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Ring-Closing Metathesis Strategies to Cyclic Sulfamide Peptidomimetics

Joseph M. Dougherty,[a] Donald A. Probst,[a] Randall E. Robinson,[b] Joel D. Moore,[a] Thomas A. Klein,[a] Kelley A. Snelgrove[a] and Paul R. Hanson[a,*]

[a]*Department of Chemistry, Malott Hall, University of Kansas, Lawrence, KS 66045-2506, USA*
[b]*Department of Chemistry, Luther College, Decorah, IA 52101, USA*

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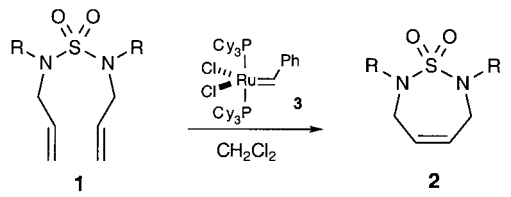
Abstract—Ring-closing metathesis (RCM) strategies toward the synthesis of a number of constrained sulfamides are discussed. This approach exploits the inherent chemistry of sulfamides and sulfonyl carbamates to generate both symmetric and unsymmetric cyclic sulfamides. Two strategies are revealed, one centers on the RCM reaction of allylated sulfamides **9a–e** to generate the C_2-symmetric cyclic sulfamides **4a–e** in high yields. A second RCM strategy utilizes the known sulfonyl carbamate **15** to prepare unsymmetric cyclic sulfamides **16** and **6** in two four-step sequences. Overall, the routes described are applicable to the synthesis of a variety of constrained dipeptidal sulfamides representing novel peptidomimetic scaffolds. © 2000 Published by Elsevier Science Ltd.

Introduction

The RCM reaction has become a powerful strategy for the construction of a number of important heterocycles[1] and constrained peptides.[2] Recently, we and others have shown that the RCM reaction catalyzed by the Grubbs ruthenium catalyst **3** is an effective method for the construction of *P*-heterocycles[3] and complex cyclic sulfonamides.[4] We have now extended this approach to report the first examples of the RCM reaction on sulfamide templates (Scheme 1). This strategy couples the RCM reaction with the unique chemistry inherent to sulfamides and sulfonyl carbamates to synthesize diverse amino acid-derived cyclic sulfamides.

Small peptides are excellent starting points for drug design due to their potential to overcome the pharmacokinetic shortcomings of larger peptides, yet retain the desirable quality of molecular recognition.[5] A number of dipeptides



Scheme 1.

are being developed as novel pharmaceutical agents.[6] Unfortunately, even small peptides suffer from proteolytic instability which limits their use as drug candidates. Recently, peptide mimics have been developed that utilize the urea moiety as a non-hydrolyzable linker and/or a hydrogen bond acceptor.[7] Further modification to cyclic ureas has led to the generation of a new sub-class of biologically active compounds.[8] Led by DuPont–Merck, a number of cyclic HIV protease inhibitors have been developed that incorporate ureas,[9] sulfamides,[10] and other urea surrogates[11] as the central lynch pin. In these cases, it has been shown that the H-bonding urea moieties may serve to replace the water molecule unique to the active site of HIV protease.[9a,9d]

Sulfamides have also served as nonhydrolyzable peptidomimetics and have been shown to be potent and selective matrix metalloprotease inhibitors,[12] serine protease inhibitors,[13] and constrained di- and tripeptides.[14,15] Our approach generates an array of constrained dipeptidal sulfamides with structures such as **2** (Scheme 1). The strategies we describe are highly flexible and applicable to the synthesis of an array of peptidomimetic scaffolds.

Two separate 3-component coupling protocols are used, followed by allylation and RCM, to yield symmetric sulfamides **4** and **5**, as well as unsymmetric sulfamide **6** (Scheme 2). With respect to the development of HIV protease inhibitors, our strategy allows for the incorporation of amino acid side chains into both the P1/P1′ and P2/P2′ regions of **4–6**. Functionalization of the internal P1/P1′ positions[16] and external P2/P2′ positions[17] in other cyclic ureas and sulfamides has been shown to influence the activity of HIV protease inhibitors. The routes to the symmetric

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* Corresponding author. Tel. +1-785-864-3094; fax: +1-785-864-5396; e-mail: phanson@ukans.edu

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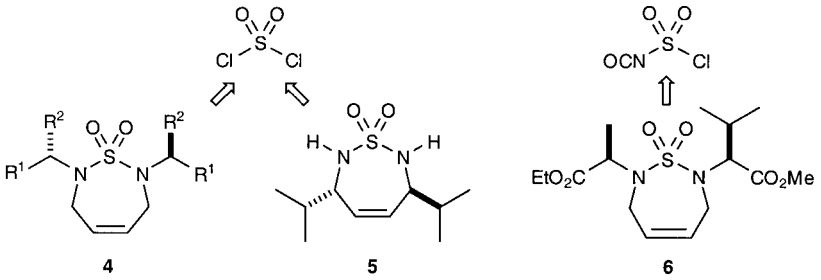
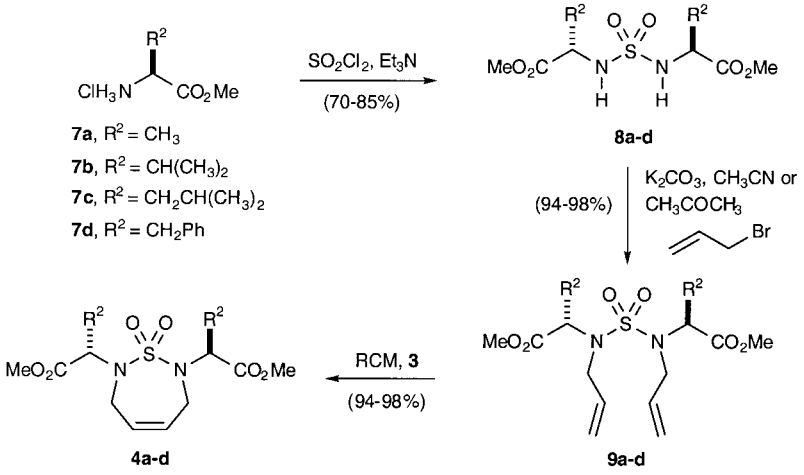


Scheme 2.



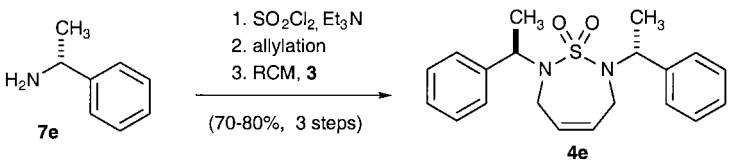
Scheme 3.

sulfamides **4** and **5** center on the coupling of two equivalents of an amine with sulfuryl chloride (SO_2Cl_2).[18] Routes to unsymmetric sulfamide **6** feature the sequential coupling of an alcohol, then an amine to chlorosulfonyl isocyanate ($OCNSO_2Cl$) followed by a Mitsunobu reaction.

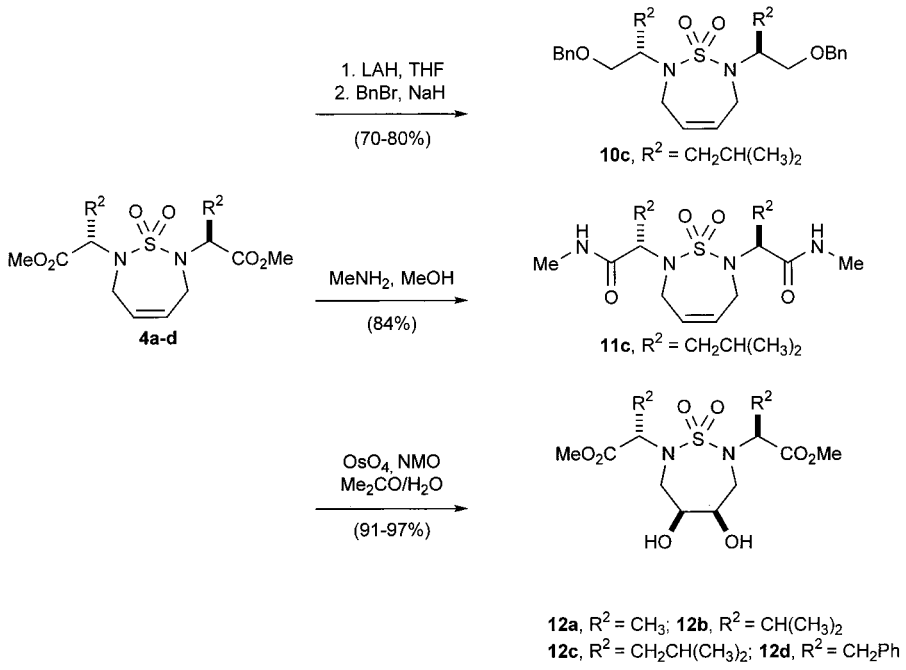
The route to the amino acid-derived C_2-symmetric sulfamides **4a–d** is outlined in Scheme 3. Condensation of a slight excess of amino esters **7a–d** with SO_2Cl_2 produces the sulfamides **8a–d** in excellent yields.[18] Subsequent diallylation to sulfamides **9a–d** proceeds quantitatively. Ring-closing metathesis using the Grubbs benzylidene catalyst **3**, gives excellent yields of the C_2-symmetric cyclic sulfamides **4a–d**. Attempts to derive unsymmetric sulfamides in this manner resulted in unacceptably low yields. In addition, attempts to directly couple secondary amines (allylated amino esters) to SO_2Cl_2 were not successful. We therefore adopted an alternative procedure employing the Mitsunobu reaction of sulfonyl carbamates, vide infra. Direct coupling does, however, work nicely with other non-racemic amines such as (*R*)-(−)-α-methyl benzylamine (**7e**) to derive non-racemic C_2-symmetric sulfamides such as **4e** (Scheme 4). Overall, the method outlined in Schemes 3 and 4 should be applicable to a host of other non-racemic amines and will prove useful for the synthesis of various cyclic sulfamide compounds.

Another attractive feature of the sulfamide group is its tolerance to various reaction conditions. In order to highlight its versatile nature, we have carried out a number of transformations on dipeptides **4a–d** as outlined in Scheme 5. A two-step protocol involving reduction and benzylation yields the sulfamide **10c** (80% yield). Exposure to CH_3NH_2/CH_3OH at room temperature gives suitable yields of the bis-carboxamide **11c**. Finally, dihydroxylation of cyclic sulfamides **4a–d** yields diols **12a–d** in excellent yields.

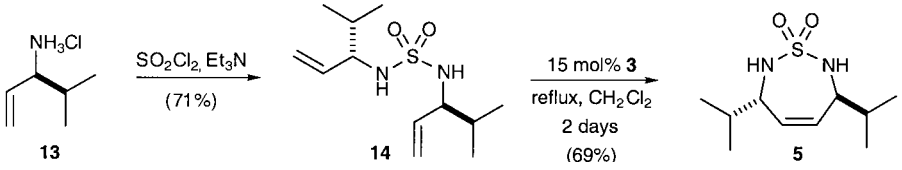
A concise route to the C_2-symmetric cyclic sulfamide **5** incorporating the valine side chain into the internal positions (P1/P1′) of sulfamide **2** is outlined in Scheme 6. As a proof of concept, we have initially developed a route to sulfamides such as **5** starting from the valine-derived non-racemic allylic amine **13**.[19] Amine **13** can be coupled with sulfuryl chloride, as described above, to yield sulfamide **14** (71%). Subsequent RCM, although sluggish, occurred over a two-day period to produce sulfamide **5** in 69% yield.



Scheme 4.

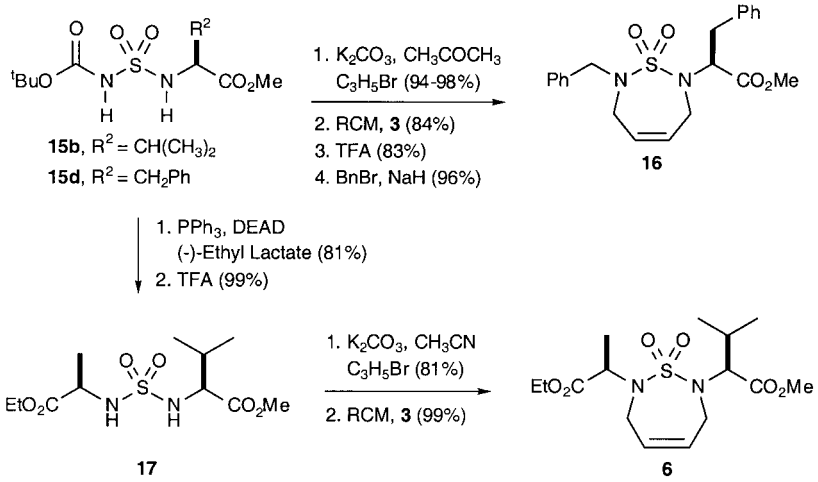


Scheme 5.



Scheme 6.

Unsymmetric cyclic sulfamides have also been shown to be potent HIV protease inhibitors.[20] We have developed a flexible strategy to unsymmetric sulfamides **16** and **6** as outlined in Scheme 7. This strategy utilizes inherent features of the sulfonyl carbamate **15** to differentiate its two nucleophilic N–H sites.[21] In the first route, after diallyation/RCM, the carbamate protecting group is unmasked and alkylated to derive the unsymmetric sulfamide **16**. In the second route, we utilize the pKa difference of the sulfonyl carbamate N–H and sulfamide N–H in a selective Mitsunobu/deprotection sequence first developed by Montero[21] and later exploited by Groutas.[22] Thus, sulfonyl carbamate **15b** is utilized in a regioselective Mitsunobu reaction to generate, after deprotection, the unsymmetric dipeptidal scaffold **17** in excellent yield. Subsequent diallylation (81%), and RCM (99%) produces the unsymmetric cyclic sulfamide **6**. These high yielding four-step routes are amenable to a number of variations which are currently being pursued.



Scheme 7.

In conclusion, we have established the strategies described herein as effective methods for the synthesis of a variety of symmetric and unsymmetric cyclic sulfamides. Current efforts are aimed at the synthesis of a diverse array of sulfur-based peptidomimetics. These compounds are currently being evaluated for biological activity and the results of those investigations will be reported in due course.

Experimental

General methods

All reactions were carried out in flame-dried glassware under argon. Toluene, THF, Et_2O, and CH_2Cl_2 were purified by passage through the Solv-Tek purification system employing activated Al_2O_3.[23] Et_3N was distilled from CaH_2. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230–400 mesh). Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, Merck). All amino acid precursors were purchased from Advanced ChemTech. ^1H and ^{13}C spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively. High resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Infrared data was obtained on an ATI-Mattson Genesis Series FTIR or a Nicolet Impact 410 FTIR. Melting points were obtained on a Thomas Hoover capillary melting point apparatus.

***N,N′*-Sulfonyl bis-L-valine dimethyl ester (8b).** H-Val-OMe·HCl (**7b**) (2.61 g, 15.56 mmol) and CH_2Cl_2 (85 mL) were added sequentially to a 250 mL round-bottom flask. The solution was cooled to 0°C, Et_3N (4.50 g, 44.5 mmol) added slowly, and the resulting solution was stirred for 15 min. SO_2Cl_2 (595 μL, 1.00 g, 7.41 mmol) was added slowly over 45 min and the resulting yellow solution was then warmed to rt over 3 h. The solvent was concentrated to 15 mL under reduced pressure, EtOAc (225 mL) was added, and the solution was washed with 10% $NaHSO_4$ (2×), aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). The solution was filtered, concentrated under reduced pressure to leave a crude oil. Flash chromatography (2:1. 1:1, Hexanes/EtOAc) afforded 1.98 g (82.6%) of sulfamide **8b** as a white solid. Mp=76–77°C; TLC R_f=0.58 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=+14.2 (c=1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.01 (d, J=9.6 Hz, 2H), 3.88 (dd, J=9.6, 4.4 Hz, 2H), 3.77 (s, 6H), 2.18–2.10 (m, 2H), 1.00 (d, J=6.9 Hz, 6H), 0.88 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 61.1, 52.4, 31.5, 18.8, 17.4; FTIR (neat) 3317, 3266, 1737, 1466, 1355, 1327, 1137 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{12}H_{25}N_2O_6S$ 325.1437, found 325.1432.

***N,N′*-Sulfonyl bis-L-alanine dimethyl ester (8a).** Coupling and flash chromatography (2:1, 1:1 Hexanes/EtOAc) produced 617 mg (31%) of sulfamide **8a** as a white solid. Mp=91–92°C; TLC R_f=0.40 in (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−75.8 (c=1.003, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.24 (d, J=8.0 Hz, 2H), 4.09 (dq, J=7.3, 7.3 Hz, 2H), 3.75 (s, 6H), 1.43 (d, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 52.7, 51.8, 19.2; FTIR (neat) 3273, 1734, 1457, 1378, 1353, 1137 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_8H_{17}N_2O_6S$ 269.0807, found 269.0791.

***N,N′*-Sulfonyl bis-L-leucine dimethyl ester (8c) and *N,N′*-Sulfonyl bis-L-phenylalanine dimethyl ester (8d)** were prepared according to literature procedure, see Ref. 18.

***N,N′*-Sulfonyl bis[(*R*)-1-phenyl-ethylamine] (8e).** Coupling and flash chromatography (3:1 Hexanes/EtOAc) produced 356 mg (63%) of sulfamide **8e** as a white solid. Mp=96–97°C; TLC R_f=0.37 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−31.2 (c=1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.21 (m, 6H), 7.17–7.14 (m, 4H), 4.74 (s, 2H), 4.43 (dq, J=12.2. 6.2 Hz, 2H), 1.46 (d, J=6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.7, 128.6, 127.5, 126.1, 53.7, 23.6; FTIR (neat) 3312, 3032, 2992, 2944, 1603, 1493, 1454, 1381, 1320, 1149, 751, 701 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{16}H_{21}N_2O_2S$ 305.1324, found 305.1322.

***N,N′*-Bis(2-propenyl)-*N,N′*-sulfonyl bis-L-valine dimethyl ester (9b).** To a stirring solution of sulfamide **8b** (500 mg, 1.54 mmol) in CH_3CN (35 mL) in a 100 mL round-bottom flask was added K_2CO_3 (1.06 g, 7.70 mmol) and allyl bromide (1.12 g, 9.24 mmol). The flask was fitted with a condenser, and the mixture was heated to 70°C for 14 h. The resulting yellow orange mixture was filtered by suction, and the solvent removed under reduced pressure to give a yellow oil. Flash chromatography (10:1 Hexanes/EtOAc) afforded 619 mg (98.7%) of sulfamide **9b** as a clear oil. TLC R_f=0.31 (10:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−89.3 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.92 (dddd, J=15.9, 10.2, 7.5, 5.7 Hz, 2H), 5.14 (dd, J=16, 1.3 Hz, 2H), 5.05 (dd, J=10.2, 1.2 Hz, 2H), 3.99–3.90 (m, 6H), 3.68 (s, 6H), 2.16–2.08 (m, 2H), 0.97 (d, J=6.7 Hz, 6H), 0.86 (d, J=6.6, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 135.2, 117.3, 66.3, 51.5, 47.7, 28.4, 19.6, 19.5; FTIR (neat) 3080, 1745, 1640, 1436, 1351, 1137 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{18}H_{33}N_2O_6S$ 405.2059, found 405.2031.

***N,N′*-Bis(2-propenyl)-*N,N′*-sulfonyl bis-L-alanine dimethyl ester (9a).** Bis-allylation and flash chromatography (10:1, Hexanes/EtOAc) produced 596 mg (92%) of **9a** as a yellow oil. TLC R_f=0.53 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−20.3 (c=1.004, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.87 (dddd, J=16.8, 10.5, 6.5, 6.3 Hz, 2H), 5.24 (dd, J=15.9, 1.4 Hz, 2H), 5.16 (dd, J=10.2, 1.2 Hz, 2H), 4.37 (q, J=7.2 Hz, 2H), 3.98 (dddd, J=16.1, 6.1, 1.1, 1.1 Hz, 2H), 3.77 (dddd, J=16.1, 6.7, 1.1, 1.1 Hz, 2H) 3.72 (s, 6H), 1.47 (d, J=4.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 134.4, 118.0, 55.0, 52.0, 48.8, 15.3; FTIR (neat) 1743, 1645, 1333, 1226 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{14}H_{25}N_2O_6S$ 349.1433, found 349.1436.

***N,N′*-Bis(2-propenyl)-*N,N′*-sulfonyl bis-L-leucine dimethyl ester (9c).** Bis-allylation and flash chromatography (2:1 Hexanes/EtOAc) produced 2.22 g (87%) of **9c** as a yellow oil. TLC R_f=0.64 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−42.5 (c=0.51, $CDCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.90 (dddd, J=17.2, 10.2, 6.8, 6.1 Hz, 2H), 5.20 (dd, J=17.2, 1.3 Hz, 2H), 5.13 (dd, J=10.2, 1.1 Hz, 2H) 4.38 (dd, J=8.2, 6.0 Hz, 2H), 3.96 (dd, J=16.2, 6.0 Hz, 2H), 3.86 (dd, J=16.2, 7.0 Hz, 2H) 3.72 (s, 6H), 1.81–1.66 (m, 6H), 0.96 (d, J=6.1 Hz, 6H), 0.91 (d, J=6.2 Hz, 6H) ^{13}C NMR

($CDCl_3$, 100 MHz) δ 172.4, 134.9, 117.8, 58.1, 52.0, 48.7, 38.7, 24.4, 22.4, 21.8; FTIR (neat) 3074, 1746, 1641, 1344, 1169 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{37}N_2O_6S$ 433.2372, found 433.2397.

***N,N′*-Bis(2-propenyl)-*N,N′*-sulfonyl bis-L-phenyl alanine dimethyl ester (9d).** Bis-allylation and flash chromatography (10:1, 5:1 Hexanes/EtOAc) produced 560 mg (95%) of **9d** as a yellow oil. TLC R_f=0.15 (10:1 Hexanes/EtOAc); $[\alpha]_D^{25}=-47.9$ (c=1.012, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.25 (m, 8H), 7.22–7.19 (m, 2H), 5.77 (dddd, J=16.8, 10.5, 6.5, 6.5 Hz, 2H), 5.17–5.13 (nfom, 4H), 4.51 (dd, J=7.3, 7.3 Hz, 2H), 3.71 (dd, J=15.9, 6.3 Hz, 2H), 3.66 (s, 6H), 3.58 (dd, J=15.9, 6.9 Hz, 2H), 3.40 (dd, J=14.1, 7.6 Hz, 2H), 3.07 (dd, J=14.1, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 137.3, 134.0, 129.2, 128.3, 126.7, 118.6, 61.0, 52.0, 48.8, 35.9; FTIR (neat) 3064, 3029, 1742, 1653, 1559, 1497, 1456, 1436, 1339, 1149, 743, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{33}N_2O_6S$ 501.2059, found 501.2043.

***N,N′*-Bis(2-propenyl)-*N,N′*-sulfonyl bis[(*R*)-1-phenylethylamine] (9e).** Bis-allylation and flash chromatography (10:1 Hexanes/EtOAc) produced 313 mg (99%) of **9e** as a colorless oil. TLC R_f=0.59 (10:1 Hexanes/EtOAc); $[\alpha]_D^{25}=+77.5$ (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J=7.4 Hz, 4H), 7.39–7.35 (m, 4H), 7.32–7.30 (m, 2H), 5.79 (dddd, J=15.7, 9.7, 7.1, 5.8 Hz, 2H), 5.19 (q, J=7.1 Hz, 2H), 5.03 (dd, J=6.1, 1.3 Hz, 2H), 5.01–4.99 (m, 2H), 3.77 (dd with small allylic coupling, J=16.3, 5.8 Hz, 2H), 3.55 (dd, J=16.3, 7.2 Hz, 2H), 1.67 (d, J=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.1, 135.9, 128.2, 127.9, 127.5, 116.9, 56.5, 47.3, 17.9; FTIR (neat) 3064, 3030, 2980, 2937, 1640, 1603, 1496, 1452, 1378, 1323, 1161, 784, 699 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{22}H_{29}N_2O_2S$ 385.1950, found 385.1958.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]-3,3′-dimethyl bis-butyric acid dimethyl ester (4b). A stirring solution of the allylated sulfamide **9b** (200 mg, 0.494 mmol) in CH_2Cl_2 (50 mL) in a 100 mL round-bottom flask was degassed by bubbling argon gas through the solution for 15 min. The Grubbs methathesis catalyst **3** (12 mg, 0.015 mmol, 3 mol%) was added, the flask was quickly fitted with a condenser containing an argon balloon, and the solution was heated to reflux for 1.5 h. The solution was cooled to rt and the flask opened up to the air. CH_2Cl_2 (40 mL) and Celite® (5.0 g) were added, and the solution was stirred for 18 h. The solvent was removed under reduced pressure, EtOAc (100 mL) was added, and the solution was filtered through a plug of silica. The solvent was again removed under reduced pressure to leave a crude solid. Flash chromatography (10:1, 5:1 Hexanes/EtOAc) gave 181 mg (97%) of the cyclic sulfamide **4b** as a white solid. Mp=57–58°C; TLC R_f=0.11 (10:1 Hexanes/EtOAc); $[\alpha]_D^{25}=-114.7$ (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.49 (t, J=2.1 Hz, 2H), 4.17–4.12 (m, 4H), 3.65 (s, 6H), 3.65–3.60 (m, 2H), 2.17–2.11 (m, 2H), 1.02 (d, J=6.8 Hz, 6H), 0.91 (d, J=6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 126.7, 65.1, 51.8, 40.4. 27.3, 19.1, 18.8; FTIR (neat) 3031, 1741, 1436, 1391, 1370, 1321, 1137, cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{16}H_{29}N_2O_6S$ 377.1746, found 377.1748.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]bis-propionic acid dimethyl ester (4a). RCM and flash chromatography (3:1 Hexanes/EtOAc) produced 223 mg (97%) of cyclic sulfamide **4a** as a brown oil. TLC R_f=0.19 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}=-62.6$ (c=0.942, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.68 (t, J=1.5 Hz, 2H), 4.76 (q, J=7.3 Hz, 2H), 4.09 (d, J=17.2 Hz, 2H), 3.73 (s, 6H), 3.68 (ddd, J=20.1, 3.2, 3.2 Hz, 2H) 1.41 (d, J=7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 127.8, 55.3, 52.3, 42.1, 16.1; FTIR (neat) 2989, 1741, 1457, 1313, 1174 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{12}H_{21}N_2O_6S$ 321.1120, found 321.1103.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]-4,4′-dimethyl bis-pentanoic acid dimethyl ester (4c). RCM and flash chromatography (2:1 Hexanes/EtOAc) produced 1.05 g (56%) of cyclic sulfamide **4c** as a white solid. Mp=89–90°C; TLC R_f=0.48 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}=-67.3$ (c=1.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 5.61 (m, 2H), 4.66 (dd, J=7.9, 6.8 Hz, 2H), 3.96–3.82 (m, 4H), 3.68 (s, 6H), 1.68–1.57 (m, 6H), 0.95 (d, J=6.1 Hz, 6H), 0.91 (d, J=6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 171.8, 127.4, 57.4, 52.1, 41.7, 38.9, 24.6, 22.9, 21.6; FTIR (neat) 3039, 2959, 2871, 1741, 1437, 1373, 1181 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{18}H_{33}N_2O_6S$ 405.2059, found 405.2033.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)] 3,3′-diphenyl bis-propionic acid dimethyl ester (4d). RCM and flash chromatography (3:1, 2:1 Hexanes/EtOAc) produced 181 mg (96%) of cyclic sulfamide **4d** as a brown oil. TLC R_f=0.39 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}=-55.2$ (c=1.098, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.19 (m, 10H), 5.46 (t, J=1.8 Hz, 2H), 4.91 (dd, J=7.8, 7.8 Hz, 2H), 3.65–3.63 (m, 10H), 3.21 (dd, J=14.2, 7.4 Hz, 2H), 2.89 (dd, J=14.2, 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 136.0, 129.2, 128.2, 127.3, 126.8, 60.3, 52.1, 41.9, 36.4; FTIR (neat) 3030, 1739, 1653, 1604, 1497, 1356, 1170, 744, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{24}H_{29}N_2O_6S$ 473.1746, found 473.1751.

1,1′-(1*R*,1′*R*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]-1,1′-diphenyl ethane (4e). RCM and flash chromatography (10:1 Hexanes/EtOAc) produced 887 mg (94%) of cyclic sulfamide **4e** as a white solid. Mp=90–92°C; TLC R_f=0.41 (10:1 Hexanes/EtOAc); $[\alpha]_D^{25}=-94.3$ (c=0.70, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, J=7.4 Hz, 4H), 7.39–7.35 (m, 4H), 7.30–7.27 (m, 2H), 5.51 (t, J=1.3 Hz, 2H), 5.44 (q, J=7.0 Hz, 2H), 3.84 (d, J=17 Hz, 2H), 3.54 (dd, J=17.5, 2.8 Hz, 2H), 1.57 (d, J=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.5, 128.4, 128.0, 127.4, 127.3, 56.1, 40.8, 17.7; FTIR (neat) 3029, 2978, 2931, 1602, 1496, 1451, 1382, 1300, 1177, 785, 698 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{25}N_2O_2S$ 357.1637, found 357.1616.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]-4,4′-dimethyl bis-pentanol. To a stirring solution of cyclic sulfamide **4c** (50 mg, 0.124 mmol) in THF (8 mL) in a 25 mL round-bottom flask fitted with argon balloon at 0°C was added lithium aluminum hydride (11 mg, 0.273 mmol). The reaction was stirred for 4 h with

the addition of another equivalent of lithium aluminum hydride. $Na_2SO_4 \cdot 10H_2O$ and several drops of distilled H_2O were added until the stirred solid turned white. The mixture was filtered and the solvent was removed under reduced pressure to gave a clear oil. Purification by flash chromatography (3:1, 1:1, 1:2 Hexanes/EtOAc) gave 42 mg (98%) of the leucinol cyclic sulfamide as clear oil. TLC R_f=0.34 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$=−6.8 (c=0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (t, J=1.8 Hz, 2H), 4.15–4.08 (m, 2H), 3.86 (d, J=17.9 Hz, 2H), 3.70 (d, J=17.9 Hz, 2H), 3.58–3.49 (m, 4H), 2.37 (s, 2H), 1.68–1.59 (m, 2H), 1.38 (ddd, J=14.3, 9.5, 4.8 Hz, 2H), 1.14 (ddd, J=14.3, 9.2, 5.0 Hz, 2H), 0.94 (d, J=6.5 Hz, 6H), 0.89 (d, J=6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.8, 64.3, 59.5, 40.9, 38.8, 25.2, 23.7, 22.4; FTIR (neat) 3463, 2955, 2870, 1468, 1379, 1290, 1176 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{16}H_{33}N_2O_4S$ 349.2161, found 349.2170.

1,1′-Bis(benzyloxy)-2,2′-(2*S*,2′*S*)-[(2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]-4,4′-dimethyl bispentane (10c). To a stirring solution of the leucinol sulfamide (39 mg, 0.112 mmol) in THF (10 mL) at 0°C was added sodium hydride (8 mg, 0.336 mmol). The mixture stirred for 45 min and benzyl bromide (57 mg, 0.336 mmol) was added. After stirring for 12 h at rt, EtOAc (20mL) was added and the mixture was washed with 10% $NaHSO_4$, $NaHCO_3$, brine, and dried ($MgSO_4$). The solution was filtered and the solvent removed under reduced pressure. Purification by flash chromatography (Hexanes, 20:1, 10:1 Hexanes/EtOAc) gave 48 mg (81%) of sulfamide **10c** as a clear oil. TLC R_f=0.78 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$=−11.5 (c=0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.27 (m, 10H), 5.57 (s, 2H), 4.51 (d, J=11.9 Hz, 2H), 4.44 (d, J=11.9 Hz, 2H), 4.31 (m, 2H), 4.07 (d, J=17.3 Hz, 2H), 3.59 (dd, J=19.2, 2.1 Hz, 2H), 3.46 (d, J=5.4 Hz, 4H), 1.73–1.65 (m, 2H), 1.50 (ddd, J=14.3, 10.0, 4.6 Hz, 2H), 1.27 (dd, J=14.2, 9.3, 5.0 Hz, 2H), 0.98 (d, J=6.5 Hz, 6H), 0.93 (d, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 128.3, 127.9, 127.6, 127.5, 72.9, 72.5, 55.5, 40.4, 38.5, 24.6, 23.4, 21.9; FTIR (neat) 3033, 2955, 2867, 1496, 1453, 1386,1366, 1301, 1183, 734, 698 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{30}H_{45}N_2O_4S$ 529.3100, found 529.3082.

***N*,*N*′-Dimethyl-[2,2′-(2*S*,2′*S*)-[(2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)]]-4,4′-dimethyl bispentanamide (11c).** A 10 mL round-bottom flask was charged with the leucine derived cyclic sulfamide (25 mg, 0.062 mmol) and $MeNH_2$ (39 mg, 1.24 mmol) in MeOH. The mixture was stirred under argon balloon for 5 days with the addition of two more equivalents of $MeNH_2$. The solvent was removed and the crude oil was purified by flash chromatography (2:1 Hexanes/EtOAc) to give 21 mg (84%) of **11c** as a clear oil. TLC R_f=0.23 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$=−158.5 (c=0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.41 (d, J=3.8 Hz, 2H), 5.69–5.68 (m, 2H), 4.41 (dd, J=9.1, 5.4 Hz, 2H), 4.05 (d, J=16.8 Hz, 2H), 3.61 (ddd, J=17.0, 4.5, 1.1 Hz, 2H), 2.82 (d, J=4.8 Hz, 6H), 1.84 (ddd, J=14.2, 8.8, 5.4 Hz, 2H), 1.66–1.57 (m, 2H) 1.48 (ddd, J=14.1, 9.1, 4.9 Hz, 2H), 0.95 (d, J=6.5 Hz, 6H), 0.91 (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 127.4, 59.2, 42.4, 38.2, 26.6, 24.8, 23.0, 21.7; FTIR (neat) 3381, 3317, 2958, 2870, 1662, 1544, 1456, 1368, 1300, 1179 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{18}H_{35}N_4O_4S$ 403.2379, found 403.2406.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-(4*R*),(5*S*)-dihydroxy-1,1-dioxido-2,7-diyl)]-4,4′-dimethyl bispentanoic acid dimethyl ester (12c). To a stirring solution of cyclic sulfamide **4c** (50 mg, 0.123 mmol) in a mixture of acetone (3 mL) and distilled water (1 mL) was added N-methyl morpholine N-oxide (32 mg, 0.248 mmol) and the mixture was stirred for 15 min. A 0.5 M aqueous solution of OsO_4 (1 mg, 4 μmol) was then added. After 19 h, Na_2SO_3 (50 mg, 0.31 mmol) was added to destroy the OsO_4. The mixture was filtered and concentrated to 1.5 mL under reduced pressure. Flash chromatography (1:2 Hexanes/EtOAc) gave 50 mg (92%) of **12c** as a clear oil. TLC R_f=0.58 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$=−21.9 (c=0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28 (dd, J=9.3, 5.8 Hz, 1H), 4.21 (dd, J=10.6, 4.6 Hz, 1H), 3.92 (t, J=4.6, 1H), 3.83–3.73 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.65 (dd, J=15.5, 8.9 Hz, 1H), 3.40, (d, J=12.4 Hz, 1H), 3.35 (dd, J=15.6, 6.9 Hz, 1H), 1.97, (ddd, J=13.8, 10.3, 3.3 Hz, 1H), 1.83–1.72 (m, 5H), 0.97 (d, J=6.3 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.2 Hz, 3H), 0.94 (d, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 173.8, 69.4, 69.0, 61.6, 59.2, 53.1, 52.8, 48.8, 46.1, 39.2, 38.8, 24.7, 24.7, 23.2, 22.9, 21.6, 21.5; FTIR (neat) 3432, 1740, 1457, 1437, 1380, 1311, 1168 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{18}H_{35}N_2O_8S$ 439.2114, found 439.2132.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-(4*R*),(5*S*)-dihydroxy-1,1-dioxido-2,7-diyl)] bis-propionic acid dimethyl ester (12a). Dihydroxylation and flash chromatography (1:2 Hexanes/EtOAc) produced 75 mg (53%) of **12a** as a colorless oil. TLC R_f=0.09 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$=−5.52 (c=1.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (q, J=7.3 Hz, 1H), 4.23(q, J=7.3 Hz, 1H), 3.88 (t, J=4.6 Hz, 1H), 3.80–3.72 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.66 (dd, J=15.6, 8.9 Hz, 1H), 3.37 (d, J=15.6 Hz, 1H), 3.35 (dd, J=15.6, 3.1 Hz, 1H), 1.56 (d, J=7.3 Hz, 3H), 1.53 (d, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 173.6, 69.4, 68.9, 58.8, 56.5, 53.0, 52.8, 48.3, 45.8, 16.3, 15.8; FTIR (neat) 3489, 3400, 2998, 1743, 1457, 1382, 1307, 1171 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{12}H_{23}N_2O_8S$ 355.1175, found 355.1161.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-(4*R*),(5*S*)-dihydroxy-1,1-dioxido-2,7-diyl)]-3,3′-dimethyl bisbutyric acid dimethyl ester (12b). Dihydroxylation and flash chromatography (1:2 Hexanes/EtOAc) produced 69 mg (96%) of **12b** as a white solid. TLC R_f=0.33 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$=−32.7 (c=0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.94 (d, J=10.1 Hz, 1H), 3.92–3.83 (m, 2H), 3.86 (d, J=10.6 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.59–3.36 (m, 4H), 2.31–2.23 (m, 1H), 2.23–2.14 (m, 1H) 1.04 (d, J=6.6 Hz, 6H), 0.97 (d, J=6.4 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 172.6, 70.0, 69.5, 67.9, 66.0, 52.5, 52.3, 47.4, 45.3, 28.5, 28.3, 20.0, 20.0, 19.6, 19.5; FTIR (neat) 3457, 1740, 1436, 1380, 1311, 1158 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{16}H_{31}N_2O_8S$ 411.1801, found 411.1809.

2,2′-(2*S*,2′*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-(4*R*),(5*S*)-dihydroxy-1,1-dioxido-2,7-diyl)]-3,3′-diphenyl

bis-propionic acid dimethyl ester (12d). Dihydroxylation and flash chromatography (1:1 Hexanes/EtOAc) produced 110 mg (97.2%) of **12d** as a white solid. Mp=153–154°C; TLC R_f=0.20 (1:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−131.8 (c=0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.21 (m, 10H), 4.36 (dd, J=10.3, 5 Hz, 1H), 4.13 (dd, J=10.6, 4.1 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.62–3.53 (nfom, 4H), 3.45 (dd, J=14.7, 5 Hz, 1H), 3.39 (dd, J=14.4, 4.1 Hz, 1H), 3.23 (dd, J=14.4, 10.6 Hz, 1H), 3.12 (dd, J=14.7, 10.4 Hz, 1H), 2.62 (d, J=12.7 Hz, 1H), 2.52 (dd, J=16.0, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 171.0, 137.0, 136.5, 129.5, 129.2, 128.6, 128.5, 127.0, 126.9, 69.8, 68.3, 68.0, 63.7, 53.6, 52.6, 51.4, 47.0, 36.9, 36.6; FTIR (neat) 3502, 3382, 3029, 1741, 1716, 1604, 1559, 1497, 1312, 1153, 753, 702 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{24}H_{31}N_2O_8S$ 507.1801, found 507.1806.

***N,N′*-Sulfonyl-(3*S*,3′*S*)-bis(4-methyl-1-penten-3-amine) (14).** Dihydroxylation and flash chromatography (3:1 Hexanes/EtOAc) produced 128 mg (56%) of **14** as a white solid. Mp=51–52°C; TLC R_f=0.48 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=85.9 (c=0.51, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.70 (ddd, J=17.7, 10.3, 7.8 Hz, 2H), 5.25 (dd, J=17, 0.9 Hz, 2H), 5.21 (d, J=10.2 Hz, 2H), 4.29 (d, J=7.7 Hz, 2H), 3.65 (dd, J=7.8, 5.4 Hz, 2H), 1.84 (m, 2H), 0.92 (d, J=6.9 Hz, 6H), 0.89 (d, J=6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.5, 117.5, 62.3, 32.4, 18.6, 17.8; FTIR (neat) 3290, 2962, 2939, 2875, 1652, 1568, 1456, 1436, 1369, 1316, 1157 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{12}H_{25}N_2O_2S$ 261.1637, found 261.1646.

(3*S*,6*S*)-[(2,3,6,7-Tetrahydro-3,6-bis(methylethyl)-1,2,7-thiadiazepine-1,1-dioxide (5). RCM and flash chromatography (3:1 Hexanes/EtOAc) produced 31 mg (69%) of **5** as a white solid. Mp=152–153°C; TLC R_f=0.35 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=50.0 (c=0.18, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.59 (s, 2H), 4.94 (d, J=10.7 Hz, 2H), 3.98 (dd, J=8.2, 4.0 Hz, 2H), 1.92–1.87 (m, 2H), 0.99 (d, J=6.7 Hz, 6H), 0.92 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.1, 56.3, 32.6, 18.7, 17.1; FTIR (neat) 3303, 3257, 2959, 2931, 2875, 1653, 1559, 1321, 1161 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{10}H_{21}N_2O_2S$ 233.1324, found 233.1321.

(*tert*-Butoxycarbonylsulfonyl) L-phenylalanine methyl ester (15d). Was prepared using literature procedure, see Groutas Ref. 17.

(*tert*-Butoxycarbonylsulfonyl) L-valine methyl ester (15b). To a stirring solution of chlorosulfonyl isocyanate (1.23 mL, 14.1 mmol) and CH_2Cl_2 (40 mL) at 0°C in a 250 mL round-bottom flask was added a solution of *t*-BuOH (1.0 M, 1.35 mL, 14.1 mmol) in CH_2Cl_2 dropwise over a period of 10 min. The resulting solution was transferred via cannula to a mixture of H-Val-OMe·HCl (2.37 g, 14.1 mmol) and Et_3N (3.94 mL, 28.3 mmol) in CH_2Cl_2 (40 mL) at 0°C. The slurry was allowed to warm to rt and stirred for an additional 2.5 h. The salts were filtered, the organic portion was washed with H_2O (2×), brine (2×), and dried (Na_2SO_4). The mixture was filtered and concentrated under reduced pressure to yield 4.19 g (96.0%) of sulfamide **15** as a pure white solid. Mp=128–129°C; TLC R_f=0.42 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=+40.6 (c=1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 5.54 (d, J=9.2 Hz, 1H), 4.04 (dd, J=9.2, 4.9 Hz, 1H), 3.76 (s, 3H), 2.18–2.10 (m, 1H), 1.49 (s, 9H), 1.18 (d, J=6.9 Hz, 3H), 0.91 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.85, 149.86, 83.75, 62.07, 52.44, 31.44, 27.89, 18.89, 17.25 ppm; FTIR (neat) 3268, 1742, 1451, 1400, 1371, 1146 cm^{-1}. HRMS $(M+H)^+$ calcd for $C_{11}H_{23}N_2O_6S$ 311.1277, found 311.1266.

***N,N′*-Bis(2-propenyl)-*N*-(*tert*-butoxycarbonylsulfonyl) L-phenylalanine methyl ester.** To a stirring solution of **15d** (0.500 g,1.40 mmol) in dry acetone (14 mL) in a 50 mL round-bottom flask was added anhydrous K_2CO_3 (0.771 g, 5.58 mmol) and allyl bromide (0.507 mL, 0.709 g, 5.86 mmol). The mixture was heated to reflux under argon for 12 h. The solution was then cooled, suction filtered, and the solvent removed under reduced pressure to give a pale yellow oil. Flash chromatography (4:1 Hexane:EtOAc) yielded 504 mg (82%) of a clear, colorless oil. TLC R_f=0.35 (4:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−27.2 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.21 (m, 5H), 5.98–5.82 (m, 2H), 5.28 (ddd, J=15.8, 3.6, 1.5 Hz, 2H), 5.17 (ddd, J=10.3, 5.1, 1.3 Hz, 2H), 4.83 (dd, J=9.0, 6.2 Hz, 1H), 5.28 (ddd, J=15.8, 3.5, 1.5 Hz, 2H), 5.17 (ddd, J=9.2, 5.1, 1.3 Hz, 2H), 4.32 (dd, J=9.0, 6.2 Hz, 1H), 4.22 (m, 3H), 4.12 (dd, J=16.6, 6.8 Hz, 1H), 3.62 (s, 3H), 3.26 (dd, J=13.6, 9.0 Hz, 1H), 3.05 (dd, J=13.6, 6.2 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 151.6, 136.9, 135.5, 133.6, 129.7, 128.9, 127.3, 118.0, 117.9, 84.0, 62.1, 52.4, 51.6, 50.0, 37.5, 28.5; FTIR (neat) 3082, 2980, 1731, 1644, 1605, 1494, 1442, 1371, 1319, 1249, 1149, 1036 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{30}N_2O_6S$ 439.1903, found 439.1882.

2-(2*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-7-*tert*-butyloxycarbonyl-2-yl)] 3-phenyl-propionic acid methyl ester. Bis-allylation and flash chromatography (4:1 Hexanes/EtOAc) produced 78 mg (84%) of cyclic sulfamide as a clear, colorless oil. TLC R_f=0.22 (4:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−37.7 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.24 (m, 5H), 5.81 (ddd, J=11.2, 5.5, 5.5 Hz, 1H), 5.67 (ddd J=11.3, 3.7, 3.7 Hz, 1H), 5.09 (t, J=7.8 Hz, 1H), 4.15 (dd, J=16.9, 5.7 Hz, 2H), 4.08 (m, 2H), 3.86 (ddd, J=16.9, 5.1, 1.3 Hz, 1H), 3.68 (s, 3H), 3.29 (dd, J=14.0, 7.6 Hz, 1H), 2.99 (dd, J=14.0, 7.9 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 151.3, 135.7, 129.2, 128.6, 128.3, 127.3, 127.1, 83.8, 61.6, 52.3, 43.8, 43.5, 37.0, 27.8; FTIR (neat) 3031, 2981, 2259, 1732, 1604, 1496, 1445, 1367, 1327, 1265, 1151, 1093, 1037, 918 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{26}N_2O_6S$ 411.1590 found 411.1582.

2-(2*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2-yl)]-3-phenyl-propionic acid methyl ester. The Boc-protected cyclic sulfamide prepared in the previous experimental (50 mg, 0.122 mmol) was added to a 5 mL round-bottom flask, followed by trifluoroacetic acid (194 mg, 0.131 mL, 1.71 mmol). The solution was stirred at ambient temperature for 36 h. CH_2Cl_2 (4 mL) was added and the resulting solution washed with saturated $NaHCO_3$ (3×). The aqueous solution was back-extracted with methylene chloride (2×) and the combined organic solutions washed with water (2×), brine (2×), and dried (Na_2SO_4).

The solution was suction filtered and the solvent removed under reduced pressure. Flash chromatography (2:1 Hexanes/EtOAc) yielded 31.2 mg (83%) of a white crystalline solid. Mp=62–64°C; TLC R_f=0.20 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−59.85 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.21 (m, 5H), 5.73–5.65 (m, 1H), 5.64–5.57 (m, 1H), 4.97 (dd, J=8.0, 5.7 Hz, 1H), 4.86(dd, J=8.9, 6.8 Hz, 1H), 4.04 (ddd, J=8.9, 2.3, 1.7 Hz, 1H), 3.81 (ddd, J=18.5, 5.1, 1.0 Hz, 1H), 3.69 (s, 3H), 3.47 (ddd, J=18.0, 4.6, 1.0 Hz, 1H), 3.44–3.34 (m, 1H), 3.29 (dd, J=26.1, 6.8 Hz, 1H), 2.96 (dd, J=14.3, 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 136.2, 129.7, 129.5, 129.2, 128.4, 128.2, 128.0, 126.9, 126.7, 61.0, 52.2, 41.9, 40.7, 36.3; FTIR (neat) 3297, 3030, 2952, 2861, 1737, 1603, 1496, 1437, 1348, 1318, 1238, 1161, 1095, 983, 917, 887 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{14}H_{18}N_2O_4S$ 311.1066 found 311.1060.

2-(2*S*)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-7-benzyl-2-yl)]-3-phenyl-propionic acid methyl ester. To a stirring solution of the cyclic sulfamide prepared in the previous experimental (49 mg, 0.159 mmol) and dry CH_3CN (1.5 mL), in a 5 mL round-bottom flask, were added anhydrous K_2CO_3 (44 mg, 0.318 mmol) and benzyl bromide (40 μL, 0.057g, 0.334 mmol). The solution was heated to 55°C and stirred for 36 h, cooled to rt, and diluted with CH_2Cl_2 (3 mL). The solution was filtered, and the solvent removed under reduced pressure. Flash chromatography (4:1 Hexanes/EtOAc) yielded 62 mg (96%) of sulfamide **16** as a white crystalline solid. Mp=56–58°C; TLC R_f=0.26 (4:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−36.8 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.20 (m, 10H), 5.83 (ddd, J=10.9, 4.4, 1.3 Hz, 1H), 5.45 (ddd, J=9.8, 5.3, 4.4 Hz, 1H), 4.97 (dd, J=9.3, 6.4 Hz, 1H), 4.03 (s, 2H), 3.98 (ddd, J=18.2, 4.0, 2.0 Hz, 1H), 3.76 (dd, J=18.2, 5.8 Hz, 1H), 3.73 (s, 3H), 3.53 (dd, J=17.8, 3.9 Hz, 1H), 3.38 (d, 2.4 Hz, 1H), 3.32 (dd J=14.3, 6.4 Hz, 1H), 2.95 (dd, J=18.2, 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 136.4, 136.1, 129.5, 128.8, 128.5, 128.4, 128.1, 127.7, 127.3, 126.9, 61.4, 52.3, 51.1, 43.5, 41.6, 36.6; FTIR (neat) 3065, 3026, 2951, 1740, 1603, 1498, 1451, 1439, 1354, 1320, 1160, 1099, 926, 753 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{24}N_2O_4S$ 401.1535 found 401.1556.

***N*-*tert*-butyloxycarbonyl-*N*′-[[(1*R*)-1-ethoxycarbonyl-ethyl-amino]sulfonyl]-L-valine methyl ester.** To a stirring solution of sulfamide **15b** (1.00 g, 3.23 mmol) in THF (2 mL) was slowly added DEAD (508 μL, 3.23 mmol) via dropwise addition. A solution consisting of (L)-(−)-Ethyl lactate (366 μL, 3.23 mmol) and PPh_3 (847 mg, 3.23 mmol) in THF (3 mL), was slowly transferred via cannula into the sulfamide solution. After 3 h, the reaction mixture was concentrated and dissolved in ether to precipitate Ph_3PO. The solution was filtered, and concentrated under reduced pressure to leave a crude oil. Flash chromatography (5:1 Hexanes/EtOAc) yielded 1.07 g (81%) of Boc-protected sulfamide as a yellow oil. TLC R_f=0.63 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=+68.8 (c=1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, J=7.6 Hz, 1H), 4.89 (q, J=6.9 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 4.09 (dd, J=7.6, 4.0 Hz, 1H), 3.77 (s, 3H), 2.18–2.15 (m, 1H), 1.57 (d, J=6.9 Hz, 3H), 1.50 (s, 9H), 1.27 (t, J=7.1 Hz, 3H), 1.01 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.15, 170.10, 150.34, 128.22, 84.82, 61.52, 61.48, 56.11, 52.29, 32.01, 27.73, 18.62, 17.14, 16.45, 14.03; FTIR (neat) 3297, 1742, 1458, 1429, 1371, 1299, 1277, 1262, 1219, 1153 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{16}H_{31}N_2O_8S$ 411.1801, found 411.1784.

***N*-[[(1*R*)-1-Ethoxycarbonyl-ethylamino]sulfonyl]-L-valine methyl ester (17).** To a stirring solution of the Boc-protected sulfamide prepared in the previous experimental (500 mg, 1.22 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.41 mL, 18.3 mmol). After 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with $NaHCO_3$ (2×), H_2O (2×), brine (2×), and dried (Na_2SO_4). The organic layer was concentrated under reduced pressure. Flash chromatography (1:1 Hexanes/EtOAc) yielded 380 mg (100%) of sulfamide **17** as a light yellow solid. Mp=79–81°C; TLC R_f=0.55 (1:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−129.2 (c=0.5, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (t, J=10.1, 8.9 Hz, 2H), 4.22 (q, J=7.1 Hz, 2H), 4.01 (m, 1H), 3.80 (dd, J=10.2, 4.9 Hz, 1H), 3.77 (s, 3H), 2.08 (m, 1H), 1.37 (d, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.01, 172.87, 61.73, 61.09, 52.36, 51.66, 31.16, 19.20, 18.88, 17.45, 14.02; FTIR (neat) 3282, 1742, 1451, 1437, 1349, 1299, 1270, 1139 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{11}H_{23}N_2O_6S$ 311.1277, found 311.1262.

***N*,*N*′-Bis(2-propenyl)-*N*-[[(1*R*)-1-ethoxycarbonyl-ethyl-amino]sulfonyl]-L-valine methyl ester.** Bis-allylation and flash chromatography (1:1 Hexanes/EtOAc) produced 152 mg (81%) of sulfamide as clear oil. TLC R_f=0.56 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−30.2 (c=1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (m, 2H), 5.21 (m, 2H), 5.15 (dd, J=10.2, 1.2 Hz, 1H), 5.11 (dd, J=10.1, 1.1 Hz, 1H), 4.19 (m, 3H), 4.07 (d, J=10.6 Hz, 1H), 3.99 (m 2H), 3.90 (dd, J=16.2, 6.16 Hz, 1H), 3.78 (dd, 16.1, 6.6 Hz, 1H), 3.70 (s, 3H), 2.20 (m, 1H), 1.48 (d, J=7.2 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 0.92 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.62, 171.52, 135.12, 134.67, 118.08, 117.60, 66.25, 61.29, 55.49, 51.69, 49.02, 47.84, 28.23, 19.62, 19.56, 15.45, 14.05 ppm; FTIR (neat) 1741, 1643, 1441, 1380, 1336, 1205, 1134 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{17}H_{31}N_2O_6S$ 391.1903, found 391.1879.

2-(2*S*)-[(7-[(1′*R*)-1′-Ethoxycarbonyl-ethyl]-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2-yl)] 3-phenyl propionic acid methyl ester (6). RCM and flash chromatography (2:1 Hexanes/EtOAc) produced 31.6 mg (67%) of the cyclic sulfamide **6** as pure brown oil. TLC R_f=0.37 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$=−24.0 (c=0.25, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (m, 2H), 4.71 (q, J=7.3, 1H), 4.18 (q, J=7.1 Hz, 2H), 4.11 (m, 3H), 3.72 (dd, J=18.8, 4.9 Hz, 1H), 3.66 (s, 3H), 3.61 (dd, J=18.3, 4.5 Hz, 1H), 2.14 (m, 1H), 1.39 (d, J=7.3 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.52, 170.87, 127.51, 127.21, 64.87, 61.43, 55.65, 51.80, 41.67, 41.02, 27.47, 19.13, 18.90, 16.29, 14.10; FTIR (neat) 1742, 1589, 1458, 1437, 1361, 1357, 1320, 1190, 1161 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{15}H_{27}N_2O_6S$ 363.1590, found 363.1575.

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