Application of a 5-*endo*-trig cyclisation in the total synthesis of (+)-preussin

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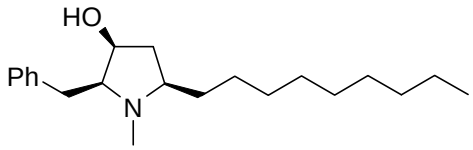
Dedicated to Professor Madeleine M. Joullié on the occasion of her 80th birthday

Abstract
The synthesis of 2,5-*syn* disubstituted pyrrolidines from *N*-SES protected aziridines is described. The key step in the methodology is a 5-*endo*-trig cyclisation. Application of this reaction in the synthesis of (+)-preussin is reported.

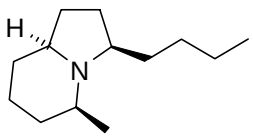
Keywords: Cyclisation, natural products, pyrrolidines, sulfones, total synthesis

Introduction

The pyrrolidine ring system has been identified as an important pharmacophore in many natural products and drug candidates.[1] Representative examples of compounds isolated from nature containing a pyrrolidine ring are the antifungal agent (+)-preussin, **1**,[2] and the pheromone (+)-monomorine I, **2**.[3]



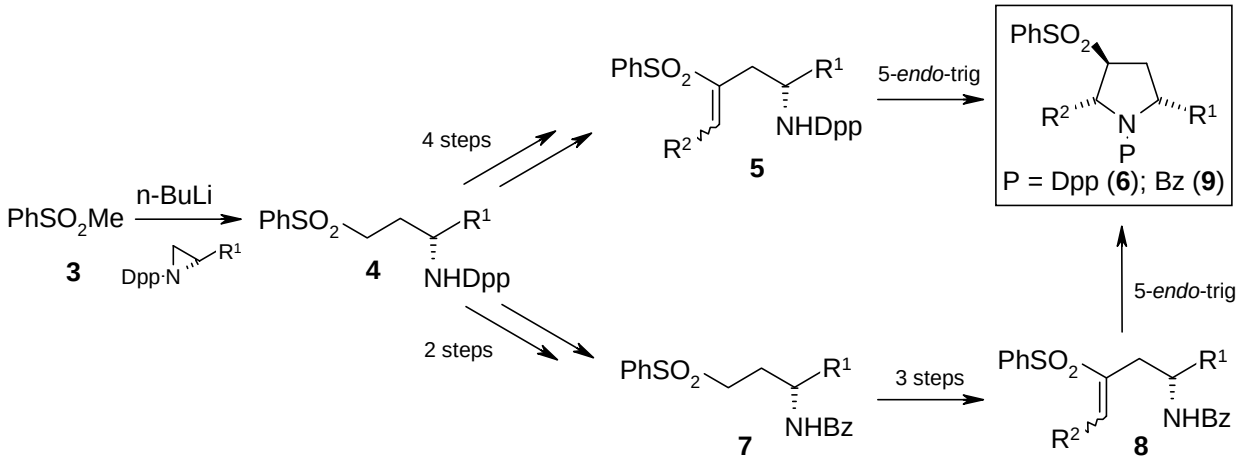
(+)-preussin
1



(+)-monomorine I
2

Figure 1. Natural products containing pyrrolidines.

As a consequence of the widespread occurrence of highly functionalised pyrrolidine containing compounds, there are a number of different methods for their construction.[4] We have been evaluating the use of the 5-*endo*-trig cyclisation (formally disfavoured according to Baldwin's guidelines)[5] for the formation of 2,5-*syn* disubstituted pyrrolidines.[6,7] This methodology is mediated by a sulfone group, which directs two carbon–carbon bond-forming reactions to construct the pyrrolidine framework prior to cyclisation (Scheme 1).



Scheme 1. 5-*Endo*-trig cyclisations to 2,5-*syn*-disubstituted pyrrolidines.

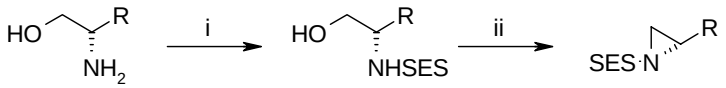
First, enantiomerically pure *N*-diphenylphosphinyl (*N*-Dpp) aziridines, derived from amino acids, were treated with the anion of methylsulfonylbenzene **3**. Double deprotonation of the resulting ring-opened products **4** was followed by introduction of a second electrophile, a non-enolisable acyl halide, to afford a β–keto sulfones (not shown). Further functionalisation gave the vinylic sulfones **5** (in some cases this was a transient species) as a mixture of *E*- and *Z*-isomers. Finally, cyclisation was achieved under basic conditions to give the 2,5-*syn* pyrrolidines **6** stereoselectively (*syn*:*anti* ≥10:1). Using this route a variety of *N*-Dpp pyrrolidines were prepared efficiently in 6 steps from *N*-Dpp aziridines. However, there were limitations in this methodology. The *N*-Dpp aziridines were particularly slow to form (often the cyclisation would take 1-2 weeks to achieve acceptable yields) and also only non-enolisable acid halides could be used in the second carbon–carbon bond-forming reaction.

To circumvent these issues, we investigated the replacement of the Dpp protecting group, via a two-step sequence, to give the benzoyl (Bz) derivative **7**. Double deprotonation of **7** now permitted the reaction with other electrophiles such as aldehydes (alkyl or aryl), which, after subsequent modification provided vinylic sulfones **8** suitable for 5-*endo*-trig cyclisation. This adaptation of the methodology expanded the range of R^2 groups that could be incorporated into the pyrrolidine products **9**. The synthetic utility of this revised protecting group strategy was demonstrated in the efficient enantioselective synthesis of (+)-monomorine I.[8]

Although the variety of 2,5-*syn* pyrrolidines accessible using the 5-*endo*-trig methodology had been improved, the necessary switch of protecting groups a (Dpp to Bz) following the ring-opening of the aziridine increased the number of synthetic steps. We were therefore keen to evaluate other aziridine protecting groups in order to simplify the methodology. This paper describes the use of the 2-(trimethylsilanyl)ethanesulfonyl (SES) protecting group in the synthesis of pyrrolidines and an application of the 5-*endo*-trig reaction in the total synthesis of (+)-preussin.

Results and Discussion

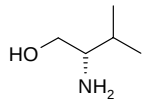
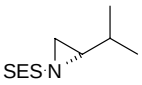
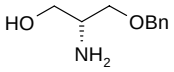
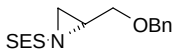
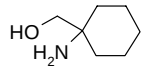
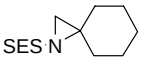
The aziridine protecting group should allow easy formation of the aziridine, activate the aziridine to nucleophilic attack, and, following ring-opening, must be readily removed under conditions that would not affect other functionality in the molecule. To satisfy these criteria, several new protecting groups were investigated, including Boc and 4-nitrobenzenesulfonyl. The optimum group was found to be the SES protecting group developed by Weinreb *et al*.[9,10] The *N*-SES protected aziridines were accessed readily from amino alcohols **10** according to the sequence outlined in Scheme 2. First, the amino alcohols **10a-c** were protected as the corresponding *N*-SES derivatives **11a-c** using SES-Cl at low temperature. For the preparation of the valine- and serine-derived aziridines **12a** and **12b**, cyclodehydration was then performed using an adaptation of the procedure reported by Wessig and co-workers[11] using toluenesulfonyl chloride and potassium hydroxide. Unfortunately, under these reaction conditions the tosyl intermediate for the cyclohexyl derivative (not shown) failed to cyclise. However, in this case aziridine formation to provide **12c** could be achieved using a modified Mitsunobu reaction according to a procedure by Tsunoda *et al*.[12] Aziridines **12a-c** were accessed via these routes (Table 1).



10a-c **11a-c** **12a-c**

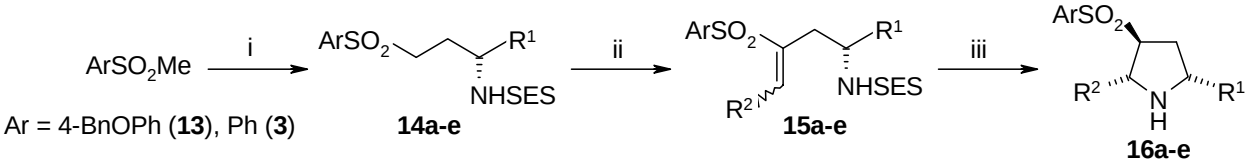
Scheme 2. Reagents and conditions: i. SESCl, Et_3N, DMF, –40 °C; ii. (a) TsCl, KOH, Et_2O, reflux or (b) ADDP, PMe_3, THF, rt.

Table 1. Synthesis of aziridines

Amino Alcohol	Aziridine	Yield[a]
		**12a**; 63%[b]
		**12b**; 59%[b]
		**12c**; 66%[c]

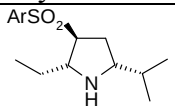
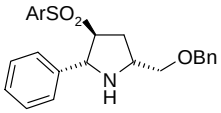
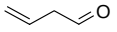
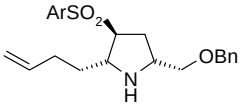
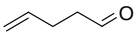
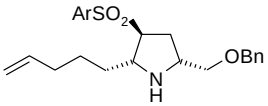
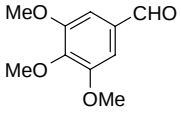
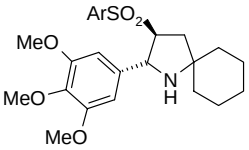
[a] Overall yield for 3 synthetic steps; [b] Cyclisation using conditions ii. (a) in Scheme 2; [c] Cyclisation using conditions ii. (b) in Scheme 2.

With the aziridines in hand, our attention turned to the synthesis of the pyrrolidines. *n*-Butyllithium-promoted deprotonation of arylsulfonyl methane (Ar = 4-benzyloxyphenyl or phenyl) was followed by the addition of the aziridine at low temperature. As expected, ring-opening of the aziridine was facile and adducts **14a-e** were isolated in good yield (79-92%). The intermediates **14a-e** were then treated with two equivalents of *n*-butyllithium to effect a double deprotonation and this was followed by the sequential addition of an aldehyde and benzoyl chloride to provide the vinylic sulfones **15a-e** (as predominantly the *E*-isomer in ratios >3:1, as evidenced by ^{1}H nmr spectroscopy). The advantage of the SES protecting group over the Bz and Dpp groups was demonstrated in the final step. In a one-pot procedure using excess tetrabutylammonium fluoride (TBAF) at either room temperature or reflux, deprotection and cyclisation occurred to provide the target pyrrolidines **16a-e** as shown in Scheme 3. We found that cesium fluoride could also effect the deprotection-cyclisation, although the yields were higher when TBAF was used. This modification of the original 5-*endo*-trig protocol provided the unprotected pyrrolidines (**Table 2**), ready for immediate modification. We were also encouraged that spirocyclic compounds (e.g. **16e**) were accessible using this chemistry as the rapid assembly of compounds containing multiple ring systems could be envisaged.



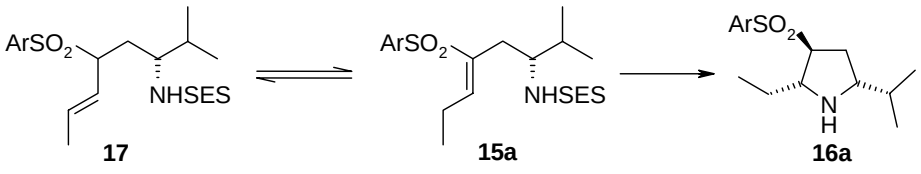
Scheme 3. *Reagents and conditions:* i. *n*-BuLi, THF:TMEDA (4:1), –78 ºC, *then* aziridine, –78 ºC to rt; ii. *n*-BuLi, THF:TMEDA (4:1), –78 ºC, *then* aldehyde R^2CHO, –78 ºC, *then* BzCl, –78 ºC to rt; iii. TBAF, THF, rt or reflux.

Table 2. Synthesis of 2,5-disubstituted pyrrolidines

Aziridine	Aldehyde	Pyrrolidine	Yield[c]	2,5-*syn*:*anti*[d]
12a			**16a**[a]; 32%	>10:1
12b	PhCHO		**16b**[b]; 36%	>25:1
12b			**16c**[b]; 32%	>10:1
12b			**16d**[b]; 28%	>10:1
12c			**16e**[b]; 33%	NA

[a] Ar = 4-BnOPh; [b] Ar = Ph; [c] Overall yield for 3 synthetic steps; [d] Ratio estimated from ^{1}H nmr integration

During the synthesis of **16a**, we observed that if the TBAF deprotection-cyclisation step was stopped prematurely then spectroscopic evidence for the formation of allylic sulfone **17** could be obtained. Fortunately, in the presence of excess quantities of TBAF, **17** was completely consumed in the reaction and only the pyrrolidine **16a** was isolated. Presumably the reaction medium is sufficiently basic that the equilibrium is driven towards the pyrrolidine via the vinylic species **15a**. This finding suggested that allylic sulfones might also be substrates for the 5-*endo*-trig cyclisation.

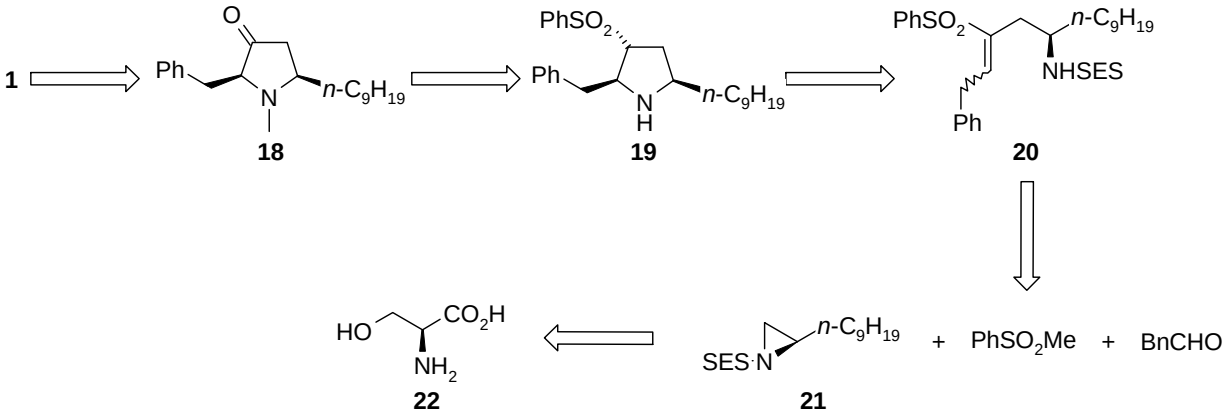


Scheme 4

In three synthetic steps (five chemical transformations) from readily accessible *N*-SES protected aziridines, highly functionalised pyrrolidines suitable for further modification were accessed in good overall yields (28-33%). We were keen to demonstrate the synthetic utility of

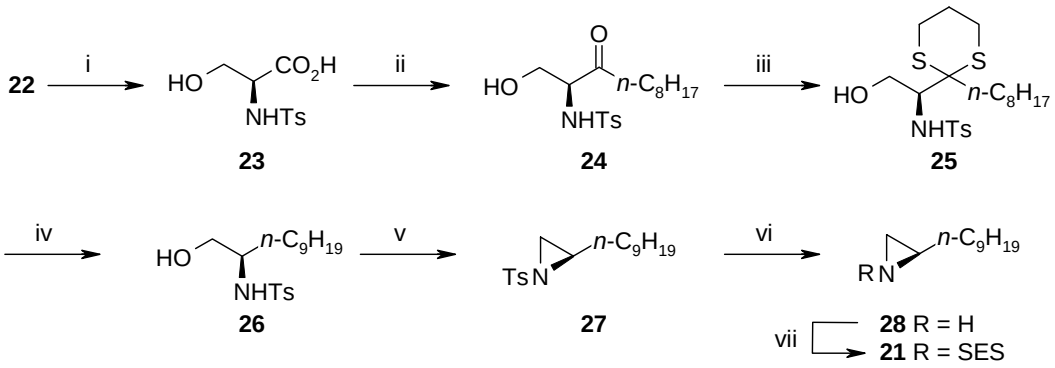
our adapted 5-*endo* trig methodology, and the natural product (+)-preussin, **1**[13-15] appeared to be an excellent target with its 2,5-*syn* disubstituted pyrrolidine core.

Our initial retrosynthetic analysis is illustrated in Scheme 4. We envisaged that the hydroxyl group in **1** could be accessed by reduction of the corresponding ketone **18**, which in turn would be made following oxidation of the sulfone-stabilised carbanion derived from **19**. The pyrrolidine ring in **19** would be prepared from vinylic sulfone **20** via the 5-*endo*-trig cyclisation. Compound **20** would be assembled according to the methodology described above, from methylsulfonylbenzene, *N*-SES protected aziridine **21** and phenylacetalaldehyde. Aziridine **21** would be accessed from L-serine **22**.



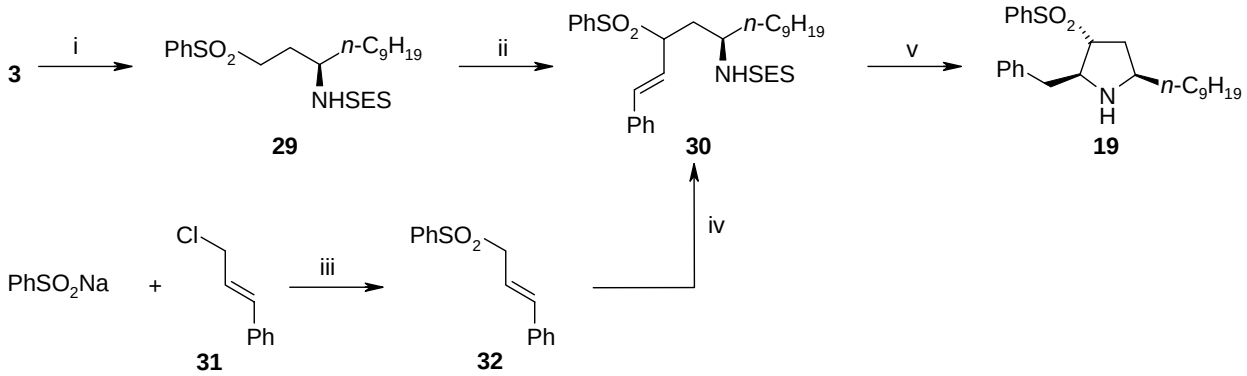
Scheme 5

Aziridine **21** was prepared in seven steps and 12% overall yield from **22** by adaptation of work described by Rapoport[16] as shown in Scheme 6. *N*-Tosyl protection of L-serine **22** was followed by the Grignard addition of *n*-octyl magnesium iodide to give ketone **24**. The ketone was reduced in a two-step sequence via dithiane **25** to give the *N*-tosyl amino alcohol **26**. Formation of aziridine **27** was achieved using the modified Wessig[12] conditions, and subsequent replacement of the *N*-tosyl group in **27** with the SES protecting group via the unprotected aziridine **28** provided the desired aziridine **21**. At the outset, we had envisaged that the SES group would be introduced at the start of the synthetic sequence thus avoiding a protection-deprotection-reprotection strategy. Unfortunately the instability of the SES group to excess organometallic reagent (4 equivalents were used in the reaction), presumably due to deprotonation α to the sulfonyl group prevented the use of this approach.



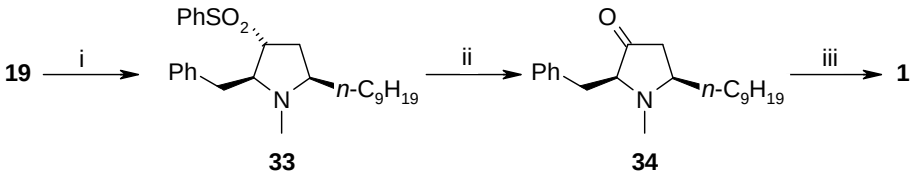
Scheme 6. *Reagents and conditions:* i. TsCl, NaOH, H_2O, EtOAc, rt, 79%; ii. *n*-BuLi, $H_{17}C_8MgI$, THF, Et_2O, –78 ºC to rt, 38%; iii. $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 ºC to rt, 83%; iv. Ni(*R*), EtOH, reflux, 91%; v. TsCl, KOH, 0 ºC to rt, 98%; vi. Na, naphthalene, THF, –78 ºC, 76%; vii SESCl, DMAP, Et_3N, CH_2Cl_2, –5 ºC, 74%.

Ring-opening of aziridine **21** using the lithio-anion of methylsulfonylbenzene provided the expected product **29**. In the subsequent carbon–carbon bond forming step, using similar conditions to those described in Scheme 3, the major product was not the desired vinylic sulfone **20** but the allylic sulfone **30**, as a mixture of diastereoisomers. We reasoned that the acidity of the α-protons in phenylacetalaldehyde was responsible for the formation of **30** as the major product. This result is also consistent with the greater thermodynamic stability of allylic sulfones over vinylic sulfones. In spite of this observation, our earlier experience, shown in Scheme 4, had suggested that **30** would also be a substrate for the 5-*endo*-trig reaction. Indeed, stirring allylic sulfone **30** with 15 equivalents of TBAF in THF at reflux for 38 hours provided the desired pyrrolidine **19** as a single diastereoisomer in 78% yield after chromatography. This observation actually made the synthesis of **19** more convergent as we were able to access **30** in two steps from the sodium salt of benzenesulfinic acid as shown in Scheme 7.



Scheme 7. *Reagents and conditions:* i. *n*-BuLi, THF:TMEDA (4:1), –78 ºC, *then* **21**, –78 ºC to rt, 89%; ii. *n*-BuLi, THF, –78 ºC, *then* phenylacetaldehyde, –78 ºC, *then* BzCl, –78 ºC to rt, 19%; iii. DMF, rt, 81%; iv. *n*-BuLi, THF:TMEDA (4:1), –78 ºC, *then* **21**, –78 ºC to rt, 95%; v. TBAF, THF, reflux, 78%.

The completion of the total synthesis of (+)-preussin was achieved as depicted in Scheme 8. Thus, the *N*-methyl derivative **33** was prepared by reductive amination of **19** using aqueous formaldehyde and sodium cyanoborohydride. With compound **33** in hand, the acidity of the sulfone α-protons, which had been pivotal during the whole synthetic route, was exploited again in an oxidative desulfonylation reaction according to the procedure described by Hwu.[17] This provided ketone **34** in good yield based on recovered starting material. The final step in the sequence was the stereoselective reduction of the ketone from the less hindered α-face using lithium aluminium hydride to provide **1** in 86% yield. The spectroscopic characteristics of the synthetic material were identical to those reported for the natural product.[2]



Scheme 8. *Reagents and conditions:* i. HCHO (aq.), $NaCNBH_3$, AcOH, MeCN, rt, 98%; ii. *n*-BuLi, THF, –78 ºC, *then* TMSOOTMS, –78 ºC, to rt, 49% (73% based on recovered starting material); iii. $LiAlH_4$, THF, –78 ºC, 86%.

In summary, we have improved the synthesis of highly decorated pyrrolidine ring systems via our 5-*endo*-trig reaction by utilizing an *N*-SES protecting group strategy. The methodology was further extended following the observation that vinylic sulfones, the precursors for the 5-*endo*-trig cyclisation, may be generated *in situ* from readily accessible allylic sulfones. These improvements to our methodology were applied to the total synthesis of (+)-preussin, which has been prepared in 12 steps and 5% overall yield from L-serine and (*E*)-3-phenyl-1-(phenylsulfonyl)-2-propene.

Experimental Section

General Procedures. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Optical rotations were measured using an Optical Activity Ltd AA-1000 polarimeter and are given in $deg.g^{-1}.cm^2$ units. Infrared spectra were recorded on a Mattson 5000 FTIR spectrometer. Proton magnetic resonance (^1H nmr) spectra and carbon magnetic resonance (^{13}C nmr) spectra were recorded in $CDCl_3$ (unless otherwise stated) on a Bruker DRX-300 spectrometer or Bruker DRX-400. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual solvent (^1H nmr: 7.27 ppm for $CDCl_3$, 3.35 for CD_3OD; ^{13}C nmr: 77.0 ppm for $CDCl_3$, 49.5 ppm for CD_3OD). Mass spectra (CI or FAB ionisation) were recorded using VG-7070B, VG707E, VG Autospec Q or Jeol SX-102 instruments. Elemental analyses were performed at the microanalytical laboratory of North

London University. Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} pre-coated glass-backed plates. Visualisation was effected with ultraviolet light, iodine, acidic ammonium molybdate (IV) or potassium permanganate. Flash chromatography was performed using BDH (40-63 μm) silica gel. Standard solvents were distilled under nitrogen prior to use; Et_2O and THF from sodium-benzophenone ketyl, CH_2Cl_2 from P_2O_5 or CaH, toluene from sodium. DMF was dried over 4Å molecular sieves. Petrol refers to the fraction bp 40–60 °C, which was distilled before use. All other solvents were reagent grade.

Compound characterization

(2*S*)-3-Methyl-2-[2-(trimethylsilanyl)ethanesulfonylamino]butan-1-ol (11a). To a solution of (2*S*)-valinol (4.58 g, 44.3 mmol, 1.5 equiv) and Et_3N (20.7 ml, 0.148 mol, 5 equiv) in DMF (70 ml) at –40 °C was added SES-Cl (5.94 g, 29.7 mmol, 1 equiv) in DMF (20 ml) over 2 h. After 16 h at –40 °C, the pale yellow suspension was poured into H_2O (50 ml) and extracted with EtOAc (3 x 50 ml). The combined organic fractions were washed with H_2O (5 x 20 ml), sat. NaCl (20 ml), separated, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to reveal a pale yellow oil. Purification by chromatography (10%-30% EtOAc-petrol) gave the product as a colourless solid (5.15 g, 65% with respect to SES-Cl); mp 94-95 °C; $[\alpha]_D^{20}$ -21.2 (*c* 1.00, $CHCl_3$); ν_{max} (film) 3394, 3208, 2956, 2898, 2877, 1450, 1320, 1278, 1249, 1172, 1129, 1085 cm^{-1}; δ_H (300 MHz) 4.52 (1H, d, *J* = 9.0 Hz, N*H*), 3.77 (1H, dd, *J* = 4.0, 11.0 Hz, H-1), 3.67 (1H, dd, *J* = 6.0, 11.0 Hz, H-1), 3.28-3.19 (1H, m, H-2), 3.05-2.98 (2H, m, CH_2SO_2N), 1.89 (1H, m, H-3), 1.90 (1H, br s, O*H*), 1.12-1.06 (2H, m, CH_2SiMe_3), 1.01 (3H, d, *J* = 7.0 Hz, Me), 0.99 (3H, d, *J* = 7.0 Hz, Me), 0.07 (9H, s, Me_3Si); δ_C (75 MHz) 63.7, 61.4, 49.9, 30.0, 19.4, 18.7, 10.6, -2.0; *m/z* (CI) 285 $[M+NH_4]^+$, 268 $[MH]^+$, 204, 90 (Found: $[M+NH_4]^+$, 285.1660; $C_{10}H_{25}NO_3SSi$ requires $[M+NH_4]^+$, 285.1668); (Found C, 45.08; H, 9.45; N, 5.16. $C_{10}H_{25}NO_3SSi$ requires C, 44.91; H, 9.42; N, 5.24%).

(2*R*)-1-Benzyloxy-2-[2-(trimethylsilanyl)ethanesulfonylamino]propan-3-ol (11b). To a solution of (2*R*)-2-amino-1-(benzyloxy)propan-3-ol, hydrochloride salt (7.35 g, 33.8 mmol, 1.2 equiv) and Et_3N (19.6 ml, 0.141 mmol, 5 equiv) in DMF (68 ml) at –40 °C was added SES-Cl 2.13 (5.64 g, 28.1 mmol, 1 equiv) in DMF (44 ml) over 2 h. The resulting pale yellow suspension was stirred at –40 °C for 16 h and then quenched with H_2O (25 ml). The two-phase mixture was extracted with EtOAc (3 x 50 ml) and the combined organic fractions were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give a yellow oil. Purification by chromatography (30%-50% EtOAc-petrol) gave the *title compound* as a colourless oil (6.67 g, 69% with respect to SES-Cl); $[\alpha]_D^{20}$ +5.5 (*c* 1.10, $CHCl_3$); ν_{max} (film) 3495, 3267, 3090, 3063, 3031, 2952, 2927, 2896, 2871, 2834, 1495, 1451, 1434, 1417, 1363, 1317, 1284, 1249, 1208, 1168, 1143, 1106, 1073, 1048, 1029 cm^{-1}; δ_H (300 MHz) 7.41-7.31 (5H, m, Ar*H*), 4.83 (1H, d, *J* = 7.5 Hz, N*H*), 4.56 (2H, s, OCH_2Ph), 3.84-3.59 (5H, m, H-1, H-2 and H-3), 3.02-2.96 (2H, m, CH_2SO_2N), 2.19 (1H, dd, *J* = 4.5, 7.5 Hz, O*H*), 1.08-1.02 (2H, m, CH_2SiMe_3), 0.04 (9H, s, Me_3Si); δ_C (75 MHz) 137.4, 128.6, 128.1, 127.8, 73.7, 71.0, 63.8, 54.9, 49.8, 10.6, -2.0; *m/z* (CI)

363 $[M+NH_4]^+$, 346 $[MH]^+$, 282, 254, 180, 91, 90 (Found: $[M+NH_4]^+$, 363.1768; $C_{15}H_{27}NO_4SSi$ requires $[M+NH_4]^+$, 363.1774); (Found C, 52.32; H, 8.02; N, 3.89. $C_{15}H_{27}NO_4SSi$ requires C, 52.14; H, 7.88; N, 4.05%).

1-(1-Aminomethyl)cyclohexan-1-ol (10c). To a solution of 1-oxaspiro[2.5]octane[18] (649 mg, 5.79 mmol, 1 equiv) in MeOH (11 ml) at rt was added NH_4Cl (0.93 g, 17.4 mmol, 3 equiv) and NaN_3 (1.13 g, 17.4 mmol, 3 equiv) and the resulting suspension was heated to reflux. After 3 h, the reaction was cooled to rt and H_2O (2 ml) was added. The mixture was extracted with EtOAc (3 x 10 ml) and the combined organic fractions were washed with sat. NaCl (5 ml), separated, dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to give 1-(1-azidomethyl)cyclohexan-1-ol as a colourless oil (694 mg, 77%). The crude product was used without further purification; ν_{max} (film) 3448, 2935, 2859, 2103, 1447, 1286, 1225, 1160 cm^{-1}; δ_H (300 MHz) 3.29 (2H, s, H-1'), 1.70-1.25 (11H, m, H-2, H-3 and H-4); δ_C (75 MHz) 71.7, 61.5, 35.0, 25.6, 21.7. To a solution of $LiAlH_4$ (6.90 ml of a 1M solution in THF, 6.90 mmol, 2 equiv) at 0 °C was added 1-(1-azidomethyl)cyclohexanol (535 mg, 3.45 mmol, 1 equiv) as a solution in THF (1 ml) dropwise. The solution was stirred at 0 °C for 1 h and then warmed to rt. After 2 h, the reaction was quenched with H_2O (0.3 ml), 15% aqueous NaOH (0.3 ml) and H_2O (0.9 ml). The white suspension was stirred for 4 h and filtered. The collected solids were washed with EtOAc (5 x 10 ml) and the filtrate was dried ($MgSO_4$), filtered and concentrated under removed under reduced pressure to reveal a colourless oil (406 mg, 91%). The crude product was used without further purification; ν_{max} (film) 3287, 2929, 2855, 1577, 1482, 1452, 1349, 1319, 1265, 1172, 1047 cm^{-1}; δ_H (300 MHz) 2.06 (2H, s, C*H*$_2$NH$_2$), 1.71-1.22 (13H, H-2, H-3, H-4, N*H*$_2$ and O*H*); δ_C (75 MHz) 70.3, 51.3, 35.4, 26.0, 22.1; *m/z* (CI) 130 $[MH]^+$ (Found: $[MH]^+$, 130.1231; $C_7H_{15}NO$ requires $[MH]^+$, 130.1232).

1-[(2-Trimethylsilanyl)ethanesulfonyl]aminomethyl]cyclohexan-1-ol (11c). To a solution of **10c** (355 mg, 2.75 mmol, 1 equiv) and Et_3N (1.92 ml, 13.8 mmol, 5 equiv) in DMF (6 ml) at –40 °C was added SES-Cl (552 mg, 2.75 mmol, 1 equiv) as a solution in DMF (2 ml) over 2 h. The colourless suspension was stirred for 16 h at –40 °C before H_2O (5 ml) was added. The reaction mixture was extracted with EtOAc (3 x 15 ml) and the combined organic fractions were washed with H_2O (2 x 5 ml), sat. NaCl (5 ml) and then separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography (30% EtOAc-petrol) gave the *title compound* as a colourless solid (651 mg, 81%); mp 123-124 °C; ν_{max} (film) 3322, 3270, 3065, 3034, 2907, 2295, 1421, 1407, 1326, 1305, 1267, 1247, 1174, 1139, 1105, 1074, 1054 cm^{-1}; δ_H (300 MHz) 4.60 (1H, t, *J* = 6.0 Hz, N*H*), 3.09 (2H, d, *J* = 6.0 Hz, C*H*$_2$NH), 3.02-2.96 (2H, m, C*H*$_2$SO$_2$N), 1.64-1.28 (11H, m, H-2, H-3, H-4 and O*H*), 1.07-1.01 (2H, m, C*H*$_2$SiMe$_3$), 0.07 (9H, s, Me$_3$Si); δ_C (75 MHz) 71.2, 52.4, 48.8, 35.4, 25.6, 21.9, 10.7, -1.9; *m/z* (CI) 311 $[M+NH_4]^+$, 293 $[MH]^+$, 276, 90 (Found: $[M+NH_4]^+$, 311.1820; $C_{12}H_{27}NO_3SSi$ requires $[M+NH_4]^+$, 311.1825); (Found C, 49.17; H, 9.22; N, 4.61. $C_{12}H_{27}NO_3SSi$ requires C, 49.11; H, 9.27; N, 4.77%).

(2*S*)-2-Methylethyl-1-[2-(trimethylsilanyl)ethanesulfonyl]aziridine (12a). To a solution of **11a** (4.86 g, 18.2 mmol, 1 equiv) in Et_2O (150 ml) at rt was added powdered KOH (5.10 g, 91.0

mmol, 5 equiv) and TsCl (3.81 g, 20.0 mmol, 1.1 equiv). After 4 h, the reaction was diluted with H_2O (60 ml) and extracted with EtOAc (3 x 60 ml). The combined organic fractions were washed with sat. NaCl, separated, dried ($MgSO_4$) and filtered. Concentration under reduced pressure gave an oil which was purified by chromatography (10%-30% EtOAc-petrol) to give the *title compound* as a colourless oil (4.37 g, 96%); $[\alpha]_D^{20}$ +38.7 (*c* 3.00, $CHCl_3$); ν_{max} (film) 2963, 2902, 2871, 1471, 1420, 1409, 1322, 1287, 1251, 1172, 1146, 1106 cm^{-1}; δ_H (300 MHz) 3.12-3.05 (2H, m, C*H*$_2$SO$_2$N), 2.60-2.52 (2H, m, H-2 and H-3), 2.14 (1H, d, *J* = 4.0 Hz, H-3), 1.53 (1H, septet, *J* = 6.5 Hz, C*H*Me$_2$), 1.20-1.14 (2H, m, C*H*$_2$SiMe$_3$), 1.06 (3H, d, *J* = 6.5 Hz, Me) 1.01 (3H, d, *J* = 6.5 Hz, Me), 0.08 (9H, s, Me$_3$Si); δ_C (75 MHz) 48.7, 44.8, 32.4, 30.2, 19.8, 19.0, 9.7, -2.0; *m/z* (CI) 516 $[2M+NH_4]^+$, 499 $[2M+H]^+$, 322, 294, 267 $[M+NH_4]^+$, 250 $[MH]^+$, 234, 84 (Found: $[MH]^+$, 250.1296; $C_{10}H_{23}NO_2SSi$ requires $[MH]^+$, 250.1297); (Found C, 48.26; H, 9.25; N, 5.54. $C_{10}H_{23}NO_2SSi$ requires C, 48.15; H, 9.29; N, 5.61%).

(2*R*)-2-(Benzyloxy)methyl-1-[2-(trimethylsilanyl)ethanesulfonyl)]aziridine (12b). Compound **12b** was prepared on a 11.9 mmol scale according to the procedure described for **12a** to give, after chromatography (10%-30% EtOAc-petrol), the *title compound* as a colourless oil (3.32 g, 85%); $[\alpha]_D^{20}$ +36.0 (*c* 2.11, $CHCl_3$); ν_{max} (film) 3087, 3063, 3032, 2971, 2952, 2898, 2866, 2826, 1496, 1453, 1419, 1382, 1365, 1322, 1288, 1250, 1231, 1218, 1170, 1153, 1096, 1023 cm^{-1}; δ_H (300 MHz) 7.39-7.29 (5H, m, Ar*H*), 4.59 (2H, s, OC*H*$_2$Ph), 3.72 (1H, dd, *J* = 4.0, 11.0 Hz, CH*H*OBn), 3.45 (1H, dd, *J* = 7.0, 11.0 Hz, C*H*HOBn), 3.16-3.10 (2H, m, C*H*$_2$SO$_2$N), 2.98 (1H, m, H-2), 2.67 (1H, d, *J* = 7.0 Hz, H-3), 2.22 (1H, d, *J* = 4.0 Hz, H-3), 1.21-1.14 (2H, m, C*H*$_2$SiMe$_3$), 0.05 (9H, s, Me$_3$Si); δ_C (75 MHz) 137.6, 128.5, 127.9, 127.7, 73.3, 69.4, 48.9, 38.2, 29.7, 9.6, -2.1; *m/z* (CI) 345 $[M+NH_4]^+$, 328 $[MH]^+$, 264, 236, 90; (Found: 328.1409 $[MH]^+$; $C_{15}H_{25}NO_3SSi$ requires 328.1403); (Found C, 54.91; H, 7.59; N, 4.17. $C_{15}H_{25}NO_3SSi$ requires C, 55.01; H, 7.69; N, 4.28%).

1-[(2-Trimethylsilanyl)ethanesulfonyl]azaspiro[2.5]octane (12c). To a solution of **11c** (460 mg, 15.7 mmol, 1 equiv) and ADDP (0.79 g, 31.4 mmol, 2 equiv) in THF (23 ml) at rt was added PMe_3 (3.14 ml of a 1M solution in THF, 31.4 mmol, 2 equiv). After 8 h, Et_2O (25 ml) was added and the suspension was filtered. The filtrate was concentrated under reduced pressure and purification of the crude material by chromatography (10% EtOAc-petrol) gave the *title compound* as a colourless solid (354 mg, 82%); mp 44 °C; ν_{max} (film) 2938, 2857, 1449, 1318, 1334, 1251, 1169, 1143, 1128, 1123 cm^{-1}; δ_H (300 MHz) 3.11-3.04 (2H, m, C*H*$_2$SO$_2$N), 2.41 (2H, s, H-2), 1.98-1.41 (10H, m, H-4, H-5 and H-6), 1.15-1.09 (2H, m, C*H*$_2$SiMe$_3$), 0.07 (9H, s, Me$_3$Si); δ_C (75 MHz) 52.0, 51.0, 41.6, 33.3, 25.5, 25.2, 9.9, -1.9; *m/z* (CI) 293 $[M+NH_4]^+$, 276 $[MH]^+$, 110 (Found: $[MH]^+$, 276.1455; $C_{12}H_{25}NO_2SSi$ requires $[MH]^+$, 276.1454); (Found C, 52.44; H, 9.25; N, 4.95. $C_{12}H_{25}NO_2SSi$ requires C, 52.32; H, 9.15; N, 5.08%).

(3*R*)-1-[4-(Benzyloxy)benzenesulfonyl]-4-methyl-3-[2-(trimethylsilanyl)ethanesulfonylamino]-pentane (14a). To a suspension of 1-benzyloxy-4-methanesulfonylbenzene[19] (644 mg, 2.45 mmol, 1 equiv) in THF:TMEDA (9.2 ml) at –78 ºC was added *n*-BuLi (1.28 ml of a 2.3 M solution in hexanes; 2.95 mmol, 1.2 equiv). The resulting red suspension was warmed to –20°C during 15 min and then the reaction was re-cooled to –78 ºC before **12a** (734 mg, 2.95 mmol,

1.20 equiv) as a solution in THF (2.70 ml) was introduced dropwise into the reaction mixture. The resulting suspension was maintained at –78 ºC for 15 min and then warmed to rt where it was left for 2 h. After this time, the reaction was quenched by the addition of sat. NH_4Cl (5 ml). The mixture was extracted with EtOAc (3 x 10 ml) and the combined extracts were washed with sat. NaCl, separated, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by chromatography (10%-30% EtOAc-petrol) gave the *title compound* as colourless crystals (1.15 g, 92%); mp 102-103 °C; $[\alpha]_D^{20}$ -3.2 (*c* 2.52, $CHCl_3$); ν_{max} (film) 3279, 2957, 2943, 2895, 2890, 1592, 1577, 1496, 1453, 1431, 1416, 1314, 1291, 1251, 1230, 1170, 1141, 1089, 1023 cm^{-1}; δ_H (300 MHz) 7.86 (2H, d, *J* = 9.0 Hz, *ortho* $ArSO_2$), 7.45-7.38 (5H, m, Ar*H*), 7.11 (2H, d, *J* = 9.0 Hz, *meta* $ArSO_2$), 5.16 (2H, s, OCH_2Ph), 4.21 (1H, d, *J* = 9.5 Hz, N*H*), 3.35-3.13 (3H, m, H-1 and H-3), 2.99-2.90 (2H, m, CH_2SO_2N), 2.06 (1H, m, H-4), 1.93-1.78 (2H, m, H-2), 1.08-1.00 (2H, m CH_2SiMe_3), 0.96 (2H, d, *J* = 6.5 Hz, Me), 0.95 (2H, d, *J* = 6.5 Hz, Me), 0.06 (9H, s, Me_3Si); δ_C (75 MHz) 163.0, 135.7, 131.0, 130.2, 128.8, 128.4, 127.5, 115.5, 70.5, 58.3, 53.7, 50.5, 32.8, 25.3, 18.5, 18.1, 10.8, -2.0; *m/z* (CI) 529 $[M+NH_4]^+$, 186, 91 (Found: $[M+NH_4]^+$, 529.2229; $C_{24}H_{37}NO_5S_2Si$ requires $[M+NH_4]^+$, 529.2226); (Found C, 56.49; H, 7.39; N, 2.52. $C_{24}H_{37}NO_5S_2Si$ requires C, 56.33; H, 7.29; N, 2.74%).

(3*R*)-4-Benzyloxy-1-phenylsulfonyl-3-[2-(trimethylsilanyl)ethanesulfonylamino]butane (14b). To a solution of methylsulfonylbenzene **3** (1.38 g, 8.86 mmol, 1 equiv) in 4:1 THF:TMEDA (40 ml) at –78 ºC was added *n*-BuLi (4.62 ml of a 2.3M solution in hexanes, 10.6 mmol, 1.2 equiv). The resulting yellow solution was stirred at –78 ºC for 15 min, before **12b** (3.04 g, 9.30 mmol, 1.05 equiv) in THF (8 ml) was introduced slowly. The reaction was left at –78 ºC for 15 min and then warmed to rt where it was maintained for 2 h. After this time, the solution was quenched with sat. NH_4Cl (10 ml) and extracted with EtOAc (3 x 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification by recrystallisation (EtOAc) gave the *title compound* as colourless crystals (3.39 g, 79%); mp 127 °C; $[\alpha]_D^{20}$ +5.0 (*c* 2.60, $CHCl_3$); ν_{max} (film) 3277, 3062, 3029, 2950, 2925, 2895, 2864, 1473, 1446, 1361, 1302, 1253, 1166, 1143, 1116, 1086, 1024 cm^{-1}; δ_H (300 MHz) 7.94-7.91 (2H, m, *ortho* $PhSO_2$), 7.70-7.55 (3H, m, Ar*H*), 7.40-7.27 (5H, m, Ar*H*), 4.70 (1H, d, *J* = 9.0 Hz, N*H*), 4.52 (2H, s, OCH_2Ph), 3.68-3.59 (1H, m, H-3), 3.55-3.44 (2H, m, H-4), 3.23 (2H, m, H-1), 3.00-2.87 (2H, m, CH_2SO_2N), 2.07-1.99 (2H, m, H-2), 1.02-0.95 (2H, m, CH_2SiMe_3), -0.01 (9H, s, Me_3Si); δ_C (75 MHz) 139.1, 137.2, 133.8, 129.4, 128.7, 128.2, 128.0, 127.9, 73.5, 72.0, 53.0, 52.6, 49.9, 26.1, 10.5, -2.0; *m/z* (CI) 501 $[M+NH_4]^+$, 361, 90; (Found: $[M+NH_4]^+$, 501.1919; $C_{22}H_{33}NO_5S_2Si$ requires $[M+NH_4]^+$, 501.1913); (Found C, 54.72; H, 6.97; N, 2.69. $C_{22}H_{33}NO_5S_2Si$ requires C, 54.63; H, 6.88; N, 2.90%).

1-[2-(Phenylsulfonyl)ethane]-1-[2-(trimethylsilanyl)ethanesulfonylamino]cyclohexane (14c). To a solution of methylsulfonylbenzene **3** (177 mg, 1.13 mmol, 1 equiv) in 4:1 THF:TMEDA (5 ml) at –78 ºC was added *n*-BuLi (567 µl of a 2.4M solution in THF, 1.36 mmol, 1.2 equiv). After 15 min, **12c** (342 mg, 1.24 mmol, 1.1 equiv) in THF (1 ml) was introduced and the reaction was stirred for a further 15 min at –78 ºC and then warmed to rt. After 16 h, the reaction was quenched with AcOH (142 mg, 2.36 mmol, 2.1 equiv) and partitioned between EtOAc (10 ml)

and H_2O (5 ml). The organic layer was separated and the aqueous phase was extracted with additional EtOAc (2 x 5 ml). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by chromatography (30%-40% EtOAc-petrol) afforded the *title compound* as a sticky, colourless gum (330 mg, 68%); mp 113-114 °C; ν_{max} (film) 3287, 2938, 2862, 1447, 1418, 1307, 1264, 1251, 1145, 1087, 1003 cm^{-1}; δ_H (300 MHz) 7.95-7.92 (2H, m, *ortho* $PhSO_2$), 7.71-7.57 (3H, m, Ar*H*), 3.97 (1H, s, N*H*), 3.30-3.24 (2H, m, C*H*$_2SO_2Ph$), 2.97-2.91 (2H, m, C*H*$_2SO_2N$), 2.16-2.10 (2H, m, C*H*$_2CH_2SO_2Ph$), 1.77-1.39 (10H, m, H-2, H-3 and H-4), 1.06-1.00 (2H, m, C*H*$_2SiMe_3$), 0.06 (9H, s, Me_3Si); δ_C (75 MHz) 138.8, 133.8, 129.3, 128.1, 58.3, 52.6, 51.4, 36.1, 31.7, 25.2, 21.7, 10.9, -1.9; *m/z* (CI) 449 $[M+NH_4]^+$, 432 $[MH]^+$, 189, 90 (Found: $[M+NH_4]^+$, 449.1959; $C_{19}H_{33}NO_4S_2Si$ requires $[M+NH_4]^+$, 449.1964); (Found C, 52.94; H, 7.87; N, 3.19. $C_{19}H_{33}NO_4S_2Si$ requires C, 52.86; H, 7.71; N, 3.24%).

(6*R*)-*E*-4-[4-(Benzyloxy)phenylsulfonyl]-7-methyl-6-[2-(trimethylsilanyl)ethanesulfonyl-amino]-oct-3-ene (15a-*E*) and (6*R*)-*Z*-4-[4-(Benzyloxy)phenylsulfonyl]-7-methyl-6-[2-(trimethylsilanyl)ethanesulfonylamino]oct-3-ene (15a-*Z*). To a solution of **14a** (330 mg, 0.645 mmol, 1 equiv) in 4:1 THF:TMEDA (6.25 ml) at –78 ºC was added *n*-BuLi (565 µl of a 2.4M solution in hexanes, 1.36 mmol, 2.1 equiv). The resulting yellow solution was stirred at –78 ºC for 15 min before propionaldehyde (56 mg, 0.969 mmol, 1.5 equiv) was introduced. This caused the colour of the mixture to fade. After 1 h at –78 ºC, BzCl (75 µl, 0.645 mmol, 1 equiv) was added and the suspension was warmed to rt where complete dissolution occurred. The reaction was maintained at rt for 1 h before it was quenched with sat. NH_4Cl (5 ml). The mixture was diluted with EtOAc (10 ml) and H_2O (2.5 ml). The organic layer was separated and the aqueous phase was extracted with additional EtOAc (2 x 5 ml). The combined organic fractions were washed with sat. NaCl (2.5 ml), separated, dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure gave a crude product which was purified by chromatography (10%-30% EtOAc-petrol) to give a mixture of *E*:*Z* (>10:1) isomers of the *title compounds* as a colourless oil (183 mg, 51%); ν_{max} (film) 3536, 3286, 3064, 3038, 2960, 2899, 2871, 1591, 1496, 1457, 1426, 1387, 1313, 1242, 1136, 1083, 1022 cm^{-1}; δ_H (300 MHz) *E* isomer 7.79 (2H, d, *J* = 9.0 Hz, *ortho* $ArSO_2$), 7.42-7.33 (5H, m, Ar*H*), 7.08 (2H, d, *J* = 9.0 Hz, *meta* $ArSO_2$), 6.89 (1H, t, *J* = 7.5 Hz, H-3), 5.12 (2H, s, OC*H*$_2Ph$), 5.07 (1H, d, *J* = 8.0 Hz, N*H*), 3.62-3.56 (1H, m, H-6), 2.99-2.93 (2H, m, C*H*$_2SO_2N$), 2.42-2.20 (4H, m, H-2 and H-5), 2.00-1.90 (1H, m, H-7), 1.11 (3H, t, *J* = 7.5 Hz, H-1), 1.02-0.97 (2H, m, C*H*$_2SiMe_3$), 0.93 (3H, d, *J* = 7.0 Hz, Me), 0.92 (3H, d, *J* = 7.0 Hz, Me), 0.07 (9H, m, Me_3Si); *Z* isomer 8.00 (2H, d, *J* = 9.0 Hz, *ortho* $ArSO_2$), 7.42-7.33 (5H, m, Ar*H*), 7.13 (2H, d, *J* = 9.0 Hz, *meta* $ArSO_2$), 6.09 (1H, t, *J* = 7.5 Hz, H-3), 5.14 (2H, s, OC*H*$_2Ph$), 4.81 (1H, d, *J* = 8.0 Hz, N*H*), 3.72-3.65 (1H, m, H-6), 2.99-2.93 (2H, m, C*H*$_2SO_2N$), 2.42-2.20 (4H, m, H-2 and H-5), 2.00-1.90 (1H, m, H-7), 1.06 (3H, t, *J* = 7.5 Hz, H-1), 1.02-0.97 (2H, m, C*H*$_2SiMe_3$), 0.91 (3H, d, *J* = 7.0 Hz, Me), 0.88 (3H, d, *J* = 7.0 Hz, Me), 0.07 (9H, m, Me_3Si); δ_C (75 MHz) *E* isomer 162.8, 145.6, 138.4, 135.7, 130.8, 130.4, 128.8, 128.4, 127.5, 115.3, 70.4, 58.0, 50.1, 32.4, 27.7, 22.3, 17.9, 17.7, 13.0, 10.5, -1.9; *Z* 163.3, 147.7, 137.5, 133.1, 131.2, 130.4, 129.6, 128.8, 127.5, 115.6, 70.0, 58.9, 50.9, 32.0, 27.0, 22.4, 18.4,

18.2, 13.5, 10.7, -1.9; *m/z* (CI) 569 $[M+NH_4]^+$, 192 (Found: $[M+NH_4]^+$, 569.2546; $C_{27}H_{41}NO_5S_2Si$ requires $[M+NH_4]^+$, 569.2539).

(2*R*)-*E*-5-Benzyloxy-1-phenyl-2-phenylsulfonyl-4-[2-(trimethylsilanyl)ethanesulfonyl amino]pent-1-ene (15b-*E*) and (2*R*)-*Z*-5-benzyloxy-1-phenyl-2-phenylsulfonyl-4-[2-(trimethylsilanyl)ethane-sulfonylamino]pent-1-ene (15b-*Z*). To a solution of **14b** (0.50 g, 1.03 mmol, 1 equiv) in 4:1 THF:TMEDA (10 ml) at –78 ºC was added *n*-BuLi (0.90 ml of a 2.4M solution in hexane, 2.17 mmol, 2.1 equiv). The resulting yellow solution was stirred at –78 ºC for 15 min before benzaldehyde (165 mg, 1.55 mmol, 1.5 equiv) in THF (2 ml) was introduced. This caused the colour of the mixture to fade. After 30 min at –78 ºC, BzCl (0.12 ml, 1.03 mmol, 1 equiv) was added and the suspension was warmed to rt where complete dissolution occurred. The reaction was maintained at rt for 1 h before it was quenched with sat. NH_4Cl (5 ml). The mixture was diluted with EtOAc (20 ml) and H_2O (5 ml). The organic layer was separated and the aqueous phase was extracted with additional EtOAc (2 x 10 ml). The combined organic fractions were washed with sat. NaCl (5 ml), separated, dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure and purification by chromatography (10%-30% EtOAc-petrol) afforded a mixture of *E*:*Z* isomers (>3:1) of the *title compounds* as a colourless oil (329 mg, 56%); ν_{max} (film) 3184, 1622, 1495, 1477, 1450, 1427, 1363, 1326, 1305, 1282, 1263, 1251, 1204, 1147, 1092, 1025 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) *E* isomer 7.95 (1H, s, H-1), 7.95-7.93 (2H, m, *ortho* $PhSO_2$), 7.69-7.23 (13H, m, Ar*H*), 5.08 (1H, d, *J* = 7.5 Hz, N*H*), 4.43, 4.39 (2H, AB q, *J* = 11.5 Hz, O*CH*$_2$Ph), 4.00 (1H, m, H-4), 3.61 (1H, dd, *J* = 4.0, 9.5 Hz, H-5), 3.48 (1H, dd, *J* = 6.0, 9.5 Hz, H-5), 3.10 (1H, dd, *J* = 15.5 Hz, H-3), 2.95-2.84 (2H, m, *CH*$_2$$SO_2$N), 2.75 (1H, dd, *J* = 8.0, 15.5 Hz, H-3), 1.05-0.94 (2H, m, *CH*$_2$$SiMe_3$), 0.02 (9H, s, Me_3Si); *Z* isomer 7.87-7.84 (2H, m, *ortho* $PhSO_2$), 7.69-7.23 (14H, m, H-1 and Ar*H*), 4.77 (1H, d, *J* = 8.5 Hz, N*H*), 4.27, 4.23 (2H, AB q, *J* = 11.5 Hz, O*CH*$_2$Ph), 3.73-3.70 (1H, m, H-4), 3.65-3.15 (3H, m, H-5 and H-3), 2.95-2.84 (2H, m, *CH*$_2$$SO_2$N), 2.55-2.48 (1H, m, H-3), 1.05-0.94 (2H, m, *CH*$_2$$SiMe_3$), 0.00 (9H, s, Me_3Si *Z*); δ_C (75 MHz) *E* isomer 140.9, 138.9, 137.8, 137.6, 133.7, 132.7, 130.3, 129.9, 129.5, 129.2, 128.5, 128.3, 127.9, 127.6, 73.2, 72.1, 51.9, 49.1, 29.9, 10.3, -1.9; *m/z* (CI) 589 $[M+NH_4]^+$, 449, 90 (Found: $[M+NH_4]^+$, 589.2214; $C_{29}H_{37}NO_5S_2Si$ requires $[M+NH_4]^+$, 589.2226).

(2*R*)-*E*-1-Benzyloxy-4-phenylsulfonyl-2-[2-(trimethylsilanyl)ethanesulfonylamino]non-4,8-diene (15c-*E*) and (2*R*)-*Z*-1-benzyloxy-4-phenylsulfonyl-2-[2-(trimethylsilanyl)ethane-sulfonylamino]-non-4,8-diene (15c-*Z*). To a solution of **14b** (2.00 g, 4.13 mmol, 1 equiv) in 4:1 THF:TMEDA (40 ml) at –78 ºC was added *n*-BuLi (3.62 ml of a 2.4M solution in hexane, 8.68 mmol, 2.1 equiv). The resulting yellow solution was stirred at –78 ºC for 15 min before 4-pentenal (487 mg, 5.79 mmol, 1.4 equiv) was introduced. This caused the colour of the mixture to fade. After 1 h at –78°C, BzCl (0.48 ml, 4.13 mmol, 1 equiv) was added and the suspension was warmed to rt where complete dissolution occurred. The reaction was maintained at rt for 1 h before it was quenched with sat. NH_4Cl (5 ml). The mixture was diluted with EtOAc (100 ml) and H_2O (10 ml). The organic layer was separated and the aqueous phase was extracted with additional EtOAc (2 x 25 ml). The combined organic fractions were washed with sat. NaCl (25

ml), separated, dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure and purification by chromatography (10%-30% EtOAc-petrol) afforded a mixture of *E*:*Z* isomers (>5:1) of the *title compounds* as a colourless oil (1.14 g, 50%); ν_{max} (film) 3287, 3064, 3030, 3001, 2951, 2920, 2898, 1639, 1474, 1492, 1434, 1361, 1304, 1288, 1106, 1085, 1023 cm^{-1}; δ_H (300 MHz) *E* isomer 7.92-7.84 (2H, m, *ortho* $PhSO_2$), 7.66-7.60 (1H, m, *para* $PhSO_2$), 7.57-7.51 (2H, m, Ar*H*), 7.40-7.26 (5H, m, Ar*H*), 7.03 (1H, t, *J* = 7.0 Hz, H-5), 5.74 (1H, dddd, *J* = 6.5, 6.5, 10.0, 17.0 Hz H-8), 5.09-5.00 (2H, m, H-9), 4.88 (1H, d, *J* = 8.5 Hz, N*H E*), 4.56, 4.49 (2H, AB q, *J* = 11.5 Hz, OCH_2Ph), 4.02-3.88 (1H, m, H-2), 3.60-3.50 (2H, m, H-1), 3.03-2.93 (2H, m, CH_2SO_2N), 2.80-2.08 (6H, m, H-3, H-6 and H-7), 1.11-0.98 (2H, m, CH_2SiMe_3), 0.05 (9H, s, Me_3Si); *Z* isomer 7.92-7.84 (2H, m, *ortho* $PhSO_2$), 7.66-7.60 (1H, m, *para* $PhSO_2$), 7.57-7.51 (2H, m, Ar*H*), 7.40-7.26 (5H, m, Ar*H*), 6.10 (1H, t, *J* = 7.0 Hz, H-5), 5.74 (1H, dddd, *J* = 6.5, 6.5, 10.0, 17.0 Hz H-8), 5.09-5.00 (2H, m, H-9), 4.71 (1H, d, *J* = 8.5 Hz, N*H*), 4.56, 4.49 (2H, AB q, *J* = 11.5 Hz, OCH_2Ph), 4.02-3.88 (1H, m, H-2), 3.60-3.50 (2H, m, H-1), 3.03-2.93 (2H, m, CH_2SO_2N), 2.80-2.08 (6H, m, H-3, H-6 and H-7), 1.11-0.98 (2H, m, CH_2SiMe_3), 0.04 (9H, s, Me_3Si *Z*); δ_C (75 MHz) *E* isomer 144.9, 139.1, 138.1, 137.5, 136.4, 133.5, 129.3, 128.5, 128.3, 128.0, 127.8, 116.4, 73.5, 71.4, 52.8, 49.5, 32.3, 29.9, 27.8, 10.5, -1.9; *Z* 146.9, 138.1, 137.6, 137.1, 136.8, 133.5, 129.3, 128.5, 128.3, 127.9, 127.5, 116.0, 73.5, 71.3, 53.3, 49.6, 37.1, 32.8, 27.9, 10.5, -1.9; *m/z* (CI) 567 $[M+NH_4]^+$, 550 $[MH]^+$, 486, 138 (Found: $[M+NH_4]^+$, 567.2373; $C_{27}H_{39}NO_5SiS_2$ requires $[M+NH_4]^+$, 567.2383).

(2*R*)-*E*-1-Benzyloxy-4-phenylsulfonyl-2-[2-(trimethylsilanyl)ethanesulfonylamino]dec-4,9-diene (15d-*E*) and (2*R*)-*Z*-1-benzyloxy-4-phenylsulfonyl-2-[2-(trimethylsilanyl)ethane-sulfonylamino]-dec-4,9-diene (15d-*Z*). To a solution of **14b** (3.63 g, 7.50 mmol, 1 equiv) in THF:TMEDA (75 ml) at –78 ºC was added *n*-BuLi (7.18 ml of a 2.3M solution in hexanes, 16.5 mmol, 2.2 equiv). The resulting yellow solution was stirred at –78 ºC for 30 min before 5-hexenal (1.10 g, 11.2 mmol, 1.5 equiv) was added as a solution in THF (15 ml) dropwise. This caused the solution to become pale yellow. After stirring the reaction mixture at –78 ºC for 1 h, BzCl (0.87 ml, 7.50 mmol, 1 equiv) was introduced, which resulted in the formation of a white precipitate. This suspension was warmed to rt whereupon the white solid dissolved. Stirring was continued for 2 h at rt and then the mixture was diluted with EtOAc (60 ml) and washed with 50% NaCl (50 ml). The organic layer was separated and the aqueous phase was extracted with additional EtOAc (3 x 25 ml). The organic fractions were combined, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude product by chromatography (30%-40% EtOAc-petrol) gave a mixture of *E*:*Z* isomers (>6:1) of the *title compounds* as a colourless oil (2.82 g, 67%); ν_{max} (film) 3285, 3069, 3031, 2954, 2929, 2897, 2858, 1719, 1639, 1603, 1583, 1495, 1474, 1447, 1415, 1360, 1306, 1287, 1265, 1250, 1208, 1145, 1107, 1086, 1024 cm^{-1}; δ_H (300 MHz) *E* isomer 7.91-7.87 (2H, m, *ortho* $PhSO_2$), 7.66-7.61 (1H, m, *para* $PhSO_2$), 7.57-7.51 (2H, m, Ar*H*), 7.40-7.32 (5H, m, Ar*H*), 7.04 (1H, t, *J* = 7.5 Hz, H-5), 5.74 (1H, dddd, *J* = 6.5, 6.5, 10.0, 17.0 Hz, H-9), 5.02-4.92 (2H, m, H-10), 4.89 (1H, d, *J* = 8.5 Hz, N*H*), 4.55, 4.49 (2H, AB q, *J* = 11.5 Hz, OCH_2Ph), 3.97-3.91 (1H, m, H-2), 3.57 (1H, dd, *J* = 4.0, 10.0 Hz, H-1), 3.49 (1H, dd, *J* = 4.5, 10.0 Hz, H-1), 3.03-2.93 (2H, m, CH_2SO_2N),

2.63-2.45 (2H, m, H-6), 2.30-2.22 (2H, m, H-3), 2.09-2.01 (2H, m, H-8) 1.63-1.53 (2H, m, H-7), 1.08-0.99 (2H, m, C*H*$_2$SiMe$_3$), 0.05 (9H, s, Me$_3$Si); *Z* isomer 7.91-7.87 (2H, m, *ortho* PhSO$_2$), 7.66-7.61 (1H, m, *para* PhSO$_2$), 7.57-7.51 (2H, m, Ar*H*), 7.40-7.32 (5H, m, Ar*H*), 6.10 (1H, t, *J* = 7.5 Hz, H-5), 5.74 (1H, dddd, *J* = 6.5, 6.5, 10.0, 17.0 Hz, H-9), 5.02-4.92 (2H, m, H-10), 4.72 (1H, d, *J* = 8.5 Hz, N*H*), 4.55, 4.49 (2H, AB q, *J* = 11.5 Hz, OC*H*$_2$Ph), 3.97-3.91 (1H, m, H-2), 3.56 (1H, dd, *J* = 4.0, 10.0 Hz, H-1), 3.48 (1H, dd, *J* = 4.5, 10.0 Hz, H-1), 3.03-2.93 (2H, m, C*H*$_2$SO$_2$N), 2.63-2.45 (2H, m, H-6), 2.30-2.22 (2H, m, H-3), 2.09-2.01 (2H, m, H-8) 1.63-1.53 (2H, m, H-7), 1.08-0.99 (2H, m, C*H*$_2$SiMe$_3$), 0.06 (9H, s, Me$_3$Si *Z*); δ_C (75 MHz) *E* isomer 145.4, 139.0, 137.8, 137.5 (2C), 133.2, 129.3, 128.5, 128.2, 128.0, 127.7, 115.6, 73.4, 71.4, 52.8, 49.5, 33.2, 29.8, 27.9, 27.5, 10.5, -1.9; *m/z* (FAB) 564 $[MH]^+$, 500, 472, 91, 73 (Found: $[MH]^+$, 564.2269; $C_{28}H_{41}NO_5S_2Si$ requires $[MH]^+$, 564.2274).

***E*-1-[(2-Phenylsulfonyl-3-(3,4,5-trimethoxyphenyl)prop-2-ene)]-1-[2-(trimethylsilanyl) ethanesulfonylamino]cyclohexane (15e).** To a solution of **14c** (298 mg, 0.691 mmol, 1 equiv) in 4:1 THF:TMEDA (7.25 ml) at –78 ºC was added *n*-BuLi (605 µl of a 2.4M solution in hexanes, 2.1 equiv). The yellow solution was stirred for 30 min at –78 ºC before 3,4,5-trimethoxybenzaldehyde (149 mg, 0.761 mmol, 1.1 equiv) in THF (1 ml) was introduced. After 30 min at –78 ºC, BzCl (80 µl, 0.691 mmol, 1 equiv) was added and the reaction was warmed to rt where it was maintained for 2 h. After this time, the mixture was partitioned between H_2O (5 ml) and EtOAc (10 ml) and the organic layer was separated. The aqueous phase was extracted with additional EtOAc (2 x 10 ml) and the combined organic fractions were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by chromatography (50%-70% Et_2O-petrol) gave a single stereoisomer (by ^{1}H nmr) of the *title compound* (255 mg, 60%) as a colourless solid; mp 65-66 °C; ν_{max} (film) 3306, 2940, 2860, 1581, 1506, 1451, 1419, 1332, 1303, 1249, 1131, 1087 cm^{-1}; δ_H (300 MHz) 8.02-7.99 (2H, m, *ortho* PhSO$_2$), 7.92 (1H, s, H-3'), 7.65-7.58 (3H, m, ArH), 6.67 (2H, s, *ortho* trimethoxyphenyl), 4.87 (1H, s, NH), 3.90 (3H, s, OMe), 3.89 (6H, s, OMe), 3.27 (2H, s, H-1'), 3.01-2.95 (2H, m, CH_2SO_2N), 2.04-2.00 (2H, m, H-2), 1.52-1.43 (8H, m, H-2, H-3 and H-4), 1.15-1.09 (2H, m, CH_2SiMe_3), 0.07 (9H, s, Me_3Si); δ_C (75 MHz) 153.4, 142.7, 139.6, 139.3, 138.8, 133.5, 129.4, 129.1, 128.4, 106.7, 61.0, 60.9, 56.4, 52.5, 38.0, 35.9, 25.1, 22.7, 22.2, 10.8, -1.2; *m/z* (CI) 627 $[M+NH_4]^+$, 610 $[MH]^+$, 487, 449, 327, 189 (Found: $[M+NH_4]^+$, 627.2587; $C_{29}H_{43}NO_7S_2Si$ requires 627.2594); (Found C, 56.98; H, 6.89; N, 2.13. $C_{29}H_{43}NO_7S_2Si$ requires C, 57.11; H, 7.11; N, 2.30%).

(2*R*,3*S*,5*R*)-3-[4-(Benzyloxy)benzenesulfonyl]-2-ethyl-5-[methylethyl]pyrrolidine (16a-*syn*) and (2*S*,3*R*,5*R*)-3-[4-(benzyloxy)benzenesulfonyl]-2-ethyl-5-[methylethyl]pyrrolidine (16a *anti*). To **15a** (160 mg, 0.290 mmol, 1 equiv) at rt was added TBAF (2.90 ml of a 1M solution in THF, 2.90 mmol, 10 equiv). The resulting yellow solution was heated to reflux. After 24 h, the solution was quenched with MeOH (1 ml) and diluted with EtOAc (10 ml). The mixture was washed with sat. $NaHCO_3$ (5 ml) and sat. NaCl (5 ml). The organics were separated, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to reveal an oil. Chromatography (40%-50% EtOAc-petrol) gave a mixture of diastereoisomers (*syn*:*anti* >10:1) of the *title compounds* as a colourless solid (77 mg, 69%); ν_{max}(film) 3340, 3064, 3035, 2960,

2933, 2873, 1456, 1413, 1386, 1311, 1295, 1257, 1191, 1178, 1142, 1087, 1002 cm^{-1}; δ_H (300 MHz) *syn* isomer 7.83 (2H, d, *J* = 9.0 Hz, *ortho* $PhSO_2$), 7.46-7.37 (5H, m, ArH), 7.11 (2H, d, *J* = 9.0 Hz, *meta* $PhSO_2$), 5.16 (2H, s, OCH_2Ph), 3.47 (1H, ddd, *J* = 4.5, 6.0, 8.5 Hz, H-2), 3.19 (1H, ddd, *J* = 2.5, 6.0, 10.0 Hz, H-5), 2.82 (1H, ddd, *J* = 6.0, 8.5, 10.0 Hz, H-3), 2.67 (1H, br s, NH), 2.32 (1H, ddd, *J* = 2.5, 6.0, 14.0 Hz, H-4), 1.61 (1H, ddd, *J* = 10.0, 10.0, 14.0 Hz, H-4), 1.54-1.27 (3H, m, H-1' and H-1"), 0.95 (3H, d, *J* = 6.5 Hz, H-2"), 0.89 (3H, d, *J* = 6.5 Hz, H-2"), 0.88 (3H, t, *J* = 7.5 Hz, H-2'); δ_C (75 MHz) *syn* isomer 162.8, 135.7, 130.8, 130.4, 128.8, 128.5, 127.6, 115.3, 70.4, 68.6, 64.8, 60.7, 33.8, 32.6 29.4, 20.5, 19.7, 11.1; *m/z* (CI) 388 $[MH]^+$ (Found: $[MH]^+$, 388.1946; $C_{22}H_{29}NO_3S$ requires $[MH]^+$, 388.1946).

(2*R*,3*S*,5*R*)-5-(Benzyloxy)methyl-2-phenyl-3-(phenylsulfonyl)pyrrolidine (16b-*syn)* and (2*S*,3*R*,5*R*)-5-(benzyloxy)methyl-2-phenyl-3-(phenylsulfonyl)pyrrolidine (16b-*anti).* Compound **16b** was prepared on a 11.9 mmol scale according to the procedure described for **16a** to give, after chromatography (40%-50% EtOAc-petrol) a mixture of diastereoisomers (*syn*:*anti* >25:1) of the *title compounds* as a colourless oil (142 mg, 81%). Some of the major diastereoisomer could be separated for full characterisation; $[\alpha]_D^{20}$ -22.5 (*c* 1.60, $CHCl_3$); ν_{max} (film) 3300, 3061, 3030, 2838, 1493, 1449, 1362, 1304, 1202, 1144, 1086, 1026, 1002 cm^{-1}; δ_H (300 MHz) 7.84-7.81 (2H, m, *ortho* $PhSO_2$), 7.62-7.57 (1H, m, *para* $PhSO_2$), 7.50-7.45 (2H, m, ArH), 7.39-7.29 (5H, m, ArH), 7.22-7.15 (5H, m, ArH), 4.66 (1H, d, *J* = 6.0 Hz, H-2), 4.57 (2H, s, OCH_2Ph), 3.74-3.61 (2H, m, H-3 and H-5), 3.63 (1H, dd, *J* = 4.0, 9.0 Hz, H-1'), 3.52 (1H, dd, *J* = 6.0, 9.0 Hz, H-1'), 2.47 (1H, ddd, *J* = 3.5, 6.5, 14.0 Hz, H-4), 2.43 (1H, br s, NH), 2.03 (1H, ddd, *J* = 10.0, 10.0, 14.0 Hz, H-4); δ_C (75 MHz) 141.9, 138.4, 138.2, 133.7, 129.2, 128.6, 128.5 (2C), 127.7, 127.6, 127.5, 126.9, 73.4, 72.7, 70.6, 62.9, 58.0, 30.4; *m/z* (CI) 408 $[MH]^+$ (Found: $[MH]^+$, 408.1636; $C_{24}H_{25}NO_3S$ $[MH]^+$, requires 408.1633); (Found C, 71.03; H, 6.07; N, 3.32. $C_{24}H_{25}NO_3S$ requires C, 70.73; H, 6.18; N, 3.44%).

(2*R*,3*S*,5*R*)-5-(Benzyloxy)methyl-2-(3-butenyl)-3-(phenylsulfonyl)pyrrolidine (16c-*syn)* and (2*S*,3*R*,5*R*)-5-(benzyloxy)methyl-2-(3-butenyl)-3-(phenylsulfonyl)pyrrolidine (16c-*anti).* To **15c** (1.08 g, 1.97 mmol, 1 equiv) at rt was added TBAF (19.7 ml of a 1M solution in THF, 19.7 mmol, 10 equiv). The dark yellow solution was stirred at rt for 2 d and then quenched with methanol (10 ml). The solvent was removed under reduced pressure and the residue that remained was purified by chromatography (30%-50% EtOAc-petrol) to afford a mixture of diastereoisomers (*syn*:*anti* >10:1) of the *title compounds* as a colourless oil (530 mg, 70%). Some of the major isomer could be separated for full characterisation; $[\alpha]_D^{20}$ +7.3 (*c* 1.10, $CHCl_3$); ν_{max} (film) 3346, 3064, 3030, 3002, 2973, 2913, 2856, 1641, 1584, 1496, 1479, 1459, 1417, 1359, 1304, 1206, 1178, 1145, 1114, 1085, 1027 cm^{-1}; δ_H (300 MHz) 7.94-7.90 (2H, m, *ortho* $PhSO_2$), 7.72-7.66 (1H, m, *para* $PhSO_2$), 7.63-7.57 (2H, m, ArH), 7.39-7.29 (5H, m, ArH), 5.71 (1H, dddd, *J* = 6.5, 6.5, 10.0, 17.0 Hz, H-3'), 4.98-4.94 (2H, m, H-4'), 4.52 (2H, s, OCH_2Ph), 3.63-3.37 (4H, m, H-2, H-5 and H-1"), 3.26 (1H, ddd, *J* = 3.5, 6.5, 10.5 Hz, H-3), 2.28 (1H, ddd, *J* = 3.5, 6.5, 13.5 Hz, H-4), 2.17-1.98 (3H, m, H-4 and H-2'), 1.90-1.79 (1H, m, H-2'), 1.66-1.39 (2H, m, H-1'); δ_C (75 MHz) 138.7, 138.1, 137.7, 133.8, 129.4, 128.6, 128.4,

127.8, 127.7, 115.2, 73.4, 72.1, 68.7, 59.2, 57.8, 35.5, 31.0, 30.7; *m/z* (CI) 386 $[MH]^+$, 264, 134, 122 (Found: $[MH]^+$, 386.1783; $C_{22}H_{27}NO_3S$ requires $[MH]^+$, 386.1790).

(2*R*,3*S*,5*R*)-5-(Benzyloxy)methyl-2-(4-pentenyl)-3-(phenylsulfonyl)pyrrolidine (16d-*syn*) and (2*S*,3*R*,5*R*)-5-(benzyloxy)methyl-2-(4-pentenyl)-3-(phenylsulfonyl)pyrrolidine (16d-*anti*). Compound **16d** was prepared on a 4.99 mmol scale according to the procedure described for **16c** to give, after chromatography (40%-50% EtOAc-petrol) a mixture of diastereoisomers (*syn*:*anti* >10:1) of the *title compounds* as a colourless oil (1.19 g, 60%). Some of the major isomer could be separated for full characterisation; mp 56 °C; $[\alpha]_D^{20}$ +6.6 (*c* 1.36, $CHCl_3$); ν_{max} (film) 3346, 3065, 3030, 2924, 2858, 1447, 1304, 1145, 1086, 1027 cm^{-1}; δ_H (300 MHz) 7.91 (2H, m, *ortho* $PhSO_2$), 7.71-7.57 (3H, m, ArH), 7.38-7.29 (5H, m, ArH), 5.72 (1H, dddd, *J* = 6.5, 6.5, 10.0, 17.0 Hz, H-4'), 5.00-4.92 (2H, m, H-5'), 4.51 (2H, s, OCH_2Ph), 3.57-3.37 (4H, m, H-2, H-5 and H-1''), 3.24 (1H, ddd, *J* = 3.5, 6.5, 14.0 Hz, H-3), 2.28 (1H, m, H-4), 2.15-1.99 (2H, m, H-3'), 1.90-1.70 (2H, m, H-4 and NH), 1.54-1.30 (4H, m, H-2' and H-3'); δ_C (75 MHz) 138.7, 138.3, 138.0, 133.8, 129.4, 128.6, 128.5, 127.7 (2C), 114.8, 73.4, 71.8, 68.7, 59.7, 57.9, 35.8, 33.5, 30.7, 26.2; *m/z* (CI) 400 $[MH]^+$, 278, 182, 136, 91 (Found: $[MH]^+$, 400.1946; $C_{23}H_{29}NO_3S$ requires $[MH]^+$, 400.1946); (Found C, 69.19; H, 7.47; N, 3.60. $C_{23}H_{29}NO_3S$ requires C, 69.14; H, 7.32; N, 3.51%).

(2*R, 3*S**)-1-Aza-3-phenylsulfonyl-2-(3,4,5-trimethoxyphenyl)-[4.5]spirodecane (16e).** Compound **16e** was prepared on a 0.210 mmol scale according to the procedure described for **16a** to give, after chromatography (70%-100% Et_2O-petrol) the *title compound* as a colourless solid (75 mg, 80%); mp 110-111 °C; ν_{max} (film) 3334, 3064, 2992, 2932, 2852, 1461, 1450, 1423, 1360, 1324, 1300, 1237, 1179, 1145, 1127, 1088, 1008 cm^{-1}; δ_H (300 MHz) 7.78-7.76 (2H, m, *ortho* $PhSO_2$), 7.57-7.53 (1H, m, *para* $PhSO_2$), 7.46-7.41 (2H, m, *meta* $PhSO_2$), 6.52 (2H, s, *ortho* trimethoxyphenyl), 4.64 (1H, d, *J* = 7.5 Hz, H-2), 3.81 (1H, ddd, *J* = 7.5, 8.5, 9.5 Hz, H-3), 3.80 (6H, s, OMe), 3.79 (3H, s, OMe), 2.27 (1H, dd, *J* = 8.5, 13.5 Hz, H-4), 2.11 (1H, dd, *J* = 9.5, 13.5 Hz, H-4), 1.85-1.38 (11H, m, H-6, H-7, H-8, H-9, H-10 and NH); δ_C (75 MHz) 152.9, 138.9, 137.2, 136.9, 133.6, 129.0, 128.3, 104.0, 70.6, 62.2, 61.7, 60.7, 56.0, 39.3, 39.0, 38.1, 25.6, 23.8, 23.5; *m/z* (CI) 446 $[MH]^+$, 304 (Found: $[MH]^+$, 446.1998; $C_{24}H_{31}NO_5S$ requires $[MH]^+$, 446.2001); (Found C, 64.53; H, 7.02; N, 3.24. $C_{24}H_{31}NO_5S$ requires C, 64.69; H, 7.01; N, 3.14%).

(*S*)-3-Hydroxy-2-(toluene-4-sulfonylamino)propionic acid (23). To a rapidly stirred solution of L-serine **22** (18.0 g, 171.2 mol) in EtOAc (400 ml) and H_2O (120 ml) at rt was added 2 M NaOH (228 ml, 456 mol) dropwise over 3 h. After a further 1 h, the phases were separated, with the aqueous layer cooled by ice bath and acidified to pH ~1 with conc. HCl. The resulting white precipitate was filtered, and the collected solid was washed with cold H_2O (50 ml) and dried to give the *title compound* as a white solid (35.0 g, 79%); $[\alpha]_D^{20}$ +11.0 (*c* 1.46, MeOH); δ_H (300 Hz) 12.6 (1H, br s, CO_2H), 7.95 (1H, d, *J* = 8.5 Hz, N*H*), 7.67 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.0 Hz, Ar*H*), 5.1 (1H, br s, O*H*), 3.75-3.68 (1H, m, C*H*N), 3.53-3.38 (2H, m, CH_2OH), 2.37 (3H, s, $ArCH_3$).

***N*-((*S*)-1-Hydroxymethyl-2-oxo-decyl)-4-methylbenzenesulfonamide (24).** To a solution of **23** (10.00 g, 38.6 mmol) in THF (400 ml) at –78 ºC was added *n*-BuLi (30.8 ml of a 2.5 M sol. in hexanes, 77.1 mmol, 2 equiv). The Grignard reagent, prepared from 1-bromooctane (29.8 g, 154 mmol, 4 equiv) and magnesium (3.84 g, 158 mmol, 4.1 equiv) in Et_2O (160 ml) was then added and the resultant grey suspension was stirred for 3 d. The mixture was then poured into 1 M HCl (400 ml), and extracted with EtOAc (3 x 200 ml). Organic phases were combined, washed with saturated aqueous $NaHCO_3$ (300 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting off white solid was purified by recrystallisation (EtOAc/petrol) to give the *title compound* as a white solid (10.31 g, 38%); $[\alpha]_D^{20}$ +56.4 (*c* 1.63, $CHCl_3$); ν_{max} (film) 3500, 3271, 3056, 2927, 2857, 1721, 1463, 1458, 1437, 1422, 1334, 1304, 1266, 1164 cm^{-1}; δ_H (300 Hz) 7.73 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ar*H*), 5.86 (1H, d, *J* = 6.0 Hz, N*H*), 3.91-3.84 (3H, m, CH_2OH, C*H*N), 2.56-2.30 (2H, m, C(O)CH_2), 2.43 (3H, s, ArCH_3), 2.20 (1H, br s, O*H*), 1.38-1.10 (12H, m, 6 x CH_2), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3); δ_C (75 Hz) 206.3, 144.2, 136.4, 130.1 (2C), 127.4 (2C), 63.5, 63.3, 39.8, 32.0, 29.5, 29.3, 29.1, 23.6, 22.8, 21.8, 14.3; *m/z* (CI) 373 $[M+NH_4]^+$, 357, 343 (Found: $[M+NH_4]^+$, 373.2166; $C_{18}H_{29}NO_4S$ requires $[M+NH_4]^+$ 373.2161); (Found C, 60.94; H, 8.01: N, 3.89. $C_{18}H_{29}NO_4S$ requires C, 60.82; H, 8.22; N, 3.94%).

***N*-[(*S*)-2-Hydroxy-1-(2-octyl-[1,3]dithian-2-yl)ethyl]-4-methylbenzene-sulfonamide (25).** To a solution of **24** (11.4 g, 32.2 mmol) in DCM (100 ml) at 0 °C was added $BF_3.OEt_2$ (5 ml) *via* syringe. The solution was then allowed to warm to rt and stirred for 24 h. The reaction mixture was quenched by addition to saturated aqueous $NaHCO_3$ (200 ml), the phases separated, and the aqueous layer extracted further with DCM (3 x 60 ml). The organic layers were combined, dried ($MgSO_4$), concentrated and purified by silica column chromatography (5% Et_2O in DCM) to give the *title compound* as a clear gum (12.2 g, 83%); $[\alpha]_D^{20}$ +47.6 (*c* 1.43, $CHCl_3$); ν_{max} (film) 3614, 3384, 3143, 3070, 3035, 3014, 2925, 2854, 1599, 1456, 1439, 1423, 1290, 1157, 1092 cm^{-1}; δ_H (300 Hz) 7.83 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.34 (2H, d, *J* = 8.0 Hz, Ar*H*), 5.47 (1H, d, *J* = 5.0 Hz, N*H*), 3.99 (1H, dd, *J* = 4.5, 12.0 Hz, C*H*OH), 3.89 (1H, dd, *J* = 3.5, 12.0 Hz, C*H*OH), 3.55-3.50 (1H, m, C*H*N), 3.0 (1H, br s, O*H*), 2.76-2.65 (2H, m, C*H*S), 2.49-2.43 (1H, m, C*H*S), 2.44 (3H, s, ArCH_3), 2.21-2.12 (1H, m, C*H*S), 1.84-1.68 (4H, m), 1.50-1.15 (12H, m), 0.89 (3H, t, 6.7 Hz, CH_2CH_3); δ_C (75 Hz) 144.1, 136.6, 129.9, 127.7, 62.8, 59.3, 56.9, 36.2, 32.0, 30.0, 29.5, 29.4, 26.3, 25.3, 24.6, 24.2, 22.8, 21.7, 14.3; *m/z* (CI) 463, 446 $[MH]^+$ (Found: $[MH]^+$, 446.1868; $C_{21}H_{35}NO_3S_3$ requires $[MH]^+$, 446.1857).

***N*-((*R*)-1-Hydroxymethyldecyl)-4-methylbenzenesulfonamide (26).** Raney nickel (approximately 6.6 g, 11 ml of settled material in ethanol) was added to **25** (2.35 g, 5.27 mmol) in ethanol (total volume 100 ml after washing). After heating at reflux for 45 min, the suspension was cooled and the Raney nickel was filtered off through a pad of silica gel, which was washed with additional ethanol. The filtrate was concentrated *in vacuo*, and the resulting crude mass purified by silica column chromatography (10% Et_2O-DCM) to give the *title compound* as a clear oil which solidified on standing (1.64 g, 91%); $[\alpha]_D^{20}$ +11.9 (*c* 1.34, $CHCl_3$); ν_{max} (film) 3600, 2925, 2854, 1599, 1460, 1428, 1323, 1093 cm^{-1}; δ_H (300 Hz) 7.79 (2H, d, *J* = 8.0 Hz,

Ar*H*), 7.32 (2H, d, *J* = 8.0 Hz, Ar*H*), 4.90 (1H, d, *J* = 8.0 Hz, N*H*), 3.59 (1H, dd, *J* = 4.0, 11.0 Hz, C*H*OH), 3.49 (1H, dd, *J* = 5.5, 11.0 Hz, C*H*OH), 3.26-3.20 (1H, m, C*H*N), 2.45 (3H, s, ArCH_3), 2.07 (1H, br s, O*H*), 1.43-1.01 (16H, m), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3); δ_C (75 Hz) 143.3, 137.9, 129.7 (2C), 127.2 (2C), 64.9, 55.7, 31.9, 31.5, 29.5, 29.5, 29.4, 29.3, 25.6, 22.7, 21.5, 14.2; *m/z* (CI) 359, 342 $[MH]^+$ (Found: $[MH]^+$, 342.2111; $C_{18}H_{31}NO_3S$ requires $[MH]^+$, 342.2103); (Found C, 63.37; H, 9.15: N, 3.99. $C_{18}H_{31}NO_3S$ requires C, 63.31; H, 9.15; N, 4.10%).

(*R*)-2-Nonyl-1-(toluene-4-sulfonyl)aziridine (27). To a solution of **26** (8.15 g, 23.9 mmol) and tosyl chloride (5.92 g, 31.0 mmol, 1.3 equiv) in THF (160 ml) at 0 °C was added freshly ground KOH (6.70 g, 0.119 mol, 5 equiv) in one portion. The white suspension was the allowed to warm to rt and stirring continued for 16 h. After this time, H_2O (200 ml) was added, the phases were separated and the aqueous layer extracted with Et_2O (3 x 100 ml). The organic phases were combined, dried ($MgSO_4$), concentrated *in vacuo*, with the resulting crude material purified by silica column chromatography (30% Et_2O in DCM) to give the *title compound* as a clear oil (7.59 g, 98%); $[\alpha]_D^{20}$ +2.0 (*c* 2.01, $CHCl_3$); ν_{max} (film) 2997, 2917, 2852, 1598, 1495, 1456, 1402, 1378, 1324, 1306, 1292, 1230, 1184, 1161 cm^{-1}; δ_H (300 Hz) 7.84 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.5 Hz, Ar*H*), 2.76-2.70 (1H, m, C*H*N), 2.66 (1H, d, *J* = 7.0 Hz, CH_2N), 2.46 (3H, s, ArCH_3), 2.07 (1H, d, *J* = 4.5 Hz, CH_2N), 1.59-1.20 (16H, m), 0.90 (3H, t, *J* = 7.0 Hz, CH_2CH_3); δ_C (75 Hz) 144.6, 135.5, 129.8 (2C), 128.2 (2C), 40.7, 34.0, 32.1, 31.5, 29.6 (2C), 29.5, 29.2, 27.0, 22.9, 21.8, 14.3.

(*R*)-2-Nonyl-1-aziridine (28). To a solution of naphthalene (11.5 g, 89.9 mmol, 4.5 equiv) in THF (175 ml) at rt was added sodium (1.84 g, 79.901 mmol, 4 equiv) in small pieces. The resultant The dark green solution was stirred for 1 h before it was cooled to –78 ºC and a solution of **27** (6.46 g, 19.9 mmol) in THF (70 ml) added *via* syringe over 5 min. After 15 min, the cooling bath was removed and the solution immediately quenched with H_2O (100 ml). The mixture was warmed to rt and the layers were separated and the aqueous layer further extracted with Et_2O (3 x 100 ml). The organic layers were combined, dried ($MgSO_4$), concentrated *in vacuo* and the resulting crude product purified by rapid passage through a basic alumina column (DCM initially, then 5% MeOH in DCM) to give the *title compound* as a pale yellow oil (2.58 g, 76%); $[\alpha]_D^{20}$ -5.8 (*c* 1.41, $CHCl_3$); ν_{max} (film) 3242, 3053, 2989, 2949, 2860, 1466 cm^{-1}; δ_H (300 Hz) 1.98-1.90 (1H, m, C*H*N), 1.75 (1H, d, *J* = 6.0 Hz, CH_2N), 1.49-1.21 (16H, m), 1.33 (1H, d, *J* = 3.5 Hz, CH_2N), 0.89 (3H, t, *J* = 6.5 Hz, CH_2CH_3); δ_C (75 Hz) 134.8, 32.1, 30.6, 29.9, 29.8, 29.7, 29.5, 27.8, 25.3, 22.9, 14.3; *m/z* (CI) 509, 340. 170 $[MH]^+$ (Found: $[MH]^+$, 170.1912; $C_{11}H_{23}N$ requires $[MH]^+$, 170.1909).

(*R*)-2-Nonyl-1-[(2-trimethylsilanyl)ethanesulfonyl)]aziridine (21). To a solution of **28** (2.54 g, 15.0 mmol), DMAP (183 mg, 1.50 mmol, 0.1 equiv) and triethylamine (12.6 ml, 90.1 mmol, 6 equiv) in DCM (16 ml) at –5 ºC was added SESCl (3.89 g, 22.5 mmol, 1.5 equiv) in DCM (16 ml) *via* syringe over 10 min. After a further 20 min, sat. NaCl (100 ml) was added and the resulting solution extracted with DCM (3 x 50 ml). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by silica column chromatography (20% Et_2O-

petrol) gave the *title compound* as a pale yellow oil (3.69 g, 74%); $[\alpha]_D^{20}$ -22.0 (*c* 6.37, $CHCl_3$); ν_{max} (film) 2966, 2945, 2897, 2862, 2850, 1460, 1421, 1408, 1324, 1286, 1252, 1171, 1145, 1109 cm^{-1}; δ_H (300 Hz) 3.11-3.05 (2H, m, C*H*$_2$SO$_2$N), 2.75-2.69 (1H, m, C*H*N), 2.60 (1H, d, *J* = 7.0 Hz, C*H*$_2$N) 2.10 (1H, d, *J* = 4.5 Hz, C*H*$_2$N), 1.61-1.27 (16H, m), 1.18-1.12 (2H, m, C*H*$_2$Si), 0.89 (3H, t, *J* = 6.5 Hz, CH$_2$C*H*$_3$) 0.08 (9H, s, TMS); δ_C (75 Hz) 48.9, 39.4, 33.6, 32.1, 31.7, 29.7 (2C), 29.5, 29.4, 27.0, 22.9, 14.3, 9.9, -1.8; *m/z* (CI) 351, 334 $[MH]^+$ (Found: $[MH]^+$, 334.2235; $C_{16}H_{35}NO_2SSi$ requires [MH]+, 334.2236).

(*E*)-1-Phenyl-3-phenylsulfonylpropene (32). To a suspension of benzenesulfinic acid, Na salt (6.45 g, 39.3 mmol, 1.2 equiv) in DMF (45 ml) at rt was added cinnamoyl chloride (5.00 g, 32.8 mmol) *via* syringe. After 16 h, the reaction was poured into H_2O (100 ml) and EtOAc (100 ml). The layers were separated, and the organic layer washed with H_2O (3 x 50 ml). The organic layer was then dried ($MgSO_4$), concentrated *in vacuo*, and recrystallised ($CHCl_3$/petrol) to give the *title compound* as a white crystalline solid (6.85 g, 81%); ν_{max} (film) 3118, 3097, 3082, 3070, 3057, 3028, 2974, 2931, 2904, 1446, 1402, 1319, 1292, 1238, 1159, 1136, 1084, 1055 cm-1; δ_H (300 Hz) 7.94-7.87 (2H, m, PhSO$_2$), 7.70-7.63 (1H, m, PhSO$_2$), 7.60-7.52 (2H, m, PhSO$_2$), 7.38-7.25 (5H, m, Ph), 6.39 (1H, d, *J* = 16.0 Hz, PhC*H*), 6.12 (1H, dt, *J* = 7.5, 16.0 Hz, PhCH=C*H*), 3.97 (2H, dd, *J* = 1.0, 7.5 Hz, C*H*$_2$SO$_2$); δ_C (75 Hz) 139.4, 138.7, 136.0, 134.0, 129.3 (2C), 128.9 (2C), 128.7 (3H), 126.8, 115.3, 30.7; *m/z* (CI) 276 $[M + NH_4]^+$ (Found: $[M+NH_4]^+$, 276.1054; $C_{15}H_{14}NO_2S$ requires $[M+NH_4]^+$, 276.1058).

(5*R*)-3-(Phenylsulfonyl)-1-phenyl-5-[2-(trimethylsilanyl)ethanesulfonylamino]-tetradec-1-ene (30). To a solution of **32** (3.10 g, 12.0 mmol, 2 equiv) in THF (35 ml) and TMEDA (9.2 ml) at –78 ºC under nitrogen was added *n*-BuLi (5.71 ml of a 2.1 M solution in hexanes, 12.0 mmol, 2 equiv) *via* syringe over 5 min. After 1 h, **21** (2.00 g, 6.00 mmol) in THF (9.2 ml) was added *via* syringe and the solution allowed to warm to rt. After 3 h, saturated aqueous NH_4Cl (100 ml) was added and resulting mixture was extracted with EtOAc (4 x 50 ml). The organic layers were combined, dried ($MgSO_4$), concentrated *in vacuo* and the resulting crude product was purified by silica column chromatography (20% EtOAc-petrol) to give the *title compound* as a clear oil (3.39 g, 95%); ν_{max} (film) 3300, 3062, 3028, 2952, 2924, 2854, 1585, 1496, 1448, 1431, 1377, 1317, 1306, 1263, 1252, 1207, 1167, 1145, 1105, 1084, 1026 cm^{-1}; δ_H (300 Hz) 7.85-7.50 (5H, m, PhSO$_2$), 7.38-7.21 (5H, m, Ph), 6.35 & 6.26 (1H, 2 x d, *J* = 16.0 Hz, PhC*H*, approx. 2:1 ratio), 5.98-5.89 (1H, m, C*H*=CHPh), 4.24-3.36 (3H, m), 3.02-2.80 (2H, m), 2.58-2.29 (1H, m), 2.07-1.91 (1H, m), 1.65-0.95 (18H, m), 0.90 (3H, t, *J* = 6.5 Hz, CH$_2$C*H*$_3$), 0.06 & 0.05 (9H, 2 x s, TMS); δ_C (75 Hz) 137.3, 136.0, 135.9, 133.9, 129.4, 129.3, 129.1, 128.8, 128.8, 128.6, 128.6, 126.8, 121.3, 120.7, 66.4, 66.3, 52.7, 51.9, 50.5, 50.3, 37.1, 35.2, 34.5, 33.3, 32.0, 29.6, 29.6, 29.4, 25.8, 25.6, 22.8, 14.2, 10.9, -1.8; *m/z* (CI) 609, 469 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 609.3239; $C_{31}H_{49}NO_4S_2Si$ requires $[M+NH_4]^+$, 609.3216).

(2*S*, 3*R*, 5*R*)-2-Benzyl-3-phenylsulfonyl-5-nonylpyrrolidine (19). To **30** (640 mg, 1.081 mmol) was added TBAF (16.22 ml of a 1 M solution in THF, 16.22 ml, 15 equiv) at rt and the resulting solution was heated to reflux. After 38 h, the reaction was then cooled to rt and MeOH (5 ml) was added followed by H_2O (50 ml). The solution was then extracted with EtOAc (2 x 50

ml), the organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the resulting crude material by chromatography on silica gave the *title compound* as a colourless oil (360 mg, 78%); $[\alpha]_D^{20}$ -9.6 (*c* 4.16, $CHCl_3$); ν_{max} (film) 3336, 3084, 3066, 3032, 3003, 2981, 2954, 2924, 2848, 2731, 2669, 1603, 1585, 1495, 1446, 1406, 1377, 1304, 1176, 1145, 1086, 1028 cm^{-1}; δ_H (300 Hz) 7.97-7.91 (2H, m, Ar*H*), 7.73-7.57 (3H, m, Ar*H*), 7.32-7.10 (5H, m, Ar*H*), 3.76 (1H, ddd, *J* = 3.5, 7.0, 9.0 Hz, H-3), 3.36 (1H, ddd, *J* = 3.5, 7.0, 10.5 Hz, H-4), 3.08 (1H, dq, *J* = 6.5, 10.0 Hz, H-7), 2.82 (1H, dd, *J* = 3.5, 13.5 Hz, H-1), 2.64 (1H, dd, *J* = 9.0, 13.5 Hz, H-2), 2.40 (1H, ddd, 13.5, 6.5, 3.5 Hz, H-5), 1.88 (1H, br s, N*H*), 1.57 (1H, dt, *J* = 10.0, 13.5 Hz, H-6), 1.49-1.15 (16H, m), 0.89 (3H, t, *J* = 6.5 Hz, CH_2CH_3); δ_C (75 Hz) 139.0, 138.4, 134.0, 129.6, 129.4, 128.8, 128.7, 126.8, 67.3, 60.7, 58.4, 41.8, 35.9, 34.3, 32.0, 29.9, 29.7 (2C), 29.5, 27.2, 22.8, 14.3; *m/z* (CI) 428 $[MH]^+$ (Found: $[MH]^+$, 428.2615; $C_{26}H_{37}NO_2S$ requires $[MH]^+$, 428.2623).

(2*S*, 3*R*, 5*R*)-1-Methyl-2-benzyl-3-phenylsulfonyl-5-nonylpyrrolidine (33). To a solution of **19** (727 mg, 1.700 mmol) in MeCN (24 ml) at rt were added aqueous formaldehyde (8.29 ml of a 37% solution, 102 mmol, 60 equiv), acetic acid (574 µl, 10.03 mmol, 5.9 equiv), and sodium cyanoborohydride (531 mg, 8.50 mmol, 5 equiv). After 1 h, the reaction mixture was concentrated *in vacuo*, H_2O (70 ml) added and extracted with DCM (4 x 30 ml). Organic layers were combined, dried ($MgSO_4$), concentrated *in vacuo* and the crude material purified by silica column chromatography (30% EtOAc-petrol) to give the *title compound* as a clear oil (735 mg, 98%); $[\alpha]_D^{20}$ -40.0 (*c* 1.10, $CHCl_3$); δ_H (300 Hz) 7.87-7.82 (2H, m, Ar*H*), 7.69-7.52 (3H, m, Ar*H*), 7.26-7.13 (5H, m, Ph), 3.31-3.15 (2H, m), 2.91 (1H, dd, *J* = 4.0, 14.0 Hz, H-1), 2.62-2.43 (2H, m), 2.34-2.22 (1H, m, H-3), 2.30 (3H, s, NCH_3) 1.65-1.55 (1H, m, H-4), 1.44-1.00 (16H, m), 0.90 (3H, t, *J* = 6.5 Hz, CH_2CH_3); δ_C (75 Hz) 138.9, 137.7, 133.8, 130.4, 129.4, 128.8, 128.2, 126.5, 67.2, 65. 5, 64.8, 38.8, 33.6, 32.1, 31.9, 30.2, 29.8, 29.7 (2C), 29.5, 25.8, 22.9, 14.3; *m/z* (CI) 442 $[MH]^+$ (Found: $[MH]^+$, 442.2791; $C_{27}H_{39}NO_2S$ requires $[MH]^+$, 442.2780).

(2*S*, 5*R*)-2-Benzyl-1-methyl-5-nonyl-3-oxopyrrolidine (34). To a solution of **33** (164 mg, 0.371 mmol) in THF (2 ml) at –78 ºC was added *n*-BuLi (165 µl of a 2.7 M sol. in hexanes, 0.446 mmol, 1.2 equiv) to give a pale yellow solution. After 15 min, a solution of TMSOOTMS (86 mg, 0.483 mmol, 1.3 equiv) in THF (0.5 ml) was added *via* syringe. The solution was then allowed to warm to rt over a 2 h, and then stirred at rt for a further 15 h. After this time, the reaction was quenched with sat. aqueous $NaHCO_3$ (15 ml) and the mixture was extracted with EtOAc (3 x 10 ml). The organic layer were combined, dried ($MgSO_4$), concentrated *in vacuo* and the resulting crude product purified by silica column chromatography (20% EtOAc-petrol) to give recovered starting material (55 mg, 34%) and the *title compound* as a pale yellow oil (57 mg, 49%, 73% based on recovered starting material); $[\alpha]_D^{20}$ -97.9 (*c* 1.43, $CHCl_3$); ν_{max} (film) 3055, 2956, 2927, 2856, 1751, 1411, 1379, 1265, 1151, 1115, 1082 cm^{-1}; δ_H (300 Hz) 7.32-7.15 (5H, m, Ph), 3.08 (1H, dd, *J* = 4.5, 14.0 Hz, PhC*H*), 2.87 (1H, dd, *J* = 5.0, 14, Hz, PhC*H*), 2.78 (1H, distorted t, C*H*(O)), 2.55-2.44 (1H, m, NC*H*), 2.41 (1H, dd, *J* = 6.0, 17.5 Hz, C(O)CH_2), 2.33 (3H, s, NMe), 1.79 (1H, dd, *J* = 10.5, 18.0 Hz, C(O)CH_2), 1.40-1.10 (16H, m), 0.91 (3H, t, *J* = 6.5 Hz, CH_3); δ_C (75 Hz) 215.0, 138.7, 129.9, 128.2, 126.3, 74.5, 62.6, 42.9, 39.4, 36.1, 33.1,

32.1, 30.0, 29.7, 29.7, 29.5, 25.8, 22.9, 14.3; *m/z* (CI) 306 $[MH]^+$ (Found: $[MH]^+$, 316.2637; $C_{21}H_{33}NO$ requires $[MH]^+$, 316.2640).

(+)-Preussin (1). To a solution of **34** (69 mg, 0.218 mmol) in THF (1 ml) at –78 ºC was added lithium aluminium hydride (0.66 ml of a 1 M solution in THF, 0.656 mmol, 3 equiv) dropwise over 3 min *via* syringe After 1 h at –78 ºC, H_2O (25 μl) was added dropwise *via* syringe, followed by 10% aqueous NaOH (25 μl). The mixture was diluted with EtOAc (3 ml) and allowed to warm to rt. After stirring at rt for 30 min, H_2O (75 μl) was added and the white solid filtered off through a pad of kieselguhr, washing with EtOAc. The filtrate was concentrated and the resulting crude product purified by silica column chromatography (40% EtOAc-petrol) to give the *title compound* as a very pale yellow oil which solidified to a waxy solid on standing (59 mg, 86%); $[\alpha]_D^{20}$ +33.3 (*c* 1.08, $CHCl_3$); ν_{max} (film) 3450, 3085, 3065, 3028, 2954, 2935, 2854, 2789, 1495, 1454, 1423, 1219, 1196, 1155, 1134, 1101, 1055, 1030 cm^{-1}; δ_H (300 Hz) 7.36-7.18 (5H, m, Ph), 3.82 (1H, m), 2.97-2.81 (2H, PhCH_2), 2.35 (3H, s, NMe), 2.35-2.00 (4H, m), 1.82-1.66 (1H, m), 1.49-1.15 (16H, m), 0.91 (3H, t, *J* = 6.5 Hz, CH_3); δ_C (75 Hz) 139.7, 129.6, 128.6, 126.2, 73.8, 70.6, 66.0, 39.6, 38.9, 35.2, 33.9, 32.1, 30.1 29.8, 29.8, 29.5, 26.5. 22.9, 14.3.

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