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Modular, One-Pot, Sequential Aziridine Ring Opening–S_NAr Strategy to 7-, 10-, and 11-Membered Benzo-Fused Sultams

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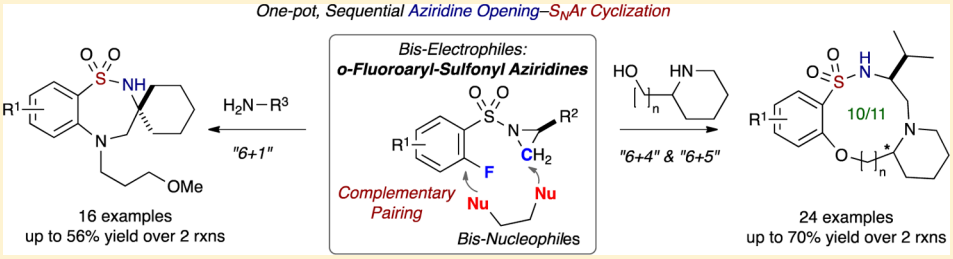
Supporting Information



ABSTRACT: The generation of common and stereochemically rich medium-sized benzo-fused sultams via complementary pairing of heretofore-unknown (*o*-fluoroaryl)sulfonyl aziridine building blocks with an array of amino alcohols/amines in a modular one-pot, sequential protocol using an aziridine ring opening and intramolecular nucleophilic aromatic substitution is reported. The strategy employs a variety of amino alcohols/amines and proceeds with 6 + 4/6 + 5 and 6 + 1 cycloetherification pathways in a highly chemo- and regioselective fashion to obtain skeletally and structurally diverse, polycyclic, 10- to 11- and 7-membered benzo-fused sultams for broad-scale screening.

INTRODUCTION

The development of efficient methods for the generation of medium- and large-sized heterocycles is an important facet of screening campaigns for facilitating drug discovery.[1] In particular, medium and macrocyclic lactams[1,2] constitute an important class of molecules in compound collections derived from target-oriented and diversity-oriented[3] synthetic approaches. Their distinct properties, which include conformational constraint, reduced polarity, increased proteolytic stability, and potential for higher target binding and selectivity,[4] are manifested in improved pharmacokinetics and pharmacodynamics,[4] rendering them as attractive lead molecules for drug development.[5] Taken collectively, these attributes have inspired production of natural product like[6] medium-sized and macrocyclic ring systems that are stereochemically rich and enhanced in terms of their fraction of sp^3 carbons,[7] enabling efforts to address emerging difficult drug targets[5,8] such as protein–protein interactions[9] and epigenetic targets.[10]

Synthetic medium-sized (8–11 membered)[11] and macrocyclic lactams have a rich biological profile and have been shown to exhibit broad activity in a variety of areas ranging from antitumor,[2a] antifungal,[12] anthelmintic,[13] neutral endopeptidase inhibitory,[14] and hepatitis C virus protease inhibitory[15] in drug discovery[16] to insecticidal agents in agriculture (Figure 1).[17] In contrast, their sulfonamide-based counterparts (amide surrogates),[18] medium[19] and macrocyclic sultams, are unnatural and less prevalent in the literature but have been found to exhibit antiproliferative,[20] anti-HIV activity,[21] inhibitory activity of trypsin-like serine protease Factor XIa involved in blood coagulation[22] and, more recently, have been shown to be modulators of lysosomal acidification involved in critical cellular function (Figure 1).[23] Despite advances in the field,[24] methods to generate functionally rich, medium- to large-sized lactams and sultams remains a significant challenge.[25]

We herein report a modular approach utilizing a heretofore-unknown class of sulfonamide building blocks, namely (*o*-fluoroaryl)sulfonyl aziridines, which react with amino alcohols via a process we term complementary pairing (CP), vide infra, with high chemo- and regioselectivity enabling access to 10- to 11-membered sultams. Overall, this one-pot protocol involves sequential aziridine ring opening by the amine component and intramolecular nucleophilic aromatic substitution (S_NAr) via the alkoxy component. In addition, dual reactivity with primary amines facilitates access to 7-membered sultams. Taken collectively, the routes reported herein generate a diverse array of polycyclic, 10- to 11- and 7-membered benzo-fused sultam scaffolds.

Previously, our group has reported a strategy termed complementary ambiphile pairing (CAP)[26,27] for the synthesis of skeletally diverse 7- and 8-membered benzo-fused sultams in a modular and efficient fashion. As shown in Figure 2A, CAP strategies unite a pair of ambiphilic compounds, possessing both electrophilic and nucleophilic components, in a synergistic

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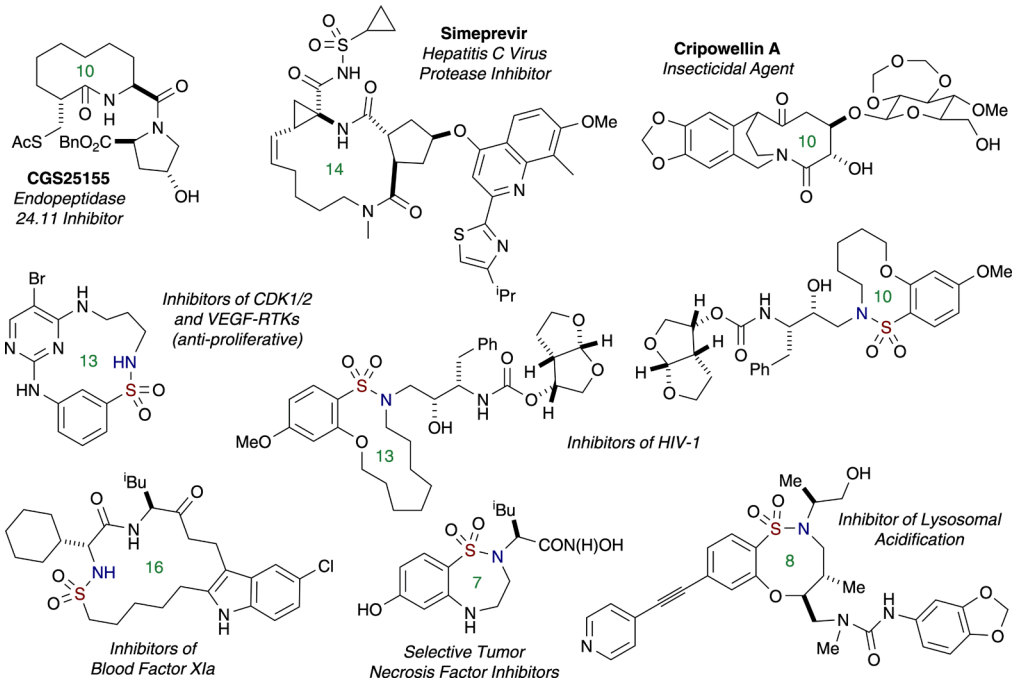

Figure 1. Bioactive lactams and sultams.

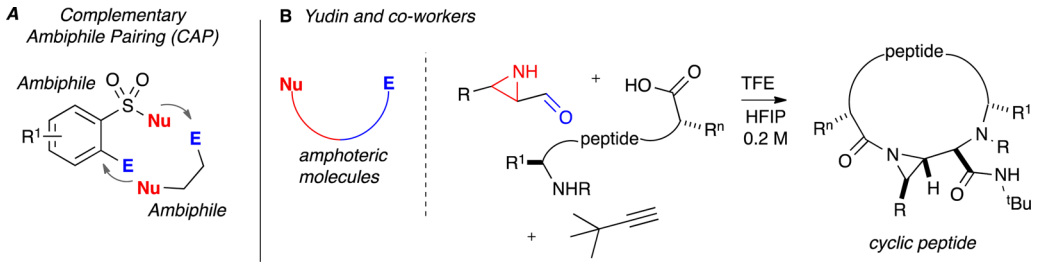

Figure 2. Complementary ambiphile pairing and amphoteric molecules.

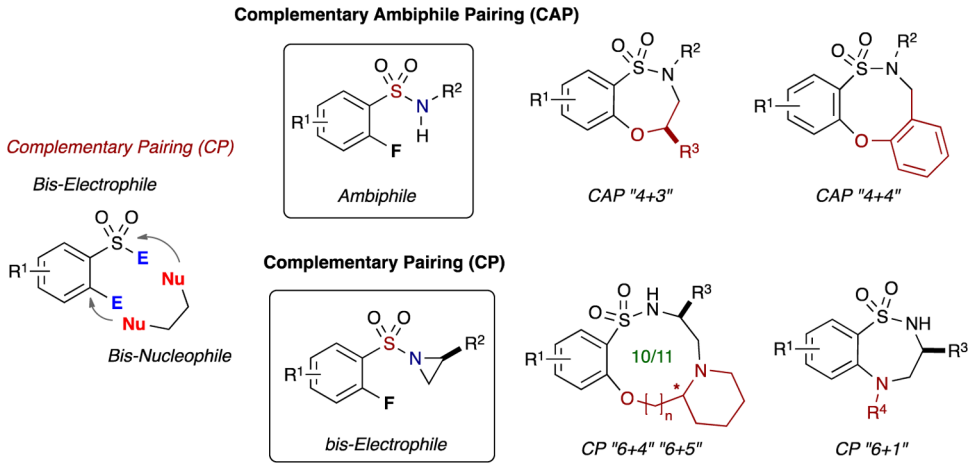

Figure 3. Summary of CAP and CP routes to benzo-fused sultams.

complementary manner [(4 + 3) and (4 + 4) cyclizations]. In contrast, Yudin and co-workers have developed a number of elegant methods using aziridine aldehydes that contain a nucleophile and electrophile on the same molecule (Figure 2B) and which they term as amphoteric molecules.[28]

We have previously investigated and reported the use of *o*-haloaryl sulfonyl chlorides in a number of pairing strategies including Click, Click, Cyclize[29] to generate a variety of bridged and benzo-fused sultams (Figure 3). Based on these studies, we sought to expand the scope to another unique class of *bis*-electrophiles, namely, heretofore unknown *o*-fluoroaryl-sulfonyl aziridines for use in complementary pairing to bis-nucleophilic counterparts, such as amino alcohols, as well as consecutive coupling with primary amines.[30] We envisioned CP of activated

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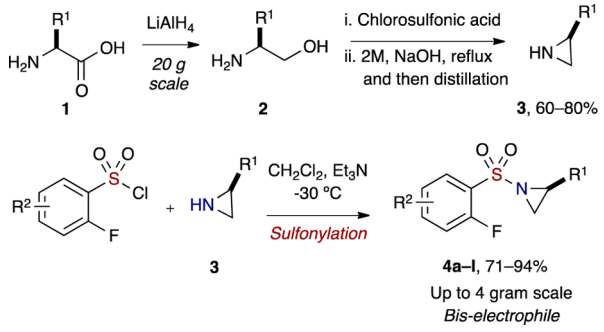
sulfonyl aziridines (simple 6-atom bis-electrophilic synthon) via "chemo- and regioselective" ring opening by the amino component of the amino alcohol (bis-nucleophiles) and subsequent S_NAr cyclization with the alcohol component to furnish unprecedented, functionally rich, medium-sized benzo-fused sultams in chemoselective "6 + 4" and "6 + 5" heterocyclization pathways. Moreover, the method can accommodate the use of (*o*-fluoroaryl)sulfonyl aziridines to generate 7-membered benzo-fused sultams via a "6 + 1" atom cyclization sequence where primary amines are utilized for sulfonyl aziridine ring opening and the resulting secondary amines cyclize via a subsequent S_NAr reaction (Figure 3).

Historically, intramolecular S_NAr cyclizations have been utilized to access common-sized rings or macrocycles comprising 5-membered indoles and indolines,[31] macrolactams such as complestatin (16-membered),[32] vancomycin (16-membered and their modified derivatives),[33] and cyclopeptide alkaloids.[34] Reports of intramolecular heteroaryl cyclizations en route to sultams first surfaced in the 1990s, when Giannotti and co-workers reported Cu-catalyzed reactions on *o*-halobenzene-sulfonamides bearing amino side chains.[35] In 2010, concurrent reports from several other laboratories detailed S_NAr arylether-ification protocols to 7- and 8-membered benzo-fused sultams.[36] Use of intramolecular S_NAr to access 10- and 11-membered sultams, however, to the best of our knowledge, is void in the literature, due to several challenging problems including methods of macrocyclization (cyclization vs oligomerization) and strain (distortion of standard bond angles, lengths and unfavorable transannular interactions) in the macrocyclic products.[37]

RESULTS AND DISCUSSION

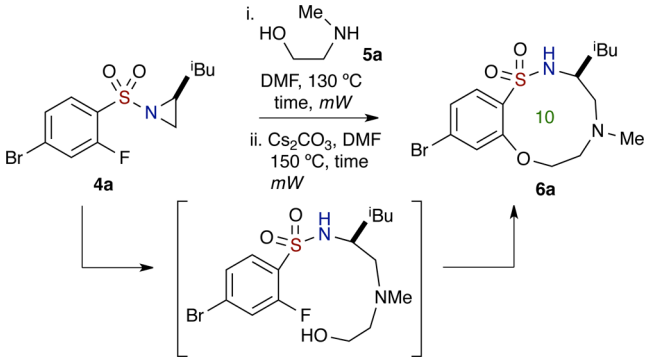
The titled investigation commenced with the preparation of chiral, nonracemic aziridines **3** via use of a mild Wenker synthesis[38] from the respective amino alcohols, with all preparations occurring in good to excellent yields. Sulfonylation of aziridines with *o*-fluorobenzenesulfonyl chlorides and Et_3N in CH_2Cl_2 at −30 °C furnished a variety of 1-((2-fluorophenyl)-sulfonyl)aziridines in good yields (71−94%) (Scheme 1).

Scheme 1. Preparation of Aziridines and Sulfonylation To Provide (*o*-Fluoroaryl)sulfonyl Aziridines



Studies on the one-pot, sequential process began with aziridinyl sulfonamide **4a** (aziridine ring opening), which was reacted with *N*-methylethanolamine **5a** (1.2 equiv) in DMF at 130 °C, using microwave (μW) irradiation for 30 min (Table 1, entry 1). The reaction was monitored by TLC, and upon disappearance of starting material, Cs_2CO_3 (2.5 equiv) was added to the crude mixture. The mixture was next subjected to 30 additional minutes of μW irradiation at 150 °C in order to facilitate the S_NAr reaction and ultimately afford the desired benzo-oxathiadiazecine 1,1-dioxide **6a** in moderate yield (43% over two reactions; 66% avg/reaction).

Table 1. Optimization of Reaction Conditions



entry[c]	conc (i−ii M)	time (i, ii min)	yield[a] (%)
1	0.3	30, 30	43[b]
2	0.3	30, 40	50[b]
3	0.3−0.1	30, 40	58[b]
4	0.3−0.08	30, 40	66[b]
5	0.3−0.05	30, 40	34[b,d]

[a]Final isolated yield over two reactions after flash chromatography. [b]Aziridine opening: **1** (1.0 equiv) and **2** (1.05−1.3 equiv) in DMF at 130 °C. S_NAr: Cs_2CO_3 (2.5 equiv) in DMF at 150 °C. [c]Reactions were monitored by TLC. [d]Reaction was run only once at 0.05.

With this result in hand, optimization of reaction conditions was carried out. Notably, it was found that solvent concentrations, reaction time, and temperature were key factors since the aziridine ring opening and S_NAr reactions are inter- and intramolecular pathways, respectively (Table 1 and Scheme 2). In particular, increased reaction time and temperature were found to effect reaction decomposition. It should also be noted that the first reaction (intermolecular aziridine ring opening) was carried out under relatively high concentrations, while the subsequent intramolecular S_NAr reaction requires dilute concentrations (Table 1, entries 3−5). Furthermore, it should also be noted that while aziridine ring opening proceeds at room temperature, the reaction took 5 days in order to go to completion, while utilization of μW irradiation allowed for completion of reaction in 30 min. Efforts to improve this reaction by screening other bases, for instance, CsF, K_2CO_3, K_3PO_4, DBU, and NaH, revealed that Cs_2CO_3 was optimal (see the Supporting Information for more data). After thorough investigation, the optimized conditions for this one-pot, sequential aziridine ring opening−S_NAr protocol was achieved, whereby arylsulfonyl aziridine **4a** and amino alcohol **5a** were subjected to μW irradiation in DMF at 130 °C for 30 min and 150 °C for 40 min, respectively. This led to 10-membered sultam **6a** in good yield (66% over two reactions; 81% avg/reaction) (Table 1, entry 4). The structure of sultam **6a** was confirmed by X-ray crystallographic analysis (Figure 4). This set of optimized conditions was also utilized for the synthesis of 7-membered benzo-fused sultams, with some substrates having a shorter reaction time for S_NAr cyclization.

With the optimization conditions in hand, the substrate scope studies commenced with the synthesis of medium-sized, fused polycyclic and spirocyclic benzo-fused sultams using several secondary acyclic and cyclic amino alcohols **5a−e** to yield the corresponding products **6a−p** in average to good overall yields (Scheme 2). Notable applications include both (*R*)- and (*S*)-

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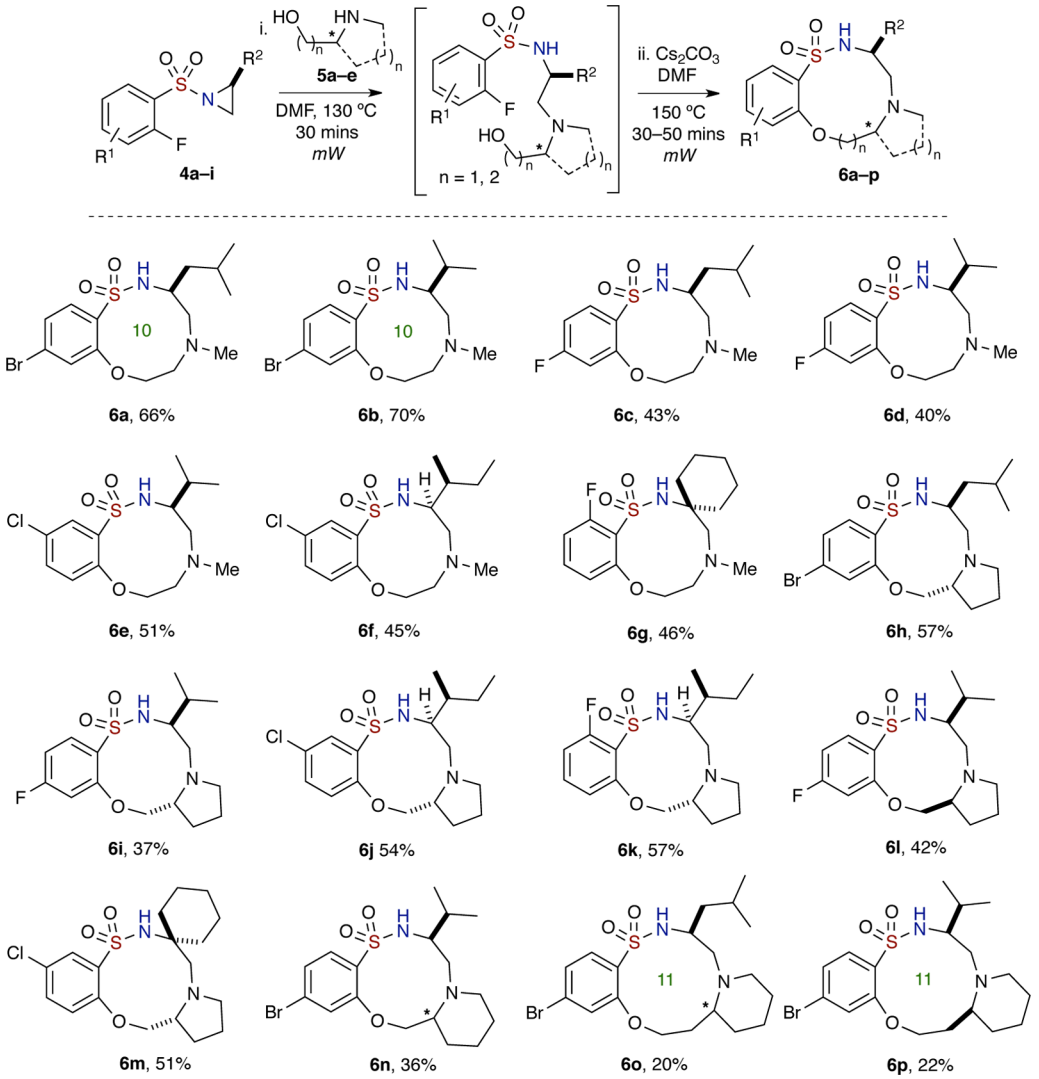
Scheme 2. "6 + 4" and "6 + 5" Cyclization to Bi- and Tricyclic 10- and 11-Membered Sultams



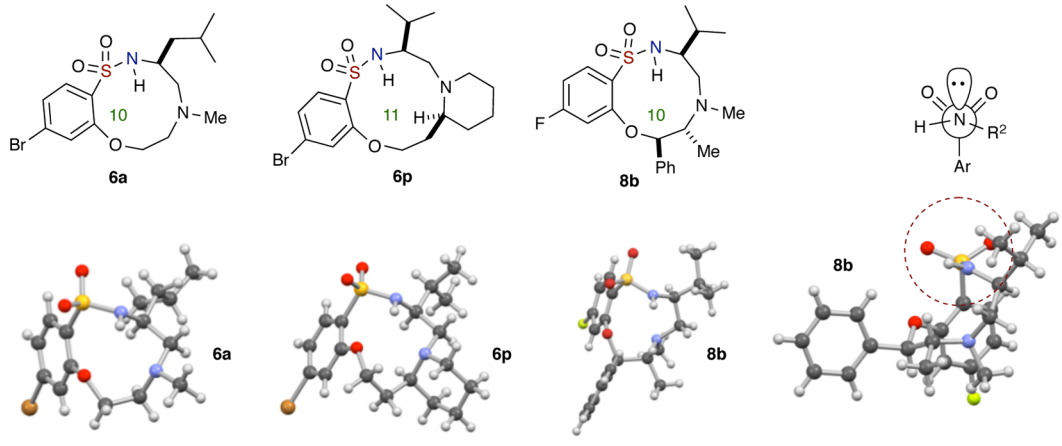


Figure 4. X-ray structures of **6a**, **6p**, and **8b**.

prolinol, racemic 2-piperidinemethanol, and 2-piperidineethanol to afford the 6,10,5-fused, 6,10,6-fused, and 6,11,6-fused tricyclic systems, respectively. During the investigation, it was determined that by increasing the reaction time for some substrates slightly higher yields were obtained. Thus, sultam **6b** was generated in 70% yield over two reactions (84% avg/reaction) when the reaction time for S_NAr reaction was extended to 50 min while maintaining all other reaction conditions (Scheme 2). In addition, two 10-membered benzo-fused sultams **6g** and **6m** were synthesized from sulfonamides derived from spiro-cyclohexyl aziridine in good yields. Finally, it is worth noting that a single diastereomer of the 6,11,6-fused tricyclic

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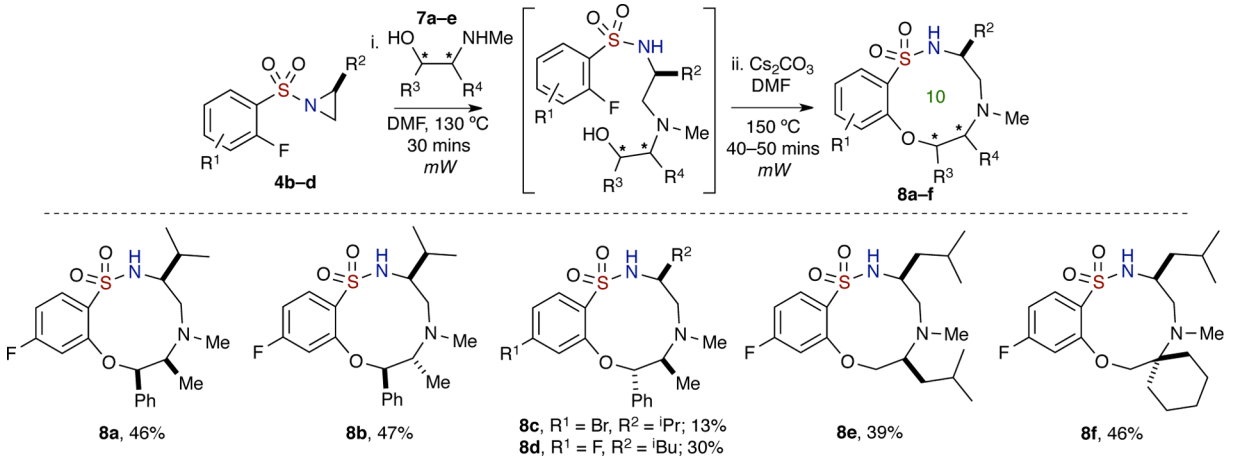
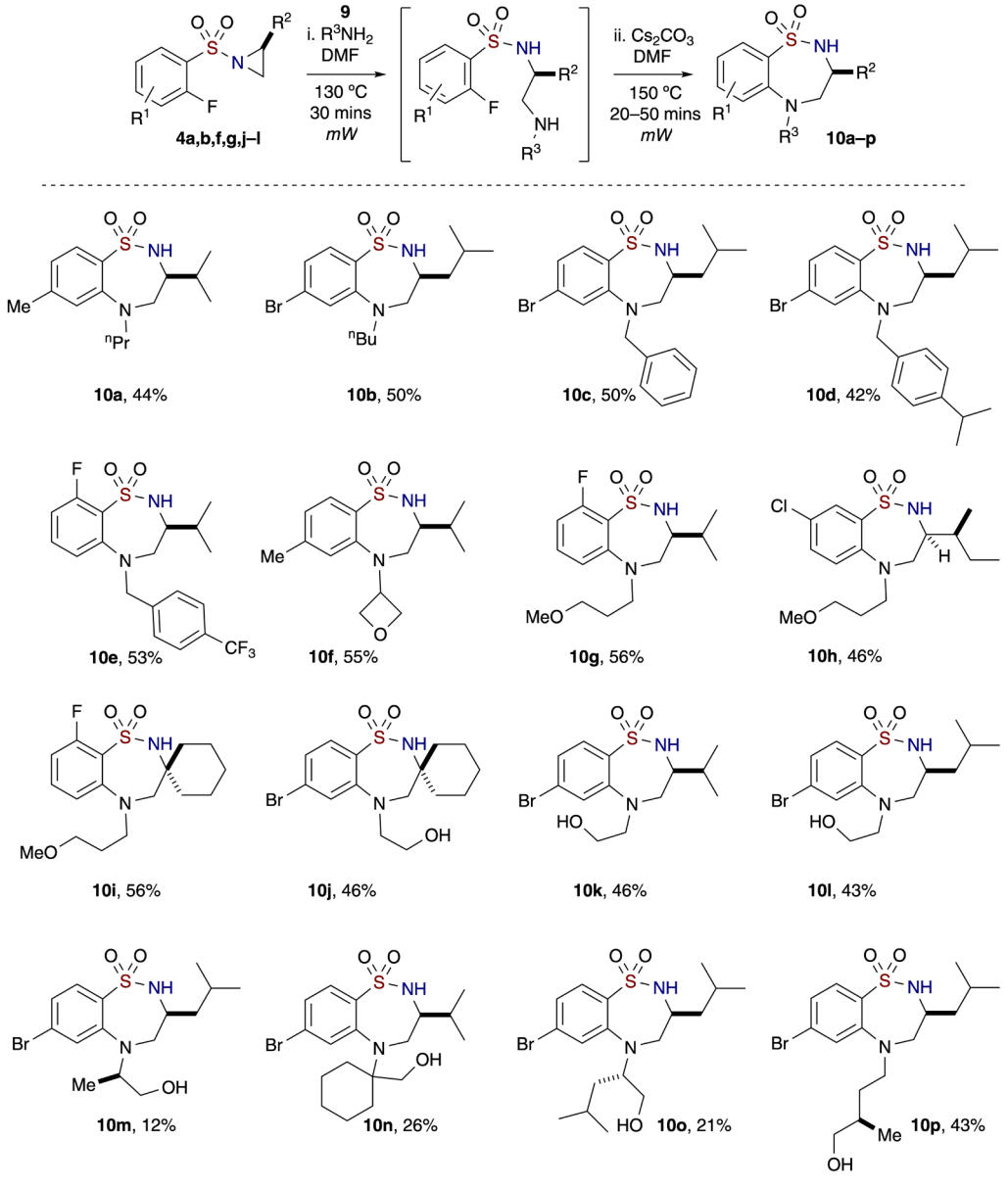
Scheme 3. Spiro- and Stereochemically Rich 10-Membered Sultams



Scheme 4. Substrate Scope of "6 + 1" Cyclization to 7-Membered Sultams



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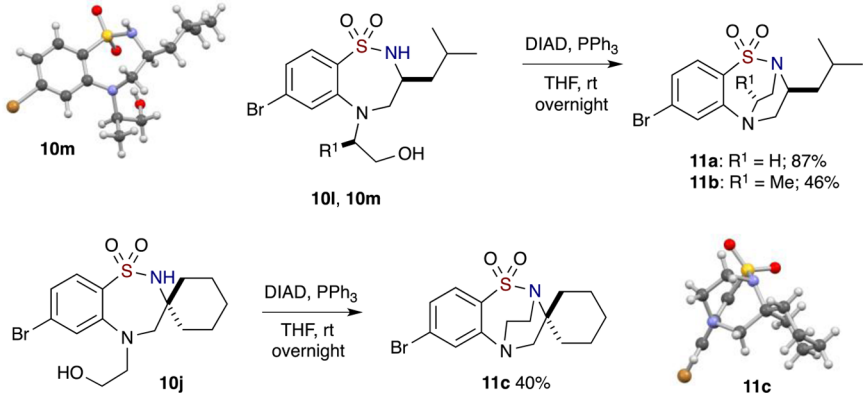
Scheme 5. Utilization of the Mitsunobu Reaction To Access Bridged 7-Membered Sultams



sultam **6p** was synthesized, starting with racemic 2-piperidineethanol, suggesting only one diastereomer intermediate underwent cyclization reaction (or potentially aziridine ring opening). The relative stereochemistry of **6p** was confirmed by X-ray crystallography (Figure 4, vide infra). Similar sultams **6n** and **6o** were also obtained as single diastereomers as observed by NMR.

A proposed plausible mechanism suggests that in all cases the secondary amino group reacts in a chemoselective fashion for the aziridine ring opening reaction, rendering the resulting tertiary amine incapable of executing the cyclization reaction (S_NAr) and thus allowing the unprotected primary or secondary hydroxyl group to cyclize under basic conditions to provide the various benzo-oxathiadiazecine 1,1-dioxides. The resulting products have stereocenters on the core medium-sized rings, which consequently imparts "non-flatland" architecture.[7]

Next, we further investigated the scope of this one-pot, sequential procedure by using chiral, nonracemic, substituted secondary amino alcohols (Scheme 3). Commercially available derivatives of ephedrine, **7a**–**e**, were subjected to the "Click" aziridine ring opening–S_NAr reaction conditions, and to our delight, the secondary alcohols proceeded smoothly to afford medium-sized sultams (**8a**–**f**) in average to good yields over two reactions, albeit in lower yield for (1*S*,2*S*)-(+)-pseudoephedrine-derived **8c**. Sultam **8b** was confirmed by X-ray crystallography where the respective stereocenters (6*R*,7*R*) correspond to the structure as shown in Figure 4. In addition, in all cases studied, both primary and branched secondary hydroxyl groups were able to undergo S_NAr cyclization to yield their respective sultams. Also, use of *N*-(methylamino) cyclohexyl methanol in the aforementioned method furnished the spiro-benzo-oxathiadiazecine-cyclohexane 1,1-dioxide **8f** in 46% yield over two reactions (68% avg/reaction) (Scheme 3).

It is worth noting that the preferred conformations of these constrained structures are governed by stereoelectronic effects innate to sulfonamides, which place the nitrogen lone pair antiperiplanar to the S–Ar bond to maximize the σ^* orbital delocalization and also bisect the O═S═O internuclear angle.[39] The bisection of the O═S═O internuclear angle by the nitrogen lone pair has been confirmed in all X-ray crystallographic structures taken in this study (Figure 4). The consequence of this stereoelectronic effect/preferred rotomer of the Ar-SO2NR^{1}R^2 moiety is that it renders the core macrocyclic in a unique conformation, whereby the N–H bond points to the inner core of the macrocycle (see the circled highlighted area in **8b** of Figure 4).[40]

With the aforementioned results in hand, the one-pot, sequential strategy was extended to several primary amines **9**, whereby their ability to have dual reactivity facilitates access to 7-membered (common-sized) benzo-fused sultams in an overall "6 + 1" atom cyclization sequence involving consecutive aziridine ring opening and S_NAr reaction (Scheme 4). The use of simple alkyl and aromatic amines containing different substituents furnished benzo-thiadiazepine 1,1-dioxides **10a**–**e** in satisfactory yields (44–53% over two reactions, 67–73% avg/reaction). Amines with both cyclic and linear ether moieties were also employed successfully to provide 7-membered benzo-fused sultams **10f**–**i** in moderate yields (46–56% over two reactions, 68–75% avg/reactions) (Scheme 4). The primary amines proceeded with aziridine ring opening, and the secondary amines generated from the first reaction were then cyclized to form cyclic sulfonamides.

Similarly, common-sized benzo-fused sultams **10j**–**p** consisting of amines having hydroxyl motifs were generated with different (*o*-fluoroaryl)sulfonyl aziridines (cyclohexyl, ^{i}Pr, and ^{i}Bu) in albeit slightly lower yields (12–56% over two reactions, 35–75% avg/reaction). On the basis of the results, when primary amines with unprotected hydroxyl groups are used as the nucleophile, the resulting secondary amines from the aziridine ring opening reaction chemoselectively proceed to S_NAr cyclization in preference to the free hydroxyl groups. A high degree of chemoselectivity was observed in the majority of cases, although in some cases formation of an unidentified side product during the S_NAr reaction and some final product decomposition were seen.

A notable feature of these 7-membered sultams possessing a free N–H is their ability to undergo an additional facile Mitsunobu reaction to synthesize bridged [3.2.2] bicyclic benzo-fused sultams. Hence, sultam **10l** was treated with Ph_3P and DIAD in THF at room temperature, stirred overnight, and upon completion, provided ethanobenzothiadiazepine 1,1-dioxide **11a** in 87% yield (Scheme 5). The structure of sultam **10m** was confirmed by X-ray crystallography and shown to display an optimal positioning of the hydroxyl group in order to participate in facile intramolecular Mitsunobu alkylation to afford sultam **11b** bearing a two-carbon bridgehead. Further demonstration of the intramolecular Mitsunobu reaction was realized in the production of the spiro-cyclohexyl-containing [3.2.2] bridged benzo-fused sultam **11c**, albeit in a lower yield of 40%. The structure of **11c** was confirmed by X-ray crystallography (Scheme 5). Sultam **10o**, on the other hand, was unsuccessful in yielding the two-carbon bridged sultam after several attempts using similar reaction conditions. The recovery of starting material and several side products present in Mitsunobu

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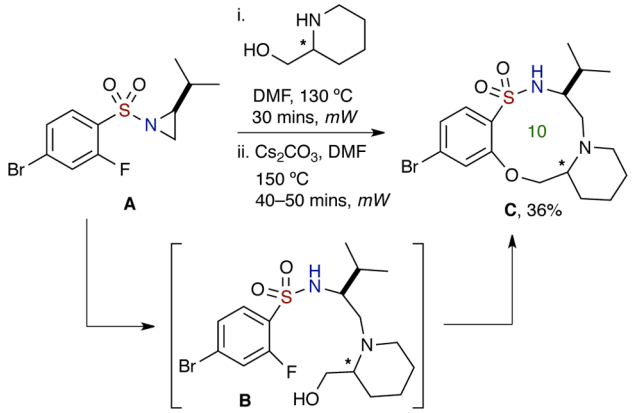
reactions as well as excess reagents that were used in the reaction were collected.

A key finding during the studies was the isolation of the intermediate, aziridine ring opened product, which was observable on ^{19}F NMR (Scheme 6). A major difference between

Scheme 6. ^{19}F NMR Studies: Comparison between Sulfonamide A, Ring-Opened B, and Product C[a]



[a]See the ^{19}F spectra in the Supporting Information.

the intermediate and the final product is the presence of the fluorine atom, and use of ^{19}F NMR provided a convenient way to monitor the progression of the S_NAr reaction. In this experiment, aziridinyl-sulfonamide **A** was chosen and shown to contain a single resonance (triplet) in the ^{19}F NMR spectrum (Figure 1a, Supporting Information). Reaction with racemic 2-piperidine-methanol furnished the ring opened intermediate **B**, which was detected as a single resonance (triplet) in the ^{19}F NMR spectrum (Figure 1b, Supporting Information) but shifted marginally upfield due to the electronic changes within the sulfonamide. After S_NAr reaction, the ^{19}F NMR of the desired product **C** (**6n**) was obtained and showed complete disappearance of the fluorine resonance (Figure 1c, Supporting Information).[41]

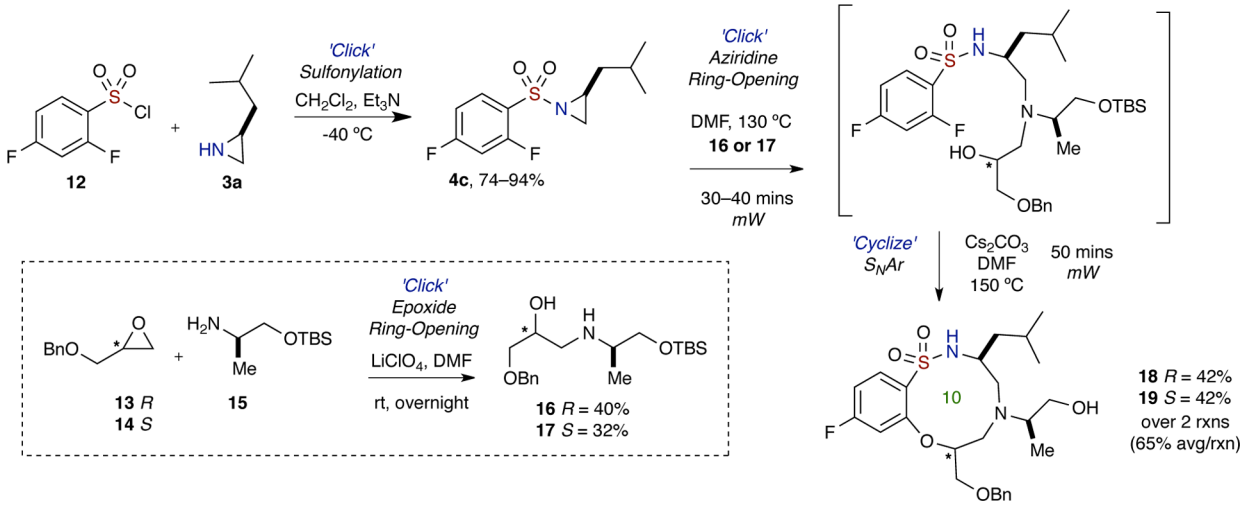
Encouraged by these results, and in an effort to further highlight the efficiency of this modular approach, studies were focused toward the extension of the method using readily available chiral, nonracemic building blocks that were obtained in one step (Scheme 7). Hence, both (*R*)- and (*S*)-benzyl glycidyl ethers were subjected to "Click" epoxide ring opening[30] with TBS-protected D-alaninol to furnish elaborate amino alcohols **16** and **17**. The chiral, nonracemic building blocks were then utilized in the established aziridine ring opening–S_NAr procedure to afford 10-membered sultams **18** and **19** with three stereocenters, along with pendant free hydroxy group, in moderate yields. In this regard, it should be noted that the TBS-ether protecting group was removed during the reaction, presumably by the displaced fluoride anion in the S_NAr reaction, thus representing an overall one-pot, sequential aziridine ring opening–S_NAr–desilylation protocol.

In summary, we have developed a one-pot CP strategy introducing (*o*-fluoroaryl)sulfonyl aziridine building blocks as versatile bis-electrophilic species for reaction with amino alcohols/amines for the preparation of common and medium-sized benzo-fused sultams containing up to three stereocenters. This approach was extended to the utilization of elaborate chiral, nonracemic building blocks as well as cyclic and spirocyclic amino alcohols to afford a diverse array of polycyclic scaffolds. Furthermore, the method is highly modular and adaptable for the preparation of sultam libraries in a one-pot, sequential manner. Work in this regard is underway and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All air- and moisture-sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_2Cl_2 was purified by passage through the purification system employing activated Al_2O_3.[42] Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2. The crude mixture was also purified using an automated flash column chromatography system. Thin-layer chromatography was performed on silica gel plates. Deuterated solvents were purchased from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer as well as a 500 spectrometer operating at 500 MHz and 126 MHz, respectively. High-resolution mass spectrometry (HRMS) spectra were obtained on a TOF-MS operating on ESI. Microwave-assisted reactions were carried out in 1 dram vials utilizing a reaction heating block in an Anton Paar Synthos 3000 synthesizer and also Biotage Initiator both using an external calibrated external infrared

Scheme 7. "Click, Click, Click, Cyclize" to Stereochemically Rich, 10-Membered Sultams



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(IR) sensor. All NMR peak assignments were assigned on the basis of both COSY and HSQC NMR methods.

General Procedure A: Preparation of (*o*-Fluoroaryl)sulfonyl Aziridines. To a round-bottom flask containing a solution of aziridine (2.2 mmol, 2.0 equiv) in dry CH_2Cl_2 (0.5 M) was added Et_3N (2.2 mmol, 2.0 equiv). The reaction mixture was cooled to −40 °C and stirred for 10 min, and sulfonyl chloride (1.1 mmol, 1.0 equiv) was added to the reaction mixture in a dropwise fashion. The reaction was then stirred for 30 min after which conversion of starting material was monitored by TLC. Upon completion of the reaction, the mixture was warmed to rt and quenched with cold water (2.2 mL), and the layers were separated. The organic portion was washed with cold 10% aq HCl, and the resulting layers were separated. This partitioning was then repeated with cold water, cold satd $NaHCO_3$, cold water again, and finally brine. The final organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford the desired aziridinyl sulfonamide.

General Procedure B: One-Pot, Sequential (Aziridine Ring Opening and S_NAr). To a microwave vial containing a solution of sulfonamide (1.0 equiv) in DMF (0.3 M) was added amine/amino alcohol (1.05−1.2 equiv). The reaction vessel was capped and heated in the Biotage Initiator microwave at 130 °C for 30−40 min, after which conversion of starting material was monitored by TLC. To the crude mixture were added DMF (0.08 M) and Cs_2CO_3 (2.5 equiv), and the mixture underwent microwave irradiation again at 150 °C for 30−50 min. Water was added to the crude mixture, which was extracted with EtOAc (4×). The organic layer was separated, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude product, which was purified by an automated flash column chromatography system.

General Procedure C: One-Pot, Sequential (Aziridine Ring Opening and S_NAr). To a microwave vial containing a solution of sulfonamide (1.0 equiv) in DMF (0.3 M) was added amine/amino alcohol (1.05−1.2 equiv). The reaction vessel was capped and heated in a Biotage Initiator microwave at 130 °C for 30−40 min, after which conversion of starting material was monitored by TLC. To the crude mixture was added Cs_2CO_3 (2.5 equiv), and the mixture underwent microwave irradiation again at 150 °C for 30−50 min. Water was added to the crude mixture, which was extracted with EtOAc (4×). The organic layer was separated, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude product, which was purified by the automated flash column chromatography system.

General Procedure D: Mitsunobu Reaction. To a flame-dried round-bottom flask containing a solution of sultam (0.047 mmol, 1.0 equiv) in dry THF (0.05 M) was added triphenylphosphine (0.140 mmol, 3.0 equiv). The reaction mixture was stirred for 10 min, and diisopropyl azodicarboxylate (0.12 mmol, 2.5 equiv) was added to the mixture in a dropwise fashion. The reaction was then stirred overnight at rt, and conversion of starting material was monitored by TLC. The solvent was removed in vacuo to yield a yellow oil and was purified by an automated flash column chromatography system.

*(S)-1-((4-Bromo-2-fluorophenyl)sulfonyl)-2-isopropylaziridine (**4b**).* According to general procedure A from 2-fluoro-4-bromosulfonyl chloride (1 g), **4b** (854.4 mg, 72%) was isolated as a yellow oil: R_f = 0.60 (1:3 EtOAc/hexane); $[\alpha]_D^{20}$ = −47.6 (*c* = 0.675, $CHCl_3$); FTIR (thin film) 3094, 2962, 1589, 1472, 1398, 1333, 1167, 879, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.88−7.76 (m, 1H, aromatic), 7.53−7.41 (m, 2H, aromatic), 2.80 (dd, *J* = 7.1, 1.1 Hz, 1H, NCH_aH_bCH), 2.72 (ddd, *J* = 7.3, 7.2, 4.8 Hz, 1H, NC*H*CH), 2.24 (d, *J* = 4.8 Hz, 1H, NCH$_aH_b$CH), 1.59−1.39 (m, 1H, CH_3CHCH_3), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 0.91 (d, *J* = 6.7 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 159.1 (d, $^1J_{C-F}$ = 262.2 Hz), 131.4, 129.4 (d, $^3J_{C-F}$ = 9.0 Hz), 127.9 (d, $^3J_{C-F}$ = 3.8 Hz), 121.0 (d, $^2J_{C-F}$ = 24.5 Hz), 120.5 (d, $^2J_{C-F}$ = 24.2 Hz), 46.6, 33.8, 30.1, 19.5, 18.9; HRMS calcd for $C_{11}H_{13}BrFNO_2SH$ (M + H)$^+$ 321.9913, found 321.9888 (TOF MS ES$^+$).

*(S)-1-((2,4-Difluorophenyl)sulfonyl)-2-isopropylaziridine (**4d**).* According to general procedure A from 2,4-difluorosulfonyl chloride (1 g), **4d** (889.4 mg, 72%) was isolated as a yellow oil: R_f = 0.51 (1:3 EtOAc/hexane); $[\alpha]_D^{20}$ = −5.0 (*c* = 1.43, $CHCl_3$); FTIR (thin film) 3103, 2964, 1603, 1481, 1429, 1335, 1167, 854, 741, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.10−7.85 (m, 1H, aromatic), 7.12−6.88 (m, 2H, aromatic), 2.80 (dd, *J* = 7.1, 1.1 Hz, 1H, NCH_aH_bCH), 2.70 (ddd, *J* = 7.3, 7.2, 4.6 Hz, 1H, NC*H*CH), 2.24 (d, *J* = 3.8 Hz, 1H, NCH$_aH_b$CH), 1.61−1.43 (m, 1H, CH_3CHCH_3), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 0.90 (d, *J* = 6.7 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.3 (dd, *J* = 258.5, 11.4 Hz), 160.4 (dd, *J* = 260.8, 12.8 Hz), 132.4 (dd, *J* = 10.6, 1.6 Hz), 111.9 (dd, *J* = 22.0, 3.8 Hz), 105.8 (dd, *J* = 25.5, 25.4 Hz), 105.4 (dd, *J* = 26.0, 25.9 Hz), 46.5, 33.7, 30.1, 19.4, 18.9; HRMS calcd for $C_{11}H_{13}F_2NO_2SH$ (M + H)$^+$ 262.0713, found 262.0720 (TOF MS ES$^+$).

*(S)-10-Bromo-3-isobutyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo-[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**6a**).* According to the reaction protocol described in general procedure B from **4a** (49.8 mg), compound **6a** (66%, 38.7 mg) was isolated after chromatography as a white solid: mp 192−195 °C; R_f = 0.44 (2:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +167.5 (*c* = 1.02, $CHCl_3$); FTIR (thin film) 3267, 3090, 2966, 1576, 1558, 1462, 1400, 1323, 1165, 1059, 824, 781, 748, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.85 (d, *J* = 8.3 Hz, 1H, aromatic), 7.34−7.28 (m, 2H, aromatic), 7.09 (s, 1H, N*H*), 4.41−4.31 (m, 2H, OCH_2CH_2), 2.73 (dddd, *J* = 9.2, 9.0, 4.7, 4.6 Hz, 1H, NHC*H*CH$_2$N), 2.66 (dd, *J* = 12.6, 4.9 Hz, 1H, NHCHCH_aH_bN), 2.58 (ddd, *J* = 14.8, 10.8, 3.3 Hz, 1H, NCH_aH_bCH$_2$O), 2.46 (s, 3H, NCH_3), 2.34 (ddd, *J* = 15.2, 1.7, 1.6 Hz, 1H, NCH$_aH_b$CH$_2$O), 2.24 (dd, *J* = 12.6, 10.5 Hz, 1H, NHCHCH$_aH_b$N), 1.85 (ddd, *J* = 13.7, 9.4, 4.2 Hz, 1H, NHCHCH_aH_b), 1.62−1.49 (m, 1H, CH_3CHCH_3), 1.33 (ddd, *J* = 13.8, 8.8, 5.0 Hz, 1H, NHCHCH$_aH_b$), 0.86 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.73 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 155.1, 132.8, 129.3, 128.4, 125.7, 120.6, 69.7, 60.0, 53.2, 49.8, 44.3, 43.1, 24.4, 23.6, 21.9; HRMS calcd for $C_{15}H_{23}BrN_2O_3SH$ (M + H)$^+$ 391.0691, found 391.0670 (TOF MS ES$^+$).

*(S)-10-Bromo-3-isopropyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo-[b][1,4,5,8]oxathiadiazecine-1,1-Dioxide (**6b**).* According to the reaction protocol described in general procedure B from **4b** (50.0 mg), compound **6b** (70%, 41.0 mg) was isolated after chromatography as a white solid: mp 175−180 °C; R_f = 0.45 (2:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +170.4 (*c* = 0.545, $CHCl_3$); FTIR (thin film) 3263, 3099, 2968, 1578, 1560, 1452, 1371, 1323, 1163 1057, 820, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (d, *J* = 8.4 Hz, 1H, aromatic), 7.36−7.29 (m, 2H, aromatic), 7.05 (s, 1H, N*H*), 4.43−4.27 (m, 2H, OCH_2CH_2), 2.68 (ddd, *J* = 11.2, 4.6, 4.5 Hz, 1H, NHC*H*CH$_2$N), 2.60 (ddd, *J* = 14.5, 10.6, 3.5 Hz, 1H, NHCHCH_aH_bN), 2.49 (dd, *J* = 12.7, 5.1 Hz, 1H, NCH_aH_bCH$_2$O), 2.46 (s, 3H, NCH_3), 2.38−2.23 (m, 3H, NHCHCH$_aH_b$N, NCH$_aH_b$CH$_2$O, CH_3CHCH_3), 0.98 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3), 0.79 (d, *J* = 7.3 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 155.2, 132.9, 129.2, 128.3, 125.7, 120.7, 69.7, 55.6, 53.7, 53.1, 44.3, 28.9, 18.3, 15.6; HRMS calcd for $C_{14}H_{21}BrN_2O_3SH$ (M + H)$^+$ 377.0535, found 377.0495 (TOF MS ES$^+$).

*(S)-10-Fluoro-3-isobutyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo-[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**6c**).* According to the reaction protocol described in general procedure C from **4c** (52.0 mg), compound **6c** (43%, 26.8 mg) was isolated after chromatography as a white solid: mp 145−148 °C; R_f = 0.33 (2:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +148.7 (*c* = 0.87, $CHCl_3$); FTIR (thin film) 3265, 2962, 1603, 1587, 1458, 1350, 1323, 1163, 1057, 818, 785, 733, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (dd, *J* = 8.6, 6.4 Hz, 1H, aromatic), 7.07 (s, 1H, N*H*), 6.92−6.78 (m, 2H, aromatic), 4.46−4.19 (m, 2H, OCH_2CH_2), 2.70 (dddd, *J* = 9.0, 8.8, 4.6, 4.4 Hz, 1H, NHC*H*CH$_2$N), 2.65 (dd, *J* = 12.4, 4.9 Hz, 1H, NHCHCH_aH_bN), 2.58 (ddd, *J* = 14.9, 8.9, 5.5 Hz, 1H, NCH_aH_bCH$_2$O), 2.46 (s, 3H, NCH_3), 2.34 (ddd, *J* = 15.1, 1.8, 1.7 Hz, 1H, NCH$_aH_b$CH$_2$O), 2.23 (dd, *J* = 12.4, 10.5 Hz, 1H, NHCHCH$_aH_b$N), 1.85 (ddd, *J* = 13.7, 9.5, 3.9 Hz, 1H, NHCHCH_aH_b), 1.61−1.52 (m, 1H, CH_3CHCH_3), 1.33 (ddd, *J* = 13.8, 8.6, 5.0 Hz, 1H, NHCHCH$_aH_b$), 0.86 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.72 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.3 (d, $^1J_{C-F}$ = 254.8 Hz), 156.3 (d, $^3J_{C-F}$ = 10.5 Hz), 133.7 (d, $^3J_{C-F}$ = 10.8 Hz), 126.2 (d, $^4J_{C-F}$ = 3.2 Hz), 109.7 (d, $^2J_{C-F}$ = 22.1 Hz), 104.9 (d, $^2J_{C-F}$ = 25.0 Hz), 69.7, 60.0, 53.2, 49.9, 44.4, 43.1, 24.4, 23.6, 21.8; HRMS calcd

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for $C_{15}H_{23}FN_2O_3SH$ $(M + H)^+$ 331.1492, found 331.1519 (TOF MS ES^+).

*(S)-10-Fluoro-3-isopropyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo-[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**6d**).* According to the reaction protocol described in general procedure C from **4d** (94.2 mg), compound **6d** (40%, 44.6 mg) was isolated after chromatography as a white solid: mp 183−188 °C; R_f = 0.30 (2:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +128.8 (c = 0.745, $CHCl_3$); FTIR (thin film) 3257, 2974, 1603, 1587, 1470, 1448, 1373, 1323, 1163, 1067, 818, 777, 756, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (dd, J = 8.6, 6.4 Hz, 1H, aromatic), 7.04 (s, 1H, N*H*), 6.93−6.73 (m, 2H, aromatic), 4.43−4.25 (m, 2H, OCH_2CH_2), 2.71−2.56 (m, 2H, $NHCHCH_2N$, $NHCHCH_aH_bN$), 2.50 (dd, J = 12.8, 5.0 Hz, 1H, $NCH_aH_bCH_2O$), 2.47 (s, 3H, NCH_3), 2.37−2.29 (m, 3H, $NHCHCH_aH_bN$, $NCH_aH_bCH_2O$, CH_3CHCH_3), 0.99 (d, J = 6.9 Hz, 3H, CH_3CHCH_3), 0.80 (d, J = 7.2 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.3 (d, $^1J_{C-F}$ = 254.7 Hz), 156.4 (d, $^3J_{C-F}$ = 10.6 Hz), 133.7 (d, $^3J_{C-F}$ = 10.8 Hz), 126.2 (d, $^4J_{C-F}$ = 3.4 Hz), 109.7 (d, $^2J_{C-F}$ = 22.1 Hz), 105.1 (d, $^2J_{C-F}$ = 25.0 Hz), 69.7, 55.7, 53.8, 53.1, 44.4, 28.9, 18.4, 15.6; HRMS calcd for $C_{14}H_{21}FN_2O_3SH$ $(M + H)^+$ 317.1335, found 317.1320 (TOF MS ES^+).

*(S)-11-Chloro-3-isopropyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo-[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**6e**).* According to the reaction protocol described in general procedure B from **4e** (75.0 mg), compound **6e** (51%, 45.8 mg) was isolated after chromatography as a yellow oil: R_f = 0.32 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +89.0 (c = 0.125, $CHCl_3$); FTIR (neat) 3149, 2962, 1587, 1469, 1371, 1307, 1222, 1161, 1107, 1060, 835, 821, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.95 (d, J = 2.7 Hz, 1H, aromatic), 7.50 (dd, J = 8.8, 2.7 Hz, 1H, aromatic), 7.14 (s, 1H, N*H*), 7.12 (d, J = 8.9 Hz, 1H, aromatic), 4.39−4.29 (m, 2H, OCH_2CH_2), 2.75−2.69 (m, 1H, $NHCHCH_2N$), 2.56 (ddd, J = 14.5, 10.5, 3.6 Hz, 1H, $NCH_aH_bCH_2O$), 2.48 (dd, J = 12.6, 5.1 Hz, 1H, $NCH_aH_bCH_2O$), 2.45 (s, 3H, NCH_3), 2.38−2.25 (m, 3H, $NHCHCH_aH_b$, $NHCHCH_aH_bN$, CH_3CHCH_3), 0.98 (d, J = 6.9 Hz, 3H, CH_3CHCH_3), 0.81 (d, J = 7.2 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 153.2, 134.1, 131.6, 131.3, 127.5, 118.7, 69.7, 55.4, 53.6, 53.0, 44.2, 28.9, 18.3, 15.5; HRMS calcd for $C_{14}H_{21}ClN_2O_3SH$ $(M + H)^+$ 333.1040, found 333.1022 (TOF MS ES^+).

*(S)-3-((S)-sec-Butyl)-11-chloro-5-methyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**6f**).* According to the reaction protocol described in general procedure B from **4f** (78.7 mg), compound **6f** (45%, 42.1 mg) was isolated after chromatography as a white solid: mp 138−142 °C; R_f = 0.31 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −93.2 (c = 0.125, $CHCl_3$); FTIR (neat) 2962, 1588, 1467, 1371, 1159, 1060, 831, 819, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.95 (d, J = 2.7 Hz, 1H, aromatic), 7.50 (dd, J = 8.8, 2.7 Hz, 1H, aromatic), 7.11 (d, J = 8.8 Hz, 1H, aromatic), 7.05 (s, 1H, N*H*), 4.44−4.24 (m, 2H, OCH_2CH_2), 2.83−2.72 (m, 1H, $NHCHCH_2N$), 2.58 (ddd, J = 14.5, 10.6, 3.5 Hz, 1H, $NCH_aH_bCH_2O$), 2.50 (dd, J = 12.6, 5.1 Hz, 1H, $NCH_aH_bCH_2O$), 2.44 (s, 3H, NCH_3), 2.35−2.25 (m, 2H, $NHCHCH_aH_bN$, $NHCHCH_aH_b$), 2.01−1.92 (m, 1H, $CH_3CHCH_aH_bCH_3$), 1.92−1.82 (m, 1H, $CH_3CHCH_aH_bCH_3$), 1.03−0.95 (m, 1H, $CH_3CHCH_aH_bCH_3$), 0.95−0.90 (m, 3H, $CH_3CHCH_2CH_3$), 0.80 (d, J = 7.1 Hz, 3H, $CH_3CHCH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 153.3, 134.1, 131.6, 131.3, 127.5, 118.6, 69.6, 55.7, 54.6, 52.8, 44.2, 36.0, 23.0, 15.3, 12.4; HRMS calcd for $C_{15}H_{23}ClN_2O_3SH$ $(M + H)^+$ 347.1196, found 347.1200 (TOF MS ES^+).

*12-Fluoro-5-methyl-4,5,6,7-tetrahydro-2H-spiro[benzo[b]-[1,4,5,8]oxathiadiazecine-3,1′-cyclohexane] 1,1-Dioxide (**6g**).* According to the reaction protocol described in general procedure B from **4g** (77.7 mg), compound **6g** (46%, 42.6 mg) was isolated after chromatography as a brownish oil: R_f = 0.35 (1:1 EtOAc/hexane); FTIR (neat) 3245, 2956, 2931, 1591, 1488, 1458, 1319, 1153, 1062, 891, 821, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.47 (ddd, J = 8.2, 8.2, 5.9 Hz, 1H, aromatic), 7.13 (ddd, J = 8.2, 1.1, 1.0 Hz, 1H, aromatic), 6.98 (ddd, J = 10.5, 8.4, 1.1 Hz, 1H, aromatic), 6.55 (s, 1H, N*H*), 5.61−5.56 (m, 1H, $OCH_aH_bCH_2$), 3.79 (dd, J = 5.1, 4.9 Hz, 1H, $OCH_aH_bCH_2$), 3.38 (d, J = 5.8 Hz, 2H, NCH_2CH_2O), 3.25−3.09 (m, 2H, $NHCCH_2N$), 2.82 (s, 3H, NCH_3), 1.99−1.87 (m, 4H, cyclohexyl), 1.70−1.44 (m, 6H, cyclohexyl); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 160.3(d, $^1J_{C-F}$ = 257.2 Hz), 154.5, 133.5 (d, $^3J_{C-F}$ = 11.2 Hz), 123.8 (d, $^3J_{C-F}$ = 10.2 Hz), 119.5 (d, $^4J_{C-F}$ = 3.2 Hz), 113.4 (d, $^2J_{C-F}$ = 24.5 Hz), 59.5, 58.9, 50.1, 42.7, 26.4 (2C), 25.0, 22.4, 22.1 (2C); HRMS calcd for $C_{16}H_{23}FN_2O_3SH$ $(M + H)^+$ 343.1492, found 343.1485 (TOF MS ES^+).

*(6S,14aR)-11-Bromo-6-isobutyl-1,2,3,5,6,7,14,14a-octahydrobenzo[b]pyrrolo[1,2-h][1,4,5,8]oxathiadiazecine 8,8-Dioxide (**6h**).* According to the reaction protocol described in general procedure C from **4a** (81.8 mg), compound **6h** (57%, 57.7 mg) was isolated after chromatography as a colorless oil: R_f = 0.34 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −48.1 (c = 1.805, $CHCl_3$); FTIR (thin film) 3275, 2955, 1578, 1466, 1317, 1159, 1063, 852, 733, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.93−7.71 (m, 1H, aromatic), 7.26−7.18 (m, 2H, aromatic), 5.69 (s, 1H, N*H*), 4.48 (dd, J = 11.5, 3.3 Hz, 1H, OCH_aH_bCHN), 3.90 (dd, J = 11.4, 11.3 Hz, 1H, OCH_aH_bCHN), 3.40−3.26 (m, 1H, $NHCHCH_2N$), 3.17 (ddt, J = 12.0, 8.1, 3.8 Hz, 1H, $NCHCH_2O$), 3.14−3.03 (m, 1H, $NCH_aH_bCH_2CH_2$), 2.50−2.38 (m, 3H, $NHCHCH_2N$, $NCH_aH_bCH_2CH_2$), 2.01−1.90 (m, 1H, $NCH_2CH_2CH_aH_b$), 1.88−1.77 (m, 3H, $NCH_2CH_2CH_2$, CH_3CHCH_3), 1.67 (ddd, J = 14.3, 8.4, 6.2 Hz, 1H, $NHCHCH_aH_b$), 1.40 (td, J = 11.4, 4.6 Hz, 1H, $NCH_2CH_2CH_aH_b$), 1.10 (ddd, J = 14.0, 7.8, 6.2 Hz, 1H, $NHCHCH_aH_b$), 0.90 (dd, J = 6.9, 6.8 Hz, 6H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 156.0, 131.1, 130.8, 128.0, 124.5, 118.2, 74.0, 62.8, 61.4, 56.7, 55.5, 40.9, 27.4, 24.7, 24.7, 22.7, 22.3; HRMS calcd for $C_{17}H_{25}BrN_2O_3SH$ $(M + H)^+$ 417.0848, found 417.0836 (TOF MS ES^+).

*(6S,14aR)-11-Fluoro-6-isopropyl-1,2,3,5,6,7,14,14a-octahydrobenzo[b]pyrrolo[1,2-h][1,4,5,8]oxathiadiazecine 8,8-Dioxide (**6i**).* According to the reaction protocol described in general procedure C from **4d** (54.3 mg), compound **6i** (37%, 26.1 mg) was isolated after chromatography as a semiwhite sticky oil: R_f = 0.28 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −6.6 (c = 1.33, $CHCl_3$); FTIR (thin film) 3300, 2961, 1603, 1587, 1468, 1387, 1323, 1157, 1070, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.99−7.76 (m, 1H, aromatic), 6.82−6.64 (m, 2H, aromatic), 4.84 (d, J = 6.9 Hz, 1H, N*H*), 4.45 (dd, J = 11.6, 3.1 Hz, 1H, OCH_aH_bCHN) 3.99 (dd, J = 11.2, 11.1 Hz, 1H, OCH_aH_bCHN), 3.32 (ddd, J = 11.3, 5.9, 5.7 Hz, 1H, $NHCHCH_2N$), 3.08 (dddd, J = 11.2, 8.7, 5.8, 3.1 Hz, 1H, $NCHCH_2O$), 2.97 (ddd, J = 9.6, 6.2, 4.5 Hz, 1H, $NCH_aH_bCH_2CH_2$), 2.71 (dd, J = 14.4, 5.6 Hz, 1H, $NHCHCH_aH_bN$), 2.56−2.43 (m, 2H, $NCH_aH_bCH_2CH_2$, $NHCHCH_aH_bN$), 2.00−1.85 (m, 2H, CH_3CHCH_3, $NCH_2CH_2CH_aH_b$), 1.79−1.69 (m, 2H, $NCH_2CH_2CH_2$), 1.45−1.31 (m, 1H, $NCH_2CH_2CH_aH_b$), 0.97 (dd, J = 6.9, 4.4 Hz, 6H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.0 (d, $^1J_{C-F}$ = 253.8 Hz), 157.5 (d, $^3J_{C-F}$ = 10.8 Hz), 132.0 (d, $^3J_{C-F}$ = 10.9 Hz), 126.7 (d, $^4J_{C-F}$ = 3.2 Hz), 107.9 (d, $^2J_{C-F}$ = 22.2 Hz), 102.6 (d, $^2J_{C-F}$ = 25.6 Hz), 74.0, 64.9, 62.8, 59.4, 57.5, 31.3, 27.2, 23.8, 18.7, 18.2; HRMS calcd for $C_{16}H_{23}FN_2O_3SH$ $(M + H)^+$ 343.1492, found 343.1492 (TOF MS ES^+).

*(6S,14aR)-6-((S)-sec-Butyl)-10-chloro-1,2,3,5,6,7,14,14a-octahydrobenzo[b]pyrrolo[1,2-h][1,4,5,8]oxathiadiazecine 8,8-Dioxide (**6j**).* According to the reaction protocol described in general procedure B from **4f** (78.8 mg), compound **6j** (54%, 54.4 mg) was isolated after chromatography as a yellow oil: R_f = 0.37 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −68.4 (c = 0.125, $CHCl_3$); FTIR (neat) 2962, 2875, 1598, 1467, 1407, 1380, 1338, 1163, 1064, 786, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (d, J = 2.7 Hz, 1H, aromatic), 7.46 (dd, J = 8.8, 2.7 Hz, 1H, aromatic), 7.06 (d, J = 8.8 Hz, 1H, aromatic), 6.85 (d, J = 5.7 Hz, 1H, N*H*), 4.35 (dd, J = 11.8, 3.2 Hz, 1H, OCH_aH_bCHN), 3.90 (t, J = 11.6 Hz, 1H, OCH_aH_bCHN), 3.20−2.95 (m, 2H, $NHCHCH_2N$, $NCHCH_2O$), 2.92−2.78 (m, 1H, $NCH_aH_bCH_2CH_2$), 2.63−2.50 (m, 2H, $NHCHCH_aH_bN$, $NCH_aH_bCH_2CH_2$), 2.41 (dd, J = 13.5, 5.1 Hz, 1H, $NHCHCH_aH_bN$), 2.02−1.86 (m, 1H, $NCH_2CH_aH_bCH_2$), 1.86−1.75 (m, 2H, $NCH_2CH_aH_bCH_2$, $NCH_2CH_aH_bCH_aH_b$), 1.76−1.62 (m, 2H, $NCH_2CH_aH_bCH_aH_b$, $CH_3CHCH_aH_bCH_3$), 1.40−1.29 (m, 1H, $CH_3CHCH_aH_bCH_3$), 1.11−0.97 (m, 1H, $CH_3CHCH_aH_bCH_3$), 0.95 (d, J = 6.8 Hz, 3H, $CH_3CHCH_2CH_3$), 0.90 (t, J = 7.3 Hz, 3H, $CH_3CHCH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 153.1, 133.6, 131.6, 130.3, 126.7, 116.4, 73.5, 61.9, 58.0, 57.2, 55.7, 37.0, 27.0, 25.4, 24.2, 15.8, 11.6; HRMS calcd for $C_{17}H_{25}ClN_2O_3SH$ $(M + H)^+$ 373.1353, found 373.1334 (TOF MS ES^+).

*(6S,14aR)-6-((S)-sec-Butyl)-9-fluoro-1,2,3,5,6,7,14,14a-octahydrobenzo[b]pyrrolo[1,2-h][1,4,5,8]oxathiadiazecine 8,8-Dioxide (**6k**).* According to the reaction protocol described in general

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procedure B from **4h** (74.4 mg), compound **6k** (57%, 54.9 mg) was isolated after chromatography as a yellowish white solid: mp 152−156 °C; R_f = 0.41 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −58.3 (*c* = 0.125, $CHCl_3$); FTIR (neat) 2962, 2875, 1598, 1467, 1380, 1338, 1163, 1064, 786, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 (ddd, *J* = 8.4, 5.8 Hz, 1H, aromatic), 7.07 (d, *J* = 6.2 Hz, 1H, N*H*), 6.89 (ddd, *J* = 8.5, 1.1, 1.1 Hz, 1H, aromatic), 6.82 (ddd, *J* = 9.6, 8.4, 1.0 Hz, 1H, aromatic), 4.42 (dd, *J* = 11.8, 3.2 Hz, 1H, OCH_aH_bCHN), 3.92 (dd, *J* = 11.5, 11.2 Hz, 1H, OCH_aH_bCHN), 3.19−3.04 (m, 2H, $NHCHCH_2N$, $NCHCH_2O$), 3.03−2.93 (m, 1H, $NCH_aH_bCH_2CH_2$), 2.64 (dd, *J* = 13.8, 5.4 Hz, 1H, $NHCHCH_aH_bN$), 2.57 (ddd, *J* = 9.3, 9.2, 6.1 Hz, 1H, $NCH_aH_bCH_2CH_2$), 2.46 (dd, *J* = 13.8, 4.9 Hz, 1H, $NHCHCH_aH_bN$), 1.99−1.88 (m, 1H, $NCH_2CH_aH_bCH_2$), 1.88−1.61 (m, 4H, $NCH_2CH_aH_bCH_2$, $NCH_2CH_aH_bCH_2$, $CH_3CHCH_aH_bCH_3$), 1.38 (dddd, *J* = 13.1, 6.8, 3.6, 3.5 Hz, 1H, $CH_3CHCH_aH_bCH_3$), 1.10−1.00 (m, 1H, $CH_3CHCH_aH_bCH_3$), 0.99 (d, *J* = 6.8 Hz, 3H, $CH_3CHCH_2CH_3$), 0.89 (t, *J* = 7.3 Hz, 3H, $CH_3CHCH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 161.1 (d, $^1J_{C-F}$ = 259.8 Hz), 155.6, 133.5 (d, $^3J_{C-F}$ = 11.0 Hz), 119.2 (d, $^3J_{C-F}$ = 13.1 Hz), 110.6 (d, $^2J_{C-F}$ = 24.2 Hz), 109.9 (d, $^4J_{C-F}$ = 3.6 Hz), 73.5, 62.1, 58.5, 57.6, 55.6, 36.8, 27.1, 25.6, 24.3, 15.9, 11.5; HRMS calcd for $C_{17}H_{25}FN_2O_3SH$ $(M + H)^+$ 357.1648, found 357.1635 (TOF MS ES^+).

*(6S,14aS)-11-Fluoro-6-isopropyl-1,2,3,5,6,7,14,14a-octahydrobenzo[b]pyrrolo[1,2-h][1,4,5,8]oxathiadiazecine 8,8-Dioxide (**6l**).* According to the reaction protocol described in general procedure B from **4d** (47.0 mg), compound **6l** (42%, 25.7 mg) was isolated after chromatography as a colorless oil: R_f = 0.1 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +74.4 (*c* = 0.36, $CHCl_3$); FTIR (thin film) 3286, 2962, 1603, 1587, 1475, 1383, 1329, 1163, 1070, 847, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.94 (dd, *J* = 8.6, 6.5 Hz, 1H, aromatic), 6.92−6.76 (m, 3H, aromatic, N*H*), 4.33 (dd, *J* = 11.9, 3.3 Hz, 1H, OCH_aH_bCHN), 3.92 (dd, *J* = 11.8, 11.7 Hz, 1H, OCH_aH_bCHN), 3.16 (ddd, *J* = 10.2, 5.5, 4.8 Hz, 1H, $NHCHCH_2N$), 3.06 (ddt, *J* = 11.9, 8.6, 3.1 Hz, 1H, $NCHCH_2O$), 2.71 (dt, *J* = 11.9, 5.9 Hz, 1H, $NCH_aH_bCH_2CH_2$), 2.64−2.50 (m, 2H, $NCH_aH_bCH_2CH_2$, $NHCHCH_aH_bN$), 2.37 (dd, *J* = 13.5, 5.0 Hz, 1H, $NHCHCH_aH_bN$), 2.02−1.89 (m, 2H, CH_3CHCH_3, $NCH_2CH_2CH_aH_b$), 1.87−1.78 (m, 2H, $NCH_2CH_2CH_2$), 1.36 (ddt, *J* = 12.6, 6.6, 3.4 Hz, 1H, $NCH_2CH_2CH_aH_b$), 0.95 (dd, *J* = 17.2, 6.8 Hz, 6H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.0 (d, $^1J_{C-F}$ = 254.3 Hz), 156.2 (d, $^3J_{C-F}$ = 10.5 Hz), 132.5 (d, $^3J_{C-F}$ = 10.8 Hz), 126.4 (d, $^4J_{C-F}$ = 3.3 Hz), 108.8 (d, $^2J_{C-F}$ = 22.2 Hz), 103.1 (d, $^2J_{C-F}$ = 25.4 Hz), 73.7, 62.0, 59.1, 57.3, 55.2, 30.5, 27.0, 25.6, 19.6, 17.5; HRMS calcd for $C_{16}H_{23}FN_2O_3SH$ $(M + H)^+$ 343.1492, found 343.1459 (TOF MS ES^+).

*(R)-10-Chloro-2,3,5,7,14,14a-hexahydro-1H-spiro[benzo[b]pyrrolo[1,2-h][1,4,5,8]oxathiadiazecine-6,1′-cyclohexane] 8,8-Dioxide (**6m**).* According to the reaction protocol described in general procedure B from **4i** (82.0 mg), compound **6m** (51%, 53.0 mg) was isolated after chromatography as a white solid: mp 154−159 °C; R_f = 0.37 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −24.0 (*c* = 0.125, $CHCl_3$); FTIR (neat) 2937, 1585, 1465, 1315, 1228, 1157, 1064, 819, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.92 (d, *J* = 2.7 Hz, 1H, aromatic), 7.45 (dd, *J* = 8.8, 2.7 Hz, 1H, aromatic), 7.05 (d, *J* = 8.8 Hz, 1H, aromatic), 6.30 (s, 1H, N*H*), 4.46 (dd, *J* = 11.9, 3.2 Hz, 1H, OCH_aH_bCHN), 3.93 (dd, *J* = 11.8, 11.5 Hz, 1H, OCH_aH_bCHN), 3.24−3.18 (m, 1H, $NCHCH_2O$), 3.13 (dddd, *J* = 12.2, 9.3, 3.4, 3.3 Hz, 1H, $NCH_aH_bCH_2CH_2$), 2.50−2.37 (m, 2H, $NHCCH_aH_bN$, $NCH_aH_bCH_2CH_2$), 2.17 (d, *J* = 14.1 Hz, 1H, $NHCCH_aH_bN$), 2.03−1.86 (m, 2H, $NCH_2CH_aH_bCH_aH_b$, $NCH_2CH_2CH_aH_b$), 1.84−1.76 (m, 2H, $NCH_2CH_aH_bCH_aH_b$, $NCH_2CH_2CH_aH_b$), 1.75−1.63 (m, 2H, cyclohexyl), 1.58−1.50 (m, 1H, cyclohexyl), 1.50−1.41 (m, 1H, cyclohexyl), 1.41−1.20 (m, 5H, cyclohexyl), 1.14−1.04 (m, 1H, cyclohexyl); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 153.0, 133.6, 133.3, 129.6, 126.5, 116.3, 73.6, 63.7, 60.3, 59.6, 38.4, 31.3, 27.3, 26.1, 25.4, 21.6, 21.4 (2C); HRMS calcd for $C_{18}H_{25}ClN_2O_3SH$ $(M + H)^+$ 385.1353, found 385.1336 (TOF MS ES^+).

*(7S)-2-Bromo-7-isopropyl-7,8,10,11,12,13,13a,14-octahydro-6H-benzo[b]pyrido[1,2-h][1,4,5,8]oxathiadiazecine 5,5-Dioxide (**6n**).* According to the reaction protocol described in general procedure C from **4b** (95.6 mg), compound **6n** (36%, 44.7 mg) was isolated after chromatography as a sticky colorless oil: R_f = 0.52 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +30.1 (*c* = 0.59, $CHCl_3$); FTIR (thin film) 3259, 2934, 1578, 1464, 1391, 1327, 1159, 1063, 812, 762, 733, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (d, *J* = 8.3 Hz, 1H, aromatic), 7.29 (d, *J* = 1.8 Hz, 1H, aromatic), 7.20 (d, *J* = 1.8 Hz, 1H, aromatic), 4.39 (dd, *J* = 10.7, 4.6 Hz, 1H, OCH_aH_bCHN), 3.75−3.60 (m, 1H, OCH_aH_bCHN), 3.42−3.25 (m, 1H, $NCHCH_2O$), 2.79−2.60 (m, 4H, $NCH_2CH_2CH_2CH_2$, $NHCHCH_2N$, $NHCHCH_aH_bN$), 2.49−2.31 (m, 1H, $NHCHCH_aH_bN$), 1.99−1.86 (m, 1H, CH_3CHCH_3), 1.87−1.77 (m, 1H, $NCH_2CH_2CH_aH_bCH_2$), 1.59−1.36 (m, 4H, $NCH_2CH_2CH_aH_bCH_aH_b$), 1.30−1.16 (m, 1H, $NCH_2CH_2CH_2CH_aH_b$), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 0.89 (d, *J* = 7.0 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 156.5, 131.9, 127.7, 127.7, 125.7, 120.3, 73.7, 59.4, 57.4 (2C), 54.2, 31.2, 23.8, 22.9, 21.6, 18.3, 17.2; HRMS calcd for $C_{17}H_{25}BrN_2O_3SH$ $(M + H)^+$ 417.0848, found 417.0838 (TOF MS ES^+).

*(7S)-2-Bromo-7-isobutyl-6,7,8,10,11,12,13,13a,14,15-decahydrobenzo[b]pyrido[1,2-h][1,4,5,8]-oxathiadiazacycloundecine 5,5-Dioxide (**6o**).* According to the reaction protocol described in general procedure C from **4a** (53.6 mg), compound **6o** (20%, 14.5 mg) was isolated after chromatography as a light yellow oil: R_f = 0.20 (2:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +132.4 (*c* = 0.69, $CHCl_3$); FTIR (thin film) 3202, 2935, 1580, 1470, 1389, 1325, 1163, 1065, 812, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.82 (d, *J* = 8.3 Hz, 1H, aromatic), 7.21 (dd, *J* = 8.3, 1.7 Hz, 1H, aromatic), 7.13 (d, *J* = 1.7 Hz, 1H, aromatic), 6.68 (s, 1H, N*H*), 4.56 (ddd, *J* = 11.9, 9.9, 4.4 Hz, 1H, $OCH_aH_bCH_2CHN$), 4.43 (ddd, *J* = 11.9, 4.7, 4.6 Hz, 1H, $OCH_aH_bCH_2CHN$), 3.20−2.99 (m, 2H, $NHCHCH_aH_bN$, $NCH_aH_bCH_2CH_2CH_2$), 2.81 (ddd, *J* = 12.8, 8.9, 4.3 Hz, 1H, $NHCHCH_2N$), 2.50 (dt, *J* = 14.1, 3.9 Hz, 1H, $NCH_aH_bCH_2CH_2CH_2$), 2.35 (dt, *J* = 12.9, 4.4 Hz, 1H, $NCHCH_2CH_2O$), 2.15−2.05 (m, 2H, $NHCHCH_aH_bN$, $NCHCH_aH_bCH_2O$), 2.01 (dt, *J* = 15.1, 5.0 Hz, 1H, $NCHCH_aH_bCH_2O$), 1.94 (ddd, *J* = 13.6, 9.2, 4.1 Hz, 1H, $NCH_2CH_2CH_aH_bCH_2$), 1.77−1.68 (m, 1H, $NCH_2CH_2CH_2CH_aH_b$), 1.68−1.50 (m, 4H, $NCH_2CH_2CH_2CH_2$, CH_3CHCH_3, $NHCHCH_aH_b$), 1.38−1.28 (m, 2H, $NCH_2CH_2CH_aH_bCH_2$, $NHCHCH_aH_b$), 1.22−1.13 (m, 1H, $NCH_2CH_2CH_2CH_aH_b$), 0.87 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.79 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 154.5, 132.3, 128.1, 126.3, 123.7, 116.2, 65.5, 55.5, 50.5 (2C), 49.0, 43.6, 28.1, 24.7, 23.9, 23.5, 22.0, 21.3, 20.6; HRMS calcd for $C_{19}H_{29}BrN_2O_3SH$ $(M + H)^+$ 445.1161, found 445.1157 (TOF MS ES^+).

*(7S,13aS)-2-Bromo-7-isopropyl-6,7,8,10,11,12,13,13a,14,15-decahydrobenzo[b]pyrido[1,2-h][1,4,5,8]-oxathiadiazacycloundecine 5,5-Dioxide (**6p**).* According to the reaction protocol described in general procedure C from **4b** (78.1 mg), compound **6p** (22%, 23.3 mg) was isolated after chromatography as a white solid: mp 152−157 °C; R_f = 0.21 (2:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +107.4 (*c* = 0.81, $CHCl_3$); FTIR (thin film) 3205, 2934, 1580, 1470, 1387, 1327, 1163, 1065, 821, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.81 (d, *J* = 8.3 Hz, 1H, aromatic), 7.20 (dd, *J* = 8.3, 1.7 Hz, 1H, aromatic), 7.13 (d, *J* = 1.7 Hz, 1H, aromatic), 6.62 (s, 1H, N*H*), 4.54 (ddd, *J* = 11.6, 9.4, 4.4 Hz, 1H, $OCH_aH_bCH_2CHN$), 4.40 (ddd, *J* = 11.6, 5.0, 4.9 Hz, 1H, $OCH_aH_bCH_2CHN$), 3.17−3.03 (m, 1H, $NCH_aH_bCH_2CH_2CH_2$), 2.96 (dd, *J* = 12.9, 4.6 Hz, 1H, $NHCHCH_aH_bN$), 2.73 (ddd, *J* = 10.4, 4.6, 4.4 Hz, 1H, $NHCHCH_2N$), 2.51 (d, *J* = 14.3 Hz, 1H, $NCH_aH_bCH_2CH_2CH_2$), 2.47−2.32 (m, 2H, CH_3CHCH_3, $NCHCH_2CH_2O$), 2.29−2.08 (m, 2H, $NHCHCH_aH_bN$, $NCHCH_aH_bCH_2O$), 1.95 (dddd, *J* = 14.6, 9.3, 5.1, 4.9 Hz, 1H, $NCHCH_aH_bCH_2O$), 1.81−1.67 (m, 1H, $NCH_2CH_2CH_2CH_aH_b$), 1.67−1.45 (m, 3H, $NCH_2CH_aH_bCH_2CH_2$), 1.37−1.20 (m, 1H, $NCH_2CH_aH_bCH_2CH_2$), 1.19−1.09 (m, 1H, $NCH_2CH_2CH_2CH_aH_b$), 0.98 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3), 0.87 (d, *J* = 7.2 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 154.8, 132.4, 128.1, 126.3, 123.7, 116.3, 66.0, 55.1, 50.4, 50.2, 49.4, 29.1, 28.4, 23.6, 21.1, 20.5, 18.9, 15.6; HRMS calcd for $C_{18}H_{27}BrN_2O_3SH$ $(M + H)^+$ 431.1004, found 431.0976 (TOF MS ES^+).

*(3S,6S,7R)-10-Fluoro-3-isopropyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**8a**).* According to the reaction protocol described in general procedure C from **4d** (52.0 mg), compound **8a** (46%, 37.2 mg) was isolated after

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chromatography as a sticky colorless oil: R_f = 0.67 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +43.1 (*c* = 1.145, $CHCl_3$); FTIR (thin film) 3267, 2962, 1603, 1585, 1475, 1454, 1371, 1323, 1163, 1068, 812, 764, 737, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.02 (dd, *J* = 8.8, 6.5 Hz, 1H, aromatic), 7.60−7.54 (m, 2H, aromatic), 7.48 (s, 1H, N*H*), 7.45−7.35 (m, 3H, aromatic), 6.94 (dd, *J* = 10.3, 2.4 Hz, 1H, aromatic), 6.87 (ddd, *J* = 8.7, 7.7, 2.3 Hz, 1H, aromatic), 5.25 (d, *J* = 2.5 Hz, 1H, OC*H*Ph), 2.93 (qd, *J* = 7.1, 2.6 Hz, 1H, NC*H*CH_3), 2.63 (ddd, *J* = 11.3, 4.6, 4.5 Hz, 1H, NHC*H*CH_2N), 2.55 (dd, *J* = 12.9, 5.2 Hz, 1H, NHCHC$H_a$$H_b$N), 2.32 (m, 1H, CH_3C*H*CH_3), 2.11 (dd, *J* = 12.1, 12.0 Hz, 1H, NHCHC$H_a$$H_b$N), 1.51 (s, 3H, N$CH_3$), 1.09 (d, *J* = 7.1 Hz, 3H, NCHCH_3), 0.98 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3), 0.78 (d, *J* = 7.2 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.3 (d, $^1J_{C-F}$ = 254.6 Hz), 155.6 (d, $^3J_{C-F}$ = 10.7 Hz), 135.0, 134.0 (d, $^3J_{C-F}$ = 10.8 Hz), 128.4, 128.3 (2C), 127.1 (2C), 125.1 (d, $^4J_{C-F}$ = 3.4 Hz), 109.5 (d, $^2J_{C-F}$ = 22.0 Hz), 104.3 (d, $^2J_{C-F}$ = 25.2 Hz), 85.3, 56.7, 55.1, 52.9, 38.9, 28.6, 18.3, 15.5, 10.6; HRMS calcd for $C_{21}H_{27}FN_2O_3SH$ (M + H)$^+$ 407.1805, found 407.1790 (TOF MS ES$^+$).

*(3S,6R,7R)-10-Fluoro-3-isopropyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**8b**).* According to the reaction protocol described in general procedure B from **4d** (53.0 mg), compound **8b** (47%, 39.0 mg) was isolated after chromatography as a white solid: mp 87−93 °C; R_f = 0.72 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +12.8 (*c* = 0.69, $CHCl_3$); FTIR (thin film) 3300, 2962, 1603, 1583, 1479, 1456, 1369, 1325, 1157, 1068, 843, 770, 735, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (dd, *J* = 8.8, 6.6 Hz, 1H, aromatic), 7.56−7.45 (m, 2H, aromatic), 7.45−7.32 (m, 3H, aromatic), 6.76 (ddd, *J* = 8.7, 7.7, 2.4 Hz, 1H, aromatic), 6.66 (dd, *J* = 10.6, 2.4 Hz, 1H, aromatic), 6.47 (s, 1H, N*H*), 4.78 (d, *J* = 9.9 Hz, 1H, OC*H*Ph), 3.10 (dq, *J* = 9.8, 6.5 Hz, 1H, NC*H*CH_3), 2.82−2.59 (m, 2H, NHC*H*CH_2N, NHCHC$H_a$$H_b$N), 2.40 (dd, *J* = 13.9, 7.2 Hz, 1H, NHCHC$H_a$$H_b$N), 2.15 (s, 3H, N$CH_3$), 1.98−1.79 (m, 1H, CH_3C*H*CH_3), 0.97 (d, *J* = 6.9 Hz, 6H, CH_3CHCH_3), 0.86 (d, *J* = 6.6 Hz, 3H, NCHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 165.9 (d, $^1J_{C-F}$ = 253.7 Hz), 158.7 (d, $^3J_{C-F}$ = 10.8 Hz), 138.5, 133.0 (d, $^3J_{C-F}$ = 10.7 Hz), 129.0 (2C), 128.8, 127.1 (2C), 124.2 (d, $^4J_{C-F}$ = 3.2 Hz), 108.5 (d, $^2J_{C-F}$ = 22.0 Hz), 104.7 (d, $^2J_{C-F}$ = 25.3 Hz), 88.3, 67.8, 58.4, 52.5, 37.7, 32.1, 19.0, 17.7, 10.6; HRMS calcd for $C_{21}H_{27}FN_2O_3SH$ (M + H)$^+$ 407.1805, found 407.1765 (TOF MS ES$^+$).

*(3S,6S,7S)-10-Bromo-3-isopropyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**8c**).* According to the reaction protocol described in general procedure C from **4b** (52.3 mg), compound **8c** (13%, 9.7 mg) was isolated after chromatography as a colorless oil: R_f = 0.55 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +73.2 (*c* = 0.335, $CHCl_3$); FTIR (thin film) 3285, 2964, 1578, 1468, 1452, 1319, 1155, 1064, 804, 756, 727, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.78 (d, *J* = 8.4 Hz, 1H, aromatic), 7.52−7.47 (m, 2H, aromatic), 7.46−7.40 (m, 2H, aromatic), 7.40−7.33 (m, 1H, aromatic), 7.07 (dd, *J* = 8.4, 1.8 Hz, 1H, aromatic), 6.95 (d, *J* = 1.8 Hz, 1H, aromatic), 4.71 (d, *J* = 9.3 Hz, 1H, OC*H*Ph), 4.41 (s, 1H, N*H*), 4.01 (bs, 1H, NHC*H*CH_2N), 3.19−3.08 (m, 1H, NC*H*CH_3), 2.78 (dd, *J* = 13.3, 2.9 Hz, 1H, NHCHC$H_a$$H_b$N), 2.23 (m, 4H, NHCHC$H_a$$H_bN, NCH_3$), 1.96−1.79 (m, 1H, CH_3C*H*CH_3), 1.09 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3), 0.75 (d, *J* = 7.0 Hz, 3H, NCHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 157.8, 138.5, 131.0, 130.8, 128.9 (2C), 128.6, 127.7, 126.7 (2C), 123.4, 118.8, 87.0, 60.4, 58.8, 58.0, 37.3, 32.3, 19.0, 18.0, 10.4; HRMS calcd for $C_{21}H_{27}BrN_2O_3SH$ (M + H)$^+$ 467.1004, found 467.1004 (TOF MS ES$^+$).

*(3S,6S,7S)-10-Fluoro-3-isobutyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]oxathiadiazecine 1,1-Dioxide (**8d**).* According to the reaction protocol described in general procedure C from **4c** (71.9 mg), compound **8d** (30%, 33.2 mg) was isolated after chromatography as a white solid: mp 165−169 °C; R_f = 0.52 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +20.0 (*c* = 0.145, $CHCl_3$); FTIR (thin film) 3265, 2960, 1602, 1586, 1473, 1451, 1373, 1323, 1163, 1066, 815, 762, 734, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (dd, *J* = 8.8, 6.6 Hz, 1H, aromatic), 7.51−7.31 (m, 5H, aromatic), 6.65 (ddd, *J* = 8.5, 8.3, 2.4 Hz, 1H, aromatic), 6.52 (dd, *J* = 10.4, 2.4 Hz, 1H, aromatic), 4.68 (d, *J* = 9.3 Hz, 1H, OC*H*Ph), 4.40 (d, *J* = 7.3 Hz, 1H, N*H*), 4.18 (bs, 1H, NHC*H*CH_2N), 3.17 (dd, *J* = 8.8, 7.1 Hz, 1H, NC*H*CH_3), 2.79 (dd, *J* = 13.6, 3.4 Hz, 1H, NHCHC$H_a$$H_b$N), 2.26 (s, 3H, N$CH_3$), 2.22−2.14 (m, 1H, NHCHC$H_a$$H_b$N), 1.94 (dt, *J* = 13.3, 6.7 Hz, 1H, CH_3C*H*CH_3), 1.50 (dd, *J* = 14.0, 7.0 Hz, 1H, NHCHC$H_a$$H_b$), 1.32 (ddd, *J* = 13.9, 7.7, 6.0 Hz, 1H, NHCHC$H_a$$H_b$), 1.04 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 1.02 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 0.77 (d, *J* = 7.0 Hz, 3H, NCHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 165.9 (d, $^1J_{C-F}$ = 253.3 Hz), 158.7 (d, $^3J_{C-F}$ = 11.0 Hz), 138.6, 131.6 (d, $^3J_{C-F}$ = 10.9 Hz), 129.0 (2C), 128.6, 127.9 (d, $^4J_{C-F}$ = 3.5 Hz), 126.7 (2C), 107.3 (d, $^2J_{C-F}$ = 22.3 Hz), 103.2 (d, $^2J_{C-F}$ = 25.5 Hz), 86.9, 60.9, 60.7, 52.5, 45.4, 37.2, 24.7, 23.1, 22.8, 10.9; HRMS calcd for $C_{22}H_{29}FN_2O_3SH$ (M + H)$^+$ 421.1956, found 421.1956 (TOF MS ES$^+$).

*(3S,6S)-10-Fluoro-3,6-diisobutyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]oxathiadiazecine-1,1-Dioxide (**8e**).* According to the reaction protocol described in general procedure B from **4c** (49.2 mg), compound **8e** (39%, 26.6 mg) was isolated after chromatography as a white solid: mp 133−137 °C; R_f = 0.66 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +106.8 (*c* = 0.825, $CHCl_3$); FTIR (thin film) 2957, 1601, 1585, 1475, 1387, 1325, 1165, 1068, 849, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.04−7.96 (m, 1H, aromatic), 7.22 (s, 1H, N*H*), 6.89−6.83 (m, 2H, aromatic), 4.22−4.08 (m, 2H, OCH_2CHN), 2.86 (dd, *J* = 13.0, 4.8 Hz, 1H, NHCHC$H_a$$H_b$N), 2.74−2.63 (m, 1H, NHC*H*CH_2N), 2.51 (tdd, *J* = 9.0, 5.3, 3.5 Hz, 1H, NC*H*CH_2), 2.35 (s, 3H, NCH_3), 2.13 (dd, *J* = 13.0, 11.0 Hz, 1H, NHCHC$H_a$$H_b$N), 1.87 (ddd, *J* = 13.7, 9.8, 3.7 Hz, 1H, NHCHC$H_a$$H_b$), 1.64−1.44 (m, 2H, NHCHCH_2C*H*, NCHCH_2C*H*), 1.39−1.20 (m, 2H, NHCHC$H_a$$H_b$, NCHC$H_a$$H_b$), 1.10 (ddd, *J* = 14.2, 8.7, 5.8 Hz, 1H, NCHC$H_a$$H_b$), 0.91 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.85 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.77 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.71 (d, *J* = 6.5 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 166.2 (d, $^1J_{C-F}$ = 254.8 Hz), 156.6 (d, $^3J_{C-F}$ = 10.5 Hz), 133.6 (d, $^3J_{C-F}$ = 10.6 Hz), 126.1 (d, $^4J_{C-F}$ = 3.4 Hz), 109.6 (d, $^2J_{C-F}$ = 22.1 Hz), 104.6 (d, $^2J_{C-F}$ = 25.0 Hz), 71.4, 57.7, 55.0, 49.4, 42.8, 36.1, 34.8, 25.3, 24.4, 23.7, 23.1, 22.0, 21.5; HRMS calcd for $C_{19}H_{31}FN_2O_3SH$ (M + H)$^+$ 387.2118, found 387.2093 (TOF MS ES$^+$).

*(S)-10-Fluoro-3-isobutyl-5-methyl-3,4,5,7-tetrahydro-2H-spiro-[benzo[b][1,4,5,8]oxathiadiazecine-6,1′-cyclohexane] 1,1-Dioxide (**8f**).* According to the reaction protocol described in general procedure B from **4c** (46.2 mg), compound **8f** (46%, 30.9 mg) was isolated after chromatography as a sticky colorless oil: R_f = 0.58 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +8.7 (*c* = 0.695, $CHCl_3$); FTIR (thin film) 2953, 1605, 1589, 1468, 1425, 1391, 1317, 1159, 1070, 847, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.97 (dd, *J* = 8.7, 6.5 Hz, 1H, aromatic), 6.84 (ddd, *J* = 8.8, 7.9, 2.4 Hz, 1H, aromatic), 6.79 (dd, *J* = 9.9, 2.4 Hz, 1H, aromatic), 4.69 (d, *J* = 10.2 Hz, 1H, OC$H_a$$H_b$C), 3.70 (d, *J* = 9.8 Hz, 1H, OC$H_a$$H_b$C), 2.99−2.84 (m, 2H, NHC*H*, NC$H_a$$H_b$), 2.43 (s, 3H, N$CH_3$), 2.25−2.12 (m, 1H, NC$H_a$$H_b$), 1.94−1.66 (m, 8H, NHCHCH_2C*H*, NHCHC$H_a$$H_b$, cyclohexyl), 1.64−1.47 (m, 1H, cyclohexyl), 1.43 (d, *J* = 12.8 Hz, 1H, cyclohexyl), 1.36−1.11 (m, 3H, NHCHC$H_a$$H_b$, cyclohexyl), 0.84 (dd, *J* = 6.6, 6.5 Hz, 6H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 165.9 (d, $^1J_{C-F}$ = 254.3 Hz), 157.7 (d, $^3J_{C-F}$ = 10.6 Hz), 132.5 (d, $^3J_{C-F}$ = 10.7 Hz), 124.8, 109.3 (d, $^2J_{C-F}$ = 22.0 Hz), 104.2 (d, $^2J_{C-F}$ = 24.9 Hz), 73.2, 59.8, 52.5, 49.3, 47.3, 36.8, 30.6, 28.1, 25.5, 24.3, 23.1, 22.8, 22.7, 22.4; HRMS calcd for $C_{20}H_{31}FN_2O_3SH$ (M + H)$^+$ 399.2118, found 399.2126 (TOF MS ES$^+$).

*(S)-3-Isopropyl-7-methyl-5-propyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10a**).* According to the reaction protocol described in general procedure B from **4j** (65.3 mg), compound **10a** (44%, 33.1 mg) was isolated after chromatography as a yellowish oil: R_f = 0.40 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −140.3 (*c* = 0.125, $CHCl_3$); FTIR (neat) 3267, 2927, 1595, 1461, 1325, 1161, 790, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 (d, *J* = 8.1 Hz, 1H, aromatic), 6.84 (s, 1H), 6.81 (ddd, *J* = 8.0, 1.5, 0.7 Hz, 1H), 4.18 (d, *J* = 9.2 Hz, 1H, N*H*CHCH_2N), 3.46 (dd, *J* = 14.8, 2.5 Hz, 1H, NHC*H*CH_2N), 3.41−3.24 (m, 2H, NHCHC$H_a$$H_bN, NCH_a$$H_bCH_2CH_3$), 3.18 (ddd, *J* = 13.1, 7.1, 6.9 Hz, 1H, NC$H_a$$H_bCH_2CH_3$), 3.01 (dd, *J* = 14.9, 9.4 Hz, 1H, NHCHC$H_a$$H_b$N), 2.35 (s, 3H, PhC$H_3$), 2.02−1.85 (m, 1H, CH_3C*H*CH_3), 1.66 (ddddd, *J* = 7.3, 7.3, 7.3, 7.3, 7.3 Hz, 2H, NCH_2CH_2CH_3), 1.04 (dd, *J* = 6.8, 5.0 Hz, 6H, CH_3CHCH_3), 0.99 (t, *J* = 7.3 Hz, 3H, NCH_2CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 148.6, 143.5, 131.1, 128.4, 121.7, 119.8, 61.4,

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56.9, 56.0, 30.3, 21.7, 21.5, 19.6, 19.0, 11.5; HRMS calcd for $C_{15}H_{24}N_2O_2SH$ $(M + H)^+$ 297.1637, found 297.1615 (TOF MS ES^+).

*(S)-7-Bromo-5-butyl-3-isobutyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]-thiadiazepine 1,1-Dioxide (**10b**).* According to the reaction protocol described in general procedure B from **4a** (50.4 mg), compound **10b** (50%, 29.0 mg) was isolated after chromatography as a colorless oil: R_f = 0.48 (1:4 EtOAc/hexane); $[\alpha]_D^{20}$ = −90.2 (*c* = 3.3, $CHCl_3$); FTIR (neat) 3258, 2957, 1578, 1468, 1369, 1319, 1151, 802, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (d, *J* = 8.5 Hz, 1H, aromatic), 7.12 (d, *J* = 1.8 Hz, 1H, aromatic), 7.07 (dd, *J* = 8.5, 1.7 Hz, 1H, aromatic), 4.33 (d, *J* = 8.1 Hz, 1H, N*H*), 3.68−3.55 (m, 1H, NHC*H*CH_2N), 3.51 (dd, *J* = 15.2, 2.9 Hz, 1H, NHCHCH_aH_bN), 3.45−3.34 (m, 1H, NC$H_aH_b$$CH_2CH_2CH_3$), 3.28−3.17 (m, 1H, NC$H_aH_b$$CH_2CH_2CH_3$), 3.05 (dd, *J* = 15.2, 8.3 Hz, 1H, NHCHCH_aH_bN), 1.86 (ddq, *J* = 12.9, 8.3, 6.5 Hz, 1H, CH_3CHCH_3), 1.68−1.57 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.57−1.49 (m, 1H, NHCHCH_aH_bCH), 1.48−1.36 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.29 (ddd, *J* = 13.9, 8.5, 5.5 Hz, 1H, NHCHCH_aH_bCH), 1.01−0.94 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.3, 131.9, 129.7, 127.0, 123.1, 121.4, 58.5, 54.3, 53.9, 40.8, 29.8, 24.6, 23.0, 21.9, 20.1, 13.9; HRMS calcd for $C_{16}H_{25}BrN_2O_2SH$ $(M + 2+H)^+$ 391.0873, found 391.0872 (TOF MS ES^+).

*(S)-5-Benzyl-7-bromo-3-isobutyl-2,3,4,5-tetrahydrobenzo[f]-[1,2,5]thiadiazepine 1,1-Dioxide (**10c**).* According to the reaction protocol described in general procedure C from **4a** (65.4 mg), compound **10c** (50%, 41.1 mg) was isolated after chromatography as a white solid: mp 140−144 °C; R_f = 0.46 (1:3 EtOAc/hexane); $[\alpha]_D^{20}$ = −75.5 (*c* = 0.14, $CHCl_3$); FTIR (thin film) 3275, 2957, 1578, 1458, 1325, 1155, 800, 783, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 (d, *J* = 8.5 Hz, 1H, aromatic), 7.42−7.29 (m, 5H, aromatic), 7.23 (d, *J* = 1.8 Hz, 1H, aromatic), 7.16 (dd, *J* = 8.4, 1.8 Hz, 1H, aromatic), 4.65 (d, *J* = 14.3 Hz, 1H, NCH_aH_bPh), 4.38 (d, *J* = 14.3 Hz, 1H, NCH_aH_bPh), 4.30−4.17 (m, 1H, N*H*), 3.51−3.28 (m, 2H, NHC*H*CH_2N, NHCHCH_aH_bN), 3.01−2.79 (m, 1H, NHCHCH_aH_bN), 1.59−1.48 (m, 1H, CH_3CHCH_3), 1.35 (ddd, *J* = 14.2, 7.4, 7.0 Hz, 1H, NHCHCH_aH_b), 1.09−0.96 (m, 1H, NHCHCH_aH_b), 0.79 (d, *J* = 6.5 Hz, 3H, CH_3CHCH_3), 0.70 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 149.8, 136.7, 129.7, 128.9 (2C), 128.3 (2C), 127.9, 127.4, 127.35 124.2, 122.4, 58.3, 57.8, 53.7, 41.0, 24.5, 22.4, 22.0; HRMS calcd for $C_{19}H_{23}BrN_2O_2SH$ $(M + H)^+$ 423.0742, found 423.0742 (TOF MS ES^+).

*(S)-7-Bromo-3-isobutyl-5-(4-isopropylbenzyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10d**).* According to the reaction protocol described in general procedure C from **4a** (58.0 mg), compound **10d** (42%, 23.5 mg) was isolated after chromatography as a light yellow solid: mp 155−161 °C; R_f = 0.54 (1:3 EtOAc/hexane); $[\alpha]_D^{20}$ = −102.9 (*c* = 0.485, $CHCl_3$); FTIR (thin film) 3258, 2959, 1578, 1468, 1375, 1325, 1155, 843, 798, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.74 (dd, *J* = 8.4, 2.0 Hz, 1H, aromatic), 7.32 (d, *J* = 7.9 Hz, 2H, aromatic), 7.26 (d, *J* = 5.0 Hz, 2H, aromatic), 7.27−7.21 (m, 1H, aromatic), 7.19−7.11 (m, 1H, aromatic), 4.60 (d, *J* = 13.9 Hz, 1H, NCH_aH_bPh), 4.32 (d, *J* = 13.9 Hz, 1H, NCH_aH_bPh), 4.23 (s, 1H, N*H*), 3.41 (dd, *J* = 14.9, 2.4 Hz, 1H, NHC*H*CH_2N), 3.38−3.30 (m, 1H, NHCHCH_aH_bN), 3.03−2.80 (m, 1H, NHCHCH_aH_bN), 1.60−1.46 (m, 1H, CH_3CHCH_3), 1.40−1.26 (m, 1H CC*H*CH_3), 1.25 (d, *J* = 6.9 Hz, 6H, CH_3CHCH_3), 1.06−0.93 (m, 1H, NHCHCH_aH_b), 0.95−0.83 (m, 1H, NHCHCH_aH_b), 0.76 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3), 0.64 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 150.0 (2C), 148.7, 134.0, 129.6, 128.5 (2C), 127.4, 126.9 (2C), 124.0, 122.3, 57.9, 57.5, 53.8, 41.0, 33.9, 24.6, 24.0, 23.9, 22.3, 22.1; HRMS calcd for $C_{22}H_{29}BrN_2O_2SH$ $(M + H)^+$ 465.1211, found 465.1184 (TOF MS ES^+).

*(S)-9-Fluoro-3-isopropyl-5-(4-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10e**).* According to the reaction protocol described in general procedure B from **4k** (70.5 mg), compound **10e** (53%, 59.6 mg) was isolated after chromatography as a brown oil: R_f = 0.42 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −149.9 (*c* = 0.125, $CHCl_3$); FTIR (neat) 3267, 2968, 1604, 1573, 1477, 1433, 1325, 1161, 854, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.93 (dd, *J* = 8.8, 6.4 Hz, 1H, aromatic), 7.65 (d, *J* = 8.0 Hz, 2H, aromatic), 7.55 (d, *J* = 8.0 Hz, 2H, aromatic), 6.78−6.69 (m, 2H, aromatic), 4.68 (d, *J* = 14.7 Hz, 1H, NCH_aH_bPh), 4.44 (d, *J* = 14.7 Hz, 1H, NCH_aH_bPh), 4.32 (d, *J* = 9.1 Hz, 1H, N*H*), 3.43 (dd, *J* = 14.8, 2.2 Hz, 1H, NHC*H*CH_2N), 3.29−3.14 (m, 1H, NHCHCH_aH_bN), 3.13−2.96 (m, 1H, NHCHCH_aH_bN), 1.85−1.66 (m, 1H, CH_3CHCH_3), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 0.79 (d, *J* = 6.7 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 165.3 (d, $^1J_{C-F}$ = 253.5 Hz), 150.6 (d, $^3J_{C-F}$ = 10.1 Hz), 140.9 (d, $^4J_{C-F}$ = 0.9 Hz), 130.8 (d, $^3J_{C-F}$ = 10.9 Hz), 130.2 (q, $^2J_{C-CF3}$ = 32.6 Hz), 130.1, 128.5 (2C), 125.8 (q, $^3J_{C-CF3}$ = 3.7 Hz, 2C), 124.0 (q, $^1J_{C-CF3}$ = 273.1 Hz), 108.7 (d, $^2J_{C-F}$ = 22.6 Hz), 106.5 (d, $^2J_{C-F}$ = 24.4 Hz), 60.7, 58.0, 56.4, 30.0, 19.0, 18.7; HRMS calcd for $C_{19}H_{20}F_4N_2O_2SH$ $(M + H)^+$ 417.1260, found 417.1271 (TOF MS ES^+).

*(S)-3-Isopropyl-7-methyl-5-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10f**).* According to the reaction protocol described in general procedure B from **4j** (69.5 mg), compound **10f** (55%, 46.1 mg) was isolated after chromatography as a white solid: mp 145−148 °C; R_f = 0.38 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −27.0 (*c* = 0.125, $CHCl_3$); FTIR (neat) 3267, 2960, 1602, 1471, 1369, 1326, 1218, 1145, 1068, 815, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 8.0 Hz, 1H, aromatic), 7.27−7.24 (m, 1H, aromatic), 7.13 (bs, 1H, aromatic), 3.80 (ddd, *J* = 14.6, 7.7, 1.6 Hz, 1H, NCHC$H_aH_b$$OCH_2$), 3.70−3.62 (m, 1H, $NCHCH_2OCH_aH_b$), 3.59 (dd, *J* = 10.9, 9.2 Hz, 1H, $NCHCH_aH_bOCH_2$), 3.54−3.42 (m, 1H, $NCHCH_2OCH_aH_b$), 3.31 (dddd, *J* = 9.7, 9.7, 7.7, 1.6 Hz, 1H, NHC*H*CH_2N), 3.20−3.12 (m, 1H, NC*H*CH_2OCH_2), 2.94 (dd, *J* = 14.5, 9.6 Hz, 1H, NHCHCH_aH_bN), 2.70 (dd, *J* = 14.5, 10.0 Hz, 1H, NHCHCH_aH_bN), 2.56 (s, 1H, N*H*), 2.40 (s, 3H, PhCH_3), 1.92−1.80 (m, 1H CH_3CHCH_3), 1.09 (d, *J* = 6.5 Hz, 3H, CH_3CHCH_3), 0.84 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 144.5, 141.1, 140.1, 130.4, 129.1, 128.7, 61.9, 60.1, 58.7, 47.6, 41.1, 29.3, 21.3, 20.6, 18.5; HRMS calcd for $C_{15}H_{22}N_2O_3SH$ $(M + H)^+$ 311.1429, found 311.1415 (TOF MS ES^+).

*(S)-9-Fluoro-3-isopropyl-5-(3-methoxypropyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10g**).* According to the reaction protocol described in general procedure B from **4k** (70.6 mg), compound **10g** (56%, 50.0 mg) was isolated after chromatography as a yellow oil: R_f = 0.37 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −140.7 (*c* = 0.125, $CHCl_3$); FTIR (neat) 3263, 2962, 1608, 1569, 1456, 1386, 1319, 1201, 1149, 1068, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.85 (dd, *J* = 8.8, 6.5 Hz, 1H, aromatic), 6.74 (dd, *J* = 11.5, 2.4 Hz, 1H, aromatic), 6.66 (ddd, *J* = 8.8, 7.5, 2.4 Hz, 1H, aromatic), 4.54 (d, *J* = 7.2 Hz, 1H, N*H*), 3.58−3.42 (m, 4H, NHCHCH_aH_bN, NHC*H*CH_2N, $NCH_2CH_2CH_2OCH_3$), 3.34 (s, 3H, $NCH_2CH_2CH_2OCH_3$), 3.33−3.30 (m, 1H, NC$H_aH_b$$CH_2CH_2OCH_3$), 3.28−3.19 (m, 2H, NHCHCH_aH_bN, NC$H_aH_b$$CH_2CH_2OCH_3$), 2.01−1.93 (m, 1H, CH_3CHCH_3), 1.92−1.83 (m, 2H, $NCH_2CH_2CH_2OCH_3$), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 1.03 (d, *J* = 6.7 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 165.2 (d, $^1J_{C-F}$ = 252.1 Hz), 150.3 (d, $^3J_{C-F}$ = 10.5 Hz), 130.8 (d, $^3J_{C-F}$ = 10.9 Hz), 129.2, 107.7 (d, $^2J_{C-F}$ = 22.7 Hz), 105.6 (d, $^2J_{C-F}$ = 24.7 Hz), 69.7, 61.6, 58.7, 56.8, 51.0, 30.2, 28.0, 19.6, 19.0; HRMS calcd for $C_{15}H_{23}FN_2O_3SH$ $(M + H)^+$ 331.1492, found 331.1481 (TOF MS ES^+).

*(S)-3-((S)-sec-Butyl)-8-chloro-5-(3-methoxypropyl)-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10h**).* According to the reaction protocol described in general procedure B from **4f** (78.7 mg), compound **10h** (46%, 44.8 mg) was isolated after chromatography as a colorless oil: R_f = 0.42 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +132.5 (*c* = 0.125, $CHCl_3$); FTIR (neat) 3267, 2931, 1506, 1488, 1458, 1386, 1326, 1220, 1157, 1058, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 2.5 Hz, 1H, aromatic), 7.34 (dd, *J* = 8.8, 2.6 Hz, 1H, aromatic), 7.05 (d, *J* = 8.8 Hz, 1H, aromatic), 4.49 (d, *J* = 9.4 Hz, 1H, N*H*), 3.60−3.48 (m, 2H, NHC*H*CH_2N, $NCH_2CH_2CH_aH_bOCH_3$), 3.48−3.42 (m, 2H, $NCH_2CH_2CH_aH_bOCH_3$, $NCH_aH_bCH_2CH_2OCH_3$), 3.38 (dd, *J* = 14.8, 2.5 Hz, 1H, NHCHCH_aH_bN), 3.33 (s, 3H, $NCH_2CH_2CH_2OCH_3$), 3.29 (dd, *J* = 13.5, 6.8 Hz, 1H, $NCH_aH_bCH_2CH_2OCH_3$), 3.04 (dd, *J* = 14.8, 9.6 Hz, 1H, NHCHCH_aH_bN), 1.90−1.78 (m, 2H, $NCH_2CH_2CH_2OCH_3$), 1.74−1.64 (m, 1H, $CH_3CHCH_2CH_3$), 1.59−1.49 (m, 1H, $CH_3CHCH_aH_bCH_3$), 1.36−1.25 (m, 1H, $CH_3CHCH_aH_bCH_3$), 1.01−0.93 (m, 6H, $CH_3CHCH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm

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146.7, 134.8, 132.6, 128.1, 125.9, 120.7, 77.2, 69.8, 61.5, 58.7, 57.1, 51.2, 30.2, 28.2, 19.6, 18.9; HRMS calcd for $C_{16}H_{25}ClN_2O_3SH$ $(M + H)^+$ 361.1353, found 361.1338 (TOF MS ES^+).

*9-Fluoro-5-(3-methoxypropyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1′-cyclohexane] 1,1-Dioxide (**10i**).* According to the reaction protocol described in general procedure B from **4g** (77.7 mg), compound **10i** (56%, 54.0 mg) was isolated after chromatography as a brownish oil: R_f = 0.38 (1:1 EtOAc/hexane); FTIR (neat) 3326, 2928, 1612, 1573, 1469, 1338, 1147, 1041, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.27−7.22 (m, 1H, aromatic), 6.97 (s, 1H, N*H*), 6.48 (d, *J* = 8.8, Hz, 1H, aromatic), 6.35 (ddd, *J* = 11.2, 8.1, 1.0 Hz, 1H, aromatic), 5.61−5.54 (m, 1H, $NCH_2CH_2CH_aH_bOCH_3$), 4.95 (dd, *J* = 6.6, 6.5 Hz, 1H, $NCH_2CH_2CH_aH_bOCH_3$), 3.54−3.44 (m, 4H, $NHCCH_2N$, $NCH_2CH_2CH_2OCH_3$), 3.36 (s, 3H, OCH_3), 3.25 (ddd, *J* = 6.7, 6.6, 5.0 Hz, 2H, $NCH_2CH_2CH_2OCH_3$), 2.00−1.84 (m, 5H, cyclohexyl), 1.65−1.55 (m, 1H, cyclohexyl), 1.54−1.39 (m, 4H, cyclohexyl); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 161.1 (d, $^1J_{C-F}$ = 248.9 Hz), 148.6 (d, $^4J_{C-F}$ = 3.4 Hz), 134.2 (d, $^3J_{C-F}$ = 12.7 Hz), 109.4 (d, $^3J_{C-F}$ = 14.0 Hz), 107.8, 101.1 (d, $^2J_{C-F}$ = 23.5 Hz), 70.2, 58.8, 50.0, 40.8, 29.0, 26.2 (2C), 25.0, 22.3, 21.9 (2C); HRMS calcd for $C_{17}H_{25}FN_2O_3SH$ $(M + H)^+$ 357.1648, found 357.1627 (TOF MS ES^+).

*7-Bromo-5-(2-hydroxyethyl)-4,5-dihydro-2H-spiro[benzo[f][1,2,5]thiadiazepine-3,1′-cyclohexane] 1,1-Dioxide (**10j**).* According to the reaction protocol described in general procedure C from **4l** (47.6 mg), compound **10j** (46%, 24.8 mg) was isolated after chromatography as a white solid: mp 178−182 °C; R_f = 0.44 (1:1 EtOAc/hexane); FTIR (thin film) 3454, 3263, 2934, 1580, 1487, 1369, 1312, 1150, 1057, 795, 733, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (dd, *J* = 8.4, 1.7 Hz, 1H, aromatic), 7.25 (s, 1H, aromatic), 7.19 (dd, *J* = 8.4, 1.7 Hz, 1H, aromatic), 4.44 (s, 1H, N*H*), 3.81−3.66 (m, 2H, NCH_2CH_2OH), 3.57 (bs, 2H, NCH_2CH_2OH), 3.26 (bs, 2H, NCH_2CNH), 2.85 (s, 1H, O*H*), 1.75−1.53 (m, 6H, cyclohexyl), 1.50−1.27 (m, 4H, cyclohexyl); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 148.1, 129.5, 127.1, 125.8, 125.3, 122.6, 65.3, 59.5, 59.1, 56.5, 25.6 (2C), 21.0 (3C); HRMS calcd for $C_{15}H_{21}BrN_2O_3SH$ $(M - H)^+$ 387.0383, found 387.0372 (TOF MS ES^-).

*(S)-7-Bromo-5-(2-hydroxyethyl)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10k**).* According to the reaction protocol described in general procedure C from **4b** (97.6 mg), compound **10k** (46%, 50.4 mg) was isolated after chromatography as a colorless oil: R_f = 0.35 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −175.5 (*c* = 0.125, $CHCl_3$); FTIR (thin film) 3466, 3252, 2964, 1578, 1470, 1371, 1319, 1157, 1059, 795, 731, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.74 (dd, *J* = 8.6, 2.1 Hz, 1H, aromatic), 7.37 (d, *J* = 2.0 Hz, 1H, aromatic), 7.29−7.22 (m, 1H, aromatic), 4.17 (d, *J* = 9.4 Hz, 1H, N*H*), 3.88−3.76 (m, 1H, $HOCH_aH_b$), 3.68−3.57 (m, 2H, NCH_2CH_2), 3.51−3.36 (m, 3H, NCH_aH_BCHNH, $NHCHCH_2$, O*H*), 3.33−3.22 (m, 1H, $HOCH_aH_b$), 2.85 (dd, *J* = 15.0, 10.4 Hz, 1H, NCH_aH_BCHNH), 1.92−1.79 (m, 1H, CH_3CHCH_3), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 1.02 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 148.9, 135.6, 129.6, 127.7, 126.1, 125.5, 60.9, 60.0, 58.9, 57.9, 30.0, 19.5, 18.3; HRMS calcd for $C_{13}H_{19}BrN_2O_3SH$ $(M + H)^+$ 363.0378, found 363.0375 (TOF MS ES^+).

*(S)-7-Bromo-5-(2-hydroxyethyl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10l**).* According to the reaction protocol described in general procedure C from **4a** (63.5 mg), compound **10l** (43%, 31.0 mg) was isolated after chromatography as a colorless oil: R_f = 0.45 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −120.8 (*c* = 0.085, $CHCl_3$); **FTIR (thin film)** 3454, 3250, 2957, 1576, 1470, 1367, 1319, 1155, 1061, 808, 789, 745, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.69 (d, *J* = 8.4 Hz, 1H, aromatic), 7.36 (d, *J* = 1.8 Hz, 1H, aromatic), 7.23 (dd, *J* = 8.5, 1.8 Hz, 1H, aromatic), 4.27 (d, *J* = 9.0 Hz, 1H, N*H*), 3.82 (ddd, *J* = 13.6, 5.6, 3.9 Hz, 1H, $HOCH_aH_b$), 3.73−3.57 (m, 3H, $NHCHCH_2$, NCH_2CH_2OH), 3.42 (s, 1H, O*H*), 3.36 (dd, *J* = 15.0, 2.1 Hz, 1H, $NHCHCH_aH_bN$), 3.32−3.21 (m, 1H, $HOCH_aH_b$), 2.85−2.71 (m, 1H, $NHCHCH_aH_bN$), 1.93−1.79 (m, 1H, CH_3CHCH_3), 1.36 (ddd, *J* = 14.3, 9.1, 5.7 Hz, 1H, $NHCHCH_aH_b$), 1.30−1.18 (m, 1H, $NHCHCH_aH_b$), 0.98 (dd, *J* = 6.5, 6.4 Hz, 6H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 148.9, 135.6, 129.6, 127.7, 126.1, 125.5, 61.3, 60.1, 58.0, 54.1, 40.7, 24.6, 23.0, 21.9; HRMS calcd for $C_{14}H_{21}BrN_2O_3SH$ $(M + H)^+$ 377.0535, found 377.0515 (TOF MS ES^+).

*(S)-7-Bromo-5-((R)-1-hydroxypropan-2-yl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10m**).* According to the reaction protocol described in general procedure C from **4a** (146.3 mg), compound **10m** (12%, 20.2 mg) was isolated after chromatography as a white solid: mp 150−154 °C; R_f = 0.55 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −143.5 (*c* = 0.365, $CHCl_3$); FTIR (thin film) 3475, 3253, 2957, 1576, 1470, 1381, 1321, 1161, 1055, 808, 777, 727, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (d, *J* = 8.4 Hz, 1H, aromatic), 7.35 (d, *J* = 1.8 Hz, 1H, aromatic), 7.27−7.24 (m, 1H, aromatic), 3.98 (s, 1H, N*H*), 3.88−3.74 (m, 1H, $NCHCH_3$), 3.62 (s, 1H, O*H*), 3.58−3.47 (m, 3H, $NHCHCH_2N$, $NHCHCH_aH_bN$, $HOCH_aH_b$), 3.40 (dd, *J* = 11.0, 10.4 Hz, 1H, $HOCH_aH_b$), 2.47−2.26 (m, 1H, $NHCHCH_aH_bN$), 1.95−1.78 (m, 1H, CH_3CHCH_3), 1.40−1.19 (m, 5H, CH_3CHN, $NHCHCH_2$), 1.00 (dd, *J* = 6.3 Hz, 6H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 150.7, 134.6, 129.5, 127.8, 125.7, 125.5, 65.6, 60.9, 54.0, 51.7, 41.1, 24.7, 23.0, 21.9, 13.9; HRMS calcd for $C_{15}H_{23}BrN_2O_3SH$ $(M + H)^+$ 391.0691, found 391.0656 (TOF MS ES^+).

*(S)-7-Bromo-5-(1-(hydroxymethyl)cyclohexyl)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10n**).* According to the reaction protocol described in general procedure C from **4b** (96.4 mg), compound **10n** (26%, 34.0 mg) was isolated after chromatography as a white solid: mp 164−168 °C; R_f = 0.66 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −187.1 (*c* = 1.29, $CHCl_3$); FTIR (thin film) 3445, 3261, 2959, 1574, 1462, 1398, 1321, 1163, 1063, 808, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 (d, *J* = 8.5 Hz, 1H, aromatic), 7.68 (d, *J* = 1.8 Hz, 1H, aromatic), 7.35 (dd, *J* = 8.4, 1.8 Hz, 1H, aromatic), 4.06 (d, *J* = 9.2 Hz, 1H, N*H*), 3.92−3.77 (m, 2H, NCH_aH_bCHNH, CH_aH_bOH), 3.68 (dd, *J* = 12.6, 4.8 Hz, 1H, CH_aH_bOH), 3.45 (ddd, *J* = 8.9, 8.8, 8.6 Hz, 1H, $NHCHCH_2N$), 3.36−3.21 (m, 1H, O*H*), 2.35 (dd, *J* = 15.6, 10.4 Hz, 1H, NCH_aH_bCHNH), 2.09 (d, *J* = 12.9 Hz, 1H, cyclohexyl), 1.88−1.68 (m, 6H, cyclohexyl, CH_3CHCH_3), 1.57 (ddd, *J* = 13.1, 12.8, 3.7 Hz, 1H, cyclohexyl), 1.48−1.34 (m, 2H, cyclohexyl), 1.31−1.17 (m, 1H, cyclohexyl), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 147.9, 139.0, 131.8, 129.3, 127.6, 126.2, 63.6, 61.5, 61.2, 50.3, 31.6, 31.2, 30.1, 25.5, 23.0, 22.8, 19.3, 18.2; HRMS calcd for $C_{18}H_{27}BrN_2O_3SH$ $(M + H)^+$ 431.1004, found 431.1019(TOF MS ES^+).

*(S)-7-Bromo-5-((S)-1-hydroxy-4-methylpentan-2-yl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[f]-[1,2,5]thiadiazepine 1,1-Dioxide (**10o**).* According to the reaction protocol described in general procedure C from **4a** (258.0 mg), compound **10o** (21%, 70.0 mg) was isolated after chromatography as a white solid: mp 86−90 °C; R_f = 0.47 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +117.3 (*c* = 0.92, $CHCl_3$); FTIR (thin film) 3470, 3250, 2955, 1578, 1470, 1402, 1323, 1163, 1068, 876, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 8.1 Hz, 1H, aromatic), 7.25−7.14 (m, 2H, aromatic), 6.70 (d, *J* = 6.4 Hz, 1H, N*H*), 4.41 (dd, *J* = 11.7, 2.9 Hz, 1H, $NCHCH_aH_bOH$), 3.87 (dd, *J* = 11.8, 11.0 Hz, 1H, $NCHCH_aH_bOH$), 3.16−2.99 (m, 1H, $NHCHCH_2N$), 2.77−2.57 (m, 2H, $NCHCH_2OH$, NCH_aH_bCHNH), 2.40 (dd, *J* = 13.6, 4.8 Hz, 1H, NCH_aH_bCHNH), 1.80−1.68 (m, 2H, CH_3CHCH_3, CH_3CHCH_3), 1.63 (ddd, *J* = 14.1, 7.2, 7.1 Hz, 1H, $NHCHCH_aH_b$), 1.24 (dd, *J* = 7.8, 6.3 Hz, 2H, $NCHCH_2$), 1.13 (ddd, *J* = 13.7, 7.0, 6.9 Hz, 1H, $NHCHCH_aH_b$), 0.98−0.88 (m, 9H, CH_3CHCH_3, CH_3CHCH_3), 0.84 (d, *J* = 6.6 Hz, 3H, CH_3CHCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 155.2, 131.8, 129.7, 128.0, 124.9, 118.5, 75.2, 54.0, 51.4, 51.3, 43.4, 42.0, 24.9, 24.3, 23.0, 22.7, 22.5, 22.4; HRMS calcd for $C_{18}H_{29}BrN_2O_3SH$ $(M + H)^+$ 435.1136, found 435.1147 (TOF MS ES^+).

*(S)-7-Bromo-5-((R)-4-hydroxy-3-methylbutyl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepine 1,1-Dioxide (**10p**).* According to the reaction protocol described in general procedure C from **4a** (81.1 mg), compound **10p** (43%, 43.1 mg) was isolated after chromatography as a colorless oil: R_f = 0.45 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = −103.1 (*c* = 0.66, $CHCl_3$); FTIR (thin film) 3512, 3252, 2957, 1578, 1543, 1470, 1371, 1315, 1150, 1040, 800, 731, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.67 (d, *J* = 8.5 Hz, 1H, aromatic), 7.20 (d, *J* = 1.8 Hz, 1H, aromatic), 7.10 (dd, *J* = 8.5, 1.8 Hz, 1H, aromatic), 4.41 (d, *J*

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= 8.2 Hz, 1H, NH), 3.68−3.56 (m, 2H, NHCHCH$_2$N, NCH$_a$H$_b$CH$_2$CHMe), 3.55−3.49 (m, 1H, HOCH$_a$H$_b$CHMe), 3.46 (dd, J = 15.1, 2.7 Hz, 1H, NHCHCH$_a$H$_b$N), 3.43−3.39 (m, 1H, HOCH$_a$H$_b$CHMe), 3.21 (ddd, J = 13.7, 8.3, 5.9 Hz, 1H, NCH$_a$H$_b$CH$_2$CHMe), 2.95 (dd, J = 15.1, 9.0 Hz, 1H, NHCHCH$_a$H$_b$N), 1.91−1.79 (m, 2H, HOCH$_2$CHMe, CH$_3$CHCH$_3$), 1.79−1.70 (m, 2H, NCH$_2$CH$_a$H$_b$CHMe, OH), 1.53−1.43 (m, 2H, NHCHCH$_a$H$_b$CH, NCH$_2$CH$_a$H$_b$CHMe), 1.27 (ddd, J = 14.0, 8.4, 5.6 Hz, 1H, NHCHCH$_a$H$_b$CH), 1.03−0.93 (m, 9H, CH$_3$CHCH$_3$, HOCH$_2$CHCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 149.3, 132.4, 129.7, 127.3, 123.8, 122.1, 67.7, 59.2, 54.0, 52.3, 40.9, 33.4, 31.4, 24.6, 22.9, 21.9, 17.0; HRMS calcd for $C_{17}H_{27}BrN_2O_3SH$ (M + H)$^+$ 421.0979, found 421.0980 (TOF MS ES$^+$).

*(3S)-7-Bromo-3-isobutyl-3,4-dihydro-2,5-ethanobenzo[f][1,2,5]-thiadiazepine 1,1-Dioxide (**11a**).* According to the reaction protocol described in general procedure D from **10l** (17.6 mg), compound **11a** (87%, 14.6 mg) was isolated after chromatography as a colorless oil: R_f = 0.53 (1:2 EtOAc/hexane); $[\alpha]_D^{20}$ = −29.1 (c = 0.945, CHCl$_3$); FTIR (thin film) 2957, 1574, 1448, 1391, 1333, 1165, 839, 797, 694 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.74 (d, J = 8.4 Hz, 1H, aromatic), 7.56 (dd, J = 8.4, 2.0 Hz, 1H, aromatic), 7.48 (d, J = 2.0 Hz, 1H, aromatic), 3.97−3.82 (m, 1H, NCHCH$_2$N), 3.72 (dddd, J = 14.7, 8.6, 2.4, 1.7 Hz, 1H, SNCH$_a$H$_b$), 3.42 (ddd, J = 14.1, 7.7, 2.5 Hz, 1H, CNCH$_a$H$_b$CH$_2$NS), 3.39−3.32 (m, 1H, CNCH$_a$H$_b$CH$_2$NS), 3.26−3.21 (m, 1H, NCH$_a$H$_b$CHN), 3.21−3.16 (m, 1H, SNCH$_a$H$_b$), 2.73 (dd, J = 14.4, 9.1 Hz, 1H, NCH$_a$H$_b$CHN), 1.89−1.75 (m, 1H, CH$_3$CHCH$_3$), 1.68 (ddd, J = 14.3, 9.8, 4.7 Hz, 1H, NCHCH$_a$H$_b$CH), 1.14 (ddd, J = 13.8, 9.0, 4.6 Hz, 1H, NCHCH$_a$H$_b$CH), 0.95 (d, J = 6.8 Hz, 3H, CH$_3$CHCH$_3$), 0.93 (d, J = 6.5 Hz, 3H, CH$_3$CHCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 148.1, 143.2, 133.9, 131.3, 129.8, 126.8, 53.3, 51.1, 51.07, 39.1, 38.3, 24.6, 23.2, 21.6; HRMS calcd for $C_{14}H_{19}BrN_2O_2SH$ (M + H)$^+$ 359.0429, found 359.0430 (TOF MS ES$^+$).

*(4R,11S)-7-Bromo-11-isobutyl-4-methyl-3,4-dihydro-2,5-ethanobenzo[f][1,2,5]thiadiazepine 1,1-dioxide (**11b**).* According to the reaction protocol described in general procedure D from **10m** (28.5 mg), compound **11b** (46%, 12.5 mg) was isolated after chromatography as a colorless oil: R_f = 0.66 (1:2 EtOAc/hexane); $[\alpha]_D^{20}$ = −2.1 (c = 0.25, CHCl$_3$); FTIR (thin film) 2957, 1574, 1456, 1381, 1331, 1161, 816, 789, 756, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.72 (d, J = 8.4 Hz, 1H, aromatic), 7.59 (dd, J = 8.4, 2.0 Hz, 1H, aromatic), 7.45 (d, J = 1.9 Hz, 1H, aromatic), 4.09−3.90 (m, 1H, NCHCH$_2$N), 3.51−3.29 (m, 4H, SNCH$_2$CHCH$_3$, NCHCH$_a$H$_b$N), 2.81 (dd, J = 14.3, 6.6 Hz, 1H, NCHCH$_a$H$_b$N), 1.84−1.77 (m, 1H, CH$_3$CHCH$_3$), 1.73 (ddd, J = 13.9, 10.2, 4.7 Hz, 1H, NCHCH$_a$H$_b$CH), 1.21 (ddd, J = 14.1, 9.0, 5.0 Hz, 1H, NCHCH$_a$H$_b$CH), 0.96 (dd, J = 6.5, 3.8 Hz, 9H, NCHCH$_3$, CH$_3$CHCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 144.3, 143.6, 136.0, 131.6, 129.1, 126.6, 56.2, 54.5, 49.2, 44.8, 40.3, 25.1, 23.2, 21.5, 20.2; HRMS calcd for $C_{15}H_{21}BrN_2O_2SH$ (M + H)$^+$ 373.0585, found 373. 0565 (TOF MS ES$^+$).

*7-Bromo-4H-spiro[2,5-ethanobenzo[f][1,2,5]thiadiazepine-3,1′-cyclohexane] 1,1-Dioxide (**11c**).* According to the reaction protocol described in general procedure D from **10j** (21.2 mg), compound **11c** (40%, 8.1 mg) was isolated after chromatography as a white solid: R_f = 0.51 (1:2 EtOAc/hexane); mp 182−185 °C; FTIR (thin film) 2935, 1574, 1452, 1393, 1327, 1167, 804, 694 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.67 (d, J = 8.4 Hz, 1H, aromatic), 7.53 (dd, J = 8.4, 2.0 Hz, 1H, aromatic), 7.47 (d, J = 2.0 Hz, 1H, aromatic), 3.88 (ddd, J = 14.8, 6.9, 5.7 Hz, 1H, SNCH$_a$H$_b$), 3.44 (ddd, J = 14.7, 8.5, 7.1 Hz, 1H, SNCH$_a$H$_b$), 3.38−3.30 (m, 2H, CNCH$_2$CH$_2$NS), 3.15 (ddd, J = 14.3, 1.3, 1.2 Hz, 1H, NCH$_a$H$_b$CNS), 2.94 (dd, J = 14.5, 0.9 Hz, 1H, NCH$_a$H$_b$CNS), 2.20−2.09 (m, 1H, cyclohexyl), 1.89−1.77 (m, 3H, cyclohexyl), 1.75−1.65 (m, 1H, cyclohexyl), 1.49−1.35 (m, 3H, cyclohexyl), 1.34−1.21 (m, 2H, cyclohexyl); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 148.9, 144.8, 133.7, 131.2, 128.7, 126.8, 60.5, 58.8, 49.8, 41.3, 37.1, 36.9, 25.1, 22.8, 22.4; HRMS calcd for $C_{15}H_{19}BrN_2O_2SH$ (M + 2 + H)$^+$ 373.0403, found 373. 0399 (TOF MS ES$^+$).

*(3S,7R)-7-((Benzyloxy)methyl)-10-fluoro-5-((R)-1-hydroxypropan-2-yl)-3-isobutyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]-oxathiadiazecine 1,1-Dioxide (**18**).* According to the reaction protocol described in general procedure B from **4c** (44.2 mg), compound **18** (42%, 33.4 mg) was isolated after chromatography as a white solid: mp 50−55 °C; R_f = 0.50 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +22.5 (c = 1.315, CHCl$_3$); FTIR (thin film) 3514, 2953, 1601, 1587, 1477, 1454, 1389, 1321, 1155, 1070, 808, 741, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.98 (dd, J = 8.8, 6.5 Hz, 1H, aromatic), 7.41−7.25 (m, 5H, aromatic), 6.79 (ddd, J = 8.7, 7.8, 2.4 Hz, 1H, aromatic), 6.72 (dd, J = 9.9, 2.4 Hz, 1H, aromatic), 5.75 (s, 1H, NH), 4.46 (d, J = 11.8 Hz, 1H, OCH$_a$H$_b$C), 4.40 (d, J = 11.9 Hz, 1H, OCH$_a$H$_b$C), 4.37 (dd, J = 12.3, 5.1 Hz, 1H, OCHCH$_a$H$_b$O), 3.90 (dd, J = 11.9 Hz, 1H, OCHCH$_a$H$_b$O), 3.64 (bs, 1H, NHCHCH$_2$N), 3.37−3.23 (m, 2H, OCHCH$_2$O, NCHCH$_3$), 3.14 (dd, J = 9.4, 4.1 Hz, 1H, HOCH$_a$H$_b$CH), 3.09−2.99 (m, 2H, NHCHCH$_a$H$_b$N, HOCH$_a$H$_b$CH), 2.53 (d, J = 12.7 Hz, 1H, NCH$_a$H$_b$CHO), 2.36−2.28 (m, 2H, NCH$_a$H$_b$CHO, OH), 2.14 (dd, J = 15.1, 10.8 Hz, 1H, NHCHCH$_a$H$_b$N), 1.95−1.81 (m, 1H, CH$_3$CHCH$_3$), 1.42 (ddd, J = 13.7, 7.7, 6.0 Hz, 1H, NHCHCH$_a$H$_b$), 1.14 (ddd, J = 13.6, 7.9, 5.6 Hz, 1H, NHCHCH$_a$H$_b$), 0.98 (d, J = 6.5 Hz, 3H, NCHCH$_3$), 0.93 (d, J = 6.5 Hz, 3H, CH$_3$CHCH$_3$), 0.89 (d, J = 6.6 Hz, 3H, CH$_3$CHCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 165.7 (d, $^1J_{C-F}$ = 254.0 Hz), 157.2, 137.7, 132.2 (d, $^3J_{C-F}$ = 10.8 Hz), 128.5 (2C), 127.9 (2C), 127.7 (2C), 108.6 (d, $^2J_{C-F}$ = 22.2 Hz), 104.1 (d, $^2J_{C-F}$ = 24.5 Hz), 73.4, 72.2, 71.9, 69.4 (2C), 57.4, 56.3, 53.7, 46.1, 24.2, 23.0, 22.5, 9.5; HRMS calcd for $C_{25}H_{35}FN_2O_5SH$ (M + H)$^+$ 495.2329, found 495.2348 (TOF MS ES$^+$).

*(3S,7S)-7-((Benzyloxy)methyl)-10-fluoro-5-((R)-1-hydroxypropan-2-yl)-3-isobutyl-2,3,4,5,6,7-hexahydrobenzo[b][1,4,5,8]-oxathiadiazecine 1,1-Dioxide (**19**).* According to the reaction protocol described in general procedure B from **4c** (40.0 mg), compound **19** (42%, 30.5 mg) was isolated after chromatography as a colorless sticky oil: R_f = 0.35 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +45.9 (c = 0.535, CHCl$_3$); FTIR (thin film) 3450, 3259, 2957, 1603, 1587, 1477, 1454, 1387, 1323, 1161, 1070, 808, 733, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.96 (ddd, J = 8.6, 6.4, 1.6 Hz, 1H, aromatic), 7.53−7.44 (m, 2H, aromatic), 7.44−7.37 (m, 2H, aromatic), 7.38−7.29 (m, 1H, aromatic), 6.87−6.79 (m, 1H, aromatic), 6.79 (ddd, J = 10.0, 1.8 Hz, 1H, aromatic), 6.42 (s, 1H, NH), 4.66 (s, 2H, OCH$_2$C), 4.56 (dd, J = 5.4, 3.1 Hz, 1H, OCHCH$_2$O), 4.01 (dd, J = 10.5, 5.1 Hz, 1H, OCHCH$_a$H$_b$O), 3.98−3.89 (m, 1H, OCHCH$_a$H$_b$O), 3.44−3.26 (m, 2H, HOCH$_2$CH), 3.06−2.96 (m, 1H, NHCHCH$_2$N), 2.95−2.87 (m, 3H, NCH$_2$CHO, OH), 2.77−2.64 (m, 1H, NCHCH$_3$), 2.33 (dd, J = 14.8, 4.9 Hz, 1H, NHCHCH$_a$H$_b$N), 2.26 (dd, J = 14.9, 3.8 Hz, 1H, NHCHCH$_a$H$_b$N), 1.65−1.53 (m, 1H, CH$_3$CHCH$_3$), 1.54−1.43 (m, 1H, NHCHCH$_a$H$_b$), 0.96 (ddd, J = 13.5, 7.9, 5.6 Hz, 1H, NHCHCH$_a$H$_b$), 0.84 (dd, J = 6.5, 1.5 Hz, 3H, CH$_3$CHCH$_3$), 0.81 (dd, J = 6.7, 1.6 Hz, 3H, NCHCH$_3$), 0.72 (dd, J = 6.6, 1.5 Hz, 3H, CH$_3$CHCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 165.9 (d, $^1J_{C-F}$ = 254.8 Hz), 155.5, 136.2, 132.3 (d, $^3J_{C-F}$ = 10.2 Hz), 129.0 (2C), 128.6 (2C), 128.4, 127.3, 109.2 (d, $^2J_{C-F}$ = 22.0 Hz), 104.1 (d, $^2J_{C-F}$ = 25.2 Hz), 78.6, 75.0, 71.0, 64.8, 61.4, 55.8, 53.5, 51.6, 43.4, 24.1, 23.1, 21.8, 10.0; HRMS calcd for $C_{25}H_{35}FN_2O_5SH$ (M + H)$^+$ 495.2329, found 495.2298 (TOF MS ES$^+$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01429.

Optimization table and ^{1}H, ^{19}F, and ^{13}C NMR spectral data (PDF)

X-ray crystallographic data for **6a**, **6p**, **8b** (CIF), **10m**, and **11c**

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125−196. and refs cited therein (b) Sharma, A.; Appukkuttan, P.; Van der Eycken, E. *Chem. Commun.* **2012**, *48*, 1623−1637. For some recent methods, see: (c) Bauer, R. A.; Wenderski, T. A.; Tan, D. S. *Nat. Chem. Biol.* **2013**, *9*, 21−29. (d) Bogdan, A. R.; Jerome, S. V.; Houk, K. N.; James, K. *J. Am. Chem. Soc.* **2012**, *134*, 2127−2138.

(2) For a review, see: (a) Cossy, J. *C. R. Chim.* **2008**, *11*, 1303−1305. (b) For selected examples of bioactive lactams, see: (c) Lou, L.; Qian, G.; Xie, Y.; Hang, J.; Chen, H.; Zaleta-Rivera, K.; Li, Y.; Shen, Y.; Dussault, P. H.; Liu, F.; Du, L. *J. Am. Chem. Soc.* **2011**, *133*, 643−645. (d) Yang, S.; Xi, Y.; Zhu, R.; Wang, L.; Chen, J.; Yang, Z. *Org. Lett.* **2013**, *15*, 812−815. (e) Floss, H. G.; Yu, T.-W. *Chem. Rev.* **2005**, *105*, 621−632. (f) Ksander, G. M.; de Jesus, R.; Yuan, A.; Ghai, R. D.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 506−514. (g) Bach, T.; Lemarchand, A. *Synlett* **2002**, 1302−1304. (h) Kawamura, T.; Tashiro, E.; Shindo, K.; Imoto, M. *J. Antibiot.* **2008**, *61*, 312−317. (i) Laumen, K.; Machauer, R.; Tintelnot-Blomley, M.; Veenstra, S. J. WO2008009750 A2 20080124, 2008. (j) Stamford, A. W.; Huang, Y.; Li, G.; Strickland, C. O.; Voigt, J. H. WO2006014944 A1 20060209, 2006.

(3) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48−56. (c) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(4) (a) Udugamasooriya, D. G.; Spaller, M. R. *Biopolymers* **2008**, *89*, 653−667. (b) Gilon, C.; Halle, D.; Chorev, M.; Selincer, Z.; Byk, G. *Biopolymers* **1991**, *31*, 745−750. (c) Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615−2623. (d) Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963−978.

(5) (a) McGeary, R. P.; Fairlie, D. P. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 208−217. (b) Fairlie, D. P.; Abbenante, G.; March, D. R. Macrocyclic peptidomimetics - forcing peptides into bioactive conformations. *Curr. Med. Chem.* **1995**, *2*, 654−686. (c) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608−624. (d) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961−2004.

(6) (a) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648−10649. (b) Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303−309. (c) Su, Q.; Beeler, A. B.; Lobkovsky, E.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.* **2003**, *5*, 2149−2152. (d) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829−837. (e) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity* **2005**, *9*, 159−169. (f) de Greef, M.; Abeln, S.; Belkasmi, K.; Dömling, A.; Orru, R. V. A.; Wessjohann, L. A. *Synthesis* **2006**, *23*, 3997−4004.

(7) Lovering, F. J.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(8) Vendeville, S.; Cummings, M. D. *Annu. Rep. Med. Chem.* **2013**, *48*, 371−386.

(9) (a) Villar, E. A.; Beglov, D.; Chennamadhavuni, S.; Porco, J. A., Jr.; Kozakov, D.; Vajda, S.; Whitty, A. *Nat. Chem. Biol.* **2014**, *10*, 723−731. (b) Nero, T. L.; Morton, C. J.; Holien, J. K.; Wielens, J.; Parker, M. W. *Nat. Rev. Cancer* **2014**, *14*, 248−262.

(10) (a) Mai, A. *ChemMedChem* **2014**, *9*, 415−417. (b) Knapp, S.; Weinmann, H. *ChemMedChem* **2013**, *8*, 1885−1891.

(11) (a) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131−9166. (b) See refs 1 and 2.

(12) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6403−6405.

(13) (a) Ayers, S.; Zink, D. L.; Mohn, K.; Powell, J. S.; Brown, C. M.; Murphy, T.; Grund, A.; Genilloud, O.; Salazar, O.; Thompson, D.; Singh, S. B. *J. Nat. Prod.* **2007**, *70*, 1371−1373. (b) Ayers, S.; Zink, D. L.; Powell, J. S.; Brown, C. M.; Grund, A.; Genilloud, O.; Salazar, O.; Thompson, D.; Singh, S. B. *J. Antibiot.* **2008**, *61*, 59−62.

(14) Johnson, E. P.; Chen, G.-P.; Fales, K. R.; Lenk, B. E.; Szendroi, R. J.; Wang, X.-J.; Carlson, J. A. *J. Org. Chem.* **1996**, *60*, 6595−6598.

(15) Lin, T.-I.; Lenz, O.; Fanning, G.; Verbinnen, T.; Delouvroy, F.; Scholliers, A.; Vermeiren, K.; Rosenquist, A.; Edlund, M.; Samuelsson, B.; Vrang, L.; de Kock, H.; Wigerinck, P.; Raboisson, P.; Simmen, K. *Antimicrob. Agents Chemother.* **2009**, *53*, 1377−1385.

(16) (a) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838−3844. (b) Lesma, G.; Colombo, A.; Silvani, A.; Sacchetti, A. *Tetrahedron Lett.* **2008**, *49*, 7423−7425. (c) Yu, X.; Sun, D. *Molecules* **2013**, *18*, 6230−6268. (d) Ksander, G. M.; de Jesus, R.; Yuan, A.; Ghai, R. D.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 506−514. (e) Ding, G.; Liu, F.; Yang, T.; Fu, H.; Zhao, Y.; Jiang, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3766−3774.

(17) Velten, R.; Erdelen, C.; Gehling, M.; Gohrt, A.; Gondol, D.; Lenz, J.; Lockhoff, O.; Wachendorff, U.; Wendisch, D. *Tetrahedron Lett.* **1998**, *39*, 1737−1740.

(18) Baldauf, C.; Günther, R.; Hofmann, H.-J. *J. Mol. Struct.: THEOCHEM* **2004**, *675*, 19−28.

(19) Gerard, B.; Duvall, J. R.; Lowe, J. T.; Murillo, T.; Wei, J.; Akella, L. B.; Marcaurelle, L. A. *ACS Comb. Sci.* **2011**, *13*, 365−374.

(20) Lücking, U.; Siemeister, G.; Schäfer, M.; Briem, H.; Krüger, M.; Lienau, P.; Jautelat, R. *ChemMedChem* **2007**, *2*, 63−77.

(21) Ghosh, A. K.; Kulkarni, S.; Anderson, D. D.; Hong, L.; Baldridge, A.; Wang, Y.-F.; Chumanevich, A. A.; Kovalevsky, A. Y.; Tojo, Y.; Amano, M.; Koh, Y.; Tang, J.; Weber, I. T.; Mitsuya, H. *J. Med. Chem.* **2009**, *52*, 7689−7705.

(22) Hanessian, S.; Larsson, A.; Fex, T.; Knecht, W.; Blomberg, N. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6925−6928.

(23) Aldrich, L. N.; Kuo, S.-Y.; Castoreno, A. B.; Goel, G.; Petric Kuballa, P.; Rees, M. G.; Seashore-Ludlow, B. A.; Cheah, J. H.; Latorre, I. J.; Stuart, L.; Schreiber, S. L.; Shamji, A. F.; Xavier, R. J. *J. Am. Chem. Soc.* **2015**, *137*, 5563−5568.

(24) (a) See refs 1 and 6e and references cited therein. (b) Hassan, H. M. A. *Chem. Commun.* **2010**, *46*, 9100−9106. (c) White, C. J.; Yudin, A. K. *Nat. Chem.* **2011**, *3*, 509−524. (d) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev.* **2013**, *113*, PR1−PR40 and references cited therein. (e) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962−16967. (f) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem.* **2005**, *243*, 137−184. For selected examples of heterocycles derived from target-oriented samples, see: (g) Lou, L.; Qian, G.; Xie, Y.; Hang, J.; Chen, H.; Zaleta-Rivera, K.; Li, Y.; Shen, Y.; Dussault, P. H.; Liu, F.; Du, L. *J. Am. Chem. Soc.* **2011**, *133*, 643−645. (h) Yang, S.; Xi, Y.; Zhu, R.; Wang, L.; Chen, J.; Yang, Z. *Org. Lett.* **2013**, *15*, 812−815. (i) Floss, H. G.; Yu, T.-W. *Chem. Rev.* **2005**, *105*, 621−632. For selected examples of heterocycles derived from diversity-oriented samples, see: (j) Tan ref 1c. (k) Hussain, A.; Yousuf, S. K.; Sharma, D. K.; Mallikharjuna Rao, L.; Singh, B.; Mukherjee, D. *Tetrahedron* **2013**, *69*, 5517−5524.

(25) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem.* **2005**, *243*, 137−184.

(26) Complementary ambiphile pairing (CAP): (a) Samarakoon, T. B.; Hur, M. Y.; Kurtz, R. D.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 2182−2185. (b) Rolfe, A.; Samarakoon, T. B.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 1216−1219.

DOI: 10.1021/acs.joc.5b01429
J. Org. Chem. 2015, 80, 9926−9941

(27) For work related to the build−couple−pair paradigm, see: (a) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48−56. (b) Uchida, T.; Rodriquez, M.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 1559−1562. (c) Luo, T.; Schreiber, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5667−5674. (d) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D., IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962−16976. (e) Gerard, B.; Duvall, J. R.; Lowe, J. T.; Murillo, T.; Wei, J.; Akella, L. B.; Marcaurelle, L. A. *ACS Comb. Sci.* **2011**, *13*, 365−374. (f) Beckmann, H. S. G.; Nie, F.; Hagerman, C. E.; Johansson, H.; Tan, Y. S.; Wilcke, D.; Spring, D. R. *Nat. Chem.* **2013**, *5*, 861−867. (g) Comer, E.; Beaudoin, J. A.; Kato, N.; Fitzgerald, M. E.; Heidebrecht, R. W.; Lee, M. d.; Masi, D.; Mercier, M.; Mulrooney, C.; Muncipinto, G.; Rowley, A.; Crespo-Llado, K.; Serrano, A. E.; Lukens, A. K.; Wiegand, R. C.; Wirth, D. F.; Palmer, M. A.; Foley, M. A.; Munoz, B.; Scherer, C. A.; Duvall, J. R.; Schreiber, S. L. *J. Med. Chem.* **2014**, *57*, 8496−8502. (h) Mamidala, R.; Babu Damerla, V. S.; Gundla, R.; Chary, M. T.; Murthy, Y. L. N.; Sen, S. *RSC Adv.* **2014**, *4*, 10619−10626. (i) Flagstad, T.; Hansen, M. R.; Le Quement, S. T.; Givskov, M.; Nielsen, T. E. *ACS Comb. Sci.* **2015**, *17*, 19−23. (j) For a review of different pairing approaches to scaffold synthesis, see: Dow, M.; Fisher, M.; James, T.; Marchetti, F.; Nelson, A. *Org. Biomol. Chem.* **2012**, *10*, 17−28 and references cited therein.

(28) For an account of the collective work in this area, see: He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029−1040 and references cited therein. Note: The nucleophilic aziridine functionality is retained in their synthesis.

(29) (a) Rolfe, A.; Young, K.; Hanson, P. R. *Eur. J. Org. Chem.* **2008**, *2008*, 5254−5262. (b) Zhou, A.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2951−2954. (c) Rolfe, A.; Young, K.; Volp, K.; Schoenen, F.; Neuenswander, B.; Lushington, G. H.; Hanson, P. R. *J. Comb. Chem.* **2009**, *11*, 732−738. (d) Zhou, A.; Rayabarapu, D. K.; Hanson, P. R. *Org. Lett.* **2009**, *11*, 531−534. (e) Rayabarapu, D. K.; Zhou, A.; Jeon, K.-O.; Samarakoon, T. B.; Rolfe, A.; Siddiqui, H.; Hanson, P. R. *Tetrahedron* **2009**, *65*, 3180−3188. (f) Ullah, F.; Samarakoon, T.; Rolfe, A.; Kurtz, R. D.; Hanson, P. R.; Organ, M. G. *Chem. - Eur. J.* **2010**, *16*, 10959−10962. (g) Rolfe, A.; Lushington, G. H.; Hanson, P. R. *Org. Biomol. Chem.* **2010**, *8*, 2198−2203. (h) Samarakoon, T. B.; Loh, J. K.; Yoon, S. Y.; Rolfe, A.; Le, L. S.; Hanson, P. R. *Org. Lett.* **2011**, *13*, 5148−5151.

(30) Ring opening of sulfonyl aziridines and epoxides with amines are among the original "Click" reactions detailed by Sharpless in their seminal paper. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(31) Chen, C.-Y.; Reamer, R. A. *Tetrahedron Lett.* **2009**, *50*, 1529−1532.

(32) Wang, Z.; Bois-Choussy, M.; Jia, Y.; Zhu, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2018−2022.

(33) (a) Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535−5542. (b) Ma, N.; Jia, Y.; Liu, Z.; Gonzalez-Zamora, E.; Bois-Choussy, M.; Malabarba, A.; Brunati, C.; Zhu, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 743−746. (c) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721−4736.

(34) (a) Boisnard, S.; Zhu, J. *Tetrahedron Lett.* **2002**, *43*, 2577−2580. (b) Temal-Laïb, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583−590.

(35) (a) Giannotti, D.; Viti, G.; Sbraci, P.; Pestellini, V.; Volterra, G.; Borsini, F.; Lecci, A.; Meli, A.; Dapporto, P.; Paoli, P. *J. Med. Chem.* **1991**, *34*, 1356−1362 and references cited therein. (b) Viti, G.; Nannicini, R.; Pestellini, V.; Bellarosa, D.; Giannotti, D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1461−1466.

(36) (a) Baxter, C. A.; O'Hagan, M.; O'Riordan, T. J. C.; Sheen, F. J.; Stewart, G. W.; Cleator, E. *Tetrahedron Lett.* **2010**, *51*, 1079−1082. (b) Pizzirani, D.; Kaya, T.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2010**, *12*, 2822−2825. (c) Gerard, B.; Duvall, J. R.; Lowe, J. T.; Murillo, T.; Wei, J.; Akella, L. B.; Marcaurelle, L. A. *ACS Comb. Sci.* **2011**, *13*, 365−374.

(37) Meutermans, W. D. F.; Gregory, T.; Bourne, G. T.; Golding, S. T.; Horton, D. A.; Campitelli, M. R.; Craik, D.; Scanlon, M.; Smythe, M. L. *Org. Lett.* **2003**, *5*, 2711−2714.

(38) Li, X.; Chen, N.; Xu, J. *Synthesis* **2010**, *20*, 3423−3428.

(39) (a) Beddoes, R. L.; Dalton, L.; Joule, J. A.; Mills, O. S.; Street, J. D.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 787−797. (b) Klug, H. P. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1968**, *24*, 792−802. (c) Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019−5022.

(40) (a) Barange, D. K.; Tu, Y.-C.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Adv. Synth. Catal.* **2011**, *353*, 41−48. (b) Chambers, C. S.; Patel, N.; Hemming, K. *Tetrahedron Lett.* **2010**, *51*, 4859−4861.

(41) As noted previously, this particular bis-nucleophile (2-piperidinemethanol) is racemic, and only one of two possible diastereomeric products was isolated resulting in a slightly lower yield (36% over two reactions), suggesting only one diastereomer intermediate underwent cyclization reaction (or potentially the aziridine ring opening was diastereoselective).

(42) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, P. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

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