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New strategies to symmetric and unsymmetric cyclic sulfamide analogs of DMP 323: a 'sulfur linchpin'/RCM approach

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Abstract—The synthesis of 7-membered cyclic sulfamides utilizing the RCM reaction is described herein. Two major synthetic strategies that expand the scope and utility of our previously reported sulfamide and sulfamoyl carbamate chemistry are employed. Both Mitsunobu alkylation and simple alkylation of core sulfamides and sulfamoyl carbamates coupled with RCM are used to efficiently install lipophilic groups into the P1/P1′ and P2/P2′ periphery of the cyclic sulfamides. Overall, the routes described are applicable to the synthesis of a variety of cyclic 7-membered sulfamides.

1. Introduction

Cyclic ureas DMP 323 and DMP 450 are the most prominent members of a class of highly potent HIV protease inhibitors initially developed at DuPont Merck Laboratories.[1] Since the discovery of DMP 323, a large number of derivatives have been synthesized and screened.[2] Extensive SAR studies have been carried out to elucidate the effects of varying P1/P1′/P2/P2′ residues,[3] as well as the absolute and relative stereochemistry at the P1/P1′ and hydroxyl-bearing stereogenic centers[4] (Fig. 1). It was found that each of these factors significantly influenced inhibitor potency by accentuating hydrophobic (P1/P1′), hydrogen bonding (P2/P2′), and catalytic aspartate (diol functionality) interactions with the enzyme. While cyclic ureas have been the most widely examined, independent studies by DuPont Merck,[5] Hallberg and co-workers,[6] and Karlén and co-workers[7] have shown that sulfamide analogs of DMP 323 also display high inhibitory activity (Fig. 2). In addition, unsymmetric DMP 323 derivatives are of particular interest due to their potential to exhibit different solubility and inhibitory profiles relative to their C_2-symmetric counterparts.[8]

Our interest in this area has led us to previously develop ring-closing metathesis[9] (RCM) strategies to the synthesis of a number of C_2-symmetric and unsymmetric analogs of DMP 323, including cyclic phosphonamides,[10,11] sulfamides,[12] and ureas.[11] In the course of this work we have developed an efficient *P*-tether/RCM approach[11a] to assemble highly functionalized 1,4-diamines that can be

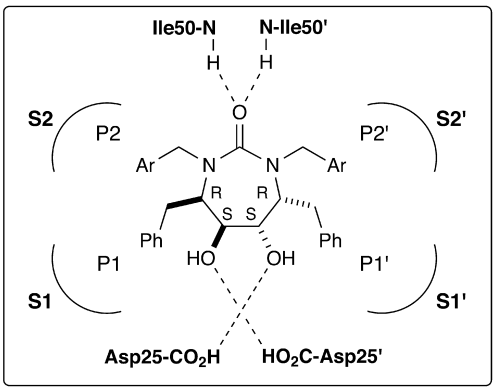

Figure 1.

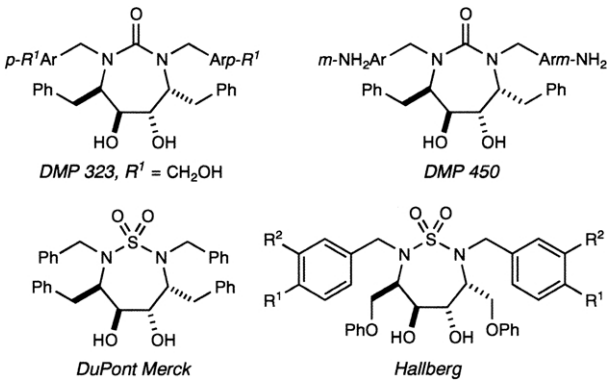

Figure 2.

Keywords: DMP 323; cyclic sulfamides; sulfur heterocycles; RCM; metathesis.

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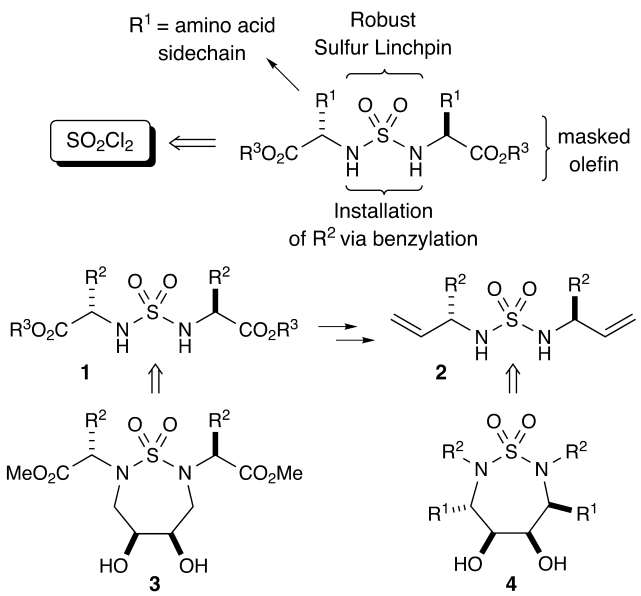
effectively converted into an array of 7-membered heterocycles related to DMP 323.[11b] In addition, we have reported a concise RCM strategy to symmetric and unsymmetric cyclic sulfamides.[12] This approach utilized the sulfur coupling reagents sulfuryl chloride (SO_2Cl_2) and chlorosulfonyl isocyanate (CSI) to produce sulfamide and sulfamoyl carbamate building blocks that could easily be functionalized via Mitsunobu and simple alkylation procedures.

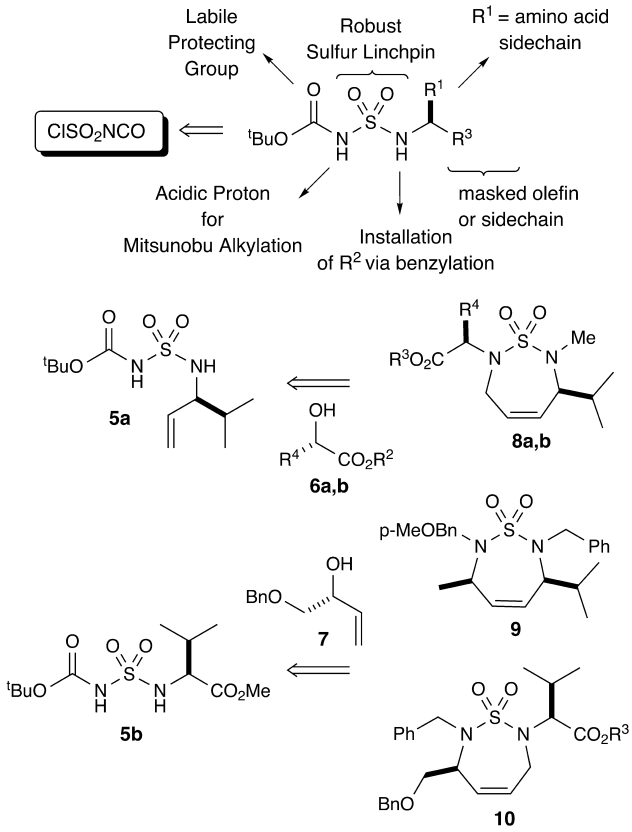
2. Discussion and results

The strategy we now report exploits the robust nature of both sulfamide and sulfamoyl carbamate moieties coupled with the power of RCM to synthesize both symmetric and unsymmetric sulfamides. Thus far, we have employed a two-fold strategy utilizing the symmetric and unsymmetric reagents, sulfuryl chloride (SO_2Cl_2, Scheme 1) and chlorosulfonyl isocyanate ($ClSO_2NCO$, Scheme 2). Overall, the strengths of these approaches lie in the ability to (i) exploit the versatility of both sulfamide and sulfamoyl carbamate groups to effectively serve as 'robust *S*-linchpins' to allow a number of simple, yet powerful transformations to occur on each respective template; (ii) implement simple ester groups in **1** as latent olefins for subsequent RCM (Scheme 1); and (iii) use the power of the Mitsunobu reaction and simple alkylation to efficiently install side-chain groups into the P1/P1′ and P2/P2′ periphery of the cyclic sulfamides (Scheme 2).

The central focus of this strategy is the development of concise synthetic pathways that allow for judicious placement of side-chain groups in each of the P1/P1′/P2/P2′ regions of the cyclic sulfamide core, with the ultimate goal of occupying the active site of HIV protease. Furthermore, these strategies will allow for the generation of cyclic sulfamides containing differentiated P1/P1′/P2/P2′ regions. This goal will be accomplished by exploiting the versatility of the core *S*-linchpins coupled with the non-racemic chiral building blocks **6** and **7** (Scheme 2).



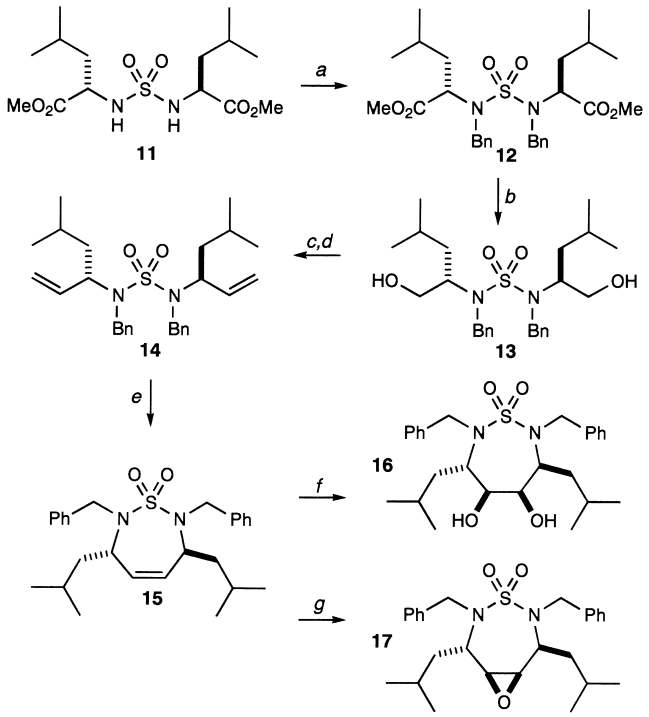
Scheme 1.



Scheme 2.

We have previously reported a synthetic route to C_2-symmetric cyclic sulfamides such as **3** that involved *bis*-coupling of an amino ester with SO_2Cl_2 to yield C_2-symmetric sulfamides such as **1** (Scheme 1).[12] These sulfamides can be readily allylated, subjected to RCM, and dihydroxylated to cleanly afford sulfamide diols such as **3** bearing hydrophobic side-chains in the P2/P2′ regions. In an analogous fashion, more elaborate allylic amines could be coupled with SO_2Cl_2 to construct **2**; subsequent RCM, benzylation, and dihydroxylation cleanly provided sulfamide diols such as **4** bearing hydrophobic side-chains in the P1/P1′ regions. While the synthesis of sulfamide **4** was concise, the production of allylic amines salts required four steps.[13] A new more efficient route has been designed to generate C_2-symmetric sulfamides bearing hydrophobic side-chains in the P1/P1′ regions as outlined in Scheme 3.

Our new route employs two-directional chain synthesis[14] on the leucine-derived, C_2-symmetric sulfamide **11**. Dialkylation of **11** with benzyl bromide under standard conditions gave the corresponding bis-benzylated sulfamide **12** in 99% yield. Next, a three-step protocol was employed on each of the homotopic ester moieties to convert the diester moiety in **11** to the diene moiety in **14**. Thus, reduction of the esters with $LiAlH_4$ (100%) cleanly produced diol **13**. Swern oxidation (99%), followed by bis-Wittig olefination with PPh_3CH_2Br (87%), yielded the diene sulfamide **14**. The efficiency of this three-step pathway further exemplifies the robust nature of the sulfamide group as it withstood a variety of reaction conditions to cleanly afford sulfamide **14**. Metathesis with 5 mol% of $(IMesH_2)(PCy_3)(Cl)_2$-Ru=CHPh[15,16] generated cyclic sulfamide **15** in 69%

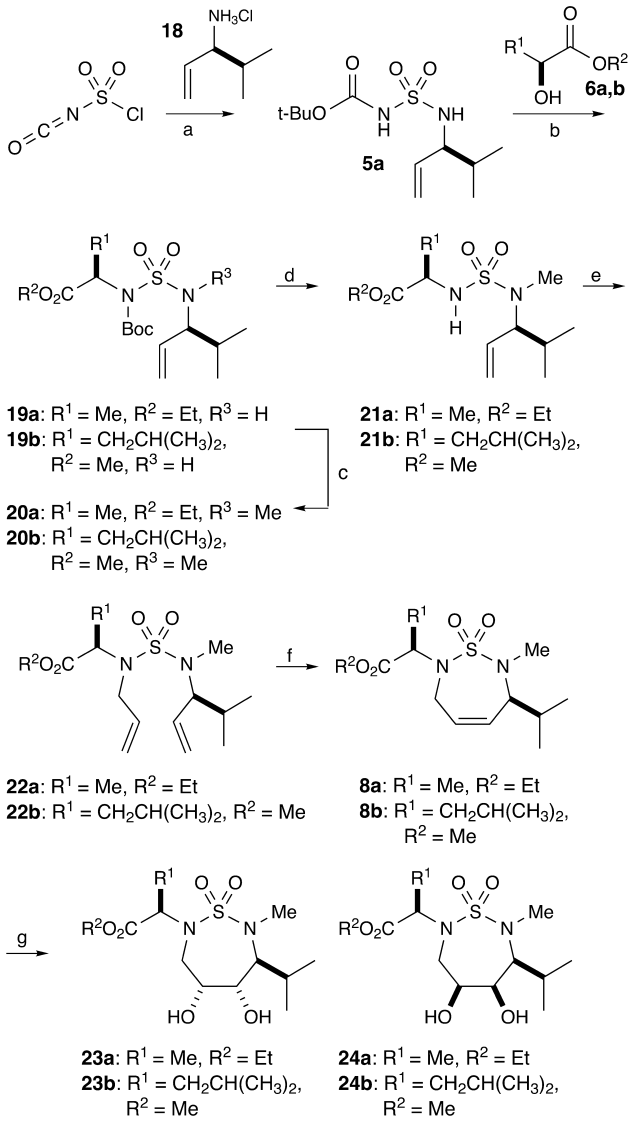


Scheme 3. *Conditions*: (a) BnBr, K_2CO_3, MeCN, 70°C, 99%; (b) LAH, THF, 100%; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 99%; (d) Ph_3PCH_2Br, BuLi, THF, 87%; (e) 5 mol% $(IMesH_2)(PCy_3)-(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 45°C, 69%; (f) OsO_4, NMO, 3:1 acetone/H_2O, 99%; (g) *m*-CPBA, CH_2Cl_2, 52%.

yield. Dihydroxylation of the C_2-symmetric sulfamide **15** bearing homotopic olefinic faces using OsO_4 proceeded smoothly to produce the cyclic sulfamide diol **16** in 99% yield. Alternatively, epoxidation was utilized to give the epoxy sulfamide **17** in modest yield (52%, unoptimized).

Our synthesis of a cyclic sulfamide bearing stereogenic centers in both the P1/P1′ and P2/P2′ positions is outlined in Scheme 4. Initially, a three-component coupling reaction of *tert*-butyl alcohol, chlorosulfonyl isocyanate (CSI), and the valine-derived allylic amine salt **18**[13] gave the corresponding sulfamoyl carbamate **5a** in 71% yield (Scheme 4). This building block, first developed by Montero and co-workers,[17] contains two nucleophilic NH sites of differing pKa that can be exploited in sequential alkylations.[18] Thus, sulfamoyl carbamate **5a** was first alkylated under Mitsunobu conditions (PPh_3, THF, DEAD) with either ethyl lactate (**6a**, R^1=Me, R^2=Et) or 2-hydroxy-4-methylpentanoic acid methyl ester (**6b**, R^1=CH_2CHMe_2, R^2=Me) to produce **19a**,**b** in good yields. Methylation of the remaining sulfamide NH, followed by Boc-deprotection and allylation generated the metathesis precursor **22a**,**b**. Final RCM with 6 mol% of the first generation Grubbs catalyst $[(PCy_3)_2(Cl)_2Ru{=}CHPh]$[19] afforded the differentiated cyclic sulfamides **8a**,**b** in excellent yields. Surprisingly, dihydroxylation of sulfamide **8a**,**b** occurred with little stereoselectivity to yield an approximate 1.3:1 mixture of diols **23a**,**b** and **24a**,**b**, respectively.

Recent work in our group has shown that dihydroxylation of sulfamide systems[11b] that are similar in structures to sulfamide **8b**, occurred with good diastereofacial selectivity (*dr*=5.9–11:1, Fig. 3). In this previous study, it was found



Scheme 4. *Conditions*: (a) *t*-BuOH, Et_3N, CH_2Cl_2, 0°C, 71%; (b) PPh_3, DEAD, THF, 84–87%; (c) MeI, K_2CO_3, MeCN, 45°C, 96–100%; (d) TFA, CH_2Cl_2, 88–100%; (e) allyl-Br, K_2CO_3, MeCN, 70°C, 91–95%; (f) 6 mol% $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 45°C, 97%; (g) OsO_4, NMO, 3:1 acetone/H_2O 97% (*dr*~1.3:1.0).

that the nature of the R group adjacent to the isopropyl side-chain influenced the diastereoselectivity where the selectivity was diminished in dihydroxylation of the benzyl substituted sulfamide **B** [**A**, R=H, *dr*=11:1 vs. **B**, R=Bn, *dr*=5.9:1]. When taken collectively, it appears that N-substitution on the sulfamide has a substantial effect on the selectivity of the dihydroxylation. We are currently

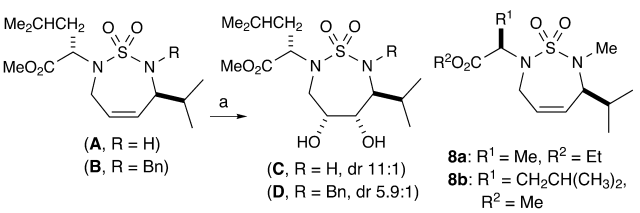
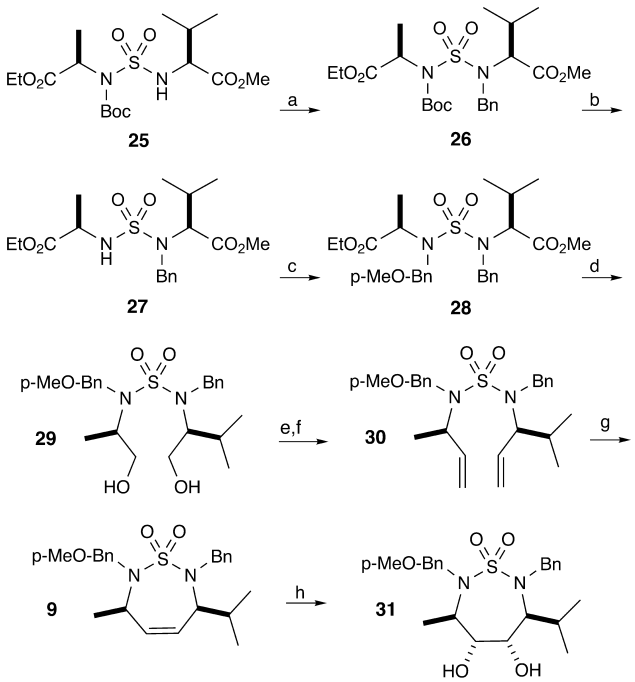


Figure 3. Dihydroxylation of sulfamides derived from P-tether approach. *Conditions*: 3 mol% OsO_4 (4 wt% solution in H_2O), 1.2 equiv. NMO·H_2O, acetone/H_2O [Ref. 11b].

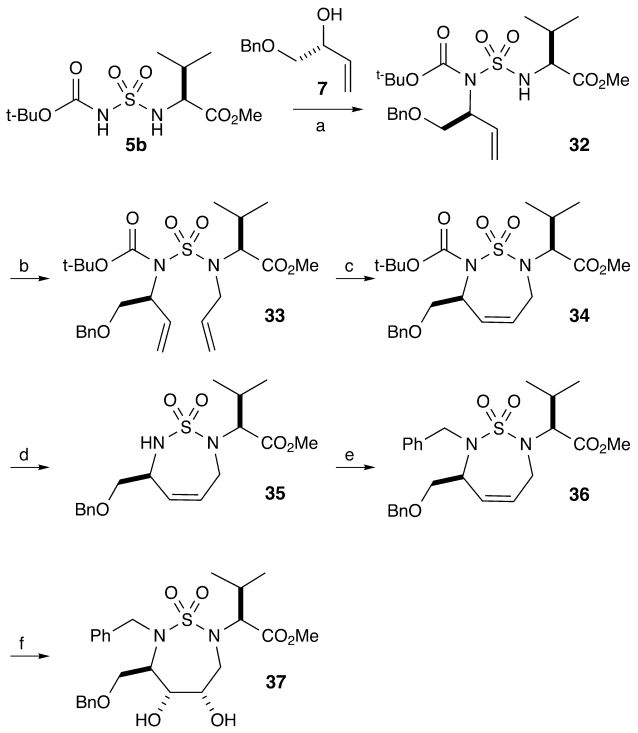
investigating the origin of this result and will report our findings at a later time.

The methods outlined in Schemes 3 and 4 were exploited further in the synthesis of an unsymmetric sulfamide bearing differentiated P1/P1′/P2/P2′ regions as outlined in Scheme 5. Thus, benzylation of our previously reported unsymmetric sulfamoyl carbamate **25**[12] (94%) followed by Boc-deprotection with TFA (97%) proceeded without incident to generate sulfamide **27** in excellent yield. Protection of the remaining sulfamide nitrogen with *p*-methoxybenzyl chloride yielded sulfamide **28** (77%). Sulfamide **28** was next subjected to two-directional chain synthesis employing the aforementioned three-step transformation of both ester groups into the corresponding olefinic groups primed for RCM. Thus, reduction with LAH (38%), Swern oxidation (99%), and Wittig olefination (69%) produced the metathesis precursor **30**. RCM with 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ proceeded smoothly to yield the unsymmetric sulfamide **9** bearing differentiated lipophilic side-chains that occupy the P1 (Me), P1′ (*i*Pr), P2 (*p*-MeOBn), and P2′ (Bn) positions. Final dihydroxylation afforded the sulfamide diol **31** in excellent yield, but with only modest stereoselectivity (*dr*=3.9:1).



Scheme 5. *Conditions*: (a) BnBr, K_2CO_3, MeCN, 70°C, 94%; (b) TFA, 97%; (c) PMBCl, K_2CO_3, MeCN, 70°C, 77%; (d) LAH, THF, 38%; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 99%; (f) Ph_3PCH_2Br, BuLi, THF, 69%; (g) 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 40°C, 69%; (h) OsO_4, NMO, 3:1 acetone/H_2O, 91% (*dr*=3.9:1.0).

The final approach that we investigated is outlined in Scheme 6. This new strategy employs the Mitsunobu reaction to install the stereogenic center occupying the P1 position. Mitsunobu alkylation of sulfamide **5b**[12] with the readily prepared nonracemic secondary allylic alcohol **7**, derived from the condensation of trimethyl sulfonium ylide with (*R*)-benzyl protected glycidol,[20] generates sulfamide **32** in good yield. It is important to note that the Mitsunobu product primarily originated from the desired S_N2 pathway



Scheme 6. *Conditions*: (a) PPh_3, DIAD, THF, 67%; (b) allyl-Br, K_2CO_3, MeCN, 70°C, 92%; (c) 5 mol% $(ImesH_2)(PCy_3)$–$(Cl)_2Ru{=}CHPh$, CH_2CH_2, 45°C, 96%; (d) TFA, 96%; (e) BnBr, K_2CO_3, MeCN, 70°C, 89%; (f) OsO_4, NMO, 3:1 acetone/H_2O 70% (*dr*=16.0:1).

rather than the competing S_N2' route. The solvent system chosen for this transformation had minor influence upon the ratio of the two observed products as seen in the following examples: THF (9.3:1 **32**:S_N2'), CH_2Cl_2 (8:1, **32**:S_N2') and benzene (>10:1, **32**:S_N2'). Currently, further investigations into this transformation are underway and will be reported in due course. Standard allylation conditions yielded sulfamide diene **33**. RCM with 5 mol% of $(ImesH_2)$-(PCy_3)–$(Cl)_2Ru{=}CHPh$ produced the cyclic sulfamides **34** in excellent yields. Boc-deprotection with TFA, and benzylation gave the desired cyclic sulfamide **36** in excellent yield. Finally, dihydroxylation with OsO_4 afforded the differentiated sulfamide diol **37** in good yield (70%) and with high diastereoselectivity (*dr*=16:1), with the major product tentatively assigned as the diastereomer resulting from dihydroxylation on the olefinic face opposite the benzyloxymethyl group of the adjacent stereocenter.

In conclusion, we have synthesized a variety of symmetric and unsymmetric cyclic sulfamides with varied substitution in their P1/P1′ and P2/P2′ periphery. These methods have been accomplished using 'robust *S*-linchpins' in combination with Mitsunobu alkylations, simple alkylations, RCM, and diastereoselective dihydroxylations. Biological evaluation of these novel sulfamides is currently in progress and will be reported in due course.

3. Experimental

3.1. 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 a purification system (Solv-Tek) employing activated Al_2O_3.[21] 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 Chem Tech. ^1H and ^{13}C spectra were recorded in $CDCl_3$ on either a Bruker DRX-400 or a Bruker AM-500 spectrometer operating at 400/100 MHz and 500/125 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 a Nicolet 320 Fourier Transform Infrared Spectrophotometers. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

3.1.1. *N*, *N*′-Bis-benzyl-*N*-*N*′-bis-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (12). To a stirring solution of the leucine-derived sulfamide **11** (500 mg, 1.43 mmol) in CH_3CN (20 mL) at rt under an argon atmosphere was added K_2CO_3 (430 mg, 3.13 mmol) and benzyl bromide (0.37 mL, 3.11 mmol). The reaction mixture was heated to reflux for 24 h, filtered, and concentrated under reduced pressure. The filtrate was extracted with EtOAc (50 mL×2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by column chromatography (10:1 hexanes/EtOAc) to afford 750 mg (99%) of the desired dibenzyl sulfamide **12** as a clear oil. TLC R_f=0.28 (10:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−35.9 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J=7.4 Hz, 4H), 7.30–7.23 (m, 6H), 4.71 (d, J=15.8 Hz, 2H), 4.44 (d, J=15.8 Hz, 2H), 4.26 (t, J=6.5 Hz, 2H), 3.64 (s, 6H), 1.82–1.77 (m, 2H), 1.58–1.49 (m, 4H), 0.85 (d, J=6.2 Hz, 6H), 0.59 (d, J=6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 137.1, 128.5, 128.4, 127.6, 58.1, 52.1, 50.3, 39.0 24.9, 22.2, 22.0; FTIR (neat) 3031, 2956, 1747, 1497, 1455, 1338, 1147, 755, 698 cm^{-1}; HRMS calcd for $C_{28}H_{41}N_2O_6S$ $(M+H)^+$ required 533.2685, found 533.2672.

3.1.2. *N*, *N*′-Bis-benzyl-*N*-*N*′-bis-[(1*S*)-2-hydroxy-1-(2-methylpropyl)ethyl]-sulfamide (13). To a stirring solution of **12** (110 mg, 0.22 mmol) in 30 mL of THF at 0°C under an argon atmosphere was added LAH (160 mg, 4.29 mmol). After 1 h, a 15% NaOH aqueous solution was added to quench the reaction, and the reaction mixture was filtered under reduced pressure. The filtrate was concentrated under reduced pressure, and extracted with EtOAc (50 mL×2). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by column chromatography (1:1 hexanes/EtOAc) to afford 100 mg (100%) of the desired sulfamide diol **13** as a clear oil. TLC R_f=0.51 (1:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+15.6 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J=7.1 Hz, 4H), 7.26–7.16 (m, 6H), 4.49 (d, J=15.8 Hz, 2H), 4.45 (d, J=15.8 Hz, 2H), 3.83–3.75 (m, 2H), 3.63–3.56 (m, 4H), 2.60 (bs, 2H), 1.54–1.44 (m, 2H), 1.44–1.37 (m, 2H), 1.19–1.12 (m, 2H), 0.79 (d, J=6.5 Hz, 6H), 0.73 (d, J=6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 128.5, 127.5, 62.5, 58.8, 49.2, 39.5, 25.1, 23.1, 21.7; FTIR (neat) 3386, 3029, 2956, 1604, 1496, 1455, 1323, 1143, 758, 698 cm^{-1}; HRMS calcd for $C_{26}H_{41}N_2O_4S$ $(M+H)^+$ required 477.2787, found 477.2808.

3.1.3. *N*, *N*′-Bis-benzyl-*N*-*N*′-bis-[(1*S*)-1-(2-methylpropyl)-2-propenyl]-sulfamide (14). To a stirring solution of oxalyl chloride (0.30 mL, 3.44 mmol) in 1 mL CH_2Cl_2 at −78°C under an argon atmosphere was added DMSO (30 μL, 4.23 mmol) in CH_2Cl_2 (1 mL) over 20 min. After 40 min, the sulfamide diol **13** (477 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added over 30 min with an addition funnel, and the funnel was rinsed with CH_2Cl_2 (10 mL). The mixture was stirred at −78°C for 5 h and monitored by TLC. Et_3N (1.5 mL, 10.76 mmol) was added over 15 min and stirred at −78°C for 2 h. THF (4 mL, 1:1 H_2O/THF) was added at −78°C for 5 min, and the mixture stirred at 0°C for 3 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL), washed with 2*M* HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 507 mg (99%) of the desired dialdehyde sulfamide as a white solid that was carried on immediately without further purification. TLC R_f=0.91 (1:1 hexanes/EtOAc).

To a stirring solution of CH_3PPh_3Br (2.69 g, 7.53 mmol) in THF (25 mL) at 0°C under an argon atmosphere was slowly added a solution of BuLi (3.75 mL, 6.0 mmol, 1.6 M in hexanes) over 3 min. After 3 h, the yellow ylide solution was cooled to −78°C and a solution of dial sulfamide (474 mg, 1.00 mmol) in THF (25 mL) at −78°C was added via cannula. After 24 h, 30 mL acetone was added to quench the reaction. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (50 mL×2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) gave 418 mg (89%) of the desired sulfamide diene **14** as white solid. Mp 86°C; TLC R_f=0.66 (10:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−18.5 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, J=7.2 Hz, 4H), 7.34–7.22 (m, 6H), 5.86 (ddd, J=17.5, 10.3, 7.8 Hz, 2H), 5.19 (d, J=10.3 Hz, 2H), 5.11 (d, J=17.2 Hz, 2H), 4.34 (d, J=15.6 Hz, 2H), 4.22 (d, J=15.6 Hz, 2H), 4.02 (dd, J=13.6, 7.8 Hz, 2H), 1.52–1.34 (m, 6H), 0.79 (d, J=6.1 Hz, 6H), 0.64 (d, J=6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 136.8, 128.6, 128.4, 127.4, 118.2, 59.8, 49.3, 41.5, 24.6, 23.1, 21.5; FTIR (neat) 3033, 2956, 2930, 1496, 1455, 1332, 1147, 700, 744 cm^{-1}; HRMS calcd for $C_{28}H_{41}N_2O_2S$ $(M+H)^+$ required 469.2889, found 469.2875.

3.1.4. (3*S*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (15). To a degassed solution of **14** (320 mg, 0.68 mmol) in benzene (25 mL) was added $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (20 mg, 0.030 mmol) at rt. After 24 h, DMSO (1.0 mL) and silica gel were added to remove the catalyst. After 24 h, the reaction mixture was filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 210 mg (69%) of the desired cyclic sulfamide **15** as white solid. Mp 108°C; TLC R_f=0.79 (5:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−55.1 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J=10.3 Hz, 4H), 7.33–7.22 (m, 6H), 5.52 (s, 2H), 4.86 (d, J=16.0 Hz, 2H), 4.23

(dd, J=9.1, 5.2 Hz, 2H), 4.20 (d, J=16.0 Hz, 2H), 1.61–1.53 (m, 2H), 1.39–1.33 (m, 2H), 1.18–1.11 (m, 2H), 0.80 (d, J=6.5 Hz, 6H), 0.48 (d, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 132.1, 128.3, 127.7, 127.2, 53.4, 50.9, 42.6, 24.2, 22.3, 21.4; FTIR (neat) 3064, 3028, 2957, 1606, 1496, 1338, 1147 cm^{-1}; HRMS calcd for $C_{26}H_{37}N_2O_2S$ $(M+H)^+$ required 441.2576, found 441.2584.

3.1.5. (3*S*,4*R*,5*S*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (16). To a stirring solution of cyclic sulfamide **15** (40 mg, 0.10 mmol) in acetone (630 μL) and water (200 μL) was added NMO (15 mg, 0.12 mmol) and OsO_4 (18 μL, 2.8 μmol, 4 wt% solution in water). After 3 days, the reaction mixture was washed with saturated Na_2SO_3, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 50 mg (99%) of the desired sulfamide diol **16** as a white solid. Mp 174°C; TLC R_f=0.28 (5:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−65.1 (c=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.45 (m, 4H), 7.35–7.26 (m, 6H), 4.92 (d, J=16.8 Hz, 1H), 4.62 (d, J=16.8 Hz, 1H), 4.52 (d, J=16.0 Hz, 1H), 4.46 (d, J=16.0 Hz, 1H), 3.81 (ddd, J=9.6, 9.6, 4.4 Hz, 1H), 3.75 (dd, J=4.0, 4.0 Hz, 1H), 3.67 (dd, J=6.9, 6.9 Hz, 1H), 3.48 (ddd, J=10, 5, 5 Hz, 1H), 2.27 (d, J=5.0 Hz, 1H), 2.12 (d, J=7.2 Hz, 1H), 1.79 (ddd, J=13.7, 8.3, 5.4 Hz, 1H), 1.67–1.47 (m, 3H), 1.46–1.36 (m, 1H), 1.31–1.17 (m, 1H), 0.90 (d, J=6.0 Hz, 3H), 0.83 (d, J=6.4 Hz, 3H), 0.69 (d, J=6.6 Hz, 3H), 0.67 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.3, 138.3, 128.6, 128.5, 128.4, 127.6, 127.5, 127.2, 73.9, 71.3, 55.4, 54.4, 51.5, 49.0, 39.8, 36.9, 24.8, 24.1, 23.1, 22.3, 22.1, 21.3; FTIR (neat) 3483, 2956, 1454, 1309, 1144 cm^{-1}; HRMS calcd for $C_{26}H_{39}N_2O_4S$ $(M+H)^+$ required 475.2631, found 475.2609.

3.1.6. (1*S*,2*R*,6*S*,7*S*)-3,5-Dibenzyl-2,6-diisobutyl-8-oxa-4-thia-3,5-diaza-bicyclo[5.1.0]octane 4,4-dioxide (17). To a stirring solution of **15** (250 mg, 0.56 mmol) in CH_2Cl_2 (5.0 mL) at 0°C was added M-CPBA (390 mg, 2.27 mmol). After 48 h, the reaction was filtered, and the filtrate was extracted with CH_2Cl_2 (50 mL×2), and washed with $NaHCO_3$ (saturated aq). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 140 mg (52%) of the desired epoxysulfamide **17** as a clear oil. $[\alpha]_D^{25}$=−33.9 (c=1.00, $CHCl_3$); TLC R_f=0.41 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.05 (m, 10H), 4.83 (d, J=17.1 Hz, 1H), 4.63 (d, J=15.5 Hz, 1H), 4.53 (d, J=15.5 Hz, 1H), 4.42 (d, J=17.1 Hz, 1H), 4.05 (dd, J=9.0, 4.8 Hz, 1H), 3.71 (ddd, J=10, 4.5, 4.5 Hz, 1H), 2.92 (dd, J=4.2, 4.2 Hz, 1H), 2.84 (d, J=4.2 Hz, 1H), 1.85 (ddd, J=14.1, 9.4, 4.9 Hz, 1H), 1.73–1.65 (m, 1H), 1.65–1.55 (m, 1H) 1.45 (ddd, J=14.2, 8.4, 6.2 Hz, 1H), 1.34–1.25 (m, 2H), 0.82 (d, J=5.8 Hz, 3H), 0.76 (d, J=5.8 Hz, 3H), 0.75 (d, J=6.0 Hz, 3H), 0.51 (d, J=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.4, 138.0, 128.5, 128.4, 128.3, 127.7, 127.1, 126.9, 59.8, 58.4, 54.0, 52.0, 51.8, 51.4, 41.3, 41.1, 24.7, 24.4, 22.5, 22.0, 21.8, 21.5; FTIR (neat) 3031, 2958, 1605, 1496, 1338, 1150 cm^{-1}; HRMS calcd for $C_{26}H_{37}N_2O_3S$ $(M+H)^+$ required 457.2525, found 457.2534.

3.1.7. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (5a). To a stirring solution of chlorosulfonyl isocyanate (610 μL, 7.0 mmol) and CH_2Cl_2 (35 mL) at 0°C in a 100 mL round-bottomed flask was added *tert*-butyl alcohol (0.67 mL, 7.0 mmol) in CH_2Cl_2 (2 mL) over 5 min and stirred for an additional 10 min. The mixture was then transferred, via cannula, to a stirring solution of valine-derived allylic amine salt **18** (1.00 g, 7.37 mmol) and Et_3N (3.91 mL, 22.1 mmol) in CH_2Cl_2 (50 mL) at 0°C in a 250 mL round-bottomed flask over 10 min. The resulting mixture was stirred for 10 h while slowly being raised to rt. CH_2Cl_2 (50 mL) was added, the solution washed with 10% $NaHSO_4$ (3×60 mL), $NaHCO_3$ (3×50 mL), brine (60 mL), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. Flash chromatography (SiO_2, hexanes/EtOAc) afforded 1.40 g (71%) of the sulfamoyl carbamate **5a** as a white solid. Mp 151°C; TLC R_f=0.48 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−26.0 (c=1.05, $CH_3C(O)CH_3$); ^{1}H NMR ($CD_3C(O)CD_3$, 400 MHz) δ 5.78 (ddd, J=17.3, 10.3, 8.1 Hz, 1H), 5.25 (dd, J=17.2, 1.0 Hz, 1H), 5.15 (d, J=10.4 Hz, 1H), 3.56 (dd, J=7.4, 7.4 Hz, 1H), 1.88–1.79 (m, 1H), 1.44 (s, 9H), 0.97 (d, J=6.8 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4, 137.2, 117.5, 82.2, 64.1, 33.4, 28.3, 19.2, 19.1; FTIR (neat) 3283, 3282, 2967, 1701, 1445, 1371, 1354, 1140 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{11}H_{23}N_2O_4S$ 279.1379, found 279.1383.

3.1.8. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-methyl-2-ethoxycarbonyl]-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (19a). To as stirring solution of **5a** (1.00 g, 3.60 mmol) and DEAD (656 μL, 3.77 mmol) in THF (1 mL) under argon in a 50 mL round-bottomed flask was added a mixture of (*S*)-ethyl lactate (**6a**) (423 μL, 3.77 mmol) and PPh_3 (989 mg, 3.77 mmol) in THF (1 mL) via drop-wise addition from a syringe. The solution was stirred for 6 h and the solvent concentrated under reduced pressure. Flash chromatography (hexanes/EtOAc) afforded 1.14 g (84%) of the sulfamoyl carbamate **19a** as a clear yellow oil. TLC R_f=0.59 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+4.0 (c=2.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.72 (ddd, J=17.3, 10.5, 6.8 Hz, 1H), 5.72 (d, J=6.7 Hz, 1H), 5.28 (d, J=17.2, 1H), 5.19 (d, J=10.5 Hz, 1H) 4.87 (q, J=7.0 Hz, 1H), 4.20 (dq, J=10.8, 7.1 Hz, 1H), 4.15 (dq, J=10.8, 7.1 Hz, 1H), 3.78 (q, J=6.7 Hz, 1H), 1.95–1.86 (m, 1H), 1.54 (d, J=7.0 Hz, 3H), 1.45 (s, 9H), 1.26 (dd, J=7.2, 7.2 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 150.9, 134.7, 117.5, 84.5, 62.2, 61.4, 55.5, 32.3, 27.9, 18.2, 17.5, 16.4, 14.1; FTIR (neat) 3313, 2978, 2876, 1744, 1721, 1456, 1369, 1151 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{16}H_{31}N_2O_6S$ 379.1903, found 379.1895.

3.1.9. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-methyl-2-ethoxycarbonyl]-*N′*-methyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (20a). Sulfamoyl carbamate **19a** (500 mg, 1.32 mmol), CH_3CN (30 mL), K_2CO_3 (910 mg, 6.60 mmol), and methyl iodide (0.826 mL, 13.2 mmol) were added sequentially to a 100 mL round-bottomed flask. The flask was fitted with a condenser, and the mixture heated to 45°C for 12 h. The resulting yellow-orange mixture was filtered by suction, and the solvent removed under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) yielded 521 mg (100%) of sulfamide **20a** as a clear oil. TLC R_f=0.35 (10:1 hexanes/EtOAc);

$[\alpha]_D^{25}$=+23.9 (c=1.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.78 (ddd, J=17.5, 10.4, 7.3 Hz, 1H), 5.33 (d, J=17.4 Hz, 1H), 5.26 (d, J=10.6 Hz, 1H), 4.91 (q, J=6.8 Hz, 1H), 4.29–4.13 (m, 2H), 3.86 (dd, J=9.3, 9.3 Hz, 1H), 2.89 (s, 3H), 1.91–1.84 (m, 1H), 1.56 (d, J=6.9 Hz, 3H), 1.45 (s, 9H), 1.28 (dd, J=7.1, 7.1 Hz, 3H), 1.00 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 150.6, 133.5, 119.0, 83.9, 65.6, 61.4, 56.7, 31.1, 28.9, 28.0, 20.1, 19.5, 16.5, 14.2; FTIR (neat) 2989, 2940, 2876, 1739, 1467, 1369, 1141 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{17}H_{33}N_2O_6S$ 393.2059, found 393.2041.

3.1.10. *N*-[(1*R*)-1-Methyl-2-ethoxycarbonyl]-*N′*-methyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (21a). Sulfamide **20a** (150 mg, 0.382 mmol), CH_2Cl_2 (380 μL), and trifluoroacetic acid (440 μL, 5.70 mmol) were added sequentially to a 10 mL round-bottomed flask and stirred for 2 h. The mixture was diluted with CH_2Cl_2 (30 mL), washed with $NaHCO_3$ (2×20 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc) yielded 111 mg (100%) of sulfamide **21a** as a yellow liquid. TLC R_f=0.52 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+35.6 (c=1.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.78 (ddd, J=17.3, 9.9, 9.9 Hz, 1H), 5.27 (d, J=16.2 Hz, 1H), 5.24 (d, J=10.2 Hz, 1H), 4.87 (d, J=6.7 Hz, 1H), 4.22–4.14 (m, 2H), 3.95–3.89 (m, 1H), 3.80 (dd, J=9.8, 9.8 Hz, 1H), 2.68 (s, 3H), 1.80–1.70 (m, 1H), 1.38 (d, J=7.2 Hz, 3H), 1.27, (t, J=7.1 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 134.8, 119.3, 67.4, 61.6, 51.2, 29.0, 29.0, 20.0, 19.7, 19.6, 14.0; FTIR (neat) 3295, 2978, 2939, 2875, 1737, 1467, 1453, 1367, 1134 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{12}H_{25}N_2O_4S$ 293.1535, found 293.1539.

3.1.11. *N*-[(1*R*)-1-Methyl-2-ethoxycarbonyl]-*N*-2-propenyl-*N′*-methyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (22a). Sulfamide **21a** (103 mg, 0.352 mmol), CH_3CN (20 mL), K_2CO_3 (243 mg, 1.76 mmol), and methyl iodide (152 μL, 13.2 mmol) were added sequentially to a 100 mL round-bottomed flask. The flask was fitted with a condenser, and the mixture was heated to 55°C for 12 h. The resulting yellow orange mixture was filtered by suction, and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc) gave 106 mg (91%) of the desired diallyl sulfamide **22a** as a clear liquid. TLC R_f=0.19 (10:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+18.3 (c=1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.86 (dddd, J=16.5, 10.2, 6.2, 6.2 Hz, 1H), 5.78 (ddd, J=17.1, 10.3, 8.1 Hz, 1H), 5.24 (dd, J=17.1, 1.0 Hz, 1H), 5.22 (dd, J=10.1, 1.0 Hz, 1H), 5.21 (dd, J=17.2, 1.4 Hz, 1H), 5.12 (dd, J=10.2, 1.3 Hz, 1H), 4.23 (q, J=7.2 Hz, 1H), 4.17 (dd, J=14.3, 3.0 Hz, 1H), 4.15 (dd, J=14.3, 3.0 Hz, 1H), 3.88 (dd, J=9.8, 9.8 Hz, 1H), 3.85 (dd, J=16.4, 6.2 Hz, 1H), 3.75 (dd, J=16.2, 6.4 Hz, 1H), 2.68 (s, 3H), 1.83–1.73 (m, 1H), 1.46 (d, J=7.2 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 0.99 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 134.9, 134.8, 118.9, 117.6, 67.5, 61.1, 55.2, 48.7, 29.2, 28.6, 20.1, 19.7, 15.6, 14.1; FTIR (neat) 2977, 2870, 1740, 1642, 1467, 1327, 1159, 1136 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{15}H_{29}N_2O_4S$ 333.1848, found 333.1831.

3.1.12. 2-(2*R*)-[6-(6*S*)-Isopropyl-7-methyl-1,1-dioxo-2,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl]-propionic acid ethyl ester (8a). To a 50 mL round-bottomed flask were added **22a** (50 mg, 0.15 mmol), and CH_2Cl_2 (15 mL) and the mixture degassed with argon for 15 min. $(PCy_3)_2$-$(Cl)_2Ru$=CHPh (4 mg, 0.005 mmol) was added, the flask fitted with a condenser containing an argon balloon, and the solution was heated to reflux for 10 h. The solution was cooled to rt and the flask opened up to air. The solvent was removed under reduced pressure, and flash chromatography (hexanes/EtOAc) afforded 44 mg (97%) of cyclic sulfamide **8a** as a clear oil. TLC R_f=0.35 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−8.7 (c=2.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.88 (dddd, J=11.5, 5.9, 5.1, 2.2 Hz, 1H), 5.65 (ddd, J=10.8, 4.3, 1.3 Hz, 1H), 4.62 (q, J=7.3 Hz, 1H), 4.21–4.10 (m, 2H), 3.97 (d, J=14.0 Hz, 1H), 3.81 (dd, J=17.5, 6.1 Hz, 1H), 3.56 (dd, J=17.6, 5.7 Hz, 1H), 2.54 (s, 3H), 1.79–1.71 (m, 1H), 1.39 (d, J=7.3 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H), 1.01 (d, J=6.5 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 132.5, 129.5, 61.6, 61.3, 55.7, 41.1, 29.7, 29.6, 19.9, 19.4, 16.5, 14.1; FTIR (neat) 2979, 2876, 1736, 1467, 1366, 1327, 1164 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{13}H_{25}N_2O_4S$ 305.1535, found 305.1513.

3.1.13. 2-(2*R*)-[(4*R*,5*S*,6*S*)-4,5-Dihydroxy-6-isopropyl-7-methyl-1,1-dioxo-2,3,6,7-tetrahydro-1,2,7-thiadiazepan-2-yl]-propionic acid ethyl ester (23a) and 2-(2*R*)-[(4*S*,5*R*,6*S*)-4,5-dihydroxy-6-isopropyl-7-methyl-1,1-dioxo-2,3,6,7-tetrahydro-1,2,7-thiadiazepan-2-yl]-propionic acid ethyl ester (24a). In a procedure similar to the preparation of **16**, sulfamide **8a** (38 mg, 0.125 mmol) was subjected to dihydroxylation conditions (OsO_4, NMO, citric acid, 3:1 acetone/H_2O). Flash chromatography (hexanes/EtOAc) yielded 43 mg (99%) of the sulfamide diols **23a** and **24a** as an inseparable mixture as a clear oil. TLC R_f=0.13 (1:1 hexanes/EtOAc); $C_{13}H_{27}N_2O_6S$ 339.1590, found 339.1570.

3.1.14. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-(2-methylpropyl)-2-methoxycarbonyl]-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (19b). In a procedure similar to the preparation of sulfamoyl carbamate **19a**, sulfamoyl carbamate **5a** (454 mg, 1.63 mmol) and 2-hydroxy-4-methyl pentanoic acid methyl ester (**6b**) (253 mg, 1.71 mmol) were subjected to Mitsunobu reaction conditions (DEAD, PPh_3, THF). Flash chromatography (hexanes/EtOAc) yielded 574 mg (87%) of sulfamoyl carbamate **19b** as a white solid. Mp 97–99°C; TLC R_f=0.59 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+79.5 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.73 (ddd, J=17.2, 10.6, 6.5 Hz, 1H), 5.41 (d, J=6.9 Hz, 1H), 5.28 (d, J=17.3 Hz, 1H), 5.20 (d, J=10.6 Hz, 1H), 4.87 (dd, J=8.8, 5.2 Hz, 1H), 3.90 (dd, J=11.8, 6.5 Hz, 1H), 3.77 (s, 3H), 1.98–1.90 (m, 2H) 1.86–1.78 (m, 1H), 1.78–1.72 (m, 1H), 1.45 (s, 9H), 0.96 (d, J=6.5 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H), 0.93 (d, J=6.2 Hz, 3H), 0.90 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 151.0, 134.8, 117.1, 84.4, 61.8, 58.4, 52.2, 39.8, 32.5, 28.0, 24.7, 23.2, 21.7, 18.1, 17.5; FTIR (neat) 3308, 2960, 2873, 1748, 1717, 1436, 1369, 1151 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{18}H_{35}N_2O_6S$ 407.2216, found 407.2195.

3.1.15. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-(2-methylpropyl)-2-methoxycarbonyl]-*N′*-methyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (20b). In a procedure similar to the preparation of **20a**, **19b** (300 mg, 0.740 mmol) was subjected to methylation conditions (MeI, K_2CO_3, CH_3CN, 55°C). Flash chromatography (hexanes/EtOAc) afforded 298 mg (96%) of sulfamide **20b** as a clear oil. TLC R_f=0.59 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+23.6 (c=3.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77 (ddd, J=17.6, 10.6, 7.2 Hz, 1H), 5.32 (d, J=17.4 Hz, 1H), 5.24 (d, J=10.6 Hz, 1H), 4.90 (dd, J=8.1, 5.5 Hz, 1H), 3.93 (dd, J=9.9, 7.4 Hz, 1H), 3.72 (s, 3H), 2.92 (s, 3H), 2.01–1.95 (m, 1H), 1.92–1.84 (m, 1H), 1.82–1.75 (m, 2H), 1.43 (s, 9H), 1.00 (d, J=6.6 Hz, 3H), 0.97 (d, J=6.3 Hz, 3H), 0.95 (d, J=6.5 Hz, 3H), 0.95 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 150.6, 133.5, 119.0, 83.9, 65.6, 61.4, 56.7, 31.1, 29.7, 28.8, 28.2, 28.0, 20.1, 19.5, 16.4, 14.1; FTIR (neat) 2959, 2873, 1735, 1469, 1368, 1337, 1154, 1140 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{19}H_{37}N_2O_6S$ 421.2372, found 421.2367.

3.1.16. *N*-[(1*R*)-1-(2-Methylpropyl)-2-methoxycarbonyl]-*N′*-methyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (21b). In a procedure similar to the preparation of **21a**, **20b** (208 mg, 0.495 mmol) was subjected to BOC-deprotection conditions (TFA, CH_2Cl_2). Flash chromatography (hexanes/EtOAc) yielded 142 mg (88%) of the deprotected sulfamide **21b** as a clear oil. TLC R_f=0.50 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+25.5 (c=1.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77 (ddd, J=17.2, 10, 9.2 Hz, 1H), 5.28 (d, J=17.3 Hz, 1H), 5.25 (d, J=10.8 Hz, 1H), 4.768 (d, J=9.8 Hz, 1H), 3.89 (ddd, J=9.2, 9.2, 5.9 Hz, 1H), 3.82 (dd, J=9.6, 9.6 Hz, 1H), 3.73 (s, 3H), 2.68 (s, 3H), 1.82–1.72 (m, 2H), 1.56–1.45 (m, 2H), 0.99 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 134.8, 119.4, 67.6, 54.1, 52.3, 42.5, 29.0, 29.0, 24.4, 22.6, 21.8, 20.0, 19.6; FTIR (neat) 3289, 2959, 2873, 1742, 1467, 1367, 1335, 1157 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{14}H_{29}N_2O_4S$ 321.1848, found 321.1834.

3.1.17. *N*-[(1*R*)-1-(2-Methylpropyl)-2-methoxycarbonyl]-*N*-2-propenyl-*N′*-methyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-propenyl]-sulfamide (22b). In a procedure similar to the preparation of **22a**, sulfamide **21b** (100 mg, 0.312 mmol) was subjected to allylation conditions (allyl bromide, K_2CO_3, CH_3CN, 70°C). Flash chromatography (hexanes/EtOAc) afforded 107 mg (95%) of diallyl sulfamide **22b** as a clear oil. TLC R_f=0.55 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+34.6 (c=1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (dddd, J=17.1, 10.2, 6.5, 6.5 Hz, 1H), 5.77 (ddd, J=17.2, 10.0, 8.8 Hz, 1H), 5.24 (d, J=17.2 Hz, 1H), 5.22 (d, J=10.3 Hz, 1H), 5.16 (d, J=17.2, 1.5 Hz, 1H), 5.09 (dd, J=10.1, 1.0 Hz, 1H), 4.30 (dd, J=8.2, 8.2 Hz, 1H), 3.90 (dd, J=16.9, 6.0 Hz, 1H), 3.90–3.82 (m, 1H), 3.87 (dd, J=16.4, 7.0 Hz, 1H), 3.69 (s, 3H), 2.65 (s, 3H), 1.80–1.64 (m, 4H), 1.00 (d, J=6.6 Hz, 3H), 0.95 (d, J=5.9 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 0.88 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 135.2, 134.7, 118.9, 117.3, 67.8, 57.9, 51.9, 48.6, 38.8, 29.2, 28.6, 24.5, 22.5, 21.8, 20.1, 19.7; FTIR (neat) 2958, 2872, 1744, 1469, 1329, 1160, 1135 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{17}H_{33}N_2O_4S$ 361.2161, found 361.2176.

3.1.18. 2-(2*R*)-[6-(6*S*)-Isopropyl-7-methyl-1,1-dioxo-2,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl]-4-methylpentanoic acid methyl ester (8b). In a procedure similar to that used for the preparation of **8a**, sulfamide **22a** (50 mg, 0.139 mmol) was subjected to standard RCM conditions (refluxing CH_2Cl_2, 3 mol% $(PCy_3)_2(Cl)_2Ru$=CHPh, 4 h). Flash chromatography (hexanes/EtOAc) afforded 45 mg (97%) of cyclic sulfamide **8b** as a clear oil. TLC R_f=0.44 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+4.6 (c=2.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.87 (dddd, J=12.3, 6.1, 4.4, 2.2 Hz, 1H), 5.67 (ddd, J=10.7, 4.4, 1.3 Hz, 1H), 4.60 (dd, J=7.9, 7.9 Hz, 1H), 3.96 (d, J=11.1 Hz, 1H), 3.78 (dd, J=17.4, 6.0 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, J=17.5, 6.1 Hz, 1H), 2.55 (s, 3H), 1.79–1.73 (m, 1H), 1.73–1.66 (m, 1H), 1.63 (d, J=7.7 Hz, 1H), 1.62 (dd, J=7.9, 2.6 Hz, 1H), 1.01 (d, J=6.5 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H), 0.93 (d, J=6.5 Hz, 3H), 0.93 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 133.0, 129.3, 61.5, 57.8, 52.0, 40.4, 39.1, 29.7, 29.6, 24.4, 22.9, 21.5, 20.0, 19.4; FTIR (neat) 2959, 2872, 1741, 1467, 1367, 1336, 1164 cm^{-1}; HRMS (M+H)$^+$ calcd for $C_{15}H_{29}N_2O_4S$ 333.1848, found 333.1824.

3.1.19. 2-(2*R*)-[(4*R*,5*S*,6*S*)-4,5-Dihydroxy-6-isopropyl-7-methyl-1,1-dioxo-2,3,6,7-tetrahydro-1,2,7-thiadiazepan-2-yl]-4-methyl-pentanoic acid methyl ester (23b) and 2-(2*R*)-[(4*S*,5*R*,6*S*)-4,5-dihydroxy-6-Isopropyl-7-methyl-1,1-dioxo-2,3,6,7-tetrahydro-1,2,7-thiadiazepan-2-yl]-4-methyl-pentanoic acid methyl ester (24b). In a procedure similar to the preparation of **16**, **8b** (44 mg, 0.132 mmol) was subjected to dihydroxylation conditions (OsO_4, NMO, citric acid, 3:1 acetone/H_2O). Flash chromatography (hexanes/EtOAc) yielded 47 mg (97%) of the sulfamide diols **23b** and **24b** as an inseparable mixture of a clear oil. TLC R_f=0.13 (1:1 hexanes/EtOAc); HRMS (M+H)$^+$ calcd for $C_{14}H_{31}N_2O_6S$ 367.1903, found 367.1905.

3.1.20. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-methyl-2-ethoxycarbonyl]-*N′*-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-sulfamide (25). To a stirring solution of **5b** (3.34 g, 10.77 mmol) and DIAD (2.4 mL, 12.19 mmol) in THF (20 mL) at rt, was added the solution of (L)-(−)-ethyl lactate (1.4 mL, 12.35 mmol) and Ph_3P (2.40 g, 9.13 mmol) in THF (20 mL). After 24 h, the reaction mixture was concentrated under reduced pressure, and purified by column chromatography (4:1 hexanes/EtOAc) to afford 3.14 g (85%) of the desired sulfamide **25** as a clear oil. TLC R_f=0.42 (4:1 hexanes/EtOAc) [For characterization data, see, reference 12].

3.1.21. *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-methyl-2-ethoxycarbonyl]-*N′*-benzyl-*N′*-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-sulfamide (26). In a procedure similar for the preparation of sulfamide **12**; sulfamide **25** (2.03 g, 4.95 mmol) in CH_3CN (50 mL) was reacted with benzyl bromide (0.75 mL, 6.52 mmol) and K_2CO_3 (1.55 g, 11.22 mmol) and refluxed at 82°C for 24 h. The reaction mixture was extracted with EtOAc (3×50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure. Flash chromatography (3:1 hexanes/EtOAc) afforded 2.11 g (94%) of the desired ester **26** as a clear oil. TLC R_f=0.62 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−13.7 (c=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.23 (m, 5H), 4.89 (d,

J=16.8 Hz, 1H), 4.86 (q, J=7.0 Hz, 1H), 4.77 (d, J=16.1 Hz, 1H), 4.25 (d, J=10.5 Hz, 1H), 4.26–4.10 (m, 2H), 3.67 (s, 3H), 1.99 (m, 1H), 1.48 (s, 9H), 1.33 (d, J=7.0 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 0.86 (d, J=6.6 Hz, 3H), 0.84 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 170.3, 150.7, 137.4, 128.7, 128.2, 127.5, 84.3, 66.7, 61.5, 56.6, 51.5, 50.3, 29.1, 28.0, 19.6, 19.5, 15.8, 14.1; FTIR (neat) 2979, 1732 (br, 3CO), 1455, 1372, 1147, 756, 695 cm^{-1}; HRMS calcd for $C_{23}H_{37}N_2O_8S$ $(M+H)^+$ required 501.2271, found 501.2287.

3.1.22. *N*-[(1*R*)-1-Methyl-2-ethoxycarbonyl]-*N*′-benzyl-*N*′-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-sulfamide (27). To a stirring solution of sulfamide **26** (2.00 g, 4.00 mmol) in CH_2Cl_2 (10 mL) at room temperature was added TFA (10 mL, 129.8 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 24 h and extracted with EtOAc (40 mL×2). The combined organic layers were washed with aqueous $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (3:1 hexanes/EtOAc) yielded 1.52 g (97%) of the desired sulfamide **27** as a clear oil. TLC R_f=0.47 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−47.0 (c=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.38 (m, 2H), 7.33–7.25 (m, 3H), 4.99 (d, J=7.5 Hz, 1H), 4.52 (d, J=15.6 Hz, 1H), 4.47 (d, J=15.6 Hz, 1H), 4.18 (q, J=7.1, 7.1 Hz, 2H), 3.97 (d, J=10.6 Hz, 1H), 4.00 (dq, J=7.2, 7.2 Hz, 1H), 3.72 (s, 3H), 2.11 (m, 1H), 1.38 (d, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 171.7, 136.9, 128.9, 128.3, 127.7, 67.2, 61.7, 51.8, 51.6, 49.7, 28.3, 19.8, 19.6, 19.5, 14.0; FTIR (neat) 3293, 2968, 1738 (br, CO), 1455, 1346, 1139, 752, 700 cm^{-1}; HRMS calcd for $C_{18}H_{29}N_2O_6S$ $(M+H)^+$ required 401.1746, found 401.1723.

3.1.23. *N*-[(1*R*)-1-Methyl-2-ethoxycarbonyl]-*N*-(4-methoxy)benzyl)-*N*′-benzyl-*N*′-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-sulfamide (28). In a benzylation procedure similar for the preparation of sulfamide **12**, sulfamide **27** (70 mg, 0.17 mmol) in CH_3CN (5 mL) was reacted with 4-methoxybenzyl chloride (0.1 mL, 0.74 mmol) and K_2CO_3 (0.12 g, 0.83 mmol) and refluxed for 24 h. Flash chromatography (3:1 hexanes/EtOAc) yielded 80 mg (77%) of the desired sulfamide **28** as a clear oil. TLC R_f=0.50 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−18.3 (c=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J=6.6 Hz, 2H), 7.26–7.18 (m, 5H), 6.77 (d, J=8.7 Hz, 2H), 4.86 (d, J=15.9 Hz, 1H), 4.49 (dd, J=15.5, 4.3 Hz, 1H) 4.40 (d, J=15.6 Hz, 1H), 4.26–4.20 (m, 1H), 4.16–3.89 (m, 3H), 3.79 (s, 3H), 3.79–3.72 (m, 1H), 3.58 (s, 3H), 1.94–1.85 (m, 1H), 1.39 (d, J=7.1 Hz, 3H), 1.20 (t, J=7.2 Hz, 3H), 0.79 (d, J=6.5 Hz, 3H), 0.77 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 171.1, 159.1, 137.4, 129.7, 129.2, 128.8, 128.2, 127.6, 113.7, 67.2, 61.2, 55.5, 55.2, 51.6, 49.5, 49.0, 28.6, 19.7, 19.4, 14.8, 13.9; FTIR (neat) 2966, 1738, 1612, 1513, 1456, 1338, 1154, 750, 701 cm^{-1}; HRMS calcd for $C_{26}H_{37}N_2O_7S$ $(M+H)^+$ required 521.2321, found 521.2325.

3.1.24. *N*-[(1*R*)-2-Hydroxy-1-methylethyl]-*N*-(4-methoxy)benzyl-*N*′-benzyl-*N*′-[(1*S*)-2-hydroxy-1-(1-methylethyl)ethyl]-sulfamide (29). In a reduction procedure similar for the preparation of sulfamide diol **13**, sulfamide **28** (1.59 g, 3.05 mmol) in THF (50 mL) was treated with LAH (0.77 g, 20.4 mmol) at 0°C for 1 h. Flash chromatography (1:1 hexanes/EtOAc) afforded 430 mg (38%) of the desired sulfamide diol **29** as a clear oil. TLC R_f=0.38 (1:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−29.1 (c=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, J=6.8 Hz, 2H), 7.38–7.27 (m, 5H), 6.84 (d, J=6.8 Hz, 2H), 4.43 (d, J=15.6 Hz, 1H), 4.38 (d, J=15.7 Hz, 1H), 4.31 (d, J=15.7 Hz, 1H), 4.24 (d, J=15.6 Hz, 1H), 4.05–3.98 (m, 1H), 3.85 (dd, J=12.1, 3.8 Hz, 1H), 3.78 (s, 3H), 3.75 (dd, J=9.5, 4.7 Hz, 1H), 3.56 (dt, J=9.8, 3.9 Hz, 1H), 3.49 (dd, J=11.6, 9.8 Hz, 1H), 3.39 (dd, J=11.6, 4.8 Hz, 1H), 2.43 (bs, 2H), 1.58–1.49 (m, 1H), 1.02 (d, J=6.9 Hz, 3H), 0.92 (d, J=6.7 Hz, 3H), 0.80 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 137.6, 130.5, 129.6, 129.1, 128.3, 127.7, 113.7, 67.8, 63.9, 61.2, 56.0, 55.1, 48.6, 47.6, 29.2, 21.0, 20.2, 15.8; FTIR (neat) 3444, 3029, 2963, 1612, 1513, 1496, 1456, 1325, 1140, 746, 700 cm^{-1}; HRMS calcd for $C_{23}H_{35}N_2O_5S$ $(M+H)^+$ required 451.2267, found 451.2256.

3.1.25. *N*-[(1*R*)-1-Methyl-2-propenyl]-*N*-(4-methoxy)-benzyl-*N*′-benzyl-*N*′-[(1*S*)-(1-methylethyl)-2-propenyl]-sulfamide (30). To a stirring solution of oxalyl chloride (0.44 mL, 5.04 mmol) in CH_2Cl_2 (1 mL) at −78°C under an argon atmosphere was added DMSO (430 μL, 6.06 mmol) in CH_2Cl_2 (1 mL) over 20 min. After 40 min, the sulfamide diol **29** (820 mg, 1.82 mmol) in CH_2Cl_2 (10 mL) was added over 30 min, and the dropping funnel was rinsed with CH_2Cl_2 (4 mL). The mixture was stirred at −78°C for 5 h and monitored by TLC. Et_3N (2.1 mL, 15.1 mmol) was added over 15 min and the reaction was stirred at −78°C for 2 h. THF (4 mL, 1:1 H_2O/THF) was added at −78°C and after 5 min, the reaction was warmed to 0°C and stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2, (50 mL) washed with 2M HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.81 g (99%) of the desired dialdehyde sulfamide that was used immediately without further purification. TLC R_f=0.91 (1:1 hexanes/EtOAc).

To a solution of methyltriphenylphosphonium bromide (4.59 g, 12.85 mmol) in THF (25 mL) was added BuLi (6.4 mL, 10.24 mmol, 1.6 M in hexane) at 0°C, the mixture stirred for 2 h, and cooled down to −78°C. A solution of dialdehyde sulfamide (0.76 g, 1.71 mmol) in THF (25 mL) at −78°C was added via cannula. After 24 h, the reaction mixture was extracted with EtOAc (50 mL×3), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 520 mg (69%) of the desired sulfamide diene **30** as a clear oil. TLC R_f=0.49 (5:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+36.8 (c=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, J=7.0 Hz, 2H), 7.33–7.26 (m, 5H), 6.81 (d, J=8.6 Hz, 2H), 5.87 (m, 1H), 5.86 (dd, J=16.6, 9.7 Hz, 1H), 5.23 (dd, J=1.5, 10.2 Hz, 1H), 5.13 (d, J=10.6 Hz, 1H), 5.08 (dd, J=6.8, 6.5 Hz, 2H), 4.30–4.14 (m, 2H), 4.31 (d, J=15.6 Hz, 1H), 4.21 (d, J=7.4 Hz, 1H), 4.16 (d, J=15.7 Hz, 1H), 3.78 (s, 3H), 3.50 (t, J=9.9 Hz, 1H), 1.87–1.80 (m, 1H), 1.19 (d, J=6.9 Hz, 3H), 0.90 (d, J=6.6 Hz, 3H), 0.69 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$. 100 MHz) δ 158.8, 138.7, 137.3, 135.9, 130.6, 129.8, 129.0, 128.3, 127.6, 119.2, 116.4, 113.5, 69.8, 55.2, 55.1, 49.7, 47.9, 30.1, 20.6, 20.4, 17.4; FTIR (neat) 3068, 2962, 1612, 1513, 1456, 1331,

1147 cm^{-1}; HRMS calcd for $C_{25}H_{35}N_2O_3S$ $(M+H)^+$ required 443.2368, found 443.2346.

3.1.26. 2-(3*S*,6*R*)-Benzyl-3-isopropyl-7-(4-methoxy-benzyl)-6-methyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide (9). To a refluxing solution of **30** (0.38 g, 0.86 mmol) in degassed benzene (10 mL) was added $(ImesH_2)(PCy_3)$-$(Cl)_2Ru$=CHPh (0.03 g, 0.04 mmol) and stirred for 1 h. The reaction mixture was cooled down to rt, and silica gel and DMSO (5 drops) were added, and the solution was stirred overnight. The reaction mixture was filtered, concentrated under reduced pressure and purified by column chromatography (5:1 hexanes/EtOAc) to yield 320 mg (89%) of the desired sulfamide **9** as a clear oil. TLC R_f=0.27 (5:1 hexanes/EtOAc); $[\alpha]_D^{25}$=+0.44 (c=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J=7.3 Hz, 2H), 7.32–7.22 (m, 5H), 6.85 (d, J=8.6 Hz, 2H), 6.02 (ddd, J=10.1, 6.1, 1.3 Hz, 1H), 5.88 (ddd, J=10.5, 5.8, 1.5 Hz, 1H), 4.75 (d, J=15.9 Hz, 1H), 4.60 (d, J=15.6 Hz, 1H), 4.57 (m, 1H), 4.04 (d, J=15.9 Hz, 1H), 3.96 (d, J=15.6 Hz, 1H), 3.93 (m, 1H), 3.79 (s, 3H), 1.78–1.72 (m, 1H), 1.17 (d, J=7.2 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H), 0.71 (d, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5, 138.1, 136.2, 134.6, 131.5, 128.2, 128.2, 128.1, 127.1, 113.6, 63.7, 55.1, 51.4, 49.9, 49.1, 30.2, 20.1, 20.0, 19.9; FTIR (neat) 3028, 2963, 1613, 1513, 1496, 1456, 1352, 1147, 826, 750, 700 cm^{-1}; HRMS calcd for $C_{23}H_{31}N_2O_3S$ $(M+H)^+$ required 415.2055, found 415.2046.

3.1.27. 2-(3*S*,4*S*,5*R*,6*R*)-Benzyl-4,5-dihydroxy-3-isopropyl-7-(4-methoxy-benzyl)-6-methyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepane 1,1-dioxide (31). To a stirring solution of **9** (25 mg, 0.06 mmol) in acetone (230 μL, 3.13 mmol) and water (100 μL, 5.55 mmol) were added NMO (21 mg, 0.15 mmol), OsO_4 (50 μL, 0.0082 mmol, 4 wt% solution in water), and citric acid monohydrate (30 mg, 0.14 mmol). After 72 h, the reaction mixture was washed with $NaHSO_3$ (30 mL), extracted with EtOAc (30 mL×2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) gave 25 mg (91%) of the desired sulfamide **31** as a white solid. TLC R_f=0.35 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$=−8.6 (c=0.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, J=7.1 Hz, 2H), 7.39–7.33 (m, 5H), 6.88 (d, J=8.6 Hz, 2H), 4.59 (d, J=14.3 Hz, 1H), 4.57 (d, J=13.8 Hz, 1H), 4.50 (d, J=13.8 Hz, 1H), 4.47 (d, J=14.7 Hz, 1H), 4.24 (d, J=3.5 Hz, 1H), 3.93 (d, J=8.5 Hz, 1H), 3.81 (s, 3H), 3.29 (m, 1H), 2.91 (dd, J=10.6, 4.4 Hz, 1H), 2.15–2.13 (m, 1H), 2.13 (d, J=5.7 Hz, 1H), 2.00 (d, J=5.7 Hz, 1H), 1.14 (d, J=6.7 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H), 0.70 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 137.3, 129.7, 129.6, 128.6, 128.0, 113.9, 68.6, 56.6, 55.2, 55.1, 53.0, 29.4, 21.2, 21.0, 18.0; FTIR (neat) 3448, 3028, 2916, 1610, 1511, 1458, 1329, 1137, 823, 753, 700 cm^{-1}; HRMS calcd for $C_{23}H_{33}N_2O_5S$ $(M+H)^+$ required 449.2110, found 449.2110.

3.1.28. *N*-[(1*S*)-1-(1-Benzyloxy)methyl-2-propenyl]-*N*-[(1,1-dimethylethoxy)carbonyl]-*N′*-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-sulfamide (32). To a stirring solution of sulfamoyl carbamate **5b** (400 mg, 1.30 mmol) in THF (1.0 mL) at rt under argon was added PPh_3 (341 mg, 1.3 mmol) and alcohol **7** (231 mg, 1.30 mmol) followed by drop-wise addition of DIAD (256 μL, 1.3 mmol). The solution was stirred for 8 h and the solvent removed under reduced pressure. Flash chromatography (20:1, heptanes/EtOAc) afforded 403 mg (67%, ~6:1 mixture of regio-isomers) of the sulfamoyl carbamate **32** as a clear yellow oil. TLC R_f=0.30 (3:1 heptane/EtOAc); $[\alpha]_D^{25}$=+33.4 (c=1.246, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.28 (m, 5H), 6.00–5.93 (m, 2H), 5.28 (dd, J=17.4, 1.0 Hz, 1H), 5.21 (dd, J=10.4, 1.0 Hz, 1H), 5.10 (dd, J=14.4, 7.1 Hz, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.57 (d, J=12.0 Hz, 1H), 4.03 (dd, J=8.3, 4.4 Hz, 1H), 3.93 (dd, J=10.0, 8.8 Hz, 1H), 3.67 (s, 3H), 3.65 (dd, J=10.0, 6.0 Hz, 1H), 2.14–2.06 (m, 1H), 1.52 (s, 9H), 0.99 (d, J=6.8 Hz, 3H), 0.83 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 151.2, 137.9, 134.0, 128.3, 127.7, 127.6, 118.4, 84.4, 72.8, 70.1, 61.8, 60.4, 52.1, 31.8, 27.9, 18.8, 17.1; FTIR (neat) 3321, 3064, 1741, 1724, 1643, 1605, 1495, 1369, 1151 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{22}H_{35}N_2O_7S$ 471.2165, found 471.2155.

3.1.29. *N*-[(1*S*)-1-(1-Benzyloxy)methyl-2-propenyl]-*N*-[(1,1-dimethylethoxy)carbonyl]-*N′*-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-*N′*-2-propenyl-sulfamide (33). To a stirring solution of **32** (119 mg, 0.25 mmol) in CH_3CN (3 mL) in a pressure tube was added K_2CO_3 (173 mg, 1.25 mmol) and allyl bromide (216 μL, 2.5 mmol). The pressure tube was heated to 70°C for 12 h. The resulting yellow-orange mixture was filtered by suction, and the solvent removed under reduced pressure. Flash chromatography (8:1 heptanes/EtOAc) afforded 120 mg (92%) of **33** as a clear yellow oil. TLC R_f=0.41 (3:1 heptane/EtOAc); $[\alpha]_D^{25}$=−37.9 (c=0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.27 (m, 5H), 6.03 (dddd, J=17.4, 10.1, 5.3, 5.3 Hz, 1H), 5.97 (ddd, J=17.0, 10.5, 6.1 Hz, 1H), 5.29 (d, J=17.4 Hz, 1H), 5.20 (d, J=10.5 Hz, 1H), 5.15 (dd, J=11.5, 1.0 Hz, 1H), 5.10–5.03 (m, 1H), 5.04 (dd, J=10.0, 1.0 Hz, 1H), 4.57 (d, J=12.2 Hz, 1H) 4.54 (d, J=12.0 Hz, 1H), 4.30 (dd, J=16.8, 7.7 Hz, 1H), 4.24 (dd, J=16.9, 5.2 Hz, 1H), 4.14 (d, J=10.5 Hz, 1H), 3.89 (dd, J=9.7, 7.7 Hz, 1H), 3.68 (s, 3H), 3.67 (dd, J=9.9, 6.8 Hz, 1H), 2.16–2.04 (m, 1H), 1.42 (s, 9H), 1.02 (d, J=6.6 Hz, 3H), 0.88 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 151.1, 137.8, 135.8, 134.5, 128.2, 127.6, 127.5, 117.6, 116.6, 83.6, 72.7, 70.6, 66.2, 60.8, 51.2, 48.8, 28.8, 27.9, 19.6, 19.2; FTIR (neat) 3081, 1726, 1640, 1367, 1140 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{25}H_{39}N_2O_7S$ 511.2478, found 511.2460.

3.1.30. 2-(2*S*)-[(6*S*)-(6-Benzyloxymethyl-7-(1,1-dimethylethoxy)carbonyl-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (34). To a stirring solution of allylated sulfamide **33** (115 mg, 0.22 mmol) in degassed CH_2Cl_2 (3 mL) in a pressure tube was added $(ImesH_2)(PCy_3)(Cl)_2Ru$=CHPh (9 mg, 0.011 mmol, 5 mol%). The solution was stirred at reflux for 3 h and opened up to air. DMSO (40 μL) was added the mixture stirred for 12 h, and the solvent concentrated. Flash chromatography (10:1 heptanes/EtOAc) yielded 104 mg (96%) of cyclic sulfamide **34** as a clear yellow oil. TLC R_f=0.32 (3:1 heptanes/EtOAc); $[\alpha]_D^{25}$=−59.8 (c=0.88, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.27 (m, 5H), 5.78–5.72 (m, 1H), 5.55–5.50 (m, 1H), 5.04 (bs, 1H), 4.57 (s, 2H), 4.28 (d, J=10.4 Hz, 1H), 4.15–4.10 (m, 1H),

3.86–3.79 (m, 3H), 3.64 (s, 3H), 2.20–2.11 (m, 1H), 1.49 (s, 9H), 1.00 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 151.1, 138.0, 128.5, 128.3, 127.6, 127.6, 125.4, 84.0, 72.8, 71.6, 65.5, 55.5, 52.0, 43.4, 28.3, 27.8, 19.2, 19.1; FTIR (neat) 3030, 1741, 1604, 1369, 1154 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{23}H_{35}N_2O_7S$ 483.2165, found 483.2156.

3.1.31. 2-(2*S*)-[(6*S*)-(6-Benzyloxymethyl-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (35). The cyclic sulfamoyl carbamate **34** was dissolved in TFA/CH_2Cl_2 (1:1). After 30 min the reaction was quenched with $NaHCO_3$ (saturated aq.) and extracted with CH_2Cl_2 (2×). The aqueous layer was re-extracted with CH_2Cl_2, and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford 49 mg (96%) of sulfamide **35** as a yellow oil. TLC R_f=0.21 (3:1 heptane/EtOAc); $[\alpha]_D^{25}$=−45.1 (c=1.025, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.30 (m, 5H), 5.64 (bs, 2H), 5.14 (d, J=10.2 Hz, 1H), 4.57 (d, J=12.0 Hz, 1H), 4.51 (d, J=12.0 Hz, 1H), 4.20–4.15 (m, 2H), 4.11 (d, J=11.0 Hz, 1H), 3.76–3.70 (m, 1H), 3.65 (s, 3H), 3.60–3.58 (m, 2H), 2.21–2.12 (m, 1H), 1.00 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 137.4, 130.9, 128.6, 128.5, 128.0, 127.8, 73.5, 72.0, 66.1, 51.8, 50.9, 41.0, 27.4, 19.2, 19.0; FTIR (neat) 3284, 3029, 1738, 1603, 1333, 1150 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{18}H_{27}N_2O_5S$ 383.1641, found 383.1662.

3.1.32. 2-(2*S*)-[(6*S*)-(7-Benzyl-6-benzyloxymethyl-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (36). To a stirring solution of cyclic sulfamide **35** (49 mg, 0.13 mmol) in CH_3CN (5 mL) in a pressure tube was added K_2CO_3 (90 mg, 0.65 mmol) and benzyl bromide (150 μL, 1.3 mmol). The reaction was heated to 70°C for ~12 h, filtered via suction filtration, and purified by column chromatography (10:1 heptane/EtOAc) to afford 54 mg (89%) of the benzylated sulfamide **36** as a yellow oil. TLC R_f=0.29 (3:1 heptanes/EtOAc); $[\alpha]_D^{25}$=−68.5 (c=0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41–7.18 (m, 10H), 5.82–5.78 (m, 1H), 5.75–5.72 (m, 1H), 4.66–4.63 (m, 2H), 4.31 (s, 1H), 4.28 (d, J=3.7 Hz, 1H), 4.22 (d, J=11.9 Hz, 1H), 4.20 (d, J=11.0 Hz, 1H), 3.99–3.94 (m, 1H), 3.82–3.76 (m, 1H), 3.72 (s, 3H), 3.54 (dd, J=9.5, 6.0 Hz, 1H), 3.42 (dd, J=9.5, 7.2 Hz, 1H), 2.22–2.14 (m, 1H), 1.06 (d, J=6.7 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 138.3, 137.6, 128.8, 128.4, 128.3, 128.3, 128.2, 127.5, 127.1, 126.9, 72.9, 70.9, 65.8, 55.4, 51.8, 51.0, 40.6, 27.8, 19.2, 19.1; FTIR (neat) 2962, 1740, 1496, 1454, 1334, 1150 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{25}H_{33}N_2O_5S$ 473.2110, found 473.2110.

3.1.33. 2-(2*S*)-[(4*S*,5*R*,6*R*)-(7-Benzyl-6-benzyloxymethyl-4,5-dihydroxy-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (37). In a procedure similar to the preparation of the sulfamide diol **16**, sulfamide **36** (93 mg, 0.200 mmol) was subjected to dihydroxylation conditions NMO·H_2O (28 mg, 0.24 mmol), citric acid (84 mg, 0.40 mmol) and OsO_4 (75 μL, 0.012 mmol, 6 mol%). Flash chromatography (1:1 heptane/EtOAc) produced 70 mg (70%) of the sulfamide diol **37** obtain as a clear oil. TLC R_f=0.49 (1:3 heptane/EtOAc); $[\alpha]_D^{25}$=−37.5 (c=0.995, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.09 (m, 10H), 4.58 (d, J=14.2 Hz, 1H), 4.39 (d, J=7.7 Hz, 1H), 4.35 (d, J=10.3 Hz, 1H), 4.29 (d, J=11.8 Hz, 1H), 4.25 (d, J=11.8 Hz, 1H), 4.22–4.20 (m, 1H), 4.05 (d, J=14.2 Hz, 1H), 3.88 (d, J=1.3 Hz, 1H), 3.84 (dd, J=10.2, 9.1 Hz, 1H), 3.78 (s, 3H), 3.69 (dd, J=14.5, 5.6 Hz, 1H), 3.42 (d, J=14.3 Hz, 1H), 3.29–3.23 (m, 2H), 3.15 (dd, J=9.0, 4.8 Hz, 1H), 2.21–2.13 (m, 1H), 1.05 (d, J=6.7 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 136.9, 136.6, 128.9, 128.5, 128.4, 127.9, 127.8, 127.4, 78.4, 74.1, 73.3, 73.2, 67.4, 59.2, 55.1, 52.1, 45.8, 28.9, 19.3, 19.2; FTIR (neat) 3468, 1739, 1345, 1140 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{25}H_{35}N_2O_7S$ 507.2165, found 507.2152.

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