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Synthesis of Cyclic Peptidosulfonamides by Ring-Closing Metathesis

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N-Protected β-aminoethanesulfonyl chlorides (**2a**−**e**) were used in the preparation of sulfonamides **4**, **8**, **11a**−**c**, and **15**. Ring-closing metathesis of sulfonamides **4** and **8** did not lead to the expected nine-membered cyclic peptidosulfonamides. In contrast, the allylated peptidosulfonamides **11a**−**c** and **15** turned out to be suitable precursor systems for ring-closing metathesis using second-generation Grubbs catalyst and nine-membered cyclic peptidosulfonamides were obtained in 47−60% yields. The possibility for incorporation of these cyclic peptidosulfonamides into a peptide sequence was illustrated by the incorporation of an amino acid on the "S"- or "N"-terminus leading to **16** and **18**−**20**, respectively. A model of cyclic peptidosulfonamide **16** hints at an extended-like structure.

Introduction

The presence of a nitro-substituted aromatic sulfonamide moiety on an amine, which increases the acidity of the resulting N−H considerably, has been exploited in a variety of ways to prepare alkylated amines, amino acids, and other functionalized amine derivatives under mild alkylation conditions using relatively weak bases or in a Mitsunobu reaction.[1]

Sulfonamide moieties are also present in peptidosulfonamide foldamers which have been introduced by us recently[2] or peptidosulfonamide−peptide hybrids.[3] Although these are *aliphatic* sulfonamide moieties, the increased acidity of a sulfonamide N−H as compared to a regular amide N−H is still apparent. This implies a difference in reactivity with respect to, for example, alkylation, and selective alkylation of sulfonamide nitrogens amidst regular amides is indeed possible.[4]

Another striking structural feature of peptidosulfonamide foldamers or peptidosulfonamide−peptide hybrids is the decreased rigidity of the sulfonamide bond as compared to the regular amide bond. To address this issue we describe in this paper an approach for preparation by ring-closing metathesis of conformationally constrained cyclic peptidosulfonamides where we have taken advantage of the increased acidity of the peptidosulfonamide NH as well as the presence of an aromatic sulfonamide N−H within the same residue for the synthesis of dialkylated cyclization precursors.

Results and Discussion

Our initial approach for the preparation of cyclization precursors for the ring-closing metathesis (RCM) leading to cyclic peptidosulfonamides[5] was to introduce the first alkene containing substituent by reaction of the Fmoc-leucine derived sulfonyl chloride **2d**[6] with allylamine to afford sulfonamide **3** in 48% yield (Scheme 1). After cleavage of the Fmoc-group with dimethylamine, the

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(2) Monnee, M. C. F.; Marijne, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41*, 7991−7995; **2001**, *42*, 965.

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(6) Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. *Synthesis* **2000**, *11*, 1579−1584.

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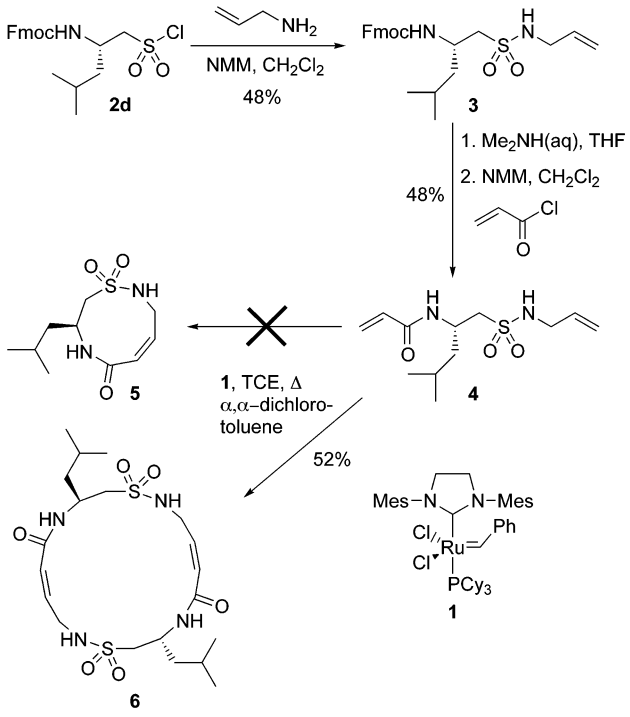
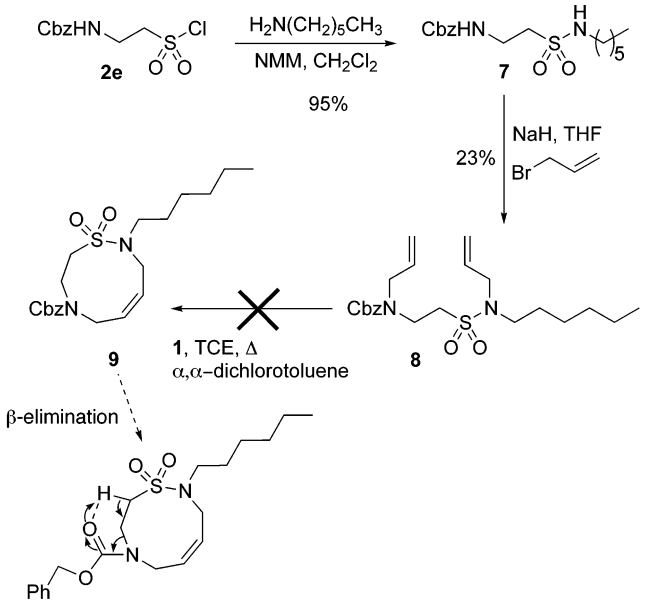
SCHEME 1



second alkene containing substituent was introduced by reaction with acryloyl chloride in the presence of a weak base (*N*-methylmorpholine: NMM) and cyclization precursor **4** was obtained in 48%. It was not possible to improve this yield by carrying out a BOP coupling reaction of the free amine with acrylic acid. For ring-closure of precursor **4**, second-generation Grubbs catalyst (**1**, 20%)[7] was used in 1,1,2-trichloroethane (TCE) as a solvent (10 mM concentration of **4**), and α,α-dichlorotoluene was added to reduce inactivation of the catalyst. Unexpectedly, only the dimeric 18-membered ring (**6**) was obtained after RCM and not the expected nine-membered cyclopeptidosulfonamide (**5**). This reaction was repeated at lower concentrations down to 1 mM, and still no nine-membered ring product was detected. It is possible that the formation of an 18-membered ring is more favorable than the corresponding nine-membered ring, since in the formation of the latter the acrylamide bond has to rotate leading to a cisoid conformation, which is clearly more difficult than rotation about the sulfonamide bond (Scheme 1).

To facilitate rotation of the alkene containing N-terminal substituent and therefore RCM to a cyclic peptidosulfonamide structure, (tertiary) carbamate **8** (Scheme 2) was prepared. Now a position of the alkene-containing substituents as in precursor **8** is more favorable, and thus, ring closure should take place. This precursor was accessible by double alkylation of taurine derivative **7**, albeit in low yield (23%). RCM of **8** showed disappearance of **8** on TLC, but after isolation only traces of a product with the correct mass were found. A possible explanation for not obtaining the desired ring closed product might be abstraction of the α-sulfonamide hydrogen atom in **9** via a six-membered ring transition-

SCHEME 2



state, which might lead to ring-opening by (thermal) *β* elimination (Scheme 2).

These negative results were now taken into account in the final approach in which cyclization precursors **11** were prepared having (a) a sulfonamide moiety facilitating a position of the alkene substituents favorable for ring-closing, and (b) the oxygens of the sulfonamide moiety of the *o*-NBS-protecting group (*o*-nitrobenzenesulfonyl) are less inclined to accept[8] a proton, and therefore, *β*-elimination, via the mechanism shown in Scheme 2, becomes less likely.

Thus, Fmoc-protected *β*-aminoethanesulfonyl chlorides **2a**−**c** were converted to the corresponding sulfonamides, after which the Fmoc-group was removed and an *o*-NBS-group was introduced, which set the stage for alkylation of the amine according to Fukuyama et al.[1a] Although his procedure was developed for the alkylation of *o*-NBS and *p*-NBS *aromatic* sulfonamides, it also worked fine for the *aliphatic* sulfonamide moiety in **10a**−**c,** and treatment of, e.g., **10c** with allyl bromide in dimethylformamide (DMF), with K_2CO_3 as a base, gave bis-allylated sulfonamide **11c** in 68% yield (Scheme 3).

Ring-closing metathesis of **11c** (5 mM in TCE) was performed analogously to the previous cyclizations in the presence of 10% of catalyst (**1**), which now afforded cyclic peptidosulfonamide **12c** in 48% yield (Scheme 3). Similarly, cyclic peptidosulfonamides **12a** and **12b** were prepared in 60% and 47% yield, respectively, indicating that cyclic peptidosulfonamides with different R^1 and R^2 groups are easily accessible.

One of the initial goals clearly was the incorporation of the cyclic peptidosulfonamides into peptides to obtain *β*-turn mimetics or to constrain the flexibility of a peptide otherwise. The used starting compounds, i.e., the Fmoc-protected aminoethanesulfonyl chlorides as well as—in a later stage of the synthesis—the presence of the removable *o*-NBS-group clearly facilitates the incorpora-

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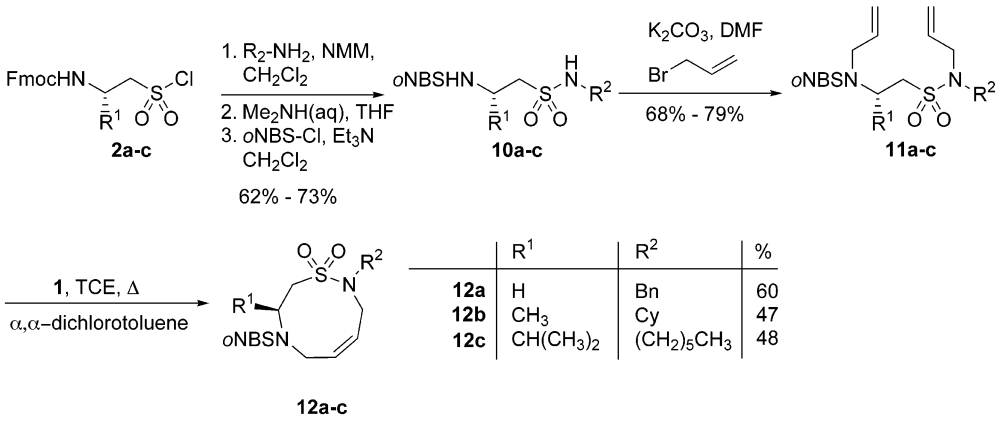
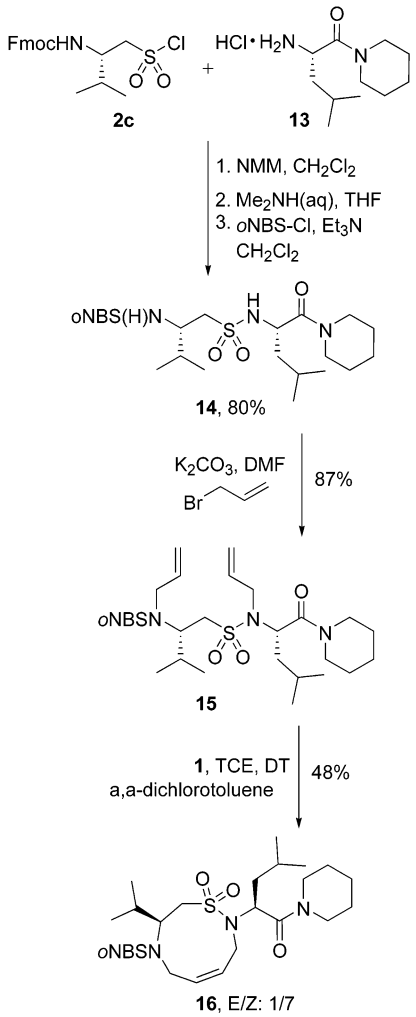
SCHEME 3



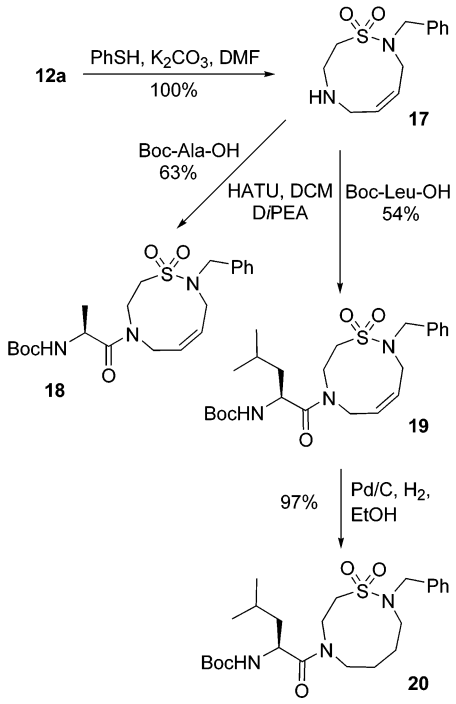
	R^1	R^2	%
12a	H	Bn	60
12b	CH_3	Cy	47
12c	$CH(CH_3)_2$	$(CH_2)_5CH_3$	48

SCHEME 4



tion of the cyclic sulfonamide in a peptide sequence. First, an amino acid residue was introduced onto the "S"-terminus as part of the ultimate cyclic peptidosulfonamide scaffold. This was achieved by coupling of sulfonyl chloride **2c** and leucine piperidine amide **13** to give **14** in a good yield (80%). Introduction of the alkene substituents by alkylation in the presence of K_2CO_3 went very well, which was followed by RCM of **15** leading to a cyclic peptidosulfonamide containing a leucine residue, i.e., **16** (Scheme 4). HPLC analysis of **16** showed two peaks (ratio

SCHEME 5



7:1). The two peaks were separated by preparative HPLC, giving two pure products of identical mass (ESI-MS). The isolated material of the minor peak was insufficient for detailed NMR measurements. However, it is assumed that the two peaks were the *E* and *Z* cyclic sulfonamides, showing that the ring-closing metathesis of this system gave—not entirely unexpectedly—cyclic sulfonamides with good *E*/*Z* selectivity (1/7).

Second, the *o*-NBS cyclic peptidosulfonamide **12a** was deprotected to give **17** in order to introduce a N-terminal residue. This was demonstrated using Boc-Ala-OH and Boc-Leu-OH to afford cyclic peptidosulfonamides **18** and **19**, respectively, in satisfactory yields (63% and 54%, respectively) (Scheme 5). The NMR spectra of **18** and **19** were much more complicated than the spectra of starting material **12a**, probably due to the presence of amide rotamers. To attempt to reduce the complexity of the NMR spectra, the double bond was reduced to give **20**. Still rotamers were present; however, the magnetic difference between rotamers, due the absence of the

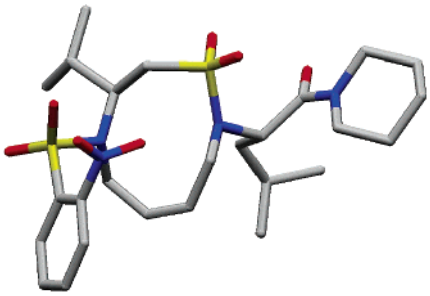


FIGURE 1. Model of cyclic peptidosulfonamide **16** obtained using MacroModel.

double bond, was apparently smaller. Remarkably, the benzyl group was not cleaved under these conditions.

Preliminary modeling studies using MacroModel[9] of, e.g., cyclic peptidosulfonamide **16** hint at an extended position of the substituents on the nitrogen atoms of the peptidosulfonamide ring (Figure 1). This might mean that amino acids attached to these nitrogen atoms also may assume a position in which the chiral α-carbon atoms are removed as far as possible from each other as is the case in an extended peptide chain.

In conclusion, cyclic peptidosulfonamides can be conveniently prepared using ring-closing metathesis following the introduction of alkene substituents which is facilitated by the presence of sulfonamide moieties. In this approach, amino acids can be attached to the cyclic peptidosulfonamide, which opens up the possibilities of incorporating this cyclic sulfonamide moiety in a peptide sequence and possibly favoring an extended-like structure. Alternatively, the cyclic peptidosulfonamide can function as a scaffold carrying a variety of functional groups. Bearing this in mind, libraries of these compounds are within reach.

Experimental Section

Cbz- and Fmoc-Protected *β*-Aminoethanesulfonyl Chlorides (2a−e). The Cbz- and Fmoc-protected amino acid derived sulfonyl chlorides (**2a**−**e**) were prepared according to the procedure described previously.[6]

Fmoc-LeuΨ[CH_2SO_2]-N(H)All (3). Fmoc-leucine derived sulfonyl chloride **(2d)** (317 mg, 0.75 mmol) was added to a solution of allylamine (37 μL, 0.5 mmol) and *N*-methylmorpholine (178 μL, 1.65 mmol) in CH_2Cl_2 (5 mL) at rt. The mixture was stirred for 3 h, and more CH_2Cl_2 (10 mL) was added. The mixture was washed with $KHSO_4$ (1 M, 8 mL) and water. After drying (Na_2SO_4), the product was isolated as a white solid (107 mg, 0.24 mmol, 48%): R_f = 0.73 (MeOH/CH_2Cl_2, 5/95); ^{1}H NMR ($CDCl_3$) δ 0.91 (4 lines, 6H, 2 × CH_3), 1.37 (m, 1H, C*H*(CH_3)$_2$), 1.57 (m, 2H, CH_2CH(CH_3)$_2$), 3.16 (m, 2H, SO_2CH_2), 3.68 (bd, 2H, CH_2CH═), 4.15 (m, 2H, NCH, CH (Fmoc)), 4.39 (bd, 2H, CH_2 (Fmoc), 5.19 (m, 2H, ═CH_2), 5.54 (bd, 1H, NHFmoc), 5.78 (bt, 1H, SO_2NH), 5.81 (m, 1H, ═CH), 7.27−7.76 (m, 8H, Ar-CH (Fmoc)); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.8 (CH_3), 24.5 (*C*H(CH_3)$_2$), 43.3 (*C*H_2CH(CH_3)$_2$), 45.4 (*C*H_2CH═), 45.9 (NCH), 47.0 (CH (Fmoc)), 56.5 (SO_2CH_2), 66.7 (CH_2 (Fmoc)), 117.6 (═CH_2), 119.8, 124.9, 125.0, 126.9, 127.6, 141.1, 143.5, 143.8 (Ar-C (Fmoc)), 133.5 (═CH), 156.6 (C═O); ESI MS *m*/*z* 443.30 [M + H]$^+$, 465.40 [M + Na]$^+$.

Acryloyl-LeuΨ[CH_2SO_2]-N(H)All (4). To a solution of **3** (105 mg, 0.237 mmol) in THF (2.4 mL) was added dimethylamine (40% m/m in water, 1.2 mL). The solution was stirred at rt for 30 min and concentrated in vacuo. After coevaporation with toluene (3×), CH_2Cl_2 (5 mL) was added and the mixture was cooled in an ice bath. After addition of *N*-methylmorpholine (78 μL, 0.71 mmol) and acryloyl chloride (39 μL, 0.48 mmol, dropwise), the mixture was stirred for 1 h at rt. Additional CH_2Cl_2 (10 mL) was added, and the organic layer was washed with $KHSO_4$ (1M, 10 mL) and water. Drying (Na_2SO_4) followed by column chromatography (MeOH/CH_2Cl_2, 3/97) afforded the product as a colorless oil (31 mg, 0.113 mmol, 48%): R_f = 0.20 (MeOH/CH_2Cl_2, 3/97); ^{1}H NMR ($CDCl_3$) δ 0.93 (4 lines, 6H, 2 × CH_3), 1.43 (m, 1H, C*H*(CH_3)$_2$), 1.66 (m, 2H, CH_2CH(CH_3)$_2$), 3.21 (m, 2H, SO_2CH_2), 3.73 (m, 2H, CH_2CH═), 4.51 (m, 1H, NCH), 5.27 (m, 2H, ═CH_2), 5.68 (m, 2H, SO_2NH, CHC═O), 5.87 (m, 1H, NCH_2CH), 6.15 (m, 1H, CH^a═CHC═O), 6.27 (m, 1H, CH^bCHC═O), 6.43 (bd, 1H, NHC═O); ^{13}C NMR ($CDCl_3$) δ 21.7, 22.8 (CH_3), 24.2 (*C*H(CH_3)$_2$), 43.2 (*C*H_2CH(CH_3)$_2$), 44.3 (NCH), 45.8 (*C*H_2CH═), 56.3 (SO_2CH_2), 118.0 (CH_2CH═*C*H_2), 127.4 (*C*H_2═CHC═O), 130.4 (═*C*HC═O), 133.4 (═*C*HCH$_2$N), 166.2 (C═O); ESI MS *m*/*z* 275.15 [M + H]$^+$, 297.15 [M + Na]$^+$.

Cbz-Tau-N(H)(CH_2)$_5$$CH_3$ (7). To a solution of *n*-hexylamine (264 μL, 2.0 mmol) and *N*-methylmorpholine (440 μL, 4.0 mmol) in CH_2Cl_2 (20 mL) was added Cbz-taurine sulfonyl chloride **(2e)** (61 mg, 2.2 mmol). After the solution was stirred for 1 h at rt, more CH_2Cl_2 (20 mL) was added. Washing with $KHSO_4$ (1 M, 20 mL) and water, followed by drying (Na_2SO_4), afforded sulfonamide **7** as a white solid (650 mg, 1.9 mmol, 95%): R_f = 0.73 (MeOH/CH_2Cl_2, 5/95); ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 3H, CH_3), 1.27 (m, 6H, CH_3(CH_2)$_3$), 1.50 (m, 2H, SO_2NHCH$_2$CH_2), 3.01 (m, 2H, SO_2NHCH_2), 3.17 (m, 2H, SO_2CH_2), 3.60 (m, 2H, CbzNHCH_2), 5.08 (bs, 3H, CH_2Ph, SO_2NH), 5.70 (bt, 1H, CbzNH), 7.32 (m, 5H, 5 × ArCH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_3CH_2), 26.1 (CH_3CH_2CH_2), 30.0 (CH_3-(CH_2)$_2$CH_2), 31.2 (CH_3(CH_2)$_3$CH_2), 35.9 (CbzNCH_2), 43.1 (SO_2-NHCH_2), 51.3 (SO_2CH_2), 66.8 (CH_2Ph), 127.9, 128.1, 128.4, 136.1 (Ar-C), 156.4 (C═O); ESI MS *m*/*z* 365.45 [M + Na]$^+$, 406.45 [M + Na + CH_3CN]$^+$.

Cbz-(*N*All)Tau-N(All)(CH_2)$_5$$CH_3$ (8). To a cooled (icebath) solution of sulfonamide **7** (685 mg, 2.0 mmol) and allyl bromide (1.39 mL, 16.0 mmol) in THF (20 mL) was added NaH (60% dispersion in mineral oil, 240 mg, 6.0 mmol). The reaction was stirred overnight at rt. After evaporation in vacuo, methanol (30 mL) and hexanes (30 mL) were added. The methanol layer was washed with hexanes (2 × 30 mL) and concentrated in vacuo. The residue was dissolved in EtOAc (30 mL) and washed with water and brine. Drying (Na_2SO_4) followed by column chromatography (gradient: CH_2Cl_2−CH_2Cl_2/MeOH (99/1)) afforded the bis-allylated sulfonamide as a colorless oil (198 mg, 0.47 mmol, 23%): R_f = 0.59 (MeOH/CH_2Cl_2, 2/98); ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 3H, CH_3), 1.27 (m, 6H, CH_3(CH_2)$_3$), 1.50 (m, 2H, SO_2NHCH$_2$CH_2), 3.18 (m, 4H, SO_2CH_2, SO_2NCH_2), 3.65 (m, 2H, CbzNCH_2), 3.70−3.96 (3m, 4H, 2 × ═CHCH_2), 5.17 (m, 6H, 2 × ═CH_2, CH_2Ph), 5.77 (m, 2H, ═CH), 7.35 (m, 5H, 5 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.5 (CH_3CH_2), 26.2 ($CH_3CH_2CH_2$), 28.3 (CH_3(CH_2)$_2$$CH_2$), 31.3 ($CH_3$($CH_2$)$_3$-*C*$H_2$), 41.4, 42.5, 46.9, 49.7, 50.2, 50.6 (CbzNCH_2, SO_2NCH_2, ═CH*C*H_2, SO_2CH_2), 67.3, 67.5 (CH_2Ph), 117.3, 118.0, 119.0 (═CH_2), 127.7, 128.0, 128.2, 128.5, 136.3 (Ar−C), 133.0, 133.2 (═CH), 156.0 (C═O); ESI MS *m*/*z* 423.30 [M + H]$^+$, 445.30 [M + Na]$^+$, 867.55 [2M + Na]$^+$.

HCl·H-Leu-piperidine Amide (13). To a solution of Boc-Leu-OH (5.8 g, 25 mmol) and BOP (12.2 g, 25 mmol) in dichloromethane (150 mL) were subsequently added dropwise piperidine (2.5 mL, 25 mmol) and D*i*PEA (9.6 mL, 55 mmol). After the solution was stirred for 1 h, the solvent was evaporated, and the residue was dissolved in ethyl acetate (300 mL). After washing (twice) with 1 M $KHSO_4$ (150 mL) and brine, the solution was dried (Na_2SO_4) and concentrated in vacuo. Boc-Leu-piperidine amide was obtained as a yellowish

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oil in quantitative yield (7.9 g): R_f = 0.62 (MeOH/DCM (3/97)); ^{1}H NMR ($CDCl_3$) δ 0.97 (dd, 6H, 2 × CH_3, J = 6.6, 6.3 Hz), 1.34−1.72 (m, 18H, C(CH_3)$_3$. NCH_2(CH_2)$_3$, CH_2CH(CH_3)$_2$), 3.44 (bs, 2H, NCH_2), 3.55 (t, 2H, NCH_2, J = 5.5 Hz), 4.66 (m, 1H, NC*H*CH_2), 5.36 (bd, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.8, 23.4 (CH(CH_3)$_2$), 24.7 (*C*H(CH_3)$_2$), 24.2, 25.4, 26.3 (NCH_2-(CH_2)$_3$), 28.1, 28.4 (C(CH_3)$_3$), 43.1, 46.4 (NCH_2, CH_2CH(CH_3)$_2$), 48.3, 48.5 (N*C*HCH_2), 79.3 (*C*(CH_3)$_3$), 155.6 (C=O (Boc)), 171.0 (NC=O); ESI MS *m*/*z* 321.35 [M + Na]$^+$, 362.45 [M + Na + CH_3CN]$^+$, 619.70 [2M + Na]$^+$. **13** was prepared by dissolving Boc-Leu-piperidine amide (1.25 g, 4.0 mmol) in dichloromethane (20 mL) and adding a saturated HCl solution in diethyl ether (20 mL) at rt, followed by concentration in vacuo. The obtained hydrochloric salt (1.40 g) was directly used for the synthesis of sulfonamide **14**.

***o*-NBS-Protected Sulfonamides 10a−c and 14: General Procedure.** To a solution of the amine (2.0 mmol, benzylamine, cyclohexylamine, *n*-hexylamine or **13**) and *N*-methylmorpholine (0.66 mL, 6.0 mmol) in CH_2Cl_2 (20 mL) was added the β-aminoethanesulfonyl chloride **(2a−c)** (2.0 mmol) in one portion. The mixture was stirred for 1 h at rt, followed by addition of CH_2Cl_2 (20 mL), and then washed with $KHSO_4$ (1 M, 20 mL) and H_2O (20 mL). After drying (Na_2SO_4) and evaporation of the solvent in vacuo, the crude and almost pure (TLC) Fmoc-protected sulfonamide was obtained. This resulting sulfonamide was dissolved in THF (20 mL), and 10 mL of a solution of dimethylamine in H_2O (40%, m/m) was added. After the solution was stirred for 30 min at rt, the solvent was evaporated in vacuo, followed by coevaporation with toluene (3×). To the crude amine were added *o*-nitrobenzenesulfonyl chloride (0.53 g, 2.4 mmol), CH_2Cl_2 (20 mL), and Et_3N (0.50 mL, 3.6 mmol). The mixture was stirred at rt overnight, and additional CH_2Cl_2 (20 mL) was added. The mixture was washed with $KHSO_4$ (1 M, 20 mL) and H_2O, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography afforded the *o*-NBS-protected sulfonamide.

***o*-NBS-Tau-N(H)Bn (10a).** Starting from 2.0 mmol (0.73 g) of **2a**: eluent gradient CH_2Cl_2−MeOH/CH_2Cl_2 (1/99)−(2/98); 67% yield (0.53 g); yellowish oil; R_f = 0.32 (MeOH/CH_2Cl_2, 2/98); ^{1}H NMR ($CDCl_3$) δ 3.14, 3.46 (2m, 4H, N*C*H_2*C*H_2SO_2), 4.23 (s, 2H, CH_2Ph), 5.38 (bs, 1H, NHBn), 6.20 (bs, 1H, *o*-NBSNH), 7.30 (m, 5H, 5 × Ar-CH (Bn)), 7.73, 7.82, 8.05 (3m, 4H, 4 × Ar-CH (*o*-NBS)); ^{13}C NMR ($CDCl_3$) δ 38.3, 46.9, 52.2 (CH_2Bn, NCH_2*C*H_2SO_2), 125.5, 127.4, 127.9, 128.2, 128.3, 128.8, 130.7, 132.9, 133.0, 133.9, 136.5, 147.7 (Ar-C (*o*-NBS, Bn)); ESI MS *m*/*z* 400.40 [M + H]$^+$, 422.20 [M + Na]$^+$, 463.25 [M + Na + CH_3CN]$^+$.

***o*-NBS-AlaΨ[CH_2SO_2]-N(H)Cy (10b).** Starting from 2.0 mmol (0.76 g) of **2b**: eluent gradient CH_2Cl_2−MeOH/CH_2Cl_2 (1/99)−(2/98); 73% yield (0.59 g); yellowish oil; R_f = 0.41 (MeOH/CH_2Cl_2, 2/98); ^{1}H NMR ($CDCl_3$) δ 1.24−1.96 (4m, 13H, CH_3, 5 × CH_2 (Cy)), 3.17 (dd, 1H, SO_2CH^a, J_{gem} = 14.3 Hz, J_{vic} = 5.6 Hz), 3.25 (m, 1H, NHC*H* (Cy)), 3.39 (dd, 1H, SO_2CH^b, J_{gem} = 14.3 Hz, J_{vic} = 6.0 Hz), 4.07 (m, 1H, NC*H*CH_3), 5.04 (bs, 2H, 2 × NH), 7.76−8.20 (3m, 4H, 4 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 24.6, 24.9, 33.9, 34.3 (CH_2 (Cy)), 47.3 (NCH (Cy)), 52.9 (NH*C*HCH_3), 59.1 (SO_2CH_2), 125.3, 130.8, 133.0, 133.8 (Ar-C^{3,4,5,6}), 133.8 (Ar-C^1), 147.6 (Ar-C^2); ESI MS *m*/*z* 406.25 [M + H]$^+$, 428.35 [M + Na]$^+$, 469.30 [M + Na + CH_3CN]$^+$, 833.55 [2M + Na]$^+$.

***o*-NBS-ValΨ[CH_2SO_2]-N(H)nHex (10c).** Starting from 2.0 mmol (0.81 g) of **2c**: eluent gradient CH_2Cl_2−MeOH/CH_2Cl_2 (1/99); 62% yield (0.54 g); yellowish oil; R_f = 0.59 (MeOH/CH_2Cl_2, 2/98); ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 9H, 3x CH_3), 1.28 (m, 6H, CH_3(CH_2)$_3$), 1.55 (m, 2H, NCH_2CH_2), 1.95 (m, 1H, C*H*(CH_3)$_2$), 3.07 (m, 2H, NHCH_2), 3.17 (dd, 1H, SO_2CH^a, J_{gem} = 14.8 Hz, J_{vic} = 4.1 Hz), 3.30 (dd, 1H, SO_2CH^b, J_{gem} = 14.8 Hz, J_{vic} = 7.4 Hz), 3.89 (m, 1H, NCH), 5.08 (t, 1H, N*H*(CH_2)$_5CH_3$, 5.96 (d, 1H, *o*-NBSNH), 7.76−8.20 (3m, 4H, 4 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3(CH_2)$_5$), 17.4, 18.2 (CH(*C*H_3)$_2$), 22.4 (CH_3CH_2), 26.1 ($CH_3CH_2CH_2$), 29.8 (CH_3(CH_2)$_2CH_2$), 31.2 (CH_3-(CH_2)$_3CH_2$), 32.0 (*C*H(CH_3)$_2$), 43.2 ($NHCH_2$), 53.0 (SO_2CH_2), 56.4 (NCH), 125.2, 130.6, 133.1, 133.8 (Ar-C^{3,4,5,6}), 134.0 (Ar-C^1), 147.4 (Ar-C^2); ESI MS *m*/*z* 436.25 [M + H]$^+$, 458.30 [M + Na]$^+$, 499.30 [M + Na + CH_3CN]$^+$, 893.45 [2M + Na]$^+$.

***o*-NBS-ValΨ[CH_2SO_2]-Leu-piperidine (14).** Starting from 4.0 mmol (1.63 g) of **2c**: eluent MeOH/CH_2Cl_2 (1/99); 80% yield (1.71 g); brownish oil; R_f = 0.19 (MeOH/CH_2Cl_2, 1/99); ^{1}H NMR ($CDCl_3$) δ 0.74, 0.88 (2d, 6H, CHCH(CH_3)$_2$, J = 6.9, 6.9 Hz), 0.95 (m, 6H, CH_2CH(CH_3)$_2$), 1.25−1.67 (2m, 8H, NCH_2CH_2-CH_2CH_2, CH_2CH(CH_3)$_2$), 1.88 (m, 1H, CH_2C*H*(CH_3)$_2$), 1.91 (m, 1H, CHC*H*(CH_3)$_2$), 3.15 (d, 1H, SO_2CH_2, J = 6.6 Hz), 3.39−3.64 (m, 4H, 2 × NCH_2), 3.94 (m, 1H, C*H*CH_2SO_2), 4.37 (m, 1H, CHC(O)N), 5.86 (bs, 2H, SO_2NH, *o*-NBSNH), 7.71−8.21 (3m, 4H, 4 × Ar-CH (*o*-NBS)); ^{13}C NMR ($CDCl_3$) δ 16.2, 18.6, 20.9, 23.1 (4 × CH_3), 24.0 (CH_2*C*H(CH_3)$_2$), 24.2, 25.4, 26.2 ($NCH_2CH_2CH_2CH_2$), 31.1 (CH*C*H(CH_3)$_2$), 42.4, 43.4 (2 × NCH_2), 46.3 (CH_2CH(CH_3)$_2$), 54.9 (SO_2CH_2), 51.6, 55.8 (2 × NCH), 125.1, 130.6, 132.7, 133.5, 133.9, 147.5 (Ar-C (*o*-NBS)), 169.9 (CO_2N); ESI MS *m*/*z* 533.45 [M + H]$^+$, 555.45 [M + Na]$^+$.

Bis-allylated *o*-NBS-Protected Sulfonamides 11a−c and 15: General Procedure. A mixture of *o*-NBS-protected sulfonamide (1.23 mmol), K_2CO_3 (680 mg, 4.92 mmol), and allyl bromide (471 μL, 5.41 mmol) in DMF (10 mL) was stirred at rt overnight. The DMF was evaporated in vacuo, followed by addition of CH_2Cl_2 and washing with H_2O (2×). The solution was dried (Na_2SO_4) and concentrated in vacuo. Column chromatography afforded the bis-allylated product.

***o*-NBS-(*N*-All)Tau-N(All)Bn (11a).** Starting from 1.32 mmol (528 mg) of **10a**: eluent hexanes/CH_2Cl_2 (1/9); 77% yield (490 mg); colorless oil; R_f = 0.63 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 3.32, 3.71 (2m, 4H, N*C*H_2*C*H_2SO_2), 3.76, 3.95 (m + d, 4H, 2 × NCH_2CH=), 4.39 (s, 2H, CH_2Ph), 5.29 (m, 4H, 2 × =CH_2), 5.78 (m, 2H, 2 × =CH), 7.33 (m, 5H, 5 × Ar-CH (Bn)), 7.72, 8.04 (2m, 4H, 4 × Ar-CH (*o*-NBS)); ^{13}C NMR ($CDCl_3$) δ 41.8, 49.0, 49.9, 51.3, 51.9 (N*C*H_2CH=, CH_2Bn, NCH_2*C*H_2SO_2), 120.0, 120.4 (=CH_2), 124.3, 127.9, 128.5, 130.9, 131.9, 132.1, 132.5, 133.9, 135.5, 147.8 (=CH, Ar-C (*o*-NBS, Bn)); ESI MS *m*/*z* 480.3 [M + H]$^+$, 502.35 [M + Na]$^+$, 518.1 [M + K]$^+$, 543.4 [M + Na + CH_3CN]$^+$, 981.1 [2M + Na]$^+$.

***o*-NBS-(*N*-All)AlaΨ[CH_2SO_2]-N(All)Cy (11b).** Starting from 1.43 mmol (580 mg) of **10b**: eluent hexanes/CH_2Cl_2 (1/9); 79% yield (549 mg); colorless oil; R_f = 0.70 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 1.02−1.82 (4m, 13H, CH_3, 5 × CH_2 (Cy)), 3.15 (dd, 1H, SO_2CH^a, J_{gem} = 13.5 Hz, J_{vic} = 9.6 Hz), 3.28 (dd, 1H, SO_2CH^b, J_{gem} = 13.5 Hz, J_{vic} = 3.0 Hz), 3.53 (m, 1H, NCH (Cy)), 3.82, 4.02 (2m, 4H, 2 × NCH_2), 4.37 (m, 1H, NC*H*CH_3), 5.20 (m, 4H, 2 × =CH_2), 5.82 (m, 2H, 2 × =CH), 7.72, 8.14 (2m, 4H, 4 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 18.8 (CH_3), 25.1, 25.9, 26.0, 32.1, 32.3 (CH_2 (Cy)), 46.0, 47.4 (NCH_2), 50.3 (NCH (Cy)), 58.1 (N*C*HCH_2), 59.1 (SO_2CH_2), 117.7, 118.6 (=CH_2), 124.2, 131.6, 131.9, 133.8, 135.3, 135.8 (=CH, Ar-C^{3,4,5,6}), 133.0 (Ar-C^1), 147.8 (Ar-C^2); ESI MS *m*/*z* = 404.20 [M − Cy + H]$^+$, 486.30 [M + H]$^+$, 508.35 [M + Na]$^+$, 449.25 [M + Na + CH_3CN]$^+$, 993.25 [2M + Na]$^+$.

***o*-NBS-(*N*-All)ValΨ[CH_2SO_2]-N(All)nHex (11c).** Starting from 1.23 mmol (535 mg) of **10c**: eluent hexanes/CH_2Cl_2 (1/9); 68% yield (433 mg); colorless oil; R_f = 0.31 (EtOAc/hexanes (2.5/7.5)); ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 9H, 3x CH_3), 1.28 (m, 6H, CH_3(CH_2)$_3$), 1.54 (m, 2H, NCH_2CH_2), 2.08 (m, 1H, C*H*(CH_3)$_2$), 3.12 (m, 2H, NCH_2(CH_2)$_4$), 3.21 (dd, 1H, SO_2CH^a, J_{gem} = 14.6 Hz, J_{vic} = 5.8 Hz), 3.40 (dd, 1H, SO_2CH^b, J_{gem} = 14.6 Hz, J_{vic} = 5.2 Hz), 3.76 (m, 2H, =CHCH_2), 3.89 (dd, 1H, =CHCH^a, J_{gem} = 16.5 Hz, J_{vic} = 7.7 Hz), 4.04 (m, 1H, NCH), 4.18 (dd, 1H, =CHCH^b, J_{gem} = 16.5 Hz, J_{vic} = 5.8 Hz), 5.23 (m, 4H, 2 × =CH_2), 5.82 (m, 2H, 2 × =CH), 7.59−8.26 (3m, 4H, 4 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H_3(CH_2)$_5$, 19.8, 19.9 (CH(CH_3)$_2$), 22.5 (CH_3CH_2), 26.2 ($CH_3CH_2CH_2$), 28.2 (CH_3(CH_2)$_2CH_2$), 31.3 (CH_2(CH_2)$_3CH_2$), 31.9 (*C*H(CH_3)$_2$), 46.9 (NCH_2(CH_2)$_4$), 49.7 (=CH*C*H_2), 55.1 (SO_2CH_2), 60.6 (NCH), 118.8, 119.1 (=CH_2), 123.8, 131.7, 131.9, 132.9, 133.6, 135.3 (Ar-C,^{3,4,5,6} =CH), 133.1 (Ar-C^1), 148.1 (Ar-C^2); ESI MS *m*/*z* 516.40 [M + H]$^+$, 538.50 [M + Na]$^+$, 479.30 [M + Na + CH_3CN]$^+$.

***o*-NBS-(*N*-All)ValΨ[CH_2SO_2]-(*N*-All)Leu-piperidine (15).** Starting from 0.97 mmol (516 mg) of **14**: eluent dichloromethane; 87% yield (515 mg); colorless oil; R_f = 0.47 (MeOH/CH_2Cl_2, 1/99); ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 12H, 4 × CH_3), 1.63 (m, 9H, $NCH_2CH_2CH_2CH_2$, $CH_2CH(CH_3)_2$), 2.06 (m, 1H, $CHCH(CH_3)_2$), 3.30−3.61 (m, 6H, SO_2CH_2, 2 × NCH_2CH_2), 3.82−4.22 (m, 5H, 2 × =$CHCH_2$, $CHCH_2SO_2$), 4.86 (t, 1H, CHC(O)N, J = 6.6 Hz), 5.22 (m, 4H, 2 × =CH_2), 5.93 (m, 2H, 2 × =CH), 7.62, 7.71, 8.23 (3m, 4H, 4 × Ar-CH (*o*-NBS)); ^{13}C NMR ($CDCl_3$) δ 19.9, 21.6, 22.4, 24.5 (4 × CH_3, $CH_2CH(CH_3)_2$), 24.4, 25.5, 26.3 ($NCH_2CH_2CH_2CH_2$), 31.7 ($CHCH(CH_3)_2$), 39.2, 43.0, 46.5, 47.8, 49.0 ($CH_2CH(CH_3)_2$, 2x NCH_2CH_2, 2 × =$CHCH_2$), 54.4, 60.4 ($NCHC(O)N$, $CHCH_2SO_2$), 55.8 (SO_2CH_2), 117.2, 118.9 (2 × =CH_2), 123.9, 131.6, 132.0, 133.2, 133.5, 135.3, 136.2, 148.1 (2 × =CH, Ar-C (*o*-NBS)), 169.2 (CO_2N); ESI MS m/z = 613.65 $[M + H]^+$, 635.60 $[M + Na]^+$, 1247.60 $[2M + Na]^+$.

Ring-Closing Metathesis: General Procedure. A solution of the bis-allylsulfonamide **11a**, **11b**, **11c**, or **15** (0.136 mmol) and α,α-dichlorotoluene (35 μL, 0.272 mmol) in 1,1,2-trichloroethane (29 mL) was refluxed for 15 min with N_2 bubbling through. Second-generation Grubbs catalyst (11.5 mg, 13.6 μmol) was then added in one portion, and refluxing was continued overnight. The mixture was concentrated in vacuo, and the residue was purified by column chromatography.

Cyclic Sulfonamide 6. Starting from 109 μmol (30.1 mg) of **11a**, the concentration of **11a** was 10 mM instead of 5 mM in 1,1,2 trichloroethane (11 mL), and 20% catalyst was used (18.5 mg): eluent MeOH/CH_2Cl_2 (5/95); 52% yield; brownish oil; R_f = 0.18 (MeOH/CH_2Cl_2 (5/95)); ^{1}H NMR ($CDCl_3$/CD_3OD) δ 0.94 (5 lines, 12H, 4 × CH_3), 1.19−1.18 (m, 6H, 2 × $CHCH_2$-$(CH_3)_2$), 3.07−3.84 (m, 8H, 2 × $CH_2SO_2NHCH_2$), 4.21 (m, 2H, 2 × NCH), 5.88 (d, 2H, 2 × =CHC=O), 6.53 (m, 2H, 2 × =$CHCH_2$); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 21.2, 22.6 (CH_3), 24.5 ($CH(CH_3)_2$), 42.7 ($CH_2CH(CH_3)_2$), 43.8 (=$CHCH_2$), 45.4 (NCH), 54.7 (SO_2CH_2), 126.1, 137.5 (CH=CH), 166.0 (C=O); ESI MS m/z 493.25 $[M + H]^+$.

Cyclic Sulfonamide 9. Starting from 81.2 μmol (34.3 mg) of **8**, the concentration of **8** was 5 mM in 1,1,2-trichloroethane (16 mL), and 20% catalyst was used (13.7 mg). Only traces of a product with the correct mass (m/z = 395.40 $[M + H]^+$, 417.55 $[M + Na]^+$, 789.65 $[2M + H]^+$, 811.40 $[2M + Na]^+$) were found by ESI-MS.

Cyclic Sulfonamide 12a. Starting from 0.136 mmol (65.4 mg) of **11a**. Eluent: gradient, EtOAc/hexanes (4/6)−(4.5/5.5); 60% yield (37.2 mg); white crystalline solid; R_f = 0.38 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 3.50, 3.82 (2m, 4H, $NCH_2CH_2SO_2$), 3.88, 4.12 (2m, 4H, 2 × NCH_2CH=), 4.40 (s, 2H, CH_2Ph), 5.86 (m, 2H, 2 × =CH), 7.39 (m, 5H, 5 × Ar-CH (Bn)), 7.67, 8.07 (2m, 4H, 4 × Ar-CH (*o*-NBS)); ^{13}C NMR ($CDCl_3$) δ 42.1, 42.3, 44.6, 51.0, 54.0 (NCH_2CH=, CH_2Bn, $NCH_2CH_2SO_2$), 124.5, 128.3, 128.4, 128.5, 128.8, 131.0, 131.1, 132.0, 132.1, 134.1, 134.8, 148.0 (=CH, Ar-C (*o*-NBS, Bn)); ESI MS m/z 452.20 $[M + H]^+$, 474.30 $[M + Na]^+$, 489.90 $[M + K]^+$, 515.25 $[M + Na + CH_3CN]^+$, 925.15 $[2M + Na]^+$; HRMS m/z calcd for $C_{19}H_{21}N_3O_6S_2$ $[M + Na]^+$ 474.0770, found 474.0769.

Cyclic Sulfonamide 12b. Starting from 0.173 mmol (83.9 mg) of **11b**: eluent gradient, EtOAc/hexanes (4/6)−(4.5/5.5); 47% yield (37.2 mg); brownish oil; R_f = 0.44 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 1.04−1.91 (4m, 13H, CH_3, 5 × CH_2 (Cy)), 3.43 (dd, 1H, SO_2CH^a, J_{gem} = 15.9 Hz, J_{vic} = 3.0 Hz), 3.65 (dd, 1H, SO_2CH^b, J_{gem} = 15.9 Hz, J_{vic} = 7.7 Hz), 3.73 (m, 1H, NCH (Cy)), 3.93−4.32 (m, 4H, 2 × NCH_2), 4.43 (m, 1H. $NCHCH_3$), 5.80 (m, 2H, 2 × =CH). 7.60−8.14 (3m, 4H, 4 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_3), 25.2, 25.9, 26.0, 31.5, 32.0 (CH_2 (Cy)), 39.7, 43.0 (NCH_2), 51.1 (NCH (Cy)), 58.7 ($NCHCH_2$), 60.0 (SO_2CH_2), 124.0, 128.5, 130.9, 131.1, 131.8, 133.9 (=CH, Ar-$C^{3,4,5,6}$), 133.7 (Ar-C^1), 148.0 (Ar-C^2); ESI MS m/z 376.15 $[M - Cy\text{-}H]^+$, 458.30 $[M + H]^+$, 480.15 $[M + Na]^+$, 496.20 $[M + K]^+$, 521.30 $[M + Na + CH_3CN]^+$, 937.30 $[2M + Na]^+$; HRMS m/z calcd for $C_{19}H_{27}N_3O_6S_2$ $[M + Na]^+$ 480.1239, found 480.1241.

Cyclic Sulfonamide 12c. Starting from 81.4 μmol (42 mg) **11c**: eluent gradient, EtOAc/hexanes (3/7)−(4/6); 48% yield (19.2 mg); brownish oil; R_f = 0.16 (EtOAc/hexanes, 2.5/7.5, v/v); an HSQC spectrum was used for interpretation of the ^{1}H NMR and ^{13}C NMR spectra; ^{1}H NMR ($CDCl_3$) δ 0.66 (d, 3H, $CHCH_3^a$, J = 6.9 Hz), 0.88 (t, 3H, $CH_3(CH_2)_4$), 1.04 (d, 3H, $CHCH_3^b$, J = 6.3 Hz), 1.28 (m, 6H, $CH_3(CH_2)_3$), 1.59 (m, 2H, NCH_2CH_2), 2.45 (m, 1H, $CH(CH_3)_2$), 3.07 (m, 2H, $NCH_2(CH_2)_4$), 3.60 (d, 2H, SO_2CH_2, J = 5.0 Hz), 3.80 (m, 2H, NCH, =$CHCH^a$), 4.07 (m, 3H, =$CHCH_2$, =$CHCH^b$), 5.73 (m, 1H, =CH), 6.05 (m, 1H, =CH), 7.59−8.10 (3m, 4H, 4 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 14.0 ($CH(CH_2)_5$), 20.5, 20.6 ($CH(CH_3)_2$), 22.5 (CH_3CH_2), 26.2 ($CH_3CH_2CH_2$), 27.4 ($CH_3(CH_2)_2CH_2$), 29.3 ($CH(CH_3)_2$), 31.4 ($CH_3(CH_2)_3CH_2$), 41.7, 42.8 (=$CHCH_2$), 46.1 (NCH_2CH_2), 53.6 (SO_2CH_2), 62.7 (NCH), 124.1, 128.7, 131.1, 131.2, 131.5, 133.9 (=CH, Ar-$C^{3,4,5,6}$), ArC^1 and Ar-C^2 were not visible. The cross-peak pattern observed in the NOESY (τ_m = 500 μs) spectrum is compatible with a cis configuration; ESI MS m/z = 488.35 $[M + H]^+$, 510.25 $[M + Na]^+$, 526.30 $[M + K]^+$, 551.40 $[M + Na + CH_3CN]^+$, 997.25 $[2M + Na]^+$; HRMS m/z calcd for $C_{21}H_{33}N_3O_6S_2$ $[M + Na]^+$ 510.1709, found 510.1673.

Cyclic Sulfonamide 16. Starting from 0.831 mmol (509 mg) of **15**: eluent MeOH/DCM (0.5/99.5); 48% yield (234 mg); brownish clear oil; R_f = 0.32 (MeOH/CH_2Cl_2, 1/99, v/v); ^{1}H NMR ($CDCl_3$) δ 0.76, 1.01 (2d, 6H, $CHCH(CH_3)_2$, J = 6.6, 6.6 Hz), 0.95 (m, 6H, $CH_2CH(CH_3)_2$), 1.47−1.64 (m, 8H, NCH_2CH_2-CH_2CH_2, $CH^aCH(CH_3)_2$), 1.83 (m, 1H, $CH^bCH(CH_3)_2$), 2.27 (m, 1H, $CHCH(CH_3)_2$), 3.44−3.62 (m, 5H, SO_2CH^a, 2 × NCH_2), 3.81−4.08 (m, 4H, =$CHCH_2$, SO_2CH^b, $CHCH(CH_3)_2$), 4.13−4.36 (m, 2H, =$CHCH_2$), 4.99 (m, 1H, CHC(O)N), 5.78 (m, 2H, 2 × =CH), 7.60, 7.69, 8.17 (3m, 4H, 4 × Ar−CH (*o*-NBS)); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.4, 22.3, 22.6 (4 × CH_3), 24.9 (CH_2CH-$(CH_3)_2$), 24.3, 25.6, 26.4 ($NCH_2(CH_2)_3$), 30.3 ($CHCH(CH_3)_2$), 39.4, 39.7, 43.2, 45.4, 46.8 ($CH_2CH(CH_3)_2$, =$CHCH_2$, NCH_2), 53.5, 63.4 ($NCHC(O)N$, $NCHCH_2SO_2$), 58.6 (SO_2CH_2), 123.9, 128.7, 129.7, 131.5, 131.6, 133.8, 133.9, 148.2 (=CH, Ar-C (*o*-NBS)), 168.4 (C(O)N); ESI MS m/z 585.55 $[M + H]^+$, 607.55 $[M + Na]^+$, 1191.70 $[2M + Na]^+$.

Cyclic Sulfonamide 18. A mixture of *o*-NBS-protected cyclic sulfonamide (31.6 mg, 70 μmol) **12a**, K_2CO_3 (29.0 mg, 210 μmol), and a DMF solution (86 μL, 84 μmol) of thiophenol (10% v/v), in DMF (0.70 mL), was stirred at rt for 40 min. After evaporation in vacuo, the residue was directly purified by column chromatography (EtOAc/hexanes 1/1), affording the secondary amine **17** quantitatively as a colorless oil (18.8 mg, 70 μmol). To this amine (9.4 mg, 35 μmol) were directly added HATU (20.1 mg, 53 μmol), BocAlaOH (10.0 mg, 53 μmol), CH_2Cl_2 (0.35 mL), and D*i*PEA (18.4 μL, 106 μmol). The mixture was stirred for 1 h at rt. More CH_2Cl_2 was added (5 mL), and the organic layer was washed with $KHSO_4$ (1 M, 3 mL), NaOH (1 M, 3 mL), and water (3 mL). Drying (Na_2SO_4) followed by column chromatography (MeOH/CH_2Cl_2, 5/95) afforded **18** as a colorless oil (9.7 mg, 63%): R_f = 0.31 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 3H, CH_3CH), 1.42, 1.44 (2s, 9H, $C(CH_3)_3$), 3.32−4.65 (m, 11H, NCH_2CH_2, CH_2Ph, 2 × CH_2CH=, NCH), 4.25 (m, 1H, NH), 5.65, 5.98, 6.24 (3m, 2H, 2 × =CH), 7.37 (m, 5H, 5 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 18.6, 18.8 (CH_3CH), 28.2, 28.3 ($C(CH_3)_3$), 40.8, 41.1, 41.8, 44.9, 45.6, 46.1, 49.4, 49.9, 52.2, 53.3, 53.4 (CH_2), 46.5, 46.6 ($C(CH_3)_3$), 127.5, 128.1, 128.3, 128.5, 128.6, 128.8, 128.9, 130.0, 131.4, 131.9, 134.9 (=CH, Ar-C), 155.2, 155.3 (C=O (Boc)), 173.4, 174.1 (C=O (amide)); ESI MS m/z 460.25 $[M + Na]^+$, 501.45 $[M + Na + CH_3CN]^+$.

Cyclic Sulfonamide 19. Cyclic sulfonamide **19** was prepared following the procedure described for the preparation of **18** starting from 9.4 mg (35 μmol) of **17** and HATU (20.1 mg, 53 μmol), BocLeuOH (13.2 mg, 53 μmol), CH_2Cl_2 (0.35 mL), and D*i*PEA (18.4 μL, 106 μmol): 54% yield (9.2 mg); colorless oil; R_f = 0.45 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 0.97 (m, 6H, 2 × CH_3), 1.41, 1.44 (2s, 9H, $C(CH_3)_3$), 1.58 (m, 2H, $(CH_3)_2CH$), 1.74 (m, 1H, $(CH_3)_2CHCH_2$), 3.35−4.46 (m, 10H, NCH_2CH_2, CH_2Ph, 2 × CH_2CH=), 4.50, 4.64 (2m, 1H, NCH),

5.11 (dd, 1H, NH), 5.66, 5.93, 6.05, 6.21 (4m, 2H, 2 × =CH), 7.37 (m, 5H, 5 × Ar-CH); ^{13}C NMR ($CDCl_3$) δ 21.7, 21.8, 23.4, 23.5 ((CH_3)$_2$)CH), 24.6, 24.7 ((CH_3)$_2$)CH), 28.2, 28.3 (C(CH_3)$_3$), 40.9, 41.2, 42.0, 42.1, 42.3, 44.9, 45.8, 46.2, 49.8, 52.3, 53.2 (CH_2), 49.1, 49.2, 49.3 (NCH), 79.8, 80.0 (C(CH_3)$_3$), 127.6, 128.1, 128.2, 128.5, 128.6, 128.7, 128.8, 130.2, 131.1, 132.0, 134.9 (=CH, Ar-C), 155.6, 155.8 (C=O (Boc)), 173.4, 174.2 (C=O (amide)); ESI MS *m*/*z* 380.25 [M − Boc + H]$^+$, 424.25 [M − tBu + H]$^+$, 502.40 [M + Na]$^+$, 543.40 [M + Na + CH_3CN]$^+$, 981.75 [2M + Na]$^+$; HRMS *m*/*z* calcd for $C_{24}H_{37}N_3O_5S$ 502.2352, found 502.2329.

Cyclic Sulfonamide 20. A mixture of cyclic sulfonamide **19** (5.2 mg, 10.8 μmol) and a catalytic amount of 10% Pd/C in ethanol (3 mL) was stirred overnight under a hydrogen atmosphere (balloon). After removal of the Pd/C by filtration, the solution was concentated in vacuo. Coevaporation with chloroform (3×) afforded the product as a colorless oil (5.1 mg, 97%): R_f = 0.47 (EtOAc/hexanes (1/1)); ^{1}H NMR ($CDCl_3$) δ 0.99 (dd, 6H, 2 × CH_3), 1.42 (s, 9H, C(CH_3)$_3$), 1.29−2.10 (m, 7H, $NCH_2CH_2CH_2$, (CH_3)$_2$CHCH_2), 2.88, 3.22, 3.54 (3m, 4H, 2 × $NCH_2CH_2CH_2$), 3.22, 3.54, 3.87, 4.18 (4m, 4H, $NCH_2CH_2SO_2$), 3.97 (d, 1H, CH^{a}Ph, J = 15.4 Hz), 4.37 (d, 1H, CH^{b}Ph, J = 15.4 Hz), 4.74 (m, 1H, NCH), 5.20 (bd, 1H, NH), 7.33 (m, 5H, 5 × Ar-CH (Ph)); ESI MS *m*/*z* 382.15 [M − Boc + H]$^+$, 426.30 [M − tBu + H]$^+$, 504.40 [M + Na]$^+$, 545.50 [M + Na + CH_3CN]$^+$, 985.65 [2M + Na]$^+$.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and two-dimensional NMR specta of all compounds as well as HPLC traces of **16**. Modeling data of **16** using MacroModel together with an atom coordinates file are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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