** (1.565 g, 96%) as a white crystalline solid, mp 117–118 °C (lit.,[17] 119–120 °C).

(3*S*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-1,2,3,4-tetrahydroisoquinoline 12[9]

To a stirred solution of **11** (0.652 g, 4 mmol) in DMF (10 mL) was added imidazole (0.408 g, 6 mmol) and TBSCl (0.903 g, 6 mmol). The resulting solution was left to stir at room temperature for 8 hours. The solvent was concentrated *in vacuo* and the slurry obtained was then diluted with water and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to afford the crude product. Flash column chromatography (10% EtOAc–hexane) on SiO_2 furnished the pure **12** (1.108 g, 100%) as an oil; $[\alpha]_D^{22}$ −51.9 (*c* 1.04 in $CHCl_3$). Remaining data identical to ref. 9.

Two diastereomers of (3*S*)-3-[(*tert*-butyldimethylsilyloxy)-methyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline 14a and 14b

To a solution of methyllithium (1.2 mL of a 1.6 M solution in Et_2O) in Et_2O (3 mL) under a nitrogen atmosphere at −78 °C was added a solution of **13** (0.275 g, 1 mmol) in Et_2O (4 mL) dropwise over 10 minutes. The resulting mixture was stirred for 4 hours before warming over one hour to −40 °C. Water (3 mL) was added dropwise with stirring, and the reaction mixture warmed rapidly to room temperature. The layers were separated and a 50% aq. solution of KOH (2 mL) was added to the aqueous layer. The aqueous layer was then extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Flash column chromatography (20% EtOAc–hexane) on SiO_2 furnished the pure *cis* diastereomer **14b** (0.166 g, 61%) as an oil; $[\alpha]_D^{22}$ −40.7 (*c* 1.08 in CH_2Cl_2); ν_{max} (solution in $CHCl_3$)/cm^{-1} 3010 (Ar C–H), 1580 (N–H), 1362 ($C(CH_3)_3$), 1258 (Si–CH_3); δ_H (250 MHz; $CDCl_3$) 0.10 (6H, s, $Si(CH_3)_2$), 0.93 (9H, s, $Si(C(CH_3)_3)$), 1.50 (3H, d, *J* 6.4, CHC*H*$_3$), 2.27 (1H, br s, NH), 2.65 (2H, d, *J* 7.0, C*H*$_2$CHNH), 3.04–3.14 (1H, m, C*H*CH_2OSi), 3.62 (1H, dd, *J* 9.8 and 7.0, C*H*HOSi), 3.77 (1H, dd, *J* 9.8 and 4.3, CH*H*OSi), 4.15 (1H, q, *J* 6.4, CC*H*NH), 7.06–7.22 (4H, m, Ar H); δ_C (63 MHz; $CDCl_3$) −5.3 (2 × q), 18.4 (s), 22.2 (q), 26.0 (3 × q), 32.2 (t), 52.2 (d), 55.0 (d), 67.1 (t), 125.2 (d), 125.9 (d), 126.0 (d), 129.2 (d), 134.4 (s), 140.2 (s); *m*/*z* (EI) 291(M^+, 23%), 276 (58), 232 (37), 218 (12), 146 (100) (Found; M^+, 291.2016. $C_{17}H_{29}NOSi$ requires 291.2018). The second fraction contained the pure *trans* diastereomer **14a** (0.070 g, 25%) as an oil; $[\alpha]_D^{22}$ −12.5 (*c* 0.32 in $CHCl_3$); ν_{max} (solution in $CHCl_3$)/cm^{-1} 3014 (Ar C–H), 2958 (CH_2/CH_3), 2930 (CH_2/CH_3), 2858 (CH_2/CH_3), 1363 ($C(CH_3)_3$), 1260 (Si–CH_3), 1223 (CH_2–OSi); δ_H (250 MHz; $CDCl_3$) 0.08 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.48 (3H, d, *J* 6.7, CHC*H*$_3$), 2.57–2.78 (2H, m, C*H*$_2$CHNH), 2.95 (1H, br s, NH), 3.25–3.35 (1H, m, C*H*CH_2OSi), 3.64 (1H, dd, *J* 9.8 and 6.7, C*H*HOSi), 3.76 (1H, dd, *J* 9.8 and 4.3, CH*H*OSi), 4.30 (1H, q, *J* 6.7, CC*H*NH), 7.06–7.15 (4H, m, Ar H); δ_C (63 MHz; $CDCl_3$) 1.0 (2 × q), 18.5 (s), 23.6 (q), 25.9 (3 × q), 31.0 (t), 49.0 (d), 50.4 (d), 66.2 (t), 125.8 (d), 126.2 (d), 126.7 (d), 129.3 (d), 133.5 (s), 139.2 (d); *m*/*z* (EI) 291 (M^+, 6%), 276 (15), 234 (16), 146 (100), 130 (22), 116 (22), 73 (15) (Found; M^+, 291.2020. $C_{17}H_{29}NOSi$ requires 291.2018).

Two diastereomers of (3*S*)-3-[(*tert*-butyldimethylsilyloxy)-methyl]-1-phenyl-1,2,3,4-tetrahydroisoquinoline 15a and 15b

Phenyllithium was prepared by the dropwise addition, over 10 minutes, of bromobenzene (0.42 mL, 4 mmol) in Et_2O (6 mL) to ^{t}BuLi (4.8 mL of a 1.7 M solution in pentane, 8 mmol) in Et_2O (6 mL) under a nitrogen atmosphere at −78 °C. The resulting yellow slurry was stirred for an additional 30 minutes before a solution of **13** (0.55 g, 2 mmol) in Et_2O (8 mL) was added dropwise over 10 minutes at −78 °C. The resulting mixture was stirred for 4 hours before warming over one hour to −40 °C. Water (6 mL) was added dropwise with stirring, and the reaction mixture warmed rapidly to room temperature. The layers were separated, and a 50% aq. solution of KOH (4 mL) was added to the aqueous layer. The aqueous layer was then extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Flash column chromatography (5% EtOAc–hexane) on SiO_2 furnished the pure *cis* diastereomer **15b** (0.240 g, 34%) as an oil; $[\alpha]_D^{22}$ +53.2 (*c* 0.47 in $CHCl_3$); ν_{max} (solution in $CHCl_3$)/cm^{-1} 3312 (N–H), 2930 (CH_2–OSi), 1492 (N–H); δ_H (250 MHz; $CDCl_3$) 0.09 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $(CH_3)_3CSi$), 2.34 (1H, br s, NH), 2.74–2.79 (2H, m, C*H*$_2$CHNH), 3.21–3.32 (1H, m, C*H*CH_2OSi), 3.67 (1H, dd, *J* 10.1 and 7.9, C*H*HOSi), 3.81 (1H, dd, *J* 10.1 and 4.0, CH*H*OSi), 5.12 (1H, s, CC*H*NH), 6.70 (1H, d, *J* 7.9, Ar H), 6.99–7.05 (1H, m, Ar H), 7.13–7.15 (2H, m, Ar H), 7.29–7.45 (5H, m, Ar H); δ_C (63 MHz; $CDCl_3$) −5.3 (2 × q), 18.4 (s), 26.0 (3 × q), 32.3 (t), 55.9 (d), 63.4 (d), 67.3 (t), 125.7 (d), 126.2 (d), 127.5 (d), 127.7 (d), 128.5 (d), 128.5 (d), 129.0 (d), 129.2 (2 × d), 134.8 (s), 139.3 (s), 144.8 (s); *m*/*z* (EI) 353 (M^+, 27%), 338 (9), 294 (54), 208 (100), 130 (10) (Found; M^+, 353.2172. $C_{22}H_{31}NOSi$ requires 353.2175). The second fraction contained the pure *trans* diastereomer **15a** (0.339 g, 48%) as an oil; $[\alpha]_D^{22}$ −9.1 (*c* 0.33 in $CHCl_3$); ν_{max} (solution in $CHCl_3$)/cm^{-1} 3319 (N–H), 2928 (CH_2–OSi), 1494 (N–H); δ_H (250 MHz; $CDCl_3$) 0.00 (6H, s, $Si(CH_3)_2$), 0.81 (9H, s, $(CH_3)_3CSi$), 2.62 (1H, dd, *J* 16.2 and 9.8, C*H*HCHNH), 2.80 (1H, dd, *J* 16.2 and 4.3, CH*H*CHNH), 3.05–3.15 (1H, m, C*H*CH_2OSi), 3.52 (1H, dd, *J* 10.1 and 7.9, C*H*HOSi), 3.81 (1H, dd, *J* 10.1 and 4.3, CH*H*OSi), 5.28 (1H, s, CC*H*NH), 6.94 (1H, d, *J* 7.3, Ar H), 7.06–7.32 (8H, m, Ar H); δ_C (63 MHz; $CDCl_3$) −5.4 (2 × q), 18.1 (s), 25.8 (3 × q), 31.2 (t), 49.0 (d), 59.3 (d), 66.3 (t), 125.6 (d), 126.5 (d), 127.0 (d), 128.2 (2 × d), 128.5 (2 × d), 128.6 (d), 129.2 (d), 135.0 (s), 136.6 (s), 145.4 (s); *m*/*z* (EI) 353 (M^+, 10%), 294 (6), 208 (100), 130 (12), 57 (5) (Found; M^+, 353.2176. $C_{22}H_{31}NOSi$ requires 353.2175).

Two diastereomers of (3*S*)-3-[(*tert*-butyldimethylsilyloxy)-methyl]-1-(1-naphthyl)-1,2,3,4-tetrahydroisoquinoline 16a and 16b

1-Naphthyllithium was prepared by the dropwise addition, over 10 minutes, of 1-bromonaphthalene (0.56 mL, 4 mmol) in Et_2O (6 mL) to ^{t}BuLi (5.3 mL of a 1.5 M solution in pentane, 8 mmol) in Et_2O (6 mL) under a nitrogen atmosphere at −78 °C. The resulting yellow slurry was stirred for an additional 30 minutes before a solution of **13** (0.55 g, 2 mmol) in Et_2O (8 mL) was added dropwise over 10 minutes at −78 °C. The resulting mixture was stirred for 4 hours before warming over one hour to −40 °C. Water (6 mL) was added dropwise with stirring, and the reaction mixture warmed rapidly to room temperature. The layers were separated, and a 50% aq. solution of KOH (4 mL) was added to the aqueous layer. The aqueous layer was then extracted Et_2O (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Flash column chromatography (5% EtOAc–hexane) on SiO_2 furnished the pure *cis* diastereomer **16b** (0.290 g, 36%) as an oil; $[\alpha]_D^{22}$ +51.0 (*c* 2.55 in $CHCl_3$); ν_{max} (solution in $CHCl_3$)/cm^{-1} 3327 (N–H), 2929 (CH_2–OSi), 1597 (N–H); δ_H (250 MHz; $CDCl_3$) 0.11 (3H, s, $Si(CH_3)_2$), 0.13 (3H, s, $Si(CH_3)_2$), 0.94 (9H, s, $(CH_3)_3CSi$), 2.56 (1H, br s, NH), 2.82–3.02 (2H, m, C*H*$_2$CHNH), 3.38–3.49 (1H, m, C*H*CH_2OSi), 3.67 (1H, dd, *J* 9.8 and 7.9, C*H*HOSi), 3.81 (1H, dd, *J* 9.8 and 4.0, CH*H*OSi), 5.85 (1H, s, CC*H*NH), 6.73 (1H, d, *J* 7.6, Ar H), 6.98 (1H, t, *J* 7.6, Ar H), 7.14–7.31 (2H, m, Ar H), 7.37–7.59 (3H, m, Ar H), 7.61–7.70 (1H, m, Ar H), 7.86–7.93 (2H, m, Ar H), 8.23 (1H, d, *J* 8.2, Ar H); δ_C (100 MHz; $CDCl_3$) −5.3 (2 × q), 18.3 (s), 25.9 (3 × q), 29.7 (d), 32.3 (t), 56.3 (d), 67.2 (t), 125.3 (d), 125.4 (d), 125.7 (d), 125.8 (d), 126.1 (d), 127.0 (d), 127.8 (d), 128.3 (d), 128.4 (d), 128.6 (d), 129.0 (d), 131.7 (s), 134.3 (s), 139.2 (2 × s), 139.8 (s); *m*/*z* (EI) 403 (M^+, 10%), 258 (100), 229 (7), 208 (6), 130 (16), 116 (6) (Found; M^+, 403.2321. $C_{26}H_{33}NOSi$ requires

403.2331). The second fraction contained the pure *trans* diastereomer **16a** (0.468 g, 58%) as an oil; $[a]_D^{22}$ +83.6 (*c* 1.46 in $CHCl_3$); ν_{max} (solution in $CHCl_3$)/cm^{-1} 3320 (N–H), 2928 (CH_2–OSi), 1598 (N–H); δ_H (250 MHz; $CDCl_3$) −0.26 (3H, s, $Si(CH_3)_2$), −0.10 (3H, s, $Si(CH_3)_2$), 0.56 (9H, s, $(CH_3)_3CSi$), 2.65 (1H, dd, *J* 16.2 and 10.4, C*H*HCHNH), 2.82 (1H, dd, *J* 16.2 and 4.0, CH*H*CHNH), 2.97–3.08 (1H, m, C*H*CH_2OSi), 3.50 (1H, dd, *J* 9.8 and 8.6, C*H*HOSi), 3.63 (1H, dd, *J* 9.8 and 4.0, CH*H*OSi), 6.18 (1H, s, CC*H*NH), 6.76 (1H, d, *J* 7.0, Ar H), 7.00 (1H, d, *J* 7.3, Ar H), 7.11–7.20 (1H, m, Ar H), 7.24–7.31 (3H, m, Ar H), 7.49–7.64 (2H, m, Ar H), 7.74 (1H, d, *J* 8.3, Ar H), 7.85 (1H, d, *J* 7.9, Ar H), 8.35 (1H, d, *J* 8.3, Ar H); δ_C (63 MHz; $CDCl_3$) −5.7 (q), −5.6 (q), 17.8 (s), 25.4 (3 × q), 31.4 (t), 49.5 (d), 55.6 (d), 66.2 (t), 123.0 (d), 124.6 (d), 125.6 (d), 125.8 (d), 126.6 (d), 126.7 (d), 127.0 (2 × d), 128.9 (d), 129.1 (2 × d), 131.4 (2 × s), 135.5 (s), 136.7 (s), 140.2 (s); *m*/*z* (EI) 403 (M^+, 17%), 258 (100), 216 (17), 130 (23), 83 (22), 71 (14), 57 (24) (Found; M^+, 403.2333. $C_{26}H_{33}NOSi$ requires 403.2331).

Two diastereomers of (3*S*)-3-[(*tert*-butyldimethylsilyloxy)-methyl]-1-mesityl-1,2,3,4-tetrahydroisoquinoline 17a and 17b

Mesityllithium was prepared by the dropwise addition, over 10 minutes, of 2-bromomesitylene (1.53 mL, 10.02 mmol) in Et_2O (15 mL) to ^{t}BuLi (13.4 mL of a 1.5 M solution in pentane, 20.04 mmol) in Et_2O (15 mL) under a nitrogen atmosphere at −78 °C. The resulting yellow slurry was stirred for an additional 30 minutes before a solution of **13** (1.378 g, 5.01 mmol) in Et_2O (20 mL) was added dropwise over 10 minutes at −78 °C. The resulting mixture was stirred for 4 hours before warming over one hour to −40 °C. Water (15 mL) was added dropwise with stirring, and the reaction mixture warmed rapidly to room temperature. The layers were separated, and a 50% aq. solution of KOH (15 mL) was added to the aqueous layer. The aqueous layer was then extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Flash column chromatography (5% EtOAc–hexane) on SiO_2 furnished the pure *cis* diastereomer **17b** (0.212 g, 11%) as a yellow oil; $[a]_D^{22}$ +59.2 (*c* 1.96 in CH_2Cl_2); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3327 (N–H), 3019 (Ar H), 2858 (CH_3), 1610 (Ar H), 1579 (Ar H), 1274 ($Si(CH_3)_2$), 1252 ($Si(CH_3)_2$); δ_H (250 MHz; $CDCl_3$) 0.06 (3H, s, $Si(CH_3)_2$), 0.07 (3H, s, $Si(CH_3)_2$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.93 (3H, s, Ar CH_3), 2.27 (3H, s, Ar CH_3), 2.47 (3H, s, Ar CH_3), 2.70 (2H, br m, CH_2CHNH), 3.23 (1H, br s, C*H*CH_2OSi), 3.60 (1H, dd, *J* 9.8 and 7.6, C*H*HOSi), 3.79 (1H, br m, CH*H*OSi), 5.62 (1H, s, CC*H*NH), 6.64 (1H, d, *J* 7.6, Ar H), 6.78 (1H, s, Ar H), 6.89 (1H, s, Ar H), 6.99 (1H, m, Ar H), 7.10 (2H, d, *J* 3.7, Ar H); δ_C (63 MHz; $CDCl_3$) −5.2 (2 × q), 18.4 (s), 19.9 (q), 20.7 (q), 21.0 (q), 26.0 (3 × q), 32.1 (t), 56.2 (d), 57.7 (d), 67.3 (t), 125.7 (d), 125.8 (d), 126.2 (d), 128.7 (d), 128.9 (d), 131.3 (d), 134.4 (s), 136.6 (s), 137.0 (2 × s), 138.5 (s), 139.4 (s); *m*/*z* (EI) 395 (M^+, 6%), 250 (100), 147 (69), 130 (12), 119 (29) (Found; M^+, 395.2638. $C_{25}H_{37}NOSi$ requires 395.2644). The second fraction contained the pure *trans* diastereomer **17a** (1.070 g, 54%) as a white crystalline solid; mp 98–99 °C (EtOAc); $[a]_D^{22}$ −10.3 (*c* 0.97 in $CHCl_3$); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3684 (N–H), 2858 (CH_3), 1580 (N–H); δ_H (250 MHz; $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.94 (3H, s, Ar CH_3), 2.27 (3H, s, Ar CH_3), 2.46 (3H, s, Ar CH_3), 2.56 (1H, d, *J* 15.9, C*H*HCHNH), 3.27–3.45 (2H, m, CH*H*NH/C*H*CH_2OSi), 3.53 (1H, dd, *J* 10.1 and 4.6, C*H*HOSi), 3.81 (1H, dd, *J* 10.1 and 9.8, CH*H*OSi), 5.64 (1H, s, CC*H*NH), 6.66 (1H, d, *J* 7.6, Ar H), 6.80 (1H, s, Ar H), 6.87 (1H, s, Ar H), 6.95–7.04 (1H, m, Ar H), 7.08 (2H, d, *J* 3.7, Ar H); δ_C (63 MHz; $CDCl_3$) −5.3 (2 × q), 18.2 (s), 20.4 (q), 20.7 (q), 20.9 (q), 25.9 (3 × q), 30.1 (t), 50.5 (d), 52.8 (d), 62.6 (t), 125.6 (d), 125.9 (2 × d), 128.6 (d), 128.9 (d), 131.2 (d), 133.3 (s), 136.4 (s), 136.9 (s), 137.4 (s), 138.7 (s), 138.8 (s); *m*/*z* (EI) 395 (M^+, 8%), 336 (5), 250 (100), 130 (20), 73 (6) (Found; M^+, 395.2650. $C_{25}H_{37}NOSi$ requires 395.2644).

(1*S*, 3*S*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-1-(2-methyl-1-naphthyl)-1,2,3,4-tetrahydroisoquinoline 18a

2-Methyl-1-naphthyllithium was prepared by the dropwise addition, over 10 minutes, of 1-bromo-2-methylnaphthalene (0.442 g, 2 mmol) in Et_2O (3 mL) to ^{t}BuLi (2.4 mL of a 1.7 M solution in pentane, 4 mmol) in Et_2O (3 mL) under a nitrogen atmosphere at −78 °C. The resulting yellow slurry was stirred for an additional 30 minutes before a solution of **13** (0.275 g, 1 mmol) in Et_2O (4 mL) was added dropwise over 10 minutes at −78 °C. The resulting mixture was stirred for 4 hours before warming over one hour to −40 °C. Water (3 mL) was added dropwise with stirring, and the reaction mixture warmed rapidly to room temperature. The layers were separated, and a 50% aq. solution of KOH (2 mL) was added to the aqueous layer. The aqueous layer was then extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Flash column chromatography (5% EtOAc–hexane) on SiO_2 furnished pure **18a** (0.340 g, 82%) as an oil; $[a]_D^{22}$ −4.4 (*c* 1.14 in $CHCl_3$); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3683 (N–H), 2858 (CH_3), 1581 (N–H); δ_H (250 MHz; $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $(CH_3)_3CSi$), 2.11 (1H, br s, NH), 2.67 (3H, s, CH_3), 2.69 (1H, m, C*H*HCHNH), 3.53–3.65 (3H, m, CH*H*C*H*NH and C*H*HOSi), 3.93 (1H, dd, *J* 9.8 and 9.8, CH*H*OSi), 5.97 (1H, s, CC*H*NH), 6.53 (1H, d, *J* 7.9, Ar H), 6.88 (1H, dd, *J* 7.9 and 7.0, Ar H), 7.07–7.36 (5H, m, Ar H), 7.70–7.75 (2H, m, Ar H), 7.98 (1H, d, *J* 8.5, Ar H); δ_C (63 MHz; $CDCl_3$) −5.24 (2 × q), 18.3 (s), 20.9 (q), 25.9 (3 × q), 30.2 (t), 50.9 (d), 53.1 (d), 62.6 (t), 124.4 (d), 125.0 (d), 125.8 (d), 126.0 (d), 126.1 (d), 127.3 (d), 127.6 (d), 128.2 (d), 128.9 (d), 129.2 (d), 131.8 (s), 132.9 (s), 134.0 (s), 134.9 (s), 136.2 (s), 139.0 (s); *m*/*z* (EI) 417 (M^+, 10%), 358 (12), 272 (100), 229 (12), 130 (22), 84 (20) (Found; M^+, 417.2490. $C_{27}H_{35}NOSi$ requires 417.2488).

(3*S*)-1,2,3,4-Tetrahydro-3-isoquinolyl tetrahydro-1*H*-pyrrol-1-yl ketone 22

To a solution of **10** (0.885 g, 5 mmol) in water (5 mL) and ^{t}BuOH (5 mL) was added NaOH (0.22 g, 5.5 mmol). To the reaction mixture was then added di-*tert*-butyl dicarbonate (1.09 g, 5 mmol) dropwise to the clear solution. After a short induction period, the temperature rose to about 30–35 °C. The reaction was then brought to completion by stirring overnight at room temperature, at which time, the clear solution had reached pH 7.5–8.5. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were then extracted with saturated aq. $NaHCO_3$ solution (2 × 10 mL) before acidifying the combined aqueous layers to pH 1–1.5 by the addition of aq. $KHSO_4$ (10 mL). The turbid reaction mixture was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water (2 × 25 mL), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. To a solution of crude **19** (1.591 g, 5.72 mmol) in DMF (30 mL) was added DCC (1.413 g, 6.86 mmol), HOBT (0.926 g, 6.86 mmol), copper(II) chloride (0.922 g, 6.86 mmol) and pyrrolidine (0.57 mL, 6.86 mmol). The reaction mixture was stirred at room temperature for 24 hours, before evaporation of the solvent under reduced pressure. The crude residue was then dissolved in CH_2Cl_2 (50 mL) and to this was added trifluoroacetic acid (5.54 mL, 65 mmol) and triethylsilane (5.61 mL, 15 mmol). The reaction mixture was left to stir at room temperature for 16 hours, and the solvent evaporated *in vacuo* to afford the crude product. Flash column chromatography on SiO_2 (10% MeOH–EtOAc) furnished pure **22** (0.713 g, 62%) as a white crystalline solid; $[a]_D^{22}$ −90.9 (*c* 0.33 in CH_2Cl_2); mp 83–84 °C (EtOH) (Found; C 72.77; H 8.05; N 12.06. $C_{14}H_{18}N_2O$ requires C 73.01; H 7.88; N 12.16%); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3340 (N–H), 3049 (Ar C–H), 1638 (C=O), 1495 (Ar C–H) (lit.,[19] ν_{max} (KBr)/cm^{-1} 3350, 2930); δ_H (250 MHz; $CDCl_3$) 1.83–2.04

(4H, m, $N(CH_2CH_2)_2$), 2.09 (1H, br s, NH), 2.80 (1H, dd, *J* 16.5 and 4.3, C*H*HCHC=O), 2.99 (1H, dd, *J* 16.5 and 11.0, CH*H*CHC=O), 3.34–3.65 (4H, m, $N(CH_2CH_2)_2$), 3.70 (1H, dd, *J* 11.0 and 4.3, CH_2CHC=O), 4.12 (2H, s, CH_2NH), 7.02–7.20 (4H, m, Ar H); δ_C (63 MHz; $CDCl_3$) 24.2 (t), 26.1 (t), 31.0 (t), 45.9 (t), 46.3 (t), 47.4 (t), 54.9 (d), 125.7 (d), 126.1 (d), 126.2 (d), 129.3 (d), 133.9 (s), 135.4 (s), 171.26 (s); *m*/*z* (FAB) 231 (M^+ + H; 100%), 132 (31) (Found; M^+, 230.1505. $C_{14}H_{18}N_2O$ requires 230.1419).

Piperidin-1-yl [(3*S*)-1,2,3,4-tetrahydro-3-isoquinolyl] ketone 23

To a solution of **10** (0.885 g, 5 mmol) in water (5 mL) and ^{t}BuOH (5 mL) was added NaOH (0.22 g, 5.5 mmol). To the reaction mixture was then added di-*tert*-butyl dicarbonate (1.09 g, 5 mmol) dropwise to the clear solution. After a short induction period, the temperature rose to about 30–35 °C. The reaction was then brought to completion by stirring overnight at room temperature, at which time, the clear solution had reached pH 7.5–8.5. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were then extracted with saturated aq. $NaHCO_3$ solution (2 × 10 mL) before acidifying the combined aqueous layers to pH 1–1.5 by the addition of aq. $KHSO_4$ (10 mL). The turbid reaction mixture was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water (2 × 25 mL), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. To a solution of crude **19** (1.591 g, 5.72 mmol) in DMF (30 mL) was added DCC (1.413 g, 6.86 mmol), HOBT (0.926 g, 6.86 mmol), copper(II) chloride (0.922 g, 6.86 mmol) and piperidine (0.68 mL, 6.86 mmol). The reaction mixture was stirred at room temperature for 24 hours, before evaporation of the solvent under reduced pressure. The crude residue was then dissolved in CH_2Cl_2 (50 mL) and to this was added trifluoroacetic acid (5.54 mL, 65 mmol) and triethylsilane (5.61 mL, 15 mmol).

The reaction mixture was left to stir at room temperature for 16 hours, and the solvent evaporated *in vacuo* to afford the crude product. Flash column chromatography on SiO_2 (10% MeOH–EtOAc) furnished pure **23** (0.695 g, 57%); $[a]_D^{22}$ −80.4 (*c* 1.12 in CH_2Cl_2); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3350 (N–H), 3048 (Ar C–H), 3021 (Ar C–H), 1637 (C=O), 1494 (Ar C–H); δ_H (250 MHz; $CDCl_3$) 1.45–1.69 (6H, m, $N(CH_2CH_2)_2CH_2$), 2.27 (1H, br s, NH), 2.72 (1H, dd, *J* 16.5 and 4.6, C*H*HCHC=O), 2.86 (1H, dd, *J* 16.5 and 10.7, CH*H*CHC=O), 3.36–3.64 (4H, br m, $N(CH_2CH_2)_2CH_2$), 3.89 (1H, dd, *J* 10.7 and 4.6, CH_2CHC=O), 4.04 (2H, s, CH_2NH), 6.95–7.13 (4H, m, Ar H); δ_C (63 MHz; $CDCl_3$) 24.6 (t), 25.6 (t), 26.6 (t), 31.7 (t), 43.0 (t), 46.5 (t), 47.1 (t), 53.0 (d), 125.7 (d), 126.1 (d), 126.2 (d), 129.2 (d), 133.7 (s), 135.4 (s), 171.0 (s); *m*/*z* (CI) 245 (M^+ + H; 50%), 132 (94), 112 (15), 84 (100), 65 (16), 51 (10) (Found; M^+ + H, 245.1646. $C_{15}H_{21}N_2O$ requires 245.1654).

(3*S*)-3-(Tetrahydro-1*H*-pyrrol-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline 24

To a solution of **22** (0.579 g, 2.52 mmol) in THF (15 mL) was added $LiAlH_4$ (0.110 g, 2.9 mmol) portionwise at 0 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and then refluxed for 14 hours. The reaction mixture was then quenched with wet Et_2O (15 mL), treated with saturated Rochelle's salt solution (10 mL), agitated vigorously and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with $NaHCO_3$ solution (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Flash column chromatography on SiO_2 (EtOAc and 1% Et_3N) furnished pure **24** (0.392 g, 72%) as an orange oil; $[a]_D^{22}$ −68.5 (*c* 1.3 in CH_2Cl_2); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3319 (N–H), 3044 (Ar C–H), 2798 (N–CH_2), 1606 (Ar C–H), 1582 (Ar C–H), 1497 (Ar C–H); δ_H (250 MHz; $CDCl_3$) 1.77–1.82 (4H, m, $N(CH_2CH_2)_2$), 2.43 (1H, dd, *J* 12.2 and 4.3, C*H*HCHNH), 2.49–2.78 (8H, m, N*H*, $N(CH_2CH_2)_2$, CH*H*CHN and $CHCH_2N$), 3.03 (1H, m, CH_2CHNH), 4.07 (2H, br s, CH_2NH), 7.00–7.13 (4H, m, Ar H); δ_C (63 MHz; $CDCl_3$) 23.6 (2 × t), 34.1 (t), 48.5 (t), 52.5 (d), 54.6 (2 × t), 61.9 (t), 125.7 (d), 126.0 (d), 126.3 (d), 129.2 (d), 134.5 (s), 135.7 (s); *m*/*z* (EI) 216 (M^+; 5%), 132 (77), 103 (5), 84 (100), 55 (8) (Found; M^+, 216.1627. $C_{14}H_{20}N_2$ requires 216.1626).

(3*S*)-3-(Piperidinomethyl)-1,2,3,4-tetrahydroisoquinoline 25

To a solution of **23** (0.368 g, 1.51 mmol) in THF (10 mL) was added $LiAlH_4$ (0.066 g, 1.74 mmol) portionwise at 0 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and then refluxed for 14 hours. The reaction mixture was then quenched with wet Et_2O (10 mL), treated with saturated Rochelle's salt solution (5 mL), agitated vigorously and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with $NaHCO_3$ solution (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Flash column chromatography on SiO_2 (10% MeOH–EtOAc and 1% Et_3N) furnished pure **25** (0.233 g, 67%) as an orange oil; $[a]_D^{22}$ −52.2 (*c* 1.04 in CH_2Cl_2); ν_{max} (solution in CH_2Cl_2)/cm^{-1} 3316 (N–H), 3043 (Ar C–H), 2804 (N–CH_2), 1583 (N–H), 1495 (Ar C–H); δ_H (250 MHz; $CDCl_3$) 1.36–1.69 (6H, m, $N(CH_2CH_2)_2CH_2$), 2.29–2.62 (7H, m, NH, $CHCH_2N$ and $N(CH_2CH_2)_2CH_2$), 2.70 (1H, dd, *J* 16.2 and 4.0, C*H*HCHNH), 3.01–3.22 (2H, br m, CH*H*CHNH and CH_2CHNH), 4.07 (2H, s, CH_2NH), 7.01–7.13 (4H, m, Ar H); δ_C (63 MHz; $CDCl_3$) 24.4 (t), 26.0 (2 × t), 33.8 (t), 48.3 (t), 50.6 (d), 55.2 (2 × t), 64.4 (t), 125.7 (d), 126.0 (d), 126.4 (d), 129.1 (d), 134.4 (s), 135.4 (s); *m*/*z* (EI) 230 (M^+; 6%), 146 (12), 132 (67), 98 (100), 55 (11) (Found; M^+, 230.1791. $C_{15}H_{22}N_2$ requires 230.1783).

General procedure for 4-*tert*-butyl-1-trimethylsilyloxycyclohex-1-ene 2[2b]

The chiral lithium amide base was prepared under a nitrogen atmosphere by the addition of ^{n}BuLi (1.88 mL of a 1.6 M solution in hexanes, 3 mmol) to a solution of the chiral amine (3 mmol) in THF (40 mL) at −78 °C. After 5 minutes the mixture was allowed to warm to room temperature over 15 minutes, and then recooled to −78 °C. TMSCl (1.085 g, 10 mmol) was added and after 2 minutes 4-*tert*-butylcyclohexanone (**1**) (0.308 g, 2 mmol) in THF (10 mL) was added dropwise over a period of 5 minutes. The mixture was stirred for a further 30 minutes at −78 °C before Et_3N (4 mL) and saturated aq. $NaHCO_3$ (10 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (2 × 40 mL) and the organic layer washed with saturated aq. NH_4Cl (2 × 20 mL), saturated aq. $NaHCO_3$ (2 × 20 mL), dried ($MgSO_4$), and filtered before the solvent was removed under reduced pressure. The crude residue was then purified by Kugelrohr distillation (bp 66–67 °C (0.44 mm Hg)) to furnish pure **2** as a colourless oil; δ_H (250 MHz; $CDCl_3$) 0.15 (9H, s, $(CH_3)_3Si$), 0.84 (9H, s, $(CH_3)_3CCH$), 1.17–1.29 (2H, m, $CH_2CH_2CH^tBu$), 1.72–1.84 (2H, m, $CH_2CH_2CH^tBu$), 1.93–2.08 (3H, m, $CHCH_2CH^tBu$), 4.80–4.83 (1H, m, $(CH_3)_3SiOCCH$) (lit.,[2b] δ_H ($CDCl_3$) 0.18 (9H, s), 0.87 (9H, s), 1.12–1.34 (2H, m), 1.73–1.88 (2H, m), 1.95–2.25 (3H, m), 4.84 (1H, m)); δ_C (63 MHz; $CDCl_3$) 0.4 (3 × q), 24.4 (t), 25.1 (t), 27.37 (3 × q), 31.0 (t), 32.1 (s), 44.0 (d), 104.0 (d), 150.3 (s) (lit.,[2b] δ_C ($CDCl_3$) 0.4 (3 × q), 24.5 (t), 25.2 (t), 27.5 (3 × q), 31.1 (t), 32.2 (s), 44.1 (d), 104.1 (d), 150.4 (s)).

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