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Synthesis of novel 1,2,5-benzothiadiazepine 1,1-dioxides

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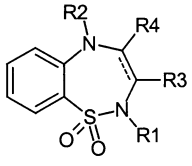
Abstract—3-Methoxycarbonyl-2-*N*-methyl-1,2,5-benzothiadiazepine 1,1-dioxide **2b** can be obtained in seven unambiguous steps starting from commercially available L-serine methyl ester. The crucial step in the synthesis of **2b** is the intramolecular Michael addition of dehydroalanine derivative **17**, which can be achieved using sodium *tert*-butoxide as a non-nucleophilic base. An initial attempt to construct the same scaffold via an alternative strategy, which was based on a nucleophilic aromatic substitution as the key ring-closing step, proofed to be unsuccessful.

1. Introduction

Over the past three decades, 1,4-benzodiazepines have elicited extensive pharmacological interest and numerous derivatives have been identified that display selective activities against a diverse array of biological targets.[1] Interestingly, the 1,2,5-benzothiadiazepine 1,1-dioxides (**1**), a subset of the 1,4-benzodiazepines, have received relatively little attention. Reported biological activities associated with the thiadioxobenzodiazepine ring system include inhibition of metalloproteinases[2] and farnesyl protein transferase[3] as well as hypolipidemic activity.[4] Tricyclic members of this class of compounds containing a pyrrole moiety have shown promise as antidepressants[5] and, notably, as inhibitors of HIV-1 replication.[6]



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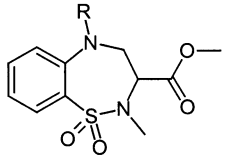

2a R = CH_2Ph
b R = H

Cyclisation strategies that have been described for the construction of the 1,2,5-benzothiadiazepine 1,1-dioxide framework involve either an intramolecular amide bond formation,[7] reductive cyclisation,[8] intramolecular S_NAr reaction,[5,6d] aza-Wittig reaction[9] or a Pictet–Spengler type condensation.[10] In addition, Field and co-workers demonstrated that the seven-membered ring system could readily be obtained via ring-expansion of a 3-chloromethyl-1,2,4-benzothiadiazine 1,1-dioxide derivative.[11] In the present paper we report a route into the novel 3-substituted 1,2,5-benzothiadiazepine 1,1-dioxides **2** following an alkoxide-catalysed intramolecular Michael addition.

2. Results and discussion

Retrosynthetic disconnection of target molecule **2** (Scheme 1) suggested the possibility of using 2,3-diaminopropionate **3** or 2-aminoacrylate **4** as key intermediates, both of which can readily be accessed from serine derivative **5**. Formation of the seven-membered core structure would be achieved either via an aromatic nucleophilic displacement (route **A**) or an intramolecular Michael addition (route **B**). Since literature precedent[5,6d] supported the former strategy, our initial focus was directed towards the preparation of the appropriate sulfonamide derivative **3** and ensuing cyclisation.

As shown in Scheme 2, target intermediate **10** could be obtained in four steps starting from the commercially available hydrochloric salt of L-serine methyl ester **5**. Thus, base-mediated sulfonylation of amine **5** with 2-fluorobenzenesulfonyl chloride furnished serine derivative **6** in quantitative yield. Selective *N*-alkylation of compound **6** with methyl iodide proceeded cleanly in the presence of sodium hydride to give tertiary sulfonamide **7**. Subsequent dehydration was carried out in a straightforward manner via base-induced β-elimination of the in situ formed triflate **8** to afford dehydroalanine derivative **9** in 80% overall yield. Finally, conjugate addition of benzylamine to acrylate **9** provided the desired diaminopropionate **10**, which was isolated in excellent yield.

Keywords: Michael addition; benzodiazepines.
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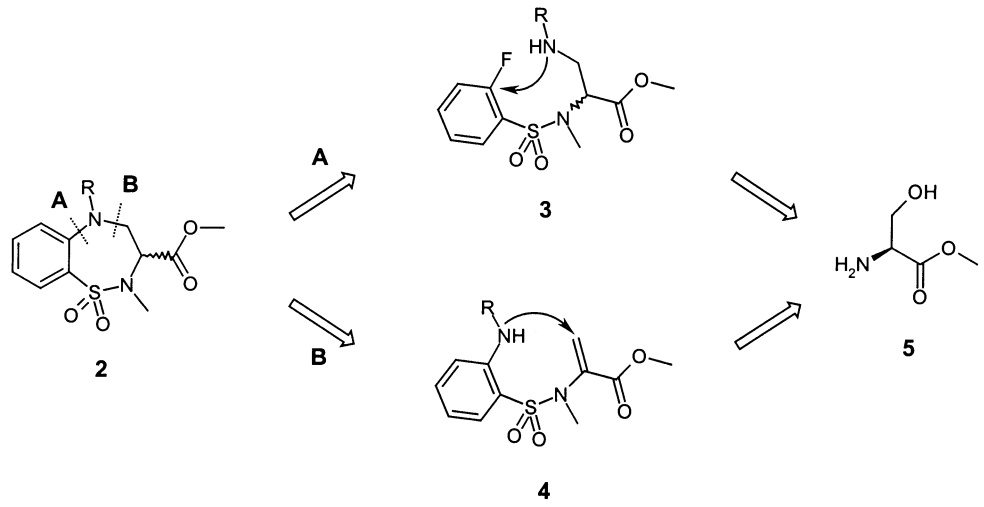
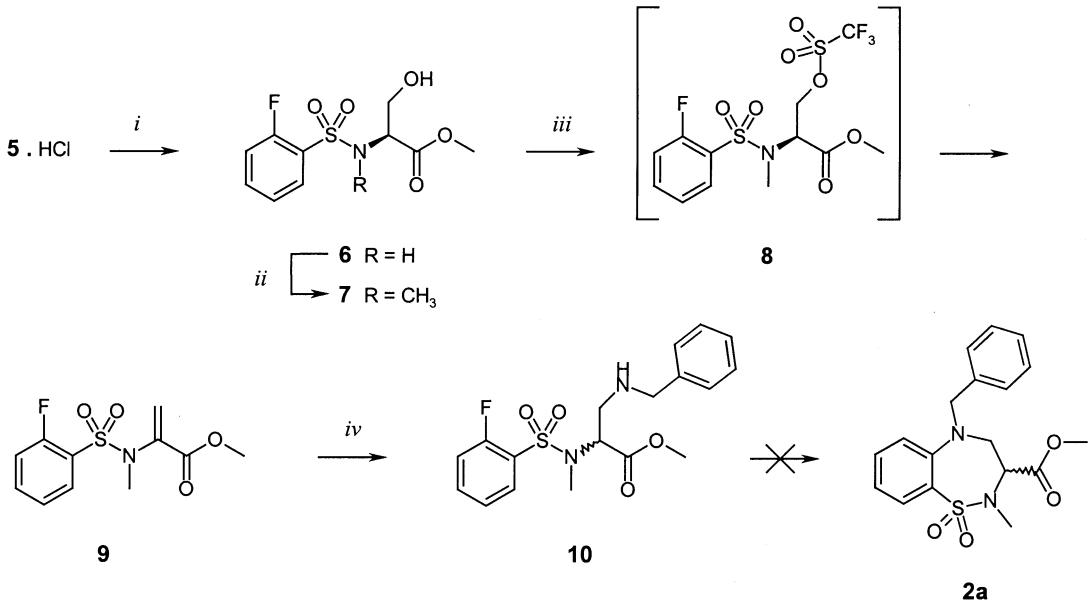
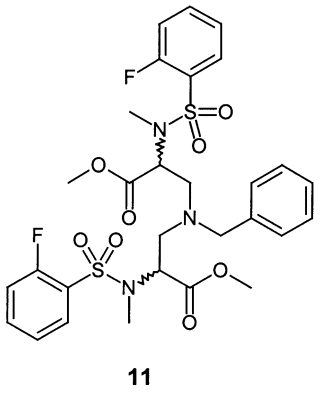


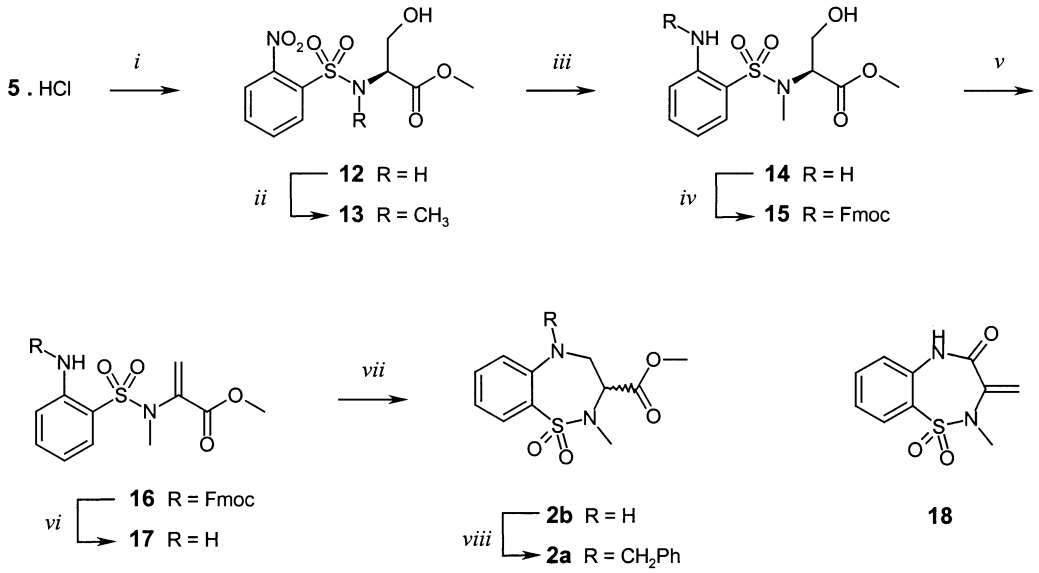
Scheme 1.



Scheme 2. (*i*) 2-Fluorobenzenesulfonyl chloride (0.5 equiv.), DIEA (1 equiv.), CH_2Cl_2, 12 h (quant.); (*ii*) MeI (3 equiv.), NaH (1.1 equiv.), DMF, 0→20°C, 4 h (74%); (*iii*) Tf_2O (1.5 equiv.), DIEA (4 equiv.), CH_2Cl_2, 0→20°C, 2 h (80%); (*iv*) benzylamine (2.8 equiv.), K_2CO_3, CH_3CN, 18 h (88%).



With intermediate **10** in hand we next set out to explore cyclisation conditions to construct the 1,2,5-thiadiazepine dioxide framework. First, thermal cyclisation of **10** was attempted in refluxing toluene or THF, however, no reaction was observed. Interestingly, heating in toluene at reflux for three days in the presence of *N*,*N*-diisopropylethylamine (DIEA) led to partial reformation of the α,β-unsaturated ester **9** which was isolated in 20% yield. The same observation was made when, for instance, THF and sodium *tert*-butoxide were used while utilisation of Ag_2O as a base furnished a mixture of starting material, olefin **9** and dimeric Michael adduct **11** in a 20:12:1 ratio. On the other hand, treatment of precursor **10** with DIEA in DMSO at 110°C for 24 h afforded only compound **9** in 35% yield and decomposed material. Furthermore, exposure of **10** to typical S_NAr reaction conditions using DMF or DMSO and an inorganic base (e.g. $NaHCO_3$ or Na_2CO_3) at elevated temperature led to rapid decomposition of starting material with no trace of either **9** or the desired cyclised product **2a**.



Scheme 3. (*i*) 2-Nitrobenzenesulfonyl chloride (1 equiv.), DIEA (2 equiv.), CH_2Cl_2, 12 h (71%); (*ii*) MeI (3 equiv.), NaH (1.1 equiv.), DMF, 0→20°C, 4 h (82%); (*iii*) 1/1 (v/v) cyclohexene/ethanol, 10% Pd/C, reflux, 48 h (86%); (*iv*) Fmoc-Cl (2.1 equiv.), $NaHCO_3$ (2.1 equiv.), CH_2Cl_2, 12 h (52%); (*v*) Tf_2O (1.5 equiv.), DIEA (4 equiv.), CH_2Cl_2, 0→20°C, 2 h (73%); (*vi*) 1/1 (v/v) DIEA/CH_2Cl_2, reflux, 48 h (70%); (*vii*) NaO*t*Bu (0.5 equiv.), THF, 0°C, 30 min (60%); (*viii*) benzyl bromide (5 equiv.), Na_2CO_3 (5 equiv.), Bu_4NI (0.5 equiv.), THF, reflux, 72 h (92%).

It is apparent from these results that the intramolecular cyclisation of **10**, despite being a favoured *seven-endo/exo-trig* process[12] is problematic. Furthermore, the intrinsic tendency of diaminopropionate derivative **10** to eliminate benzylamine precludes the intramolecular cyclisation by this approach.

At this stage, we turned our efforts to investigate the synthesis of target molecule **2** via route B. Requisite sulfonamide derivative **12** was obtained in a straightforward manner, analogous to the synthesis of serine derivative **6** (vide supra), by treatment of L-serine methyl ester hydrochloride (**5**·HCl) with 2-nitrobenzenesulfonyl chloride under basic conditions. Similarly, selective alkylation of the secondary sulfonamide moiety with methyl iodide (cf. synthesis of **7**) was uneventful, yielding compound **13**. Subsequent reduction of the nitro group was achieved via hydrogen-transfer hydrogenolysis to give amine **14** which was then treated with 9-fluorenylmethyl chloroformate in the presence of tertiary base to afford the Fmoc-protected compound **15** in 45% overall yield. Dehydroalanine derivative **16** was subsequently obtained, as described for the preparation of **9**, by treatment with triflic anhydride under the agency of a tertiary base.

In the next step, it was anticipated that removal of the Fmoc-group using standard conditions, i.e. piperidine/DMF, would rapidly lead to the formation of the corresponding piperidyl adduct (cf. synthesis of **10**). Therefore, alternative conditions for the deprotection of Fmoc-derivative **16** were studied. It was found that clean reaction could be achieved using a 1:1 mixture of dichloromethane and DIEA. However, the reaction was extremely slow. Fortunately, heating the mixture at reflux for 48 h afforded aniline derivative **17** in 70% yield. It is important to note that no cyclisation was observed under these conditions (Scheme 3).

On the basis of the latter result it was considered that in order for the ring closure to take place a base would be required that is able to deprotonate the aniline moiety. A suitable base that meets this criterion is sodium *tert*-butoxide. However, a possible complication that was envisaged was that cyclisation onto the ester functionality could take place under strong basic conditions giving benzothiadiazepin-3-one 1,1-dioxide **18**. Indeed, Mayer et al.[13] previously showed that sodium *tert*-butoxide could successfully be used to affect the cyclisation of solid-supported amino acid anthranilate derivatives to form and simultaneously release 1,4-benzodiazepine-2,5-diones. Nonetheless, when precursor **17** was treated with sodium *tert*-butoxide in THF, rapid formation of desired benzothiadiazepine dioxide **2b** as the sole product took place. This observation likely reflects the high reactivity of acrylate **17** towards Michael additions. Optimal results were obtained by using a half an equivalent of sodium *tert*-butoxide in THF at 0°C for 30 min, which furnished **2b** in 60% yield.

The obtained benzothiadiazepine dioxide **2b** can be further functionalised at the 5-position by, for instance, alkylation using benzylbromide in the presence of sodium carbonate and tetrabutylammonium iodide to give tertiary aniline **2a** in excellent yield. Interestingly, compound **2a** is completely stable towards treatment with DIEA in toluene under reflux for 24 h.

In summary, we have developed an expedient route for the synthesis of novel 3-substituted 1,2,5-benzothiadiazepine 1,1-dioxides. Construction of the core structure follows a favourable *seven-endo-trig* Michael addition employing suitably protected aniline derivative **17**. Application of this methodology should provide an entry into the synthesis of a diverse range of 1,2,5-benzothiadiazepine 1,1-dioxides showing interesting biological activities.

3. Experimental

3.1. General

Commercially available reagents and solvents were used as received. Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). Melting points were measured using a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR. Optical rotations were measured using a Perkin–Elmer 241 polarimeter with a path length of 1 dm; concentrations are expressed in g/100 mL. Mass spectra were recorded using an API 165 Perkin–Elmer workstation with TIS interface. ^{1}H NMR spectra were recorded on a Bruker DPX 250 spectrometer at 250.1 MHz in $CDCl_3$ and are referenced to internal tetramethylsilane. ^{13}C NMR spectra were recorded on a Bruker DPX 250 or a Bruker AMX 500 spectrometer using the Attached Proton Test (APT) technique at 62.5 or 125 MHz, respectively, and referenced to the corresponding deuterated solvent peaks. Microanalyses were performed by Elemental Microanalysis Ltd. (Okehampton, UK).

3.1.1. *N*-(2-Fluorobenzenesulfonyl)-L-serine methyl ester (6). L-Serine methyl ester hydrochloride (3.5 g, 23 mmol) and DIEA (6.0 mL, 35 mmol) were added to a solution of 2-fluorobenzenesulfonyl chloride (2.2 g, 11 mmol) in dichloromethane (50 mL) and stirred for 12 h at room temperature. Then, the mixture was diluted with dichloromethane (200 mL) and washed with water (50 mL), saturated aq. NaCl (50 mL), dried ($MgSO_4$) and filtered. Concentration in vacuo yielded sulfonamide **6** (3.1 g, 100%) as a colourless oil. IR (neat): ν_{max} 3274 (br), 1744 (s, C=O), 1342 (s, SO_2), 1169 (s, SO_2) cm^{-1}; $[\alpha]_D^{22}=+9.7$ (4.4, $CHCl_3$); MS (ESI+, *m/z*): 300 ($M+Na^+$); MS (ESI−, *m/z*): 276 ($M-H^+$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.49 (t, 1H, *J*=6.3 Hz, OH), 3.63 (s, 3H, OMe), 3.86–4.02 (m, 2H, Hβ), 4.16 (m, 1H, Hα), 5.96 (bd, 1H, *J*=7.0 Hz, NH), 7.18–7.30 (m, 2H, H-arom.), 7.58 (m, 1H, H-arom.), 7.87 (dt, 1H, J_1=1.7 Hz, J_2=7.5 Hz, 1H-arom.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=53.2 (OMe), 58.3 (Cα), 64.1 (Cβ), 117.4 (d, $J_{C,F}$=21.1 Hz, CH-arom.), 124.7 (d, $J_{C,F}$=3.8 Hz, CH-arom.), 128.4 (d, $J_{C,F}$=13.8 Hz, CSO_2), 130.3 (CH-arom.), 135.5 (d, $J_{C,F}$=8.5 Hz, CH-arom.), 159.4 (d, $J_{C,F}$=254 Hz, CF), 170.5 (C=O). Anal. Calcd for $C_{10}H_{12}FNO_5S$: C 43.32; H 4.36; N 5.05; Found: C 43.03; H 4.51; N 4.90.

3.1.2. *N*-(2-Fluorobenzenesulfonyl)-*N*-methyl-L-serine methyl ester (7). Serine derivative **6** (3.1 g, 11 mmol) was dissolved in anhydrous DMF (50 mL) and cooled to 0°C. Next, methyl iodide (2.0 mL, 32 mmol) and sodium hydride (0.5 g, 60% dispersion in mineral oil) were added and the mixture was stirred for 3 h at 0°C. After removal of the ice bath and additional stirring for 1 h, the solution was poured into saturated aq. NaCl (300 mL) and extracted with ethyl acetate (4×50 mL). The combined extracts were washed with saturated aq. NaCl (50 mL), dried ($MgSO_4$), filtered and evaporated to dryness. Purification of the residue by silica gel flash chromatography (eluent: 1/1 hexane/ethyl acetate) afforded tertiary sulfonamide **7** (2.4 g, 74%) as a colourless oil. IR (neat): ν_{max} 3526 (br), 1744 (s, C=O), 1342 (s, SO_2), 1172 (s, SO_2) cm^{-1}; $[\alpha]_D^{22}=-16.0$ (2.4, $CHCl_3$); MS (ESI+, *m/z*): 292 ($M+H^+$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.10 (t, 1H, *J*=6.6 Hz, OH), 2.98, 2.99 (2×s, 3H, NMe), 3.61 (s, 3H, OMe), 3.88–4.08 (m, 2H, Hβ), 4.78 (dd, 1H, J_1=5.3 Hz, J_2=7.0 Hz, Hα), 7.16–7.30 (m, 2H, H-arom.), 7.57 (m, 1H, H-arom.), 7.90 (dt, 1H, J_1=1.7 Hz, J_2=7.5 Hz, H-arom.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=31.7 (NMe), 52.7 (OMe), 61.2 (Cβ), 61.4 (Cα), 117.3 (d, $J_{C,F}$=21.6 Hz, CH-arom.), 124.6 (d, $J_{C,F}$=3.8 Hz, CH-arom.), 127.4 (d, $J_{C,F}$=14.3 Hz, CSO_2), 131.2 (CH-arom.), 135.5 (d, $J_{C,F}$=8.5 Hz, CH-arom.), 159.4 (d, $J_{C,F}$=253 Hz, CF), 169.8 (C=O). Anal. Calcd for $C_{11}H_{14}FNO_5S$: C 45.36; H 4.84; N 4.81; Found: C 45.22; H 4.92; N 4.71.

3.1.3. Methyl 2-[*N*-(2-fluorobenzenesulfonyl)methylamino]acrylate (9). Compound **7** (0.35 g, 1.2 mmol) was dissolved in dry dichloromethane (15 mL) under argon and cooled to 0°C. Then, DIEA (0.85 mL, 4.9 mmol) and trifluoromethanesulfonic anhydride (0.30 mL, 1.8 mmol) were added successively before the ice bath was removed. After additional stirring for 2 h at room temperature, the mixture was concentrated and purified by silica gel flash chromatography (eluent: 2/1 hexane/ethyl acetate) to give α,β-unsaturated ester **9** (0.27 g, 80%) as a colourless oil. IR (neat): ν_{max} 1732 (s, C=O), 1632 (w, C=C), 1356 (s, SO_2), 1223 (s), 1173 (s, SO_2) cm^{-1}; MS (ESI+, *m/z*): 296 ($M+Na^+$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.16, 3.17 (2×s, 3H, NMe), 3.66 (s, 3H, OMe), 5.85, 6.34 (2×s, 2H, Hβ), 7.17–7.28 (m, 2H, H-arom.), 7.57 (m, 1H, H-arom.), 7.83 (dt, 1H, J_1=1.8 Hz, J_2=7.8 Hz, H-arom.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=37.6 (NMe), 52.8 (OMe), 117.4 (d, $J_{C,F}$=21.6 Hz, CH-arom.), 124.5 (d, $J_{C,F}$=3.8 Hz, CH-arom.), 127.1 (d, $J_{C,F}$=14.3 Hz, CSO_2), 127.4 (Cβ), 131.4 (CH-arom.), 135.6 (d, $J_{C,F}$=8.4 Hz, CH-arom.), 137.9 (Cα), 159.6 (d, $J_{C,F}$=255 Hz, CF), 164.1 (C=O). Anal. Calcd for $C_{11}H_{12}FNO_4S$: C 48.35; H 4.43; N 5.13; Found: C 48.54; H 4.50; N 5.08.

3.1.4. Methyl 3-benzylamino-2-[*N*-(2-fluorobenzenesulfonyl)methylamino]propionate (10). Potassium carbonate (0.14 g, 1.0 mmol) and benzylamine (0.20 mL, 1.8 mmol) were added to a solution of acrylate **9** (0.18 g, 0.64 mmol) in acetonitrile (8 mL). The mixture was stirred for 15 h at room temperature, filtered and evaporated to dryness. Purification by silica gel flash chromatography (eluent: 1/1 hexane/ethyl acetate) gave diaminopropionate **10** (0.22 g, 88%) as a colourless oil. IR (neat): ν_{max} 1742 (s, C=O), 1344 (s, SO_2), 1171 (m, SO_2) cm^{-1}; MS (ESI+, *m/z*): 381 ($M+H^+$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.91, 2.92 (2×s, 3H, NMe), 2.94 (dd, 1H, J_1=9.1 Hz, J_2=13.1 Hz, Hβ), 3.11 (dd, 1H, J_1=5.4 Hz, J_2=13.1 Hz, Hβ), 3.53 (s, 3H, OMe), 3.74, 3.89 (2×d, 2H, J_{gem}=13.2 Hz, CH_2Ph), 4.85 (dd, 1H, J_1=5.4 Hz, J_2=9.1 Hz, Hα), 7.10–7.36 (m, 7H, CH-arom.), 7.53 (m, 1H, CH-arom.), 7.88 (dt, 1H, J_1=1.7 Hz, J_2=7.7 Hz, CH-arom.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=30.9 (NMe), 47.6, 53.2 (2×NCH_2), 52.5 (OMe), 117.4 (d, $J_{C,F}$=21.7 Hz, CH-arom.), 124.6 (d, $J_{C,F}$=3.8 Hz, CH-arom.), 127.5, 128.6, 128.8 (CH-arom.), 127.7 (d, $J_{C,F}$=14.4 Hz, CSO_2), 131.3 (CH-arom.), 135.4 (d, $J_{C,F}$=8.5 Hz, CH-arom.), 140.2 (ipso C-phenyl), 159.5 (d, $J_{C,F}$=253.6 Hz, CF), 170.4 (C=O). Anal. Calcd for $C_{18}H_{21}FN_2O_4S$: C 56.83; H 5.56; N 7.36; Found: C 56.58; H 5.57; N 7.29.

3.1.5. *N*-(2-Nitrobenzenesulfonyl)-L-serine methyl ester (12). DIEA (23.5 mL, 0.14 mol) was added dropwise to a suspension of L-serine methyl ester hydrochloride (10.5 g, 0.68 mol) and 2-nitrobenzenesulfonyl chloride (15.0 g, 0.68 mol) in dichloromethane (250 mL). After stirring for 12 h at room temperature, the solution was further diluted with dichloromethane (250 mL), successively washed with water (3×100 mL) and saturated aq. NaCl (100 mL), dried ($MgSO_4$), filtered and evaporated to dryness. Crystallisation of the crude product from ethyl acetate afforded sulfonamide **12** (14.5 g, 71%) as off-white crystals. Mp: 125–127°C (ethyl acetate); IR (neat): ν_{max} 3488 (br), 1752 (s, C═O), 1539 (s, NO_2), 1354 (s, SO_2), 1156 (s, SO_2), 1074 (s) cm^{-1}; $[\alpha]_D^{22}=-96.5$ (2.3, MeOH), lit.[14] $[\alpha]_D^{24}=-103$ (3.0, MeOH); MS (ESI+, *m/z*): 327 ($M+Na^+$); MS (ESI−, *m/z*): 303 ($M-H^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=2.12 (t, 1H, OH), 3.60 (s, 3H, OMe), 3.92–4.08 (m, 2H, Hβ), 4.27 (m, 1H, Hα), 6.46 (bd, 1H, *J*=7.7 Hz, NH), 7.71–8.13 (3 m, 4H, H-arom.); ^{13}C NMR (125 MHz, DMSO-*d*6): δ=52.3 (OMe), 58.7 (Cα), 62.3 (Cβ), 124.6, 130.2, 132.8, 133.7 (CH-arom.), 134.4 (CSO_2), 147.6 (CNO_2), 170.4 (s, C═O). Anal. Calcd for $C_{10}H_{12}N_2O_7S$: C 39.47; H 3.98; N 9.21; Found: C 39.40; H 3.93; N 9.12.

3.1.6. *N*-Methyl-*N*-(2-nitrobenzenesulfonyl)-L-serine methyl ester (13). Compound **12** (11.0 g, 36.2 mmol) was *N*-methylated as described for the synthesis of **7** using methyl iodide (6.8 mL, 0.11 mol) and sodium hydride (1.5 g, 60% dispersion in mineral oil) in anhydrous DMF (100 mL). Purification by silica gel flash chromatography (eluent: 1/3 hexane/ethyl acetate) gave tertiary sulfonamide **13** (9.5 g, 82%) as a colourless oil. IR (neat): ν_{max} 3529 (br), 1740 (s, C═O), 1541 (s, NO_2), 1372 (s), 1344 (s), 1171 (s, SO_2) cm^{-1}; $[\alpha]_D^{22}=-24.8$ (0.25, $CHCl_3$); MS (ESI+, *m/z*): 341 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=2.26 (t, 1H, OH), 3.04 (s, 3H, NMe), 3.68 (s, 3H, OMe), 3.86–4.12 (m, 2H, Hβ), 4.81 (dd, 1H, J_1=4.8 Hz, J_2=7.5 Hz, Hα), 7.61–7.76 (m, 3H, H-arom.), 8.09 (m, 1H, H-arom.); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=32.0 (NMe), 53.0 (OMe), 61.1 (Cβ), 61.6 (Cβ), 124.7, 131.8, 132.3, 134.2 (CH-arom.), 132.7 (CSO_2), 148.3 (CNO_2), 169.7 (C═O). Anal. Calcd for $C_{11}H_{14}N_2O_7S$: C 41.51; H 4.43; N 8.80; Found: C 41.34; H 4.46; N 8.63.

3.1.7. *N*-(2-Aminobenzenesulfonyl)-*N*-methyl-L-serine methyl ester (14). A suspension of compound **13** (9.5 g, 30 mmol) and 10% palladium on activated carbon (0.99 g) in a mixture of ethanol (200 mL) and cyclohexene (20 mL) was stirred under reflux. After 48 h, mass spectroscopic analysis revealed that all starting material had disappeared. The mixture was filtered over Celite, evaporated to dryness and purified by silica gel flash chromatography (eluent: 1/2 hexane/ethyl acetate) to furnish aniline **14** (7.3 g, 86%) as a colourless oil. IR (neat): ν_{max} 3471 (br), 1736 (s, C═O), 1619 (s), 1320 (s, SO_2), 1136 (s, SO_2) cm^{-1}; $[\alpha]_D^{22}=-7.5$ (2.8, $CHCl_3$); MS (ESI+, *m/z*): 311 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=2.76 (s, 1H, OH), 2.84 (s, 3H, NMe), 3.67 (s, 3H, OMe), 3.83 (m, 1H, Hβ), 4.00 (m, 1H, Hβ), 4.83 (dd, 1H, J_1=5.3 Hz, J_2=8.4 Hz, Hα), 4.95 (bs, 2H, NH_2), 6.74 (dd, 1H, J_1=<1.0 Hz, J_2=8.1 Hz, H-arom.), 6.81 (t, 1H, H-arom.), 7.31 (m, 1H, H-arom.), 7.70 (dd, 1H, J_1=1.5 Hz, J_2=8.0 Hz, H-arom.); ^{13}C NMR (125 MHz, DMSO-d_6): δ=31.2 (NMe), 52.2 (OMe), 60.1 (Cβ), 60.7 (Cα), 115.6, 117.7, 129.9, 134.3 (CH-arom.), 118.8 (CSO_2), 147.3 (CNH_2), 169.9 (C═O). Anal. Calcd for $C_{11}H_{16}N_2O_7S$: C 45.82; H 5.59; N 9.72; Found: C 45.69; H 5.63; N 9.52.

3.1.8. *N*-[2-*N'*-(9-Fluorenylmethylcarbonyl)aminobenzenesulfonyl]-*N*-methyl-L-serine methyl ester (15). Sodium hydrogen carbonate (2.4 g, 28 mmol) and 9-fluorenylmethyl chloroformate (7.0 g, 27 mmol) were added to a solution of compound **14** (3.7 g, 12.7 mmol) in dichloromethane (100 mL). After stirring for 12 h at room temperature, the mixture was distributed between dichloromethane (200 mL) and water (100 mL). The organic layer was washed with water (100 mL) and saturated aq. NaCl (100 mL), dried ($MgSO_4$), filtered and concentrated. Silica gel flash chromatography (eluent: 1/1 hexane/ethyl acetate) of the resulting oil gave carbamate **15** (3.4 g, 52%) as a colourless foam. IR (neat): ν_{max} 3350 (br), 1732 (br, C═O), 1525 (s), 1437 (s), 1326 (s, SO_2), 1210 (s), 1145 (s, SO_2) cm^{-1}; $[\alpha]_D^{22}=-15.5$ (1.1, $CHCl_3$); MS (ESI+, *m/z*): 383 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=2.09 (t, 1H, *J*=6.4 Hz, OH), 2.81 (s, 3H, NMe), 3.52 (s, 3H, OMe), 3.78–4.00 (m, 2H, Hβ), 4.27 (t, 1H, *J*=6.7 Hz, CH-Fmoc), 4.49 (dd, 1H, J_1=6.6, Hz J_2=10.6 Hz, CH_2-Fmoc), 4.56 (dd, 1H, J_1=6.9 Hz, J_2=10.6 Hz, CH_2-Fmoc), 4.64 (dd, 1H, J_1=5.2 Hz, J_2=7.5 Hz, Hα), 7.13–7.79 (m, 10H, CH-arom.), 7.85 (dd, 1H, J_1=1.5 Hz, J_2=8.0 Hz, CH-arom.), 8.13 (d, 1H, *J*=8.3 Hz, CH-arom.), 8.76 (bs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ=31.6 (NMe), 47.4 (CH-Fmoc), 53.0 (OMe), 60.9 (Cβ), 61.1 (Cα), 67.8 (CH_2-Fmoc), 120.5, 122.6, 123.6, 125.4, 127.6, 128.3, 130.5, 134.7 (CH-arom.), 126.7 (CSO_2), 136.9, 141.8, 144.0 (C-arom.), 153.6 (CONH), 169.5 (C═O).

3.1.9. Methyl 2-*N*-[[2-*N'*-(9-fluorenylmethylcarbonyl)-aminobenzenesulfonyl]methyl-amino]acrylate (16). In situ *O*-triflation and β-elimination of compound **15** (0.55 g, 1.1 mmol) was carried out as described for the preparation of acrylate **9** using DIEA (0.75 mL, 4.3 mmol) and trifluoromethanesulfonic anhydride (0.25 mL, 1.5 mmol) in dichloromethane (10 mL). Purification by silica gel flash chromatography (eluent: 5/2 hexane/ethyl acetate) gave α,β-unsaturated ester **15** (0.39 g, 73%) as a colourless oil. IR (neat): ν_{max} 3346 (br), 1728 (br, C═O), 1585 (s), 1526 (s), 1437 (s), 1321 (s, SO_2), 1210 (s), 1149 (m, SO_2) cm^{-1}; MS (ESI+, *m/z*): 515 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=3.00 (s, 3H, NMe), 3.59 (s, 3H, OMe), 4.28 (t, 1H, *J*=7.0 Hz, CH-Fmoc), 4.48 (d, 2H, *J*=7.0 Hz, CH_2-Fmoc), 5.84, 6.60 (2×s, 2H, Hβ), 7.12–7.79 (m, 10H, CH-arom.), 7.82 (dd, 1H, J_1=1.6 Hz, J_2=8.0 Hz, CH-arom.), 8.23 (d, 1H, *J*=8.3 Hz, CH-arom.), 8.88 (bs, 1H, NH); ^{13}C NMR (125 MHz, DMSO-*d*6): δ=37.6 (NMe), 47.4 (CH-Fmoc), 53.0 (OMe), 67.9 (CH_2-Fmoc), 120.5, 121.8, 123.1, 125.6, 127.6, 128.3, 130.6, 134.9 (CH-arom.), 125.3, 127.7 (CSO_2, Cβ), 137.4, 138.0, 141.8, 144.1 (Cα, C-arom.), 153.4 (CONH), 164.0 (C═O). Anal. Calcd for $C_{26}H_{24}N_2O_6S.H_2O$: C 61.16; H 5.13; N 5.49; Found: C 61.26; H 4.85; N 5.40.

3.1.10. Methyl 2-*N*-[(2-aminobenzenesulfonyl)methyl-amino]acrylate (17). Compound **16** (0.30 g, 0.62 mmol) was dissolved in a mixture of dichloromethane (5 mL) and DIEA (5 mL) and stirred under reflux for 48 h. The solution was then concentrated and the residue purified by silica gel

flash chromatography (eluent: 5/2→1/1 hexane/ethyl acetate) to give amine **17** (0.12 mg, 70%) as a yellow oil. IR (neat): ν_{max} 3476 (br), 1727 (s, C=O), 1616 (s, C=C), 1317 (s, SO_2), 1211 (s), 1138 (s, SO_2) cm^{-1}; MS (ESI+, *m/z*): 293 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=3.00 (s, 3H, NMe), 3.74 (s, 3H, OMe), 5.12 (bs, 2H, NH_2), 5.74, 6.26 (2×s, 2H, Hβ), 6.68–6.75 (m, 2H, CH-arom.), 7.30 (m, 1H, CH-arom.), 7.64 (d, 1H, J_1=1.4 Hz, J_2=8.0 Hz, CH-arom.); ^{13}C NMR (125 MHz, $CDCl_3$): δ=37.2 (NMe), 53.0 (OMe), 116.2, 118.2, 131.1, 135.1 (CH-arom.), 118.3 (CSO_2), 124.6 (Cβ), 139.2 (Cα), 147.1 (CNH_2), 165.1 (C=O). Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C 48.88; H 5.22; N 10.36; Found: C 48.90; H 5.24; N 10.26.

3.1.11. (±)-3-Methoxycarbonyl-2-*N*-methyl-1,2,5-benzothiadiazepine 1,1-dioxide (2b). Sodium *tert*-butoxide (15 mg, 0.15 mmol) was added to a solution of compound **17** (77 mg, 0.29 mmol) in anhydrous THF (10 mL) at 0°C under argon. After stirring for 30 min, the mixture was diluted with ethyl acetate (100 mL) and successively washed with water (20 mL) and saturated aq. NaCl (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (eluent: 1/1 hexane/ethyl acetate) to give benzothiadiazepine **2b** (46 mg, 60%) as a white solid. Mp: 112–114°C (hexane/ethyl acetate); IR (neat): ν_{max} 3384 (s), 1736 (br, C=O), 1481 (s), 1318 (s, SO_2), 1261 (s), 1147 (s, SO_2) cm^{-1}; MS (ESI+, *m/z*): 293 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=2.97 (s, 3H, NMe), 3.75 (ddd, 1H, J_1=4.8 Hz, J_2=7.7 Hz, J_{gem}=14.8 Hz, H-4), 3.80 (s, 3H, OMe), 4.10 (m, 1H, H-4), 4.32 (dd, 1H, J_1=4.8 Hz, J_2=10.6 Hz, H-3), 4.47 (bd, 1H, NH), 6.77 (dd, 1H, J_1<1.0 Hz, J_2=8.1 Hz, CH-arom.), 6.93 (dt, 1H, J_1<1.0 Hz, J_2=7.6 Hz, CH-arom.), 7.30 (dt, 1H, J_1<1.0 Hz, J_2=7.6 Hz, CH-arom.), 7.77 (dd, 1H, J_1=1.5 Hz, J_2=8.1 Hz, CH-arom.); ^{13}C NMR (125 MHz, DMSO-*d*6): δ=38.1 (NMe), 46.0 (C-4), 52.4 (OMe), 64.9 (C-3), 118.6, 119.4, 128.8, 133.3 (CH-arom.), 124.4 (C-7), 147.4 (C-6), 169.8 (C=O). Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C 48.88; H 5.22; N 10.36; Found: C 48.89; H 5.31; N 10.29.

3.1.12. (±)-5-*N*-Benzyl-3-methoxycarbonyl-2-*N*-methyl-1,2,5-benzothiadiazepine 1,1-dioxide (2a). Benzylbromide (0.70 mL, 5.9 mmol), sodium carbonate (0.60 g, 5.7 mmol) and tetrabutylammonium iodide (0.20 g, 0.54 mmol) were added to a solution of compound **2b** (0.30 g, 1.1 mmol) in anhydrous THF (10 mL). The mixture was stirred under reflux for 72 h, filtered and evaporated to dryness. Purification by silica gel flash chromatography (eluent: 2/1→1/1 hexane/ethyl acetate) furnished tertiary amine **2a** (0.37 g, 92%) as a colourless wax. IR (neat): ν_{max} 1750 (s, C=O), 1492 (s), 1322 (s, SO_2), 1206 (s), 1144 (s, SO_2) cm^{-1}; MS (ESI+, *m/z*): 383 ($M+Na^+$); ^1H NMR (250 MHz, $CDCl_3$): δ=2.89 (s, 3H, NMe), 3.65 (dd, J_1=3.8 Hz, J_{gem}=15.2 Hz, H-4), 3.72 (s, 3H, OMe), 4.05 (m, 1H, H-4), 4.20 (dd, 1H, J_1=3.8 Hz, J_2=10.5 Hz, H-3), 4.52, 4.70 (2×d, 2H, J_{gem}=15.4 Hz, CH_2Ph), 6.97–7.03 (m, 2H, CH-arom.), 7.25–7.41 (m, 6H, CH-arom.), 7.86 (dd, 1H, J_1=1.7 Hz, J_2=8.1 Hz, CH-arom.); ^{13}C NMR (125 MHz, $CDCl_3$): δ=36.9 (NMe), 51.1 (C-4), 52.9 (OMe), 58.0 (CH_2Ph), 63.3 (C-3), 119.5, 121.4, 128.0, 128.1, 129.3, 130.3, 133.7 (CH-arom.), 129.7 (C-7), 137.6 (ipso C-phenyl), 148.1 (C-6), 169.7 (C=O). Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C 59.98; H 5.59; N 7.77; Found: C 59.74; H 5.65; N 7.24.

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