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α-Haloarylsulfonamides: multiple cyclization pathways to skeletally diverse benzofused sultams

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ABSTRACT

The development of new methods to skeletally diverse sultams based on a central α-halo benzene sulfonamide building block is reported. Several salient features of this building block are utilized in multiple reaction pathways, including the Heck reaction, C- and O-arylation, Sonogashira–Pauson–Khand, Sonogashira-intramolecular hydroamination, and domino aza-Michael–Heck for the generation of five-, six-, and seven-membered benzofused bicyclic and tricyclic sultams.

1. Introduction

In recent years, there has been a rapidly growing demand for libraries of small molecules for high-throughput screening (HTS). This demand has presented challenging opportunities in molecular library development. In this regard, Diversity-Oriented Synthesis (DOS)[1,2] has emerged as an enabling platform for the production of multiple scaffolds displaying skeletal diversity, where a lack there of has been cited as a bottleneck in the drug discovery process.[1] Among several features that define DOS, functional group pairing[3] has surfaced as a significant component, which aims to selectively pair functional groups resulting in the generation of multiple scaffolds. Interest in the facile production of new sultams for biological screening has provided recent impetus for exploring new FG-pairing cyclization pathways of α-halo benzene sulfonamides. We herein report studies toward this goal revealing α-halo benzene sulfonamides as versatile starting materials whose features can be exploited in multiple reaction pathways to produce an array of five-, six-, and seven-membered benzofused sultams. Ultimately, we aim to utilize these methods in a broader DOS strategy for library production of sultams (Fig. 1).

Sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties.[4] In particular, a number of benzofused sultams have recently been reported that exhibit broad inhibitory properties against a variety of enzymes including: COX-2,[5] HIV integrase,[6] lipoxygenase,[7] Calpain I,[8] and MMP-2.[9] Moreover, a number of additional sultams have shown promising bioactivity, such as antiviral,[10] anticancer,[11] antimicrobial,[12] antimalarial,[13] antileukemic,[14] and AMPA receptor modulatory properties with potential for treating disorders of the brain.[15] This impressive biological profile is augmented by a number of chemical properties inherent to sulfonamides including facile coupling/alkylation pathways for sulfonamide formation, stability to hydrolysis, polarity, and their crystalline nature.[16]

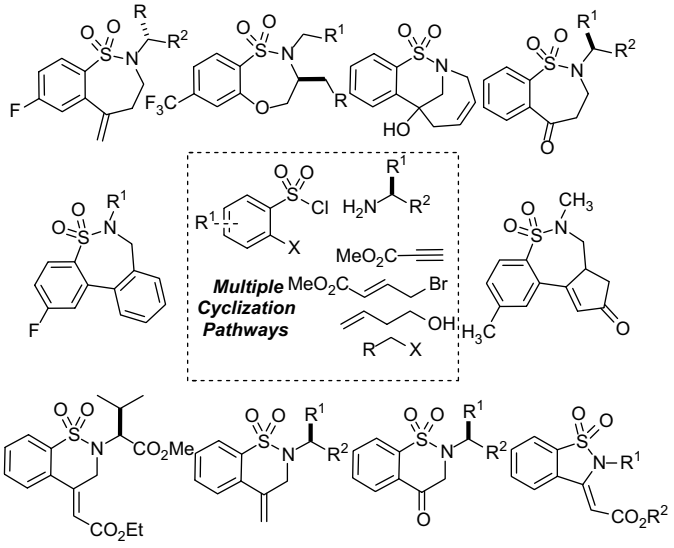

Figure 1. Multiple cyclization pathways toward skeletally diverse sultams.

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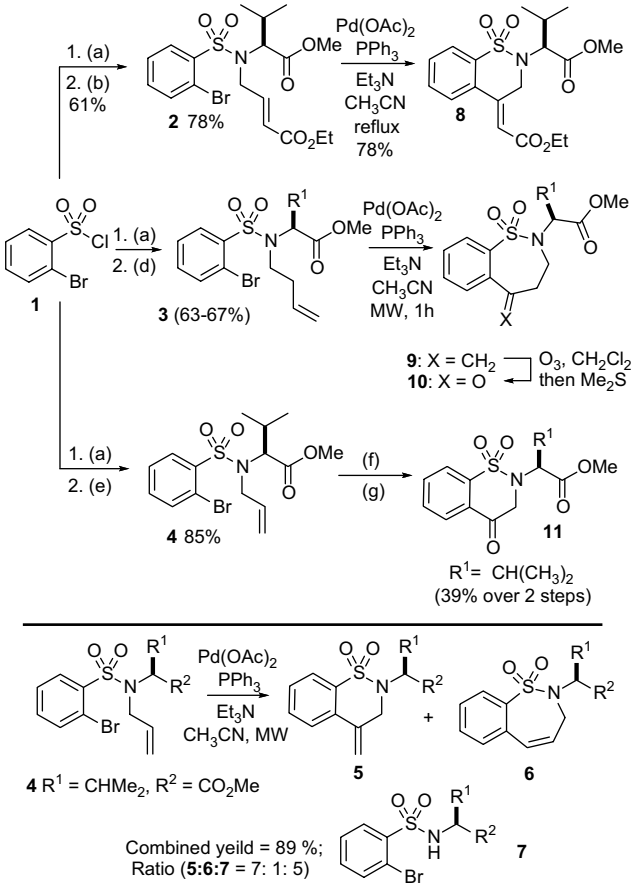
α-Haloarylsulfonamides represent an attractive building block for the production of benzofused sultams,[17] due to a number of key features. The most prominent include: (i) click coupling between starting α-halobenzenesulfonyl chlorides and amines under mild conditions generating the corresponding sulfonamides in quantitative yield, (ii) the α-halo group enhances the acidity of the aryl sulfonamide N–H enabling Mitsunobu and conventional alkylation reactions to occur under mild conditions, (iii) the α-halo group can be utilized in metal-catalyzed cross coupling or Li-halogen exchange chemistry, and (iv) a number of substituted α-halo benzene sulfonyl chlorides are commercially available. Taken collectively, these attributes guided our efforts in this study.

2. Results and discussion

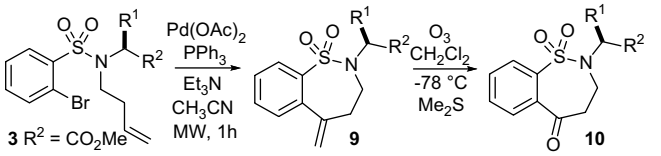
As outlined in Scheme 1, we began our initial investigation exploring Pd(0)-catalyzed Heck reactions with olefin containing sulfonamides **2**, **3**, and **4** (Scheme 1). Substrates **2** and **3** were designed to alleviate any potential issues with regioselective Heck reactions. Substrate **4** was a more promiscuous Heck substrate and deserves mention first. Sulfonamide **4** was prepared via simple coupling of sulfonyl chloride **1** with L-amino methyl ester·HCl under standard conditions (CH_2Cl_2, Et_3N, DMAP) and allylation with allyl bromide. Subsequent Heck conditions were explored [$Pd(OAc)_2$, Et_3N, 0.25 M in CH_3CN at 100 °C in a microwave] and produced a mixture of products via 6-*exo*-*trig* (**5**) and 7-*endo*-*trig* (**6**) pathways, along with product **7** resulting from deallylation.[18]

The regioselectivity concern of 6-*exo* versus 7-*endo* cyclization was not an issue when sulfonamide **2** was subjected to standard



Scheme 1. Intramolecular Heck reaction. (a) Amino ester, Et_3N, DMAP, CH_2Cl_2; (b) ethyl 4-bromocrotonate, K_2CO_3, CH_3CN, 60 °C; (c) amino ester, Et_3N, DMAP, CH_2Cl_2; (d) 4-buten-1-ol, DIAD, PPh_3, CH_2Cl_2, rt; (e) allyl bromide, K_2CO_3, CH_3CN, rt; (f) $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN; (g) O_3, CH_2Cl_2, −78 °C then Me_2S.

Table 1
Pd(0)-catalyzed Heck cyclizations of substrate **3**[a]



Entry	SM	Product	**9** yield[b] %	**10** yield[c] %
1	**3a**	R^1=CH_3	**9a** (72)	**10a** (84)
3	**3b**	R^1=CH_2CHMe_2	**9b** (91)	**10b** (82)
4	**3c**	R^1=H	**9c** (70)	**10c** (78)
5	**3d**	R^1=H, R^2=C_6H_5	**9d** (62)	**10d** (78)

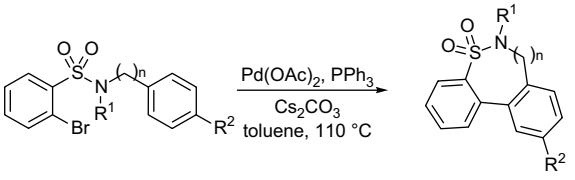
[a] Isolated yields.
[b] Heck conditions: substrate (1.00 mmol), $Pd(OAc)_2$ (0.1 mmol, 10.0 mol %), PPh_3 (0.2 mmol) in CH_3CN (0.25 M) at 100 °C for 1 h under microwave.
[c] O_3, −78 °C, CH_2Cl_2 then Me_2S.

Heck reaction conditions. Thus, treatment of **1** with L-amino methyl ester·HCl under the aforementioned conditions, followed by alkylation with ethyl 4-bromocrotonate, yielded the alkylated sulfonamide **2**, which upon subjection to Heck conditions in refluxing CH_3CN, afforded the desired δ-sultam **8** as the sole product via a selective 6-*exo* cyclization pathway.

The straightforward syntheses of the seven-membered sultams **9** were also realized as outlined in Scheme 1. Homo-allylation of the sulfonamide with 4-bromo-1-butene produced the alkylated product **3** in low yield. However, we found that performing the Mitsunobu reaction with 3-buten-1-ol in the presence of DIAD and PPh_3 gave superior yields of **3**.[19] Subsequent intramolecular Heck reaction of **3**, cleanly afforded the 7-*exo*-*trig* cyclization products **9** in excellent yields (Table 1). Ozonolysis of **9** produced the benzothiazepenones **10** in good to excellent yields. Similarly, the inseparable mixture of Heck products **5** and **6** was subjected to ozonolysis furnishing benzothiazenone **11** in pure form after isolation.

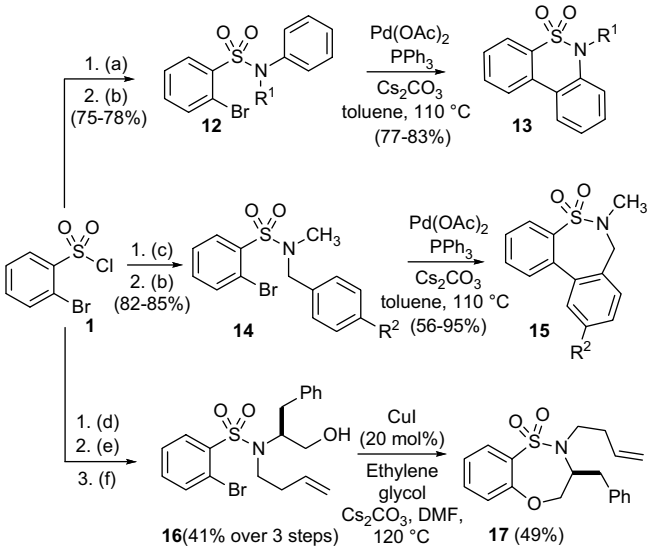
The chemistry of benzene sulfonamide was further extended to an intramolecular arylation reaction whereby the α-bromo aryl sulfonamide group was paired with an aromatic group.[20] The literature contains a single example of a six-membered sultam produced from an α-halobenzenesulfonamide using Pd(0)-catalysis.[21] However, in this intramolecular direct C-arylation, the yield was low. Treating **1** with aniline and subsequent alkylation with methyl iodide or ethyl iodide produced the corresponding sulfonamide **12**, which was subjected to $Pd(OAc)_2$, PPh_3, Cs_2CO_3 in toluene at 110 °C affording cyclized product **13** via a C-arylation pathway. The present method offers a practical method for synthesis of dibenzothiazine dioxides in excellent yields (Table 2, Scheme 2).

Table 2
Pd(0)-catalyzed C-arylation of substrates **12** and **14**[a]

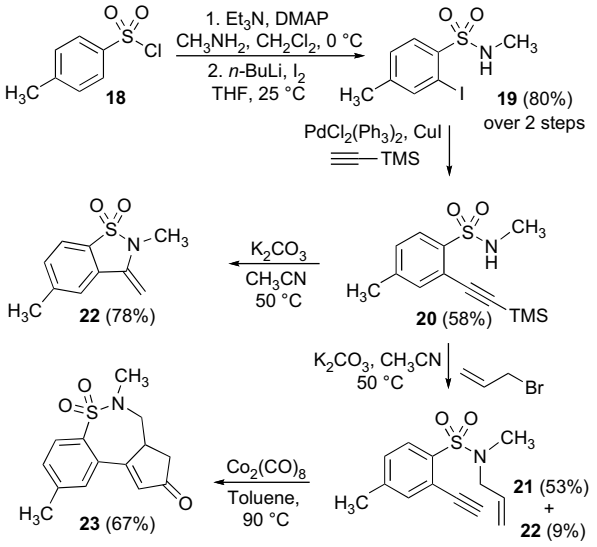


Entry	SM	Product	Yield[b] (%)
1	**12a**	n=0, R^1=Me, R^2=H	**13a** (83)
2	**12b**	n=0, R^1=Et, R^2=H	**13b** (77)
3	**14a**	n=1, R^1=Me, R^2=H	**15a** (85)
4	**14b**	n=1, R^1=Me, R^2=OMe	**15b** (56)
5	**14c**	n=1, R^1=Bn, R^2=H	**15c** (95)

[a] Isolated yields.
[b] Conditions: substrate (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol, 10.0 mol %), PPh_3 (0.2 mmol), Cs_2CO_3 (2.0 mmol) in toluene (4.0 mL) at 110 °C in sealed tube for 12–24 h.



Scheme 2. C- and O-arylation reactions. (a) Aniline, pyridine, CH_2Cl_2; (b) methyl iodide or ethyl iodide, K_2CO_3, CH_3CN, 50 °C; (c) benzyl amine, Et_3N, DMAP, CH_2Cl_2; (d) phenylalanine methyl ester, Et_3N, DMAP, CH_2Cl_2; (e) DIAD, PPh_3, 4-buten-1-ol; (f) $LiAlH_4$, THF, 0 °C to rt.



Scheme 3. Sonogashira-PK and Sonogashira-IHA strategies.

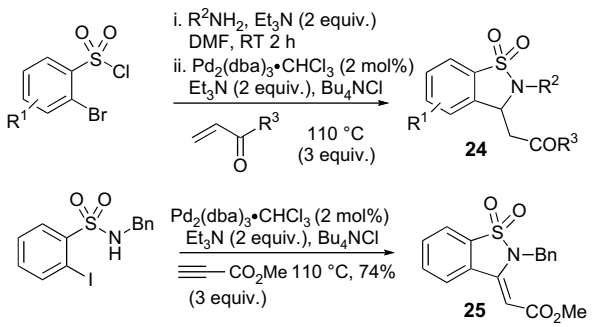
With this result in hand, we attempted the direct C-arylation to furnish a seven-membered sultam **15**. Treatment of **1** with benzyl amine and subsequent alkylation with methyl iodide furnished **14**, which was again subjected to $Pd(OAc)_2$ conditions at 110 °C for 24 h to afford the seven-membered benzofused sultam **15** in 85% yield (Scheme 2).

The method was next applied to an intramolecular O-arylation reaction[22] whereby the α-bromo aryl sulfonamide group was paired with an alcohol. Thus, **1** was coupled with phenylalanine methyl ester, followed by Mitsunobu reaction with 3-buten-1-ol and reduction with $LiAlH_4$ to furnish sulfonamide **16** in 41% over 3 steps. Sulfonamide **16** was treated with CuI (20 mol %) in the presence of $HOCH_2CH_2OH$ as a ligand in DMF at 120 °C to afford the O-arylation, cyclized product **17** in 49% yield (Scheme 2).

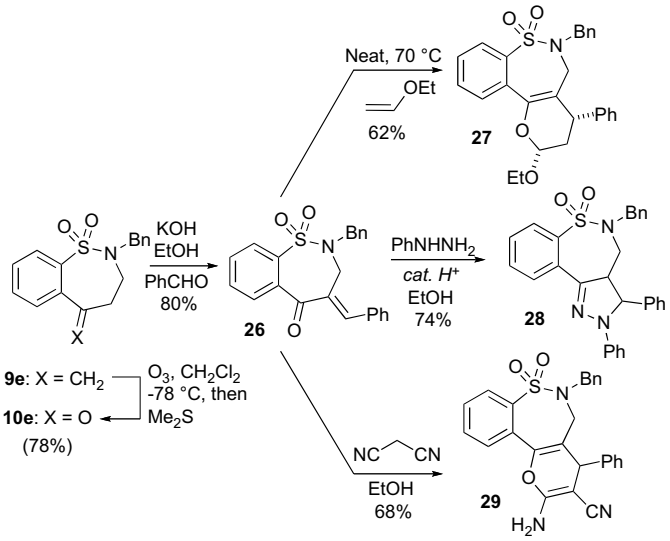
The chemistry of α-halobenzenesulfonamide was further extended to both Pauson–Khand (PK) and intramolecular hydroamination (IHA) reactions.[23] In this method, the α-bromo aryl sulfonamide group was attached to an alkyne under Sonogashira conditions and subsequently paired with both an alkene (PK) as well as an N–H (IHA). The reaction sequence began with the sulfonylation of methylamine with tosyl chloride **18** followed by iodination to afford 2-iodosulfonamide **19** in 80% over 2 steps (Scheme 3).[24] Compound **19** was subjected to Sonogashira reaction with trimethylsilyl acetylene in presence of $PdCl_2(PPh_3)_2$ and CuI to furnish sulfonamide **20**.[25] Alkylation of **20** with allyl bromide in presence of K_2CO_3 in CH_3CN at 50 °C afforded allylated enyne product **21** along with a small amount of the corresponding IHA product **22**. However, when the reaction of **20** was carried out in the same conditions in the absence of allyl bromide, sultam **22** was produced as the sole product in 78% yield, representing a formal intramolecular hydroamination of an acetylene via a 5-*exo* cyclization pathway. Finally, treatment of sulfonamide enyne **21** with $[Co_2(CO)_8]$ under thermal conditions (90 °C) furnished the tricyclic Pauson–Khand product **23** in 67% yield.

The production of sultam **22** via an intramolecular hydroamination pathway prompted us to explore the development of a one-pot protocol that would take advantage of the inherent nucleophilicity of the sulfonamide N–H. In this regard, we have previously reported a one-pot domino Heck-aza-Michael protocol for the synthesis of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides **24** (Scheme 4).[26] Such domino protocols are attractive strategies for the incorporation of multiple points of diversity in a one-pot multicomponent transformation. Thus, we investigated the application of α-haloaryl sulfonamides toward a domino aza-Michael–Heck protocol, whereby initial Michael addition of the sulfonamide into methyl propiolate, followed by an intramolecular Heck reaction yields the corresponding benzofused sultam. Thus, *N*-benzyl-2-iodobenzenesulfonamide was reacted with methyl propiolate under standard reaction conditions at 110 °C to cleanly afford the desired sultam **25** in 74% yield. We are currently investigating additional variants of this protocol.

As a final example, we explored additional chemistry of the seven-membered benzothiazepenones using a classical aldol reaction to produce enone **26**. The underlying principle behind this was a reagent-based DOS approach toward skeletal diversity. Thus, treatment of **10e** with benzaldehyde in the presence of KOH furnished **26** bearing an unsaturated ketone as a single isomer in 80% yield. This aldol condensation set the stage for further modifications as outlined in Scheme 5.[2a] Subsequent hetero-Diels–Alder (HDA) reaction of ethyl vinyl ether and **26** under neat conditions at 70 °C generated the tricyclic benzosultam **27** as a single regio- and diastereoisomer in 62% yield. Condensation reaction of **26** with phenyl hydrazine produced the pyrozoline-containing sultam **28** in 82% yield as a 1:1 mixture of diastereomers.[27] Finally, reaction of malononitrile with **26** produced the tricyclic sultams **29** in 68% yield.



Scheme 4. Domino aza-Michael–Heck strategy.



Scheme 5. Reagent-based DOS approach.

3. Conclusion

In conclusion, we have developed a variety of new reaction pathways toward the synthesis of skeletally diverse benzofused sultams. These methods employ commercially available α-haloaryl sulfonyl chlorides in achieving multiple reaction pathways such as Heck, Sonogashira-NH addition, Sonogashira–Pauson–Khand, C- and O-arylations to produce five-, six-, and seven-membered sultams in good to excellent yields. We also demonstrated that Heck reaction products undergo facile ozonoly sis/aldol to produce an intermediate unsaturated ketone, which was utilized in a reagent-based DOS approach to furnish additional diverse sultams. All the sultam reported herein have been submitted to NIH biological outreach partners for biological screening through the NIH Molecular Library Screening Network (NIH-MLSCN). The utilization of the reported method is currently being employed in library production and the results will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out in flame-dried glassware under argon. Toluene, THF, Et_2O, and CH_2Cl_2 were purified by passage through a purification system (Solv-Tek) employing activated Al_2O_3.[28] Et_3N was distilled from CaH_2. Flash column chromatography was performed with Merck silica gel (230–400 mesh). Thin layer chromatography was performed on silica gel $60F_{254}$ plates. ^1H and ^{13}C spectra were recorded in $CDCl_3$ on either a Bruker DRX-400 or a Bruker AM-500 spectrometer operating at 400/100 MHz and 500/125 MHz, respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Infrared data was obtained on a Nicolet 320 Fourier Transform Infrared Spectrophotometer. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

4.2. Synthetic studies

*4.2.1. (S,E)-Ethyl-4-(2-bromo-N-(1-methoxy-3-methyl-1-oxobutan-2-yl)phenylsulfonamido)but-2-enoate (**2**)*

Into a flame-dried flask were added **1** (2.0 g, 7.82 mmol), H-Leu-OMe (1.42 g, 7.82 mmol), and CH_2Cl_2 (20 mL). After stirring for 5 min at rt, Et_3N (2.32 mL, 16.4 mmol) was added and the reaction flask stirred at rt for 2 h. The crude reaction mixture was filtered and concentrated under reduced pressure. A portion of the crude material (208 mg, 0.56 mmol) was added to a flame-dried flask, to which Cs_2CO_3 (294 mg, 1.165 mmol) and dry CH_3CN (6 mL, 0.1 M) were added. After stirring for 5 min, (*E*)-ethyl 4-bromobut-2-enoate (0.66 mmol) was added and the reaction mixture was stirred at 60 °C until completion of reaction (as monitored by TLC). The crude reaction mixture was filtered through a pad of Celite, washed with CH_2Cl_2, concentrated under reduced pressure, and subjected to flash chromatography (1:1 EtOAc/hexane) to provide **2** (201 mg, 0.44 mmol, 78%) as a clear oil. FTIR (neat): 2972, 1739, 1720, 1342,1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.11 (dd, *J*=1.7, 7.9 Hz, 1H), 7.71 (dd, *J*=7.8, 1.3 Hz, 1H), 7.43 (td, *J*=7.7, 1.3 Hz, 1H), 7.37 (dt, *J*=7.5, 1.8 Hz, 1H), 6.84 (ddd, *J*=15.8, 7.8, 5.1 Hz, 1H), 5.87 (dt, *J*=15.8, 1.5 Hz, 1H), 4.41 (dddd, *J*=18.4, 9.0, 6.4, 1.5 Hz, 2H), 4.14 (q, *J*=7.1 Hz, 2H), 4.09 (d, *J*=10.3 Hz, 1H), 3.54 (s, 3H), 2.15–2.06 (m, 1H), 1.29–1.23 (m, 3H), 1.02 (d, *J*=6.6 Hz, 3H), 0.91 (dd, *J*=9.0, 3.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.0, 165.7, 144.4, 139.2, 135.4, 133.8, 133.1, 127.6, 123.1, 120.3, 65.5, 60.4, 51.7, 46.5, 28.9, 19.8, 19.3, 14.2; HRMS calcd for $C_{18}H_{24}BrNNaO_6S$ $(M+Na)^+$ 484.0405, found 484.0379.

*4.2.2. (S)-Methyl-2-(2-bromo-N-(but-3enyl)phenylsulfonamido)-propanoate (**3a**)*

Into a flame-dried flask under argon were added **1** (7.82 mmol), amino ester/amine (7.82 mmol), and CH_2Cl_2 (20 mL). Et_3N (16.4 mmol) was added and the reaction flask stirred at rt for 2 h. The crude reaction mixture was filtered and concentrated under reduced pressure. A portion of the crude (2.56 g, 7.64 mmol) was added to a flame-dried flask under argon (2.56 g, 7.64 mmol), to which were added PPh_3 (2.21 g, 8.45 mmol) and dry CH_2Cl_2 (40 mL). After stirring for 5 min, 3-buten-1-ol (0.72 mL, 8.45 mmol) was added followed by dropwise addition of diisopropyl azodicarboxylate (DIAD) (1.71 mL, 8.45 mmol) at rt. The reaction mixture was stirred for 3 h, after which time the crude mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 EtOAc/hexane) to provide **3a** (2.34 g, 79% yield) as a white solid. FTIR (neat): 3064, 2950, 1795, 1448, 1434, 1342, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.15 (dd, *J*=7.9, 1.7 Hz, 1H), 7.71 (dd, *J*=7.8, 1.3 Hz, 1H), 7.44 (td, *J*=7.7, 1.3 Hz, 1H), 7.37 (td, *J*=7.6, 1.7 Hz, 1H), 5.62 (ddt, *J*=17.2, 10.5, 7.7 Hz, 1H), 4.96 (dd, *J*=3.4, 1.8 Hz, 1H), 4.94 (dq, *J*=11.8, 1.7 Hz, 1H), 4.82 (q, *J*=7.4 Hz, 1H), 3.63 (s, 3H), 3.57–3.47 (m, 1H), 3.17 (ddd, *J*=15.3, 9.3, 7.2 Hz, 1H), 2.28–2.21 (m, 2H), 1.50 (d, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.06, 135.44, 134.40, 133.47, 132.16, 127.50, 116.92, 55.43, 52.29, 45.14, 34.69, 16.48; HRMS calcd for $C_{14}H_{18}BrNNaO_4S$ $(M+Na)^+$ 398.0038, found 398.0045.

*4.2.3. (S)-Methyl 2-(2-bromo-N-(but-3-enyl)phenylsulfonamido)-4-methylpentanoate (**3b**)*

Using a similar procedure as that used to produce sultam **3a**, sultam **3b** was produced in 69% yield. FTIR (neat): 3064, 2955, 1795, 1448, 1434, 1336, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.14 (dd, *J*=7.9, 1.7 Hz, 1H), 7.45 (td, *J*=7.7, 1.3 Hz, 1H), 7.38 (td, *J*=7.6, 1.7 Hz, 2H), 5.72 (ddt, *J*=17.1, 10.2, 6.8 Hz, 1H), 5.04 (dddd, *J*=16.0, 1.5, 1.5, 1.5 Hz, 1H), 5.03 (m, 1H), 4.56 (dd, *J*=8.8, 5.6 Hz, 1H), 3.59–3.51 (m, 1H), 3.54 (s, 3H), 3.32 (ddd, *J*=16.0, 11.0, 5.2 Hz, 1H), 2.57–2.48 (m, 1H), 2.34–2.25 (m, 1H), 1.78–1.69 (m, 2H), 1.65–1.56 (m, 1H), 0.93 (dd, *J*=17.1, 6.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 139.2, 135.5, 134.7, 133.4, 132.4, 127.5, 120.4, 117.0, 58.3, 52.1, 45.8, 39.4, 35.5, 24.5, 22.6, 21.7; HRMS calcd for $C_{17}H_{24}BrNNaO_4S$ $(M+Na)^+$ 440.0507, found 440.0500.

*4.2.4. Methyl-2-(2-bromo-N-(but-3-enyl)phenylsulfonamido)-acetate (**3c**)*

Using a similar procedure as that used to produce sultam **3a**, sultam **3c** was produced in 87% yield. FTIR (neat): 2951, 1753, 1340,

1161, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (dd, J=7.8, 1.8 Hz, 1H), 7.74 (dd, J=7.8, 1.3 Hz, 1H), 7.45 (td, J=7.5, 1.3 Hz, 1H), 7.40 (td, J=7.5, 1.7 Hz, 1H), 5.59 (ddt, J=17.0, 10.2, 6.8 Hz, 1H), 5.01 (ddd, J=11.0, 6.6, 5.5 Hz, 2H), 4.28 (s, 2H), 3.71 (s, 3H), 3.57–3.38 (m, 2H), 2.34–2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.5, 139.3, 135.5, 134.1, 133.6, 132.2, 127.5, 120.5, 117.5, 52.3, 48.5, 47.6, 32.0; HRMS calcd for $C_{13}H_{16}BrNNaO_4S$ $(M+Na)^+$ 383.9881, found 383.9882.

4.2.5. *N-Benzyl-2-bromo-N-(but-3-enyl)benzenesulfonamide (**3d**)*

Using a similar procedure as that used to produce sultam **3a**, sultam **3d** was produced in 67% yield. FTIR (neat): 3064, 2927, 1641, 1448, 1434, 1332, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.16 (dd, J=7.8, 1.8 Hz, 1H), 7.76 (dd, J=7.8, 1.4 Hz, 1H), 7.44 (td, J=7.6, 1.4 Hz, 1H), 7.40 (td, J=7.6, 1.9 Hz, 1H), 7.34–7.26 (m, 5H), 5.56–5.47 (m, 1H), 4.94–4.92 (m, 1H), 4.90 (t, J=1.3 Hz, 1H), 4.57 (s, 2H), 3.26 (dd, J=8.4, 6.8 Hz, 2H), 2.16–2.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.47, 135.90, 135.53, 134.30, 133.49, 132.34, 128.63, 128.26, 127.80, 127.51, 120.52, 117.13, 77.25, 77.00, 76.75, 51.26, 46.01, 31.90; HRMS calcd for $C_{17}H_{18}BrNNaO_2S$ $(M+Na)^+$ 402.0140, found 402.0139.

4.2.6. *(S)-Methyl 3-(N-allyl-2-bromophenylsulfonamido)-5-methyl-2-oxohexanoate (**4**)*

Using a similar procedure as that used to produce sultam **2**, sultam **4** was produced as a clear oil in 85% yield. $[\alpha]_D^{20}$ −42.8 (*c* 3.38, CH_2Cl_2), colorless oil; FTIR (neat): 2966, 1740, 1340, 1163, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.01–7.28 (aromatic H, 4H), 5.80 (m, 1H), 5.06 (d, J=17.2 Hz, 1H), 4.91 (d, J=10.2 Hz, 1H), 4.49 (dd, J=6.4, 3.9 Hz, 1H), 4.10 (dd, J=16.4, 8.0 Hz, 1H), 3.93 (d, J=10.4 Hz, 1H), 3.40 (s, 3H), 2.10 (m, 1H), 0.94 (d, J=6.6 Hz, 3H), 0.80 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.7, 139.4, 135.5, 135.3, 133.6, 132.8, 127.5, 120.1, 117.3, 65.5, 51.3, 48.6, 28.5, 19.5, 18.8; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}BrNO_4SNa$ 412.0194 $(M+Na)^+$, found 412.0181.

4.2.7. *Sultam (**5**)*

Into a microwave vial were added sulfonamide **4** (1.77 g, 4.30 mmol), $Pd(OAc)_2$ (0.43 mmol, 96 mg), PPh_3 (0.86 mmol, 225 mg), CH_3CN (17 mL), and Et_3N (1.8 mL, 12.9 mmol). After stirring for 5 min, the reaction was run in the microwave at 100 °C for 1 h. After 1 h, the reaction mixture was cooled to rt, filtered through a small Celite pad, and thoroughly washed with CH_2Cl_2. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane/EtOAc) to provide a 1.24 g (89%) of a mixture of compounds **5**/**6**/**7** [1:0.14:0.74 based on ^1H NMR] as a yellow oil. FTIR (neat): 2964, 1740, 1340, 1170, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.06–7.41 (aromatic H, 4H), 5.78 (s, 1H), 5.25 (s, 1H), 4.67 (d, J=6.7 Hz, 1H), 4.49 (d, J=6.8 Hz, 1H), 4.11 (d, J=10.6 Hz, 1H), 3.25 (s, 3H), 1.68 (m, 1H), 0.92 (d, J=6.8 Hz, 3H), 0.06 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.2, 136.0, 134.3, 133.5, 131.1, 127.6, 125.3, 120.4, 113.8, 64.3, 51.4, 47.9, 27.9, 19.2, 18.8; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}NO_4SNa$ 332.0932 $(M+Na)^+$, found 332.0936.

4.2.8. *Intramolecular Heck reaction to sultam **8***

To the alkylated sulfonamide **2** were added $Pd(OAc)_2$ (12.5 mg, 0.056 mmol), PPh_3 (29 mg, 0.11 mmol), and Et_3N (0.23 mL, 1.68 mmol) and the reaction mixture was heated at 70 °C for overnight. After 12 h the reaction mixture was cooled to rt, filtered through a small Celite pad, and thoroughly washed with CH_2Cl_2. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane/EtOAc) to provide **8** (67% yield) as a yellow oil. $[\alpha]^{25}$ −12.1 (*c* 0.05, $CHCl_3$); FTIR (neat): 2968, 1739, 1332, 1199, 1117, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.94 (dd, J=7.9, 0.9 Hz, 1H), 7.68–7.58 (m, 1H), 7.51 (ddd, J=8.0, 6.4, 2.5 Hz, 2H), 6.96 (s, 1H), 4.56 (d, J=10.4 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.78 (s, 3H), 3.59 (s, 2H), 2.24 (ddt, J=13.3, 10.4, 6.7 Hz, 1H), 1.22 (t, J=7.1 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 0.79 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.7, 170.6, 132.5, 132.1, 131.4, 128.1, 127.8, 124.0, 122.1, 113.5, 62.5, 61.2, 52.5, 36.6, 29.9, 19.1, 18.6, 14.1; HRMS calcd for $C_{18}H_{23}NO_6SNa$ $(M+Na)^+$ 404.1144, found 404.1146.

4.2.9. *(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-5-methylene-α-(2-methylpropyl)-, methyl ester, 1,1-dioxide (**9b**)*

Into a microwave vial were added sulfonamide **3b** (1.8 g, 4.30 mmol), $Pd(OAc)_2$ (0.43 mmol, 96 mg), PPh_3 (0.86 mmol, 225 mg), CH_3CN (17 mL), and Et_3N (1.8 mL, 12.9 mmol). After stirring for 5 min, the reaction was run in the microwave at 100 °C for 1 h. After 1 h, the reaction mixture was cooled to rt and filtered through a small Celite pad and thoroughly washed with CH_2Cl_2. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane/EtOAc) to provide 1.29 g (89%) of the title compound **9b** as a yellow oil. $[\alpha]^{25}$ −35.4 (*c* 7.30, $CHCl_3$); colorless liquid; FTIR (neat): 2954, 2869, 1741, 1467, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.46 (dd, J=7.8, 1.1 Hz, 1H), 8.03 (td, J=7.5, 1.3 Hz, 1H), 7.97–7.89 (m, 2H), 5.86 (d, J=0.7 Hz, 1H), 5.82 (d, J=1.2 Hz, 1H), 5.23 (dd, J=9.4, 6.0 Hz, 1H), 4.32 (ddd, J=13.0, 8.2, 4.6 Hz, 1H), 4.19 (dt, J=10.7, 5.1 Hz, 1H), 3.92 (s, 3H), 3.22–2.96 (m, 2H), 2.19 (dq, J=17.1, 8.7 Hz, 2H), 2.04 (ddd, J=13.6, 6.7, 6.5 Hz, 1H), 1.44 (d, J=6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.4, 147.0, 139.7, 139.7, 132.2, 129.9, 127.2, 126.1, 119.0, 57.5, 51.7, 45.0, 38.1, 35.0, 24.3, 22.8, 21.3; HRMS calcd for $C_{17}H_{23}NNaO_4S$ $(M+Na)^+$ 360.1245, found 360.1224.

4.2.10. *(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-α-methyl-5-methylene-, methyl ester, 1,1-dioxide (**9a**)*

Using a similar procedure as that used to produce sultam **9b**, sultam **9a** was produced in 72% yield. $[\alpha]^{25}$ −34.0 (*c* 3.45, $CHCl_3$); colorless liquid; FTIR (neat): 2951, 1750, 1365, 1170, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.88 (dd, J=7.9, 1.1 Hz, 1H), 7.46 (td, J=7.6, 1.3 Hz, 1H), 7.36 (td, J=7.7, 1.5 Hz, 2H), 5.29 (s, 1H), 5.26 (s, 1H), 4.69 (q, J=7.3 Hz, 1H), 3.70 (t, J=4.3 Hz, 2H), 3.46 (s, 3H), 2.52 (ddd, J=14.4, 6.2, 5.9 Hz, 2H), 1.33 (d, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.7, 147.0, 139.8, 139.7, 132.2, 130.1, 127.3, 126.2, 119.3, 55.1, 52.0, 45.5, 35.5, 16.1; HRMS calcd for $C_{14}H_{17}NNaO_4S$ $(M+Na)^+$ 318.0776, found 318.0780 (FAB).

4.2.11. *(S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-5-methylene-, methyl ester, 1,1-dioxide (**9c**)*

Using a similar procedure as that used to produce sultam **9b**, sultam **9c** was produced in 70% yield. FTIR (neat): 2952, 1755, 1417, 1128, 860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.92 (dd, J=7.8, 1.2 Hz, 1H), 7.52 (td, J=7.5, 1.4 Hz, 1H), 7.44–7.35 (m, 2H), 5.36 (d, J=0.9 Hz, 1H), 5.28 (d, J=1.2 Hz, 1H), 3.83 (s, 4H), 3.70 (s, 3H), 2.58 (t, J=4.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 168.9, 146.8, 140.2, 137.7, 132.8, 130.5, 127.5, 127.5, 119.7, 52.2, 50.5, 48.8, 32.6; HRMS calcd for $C_{13}H_{15}NNaO_4S$ $(M+Na)^+$ 304.0619, found 304.0613.

4.2.12. *1,2-Benzothiazepine, 2,3,4,5-tetrahydro-5-methylene-2-(phenylmethyl)-, 1,1-dioxide (**9d**)*

Using a similar procedure as that used to produce sultam **9b**, sultam **9d** was produced in 62% yield. FTIR (neat): 2943, 1352, 1336, 1163, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (dd, J=7.7, 1.3 Hz, 1H), 7.56 (td, J=7.5, 1.4 Hz, 1H), 7.45 (ddd, J=16.2, 7.6, 1.3 Hz, 2H), 7.38–7.29 (m, 5H), 5.38 (d, J=0.7 Hz, 1H), 5.31 (t, J=2.0 Hz, 1H), 4.18 (s, 2H), 3.60 (s, 2H), 2.55 (t, J=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.1, 140.6, 137.4, 135.7, 132.8, 130.6, 128.6, 128.3, 128.2, 128.2, 127.9, 127.6, 119.7, 50.0, 47.6, 31.5; HRMS calcd for $C_{17}H_{17}NNaO_2S$ $(M+Na)^+$ 322.0878, found 322.0865.

*4.2.13. (S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-α-(2-methylpropyl)-5-oxo-, methyl ester, 1,1-dioxide (**10b**)*

To a round bottom flask were added **9b** (1.88 g, 5.57 mmol), Sudan III (1 mg), and CH_2Cl_2 (50 mL). The reaction mixture was cooled down to −78 °C and O_3 was bubbled into the solution for 15 min. After such time, Me_2S (5 mL) was added dropwise upon disappearance of the pink color of the crude reaction mixture. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (4:1 hexanes/EtOAc) to provide 82% yield of the desired product (**10c**) as a colorless oil. $[\alpha]^{25}$ 8.7 (*c* 1.39, $CHCl_3$); FTIR (neat): 2956, 1741, 1693, 1342, 1203, 1172, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.00 (ddd, *J*=7.0, 4.4, 2.5 Hz, 1H), 7.90 (ddd, *J*=8.8, 4.8, 2.2 Hz, 1H), 7.65–7.62 (ddd, *J*=5.0, 2.4, 2.1 Hz, 2H), 4.78 (dd, *J*=8.3, 7.3 Hz, 1H), 3.75–3.50 (m, 2H), 3.49–3.36 (m, 3H), 3.18 (dt, *J*=13.9, 5.0 Hz, 1H), 1.81–1.57 (m, 4H), 1.02 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 198.9, 171.1, 140.8, 135.6, 132.4, 132.0, 129.4, 126.3, 58.9, 52.0, 42.3, 39.9, 38.0, 24.5, 23.1, 21.0; HRMS calcd for $C_{16}H_{21}NNaO_5S$ $(M+Na)^+$ 362.1038, found 362.1047.

*4.2.14. (S)-1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-α-methyl-5-oxo-, methyl ester, 1,1-dioxide (**10a**)*

Using a similar procedure as that used to produce sultam **10b**, sultam **10a** was produced in 84% yield as a colorless oil. $[\alpha]^{25}$ 30.5 (*c* 0.67, $CHCl_3$); FTIR (neat): 2935, 1693, 1589, 1315, 1280, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.99 (ddd, *J*=8.8, 4.8, 2.4 Hz, 1H), 7.87 (ddd, *J*=9.2, 4.8, 2.4 Hz, 1H), 7.66 (ddd, *J*=8.8, 4.4, 2.0 Hz, 2H), 4.81 (q, *J*=7.2 Hz, 1H), 3.50 (s, 3H), 3.45–3.64 (m, 3H), 3.24 (ddd, *J*=10.8, 6.4, 4.4 Hz, 1H), 1.45 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.1, 171.1, 140.7, 135.7, 132.4, 132.0, 129.4, 126.2, 56.2, 52.2, 42.3, 40.0, 16.0; HRMS calcd for $C_{13}H_{15}NNaO_5S$ $(M+Na)^+$ 320.0569, found 320.0570.

*4.2.15. 1,2-Benzothiazepine-2(3H)-acetic acid, 4,5-dihydro-5-oxo-, methyl ester, 1,1-dioxide (**10c**)*

Using a similar procedure as that used to produce sultam **10b**, sultam **10c** was produced in 78% yield as a colorless oil. FTIR (neat): 2954, 1751, 1693, 1342, 1163, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.95 (ddd, *J*=9.0, 5.6, 3.2 Hz, 1H), 7.83 (ddd, *J*=9.0, 6.4, 3.0 Hz, 1H), 7.68 (ddd, *J*=10.0, 5.7, 3.3 Hz, 2H), 4.11 (s, 2H), 3.66 (s, 3H), 3.62 (t, *J*=6.0 Hz, 2H), 3.34 (t, *J*=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 199.8, 168.8, 138.8, 136.0, 132.7, 132.0, 129.5, 126.3, 52.3, 51.2, 45.3, 41.7; HRMS calcd for $C_{12}H_{13}NNaO_5S$ $(M+Na)^+$ 306.0412, found 306.0425.

*4.2.16. 1,2-Benzothiazepin-5(2H)-one, 3,4-dihydro-2-(phenylmethyl)-, 1,1-dioxide (**10d**)*

Using a similar procedure as that used to produce sultam **10b**, sultam **10d** was produced in 78% yield as a colorless oil. FTIR (neat): 2956, 1693, 1512, 1340, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.06 (ddd, *J*=8.8, 5.6, 3.6 Hz, 1H), 7.83–7.60 (m, 3H), 7.49–7.24 (m, 5H), 4.30 (s, 2H), 3.49 (t, *J*=6.0 Hz, 2H), 3.14 (t, *J*=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 200.6, 137.5, 137.2, 135.0, 132.9, 131.7, 129.3, 128.8, 128.3, 128.2, 127.2, 52.5, 43.5, 41.2; HRMS calcd for $C_{16}H_{15}NNaO_3S$ $(M+Na)^+$ 324.0670, found 324.0667 (FAB).

*4.2.17. Sultam (**11**)*

Using a similar procedure as that used to produce sultam **8**, sultam **4** was produced and carried through crude using a similar procedure as that used to produce sultam **10**, to yield **11** (39% over 2 steps) as a clear oil. FTIR (neat): 2964, 1739, 1469, 1340, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (d, *J*=7.3 Hz, 1H), 7.82 (d, *J*=7.5 Hz, 1H), 7.78–7.66 (m, 2H), 4.70 (d, *J*=18.8 Hz, 1H), 4.39 (d, *J*=18.9 Hz, 1H), 4.22 (d, *J*=10.0 Hz, 1H), 3.20 (s, 3H), 2.28–2.03 (m, 1H), 1.05 (d, *J*=6.7 Hz, 4H), 0.96 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 188.4, 170.3, 140.1, 134.2, 132.9, 129.9, 128.1, 123.4, 65.3, 54.0, 51.6, 28.4, 19.1, 19.1; HRMS calcd for $C_{14}H_{17}NNaO_5S$ $(M+Na)^+$ 334.0725, found 334.0737.

*4.2.18. N-Benzyl-2-bromo-N-methylbenzenesulfonamide (**12a**)*

Into a flame-dried flask under argon were added sulfonyl chloride **1** (1.0 g, 3.9 mmol), aniline (0.36 mL, 3.9 mmol), dry CH_2Cl_2 (39 mL, 0.1 M), and pyridine (1.58 mL, 1.95 mmol). After stirring at rt for 2 h the crude reaction mixture was filtered, washed with water (2×20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. A portion of the crude material (1.0 g, 0.32 mmol) was added to a flame-dried flask followed by the addition of CH_3I (1.0 mL, 1.61 mmol), K_2CO_3 (2.22 g, 1.61 mmol), and dry CH_3CN (12 mL, 0.1 M) and the reaction mixture was stirred at rt, until the starting material disappeared as monitored by TLC. The crude reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane/EtOAc) to provide **12a** (88% yield) as a clear oil; FTIR (neat): 1493, 1339, 1157, 741, 565 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.83 (dd, *J*=7.1, 2.0 Hz, 1H), 7.66 (dd, *J*=7.0, 2.0 Hz, 1H), 7.36–7.07 (m, 7H), 3.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 141.0, 138.2, 135.8, 133.9, 133.1, 129.4, 127.6, 127.6, 127.2, 120.7, 39.7; HRMS calcd for $C_{13}H_{12}BrNNaO_2S$ $(M+Na)^+$ 347.9670, found 347.9636.

*4.2.19. N-Benzyl-2-bromo-N-ethylbenzenesulfonamide (**12b**)*

Using a similar procedure as that used to produce sultam **12a**, sultam **12b** was produced as a yellow oil in 85% yield. FTIR (neat): 2974, 1490, 1336, 1174, 741, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.77 (dd, *J*=7.8, 1.8 Hz, 1H), 7.65 (dd, *J*=7.8, 1.3 Hz, 1H), 7.33–7.08 (m, 7H), 3.86 (q, *J*=7.1 Hz, 2H), 1.09 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 138.8, 138.3, 135.6, 133.7, 133.1, 129.7, 129.4, 128.2, 127.5, 120.6, 47.7, 14.9; HRMS calcd for $C_{14}H_{14}BrNNaO_2S$ $(M+Na)^+$ 361.9827, found 361.9830.

*4.2.20. Intramolecular C-arylation to 6H-dibenzo[c,e][1,2]thiazine, 6-methyl-, 5,5-dioxide (**13a**)*

To **12a** were added $Pd(OAc)_2$ (3.02 mg, 0.0135 mmol), PPh_3 (7.08 mg, 0.027 mmol), Cs_2CO_3 (131 mg, 0.405 mmol), and toluene (4 mL). The crude reaction mixture was heated at 110 °C for 12–24 h, until the SM was consumed, as indicated by TLC. After 24 h the reaction mixture was cooled to rt, filtered through a small Celite pad, and thoroughly washed with CH_2Cl_2. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (4:1 hexane/EtOAc) to afford the desired product **13a** in 83% yield as a yellow oil. FTIR (neat): 1477, 1327, 1174, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.03 (td, *J*=6.5, 1.4 Hz, 2H), 7.98 (d, *J*=8.0 Hz, 1H), 7.72 (td, *J*=7.5, 1.4 Hz, 1H), 7.58 (td, *J*=7.7, 1.1 Hz, 1H), 7.52 (ddd, *J*=8.1, 7.5, 1.5 Hz, 1H), 7.38–7.29 (m, 2H), 3.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 139.4, 134.1, 132.4, 132.3, 130.4, 128.2, 125.5, 125.4, 124.6, 123.9, 122.4, 119.3, 32.7; HRMS calcd for $C_{13}H_{11}NNaO_2S$ $(M+Na)^+$ 268.0408, found 268.0430.

*4.2.21. 6H-Dibenzo[c,e][1,2]thiazine, 6-ethyl-, 5,5-dioxide (**13b**)*

Using a similar procedure as that used to produce sultam **13a**, sultam **13a** was produced in 77% yield as a yellow oil. FTIR (neat): 1635, 1336, 1166, 1095, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.03–7.95 (m, 3H), 7.71 (td, *J*=7.6, 1.3 Hz, 1H), 7.62 (dd, *J*=7.7, 1.0 Hz, 1H), 7.57 (td, *J*=7.7, 1.1 Hz, 1H), 7.50 (ddd, *J*=8.3, 7.3, 1.5 Hz, 1H), 7.40 (dd, *J*=8.0, 1.1 Hz, 1H), 7.37 (td, *J*=7.6, 1.1 Hz, 1H), 3.99 (q, *J*=7.1 Hz, 2H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 140.9, 139.4, 134.8, 133.5, 133.3, 130.2, 129.9, 129.5, 129.0, 128.5, 128.3, 127.5, 56.1, 39.0; HRMS calcd for $C_{14}H_{13}NNaO_2S$ $(M+Na)^+$ 282.0565, found 282.0553.

*4.2.22. 2-Bromo-N-(4-methoxybenzyl)-N-methylbenzene-sulfonamide (**14b**)*

Into a flame-dried flask under argon were added 2-bromobenzenesulfonyl chloride (150 mg, 0.58 mmol), methylamine (1.76 mmol), and dry CH_2Cl_2 (6 mL). Et_3N (0.11 mL, 0.76 mmol) and DMAP (5 mg, 0.1 mmol) were added and the reaction flask stirred at rt for 2 h. The crude reaction mixture was filtered and washed with water. The mixture was dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography (1:1 hexane/EtOAc) to provide the corresponding *N*-methyl sulfonamide in 98% yield as a yellow solid. To the 2-bromo-*N*-methylbenzene sulfonamide (0.56 mmol) in dry CH_3CN (6 mL, 0.1 M) was added Cs_2CO_3 (294 mg, 1.165 mmol). *p*-Methoxy benzyl bromide (0.66 mmol) was added and the reaction mixture was stirred at 60 °C, until the SM disappeared as monitored by TLC. The crude reaction mixture was filtered through a pad of Celite, washed with CH_2Cl_2, concentrated under reduced pressure, and purified by flash chromatography (1:1 hexane/EtOAc) to provide 2-bromo-*N*-(4-methoxybenzyl)-*N*-methylbenzene sulfonamide **14b** in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.15 (dd, *J*=7.8, 1.8 Hz, 1H), 7.78 (dd, *J*=7.8, 1.3 Hz, 1H), 7.47 (td, *J*=7.6, 1.3 Hz, 1H), 7.41 (td, *J*=7.6, 1.8 Hz, 1H), 7.24 (d, *J*=7.8 Hz, 1H), 6.89 (d, *J*=7.5 Hz, 1H), 6.86 (d, *J*=2.2 Hz, 1H), 6.83 (dd, *J*=8.1, 2.2 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.8, 135.6, 133.6, 132.4, 129.6, 127.5, 120.5, 113.6, 113.2, 55.20, 54.04, 33.94; HRMS calcd for $C_{15}H_{16}BrNNaO_3S$ $(M+Na)^+$ 391.9932, found 398.9906.

*4.2.23. N-Benzyl-2-bromo-N-methylbenzenesulfonamide (**14a**)*

Using a similar procedure as that used to produce sultam **14b**, sultam **14a** was produced as a yellow oil in 71% yield. FTIR (neat): 3062, 2912, 1795, 1446, 1434, 1332, 1163 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.15 (dd, *J*=7.8, 1.8 Hz, 1H), 7.78 (dd, *J*=7.8, 1.3 Hz, 1H), 7.47 (td, *J*=7.6, 1.4 Hz, 1H), 7.41 (td, *J*=7.6, 1.8 Hz, 1H), 7.36–7.34 (m, 1H), 7.33–7.32 (m, 2H), 7.31 (d, *J*=1.0 Hz, 1H), 7.30–7.27 (m, 1H), 4.44 (s, 2H), 2.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 138.4, 135.8, 135.7, 133.6, 132.4, 128.7, 128.2, 127.8, 127.6, 120.3, 77.2, 77.0, 76.7, 54.1, 33.9; HRMS calcd for $C_{14}H_{14}BrNNaO_2S$ $(M+Na)^+$ 361.9827, found 361.9843.

*4.2.24. N,N-Dibenzyl-2-bromobenzenesulfonamide (**14c**)*

Using a similar procedure as that used to produce sultam **14b**, sultam **14a** was produced as a white solid in 96% yield. Mp: 110 °C; FTIR (neat): 1332, 1159, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.48–8.09 (m, 1H), 8.09–7.65 (m, 1H), 7.58–7.16 (m, 8H), 7.16–6.91 (m, 4H), 4.42 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 139.7, 135.6, 135.4, 133.6, 132.5, 128.6, 128.6, 127.8, 127.6, 120.8, 50.2; HRMS calcd for $C_{20}H_{18}BrNNaO_2S$ $(M+Na)^+$ 452.0170, found 452.0238.

*4.2.25. Dibenzo[d,f][1,2]thiazepine, 6,7-dihydro-6-methyl-, 5,5-dioxide (**15a**)*

Using a similar procedure as that used to produce sultam **13a**, sultam **15a** was produced in 85% yield as a yellow oil. FTIR (neat): 1635, 1336, 1166, 1095, 977 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, *J*=7.8, 1.0 Hz, 1H), 7.73 (td, *J*=7.6, 1.3 Hz, 1H), 7.62 (dd, *J*=7.7, 1.0 Hz, 1H), 7.57 (td, *J*=7.7, 1.3 Hz, 1H), 7.54–7.42 (m, 4H), 3.78 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 140.9, 139.4, 134.8, 133.5, 133.3, 130.2, 129.9, 129.5, 129.0, 128.5, 128.3, 127.5, 56.1, 39.0; HRMS calcd for $C_{14}H_{13}NNaO_2S$ $(M+Na)^+$ 282.0565, found 282.0553.

*4.2.26. Sultam (**15b**)*

Using a similar procedure as that used to produce sultam **13a**, sultam **15b** was produced in 56% yield as a yellow oil. FTIR (neat): 3335, 1636, 1340, 1120, 967 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.00 (dd, *J*=1.1, 7.8 Hz, 1H), 7.71 (td, *J*=7.6, 1.3 Hz, 1H), 7.60 (dd, *J*=7.7, 1.0 Hz, 1H), 7.56 (td, *J*=7.7, 1.3 Hz, 1H), 7.34 (d, *J*=8.3 Hz, 1H), 6.99 (d, *J*=2.6 Hz, 1H), 6.93 (dd, *J*=2.7, 8.3 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 2H), 2.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.2, 142.1, 139.3, 134.7, 133.3, 131.4, 128.4, 127.5, 125.6, 114.6, 113.7, 55.5, 55.3, 38.9; HRMS calcd for $C_{15}H_{15}NNaO_3S$ $(M+Na)^+$ 312.0670, found 312.0652.

*4.2.27. Sultam (**15c**)*

Using a similar procedure as that used to produce sultam **13a**, sultam **15c** was produced in 95% yield as a yellow oil. FTIR (neat): 3058, 3028, 1446, 1334, 1168, 912, 746 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.07 (dd, *J*=7.8, 1.1 Hz, 1H), 7.71 (td, *J*=7.6, 1.2 Hz, 1H), 7.58 (ddd, *J*=10.5, 8.7, 4.4 Hz, 2H), 7.60 (d, *J*=7.6 Hz, 1H), 7.57 (td, *J*=7.6, 1.1 Hz, 1H), 7.42 (d, *J*=7.1 Hz, 2H), 7.40–7.34 (m, 3H), 7.33 (d, *J*=7.1 Hz, 1H), 7.24 (d, *J*=7.5 Hz, 1H), 4.45 (s, 2H), 3.70 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 135.8, 133.6, 133.2, 130.1, 129.9, 129.4, 129.0, 128.7, 128.6, 128.5, 128.3, 127.9, 127.0, 55.0, 52.7; HRMS calcd for $C_{20}H_{17}NNaO_2S$ $(M+Na)^+$ 358.0878, found 358.0868.

*4.2.28. (S)-2-Bromo-N-(but-3-enyl)-N-(1-hydroxy-3-phenyl-propan-2-yl)benzenesulfonamide (**16**)*

A flame-dried flask was charged with the homo allylated sulfonamide (0.917 g, 2.027 mmol) and Et_2O (4 mL) and cooled to 0 °C. $LiAlH_4$ (81 mg, 2.128 mmol) was added portionwise to the reaction mixture over 10 min after which the reaction was allowed to warm to rt and stirred for 1 h. The reaction was quenched using the Fieser workup procedure. The organic layer was extracted with Et_2O (5 mL×2), dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (1:1 hexane/EtOAc) to afford the alcohol in 95% yield. FTIR (neat): 3527, 3028, 1446, 1326, 1124, 919, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.83–7.79 (m, 2H), 7.58–7.54 (m, 1H), 7.50–7.45 (m, 1H), 7.24–7.16 (m, 2H), 7.02–6.98 (m, 1H), 5.78 (ddt, *J*=17.1, 10.2, 6.9 Hz, 1H), 5.12 (dd, *J*=3.1, 1.5 Hz, 1H), 5.09 (td, *J*=3.3, 1.9 Hz, 1H), 5.07 (s, 1H), 4.03–3.97 (m, 1H), 3.60 (t, *J*=6.1 Hz, 1H), 3.41 (dt, *J*=8.3, 7.3 Hz, 1H), 3.31–3.23 (m, 1H), 2.70 (dd, *J*=13.5, 9.5 Hz, 1H), 2.61 (dd, *J*=13.5, 5.3 Hz, 1H), 2.47 (dt, *J*=14.5, 7.2 Hz, 1H), 1.97 (t, *J*=5.9, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 137.4, 134.9, 132.6, 129.1, 128.9, 128.6, 127.2, 126.7, 117.4, 77.3, 77.2, 77.0, 76.8, 62.2, 62.1, 44.3, 36.3, 35.4; HRMS calcd for $C_{19}H_{22}NBrNaO_3S$ $(M+Na)^+$ 446.0401, found 446.0402.

*4.2.29. Procedure for intramolecular O-arylation reaction **17***

To sulfonamide **16** (0.301 g, 0.70 mmol) were added CuI (0.117 mmol, 22 mg), ethylene glycol (0.26 mL, 4.702 mmol), Cs_2CO_3 (1.53 g, 4.70 mmol), and DMF (3 mL) under Ar. The crude mixture was heated at 120 °C for 12–24 h, till the SM is consumed, as indicated on TLC. After 24 h the reaction mixture was cooled to rt, filtered through a small Celite pad, thoroughly washed with CH_2Cl_2, concentrated under reduced pressure, and purified using flash chromatography (4:1 hexane/EtOAc) to provide **17** in 49% yield as a yellow oil. $[\alpha]^{25}$ −56.7 (*c* 2.39, $CHCl_3$); FTIR (neat): 3064, 1593, 1440, 1218, 1153, 1008, 918 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (dd, *J*=7.9, 1.6 Hz, 1H), 7.36 (dddd, *J*=19.4, 17.4, 12.1, 4.5 Hz, 6H), 7.17–7.11 (m, 1H), 7.03–6.97 (m, 1H), 5.56 (dddd, *J*=16.3, 13.6, 9.5, 6.8 Hz, 1H), 4.94 (s, 1H), 4.91 (dd, *J*=3.7, 2.1 Hz, 1H), 4.78 (t, *J*=12.0 Hz, 1H), 4.34 (dd, *J*=13.2, 4.6 Hz, 1H), 3.86 (s, 1H), 3.21 (dd, *J*=13.7, 7.9 Hz, 1H), 3.06 (t, *J*=7.7 Hz, 2H), 2.91 (dd, *J*=13.6, 7.3 Hz, 1H), 2.14–2.03 (m, 1H), 1.96 (dt, *J*=14.1, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.5, 137.6, 134.4, 133.4, 132.1, 129.5, 129.4, 128.8, 128.7, 126.8, 123.2, 121.3, 117.0, 73.8, 64.6, 51.4, 37.3, 32.9; FTIR (neat): 3064, 1593, 1440, 1218, 1153, 1008, 918 cm^{-1}; HRMS calcd for $C_{19}H_{21}NNaO_3S$ $(M+Na)^+$ 366.1140, found 366.1136.

*4.2.30. N,4-Dimethyl-2-((trimethylsilyl)ethynyl)-benzenesulfonamide (**20**)*

To a stirring solution of tosyl chloride (1.0 g, 5.24 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (2.2 mL) and methylamine

(0.23 mL, 5.24 mmol). After stirring for 2 h, the reaction was quenched with H_2O (10 mL), the organic layer removed, and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with satd brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the desired sulfonamide as a pale yellow solid. A portion of this crude (0.8 g, 4.31 mmol) in Et_2O (43 mL) was cooled to −78 °C and stirred for 15 min. After such time *n*-BuLi (1.0 M, 4.31 mmol) was added dropwise to the crude mixture and the reaction was stirred for an additional 15 min. Elemental I_2 (0.65 g, 5.17 mmol) was added to the reaction mixture and after 15 min was warmed to rt and stirred for 2 h. The reaction was quenched with aqueous satd NH_4Cl (10 mL), extracted with EtOAc (2×20 mL), and the combined organic layers were washed with aqueous satd Na_2SO_3 (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford sulfonamide **19** as pale yellow solid. To a portion of crude material (500 mg, 1.6 mmol) in DMF (8.2 mL) were added $PdCl_2(PPh_3)_2$ (33.8 mg, 0.048 mmol), PPh_3 (51 mg, 0.192 mmol), CuI (8.8 mg, 0.08 mmol), and Et_3N (0.67 mL, 4.818 mmol). After the addition of TMS acetylene (0.68 mL, 4.818 mmol), the reaction was heated to 80 °C and stirred for 14 h after which time the crude mixture was cooled to rt and concentrated under reduced pressure. The crude material was purified using flash chromatography (1:1 hexane/EtOAc) to provide **20** in 46% yield over 3 steps as a yellow oil. FTIR (neat): 2359, 1731, 1330, 1315, 1174, 1141, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.72 (d, *J*=8.1 Hz, 1H), 7.27 (dd, *J*=1.1, 0.5 Hz, 1H), 7.09–7.05 (m, 1H), 2.40 (d, *J*=5.5 Hz, 3H), 2.21 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.9, 137.2, 135.0, 129.6, 129.6, 120.0, 103.1, 101.5, 29.4, 21.1; HRMS calcd for $C_{13}H_{19}NNaO_2SSi$ $(M+Na)^+$ 304.0803, found 304.0806.

*4.2.31. Sultam (**22**)*

To a flame-dried round bottom flask charged with **20** (0.5 g, 0.177 mmol) were added CH_3CN (2.0 mL) and K_2CO_3 (0.7 g, 0.523 mmol) and the reaction mixture was stirred at 60 °C for 2 h. After such time, the crude reaction mixture was filtered through a silica pad, concentrated under pressure, and purified by flash chromatography (4:1 hexane/EtOAc) to provide **22** in 67% yield as a yellow oil. FTIR: (neat) 2358, 2341, 1298, 1140, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J*=8.0 Hz, 1H), 7.55–7.39 (m, 1H), 7.31 (dd, *J*=8.0, 0.7 Hz, 1H), 4.89 (d, *J*=2.8 Hz, 1H), 4.35 (d, *J*=2.8 Hz, 1H), 3.05 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 144.0, 138.9, 131.3, 130.6, 129.4, 121.5, 120.7, 84.2, 25.8, 21.8; HRMS calcd for $C_{10}H_{11}NNaO_2S$ $(M+Na)^+$ 232.0408, found 232.0392.

*4.2.32. Sultam (**23**)*

To a flame-dried round bottom flask charged with **21** (45 mg, 0.14 mmol) and toluene (5 mL) was added $Co_2(CO)_8$ (52 mg, 0.15 mmol). The reaction mixture was heated at 90 °C for 2 h, concentrated, and the crude product was purified by column chromatography (1:1 hexanes/EtOAc) furnishing the tricyclic product in 67% yield as a yellow oil. FTIR (neat): 2948, 1780, 1323, 1147, 1122, 946, 906 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.03 (s, 1H), 7.81 (d, *J*=8.2 Hz, 1H), 7.30–7.23 (m, 1H), 7.20 (s, 1H), 4.57 (d, *J*=14.4 Hz, 1H), 3.46–3.33 (m, 1H), 3.29 (dd, *J*=14.4, 1.3 Hz, 1H), 2.83 (s, 3H), 2.77–2.62 (m, 1H), 2.44 (s, 3H), 2.33 (dd, *J*=17.6, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 206.0, 164.4, 143.7, 143.1, 142.0, 130.4, 130.0, 129.9, 129.2, 60.4, 43.6, 40.3, 39.0, 21.4; HRMS calcd for $C_{14}H_{15}NNaO_3S$ $(M+Na)^+$ 300.0670, found 300.0677.

*4.2.33. (Z)-Methyl 2-(2-benzyl-3-benzisothiazoline-1-ylidene)-acetate (**25**)*

Into a 1 dram vial were added *N*-benzyl-2-idobenzenesulfonamide (50 mg, 0.13 mmol), Et_3N (37μL, 0.26 mmol), Bu_4NCl (50 mg, 0.13 mmol), $Pd_2(dba)_3\cdot CHCl_3$ (2 mol %, 2.8 mg, 0.0027 mmol), and dry DMF (0.98 mL). After stirring for 5 min at rt, methyl propiolate (33 μL, 0.40 mmol) was added and the reaction vial was placed immediately into a preheated reaction block. The reaction was stirred at 110 °C for 14 h after which time the reaction was cooled and concentrated under reduced pressure. The crude product was purified using flash chromatography (8:1 hexane/EtOAc) to yield **25** as a yellow oil (31.6 mg, 76%, 0.096 mmol). FTIR (neat): 2362, 1730, 1291, 1172 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.26 (dd, *J*=17.2, 1.3 Hz, 1H), 7.92–7.83 (m, 1H), 7.73–7.63 (m, 2H), 7.38–7.21 (m, 3H), 5.25 (s, 1H), 4.79 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 166.1, 143.1, 133.9, 133.7, 132.8, 132.1, 129.6, 129.0, 128.1, 127.3, 126.9, 121.1, 96.1, 53.6, 44.4; HRMS calcd for $C_{17}H_{15}NO_4SNa$ $(M+Na)^+$ 352.0619, found 352.0593 (TOF MS EI^+).

*4.2.34. Sultam (**26**)*

Into a flame-dried round bottom flask were added benzothiazepenone **10e** (0.1 g, 0.33 mmol), benzaldehyde (0.5 mL, 0.49 mmol), and EtOH (2 mL). To this mixture was added KOH (0.48 mmol) and the reaction mixture was heated at 50 °C for 4 h. After such time, the crude mixture was filtered and recrystallized from EtOH to produce **26** (80% yield) as a white solid. Mp: 171 °C; FTIR (neat): 3060, 1676, 1607, 1172, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.94 (s, 1H), 7.91 (m, 2H), 7.73–7.65 (m, 2H), 7.36–7.24 (m, 7H), 7.19 (m, 2H), 7.09 (t, *J*=7.5 Hz, 1H), 4.24 (s, 2H), 3.52 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 192.1, 143.3, 136.9, 134.8, 134.6, 134.0, 133.4, 132.7, 130.8, 130.7, 129.9, 129.7, 129.5, 128.8, 128.6, 128.4, 126.3, 55.9, 47.8; HRMS calcd for $C_{23}H_{19}NNaO_3S$ $(M+Na)^+$ 412.0984, found 412.0983.

*4.2.35. Sultam (**27**)*

To a flame dried round bottom flask were added benzothiazepenone (0.1 g, 0.33 mmol) and benzaldehyde (0.5 mL, 0.49 mmol) dissolved in EtOH (2 mL). The reaction mixture was treated with KOH (0.48 mmol) and heated at 50 °C for 4 h. The crude product was filtered and recrystallized from EtOH producing the desired aldol product in 80% yield. To a flame-dried screw cap vial, aldol product (0.1 mmol) and ethyl vinyl ether (0.30 mmol) were heated at 70 °C in neat condition for overnight. The TLC analysis indicated that the reaction was complete and the crude product was purified by column chromatography (2:1 hexanes/EtOAc) to afford desired hetero-Diels–Alder product in 62% yield as a yellow oil. FTIR (neat): 2974, 1336, 1296, 1168, 1081 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.95 (dd, *J*=7.8. 1.1 Hz, 1H), 7.72 (d, *J*=7.8 Hz, 1H), 7.56 (td, *J*=7.7, 1.3 Hz, 1H), 7.44 (td, *J*=7.7, 1.2 Hz, 1H), 7.35–7.29 (m, 2H), 7.29–7.17 (m, 3H), 7.06–7.01 (m, 3H), 6.77 (d, *J*=7.1 Hz, 2H), 5.20 (t, *J*=3.0 Hz, 1H), 4.13 (d, *J*=14.6 Hz, 1H), 3.95 (dq, *J*=9.5, 7.1 Hz, 1H), 3.82 (d, *J*=14.6 Hz, 1H), 3.66 (dq, *J*=9.5, 7.1 Hz, 1H), 3.51 (t, *J*=8.2 Hz, 1H), 3.08 (d, *J*=13.8 Hz, 1H), 2.93 (d, *J*=13.7 Hz, 1H), 2.20–2.04 (m, 2H), 1.21 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 147.3, 142.3, 136.9, 135.7, 134.4, 132.4, 129.3, 128.8, 128.6, 128.6, 128.4, 127.8, 127.3, 127.0, 126.9, 111.3, 97.0, 64.3, 54.0, 48.9, 39.4, 36.0, 15.3; HRMS calcd for $C_{27}H_{27}NNaO_4S$ $(M+Na)^+$ 484.1558, found 484.1534.

*4.2.36. Sultam (**28**)*

To a solution of aldol **26** (0.1 g, 0.25 mmol) in EtOH (3 mL) were added phenyl hydrazine (0.1 mL, 1.0 mmol) and a drop of sulfuric acid. The reaction mixture was stirred at rt overnight. The product was obtained after concentration of the solution, filtration, and recrystallization from hexanes to afford **28** in 74% yield as a yellow oil. FTIR (neat): 1593, 1493, 1336, 1163, 1139, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.08–7.91 (m, 2H), 7.54 (td, *J*=7.6, 1.3 Hz, 1H), 7.43 (td, *J*=7.6, 1.3 Hz, 1H), 7.32–7.17 (m, 6H), 7.16–7.00 (m, 6H), 6.95 (d, *J*=7.8 Hz, 2H), 6.77 (t, *J*=7.3 Hz, 1H), 4.69 (d, *J*=7.0 Hz, 1H), 4.37 (d, *J*=13.6 Hz, 1H), 3.97–3.74 (m, 2H), 3.61 (s, 1H), 3.36 (d, *J*=8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 145.8, 143.7,

140.6, 138.3, 135.0, 132.6, 130.8, 130.5, 129.5, 129.0, 128.8, 128.8, 128.5, 128.3, 128.2, 125.3, 120.4, 113.7, 76.8, 69.6, 54.4, 48.7; HRMS calcd for $C_{29}H_{25}N_3NaO_2S$ $(M+Na)^+$ 502.1565, found 502.1560.

*4.2.37. Sultam (**29**)*

To a solution of aldol product **26** (50 mg, 0.128 mmol) in EtOH (3 mL) were added malononitrile (9.3 mg, 0.14 mmol) and a drop of piperidine. The reaction mixture was stirred at rt for overnight, after which time the crude reaction mixture was concentrated and the crude product was purified by column chromatography (4:1 hexanes/EtOAc) furnishing the desired product **29** in 68% yield as a clear oil. FTIR (neat): 2974, 1650, 1512, 1336, 1168, 1081, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.10 (dd, J=7.8, 1.3 Hz, 1H), 8.02 (dd, J=8.1, 1.0 Hz, 1H), 7.68 (td, J=1.4, 7.8 Hz, 1H), 7.54 (td, J=7.7, 1.1 Hz, 1H), 7.36–7.27 (m, 3H), 7.22–7.12 (m, 5H), 6.92–6.84 (m, 2H), 4.65 (s, 2H), 4.02 (d, J=14.1 Hz, 1H), 3.86 (s, 1H), 3.80 (d, J=17.8 Hz, 1H), 3.53 (d, J=14.1 Hz, 1H), 3.45 (d, J=17.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 158.7, 141.9, 140.3, 137.4, 134.5, 132.9, 129.2, 129.1, 128.8, 128.7, 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 118.9, 116.40, 76.8, 60.4, 52.4, 48.2, 42.8; HRMS calcd for $C_{26}H_{21}N_3NaO_3S$ $(M+Na)^+$ 478.1201, found 478.1211.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.053.

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