

# Synthesis and evaluation of *N,S*-compounds as chiral ligands for transfer hydrogenation of acetophenone †

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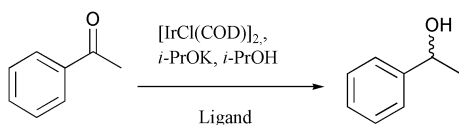
New nitrogen- and sulfur-containing compounds, bicyclic and monocyclic, were prepared and evaluated as ligands in the transfer hydrogenation of acetophenone. Utilising  $[\text{Ir}(\text{COD})\text{Cl}]_2$  as metal precursor the best result, 80% ee, was obtained using a bicyclic sulfoxide ligand.

## Introduction

Sulfur-containing ligands have been studied in a variety of applications in asymmetric catalysis.<sup>1</sup> The different electronic properties of sulfur compared to oxygen<sup>2</sup> as the chelating atom and the fact that sulfur can become chiral when coordinated to a metal have challenged many scientists.<sup>3–6</sup> Utilisation of nitrogen and sulfur as chelating atoms in ligands have afforded moderate to excellent results in *e.g.* allylic alkylation,<sup>1,3,7</sup> hydrogenation,<sup>1,8</sup> diethylzinc addition,<sup>9–11</sup> conjugate addition to enones,<sup>1,12</sup> metal-catalysed cross-coupling<sup>1</sup> and hydrosilylation of imines and ketones.<sup>1</sup>

Prior to work done by the groups of Lemaire<sup>13–16</sup> and van Leeuwen<sup>17,18</sup> very little has been reported regarding sulfur-containing ligands for the transfer hydrogenation reaction.<sup>1</sup> Enantioselective transfer hydrogenation of ketones is a well explored reaction in asymmetric catalysis.<sup>19,20</sup> The attractive feature of this reaction lies primarily in the use of isopropyl alcohol or formic acid as the hydrogen source instead of molecular hydrogen. We have previously reported that 2-azanobornan-3-ylmethanol is an efficient ligand in Ru(arene)-catalysed asymmetric transfer hydrogenation.<sup>21–24</sup>

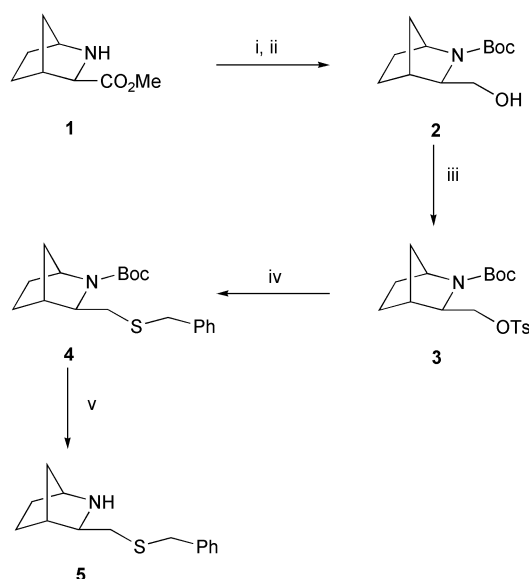
Here we report the synthesis and evaluation of two new classes of *N,S*-ligands for transfer hydrogenation. With the results of the 2-azanobornanyl amino alcohols in mind, we prepared the corresponding amino sulfides bearing this bicyclic backbone. Aiming for access to active ligands that can be easily prepared and modified, we also developed a class of cyclohexyl-based amino sulfides. A short synthetic protocol afforded these compounds as racemic mixtures easily separated by chiral HPLC. The influence of different backbones and substituents in the amino sulfides was investigated by subjecting them to the transfer hydrogenation conditions using  $[\text{Ir}(\text{COD})\text{Cl}]_2$  as the metal precursor and *i*-PrOH as the hydrogen donor (Scheme 1).



Scheme 1 Asymmetric transfer hydrogenation of acetophenone.

## Results and discussion

Amino sulfide **5** was synthesised in five steps from amino ester **1**, prepared according to literature procedures (Scheme 2).<sup>21,25</sup> Boc-protection of **1** and reduction of the ester with  $\text{LiAlH}_4$



Scheme 2 (i)  $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , THF, rt, overnight; (ii) LAH, THF, 0 °C 2 h; (iii)  $\text{TsCl}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ , 0 °C, rt 5 h; (iv)  $\text{BnSH}$ , *n*-BuLi, THF, 0 °C 1 h, rt overnight; (v) TFA,  $\text{CH}_2\text{Cl}_2$ , rt, 2 h.

gave alcohol **2**, which was subjected to tosylation to give **3**. Nucleophilic substitution of the tosylate with deprotonated toluene- $\alpha$ -thiol and subsequent deprotection yielded compound **5**.

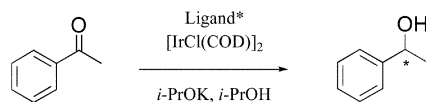
In earlier reports<sup>17,26</sup> on *N,S*-ligands in asymmetric transfer hydrogenation, it has been revealed that  $[\text{Ir}(\text{COD})\text{Cl}]_2$  is the most active pre-catalyst. Amino sulfide **5** was therefore evaluated in the transfer hydrogenation of acetophenone in *i*-PrOH using this iridium salt and *i*-PrOK as the base (entry 1, Table 1). Under these conditions acetophenone was reduced to the corresponding alcohol with high rate but low selectivity (95% conversion after 1 h, 63% ee).

Monooxidation of the sulfur atom introduces new centre of chirality into the ligand. This was performed with Boc-protected **4** using sodium periodate in a  $\text{MeOH-H}_2\text{O}$  solution (Scheme 3). The product was formed as a 3:2 mixture of diastereomers that were separated by preparative chiral HPLC. Boc-deprotection yielded sulfoxides major-**7** and minor-**7**.

Major-**7** and minor-**7** were evaluated in the transfer hydrogenation reaction and the results are shown in Table 1, entries 2 and 3. Both were found to yield less active catalysts compared to **5**, (respectively, 10 and 52% conversion after 1 h), but a higher enantiomeric excess was recorded for minor-**7**: 80% ee of (*R*)-1-phenylethanol. In addition, ligands **5**, and minor- and major-**7** were evaluated in the asymmetric transfer hydrogen-

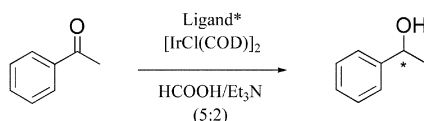
† Electronic supplementary information (ESI) available: NMR spectra. See <http://www.rsc.org/suppdata/ob/b2/b208907f/>

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**Table 1** Transfer hydrogenation of acetophenone using ligands **5** and **7**<sup>a</sup>

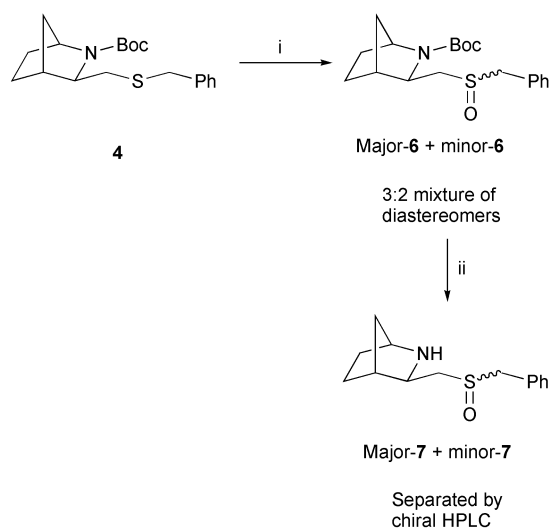
Entry	Ligand <sup>b</sup>	Time (t/h)	Conv. (%) <sup>c</sup>	Ee (%) <sup>c</sup>	Config. of product
1	<b>5</b>	1	95	63	<i>R</i>
2	Major-7	1	10	55	<i>S</i>
3	Minor-7	1	52	80	<i>R</i>

<sup>a</sup> See the Experimental section for procedure. <sup>b</sup> Substrate:metal:ligand:base = 200:1:2.5:6.25. <sup>c</sup> Determined by chiral GC.

**Table 2** Transfer hydrogenation of acetophenone using formic acid as the hydrogen donor<sup>a</sup>

Entry	Ligand <sup>b</sup>	Temp. (T/°C)	Time (t/h)	Conv. (%) <sup>c</sup>	Ee (%) <sup>c</sup>	Config. of product
1	<b>5</b>	60	6	100	15	<i>R</i>
2	<b>5</b>	Rt	96	30	28	<i>S</i>
3	Major-7	No reaction				
4	Minor-7	No reaction				

<sup>a</sup> See the Experimental section for procedure. <sup>b</sup> Substrate:metal:ligand = 200:1:2.5. <sup>c</sup> Determined by chiral GC.

**Scheme 3** (i) NaIO<sub>4</sub>, MeOH–H<sub>2</sub>O, 0 °C to rt; (ii) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h.

ation of acetophenone using formic acid as the hydrogen donor (Table 2).

Using ligand **5**, full conversion was reached after 6 h at 60 °C and the enantiomeric excess of the (*R*)-product was 15%. At room temperature the reaction was very slow, 30% conversion after 96 h, but interestingly this led to a reversal of the stereoselectivity and the (*S*)-product was obtained in 28% ee. With ligands minor- and major-7 there was no reaction at all.

To obtain ligands prepared according to a shorter synthetic protocol with more possibilities to change substituents on nitrogen and sulfur, a class of cyclohexylamino sulfides was prepared. Aziridine **8**, derived from cyclohexene oxide served as the starting point for these new ligands (Scheme 4).<sup>27–29</sup>

Ring opening of **8** with sulfur nucleophiles yielded racemic **9a–c**. After Cbz-protection of these primary amines, the enantiomers could be separated by chiral HPLC. Deprotection of the Cbz-group using 6 M HCl was performed in clean reactions yielding enantiomerically pure amino sulfides **11a,b**.

Attempts to ring open **8** with 2-methylpropane-2-thiol were not successful, probably due to the large degree of steric hindrance in the thiol. However, we found that with the activated Cbz-protected aziridine **12** in combination with BF<sub>2</sub>·OEt<sub>2</sub>, ring opening was possible with 2-methylpropane-2-thiol (Scheme 4). The resulting amino sulfide **10d** was resolved into the pure enantiomers by chiral HPLC and thereafter deprotected yielding **11d**.

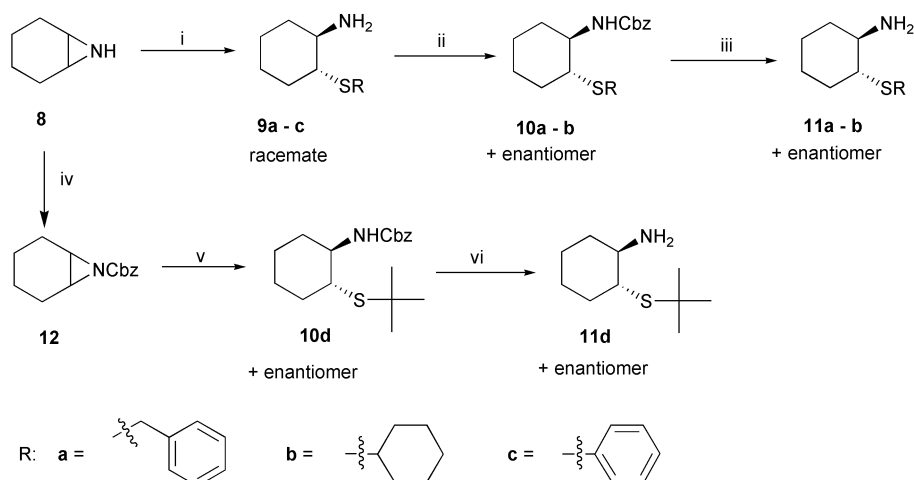
Racemic **9a** and **9c** was benzylated *via* reductive amination yielding compounds with a secondary amine functionality (Scheme 5). The two enantiomers of the resulting compounds **14** and **15** were separated by chiral HPLC. Alkylation with an isopropyl group was done using enantiomerically pure **11a** since the enantiomers of product **13** did not separate on chiral HPLC (Scheme 5). Attempts to monooxidise sulfide **14** in the same manner as for the bicyclic compound were also made but it was not possible to purify or characterise satisfactorily the oxidised product.

Faster access to *N*-benzylamino sulfides such as **14** and **15** was obtained using aziridine **16**, derived from cyclohexene oxide and benzylamine (Scheme 6).<sup>30–32</sup> This aziridine was ring opened with four different substituted phenyl thiols resulting in compounds **17a–d**. These ligands enabled us to study substituent effects in the aryl ring.

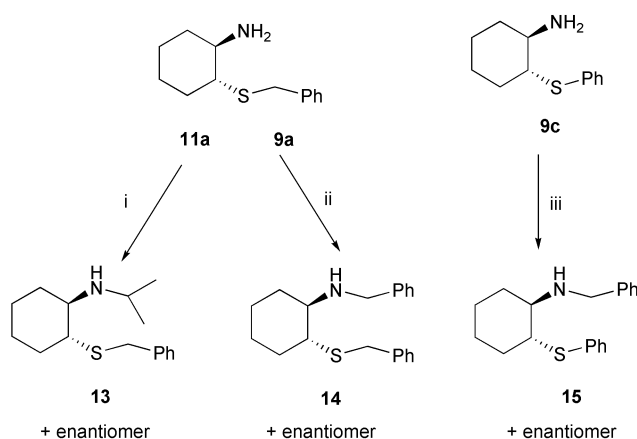
A third chiral center in the ligand structure was introduced *via* ring opening of chiral aziridine **18**, derived from (*S*)-1-phenylethylamine and cyclohexene oxide (Scheme 7).<sup>30,31</sup> A 3:1 mixture of diastereomers was obtained when **18** was ring opened with toluene-*α*-thiol (major-**19** and minor-**19**, ratio determined by NMR analysis), which could be separated by flash chromatography.

The effect of a smaller ring in the ligand backbone was studied using compound **22** (Scheme 8). Aziridine **20**, synthesised according to a literature procedure,<sup>29</sup> was ring opened with toluene-*α*-thiol, *N*-benzylated and separated into the pure enantiomers in the same manner as for **14**.

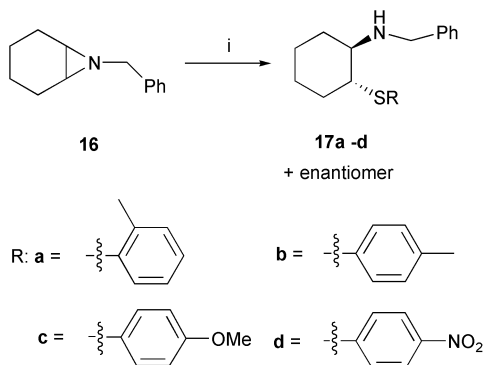
Compounds **11a,b,d,13**, **14**, **15**, **17a–d**, major-**19**, minor-**19** and **22** were evaluated in the transfer hydrogenation reaction and the results are shown in Table 3. Primary amine **11a** gave



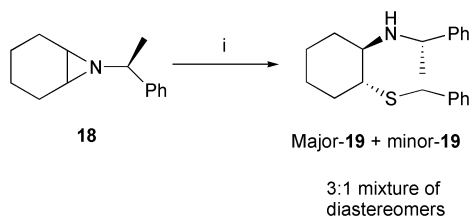
**Scheme 4** (i) RSH, MeOH, reflux, 7 h; (ii) CbzCl, Et<sub>3</sub>N, Et<sub>2</sub>O, 0 °C, 2 h and then separation on chiral HPLC; (iii) 6 M HCl, reflux, over night; (iv) CbzCl, Et<sub>3</sub>N, Et<sub>2</sub>O, 0 °C, 1.5 h; (v) *t*-BuSH, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C 3 h, rt overnight and then separation on chiral HPLC; (vi) Pd-C, NH<sub>4</sub><sup>+</sup>COO<sup>-</sup>, MeOH, rt 1 h.



**Scheme 5** (i) Acetone, NaCNBH<sub>3</sub>, MeOH, rt overnight; (ii) benzaldehyde, NaCNBH<sub>3</sub>, MeOH, rt overnight and then separation on chiral HPLC; (iii) benzaldehyde, MgSO<sub>4</sub>, EtOH, rt 4 h and then NaBH<sub>4</sub>, rt overnight and then separation on chiral HPLC.

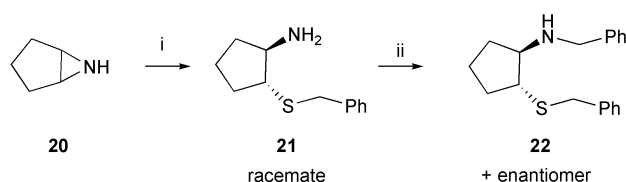


**Scheme 6** (i) RSH, MeOH, reflux overnight and then separation on chiral HPLC.



**Scheme 7** (i) BnSH, MeOH, reflux 7 h.

rise to a more efficient catalyst than the bicyclic ligands **5** and minor-**7** (97% conversion in 0.5 h), but which was less selective, 59% ee. The primary amines with more bulky substituents on



**Scheme 8** (i) BnSH, MeOH, reflux, 6 h; (ii) benzaldehyde, MgSO<sub>4</sub>, EtOH, rt, 4 h and then NaBH<sub>4</sub>, EtOH, rt, overnight, separation on chiral HPLC.

sulfur, **11b** and **d**, showed a decrease in both activity and selectivity of the catalyst (entries 2 and 3). Amino sulfides **13** and **14**, with a secondary amine, both gave a higher enantiomeric excess than the corresponding primary amine **11a**, 63 and 70% ee, respectively (entries 4 and 5). For **14** the same rate as for the primary amine **11a** was recorded (approximately full conversion in 0.5 h, entry 5). Ligand **15** afforded a low ee (33%, entry 6) probably due to too much steric bulk around the sulfur. The results obtained with the aryl substituted analogues **17a-d**, (entries 7–10) showed that electron-donating aryl substituents gives a slight increase in the enantiomeric excess (*cf.* entries 6–9) whilst an electron-withdrawing group lowered the enantiomeric excess (*cf.* entries 6 and 10). The introduction of steric bulk into the aryl ring close to the metal centre did not effect the selectivity much (*cf.* entries 6 and 7). Ligands major- and minor-**19** (entries 11 and 12), differed significantly in rate, 94 and 20% conversion, respectively, in 1 h, even though both of them gave very low enantiomeric excesses. A one-carbon decrease in ring size (ligand **22**, entry 13) was not beneficial either (38% ee); one reason might be the change in dihedral angle between the heteroatoms.

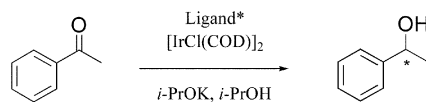
## Conclusions

Two new classes of nitrogen and sulfur containing ligands have been synthesised and evaluated in the asymmetric transfer hydrogenation of acetophenone. Bicyclic sulfoxide minor-**7** gave rise to a catalyst of good selectivity, 80% ee. A synthetic protocol for rapid access to a number of monocyclic ligands, open to different structural modifications, was also developed. Dibenzyl ligand **14** afforded the most efficient catalyst in this study, 98% conversion in 0.5 h using a substrate:catalyst ratio of 200:1.

## Experimental

### General

All reactions were run under argon or nitrogen using dry glassware and magnetic stirring. THF and Et<sub>2</sub>O were freshly distilled

**Table 3** Transfer hydrogenation of acetophenone using ligands **11a,b,d**, **13**, **14**, **15**, **17a–d**, major-**19**, minor-**19** and **22**<sup>a</sup>

Entry	Ligand <sup>b,c</sup>	Time (t/h)	Conv. (%) <sup>d</sup>	Ee (%) <sup>d</sup>	Config. of product
1	<b>11a</b>	0.5	97	59	S
2	<b>11b</b>	2.5	100	16	S
3	<b>11d</b>	1	41	28	S
4	<b>13</b>	1	96	63	S
5	<b>14</b>	0.5	98	70	S
6	<b>15</b>	0.5	79	33	S
7	<b>17a</b>	1	80	35	S
8	<b>17b</b>	1	91	35	S
9	<b>17c</b>	1	92	44	S
10	<b>17d</b>	1	59	29	S
11	Major- <b>19</b>	1	94	24	R
12	Minor- <b>19</b>	1	20	32	S
13	<b>22</b>	1	89	38	S

<sup>a</sup> See the Experimental section for procedure. <sup>b</sup> Substrate:metal:ligand:base = 200:1:2.5:6.25. <sup>c</sup> For ligands prepared as racemates and then separated into pure enantiomers by chiral HPLC, the enantiomer first eluted from the column was used. <sup>d</sup> Determined by chiral GC.

under nitrogen from a deep-blue solution of sodium–benzophenone ketyl just prior to use. CH<sub>2</sub>Cl<sub>2</sub> and *i*-PrOH were freshly distilled under nitrogen from powdered CaH<sub>2</sub> just prior to use. Flash chromatography was performed using Matrex silica gel 60 Å (37–70 μm). Analytical TLC was carried out utilising 0.25 mm precoated plates from Merck, silica gel 60 UV<sub>254</sub>, and spots were visualised by use of UV light and ethanolic phosphomolybdic acid followed by heating. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Gemini 200 or a Varian Unity 400 spectrometer at ambient temperature for CDCl<sub>3</sub> solutions. Chemical shifts for protons are reported using the residual CHCl<sub>3</sub> as internal reference (δ 7.26). Carbon signals are referenced to the shift from the <sup>13</sup>C signal of CDCl<sub>3</sub> (δ 77.0). Infrared spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Mass spectra were recorded using a Finnigan MAT GCQ PLUS system (EI; 70 eV) or a Varian Saturn 2100T GC/MS (EI). GC analysis was performed using a Varian 3400 instrument equipped with a CP-Chirasil-Dex CB column with N<sub>2</sub> as the carrier gas at 15 psi and a FID detector. Preparative separations were performed using a Gilson HPLC with a Chiralcel OD column (25 cm/2 cm id) and UV detector.

Elementary analysis was performed by Mikro Kemi AB and Analytische Laboratorien AG. For some of the compounds it was not possible to obtain satisfactory analysis data. <sup>1</sup>H and <sup>13</sup>C NMR spectra are included in the supplementary data. †

#### General procedure for transfer hydrogenation of acetophenone

To a dry 50 ml Schlenk flask under argon was added [IrCl(COD)]<sub>2</sub> (0.00335 g, 0.005 mmol), ligand (0.025 mmol) and *i*-PrOH (2 ml). The solution was stirred for 30 minutes at 80 °C and then cooled to rt. *i*-PrOH (18 ml) was added, followed by acetophenone (235 μl, 2.0 mmol) and *i*-PrOK (63 μl, 0.063 mmol, 1.0 M solution in *i*-PrOH). The reaction was stirred at room temperature until completion and quenched by addition of 2 drops of 1 M hydrochloric acid. Evaporation of the solvent *in vacuo* and flash chromatography (Et<sub>2</sub>O–pentane) gave the pure 1-phenylethanol. The enantiomeric excess was determined by chiral GC analysis.

#### General procedure for transfer hydrogenation of acetophenone with formic acid–triethylamine as reductant

To a dry round-bottomed flask was added [IrCl(COD)]<sub>2</sub> (0.00335 g, 0.005 mmol) and ligand (0.025 mmol). Acetophenone (235 μl, 2 mmol) was added and the mixture was stirred for 30 min at 60 °C. A 5:2 HCOOH–Et<sub>3</sub>N azeotropic

mixture (3 ml) was added and the reaction was stirred at the indicated temperature and time in an open-air vessel. The reaction was quenched by the addition of water (10 ml) and extracted with diethyl ether (3 × 4 ml). The combined organic fractions were dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The resulting red oil was analysed as described above.

#### (1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-carboxylic acid methyl ester **1**

This compound was prepared according to literature procedures *via* an aza-Diels–Alder reaction<sup>25</sup> followed by hydrogenation and hydrogenolysis of the resulting adduct.<sup>21</sup> Amino ester **1** was used without further purification.

#### (1*S*,3*R*,4*R*)-3-Hydroxymethyl-2-azabicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **2**

To a stirred solution of (Boc)<sub>2</sub>O (9.70 g, 44.4 mmol) and Et<sub>3</sub>N (10.9 ml, 78.2 mmol) in THF (60 ml), amino ester **1** (5.70 g, 36.7 mmol) as a solution in THF (60 ml) was added slowly over a 20 min period. The reaction mixture was stirred at rt overnight. After evaporation of the solvent the residue was dissolved in Et<sub>2</sub>O (50 ml) and extracted with 1 M HCl (2 × 50 ml), NaHCO<sub>3</sub> (sat., 50 ml) and brine (50 ml). Drying (MgSO<sub>4</sub>) and evaporation afforded Boc-protected **1** as a colourless oil that was reduced without further purification. To a stirred suspension of LAH (2.1 g, 55.1 mmol) in THF (70 ml) Boc-protected **1** (10.8 g, 36.7 mmol) as a solution in THF (45 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and thereafter quenched with water (2.1 ml), 1 M NaOH (2.1 ml) and water (6.3 ml). Filtration followed by drying (MgSO<sub>4</sub>) gave **2** (8.04 g, 96%) as a colourless oil. [In the case of impure product, flash chromatography could be performed (pentane–EtOAc, 95:5 to 40:60)]. *R*<sub>f</sub> 0.57 (EtOAc–pentane, 60:40); [α]<sub>D</sub><sup>24</sup> +71.6 (*c* 0.87 in CHCl<sub>3</sub>); (Found: C, 62.9; H, 9.7; N, 6.2. Calc. for C<sub>12</sub>H<sub>21</sub>NO<sub>3</sub>: C, 63.4; H, 9.3; N, 6.2%); ν<sub>max</sub>(film)/cm<sup>-1</sup> 3420, 1697, 1670, 1397, 1165; δ<sub>H</sub>(200 MHz) 1.24 (m, 2H), 1.45 (s, 9H), 1.65 (m, 4H), 2.28 (s, 1H), 3.45 (m, 1H), 3.56 (m, 2H), 4.08 (s, 1H), 4.46 (m, 1H); δ<sub>C</sub>(50.2 MHz) 27.9, 28.4, 29.7, 35.7, 39.7, 57.9, 66.6, 67.3, 80.2, 157.4; *m/z* (EI) 227 (M<sup>+</sup>, 1%), 68 (42), 96 (15), 112 (18), 140 (100), 196 (26).

#### (1*S*,3*R*,4*R*)-3-(4-Tolylsulfonyloxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester **3**

Compound **2** (8.04 g, 35.4 mmol) was dissolved in pyridine (72 ml) and cooled to 0 °C. TsCl (8.82 g, 46.0 mmol) was added

at 0 °C and then the reaction mixture was stirred at rt for 5 h. CH<sub>2</sub>Cl<sub>2</sub> (300 ml) was added and the solution was extracted with 1 M HCl (4 × 100 ml), NaHCO<sub>3</sub> (sat., 100 ml) and water (100 ml). Purification by flash chromatography (EtOAc–pentane, 1:10 to 1:4) afforded **3** (9.94 g, 74%) as a colourless oil. *R*<sub>f</sub> 0.82 (EtOAc–pentane, 60:40); [α]<sub>D</sub><sup>24</sup> +65.5 (*c* 1.11 in CHCl<sub>3</sub>); (Found: C, 59.1; H, 7.2; N, 3.6. Calc. for C<sub>19</sub>H<sub>27</sub>NO<sub>5</sub>S: C, 59.8; H, 7.1; N, 3.7%); ν<sub>max</sub>(film)/cm<sup>-1</sup> 1698, 1366, 1177; δ<sub>H</sub>(200 MHz, 1:1 mixture of rotamers) 1.22 (m, 2H), 1.32 (s, 9H), 1.39 (s, 9H), 1.65 (m, 8H), 2.43 (s, 6H), 2.51 (m, 2H), 3.30 (m, 1H), 3.44 (m, 1H), 3.64 (m, 1H), 3.77 (m, 1H), 4.10 (m, 6H), 7.33 (m, 4H), 7.77 (m, 4H); δ<sub>C</sub>(50.2 MHz, 1:1 mixture of rotamers) 21.6, 27.2, 28.3, 28.4, 29.6, 30.1, 33.8, 34.6, 38.6, 39.2, 56.7, 57.6, 61.5, 61.7, 68.4, 68.6, 79.8, 127.9, 129.8, 133.0, 145.2; *m/z* (EI) 281 (M<sup>+</sup> – Boc, <1%), 53 (17), 54 (30), 65 (28), 66 (32), 67 (100), 68 (74), 77 (11), 78 (10), 79 (14), 80 (68), 81 (17), 82 (12), 94 (72), 108 (54), 112 (29), 138 (17), 153 (66).

**(1S,3R,4R)-3-Benzylsulfanyl-methyl-2-azabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester 4**

Toluene-*α*-thiol (0.882 g, 7.08 mmol) was dissolved in THF (20 ml). The solution was cooled to 0 °C and *n*-BuLi (4.42 ml, 7.08 mmol, 1.6 M in hexanes) was added dropwise *via* syringe. The reaction was stirred for 10 min then more *n*-BuLi was added until the solution turned deep red. The reaction was stirred for an additional 40 min. The mixture was added to an ice-cooled solution of **3** (1.80 g, 4.72 mmol) as a solution in THF (20 ml). The mixture was stirred at rt overnight. The solvent was evaporated and the mixture was extracted with water (30 ml) and Et<sub>2</sub>O (30 ml). The water phase was then extracted with Et<sub>2</sub>O (2 × 30 ml) and the combined organic phases were dried (MgSO<sub>4</sub>) and filtrated. The crude product was purified by column chromatography (pentane–EtOAc, 10:1) to give **4** (1.00 g, 64%) as a colourless oil. [α]<sub>D</sub><sup>24</sup> –67.0 (*c* 0.941 in CHCl<sub>3</sub>); (Found: C, 68.6; H, 8.3; N, 4.35. Calc. for C<sub>19</sub>H<sub>27</sub>NO<sub>2</sub>S: C, 68.4; H, 8.2; N, 4.2%); ν<sub>max</sub>(CDCl<sub>3</sub>)/cm<sup>-1</sup> 2973, 2873, 1693, 1391, 1175; δ<sub>H</sub>(400 MHz, 1:1 mixture of rotamers) 1.17 (m, 1H), 1.20 (m, 1H), 1.25–1.76 (m, 15H), 2.17–2.31 (m, 1H), 2.51–2.57 (m, 1H), 2.86 (dd, 1H, *J* = 13.4, 3.1 Hz), 2.94 (dd, 1H, *J* = 13.4, 3.1 Hz), 3.18–3.24 (m, 1H), 3.39–3.43 (m, 1H), 3.76 (s, 1H), 3.80 (s, 1H), 4.00–4.04 (m, 1H), 4.11–4.15 (m, 1H), 7.38–7.17 (m, 10H); δ<sub>C</sub>(100.6 MHz, 1:1 mixture of rotamers) 27.8, 28.7, 28.8, 29.9, 30.5, 34.1, 34.4, 34.8, 35.0, 37.6, 38.5, 39.9, 40.6, 57.3, 58.2, 63.8, 64.1, 79.1, 79.4, 126.8, 127.0, 128.3, 128.5, 128.7, 128.9, 138.3, 138.7, 154.9; *m/z* (EI) 334 (M<sup>+</sup> + 1, 100%), 278 (14), 234 (20), 196 (9), 140 (33), 96 (40), 91 (18), 68 (30).

**(1S,3R,4R)-3-Benzylsulfanyl-methyl-2-azabicyclo[2.2.1]heptane 5**

Compound **4** (0.820 g, 0.36 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (16 ml) and cooled to 0 °C after which TFA (8.2 ml) was added dropwise. The ice bath was removed and the reaction mixture was stirred at rt for 2 h. The solvent and TFA were then evaporated off *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and K<sub>2</sub>CO<sub>3</sub> was added until no evolution of CO<sub>2</sub> (g) could be seen. The solution was filtered through Celite and extracted with 2 M HCl (10 ml), and the water phase was made basic (pH 9–10) by addition of 2 M NaOH, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 ml). The combined organic phases were dried (MgSO<sub>4</sub>), filtered through Celite and evaporated. Purification by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 100:0 to 80:20) yielded **5** (0.399 g, 70%) as a pale yellow oil. [α]<sub>D</sub><sup>24</sup> –32.6 (*c* 0.276 in CHCl<sub>3</sub>); ν<sub>max</sub>(CDCl<sub>3</sub>)/cm<sup>-1</sup> 3392, 2944, 2861, 1600, 1412; δ<sub>H</sub>(400 MHz) 1.12–1.16 (m, 1H), 1.30 (m, 1H), 1.47–1.51 (m, 1H), 1.52–1.68 (m, 1H), 2.28 (m, 1H), 2.38–2.22 (m, 3H), 2.73 (m, 1H), 3.42 (m, 1H), 3.72 (s, 2H), 7.35–7.15 (m 5H); δ<sub>C</sub>(100.6 MHz) 28.8, 32.6, 34.3, 36.6, 38.3, 40.5, 56.2, 60.7, 126.9, 128.4, 128.8, 138.6; *m/z* (EI) 234 (M<sup>+</sup> + 1, 15%), 223 (9), 123 (12), 96 (61), 91 (51), 68 (100).

**(1S,3R,4R)-3-Benzylsulfanyl-methyl-2-azabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester 6**

Compound **4** (0.300 g, 0.9 mmol) was dissolved in MeOH (10 ml) and cooled to 0 °C. NaIO<sub>4</sub> (0.222 g, 1.04 mmol) was dissolved in H<sub>2</sub>O (5 ml) and added dropwise. The reaction was stirred for one hour at 0 °C then the ice bath was removed and the reaction was stirred at rt for 3.5 h. The solvent was removed *in vacuo* and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 ml). The combined organic phases were dried (MgSO<sub>4</sub>) and the solvent was evaporated. Purification of the residue by flash chromatography (EtOAc–MeOH, 20:0.3) afforded **6** (0.200 g, 64%) as a 3:2 mixture of diastereomers, as pale yellow crystals. The diastereomers were separated on an OD column [hexane–*i*-PrOH, 85:15, 6 ml min<sup>-1</sup>, retention times 24 min (major), 33 min (minor)].

Major-**6**: [α]<sub>D</sub><sup>24</sup> +46.2 (*c* 1.01 in CHCl<sub>3</sub>); ν<sub>max</sub>(CDCl<sub>3</sub>)/cm<sup>-1</sup> 3063, 2973, 2875, 1690, 1392, 1033; δ<sub>H</sub>(400 MHz, mixture of rotamers) 1.30 (s, 9H), 1.26–1.32 (m, 1H), 1.45 (s, 9H), 1.54–1.74 (m, 5H), 2.46–2.55 (m, 1H), 2.69–2.74 (m, 1H), 2.79–2.85 (m, 1H), 3.04–3.11 (m, 1H), 3.49–3.54 (m, 1H), 3.62–3.68 (m, 1H), 3.86–3.93 (m, 1H), 4.02–4.08 (m, 1H), 4.11–4.18 (m, 1H), 7.26–7.40 (m, 5H); δ<sub>C</sub>(100.6 MHz, mixture of rotamers) 27.4, 28.3, 28.5, 29.8, 30.3, 34.2, 34.9, 41.2, 42.1, 55.2, 56.6, 57.6, 58.9, 60.2, 60.6, 60.7, 128.2, 128.5, 128.7, 129.1, 129.9, 130.3; *m/z* (EI) 350 (M<sup>+</sup> + 1, 20%), 334 (26), 294 (16), 278 (19), 250 (27), 232 (11), 202 (36), 186 (7), 154 (16), 140 (45), 91 (100), 68 (20).

Minor-**6**: [α]<sub>D</sub><sup>24</sup> +91.7 (*c* 0.86 in CHCl<sub>3</sub>); ν<sub>max</sub>(CDCl<sub>3</sub>)/cm<sup>-1</sup> 2975, 2873, 1691, 1393, 1026; δ<sub>H</sub>(400 MHz, mixture of rotamers) 1.23–1.32 (m, 1H), 1.37 (s, 9H), 1.46 (s, 9H), 1.54–1.64 (m, 1H), 2.32–2.38 (m, 1H), 2.53–2.57 (m, 1H), 2.68–2.74 (m, 1H), 2.89–2.98 (m, 1H), 3.62–3.66 (m, 1H), 3.68–3.73 (m, 1H), 3.98–4.05 (m, 1H), 4.08 (m, 1H), 4.16 (m, 1H), 4.29–4.33 (m, 1H), 7.25–7.41 (m, 5H); δ<sub>C</sub>(100.6 MHz, mixture of rotamers) 27.4, 28.4, 28.5, 29.6, 30.1, 34.1, 35.0, 40.8, 41.5, 54.1, 54.7, 56.8, 57.8, 57.8, 57.9, 58.6, 128.1, 128.4, 128.7, 128.9, 130.1, 130.3; *m/z* (EI) 350 (M<sup>+</sup> + 1, 20%), 334 (26), 294 (16), 278 (19), 250 (27), 232 (11), 202 (36), 186 (7), 154 (16), 140 (45), 91 (100), 68 (20).

**(1S,3R,4R)-3-Benzylsulfanyl-methyl-2-azabicyclo[2.2.1]heptane: major-7**

Use of the same procedure as reported for **5** using major-**6** (0.120 g, 0.36 mmol) and TFA (1.25 ml), afforded major-**7** (0.0801 g, 94%) as white crystals. [α]<sub>D</sub><sup>24</sup> –163.2 (*c* 0.95 in CHCl<sub>3</sub>); ν<sub>max</sub>(CDCl<sub>3</sub>)/cm<sup>-1</sup> 3435, 2960, 2897, 1640, 1023; δ<sub>H</sub>(400 MHz) 1.20–1.24 (m, 1H), 1.30–1.49 (m, 2H), 1.53–1.71 (m, 3H), 1.83 (br s, 1H), 2.24 (m, 1H), 2.43 (dd, 1H, *J* = 12.2, 10.1 Hz), 2.57 (dd, 1H, *J* = 12.2, 3.6 Hz), 3.49 (m, 1H), 3.95 (d, 1H, *J* = 13.1 Hz), 3.97 (d, 1H, *J* = 13.1 Hz), 7.27–7.38 (m, 5H); δ<sub>C</sub>(100.6 MHz) 28.7, 32.9, 34.3, 41.4, 54.9, 56.4, 58.7, 59.4, 128.2, 128.8, 130.0, 130.1; *m/z* (EI) 250 (M<sup>+</sup> + 1, 59%), 232 (15), 197 (25), 185 (15), 140 (19), 109 (74), 91 (100), 68 (94).

**(1S,3R,4R)-3-Benzylsulfanyl-methyl-2-azabicyclo[2.2.1]heptane: minor-7**

Use of the same procedure as reported for **5** using minor-**6** (0.130 g, 0.39 mmol) and TFA (1.25 ml) yielded minor-**7** (0.0534 g, 58%) as white crystals. [α]<sub>D</sub><sup>24</sup> +57.4 (*c* 0.35 in CHCl<sub>3</sub>); ν<sub>max</sub>(CDCl<sub>3</sub>)/cm<sup>-1</sup> 3400, 3031, 2960, 2873, 1685, 1201, 1026; δ<sub>H</sub>(400 MHz) 1.27 (m, 1H), 1.47 (m, 2H), 1.49 (m, 1H), 1.63 (m, 3H), 1.8 (br s), 2.35 (m, 1H), 2.54 (dd, 1H, *J* = 13.1, 8.0 Hz), 2.79 (dd, 1H, *J* = 13.1, 6.1 Hz), 3.25–3.62 (m, 3H), 4.08 (s, 2H), 7.20–7.42 (m, 5H); δ<sub>C</sub>(100.6 MHz) 28.7, 32.9, 34.3, 41.4, 54.9, 56.4, 58.7, 59.4, 128.2, 128.8, 130.0, 130.1; *m/z* (EI) 250 (M<sup>+</sup> + 1, 58%), 232 (10), 197 (25), 185 (15), 140 (19), 109 (33), 91 (100), 68 (69).

## 7-Azabicyclo[4.1.0]heptane 8

This compound was prepared according to literature procedures, namely, ring opening of cyclohexene oxide with sodium azide<sup>27</sup> and ring closure using PPh<sub>3</sub> in MeCN.<sup>28</sup> All spectroscopic and physical data for **8** were in complete agreement with those published.<sup>29</sup>

### trans-2-Benzylsulfanylcyclohexylamine 9a

To a solution of **8** (1.5 g, 15.4 mmol) in MeOH (20 ml) was added toluene- $\alpha$ -thiol (2.76 ml, 2.92 g, 23.5 mmol) *via* syringe at rt, and the mixture was refluxed for 7 h. The solvent was then evaporated *in vacuo* and flash chromatography of the residue (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 90:10) yielded **9a** (3.30 g, 97%) as a colourless oil.  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3360, 3027, 2928, 2360, 1601 and 1447;  $\delta_{\text{H}}(400 \text{ MHz})$  1.02–1.35 (m, 3H), 1.38–1.52 (m, 1H), 1.58 (br s, 2H), 1.64–1.74 (m, 2H), 1.90–2.09 (m, 2H), 2.15–2.25 (m, 1H), 2.47–2.55 (m, 1H), 3.76 (s, 1H), 3.77 (s, 1H) and 7.22–7.39 (m, 5H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  24.9, 26.4, 33.4, 34.6, 35.5, 53.7, 53.8, 126.8, 128.3, 128.6 and 138.7;  $m/z$  (EI) 221 (M<sup>+</sup>, <1%), 204 (30), 123 (40), 113 (65), 91 (74) and 79 (100).

### trans-2-Cyclohexylsulfanylcyclohexylamine 9b

Use of the same procedure as reported for **9a** using **8** (0.250 g, 2.57 mmol) and cyclohexanethiol (0.47 ml, 3.86 mmol) yielded **9b** in quantitative yield as a colourless oil. (Found: C, 67.35; H, 11.0; N, 6.7. Calc. for C<sub>12</sub>H<sub>23</sub>NS: C, 67.5; H, 10.9; N, 6.6%);  $\nu_{\max}(\text{Et}_2\text{O})/\text{cm}^{-1}$  2977, 2932, 2861, 1383, 1124;  $\delta_{\text{H}}(400 \text{ MHz})$  2.71 (m, 1H), 2.48 (dt, 1H,  $J = 4.0, 10.5 \text{ Hz}$ ), 2.27 (ddd, 1H,  $J = 4.0, 10.1, 11.9 \text{ Hz}$ ), 2.07 (m, 1H), 1.97 (m, 3H), 1.81–1.52 (m, 8H), 1.45–1.06 (m, 8H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  54.4, 52.6, 43.2, 35.6, 35.1, 34.8, 34.5, 26.7, 26.2, 26.2, 25.7, 25.1;  $m/z$  (EI) 214 (M<sup>+</sup> + 1, 14%), 197 (16), 131 (50), 114 (27), 82 (100).

### trans-2-Phenylsulfanylcyclohexylamine 9c

Use of the same procedure as reported for **9a** using **8** (0.490 g, 5.04 mmol) and thiophenol (0.62 ml, 6.05 mmol) yielded **9c** in quantitative yield as a colourless oil. (Found: C, 69.0; H, 8.2; N, 6.4. Calc. for C<sub>12</sub>H<sub>17</sub>NS: C, 69.5; H, 8.3; N, 6.8%);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3365, 3056, 2931, 2854;  $\delta_{\text{H}}(400 \text{ MHz})$  1.12–1.43 (m, 4H), 1.60–1.79 (m, 4H), 1.93–2.18 (m, 2H), 2.57 (dt, 1H,  $J = 4.05, 10.1 \text{ Hz}$ ), 2.64 (m, 1H), 7.18–7.34 (m, 3H), 7.38–7.56 (m, 2H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  24.9, 26.4, 33.5, 35.6, 54.0, 57.1, 127.2, 128.8, 133.1, 134.0;  $m/z$  (EI) 207 (M<sup>+</sup>, 44%), 135 (26), 109 (28), 98 (100), 56 (70).

### trans-2-Benzylsulfanylcyclohexylcarbamic acid benzyl ester 10a

To **9a** (0.615 g, 2.76 mmol) and Et<sub>3</sub>N (0.41 ml, 2.93 mmol) in Et<sub>2</sub>O (7 ml) was added dropwise benzyl chloroformate (0.37 ml, 2.47 mmol) in Et<sub>2</sub>O (1.5 ml) at 0 °C. The reaction mixture was stirred for 1.5 h, after which it was extracted with saturated NaHCO<sub>3</sub> (aq.) and brine. The organic phase was dried (MgSO<sub>4</sub>) and evaporated *in vacuo* and the crude product obtained was purified by flash chromatography (pentane-EtOAc, 4:1) to give racemic **10a** (0.405 g, 65%) as a white solid. The enantiomers were separated with a preparative OD column (HPLC) with hexane-*i*-PrOH as the eluent (85:15, 6 ml min<sup>-1</sup>, retention times, respectively, 15 and 23 min).  $[a]_{\text{D}}^{20} -63.4$  (first peak eluted from HPLC,  $c$  3.5 in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3321, 2931, 2359, 1683 and 1539;  $\delta_{\text{H}}(400 \text{ MHz})$  1.16–1.21 (m, 2H), 1.22–1.38 (m, 1H), 1.51–1.55 (m, 1H), 1.63–1.72 (m, 2H), 2.08–2.20 (m, 2H), 2.37–2.43 (ddd,  $J = 10.4, 10.4, 4.0 \text{ Hz}$ , 1H), 3.47–3.73 (m, 1H), 3.72 (s, 1H), 3.73 (s, 1H), 4.73 (br s, 1H), 5.11 (s, 2H) and 7.19–7.39 (m, 10H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  24.3, 25.4, 32.8, 33.1, 34.4, 48.4, 53.3, 66.5, 126.9, 127.9, 128.0, 128.4, 128.8, 136.6, 138.3 and 155.8;  $m/z$  (EI) 354 (M<sup>+</sup>, <1%), 310 (100), 197 (54), 196, (57), 186 (38) and 106 (75).

### trans-2-Cyclohexylsulfanylcyclohexylcarbamic acid benzyl ester 10b

Use of the same procedure as reported for **10a** using **9b** (0.127 g, 0.595 mmol), benzyl chloroformate (0.089 ml, 0.625 mmol) and Et<sub>3</sub>N (0.087 ml, 0.625 mmol) afforded **10b** (0.202 g, 98%) as white crystals. The enantiomers were separated with a preparative OD column (HPLC) with hexane-*i*-PrOH as the eluent (90:10, 5 ml min<sup>-1</sup>, retention times, respectively, 21 and 27 min.).  $[a]_{\text{D}}^{24} -40.0$  (first peak eluted from HPLC,  $c$  0.80 in CHCl<sub>3</sub>); (Found: C, 69.2; H, 8.4; N, 3.8. Calc. for C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>S: C, 69.1; H, 8.4; N, 4.0%);  $\nu_{\max}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$  3438, 2936, 2361, 1717, 1508;  $\delta_{\text{H}}(400 \text{ MHz})$  1.14–1.44 (8H, m), 1.48–1.80 (6H, m), 1.91 (2H, m), 2.08 (1H, m), 2.22 (1H, m), 2.61 (1H, m), 2.68 (1H, m), 3.43 (1H, m), 4.92 (1H, br s), 5.11 (2H, s), 7.28–7.41 (5H, m);  $\delta_{\text{C}}(100.6 \text{ MHz})$  23.9, 25.2, 25.7, 26.1, 26.2, 32.5, 33.4, 34.3, 34.5, 42.7, 47.0, 53.9, 66.6, 128.1, 128.5, 136.7, 155.8, 128.0;  $m/z$  (EI) 347 (M<sup>+</sup>, 1%), 196 (100), 115 (96), 91 (77), 81 (59).

### trans-(2-tert-Butylsulfanyl)cyclohexylcarbamic acid benzyl ester 10d

To **12** (2.4 g, 10.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> under N<sub>2</sub> at 0 °C was added 2-methylpropane-2-thiol (1.22 ml, 10.8 mmol) followed by the dropwise addition of boron trifluoride-diethyl ether (1.37 ml, 10.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) *via* syringe. The reaction was stirred at 0 °C for 3 h and was then allowed to reach rt and stirred at this temperature overnight. The mixture was extracted with NaHCO<sub>3</sub> (sat.) and brine, and the organic phase was dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. This crude product was purified by flash chromatography (EtOAc-pentane, 1:9) to yield **10d** (2.25 g, 68%) as a white solid. The enantiomers were separated with a preparative OD column (HPLC) with hexane-*i*-PrOH as the eluent (85:15, 6 ml min<sup>-1</sup>, retention times, respectively, 15 and 22 min).  $[a]_{\text{D}}^{20} -16.8$  (first peak eluted from HPLC,  $c$  3.2 in CH<sub>2</sub>Cl<sub>2</sub>); (Found: C, 67.1; H, 8.5; N, 4.4. Calc. for C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub>S: C, 67.3; H, 8.5; N, 4.4%);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3345, 2935, 1691, 1545;  $\delta_{\text{H}}(400 \text{ MHz})$  1.32 (s, 9H), 1.33–1.44 (m, 3H), 1.51–1.63 (m, 3H), 2.04–2.17 (m, 2H), 2.62–2.66 (m, 1H), 3.44–3.50 (m, 1H), 4.92 (br s, 1H), 5.11 (s, 2H), 7.28–7.34 (m, 5H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  23.1, 24.4, 31.0, 31.4, 34.0, 43.4, 45.0, 53.6, 66.6, 128.0, 128.1, 128.5, 136.6, and 155.9;  $m/z$  (EI) 321 (M<sup>+</sup>, <1%), 170 (56), 114 (100), 91 (85).

### trans-2-Benzylsulfanylcyclohexylamine 11a

To enantiomerically pure **10a** (0.200 g, 0.564 mmol) was added HCl (aq., 6 M, 10 ml) and the solution was refluxed overnight. The reaction was cooled to 0 °C, after which CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added, the organic phase was made basic by addition of NaOH (aq., 2 M) and the phases were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and the combined organic phases were washed with brine (10 ml). Drying (MgSO<sub>4</sub>), evaporation of the solvent and flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 100:0 to 70:30) afforded **11a** (0.115 g, 92%) as a colourless oil.  $[a]_{\text{D}}^{20} -70.8$  (first peak eluted from HPLC,  $c$  2.2 in CH<sub>2</sub>Cl<sub>2</sub>). For full characterisation see **9a**.

### trans-2-Cyclohexylsulfanylcyclohexylamine 11b

By following the same procedure as reported for **11a** compound **11b** was obtained as a colourless oil in 90% yield.  $[a]_{\text{D}}^{20} -76.7$  (first peak eluted from HPLC,  $c$  2.1 in CH<sub>2</sub>Cl<sub>2</sub>). For full characterisation see **9b**.

### trans-2-(tert-Butylsulfanyl)cyclohexylamine 11d

To a suspension of Pd-C (10%, 0.100 g) in MeOH (2 ml) was added ammonium formate (0.155 g, 2.46 mmol) and **10d** (0.250 g, 0.778 mmol) in MeOH (2 ml) *via* syringe. The mixture was stirred at rt for 1 h and then filtered through Celite. The product

was extracted using CH<sub>2</sub>Cl<sub>2</sub>-brine and the organic phase was the dried (MgSO<sub>4</sub>) and evaporated to give **11d** (0.134 g, 92%) as a colourless oil.  $[\alpha]_D^{20}$  -66.8 (*c* 1.87 in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3364, 2926, 1579, 1447;  $\delta_{\text{H}}(400 \text{ MHz})$  1.11–1.24 (m, 1H), 1.24–1.31 (m, 4H), 1.34 (s, 9H), 1.39–1.67 (m, 1H), 1.66 (br s, 2H), 1.65–1.73 (m, 2H), 1.97–2.03 (m, 1H), 2.07–2.13 (m, 1H), 2.16–2.26 (m, 1H), 2.35–2.42 (m, 1H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  25.1, 26.9, 31.8, 35.5, 37.1, 43.2, 51.2, 54.0; *m/z* (EI) 187 (M<sup>+</sup>, 50%), 130 (100), 113 (51), 79 (56).

#### 7-Azabicyclo[4.1.0]heptane-7-carboxylic acid benzyl ester **12**

To **8** (0.200 g, 2.06 mmol) and Et<sub>3</sub>N (0.35 ml, 2.47 mmol) in Et<sub>2</sub>O (7 ml) was added dropwise benzyl chloroformate (0.37 ml, 2.47 mmol) in Et<sub>2</sub>O (1.5 ml) at 0 °C. After being stirred for 1.5 h, the reaction mixture was extracted with saturated NaHCO<sub>3</sub> (aq.) and brine. The organic phase was dried (MgSO<sub>4</sub>) and evaporated *in vacuo* and the crude product obtained was purified by flash chromatography (pentane–EtOAc, 4:1) to give **12** (0.405 g, 85%) as a colourless oil.  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3032, 2937, 1718, 1440, 1219;  $\delta_{\text{H}}(400 \text{ MHz})$  1.21–1.25 (m, 2H), 1.37–1.41 (m, 2H), 1.78–1.81 (m, 2H), 1.90–1.97 (m, 2H), 2.65 (dd, *J* = 3.2, 1.6 Hz, 2H), 5.11 (s, 2H), 7.31–7.39 (m, 5H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  19.7, 23.6, 37.0, 67.7, 128.0, 128.1, 128.3, 128.5, 163.2; *m/z* (EI) 231 (M<sup>+</sup>, 1%), 91 (100), 69 (9) and 65 (18).

#### *trans*-N-Isopropyl-2-benzylsulfanyl cyclohexylamine **13**

To a suspension of NaCNBH<sub>3</sub> (0.034 g) in MeOH (0.5 ml) was added *via* syringe acetone (0.071 g, 1.08 mmol) followed by **11a** (0.119 g, 0.54 mmol), in MeOH (0.5 ml) at rt and the mixture was stirred overnight. The reaction was quenched by the addition of water (0.6 ml) and 10% NaOH (aq., 0.6 ml). Extraction with CH<sub>2</sub>Cl<sub>2</sub> (3 × 1 ml), drying (MgSO<sub>4</sub>) and evaporation *in vacuo* yielded **13** (0.102 g, 72%) as a colourless oil that was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 90:10).  $[\alpha]_D^{20}$  -81.3 (*c* 2.6 in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3028, 2854, 2360, 1452, 1170;  $\delta_{\text{H}}(400 \text{ MHz})$  1.01 (d, 3H, *J* = 6 Hz), 1.05 (d, 3H, *J* = 6 Hz), 1.02–1.14 (m, 1H), 1.20–1.29 (m, 2H), 1.48–1.53 (m, 1H), 1.65–1.71 (m, 2H), 1.77 (s, 1H), 2.03–2.11 (m, 2H), 2.38–2.49 (m, 2H), 2.81–2.87 (m, 1H), 3.74 (s, 1H), 3.75 (s, 1H), 7.20–7.34 (m, 5H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  22.4, 24.4, 24.6, 26.12, 33.2, 33.5, 34.6, 45.7, 50.7, 57.1, 126.9, 128.4, 128.7, 138.6; *m/z* (EI) 263 (M<sup>+</sup>, 92%), 172 (54), 113 (43), 91 (17), 79 (32), 58 (100).

#### *trans*-N-Benzyl-2-benzylsulfanyl cyclohexylamine **14**

By following the same procedure as reported for **13** compound **14** (76%) was obtained as a colourless oil.  $[\alpha]_D^{20}$  -82.2 (first peak eluted from HPLC, *c* 3.1 in CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3026, 2929, 2360, 1453;  $\delta_{\text{H}}(400 \text{ MHz})$  1.16–1.27 (m, 3H), 1.45–1.51 (m, 1H), 1.67–1.74 (m, 2H), 2.03 (s, 1H), 2.02–2.07 (m, 1H), 2.10–2.18 (m, 1H), 2.33–2.40 (m, 1H), 2.50–2.58 (ddd, 1H, *J* = 11.6, 11.6, 4.0 Hz), 3.59 (d, 1H, *J* = 13.2 Hz), 3.67 (s, 2H), 3.86 (d, 1H, *J* = 13.2 Hz), 7.20–7.35 (m, 10H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  24.4, 26.2, 31.5, 33.5, 34.3, 50.0, 50.3, 58.4, 126.9, 127.0, 128.0, 128.8, 129.0, 138.6, 139.7; *m/z* (EI) 312 (M<sup>+</sup>, 13%), 220 (22), 106 (100), 91 (54).

#### *trans*-N-Benzyl-2-phenylsulfanyl cyclohexylamine **15**

The same procedure as reported for **22** (below) was followed using **9c** (1.05 g, 5.06 mmol), benzaldehyde (0.51 ml, 5.06 mmol) and NaBH<sub>4</sub> (0.37 g, 9.88 mmol) to afford **15** (0.827 g, 55%) as a colourless oil. The enantiomers were separated with a preparative OD column (HPLC) with hexane-*i*-PrOH as the eluent (90:10, 5 ml min<sup>-1</sup>, retention times 19 and 35 min).  $[\alpha]_D^{27}$  -111 (first peak eluted from HPLC, *c* 0.98 in CHCl<sub>3</sub>); (Found: C, 76.4; H, 7.8; N, 4.5. Calc. for C<sub>19</sub>H<sub>23</sub>NS: C, 76.7; H, 7.8; N, 4.7%);  $\nu_{\max}(\text{CDCl}_3)/\text{cm}^{-1}$  3292, 3065, 3022, 2934, 2858, 2246;  $\delta_{\text{H}}(400 \text{ MHz})$  1.17–1.48 (m, 4H), 1.71 (m, 2H), 2.09 (m, 1H),

2.21 (m, 1H), 2.45 (m, 1H), 2.88 (br s, 1H), 2.96 (ddd, 1H, *J* = 4.0, 10.0, 11.3 Hz), 3.74 (d, 1H, *J* = 13.1 Hz), 3.94 (d, 1H, *J* = 13.1 Hz), 7.22–7.30 (m, 4H), 7.31–7.40 (m, 6H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  24.3, 26.2, 32.0, 33.4, 50.8, 53.5, 59.0, 126.9, 127.2, 128.1, 128.4, 128.7, 133.2, 133.6, 140.2; *m/z* (EI) 298 (M<sup>+</sup> + 1, 4%), 188 (9), 146 (25), 106 (100), 91 (84).

#### 7-Benzyl-7-azabicyclo[4.1.0]heptane **16**

Ring opening of cyclohexene oxide with benzylamine was performed according to a literature procedure<sup>30</sup> and ring closure of the resulting amino alcohol yielding **16** was done according to a slightly modified literature procedure<sup>31</sup> where DEAD replaced DIAD, which was used in the reference. All spectroscopic and physical data for **16** were in complete agreement with those published.<sup>32</sup>

#### *trans*-N-Benzyl-2-(2-methylphenylsulfanyl) cyclohexylamine **17a**

Compound **16** (0.100 g, 0.53 mmol) was dissolved in MeOH (5 ml) and *o*-thiocresol (0.073 g, 0.58 mmol) was added. The solution was refluxed overnight and then cooled to rt after which the solvent was evaporated off. Purification of the residue by flash chromatography (silica, Et<sub>2</sub>O–pentane 10:90) afforded **17a** (0.080 g, 49%) as a colourless oil. The enantiomers were separated on a chiral OD column (HPLC) using hexane-*i*-PrOH as the eluent (90:10, 6 ml min<sup>-1</sup>, retention times 15 and 19 min, respectively).  $[\alpha]_D^{30}$  +65.5 (second peak eluted from HPLC, *c* 1.00 in CHCl<sub>3</sub>);  $\nu_{\max}(\text{CDCl}_3)/\text{cm}^{-1}$  3436, 3061, 2931, 2855, 1642, 1455;  $\delta_{\text{H}}(400 \text{ MHz})$  1.25 (m, 3H), 1.42 (m, 1H), 1.70 (m, 2H), 2.06 (m, 1H), 2.20 (m, 1H), 2.41 (s, 3H), 2.54 (m, 1H), 3.02 (m, 1H), 3.74 (d, 1H, *J* = 13.4 Hz), 3.92 (d, 1H, *J* = 13.4 Hz), 7.07–7.19 (m, 3H), 7.25 (m, 1H), 7.33 (m, 5H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  21.1, 24.3, 26.1, 32.1, 33.3, 51.0, 53.2, 59.6, 126.3, 126.8, 126.9, 128.1, 128.4, 130.3, 132.4, 140.0, 140.5; *m/z* (EI) 313 (M<sup>+</sup> + 1, 9%), 312 (36), 204 (21), 188 (26), 187(17), 147 (14), 146 (33), 107 (87), 106 (100), 92 (90), 91 (69), 79 (16).

#### *trans*-N-Benzyl-2-(4-methylphenylsulfanyl) cyclohexylamine **17b**

The same procedure as reported for **17a** was followed, using **16** (0.100 g, 0.53 mmol) and 4-methylbenzenethiol (0.073 g, 0.58 mmol), to afford **17b** (0.073 g, 44%) as a colourless oil. The enantiomers were separated on a chiral OD column (HPLC) using hexane-*i*-PrOH as the eluent (90:10, 6 ml min<sup>-1</sup>, retention times 15 and 20 min).  $[\alpha]_D^{30}$  +154.2 (second peak eluted from HPLC, *c* 0.54 in CHCl<sub>3</sub>);  $\nu_{\max}(\text{CDCl}_3)/\text{cm}^{-1}$  3412, 3025, 2931, 2855, 1601, 1493, 1452;  $\delta_{\text{H}}(400 \text{ MHz})$  1.11–1.40 (m, 4 H), 1.69 (m, 2H), 2.05 (m, 1H), 2.20 (m, 1H), 2.32 (s, 3H), 2.40 (m, 1H), 2.84 (m, 1H), 3.72 (d, 1H, *J* = 13.3 Hz), 3.94 (d, 1H, *J* = 13.3 Hz), 7.06 (m, 2H), 7.26 (m, 3H), 7.34 (m, 4H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  21.1, 24.4, 26.3, 32.1, 33.4, 50.9, 53.9, 58.9, 126.8, 128.2, 128.4, 129.5, 134.0, 137.5, 138.3, 140.5; *m/z* (EI) 313 (M<sup>+</sup> + 1, 5%), 312 (18), 205 (7), 188 (24), 187 (11), 146 (25), 107 (83), 106 (100), 91 (75), 79 (17).

#### *trans*-N-Benzyl-2-(4-methoxyphenylsulfanyl) cyclohexylamine **17c**

The same procedure as reported for **17a** was followed, using **16** (0.100 g, 0.53 mmol) and 4-methoxybenzenethiol (0.081 g, 0.58 mmol) to afford **17c** (0.075 g, 43%) as a colourless oil. The enantiomers were separated on a chiral OD column (HPLC) using hexane-*i*-PrOH as the eluent (90:10, 6 ml min<sup>-1</sup>, retention times 24 and 25 min).  $[\alpha]_D^{30}$  +116.1 (second peak eluted from HPLC, *c* 1.00 in CHCl<sub>3</sub>);  $\nu_{\max}(\text{CDCl}_3)/\text{cm}^{-1}$  3420, 3026, 2931, 2855, 1592, 1494, 1461, 1285;  $\delta_{\text{H}}(400 \text{ MHz})$  1.10–1.41 (m, 4H), 1.69 (m, 2H), 2.04 (m, 1H), 2.20 (m, 1H), 2.36 (m, 1H), 2.64 (br s, 1H), 2.74 (m, 1H), 3.75 (d, 1H, *J* = 13.0 Hz), 3.78 (s, 3H), 2.93 (d, 1H, *J* = 13.0 Hz), 6.78 (m, 2H), 7.28 (m, 3H), 7.36 (m, 4H);  $\delta_{\text{C}}(100.6 \text{ MHz})$  24.4, 26.3, 32.0, 33.2, 50.8, 54.2, 55.2,

58.5, 114.2, 122.9, 126.8, 128.2, 128.4, 136.5, 140.5, 159.6; *m/z* (EI) 329 ( $M^+ + 1$ , 7%), 328 (31), 327 (17), 221 (14), 188 (33), 187 (9), 147 (13), 146 (21), 107 (100), 106 (87), 92 (83), 91 (53), 79 (12).

#### *trans*-*N*-Benzyl-2-(4-nitrophenylsulfanyl)cyclohexylamine **17d**

The same procedure as reported for **17a** was followed, using **16** (0.100 g, 0.53 mmol) and 4-nitrobenzenethiol (0.081 g, 0.58 mmol) to afford **17d** (0.080 g, 46%) as yellow crystals. The enantiomers were separated on a chiral OD column (HPLC) using hexane-*i*-PrOH as the eluent (70:30, 6 ml min<sup>-1</sup>, retention times 30 and 35 min). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -2.6 (first peak eluted from HPLC, *c* 1.00 in CHCl<sub>3</sub>);  $\nu_{\max}$ (CDCl<sub>3</sub>)/cm<sup>-1</sup> 3436, 2929, 2847, 1640;  $\delta_{\text{H}}$ (400 MHz) 1.10–1.60 (m, 5H), 1.65–1.82 (m, 2H), 2.12–2.29 (m, 3H), 2.57 (m, 1H), 3.25 (m, 1H), 3.78 (d, 1H, *J* = 13.1 Hz), 3.95 (d, 1H, *J* = 13.1 Hz), 7.20–7.50 (m, 7H), 8.05 (m, 2H);  $\delta_{\text{C}}$ (100.6 MHz) 24.1, 25.9, 31.9, 33.0, 50.9, 52.5, 59.0, 123.8, 125.8, 127.1, 128.0, 128.5, 128.7, 129.0, 146.1; *m/z* (EI) 343 ( $M^+ + 1$ , 17%), 239 (51), 149 (25), 146 (16), 106 (100), 91 (77).

#### 7-[(*S*)-1-Phenylethyl]-7-azabicyclo[4.1.0]heptane **18**

Ring opening of cyclohexene oxide with (*S*)-1-phenylethylamine was performed according to a literature procedure<sup>30</sup> and ring closure of the resulting amino alcohol yielding **18** was done according to a slightly modified literature procedure<sup>31</sup> where DEAD replaced DIAD, which was used in the reference. Spectroscopic and physical data for **18** were in complete agreement with those published.<sup>30</sup>

#### *trans*-*N*-[(*S*)-1-Phenylethyl]-2-benzylsulfanyl cyclohexylamine **19**

Compound **18** (0.480 g, 2.38 mmol) was dissolved in MeOH (20 ml) and BnSH (0.340 ml, 2.86 mmol) was added. The reaction mixture was refluxed for 7 h and then cooled to rt, after which the solvent was evaporated off. Purification of the residue by flash chromatography (Et<sub>2</sub>O–pentane, 30:70 to 40:60) afforded **19** as a colourless oil (0.123 g of the minor isomer, 0.248 g of the major isomer, 48%).

Major-**19**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +38.9 (*c* 1.03 in CHCl<sub>3</sub>); (Found: C, 77.3; H, 8.3; N, 4.1. Calc. for C<sub>21</sub>H<sub>27</sub>NS: C, 77.5; H, 8.4; N, 4.3%);  $\nu_{\max}$ (film)/cm<sup>-1</sup> 3308, 3061, 3027, 2928, 1494, 1451;  $\delta_{\text{H}}$ (400 MHz) 0.97 (1H, m), 1.19 (2H, m), 1.33 (3H, d, *J* = 6.6 Hz), 1.54 (2H, m), 1.66 (1H, m), 1.75 (1H, m), 2.08 (2H, m), 2.43 (dt, 1H, *J* = 4.0, 9.5 Hz), 2.52 (1H, m), 3.79 (3H, m), 7.19–7.39 (10H, m);  $\delta_{\text{C}}$ (100.6 MHz) 24.2, 24.3, 25.8, 33.1, 33.6, 34.7, 50.4, 56.9, 58.9, 126.57, 126.58, 126.9, 128.2, 128.5, 128.8, 138.8, 147.1; *m/z* (EI) 325 (16), 234 (95), 203 (45), 105 (100), 91 (55).

Minor-**19**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -52.5 (*c* 1.09 in CHCl<sub>3</sub>); (Found: C, 77.4; H, 8.4; N, 4.3. Calc. for C<sub>21</sub>H<sub>27</sub>NS: C, 77.5; H, 8.4; N, 4.3%);  $\nu_{\max}$ (film)/cm<sup>-1</sup> 3308, 3061, 3027, 2928, 1494, 1451;  $\delta_{\text{H}}$ (400 MHz) 1.00–1.45 (m, 7H), 1.64 (m, 2H), 1.99 (m, 1H), 2.12 (m, 2H), 2.50 (m, 1H), 3.57 (d, 1H, *J* = 12.7 Hz), 3.64 (d, 1H, *J* = 12.7 Hz), 3.90 (m, 1H), 7.21–7.38 (m, 10H);  $\delta_{\text{C}}$ (100.6 MHz) 24.5, 25.3, 26.6, 32.1, 33.6, 34.4, 51.1, 54.3, 55.8, 126.7, 127.1, 127.2, 128.73, 128.74, 129.1, 138.7, 140.9; *m/z* (EI) 325 (13), 234 (92), 203 (44), 105 (100), 91 (54).

#### 6-Azabicyclo[3.1.0]hexane **20**

This compound was prepared according to a literature procedure.<sup>29</sup> All physical and spectroscopic data were in agreement with the published data.

#### *trans*-2-Benzylsulfanyl cyclopentylamine **21**

Compound **20** (0.830 g, 10.0 mmol) was dissolved in MeOH (20 ml) and toluene- $\alpha$ -thiol (1.86 g, 15.0 mmol) was added *via* syringe. The mixture was refluxed for 6 h and then evaporated.

Purification of the residue by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>–MeOH 100:0 to 90:10) afforded racemic **21** (0.530 g, 24%) as a yellow oil.  $\nu_{\max}$ (CDCl<sub>3</sub>)/cm<sup>-1</sup> 3359, 3061, 3027, 2953, 2865, 2344, 2359, 1601, 1495, 1453;  $\delta_{\text{H}}$ (400 MHz) 1.33 (m, 1H), 1.45 (br s, 2H), 1.62 (m, 3H), 2.25 (m, 2H), 2.53 (ddd, 1H, *J* = 7.6, 6.7, 0.4 Hz), 3.04 (ddd, 1H, *J* = 7.4, 6.9, 0.4 Hz), 3.72–3.76 (d, 1H, *J* = 13.4 Hz), 3.77–3.82 (d, 1H, *J* = 13.4 Hz), 7.20–7.36 (m, 5H);  $\delta_{\text{C}}$ (100.6 MHz) 21.8, 32.5, 34.1, 36.0, 53.1, 58.8, 126.9, 128.4, 128.7, 138.7; *m/z* (EI) 208 ( $M^+ + 1$ , 100%), 191 (8), 150 (12), 115 (37).

#### *trans*-*N*-Benzyl-2-benzylsulfanyl cyclopentylamine **22**

Compound **21** (0.300 g, 1.40 mmol) was dissolved in EtOH (10 ml), MgSO<sub>4</sub> was added and the mixture was cooled to 0 °C. Benzaldehyde (0.153 g, 1.40 mmol) was added *via* syringe and the reaction mixture was stirred at rt for 4 h. NaBH<sub>4</sub> (0.106, 2.80 mmol) was added and the reaction mixture was stirred at rt overnight. The solvent was evaporated off and the crude product was extracted with CH<sub>2</sub>Cl<sub>2</sub> and brine (3 × 10 ml). The combined organic phases were dried (MgSO<sub>4</sub>) and evaporation of the solvent afforded **22** (0.300 g, 72%) as a yellow oil. The enantiomers were separated on a chiral OD (HPLC) column using hexane-*i*-PrOH as the eluent (90:10, 6 ml min<sup>-1</sup>, retention times 15 and 17 min). [ $\alpha$ ]<sub>D</sub><sup>23</sup> -44.6 (first peak eluted from HPLC, *c* 0.87 in CHCl<sub>3</sub>);  $\nu_{\max}$ (CDCl<sub>3</sub>)/cm<sup>-1</sup> 3401, 3084, 3061, 3027, 2952, 1495, 1453;  $\delta_{\text{H}}$ (400 MHz) 1.36–1.46 (m, 1H), 1.54–1.73 (m, 3H), 1.75 (br s, 1H), 1.95–2.13 (m, 2H), 2.78 (ddd, 1H, *J* = 0.4, 6.7, 7.9 Hz), 2.93 (ddd, 1H, *J* = 0.4, 6.5, 6.8 Hz), 3.67 (d, 1H, *J* = 13.2 Hz), 3.74 (d, 1H, *J* = 2.7 Hz), 3.75–3.80 (d, 1H, *J* = 13.2 Hz), 7.19–7.39 (m, 10H);  $\delta_{\text{C}}$ (100.6 MHz) 22.5, 32.0, 32.6, 36.0, 49.9, 52.5, 64.3, 124.4,<sup>33</sup> 126.4, 128.1, 128.3, 128.4, 128.7, 138.7, 140.2; *m/z* (EI) 298 ( $M^+ + 1$ , 100%), 207 (45), 191 (10), 174 (20), 146 (12), 106 (30), 91 (70), 65 (9).

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