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SYNTHESIS OF A LIBRARY OF 1,5,2-DITHIAZEPINE 1,1-DIOXIDES. PART 1: A ONE-POT SULFONYLATION/THIA-MICHAEL PROTOCOL

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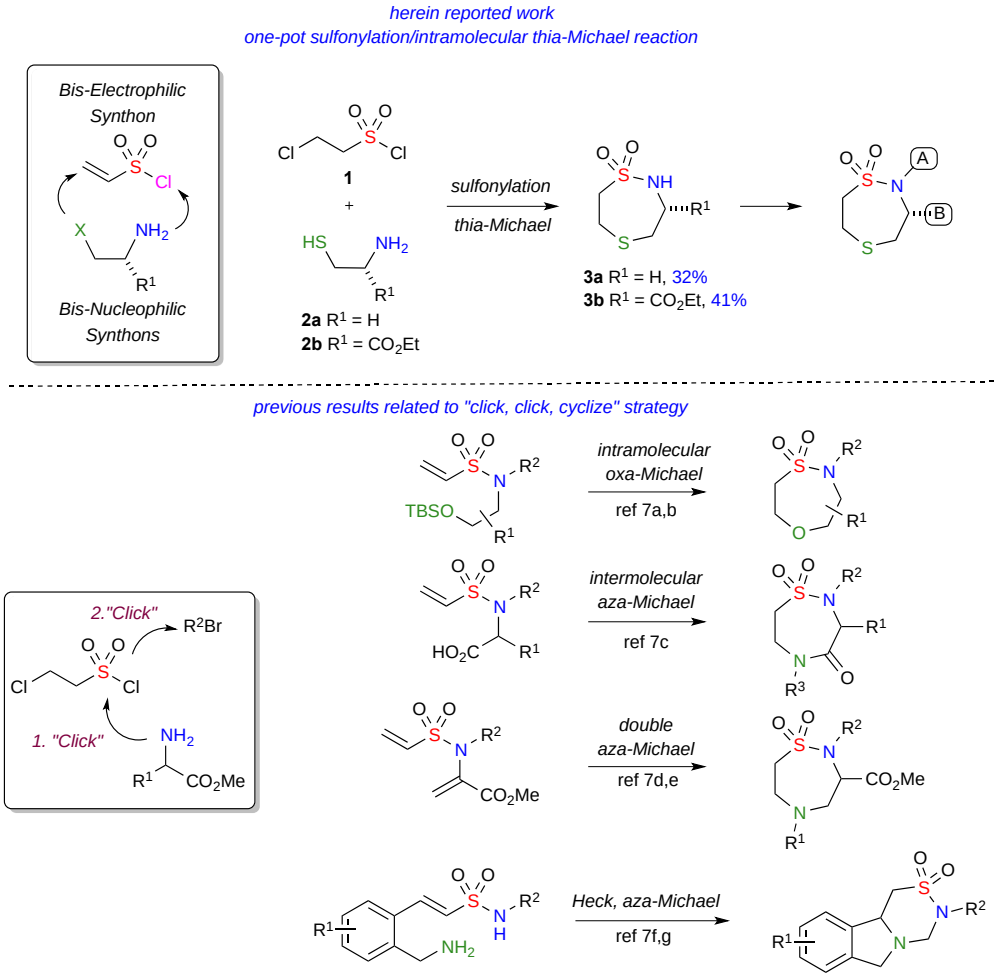
Abstract – A novel one-pot sulfonylation/intramolecular thia-Michael protocol is reported for the synthesis of 1,5,2-dithiazepine 1,1-dioxides. Sulfonylation between cysteine ethyl ester/cysteamine and 2-chloroethanesulfonyl chloride, followed by *in situ* intramolecular thia-Michael addition, was achieved and afforded the titled 1,5,2-dithiazepine-1,1-dioxide scaffolds. Diversification was demonstrated for future library synthesis.

Heterocyles have a storied history in drug development due to their diverse pharmacological properties, which when coupled with advances in high-throughput screening and the need for new pharmaceutical leads, drive discovery efforts for their efficient synthesis.[1] Hetero Michael reactions aspire to this goal, and have been broadly used in the synthesis of azacycles,[2] oxacycles,[3,4] thiacycles,[5] and *bis*-heterocycles,[6] all of which can be characterized as versatile pathways that are mild, catalytic, and adhere to atom and step economy. Vinyl sulfones are one particular class of Michael acceptors that have been well documented in the literature,[7] however, their vinyl sulfonamide counterparts have assumed a far less prominent role. To this end, we have utilized the hetero-Michael addition on vinyl sulfonamides to synthesize a series of sultams (cyclic sulfonamides, Scheme 1).[8] These efforts include a "click, click,

Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

cyclize" strategy in the synthesis of 1,4,5-oxathiazepane 4,4-dioxides utilizing an intramolecular oxa-Michael pathway,[8a,b] an automated synthesis of 1,2,5-thiadiazepane 1,1-dioxide via an aza-Michael pathway,[8c] a double aza-Michael protocol in the synthesis of 1,2,5-thiadiazepane 1,1-dioxide,[8d,e] and a Heck-aza-Michael strategy in the synthesis of isoindoline/tetrahydroisoquinoline-based tricyclic sultams.[8f,g] Taken collectively, use of "click" sulfonylation,[9] "click" sulfonamide alkylation and subsequent Michael additions greatly simplify sultam construction. In this context, we herein report a one-pot sulfonylation/intramolecular thia-Michael protocol, which combines the "click" sulfonylation and the cyclization steps in one pot, to readily assemble the titled sultam scaffolds.

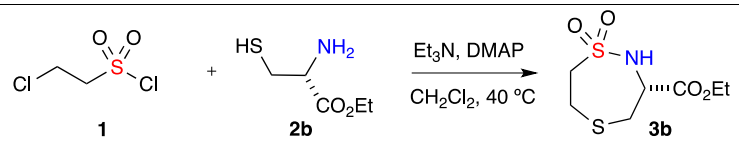


Scheme 1. One-pot sulfonylation and intramolecular thia-Michael protocol

As a precursor of the bis-electrophilic synthon vinylsulfonyl chloride, 2-chloroethanesulfonyl chloride (**1**) can react with a wide range of bis-nucleophilic synthons, such as substituted 2-amino alcohols, to generate 7-membered sultams.[8] Previous oxa-Michael studies from our laboratories has shown that the use of a tertiary sulfonamide is necessary for the Michael addition to take place. However, when **1** was treated with cysteine ethyl ester (**2a**) or cysteamine (**2b**), intramolecular thia-Michael and sulfonylation occur simultaneously, leading to a one-pot synthesis of 1,5,2-dithiazepine 1,1-dioxide scaffolds **3** that

bear free sulfonamide N-H groups (Scheme 1). A survey of base, additive, solvent and temperature (Entries 1 to 8, Table 1) showed 3.5 equivalent of Et_3N, 0.1 equivalent of DMAP, 40 ºC in CH_2Cl_2 gives the highest yield. Although the yield in this protocol is only moderate, the reaction is carried out under mild conditions and the products were conveniently recrystallized and isolated as colorless needles. We assume the moderate yield may be caused by the polymerization via intermolecular pathways,[10] as some residue that didn't dissolve in any solvent was observed during recrystallization, as well as the fact that slightly enhanced yield in more diluted concentration (Entry 9). Another possible reason accounting for the difficulty in approving the yield could be the decomposition of cysteine ethyl ester. It was supported by the detection of hydrogen sulfide smell, which is void in either starting cysteine ethyl ester or the cyclized product. To check this possibility, the ratio of sulfonyl chloride and cysteine ethyl ester was changed. In the case of excess sulfonyl chloride (Entry 10), the yield was similar to the original result (Entry 3), while when cysteine ethyl ester was in excess the yield was increased to 42% (Entry 11). Further increasing cysteine ethyl ester to 4 equivalents resulted in an inseparable byproduct along with the product (not shown). Finally, the reaction was carried out up to 40-gram scale (cysteine ethyl ester) using the condition in Entry 3, and roughly 20 grams of the desired product was obtained after recrystallization ($CHCl_3$) in a single reaction step (Entry 12). The structure of **3b** was confirmed via X-ray crystallography (Figure 1).

Table 1. The synthesis of core scaffolds **3**



Entry	1 (equiv.)	2 (equiv.)	Base (equiv.)	Additive (equiv.)	Solvent (conc.)	Temp. (ºC) [a]	Yield (%) [b]
1	1	1.1	Et_3N (3.5)	DMAP (0.1)	MeOH (0.2 M)	40	0
2	1	1.1	Et_3N (3.5)	DMAP (0.1)	DMF (0.2 M)	40	30
3	1	1.1	Et_3N (3.5)	DMAP (0.1)	CH_2Cl_2 (0.2 M)	40	31
4	1	1.1	Na_2CO_3	-	DCM/H_2O (0.2 M)	40	25
5	1	1.1	-	-	Pyridine (0.2 M)	40	0
6	1	1.1	Et_3N (3.5)	DMAP (0.1)	CH_2Cl_2 (0.2 M)	rt	15
7	1	1.1	Et_3N (3.5)	DMAP (0.1)	DMF (0.2 M)	120 ºC [c]	24
8	1	1.1	Et_3N (3.5)	DBU (0.1)	CH_2Cl_2 (0.2 M)	40	19
9	1	1.1	Et_3N (3.5)	DMAP (0.1)	CH_2Cl_2 (0.05 M)	40	35
10	2	1	Et_3N (5)	DMAP (0.1)	CH_2Cl_2 (0.2 M)	40	26
11	1	2	Et_3N (5)	DMAP (0.1)	CH_2Cl_2 (0.2 M)	40	42
12	1	1.1	Et_3N (3.5)	DMAP (0.1)	CH_2Cl_2 (0.2 M)	40	41 [d]

[a] Reaction time is 14 h.
[b] Isolated yield after flash chromatography.
[c] Microwave for 10 minutes.
[d] Isolated yield for a 40 gram-scale reaction. The product was purified via recrystallization.

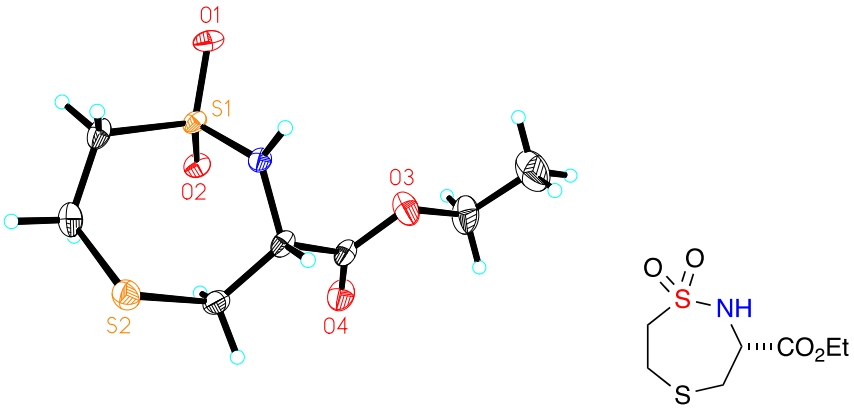
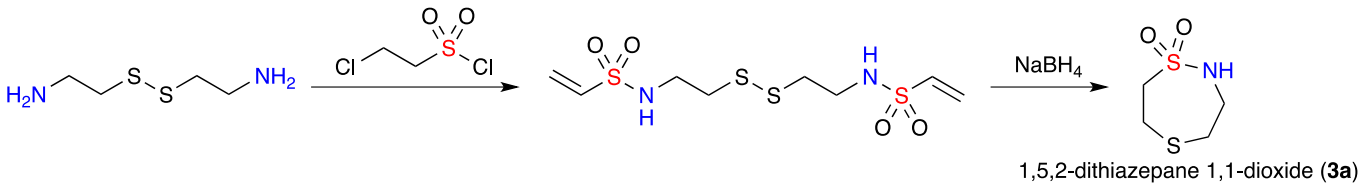


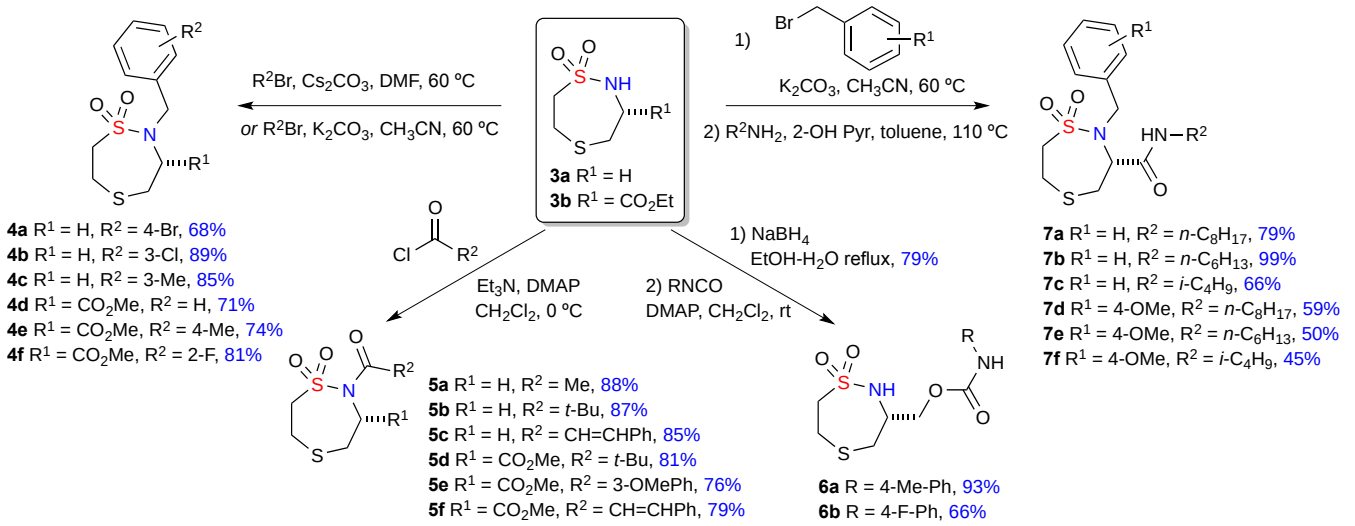
Figure 1. ORTEP diagram of **3b**

Notably, the only report of synthesis of 1,5,2-dithiazepane 1,1-dioxide (**3a**) involves the usage of 2,2'-dithiobis(ethylamine) dihydrochloride in a two-step sequence using two chromatographic separations (Scheme 2).[11]



Scheme 2. Reported synthesis of 1,5,2-dithiazepane 1,1-dioxide (**3a**)

With the convenient synthesis of sultam **3** in hand, various diversification pathways were explored as outlined in Scheme 3. Benzylation of sultam scaffolds **3** using substituted benzyl bromides gave products **4** in good yield. In addition, benzylation of **3a** required Cs_2CO_3 in DMF, but milder conditions (K_2CO_3 in MeCN) were sufficient for substrate **3b** presumably due to the electron withdrawing ester group in **3b**. Treating of **3** with acyl chloride, in the presence of Et_3N and DMAP resulted in acyl-products **5**. Alternatively, reduction of the ester group of **3b** followed by isocyanate coupling with the resulting alcohol provided carbamate **6**. Finally, amides **7** were synthesized via a two-step sequence of benzylation and direct amidation of the ester.



Scheme 3. Diversification leading to 1,5,2-dithiazepane 1,1-dioxides

In summary, a one-pot sulfonylation/intramolecular thia-Michael protocol was developed for the synthesis of 1,5,2-dithiazepine 1,1-dioxide scaffold on multi-gram scale, incorporating stereochemistry and additional handles for further diversification. A demonstrative library was generated from the scaffolds. The compounds produced are currently being broadly screened within the NIH Molecular Library Screening Network (NIH-MLSCN) and additional biological collaborators.

EXPERIMENTAL

All reactions were carried out under argon atmosphere. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, toluene, THF and CH_2Cl_2 were either purchased through Sigma-Aldrich or purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (R. H. Grubbs, R. K. Rosen, and F. J. Timmers, *Organometallics*, 1996, **15**, 1518–1520). Et_3N was purified by passage over basic alumina or distilled over CaH and stored over KOH. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H, ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz, 100 MHz respectively as well as a Bruker DRX-500 spectrometer operating at 500 MHz, 125 MHz respectively and a Avance AV-III 500 with a dual carbon/proton (CPDUL) cryoprobe operating at 500 MHz, 125 MHz respectively. Observed rotations at 589 nm were measured using AUTOPOL IV Model automatic polarimeter. Weights were taken on a Flexiweigh Automatic Weigher; weight tolerance +/- 0.3mg. Samples were concentrated on a GeneVac EZ personal evaporator and placed under high vacuum for ≥ 2 hours before final weights were taken.

General procedure for the one-pot sulfonylation/intramolecular thia-Michael protocol.

2-Chloroethanesulfonyl chloride (20.9 mL, 0.2 mol) was added drop wise to a stirred solution of cysteine ethyl ester (40.9 g, 1.1 equiv.) or cysteamine hydrochloride (25.0 g, 1.1 equiv.), Et_3N (111.3 mL, 4 equiv.) and DMAP (2.44 g, 0.1 equiv.) in CH_2Cl_2 (500 mL) at 0 ºC. After addition, the reaction was allowed to warm to room temperature and stirred overnight. The mixture was washed with 1 M HCl, brine, dried (Na_2CO_3), and concentrated under reduced pressure. The crude mixture was recrystallized with $CHCl_3$ to afford the product **3a** or **3b** as colorless needles.

1,5,2-Dithiazepane 1,1-dioxide (3a).[12]

Colorless needles, yield 32%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95–4.77 (brs, 1H), 3.55–3.47 (m, 2H), 3.29 (t, *J* = 6.3 Hz, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 2.95–2.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 58.9, 41.8, 35.1, 28.1.

(*R*)-Ethyl 1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (3b).

Colorless needles, yield 41%. mp 168–169 °C. $[\alpha]_D^{20}$ -64.8 (c 0.75, CH_2Cl_2). FTIR: 2947, 1491, 1339, 1140, 1109, 758 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (s, 1H), 4.33–4.24 (m, 3H), 3.72 (ddd, *J* = 14.4, 3.7 Hz, 3.7 Hz, 1H), 3.53 (dd, *J* = 15.8, 5.8 Hz, 1H), 3.44 (dd, *J* = 15.8, 2.9 Hz, 1H), 3.41–3.34 (m, 1H), 2.92–2.88 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 62.9, 59.3, 54.1, 37.3, 28.1, 14.1. HRMS (ESI) *m/z* calculated for $C_7H_{13}NNaO_4S_2$ 262.0184 $(M+Na)^+$, found 262.0184.

General procedure for the synthesis of 4a-c from scaffolds 3a.

To a stirred solution of 3a (0.2 mmol, 1 equiv.) and benzyl bromide (0.22 mmol, 1.1 equiv.) in DMF (1 mL) was added Cs_2CO_3 (0.3 mmol, 1.5 equiv.). The mixture was stirred at 60 ºC overnight, before quenching with addition of H_2O. The mixture was diluted with Et_2O, washed with H_2O and brine, dried (Na_2CO_3), and concentrated under reduced pressure. The crude product was purified via flash chromatography.

2-(4-Bromobenzyl)-1,5,2-dithiazepane 1,1-dioxide (4a).

White solid, yield 68%. mp 164–165 °C. FTIR: 2924, 2887, 1331, 1142, 914 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 4.48 (s, 2H), 3.52–3.45 (m, 2H), 3.19 (dd, *J* = 9.8, 3.5 Hz, 2H), 3.10 (dd, *J* = 9.7, 3.6 Hz, 2H), 2.94–2.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 131.8, 129.9, 121.9, 55.9, 54.1, 45.5, 34.4, 27.5. HRMS (ESI) *m/z* calculated for $C_{11}H_{15}BrNO_2S_2$ 335.9728 $(M+H)^+$, found 335.9733.

2-(3-Chlorobenzyl)-1,5,2-dithiazepane 1,1-dioxide (4b).

White solid, yield 89%. mp 125–126 °C. FTIR: 2924, 1327, 1140, 1121, 854, 735, 494 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.39 (m, 1H), 7.30 (t, *J* = 1.4 Hz, 3H), 4.52 (s, 2H), 3.54–3.47 (m, 2H), 3.22 (t, *J* = 6.3 Hz, 2H), 3.12 (dd, *J* = 9.6, 3.5 Hz, 2H), 2.95–2.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 134.7, 130.0, 128.2, 128.2, 126.3, 56.0, 54.2, 45.6, 34.5, 27.5. HRMS (ESI) *m/z* calculated for $C_{11}H_{15}NO_2S_2Cl$ 292.0233 $(M+H)^+$, found 292.0222.

2-(3-Methylbenzyl)-1,5,2-dithiazepane 1,1-dioxide (4c).

White solid, yield 85%. mp 88–89 °C. FTIR: 2919, 1335, 1146, 1124, 854, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 4.51 (s, 2H), 3.54–3.47 (m, 2H), 3.22 (t, *J* = 6.4 Hz, 2H), 3.11 (dd, *J* = 9.7, 3.4 Hz, 2H), 2.94–2.89 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 135.9, 128.9, 128.7, 128.5, 125.3, 56.0, 54.5, 45.2, 34.5, 27.5, 21.4. HRMS (ESI) *m/z* calculated for $C_{12}H_{17}NO_2S_2Na$ 294.0598 $(M+H)^+$, found 294.0596.

General procedure for the synthesis of 4d–f from scaffolds 3b.

To a stirred solution of **3b** (0.20 mmol, 1 equiv.) and benzyl bromide (0.22 mmol, 1.1 equiv.) in MeCN (1 mL) was added K_2CO_3 (0.30 mmol, 1.5 equiv.). The mixture was stirred at 60 ºC overnight, before quenching with addition of H_2O. The mixture was diluted with Et_2O, washed with H_2O and brine, dried (Na_2CO_3), and concentrated under reduced pressure. The crude product was purified via flash chromatography.

(*R*)-Ethyl 2-benzyl-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4d).

White solid, yield 71%. $[\alpha]_D^{20}$ -31.7 (c 0.70, CH_2Cl_2). FTIR: 2982, 2926, 1732, 1339, 1148, 854, 727, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2H), 7.40–7.30 (m, 3H), 4.78 (d, *J* = 14.6 Hz, 1H), 4.49 (d, *J* = 14.6 Hz, 1H), 4.09–4.02 (m, 2H), 3.72 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.59 (ddd, *J* = 14.5, 3.1, 3.1 Hz, 1H), 3.53 (dd, *J* = 15.6, 11.0 Hz, 1H), 3.43 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.29 (ddd, *J* = 14.5, 12.4, 4.2 Hz, 1H), 2.98 (ddd, *J* = 15.2, 12.4, 2.8 Hz, 1H), 2.90 (ddd, *J* = 15.3, 3.6, 3.6 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 135.1, 129.6, 128.5, 128.2, 61.6, 59.6, 56.2, 55.3, 37.5, 28.4, 13.9. HRMS (ESI) *m/z* calculated for $C_{14}H_{19}NO_4S_2K$ 368.0393 $(M+K)^+$, found 303.0392.

(*R*)-Ethyl 2-(4-methylbenzyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4e).

Yellow solid, yield 74%. mp 85–86 °C. $[\alpha]_D^{20}$ -19.5 (c 1.00, CH_2Cl_2). FTIR: 2980, 2924, 1728, 1340, 1146, 854 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 4.73 (d, *J* = 14.4 Hz, 1H), 4.47 (d, *J* = 14.4 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.71 (dd, *J* = 10.9, 7.1 Hz, 1H), 3.58 (dt, *J* = 14.5, 3.1 Hz, 1H), 3.52 (dd, *J* = 15.6, 11.0 Hz, 1H), 3.41 (dd, *J* = 15.6, 7.1 Hz, 1H),

3.28 (ddd, *J* = 14.5, 12.2, 4.3 Hz, 1H), 2.97 (ddd, *J* = 15.0, 12.2, 2.8 Hz, 1H), 2.88 (dt, *J* = 15.3, 3.9 Hz, 1H), 2.35 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 138.0, 131.9, 129.5, 129.1, 61.6, 59.3, 55.8, 55.3, 37.5, 28.3, 21.1, 13.9. HRMS (ESI) *m/z* calculated for $C_{15}H_{21}NO_4S_2Na$ 366.0810 $(M+Na)^+$, found 366.0813.

(*R*)-Ethyl 2-(2-fluorobenzyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4f).

Yellow oil, yield 81%. $[\alpha]_D^{20}$ -6.4 (c 1.00, CH_2Cl_2). FTIR: 2982, 2926, 1732, 1493, 1342, 1229, 1148, 854, 760 cm^{-1}. 1H NMR (500 MHz, $CDCl_3$) δ 7.60 (td, *J* = 7.6, 1.7 Hz, 1H), 7.35–7.29 (m, 1H), 7.16 (td, *J* = 7.5, 1.1 Hz, 1H), 7.11–7.04 (m, 1H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.55 (d, *J* = 15.2 Hz, 1H), 4.10 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.81 (dd, *J* = 10.6, 7.4 Hz, 1H), 3.54 (ddd, *J* = 14.4, 3.0, 3.0 Hz, 1H), 3.50–3.36 (m, 2H), 3.20 (ddd, *J* = 14.4, 12.5, 4.1 Hz, 1H), 2.96–2.88 (m, 1H), 2.82 (ddd, *J* = 15.3, 3.7, 3.7 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 161.2 (d, $^1J_{CF}$ = 246.7 Hz), 132.3 (d, $^3J_{CF}$ = 3.8 Hz), 130.1 (d, $^3J_{CF}$ = 8.3 Hz), 124.2 (d, $^4J_{CF}$ = 3.6 Hz), 122.5 (d, $^2J_{CF}$ = 14.6 Hz), 115.4 (d, $^2J_{CF}$ = 21.9 Hz), 61.6, 60.1 (d, $^5J_{CF}$ = 1.2 Hz), 55.6, 49.1 (d, $^3J_{CF}$ = 2.9 Hz), 37.1, 28.2, 13.9. HRMS (ESI) *m/z* calculated for $C_{14}H_{18}FNO_4S_2Na$ 370.0559 $(M+Na)^+$, found 370.0555.

General procedure for the synthesis of 5 from scaffolds 3.

To a stirred solution of **3** (0.20 mmol, 1 equiv.), Et_3N (0.60 mmol, 3 equiv.), DMAP (0.02 mmol, 0.1 equiv.) in CH_2Cl_2 (1 mL) was slowly added acyl chloride (0.22 mmol, 1.1 equiv.) at 0 ºC. The mixture was kept stirring at 0 ºC for 1 h, before quenching with addition of H_2O. The mixture was diluted with Et_2O, washed with H_2O and brine, dried (Na_2CO_3), and concentrated under reduced pressure. The crude product was purified via flash chromatography.

1-(1,1-Dioxido-1,5,2-dithiazepan-2-yl)ethanone (5a).

Yellow solid, yield 88%. mp 104–105 °C. FTIR: 2984, 2926, 1697, 1352, 1157, 849 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (d, *J* = 6.7 Hz, 2H), 3.68–3.62 (m, 2H), 3.10 (d, *J* = 6.6 Hz, 2H), 2.92–2.87 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 55.4, 42.9, 33.5, 27.4, 25.1. HRMS (ESI) *m/z* calculated for $C_6H_{11}NO_3S_2Na$ 232.0078 $(M+Na)^+$, found 232.0078.

1-(1,1-Dioxido-1,5,2-dithiazepan-2-yl)-2,2-dimethylpropan-1-one (5b).

White solid, yield 87%. mp 125–126 °C. FTIR: 2976, 2935, 1688, 1352, 1157, 1095 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (t, *J* = 6.5 Hz, 2H), 3.90–2.83 (m, 2H), 3.16 (t, *J* = 6.5 Hz, 2H), 2.91–2.86 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.2, 54.2, 44.5, 41.7, 35.9, 28.8, 28.0. HRMS (ESI) *m/z* calculated for $C_9H_{17}NO_3S_2Na$ 274.0548 $(M+Na)^+$, found 274.0530.

(*E*)-1-(1,1-Dioxido-1,5,2-dithiazepan-2-yl)-3-phenylprop-2-en-1-one (5c).

White solid, yield 85%. mp 150–151 °C. FTIR: 2926, 1676, 1616, 1356, 1155, 1122 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 15.4 Hz, 1H), 7.60 (dd, *J* = 6.8, 2.8 Hz, 2H), 7.48–7.41 (m, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.71–3.65 (m, 2H), 3.15 (t, *J* = 6.6 Hz, 2H), 2.93–2.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 147.3, 134.3, 130.8, 129.0, 128.5, 117.3, 56.8, 42.6, 33.9, 27.7. HRMS (ESI) *m/z* calculated for $C_{13}H_{15}NO_3S_2Na$ 320.0391 $(M+Na)^+$, found 320.0393.

(*R*)-Ethyl 2-pivaloyl-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (5d).

White solid, yield 81%. mp 152–153 °C. $[\alpha]_D^{20}$ -102.2 (c 0.92, CH_2Cl_2). FTIR: 2954, 1738, 1690, 1358, 1159, 1111 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 9.2, 8.1 Hz, 1H), 4.29 (qd, *J* = 7.1, 1.6 Hz, 2H), 4.21 (ddd, *J* = 14.8, 9.2, 7.9 Hz, 1H), 3.60 (dd, *J* = 15.7, 9.4 Hz, 1H), 3.55–3.47 (m, 2H), 2.91 (dd, *J* = 2.9, 1.5 Hz, 1H), 2.90 (d, *J* = 3.0 Hz, 1H), 1.37 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.8, 168.9, 62.3, 57.4, 53.3, 41.6, 38.4, 28.8, 28.2, 14.0. HRMS (ESI) *m/z* calculated for $C_{12}H_{21}NO_5S_2Na$ 346.0759 $(M+Na)^+$, found 346.0741.

(*R*)-Ethyl 2-(3-methoxybenzoyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (5e).

White solid, yield 76%. mp 112–113 °C. $[\alpha]_D^{20}$ -83.2 (c 1.00, CH_2Cl_2). FTIR: 2981, 1740, 1690, 1364, 1231, 1161, 841, 746 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.27–7.25 (m, 1H), 7.07 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.60 (dd, *J* = 10.0, 7.7 Hz, 1H), 4.41–4.30 (m, 3H), 3.83 (s, 3H), 3.64 (dt, *J* = 14.9, 3.0 Hz, 1H), 3.50 (dd, *J* = 15.6, 10.0 Hz, 1H), 3.36 (dd, *J* = 15.6, 7.7 Hz, 1H), 3.04–2.91 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 168.6, 159.8, 135.1, 130.2, 119.8, 118.4, 112.5, 62.5, 60.3, 55.4, 53.6, 38.2, 29.0, 14.1. HRMS (ESI) *m/z* calculated for $C_{15}H_{19}NO_6S_2Na$ 396.0551 $(M+Na)^+$, found 396.0567.

(*R*)-Ethyl 2-cinnamoyl-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (5f).

Yellow solid, yield 79%. mp 123–124 °C. $[\alpha]_D^{20}$ -83.2 (c 1.00, CH_2Cl_2). FTIR: 2981, 1740, 1690, 1364, 1231, 1161, 841, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 15.4 Hz, 1H), 7.64–7.58 (m, 2H), 7.53 (d, *J* = 15.4 Hz, 1H), 7.43 (dd, *J* = 5.1, 1.9 Hz, 3H), 5.56 (dd, *J* = 11.4, 6.4 Hz, 1H), 4.32 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.72 (dt, *J* = 14.6, 3.4 Hz, 1H), 3.66–3.56 (m, 1H), 3.52 (d, *J* = 9.0 Hz, 2H), 3.04–2.88 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 166.2, 148.1, 134.2, 131.0, 129.0, 128.6, 116.6, 62.1, 56.9, 55.1, 36.1, 28.0, 14.1. HRMS (ESI) *m/z* calculated for $C_{16}H_{19}NO_5S_2Na$ 392.0602 $(M+Na)^+$, found 392.0605.

General procedure for the synthesis of 6 from scaffolds 3b.

A solution of $NaBH_4$ (24 mmol, 4 equiv.) in 50% EtOH/H_2O (10 mL) was added to a suspension of **3b** (6 mmol, 1 equiv.) in 50% EtOH/H_2O (10 mL). After the reaction was stirred at 80 ºC for 4 h, solvent was evaporated to afford the crude alcohol, which was purified via flash chromatography. The resulting alcohol (0.2 mmol, 1 equiv.), DMAP (0.02 mmol, 0.1 equiv.) was dissolved in CH_2Cl_2 (1 mL), then isocyanate (0.21 mmol, 1.05 equiv.) was added at rt. The reaction was stirred at rt for 2 h and the solvent was removed under reduced pressure. The resulted residue was dissolved back into EtOAc, washed with 10% HCl and brine, and dried (Na_2SO_4). The crude product was purified via flash chromatography.

(*R*)-(1,1-Dioxido-1,5,2-dithiazepan-3-yl)methyl *p*-tolylcarbamate (6a).

White solid, yield 93%. mp 192–193 °C. $[\alpha]_D^{20}$ 16.3 (c 0.40, MeOH). FTIR: 3304, 2918, 1728, 1531, 1315, 1294, 1223, 1207, 1128, 1063, 816 cm^{-1}. ^1H NMR (500 MHz, DMSO) δ 9.62 (s, 1H), 7.85 (d, *J* = 6.4 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 4.03 (ddd, *J* = 17.3, 10.9, 7.0 Hz, 2H), 3.56–3.35 (m, 3H), 3.10 (dd, *J* = 15.1, 4.9 Hz, 1H), 2.91 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.86 (dd, *J* = 8.2, 3.8 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 153.1, 136.4, 131.3, 129.1, 118.2, 65.6, 59.1, 52.4, 35.9, 27.3, 20.3. HRMS (ESI) *m/z* calculated for $C_{13}H_{18}N_2O_4S_2Na$ 353.0606 $(M+Na)^+$, found 353.0611.

(*R*)-(1,1-Dioxido-1,5,2-dithiazepan-3-yl)methyl (4-fluorophenyl)carbamate (6b).

White solid, yield 66%. mp 163–164 °C. $[\alpha]_D^{20}$ 16.0 (c 0.40, MeOH). FTIR: 3308, 2918, 1717, 1508, 1325, 1213, 1128, 1063, 816 cm^{-1}. ^1H NMR (500 MHz, Acetone) δ 8.81 (s, 1H), 7.57 (dd, *J* = 8.8, 4.8 Hz, 2H), 7.12–7.03 (m, 2H), 6.79 (d, *J* = 5.4 Hz, 1H), 4.18 (qd, *J* = 10.9, 6.9 Hz, 2H), 3.66–3.58 (m, 1H), 3.56–3.49 (m, 1H), 3.44 (ddd, *J* = 14.4, 7.2, 5.3 Hz, 1H), 3.21 (dd, *J* = 15.3, 5.2 Hz, 1H), 3.04 (dd, *J* = 15.3, 8.6 Hz, 1H), 2.96–2.91 (m, 2H). 13C NMR (126 MHz, Acetone) δ 159.2 (d, $^1J_{CF}$ = 239.5 Hz), 154.0, 136.2, 120.7, 115.9 (d, $^2J_{CF}$ = 22.5 Hz), 79.0, 66.9, 59.9, 36.7, 28.5. HRMS (ESI) *m/z* calculated for $C_{12}H_{15}FN_2O_4S_2Na$ 357.0355 $(M+Na)^+$, found 357.0353.

General procedure for the synthesis of 7 from scaffolds 4.

A solution of scaffold 4 (0.2 mmol, 1 equiv.), amine (2 mmol, 10 equiv.) and 2-hydroxypyridine (0.04 mmol, 0.2 equiv.) in toluene (1 mL) was refluxed for 14 h. The solvent was evaporated under reduced pressure and the crude product was purified via flash chromatography.

(*R*)-2-Benzyl-*N*-octyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7a).

White solid, yield 79%. mp 136–137 °C. $[\alpha]_D^{20}$ -0.8 (c 1.00, CH_2Cl_2). FTIR: 3429, 2922, 2851,

1668, 1327, 1140, 1051, 854, 733, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.41–7.32 (m, 3H), 6.33 (s, 1H), 4.86 (d, *J* = 14.1 Hz, 1H), 4.22 (d, *J* = 14.1 Hz, 1H), 3.77–3.70 (m, 2H), 3.57 (dd, *J* = 15.8, 5.8 Hz, 1H), 3.47–3.35 (m, 2H), 3.01 –2.93 (m, 3H), 2.88 (dt, *J* = 15.3, 3.5 Hz, 1H), 1.36–1.09 (m, 12H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 135.1, 129.3, 129.1, 128.8, 64.6, 57.5, 56.1, 39.5, 37.7, 31.8, 29.1, 29.1, 29.1, 27.8, 26.6, 22.6, 14.1. HRMS (ESI) *m/z* calculated for $C_{20}H_{32}N_2O_3S_2Na$ 435.1752 $(M+Na)^+$, found 435.1756.

(*R*)-2-Benzyl-*N*-hexyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7b).

White solid, yield 99%. mp 138–140 °C. $[\alpha]_D^{20}$ -1.6 (c 0.75, CH_2Cl_2). FTIR: 3431, 2951, 2926, 2856, 1668, 1327, 1140, 1051, 854, 733, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.42–7.35 (m, 3H), 6.33 (s, 1H), 4.86 (d, *J* = 14.1 Hz, 1H), 4.22 (d, *J* = 14.1 Hz, 1H), 3.73 (ddd, *J* = 14.6, 8.9, 4.4 Hz, 2H), 3.57 (dd, *J* = 15.8, 5.8 Hz, 1H), 3.47–3.35 (m, 2H), 3.04–2.93 (m, 3H), 2.88 (dt, *J* = 15.4, 3.4 Hz, 1H), 1.34–1.11 (m, 8H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 135.1, 129.3, 129.1, 128.8, 64.6, 57.5, 56.1, 39.4, 37.7, 31.4, 29.0, 27.8, 26.3, 22.5, 14.0. HRMS (ESI) *m/z* calculated for $C_{18}H_{28}N_2O_3S_2Na$ 407.1439 $(M+Na)^+$, found 407.1440.

(*R*)-2-Benzyl-*N*-isobutyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7c).

White solid, yield 66%. mp 196–197 °C. $[\alpha]_D^{20}$ -0.9 (c 1.00, CH_2Cl_2). FTIR: 3427, 2957, 2918, 2870, 1668, 1522, 1329, 1138, 1049, 854, 735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.42–7.33 (m, 3H), 6.42 (s, 1H), 4.85 (d, *J* = 14.1 Hz, 1H), 4.24 (d, *J* = 14.1 Hz, 1H), 3.80–3.69 (m, 2H), 3.58 (dd, *J* = 15.7, 5.8 Hz, 1H), 3.47–3.36 (m, 2H), 3.00 (ddd, *J* = 15.3, 12.6, 2.7 Hz, 1H), 2.92–2.85 (m, 2H), 2.77–2.69 (m, 1H), 1.53 (td, *J* = 13.4, 6.7 Hz, 1H), 0.79 (d, *J* = 6.7 Hz, 2H), 0.76 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 135.1, 129.3, 129.2, 128.8, 64.5, 57.4, 56.0, 46.7, 37.8, 28.2, 27.9, 19.9, 19.9. HRMS (ESI) *m/z* calculated for $C_{16}H_{24}N_2O_3S_2Na$ 379.1126 $(M+Na)^+$, found 379.1128.

(*R*)-2-(4-Methoxybenzyl)-*N*-octyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7d).

White solid, yield 59%. mp 159–160 °C. $[\alpha]_D^{20}$ -0.8 (c 0.75, CH_2Cl_2). FTIR: 3431, 2953, 2922, 2851, 1664, 1512, 1327, 1151, 1140, 1057, 847 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 6.92–6.86 (m, 2H), 6.32 (s, 1H), 4.80 (d, *J* = 14.1 Hz, 1H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.78–3.68 (m, 2H), 3.56 (dd, *J* = 15.7, 5.8 Hz, 1H), 3.45–3.32 (m, 2H), 2.99 (tdd, *J* = 12.1, 7.4, 4.7 Hz, 3H), 2.86 (dt, *J* = 15.3, 3.5 Hz, 1H), 1.34–1.10 (m, 12H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 159.9, 130.6, 127.0, 114.4, 64.4, 56.9, 56.1, 55.2, 39.5, 37.6, 31.8, 29.2, 29.1, 27.8, 26.7, 22.6, 14.1. HRMS (ESI) *m/z* calculated for $C_{21}H_{35}N_2O_4S_2$ 443.2038 $(M+H)^+$, found 443.2046.

(*R*)-*N*-Hexyl-2-(4-methoxybenzyl)-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7e).

White solid, yield 50%. mp 165–166 °C. $[\alpha]_D^{20}$ -1.2 (c 0.85, CH_2Cl_2). FTIR: 3431, 2955, 2924, 2854, 1664, 1512, 1327, 1151, 1140, 1057, 849 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 6.92–6.87 (m, 2H), 6.32 (s, 1H), 4.80 (d, *J* = 14.0 Hz, 1H), 4.16 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.77–3.67 (m, 2H), 3.57 (dd, *J* = 15.7, 5.8 Hz, 1H), 3.48–3.32 (m, 2H), 3.07–2.92 (m, 3H), 2.86 (dt, *J* = 15.4, 3.5 Hz, 1H), 1.36–1.10 (m, 8H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 159.9, 130.6, 127.0, 114.4, 64.4, 56.9, 56.1, 55.2, 39.4, 37.6, 31.4, 29.1, 27.8, 26.3, 22.5, 14.0. HRMS (ESI) *m/z* calculated for $C_{19}H_{30}N_2O_4S_2Na$ 437.1545 $(M+Na)^+$, found 437.1552.

(*R*)-*N*-Isobutyl-2-(4-methoxybenzyl)-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7f).

White solid, yield 45%. mp 175–176 °C. $[\alpha]_D^{20}$ -0.7 (c 0.90, CH_2Cl_2). FTIR: 3427, 2955, 2926, 1664, 1514, 1327, 1153, 1140, 1126, 1057, 855, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.33 (m, 2H), 6.94–6.85 (m, 2H), 6.42 (s, 1H), 4.79 (d, *J* = 14.0 Hz, 1H), 4.19 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, *J* = 11.9, 5.9 Hz, 1H), 3.70 (dt, *J* = 14.7, 3.0 Hz, 1H), 3.57 (dd, *J* = 15.7, 5.8 Hz, 1H), 3.43 (dd, *J* = 15.7, 12.0 Hz, 1H), 3.37 (ddd, *J* = 14.6, 12.7, 3.9 Hz, 1H), 2.99 (ddd, *J* = 15.3, 12.7, 2.7 Hz, 1H), 2.93–2.84 (m, 2H), 2.81–2.74 (m, 1H), 1.57–1.51 (m, 1H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 159.9, 130.6, 127.0, 114.5, 64.3, 56.9, 56.0, 55.3, 46.8, 37.8, 28.2, 27.9, 19.9, 19.8. HRMS (ESI) *m/z* calculated for $C_{17}H_{26}N_2O_4S_2Na$ 409.1232 $(M+Na)^+$, found 409.1221.

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