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Sulfinamides as Highly Effective Amine Protecting Groups and Their Use in the Conversion of Amino Alcohols into Morpholines

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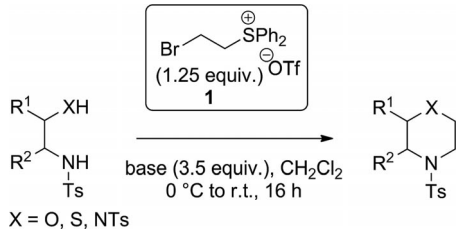
1,2-Amino alcohols have been converted into morpholines by using sulfinamides as temporary protecting/activating groups on the amine. We have developed a procedure for the selective synthesis of monoprotected *N*-sulfinyl amino alcohols through a double sulfinylation/hydrolysis strategy. Following the reaction of the sulfinamides with bromoethyldiphenylsulfonium triflate, protected morpholines were obtained in high yields. Subsequent treatment with HCl liberated the morpholine hydrochloride salts. The usefulness of this high yielding and efficient methodology has been demonstrated in the formal synthesis of the antidepressant drug (*S*,*S*)-reboxetine.

Introduction

Efficient methods for the synthesis of saturated heterocycles are especially important in medicinal chemistry where such motifs are ubiquitous.[1] We have previously reported the synthesis of pharmaceutically important building blocks such as morpholines and benzodiazepines from readily available amino alcohols and bromoethylsulfonium salt **1**, which is now commercially available (Scheme 1).[2,3]



Scheme 1. Methodology for the preparation of heterocycles from amino alcohols.[2c]

For cleavable groups on nitrogen, only sulfonyl groups in the form of Ts, Ns, Bts or SES have been reported, but occasionally issues relating to functional group compatibility and/or ease of removal (especially for Ts) can make these groups unsuitable. We have therefore considered alternative groups that are both easy to introduce and easy to remove. However, standard amine protecting groups, for example, Boc, Cbz and Ac, were not suitable in the annulation process as their use led to alternative products.[4] We therefore considered the possibility of using sulfinamides. Although the extensive practical and pioneering work of Davis and Ellman has demonstrated their use in highly stereoselective amine synthesis[5–7] and simple mild methods for their deprotection have been developed,[8] sulfinamides have not been commonly employed as direct amine protecting groups.

In this paper we describe the (nontrivial) synthesis of sulfinamides[9] derived from amino alcohols, their successful use in annulation and their straightforward deprotection. Furthermore, we illustrate the application of the methodology in a formal synthesis of the antidepressant (*S*,*S*)-reboxetine.

Results and Discussion

Our initial efforts focused on the preparation of sulfinamide **4a** derived from the amino alcohol **3a**. The use of *n*BuLi with methyl *p*-tolylsulfinate ester **5**[10] gave the desired product, but the reaction was found to be somewhat capricious in our case and partial reaction with the OH could not be avoided. The use of *p*-tolylsulfinyl chloride (**6**), which had to be freshly prepared due to its instability, or the much more stable *p*-tolylsulfinyl *p*-tolyl sulfone (**7**)[11,12] led to a mixture of starting material **3a**, the desired sulfinamide **4a** and the bis-protected adduct **8a** under a variety of conditions (Scheme 2). The difficulty in generating monosulfinamides in high yields from amines could be one of the reasons why this group has not been used extensively for

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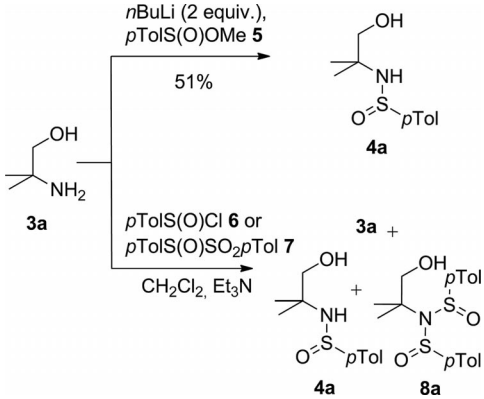
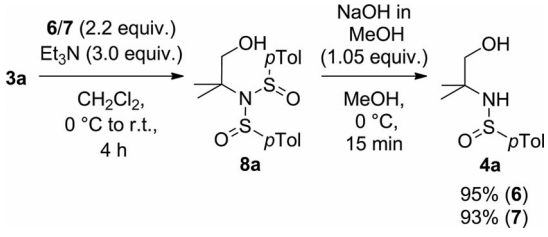
amine protection especially as it would share some of the benefits of the ubiquitous tosyl group but with the added benefit of a much simpler deprotection.



Scheme 2. Initial investigation of sulfinamide formation.

The mixture of products obtained (Scheme 2) indicated to us that under the mildly basic conditions the desired product **4a** was easily deprotonated and that the resulting anion had similar nucleophilicity to the neutral amine **3a**, thus leading to the bis-protected adduct **8a**. We therefore sought to exploit the reactivity of sulfinamide **4a** in a double protection/hydrolysis strategy. Thus, treatment of amino alcohol **3a** with 2.2 equiv. of *p*-tolylsulfinyl *p*-tolyl sulfone (**7**) led to full conversion to **8a**. Subsequent treatment with NaOH in MeOH selectively cleaved one of the sulfinyl groups to give the desired sulfinamide **4a** in high overall yield (Scheme 3). This protocol was general for a series of amino alcohols furnishing the sulfinamides **4a**–**f** in high yields as mixtures of isomers (Table 1).



Scheme 3. Optimised synthesis of mono-*N*-protected sulfinamide.

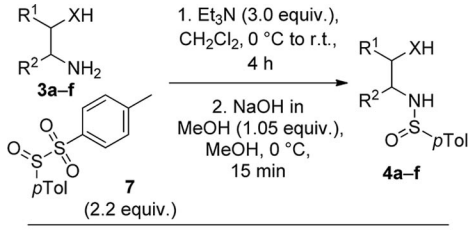
We then turned to the annulation reaction with the bromoethylsulfonium salt **1**. A number of bases were tested in this reaction (Table 2) and NaH in CH_2Cl_2 was found to be optimum.[13]

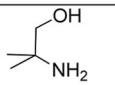
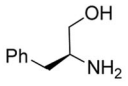
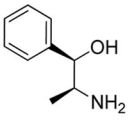
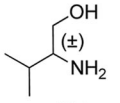
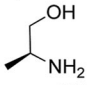
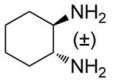
When applied to our sulfinamides **4a**–**f**, the protected morpholines **9a**–**e** and the piperazine **9f** were all obtained in high yields (Table 3).

The annulation reaction is believed to proceed via the intermediate vinyl sulfonium salt **2** and involves conjugate addition, proton transfer and cyclisation (Scheme 4).

To complete our synthetic strategy, we deprotected two representative substrates by facile treatment with HCl in Et_2O. The amine hydrochloride salts **12a**/**12e** precipitated

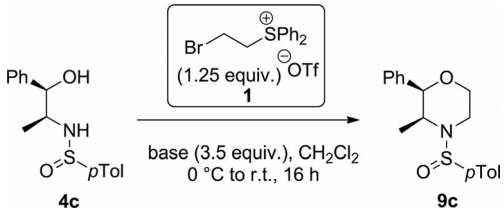
Table 1. Synthesis of *N*-*p*-tolylsulfinyl-protected amino alcohols **4a**–**e** and diamine **4f**.



Entry	Substrate	Yield of **4** (%) [a]
1		93/ 95 [b]
2		80
3		81
4		93
5		91
6		84 [c]

[a] Isolated yield. Obtained as a mixture of isomers (epimeric at sulfur). [b] With sulfinyl chloride as sulfinylating agent. [c] X = NS(O)*p*Tol.

Table 2. Optimisation of the conditions for annulation.

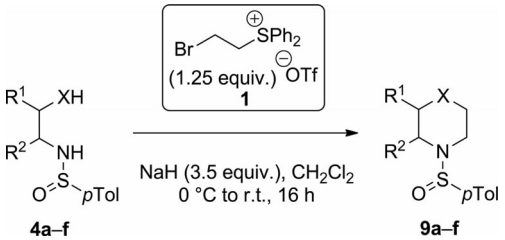


Entry	Base	Yield [%]
1	Et_3N	no conversion observed
2	DBU	49
3	NaH	93

and were isolated by simple filtration (Table 4). Salt **12e** is an especially notable morpholine that has been incorporated into a number of potential drug molecules.[14]

Finally, the methodology was applied to a formal synthesis of (*S*,*S*)-reboxetine, an antidepressant drug marketed by Pfizer.[15–17] Starting from the amino diol **13**, the reaction with excess *p*-tolylsulfinyl chloride (**6**) or *p*-tolylsulfinyl *p*-tolyl sulfone (**7**) followed by partial hydrolysis gave the required sulfinamide **14**. The primary alcohol was then protected as the trityl ether and the β-hydroxy sulfinamide **15**

Table 3. Synthesis of *N*-*p*-tolylsulfinyl-protected morpholines and piperazines.

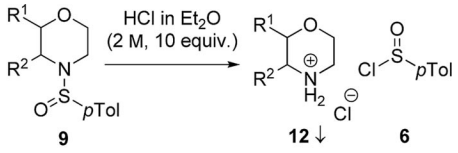


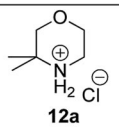
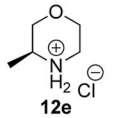
4a–f 9a–f

Entry	Substrate	Yield of **9** [%] [a]
1	**4a**	92
2	**4b**	92
3	**4c**	93
4	**4d**	73
5	**4e**	82
6	**4f**	71[b]

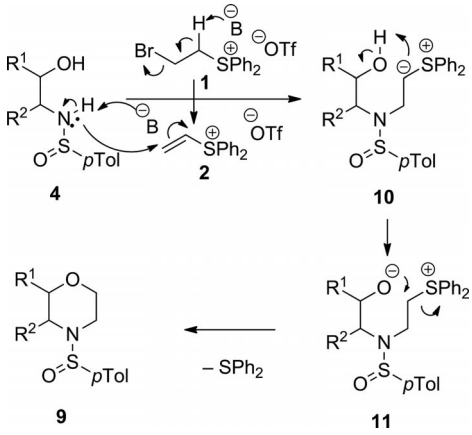
[a] Isolated yield. Obtained as a mixture of isomers (epimeric at sulfur). [b] X = NS(O)*p*Tol.

Table 4. Representative examples of deprotection.



Entry	Product	Yield of **12** (%)
1[a]	 **12a**	94
2	 **12e**	93

[a] *p*-Tolylsulfinyl chloride was reisolated from Et_2O as a yellow oil in 87% yield.

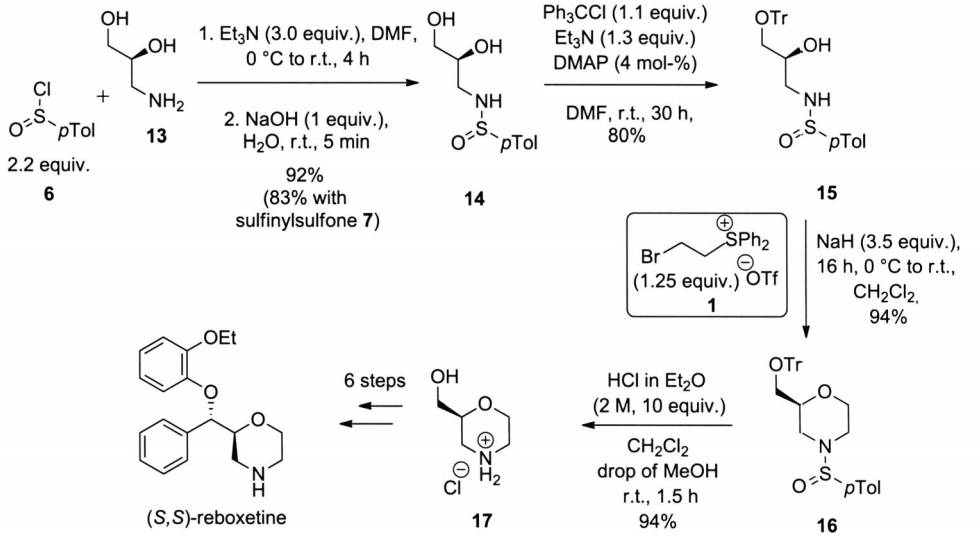


Scheme 4. Proposed mechanism for the annulation reaction.

was subjected to our standard annulation reaction, which furnished **16** in 94% yield. Without protection of the primary alcohol we found that competing formation of a seven-membered ring occurred, leading to a mixture of two heterocycles. Finally, simultaneous deprotection of both the trityl and sulfinamide groups was achieved with HCl in Et_2O, giving the morpholine hydrochloride **17** in 94% yield. This material was converted into (*S*,*S*)-reboxetine,[16] thus completing a formal synthesis of the drug (Scheme 5).

Conclusions

We have found that the *p*-tolylsulfinyl group is an ideal amine protecting group in the synthesis of morpholines from amino alcohols. Not only does it enable the annu-



Scheme 5. Formal synthesis of (*S*,*S*)-reboxetine.

lation reaction to proceed in high yield with the stable and crystalline bromoethylsulfonium salt **1** but it is also very easily deprotected to give the HCl salt of the morpholine. Furthermore, we have developed a highly effective method for installing the sulfinyl group onto primary amines. We expect this will increase the use of the sulfinyl group as a highly effective amine protecting group. Application of this significantly improved annulation methodology has been demonstrated in a formal synthesis of (*S*,*S*)-reboxetine.

Experimental Section

Sulfinyl Protection. General Method A: A mixture of Et_3N (3.0 equiv.) and β-amino alcohol (1.0 equiv.) or diamine (0.5 equiv.) **3a**–**f** in CH_2Cl_2 (0.5 M) was added dropwise over 5 min to a stirred mixture of sulfinylating agent (2.2 equiv.) **6** or **7** in CH_2Cl_2 (0.5 M) at 0 °C. The mixture was stirred at 0 °C for 1 h and then the ice bath was removed and the reaction stirred at room temp. for a further 3–4 h (Completion was monitored by TLC, EtOAc/PE, 1:1, for near-disappearance of the mono-protected substrate). The mixture was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$ before in vacuo solvent removal. The residue was dissolved in MeOH (0.1 M) and the stirred solution cooled to 0 °C. A 1 M solution of NaOH in MeOH (1.05 equiv. of base) was added dropwise over 5 min and the reaction stirred for a further 5 min (completion was monitored by TLC, 1:1 EtOAc/PE, for disappearance of the bis-protected substrate). After completion, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$ before in vacuo solvent removal. The residue was purified by flash chromatography (1:1 EtOAc/PE) to afford the *N*-mono-protected amino alcohol or diamine **4a**–**f**.

Annulation. General Method B: NaH (3.5 equiv., 60% in mineral oil) and then bromoethylsulfonium triflate (**1**, 1.2 equiv.) were slowly added (***Caution:*** **hydrogen gas is released**) to a stirred solution of the *N*-sulfinyl-protected β-amino alcohol or diamine **4a**–**f** (1 equiv.) in CH_2Cl_2 at 0 °C. The reaction was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for an additional 14 h. The mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (1:1 EtOAc/PE) to give *N*-sulfinyl-protected morpholines or piperazine **9a**–**f**.

Deprotection. General Method C: *N*-Sulfinyl-protected morpholine **9a** or **9e** was treated with 10 equiv. of HCl in Et_2O (2 M) and stirred for 10 min, during which morpholine hydrochloride precipitated. The now slightly yellow Et_2O solution (containing sulfinyl chloride **6**) was decanted by syringe. The precipitate was washed twice with small amounts of Et_2O and dried in vacuo to afford pure morpholine hydrochloride **12a** or **12e**.

Protection/Sulfinylating Reagents

4-Methylbenzene-1-sulfinyl Chloride[18,19] **(6):** Sulfuryl chloride (1.98 mL, 24.4 mmol, 3 equiv.) was added dropwise over 30 min to a vigorously stirred solution of *p*-tolyl disulfide (2.00 g, 8.1 mmol) in acetic acid (0.93 mL, 16 mmol, 2 equiv.) at –40 °C. The mixture was stirred for 3 h at –40 °C and then warmed to +35 °C for 1 h. Acetyl chloride was carefully removed in vacuo to afford the pure product (1.40 g, 99%) as a bright-yellow oil. Stored at –20 °C under argon, the compound was stable for approximately 48 h. The spectroscopic data were consistent with those reported in the literature.[18,19]

4-Methylphenyl (4-Methylphenyl)sulfinyl Sulfone[11,20] **(7a) and (7b):** In an open flask, sodium *p*-toluenesulfinate (3.40 g, 19.2 mmol, 1 equiv.) was added to thionyl chloride (1.40 mL, 19.2 mmol, 1 equiv.) in PE containing 12 drops of DMF. After the vigorous reaction had ceased a second portion of sodium *p*-toluenesulfinate (3.40 g, 19.2 mmol, 1 equiv.) was added and the reaction mixture was stirred for 24 h at room temp. under nitrogen. If necessary some additional PE was added to replace the solvent, which had evaporated. The reaction was poured into ice–water and the precipitated solid was collected by filtration, washed with PE and dried in vacuo to afford the named product as a white powder (4.51 g, 80%). To obtain analytically pure samples, the compound was dissolved in CH_2Cl_2 and the resulting suspension filtered. The pure product was crystallized from the filtrate by addition of *n*-hexane; m.p. 86–87 °C (from CH_2Cl_2/*n*-hexane) [ref.[11] 83–85 °C (CH_2Cl_2/*n*-hexane)]. IR (neat): $\tilde{\nu}_{max}$ = 2922–1653 (br. w, C–H), 1590, 1488, 1401, 1383, 1321, 1292 cm^{-1}. In $CDCl_3$, compound **7** is a mixture of isomers in rapid equilibrium; both isomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.04–8.00 (m, 8 H, Ar*H*), 2.49/2.44/2.40 (3 × s, 6 H, 3 × ArC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6 (C), 144.6 (C), 142.0 (C), 140.2 (C), 136.4 (CH), 133.0 (C), 130.1 (CH), 129.9 (CH), 129.3 (CH), 128.5 (CH), 127.4 (CH), 124.4 (C), 21.7 (CH_3), 21.6 (CH_3), 21.4 (CH_3) ppm. MS (EI+): *m*/*z* = 278 $[M - O]^+$, 155 $[p\text{TolSO}_2]^+$, 139 $[p\text{Tol S(O)}]^+$.

The spectroscopic data (^1H) are consistent with those reported in the literature.[11c]

***N*-(1-Hydroxy-2-methylpropan-2-yl)-4-methyl-*N*-(*p*-tolylsulfinyl)-benzenesulfinamide (8a):** According to general method A, **8a** (a yellow oil) was identified by ^1H NMR prior to treatment with NaOH/MeOH. It was obtained as a 1:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.5. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.63 (m, 8 H, ArH), 7.22–7.35 (m, 8 H, ArH), 4.23 (br. s, 1 H, OH), 4.15 (br. s, 1 H, OH), 3.95 (d, *J* = 9.8 Hz, 1 H, C*H*H), 3.92 (d, *J* = 9.8 Hz, 1 H, C*H*H), 3.51 (d, *J* = 9.8 Hz, 1 H, C*H*H), 3.42 (d, *J* = 9.8 Hz, 1 H, C*H*H), 2.41 (s, 6 H, 2 × ArCH_3), 2.39 (s, 6 H, 2 × ArCH_3), 1.41 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm.

***N*-(1-Hydroxy-2-methylpropan-2-yl)-4-methylbenzenesulfinamide (4a):** According to general method A, using either 4-methylphenyl (4-methylphenyl)sulfinyl sulfone (**7**; 783 mg, 2.66 mmol) or 4-methylbenzene-1-sulfinyl chloride (**6**; 465 mg, 2.66 mmol), 2-amino-2-methylpropan-1-ol (108 mg, 1.21 mmol) and Et_3N (0.51 mL, 3.6 mmol) in a total volume of 5 mL of CH_2Cl_2. The residue was dissolved in MeOH (12 mL) and a 1 M NaOH solution in MeOH (1.27 mL) was added dropwise. This afforded the sulfinamide [255 mg, 93% (from **7**) or 261 mg, 95% (from **6**)] as a yellow oil. R_f (EtOAc/PE, 1:1): 0.2. IR (neat): $\tilde{\nu}_{max}$ = 3240–3380 (O–H and N–H), 3050 (ArC–H), 2890–2970 (C–H), 952–1086 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.2 Hz, 2 H, ArH), 7.29 (d, *J* = 8.2 Hz, 2 H, ArH), 4.16 (br. s, 1 H, NH), 3.77 (br. s, 1 H, OH), 3.54–3.67 (dd, *J* = 11.8, 7.0 Hz, 1 H, CH), 3.42 (dd, *J* = 11.8, 5.9 Hz, 1 H, CH), 2.41 (s, 3 H, ArCH_3), 1.42 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9 (C), 141.4 (C), 129.5 (CH), 125.5 (CH), 70.9 (CH_2), 58.2 (C), 26.5 (CH_3), 23.3 (CH_3), 21.3 (ArCH_3) ppm. MS (ESI^+): *m*/*z* = 250 $[M + Na]^+$. HRMS (ESI^+): calcd. for $C_{11}H_{17}NO_2SNa^+$ $[M + Na]^+$ 250.0872; found 250.0872.

***N*-[(*S*)-1-Hydroxy-3-phenylpropan-2-yl]-4-methylbenzenesulfinamide (4b):** According to general method A, using 4-methylphenyl (4-methylphenyl)sulfinyl sulfone (**7**; 556 mg, 1.89 mmol), (*S*)-2-amino-

3-phenylpropan-1-ol (130 mg, 0.86 mmol) and Et_3N (0.36 mL, 2.6 mmol) in a total volume of 3.5 mL of CH_2Cl_2. The residue was dissolved in MeOH (9 mL) and a 1 M NaOH solution in MeOH (0.9 mL) was added dropwise. This afforded the sulfinamide (199 mg, 80%) as a pale-yellow gum after work-up as a 1:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.3. IR (neat): $\tilde{\nu}_{max}$ = 3200–3300 (O–H and N–H), 3020 (ArC–H), 2855–2921 (C–H), 941–1080 (S=O) cm^{-1}. Both diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.09–7.41 (m, 16 H, Ar*H*, mix), 6.91 (dd, *J* = 6.6, 2.9 Hz, 2 H, Ar*H*, mix), 5.16 (d, *J* = 9.3 Hz, 1 H), 4.69 (d, *J* = 9.3 Hz, 1 H), 3.48–3.84 (m, 4 H), 3.40 (dd, *J* = 11.6, 7.6 Hz, 1 H), 3.15–3.28 (m, 1 H), 2.82–3.00 (m, 2 H, CH_2Ph), 2.55–2.77 (m, 2 H, CH_2Ph), 2.39 (s, 3 H, ArCH_3), 2.37 (s, 3 H, ArCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5 (C), 141.2 (C), 141.0 (C), 138.1 (C), 138.0 (C), 137.4 (C), 129.40 (CH), 129.37 (CH), 129.31 (CH), 129.29 (CH), 128.3 (CH), 128.2 (CH), 126.34 (CH), 126.30 (CH), 126.1 (CH), 125.6 (CH), 65.14 (CH_2OH), 65.12 (CH_2OH), 60.4 (CH), 57.9 (CH), 38.9 (CH_2Ph), 38.4 (CH_2Ph), 21.2 (CH_3), 21.1 (CH_3) ppm. MS (ESI^+): *m*/*z* = 290 $[M + H]^+$, 242, 150, 139 $[p\text{TolS(O)}]^+$. HRMS (ESI^+): calcd. for $C_{16}H_{20}NO_2S^+$ $[M + H]^+$ 290.1215; found 290.1213.

***N*-[(1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl]-4-methylbenzenesulfinamide (4c):** According to general method A using 4-methylphenyl (4-methylphenyl)sulfinyl sulfone (**7**; 783 mg, 2.66 mmol), (1*R*,2*S*)-2-amino-1-phenylpropan-1-ol (183 mg, 1.21 mmol) and Et_3N (0.51 mL, 3.6 mmol) in a total volume of 5 mL of CH_2Cl_2. The residue was dissolved in MeOH (12 mL) and a 1 M NaOH solution in MeOH (1.27 mL) was added dropwise. This afforded the sulfinamide (315 mg, 81%) as a clear oil after work-up as a 1.3:1 mixture of diastereoisomers. R_f (EtOAc/PE, 4:6): 0.35. IR (neat): $\tilde{\nu}_{max}$ = 3240–3370 (O–H and N–H), 3050 (ArC–H), 2850–2924 (C–H), 969–1085 (S=O) cm^{-1}. Both diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.67 (m, 4 H, Ar*H*, mix.), 7.11–7.42 (m, 14 H, Ar*H*, mix.), 5.29 (d, *J* = 7.9 Hz, 1 H, N*H*, min.), 4.78 (br. s, 1 H, N*H*, maj.), 4.62 (d, *J* = 9.2 Hz, 2 H, PhC*H* and br. s, OH, mix.), 4.49 (d, *J* = 9.7 Hz, 1 H, PhC*H*, min.), 4.39 (br. s, 1 H, O*H*, min.), 3.70 (m, 1 H, NC*H*, maj.), 3.29–3.49 (m, 1 H, NC*H*, min.), 2.39 (s, 3 H, ArCH_3, min.), 2.38 (s, 3 H, ArCH_3, maj.), 1.06 (d, *J* = 6.8 Hz, 3 H, CH_3, maj.), 0.90 (d, *J* = 7.0 Hz, 3 H, CH_3, min.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4 (C), 141.32 (C), 141.26 (C), 140.5 (C), 140.1 (C), 139.0 (C), 129.5 (CH), 129.4 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.3 (CH), 126.2 (CH), 125.6 (CH), 76.2 (PhCH), 75.0 (PhCH), 56.9 (CH), 55.2 (CH), 21.2 ($ArCH_3$), 17.8 (CH_3), 16.4 (CH_3) ppm. MS (CI^+): *m*/*z* = 290 $[M + H]^+$, 272, 209, 139 $[p\text{TolS(O)}]^+$. HRMS (CI^+): calcd. for $C_{16}H_{19}NO_2SH^+$ $[M + H]^+$ 290.1215; found 290.1224.

The spectroscopic data are comparable to those reported in the literature (1*R*,2*R* and 1*S*,2*S* diastereomers).[10]

***N*-(±)-(1-Hydroxy-3-methylbutan-2-yl)-4-methylbenzenesulfinamide (4d):** According to general method A, using 4-methylphenyl (4-methylphenyl)sulfinyl sulfone (**7**; 783 mg, 2.66 mmol), (±)-2-amino-3-methylbutan-1-ol (125 mg, 1.21 mmol) and Et_3N (0.51 mL, 3.6 mmol) in a total volume of 5 mL of CH_2Cl_2. The residue was dissolved in MeOH (12 mL) and a 1 M NaOH solution in MeOH (1.27 mL) was added dropwise. After work-up, this afforded the sulfinamide (272 mg, 93%) as a clear oil as a 1.2:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.4. IR (neat): $\tilde{\nu}_{max}$ = 3200–3390 (O–H and N–H), 3050 (ArC–H), 2870–2958 (C–H), 1015–1100 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.54 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 7.21–7.34 (m, 4 H, Ar*H*, mix.), 4.64–4.84 (m, 2 H, N*H*, mix.), 4.13 (d, *J* = 10.1 Hz, 1 H, O*H*), 3.67–3.92 (m, 2 H, C*H*HOH and O*H*), 3.44–3.63 (m, 2 H, mix.), 3.29–3.42 (m, 1 H, C*H*HO), 3.14–3.27 (m, 1 H, NC*H*), 2.76 (dddd, *J* = 9.7, 8.3, 5.6, 2.4 Hz, 1 H, NC*H*), 2.40 (s, 6 H, ArCH_3, mix.), 1.77–1.96 (dqq, *J* = 5.6, 6.8, 6.8 Hz, 1 H, C*H*Me_2), 1.55–1.74 (dqq, *J* = 5.6, 6.8, 6.8 Hz, 1 H, C*H*Me_2), 1.01 (d, *J* = 6.8 Hz, 3 H, CH_3, min.), 0.95 (d, *J* = 6.8 Hz, 3 H, CH_3, min.), 0.79 (d, *J* = 6.8 Hz, 3 H, CH_3, maj.), 0.72 (d, *J* = 6.8 Hz, 3 H, CH_3, maj.) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): 141.9 (C), 141.6 (C), 141.5 (C), 138.3 (C), 129.6 (CH), 129.4 (CH), 126.3 (CH), 125.5 (CH), 65.7 (CH), 64.6 (CH_2), 64.3 (CH_2), 61.8 (CH), 30.6 (CH), 30.2 (CH), 21.29 (CH_3), 21.28 (CH_3), 19.8 (CH_3), 19.6 (CH_3), 18.3 (CH_3), 18.0 (CH_3) ppm. MS (CI^+): *m*/*z* = 242 $[M + H]^+$, 225, 139 $[p\text{TolS(O)}]^+$, 102, 86. HRMS (CI^+): calcd. for $C_{12}H_{20}NO_2S$ $[M + H]^+$ 242.1215; found 242.1214.

***N*-[(*S*)-1-Hydroxypropan-2-yl]-4-methylbenzenesulfinamide (4e):** According to general method A, using 4-methylphenyl (4-methylphenyl)sulfinyl sulfone (**7**; 1.29 g, 4.4 mmol), (*S*)-2-aminopropan-1-ol (150 mg, 2.0 mmol) and Et_3N (0.84 mL, 6.0 mmol) in a total volume of 8 mL of CH_2Cl_2. The residue was dissolved in MeOH (18 mL) and a 1 M NaOH solution in MeOH (2.0 mL) was added dropwise. After work-up, this afforded the sulfinamide (388 mg, 91%) as a clear oil as a 1.2:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.2. IR (neat): $\tilde{\nu}_{max}$ = 3200–3390 (O–H and N–H), 2870–2958 (C–H), 1015–1085 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.60 (4 H, m, Ar*H*, mix.), 7.19–7.34 (m, 4 H, Ar*H*, mix.), 4.97 (d, *J* = 9.0 Hz, 1 H, N*H*), 4.57 (br. s, 2 H, N*H* and O*H*), 3.89 (br. s, 1 H, O*H*), 3.37–3.67 (4 H, CH_2, mix.), 3.23–3.32 (m, 1 H, C*H*), 3.08–3.22 (m, 1 H, C*H*), 2.40 (s, 3 H, ArCH_3, maj.) 2.38 (s, 3 H, ArCH_3, min.), 1.24 (d, *J* = 6.6 Hz, 3 H, CH_3, min.), 1.03 (d, *J* = 6.8 Hz, 3 H, CH_3, maj.) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.5 (C), 141.33 (C), 141.27 (C), 139.0 (C), 129.6 (CH), 129.5 (CH), 126.2 (CH), 125.6 (CH), 67.2 (CH_2), 66.7 (CH_2), 53.8 (CH), 52.4 (CH), 21.2 ($ArCH_3$), 18.5 (CH_3), 18.2 (CH_3) ppm. MS (CI^+): *m*/*z* = 214 $[M + H]^+$, 197, 166, 139 $[p\text{TolS(O)}]^+$. HRMS (CI^+): calcd. for $C_{10}H_{16}NO_2S$ $[M + H]^+$ 214.0902; found 214.0901.

(±)-*N*,*N*′-(Cyclohexane-1,2-diyl)bis(4-methylbenzenesulfinamide) (4f): According to general method A, using 4-methylphenyl (4-methylphenyl)sulfinyl sulfone (**7**; 783 mg, 2.66 mmol), (±)-*trans*-cyclohexane-1,2-diamine (69 mg, 0.61 mmol) and Et_3N (0.51 mL, 3.6 mmol) in a total volume of 5 mL of CH_2Cl_2. The residue was dissolved in MeOH (12 mL) and a 1 M NaOH solution in MeOH (1.27 mL) was added dropwise. After work-up, this afforded the sulfinamide (197 mg, 84%) as a yellow oil as an approximate 1:6:6:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.17. IR (neat): $\tilde{\nu}_{max}$ = 3170 (N–H), 3050 (ArC–H), 2858–2928 (C–H), 1016–1087 (S=O) cm^{-1}. Two major diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.71 (m, 8 H, ArCH, mix.), 7.08–7.26 (m, 8 H, ArCH, mix.), 5.60 (d, *J* = 4.8 Hz, 2 H, NH), 5.08 (d, *J* = 7.9 Hz, 2 H, NH), 2.93 (m, 2 H, 2× NC*H*), 2.65–2.80 (m, 2 H, 2× NC*H*), 2.41 (s, 6 H, CH_3, maj.), 2.39 (s, 6 H, CH_3, maj.), 2.16 (dd, *J* = 11.9, 2.7 Hz, 2 H, CH_2), 1.59–1.73 (m, 2 H, CH_2), 1.46–1.57 (m, 4 H, CH_2), 1.10–1.32 (m, 6 H, CH_2), 0.79–1.28 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9 (C), 141.3 (C), 141.1 (C), 140.5 (C), 129.5 (CH), 129.3 (CH), 126.1 (CH), 125.2 (CH), 57.8 (NCH), 54.6 (NCH), 35.0 (CH_2), 34.8 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 21.4 (CH_3), 21.3 (CH_3) ppm. Distinguishable peaks of minor diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3, min.), 2.31 (s, 3 H, CH_3, min.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.6 (CH), 129.5 (CH), 127.1 (CH), 125.6 (CH) ppm. MS (ESI^+): *m*/*z* = 391 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_{20}H_{27}N_2O_2S_2$ $[M + H]^+$ 391.1523; found 391.1508.

3,3-Dimethyl-4-(*p*-tolylsulfinyl)morpholine (9a): According to general method B, using *N*-(1-hydroxy-2-methylpropan-2-yl)-4-methyl-

benzenesulfinamide (**4a**; 50 mg, 0.22 mmol, 1 equiv.), bromoethylsulfonium triflate (**1**; 1.2 equiv.) and NaH (3.5 equiv.) afforded *N*-sulfinyl-protected morpholine **9a** (51 mg, 92%) as a brown oil. R_f (EtOAc/PE, 1:1): 0.43. IR (neat): $\tilde{\nu}_{max}$ = 3020 (ArC–H), 2852–2970 (C–H), 984–1118 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.3 Hz, 2 H, Ar*H*), 7.23 (d, J = 8.3 Hz, 2 H, Ar*H*), 3.76 (dddd, J = 11.1, 3.4, 2.7, 0.6 Hz, 1 H, OC*H*H), 3.41 (dd, J = 11.1, 0.6 Hz, 1 H, OCH*H*), 3.27–3.37 (m, 2 H, OC*H*H and OC*H*H), 3.16 (ddd, J = 12.6, 11.1, 3.4 Hz, 1 H, NC*H*H), 2.43 (dt, J = 12.6, 2.7 Hz, 1 H, NC*H*H), 2.37 (s, 3 H, ArCH_3), 1.54 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9 (C), 140.4 (C), 129.5 (CH), 126.4 (CH), 77.8 (OCH_2), 67.6 (OCH_2), 56.7 (NC), 36.9 (NCH_2), 25.5 (CH_3), 22.1 (CH_3), 21.3 (CH_3) ppm. MS (ESI^+): m/z = 276 $[M + Na]^+$. HRMS (ESI^+): calcd. for $C_{13}H_{19}NO_2SNa^+$ $[M + Na]^+$ 276.1038; found 276.1028.

(3*S*)-3-Benzyl-4-(*p*-tolylsulfinyl)morpholine (9b): According to general method B, using *N*-[(*S*)-1-hydroxy-3-phenylpropan-2-yl]-4-methylbenzenesulfinamide (**4b**; 64.0 mg, 0.22 mmol, 1 equiv., *dr* 1:1), bromoethylsulfonium triflate (**1**; 1.2 equiv.) and NaH (3.5 equiv.) afforded *N*-sulfinyl-protected morpholine **9b** (64 mg, 92%) as a clear oil as a 1:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.4. IR (neat): $\tilde{\nu}_{max}$ = 3025 (ArC–H), 2860–2952 (C–H), 982–1104 (S=O) cm^{-1}. Both diastereoisomers: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, J = 8.2 Hz, 2 H, Ar*H*), 7.25 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.09–7.22 (m, 10 H, Ar*H*), 7.04–7.08 (m, 2 H, Ar*H*), 6.94 (d, J = 6.9 Hz, 2 H, Ar*H*), 3.50–3.95 (m, 11 H, mix.), 3.36 (dd, J = 13.8, 7.7 Hz, 1 H, C*H*), 3.14 (dd, J = 13.4, 10.0 Hz, 1 H, C*H*), 2.86–3.00 (m, 5 H, mix.), 2.34 (s, 3 H, $ArCH_3$), 2.30 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.19 (C), 141.18 (C), 140.1 (C), 140.0 (C), 138.2 (C), 138.0 (C), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 126.5 (CH), 126.4 (CH), 126.3 (CH), 126.2 (CH), 70.0 (CH_2O), 68.9 (CH_2O), 68.1 (CH_2O), 67.4 (CH_2O), 59.2 (CH), 57.6 (CH), 42.4 (CH_2Ph), 40.5 (CH_2Ph), 36.2 (NCH_2), 35.8 (NCH_2), 21.3 (CH_3), 21.2 (CH_3) ppm. MS (ESI^+): m/z = 316 $[M + H]^+$, 224, 176, 139 $[p\text{TolS(O)}]^+$. HRMS (ESI^+): calcd. for $C_{18}H_{22}NO_2S^+$ $[M + H]^+$ 316.1371; found 316.1384.

(2*R*,3*S*)-3-Methyl-2-phenyl-4-(*p*-tolylsulfinyl)morpholine (9c): According to general method B, using *N*-[(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-4-methylbenzenesulfinamide (**4c**; 71.0 mg, 0.25 mmol, 1 equiv., *dr* 1.3:1), bromoethylsulfonium triflate (**1**; 1.2 equiv.) and NaH (3.5 equiv.) afforded *N*-sulfinyl-protected morpholine **9c** (74 mg, 93%) as a brown oil. Isolated as a 1.3:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.5. IR (neat): $\tilde{\nu}_{max}$ = 3020 (ArC–H), 2861–2940 (C–H), 912–1122 (S=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.64 (m, 4 H, Ar*H*, mix.), 7.20–7.37 (m, 14 H, Ar*H*, mix.), 4.81 (d, J = 2.9 Hz, 1 H, OC*H*Ph, min.), 4.75 (d, J = 2.9 Hz, 1 H, OC*H*Ph, maj.), 4.05 (m, 2 H, mix.), 3.90 (m, 1 H, OC*H*H, mix.), 3.78–3.81 (m, 2 H, mix.), 3.72 (ddd, J = 12.4, 11.4, 3.1 Hz, 1 H, NC*H*H, min.), 3.50 (ddd, J = 13.3, 12.4, 3.7 Hz, 1 H, NC*H*H, min.), 3.34 (ddd, J = 13.6, 12.3, 3.8 Hz, 1 H, NC*H*H, maj.), 3.11 (dd, J = 13.6, 3.2 Hz, 1 H, NC*H*H, maj.), 2.88 (dd, J = 13.3, 3.1 Hz, 1 H, NC*H*H, min.), 2.45 (s, 3 H, ArCH_3, maj.), 2.43 (s, 3 H, ArCH_3, min.), 1.08 (d, J = 6.8 Hz, 3 H, CH_3, maj.), 1.03 (d, J = 6.8 Hz, 3 H, CH_3, min.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.30 (C), 141.25 (C), 140.28 (C), 140.25 (C), 139.2 (C), 139.1 (C), 129.7 (CH), 129.6 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 127.2 (CH), 126.30 (CH), 126.26 (CH), 125.4 (CH), 125.3 (CH), 81.3 (CHPh), 80.8 (CHPh), 68.9 (OCH_2), 67.7 (OCH_2), 57.3 (N*C*HMe), 56.8 (N*C*HMe), 40.1 (NCH_2), 38.9 (NCH_2), 21.33 ($ArCH_3$), 21.30 ($ArCH_3$), 12.0 (CH_3), 11.3 (CH_3) ppm. MS (ESI^+): m/z = 338 $[M + Na]^+$. HRMS (ESI^+): calcd. for $C_{18}H_{21}NO_2SNa^+$ $[M + Na]^+$ 338.1180; found 338.1185.

(±)-3-Isopropyl-4-(*p*-tolylsulfinyl)morpholine (9d): According to general method B, using *N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylbenzenesulfinamide (**4d**; 50 mg, 0.20 mmol, 1 equiv., *dr* 1.2:1), bromoethylsulfonium triflate (**1**; 1.2 equiv.) and NaH (3.5 equiv.) afforded *N*-sulfinyl-protected morpholine **9d** (40.4 mg, 73%) as a brown oil as a 1.4:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.7. IR (neat): $\tilde{\nu}_{max}$ = 3025 (ArC–H), 2772–2972 (C–H), 1007–1207 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.60 (m, 4 H, Ar*H*, mix.), 7.27–7.34 (m, 4 H, Ar*H*, mix.), 3.80–3.95 (m, 4 H, mix.), 3.69–3.79 (m, 2 H, mix.), 3.63 (ddd, J = 10.9, 3.2, 3.2 Hz, 1 H, NC*H*, maj.), 3.57 (ddd, J = 11.2, 3.8, 3.8 Hz, 1 H, NC*H*, min.), 3.43 (ddd, J = 14.1, 10.6, 3.7 Hz, 1 H, NC*H*H, maj.), 3.10–3.19 (m, 2 H, mix.), 2.98 (dt, J = 13.7, 3.8 Hz, 1 H, NC*H*H, min.), 2.75–2.86 (m, 2 H, mix.), 2.47–2.59 (m, 1 H, isoprop-C*H*, min.), 2.42 (s, 6 H, 2× ArCH_3, mix.), 2.30 (m, 1 H, isoprop-C*H*, maj.), 1.08 (d, J = 6.8 Hz, 3 H, CH_3, min.), 1.05 (d, J = 6.8 Hz, 3 H, CH_3, min.), 0.87 (d, J = 6.6 Hz, 3 H, CH_3, maj.), 0.76 (d, J = 6.8 Hz, 3 H, CH_3, maj.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3 (C), 141.2 (C), 140.6 (C), 140.5 (C), 129.6 (CH), 129.3 (CH), 126.27 (CH), 126.25 (CH), 69.0 (CH_2), 68.0 (CH_2), 67.7 (CH_2), 67.3 (CH_2), 64.9 (CH), 61.3 (CH), 44.8 (CH_2), 40.6 (CH_2), 26.3 (CH), 25.4 (CH), 21.35 (CH_3), 21.32 (CH_3), 20.31 (CH_3), 20.28 (CH_3), 19.8 (CH_3), 18.8 (CH_3) ppm. MS (CI^+): m/z = 268 $[M + H]^+$, 224, 195, 139 $[p\text{TolS(O)}]^+$, 128. HRMS (CI^+): calcd. for $C_{14}H_{22}NO_2S^+$ $[M + H]^+$ 268.1371; found 268.1368.

(3*S*)-3-Methyl-4-(*p*-tolylsulfinyl)morpholine (9e): According to general method B, using *N*-[(*S*)-1-hydroxypropan-2-yl]-4-methylbenzenesulfinamide (**4e**; 100 mg, 0.47 mmol, 1 equiv., *dr* 1:1), bromoethylsulfonium triflate (**1**; 1.2 equiv.) and NaH (3.5 equiv.) afforded *N*-sulfinyl-protected morpholine **9e** (92 mg, 82%) as a clear oil as a 1:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.4. IR (neat): $\tilde{\nu}_{max}$ = 3077 (ArC–H), 2856–2969 (C–H), 1062–1114 (S=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.58 (m, 4 H, Ar*H*, mix.), 7.28–7.35 (m, 4 H, Ar*H*, mix.), 3.69–3.86 (m, 4 H, mix.), 3.35–3.62 (m, 6 H, mix.), 3.30 (dd, J = 11.2, 8.6 Hz, 1 H, C*H*H), 3.01 (ddd, J = 12.7, 9.7, 3.3 Hz, 1 H, C*H*H), 2.63–2.75 (m, 2 H, mix.), 2.41 (s, 6 H, 2× ArCH_3), 1.41 (d, J = 6.8 Hz, 3 H, CH_3), 1.40 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.22 (C), 141.18 (C), 140.0 (C), 139.5 (C), 129.6 (CH), 129.5 (CH), 126.3 (CH), 126.1 (CH), 73.1 (CH_2), 72.6 (CH_2), 67.3 (CH_2), 67.0 (CH_2), 52.9 (CH), 52.8 (CH), 41.1 (CH_2), 40.7 (CH_2), 21.30 (CH_3), 21.29 (CH_3), 15.8 (CH_3), 15.7 (CH_3) ppm. MS (CI^+): m/z = 240 $[M + H]^+$, 153, 139 $[p\text{TolS(O)}]^+$, 125, 102. HRMS (CI^+): calcd. for $C_{12}H_{18}NO_2S^+$ $[M + H]^+$ 240.1058; found 240.1062.

(±)-1,4-Bis(*p*-tolylsulfinyl)decahydroquinoxaline (9f): According to general method B, using *N*,*N*′-(cyclohexane-1,2-diyl)bis(4-methylbenzenesulfinamide) (**4f**; 50 mg, 0.13 mmol, 1 equiv., *dr* 1:6:6:1), bromoethylsulfonium triflate (**1**; 1.2 equiv.) and NaH (3.5 equiv.) to afford *N*-sulfinyl-protected piperazine **9f** (38 mg, 71%) as a brown oil as an approximate 1:6:6:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:1): 0.4. IR (neat): $\tilde{\nu}_{max}$ = 3050 (ArC–H), 2858–2928 (C–H), 1016–1087 (S=O) cm^{-1}. Two major diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.51 (m, 8 H, ArH, mix.), 7.23–7.29 (m, 8 H, ArH, mix.), 3.33 (td, J = 9.8, 3.7 Hz, 2 H), 3.21–3.28 (m, 2 H), 3.05–3.19 (m, 2 H), 2.96 (ddd, J = 12.1, 9.2, 3.5 Hz, 2 H), 2.76–2.87 (m, 2 H), 2.62–2.74 (m, 2 H), 2.40 (s, 2× 3 H, $ArCH_3$, maj.), 2.38 (s, 2× 3 H, $ArCH_3$, maj.), 2.24–2.34 (m, 4 H), 1.89–2.05 (m, 8 H), 1.37–1.60 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.03 (C), 140.96 (C), 140.4 (C), 140.0 (C), 129.54 (CH), 129.49 (CH), 126.35 (CH), 125.9 (CH), 64.9 (NCH), 63.0 (NCH), 44.4 (CH_2), 43.3 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 25.3 (CH_2), 24.4 (CH_2), 21.29 (CH_3), 21.25 (CH_3) ppm. Distinguishable peaks of minor diastereoisomers: ^1H NMR (400 MHz,

$CDCl_3$): δ = 2.40 (s, 2× 3 H, $ArCH_3$, min.), 2.39 (s, 2× 3 H, $ArCH_3$, min.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.63 (CH, min.), 129.59 (CH, min.) 126.30 (CH, min.), 126.0 (CH, min.) ppm. MS (ESI^+): *m*/*z* = 417 $[M + H]^+$, 139 $[p\text{TolS(O)}]^+$. HRMS (ESI^+): calcd. for $C_{22}H_{29}N_2O_2S_2^+$ $[M + H]^+$ 417.1677; found 417.1665.

3,3-Dimethylmorpholin-4-ium Chloride (12a): According to general method C, using 3,3-dimethyl-4-(*p*-tolylsulfinyl)morpholine (**9a**; 33.8 mg, 0.13 mmol) and HCl in Et_2O (2 M, 0.66 mL, 1.3 mmol, 10 equiv.) afforded pure morpholine hydrochloride **12a** (18.6 mg, 93%) as a white salt; m.p. 194–195 °C (directly from synthesis) (ref.[6] 196–197 °C). IR (neat): $\tilde{\nu}_{max}$ = 3356 (N–H), 2511 (NH_2^+), 1639 (N^+–H), 1384–1463 (C–H) cm^{-1}. ^1H NMR (400 MHz, [D_4]methanol): δ = 3.87 (m, 2 H, OCH_2), 3.61 (s, 2 H, CCH_2O), 3.27 (t, *J* = 5.4 Hz, 2 H, NCH_2), 1.41 (s, 6 H, 2× CH_3) ppm. ^{13}C NMR (100 MHz, [D_4]methanol): δ = 74.4 (CH_2O), 64.9 (CH_2O), 55.2 (C), 40.5 (NCH_2), 21.9 (CH_3) ppm. MS (CI^+): *m*/*z* = 116 $[M - Cl]^+$, 93.0, 65.0, 57.0. HRMS (CI^+): calcd. for $C_6H_{14}NO^+$ $[M - Cl]^+$ 116.1075; found 116.1076.

The ^1H NMR spectroscopic data are comparable to those reported in the literature (δ_H recorded in [D_6]DMSO).[21]

(*S*)-3-Methylmorpholin-4-ium Chloride (12e): According to general method C, using (3*S*)-3-methyl-4-(*p*-tolylsulfinyl)morpholine (**9e**; 38 mg, 0.16 mmol) and HCl in Et_2O (2 M, 0.8 mL, 1.6 mmol, 10 equiv.) afforded pure morpholine hydrochloride **12e** (20 mg, 93%) as a white salt; m.p. >200 °C (directly from synthesis). $[\alpha]_D^{20}$ = +3.0 (*c* = 1.0, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 3372 (br., N–H), 2988 (C–H), 2508 (br., NH_2^+), 1639 (N^+–H), 1306–1452 (C–H) cm^{-1}. ^1H NMR (400 MHz, [D_4]methanol): δ = 3.91–4.02 (m, 2 H, 2× OC*H*H), 3.74 (ddd, *J* = 12.9, 11.3, 2.7 Hz, 1 H, OC*H*H), 3.44–3.52 (m, 1 H), 3.34–3.44 (m, 1 H), 3.29 (dt, *J* = 13.1, 2.4 Hz, 1 H, NC*H*H), 3.20 (ddd, *J* = 12.9, 11.4, 3.9 Hz, 1 H, NC*H*H), 1.26 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D_4]methanol): δ = 70.5 (CH_2), 64.5 (CH_2), 52.3 (CH), 44.5 (CH_2), 14.6 (CH_3) ppm. MS (CI^+): *m*/*z* = 102 $[M - Cl]^+$, 86, 72. HRMS (CI^+): calcd. for $C_5H_{12}NO^+$ $[M - Cl]^+$ 102.0919; found 102.0920.

The ^1H NMR spectroscopic data are comparable to those reported in the literature (other enantiomer reported).[22]

Formal Synthesis of (*S*,*S*)-Reboxetine

***N*-[(2*S*)-2,3-Dihydroxypropyl]-4-methylbenzenesulfinamide (14):** 4-Methylphenyl (4-methylphenyl)sulfinyl sulfone (712 mg, 2.42 mmol, **7**) or 4-methylbenzenesulfinyl chloride (422 mg, 2.42 mmol, **6**) was added portion/dropwise over 5 min to a stirred mixture of (*S*)-3-aminopropane-1,2-diol (**13**; 100 mg, 1.1 mmol) and Et_3N (0.46 mL, 3.3 mmol) in DMF (0.25 M, 4.4 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h before being allowed to warm up and stirred for another 24 h (with **7**) or 3 h (with **6**). The mixture was injected on to the top of a long silica plug and eluted with PE (400 mL) to remove impurities and most of the DMF. The eluting solvent was changed to 95:5 EtOAc/MeOH and the collected fraction was concentrated in vacuo to afford a mixture of the bis-protected amino diol in a small amount of DMF. DMF was carefully removed under high vacuum, assisted by an oil bath, heated to 80 °C, using a trap setup with a room-temperature (water bath) trap. The resulting yellow residue was dissolved in water (10 mL) and 1 M aq. NaOH (1.1 mL) was added (monitored by TLC, 95:5 EtOAc/MeOH). The mixture was stirred for 15 min and then concentrated in vacuo. The resulting residue was purified by flash chromatography, eluting with 95:5 EtOAc/MeOH, to give the monoprotected product [209 mg, 83% (with **7**) and 231 mg, 92% (with **6**)] as a clear oil as a 1:1 mixture of diastereoisomers. R_f (EtOAc/MeOH, 92.5:7.5): 0.3. IR (neat): $\tilde{\nu}_{max}$ = 3200–3300 (OH and NH), 2890–2922 (C–H), 909–1085 (S=O) cm^{-1}. Both diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.2 Hz, 2× 2 H, Ar*H*, mix.), 7.29 (d, *J* = 8.2 Hz, 2× 2 H, Ar*H*, mix.), 5.45 (d, *J* = 7.5 Hz, 1 H, 5.0 Hz, N*H*), 5.35 (t, *J* = 6.1 Hz, 1 H, N*H*), 3.67–3.76 (m, 2 H, 2× C*H*OH, mix.), 3.54–3.63 (m, 3 H, 3× CH*H*OH, mix.) 3.43–3.51 (m, 1 H, CH*H*OH, mix.), 2.87–3.14 (m, 4 H, 4× NC*H*H, mix.), 2.40 (2× 3 H, s, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.53 (C), 141.52 (C), 139.3 (C), 139.2 (C), 129.73 (CH), 129.71 (CH), 126.24 (CH), 126.22 (CH), 70.8 (CH), 70.1 (CH), 64.4 (CH_2OH), 64.1 (CH_2OH), 45.3 (NCH_2), 45.0 (NCH_2), 21.29 ($ArCH_3$), 21.27 ($ArCH_3$) ppm. MS (CI^+): *m*/*z* = 230 $[M + H]^+$. HRMS (CI^+): calcd. for $C_{10}H_{16}NO_3S^+$ $[M + H]^+$ 230.0851; found 230.0841.

***N*-[(2*S*)-2-Hydroxy-3-(trityloxy)propyl]-4-methylbenzenesulfinamide (15):** A stirred mixture of *N*-[(2*S*)-2,3-dihydroxypropyl]-4-methylbenzenesulfinamide (**14**; 100 mg, 0.44 mmol, 1 equiv.), Et_3N (0.09 mL, 0.7 mmol, 1.5 equiv.) and DMAP (2.2 mg, 0.02 mmol, 0.04 equiv.) in DMF (0.5 M, 0.8 mL) was treated with Ph_3CCl (134 mg, 0.48 mmol, 1.1 equiv.). After 24 h, the reaction was quenched with ice–water (1 mL) and extracted with CH_2Cl_2 (3× 30 mL). The combined organic phases were washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography, eluting with 6:4 EtOAc/PE, afforded the product (166 mg, 80%) as a clear oil as a 1:1 mixture of diastereoisomers. R_f (EtOAc/PE, 6:4): 0.3. IR (neat): $\tilde{\nu}_{max}$ = 3296 (OH and NH), 2872–3057 (C–H, aromatic and aliphatic), 1960 (C–H aromatic overtones), 1665 and 1596 (C–C aromatic), 1448 (C–O–H) 1016–1085 (S=O and C–O) cm^{-1}. Both diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98–7.54 (m, 38 H, Ar*H*, mix.), 4.38–4.68 (m, 2 H), 3.77–4.11 (m, 2 H), 3.67 (m, 2 H, 2× C*H*, mix.), 3.20 (dd, *J* = 10.1, 4.7 Hz, 1 H, TrOC*H*H), 2.84–3.10 (m, 7 H, mix.), 2.31 (s, 3 H, $ArCH_3$), 2.30 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6 (C), 143.5 (C), 141.30 (C), 141.28 (C), 139.9 (C), 139.1 (C), 129.54 (CH), 129.51 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH), 126.2 (CH), 126.0 (CH), 86.7 (C), 86.6 (C), 69.5 (CH), 67.9 (CH), 65.1 (CH_2), 64.5 (CH_2), 46.6 (CH_2), 46.1 (CH_2), 21.3 (CH_3), 21.2 (CH_3) ppm. MS (ESI^+): *m*/*z* = 494 $[M + Na]^+$, 243. HRMS (ESI^+): calcd. for $C_{29}H_{29}NO_3SNa^+$ $[M + Na]^+$ 494.1764; found 494.1760.

(2*S*)-4-(*p*-Tolylsulfinyl)-2-[(trityloxy)methyl]morpholine (16): Bromoethylsulfonium triflate (**1**; 176 mg, 0.40 mmol, 1.25 equiv.) was slowly (H_2 is set free) added to a stirred solution of *N*-[(*S*)-2-hydroxy-3-(trityloxy)propyl]-4-methylbenzenesulfinamide (**15**; 150 mg, 0.32 mmol, 1 equiv.) and NaH (45 mg, 1.1 mmol, 3.5 equiv.) in CH_2Cl_2 (1.3 mL, 0.25 M) at 0 °C. The reaction was stirred at 0 °C for 2 h and then being allowed to warm up to room temperature and stirred for an additional 14 h. The mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3× 30 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, eluting with 1:3 EtOAc/PE, to give the product (150 mg, 94%) as a clear oil in a 1:1 mixture of diastereoisomers. R_f (EtOAc/PE, 1:3): 0.33. IR (neat): $\tilde{\nu}_{max}$ = 2862–3057 (C–H, ar. and aliph.), 1960 (C–H Ar.), 1596 (C–C Ar.), 1068–1090 (S=O and C–O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.6 Hz, 4 H, ArH, mix.), 7.31–7.39 (m, 6 H, ArH, mix.), 7.06–7.30 (m, 28 H, ArH, mix.), 3.55–3.92 (m, 4 H, CH, OCH_2), 3.19–3.55 (m, 3 H, OCH_2, NCH_2, mix.), 2.80–3.19 (m, 9 H, OCH_2, NCH_2, NCH_2, mix.), 2.64 (dd, *J* = 12.2, 10.5 Hz, 2 H, NCH_2) 2.36 (s, 3 H, $ArCH_3$), 2.34 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 (C), 143.6 (C), 141.49 (C), 141.46 (C), 139.3 (C), 139.2 (C), 129.6 (CH), 128.65 (CH), 128.55 (CH), 127.85 (CH), 127.76 (CH), 127.1 (CH), 127.0 (CH), 126.18 (CH), 126.15 (CH), 86.7

(Trityl-C), 86.5 (Trityl-C), 75.5 (CH), 74.9 (CH), 66.9 (CH_2), 66.3 (CH_2), 64.5 (CH_2), 64.3 (CH_2), 51.1 (CH_2), 47.8 (CH_2), 46.0 (CH_2), 42.7 (CH_2), 21.44 (CH_3), 21.38 (CH_3) ppm. MS (ESI^+): *m*/*z* = 520 $[M + Na]^+$, 498 $[M + H]^+$, 243. HRMS (ESI^+): calcd. for $C_{31}H_{31}NO_3SNa^+$ $[M + Na]^+$ 520.1927; found 520.1916.

(2*S*)-Morpholin-2-ylmethanol: A solution of (2*S*)-4-(*p*-tolylsulfinyl)-2-[(trityloxy)methyl]morpholine (**16**; 120 mg, 0.241 mmol, 1 equiv.) in CH_2Cl_2 (0.48 mL, 0.5 M) was treated with 2 M HCl in Et_2O (1.2 mL, 2.4 mmol, 10 equiv.) at room temp. under nitrogen. After 1 h, a drop of methanol was added to the vigorously stirred reaction and stirring was continued for 0.5 h. During this time the colour of the solution turned slightly yellow due to the formation of *p*-tolylsulfinyl chloride (**6**). Furthermore, precipitation of the hydrochloride salt **17** as a coating inside the flask was observed. The solvent was removed by syringe and in the same manner the mixture was washed with Et_2O (2× 2 mL). Drying in vacuo afforded (*S*)-2-(hydroxymethyl)morpholine hydrochloride (**17**) as a white solid (36.3 mg, 94%). The product was deprotonated by addition of NaOH (9.1 mg, 1 equiv.) to a solution of the hydrochloride salt in CD_3OD. Following solvent removal in vacuo, the resulting mixture of the reported product and NaCl was subjected to NMR analysis for comparison with previously reported data.

The spectroscopic data are consistent with those reported in the literature.[16]

(*S*)-*tert*-Butyl 2-(Hydroxymethyl)morpholine-4-carboxylate: To verify its stereochemistry, **17** (19.9 mg, 0.13 mmol) was converted into the Boc-protected morpholine according to a known procedure (Boc_2O, NEt_3, CH_2Cl_2).[23] After purification by flash chromatography, eluting with 1:1 EtOAc/hexane, this procedure afforded **19** (20.3 mg, 72%). R_f (EtOAc/hexane, 1:1): 0.2; $[a]_D^{19}$ = +18.8 (*c* = 1.0, $CHCl_3$) [ref.[16] +20.7 (*c* = 1.01, $CHCl_3$)].

The spectroscopic data are consistent with those reported in the literature.[16,23]

Supporting Information (see footnote on the first page of this article): General directions, experimental procedures, spectroscopic and analytical data for all compounds.

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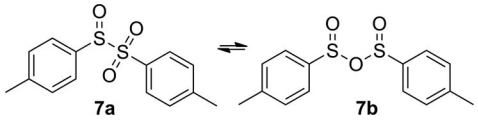

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