

# Chirally templated boronic acid Mannich reaction in the synthesis of optically active $\alpha$ -amino acids

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Adducts from diastereoselective Mannich-type reactions of aldehydes, 2-furylboronic acid and the chiral amine template (*S*)-5-phenylmorpholin-2-one, have been used in the synthesis of a series of enantiomerically pure D- $\alpha$ -amino acids.

## Introduction

$\alpha$ -Amino acids represent an extremely important class of naturally occurring compound, not only as vital components in metabolism in their own right, but also as the essential building blocks of a wide selection of synthetically and clinically interesting primary and secondary metabolites.<sup>1</sup> Not only are amino acids constituents of synthetic targets, but their derivatives also hold utility for the synthetic chemist as chiral auxiliaries, for example, for the induction of stereocontrol into molecular structure. Classic examples being SAMP and RAMP,<sup>2</sup> and Evans' auxiliary.<sup>3</sup>

Extensive work within our group has focused on the diastereocontrolled cycloaddition reactions of azomethine ylides derived from (*S*)-5-phenylmorpholin-2-one † **1**,<sup>4</sup> and the stereochemical outcome has been rationalised by axial approach of the dipolarophile to the azomethine ylide, lying in a *quasi* chair conformation, in which the 5-phenyl substituent lies in an equatorial environment. As an extension to this work we reasoned that, in the presence of suitable nucleophiles, **1** could be a candidate for generating iminium species capable of undergoing diastereocontrolled Mannich reactions leading to optically active amine derivatives. Initial attempts using electron rich alkenes, such as enol ethers, vinyl thioethers, pyrroles and furan as the nucleophilic species, proved limited in application, with low yields of adducts being observed solely with paraformaldehyde.<sup>5</sup> However, a report by Petasis and Akritopoulou, that geometrically pure tertiary allyl amines may be constructed from paraformaldehyde, vinylboronic acids and secondary amines in refluxing dioxane by a boronic acid Mannich reaction (Scheme 1),<sup>6</sup> prompted us to investigate the application of this system to iminium species derived from morpholinone **1**.



**Scheme 1** Reagents and conditions: (i) [HCHO]<sub>n</sub>, dioxane, reflux.

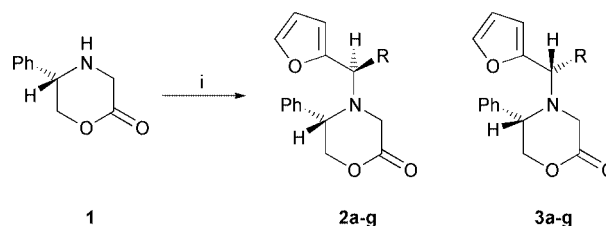
† The trivial morpholin-2-one nomenclature is used for 3,4,5,6-tetrahydro-2H-1,4-oxazin-2-one in this paper.

**Table 1** Diastereocontrolled formation of adducts **2**

Product <b>2</b>	R	Major isomer	
		Yield (%)	De (%)
<b>a</b>	Bu	69	90
<b>b</b>	Pr	59	93
<b>c</b>	BnCH <sub>2</sub>	66	89
<b>d</b>	<sup>t</sup> BuCH <sub>2</sub>	75	86
<b>e</b>	BnOCH <sub>2</sub>	64	86
<b>f</b>	C-C <sub>6</sub> H <sub>11</sub>	6	>95
<b>g</b>	<sup>i</sup> Pr	7	>95

## Results and discussion

An initial survey with paraformaldehyde indicated that the reaction proceeded with high efficiency utilising 2-furylboronic acid as the nucleophile. Applying our optimised conditions to a range of aldehydes resulted in the formation of mixtures of adducts in high material yield and with diastereomeric excesses in the range of 86–>95% (Table 1), ‡ each diastereomer being readily separable by column chromatography (Scheme 2).<sup>7</sup>  $\alpha$ -Branched aldehydes gave reduced yields and sluggish reaction times, presumably as a consequence of a more sterically



**Scheme 2** Reagents and conditions: (i) 2-furylboronic acid, RCHO, THF,  $\Delta$ .

‡ Quoted diastereomeric excesses are based on isolated yields since the complexity of the NMR spectra of crude reaction mixtures did not allow for accurate analysis of the minor isomer signal integrations. Where possible, analysis of spectra gave results in good agreement with those from isolated yields.

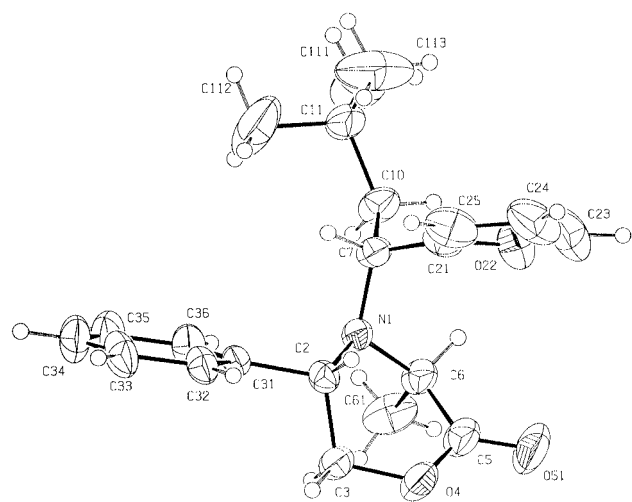
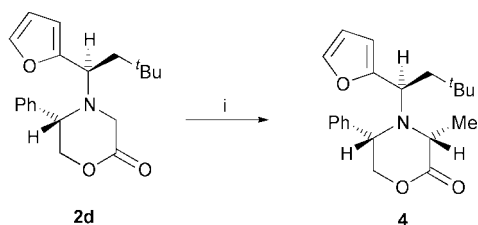


Fig. 1 X-Ray crystal structure of **4**.

restrictive situation leading to the transition state. The resulting major adducts represent a potential entry point for the synthesis of optically pure  $\alpha$ -amino acids, after degradation of the template to the amine functionality; the furyl group representing a masked carboxy moiety. Subsequent to our initial communication, Petasis and co-workers have also demonstrated the stereocontrolled boronic acid Mannich reaction to an extensive range amino derivatives.<sup>8</sup>

Analysis of NOE difference spectra obtained on the major adducts did not permit unambiguous structural assignment and the direction of diastereocontrol was eventually proven by X-ray crystallographic analysis of crystalline derivative **4** (Fig. 1),§ obtained in 71% isolated yield (84% based upon recovered starting material) by alkylation of the sodium enolate of **2d** with iodomethane (Scheme 3).



Scheme 3 Reagents and conditions: (i) NaHMDS, THF-DME,  $-78\text{ }^{\circ}\text{C}$ ; (ii) MeI.

The stereochemistry of the reaction products is supportive of our mechanistic rationale which, by analogy with earlier studies, invokes nucleophilic attack of the 2-furylboronic acid on the more accessible face of a conformationally locked *E*-iminium ion, predicting the major diastereoisomers to be **2a–g** (Fig. 2).

With the series of Mannich products **2a–e** listed in Table 1 in hand, attention was then focused on the removal of the template. Our initial strategy hinged on opening the lactone **2** with lithium aluminium hydride to give the diol **5**, followed by cleavage of the pendant hydroxyethyl groups with glycol cleaving reagents. The desired diol **5** was easily prepared in

§ X-Ray crystallographic data:  $\text{C}_{21}\text{H}_{27}\text{NO}_3$ ,  $M = 341.44$ , monoclinic, space group  $C2$ ,  $a = 16.120(9)$ ,  $b = 11.511(9)$ ,  $c = 11.189(8)$  Å,  $\beta = 96.33(1)^{\circ}$ ,  $U = 2064$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.099$  g cm<sup>-3</sup>,  $F(000) = 736$ , 3218 independent reflections were obtained from  $95 \times 2^{\circ}$  frames, each collected for 2 min on the MARresearch Image Plate system. Data analysis was carried out with the XDS program. The structure was determined by direct methods using SHELXL86 to  $R$  0.0617. Atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference number 207/454. See <http://www.rsc.org/suppdata/p1/b0/b003067h>

Table 2 Isolated yields of intermediates **5**, **7**, **9–11** and **13**

	Purified yields (%)					
	<b>5</b>	<b>7</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>13</b>
<b>a</b>	98	74	92	82	66	99
<b>b</b>	98	60	76	83	71	78
<b>c</b>	99	69	85	72	66	71
<b>d</b>	99	62	90	84	68	71
<b>e</b>	97	47	78	82	61	78

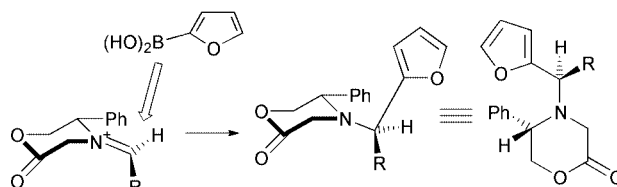
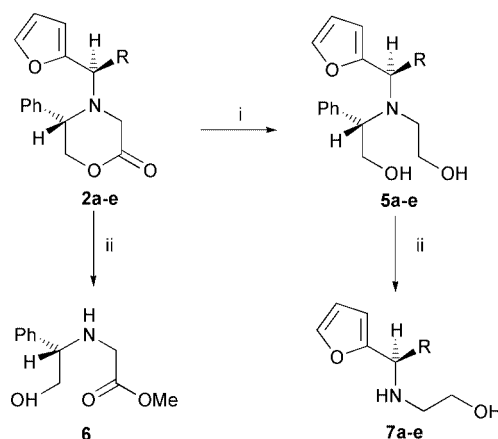


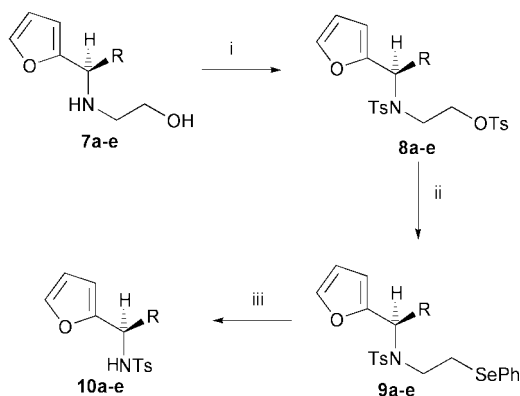
Fig. 2 Model of nucleophile approach to *E*-iminium ion.



Scheme 4 Reagents and conditions: (i)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $\Delta$ ; (ii)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , MeOH, TFA,  $\text{H}_2\text{O}$ .

essentially quantitative yield (Scheme 4), although attempts at revealing the free amine with reagents such as lead tetraacetate,<sup>9</sup> or sodium periodate,<sup>10</sup> met with failure. Attention was then moved towards cleavage of the *N*-benzyl bond. Use of debenzylation protocols such as alkyl chloroformate esters<sup>11</sup> or von Braun conditions<sup>12</sup> gave only starting material, whilst treatment of **2a** with Pearlman's catalyst under standard hydrogenolysis conditions gave a low yield of the desired product as the methyl ester, the major product of the reaction being the amino alcohol **6** resulting from preferential cleavage of the furfurylamine bond. This selectivity problem was successfully overcome by treatment of the diols **5a–e**, under the same hydrogenation conditions, furnishing the desired amino alcohols **7a–e** in 60–70% yield after purification on alumina (Table 2). It is interesting to note that, in the case of the *O*-benzyl substrate **5e**, no loss of the protecting group was observed.

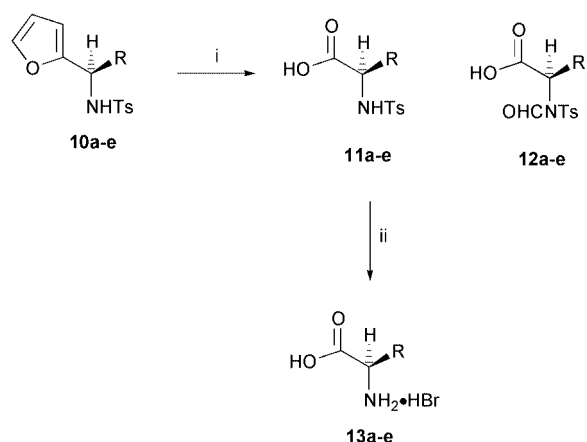
Studies into the removal of the remaining section of the template once again revealed that glycol cleaving reagents were ineffective, so efforts turned towards elimination of the hydroxy group, followed by hydrolysis of the resultant enamine. The most satisfactory method developed hinged upon one-pot oxidation, elimination and hydrolysis starting from aryl selenides **9a–e** (Scheme 5). The amino alcohols **7a–e** were treated with toluene-*p*-sulfonic anhydride, yielding the unstable *N,O*-ditosylated products, which were subsequently treated with diphenyl diselenide and sodium borohydride in refluxing ethanol, to deliver the aryl selenides **9a–e**.<sup>13</sup> Oxidation of the aryl selenide with sodium periodate furnished the selenoxides, which proved unusually thermally stable, requiring refluxing



**Scheme 5** Reagents and conditions: (i)  $(\text{Tos})_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DCM; (ii)  $\text{PhSeSePh}$ ,  $\text{NaBH}_4$ ,  $\text{EtOH}$ ,  $\Delta$ ; (iii)  $\text{NaHCO}_3$ ,  $\text{NaIO}_4$ ,  $\text{MeOH}$ ,  $\text{H}_2\text{O}$ ; (iv) 1,4-dioxane,  $\Delta$  followed by  $\text{HCl}$ .

in dioxane for 30 mins to effect complete elimination. Subsequently, aqueous hydrochloric acid was added with refluxing continued for a further hour, furnishing the desired sulfonamides **10a–e**. Several of these compounds have been claimed to have been prepared in enantiomerically pure form, by a kinetic resolution procedure involving oxidative transformation of the racemic *N*-toluenesulfonylfurfurylamines, using a modified Sharpless epoxidation and isolation of unreacted starting material.<sup>14</sup> However, our materials consistently showed greater specific rotations than previously reported.<sup>15</sup> Application of a similar strategy to diol **5**, attempting to convert the hydroxy functionalities into suitable leaving groups for elimination to a bis(enamine), led only to polymerization.

Oxidative modification of furan rings to carboxy groups is well known in the literature and reports by Zhou *et al.* had shown that oxidation of the furan ring in similar compounds to ours could be best achieved by ozonolysis.<sup>14</sup> However, in our hands, such a procedure gave only complex reaction mixtures and the ruthenium dioxide oxidation procedure, developed by Sharpless, was used instead.<sup>16</sup> Treatment of the sulfonamides **10a–e** with ruthenium dioxide, using sodium periodate as the co-oxidant in a 2:2:3 mixture of water, carbon tetrachloride and acetonitrile, gave the *N*-tosylated amino acids **11a–e** accompanied by lesser amounts (~7%) of the formamides **12a–e** (Scheme 6). Finally, *N*-deprotection using



**Scheme 6** Reagents and conditions: (i)  $\text{RuO}_2$ ,  $\text{NaIO}_4$ ,  $\text{MeCN}$ ,  $\text{CCl}_4$ ,  $\text{H}_2\text{O}$ ; (ii)  $\text{HBr}$  (30% w/w  $\text{AcOH}$ ),  $\text{PhOH}$ .

30% w/w  $\text{HBr}$ – $\text{AcOH}$ , gave the desired amino acids as their hydrobromide salts **13a–e**, with concomitant *O*-debenzylation in the case of substrate **10e**. One-pot deprotection and deformylation of the formamides **12a–e** in refluxing aqueous  $\text{HBr}$  occurred readily and the enantiomeric excesses of the *D*-amino acid salts **13a–e** were estimated to be greater than 95% based upon specific rotation values of synthesised compounds

compared to hydrobromide salts prepared from commercially available *D*-amino acids.

In conclusion, we have demonstrated that sequential degradation of diastereomically pure *N*-furfurylmorpholinones **2**, obtained by boronic Mannich condensation, can be carried out to furnish amino acids of high optical purity. Although demonstrated for the *D*-series, use of (*R*)-5-phenylmorpholinone would equally give rise to the *L*-enantiomers.

## Experimental

Melting points were recorded on a Kofler hot stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer PARAGON 1000 FT-IR spectrophotometer as KBr disks or thin films as stated. NMR spectra were recorded on either a Bruker AMX 400 NMR (400 MHz) or a Bruker DPX Cryospec WM 250 (250 MHz). Spectra were referenced to an internal standard, tetramethylsilane, or to residual solvent peaks. Mass spectrometric data were recorded on a Fisons VG Autospec, using chemical ionisation with ammonia. X-Ray crystallography was performed at Reading University on a MARresearch Image Plate.† Flash column chromatography was performed using Merck 60 silica gel. TLC analysis was performed on glass backed plates coated with 0.2 mm silica 60<sub>F254</sub>. All solvents were distilled prior to use. THF, 1,4-dioxane and diethyl ether were distilled over sodium and benzophenone ketyl radical and dichloromethane from  $\text{CaH}_2$ . Methanol was distilled from magnesium turnings and iodine prior to use. MeCN was distilled from  $\text{P}_2\text{O}_5$  and stored over molecular sieves. Petrol refers to the fraction boiling between 30 and 40 °C.

### General procedure for (5*S*,1'*S*)-*N*-[1'-(2-furyl)alkyl]-5-phenylmorpholin-2-ones (**2a–e**)

To a stirred solution of morpholinone (0.56 mmol) and 2-furylboronic acid (2.24 mmol) in THF (10 ml) was added the requisite aldehyde (0.62 mmol) in THF (2 ml). The reaction mixture was then refluxed for 3 hours, until TLC indicated complete consumption of morpholinone. The solvent was then removed under reduced pressure, DCM (1 ml) added and the resulting suspension filtered through Celite®. The solvent was then removed under reduced pressure and the resultant oil purified by flash column chromatography with gradient elution (silica, typically 9:1 petrol–ether to 5:1 petrol–ether) to afford the product as a colourless oil.

#### (5*S*,1'*S*)-*N*-[1'-(2-Furyl)pentyl]-5-phenylmorpholin-2-one

**(2a)**. Colourless oil (122 mg, 69%);  $\nu_{\text{max}}$  (film) 1751  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.45–7.36 (6H, m, *Ph*), 6.32 (1H, dd,  $J$  3.2,  $J'$  1.9 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 6.03 (1H, d,  $J$  3.2 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 4.26 (1H, t,  $J$  11.0 Hz, 6 $\alpha$ -H), 4.18 (1H, dd,  $J$  11.2 Hz,  $J'$  3.8 Hz, 6 $\beta$ -H), 3.87 (1H, dd,  $J$  10.4,  $J'$  3.8 Hz, 5-H), 3.83 (1H, d,  $J$  17.9 Hz, 3 $\alpha$ -H or 3 $\beta$ -H), 3.71 (1H, t,  $J$  7.3 Hz,  $\text{PhCHNCH}$ ), 3.33 (1H, d,  $J$  17.9 Hz, 3 $\alpha$ -H or 3 $\beta$ -H), 1.83–1.75 (1H, m,  $\text{CHHCH}_2\text{CH}_2\text{CH}_3$ ), 1.73–1.65 (1H, m,  $\text{CHHCH}_2\text{CH}_2\text{CH}_3$ ), 1.42–1.33 (1H, m,  $\text{CH}_2\text{CHHCH}_2\text{CH}_3$ ), 1.28–1.12 (3H, m,  $\text{CH}_2\text{CHHCH}_2\text{CH}_3$ ), 0.87 (3H, t,  $J$  7.2 Hz,  $\text{CH}_2\text{CHHCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 169.1, 152.8, 142.2, 136.8, 128.9, 128.7, 128.7, 109.8, 109.1, 73.0, 60.7, 55.5, 47.6, 29.9, 28.4, 22.4, 13.9;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 314 ( $\text{MH}^+$ ), 256, 178, 137; HRMS for  $\text{C}_{19}\text{H}_{23}\text{NO}_3$   $\text{MH}^+$  requires 314.1757, found 314.1756;  $[\alpha]_{\text{D}}^{20} +179$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

#### (5*S*,1'*S*)-*N*-[1'-(2-Furyl)butyl]-5-phenylmorpholin-2-one (**2b**)

Colourless oil (99 mg, 59%);  $\nu_{\text{max}}$  (film) 1741  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.45–7.36 (6H, m,  $\text{CH}=\text{CH}-\text{O}$  and *Ph*), 6.32 (1H, dd,  $J$  3.2,  $J'$  1.9 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 6.03 (1H, d,  $J$  3.2 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 4.26 (1H, t,  $J$  11.0 Hz, 6 $\alpha$ -H), 4.18 (1H, dd,  $J$  11.2 Hz,  $J'$  3.8 Hz, 6 $\beta$ -H), 3.87 (1H, dd,  $J$  10.4,  $J'$  3.8 Hz, 5-H),

3.83 (1H, d,  $J$  17.9 Hz, 3 $\alpha$ -H or 3 $\beta$ -H), 3.73 (1H, t,  $J$  7.2 Hz, PhCHNCH), 3.34 (1H, d,  $J$  17.9 Hz, 3 $\alpha$ -H or 3 $\beta$ -H), 1.82–1.74 (1H, m, CHHCH<sub>2</sub>CH<sub>3</sub>), 1.70–1.63 (1H, m, CHHCH<sub>2</sub>CH<sub>3</sub>), 1.46–1.37 (1H, m, CHHCH<sub>3</sub>), 1.28–1.17 (1H, m, CHHCH<sub>3</sub>), 0.85 (3H, t,  $J$  7.4 Hz, CH<sub>3</sub>);  $\delta_C$  (125.7 MHz, CDCl<sub>3</sub>) 169.0, 152.7, 142.2, 136.7, 128.9, 128.7, 128.6, 109.8, 109.0, 73.0, 60.7, 55.2, 47.5, 32.3, 19.5, 13.8;  $m/z$  (CI + {NH<sub>3</sub>}) 300 (MH<sup>+</sup>), 256, 178, 123; HRMS for C<sub>18</sub>H<sub>22</sub>NO<sub>3</sub> MH<sup>+</sup> requires 300.1600, found 300.1600;  $[a]_D^{20} +194$  ( $c = 1.0$ , CHCl<sub>3</sub>).

**(5*S*,1'*S*)-*N*-[1'-(2-Furyl)-3'-phenylpropyl]-5-phenylmorpholin-2-one (2c).** Colourless oil (134 mg, 66%);  $\nu_{\max}$  (film) 1747 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.43 (1H, d,  $J$  1.8 Hz, CH=CH-O), 7.40–7.33 (5H, m, PhCHN), 7.20 (2H, t,  $J$  7.6 Hz, CH<sub>2</sub>Ph), 7.14 (1H, t,  $J$  7.2 Hz, CH<sub>2</sub>Ph), 7.10 (2H, d,  $J$  7.7 Hz, CH<sub>2</sub>Ph), 6.35 (1H, dd,  $J$  3.2,  $J'$  1.9 Hz, CH=CH-O), 6.06 (1H, d,  $J$  3.2 Hz, CHCH=CH-O), 4.28 (1H, t,  $J$  11.0 Hz, 6 $\alpha$ -H), 4.19 (1H, dd,  $J$  11.3,  $J'$  3.8 Hz, 6 $\beta$ -H), 3.91–3.87 (2H, m, 5-H and 3 $\alpha$ -H or 3 $\beta$ -H), 3.81 (1H, t,  $J$  7.6 Hz, PhCHNCH), 3.38 (1H, d,  $J$  17.9 Hz, 3 $\alpha$ -H or 3 $\beta$ -H), 2.73–2.67 (1H, m, PhCH<sub>2</sub>), 2.56–2.50 (1H, m, PhCH<sub>2</sub>), 2.13–2.08 (2H, m, PhCH<sub>2</sub>CH<sub>2</sub>);  $\delta_C$  (50.3 MHz, CDCl<sub>3</sub>) 169.2, 152.4, 142.7, 141.6, 136.7, 129.2, 128.9, 128.6, 128.5, 126.2, 110.1, 109.1, 73.1, 60.8, 55.1, 47.7, 32.5, 31.9;  $m/z$  (CI + {NH<sub>3</sub>}) 362 (MH<sup>+</sup>), 256, 185, 178; C<sub>23</sub>H<sub>23</sub>NO<sub>3</sub> requires C, 76.4; H, 6.4; N, 3.90%, found C, 76.7; H, 6.10; N, 3.70%;  $[a]_D^{20} +113$  ( $c = 1.0$ , CHCl<sub>3</sub>).

**(5*S*,1'*S*)-*N*-[1'-(2-Furyl)-3',3'-dimethylbutyl]-5-phenylmorpholin-2-one (2d).** Colourless oil (139 mg, 75%);  $\nu_{\max}$  (film) 1752 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.45–7.38 (6H, *Ph* and CH=CH-O), 6.32 (1H, dd,  $J$  3.2,  $J'$  2.0 Hz, CH=CH-O), 5.99 (1H, d,  $J$  3.2 Hz, CHCH=CH-O), 4.24 (1H, t,  $J$  10.8 Hz, 6 $\alpha$ -H), 4.16 (1H, dd,  $J$  11.2,  $J'$  3.8 Hz, 6 $\beta$ -H), 3.90–3.84 (2H, m, NCHCH<sub>2</sub>Bu' and 3 $\alpha$ -H), 3.69 (1H, dd,  $J$  10.4,  $J'$  3.9 Hz, 5-H), 3.36 (1H, d,  $J$  17.9 Hz, 3 $\beta$ -H), 1.97 (1H, dd,  $J$  13.6,  $J'$  9.2 Hz, NCHCHHBu'), 1.64 (1H, dd,  $J$  13.6,  $J'$  3.5 Hz, NCHCHHBu'), 0.70 (9H, s, Bu');  $\delta_C$  (50.3 MHz, CDCl<sub>3</sub>) 168.9, 152.3, 142.0, 136.6, 128.9, 128.8, 128.7, 110.0, 109.3, 73.0, 60.6, 52.8, 48.3, 44.9, 30.5, 29.4;  $m/z$  (CI + {NH<sub>3</sub>}) 328 (MH<sup>+</sup>), 256, 178, 151; C<sub>20</sub>H<sub>25</sub>NO<sub>3</sub> requires C, 73.4, H, 7.70, N, 4.30% found C, 73.5, H, 7.55, N, 3.95%;  $[a]_D^{20} +199$  ( $c = 1.0$ , CHCl<sub>3</sub>).

**(5*S*,1'*S*)-*N*-[1'-(2-Furyl)-2'-benzyloxyethyl]-5-phenylmorpholin-2-one (2e).** Colourless oil (136 mg, 64%);  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.48–7.26 (11H, *Ph* and CH=CH-O), 6.34 (1H, dd,  $J$  3.2,  $J'$  1.9 Hz, CH=CH-O), 6.13 (1H, d,  $J$  3.2 Hz, CHCH=CH-O), 4.50 (2H, s, PhCH<sub>2</sub>O), 4.29 (1H, t,  $J$  11.1 Hz, 6 $\alpha$ -H), 4.20 (1H, dd,  $J$  11.3,  $J'$  3.8 Hz, 6 $\beta$ -H), 4.10 (1H, t,  $J$  6.7 Hz, PhCHNCH), 3.95 (1H, dd,  $J$  10.4,  $J'$  3.8 Hz, 5-H), 3.87 (1H, d,  $J$  17.8 Hz, 3 $\alpha$ -H or 3 $\beta$ -H), 3.82 (1H, dd,  $J$  10.0,  $J'$  6.8 Hz, NCHCH<sub>2</sub>OCH<sub>2</sub>Ph), 3.73 (1H, dd,  $J$  10.0,  $J'$  6.6 Hz, NCHCH<sub>2</sub>OCH<sub>2</sub>Ph), 3.40 (1H, d,  $J$  17.8 Hz, 3 $\alpha$ -H or 3 $\beta$ -H);  $\delta_C$  (50.3 MHz, CDCl<sub>3</sub>) 168.7, 150.3, 142.5, 138.0, 136.4, 129.0, 128.8, 128.7, 128.4, 127.7, 127.6, 110.1, 73.1, 72.9, 69.0, 60.8, 55.5, 48.8;  $m/z$  (CI + {NH<sub>3</sub>}) 378 (MH<sup>+</sup>), 256, 201, 178, 91; C<sub>23</sub>H<sub>23</sub>NO<sub>4</sub> requires C, 73.2; H, 6.15; N, 3.70%, found C, 73.4; H, 6.20; N, 4.00%;  $[a]_D^{20} +116$  ( $c = 1.0$ , CHCl<sub>3</sub>).

**(3*R*,5*S*,1'*R*)-*N*-[1'-(2-Furyl)-3',3'-dimethylbutyl]-5-phenyl-3-methylmorpholin-2-one (4).** Morpholinone (2d) (147 mg, 0.45 mmol) was dissolved in DME (1 ml) and THF (0.6 ml) under an atmosphere of nitrogen at –78 °C and sodium hexamethyldisilazide (0.45 ml, 1 M in THF, 0.45 mmol) was added dropwise. The solution was stirred for 30 minutes before methyl iodide (280  $\mu$ l, 4.5 mmol) was added. The reaction mixture was warmed to room temperature and stirred for a further 30 minutes. Saturated aqueous ammonium chloride (1 ml) was added and the mixture was shaken with DCM (20 ml) and brine (15 ml). The aqueous solution was washed with additional

DCM (15 ml) and the organic solutions were combined, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica, 7:1 petrol–ether) to afford (4) as a colourless solid (108 mg, 71%); mp 120–122 °C;  $\nu_{\max}$  (film) 1752 cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.48–7.28 (6H, *Ph* and CH=CH-O), 6.27 (1H, dd,  $J$  3.1,  $J'$  1.9 Hz, CH=CH-O), 6.07 (1H, d,  $J$  3.1 Hz, CHCH=CH-O), 4.23–4.15 (2H, m, 6 $\alpha$ -H and 3-H), 4.10 (1H, dd,  $J$  11.5,  $J'$  3.9 Hz, 5-H or 6 $\beta$ -H), 4.01 (1H, dd,  $J$  11.2,  $J'$  3.8 Hz, 5-H or 6 $\beta$ -H), 3.61 (1H, dd,  $J$  10.1,  $J'$  2.6 Hz, CHCH<sub>2</sub>Bu'), 2.03 (1H, dd,  $J$  13.3,  $J'$  10.1 Hz, CHHBu'), 1.72–1.60 (4H, m, CH<sub>3</sub>CH and CHHBu'), 0.62 (9H, s, Bu');  $\delta_C$  (62.9 MHz, CDCl<sub>3</sub>) 172.6, 153.8, 142.0, 138.1, 128.7, 128.3, 127.8, 109.9, 108.4, 70.0, 60.4, 54.4, 53.0, 46.3, 30.3, 29.3, 24.9;  $m/z$  (CI + {NH<sub>3</sub>}) 342 (MH<sup>+</sup>), 270, 192, 151; HRMS for C<sub>21</sub>H<sub>28</sub>NO<sub>3</sub> MH<sup>+</sup> requires 341.1991, found 341.1990;  $[a]_D^{20} +65.4$  ( $c = 0.5$ , CHCl<sub>3</sub>).

#### General procedure for (2*S*,1'*R*)-*N*-[1'-(2-furyl)alkyl]-*N*-(2-hydroxyethyl)-2-phenylglycinols (5a–e)

Adducts 2a–e (1 mmol) were stirred at room temperature in ether (80 ml), under a nitrogen atmosphere, with LiAlH<sub>4</sub> (1.2 mmol) added slowly in small portions and the reaction was then heated to reflux for 1.5 hours. After cooling to room temperature, water (1 ml), NaOH (2 M, 1 ml) and water (3 ml) were added consecutively. Once effervescence had stopped, the reaction mixture was filtered through a pad of silica. The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica, typically 1:1 petrol–ether) to yield the diols as colourless oils.

**(2*S*,1'*R*)-*N*-[1'-(2-Furyl)pentyl]-*N*-(2-hydroxyethyl)-2-phenylglycinol (5a).** Colourless oil (6.55 g, 96%);  $\nu_{\max}$  (film) 3333, 1602, 1499 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.29–7.16 (6H, m, CH=CH-O and *Ph*), 6.19 (1H, dd,  $J$  3.2,  $J'$  1.9 Hz, CH=CH-O), 5.87 (1H, d,  $J$  3.2 Hz, CHCH=CH-O), 4.02 (1H, t,  $J$  6.0 Hz, PhCHCHHOH or PhCHCHHOH), 3.87–3.79 (3H, m, PhCHNCH and PhCHCHHOH or PhCHCHHOH), 3.68–3.57 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.15–3.09 (1H, m, NCHHCH<sub>2</sub>OH), 2.88 (2H, br s, CH<sub>2</sub>OH), 2.81 (1H, dt,  $J$  14.7,  $J'$  4.3 Hz, NCHHCH<sub>2</sub>OH), 1.90–1.82 (1H, m, CHHCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.80–1.74 (1H, m, CHHCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.37–1.16 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.87 (3H, t,  $J$  7.1 Hz, CH<sub>3</sub>);  $\delta_C$  (125.7 MHz, CDCl<sub>3</sub>) 156.0, 146.0, 141.4, 128.6, 128.4, 127.3, 109.8, 107.5, 65.2, 63.7, 61.5, 56.8, 48.6, 31.9, 28.8, 22.5, 13.9;  $m/z$  (CI + {NH<sub>3</sub>}) 318 (MH<sup>+</sup>), 182, 137; C<sub>19</sub>H<sub>27</sub>NO<sub>3</sub> requires C, 71.9; H, 8.55; N, 4.40%, found C, 72.0; H, 8.85; N, 4.30%;  $[a]_D^{20} +91.0$  ( $c = 1.0$ , CHCl<sub>3</sub>).

**(2*S*,1'*R*)-*N*-[1'-(2-Furyl)butyl]-*N*-(2-hydroxyethyl)-2-phenylglycinol (5b).** Colourless oil (352 mg, 98%);  $\nu_{\max}$  (film) 3340, 1602, 1583 cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.21–7.03 (6H, m, *Ph* and OCH=CH), 6.17 (1H, dd,  $J$  1.9,  $J'$  1.2 Hz, OCH=CH), 5.84 (1H, d,  $J$  3.3 Hz, OCH=CHCH), 4.00 (1H, t,  $J$  6.2 Hz, NCHPh or NCHPhCH<sub>2</sub>), 3.86–3.78 (2H, m, NCHPhCH<sub>2</sub> and NCHCH<sub>2</sub>), 3.66–3.58 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.11–3.06 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.01 (2H, br s, OH), 2.82 (1H, dt,  $J$  4.2,  $J'$  14.7 Hz, NCH<sub>2</sub>CH<sub>2</sub>OH), 1.82–1.77 (2H, m, NCHCH<sub>2</sub>), 1.17–1.34 (2H, m, NCHCH<sub>2</sub>CH<sub>2</sub>), 0.87 (3H, t,  $J$  7.3 Hz, CH<sub>3</sub>);  $\delta_C$  (62.8 MHz, CDCl<sub>3</sub>) 155.6, 141.2, 140.2, 128.4, 128.2, 127.2, 109.7, 107.4, 65.2, 63.7, 61.5, 56.6, 48.6, 34.4, 19.9;  $m/z$  (CI + {NH<sub>3</sub>}) 304 (MH<sup>+</sup>), 272, 182, 150, 123, 81; HRMS for C<sub>18</sub>H<sub>25</sub>NO<sub>3</sub> MH<sup>+</sup> requires 304.1913, found 304.1902;  $[a]_D^{20} +84.2$  ( $c = 0.92$ , EtOH).

**(2*S*,1'*R*)-*N*-[1'-(2-Furyl)-3'-phenylpropyl]-*N*-(2-hydroxyethyl)-2-phenylglycinol (5c).** Colourless oil (1.18 g, 99%);  $\nu_{\max}$  (film) 3414, 1644 cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.21–7.03 (13H, m, *Ph* and OCH=CH), 6.12 (1H, dd,  $J$  2.9,  $J'$  1.7 Hz,

OCH=CH), 5.77 (1H, d, *J* 2.9, OCH=CHCH), 3.94 (1H, t, *J* 6.2 Hz, NCHPh or NCHPhCH<sub>2</sub>), 3.81 (1H, t, *J* 7.3 Hz, NCHPhCH<sub>2</sub> or NCHCH<sub>2</sub>), 3.76–3.68 (1H, m, NCHPhCH<sub>2</sub>OH), 3.52 (2H, br, s, NCH<sub>2</sub>CH<sub>2</sub>OH), 2.76–2.73 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 2.58–2.45 (4H, m, OH and NCHCH<sub>2</sub>) 2.14–1.92 (1H, m, NCHCH<sub>2</sub>CHHPh), 2.20–2.14 (1H, m, NCHCH<sub>2</sub>CHHPh);  $\delta_c$  (67.9 MHz, CDCl<sub>3</sub>) 152.5, 141.5, 138.6, 136.8, 128.3, 128.1, 127.7, 109.9, 107.4, 73.5, 69.1, 62.9, 62.0, 60.2, 53.7, 47.6; *m/z* (CI + {NH<sub>3</sub>}) 366 (MH<sup>+</sup>), 334, 185, 150, 117, 91; HRMS for C<sub>23</sub>H<sub>28</sub>NO<sub>3</sub> MH<sup>+</sup> requires 366.2069, found 366.2062;  $[\alpha]_D^{20} + 70.6$  (*c* = 1.0, EtOH).

**(2*S*,1'*R*)-*N*-[1'-(2-Furyl)-3',3'-dimethylbutyl]-*N*-(2-hydroxyethyl)-2-phenylglycinol (5d).** Colourless oil (1.58 g, 99%);  $\nu_{\max}$  (film) 3361 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.34–7.16 (6H, m, Ph and OCH=CH), 6.18 (1H, dd, *J* 1.7, *J'* 1.3 Hz, OCH=CH), 5.82 (1H, d, *J* 3.1 Hz, OCH=CHCH), 3.94–3.89 (2H, m, NCHPh or NCHPhCH<sub>2</sub>), 3.84–3.74 (2H, m, NCHPhCH<sub>2</sub> and NCHCH<sub>2</sub>), 3.74–3.57 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.17–3.11 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 2.75 (1H, dt, *J* 14.7, *J'* 4.4 Hz, NCH<sub>2</sub>CH<sub>2</sub>OH), 2.15 (1H, dd, *J* 10.5, *J'* 2.9 Hz, NCHCH<sub>2</sub>), 1.61 (1H, dd, *J* 2.2, *J'* 11.3 Hz, NCHCH<sub>2</sub>), 0.69 (9H, s, 'Bu);  $\delta_c$  (67.8 MHz, CDCl<sub>3</sub>) 155.0, 140.9, 140.4, 128.4, 127.3, 109.9, 107.8, 66.0, 65.8, 64.0, 61.4, 53.5, 48.8, 46.9, 30.5, 29.6, 15.2; *m/z* (CI + {NH<sub>3</sub>}) 332 (MH<sup>+</sup>), 300, 182, 151, 90, 57; HRMS for C<sub>20</sub>H<sub>30</sub>NO<sub>3</sub> MH<sup>+</sup> requires 332.2226, found 332.2223;  $[\alpha]_D^{23} + 77.1$  (*c* = 1.0, EtOH).

**(2*S*,1'*R*)-*N*-[1'-(2-Furyl)-2'-benzyloxyethyl]-*N*-(2-hydroxyethyl)-2-phenylglycinol (5e).** Colourless oil (857 mg, 97%);  $\nu_{\max}$  (film) 3411 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.44–7.11 (11H, m, Ph and OCH=CH), 6.14 (1H, dd, *J* 1.5, *J'* 1.8 Hz, OCH=CH), 5.58 (1H, d, *J* 4.5 Hz, OCH=CHCH), 4.64 (2H, dd, *J* 15.6, *J'* 11.4 Hz, NCHCH<sub>2</sub>OBn), 4.40 (1H, dd, *J* 6.7, *J'* 4.0 Hz, NCHCH<sub>2</sub>), 4.11–3.90 (3H, m, OCH<sub>2</sub>Ph and NCHPhCH<sub>2</sub>), 3.81–3.52 (5H, m, NCH<sub>2</sub>CH<sub>2</sub>OH and NCHPhCH<sub>2</sub> and OH), 3.03–2.95 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>OH), 2.79 (1H, dt, *J* 10.9, *J'* 3.4 Hz, NCH<sub>2</sub>CH<sub>2</sub>OH);  $\delta_c$  (68.0 MHz, CDCl<sub>3</sub>) 152.5, 141.5, 138.6, 136.8, 129.3, 128.3, 127.7, 127.5, 109.9, 107.4, 73.5, 69.1, 62.9, 61.9, 60.2, 53.7, 47.6; *m/z* (CI + {NH<sub>3</sub>}) 382 (MH<sup>+</sup>), 350, 260, 201, 139, 91; HRMS for C<sub>23</sub>H<sub>28</sub>NO<sub>4</sub> MH<sup>+</sup> requires 382.2016, found 382.2018;  $[\alpha]_D^{22} + 51.5$  (*c* = 0.13, EtOH).

#### General procedure for (*R*)-*N*-[1'-(2-furyl)alkyl]-2-aminoethanols (7a–e)

To a solution of the diol (5a–e) (1 mmol) in MeOH (4 ml) were added TFA (2 drops) and water (2 drops). The reaction was stirred for 15 mins, before the addition of palladium hydroxide (25% w/w). The reaction was then left to stir under a hydrogen balloon until TLC analysis indicated complete consumption of starting material, typically 10 hours. The reaction mixture was then filtered through Celite® and the solvent removed under reduced pressure. The residual yellow oil was purified by flash column chromatography with gradient elution (alumina, Brockman Grade IV, typically 6:4 petrol–ether to 1:9 petrol–ether).

**(*R*)-*N*-[1'-(2-Furyl)pentyl]-2-aminoethanol (7a).** Colourless oil (0.71 g, 74%);  $\nu_{\max}$  (film) 3305 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.35 (1H, d, *J* 1.8 Hz, CH=CH-O), 6.30 (1H, dd, *J* 3.1, *J'* 1.8 Hz, CH=CH-O), 6.13 (1H, d, *J* 3.1 Hz, CHCH=CH-O), 3.67–3.56 (2H, m, CH<sub>2</sub>NCH and NCH<sub>2</sub>CH<sub>2</sub>O), 3.55–3.49 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>O), 2.71–2.59 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>O), 2.08 (2H, br s, NH and OH), 1.75 (2H, q, *J* 7.3 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.40–1.18 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.88 (3H, t, *J* 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>);  $\delta_c$  (50.3 MHz, CDCl<sub>3</sub>) 156.5, 141.4, 109.8, 106.5, 61.0, 56.1, 48.6, 34.4, 28.4, 22.5, 14.0; *m/z* (CI + {NH<sub>3</sub>}) 198 (MH<sup>+</sup>), 140, 137; HRMS for C<sub>11</sub>H<sub>20</sub>NO<sub>2</sub> MH<sup>+</sup> requires 198.1494, found 198.1499;  $[\alpha]_D^{23} + 32.7$  (*c* = 1.0, CHCl<sub>3</sub>).

**(*R*)-*N*-[1'-(2-Furyl)butyl]-2-aminoethanol (7b).** Colourless oil (813 mg, 60%);  $\nu_{\max}$  (film) 3302, 1460 cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.27 (1H, d, *J* 1.5 Hz, OCH=CH), 6.23 (1H, dd, *J* 2.9, *J'* 1.8 Hz, OCH=CH), 6.08 (1H, d, *J* 2.9 Hz, OCH=CHCH), 3.62 (1H, t, *J* 14.3 Hz, NCHCH<sub>2</sub>), 3.58–3.50 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>), 3.49–3.44 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.68 (2H, s, OH and NH), 2.64–2.53 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 1.73–1.64 (2H, m, NCHCH<sub>2</sub>CH<sub>2</sub>), 1.31–1.13 (2H, m, NCHCH<sub>2</sub>CH<sub>2</sub>), 0.82 (3H, t, *J* 7.3 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>);  $\delta_c$  (62.8 MHz, CDCl<sub>3</sub>) 156.3, 141.5, 109.8, 106.6, 60.9, 55.7, 48.5, 36.8, 19.5, 13.9; *m/z* (CI + {NH<sub>3</sub>}) 184 (MH<sup>+</sup>), 140, 62; HRMS for C<sub>10</sub>H<sub>18</sub>NO<sub>2</sub> MH<sup>+</sup> requires 184.1338, found 184.1339;  $[\alpha]_D^{21} + 29.4$  (*c* = 0.93, EtOH).

**(*R*)-*N*-[1'-(2-Furyl)-3'-phenylpropyl]-2-aminoethanol (7c).** Colourless oil (900 mg, 62%);  $\nu_{\max}$  (film) 3308 cm<sup>-1</sup>;  $\delta_H$  (250 MHz, CDCl<sub>3</sub>) 7.51 (1H, d, *J* 0.8 Hz, OCH=CH), 7.36–7.07 (5H, m, Ph), 6.31 (1H, dd, *J* 1.9 Hz, *J'* 1.3 Hz, OCH=CH), 6.17 (1H, d, *J* 3.1 Hz, OCH=CHCH), 3.62 (1H, t, *J* 5.9 Hz, NCHCH<sub>2</sub>), 3.59–3.48 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.88 (2H, br s, OH and NH), 2.69–2.50 (4H, m, NCH<sub>2</sub>CH<sub>2</sub> and NCHCH<sub>2</sub>CH<sub>2</sub>), 2.18–1.97 (2H, m, NCHCH<sub>2</sub>);  $\delta_c$  (62.83 MHz, CDCl<sub>3</sub>) 156.0, 141.6, 128.4, 125.9, 109.9, 106.9, 61.0, 60.4, 55.4, 48.6, 36.7, 32.4; *m/z* (CI + {NH<sub>3</sub>}) 246 (MH<sup>+</sup>), 185, 139, 117, 90, 66; HRMS for C<sub>15</sub>H<sub>20</sub>NO<sub>2</sub> MH<sup>+</sup> requires 246.1494, found 246.1489;  $[\alpha]_D^{19} + 31.7$  (*c* = 1.0, EtOH).

**(*R*)-*N*-[1'-(2-Furyl)-3',3'-dimethylbutyl]-2-aminoethanol (7d).** Colourless oil (642 mg, 69%);  $\nu_{\max}$  3299, 1504, 1365 cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CD<sub>3</sub>OD) 7.42 (1H, s, OCH=CH), 6.33 (1H, d, *J* 1.6 Hz, OCH=CH), 6.25 (1H, d, *J* 2.9 Hz, OCH=CHCH), 3.79 (1H, dd, *J* 6.2, *J'* 3.4 Hz, NCHCH<sub>2</sub>), 3.59–3.48 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.56 (2H, t, *J* 5.3 Hz, NCH<sub>2</sub>CH<sub>2</sub>), 2.52 (2H, br s, OH and NH), 1.91 (1H, dd, *J* 9.8, *J'* 3.8 Hz, NCH<sub>2</sub>C'Bu), 1.63 (1H, dd, *J* 10.2, *J'* 3.5 Hz, NCHCH<sub>2</sub>C'Bu), 0.81 (9H, s, NCHCH<sub>2</sub>C'Bu);  $\delta_c$  (67.9 MHz, CD<sub>3</sub>OD) 157.2, 142.6, 130.0, 129.4, 127.2, 111.9, 108.6, 61.4, 54.3, 40.3, 31.3, 29.6; *m/z* (CI + {NH<sub>3</sub>}) 212 (MH<sup>+</sup>) 151, 140, 95, 57; HRMS for C<sub>12</sub>H<sub>22</sub>NO<sub>2</sub> requires 212.1651, found 212.1641;  $[\alpha]_D^{24} + 36.4$  (*c* = 1.5, EtOH).

**(*R*)-*N*-[1'-(2-Furyl)-2'-benzyloxyethyl]-2-aminoethanol (7e).** Colourless oil (189 mg, 47%);  $\nu_{\max}$  (film) 3408 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.42–7.17 (6H, m, Ph and OCH=CH), 6.31 (1H, dd, *J* 1.8, *J'* 1.5 Hz, OCH=CH), 6.26 (1H, d, *J* 2.9 Hz, OCH=CHCH), 4.53 (2H, dd, *J* 12.0, *J'* 2.5 Hz, NCHCH<sub>2</sub>O), 4.15 (1H, t, *J* 6.2 Hz, NCHCH<sub>2</sub>), 3.70 (2H, d, *J* 6.2 Hz, CH<sub>2</sub>OCH<sub>2</sub>Ph), 3.64–3.52 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 3.41 (2H, br s, OH and NH), 2.71 (2H, t, *J* 5.1 Hz, NCH<sub>2</sub>CH<sub>2</sub>);  $\delta_c$  (67.89 MHz, CDCl<sub>3</sub>) 153.4, 141.9, 137.8, 128.4, 128.1, 110.2, 107.5, 73.2, 71.7, 60.8, 55.8, 48.6; *m/z* (CI + {NH<sub>3</sub>}) 262 (MH<sup>+</sup>), 201, 140, 122, 91, 65; HRMS for C<sub>15</sub>H<sub>20</sub>NO<sub>3</sub> MH<sup>+</sup> requires 262.1443, found 262.1445;  $[\alpha]_D^{24} + 20.7$  (*c* = 0.19, EtOH).

#### General procedure for (*R*)-*N*-[1'-(2-furyl)alkyl]-*N*-[2-(*p*-tolylsulfonyl)ethyl]toluene-*p*-sulfonamides (8a–e)

To a solution of the amino alcohols (7a–e) (1 mmol) in DCM (8 ml) at 0 °C, were added triethylamine (2.5 mmol) and toluene-*p*-sulfonic anhydride (2.5 mmol). The reaction was warmed to room temperature and stirred for 3 days, until TLC showed no starting material or monotosylated products. The reaction was then added to a separating funnel and shaken with ether (20 ml) and HCl (2 M, 10 ml). The organic layer was further washed with sodium bicarbonate (5% w/w, 10 ml), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was rapidly purified by flash column chromatography (silica, typically 6:4 ether–petrol), and used directly in the next step. Mass spectrometric analysis was not possible due to instability of the compounds under the chemical ionisation conditions.

**(R)-N-[1'-(2-Furyl)pentyl]-N-[2-(*p*-tolylsulfonyl)ethyl]-toluene-*p*-sulfonamide (8a).** Colourless solid (82 mg, 64%); mp 59–63 °C;  $\nu_{\max}$  (film) 1599  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.75 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.66 (2H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.35 (2H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.26 (2H, d,  $J$  8.1 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.14 (1H, d,  $J$  1.6 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 6.20 (1H, dd,  $J$  3.1,  $J'$  1.8 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 6.04 (1H, d,  $J$  3.2 Hz,  $\text{CHCH}=\text{CH}-\text{O}$ ), 4.92 (1H, t,  $J$  7.6 Hz,  $\text{CH}_2\text{NCH}$ ), 4.08–3.95 (1H, m,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.91–3.82 (1H, m,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.32–3.14 (2H, m,  $\text{NCH}_2\text{CH}_2\text{O}$ ), 2.46 (3H, s,  $\text{C}_6\text{H}_4\text{CH}_3$ ), 2.42 (3H, s,  $\text{C}_6\text{H}_4\text{CH}_3$ ), 1.92–1.79 (1H, m,  $\text{CHHCH}_2\text{CH}_2\text{CH}_3$ ), 1.69–1.56 (1H, m,  $\text{CHHCH}_2\text{CH}_2\text{CH}_3$ ), 1.36–1.15 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.85 (3H, t,  $J$  7.2 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (50.3 MHz,  $\text{CDCl}_3$ ) 152.0, 145.0, 143.6, 142.2, 136.6, 132.6, 129.9, 129.5, 128.0, 127.5, 110.2, 108.7, 68.4, 55.4, 42.4, 31.3, 28.3, 22.2, 21.6, 21.5, 13.9;  $[\alpha]_{\text{D}}^{25} + 72.8$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

**(R)-N-[1'-(2-Furyl)butyl]-N-[2-(*p*-tolylsulfonyl)ethyl]toluene-*p*-sulfonamide (8b).** Colourless oil (1.43 g, 88%);  $\nu_{\max}$  (film) 1361, 1179  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 7.84 (1H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.65 (1H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.35 (1H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.25 (1H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.13 (1H, dd,  $J$  3.8,  $J'$  1.8 Hz,  $\text{OCH}=\text{CH}$ ), 6.20 (1H, dd,  $J$  1.4,  $J'$  1.9 Hz,  $\text{OCH}=\text{CH}$ ), 6.04 (1H, d,  $J$  3.3 Hz,  $\text{OCH}=\text{CHCH}$ ), 4.94 (1H, t,  $J$  7.6 Hz,  $\text{NCHCH}_2$ ), 4.03–4.00 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.91–3.87 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.26–3.18 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.46 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.42 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 1.89–1.78 (1H, m,  $\text{NCHCH}_2$ ), 1.65–1.60 (1H, m,  $\text{NCHCH}_2$ ), 1.32–1.80 (2H, m,  $\text{NCHCH}_2-\text{CH}_2$ ), 0.89 (3H, t,  $J$  7.4 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 154.2, 144.4, 142.6, 142.3, 141.8, 137.9, 129.9, 129.5, 128.0, 127.6, 109.6, 108.0, 67.7, 55.0, 42.1, 33.9, 22.1, 19.4, 14.1;  $[\alpha]_{\text{D}}^{25} + 63.2$  ( $c = 1.0$ ,  $\text{EtOH}$ ).

**(R)-N-[1'-(2-Furyl)-3'-phenylpropyl]-N-[2-(*p*-tolylsulfonyl)ethyl]toluene-*p*-sulfonamide (8c).** Colourless oil (1.39 g, 75%);  $\nu_{\max}$  (film) 1364, 1178  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.85 (2H, d,  $J$  8.1 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.71 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.59 (2H, d,  $J$  8.1 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.53 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.31–7.17 (6H, m, Ph and  $\text{OCH}=\text{CH}$ ), 6.22 (1H, d,  $J$  1.8 Hz,  $\text{OCH}=\text{CH}$ ), 6.07 (1H, d,  $J$  3.3 Hz,  $\text{OCH}=\text{CHCH}$ ), 4.95 (1H, t,  $J$  7.5 Hz,  $\text{NCHCH}_2$ ), 4.06–4.01 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.93–3.89 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.30–3.23 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.59–2.54 (2H, m,  $\text{NCHCH}_2\text{CH}_2$ ), 2.44 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.42 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.23 (1H, m,  $\text{NCHCH}_2\text{CH}_2$ ), 1.94–1.90 (1H, m,  $\text{NCHCH}_2\text{CH}_2$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 151.9, 145.4, 144.0, 142.8, 141.2, 136.8, 133.0, 130.3, 130.0, 129.0, 128.9, 128.4, 127.9, 126.6, 110.7, 109.6, 68.9, 66.3, 55.4, 43.1, 33.8, 32.9, 22.0, 15.7;  $[\alpha]_{\text{D}}^{20} + 51.0$  ( $c = 0.61$ ,  $\text{EtOH}$ ).

**(R)-N-[1'-(2-Furyl)-3',3'-dimethylbutyl]-N-[2-(*p*-tolylsulfonyl)ethyl]toluene-*p*-sulfonamide (8d).** Colourless oil (294 mg, 79%);  $\nu_{\max}$  (film) 1365, 1343, 1177, 1160  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 7.75 (2H, d,  $J$  19.1 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.64 (2H, d,  $J$  21.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.35 (2H, d,  $J$  21.8 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.26 (2H,  $J$  20.0 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.19 (1H, d,  $J$  0.73 Hz,  $\text{OCH}=\text{CH}$ ), 6.20 (1H, dd,  $J$  1.8,  $J'$  1.5 Hz,  $\text{OCH}=\text{CH}$ ), 6.01, (1H, d,  $J$  3.3 Hz,  $\text{OCH}=\text{CHCH}$ ), 5.00 (1H, dd,  $J$  7.6,  $J'$  3.1 Hz,  $\text{NCHCH}_2$ ), 4.04 (1H, dt,  $J$  10.3,  $J'$  7.6 Hz,  $\text{NCH}_2\text{CH}_2$ ), 3.73 (1H, dt,  $J$  10.2,  $J'$  6.9 Hz,  $\text{NCH}_2\text{CH}_2$ ), 3.35 (2H, t,  $J$  7.1 Hz,  $\text{NCH}_2\text{CH}_2$ ), 2.45 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.41 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.05 (1H, dd,  $J$  10.5,  $J'$  2.9 Hz,  $\text{NCHCH}_2$ ), 1.38 (1H, dd,  $J$  10.5,  $J'$  2.9 Hz,  $\text{NCHCH}_2$ ), 0.75 (9H, s,  $\text{NCHCH}_2\text{tBu}$ );  $\delta_{\text{C}}$  (67.9 MHz,  $\text{CDCl}_3$ ) 152.4, 144.9, 143.5, 141.8, 136.6, 132.7, 130.0, 129.5, 128.3, 127.4, 110.5, 108.8, 68.2, 52.2, 45.2, 42.6, 31.5, 29.3, 21.6;  $[\alpha]_{\text{D}}^{25} + 70.0$  ( $c = 1.0$ ,  $\text{EtOH}$ ).

**(R)-N-[1'-(2-Furyl)-2'-benzyloxyethyl]-N-[2-(*p*-tolylsulfonyl)ethyl]toluene-*p*-sulfonamide (8e).** Colourless oil (143 mg, 78%);  $\nu_{\max}$  (film) 1360, 1170  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 7.76–7.63 (4H, m,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.43–7.10 (10H, m, Ph,  $\text{OCH}=\text{CH}$  and  $\text{C}_6\text{H}_4\text{Me}$ ), 6.22 (1H, dd,  $J$  1.8,  $J'$  1.5 Hz,  $\text{OCH}=\text{CH}$ ), 6.14 (1H,

d,  $J$  4.7 Hz,  $\text{OCH}=\text{CHCH}$ ), 5.26 (1H, t,  $J$  6.4 Hz,  $\text{NCHCH}_2$ ), 4.47 (2H, dd,  $J$  12.0,  $J'$  6.4 Hz,  $\text{NCHCH}_2$ ), 4.13–4.04 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.94–3.82 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 3.78 (2H, d,  $J$  6.7 Hz,  $\text{NCHCH}_2\text{OCH}_2$ ), 3.36–3.16 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.44 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.39 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ );  $\delta_{\text{C}}$  (67.8 MHz,  $\text{CDCl}_3$ ) 149.8, 145.0, 144.9, 143.5, 142.4, 132.7, 132.3, 137.5, 136.4, 130.0, 128.4, 129.9, 128.7, 127.6, 110.4, 109.5, 73.1, 69.2, 68.9, 68.2, 54.7, 43.0, 31.5, 21.6, 21.5;  $[\alpha]_{\text{D}}^{25} + 31.8$  ( $c = 0.3$ ,  $\text{DCM}$ ).

#### General procedure for (R)-N-[1'-(2-furyl)alkyl]-N-(2-phenylselenoethyl)toluene-*p*-sulfonamides (9a–e)

Sodium borohydride (3.0 mmol) was added portion-wise to a suspension of diphenyl diselenide (1.1 mmol) in ethanol (15 ml). The mixture was stirred for 30 mins until a colourless solution resulted. The ditosylate (8a–e) (1.0 mmol) was then added in THF (1 ml) and the reaction heated to reflux for 5 h. After cooling to room temperature, the mixture was shaken with sodium hydroxide (2 M, 50 ml) and ether (50 ml). The aqueous layer was further washed with ether (50 ml) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The *aryl selenide* was then purified by flash column chromatography (silica, typically 7:3 petrol–ether).

**(R)-N-[1'-(2-Furyl)pentyl]-N-(2-phenylselenoethyl)toluene-*p*-sulfonamide (9a).** Colourless crystals (737 mg, 92%); mp 30–32 °C;  $\nu_{\max}$  (film) 1598, 1579, 1339, 1160  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.59 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.49–7.40 (2H, m,  $\text{SePh}$ ), 7.29–7.25 (3H, m,  $\text{SePh}$ ), 7.19 (2H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.14 (1H, d,  $J$  1.4 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 6.18 (1H, dd,  $J$  3.1,  $J'$  1.9 Hz,  $\text{CH}=\text{CH}-\text{O}$ ), 5.91 (1H, d,  $J$  3.3 Hz,  $\text{CHCH}=\text{CH}-\text{O}$ ), 4.98 (1H, t,  $J$  7.7 Hz,  $\text{CH}_2\text{NCH}$ ), 3.21–3.10 (2H, m,  $\text{NCH}_2\text{CH}_2\text{SePh}$ ), 2.95–2.83 (1H, m,  $\text{NCHHCH}_2\text{SePh}$ ), 2.78–2.68 (1H, m,  $\text{NCHHCH}_2\text{SePh}$ ), 2.40 (3H, s,  $\text{C}_6\text{H}_4\text{CH}_3$ ), 1.78–1.71 (1H, m,  $\text{CHHCH}_2\text{CH}_2\text{CH}_3$ ), 1.67–1.50 (1H, m,  $\text{CHHCH}_2\text{CH}_2\text{CH}_3$ ), 1.34–1.15 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.85 (3H, t,  $J$  6.6 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.9 MHz,  $\text{CDCl}_3$ ) 152.6, 142.9, 141.9, 137.5, 132.9, 129.2, 129.0, 128.0, 127.3, 127.0, 110.1, 108.3, 55.1, 44.8, 31.4, 28.4, 26.7, 22.2, 21.4, 13.8;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 491 ( $\text{MH}^+$ ), 336, 198, 137; HRMS for  $\text{C}_{24}\text{H}_{30}\text{NO}_3\text{Se}$   $\text{MH}^+$  requires 491.1033, found 491.1023;  $[\alpha]_{\text{D}}^{24} + 52.6$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

**(R)-N-[1'-(2-Furyl)butyl]-N-(2-phenylselenoethyl)toluene-*p*-sulfonamide (9b).** Colourless oil (933 mg, 76%);  $\nu_{\max}$  (film) 1341, 1162, 739, 724  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.59 (2H, d,  $J$  8.3 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.46–7.45 (2H, m,  $\text{Ph}$ ), 7.29–7.26 (3H, m,  $\text{Ph}$ ), 7.19 (2H, d,  $J$  8.0 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.14 (1H, d,  $J$  50.8 Hz,  $\text{OCH}=\text{CH}$ ), 6.18 (1H, dd,  $J$  1.9,  $J'$  1.4 Hz,  $\text{OCH}=\text{CH}$ ), 5.91 (1H, d,  $J$  7.7 Hz,  $\text{OCH}=\text{CHCH}$ ), 5.00 (1H, t,  $J$  7.7 Hz,  $\text{NCHCH}_2$ ), 3.21–3.14 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.92–2.81 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.78–2.72 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.39 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 1.81–1.76 (1H, m,  $\text{NCHCH}_2$ ), 1.61–1.56 (1H, m,  $\text{NCHCH}_2$ ), 1.37–1.29 (2H, m,  $\text{NCHCH}_2\text{CH}_2$ ), 0.89 (3H, t,  $J$  7.3 Hz,  $\text{NCHCH}_2\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 153.0, 143.5, 142.4, 137.8, 133.3, 129.8, 129.1, 128.7, 127.2, 127.8, 110.5, 108.7, 55.3, 45.1, 34.2, 27.1, 21.9, 19.9, 15.7;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 477 ( $\text{M}^+$ ), 353, 322, 184, 123, 81; HRMS for  $\text{C}_{23}\text{H}_{26}\text{NSO}_3\text{Se}$   $\text{M}^+$  requires 477.0877, found 477.0864;  $[\alpha]_{\text{D}}^{20} + 29.0$  ( $c = 0.95$ ,  $\text{EtOH}$ ).

**(R)-N-[1'-(2-Furyl)-3'-phenylpropyl]-N-(2-phenylselenoethyl)toluene-*p*-sulfonamide (9c).** Colourless oil (1.04 g, 90%);  $\nu_{\max}$  (film) 1341, 1158, 738, 712  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 7.47 (2H, d,  $J$  10.7 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.26–7.08 (11H, m,  $\text{OCH}=\text{CH}$ ,  $\text{SePh}$  and  $\text{Ph}$ ), 7.02 (2H, d,  $J$  6.7 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 6.13 (1H, dd,  $J$  1.8,  $J'$  1.4 Hz,  $\text{OCH}=\text{CH}$ ), 5.86 (1H, d,  $J$  3.3 Hz,  $\text{OCH}=\text{CHCH}$ ), 4.95 (1H, t,  $J$  7.7 Hz,  $\text{NCHCH}_2$ ), 3.17–3.10 (2H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.91–2.80 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.75–2.66 (1H, m,  $\text{NCH}_2\text{CH}_2$ ), 2.53 (2H, t,  $J$  7.5 Hz,  $\text{NCHCH}_2\text{CH}_2$ ), 2.33

(3H, s, C<sub>6</sub>H<sub>4</sub>Me), 2.12–2.03 (1H, m, NCHCH<sub>2</sub>), 1.84–1.58 (1H, m, NCHCH<sub>2</sub>);  $\delta_C$  (62.8 MHz, CDCl<sub>3</sub>) 152.4, 143.6, 142.6, 141.3, 137.6, 133.4, 129.8, 129.1, 129.5, 128.8, 128.9, 127.8, 127.6, 110.7, 109.1, 55.2, 45.4, 33.9, 33.0, 27.2, 21.9; *m/z* (CI + {NH<sub>3</sub>}) 539 (M<sup>+</sup>), 384, 198, 185, 91; HRMS for C<sub>28</sub>H<sub>29</sub>NO<sub>3</sub>SSe MH<sup>+</sup> requires 539.1033, found 5239.1035; [α]<sub>D</sub><sup>25</sup> +25.2 (*c* = 1.0, EtOH).

**(R)-N-[1'-(2-Furyl)-3',3'-dimethylbutyl]-N-(2-phenylselenoethyl)toluene-*p*-sulfonamide (9d).** Colourless oil (276 mg, 85%);  $\nu_{\max}$  (film) 1338, 1158, 738, 717 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.57 (2H, d, *J* 6.9 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.54–7.45 (2H, m, Ph), 7.31–7.23 (3H, m, Ph), 7.15 (2H, d, *J* 6.7 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.14 (1H, d, *J* 1.8 Hz, OCH=CH), 6.19 (1H, dd, *J* 2.0, *J'* 1.3 Hz, OCH=CH), 5.93 (1H, d, *J* 3.3 Hz, OCH=CHCH), 5.06 (1H, dd, *J* 7.4, *J'* 3.1 Hz, NCHCH<sub>2</sub>), 3.41–3.20 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 3.06–2.91 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.65–2.50 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.39 (3H, s, C<sub>6</sub>H<sub>4</sub>Me), 2.01 (1H, dd, *J* 10.7, *J'* 2.9 Hz, NCHCH<sub>2</sub>), 1.44 (1H, dd, *J* 10.5, *J'* 3.1 Hz, NCHCH<sub>2</sub>), 0.75 (9H, s, 'Bu);  $\delta_C$  (67.9 MHz, CDCl<sub>3</sub>) 152.9, 143.1, 141.6, 137.4, 132.9, 129.4, 129.1, 128.8, 127.3, 127.1, 110.5, 108.6, 52.0, 45.5, 45.2, 30.3, 29.4, 26.7, 21.4; *m/z* (CI + {NH<sub>3</sub>}) 505 (M<sup>+</sup>) 350, 198, 151, 91; HRMS for C<sub>25</sub>H<sub>31</sub>NSO<sub>3</sub>Se M<sup>+</sup> requires 505.1190, found 505.1180; [α]<sub>D</sub><sup>24</sup> +34.5 (*c* = 1.0, EtOH).

**(R)-N-[1'-(2-Furyl)-2'-benzyloxyethyl]-N-(2-phenylselenoethyl)toluene-*p*-sulfonamide (9e).** Colourless oil (176 mg, 78%);  $\nu_{\max}$  (film) 1337, 1160 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.62 (2H, d, *J* 10.4 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.58–7.07 (11H, m, SePh, Ph, OCH=CH), 6.20 (1H, dd, *J* 16.2, *J'* 13.6 Hz, OCH=CH), 6.04 (1H, d, *J* 0.9 Hz, OCH=CHCH), 5.30 (1H, t, *J* 6.4 Hz, NCHCH<sub>2</sub>), 4.44 (2H, dd, *J* 11.8, *J'* 10.9 Hz, NCHCH<sub>2</sub>), 3.79–3.66 (2H, m, NCHCH<sub>2</sub>OCH<sub>2</sub>), 3.33–3.06 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 3.00–2.89 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.76–2.64 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.36 (3H, s, C<sub>6</sub>H<sub>4</sub>Me);  $\delta_C$  (67.9 MHz, CDCl<sub>3</sub>) 150.2, 143.0, 142.2, 137.5, 137.1, 132.7, 129.3, 129.0, 128.4, 127.5, 127.5, 127.3, 110.3, 109.2, 73.1, 69.1, 54.4, 45.3, 26.2, 21.4; *m/z* (CI + {NH<sub>3</sub>}) 556 (MH<sup>+</sup>), 354, 198, 170, 91; HRMS for C<sub>28</sub>H<sub>29</sub>NO<sub>4</sub>SSe M<sup>+</sup> requires 555.0983, found 555.0998; [α]<sub>D</sub><sup>24</sup> +23.4 (*c* = 1.0, EtOH).

#### General procedure for (R)-N-[1'-(2-furyl)alkyl]toluene-*p*-sulfonamides (10a–e)

The phenyl selenides (9a–e) (1 mmol) were dissolved in methanol (25 ml). Sodium bicarbonate (1.25 mmol) and sodium periodate (3.0 mmol) in water (4.5 ml) were added and the mixture stirred for 1 hour. The suspension was shaken with water (25 ml) and DCM (70 ml). The layers were separated and the aqueous layer extracted further with DCM (1 × 40 ml), dried over magnesium sulfate, filtered and solvent removed. The selenoxides were then added to refluxing dioxane (75 ml) in DCM (1 ml) under nitrogen. After 1 hour, HCl (2 M, 1.5 ml) was added with refluxing for a further hour. The reaction was then cooled, triethylamine (1 ml) added and the solvent removed under reduced pressure. The residue was then taken up in DCM (25 ml) and washed with water (2 × 25 ml). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude oil was the purified by flash column chromatography (silica, typically 6:4 petrol–ether).

**(R)-N-[1'-(2-Furyl)pentyl]toluene-*p*-sulfonamide (10a).** Colourless needles (169 mg, 82%); mp 73–76 °C;  $\nu_{\max}$  (film) 3278 cm<sup>-1</sup>;  $\delta_H$  (250 MHz, CDCl<sub>3</sub>) 7.61 (2H, d, *J* 8.3 Hz, C<sub>6</sub>H<sub>4</sub>), 7.20 (2H, d, *J* 8.1 Hz, C<sub>6</sub>H<sub>4</sub>), 7.14–7.13 (1H, m, OCH=CH), 6.12 (1H, dd, *J* 3.2, *J'* 1.8 Hz, OCH=CH), 5.89 (1H, d, *J* 3.2 Hz, OCH=CHCH), 4.77 (1H, br d, *J* 8.7 Hz, TsNH), 4.39 (1H, q, *J* 7.8 Hz, NCHCH<sub>2</sub>), 2.39 (3H, s, C<sub>6</sub>H<sub>4</sub>Me), 1.77 (2H, q, *J* 7.3 Hz, NCHCH<sub>2</sub>CH<sub>2</sub> and NCHCH<sub>2</sub>CH<sub>2</sub>), 1.29–1.12 (4H, m), 0.84 (3H, t, *J* 7.0 Hz, CH<sub>3</sub>);  $\delta_C$  (62.9 MHz, CDCl<sub>3</sub>) 141.6, 129.2,

126.9, 109.8, 106.6, 51.7, 34.6, 27.6, 22.0, 21.3, 13.7; *m/z* (EI+) 307 (M<sup>+</sup>), 250, 155, 152, 91; C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub>S requires C, 62.5; H, 6.90; N, 4.55%, found C, 62.4; H, 7.00; N, 4.80%; [α]<sub>D</sub><sup>20</sup> +56.4 (*c* = 1.0, EtOH) [lit.<sup>14</sup> (ent-10a) [α]<sub>D</sub><sup>20</sup> -5.0 (*c* = 0.83, EtOH)].

**(R)-N-[1'-(2-Furyl)butyl]toluene-*p*-sulfonamide (10b).** Colourless solid (154 mg, 83%); mp 84–85 °C (lit.<sup>14</sup> mp 94–95 °C);  $\nu_{\max}$  (KBr disk) 3437, 1320, 1124 cm<sup>-1</sup>;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.60 (2H, d, *J* 8.3 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.17 (2H, d, *J* 8.0 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.12 (1H, d, *J* 1.1 Hz, OCH=CH), 6.09 (1H, dd, *J* 3.2, *J'* 1.4 Hz, OCH=CH), 5.88 (1H, d, *J* 3.2 Hz, OCH=CHCH), 4.87 (1H, br d, *J* 8.6 Hz, TsNH), 4.39 (1H, dd, *J* 16.0, *J'* 8.6 Hz, NCHCH<sub>2</sub>), 2.88 (3H, s, C<sub>6</sub>H<sub>4</sub>Me), 1.79–1.70 (2H, m, NCHCH<sub>2</sub>), 1.38–1.17 (2H, m, NCHCH<sub>2</sub>CH<sub>2</sub>), 0.85 (3H, t, *J* 7.3 Hz, CH<sub>3</sub>);  $\delta_C$  (62.8 MHz, CDCl<sub>3</sub>) 153.4, 143.4, 142.1, 138.1, 129.7, 127.4, 110.3, 107.2, 51.9, 37.4, 21.9, 19.3, 13.9; *m/z* (CI + {NH<sub>3</sub>}) 294 (MH<sup>+</sup>) 250, 155, 138, 123, 108, 91, 65; HRMS for C<sub>15</sub>H<sub>20</sub>NSO<sub>3</sub> MH<sup>+</sup> requires 294.1164, found 294.1161; [α]<sub>D</sub><sup>24</sup> +50.7 (*c* = 0.18, EtOH) [lit.<sup>14</sup> (ent-10b) [α]<sub>D</sub><sup>20</sup> -5.3 (*c* = 1.0, EtOH)].

**(R)-N-[1'-(2-Furyl)-3'-phenylpropyl]toluene-*p*-sulfonamide (10c).** Colourless solid (304 mg, 84%); mp 78–81 °C;  $\nu_{\max}$  (KBr disc) 3287, 1343, 1155 cm<sup>-1</sup>;  $\delta_H$  (250 MHz, CDCl<sub>3</sub>) 7.59 (2H, d, *J* 10.3 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.26–7.07 (8H, m, OCH=CH, Ph and C<sub>6</sub>H<sub>4</sub>Me), 6.11 (1H, dd, *J* 1.9, *J'* 1.4 Hz, OCH=CH), 5.90 (1H, d, *J* 3.2 Hz, OCH=CHCH), 5.05 (1H, d, *J* 14.4 Hz, TsNH), 4.40 (1H, q, *J* 7.3 Hz, NCHCH<sub>2</sub>), 2.63–2.50 (2H, m, NCHCH<sub>2</sub>), 2.37 (3H, s, C<sub>6</sub>H<sub>4</sub>Me), 2.08 (2H, q, *J* 7.9 Hz, NCHCH<sub>2</sub>CH<sub>2</sub>);  $\delta_C$  (62.8 MHz, CDCl<sub>3</sub>) 152.6, 143.1, 142.0, 140.8, 137.6, 129.4, 128.4, 127.0, 126.1, 109.9, 107.1, 51.3, 36.5, 31.8, 21.5; *m/z* (CI + {NH<sub>3</sub>}) 356 (MH<sup>+</sup>), 288, 250, 185, 155, 117, 91, 69; HRMS for C<sub>20</sub>H<sub>22</sub>NO<sub>3</sub>S MH<sup>+</sup> requires 356.1320, found 356.1317; [α]<sub>D</sub><sup>20</sup> +47.4 (*c* = 1.0, EtOH).

**(R)-N-[1'-(2-Furyl)-3',3'-dimethylbutyl]toluene-*p*-sulfonamide (10d).** Colourless solid (112 mg, 72%); mp 93–94 °C;  $\nu_{\max}$  (KBr disk) 3278, 1317, 1154 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.56 (2H, d, *J* 8.1 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.15 (2H, d, *J* 8.1 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.09 (1H, d, *J* 1.8, OCH=CH), 6.04 (1H, dd, *J* 1.8 Hz, *J'* 1.1 Hz, OCH=CH), 5.82 (1H, d, *J* 2.0 Hz, OCH=CHCH), 4.96 (1H, br d, *J* 8.7 Hz, TsNH), 4.52 (1H, q, *J* 6.2 Hz, NCHCH<sub>2</sub>), 2.37 (3H, s, C<sub>6</sub>H<sub>4</sub>Me), 1.84–1.65 (2H, m, NCHCH<sub>2</sub>), 0.82 (9H, s, 'Bu);  $\delta_C$  (67.9 MHz, CDCl<sub>3</sub>) 153.5, 142.8, 141.4, 132.6, 129.5, 126.9, 109.9, 106.7, 65.5, 49.2, 48.2, 30.2, 29.6, 21.4; *m/z* (CI + {NH<sub>3</sub>}) 322 (MH<sup>+</sup>), 250, 166, 151, 91; HRMS for C<sub>17</sub>H<sub>24</sub>NSO<sub>3</sub> MH<sup>+</sup> requires 322.1477, found 322.1501; [α]<sub>D</sub><sup>21</sup> +45.0 (*c* = 1.0, EtOH).

**(R)-N-[1'-(2-Furyl)-2'-benzyloxyethyl]toluene-*p*-sulfonamide (10e).** Colourless solid (90 mg, 82%); mp 86–87 °C;  $\nu_{\max}$  (KBr disc) 3441, 1314, 1161 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 7.68 (2H, d, *J* 8.1 Hz, C<sub>6</sub>H<sub>4</sub>Me), 7.33–7.27 (3H, m, Ph), 7.22–7.16 (5H, m, C<sub>6</sub>H<sub>4</sub>Me, Ph and OCH=CH), 6.20 (1H, dd, *J* 3.3, *J'* 1.8 Hz, OCH=CHCH), 6.12 (1H, dt, *J* 3.3, *J'* 0.7 Hz, OCH=CHCH), 5.40 (1H, br d, *J* 7.6 Hz, TsNH), 4.61 (1H, dt, *J* 7.6, *J'* 5.3 Hz, NCHCH<sub>2</sub>), 3.71 (2H, dd, *J* 9.6, *J'* 5.3 Hz, NCHCH<sub>2</sub>), 3.60 (2H, dd, *J* 9.8, *J'* 5.1 Hz, NCHCH<sub>2</sub>OCH<sub>2</sub>), 2.17 (3H, s, C<sub>6</sub>H<sub>4</sub>Me);  $\delta_C$  (67.9 MHz, CDCl<sub>3</sub>) 151.2, 143.2, 141.9, 137.4, 129.4, 128.4, 127.6, 127.1, 110.3, 108.0, 73.1, 70.6, 67.0, 53.7, 51.3, 29.7; *m/z* (CI + {NH<sub>3</sub>}) 371 (M<sup>+</sup>), 250, 201, 155, 91; HRMS for C<sub>20</sub>H<sub>21</sub>NSO<sub>4</sub> M<sup>+</sup> requires 371.1191, found 372.1184; [α]<sub>D</sub><sup>22</sup> +54.3 (*c* = 1.0, EtOH).

#### General procedure for (R)-2-(*p*-tolylsulfonamido) acids (11a–e) and *N*-formyl-(R)-2-(*p*-tolylsulfonamido) acids (12a–e)

To a mixture of water (8 ml), acetonitrile (10 ml) and carbon tetrachloride (8 ml) was added ruthenium dioxide (0.05 mmol)

and sodium periodate (14.67 mmol). The furyl toluenesulfonamide (**10a–e**) (1.0 mmol) was then added in acetonitrile (2 ml) and the reaction rapidly stirred for 1 hour until TLC analysis indicated consumption of starting material. The mixture was then shaken with water (20 ml) and ether (50 ml). The aqueous layer was then further extracted with ether (2 × 50 ml) and DCM (2 × 50 ml). The combined organic layers were dried over magnesium sulfate and filtered through a pad of Celite® and activated charcoal. The solvent was then removed under reduced pressure and the crude oil purified by flash column chromatography (silica, typically 60:40:1 petrol–ether–acetic acid).

**(R)-2-(p-Tolylsulfonamido)norleucine (11a).** Colourless solid (102 mg, 66%); mp 122–123 °C;  $\nu_{\max}$  (KBr disc) 3362, 3246, 1716  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 7.73 (2H, d,  $J$  8.2 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.28 (2H, d,  $J$  8.3 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.08 (1H, br s,  $\text{CO}_2\text{H}$ ), 5.36 (1H, br d,  $J$  8.9 Hz,  $\text{NH}$ ), 3.91 (1H, m,  $\text{CHNHTs}$ ), 2.41 (3H, s,  $\text{C}_6\text{H}_4\text{CH}_3$ ), 1.80–1.53 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.33–1.14 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.84 (3H, t,  $J$  6.9 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.9 MHz,  $\text{CDCl}_3$ ) 176.3, 143.7, 136.8, 129.5, 127.1, 55.3, 32.7, 26.8, 21.9, 21.4, 13.6;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 303 ( $\text{MNH}_4^+$ ), 286 ( $\text{MH}^+$ ), 240, 155, 91; HRMS for  $\text{C}_{13}\text{H}_{20}\text{NO}_5\text{S}$   $\text{MH}^+$  requires 286.1113, found 286.1113;  $[\alpha]_{\text{D}}^{25}$   $-1.9$  ( $c = 2.0$ ,  $\text{CHCl}_3$ ).

**N-Formyl-(R)-2-(p-tolylsulfonamido)norleucine (12a).** Colourless oil (15 mg, 9%);  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 9.03 (1H, s,  $\text{NCHO}$ ), 7.76 (2H, d,  $J$  8.3 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.57 (1H, br s,  $\text{CO}_2\text{H}$ ), 7.36 (2H, d,  $J$  8.1 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.08 (1H, br s,  $\text{CO}_2\text{H}$ ), 4.46 (1H, dd,  $J$  8.9,  $J'$  5.5 Hz,  $\text{CHNCHO}$ ), 2.45 (3H, s,  $\text{C}_6\text{H}_4\text{CH}_3$ ), 2.20–1.85 (2H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.36–1.08 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.82 (3H, t,  $J$  6.9 Hz,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.9 MHz,  $\text{CDCl}_3$ ) 173.5, 161.0, 145.6, 134.9, 129.9, 127.8, 57.1, 28.6, 28.5, 22.1, 21.6, 13.6.

**(R)-2-(p-Tolylsulfonamido)norvaline (11b).** Colourless solid (117 mg, 71%); mp 91–93 °C;  $\nu_{\max}$  (KBr disc) 3265, 2854, 2924, 1334, 1160  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.73 (2H, d,  $J$  8.3 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.27 (2H, d,  $J$  8.3 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 5.47 (1H, br s,  $\text{TsNH}$ ), 3.97–3.88 (1H, m,  $\text{NCHCH}_2$ ), 2.41 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 1.75–1.58 (2H, m,  $\text{NCHCH}_2$ ), 1.44–1.26 (2H, m,  $\text{NCHCH}_2\text{CH}_2$ ), 0.87 (3H, t,  $J$  6.9 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 177.1, 143.9, 136.6, 129.7, 127.2, 55.2, 35.0, 21.5, 18.2, 13.4;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 272 ( $\text{MH}^+$ ), 226, 155, 139, 116, 91, 72; HRMS for  $\text{C}_{12}\text{H}_{18}\text{NSO}_4$   $\text{MH}^+$  requires 272.0957, found 272.0961;  $[\alpha]_{\text{D}}^{19}$   $-1.02$  ( $c = 1.0$ ,  $\text{EtOH}$ ).

**N-Formyl-(R)-2-(p-tolylsulfonamido)norvaline (12b).** Colourless oil (14 mg, 7%);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 9.04 (1H, s,  $\text{NCHO}$ ), 7.97 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.38 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 4.47 (1H, m,  $\text{NCHCH}_2$ ), 2.46 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 1.75–1.48 (2H, m,  $\text{NCHCH}_2$ ), 1.44–1.26 (2H, m,  $\text{NCHCH}_2\text{CH}_2$ ), 0.85 (3H, t,  $J$  7.1 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 161.4, 145.8, 134.8, 130.1, 127.9, 126.4, 54.1, 30.8, 21.7, 19.7, 13.0.

**(R)-2-(p-Tolylsulfonamido)phenylalanine (11c).** Colourless solid (99 mg, 68%); mp 91–93 °C;  $\nu_{\max}$  (KBr disc) 3265, 2854, 2924, 1334, 1160  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 7.68 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.34–7.28 (5H, m, Ph), 7.27 (2H, d,  $J$  6.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 5.60 (1H, br d,  $J$  8.9 Hz,  $\text{TsNH}$ ), 3.99–3.90 (1H, m,  $\text{NCHCH}_2$ ), 2.69–2.62 (2H, m,  $\text{NCHCH}_2$ ), 2.39 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.07–1.91 (2H, m,  $\text{NCHCH}_2\text{CH}_2$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 177.1, 143.9, 136.6, 131.4, 129.7, 128.3, 127.2, 56.2, 55.2, 35.0, 21.5, 18.2, 13.4;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 334 ( $\text{MH}^+$ ), 288, 178, 134, 91, 65; HRMS for  $\text{C}_{17}\text{H}_{20}\text{NSO}_4$   $\text{MH}^+$  requires 334.1113, found 334.1109;  $[\alpha]_{\text{D}}^{20}$   $-1.02$  ( $c = 1.0$ ,  $\text{EtOH}$ ).

**N-Formyl-(R)-2-(toluene-p-sulfonamido)phenylalanine (12c).**

Colourless oil (18 mg, 11%);  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 9.04 (1H, s,  $\text{NCHO}$ ), 7.79 (2H, d,  $J$  8.4 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.38 (2H, d,  $J$  8.6 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.28–7.11 (5H, Ph, m), 4.46 (1H, dd,  $J$  6.0,  $J'$  2.1 Hz,  $\text{NCHCH}_2$ ), 2.44 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 1.75–1.48 (2H, m,  $\text{NCHCH}_2$ ), 1.44–1.26 (2H, m,  $\text{NCHCH}_2\text{CH}_2$ );  $\delta_{\text{C}}$  (62.8 MHz,  $\text{CDCl}_3$ ) 178.4, 174.3, 161.4, 145.8, 134.8, 130.1, 127.9, 126.4, 57.4, 30.8, 21.7, 19.7, 13.5.

**(R)-2-(p-Tolylsulfonamido)neopentylglycine (11d).** Chromatography yielded an inseparable mixture of the *formamide* and the *acid* as a colourless solid (37 mg, 66%);  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.77 (2H, d,  $J$  7.8 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.27 (2H, d,  $J$  8.1 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 5.05 (1H, d,  $J$  10.2 Hz,  $\text{TsNH}$ ), 3.95 (1H, m,  $\text{NCHCH}_2$ ), 2.41 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 1.61 (1H, dd,  $J$  10.9,  $J'$  3.4 Hz,  $\text{NCHCH}_2$ ), 1.44 (1H, dd,  $J$  8.9,  $J'$  5.6 Hz,  $\text{NCHCH}_2$ ), 0.91 (s, 'Bu).

**N-Formyl-(R)-2-(p-tolylsulfonamido)neopentylglycine (12d).**  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 9.02 (1H, s,  $\text{NCHO}$ ), 7.79 (2H, d,  $J$  7.9 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.34 (2H, d,  $J$  8.0 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 4.67 (1H, dd,  $J$  4.9,  $J'$  1.1 Hz,  $\text{NCHCH}_2$ ), 2.46 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ ), 2.27 (1H, dd,  $J$  10.7,  $J'$  4.5 Hz,  $\text{NCHCH}_2$ ), 1.81 (1H, dd,  $J$  8.7,  $J'$  5.9 Hz,  $\text{NCHCH}_2$ ), 0.91 (s, 'Bu).

**N-Formyl-(R)-2-(p-tolylsulfonamido)serine (12e).** Colourless oil (2 mg, 4%);  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 9.01 (1H, s,  $\text{TsNCHO}$ ), 7.76 (2H, d,  $J$  8.9 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.35–7.09 (7H, m, Ph and  $\text{C}_6\text{H}_4\text{Me}$ ), 4.47 (2H, s,  $\text{OCH}_2\text{Ph}$ ), 4.11–4.06 (1H, m,  $\text{NCHCH}_2$ ), 3.86 (1H, dd,  $J$  6.0,  $J'$  3.6 Hz,  $\text{NCHCH}_2$ ), 3.61 (1H, dd,  $J$  5.3,  $J'$  4.4 Hz,  $\text{NCHCH}_2$ ), 2.41 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ );  $\delta_{\text{C}}$  (67.9 MHz,  $\text{CDCl}_3$ ) 172.6, 169.3, 140.7, 135.8, 130.8, 128.1, 127.6, 127.5, 127.1, 69.4, 65.4, 55.4, 22.9.

**(R)-2-(p-Tolylsulfonamido)serine (11e).** Colourless solid (28 mg, 61%); mp 125–128 °C;  $\nu_{\max}$  (KBr disc) 3347, 3281, 1731, 1317, 1164  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 7.70 (2H, d,  $J$  8.6 Hz,  $\text{C}_6\text{H}_4\text{Me}$ ), 7.36–7.13 (7H, m, Ph and  $\text{C}_6\text{H}_4\text{Me}$ ), 5.53 (1H, d,  $J$  8.3 Hz,  $\text{TsNH}$ ), 4.47 (2H, s,  $\text{OCH}_2\text{Ph}$ ), 4.12–4.06 (1H, m,  $\text{NCHCH}_2$ ), 3.86 (1H, dd,  $J$  6.0,  $J'$  3.6 Hz,  $\text{NCHCH}_2$ ), 3.60 (1H, dd,  $J$  5.2,  $J'$  4.4 Hz,  $\text{NCHCH}_2$ ), 2.39 (3H, s,  $\text{C}_6\text{H}_4\text{Me}$ );  $\delta_{\text{C}}$  (67.9 MHz,  $\text{CDCl}_3$ ) 173.0, 143.9, 136.7, 129.8, 128.1, 128.0, 127.8, 127.1, 73.6, 70.1, 55.5, 21.5;  $m/z$  ( $\text{CI} + \{\text{NH}_3\}$ ) 350 ( $\text{MH}^+$ ), 194, 157, 139, 91, 66; HRMS for  $\text{C}_{17}\text{H}_{19}\text{NSO}_5$   $\text{MH}^+$  requires 350.1062, found 350.1073;  $[\alpha]_{\text{D}}^{21}$   $-2.08$  ( $c = 1.0$ ,  $\text{EtOH}$ ).

#### General procedure for (R)- $\alpha$ -amino acid hydrobromide salts (**13a–e**)

To a sample of the toluene-*p*-sulfonated amino acids (**11a–e**) (1 mmol) in hydrobromic acid (30% in  $\text{AcOH}$ , 7 ml) was added phenol (5 mmol) and the reaction mixture was stirred for 24 hours. The aqueous solution was cooled to 0 °C then diluted with water (30 ml) and shaken with ethyl acetate (20 ml). The organic layer was then extracted with water (1 × 15 ml) and the combined aqueous fractions concentrated under reduced pressure and freeze dried, furnishing the *amino acid salts* as pale orange solids. Further purification could be achieved by ion exchange chromatography as required.

**(R)-Norleucine hydrobromide (13a).** Yellow oil (37 mg, quant.),  $\nu_{\max}$  (film) 3447, 2964, 1734, 1617, 1507, 1249  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (250 MHz,  $\text{D}_2\text{O}$ ) 4.02 (1H, t,  $J$  6.2 Hz,  $\text{NCHCO}_2\text{H}$ ), 1.97–1.78 (2H, m,  $\text{NCHCH}_2$ ), 1.40–1.23 (4H, m,  $\text{NCHCH}_2\text{CH}_2$ ), 0.84 (3H, t,  $J$  6.8 Hz,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz,  $\text{D}_2\text{O}$ ) 173.3, 53.9, 30.3, 27.1, 22.4, 13.8;  $m/z$  (FAB) 132 ( $\text{MH}^+$ ), 86, 79; HRMS for  $\text{C}_6\text{H}_{13}\text{NO}_2$   $\text{MH}^+$  requires 132.1821, found 132.2013;  $[\alpha]_{\text{D}}^{27}$   $-10.1$  ( $c = 2.2$ ,  $\text{H}_2\text{O}$ ).

**(R)-Norvaline hydrobromide (13b).** Pale orange solid (22 mg, 78%);  $\nu_{\max}$  (KBr disc) 3146, 2928, 1714  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (250 MHz,  $\text{D}_2\text{O}$ ) 3.69 (1H, t,  $J$  6.30 Hz,  $\text{NCHCO}_2\text{H}$ ), 1.74–1.64 (2H, m,

NCHCH<sub>2</sub>), 1.30–1.21 (2H, m, CHCH<sub>2</sub>CH<sub>2</sub>), 0.81 (3H, t, *J* 5.9 Hz, CH<sub>3</sub>);  $\delta_{\text{C}}$  (62.8 MHz, D<sub>2</sub>O) 173.7, 53.2, 31.1, 16.4, 11.5; *m/z* (FAB) 118 (MH<sup>+</sup>), 72, 43; HRMS for C<sub>5</sub>H<sub>13</sub>NO<sub>2</sub> MH<sup>+</sup> requires 118.0868, found 118.0863;  $[\alpha]_{\text{D}}^{20} +12.6$  (*c* = 1.0, 5 M HBr).

**(R)-Phenylalanine hydrobromide (13c).** Pale orange solid (12 mg, 71%);  $\nu_{\text{max}}$  (KBr disc) 3399, 3017, 1735, 769, 759, 742, 698 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (250 MHz, D<sub>2</sub>O) 7.36–7.22 (5H, m, Ph) 4.02 (1H, t, *J* 6.3 Hz, NCHCO<sub>2</sub>H) 2.79–2.68 (2H, m, NCHCH<sub>2</sub>) 2.33–2.13 (CHCH<sub>2</sub>CH<sub>2</sub>);  $\delta_{\text{C}}$  (62.8 MHz, D<sub>2</sub>O) 174.3, 142.5, 129.2, 128.8, 127.0, 53.4, 32.7, 30.8; *m/z* (CI + {NH<sub>3</sub>}) 180 (MH<sup>+</sup>), 162, 134, 91; HRMS for C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub> MH<sup>+</sup> requires 180.2261, found 180.1016;  $[\alpha]_{\text{D}}^{20} +22.6$  (*c* = 1.0, 5 M HBr).

**(R)-Neopentylglycine hydrobromide (13d).** Pale orange solid (12 mg, 71%);  $\nu_{\text{max}}$  (KBr disc) 3285, 2993, 1683 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (250 MHz, D<sub>2</sub>O) 3.56 (1H, dd, *J* 5.1, *J'* 7.3 Hz, NCHCO<sub>2</sub>H), 1.77 (1H, dd, *J* 4.8, *J'* 15.2 Hz, NCHCH<sub>2</sub>), 1.46 (1H, dd, *J* 7.2, *J'* 14.8 Hz, NCHCH<sub>2</sub>), 0.83 (9H, s, 'Bu);  $\delta_{\text{C}}$  (62.8 MHz, D<sub>2</sub>O) 176.9, 53.8, 45.8, 33.2, 30.6, 29.5, 21.5;  $[\alpha]_{\text{D}}^{20} +3.70$  (*c* = 1.0, 5 M HBr).

**(R)-Serine hydrobromide (13e).** Pale orange solid (33 mg, 78%);  $\nu_{\text{max}}$  (KBr disc) 3337, 2298, 1945, 1728 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (250 MHz, D<sub>2</sub>O) 4.10 (1H, dd, *J* 3.6, *J'* 0.7 Hz NCHCO<sub>2</sub>H) 4.03–3.87 (2H, m, NCHCH<sub>2</sub>);  $\delta_{\text{C}}$  (62.8 MHz, D<sub>2</sub>O) 170.6, 59.7, 55.1; *m/z* (FAB) 106 (MH<sup>+</sup>), 60; HRMS for C<sub>3</sub>H<sub>8</sub>NO<sub>3</sub> MH<sup>+</sup> requires 106.0504, found 106.0499;  $[\alpha]_{\text{D}}^{20} +6.3$  (*c* = 1.0, HBr).

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